Nitrogen-Containing Ligands for Asymmetric Homogeneous and Heterogeneous Catalysis

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I. Introduction

Practical asymmetric catalysis using transition metal complexes was inspired by the work of Kagan[1] and Knowles.[2] Their important results, based on the use of chiral phosphines as ligands for asymmetric hydrogenation, have induced a tremendous amount of work dealing with the synthesis and use of new chiral phosphine-containing complexes as catalysts. Numerous catalytic reactions allowing the enantioselective formation of C−H, C−C, C−O, C−N, and other bonds have been discovered over the last 30 years, often with spectacular results in terms of efficiency and selectivity.

More recently, asymmetric catalysis has been developed on a practical scale, since some very efficient catalytic industrial processes are currently carried out to produce chiral building blocks. For economic, environmental, and social reasons, interest

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Fabienne Fache graduated from Ecole Supérieure de Chimie Industrielle de Lyon in 1987. She went to the University of Strasbourg where she worked on geochemistry and steroid synthesis during her Ph.D. studies in the laboratory of Dr. P. Albrecht. In 1991, she joined the Centre National de la Recherche Scientifique in the group of Professor M. Lemaire. Apart from asymmetric catalysis, she is particularly interested in finding new methods for organic synthesis using heterogeneous catalysis.

Emmanuelle Schulz was born in Cayenne. She graduated from Ecole Supérieure de Chimie Industrielle de Lyon in 1989 and received her Ph.D. degree from the University of Lyon in 1992 for studies concerning the total synthesis of Strigol, under the direction of Professor P. Welzel at the Ruhr-Universität Bochum, RFA. After an industrial postdoctoral position at the Research Center La Dargoire (Rhône-Poulenc Agrochimie), she joined the group of Marc Lemaire in 1993. In 1997 she obtained a permanent position at the "Centre National de la Recherche Scientifique" (CNRS). Her research topics include the preparation of "organic materials" for various applications: chiral ligands for the heterogeneous asymmetric catalysis, organic conducting polymers for asymmetric electrocatalysis, and specific resins for depollution (especially useful for the petroleum industry).

in the preparation of enantiomerically pure compounds is growing. More than 30 years after the discovery of the above-mentioned methods, however, most chiral synthons are still produced from natural chiral building blocks or by performing racemic resolution (either diastereomer separation or kinetic resolution). There is, indeed, no simple and versatile method for the preparation of chiral molecules: numerous competitive methodologies have to be tested to offer, in each particular case, an optimal solution.

It appears that the contribution of asymmetric catalysis in the overall production of chiral chemicals is much lower than originally expected, which is surprising given the huge amount of work devoted to this subject, in both academic and industrial

M. Lorraine Tommasino was born in Mexico and received her Chemistry degree and the Gabino Barreda Medal in 1990 at the University of Mexico (UNAM). She then came to France and studied ruthenium dihydrogen complexes and their applications in homogeneous catalysis with Bruno Chaudret and received her Ph.D. degree from the University of Toulouse in 1994. In her postdoctoral stay in Paris in Eric Rose's group, she studied asymmetric oxidations catalyzed with metalloporphyrins. Since 1996 she has had a permanent teaching position "Maître de conférences" at the University of Lyon. Her research interests involve asymmetric homogeneous catalysis mainly in hydrogenation, hydrosilylation, and hydroformylation reactions.

Professor Marc Lemaire was born in 1949 in Paris (France). He was employed several years in the pharmaceutical industry as a technician,and then he obtained the engineer level (CNAM Paris 1979) and his Ph.D. degree at the Paris VI University (Professor J. P. Guetté; "New chlorinating reagent"). In 1983 he obtained a postdoctoral position in the University of Groningen (The Netherlands; Professor R. M. Kellogg; "Thiamacrocycles as ligand for asymmetric catalysis"). He returned to Paris and obtained an assistant position at CNAM, and then he became a professor at the Unversity of Lyon. His group is working in five main areas: (1) heterogeneous catalysis in fine chemistry, (2) asymmetric catalysis, (3) separation science, including new ligands for liquid–liquid extraction, new ionoselective materials, new complexing agents for nanofiltration-complexation systems, (4) organic conductors, including poly(thiophenes) and poly(pyrroles), and (5) deep desulfurization of gasoil.

research centers. Several factors are responsible for this lack of practical application, particularly the price of the catalyst precursor (both precious metal and optically pure ligand) and the difficulties encountered in the separation and recycling of the catalyst. A few processes have, however, permitted high turnovers. In these cases, the cost of the catalyst was considered to be negligible and so the catalyst was sacrificed during the workup procedure. Apart from these economic considerations, it is almost impossible to recycle phosphine-containing catalysts due to their low stability toward oxidation. Moreover,

this strategy is obviously in total contradiction with the general tendency toward ecological care in chemical industry. In summary, we can conclude that the chemical and economic characteristics of these catalysts were partly responsible for many problems encountered in the development of catalytic asymmetric processes.

Many evaluations of new chiral phosphorus-containing ligands are found in every issue of the major organic chemical journals, but they focus more often on interesting and original properties than on easy and straightforward synthesis, which is usually complicated. To facilitate separation of the product from the bulk of the reaction and recycling of the catalyst, some ligands have been modified to lead to elegant solutions, such as, for example, homogeneous supported catalysis, biphasic and supported biphasic systems, or use of supercritical solvents. All of these possibilities are interesting but require additional modifications of the catalyst and thus increase the difficulty of synthesis and the cost. As a consequence, catalyst recycling becomes even more important with such approaches, but this frequently leads to partial loss of activity and/or selectivity.

Although nitrogen-containing ligands were only rarely used in the 1970s and the 1980s, some of the first historic asymmetric catalysts were heterogeneous nitrogen-containing chiral systems. Very early, asymmetric reduction was reported on silk fibroin with palladium[3] and with Raney nickel modified by amino acids. The use of platinum as the metal modified with cinchona alkaloids has received much interest in the reduction of α-ketoesters.[4] Recently, many promising results have been revealed for nitrogen-containing ligands in asymmetric catalysis, as summarized in a 1994 review by Togni and Venanzi.[5] Considering the need for easy separation and an inexpensive recycling as already mentioned, these nitrogen-containing compounds appear to be interesting: in a short recent review devoted to functionalized polymers in organic synthesis,[6] only three references dealt with supported catalysts based on phosphine-containing ligands. On the contrary, most of the recent heterogeneous catalysts contained nitrogen as a chelating atom.

The aim of this review is to present a selection of some of the most important new results in the field of asymmetric catalysis by transition metal complexes with nitrogen-containing ligands. This report is also the occasion to point out the general potential of such ligands, especially when they give rise to stable, easily separable and recyclable catalytic systems.

Nitrogen-containing ligands present several distinct advantages. First, they are largely available in enantiomerically pure form, both in the chiral pool or as cheap industrial chemical intermediates. In addition, the production of chiral amines by resolution of racemates[7] is probably one of the easiest and best documented methods of enantiomer separation. Chirality on the nitrogen atom is nevertheless difficult to obtain: contrary to chiral phosphines, like DIPAMP,[8] the chiral nitrogen atoms are instantaneously epimerized at room temperature. The formation of a stable chiral center on a nitrogen atom is, however, possible by using bicyclic structures. Indeed, many chiral centers on nitrogen atoms exist in the chiral pool such as quinine, cinchonine, sparteine, strychnine, and emetine. Some of these easily available chemicals have already given rise to very efficient and enantioselective catalysts for both homogeneous and heterogeneous systems.

The second advantage of nitrogen-containing ligands lies in the chemistry of the nitrogen functional group itself. The chemistry of nitrogen is not always easy but has received abundant attention so that there exist, in most cases, numerous synthetic solutions to each possible transformation of these compounds. As a result, these synthetic facilities allow tailor-made modifications toward the preparation of ligands with specific physicochemical properties. Particularly, the interactions with the transition metals could be widely varied by preparing X-type ligands (amides, sulfonamides), L-type ligands (amines), or π-type ligands (such as imines, for example). Furthermore, a nitrogen-containing functional group can act as a strong base, as in guanidines, or as a strong nucleophile, as in hydrazines. The absence of an available d-orbital in such functionalities could, at first glance, be considered as a limitation for an effective interaction with transition metal complexes. This weakness could, nevertheless, be counterbalanced by numerous other types of interactions. Indeed, natural metal transition complexes (i.e., porphyrines) in which nitrogen acts as a ligand have already proven their efficiency not only for precious metal complexes (such as Rh, Pd, Ru,...) but also for early transition metal complexes (such as Mn, Cu, Ni, Co,...).

In this article, we will describe the most recent results concerning the use of nitrogen-containing ligands for asymmetric catalysis. We have chosen to classify these results according to the type of catalytic reaction involved, i.e., regarding the formation of new bonds (C−H, C−N, C−S, N−S, C−O, S−O, and C−C). The reactions will be described in relation to the structure of the N-containing ligand used, where homogeneous systems and, as often as possible, their heterogeneous counterparts are reported.

II. C–H Bond Formation

The catalytic formation of the C−H bond is accomplished mainly by using molecular hydrogen, metallic hydrides, or organic hydrides by a hydride transfer reaction. From a mechanistic point of view, the first reaction is obtained via an oxidative addition and the others are Meerwein−Ponndorf−Verley-type reactions. We have chosen to organize our article according to this scheme.

II.1. Hydrogen as Reducing Agent

The first example of enantioselective hydrogenation was performed in 1939 using PtO_2 and cinchonine as a chiral modifier.[9,10] Eight percent enantiomeric excess (ee) was measured for the reduction of β-methylcinnamic acid. With a silk fibroin support, up to 66% ee was reached.[3] In the late 1960s, Knowles[11] and Kagan[12] independently developed Rh(I) com-

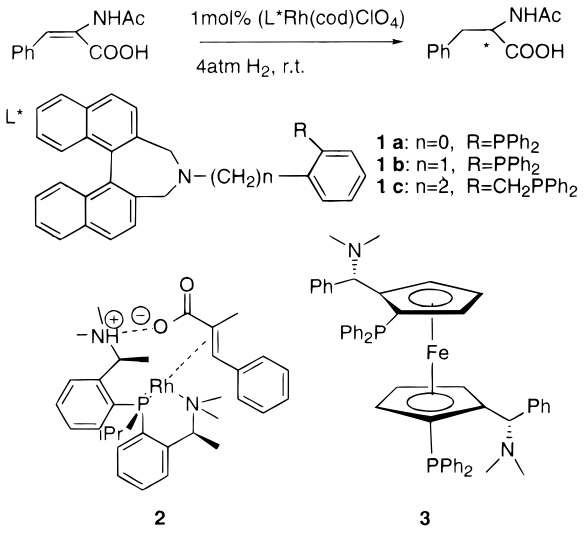
plexes of chiral chelating phosphines leading to 90% ee. Until then, a tremendous amount of work was done on this class of ligands, excluding most of the other types of Lewis bases, and reached its highest point with Noyori's BINAP ligand (almost 100% ee).[13] Nevertheless, with the beginning of the 1990s, more and more articles dealing with ligands containing nitrogen functional groups appeared in the literature.

II.1.1. Homogeneous Systems

Literature data have been classified according to the function to be reduced.

II.1.1.1. Reduction of C=C Bonds. In 1995, Wimmer and Widhalm showed that chiral aminophosphines[14] allowed the enantioselective hydrogenation of C=C bonds with Rh catalysts and with cationic complexes of **1b**. The reduction of (*Z*)-acetamidocinnamic acid was performed with 77% ee (Scheme 1).

Scheme 1

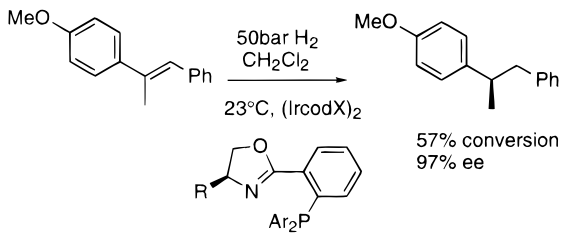


Yamagishi et al.[15] reported the easy synthesis and use of chiral phosphinediamines and Rh (Scheme 1; **2**) for the enantioselective hydrogenation of acrylic acid derivatives. NMR studies proved that the two N atoms of the ligands acted differently. One nitrogen atom, acting as a ligand, was bound to the rhodium, and the other interacted with the functional group of the substrate. Up to 92% ee was reached with this system.

Recently, Knochel et al.[16] reported the use of C_2-symmetric ferrocenyl diaminodiphosphines (diamino FERRIPHOS, **3**; Scheme 1) for the rhodium-catalyzed enantioselective hydrogenation of methyl α-acetamidoacrylates. More than 99% ee was measured on the resulting acetamido alanine, which is one of the best results obtained for such a reduction.

We note that until now ligands containing only nitrogen atoms are not suitable for the reduction of dehydroamino acids and that the simultaneous presence of phosphorus and nitrogen atoms in the ligands is necessary. Nevertheless, Noyori's BINAP is one of the most efficient ligands and by far the most used ligand for this transformation. For a review on the reduction of dehydroamino acids, see Nagel and Albrecht.[17] Olefins were also reduced with P,N-ligands[18] using iridium catalysts (Scheme 2).

Scheme 2

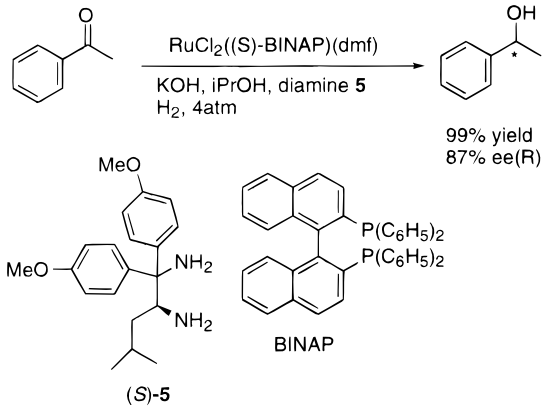


4 : R= tBu, Ar= o-Tol, X=PF_6^-

We wish to emphasize the excellent enantioselectivity reported for such unfunctionalized olefins, for which no efficient reaction with rhodium− or ruthenium−phosphine catalysts has been described.

II.1.1.2. Reduction of C=O Bonds. Diphosphine complexes of Rh and Ru have been used successfully for the asymmetric hydrogenation of functionalized ketones with almost 100%[19] ee. For β-diketones, Genêt's group[20] has developed efficient systems. High enantioselectivity was, nevertheless, difficult to attain with phosphine ligands for the reduction of α-diketones and of simple ketones lacking heteroatoms that anchor the metal. For such compounds, the use of chiral nitrogen ligands complexed with Rh and Ir appeared to be much more efficient. In 1995, Noyori[21] reported the use of both BINAP−Ru catalysts and a chiral diamine as an additional ligand, allowing the reduction of various simple aromatic ketones with high ee (up to 99%). The synergetic effect of the amine is noteworthy, as BINAP−Ru catalysts alone were unable to hydrogenate simple ketones devoid of heteroatoms to interact with the catalyst (Scheme 3).

Scheme 3

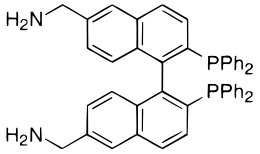


Despite the use of conditions close to those of hydrogen transfer reactions (KOH, ^{i}PrOH), the authors claimed that H_2 was the real reductant. It is very revealing to see that Noyori's group, famous for its work on phosphines, moved onto nitrogen ligands. The same system[22] turned out to be efficient for the selective hydrogenation of unsaturated ketones into the corresponding unsaturated alcohols with a chemioselectivity comparable to that obtained with stoichiometric $NaBH_4$ (> 98.5%) and enantioselectivity up to 98%. Using racemic TolBINAP and the chiral

(*S*,*S*)-1,2-diphenylethylenediamine, the same group performed the asymmetric activation of racemic phosphines.[23] Thus, 95% ee (100% yield) was reached for the hydrogenation of 2,4,4-trimethyl-2-cyclohexenone instead of 96% with enantiomerically pure (*R*)-TolBINAP. Further optimization led to a particularly efficient catalytic system, as TON as high as 2 400 000 can be measured with 80% ee (100% yield) for the reduction of acetophenone.[24] This synergetic effect of phosphines and diamines as ligands is by far the most important result in this field of the recent years and might be a solution for numerous problems in asymmetric catalysis.

Taking into account the efficiency of the dual phosphine−diamine catalysis, we have synthesized a BINAP derivative containing two amine functionalities[25] (Scheme 4).

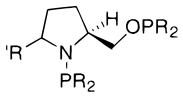
Scheme 4



At total conversion, only 18% ee was measured for the reduction of acetophenone. In contrast, BINAP alone does not react under these conditions.

Phosphorus−nitrogen-containing[26,27] ligands such as amino(amido)phosphinephosphinite bisphosphines complexed with ruthenium(II) were used in the asymmetric hydrogenation of activated ketones and led to 95% ee in the case of α-ketoesters (Scheme 5).

Scheme 5



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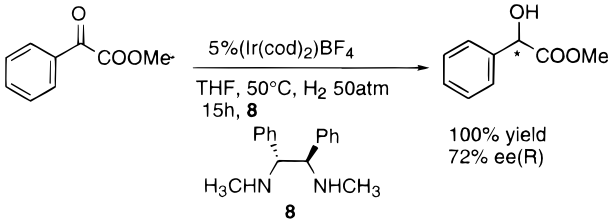
R = cyclohexyl, phenyl
R' = H, =O

It could be assumed, however, that in these compounds the nitrogen atom did not chelate the metal.

C_2-symmetric chiral diamines complexed to transition metals were also used in the hydrogenation of the prochiral keto group. With cationic iridium, up to 72% ee was measured[28] (Scheme 6).

Scheme 6



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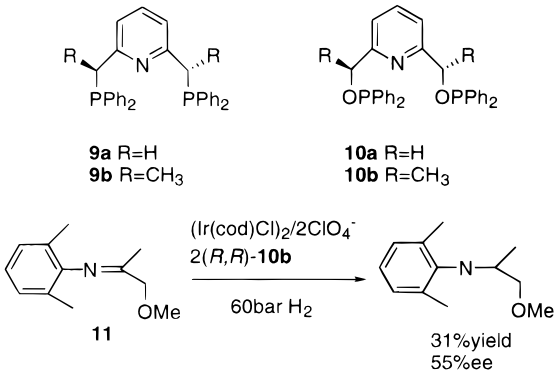
In the case of rhodium catalyst, the hydrophilic character of the diamine and the addition of 1 equiv of β-cyclodextrine (β-CD) per metal atom allowed Lemaire et al. to work in aqueous media without further modifications of the ligand structure.[29] This feature is of particular interest due to the large potential scope of applications of catalysis in water. There are, as yet, only a few examples of asymmetric catalysis in aqueous media;[30] they are performed with modified (usually sulfonated) phosphines which are difficult to synthesize. Modifications of the ligands are not necessary when diamines and cyclodextrine are combined. This can be considered as one of the main advantages of N-ligands over P-ligands.

II.1.1.3. Reduction of C=N Bonds. Imines[31] were also reduced by [M(PNP)(diene)]$^+$ complexes (M = Ir or Rh; diene = COD or NBD) with PNP representing a tridentate diphosphine ligand of C_2-symmetry (Scheme 7).

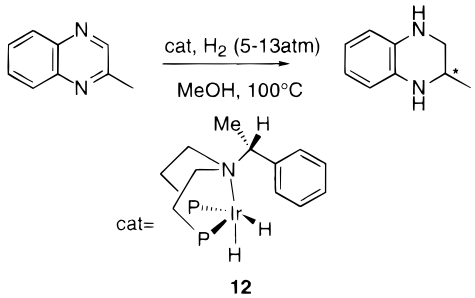
Scheme 7



The best results were obtained for the reduction of **11**, an intermediate in the synthesis of pesticides. The authors explained the low chemical yield by a deactivation of the catalyst due to the irreversible formation of the dihydride complex [Ir(PNP)H_2]$^+$. Even if both activity and selectivity are low compared to the results obtained by other groups with phosphine ligands[32] (80% ee for ferrocenyl−diphosphine-type ligands), these primary results are encouraging because the ligand structures can be modified. Protic amines[33] or phthalimides[34] were also used as cocatalysts for the asymmetric hydrogenation of imines by diphosphine-iridium(I) catalysts. For a review on the reduction of imines, see ref 35.

Other P,N,P-ligands were used with Ir as in the hydrogenation of 2-methylquinoxaline (90% ee) into the corresponding tetrahydro compound (Scheme 8).

Scheme 8



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It is noteworthy that for the reduction of imine derivatives, no ligand containing only nitrogen as a heteroatom was described: phosphorus atoms were always necessary. This could be due to competition between the ligand and the amine, formed after reduction of the corresponding imine, to chelate the

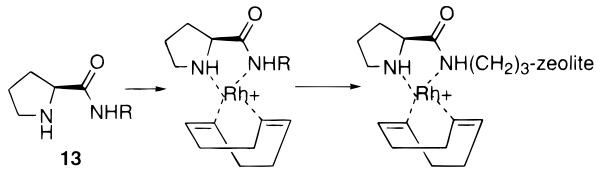
metal. The phosphorus part of the ligand increases the stability of the active complexes. This property of complex formation between transition metals and amines was explored by Baiker et al.,[36−38] who enantioselectively hydrogenated α-ketoesters via imine formation with Pt/Al_2O_3 modified by 1-(1-naphthyl)ethylamine. This result will be discussed later.

II.1.2. Heterogeneous Systems

Several types of heterogeneous systems can be considered. The oldest system is a metal particle with a small chiral molecule (a modifier) interacting with noncovalent bonds. The second type of system, which is probably the most developed system up to now, is supported homogeneous catalysis using organic or inorganic supports. These two strategies were successfully applied with nitrogen-containing ligands. New approaches using biphasic or supported liquid−liquid systems, organic salts, or supercritical liquids as solvants are currently studied in numerous industrial and academic laboratories. To our knowledge very few of these approaches have been applied to nitrogen-containing ligands.

II.1.2.1. Reduction of C═C Bonds. In 1991, Corma's group proposed catalytic systems based on Rh-complexes with N-containing chiral ligands anchored on modified USY zeolites[39] (Scheme 9).

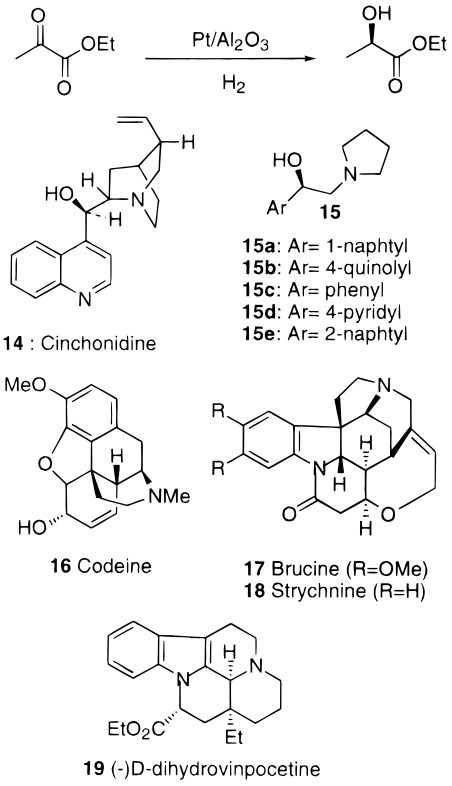
Scheme 9



This heterogenization of the homogeneous system produced a remarkable increase of enantioselectivity in the hydrogenation of *N*-acyldehydrophenylalanine derivatives. In some cases, ee increased from 54% with the homogeneous system to 94% with its zeolite counterpart. The catalytic system was claimed to be reusable several times without any decrease in activity or rhodium content. Later, the same group tried various other bulkier ligands, but the enantioselectivity obtained with the heterogeneous system remained close to that measured with the homogeneous one.[40] The heterogenized complexes are, nevertheless, still more stable than their homogeneous counterparts. It seems that a compromise between the steric hindrance of the substrates and of the ligands and the size of the mesopores or channels in the zeolite is crucial if activity and enantioselectivity are to be controlled. This result, which is obtained with several approaches (organic, inorganic, and organometallic) highlights the value of nitrogen-containing ligands in homogeneous supported asymmetric catalysis.

II.1.2.2. Reduction of C═O Bonds. The heterogeneous reduction of α-ketoesters has been extensively studied. Thus, the Pt/Al_2O_3 catalyst modified by cinchona alkaloids is one of the oldest heterogeneous catalytic systems using surface modifiers studied in the literature[4] (Scheme 10).

Scheme 10



Pt/Al_2O_3 modified by cinchona alkaloids allowed the reduction of α-ketoesters, and since its discovery by Orito[41] in 1978, no new chiral catalyst with similar efficiency has been reported. Finely dispersed poly(vinylpyrrolidone)-stabilized platinum clusters[42] were used with success in the same reaction. Up to 97% ee in favor of the (*R*)-(+)-methyl lactate was measured in the presence of cinchonodine. Contrary to most observations of the Pt/cinchonidine system, the smallest Pt clusters gave the best results despite having no flat surface large enough for the adsorption of cinchonidine.

Various groups have studied the modifier/catalyst/substrate interaction to find new classes of ligands for this system. Studies on the structural requirements for the modifiers to reach good to excellent ee led Pfaltz and Baiker[43] to the conclusion that it was the interaction of the substrate and the quinuclidine part of the ligand which determined the ee. They, therefore, proposed ligands with simpler structures (Scheme 10, structures **15**). With structure **15a**, 75% ee was reached at 100% conversion compared to the maximum of 95% ee obtained with the more classic dihydrocinchonidine.[44] Wells et al.[45] proposed codeine **16** and strychnos alkaloids **17** and **18** to induce enantioselectivity at Pt surfaces (Scheme 10). Only low ee's were measured, however (<15%). (−)D-Dihydrovinpocetine **(19)**[46,47] was also used as a modifier for the reduction of ethylpyruvate (ee < 50%) and for the reduction of the prochiral C═C bond of isophorone (38% ee with a Pd black catalyst).

To summarize, the best ligand remained the cinchona alkaloid for high-pressure conditions and 1-(1-naphthyl)ethylamine for low-pressure conditions. Various other substrates, like ketoacids,[48] trifluoro-

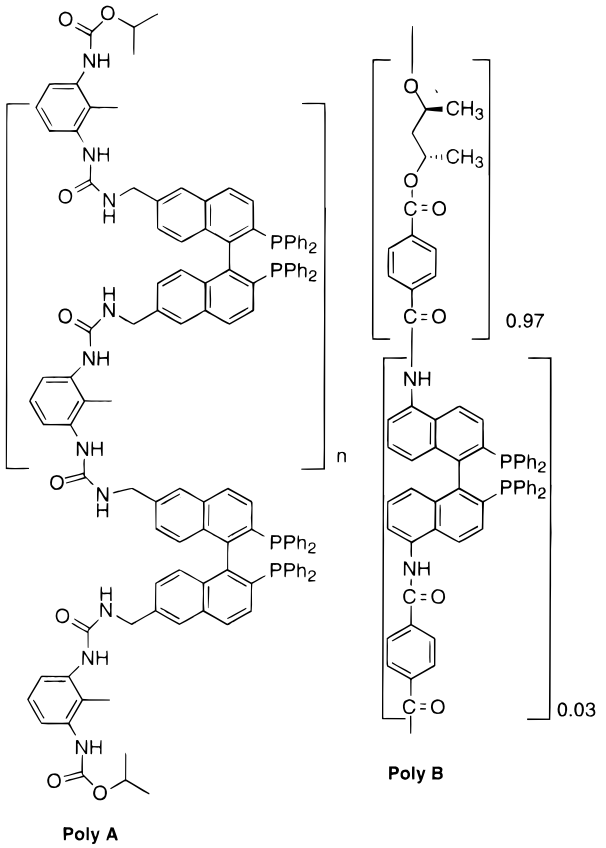
acetophenones,[49] and conjugated diketones,[50] were successfully reduced with the same system. Recently, α-ketoamides were also reduced into the corresponding alcohols with up to 60% ee over Pt/Al_2O_3 modified by cinchonidine.[51] Up to 91% ee was reached in the case of cyclic imidoketones.[52]

Dihydrocinchonidine derivatives have recently been used with platinum colloids[53] to reduce α-ketoesters. The colloidal system led to 81% ee instead of 91% for the conventional system. The activity is, nevertheless, 3 times higher with colloids.[53] For a review on chirally modified Pt metal catalyst, see Baiker[49] and for the kinetic studies see Blackmond.[55]

The work of Baiker et al. in supercritical fluids[56] is of high interest. Ethylpyruvate was reduced using a Pt/Al_2O_3 catalyst modified by cinchonidine in ethane under supercritical conditions. The same ee as in nonsupercritical conditions was measured, but the reaction rate was higher (by a factor of 3.5). Supercritical conditions allowed a high substrate/catalyst ratio, which is important in view of a possible industrialization of the reaction via a continuous fixed-bed reactor.

Finally, we reported the heterogenization of the BINAP system described in Scheme 4. The polymerization by polyaddition of *diam*-BINAP with 2,6-tolylene diisocyanate afforded a polyurea[25] (Scheme 11). With diphenylethylenediamine as auxiliary and

Scheme 11

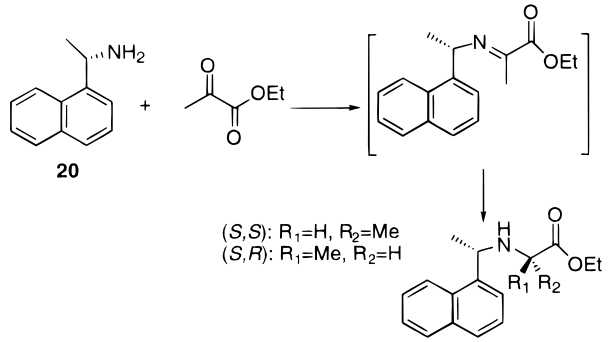


$[RuCl_2(benzene)]_2$, 96% ee at 100% conversion was reached for the reduction of naphthylmethyl ketone. The same ee was obtained by Noyori with BINAP and the same amine. Polymer **A** (poly **A**) was reused with success 4 times without loss of activity or selectivity. At the same time, Chan et al. published up to 94% ee with the same type of polymer (poly **B**) for the reduction of dehydronaproxen.[57]

The use of material having ligand in the main chain of a polymer appears to be one of the recent advances in homogeneous supported catalysis. These two last examples illustrate the need of nitrogen functionnal groups in order to obtain reusable catalytic material even in the case of well-known diphosphine ligands.

II.1.2.3. Reductive Amination. Recently, a new family of modifiers derived from 1-(1-naphthyl)-ethylamine **20** was reported. In fact, the actual modifier is the product of reaction between the substrate ethylpyruvate reduced in situ over Pt/alumina.[36−38] The reaction proceeds via the formation and the subsequent reduction of the imine. Up to 82% de was measured with a modifier/reactant molar ratio of 1:15 000, which corresponds to a modifier:Pt (surface) molar ratio of 1:1. This is an example of heterogeneous catalytic self-replication. This strategy of reductive alkylation of **20** with various aldehydes or ketones provides access to numerous modifiers (Scheme 12).

Scheme 12



II.2. Borohydride and Other Inorganic Hydrides as Reducing Agents

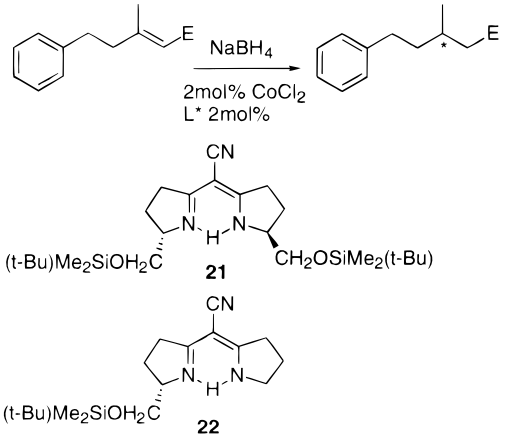
The use of inorganic hydrides for asymmetric catalytic reduction is of special interest due to the simplicity of the procedure and of the required equipment. Two main classes of boron derivatives have been used as reducing agents in asymmetric catalysis with nitrogen-containing ligands. The first class of boron derivatives are oxazaborolidines prepared from amino alcohols[58] in catalytic amounts in addition to stoichiometric or substoichiometric quantities of borane (BH_3 or catecholborane), the hydride being transferred via a concerted mechanism. Oxazaborolidines contain a Lewis-acidic center and a Lewis-basic center side by side able to activate both the carbonyl function and the borane. This unique property explains the high reactivity of the system toward reduction and the fact that phosphorus analogues could not be obtained. The second class of boron derivatives used as reducing agents are inorganic borohydrides, mostly with cobalt as a catalyst. This involves a hydride transfer reaction via a transition metal complex, which acts as a chiral reagent regenerated in situ by the inorganic hydride.

For a review on asymmetric boron-catalyzed reactions, see refs 59 and 60.

II.2.1. Homogeneous Systems

II.2.1.1. Reduction of C=C Bonds. Pfaltz et al.[61] developed chiral semicorrin ligands and used them for the reduction of electrophilic C=C bonds, typically those found in α,β-unsaturated carboxylic esters, carboxamides, nitriles, and sulfones (Scheme 13).

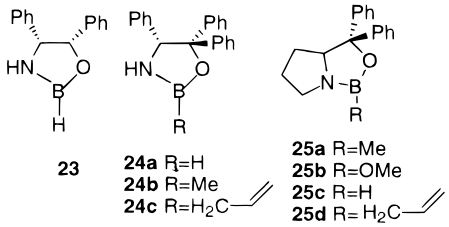
Scheme 13



High ees were measured (up to 96%), and it is interesting to note that the C_2-symmetry of ligand **21** favors a good ee in all the cases except for α,β-unsaturated sulfones, for which disymmetric "semicorrins" **22** proved to be superior. For a review on chiral semicorrin ligands in asymmetric catalysis, see refs 62 and 63.

II.2.1.2. Reduction of C=O Bonds. Since the first results on the use of oxazaborolidines by Itsuno[64] et al. and their improvement by Corey[53] et al., numerous examples have been published in the literature using various structures (Scheme 14).

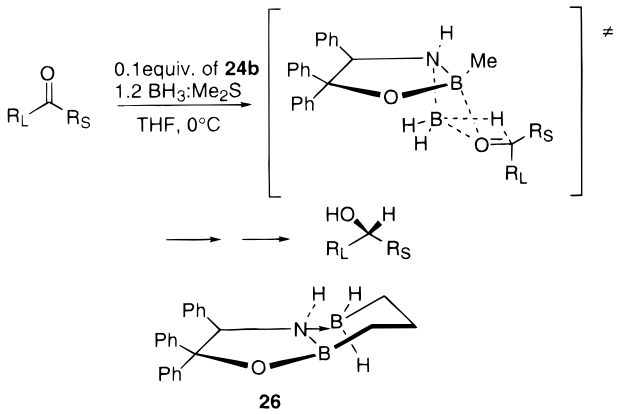
Scheme 14



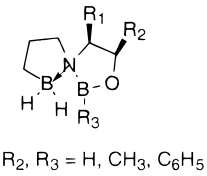
Stucture **23** allows the reduction of acetophenone with 99% ee, but reduction of aliphatic ketones gives low ee (<30%[66]). Addition of alkylaluminum[67] significantly accelerates the rate of the reduction. The authors claim that it is not a simple Lewis acid effect. Structure **24b** leads to the same ee for acetophenone as **23** but is more effective for aliphatic ketones: thus, 72% ee is obtained with 2-octyl ketone, which is particularly high for such products.[68] The reaction parameters have been extensively studied, and among them the temperature appears to be of special importance.[69,70] The intermediate generally proposed is depicted in Scheme 15.[68]

Cai et al.[71] reported that two hydrogen atoms could react from each BH_3, the second transfer thus being less selective. The corresponding β-allyloxazaborolidines were, therefore, synthesized (structures **24** and **25**) leading to more constricted transition states. In this hypothesis, only one hydride of the BH_3 could be transferred to the substrate (**26**, Scheme 15). With these new ligands, the activity is maintained but the selectivity is slightly lower (59% ee for 2-octanone instead of 64%). Recently, LeToumelin and Baboulène[72] synthesized *N*-spiroazaborolidine for the same purpose (Scheme 16). Despite high activity (yield reduction > 95%) the enantioselectivity remains low (ee < 38%).

Scheme 15

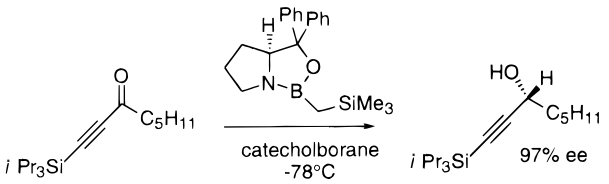


Scheme 16



Studies were also performed to quantify the influence of the acidity of the oxazaborolidine boron. Replacing trimethylborane by trimethylborate (structure **25b**) allowed an increase of both activity and selectivity. Thanks to this modification, 2-, 3-, and 4-acetylpyridine were reduced with high ee (up to 99%).[73] Corey[74] et al. reported that substitution of the borane by a larger alkyl group resulted in marked enhancement of ee in the enantioselective reduction of achiral α,β-ynones (Scheme 17).

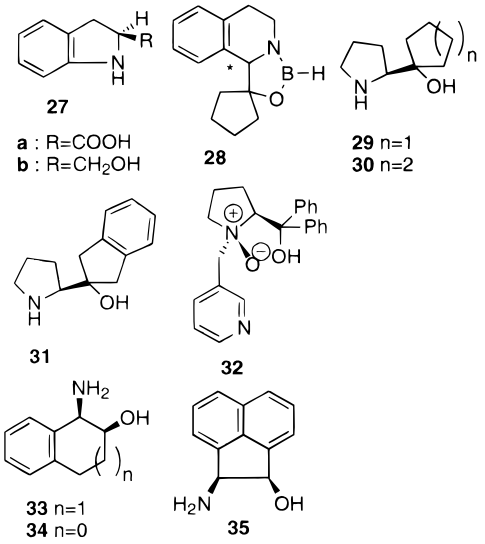
Scheme 17



This high ee is due to a novel remote steric effect across the C−C triple bond involving both the distal $^i Pr_3Si$ group on the substrate and the Me_3SiCH_2 substituent on the boron atom of the catalyst. This catalyst was also efficient for the reduction of β-silyl- or β-stannyl-substituted α,β-enones (ee up to 94%).[75] Catalyst **25c** allows the reduction of imides[76] with up to 94% ee and moderate to good yields.

To increase rigidity and to limit the number of possible conformations of the intermediates, cyclic α-amino acids were also tested in the same reaction in comparison to their corresponding amino alcohols.[77] The later gave better ee than the former even though the enantioselectivity remained moderate (<52%) with this type of structure (Scheme 18).

Scheme 18

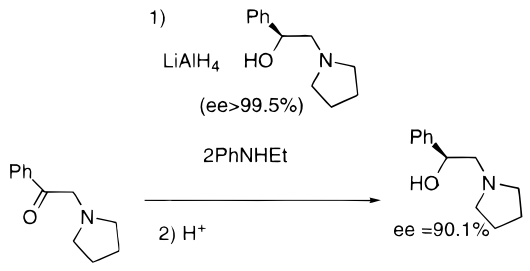


After modification of structure **27**, 88% ee was obtained in the case of acetophenone with the in-situ-formed oxazaborolidine[78,79] **28**. Other structures (**29**−**31**) derived from proline also gave good selectivities (57−96% ee). Among these structures, indanol **31** was shown to be the most effective catalyst for reduction by borane of prochiral ketones into the corresponding alcohols.[80]

Homochiral prolinol *N*-oxide derivatives (**32**) have been synthesized by oxidation of the appropriate tertiary amine, the *N*-oxide being formed syn to the side chain hydroxyl group.[81] In particular, catalysts obtained from **32** gave 96% ee for the reduction of α-chloroacetophenone. All these catalytic systems were derived from the chiral pool. There are also examples of man-made chiral auxiliaries such as *cis*-1-amino-1,2,3,4-tetrahydro-2-naphthalenol **(33)**,[82,83] *cis*-1-amino-2-indanol **(34)**,[84] and *cis*-2-amino-1-acenaphthenol **(35)**.[85] They give good ee (up to 95%) with BH_3·SMe_2 as reductor. Boron derivatives with a structure similar to that of **34** have been patented for the enantioselective reduction of ketones.[86]

Enantioselective self-replication in the asymmetric autoinductive reduction of ketones has been reported for the same reaction with high ee[87] (Scheme 19).

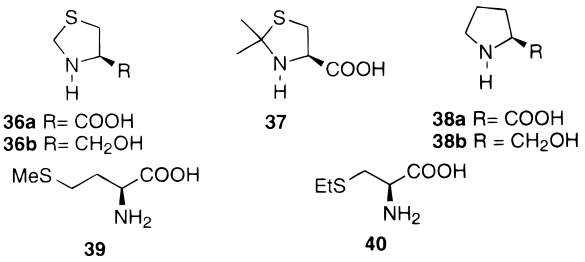
Scheme 19



Aside from the alkylation of aldehydes, this is the only example of self-replication in asymmetric catalysis. This introduces a new concept into asymmetric catalysis.

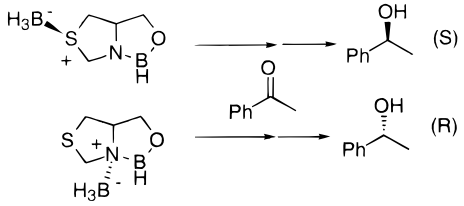
Various sulfur-containing ligands were also tested[88,89] (Scheme 20).

Scheme 20



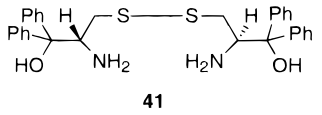
Moderate ee were measured (<50% with acetophenone). This can be explained by the ability of BH_3 to coordinate with either the nitrogen atom or the sulfur atom. As the boron of the oxazaborolidine moiety coordinates with the prochiral ketone cis to the BH_3, the two enantiomers could be obtained, which lowered the ee (Scheme 21).

Scheme 21



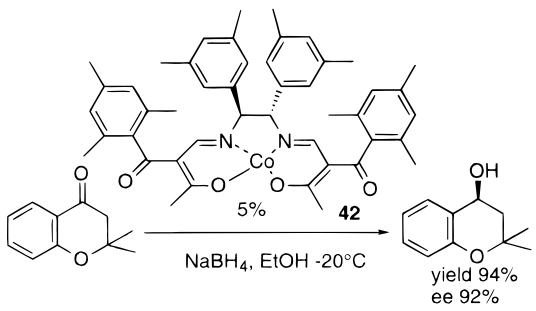
With C_2-symmetric bis-β-amino alcohols the enantioselectivity was improved (up to 98% ee with **41**). The presence of a primary amino group combined with a less sterically demanding α-substitution in the borane reduction seemed to be crucial for a good induction[90] (Scheme 22).

Scheme 22



Mukaiyama[91,92] et al. reduced ketones with $NaBH_4$ and catalytic amounts of optically active cobalt(II) complexes (**42**) having β-oxoaldimine ligands (Scheme 23).

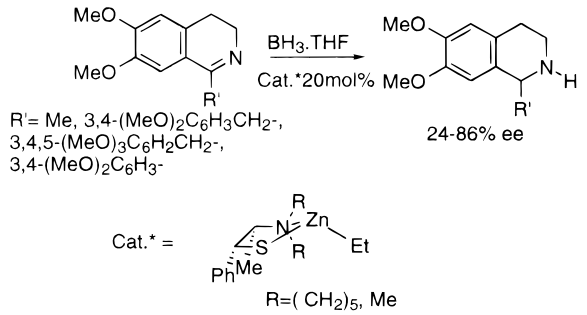
Scheme 23



A patent was obtained by Mitsui Petrochemical Ind. for the preparation of optically active alcohols by this method.[93] The addition of an appropriate alcohol (tetrahydrofurfuryl alcohol, methanol, or ethanol) as a modifier of the borohydride, combined with the use of a suitable aldimine ligand for the cobalt catalyst, led to very high ee (>90%) for the reduction of aromatic ketones with $NaBH_4$.[94]

II.2.1.3. Reduction of C═N Bonds. Recently, Kang et al. reported the enantioselective catalytic reduction of dihydroisoquinoline derivatives with BH_3·THF using thiazazincolidine complexes[95] (Scheme 24).

Scheme 24



The chiral Lewis acid can coordinate to the lone pair on the nitrogen of the dihydroisoquinoline in two ways. For both electronic and steric reasons, one of the two species thus obtained is much lower in energy than the other ,which explains the good enantioselectivity obtained with this system.

Oxazaborolidines of type **21** were also used successfully in the asymmetric reduction of ketoxime ethers into optically active O-substituted hydroxylamines as up to 99% ee's were obtained.[96]

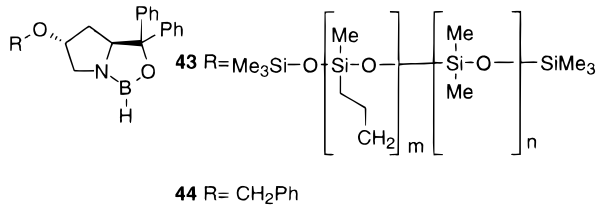
Aldiminato cobalt(II) complexes are also applicable to the reduction of C═N bonds in aromatic imines.[97] In particular, *N*-phosphinyl imines led to better ee (>90%)[82] than those measured with *N*-tosyl, and the resulting *N*-phosphinylamines were smoothly deprotected. Surprisingly, this system is not suitable for oxime and oxime methyl ether derivatives.

II.2.2. Heterogeneous Systems

Very selective and efficient methods using inorganic hydrides have been reported during the past few years. There are, nevertheless, two main drawbacks to the development of such methodology on a larger scale, the most important being the relatively low substrate/catalyst ratio. Several attempts to separate and recycle the catalysts have been made. For example, Wandrey et al. reported the use of a polymer-enlarged soluble oxazaborolidine catalyst[98] (Scheme 25).

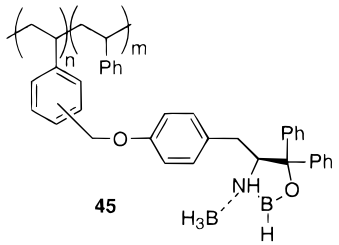
Reduction of acetophenone was carried out at room temperature in THF, with **43** and BH_3·SMe_2 complex as reducing agent to give phenylethanol of 97% optical purity. The same enantioselectivity was reached with the non-polymer-enlarged oxazaborolidine **44**. The polymeric-enlarged catalyst **43** could

Scheme 25



be retained by a nanofiltration membrane. Thus, with polymer **45** (Scheme 26) the reduction of ketones

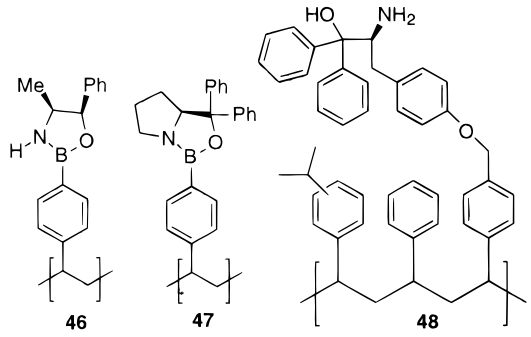
Scheme 26



could be performed in a continuously operated membrane reactor equipped with a nanofiltration membrane with an enhancement of total turnover number from 10 to 560 (equivalent to 0.18 mol % catalyst for an average ee of 91%).[99]

Other examples of heterogeneous polymeric systems have been published. Two possibilities of binding are described: via the boron atom **46**,**47**[100,101] or via the amino alcohol **48**[102] (Scheme 27).

Scheme 27



In the case of catalysts **46** and **47**, the selectivity achieved with the heterogeneous system is the same as the selectivity measured with the nonpolymeric catalysts (respectively 86% ee for **46** and 98% ee for **47** in the case of acetophenone). With **48** the ee is lower. In all the cases the catalyst can be recovered by simple filtration and reused at least 3 times without loss of activity and selectivity.

Finally, chiral reverse micelles formed from chiral surfactants derived from enantiomerically pure ephedrine were tested for the reduction of prochiral ketones with $NaBH_4$.[103] Only modest ee's were measured (<27%), but improvement may be obtained by modification of the nature of the chiral surfactant. Using the same approach, Rico-Lattes and co-workers obtained up to 99% ee on acetophenone at the "pseudo-micellar" interface of a chiral amphiphilic

dendrimer[104] with a polyamine core and sugar derivatives at the surface.

II.3. Hydride Transfer Reduction

Hydride transfer reactions use sources of hydrogen other than molecular hydrogen such as cyclohexene, cyclohexadiene, alcohols, formic acid, or inorganic reagents such as hydrazine.

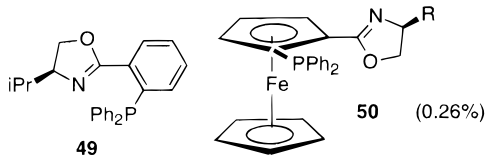
$$DH_2 + A \overset{cat}{\rightleftharpoons} D + AH_2$$

This method avoids all the risks inherent to molecular hydrogen, and chemoselectivities can be modulated by the proper choice of hydride donor. Several functions can thus be reduced, and various metals have also been tested with success. These different parameters will be discussed in the following part of the review. For a more complete review on hydride transfer reactions, see Gladiali et al.[105] Unlike with asymmetric hydrogenation with molecular hydrogen, the most used ligands contain nitrogen atoms and not phosphorus atoms.

II.3.1. Homogeneous Systems

II.3.1.1. Reduction of C=O Bonds. Historically, phosphorus compounds were the first type of ligands used in hydride transfer reduction. Introduction of nitrogen atoms in the structure of the ligands was the key for the increase in the use of these types of structures in hydride transfer reactions. Thus, complexes of ruthenium and phosphinooxazolines were found to proceed with excellent turnover and with up to 94% ee on acetophenone (ligand **49**).[106] An ee of 60% was measured on cyclohexyl methyl ketone, the enantioselective reduction of which is still unsolved (Scheme 28).

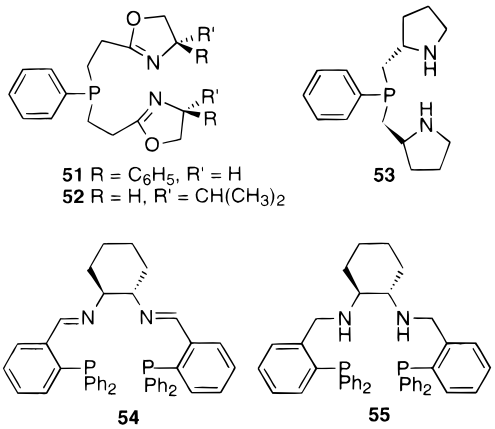
Scheme 28



Chiral ferrocenyl ligands were also tested in hydride transfer reduction with ruthenium,[107,108] leading to 94% ee on acetophenone (**50**, Scheme 28). The authors have shown that the phosphine part of the (phosphinoferrocenyl)oxazoline **(50)** was necessary for the reaction to proceed with high activity and selectivity. These two types of ligands are devoid of C_2-symmetry and thus potentially lead to several diastereoisomeric complexes which could exhibit different reactivities and selectivities. It is therefore difficult to rationalize the structure/reactivity relationship. Tri- or tetradentate ligands with C_2-axis structures were thus proposed[109,110] (Scheme 29).

Curiously, ruthenium complexes of **51** exhibited higher selectivities with dialkyl ketones (63−92% ee) than with alkyl−aryl ketones. For example, 92% ee

Scheme 29

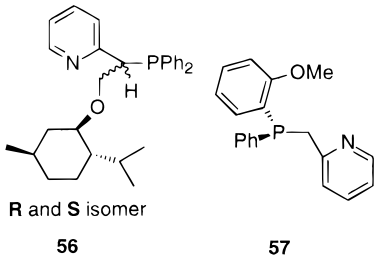


in 25 h at room temperature was measured with terbutyl methyl ketone (85% conversion), which is the highest enantioselectivity achieved so far for dialkyl ketones in hydride transfer reduction.

Other P,N-ligands were reported, such as the C_2-symmetric diphosphine/diamine tetradentate ligands described by Noyori[111] (Scheme 29). These compounds have two phosphorus atoms and two harder nitrogen atoms. Interestingly, the two ligands react very differently, depending on the type of nitrogen atoms. In the reduction of acetophenone, the diimino ligand **54** is almost inactive whereas the diamino ligand **55** gives 97% ee in 91% yield after reaction for 25 h at room temperature. NMR studies show that the difference between the sp^2- and sp^3-hybridized nitrogen atoms does not seem to have a significant electronic influence on the Ru center. The absence of available p-orbitals is the only difference which could be taken into account to explain this behavior. The NH function should be responsible for the high reactivity of the $P_2(NH)_2$-based catalyst.

Hemilabile P,N,O-tridentate ligands lead to stable complexes with ruthenium (Scheme 30).[112] Depend-

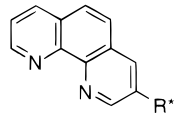
Scheme 30



ing on the isomer, the hemilabile character in solution is due either to the pyridyl arm or to the ether arm. Nevertheless, even if these ligands exhibit high activity, they lead to moderate enantioselectivity (no more than 60% ee for the reduction of acetophenone).

Optically active ligands containing pyridine-derived ring systems have been used in asymmetric hydride transfer reduction with various metals and hydride sources. Thus, Gladiali et al.[113] obtained 65% ee in the reduction of acetophenone with a dissymmetric chiral 3-alkyl phenanthroline-rhodium catalyst and ^{i}PrOH as hydride donor (Scheme 31).

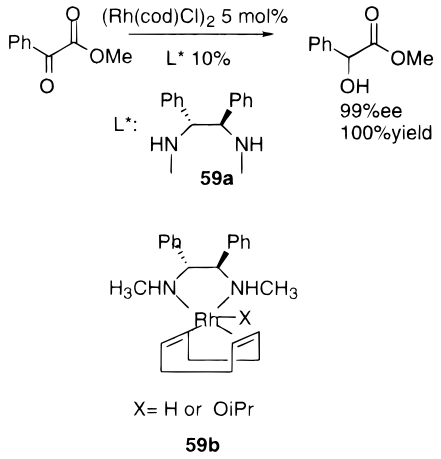
Scheme 31



58a R*= EtMeCH-
58b R* = tBuMeCH-

With C_2-symmetric chiral phenanthrolines, no induction was detected. The rhodium precursor was also important: $[Rh(cod)Cl]_2$ was more selective but less active than $[Rh(hd)Cl]_2$, and the temperature has no effect on the ee. In 1993, 67% ee was measured in the same reaction on acetophenone with C_2-symmetric diamines, up to 99% ee was obtained in some cases (Scheme 32).[114]

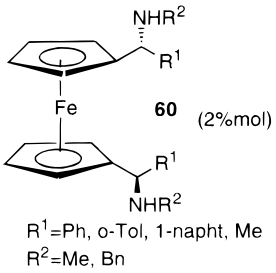
Scheme 32



These results were particularly interesting since complexes with nitrogen donors containing N−H bonds are generally not suitable for most organometallic reactions, the H on the N being acidic enough to react with nucleophiles. In the case of diamines **59a**,[115] it was postulated that the nitrogen atom became a stereogenic center when bound to the rhodium. The chirality was therefore closer to the metal center than for sp^2 ligands such as phenanthrolines, for which the stereogenic center has to be located far away on the aromatic ring. Moreover, with diamines, $[Rh(hd)Cl]_2$ turned out to be more selective but less active than the cod precursor and there was an increase of ee with the decrease of temperature. The difference of behavior between these two classes of ligands may be due to the fact that phenanthrolines are sp^2-type ligands whereas diamines are sp^3 ligands. As for the mechanism, Gladiali et al. claimed that there are two bidentate ligands on the rhodium whereas studies with diamines show that only one diamine chelates the metal[116] and that one diene is still present on the metal center (**59b**).

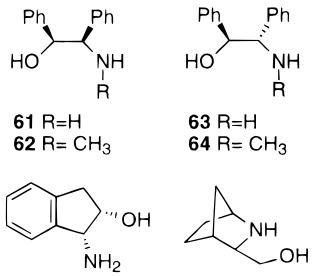
Finally, with ligands containing only nitrogen as heteroatoms, C_2-symmetric diaminoferrocenyl derivatives (Scheme 33) were found to be highly active ligands for the hydride transfer reduction of ketones[107,117] (up to 80% ee on acetophenone with $[Ru(p\text{-cymene})Cl_2]_2$.

Scheme 33



Amino alcohols are also suitable ligands for the enantioselective reduction of aromatic ketones with 2-propanol (Scheme 34).

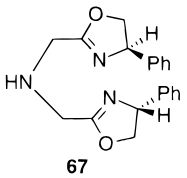
Scheme 34



For this reaction, Noyori[118] reported the use of various chiral 2-amino-1,2-diphenylethanol compounds with up to 92% ee and greater than 90% yield with structure **64**. It is noteworthy that **64** permitted the reduction of cyclohexylmethyl ketone with 75% ee, a particularly high ee value for that type of substrate. Wills et al.[119] obtained excellent ee too (up to 98%) with the more rigid (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol **(65)**. In this case, the *N*-methyl derivatives led to lower asymmetric induction. 2-Azanorbornylmethanol **(66)**, developed by Andersson's group, led to similar results.[120] In all cases, the catalyst precursor turned out to be very important and $RuCl_2(C_6Me_6)_2$ led to better ee and higher reaction rates.

Other N,O-containing ligands have been described. Bis(oxazolinylmethyl)amine ligands (Scheme 35)

Scheme 35



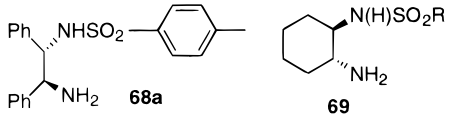
turned out to be particularly efficient, as a reaction rate of 2000 turnovers/cat./h can be reached for ee up to 98% on acetophenone with ruthenium.[121]

The presence of an NH moiety is crucial for activity and selectivity. The main drawback of this system is that high performances require an additional phosphine ligand (PPh_3), which could interfere with the reduction reaction.

Modification of the basic structure **59a** led to the most selective ligand ever reported for hydride trans-

fer reaction, described by Noyori, the (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine **(68a)**. It gave 97% ee in the reduction of acetophenone[122] with 2-propanol as the hydride source and ruthenium (Scheme 36).

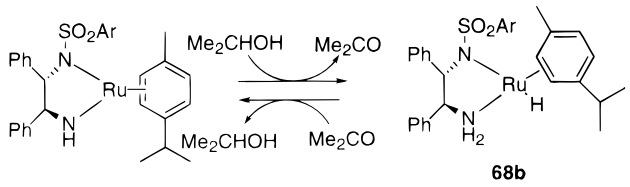
Scheme 36



The counterpart of **68a**, the *N*-monosulfonylated-1,2-diaminocyclohexane **(69)**, gives 94% ee (>99% conversion) in the same conditions.[107]

Cobalt and iridium have also been tested in such reactions. Chiral cobalt−diamine **59a** leads to encouraging ee (up to 58%) but low conversion. The use of iridium precursors with **68a** appears to be particularly relevant as 92% ee at 87% conversion is measured with acetophenone.[123] Both kinetic studies and X-ray structures show that the key intermediate is the metal hydride complex **68b** instead of the alkoxide derivative (Scheme 37).[124] α,*β*-Acetylenic

Scheme 37



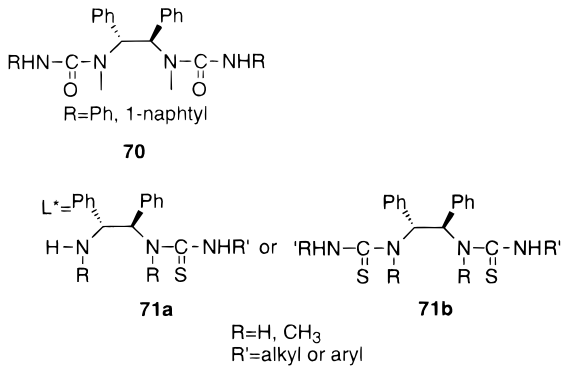
ketones were reduced by this system with ee better than 90%.[125]

Ligand **68a** was also efficient for the reduction of prochiral aromatic ketones using the formic acid/triethylamine 5/2 system as hydride source,[126] and 98% ee was reached with acetophenone. Rhodium and iridium complexes of the same type were also efficient with the same ligands with up to 97% ee.[127]

To find new types of ligands for asymmetric catalysis, amides, ureas, diureas, thioureas, and dithioureas were tested in hydride transfer reactions. Although amides, diamides, and monoureas turned out to be of little interest for this reaction, diureas and especially dithioureas appear to be new ligands of high potentiality for hydride transfer reductions. Diureas (**70**) led to moderate ee (43% with acetophenone)[128] with rhodium catalyst and 2-propanol as the donor (Scheme 38).

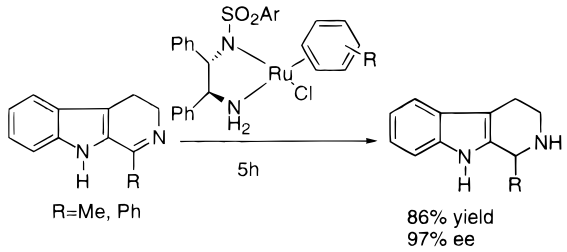
Monothioureas (**71a**) give moderate ee (best results <60% with ruthenium). As for dithioureas (**71b**), they can also be used with rhodium and iridium precursors. $[RuCl_2(C_6H_6)]_2$ leads to up to 89% ee over 24 h with 94% conversion for the reduction of acetophenone (R = CH_3, R′ = phenyl).[129,130] These ligands are easily obtained by reacting a diamine with 1 or 2 equiv of isothiocyanate. The chirality can be introduced either by the diamine moiety or by the isothiocyanate part, which gives access to a wide variety of structures. The easy synthesis of such ligands is probably one of their main advantages in view of further development.

Scheme 38



II.3.1.2. Reduction of C=N Bonds. The system $Ru/HCO_2H-(C_2H_5)_3N$/aminosulfonamide **(68a)** allowed the reduction of imines with ee up to 97% for the reduction of indoles (Scheme 39).[131,132] Probably

Scheme 39



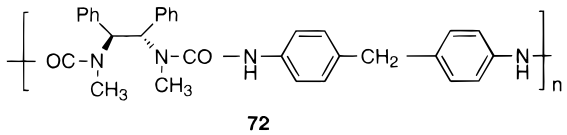
because of their lower stability in reaction conditions, few acyclic imines have been enantioselectively reduced by this method.

II.3.2. Heterogeneous Systems

One advantage of nitrogen ligands over phosphines and of NH-containing ligands over tertiary or aromatic amines is that they can be polymerized and then form heterogeneous catalytic systems with metals.

II.3.2.1. Reduction of C=O Bonds. Diamine **59a** was incorporated into polymer backbones leading to pseudo-C_2-symmetric urea. A series of chiral poly(urea)s (Scheme 40) was synthesized by polyaddition

Scheme 40



First use : 60% ee, 100% conversion, 1 day
Second use : 60% ee, 100% conversion, 1 day
Third use : 59% ee, 100% conversion, 1 day

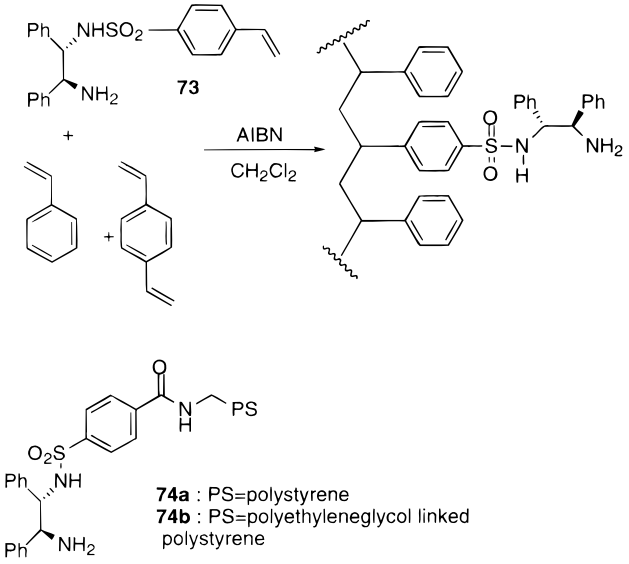
and tested in the reduction of carbonyl compounds by hydride transfer.[133] Cross-linked polymers with 70% of triisocyanate gave rise to higher selectivity compared to linear polymers (from 40% ee to 60% ee). Moreover, the reaction rate appears to be even higher than in the homogeneous phase. This could be due to the greater stability of the insoluble catalyst. The polymer was recycled and reused 3 times without loss of activity or selectivity.

An increase in enantioselectivity was also possible using the molecular imprinting technique. Thus, polymerization of the active complex containing the proper enantiomer leads to an 18% increase in ee, in the case of acetophenone.[134]

Another way to heterogenize a catalytic system is to anchor it to a support. Thus, taking into account the basicity of nitrogen-containing ligands and the acidity of silica as support, the metal/ligand catalytic system can be supported by noncovalent interactions. Using silica and diamine **59a** complexed with rhodium, a continuous flow reactor was built, affording the same selectivity as in the homogeneous phase and a much higher efficiency in the reduction of carbonyl groups by hydride transfer[135] (turnover number = 300 instead of 20).

To heterogenize ligand **68**, two strategies have already been tested. The first one required the synthesis of monomer **73**, which is copolymerized with divinylbenzene and styrene. The second one led to the fixation of the ligand on aminostyrene resins (**74**). The two approaches give rise to similar results and drawbacks, although tested in very different conditions and with different metals (Scheme 41).

Scheme 41



The copolymers of **73** led to up to 94% ee at 96% conversion with iridium.[136] With copolymers of **74**, depending on the type of polymer used, the nature of the hydride donor is different.[137] With **74a**, isopropyl alcohol led to 90% ee at 88% conversion, whereas for **74b**, best results were obtained with HCO_2H:Et_3N (97% ee at 96% conversion). Nevertheless, in both cases, recycling is still a problem.

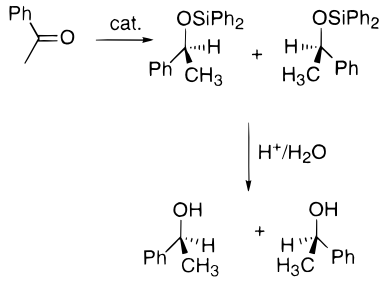
Similarly, diimines were polymerized.[138] The degree of cross-linking is important, and in the best conditions, up to 70% ee was measured on acetophenone. Here again, the polymer could not be recycled.

II.4. Hydrosilylation

Asymmetric hydrosilylation of ketones, imines, and olefines leads to valuable chiral compounds such as alcohols, amines, and alkanes. In the early 1970s, the catalytic activity of the Wilkinson catalyst was proven to be efficient for the hydrosilylation of ketones. The first results in asymmetric hydrosilylation were reported soon afterward using rhodium catalysts and chiral phosphine ligands.[139] Only moderate enantioselectivity (<85%) was nevertheless obtained. Since the early 1980s, the development of chiral nitrogen-containing ligands has allowed a considerable increase in enantioselectivity (up to 99%). Asymmetric hydrosilylation is one of the reactions for which the move from phosphine ligands to nitrogen-containing ligands has much improved the enantioselectivity. Indeed, complexes with Pybox, Pymox, or Pythia ligands allow the hydrosilylation of ketones with very high enantioselectivity. Such structures are all the more successful as they are easy to synthesize from pyridine, carboxylic acids, and natural amino acids. For a review on asymmetric hydrosilylation through 1993, see ref 140. Only the hydrosilylation of ketones will be treated in this chapter.

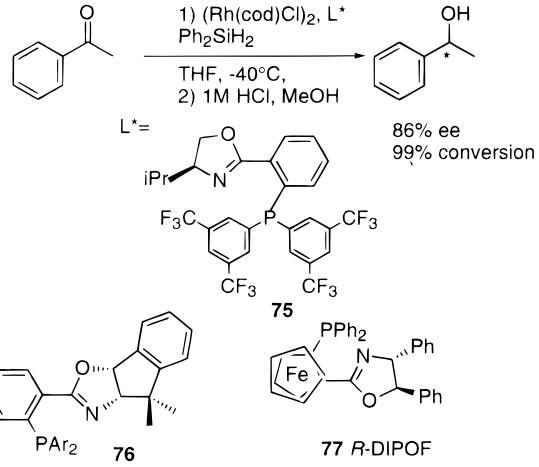
Acetophenone has been widely used as a model for ketones, and the general reaction scheme is depicted in Scheme 42.

Scheme 42



Combinations of oxazolynil and phosphine structures lead to new ligands[141,142] (Scheme 43).

Scheme 43

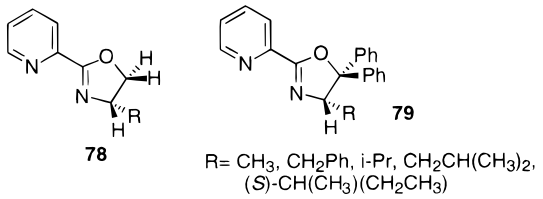


With phosphorus-containing oxazolines, up to 86% ee was obtained in the conversion of acetophenone into phenethyl alcohol using a rhodium complex of ligand **75**. (Phosphinooxazoline)rhodium(I) can efficiently catalyze hydrosilylation of aromatic as well as aliphatic ketones. Improvement of structure **75** leads to ligand **76**, which increases the ee up to 94% for acetophenone[143] (Scheme 43).

Oxazolylferrocene−phosphine hybrid ligands are a very effective class of ligands for the Rh(I)-catalyzed hydrosilylation of ketones lacking a secondary coordinating functional group (up to 91% ee)[144,145] (Scheme 43). Using Ir(I), 1-phenylethanol of the opposite configuration was produced from acetophenone (96% ee). Studies are in progress to clarify this feature.

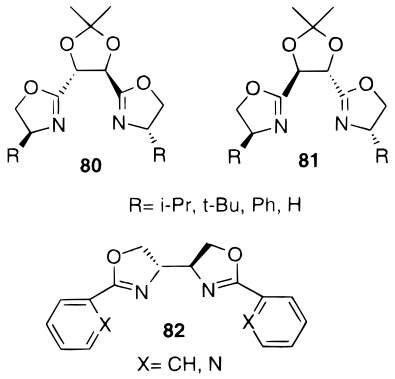
Various new oxazoline ligands have been described or developed over the past few years. Thus, with 2-(2-pyridinyl)oxazolines **78**, substitution at the 5 position by two phenyl groups leads to compound **79**, which gives ee values10−34% higher than with **78** (best result 89% ee with R = ^{i}Pr) (Scheme 44).[146]

Scheme 44



Chiral bis(oxazoline) ligands with four asymmetric centers were synthesized from the two enantiomers of tartaric acid and from several amino acids which gave access to a wide range of molecules[147] (Scheme 45).

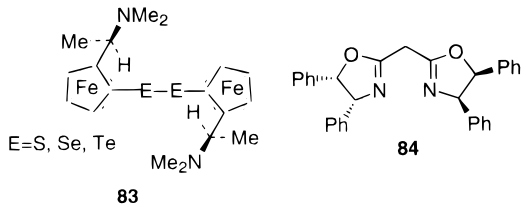
Scheme 45



From this study, it appears that the sense of asymmetric induction is determined by the amino acid part of the ligand whereas the degree of enantioselectivity is affected by the tartaric acid backbone (**80**, **81**). Nevertheless, only 65% ee are reached with the best structure (R = t-Bu). Other C_2-symmetric bis(oxazoles) possessing chirality on their backbone are reported but the ee remain modest (50%, **82**).[148]

Diferrocenyl dichalcogenides also worked as chiral ligands for the Rh(I)-catalyzed asymmetric hydrosilylation of several alkyl aryl ketones (Scheme 46).[149]

Scheme 46



Up to 85% ee over 1.5 days was obtained on acetophenone with E = Se but with a low conversion (31%). Nevertheless, it is the first example of the use of organic dichalcogenides as ligands in asymmetric metal-catalyzed enantioselective reaction.

Finally, bis(oxazoline) can be used with early transition metals. Thus, titanium complexes lead to up to 61% ee with 86% yield (48 h) for the reduction of acetophenone. Even if this ee is modest compared to some already published results, it is the first time that early transition metals with C_2-chiral bis(oxazolines) (Scheme 46) have been used in asymmetric catalysis.[150]

III. C–O Bond Formation

C−O bonds are generally formed by oxidation. Significant successes in enantioselective oxidation appeared much later than for reduction. It was only in the 1980s that Sharpless's work demonstrated the feasibility of asymmetric C−O bond formation. Nitrogen- and oxygen-containing ligands are almost exclusively used, to the detriment of easily oxidizable phosphine ligands.

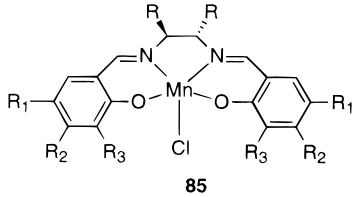
III.1. Epoxidation of Unfunctionalized Olefins

In the 1970s, several groups discovered the ability of metal catalysts and alkyl peroxides to generate epoxides from alkenes.[151] The asymmetric version of this work was first reported by Sharpless and Katsuki on allylic alcohols using tBuOOH, Ti(O-^{i}Pr)$_4$, and diethyl tartrate with up to 90% ee.[152] Groves[153] showed that chiral transition metal porphyrin complexes catalyzed epoxidation of styrenes with up to 51% ee. Finally, in 1990 Jacobsen reported the epoxidation of simple olefins with chiral manganese salen catalysts.[154] This last system, easy to handle and with a wide scope of applications, is one of the most relevant methods of building chiral epoxides. Salen and porphyrin ligands will be studied in more detail in the following part of this review. Other kinds of ligands will also be presented, and finally, heterogeneous systems will be reported.

III.1.1. Homogeneous Catalysis

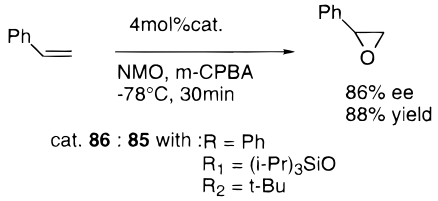
III.1.1.1. Salen Ligands.[155] The asymmetric epoxidation of simple olefins has been successfully performed using chiral derivatives of [Mn(salen)]$^+$ complexes with oxidants such as PhIO or aqueous NaOCl under phase transfer conditions. More than 50 different structures of type **85** have been synthesized and tested in epoxidation, and often more than 90% ee's were obtained with such systems for cis-disubstituted and trisubstituted olefins (Scheme 47).[156,157]

Scheme 47



Jacobsen's group has shown that a *tert*-butyl group is necessary to achieve high ee with NaOCl as an oxidant. Ligand **85** with R = cyclohexyl, $R_1 = R_3 =$ *t*-Bu, $R_2 = H$ will be referred to as Jacobsen's catalyst. Katsuki et al.[158,159] obtained better results with PhIO as an oxidant using a second stereogenic center (*R*)- or (*S*)-1-phenylpropyl. Nevertheless, with terminal olefins such as styrene, only moderate ee's (50−70%) were reported. This could be due to a lower enantiofacial selectivity with such compounds than with cis-disubstituted and trisubstituted olefins and/or to a special type of enantiomeric "leakage" pathway.[160,161] By lowering the temperature to −78 °C, 86% ee was reached for the epoxidation of styrene. In this case, NaOCl, which is frozen at such a temperature, was replaced by the *m*-CPBA/*N*-methylmorpholine-*N*-oxide (NMO) system (Scheme 48).

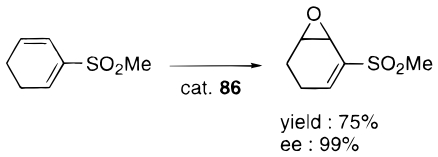
Scheme 48



Tetrabutylammonium monopersulfate (Bu_4NHSO_5) turned out to be a good oxidant together with *N*-methylmorpholine-*N*-oxide as an additive with Jacobsen's catalyst. This system led to 93% ee at 97% conversion on 2,2-dialkylchromenes and trisubstituted alkenes.[162]

With catalyst **86**, 2-sulfonyl-1,3-cyclic dienes were epoxidized with ee up to 99%. Incorporation of the sulfone moiety increases the enantioselectivity by up to 30% relative to unsubstituted 1,3-cyclic dienes.[163] Linear sulfonyl-1,3-dienes are not very reactive in these conditions (Scheme 49).

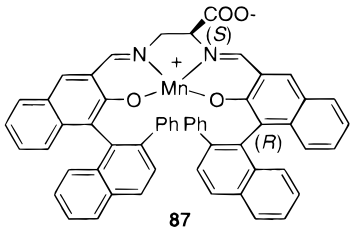
Scheme 49



Achiral Mn−salen complex was also used as an effective enantioselective catalyst for the epoxidation of 2,2-dimethylchromenes in the presence of chiral amine. Up to 73% ee's were reported using sparteine.[164] Addition of this external axial chiral ligand favors one of the two enantiomeric nonplanar conformers of the achiral complex and renders the complex chiral. The nonplanarity of the salen−amine−Mn complex has been demonstrated to be of high importance for the asymmetric induction. To quantify this effect, the same group has synthesized complex **87**,[165] which led to a nonplanar Mn complex by coordination of the metal by the carboxylate group, Scheme 50.

Up to 99% ee is reported. It shows that this system, which does not use any additional axial ligand, leaves one axial coordination site unoccupied, which can partly explain the high level of induction.

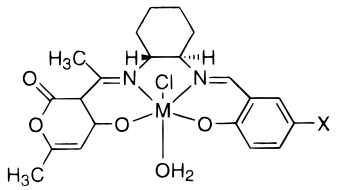
Scheme 50



87

A series of dissymmetric chiral Schiff base complexes of Mn(III) and Ru(III) were tested in the enantioselective epoxidation of nonfunctionalized prochiral olefins (*cis*-stilbene, *trans*-3-nonene, *trans*-4-octene) with iodosylbenzene as oxidant[166] (Scheme 51).

Scheme 51



X = H, Cl, OMe, NO_2
M = Mn(III), Ru(III)

88

Regardless of the ligand used, Mn catalysts gave better results than Ru catalysts. The presence of a nitro substituent on the aromatic part of the ligand led to a better conversion and a higher cis/trans ratio compared to the methoxy group (cis/trans 16/84 compared to 48/52). This could be due to a difference in the electron density around the metal but also to a difference in the path of the incoming substrate. Nevertheless, the enantioselectivity obtained with these ligands remains modest (<60%).

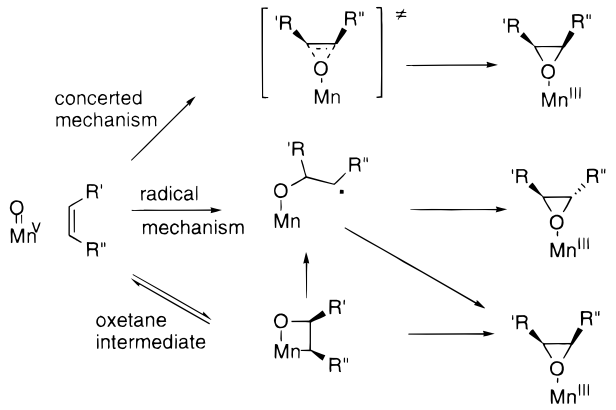
Aerobic epoxidation using chiral salen complexes of type **85** was also reported with cobalt or manganese catalysts.[167,168] The authors used aldehydes or esters as sacrificial reductants, but the enantioselectivity measured with these systems was lower than with Jacobsen's ligand. With Ni(II) and chiral Schiff base complexes, in the same conditions, the activity is good but the selectivity remains low.[169]

The mechanism of enantioselective epoxidation using the Jacobsen−Katsuki system is still controversial.[170,171] It has been claimed to proceed either in a concerted manner, via a radical intermediate,[172] or via a manganaoxetane intermediate[173] (Scheme 52). Moreover, Janssen et al. recently reported the occurrence of a nonselective blank reaction which competes with the catalyzed reaction and thus lowers the enantioselectivity.[174]

Mn^{V}−oxo complexes have been detected as catalytically active species.[175] The nitrogen analogue of this intermediate was studied by Jorgensen et al.[176] The comparison of crystallographic data and ab initio DFT calculations shows a weaker Mn=O bond in the oxo−manganese(V) complex than in the nitrido−manganese(V) analogue.

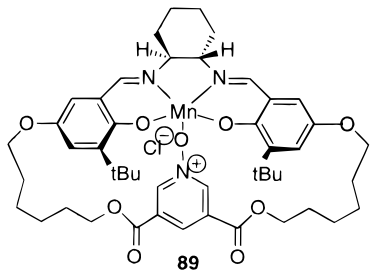
Concerning the influence of additives, analysis of the structure of catalyst **89** synthesized by Jacob-

Scheme 52



sen[172] proves that the amine *N*-oxide acts as an axial coligand (Scheme 53).

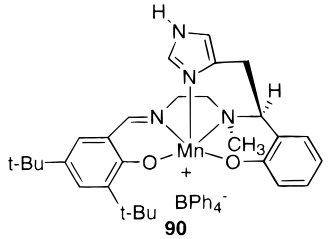
Scheme 53



Addition of 4-phenylpyridine *N*-oxide has no influence with catatalyst **89**, whereas it dramatically increased activity and selectivity with catalysts of type **85**. Ligands bearing electron-donating substituents afforded higher ee. This can be correlated to a modification of a transition state position along the reaction coordinate.[177]

Salens bearing a fifth axial donor imidazole group were also synthesized for the enantioselective epoxidation of unfunctionalized olefins with hydrogen peroxide as the source of oxygen. No coligand was necessary (Scheme 54).[178]

Scheme 54

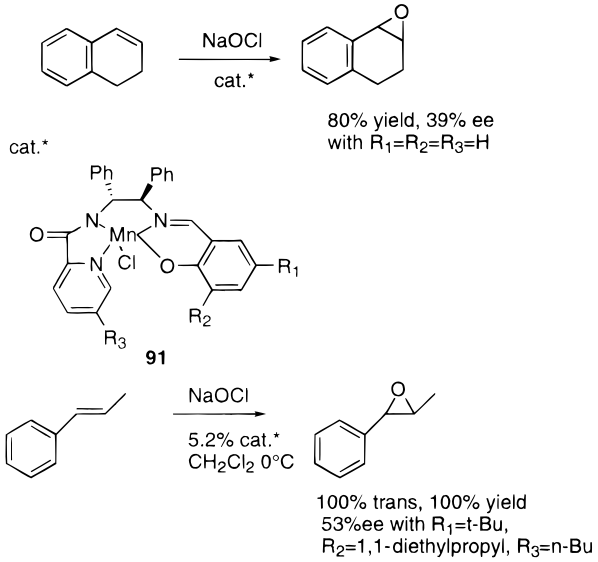


These structures combined the features of a peroxidase-like coordination sphere and a chiral manganese(III) salen complex. Up to 64% ee was achieved with 1,2-dihydronaphthalene. Suppression of the imidazole led to tetradentate chelate which is devoid of activity. It is noteworthy that other oxidants can be used as well.

Chromium salen also catalyzed asymmetric alkene epoxidation.[179] Nevertheless, enantiomeric excesses are lower than with Mn. In contrast with the manganese series, any 3,3′-substituent on **85** is effective for enantioselectivity. Moreover, electron-withdrawing substituents increase the reaction rate. Dissymmetrical salen ligands were also used with Cr but led to lower ee.[180]

III.1.1.2. Other Ligands. Chiral manganese–salen systems are highly enantioselective for epoxidation of cis olefins but the turnover numbers are low (<30) due to the oxidation of the imine and phenoxide parts of the ligands. Replacement of these functions by less oxidizable amide and pyridine moieties increases the turnover number from 25 for Jacobsen's catalyst to 100 in the epoxidation of dihydronaphthalene (Scheme 55).[181]

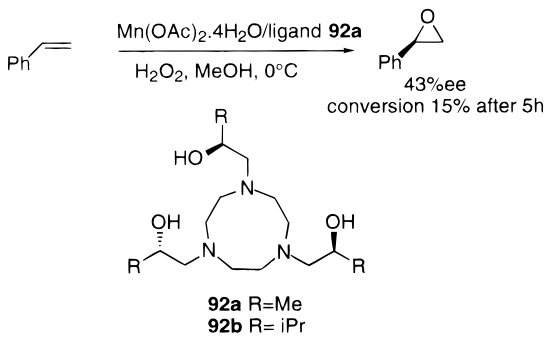
Scheme 55



Unlike the salen ligands, these ligands are devoid of C_2-symmetry. Moreover, a five-membered metallacycle is formed with Mn via the picolinamide moiety, whereas a six-membered metallocycle is obtained with the salicylidene moiety. These two geometrical differences should be of high importance for the enantioselectivity of the reaction. Even if this new class of ligands leads to lower ee than the family obtained with salen complexes, their structure could be improved and they could be a solution for the still difficult epoxidation of *trans*-olefins. Thus, 53% ee was measured for the epoxidation of *trans*-*β*-methylstyrene, which was one of the best results ever published up to now (Scheme 55).

Very original C_3-axis chiral 1,4,7-triazacyclononane complexes **92** of manganese also catalyze the asym-

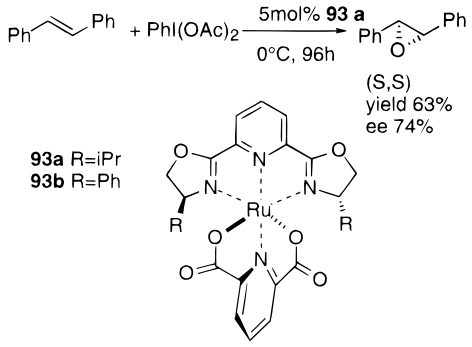
Scheme 56



metric oxidation of unfunctionalized olefins with hydrogen peroxide. Only moderate ee's are measured (Scheme 56).[182]

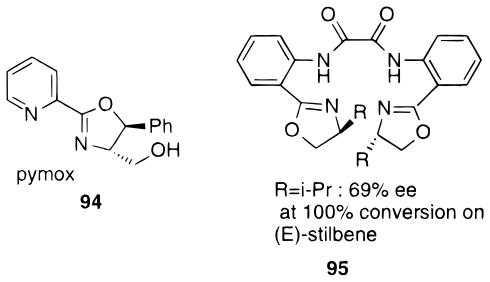
Ruthenium-pyridinedicarboxylate (Ru−pydic) complexes **93** of terpyridine and chiral bis(oxazolinyl)-pyridine (pybox) were also used for alkene epoxidation with [bis(acetoxy)iodo]benzene as an oxygen donor.[183] Variations of the ligand structure have shown that the rigidity of the tridentate pydic is a key to obtain enantioselectivity (Scheme 57).

Scheme 57



A modest ee (13%) was also obtained with pymox ligand **94** [184] (Scheme 58).

Scheme 58

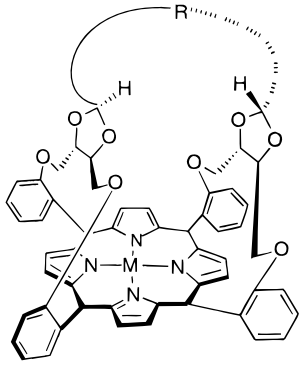


With chiral tetradentate bisamide ligands **95**, ruthenium, and $NaIO_4$ as an oxidant, only modest ee's were obtained (Scheme 58).[185]

Jacobsen et al. used combinatorial chemistry to discover novel epoxidation catalysts. Moderate ee's were obtained up to now, but the strategy is efficient and currently under evaluation.[186]

III.1.1.3. Porphyrin Ligands. The major limitation of metallosalens is their oxidizability. On the contrary, metalloporphyrins are much more stable and up to 2800 turnovers were measured in enantioselective epoxidation. Nevertheless, metalloporphyrins give rise to lower ee than the salen systems. Moreover, the access to porphyrins is not straightforward. Collman et al.[187a] developed threitol-strapped manganese porphyrins for the enantioselective epoxidation of unfunctionalized olefins. They chose mono-faced porphyrin systems: bulky ligands block the unsubstituted face of the porphyrin, and the substrate is thus forced to arrive by the substituted face. They use tartaric acid as the chiral source, which gives access to several different molecules by simple modification of the protecting groups of the tartrate. Bridged threitol-strapped systems were also synthesized (Scheme 59).

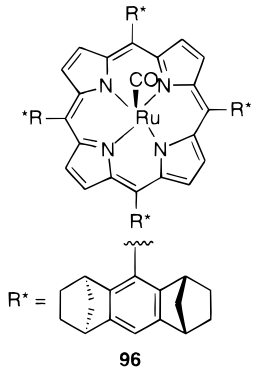
Scheme 59



Addition of imidazole ligands can lead to 70% ee in the epoxidation of 4-chlorostyrene and up to 77% for the *cis*-β-methylstyrene. The imidazole effect can be explained by the binding of these ligands to the open face of the catalyst, forcing the oxidation to occur between the chiral straps. With a C_2-symmetric iron porphyrin and PhIO, the same group obtained impressive high ee on terminal olefins. Thus, 82% ee was measured on chlorostyrene (90% conversion) and 83% ee on styrene.[187b] These are some of the best results ever reported for olefins with chiral metalloporphyrin catalysts and can be compared to the 81% ee obtained with salens.[156]

In 1996, a C_4 ruthenium porphyrin catalyst was described[188] for the epoxidation of styrene with up to 57% ee (16% conversion). This system turned out to be remarkably sensitive to the solvent and to the oxidant. Nevertheless, even if the selectivities are significant for unsubstituted olefins, the activity remains low (<50%) (Scheme 60).

Scheme 60

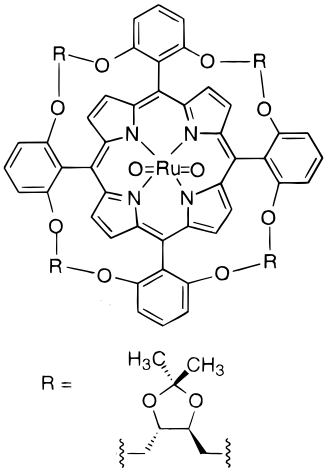


Other ruthenium porphyrins with 2,6-dichloropyridine *N*-oxide as the terminal oxidant reached 100% conversion over 2 days with 70% ee and 79% yield[189] with styrene, which is the best result ever obtained with any metalloporphyrin-based system (Scheme 61). With this ligand, Ru gives better results than Fe and Mn.[190] The use of an aromatic solvent and a primary oxidant (*N*-oxides > iodosylarenes) also allows an increase in enantioselectivity. Thus, up to 6000 catalytic turnovers were achieved for epoxidation of olefins with iron complexes.

III.1.2. Heterogeneous System

Although Jacobsen-type catalysts are rather cheap and easy to obtain (both metal and ligand), several

Scheme 61

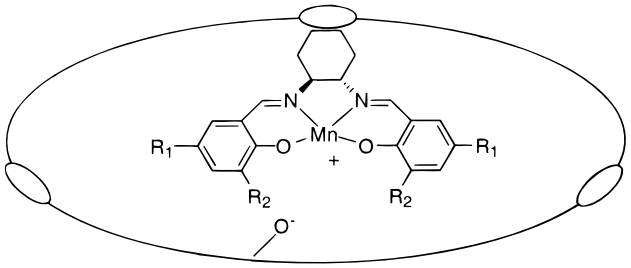


97

attempts to build heterogeneous systems have been made. An increase in stability (turnover) and an easier separation are the main objectives of such research.

A chiral salen manganese complex was encapsulated within a zeolite and used successfully for the epoxidation of alkenes (Scheme 62).

Scheme 62



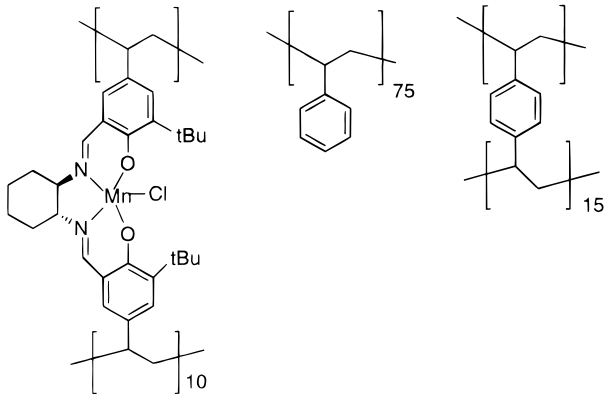
With zeolite Y[191] ($R_1 = R_2 = H$), both activity and selectivity were inferior to those obtained with the corresponding homogeneous system. This is probably due to problematic diffusion of the substrate into the zeolite framework, as far as the activity is concerned. Jacobsen's catalyst, with four *tert*-butyl groups on the phenyl rings, does not fit into the zeolite supercages.

With zeolite EMT[192] (an hexagonal form of the faujasite structure) and $R_1 = t$-Bu and $R_2 =$ Me, better results were obtained. For example, 88% ee was measured for the epoxidation of (Z)-methylstyrene instead of 58% with zeolite Y. Nevertheless, as both zeolites and salen structures were different, it is difficult to draw conclusions on the influence of the zeolite structure. With zeolite EMT, the recycled catalyst led to significantly lower ee for reasons still unknown.

Another way to heterogenize the salen system is to polymerize it. Thus, Salvadori et al. incorporated the chiral (salen)Mn(III) complex in a polystyrene−divinylbenzene polymer (Scheme 63).[193]

The oxidant PhIO has to be replaced by the *m*-CPBA/NMO system because its product of disproportionation, $PhIO_2$, is insoluble in the reaction medium. It is thus impossible to get rid of $PhIO_2$ by washing the polymer, and no recycling is possible.

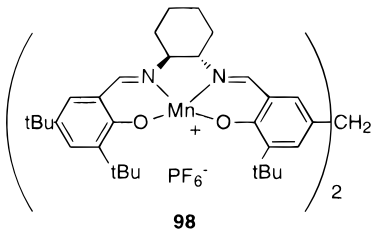
Scheme 63



With the modified oxidative system, recycled 5 times, the selectivity and activity remain the same. Nevertheless, the ee is still low if compared to what has been measured with the homogeneous systems (14% ee on styrene). Sherrington et al., by an appropriate modification of the polymer matrix, achieved the highest ee ever measured with a polymer-supported chiral Mn^{III} (salen) catalyst. Thus, 91% ee at 49% conversion was reached with a methacrylate-based resin for 1-phenylcyclohex-1-ene epoxidation.[194] With soluble Jacobsen's catalyst, 92% ee at 72% conversion was obtained.

Around the same time, Vankelecom et al.[195] described the occlusion of Jacobsen's catalyst in a poly(dimethylsiloxane) (PDMS) membrane. The complex is kept in the elastomer network by steric restrictions, whereas covalent bonds are necessary in the preceding example. The catalyst membrane is regenerated by a simple washing procedure and reused twice without loss of activity and selectivities (regio and enantio) and with no leaching (52% ee, 84% conversion on styrene). This new method of heterogenization has the advantage of maintaining the structure of the chiral catalyst without any supplementary chemical bonding. Nevertheless, leaching is still a problem. To improve steric retention of Mn(III)(salen)-type complexes in PDMS membranes, the same group synthesized a dimeric complex[196] (Scheme 64).

Scheme 64

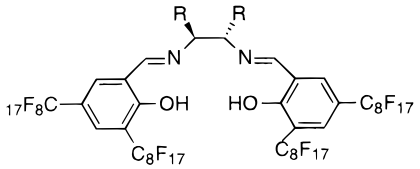


98

The dimer tested in homogeneous conditions is about as active as Jacobsen's catalyst. In a membrane, the dimer leaches less than the monomer but the enantioselectivity is the same. Nevertheless, the system remains very solvent sensitive.

Chiral (salen)Mn complexes (Scheme 65) bearing perfluorinated groups on the aromatic rings were used in fluorous biphase systems (FBS).[197]

Scheme 65



99 : R-R = -$(CH_2)_4$-
100: R = Ph

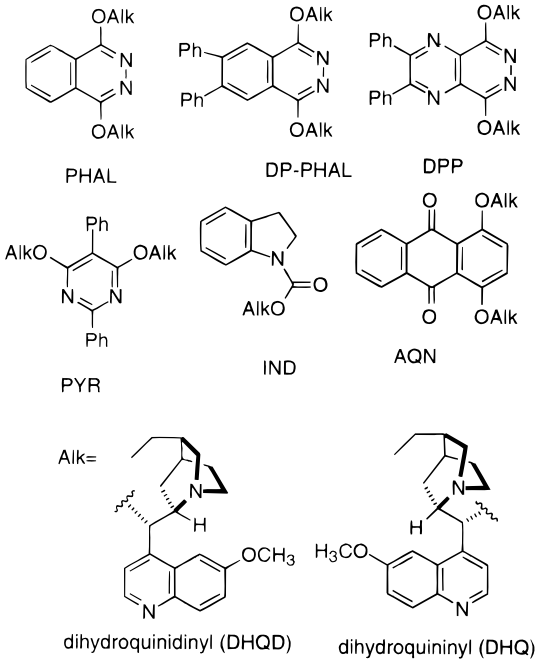
With indene and catalyst Mn-**99**, 92% ee was reported using O_2 as oxidant. With other substrates and/or oxidizing agents, ee's were much lower. Nevertheless, this method of heterogenization was competitive if compared to other heterogenized Jacobsen−Katsuki catalysts. In particular, the catalyst is easy to separate and recycle.

III.2. Dihydroxylation of Olefins

III.2.1. Homogeneous Systems

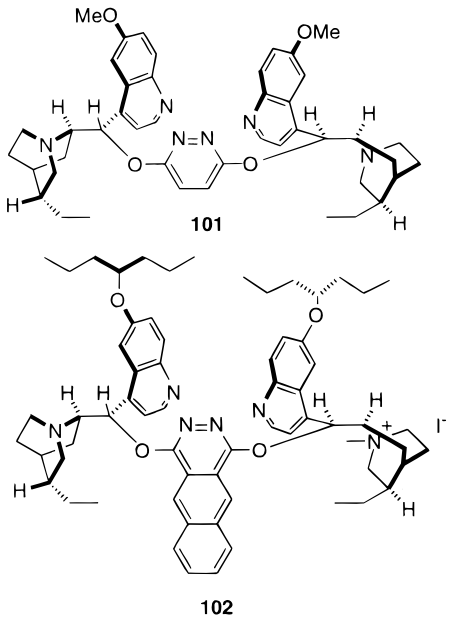
The asymmetric dihydroxylation (AD) of olefins is one of the most recent successes in asymmetric catalysis. Since 1987[198] with Sharpless's discovery of cinchona-catalyzed enantioselective dihydroxylation using catalytic OsO_4, interest in this method has considerably increased. Numerous papers have been published on the subject by Sharpless and other groups, and good to excellent ee's were reported depending on the class of olefins.[199,200] As for the ligands, Sharpless's group synthesized and tested over 500 different compounds. The basic structure contains dihydroquinidine or dihydroquinine, one of the most popular chiral inductors containing nitrogen atoms. The two cinchona alkaloids (dihydroquinidinyl (DHQD) or dihydroquininyl (DHQ)) are bridged by various aromatic moieties such as phthalazine (PHAL), diphenylphthalazine (DP−PHAL), diphenylpyrazinopyridazine (DPP), and pyrimidine (PYR).[201] Recently,[202] 1,4-bis(dihydroquinidinyl)anthraquinone [$(DHQD)_2$AQN] and 1,4-bis(dihydroquininyl)anthraquinone [$(DHQ)_2$AQN] were developed (Scheme 66). These modifications were performed in order to improve both enantioselectivity and separation.

Scheme 66



These new ligands turned out to be superior to the others for the asymmetric dihydroxylation (AD) of olefins having aliphatic substituents. For sterically congested olefins, the pyrimidine-based ligands remain the best. A mechanistic model shows that the ligand formed a U-shaped binding pocket.[203] On the basis of this proposed transition-state model, modified ligands were synthesized with a structure appropriate to the substrate to be dihydroxylated (Scheme 67).[204]

Scheme 67



As for the mechanism, two pathways were proposed: a [2 + 2] cycloaddition model (Sharpless) or a [3 + 2] one (the CCN model for Criegee−Corey−Noe).[205] Numerous articles have been published on the subject, but for the moment, the latest results by Sharpless and co-workers using experimental and theoretical kinetic isotope effects supported a rate-limiting [3 + 2] cycloaddition.[206]

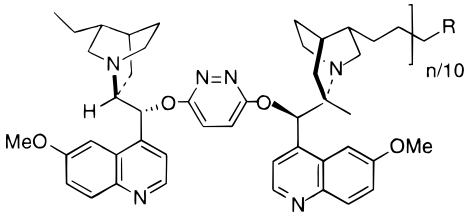
Plenty of examples of application of AD are reported in the literature, such as the AD of halogenated propenes,[207] the oxidation of allylselenides,[208] or the synthesis of the biologically active tetracyclic marine sesterterpene, the scalarenedial.[209]

III.2.2. Heterogeneous System

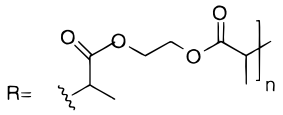
Several groups have tried to heterogenize this powerful system, due to its high interest (it is nevertheless noteworthy that the AD catalyst is already almost unsoluble in the reaction medium). The reported catalytic AD reaction using chiral cinchona alkaloids on different polymer backbones led to inferior activity and selectivity until Lohray et al. published pyridazine-based cinchona alkaloid supported on poly(ethylene glycol) dimethacrylate, which exhibited almost the same behavior as the

homogeneous system in numerous cases (Scheme 68).[210] Nevertheless, low ee's were obtained with

Scheme 68



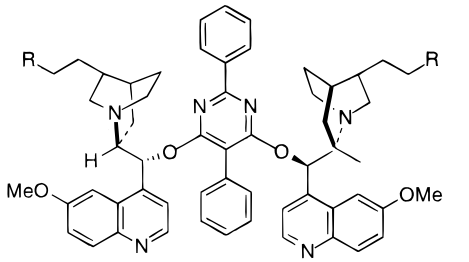
103 : DHQ_2-Py-Polymer



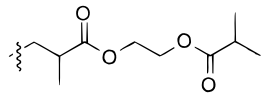
aliphatic olefins.

Polymer **104** and **105** exhibited higher enantioselectivity in the case of aliphatic terminal olefins (76% ee, 80% yield with 3,3-dimethyl-1-butene) (Scheme 69). Nevertheless, the polymer was recycled and the

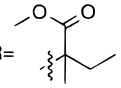
Scheme 69



Polymer **104** : **R=**



Polymer **105** : R=



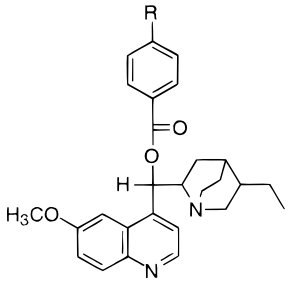
activity dramatically decreased due to the loss of OsO_4 during filtration.[211]

Polymers obtained by radical copolymerization of cinchona alkaloid derived monomers and hydroxyethyl methacrylate using ethylene glycol dimethacrylate as a cross-linking agent also give good enantioselectivity on aliphatic olefins (up to 88% ee on 5-decene).[212]

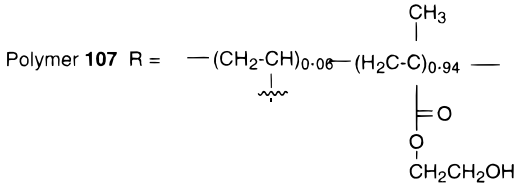
The influence of the polymer backbone polarity on enantioselectivity was demonstrated by Song et al. in connection with the nature of the reaction medium and conditions.[213] Thus, homopolymers of type **106** were highly efficient in t-BuOH/H_2O solvent using $K_3Fe(CN)_6$ as a secondary oxidant, whereas for an NMO−acetone/H_2O system, the enantioselectivity was drastically improved by increasing the polarity of the polymer backbone (polymer **107** Scheme 70).

Cinchona alkaloids were also supported on silica gel. With DHQ_2−PY polymers, Lohray et al.[214] reported an activity comparable to that of the homogeneous system but a much lower ee. With $(QN)_2$−

Scheme 70



Polymer **106** R = —$(CH_2$-$CH)_n$—

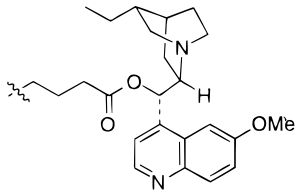


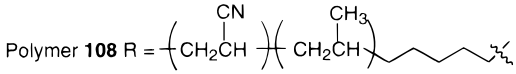
Polymer **107** R = —$(CH_2$-$CH)_{0.06}$—$(H_2C$-$C)_{0.94}$—

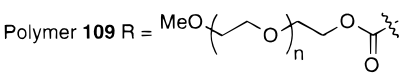
PHAL, Song et al. obtained much better results in the case of vinylic olefins (92−99% ee).[215] The catalyst was reused once with only a slight loss of activity and selectivity. It seems that the alkaloid moiety adopts a conformation favorable to the catalytic activity and selectivity on silica gel.

With heterogeneous catalytic polymeric systems, the ligand resides in the insoluble phase whereas OsO_4 and the olefin are in solution. This classic behavior of a heterogeneous catalyst induces a decrease in the reaction rate and causes diffusion problems. The conditions are thus less favorable than in homogeneous phase. Therefore, Han and Janda synthesized a soluble polymer-bound ligand system which allows the reaction to occur in the homogeneous phase, the catalyst/polymer-bound ligand being recovered by filtration after addition of diethyl ether and subsequent precipitation.[216] The comparison between a soluble system **109** and its insoluble (cross-linked) analogue **108** shows a slight increase in selectivity but a tremendous jump in activity (5 h instead of 48 h for the same conversion, Scheme 71).

Scheme 71



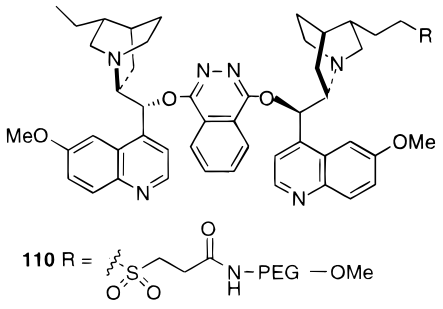
Polymer **108** R = 

Polymer **109** R = 

Nevertheless, the ee remains lower than those measured with the free ligands (99% ee).[217]

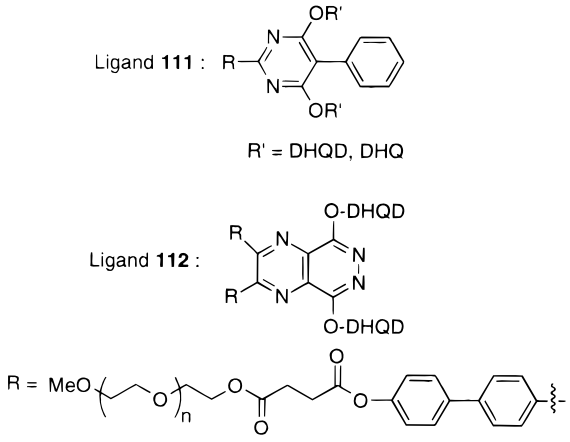
Han and Janda considerably improved the polymer structure (Scheme 72) with polymer **110**, which led to better ee (99% ee on *trans*-stilbene).[218]

Scheme 72



Bolm and Gerlach[219] synthesized ligands **111** and **112** for which the symmetry of the DHQ and DHQD ligands was retained (Scheme 73).

Scheme 73



These ligands remain soluble in the reaction mixture, the reaction is fast, and the enantioselectivities are almost as high as with the free ligands (99% ee on stilbene, 91% yield, <5 h). Moreover, these ligands are recovered after precipitation with *tert*-butyl methyl ether and filtration. After six sequential reuses of **112**, the enantioselectivity on styrene decreases only from 98% to 96%, due to a minor ester hydrolysis under the basic reaction conditions.

A multipolymer-supported approach for which both the substrate and the ligand were supported was also developed for the AD reaction.[220] Thus, the substrate was supported on resins of various hydrophilicity and tested with polymeric or nonpolymeric ligands. With the free ligand, a non-cross-linked soluble resin provided the best overall results (0.5 h, 10% OsO_4, 100% conversion, 99% ee) whereas an insoluble resin was more suitable in combination with the soluble polymeric catalyst. The nonimmobilized substrate led to higher activity for similar selectivity. This dual approach seems, nevertheless, particularly interesting for automation purpose.

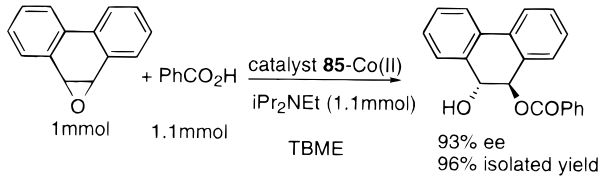
Salvadori et al. published a comparative study on insoluble (IPB) and soluble polymer-bound ligands (SPB) and provided evidence that the two approaches were competitive.[221] They pointed out that IPB systems are well suited to industrial purposes, as they can be directly recovered without addition of a solvent.

To the present day, several efficient systems allowing an easy recovery of the different components of the reaction are available for the AD reaction, which is not the case for most of the other asymmetric reactions commonly studied. This emphasizes the importance of this reaction.

III.3. Ring Opening of Meso Epoxides

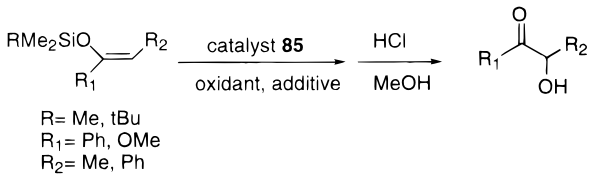
The opening of epoxides is a very powerful reaction which can provide access to numerous products depending on the nature of the nucleophile (amino alcohols when the nucleophile is an amine, diols in the case of water, ...). Salen complexes have been used for the enantioselective ring opening of epoxides. For terminal epoxides, with $TMSN_3$, (salen)CrN_3 complexes are used.[222] In the case of meso epoxides, the nature of the nucleophile is important: with Me_3SiN_3, (salen)Cr(III) derivatives give the best results,[223] whereas with benzoic acid, (salen)Co(II) complexes are particularly relevant.[224] In all cases, excellent ee's may be reached (Scheme 74).

Scheme 74



Jacobsen's catalyst was also used in the enantioselective synthesis of optically active α-hydroxycarbonyl compounds by (salen)Mn(III)-catalyzed oxidation of silyl enol ethers and silyl ketene acetals.[225,226] Values of ee up to 89% for α-hydroxy ketones and 68% for α-hydroxy esters were obtained (Scheme 75).

Scheme 75



The nature of the oxygen source and of the different additives are determining factors for both activity and selectivity.

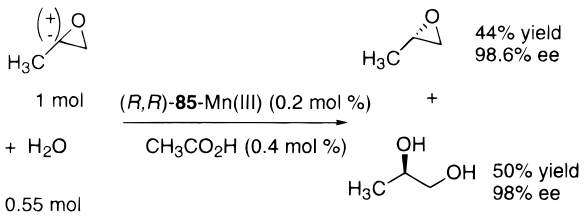
III.4. Kinetic Resolution

III.4.1. Terminal Epoxides

Terminal epoxides are relatively inexpensive materials readily available as racemic mixtures. Hydrolytic kinetic resolution of these compounds leads to valuable chiral epoxides and to chiral diols, using water as the only reagent and chiral cobalt−salen catalysts. Thus, more than 95% ee in both products can be reached[227,228] (Scheme 76).

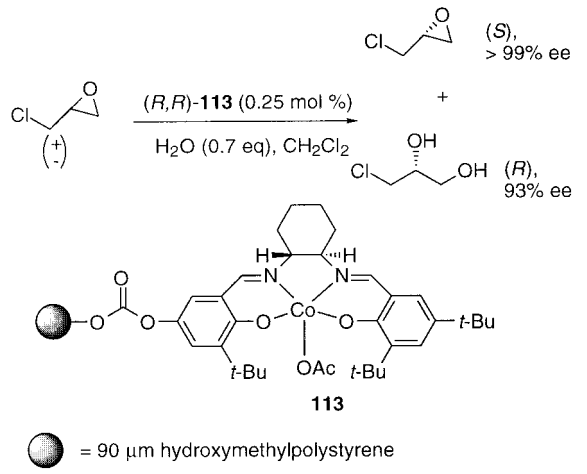
Polystyrene- and silica-bound chiral Co(salen) complexes were used for the heterogeneous version of the reaction. Enantiomeric excesses as high as those in the homogeneous phase are obtained, and this system provides a practical method for product separation. Moreover, the catalytic system can be recycled, and

Scheme 76



the silica-bound catalyst is suitable for a continuous-flow system[229] (Scheme 77).

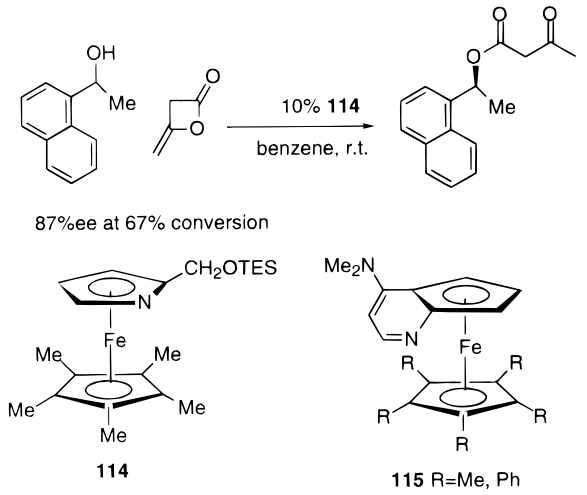
Scheme 77



III.4.2. Secondary Alcohols

Planar−chiral π-complexes of nitrogen-containing heterocycles with transition metals such as Fe have been used for the kinetic resolution of secondary alcohols via acylation[230] (Scheme 78).

Scheme 78



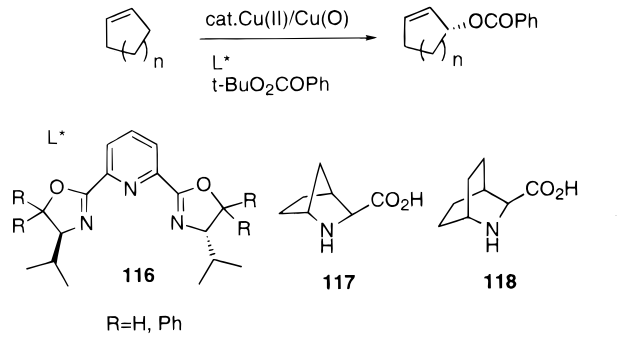
Catalyst **114** gives good enantioselectivity with ketenes as alkylating agents. Modification of its structure led to catalyst **115**. With R = Me, almost no activity and selectivity are reported. Replacing Me by Ph allows kinetic resolution with high enantioselectivity using acetic anhydride for acylation.[231] It is the first time that an increase in the steric bulk of the cycopentadienyl ring has led to a significant improvement in enantioselectivity. At 50−70% conversion, ee > 92% of unreacted alcohol are measured with a selectivity factor between 12 and 52 (E = k(fast reacting enantiomer)/k(slow reacting enantiomer)). This is particularly high for nonenzymatic chiral acylation catalysts. Moreover, catalyst **115** is stable under air and can easily be recovered.

IV. C–H Bond Oxidation

IV.1. Allylic and Benzylic Oxidation

Enantioselective allylic oxidation of olefins with *tert*-butyl perbenzoate leading to allylic benzoate (known as the Kharasch−Sosnovsky reaction) is one of the possible approaches to allylic alcohols and is thus a very promising method for synthetic chemists. Copper complexes of chiral nitrogen-containing ligands are the catalysts of choice for such a reaction. Essentially, two types of ligands have been developed for the oxidation of acyclic olefins: bis(oxazolinyl)-pyridine[232,233] and proline[234−236] derivatives (Scheme 79).

Scheme 79



With the former (**116**), up to 81% ee's[233] were obtained on cyclohexene but over 15 days with only 58% isolated yield using the precursor Cu(OTf) prepared in situ by reduction (ligand R = Ph). With the latter, the best results are 65% ee with 63% isolated yield with ligand **117** over 2 days.[236,237] It is noteworthy that although the enantioselectivity and catalytic efficiency are still to be improved, a first step toward a practical catalytic system has been taken. Nevertheless, efforts need to be made to find conditions for the allylic oxidation of acyclic olefins, as no results have been reported on such compounds until now. Propargylic oxidation was also possible with the same kind of system with moderate induction (<52% ee).[238] Using t-BuOOH as oxidant instead of t-BuO_2-COPh leads to chiral peroxides with up to 84% ee.[239]

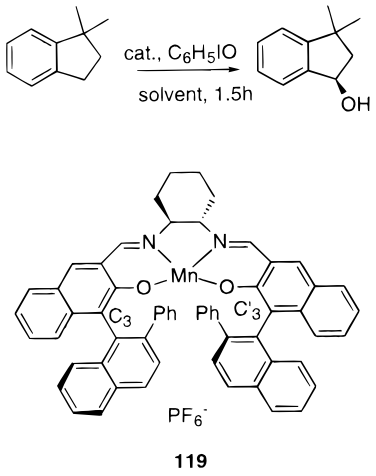
Mn−salen complexes were also used for asymmetric benzylic oxidation of various compounds into the corresponding alcohols.[240] Nevertheless, the enantioselectivity remains low, as only up to 64% ee's are reached with ligand **119** (Scheme 80).

The presence of chirality on C_3 and C_3' substituents (atropochirality) seemed to be a determining factor as Jacobsen's catalyst, which is not chiral at those sites, gives almost no enantioselectivity.

IV.2. Baeyer–Villiger-type Reaction

The enantioselective Baeyer−Villiger oxidation of ketones has previously been performed only with the

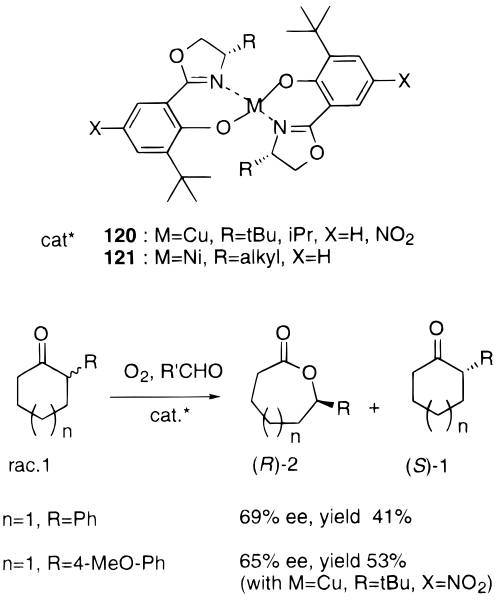
Scheme 80



119

help of enzymes.[241] Bolm et al.[242] developed a metal-catalyzed variant of this reaction using oxygen and chiral copper complexes of nitrogen-containing ligands. Moreover, an aldehyde, present in a stoichiometric amount, is necessary as an oxygen acceptor (Scheme 81).

Scheme 81

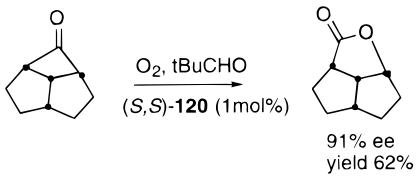


The best results were obtained with *p*-nitro-substituted copper complexes in water-saturated benzene and with pivalaldehyde as the oxygen acceptor. It is noteworthy that without the *tert*-butyl substituent on the arene, the copper complexes are only weakly active. The remaining ketone is enriched, which corresponds to a kinetic resolution. The over-oxidation of the lactone into the corresponding ketoacid is observed. This can be partially suppressed by addition of 2,6-di-*tert*-butylcresol as a radical trap.

With the same system, cyclobutanone derivatives gave the corresponding butyrolactones with up to 95% ee, and 91% ee was measured on Kelly's tricyclic ketone (Scheme 82).[243]

Other catalytic systems using Ti in Sharpless's oxidation conditions[244] or Pt and various chiral phosphines[245,246] have also been developed, but nitrogen-

Scheme 82

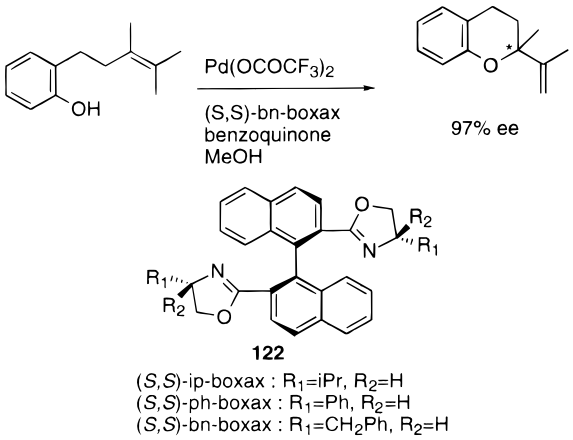


containing ligands give the best enantioselectivity in the Baeyer−Villiger oxidation of cyclic ketones.

IV.3. Wacker-type Cyclization

Palladium bis(trifluoroacetate), (*S*,*S*)-2,2′-bis[4-(alkyl)oxazolyl]-1,1′-binaphthyls, and *p*-benzoquinone turned out to be a good catalytic system for the enantioselective cyclization of unsaturated alkylphenols (Scheme 83).[247]

Scheme 83



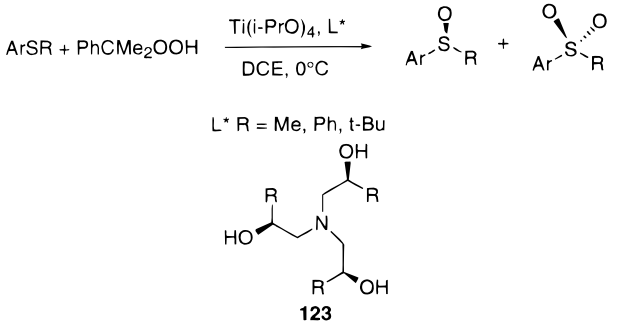
Both the central chirality of the oxazoline part and the axial chirality on the binaphthyl are important in determining the level of enantioselectivity. The two parts of the ligands are necessary to achieve high enantioselectivity as bis(oxazolines) alone or binaphthyl derivatives deprived of the oxazoline part are inactive.

V. S–O Bond Formation

Excellent results have been obtained by Kagan and others with Ti(IV)/chiral diol/alkyl or aryl hydroperoxide reagents for the enantioselective oxidation of sulfides to sulfoxides.[248−250] High enantiomeric purity was reached by addition of 1 mol equiv of water. Modena et al.[251] reported at the same time that a large excess of diethyl tartrate (4 mol equiv) was of high interest. The two approaches seemed to involve closely related complexes. These systems were originally stoichiometric, but catalytic versions were published a few years ago. The turnover number remains relatively low, despite the use of activated molecular sieves which allow a reduction of the Ti(IV)/hydroperoxide ratio by controling the water content. Ligands other than tartrates have been reported. Alkyltriethanolamines have been developed.[252] Both the nature of the ligand and the nature of the hydroperoxide are important parameters. Moreover, two enantioselective processes are in-

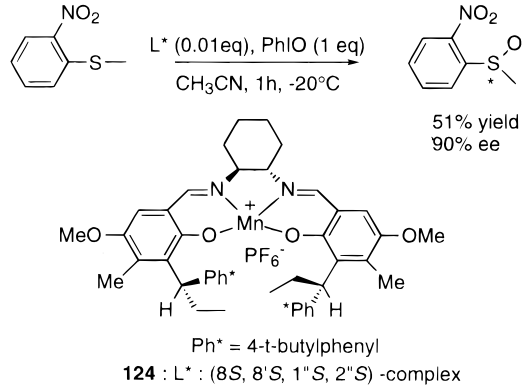
volved: asymmetric oxidation to sulfoxide and kinetic resolution via oxidation to sulfone. The best results are obtained with phenyl benzyl sulfide (84% ee, R = Ph for 88% ee) with Kagan's system[253] (Scheme 84).

Scheme 84



(Salen)Mn(III) complexes (Scheme 85) are also

Scheme 85

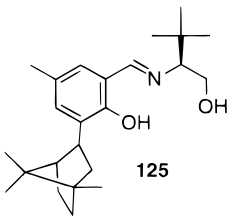


suitable catalysts for asymmetric sulfide oxidation.[254]

It is noteworthy that the diastereomeric (8*R*, 8′*R*, 1″*S*, 2″*S*)-complex of **124** gives very low ee, and Jacobsen's catalyst gives only 34% ee (but at 94% yield) on the same substrate.[255]

Vanadium catalysts turned out to be good candidates for thioether and dithiane oxidation using aza ligands. Thus, Schiff base ligands (Scheme 86) car-

Scheme 86

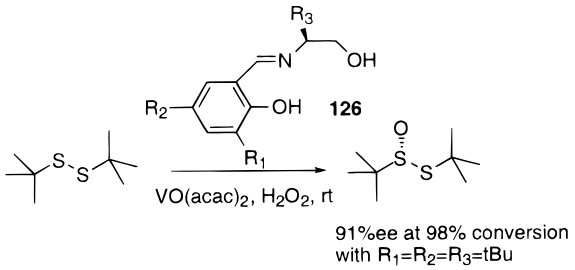


rying two elements of chirality led to 78% ee at 97% yield for the sulfoxidaton of thioethers.[256]

Bolm[257,258] reported 53−70% ee for thioethers and 85% ee for 2-phenyl-1,3-dithiane. The same system was also used for the oxidation of *tert*-butyl disulfide (Scheme 87).[259,260]

Steric effects at the 5-position of the aromatic ring of the ligand (R_2) are not important, but electronic effects are crucial. At the 3-position, both electronic and steric factors are relevant. For R_3, the *tert*-butyl

Scheme 87



group gives the best results. Thus, in $CHCl_3$ with 1% catalyst, 96−98% yield of pure product with 91% ee is obtained.

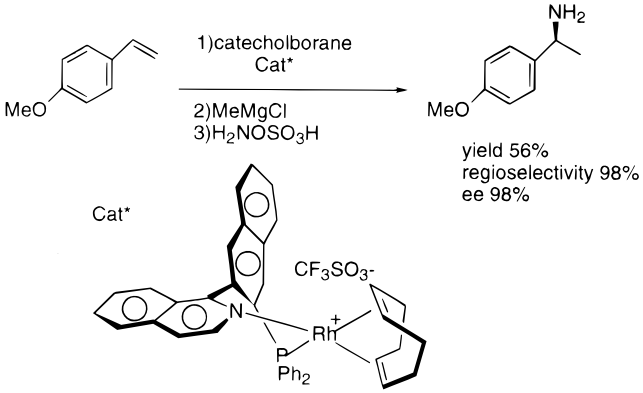
VI. C–N Bond Formation

The formation of C−N bonds is of great importance in organic synthesis as numerous biologically active compounds contain nitrogen atoms. Several possibilities for creating this bond have been reported so far and are illustrated in the following part of this review.

VI.1. Hydroboration/Amination

Primary amines were synthesized via catalytic hydroboration of vinylarenes followed by addition of MeMgCl and H_2NOSO_3H (Scheme 88).

Scheme 88



The ee values reflected the enantioselectivity of the catalyzed hydroboration step.[261] The catechol residue is then displaced by MeMgCl leading to the mixed trialkylborane and the nitrogen atom is introduced via H_2NOSO_3H addition.

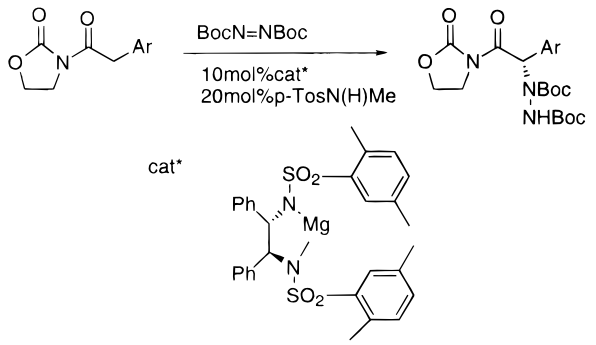
VI.2. Enolate Amination

Magnesium−bis(sulfonamide) complexes turned out to be effective catalysts for the enantioselective enolate amination of carboxylates esters (Scheme 89). A ee value of 97% was reported (>99% after recrystallization).[262]

VI.3. Aza-Claisen Rearrangement

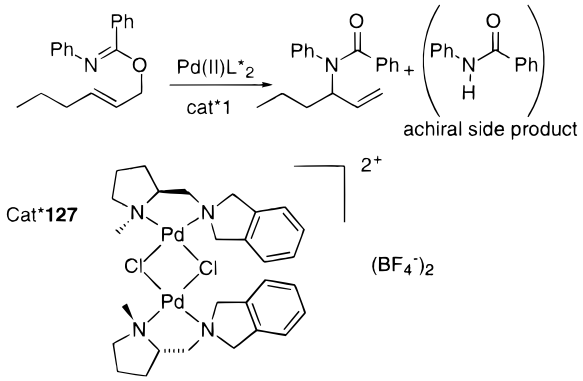
Chiral diamine ligands were tested in the Pd-catalyzed enantioselective allylic imidate rearrange-

Scheme 89



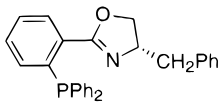
ment in allylic amides. The first results were obtained with catalyst **127**[263] (Scheme 90).

Scheme 90



Analysis of the ligand structure indicates that the isoindole group is particularly relevant. Moreover, an increase of the proximal nitrogen substituent (H to Me) improves the asymmetric induction. Even if the catalytic performances of this system were moderate (69% yield, 60% ee), this study was promising. Recently, up to 81% ee was reported in the same reaction using ligand **128**, but with only 30% isolated yield due to the abundance of the achiral side product[264] (Scheme 91).

Scheme 91



128

Planar−chiral cyclopalladated ferrocenylamines and imines were also reported for the same reaction with almost the same performances.[265]

VI.4. Azide Synthesis

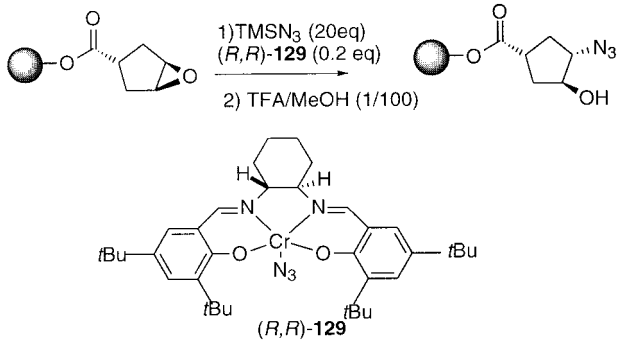
Asymmetric catalytic ring opening of polymer-bound meso epoxides with trimethylsilyl azide using (salen)CrN_3 was reported by Jacobsen's group[266] with up to 94% ee (Scheme 92).

The optically active azido alcohols thus obtained were then used for the synthesis of cyclic 1,2-amino alcohols or cyclic peptides containing the RGD (Arg-Gly-Asp) sequence.[267,268]

VI.5. Aminohydroxylation

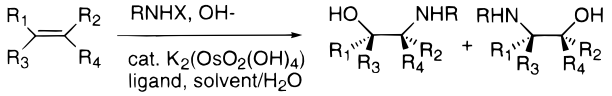
The AD procedure was adapted by Sharpless's group to the asymmetric aminohydroxylation (AA) of

Scheme 92



olefins using an osmium catalyst and $(DHQ)_2$−PHAL or $(DHQD)_2$−PHAL (see section III.2.) as ligands (Scheme 93).[269]

Scheme 93



Up to 99% ee can be reached with this system.[270] In the absence of a ligand, a large amount of diol is formed and the regioselectivity of the reaction decreases.

There are six different methods for AA which differ only in the nature of the N-protecting group.[271] The nature of the nitrogen source is thus of great importance and depends on the substrate to be aminohydroxylated.[272−276] Water appears to be necessary as cosolvent in order to reach high reactivity. This method is also suitable for the aminohydroxylation of α,*β*-unsaturated amides in its racemic version.[277]

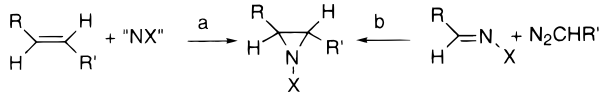
Recently, Sharpless and co-workers reported that the use of the AQN core instead of PHAL caused changes in regioselectivity in the AA of cinnamates.[278]

The heterogeneous version of AA was reported by Song et al. using a silica gel-supported bis-cinchona alkaloid.[279] Up to 99% ee has been achieved with *trans*-cinnamate.

VI.6. Aziridine Synthesis[280]

Aziridines are useful building blocks in synthesis, and chiral derivatives have also served as ligands in asymmetric catalysis. Aziridines can be obtained in chiral nonracemic form either by starting from the chiral pool (by cyclization of amino acids, for example[281]) or by asymmetric catalysis. There are two main catalytic ways to synthesize such compounds: the asymmetric metal-catalyzed nitrene transfer to olefins (path a) or its alternative, the transfer of carbenes to imines (path b) (Scheme 94).

Scheme 94

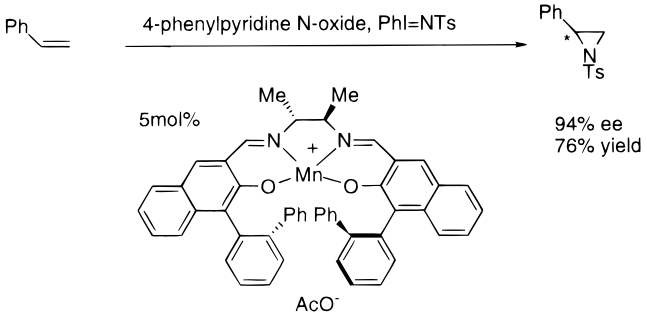


Copper-chiral bis(oxazoline) systems allowed both reactions but with low yields and ee (<12%).[282,283] Dissymmetric chiral diamine and diimine ligands having a 1,1′-binaphthyl or 1,1′-biphenyl moiety have

been tested with copper for the aziridination of styrene derivatives, but ee values do not surpass 22%.[284]

With chiral (salen) manganese(III) complexes,[285] results are better as up to 94% ee (74% yield) was reached for the aziridination of styrene derivatives (Scheme 95).

Scheme 95

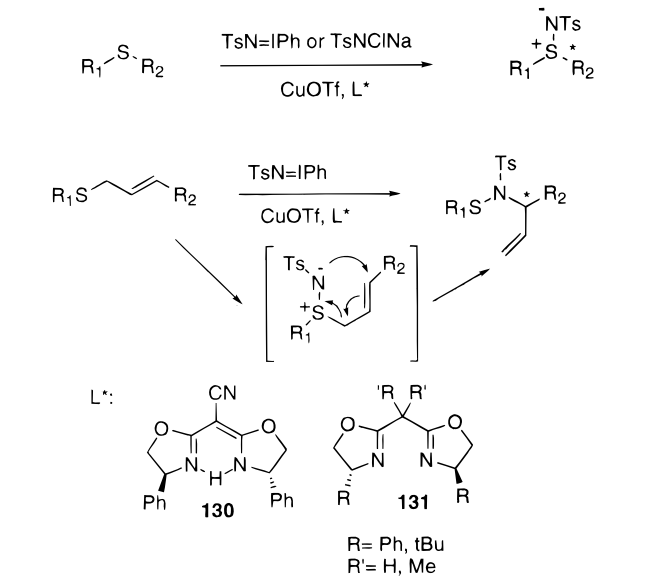


Additives play an important role in the reaction for activation of the catalyst (trifluoroacetic anhydride, toluenesulfonic anhydride, ...), and most of the time, the use of pyridine *N*-oxide is crucial to reach high enantioselectivity.[286]

VI.7. C–N Bond Formation via S–N Bond Formation

Enantioselective C−N bond formation have been obtained via copper-catalyzed asymmetric S−N bond formation and sigmatropic rearrangement. Chiral bis(oxazolines) were used in the enantioselective catalytic direct imidation of sulfides to sulfimides using copper triflate as a catalyst.[287] Enantiomeric excesses of up to 71% were measured. When allylic sulfides were used, the corresponding chiral sulfonamides were produced via [2,3]-sigmatropic rearrangement of the intermediar allylic sulfimides (up to 58% ee) (Scheme 96).

Scheme 96

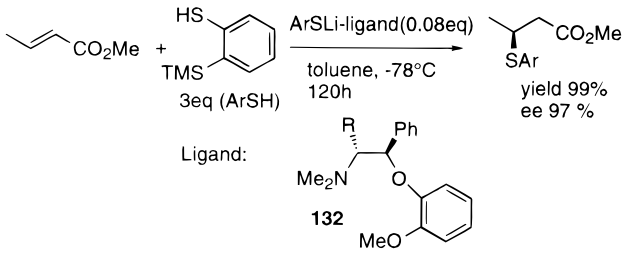


The nature of the substrate, the solvent, and the nitrene source played an important role. As for the ligand, bis(oxazolines) with the *gem*-dimethyl group (R′) and with the possibility of π-stacking interaction (R group) led to the best results for reasons still unclear.

VII. C–S Bond Formation

Enantioselective formation of C−S bonds is performed using chiral bases or transition metal complexes. The first method seems to be the more successful, so the catalytic asymmetric addition of thiophenol to α,β-unsaturated esters was reported using tridentate amino ether ligands (Scheme 97) in

Scheme 97

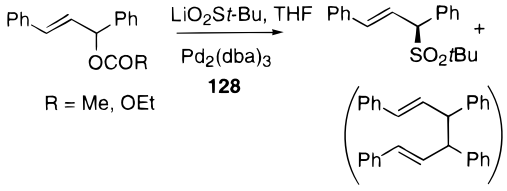


catalytic amount.[288,289]

The relative stereochemistry of the aminoether type **132** was studied, and the need for a *threo* configuration of the aminoether fragment was demonstrated. Moreover, bidentate ligands are less selective.

Allylic *tert*-butyl sulfones and sulfides were synthesized by a Pd-catalyzed allylic alkylation with up to 98% ee using the phosphine−oxazoline ligand[290] **128** (Scheme 98).

Scheme 98



It is noteworthy that the sense and degree of asymmetric induction are the same as with C- or N-nucleophiles.

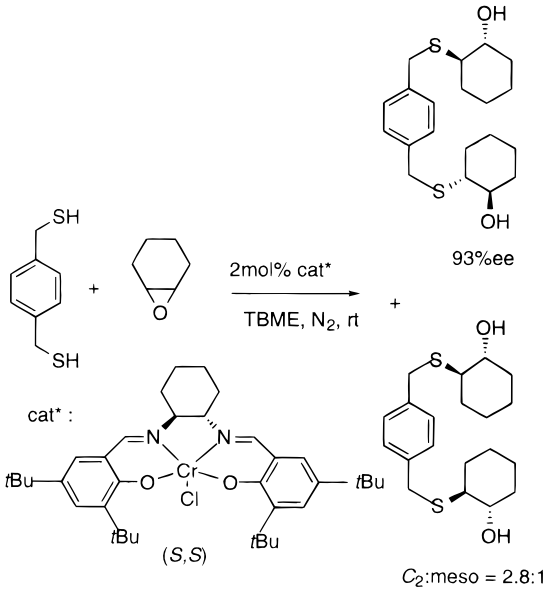
Ring opening of meso epoxides was performed with thiols using (salen)Cr(III) catalysts. Only 59% ee was reached. Using dithiols, a double asymmetric ring opening (ARO) reaction (Scheme 99) was realized with 85% ee and excellent yield.[291]

VIII. C–C Bond Formation

VIII.1. Allylic Substitutions

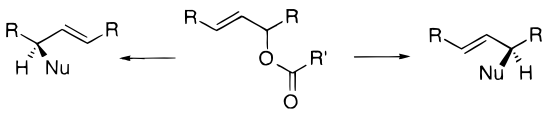
Activated allylic substrates are easily available and are very useful for creating C−C bonds by substitution. S_N1, S_N2 and S_N2' type reactions are now well-documented and easily performed with such compounds. Pd-catalyzed allylic substitutions, i.e., Tsuji−Trost reactions,[292] have been intensively studied over the past few years. Although these transformations require rather sophisticated conditions depending

Scheme 99



mainly on the nature of the catalytic species, they allow control of regio-, diastereo-, and even enantioselectivity. Very often the test reaction to evaluate the selectivity of the chiral ligand involves the transformation of the 1,3-diphenylallylsystem with various nucleophiles but mainly dimethyl malonate (Scheme 100, R = Ph). This reaction allows a facile

Scheme 100

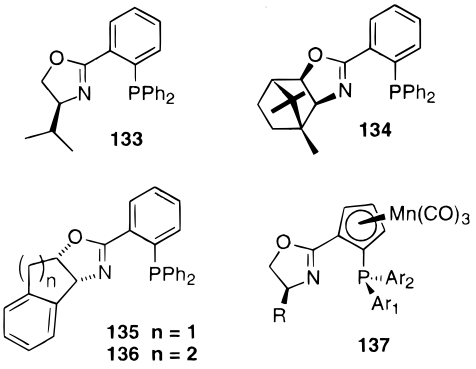


comparison and analysis of the results, since this substrate, despite its slight practical interest, usually gives rise to rather high ee values and good yields, compared to the analogous 1,3-dimethylallylsystem (R = Me), for example.

On the contrary, cyclopentenyl or hexenyl derivatives, or other aliphatic-activated allylic substrates, which after transformation could potentially lead to valuable synthons, often give rise to very weak enantiomeric excesses. The enantioselective alkylation of 1,3-diphenyl-2-propenyl acetate is therefore described with almost all the newly created catalytic systems. Only catalysts allowing good conversions and ee values with other allyllic substrates are of general interest. This situation applies to chiral phosphine-containing ligands[293] for this transformation. Excellent results are obtained only with what we will from now on call the test reaction, i.e., the alkylation of 1,3-diphenyl-2-propenyl acetate. It is only recently that, thanks to the use of N,P- or N_2,P_2-containing ligands, high enantioselectivities could be obtained for the Tsuji−Trost transformation of many useful substrates.

Hence, Helmchen and co-workers reported chiral phosphinoaryldihydrooxazoles (phosphinooxazolines) to be particularly efficient.[294] Ligand **133** (Scheme 101) furnished excellent results with large acyclic substrates, particularly in the test reaction (97% yield, 99% ee).[295] Helmchen successfully studied the

Scheme 101

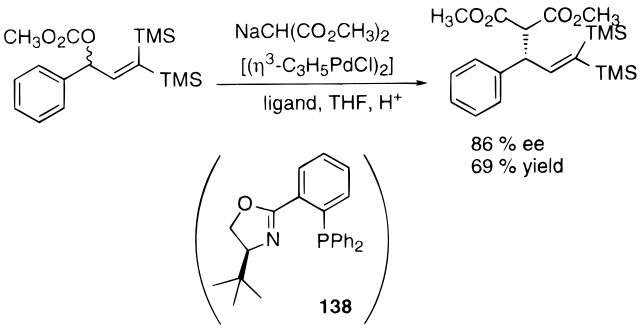


use of nitronates derived from nitromethane as nucleophiles for this catalytic allylic alkylation in the presence of **133** to obtain enantioselectivities exceeding 99%.[296] These workers have thus obtained highly valuable synthons for their transformation into synthetically important molecules. This standard phosphinooxazoline is not efficient enough for the transformation of cyclic or small acyclic substrates, however. This ligand has then been modified following various observations concerning mechanistic aspects of allylic substitutions with Pd complexes.[297] This resulted in the design of new ligands containing larger substituents at the oxazoline moiety (Scheme 101).

As expected, palladium-catalyzed allylic alkylation of 1,3-dimethylallyl acetate with the sterically demanding phosphonooxazoline ligand **136** yielded products with up to 89.5% ee. Cyclic substrates furnished low enantioselectivities with these ligands, however, due to the absence of differentiation between the intermediate π-allylpalladium complexes. Helmchen thus prepared P,N-chelate ligands with a cymanthrene unit (structure **137** in Scheme 101) that led, as expected, to higher reactivities and selectivities for the reaction with cyclic allyl acetates than with the previously reported chiral ligands.[298]

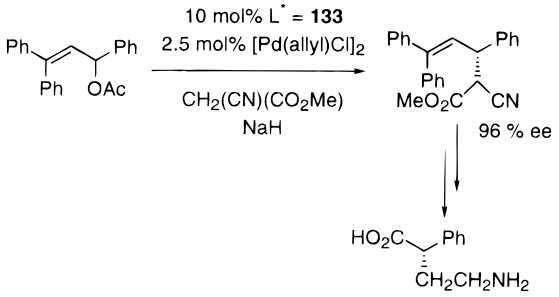
Romero and Fritzen[299] investigated the palladium-catalyzed asymmetric alkylation of a bis(trimethylsilyl)-substituted propenyl acetate and carbonate using various chiral ligands and reaction conditions. One more time, chiral phosphinooxazoline ligand **138** (Scheme 102) led to the best enantioselectivity.

Scheme 102



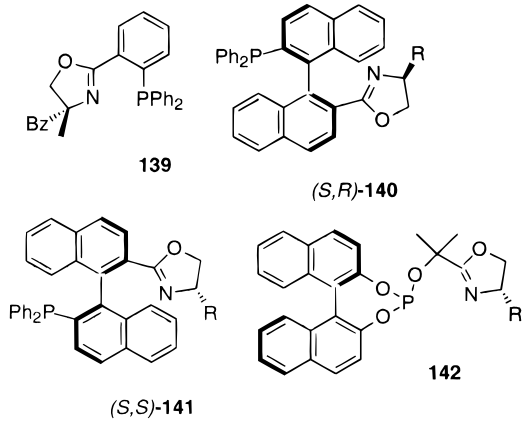
This type of phosphinooxazoline ligand also proved its efficiency in promoting enantioselective Pd-catalyzed allylic substitution reactions as a key step in the synthesis of enantiomerically enriched γ-amino acides[300] (Scheme 103).

Scheme 103



Several groups have prepared various oxazoline derivatives and tested their performance as chiral ligands for Pd-catalyzed allylic alkylations. 4,4-Disubstituted 4,5-dihydro-2-(phosphinoaryl)oxazole ligand was prepared by Zehnder[301] (structure **139** in Scheme 104) and used in the test reaction with

Scheme 104



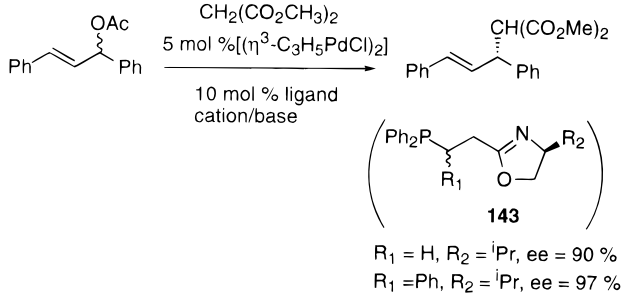
dimethylmalonate but led to very poor ee values (26%), whereas the analoguous monosubstituted oxazolines induced the asymmetry with ee values greater than 90%. Furthermore, Ikeda[302] and Hayashi[303] simultaneously prepared and tested chiral phosphino-oxazoline ligands with a 1,1′-binaphthyl skeleton (Scheme 104).

Used in the test reaction, these ligands gave alkylation products with enantiomeric excesses of up to 91%. Interestingly, Ikeda noticed that the enantioselection was governed by the biphenyl moieties, regardless of the identical *(S)*-oxazoline ring existing in both ligands.

Pfaltz prepared new chiral ligands (Scheme 104, structure **142**) derived from an oxazoline backbone with the aim to introduce electronegative substituents at the coordinating P atom that render the Pd center more electrophilic.[304] Furthermore, steric hindrance was required to affect the equilibrium between allyl intermediates. They demonstrated how the enantio- and regioselectivities of allylic alkylations with 1- and 3-aryl-2-propenyl acetates were changed by systematic modifications of the electronic and steric properties of the ligand. Very good enantioselectivities (up to 96%) were achieved.

Gilbertson and Chang[305] developed a new route toward the preparation of various phosphinodihydrooxazoles such as **143** (Scheme 105). The phosphine and oxazoline groups are linked with a two-carbon

Scheme 105

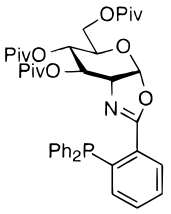


alkyl chain, forming a six-membered chelate upon palladium coordination as with the efficient ligand **133** developed by Helmchen.

They further reported the use of combinatorial chemistry[306] to synthesize and evaluate new phosphine−oxazoline ligands possessing a structure related to **143**, Scheme 105. This technology, allowing the rapid synthesis of large numbers of compounds, may have great potential in the development of new catalysts. Indeed, Burgess and co-workers[307,308] used the same high throughput screening techniques to develop similar ligands. The large amount of data accumulated allowed them to find a correlation between the substituent on the oxazoline ring, the ligand-to-metal ratios, and the observed enantioselectivities.

As part of a search for new chiral ligands derived from inexpensive natural products, Kunz prepared the carbohydrate-derived phosphinoaryloxazoline ligand **144** (Scheme 106) and tested it in Pd-catalyzed

Scheme 106



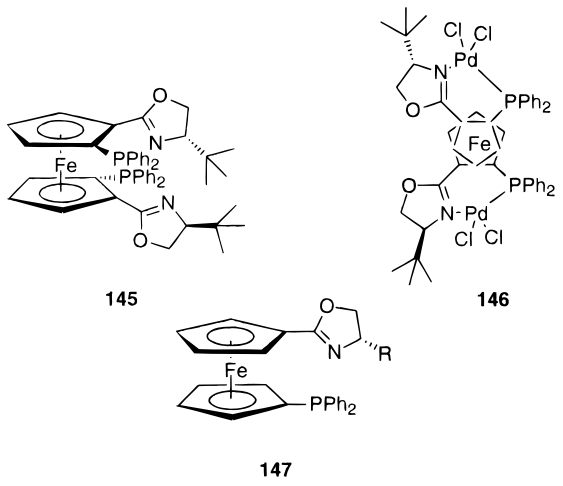
allylic substitutions of symmetrically and nonsymmetrically substituted allyl acetates.[309]

Up to 98% ee was obtained for the test reaction. The enantioselectivities observed for other substrates support the strategy of using carbohydrates with a bicyclic oxazoline structure and bulky protecting groups to optimize the stereodifferentiation.

Ikeda and co-workers[310] reported the synthesis of the novel C_2-symmetric tetrasubstituted ferrocene compound **145** (Scheme 107) and studied its complexation behavior with Pd(II) for the Pd-catalyzed asymmetric allylic alkylation. They were able to detect that a C_2-symmetric 1/2 (ligand/metal) P,N-chelate (**146**) was formed upon addition of 2 equiv of dichlorobis(acetonitrile) palladium(II). Up to 99% ee was obtained in the test reaction.

They further studied this reaction with a new kind of chiral P,N-ferrocene ligand, in which the phosphine and the oxazoline groups are attached to the two different C_p-rings of ferrocene[311] (structure **147** in Scheme 107). Up to 91% ee with 99% chemical yield

Scheme 107

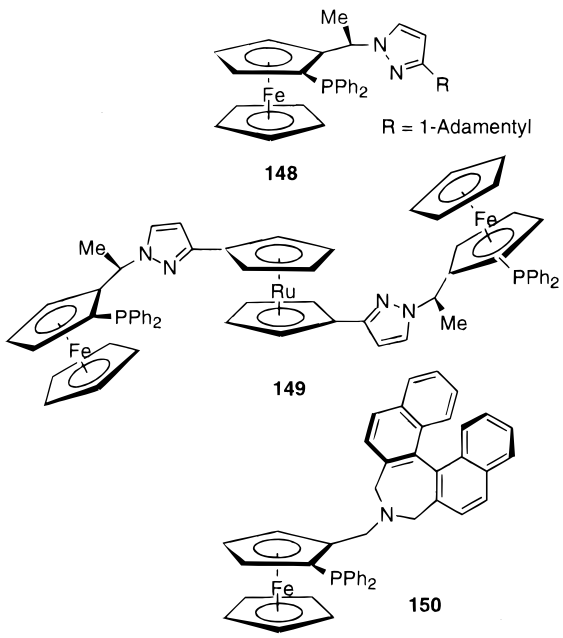


145 146 147

was afforded with these ligands, which do not possess planar chirality on the ferrocene backbone. When coordinating with a metal, however, a new chirality is induced by the C_p-ring twist. At the same time, Ahn and co-workers[312] reported the synthesis and evaluation of similar ligands having various planar chiralities. They were interested in understanding the coordination mode to palladium and were able to reject a N,N′-type ligation. They assumed that the coordination mode is dependent on the palladium source used, but contrary to Ikeda et al., they proposed a preferred P,P′-chelation for the N,N′,P,P′-type ligands studied during the catalytic reaction.

Following the same methodology, but for the creation of a new C−N bond, Togni et al.[313,314] reported the successful application of ferrocenyl ligands of type **148** (Scheme 108), containing a phosphine and a

Scheme 108



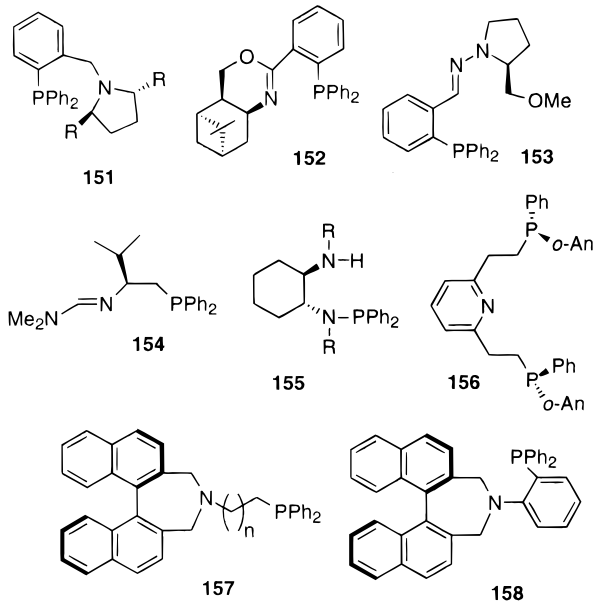
148 149 150

pyrazole ring as chelating units, in Pd-catalyzed reactions (more than 99.5% ee, in the reaction of 1,3-diphenylallylcarbonate with benzylamine). They then prepared a new ligand system by the incorporation of more than one catalyst unit into the same molecule (**149**), as a first step toward the realization of dendritic asymmetric catalysis.[315] This bimetallic catalyst (with respect to Pd, one Pd center per P,N-unit) affords very high enantioselectivities (99.3%), however, comparable to the analogous mononuclear system. But because of its lowered solubility, the system containing ligand **149** was successfully recovered and reused. The palladium-catalyzed allylic amination reaction has been further studied by several groups[316,317,318] using the same methodology as that for the creation of C−C bonds and testing similar chiral auxiliaries. This reaction will thus not be discussed in detail here.

Widhalm et al.[319] tested the ability of aminophosphine ligands containing axial and planar chiral elements to perform enantioselective π-allylic substitutions. They indeed prepared ligand **150** (Scheme 108) in four steps from ferrocene with good yields. It led to 71% ee for the Pd-catalyzed transformation of 2-cyclopent-1-yl acetate with dimethylmalonate.

Another type of P,N-ligand, in which the nitrogen atom is not part of an oxazoline group, has been tested by Cahill and Guiry.[320] They synthesized cationic palladium complexes possessing an enantiopure *trans*-2,5-dialkylpyrrolidinyl unit (structure **151** in Scheme 109). Applied to the test reaction, they

Scheme 109



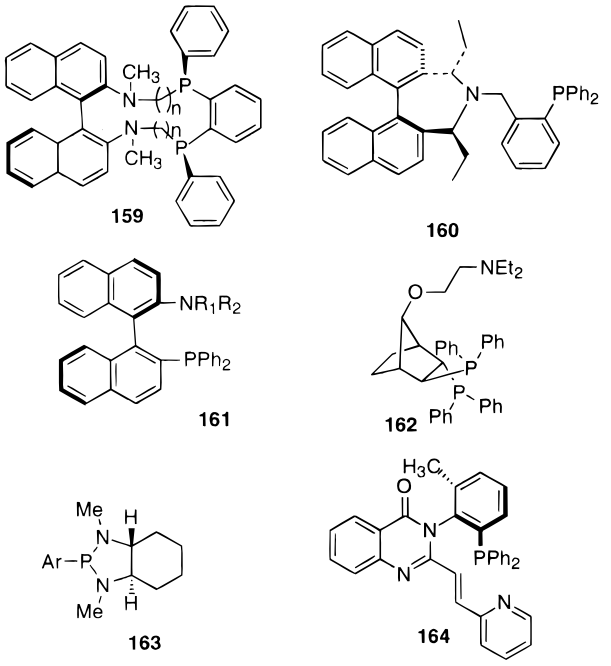
151 152 153 154 155 156 157 158

led to high conversion (90%) and up to 90% ee. Moreover, Evans et al.[321] reported that treatment of 1,3-diphenyl-2-propenyl acetate with the sodium salt of dimethyl malonate and the palladium complex of the phosphino-1,3-oxazine ligand **152** (Scheme 109) gave the allylic substitution product in 99% yield and 95% ee.

Yamashita et al. investigated the use of chiral hydrazones as ligands in asymmetric catalysis.[322] They prepared phosphine−hydrazone ligands such as **153**, which transformed 1,3-diphenyl-2-propenyl acetate in high yields with up to 92% ee. Morimoto used another P,N-bidentate ligand, the phosphorus-containing chiral amidine **154**, for enantioselective allylic

substitutions using ketene silyl acetals as nucleophiles, thus extending the scope of asymmetric allylic substitutions.[323] Spilling prepared and tested the less successful amino phosphine ligands of type **155** derived from the phosphinylation of disubstituted chiral diamines.[324] A chiral tridentate ligand based on 2,6-disubstituted pyridine (structure **156** in Scheme 109) has been prepared by Zhang[325] to yield 75% ee in the test reaction. The preparation of a ligand similar to **156** with a benzene unit instead of the pyridine moiety led to comparable results, however, suggesting that only the bidentate diphosphine coordination was responsible for the asymmetric induction. Kubota and Koga[326] reported the synthesis and use of the P,N-containing C_2-symmetric chiral ligands **157** for the asymmetric allylic substitution with high (up to 96%) enantiomeric excesses. Wimmer and Widhalm[327] prepared the chiral aminophosphine **158,** which was very efficient (96% ee) in the test reaction. The same group prepared and tested macrocyclic diphosphine ligands[328] (**159** in Scheme 110) with

Scheme 110

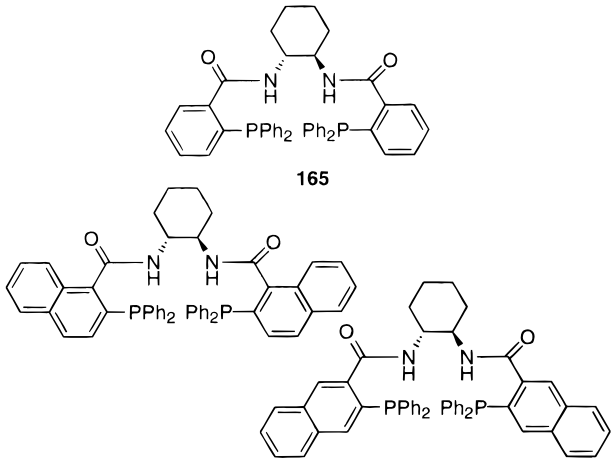


potential N_2,P_2 coordination sites owing their chirality to the incorporation of an axial−chiral binaphthyl unit. Only 77% ee was reached in the test reaction.

The new aminophosphine ligand **160** with increased steric interaction in proximity to the N-coordination site has been prepared,[329] but these structural changes did not lead to improved enantioselectivities. Vyskocil et al.[330] prepared derivatives of 2-amino-2′-diphenylphosphino-1,1′-binaphthyl (structure **161**) which were efficient P,N-coordinating ligands for the test reaction with malonate nucleophiles (up to 73% ee). Achiwa and co-workers[331] prepared a novel type of chiral biphosphine ligand (Norphos-7-NEt_2, **162**) with a pendant amino function. Interestingly, this *(S,S)*-ligand gave a product with the same absolute configuration (99% ee) as that obtained with *(R,R)*-Norphos (73% ee). This clearly indicates the interaction of the amino group on the ligand with the incoming nucleophile and the importance of the neighboring participation in enantioselection of asymmetric allylic alkylation. Wills et al.[332] discussed the capacity of ligand **163** to perform enantioselective allylic alkylations and were able to obtain up to 89% ee. The type of chelation of these ligands toward Pd (i.e., N- or P-type chelation) is, however, not determined. Dai and Virgil[333] described a mixed P,N-bidentate ligand derived from quinazolinone (structure **164** in Scheme 110) able to perform palladium-catalyzed allylic alkylation reactions with asymmetric inductions up to 87% ee. The facile modification of the structure of this ligand by electrophilic substitution should allow easy use for a variety of substrates and catalytic reactions.

Trost, particularly, has conducted very important studies to understand the asymmetric induction in this catalytic reaction. He proposed the concept of a "chiral pocket" created by the ligand.[334] It is indeed well-known that the ee decreases as the size of the substituents on the substrate (Scheme 100) decreases because of the facile interconverting of syn and anti π-allylpalladium intermediates with small R groups. When R is large, however, the *syn*,*syn*-complex is strongly favored. The use of a chiral ligand creating such a "chiral pocket" would inhibit these interconversions and thereby lead to higher levels of asymmetric induction. This concept was verified by preparing ligand **165** and its derivatives[335] (Scheme 111)

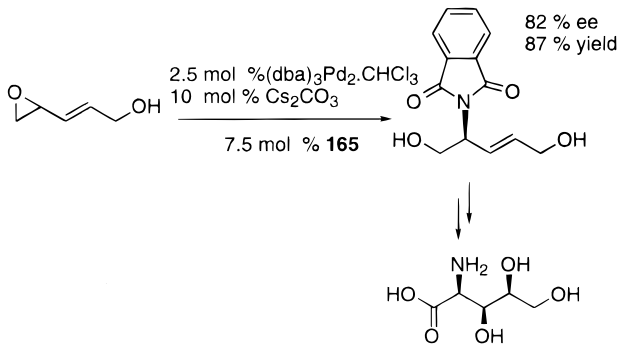
Scheme 111



for which rotation about bonds is restricted. Hence, the chiral moiety communicates its chirality to the conformationally chiral space created by the diphenylphosphino unit.

For the first time, high ee (92%) was obtained for the dimethyl case (R = Me in Scheme 100) using ligand **165** (the substrate fit well into the "chiral pocket"). The results are, however, not satisfactory for the 1,3-diphenyl analogue, indicating that, as postulated, the catalyst imposes a size restriction on the substrate. Furthermore, the authors noticed a dependence of the ee on the metal cation, revealing that the structure of the ion pair that constitutes the nucleophile is critical for good molecular recognition. Trost developed the synthesis of (+)-polyoxamic acid (a precursor for the synthesis of antifungal agents, Scheme 112), starting from a vinyl epoxide leading

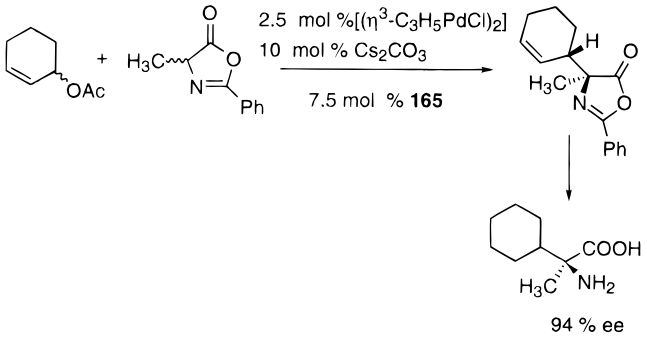
Scheme 112



to the formation of an intermediate phthalimide with 82 % ee. This example provides a particularly cheap and flexible asymmetric starting material for the obtention of numerous targets.

Hence, Trost reported a catalytic asymmetric method for the preparation of α-alkylated amino acids[336] by allylation of readily available azalactones (Scheme 113).

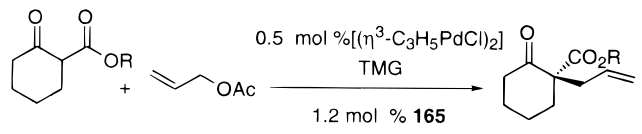
Scheme 113



The intermediate can be easily obtained as a single diastereoisomer and hydrolysis provides the amino acid without racemization.

Trost also studied the feasibility of creating other quaternary carbon centers by this methodology and worked on the catalytic asymmetric alkylation of β-ketoesters.[337] The reaction of 2-carboalkoxycyclohexanone with allyl acetate using the chiral ligand **165** in a Pd-catalyzed reaction was examined (Scheme 114) according to the choice of base and solvent which

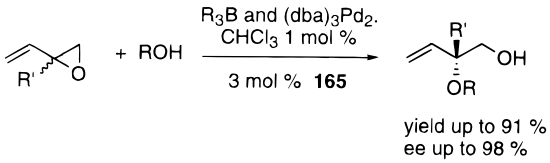
Scheme 114



leads to important variations in selectivity. The best results were obtained (81% yield, 86% ee) in toluene with tetramethylguanidine as base.

The presence of three different functional groups on the stereogenic center provides great flexibility for the transformation of this chiral synthon. As an example, the authors reported a facile synthesis of the spiroalkaloid nitramine starting from this compound. Trost also focused on the effect on enantiomeric excess of the metal ion associated to the incoming nucleophile.[338] Recently, his group worked on the Pd-catalyzed allylic alkylation of phenols as a key step for the preparation of (−)-Calanolides.[339] He also applied this technology to the asymmetric synthesis of (+)-Cyclophellitol.[340] Very recently, his research team[341] studied the palladium-catalyzed asymmetric additions of alcohols to vinyl epoxides for the preparation of useful vinylglycidols, which, in their chiral nonracemic form, are important building blocks for the synthesis of biological target molecules. They prepared a two-component catalyst system in which trialkylboranes promoted the nucleophilic addition of alcohols to vinyl epoxides in a dynamic kinetic resolution, and palladium activated the electrophile (Scheme 115).

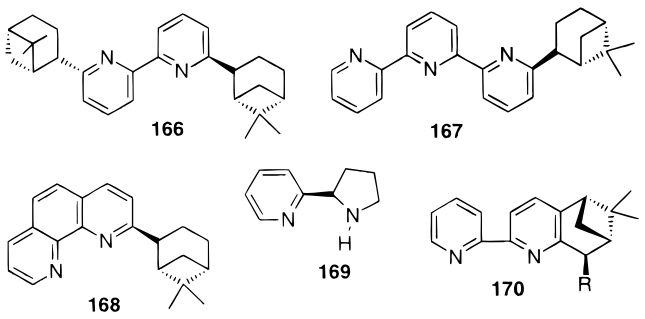
Scheme 115



They thus obtained a variety of diols with excellent yields and selectivities, wherein the more substituted alcohol is selectively "protected" by various groups such as alkyl, allyl, silyl, or benzyl derivatives, a type of differentiation not readily accessible by selective monoprotection of the diol. As summarized above, Trost obtained excellent selectivities in Pd-catalyzed allylic alkylations by using P,N-chelate ligands. This type of ligand is indeed the most successful for this reaction: it is demonstrated that different σ-donor/π-acceptor behaviors of nitrogen and phosphorus give rise to a selective attack of the nucleophile.

As we have seen, P,N-chelating ligands are mostly used to perform Pd-catalyzed enantioselective allylic substitution. Reports on the use of optically active nitrogen ligands have appeared only very recently: Pd(0) species are involved in the catalytic cycle, and it is commonly accepted that nitrogen donors are rather poor ligands for the stabilization of low oxidation states of late transition metals. Some examples are, however, to be found, in which the chelation is performed via two nitrogen atoms, leading to high enantioselectivities. Chelucci et al. prepared chiral nitrogen-containing ligands with pyridine[342] and phenanthroline derivatives.[343] They prepared bipyridines, terpyridines, and phenanthrolines bearing the 6,6-dimethyl-norpynan-2-yl group as the common chiral substituent. Examples of structures are listed in Scheme 116.

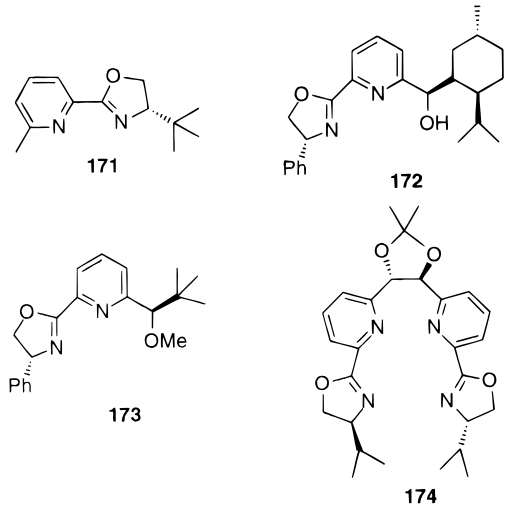
Scheme 116



These ligands are active for allylic substitutions but lead to poor selectivities (40% ee for **167**, 50% ee for **168,** and 64% ee for **169**). The process was not enantioselective when ligand **166**, with a C_2-symmetric axis, was used. By varying the structure of this bipyridine (see **170**, a chiral C_1-symmetric 2,2′-bipyridine),[344] enantioselectivities up to 89% were obtained. Helquist et al.[345] performed molecular mechanics calculations to predict the suitability of a number of chiral substituted phenanthrolines and their η^3-allylpalladium complexes for use in asymmetric palladium-catalyzed substitution reactions of allylic acetates. Good correlations were obtained with experimental results. The highest levels of asymmetric induction were predicted and obtained with a readily available 2-(2-bornyl)phenanthroline ligand (see **168**). Moreover, this work provides indications of the potential utility of a combined calculatory/experimental approach for the design of chiral catalysts.

Another class of dinitrogen ligands, namely, chiral oxazolinylpyridines, has been prepared and tested by Chelucci.[346] An enantioselectivity of up to 91% was obtained with ligand **171** (Scheme 117) for the test reaction.

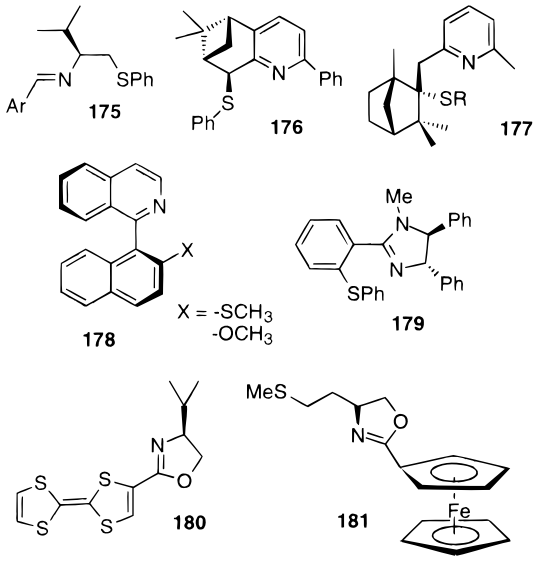
Scheme 117



Moberg modified a similar structure (**172**, Scheme 117) and prepared [(hydroxyalkyl)pyridinooxazoline] and [(alkoxyalkyl)pyridinooxazoline] palladium complexes that were highly selective for the test reaction.[347,348] The results were dependent on the nature of the substituents, on the ligand, and on the relative configuration of the two stereogenic centers present in the ligand. Better than 99% ee was obtained with ligands **172** and **173**. The authors recently reported the use of this type of ligand for asymmetric transition metal-catalyzed reactions promoted by microwave flash heating.[349] They thus demonstrated that very fast allylic alkylation reactions were accomplished in high yields and with fair enantioselectivities. The selectivities encountered were, however, somewhat lower than those obtained under classic conditions at room temperature. Chelucci finally prepared new chiral C_2-symmetric bis(oxazolinylpyridinyl)dioxolane ligands such as **174**.[350] On the basis of molecular modeling studies, he proposed two limiting conformations leading to possible bidentate ligands or tetradentate chelates. He assumed that a proper selection of both the configuration of the stereocenter and the hindrance generated by the substituents on the oxazoline ring should be chosen in agreement with the specific requirement of a particular metal-catalyzed reaction. Ligand **174** hence led to a high selectivity (ee > 98%) in the classic palladium-assisted allylic substitution. Several enantiomerically pure bis(oxazolines), with asymmetric centers on the oxazoline rings and on the side chains, have been recently used for the palladium-catalyzed allylic substitution to yield the desired products in up to 90% ee.[351]

Another class of N-containing ligands is reported in the literature to efficiently carry out the palladium-catalyzed π-allylic substitutions, i.e., N,S-chelates. Sulfur-containing ligands have rarely been used for the transition metal-catalyzed reactions, probably because of their propensity to poison the catalyst. Anderson et al.[352] developed a new series of sulfur−imine mixed donor chiral ligands (**175** in Scheme 118) easily prepared from commercially

Scheme 118



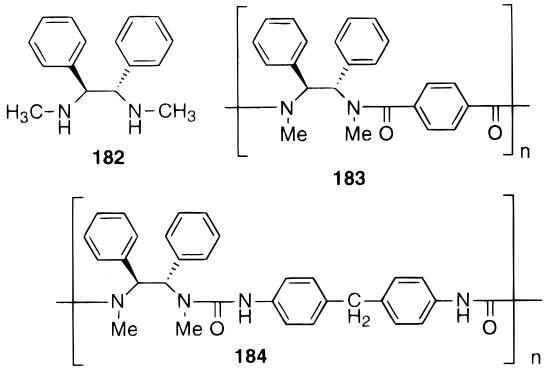
available amino alcohols. They chose to prepare imine ligands instead of amine because the unsaturated nitrogen atom could offer greater stability to the low oxidation state, electron-rich palladium, due to the N=C π^* orbital of lower energy. They indeed obtained 94% ee in the test reaction.

Chelucci developed allylic substitutions with sulfur-containing ligand, such as **176**.[353] The reactions were carried out employing $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as pro-catalyst and a mixture of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide, and potassium acetate (Trost's procedure) to yield up to 83% ee. Similar S,N-chelates (structure **177**) were developed by Kellogg et al.[354] by base-induced addition of 2,6-lutidine to thiofenchone. The corresponding thioether derivatives were also prepared, and these chiral ligands led to nearly absolute enantiomeric excess (98%) and high chemical yield (96%) in the classic test reaction

for the allylic substitution. Chelucci and his team[355] recently reported the synthesis and resolution of 1-(2-methoxy-1-naphthyl)isoquinoline and 1-(2-methylthio-1-naphthyl)isoquinoline (structures **178** in Scheme 118). Used in the test reaction, however, these molecules led to poor activities and moderate ee (68% for X = $-OCH_3$ in structure **178**). It is nevertheless noteworthy that this result is the highest asymmetric induction reported for a ligand based on the 1,1′-binaphthylbackbone not containing phosphorus as a donor atom. Chiral thioimidazoline ligands were developed by Morimoto.[356] This group described the preparation of ligand **179** and its successful application as a chiral chelate (96% ee) for the allylic substitution of 1,3-diphenyl-2-propenyl pivalate with dimethyl malonate. Chesney and Bryce were interested in preparing chiral oxazolines linked to tetrathiafulvalene as redox-active ligands (structure **180**) for asymmetric synthesis.[357] However, they obtained very poor results in terms of enantioselectivity (ee = 21%) and yield (around 30%). The authors nevertheless performed electrochemical experiments to show that the binding of palladium to this type of ligands may be electrochemically controlled. They further studied the electrochemical recycling of the catalyst. They thus prepared chiral ferrocenyl−oxazolines (**181**, Scheme 118) incorporating thioether units.[358] These systems were successfully used in the palladium-catalyzed allylic substitution reactions (up to 93% ee). The binding of palladium to these systems was shown to be reversible by electrochemical techniques. The authors wish to apply analogous catalysts in reactions for which electrochemical recycling is the key step in the catalytic cycle.

This catalytic enantioselective transformation has rarely been studied in its heterogeneous version. One example has been studied in our group[359] in which the activity and enantioselectivity of various chiral C_2-diamines are described for the asymmetric transformation of various allyl acetates. The structures tested are represented in Scheme 119.

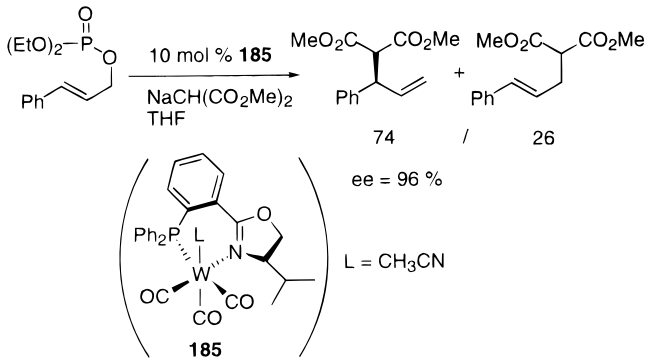
Scheme 119



Diamine **182** led to 95% ee for the alkylation of 1,3-diphenyl-2-propenyl acetate with 90% yield. This ligand reacted with a diisocyanate or a diacid chloride to lead by polyaddition or polycondensation, respectively, to an insoluble poly(urea) **184** or poly(amide) **183** with excellent yields. Poly(amide) **183** gave a better ee (80%) than poly(urea) **184** (38%) with a lower conversion (respectively, 38 and 72%) for the same transformation tested with the homogeneous ligand **182**. Efforts to reuse these heterogeneous catalysts after filtration remained vain: the palladium turned black and the recovered catalyst was no longer active. This was, however, one of the first examples of carbon−carbon bond formation in heterogeneous phase with enantioselective control.

Enantioselective allylic substitutions were thus finally performed successfully in the past few years with many useful substrates. In this particular transformation, N,N- but especially N,P- and N_2P_2-containing ligands were the best systems described to reach high efficiencies and selectivities. If selectivity problems are now well understood and even solved (see the "chiral pocket" described by Trost), the reaction still suffers from several drawbacks, essentially due to the use of Pd(0) complexes. Indeed, the rather low stability of theses complexes involves difficult separation and recycling of the catalyst. The difficulties encountered in the attempts to perform heterogeneous versions of these systems are hence not so surprising. The preparation of complexes that are active under biphasic conditions have already been reported, albeit without particularly good enantioselectivity until now. It now seems, however, that research is directed toward the use of transition metal species other than palladium. Indeed, Pfaltz[360] reported the use of chiral phosphanodihydrooxazoles in tungsten-catalyzed allylic substitutions. The active complex derived from **185** (Scheme 120) is the first

Scheme 120

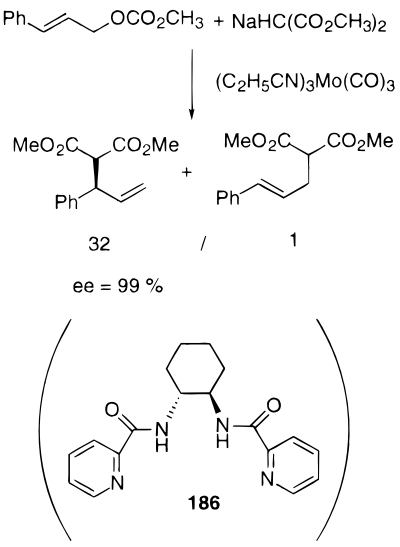


example of an enantioselective tungsten catalyst for allylic alkylation. Interestingly, the regio- and enantioselectivities with arylpropenyl phosphates are opposite to those obtained by using analogous Pd-(phosphinodihydrooxazole) catalysts.

Trost explained[361] that with aryl-substituted allyl systems, palladium-catalyzed reactions normally lead to products obtained by attack at the less substituted carbon atom, whereas molybdenum and tungsten catalysts favor attack at the most substituted sp^2-C. These results were illustrated with the transformation reported in Scheme 121 with ligand **186**. The metallic precursor used is $(C_2H_5{-}CN)_3Mo(CO)_3$.

The copper(I)-catalyzed enantioselective substitution of allyl chlorides with diorganozinc compounds has been described by Knochel[362] using a ferrocenylamine as the chiral ligand. The allylated products are obtained with moderate to good enantioselectivi-

Scheme 121



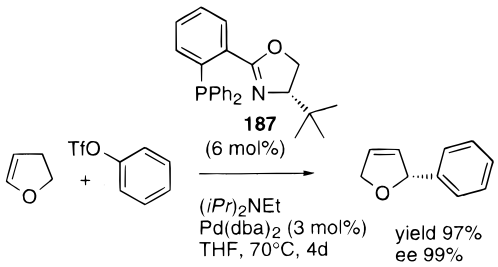
ties (up to 87% ee) and excellent S_N2' regioselectivities.

VIII.2. Heck Reactions

The development of enantioselective variants of the Heck reaction has been reviewed by Schmalz[363] and Mayer.[364] This important method for C−C bond formation leads to excellent enantioselectivities especially when BINAP is used as a ligand for this palladium-catalyzed reaction. This reaction is often limited by low activity with certain classes of substrates, however, and also by the formation of byproducts (resulting from a C=C bond migration) leading to mixtures of isomers. There is thus a need for the design of new ligands to widen the scope and applications of enantioselective Heck reactions. N,P-Containing chelates have proven to be efficient for such a transformation.

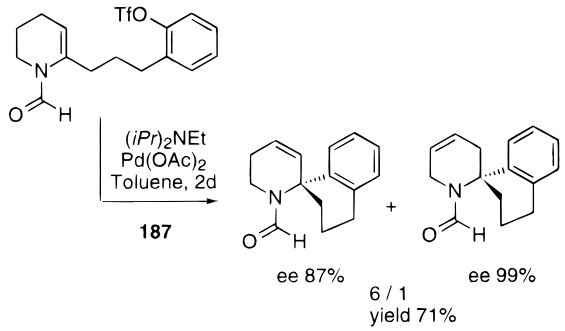
Pfaltz and co-workers[365] described the remarkable selectivities obtained with the phosphanyldihydrooxazole derivative **187** for enantioselective Heck reactions (Scheme 122).

Scheme 122



They proved that this system does not promote C=C bond migration, in contrast to the Pd(BINAP) analogue. Indeed, this last catalyst yields the thermodynamically more stable 2,3-dihydro isomer as the major product, with 58% yield and 87% ee. These types of P,N-ligands are quite attractive because of their availability and the possibility to easily modify their structure either on the dihydrooxazole ring or on the phosphane group. Hallberg and his team[366] worked on the intramolecular, enantioselective palladium-catalyzed Heck arylation of cyclic enamides to provide spiro compounds as efficient synthons for valuable bioactive molecules. The more efficient asymmetric N-containing ligand once again was proven to be the chiral (phosphinoaryl)oxazoline **187** (Scheme 123), which furnished higher enantiomeric

Scheme 123



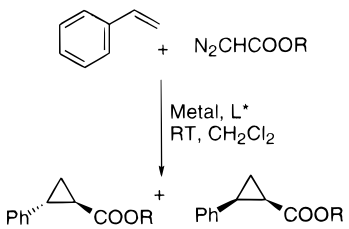
excesses and better regioselectivities than chiral phosphine ligands such as BINAP.

The remarkable selectivities obtained with phosphanyldihydrooxazoles show the important potential of P,N-containing ligands for enantioselective Heck reactions. To our knowledge, few or no other N-containing ligands have been tested in such a transformation.

VIII.3. Cyclopropanations

Asymmetric catalytic cycloaddition of electrophilic metal carbenes to prochiral olefins is a facile methodology for highly enantioselective cyclopropane synthesis. The method consists of the metal-catalyzed decomposition of substituted diazo compounds in the presence of various alkenes, which leads to the synthesis of highly functionalized cyclopropanes, important building blocks for the obtention of several natural compounds and agrochemical active species. The reaction of styrene with methyldiazoacetate (Scheme 124) has been widely studied and plays more

Scheme 124



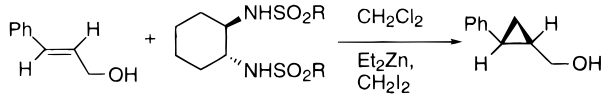
or less the same role for asymmetric cyclopropanation as the transformation of the 1,3-diphenylallyl-system with various nucleophiles plays for the Tsuji−Trost reaction. Some attempts have been made to perform asymmetric cyclopropanation with palladium as the catalytic species, and several examples using the Simmons−Smith transformation are also proposed. However, the most successful catalysts are complexes of ruthenium, rhodium, and especially copper derivatives. Excellent control of both diastereo- and enantioselectivity are observed when chiral nitrogen-

containing ligands are used. For this transformation, N-containing ligands proved to lead to better activities and selectivities than all other types of ligands. Indeed, few examples of efficient and selective systems were described using phosphine ligands.

Several examples of this methodology, in which the reactions are classified according to the nature of the catalytic system used, are given below.

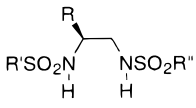
First, it is worthwhile to mention a procedure based on the Simmons−Smith reaction, recently reported by Kobayashi[367] and improved by Denmark and coworkers,[368,369] in which the carbene is typically generated from CH_2I_2. This catalytic enantioselective cyclopropanation of allylic alcohols requires the use of diethylzinc, diiodomethane, and chiral promoters, in this case chiral sulfonamide derivatives (Scheme 125).

Scheme 125



The rate and selectivity of this reaction proved to be highly dependent on the order of addition of the reagents. The prior formation of a zinc alkoxide derivative and the use of ZnI_2 as cocatalyst are necessary to obtain high enantioselectivities (up to 86% with this system). The same authors studied the dependence of the enantiomeric excess on the structure of the chiral N-containing promoter.[370] They then synthesized numerous diamine ligands by varying the sulfonamide structure (R-group in Scheme 125) of *trans*-1,2-diaminocyclohexane, thus demonstrating the superiority of the methanesulfonamido group. Next, a variety of diamine skeletons were tested to probe their effect on activity and enantiomeric excess. The best results are obtained when a nonsterically hindered NH-bis(sulfonamide) can chelate the metal with a 60−75° bite angle. The stereoselectivity of cyclopropanation was found to be independent of the olefin geometry and remained very high with allylic alcohols bearing aliphatic and/or aromatic substituents.[371] It has recently been assumed[372] that the addition of zinc iodide in the reaction course allowed a spectacular enhancement of both the reaction rate and the enantiomeric excess (80 to 89%). This is probably due to a reagent modification via a Schlenk equilibrium leading to the formation of the reactive and selective (iodomethyl)zinc iodide, "ICH_2-Zn-I". Attempts to optimize the structure of the chiral N-containing promoter have been made, and Imai and Nokami[373] reported the synthesis of new disulfonamides prepared from α-amino acids (general structure in Scheme 126). Unfortunately, none of the

Scheme 126

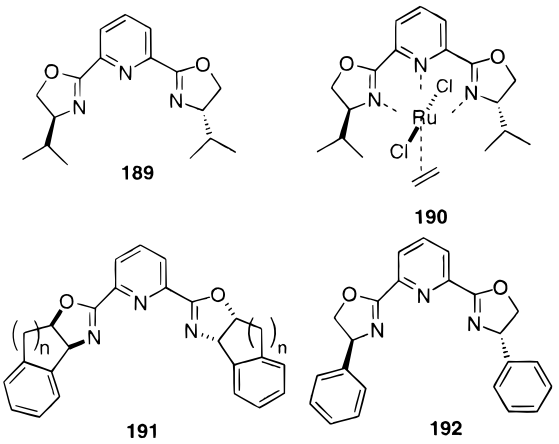


188

synthesized structures of type **188** led to excellent enantioselectivities.

There exist some examples of other metals that are efficiently used for the asymmetric cyclopropanation of olefins. The catalytic activity of several ruthenium complexes for cyclopropanation with diazoacetates has been reported mainly by Nishiyama[374] who, in this case, used bis(oxazolinyl)pyridine derivatives (pybox) as chiral nitrogen-containing ligands (Scheme 127, structure **189**). The catalyst prepared in situ

Scheme 127



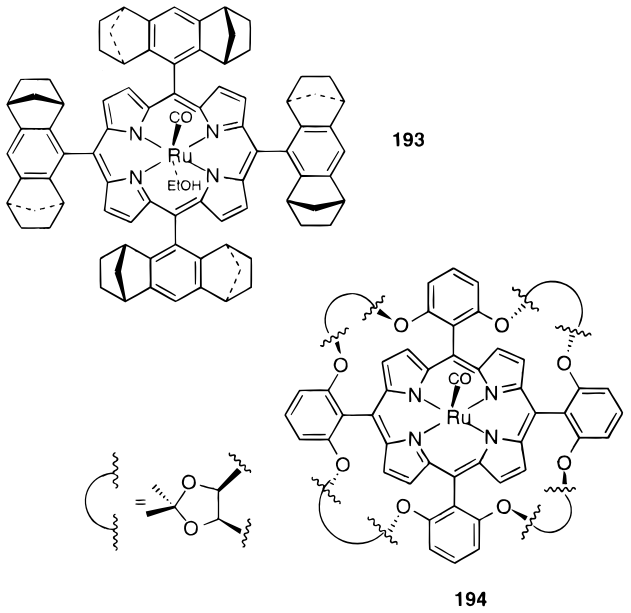
from **189** and $[RuCl_2(p\text{-cymene})_2]$ or complex **190** were found to be highly active and selective in the model reaction depicted in Scheme 124 (*trans*/*cis* selectivities up to 98/2 and 97% ee). Recently, the same group[375] reported the synthesis of single, chiral bis(oxazolinyl)pyridine ligands and their activity in the same transformation. Enantioselectivities up to 94% were indeed observed. The authors explained these good results by proposing structures for the intermediate carbene complexes, for which a chirality in pybox is sufficient to guide the selective attack of the olefin.

Davies[376] worked on the determination of pybox-induced conformational effects by testing several ligands which were sterically hindered on the oxazoline moieties (Scheme 127, structures **191** and **192**). These new ligands gave poorer results in terms of yields and enantioselectivities than ligand **189** for the Ru-catalyzed cyclopropanation reaction, indicating unfavorable steric interactions between styrene and the carbene complex.

Metalloporphyrins are also effective catalysts for cyclopropanation. Two groups[377,378] reported their use as ruthenium carbonyl ligands for the enantioselective cyclopropanation of styrene.

Structure **193** drawn in Scheme 128 proved to be extremely active: at a catalyst loading of only 0.15 mol %, quantitative transformations of olefines were obtained. Moreover, excellent diastereoselectivities (*trans*/*cis* 96/4) and high enantiomeric excesses (up to 91%) were obtained in the cyclopropanation of styrene with ethyl diazoacetate. Recently, Simonneaux and his group[379] reported that the homochiral porphyrin ruthenium(II) complex (structure **194** in Scheme 128) catalyzed the cyclopropanation of styrene derivatives with good yields. Only moderate enantiomeric excesses (up to 52%) were achieved, however. Gross studied an alternative approach,[380]

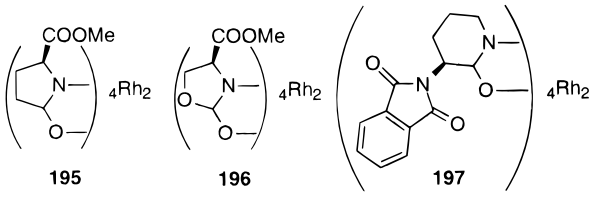
Scheme 128



in which the asymmetric cyclopropanation of olefins occurred by an enantiopure carbenoid by catalysis with achiral metalloporphyrins. This methodology provided significant insight into the mechanistic aspects which determine the selectivity. Up to 80% de (>98% de after recrystallization) was obtained by this interesting alternative approach.

The catalyzed cyclopropanation of prochiral olefins with diazoacetates has also been successfully described with rhodium as the active transition metal. Doyle et al. worked on the synthesis and evaluation of dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5-carboxylate (structure **195**, Rh_2(5*S*-MEPY)$_4$ in Scheme 129) and dirhodium(II) tetrakis[methyl 2-oxazolidi-

Scheme 129

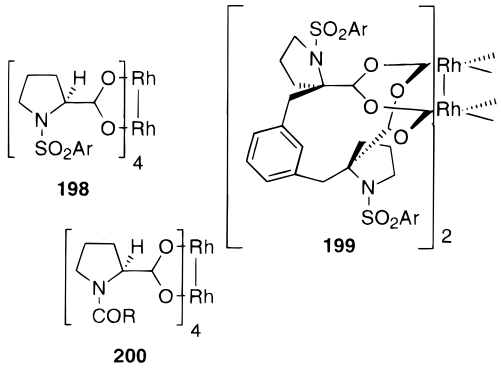


none-4-carboxylate (structure **196**, Rh_2(4*S*-MEOX)$_4$ in Scheme 129).

These two chiral dirhodium(II) carboxamidates were particularly effective for the enantioselective catalytic intramolecular cyclopropanation of allylic α-diazopropionates: structure **195** allowed the formation of the corresponding cyclopropane-fused bicyclic lactones in high yields and ee values up to 94%.[381] With Rh_2(4*S*-MEOX)$_4$ in similar conditions, 85% ee was obtained.[382,383] These types of reactions found their synthetic utility for the efficient synthesis of chiral macrocyclic lactones.[384] Dirhodium(II) tetrakis-[3(*S*)-phthalimido-2-piperidinonate] **197**, when employed in the rarely used ether as solvent, affords the highest levels of enantioselectivity (98%) reported to date, albeit with a limited number of substrates (alkenes and substituted diazoalkanes).[385]

Other N-containing ligands derived from proline (**198** and **199** in Scheme 130) are particularly effec-

Scheme 130

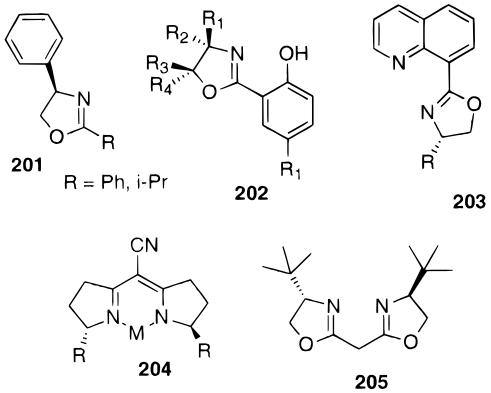


tive for enantioselective intermolecular cyclopropanation reactions with methyl phenyldiazoacetate,[386,387] whereas in these cases the nitrogen atom is not directly involved in the metal coordination.

Studies have been conducted on the rhodium *N*-(arylsulfonyl)prolinate derivative catalyzed decomposition of vinyldiazomethanes in the presence of olefins for the effective preparation of functionalized cyclopropanes with high diastereo- and enantioselectivities.[388,389] Chiral *N*-acyl pyrrolidine carboxylic acid ligands[390] (structure **200**) have been tested for the dirhodium-catalyzed asymmetric cyclopropanation with vinyldiazoacetates. Davies recently illustrated the synthetic utility of these complexes for vinylcarbenoid cyclopropanations[391] and for the construction of 1,4-cycloheptadienes by tandem asymmetric cyclopropanation/Cope rearrangement.[392]

Finally, asymmetric cyclopropanation of olefins is by far the most successful application of the Cu(I) bis(oxazoline) catalytic system. We first wish to summarize several articles in which the authors studied the possibility of using monodentate oxazoline ligands. Hence, Dakovic et al.[393] described the inefficiency (in terms of selectivity) of such oxazoline ligands in asymmetric copper cyclopropanation but reported that when the N-containing ligand bore a phenyl group (structure **201** in Scheme 131), an

Scheme 131



asymmetric induction, comparable to the usual ee obtained with bis(oxazoline) ligand, was observed. This behavior was explained by the participation of 2:1 (ligand:Cu) complexes, stabilized by π-stacking

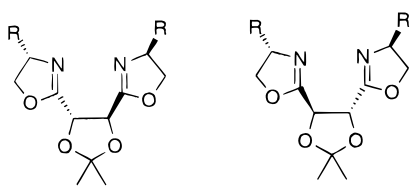
of phenyl groups on the chiral center, in the catalytic cycles. Similarly, Brunner and Berghofer[394] reported the synthesis of salicyloxazolines **202** (Scheme 131) and their use in the enantioselective Cu-catalyzed cyclopropanation of styrene with ethyl diazoacetate. Optical inductions of up to 60% ee were achieved with these ligands. Zhou et al.[395] prepared chiral quinolinyl-oxazoline ligands of type **203** (Scheme 131). The electronic properties of these ligands are similar to those of pyridine−oxazoline chelates. The size of the chelating ring in the formed complexes with metals is different, thus influencing their stability, stereochemistry, and enantioselectivity. When tested in the asymmetric cyclopropanation of styrene with diazoacetates in the presence of copper(I) triflate, however, they led to moderate stereo- and enantioselectivities (up to 64% ee).

Chiral C_2-symmetric semicorrins, developed 10 years ago by Pfaltz,[396] were proven to be highly efficient ligands for the copper-catalyzed enantioselective cyclopropanation of olefins (structure **204**). Variations of the substituents at the stereogenic centers have led to optimized structures and very high enantioselectivities.[397]

Evans[398] reported the cyclopropanation of styrene with ethyl diazoacetate in the presence of the catalyst generated in situ from Cu(I) triflate and bis(oxazoline) **205** (Scheme 131) with high asymmetric induction (54% de and, respectively, 98% and 93% ee for each cyclopropane derivative formed).

Structure **205**, commonly named Evans's ligand, is widely used for performing highly enantioselective Cu(I)-catalyzed cyclopropanation. For example, it was efficient for the cyclopropanation of cyclic enol ethers, described by Andersson,[399] toward the asymmetric total synthesis of (+)-Quebrachamine. A lot of work has been done to improve the structure of the C_2-symmetric chiral bis(oxazoline) **205**, namely, by varying the size of the oxazoline substituent and the length and/or nature of the bridge between the two heterocycles. In particular, Andersson et al.[400,401] (and simultaneously Knight[402] and Imai[403]) worked on the effect of the length and structure of the bridge between the two oxazoline moieties. The most widely studied ligands in this series formed a six-membered chelate with the metal (structure **205** in Scheme 131). They prepared and tested a new class of bis(oxazoline)s in which both heterocycles were separated by a tartrate backbone and thus formed a seven-membered chelate with the metal (Scheme 132).

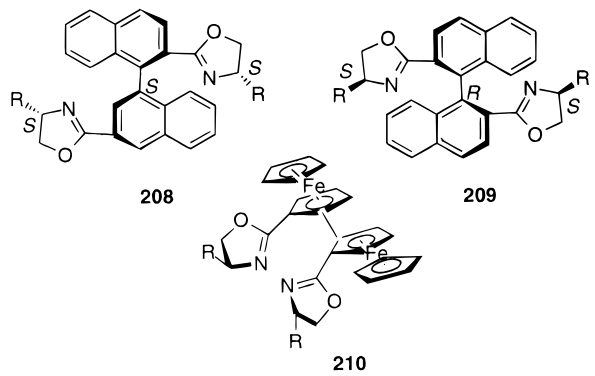
Scheme 132



This model, as a result of the twist imparted by the 1,3-dioxolane ring, allows control of the orientation (and the proximity) of the oxazolinyl-R substituent around the reactive metallic site. Higher enantioselectivities are thus obtained with ligand **207** (R = $CHMe_2$, 84% ee for the trans product, Scheme 132) in which the R groups are brought closer to the metal. The effect of increasing the steric bulk of the diazoacetate in the cyclopropanation of styrene was also studied and permitted to raise the ee (up to 96% for (−)-8-phenylmenthyldiazoacetate). The comparison of isopropyl derivatives of these ligands with previously reported five- and six-membered bis(oxazoline)s clearly indicates the beneficial effect of the larger chelate size of the tartrate-derived ligands (ee values around 70% for **206** and **207**, whereas they only reached 8% and 36% for the five- and six-membered corresponding chelates, respectively). Obviously, the effect of the ring size is difficult to separate from the effect of the double induction coming from the tartric backbone.

Other very attractive bis(oxazoline) derivatives have been prepared by Hayashi's[404] group. This group synthesized both diastereoisomers of 2,2′-bis[4-(alkyl)oxazol-2-yl]-1,1′-binaphthyl, which are reported in Scheme 133.

Scheme 133



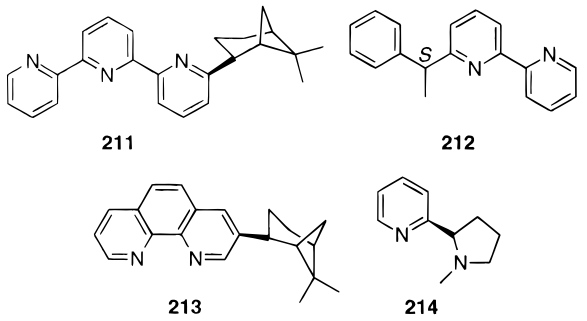
These ligands, which possess both binaphthyl axial chirality and carbon-centered chirality, led to excellent enantioselectivity or diastereoselectivity, particularly for the cyclopropanation of styrene with *l*-menthyldiazoacetate. The catalytic system CuOTf−*(S,S)*-bis(oxazolyl)binaphthyl (R = ^{t}Bu) gave 95% ee for the corresponding *trans*-cyclopropane and 97% ee for the *cis*, the *trans*/*cis* ratio being 68/32. In these structures (**208** and **209**, in Scheme 133), the angle for the metal chelation is larger than in the model structure **205** (Scheme 131) and led to improved enantioselectivities. Corey et al.[405] simultaneously reported similar studies concerning asymmetric intramolecular cyclopropanation with a 2,2′-bis(oxazolyl)-6,6′-dimethyl-1,1′-biphenyl as copper(I) triflate chelate. They applied this highly enantioselective methodology to the synthesis of Sirenin. Encouraged by this result, Ahn et al.[406] reported the synthesis of enantiomerically pure bis(oxazolinyl)biferrocene ligands (structure **210** in Scheme 133) which also have both planar and central chirality. The results obtained (regarding *cis*/*trans* selectivity and enantioselectivity) are indeed comparable to those achieved with the binaphthyl derivatives mentioned above, since 2-(phenyl)cyclopropane carboxylates were synthesized in up to 99% ee and a *trans*/*cis* selectivity of up to 88/12. Several homochiral bis(oxazolines), with asymmetric centers on the oxazoline rings and

on the side chains, were recently prepared by Aït-Haddou and Balavoine.[407] Ethyl 2-phenylcyclopropanecarboxylate could be obtained in up to 85% ee in the copper-catalyzed cyclopropanation of styrene with these ligands.

It is noteworthy that all the preceding results report oxazoline copper-catalyzed cyclopropanations. Attempts have been made with bis(oxazoline)palladium(II) complexes,[408] which were all efficient for this reaction but led to racemic compounds. A partial or complete decomplexation of the bis(oxazoline) ligand during the course of the reaction was the explanation given for this lack of selectivity.

Another class of N-containing chiral ligands, based on the pyridine framework, has been tested to extend the scope of the copper-catalyzed cyclopropanation reaction of olefins. Hence, Chelucci et al.[409] examined the efficiency of a number of chiral pyridine derivatives as bidentate ligands (mainly 2,2′-bipyridines, 2,2′:6′,2″-terpyridines, phenanthrolines, and aminopyridine) in the copper-catalyzed cyclopropanation of styrene by ethyl diazoacetate. Some examples of the structures studied are presented in Scheme 134.

Scheme 134

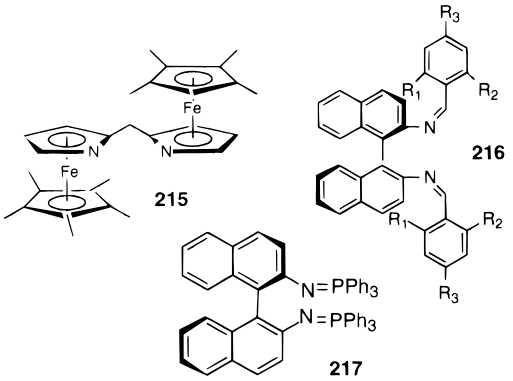


The corresponding copper complexes proved to be only moderatly active and enantioselective (ee up to 32%), however. These structures have to be improved, particularly if the asymmetric control of the reaction is governed by the steric hindrance generated by the substituents at the asymmetric centers: the structures which are selected must be able to accommodate the metal ion during complex formation.

Several new N-containing ligands have recently been described as effective chiral inductors for copper-catalyzed asymmetric cyclopropanation. Hence, Fu and Lo[410] prepared a new class of planar, chiral ligands, namely, the C_2-symmetric bisazaferrocene (structure **215** in Scheme 135), which was found to be efficient for the cyclopropanation of various olefins with large diastereomeric excesses and ee values up to 95%.

Suga and Ibata[411] prepared binaphthyldiimine derivatives (structure **216** in Scheme 135); the best selectivity, 98% de for the transformation of 1,1-diphenylethylene with *l*-menthyl diazoacetate, was obtained by using double induction for the copper-catalyzed cyclopropanation. Chiral diamines were converted into the corresponding diimino(triphenyl)-phosphoranes (structure **217** in Scheme 135) by Reetz and co-workers.[412] Preliminary studies using this chiral copper complex for the cyclopropanation led

Scheme 135

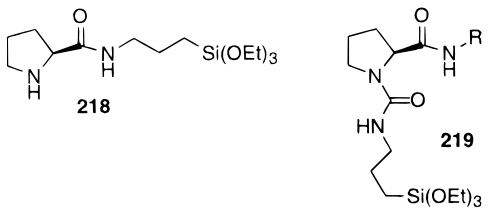


to important ee values (up to 90%) for the reaction between styrene and ethyl diazoacetate.

We have presented several structures of N-containing ligands which are effective for the enantioselective cyclopropanation of prochiral olefins with diazoacetates. The diastereo- and enantioselectivities obtained are not yet well understood and depend both on steric and electronic factors. To compare the efficiency of these various ligands for specific reactions, we mention the recent work of Doyle, which evaluated the enantiocontrol of cyclopropanation with different chiral catalysts.[413,414] Reissig similarly screened N-containing catalysts for their evaluation in the asymmetric cyclopropanation of silyl enol ethers.[415]

Efforts have been made to heterogenize copper complexes as immobilized catalysts for the asymmetric cyclopropanation of alkenes. Corma et al.[416] prepared chiral Cu(I) complexes with substituted pyrrolidine ligands bearing a triethoxysilyl group (Scheme 136).

Scheme 136



These N-anchoring ligands were then supported on a modified ultrastable Y-zeolite containing supermicropores by a covalent bond. The complexes anchored on the zeolite have been compared to the free complexes in homogeneous medium regarding their efficiency for the catalytic cyclopropanation of styrene with ethyldiazoacetate. The selectivities observed were low (up to 11% ee) but led to similar values when comparing the unsupported and zeolite-supported Cu complexes. Interestingly, however, the zeolite catalysts could be recovered and reused several times with no loss of activity or copper content. Another example of heterogeneous complexes used for asymmetric cyclopropanation was reported in 1997 by Fraile et al.[417] The authors used cationic bis(oxazoline)Cu(II) complexes intercalated into lamellar solids (in this case clays) as catalysts for C−C bond formation reactions. They used cationic

complexes (starting from $CuCl_2$) supported by electrostatic interactions with aluminosilicate sheets of clays with cation exchange capacity. Interestingly, the heterogeneous catalysts led to higher conversions and selectivities than their homogeneous counterpart. Changes in the microenvironment (solvent, negatively charged sheets, site isolation, dimensionality, ...) of the bis(oxazoline)Cu(II) complexes can explain these results. Furthermore, these catalysts have been recovered and reused without loss of their catalytic activity. Recently, Fraile et al.[418] reported good results when Laponite is used as the support. The interaction with the support leads to a modification of the stereochemical course of the reaction, giving rise to an increase of the *cis*-cyclopropanes with regard to what was observed in the homogeneous phase. Some of the catalysts could be recovered and reused, retaining the same catalytic activity and leading to the same enantioselectivity.

To conclude, there are two main difficulties in performing useful cyclopropanation: the first one consists of obtaining high enantioselectivity, the second one is reaching high diastereoselectivity. This last requirement is very important when one considers that potential useful target molecules often possess several substituents on the cyclopropane ring, with precise spatial orientation. The parameters allowing the control of the diastereoselectivity are still not fully understood. It has to be noticed, however, that asymmetric cyclopropanation has been performed with excellent diastereo- and enantiocontrol when copper catalysts were used, especially those containing bis(oxazoline) derivatives. Moreover, some of the best results published have been obtained with more expensive rhodium complexes. This catalytic organic transformation is a particular example in which such good selectivities could not be obtained with P-containing ligands as chiral auxiliaries.

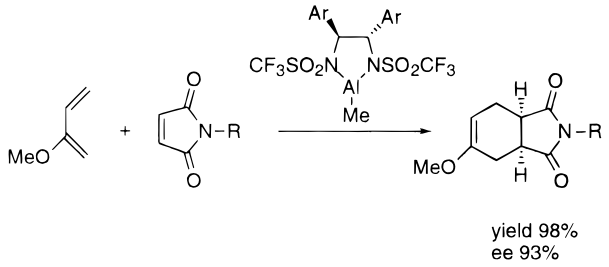
VIII.4. Cycloaddition Reactions

VIII.4.1. Diels–Alder Reactions

The Diels−Alder reaction is one of the most powerful synthetic methods that fits the modern concept of atom economy.[419,420] For this reason, the recent development of highly enantioselective catalytic Diels−Alder reactions[421] represents a great advance in synthetic chemistry. A large number of metals, ligands, and dienophiles have been studied. Until recently, most of the successful catalysts contain chelating oxygen ligands, but some recent success was obtained using diphosphine ligands such as BINAP. Most of the studies are now focused on the use of optically active N-containing ligands. Their better stability can probably explain this general trend. Indeed, the best results are currently obtained using bis(oxazoline) derivatives that complex copper. The most recent results will be reported here and classified according to the metal used for the preparation of the catalytic N-containing complex.

Regarding the N-containing chiral ligands used for this reaction, Corey et al.[422] reported the use of diazaaluminolidine, which led to excellent enantiomeric excess (Scheme 137).

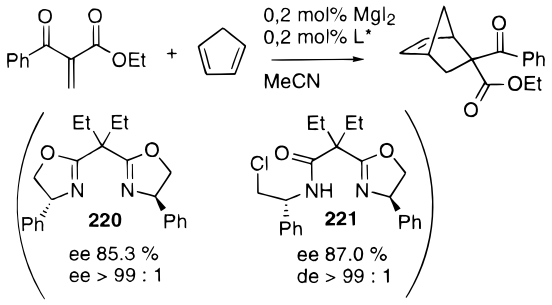
Scheme 137



It appears that substitution of the sulfonamide aromatic ring is crucial to afford high selectivities, as the steric factors in the dienophile are important: indeed, the Diels−Alder reaction with maleic anhydride proceeds in a completely racemic manner. The enantioselective Diels−Alder reactions of *N*-arylmaleimides are potentially useful for the obtention of natural substances such as Gracilin B.

Furthermore, Yamauchi[423] described the magnesium-catalyzed Diels−Alder reaction of 2-benzoylacrylate using two chiral oxazoline ligands, a C_2-symmetric one and an unsymmetric one (Scheme 138,

Scheme 138

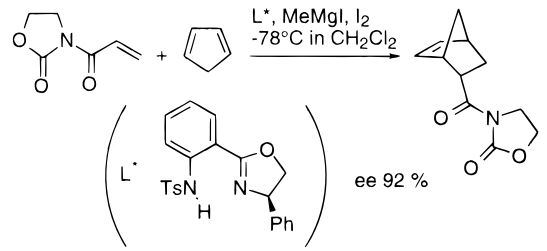


structures **220** and **221**).

The excellent diastereoselectivity obtained in this reaction was explained by considering the steric hindrance generated by the phenyl substituent of the acyl group. It is not yet clear which mechanism governs the high enantioselectivity obtained when the mono(oxazoline) ligand **221** is used.

Fujisawa et al.[424] reported that the magnesium complex prepared from chiral 2-[2-[(tolylsulfonyl)-amino]phenyl]-4-phenyl-1,3-oxazoline and methylmagnesium iodide was an effective catalyst for the enantioselective Diels−Alder reaction of 3-alkenoyl-1,3-oxazolidin-2-one with cyclopentadiene (Scheme 139).

Scheme 139

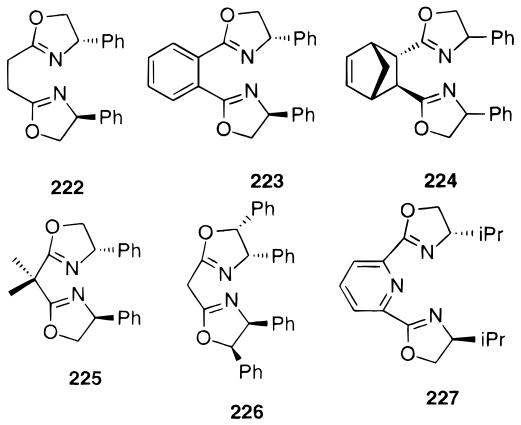


The endo adducts were exclusively obtained in up to 92% ee. It was found, furthermore, that the substituent on the sulfonamide group on the chiral

ligand strongly influenced the enantiofacial selectivity. The presence of iodine as an additive was proven to be a determining factor for enantioselectivity by dissociating the iodide anion from the magnesium cation.

Zinc(II) salts also constitute useful precursors for Lewis-acid-catalyzed transformations in organic synthesis. Takacs et al.[425] examined their ability to perform enantioselective Diels−Alder reactions of *N*-crotonyloxazolidinone with cyclopentadiene, compared to the two metals already mentioned. Assuming that the various metals should demand different optimal distances for tethering the two nitrogen atoms and for accommodating intrinsic differences in ionic radii and/or coordination geometry, the authors prepared and tested various chiral bis(oxazoline) ligands differing in the length of the chain binding the two oxazoline moieties and in the nature of the substituent at the stereogenic center. The best $Zn(OTf)_2$ catalyst is derived from a 1,4-bis(oxazoline) ligand (structure **222**, Scheme 140). These results

Scheme 140

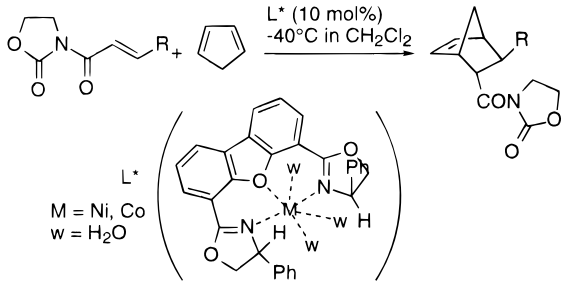


prompted the authors to diversify the structure of this N-containing ligand.[426]

Ligand **223** failed to give good ee, whereas ligand **224** led to significant ee values in the Zn-catalyzed Diels−Alder reaction (poor enantioselectivity is obtained when magnesium is used instead of Zn or Cu). Jørgensen[427] also studied the zinc(II)-catalyzed hetero-Diels−Alder reaction of different conjugated dienes such as 2,3-dimethylbuta-1,3-diene and cyclohexa-1,3-diene with ethyl glyoxylate in the presence of different C_2-symmetric bis(oxazoline)s (structures **225**−**227** in Scheme 140). The reaction involving the noncyclic diene gave both the hetero-Diels−Alder and -ene products, the former being the major compound with an enantiomeric excess of 87%. With the cyclic diene, only 65% ee was achieved, the selectivity being largely dependent on the solvent used.

An interesting report has been published by Kanemasa et al.,[428,429] who used a trans-chelating tridentate ligand, again containing the efficient oxazoline structure, for the formation of a new class of cationic aqua complex catalysts. A variety of transition metal perchlorates show high catalytic activity in the Diels−Alder reaction of cyclopentadiene with 3-acryloyl-2-oxazolidinone. In particular, complexes of $Co(ClO_4)_2 \cdot 6H_2O$ and $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol %) gave the endo cycloadduct as a single enantiomer (endo/exo = 97/3, Scheme 141). These catalytic complexes

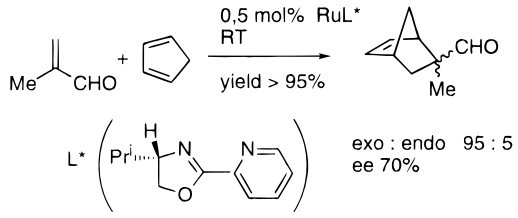
Scheme 141



show advantageously high water tolerance and maintain their activity and selectivity after several weeks of storage in air.

Ruthenium complexes have also been reported as active species for enantioselective Diels−Alder reactions. For example, Davies[430] prepared the complex $[Ru(H_2O)L^*(\eta^6\text{-mesitylene})][SbF_6]_2$ (see Scheme 142

Scheme 142

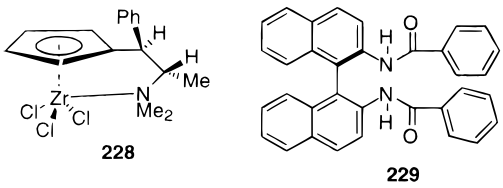


for the structure of L*) and tested its activity in the reaction between methacrolein and cyclopentadiene. One of the best results obtained is summarized in Scheme 142.

The same group[431] studied the parent chiral sandwich rhodium oxazoline complexes, which led to very similar results in terms of activity and enantioselectivity, however.

Tests were attempted to diversify the structure of the N-containing chelates. In this context, Zeijden[432] used chiral N-functionalized cyclopentadiene ligands for the preparation of a series of transition metal complexes. The zirconium derivative (structure **228** in Scheme 143) behaves as a moderate Lewis acid

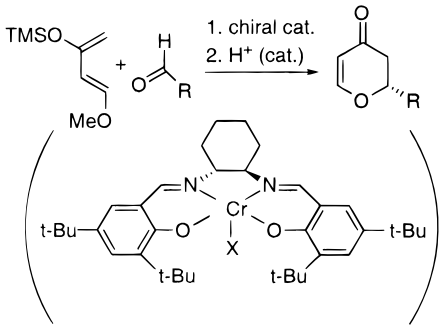
Scheme 143



and catalyzes the Diels−Alder reaction between methacroleine and cyclopentadiene, albeit with no measurable enantiomeric excess. Nakagawa[433] reported 1,1′-(2,2′-bisacylamino)binaphthalene (structure **229** in Scheme 143) to be effective in the ytterbium-catalyzed asymmetric Diels−Alder reaction between cyclopentadiene and crotonyl-1,3-oxazolidin-2-one. The adduct was obtained with high yield and enantioselectivity (97% yield, endo/exo = 91/9, >98% ee for the endo adduct).

Jacobsen[434] has evaluated a series of chiral (salen)-metal complexes and found that (salen)Cr(III)Cl complexes were efficient catalysts for the hetero-Diels−Alder reaction between Danishefsky's diene and aldehydes leading to dihydropyranones (Scheme 144). Enantioselectivities up to 90% were obtained

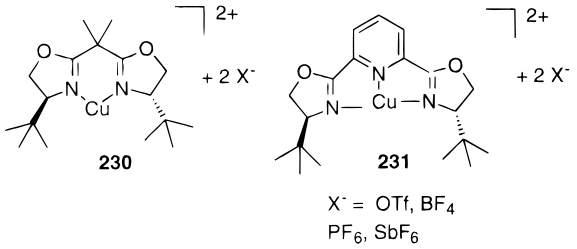
Scheme 144



by modifying the structure of the catalyst.

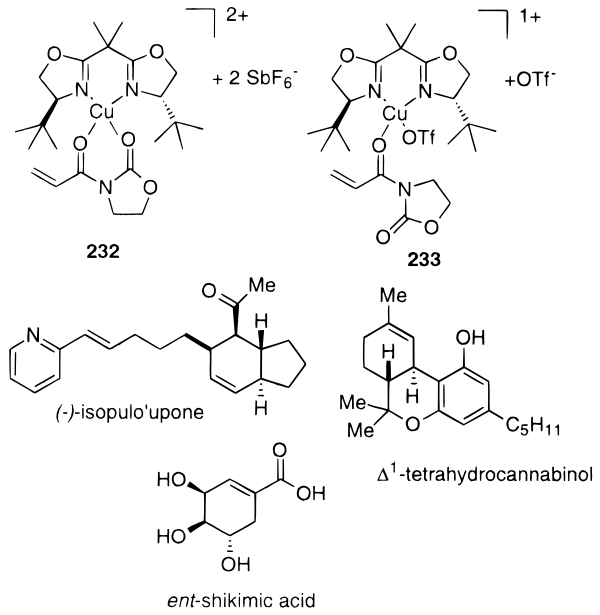
N-Containing chiral ligands are most widely used to perform the asymmetric catalytic Diels−Alder reaction, and in particular, bis(oxazoline) derivatives associated with copper salts form active asymmetric catalysts. Moreover, Ghosh et al.[435] recently reviewed the utility of C_2-symmetric chiral bis(oxazoline)−metal complexes for catalytic asymmetric synthesis, in which an important place is reserved for this and related transformations. Bis(oxazoline)copper(II) triflate derivatives[436] have indeed been described as effective catalysts for the asymmetric Diels−Alder reaction. To broaden the scope of the utilization of Lewis acidic chiral Cu(II) complexes, Evans et al. prepared and tested bis(oxazolinyl)pyridine (pybox, structure **231**, Scheme 145) as a ligand.[437]

Scheme 145



The bis(oxazoline) ligand **230** allowed the Diels−Alder transformation of two-point binding *N*-acylimide dienophiles in good yields and excellent ee values (up to 99%). The tridentate pybox ligands were far more widely effective for the transformation of carbonyl-derived dienophiles with a single accessible coordination site (high exo/endo selectivities and up to 96% ee). Evans's group found that the nature of the counterion implicated in the catalytic cycle is of major importance regarding the enantioselectivity, with SbF_6^- leading to the best results. A square-planar catalyst−substrate complex (**232** in Scheme 146) is assumed to be responsible for the high enantioselectivities observed with a counterion with

Scheme 146

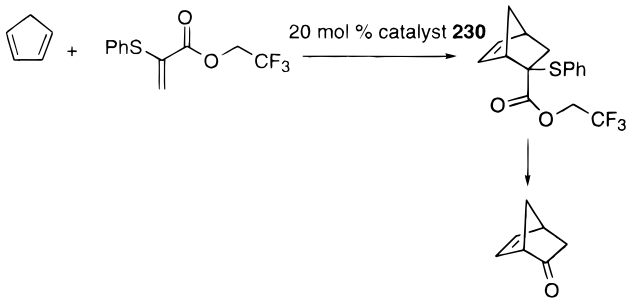


weak coordinating properties such as SbF_6^-, as a less organized one-point complex (**233**) may explain the lower enantioselectivity observed in the case of triflate complexes.

Interestingly, this group very recently applied these findings to the efficient synthesis of several natural compounds (Scheme 146): the marine toxin (−)-isopulo'upone,[438] *ent*-Δ^1-tetrahydrocannabinol,[439] and *ent*-Shikimic acid.[440]

Due to the success of copper−bis(oxazoline) complexes in Diels−Alder reactions, Aggarwal et al.[441] chose this type of catalyst for the reaction between cyclopentadiene and α-thioacrylates. They obtained the corresponding cycloadducts in up to 92% yield, 88% de, and >95% ee for the endo product (Scheme 147). This compound was then easily converted to

Scheme 147

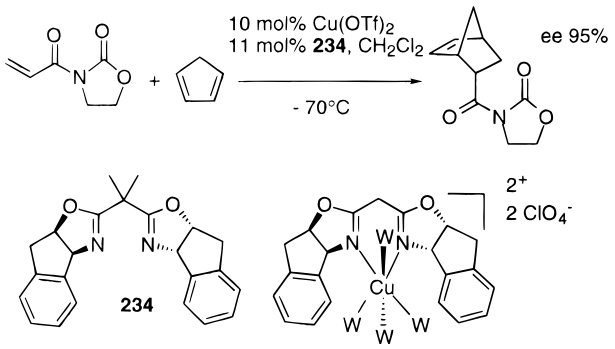


norbornenone with high enantioselectivity.

Davies et al.[442] recently published results in which they proposed explanations for the enantioselectivity values related to the conformation of the chiral complex. They synthesized and tested several Evans-type auxiliaries, i.e., bis(oxazolines) or pyridine−bis-(oxazolines), bearing various sterically hindering substituents. The best results are presented in Scheme 148.

They assumed that the ligand bite angle played an important role in enantioselectivity and could be

Scheme 148

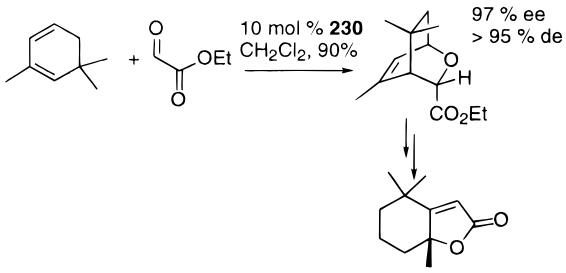


correlated with the magnitude of the angle of the uncomplexed ligand. They thus developed a single force field for modeling bis(oxazoline) and pyridine−bis(oxazoline) copper(II)-complexes. They were then able to confirm the role of this angle and propose explanations for this influence of C_4-oxazoline substituents on the selectivity.[443]

Ghosh et al.[444] prepared a cationic aquo complex of inexpensive $Cu(ClO_4)_2 \cdot 6H_2O$ and constrained bidentate bis(oxazoline) (**235** in Scheme 148) to provide a highly effective system for enantioselective Diels−Alder reactions. For the transformation depicted in Scheme 148, 98% ee (endo/exo > 99/1) could be obtained at low temperature (−30 °C).

The copper complex **230** (Scheme 145) has successfully been involved in the catalytic hetero-Diels−Alder reaction of a substituted cyclohexadiene with ethyl glyoxylate,[445] a key step in the total synthesis of (*R*)-dihydroactinidiolide (Scheme 149).

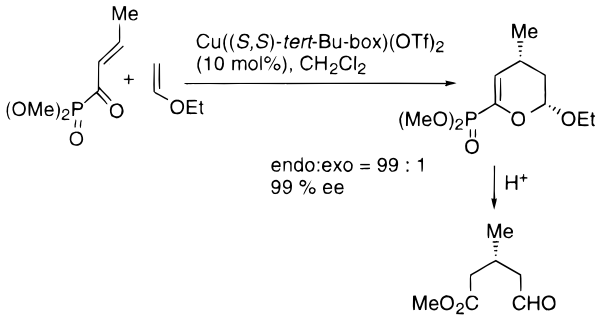
Scheme 149



After having reported numerous examples of Cu(II) bis(oxazoline) complexes that catalyze Diels−Alder reactions, Evans et al.[446] reported that α,β-unsaturated acyl phosphonates undergo enantioselective hetero-Diels−Alder reactions with enol ethers. This reaction was particularly efficient with chiral Cu(II) complexes such as **230** and afforded cyclic enol phosphonates (Scheme 150), efficient synthons for asymmetric synthesis.

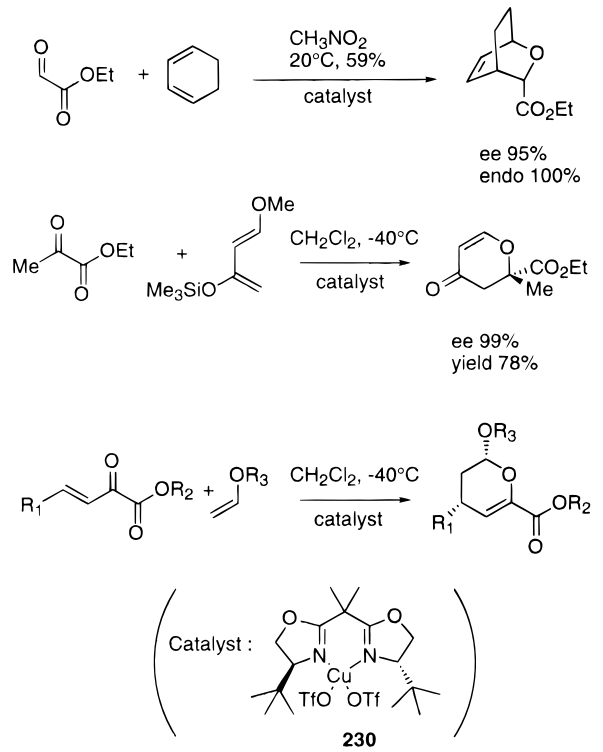
Solvent effects influencing the course of Diels−Alder reactions catalyzed by copper(II)−bis(oxazoline) have been studied by Jørgensen et al.[447] They assumed that the use of polar solvents (generally nitroalkanes) improved the activity and selectivity of the cationic copper−Lewis acid used in the hetero-

Scheme 150



Diels−Alder reaction of alkylglyoxylates with dienes (Scheme 151). The explanation, close to that given

Scheme 151



by Evans regarding the crucial role of the counterion, is a stabilization of the dissociated ion, leading to a more defined complex conformation. They also used this reaction for the synthesis of a precursor for highly valuable sesquiterpene lactones with an enantiomeric excess exceeding 99.8%.

Similar transformations have been performed with Danishefsky's diene and glyoxylate esters[448] catalyzed by bis(oxazoline)−metal complexes to afford the hetero-Diels−Alder product in 70% isolated yield and up to 72% ee.

Jørgensen[449,450] reported a highly enantioselective, catalytic hetero-Diels−Alder reaction of ketones and similar chiral copper(II) complexes which led to enantiomeric excesses up to 99.8% (Scheme 151).

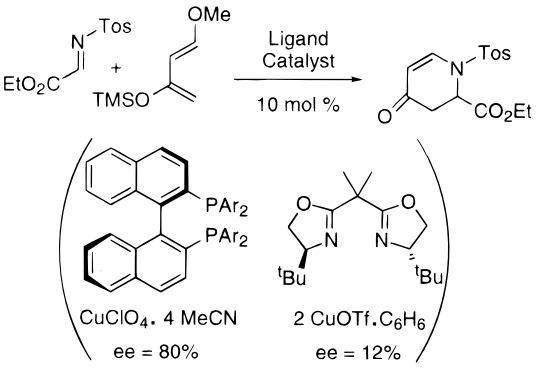
This same research group[451] reported a highly diastereo- and enantioselective, catalytic hetero-Diels−Alder reaction of β,γ-unsaturated α-ketoesters with electron-rich alkenes (Scheme 151) to give dihydropyran adducts (more than 99% ee, total conversion). These compounds are highly valuable

synthons for the obtention of carbohydrates and natural products.

Evans et al.[452] proposed a simplified procedure for this last reaction including particularly low catalyst loadings, the use of aqua complexes (easier to store without special precaution), and a catalyst recycling procedure. They ran the cycloaddition in hexane in the presence of an adsorbent (florisil). In these conditions, the catalyst is insoluble, so the product solution was decanted at the end of the reaction and the catalyst reused without significant loss of yield and selectivity.

Catalytic enantioselective aza Diels−Alder reactions, which provide optically active piperidine and tetrahydroquinoline heterocycles, have not yet been as extensively studied. Jørgensen et al.[453] recently reported the reaction between imines derived from ethylglyoxylate with activated dienes, catalyzed particularly with various chiral ligands and copper complexes (Scheme 152). In this case, however, use

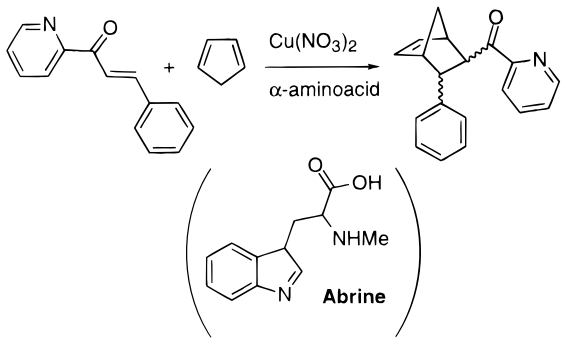
Scheme 152



of bis(oxazoline) ligands resulted in very low ee values, whereas use of tol-BINAP ligand led to a much higher enantioselectivity.

Last, a very interesting study has been reported by Engberts and co-workers,[454] who studied enantioselective, Lewis-acid-catalyzed Diels−Alder reactions in water. They thus performed the Diels−Alder reaction of 3-phenyl-1-(2-pyridyl)-2-propen-1-one with cyclopentadiene (Scheme 153) by coordinating chiral,

Scheme 153

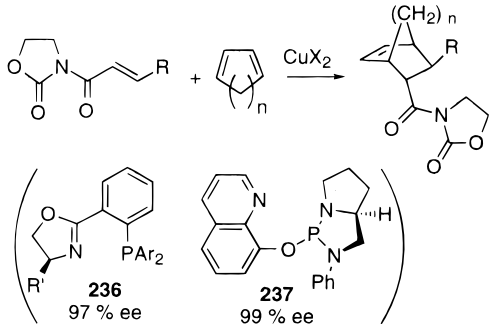


commercially available α-amino acids and their derivatives with copper salts. Yields generally exceeded 90% and with L-abrine; an enantiomeric excess of 74% could be achieved. Moreover, the catalyst solution was reused with no loss of enantioselectivity.

Significant enantioselectivities were obtained exclusively with ligands containing an aromatic side group. The authors assumed that π-stacking must, therefore, be of major importance in achieving high selectivities. This hypothesis is in complete agreement with the fact that enantioselectivity, using the described copper complex largely benefits from the use of water as solvent instead of other typical organic solvents. Arene−arene interactions are indeed less efficient in organic solvents than in water.

Helmchen[455] also worked on the preparation of efficient catalysts for enantioselective Diels−Alder reactions; he synthesized (phosphino−oxazoline)-copper(II) complexes (Scheme 154) for this purpose.

Scheme 154



The phosphorus σ-donor/π-acceptor ligand was expected to enhance the Lewis acidity and thus the catalytic activity of the complexes. Therefore, ligands containing bulky aryl goups at the phosphorus atom (structure **236**) were tested with a range of substrates derived from 3-acryloyl-1,3-oxazolidin-2-one. Enantioselectivities of up to 97% were achieved.

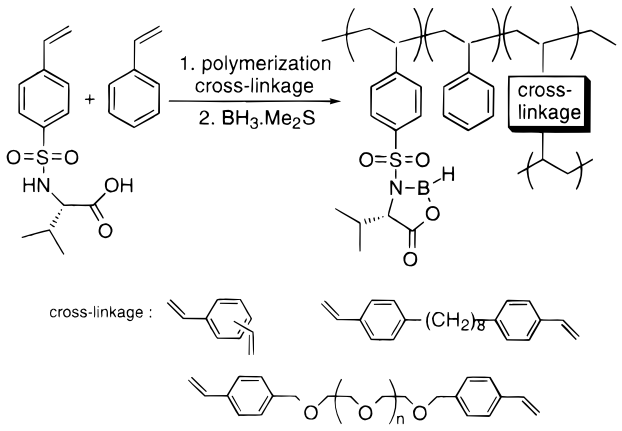
Buono et al.[456] proposed the use of new, chiral copper(II) catalysts with P,N-ligands (see the chiral pyridine−phosphine ligand **237** in Scheme 154) for the efficient Diels−Alder reaction of 3-acryloyl-1,3-oxazolidine-2-one with cyclopentadiene (up to 99% ee).

The great versatility of the Diels−Alder reaction has certainly been demonstrated here by numerous examples concerning very different catalytic systems. As an illustration of this variety, Whiting et al.[457] reported a parallel, combinatorial approach to identifying new catalysts for the asymmetric aza Diels−Alder reaction of an imino dienophile. They studied a different metal salt for each of four metals (ytterbium, magnesium, copper, and iron), three different homochiral ligands (a bis(oxazoline) of structure type **230** (see Scheme 145), BINOL, and (1*S*,2*S*)-1,2-diphenylethylenediamine), various solvents, and additives. They rapidly recognized that all salts chosen were capable of catalyzing the reaction with ee values exceeding 80% for certain ligands, which shows the value of combinatorial methods for the discovery of new asymmetric catalysts.

Finally, it is worth mentioning that the asymmetric Diels−Alder reaction of methacrolein with cyclopentadiene has been reported[458] using polymer-supported catalysts of chiral oxazaborolidinone (Scheme 155) having different cross-linking structures.

The polymers were prepared by copolymerization of the chiral *N*-sulfonylamino acid derivative, styrene,

Scheme 155



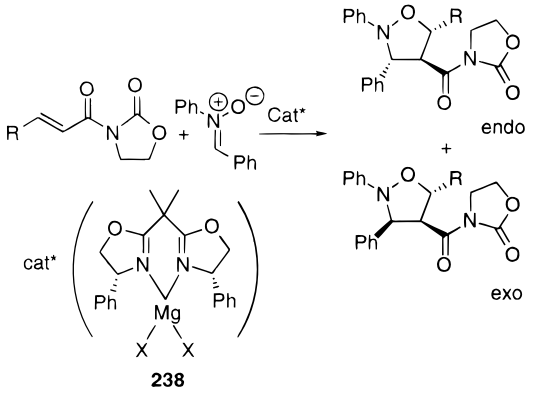
and a cross-linking agent in the presence of benzoyl peroxide as a radical initiator. The Diels−Alder reaction occurs smoothly even at −78 °C in the presence of the polymeric catalyst to afford highly selective *exo*-cycloadduct in excellent yield. The authors assumed that the cross-linking structure greatly affected the performance of the catalyst: 65% ee was obtained when divinylbenzene was used as cross-linker, whereas the ee improved to 95% with the polymeric catalyst containing long oxyethylene chains. Moreover, these results are surprisingly better than those obtained with their homogeneous counterparts, but the reasons behind this effect remain unclear. The authors have tested their catalytic system in a flow reactor at −30 °C, with a solution of methacrolein and cyclopentadiene in dichloromethane continuously eluted through a column filled with the solid polymeric catalyst. The results, in terms of activity and enantioselectivity, are analogous to those obtained from the batch system.

N-Containing ligands are highly efficient for the preparation of chiral complexes for asymmetric Diels−Alder cycloadditions. In particular, bis(oxazoline)s associated with copper salts have been reported to lead to selective reactions with various substrates. Indeed, the most successful system associated a bidentate ligand (which complexes to the metal) and a dienophile (which acts as a two-point binder to the ligand−metal complex). Heterogeneous catalysis has successfully been developed in this field and generally leads to better enantioselectivities than the corresponding homogeneous system. The use of other metal ions is one of the new trends for achieving this reaction. Although bis(oxazoline)s are often successful chelates for this transformation, the development of other types of ligands (such as amines or sulfonimides instead of imines) seems to have considerable potential. Hydrophobic styrene-type resins have already been tested and eliminate the necessity for dry conditions.

VIII.4.2. 1,3-Dipolar Cycloadditions

The 1,3-dipolar cycloaddition of alkenes with nitrones is now one of the most useful synthetic methods, catalyzed by various chiral metal complexes leading to isooxazolidines with good control of stereoselectivity.[459] Among these reactions, the most widely studied is the addition of crotonoyl- and acryloyloxazolidinones with *C,N*-diphenyl nitrone, usually catalyzed by magnesium(II)−bis(oxazoline) catalysts (Scheme 156). This system has been chosen

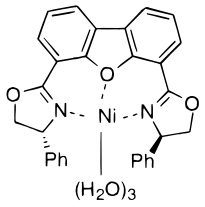
Scheme 156



because a variety of efficient combinations between chiral Lewis acids and electron-deficient alkenes have already been investigated with success, for example, in the study of catalyzed enantioselective Diels−Alder reactions.

Jørgensen et al.[460] recently studied the influence of molecular sieves on the course of the reaction. The transformation depicted in Scheme 156 was run in the presence of molecular sieves to reach one enantiomer of the endo product with up to 82% ee, whereas in the absence of molecular sieves, the mirror image enantiomer is obtained with up to 73% ee. This new aspect of molecular sieves in metal-catalyzed reactions, as the absolute stereochemistry of the isoxazolidine formed by 1,3-dipolar cycloaddition, has been ascribed to a possible bonding of the Mg(II)−bis(oxazoline)−alkenoyl−oxazolidinone intermediate to the surface of the molecular sieves. Kanemasa et al.[461] reported the use of the aqua complex of 4,6-dibenzofurandiyl-2,2′-bis(4-phenyl)-oxazoline)nickel(II) perchlorate to efficiently catalyze the same reaction (Scheme 157). The simple prepara-

Scheme 157



tion procedure of the aqua catalyst is attractive. Moreover, this catalyst can be stored for a long time without special precautions.

However, here again, the presence of molecular sieves is essential to reach excellent yields and enantioselectivities. With this procedure, ee values exceeding 99% were obtained with complete diastereoselectivities. Furthermore, this complex presented the most promising features with respect to the catalytic cycle yet reported, since such low catalyst loadings as 2 mol % led to excellent activities. The authors assume these results arise from the transi-

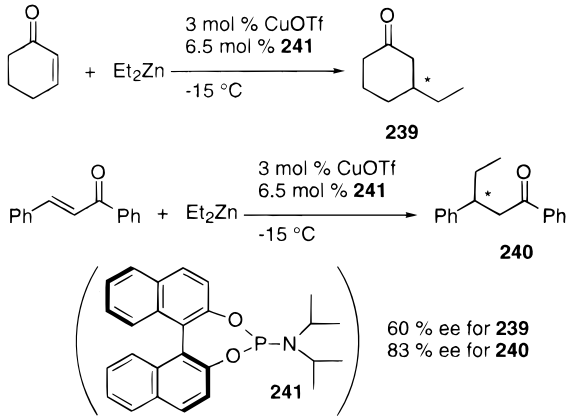
tion structure involving a trigonal-bipyramid substrate complex.

VIII.5. Addition of Nucleophiles to C=C Bonds

VIII.5.1. Michael Additions

Enantioselective Michael additions of organolithium, Grignard, or diorganozinc derivatives are attractive ways to introduce chirality into organic compounds. A number of successful methods have been described for stereoselective 1,4-addition based on chiral auxiliaries or stoichiometric additions of organometallic reagents. The "catalytic version" of those reactions has been recently studied and described mostly with copper, nickel, or cobalt salts as catalytic precursors. Copper catalysis, which has been described the most, led to the best selectivities. Krause briefly reviewed this subject.[462] Mainly in the presence of phosphorus ligands derived from chiral diols, ephedrine, or oxazolines, significant levels of enantioselectivity have been reached for organometallic addition to cyclohexen-2-one and benzylideneacetone. Feringa et al.[463] reported on chiral copper catalysts containing chiral N,P-ligands which catalyzed conjugate addition of dialkylzinc reagents to cyclic and acyclic enones in high yields and ee values up to 90% (Scheme 158).

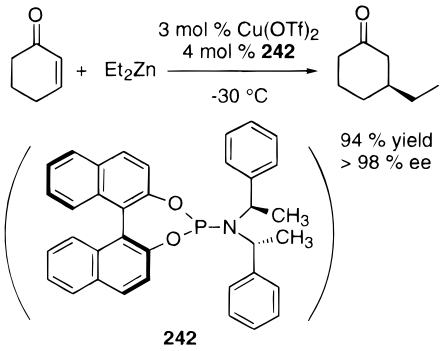
Scheme 158



Significant improvement in ee was observed with ligand **241**, in which more sterically demanding substituents were introduced onto the nitrogen atom. Feringa's group noticed, interestingly, that the use of Cu(II) salts enhanced the selectivity. The authors also incorporated two chiral structural units (structure **242**, in Scheme 159)[464] into the basic structure of the ligand, which resulted in a successfully matched combination. This ligand indeed permitted the preparation of a highly selective catalyst (ee around 98%) for the addition of dialkylzinc to various substituted enones.

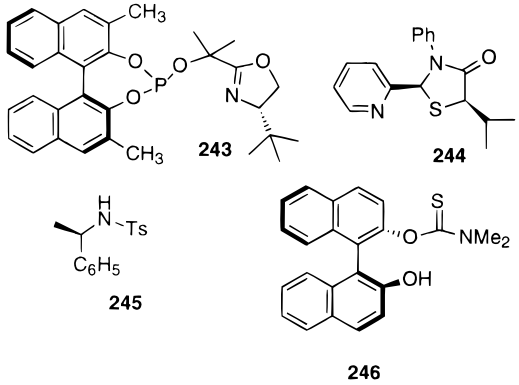
The authors applied their methodology to the construction of carbocyclic compounds by a highly enantioselective annulation reaction (1,4-addition−aldol cyclization) for cyclohexenones, cycloheptenones, and cyclooctenones with use of functionalized organozinc reagents.[465] It is clear that the amine moiety has an important influence on the enantioselectivity (double induction), although the nitrogen

Scheme 159



atom does not act as a ligand in this case. Conversely, Pfaltz and co-workers[466] modified the binaphthyl phosphite structure (compound **243**, Scheme 160) by

Scheme 160



adding an oxazoline ring as a chiral coordinating unit. This led to efficient catalysts for the enantioselective, copper-catalyzed 1,4-addition of organozinc reagents to cyclic enones. They indeed obtained 87−96% ee for reactions with cyclohexenone. Moderate enantioselectivities were achieved with cyclopentenone (72% ee) and cycloheptenone (77−80% ee), but these results were significantly better than with other catalysts. Furthermore, the ligand structures allowed easy modification on the phosphite part, on the spacer, and on the oxazoline moiety.

Several other N-containing ligands have been developed to perform such 1,4-additions. Feringa and Kellogg[467] were particularly interested in preparing N,S-containing ligands, derived from pure β-amido thiols. Because sulfides and pyridines have a pronounced affinity for Cu(I), the authors prepared several 2-pyridylthiazolidin-4-ones (Scheme 160, ligand **244**) and tested them in the copper-catalyzed, enantioselective conjugate addition of dialkylzinc to enones. Ligand **244** led to an ee of 62% for the quantitative transformation of cyclohexenone with diethylzinc in the presence of catalytic quantities of CuOTf. This moderate selectivity represents, however, the first successful use of an N,S-containing ligand for such a transformation.

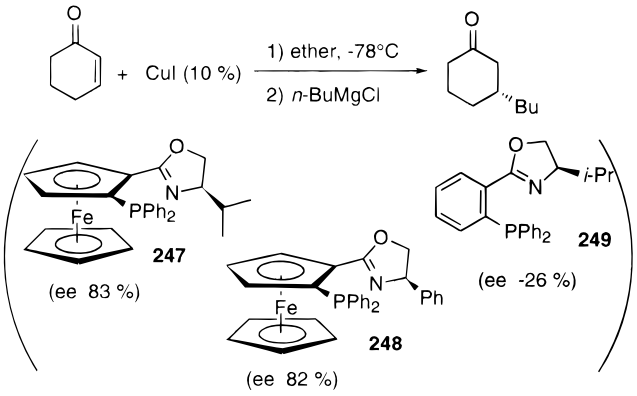
Wendisch and Sewald[468] also studied the enantioselective conjugate addition of diethylzinc to cyclic enones in the presence of chiral sulfonamides (ligand **245**). The enantioselectivities were quite low (ee < 30%), but interestingly, the authors noticed that the

anion of the copper salt used as catalyst significantly influenced the sense of the addition. With the same absolute configuration of the chiral catalyst, CuCN favored the formation of *(R)*-3-ethylcyclohexanone while all other copper salts tested led to the *(S)*-enantiomer. The complexity of the reaction and the possibility of various equilibria between monomeric or higher aggregated species prevented a direct explanation of these results.

Woodward et al.[469] recently published preliminary studies in which thiourethanes were tested as copper(I) ligands for 1,4-addition to acyclic enones. Moderate results were obtained with structure **246** (Scheme 160), which afforded 51% ee for the addition of $AlMe_3$ to *(E)*-non-3-en-2-one in the presence of $[Cu(MeCN)_4]BF_4$.

Apart from dialkyl zinc derivatives, Grignard reagents have also been studied for the asymmetric copper-catalyzed conjugate addition to enones. Stangeland and Sammakia[470] reported that the use of ferrocenyl phosphine oxazolines as chiral auxiliaries provided useful levels of asymmetric induction (Scheme 161).

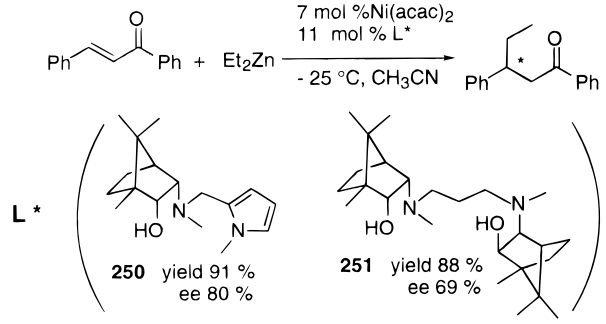
Scheme 161



The authors noticed, by comparing ligands **247** and **248** with **249**, that additional planar chirality imparted by the ferrocenyl template was essential to produce high levels of asymmetric induction.

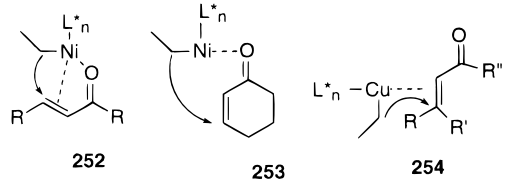
Nickel-catalyzed enantioselective conjugate additions of dialkylzinc reagents have been reported by Feringa.[471] Interesting enantioselectivities were reached with these catalysts only for the transformation of acyclic enones. Feringa's group has synthesized tri- and tetradentate amino alcohol ligands derived from (+)-camphor (**250** and **251** in Scheme 162).

Scheme 162



The authors explained the different selectivities obtained with cyclic or acyclic substrates by taking into account a chiral alkyl transfer via an alkyl−nickel species possessing affinity for the carbonyl, as shown in Scheme 163. With cyclic substrates, this

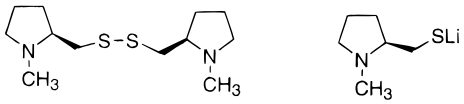
Scheme 163



type of coordination resulted in a chiral alkyl−nickel species (**253** in Scheme 163) too far away from the β-position to introduce high enantioselectivity. With the alkyl−copper species, however, because of a probable coordination to the carbon−carbon double bond of the enone, the enantioselective transfer occurred similarly with cyclic or acyclic substrates (structure **254**).

Gibson reported the enantioselective addition of diethylzinc to chalcone catalyzed by nickel(II) using an enantiopure β-amino thiolate or a β-amino disulfide (Scheme 164) to achieve enantiomeric excesses

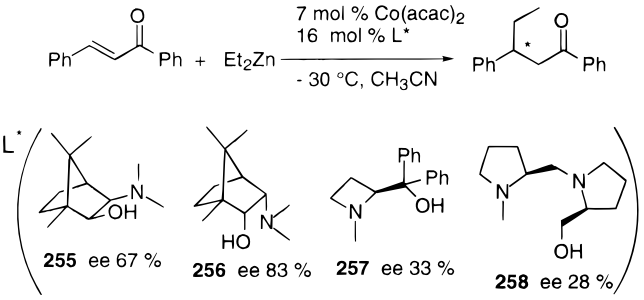
Scheme 164



exceeding 50%.[472]

De Vries and Feringa described the use of cobalt for the catalytic enantioselective conjugate addition reactions of diethylzinc to chalcone using several chiral amino alcohols (Scheme 165).[473]

Scheme 165

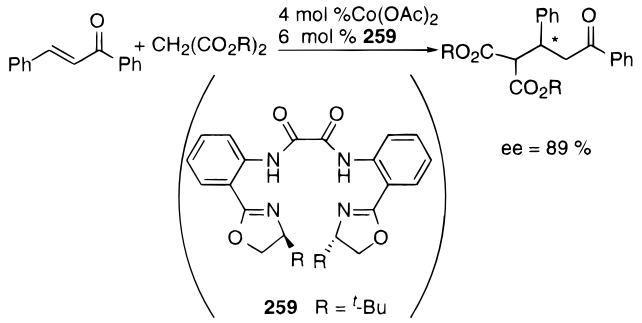


The cobalt conjugate addition occurred relatively slowly compared to the nickel-catalyzed reaction, and significant reduction of the carbon−carbon double bond (especially with ligands **257** and **258**) was observed. However, transmetalation processes of organozinc reagents to cobalt seemed more applicable to enantioselective organic reactions than transmetalation to other metal salts. With Pd or Fe salts as catalysts in the model reaction depicted in Scheme 165, only traces of the 1,4-product were formed.

Pfaltz reported the cobalt-catalyzed Michael reaction of malonates with chalcone to proceed with high enantioselectivities (up to 89% ee) when a new class

of tetradentate ligands, i.e., bis(dihydrooxazolylphenyl)oxalamides (Scheme 166), was used.[474]

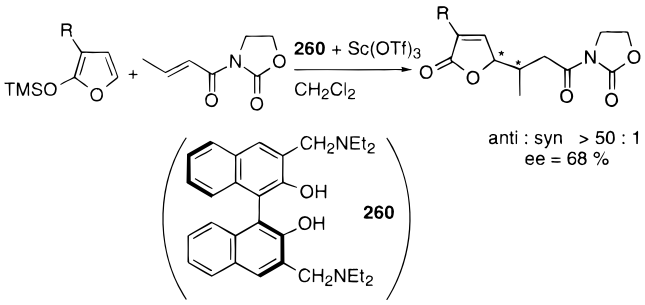
Scheme 166



The analogous copper or nickel complexes did not catalyze the reaction. A wider application of this reaction was not envisaged, however, because of the low conversions usually observed.

Lewis-acid-promoted Michael additions have been studied by Kitajima and Katsuki.[475] For the preparation of optically active butenolides, an important class of synthons for the obtention of naturally occurring compounds, they studied the reaction depicted in Scheme 167, catalyzed by a 1:1 complex prepared

Scheme 167



from scandium triflate and ligand **260**.

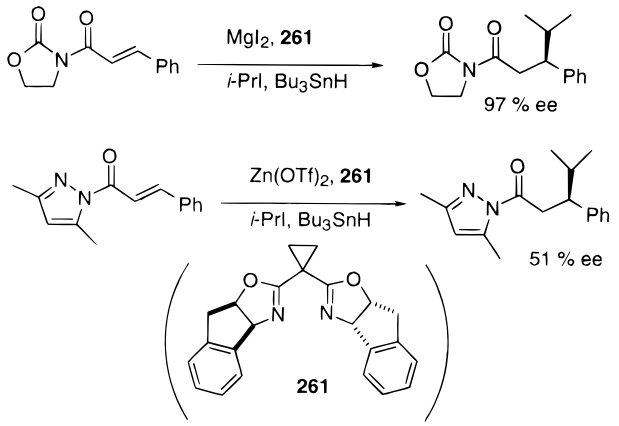
They obtained excellent anti selectivity and moderate enantioselectivity, while the Cu(II)−bis(oxazoline) complex exhibited excellent enantioselectivity and moderate to good anti selectivity (anti:syn = 8.5:1; ee = 95%).

No general solutions have yet been found to perform the asymmetric version of Michael additions in good conditions (i.e., high conversion and high enantioselectivity) for each substrate. Promising results have, however, already been described for individual substrates. It is worth noting that most of the newly developed ligands are nitrogen-containing chelates.

VIII.5.2. Free Radical Conjugate Additions

Free radical reactions have received renewed interest because of relatively recent discoveries demonstrating that the stereochemistry of these transformations can be controlled.[476] Numerous chemists are interested in enantioselective carbon−carbon bond formation using free radical intermediates. Sibi et al. reported an example of chiral, Lewis-acid-mediated, conjugate radical additions.[477] They studied the radical addition of isopropyl iodide to cinnamoyl oxazolidinone (Scheme 168) using bis(oxazoline) ligands

Scheme 168



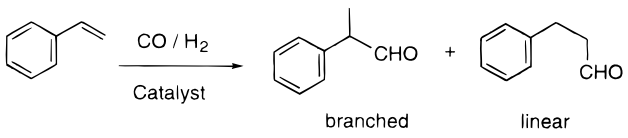
and magnesium iodide as a Lewis acid.

The authors noticed that the stoichiometry of the Lewis acid led to important changes in the enantioselection. The use of substoichiometric amounts of the chiral Lewis acid gave very high ee values for the conjugate addition (around 97% ee). Decreasing the amount of the Lewis acid to 5 mol % led to a small decrease in the enantioselectivity (90% ee), while use of only 1 mol % catalyst led to a large decrease in enantioselectivity (63%) as well as in chemical yield. The use of pyrazole derivatives as the achiral platform was further examined in enantioselective conjugate radical addition leading to moderate enantioselectivities.[478] It was noticed that the pyrazole and oxazolidinone templates gave products of opposite configuration using the same chiral Lewis acid.

VIII.6. Hydroformylation

Even if the use of nitrogen-containing ligands is becoming more widespread in asymmetric catalytic reactions involving carbon monoxide, there are fewer examples than for other catalytic reactions discussed in this paper. We have covered all ligands containing at least one nitrogen atom as a possible binding site for the metal. Catalytic reactions of olefins with carbon monoxide as carbonylation or hydroformylation must reach high regioselectivities and enantioselectivities. As shown in Scheme 169, the hydro-

Scheme 169



formylation of styrene can lead to both the linear and the branched aldehyde.

The branched product is often more interesting for pharmaceutical applications (ibuprofen, naproxen).[479−482] This explains the need for catalytic systems with regioselectivity toward the branched isomer (see section VIII.6.1.). Even if cobalt and rhodium are employed the most, catalytic hydroformylation reactions have been carried out in the

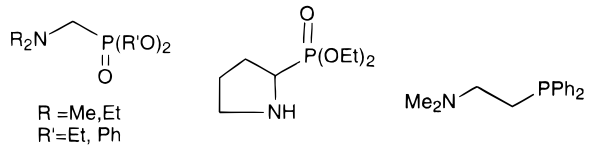
presence of iridium, ruthenium, osmium, platinum, palladium, iron, and nickel complexes.[480,481] Cobalt was the first metal used in asymmetric hydroformylation, and rhodium was rapidly studied afterward in the presence of chiral mono- or diphosphine ligands. Ruthenium, iridium, and palladium have also been employed for this purpose.[482,483] Currently, the most promising asymmetric systems are formed with $Pt/SnCl_2$ or Rh catalysts.[482]

Asymmetric hydroformylation was first reported in 1972, and one of the catalytic systems then employed was a cobalt chiral Schiff base complex.[483] Nitrogen-containing ligands thus seemed promising for enantioselective hydroformylation. Hydroformylation reactions have been largely reviewed,[480−485] and two reviews on asymmetric hydroformylation reactions[482,486] were published in 1995. We will focus on progress made since then. In fact, good enantioselectivities have been achieved by means of rhodium species containing chiral diphosphine ligands such as diphosphites (87% ee)[487] or the phosphine−phosphite BINAPHOS ligand (95% ee).[488] Even if most of the asymmetric catalytic systems reported involve chiral phosphorus ligands, there are, however, some examples with N-ligands which are reported in section VIII.6.2.

VIII.6.1. Regioselective Hydroformylation

We will describe only a few representative examples of such catalysts in a nonasymmetric hydroformylation reaction. For instance, bifunctional P,N-ligands (Scheme 170) have given rise to high regio-

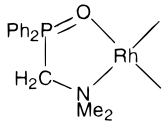
Scheme 170



selectivities in the rhodium-catalyzed hydroformylation of styrene.[489] After 1 h, the conversions varied from 9% to 82% and the reported values of branched/linear ratios went from 64/36 to 90/10. No conversion was observed when the nitrogen function of the mixed ligand was a primary amine. Two trials were performed in the same conditions with monofunctional N-ligands, NEt_3 and $HNEt_2$. Poor activity was observed (less than 6% conversion), and branched/linear ratios were high, 86/14 and 100/0, respectively.

Amer et al. also studied bifunctional ligands for the hydroformylation of styrene.[490] In the case of O═P,N-ligands, they suggested that the number of carbon atoms between the N and the P functions can determine the conversion. The best results were achieved with only one carbon atom as a spacer, leading to a stable, cyclic five-membered rhodium complex (Scheme 171), giving regioselectivities up to

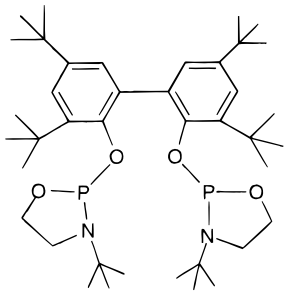
Scheme 171



91% toward the branched aldehyde.

Regioselectivity can be orientated in the presence of some P,N-ligands. A representative example is given by rhodium complexes formed in the presence of phosphoramidites.[491] The use of the ligand shown in Scheme 172 induces very active and regioselective

Scheme 172

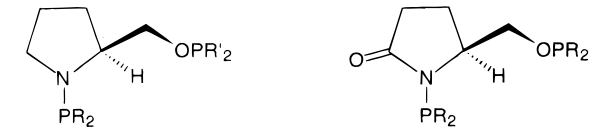


catalysts for hydroformylation reactions. 1-Octene has been hydroformylated at 80 °C with a 870 mol·[mol Rh]$^{-1}$·h^{-1} turnover frequency. The linear aldehyde was the main product (87%). At 40 °C, styrene was mainly transformed into the branched product (89%) but the reaction rate decreased to 25 mol·[mol Rh]$^{-1}$·h^{-1}. No attempts to use the chiral versions have yet been made, or reported, with these types of ligands.

VIII.6.2. Enantioselective Hydroformylation

In recent years, the nitrogen-containing ligands used in catalytic asymmetric hydroformylation reactions have always been mixed P,N-ligands. Platinum catalysts were used in the presence of $SnCl_2$ by Mortreux et al.[492] for the asymmetric hydroformylation of styrene. The aminophosphine and amidophosphine-phosphinite complexes, $[Pt(AMPP)Cl_2]$, were prepared from (*S*)-2-(hydroxymethyl)pyrrolidine **(262)** or (*S*)-2-(hydroxymethyl)-5-pyrrolidinone **(263)** and $Pt(COD)Cl_2$ (Scheme 173). The combination of these

Scheme 173



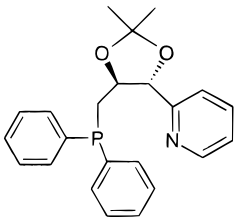
262 R, R' = Cy, Ph

263 R = Ph, Cy, CP

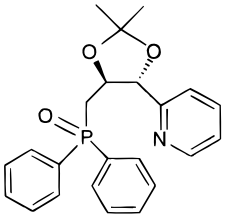
complexes with $SnCl_2·2H_2O$ catalyzed the asymmetric hydroformylation of styrene. Various linear-to-branched ratios were reported (0.4−0.8) with enantiomeric excesses between 40% and 56%. Even if there is no nitrogen−platinum bond (X-ray structure of the complex with ligand **262** and R = R′ = Ph), the catalytic activity of these systems depends strongly on the aminophosphine part of the ligand.

In the case of rhodium catalysts, Marchetti et al.[493] studied the use of pyridylphosphine Pydiphos **264** and its P-oxide **265** as ligands (Scheme 174). The hydroformylation reactions were carried out at 90 bar of CO/H_2 (1:1) with a substrate to $[Rh(CO)_2(acac)]$ ratio of 300:1. After 20 h, the hydroformylation of styrene at 30 °C gave 70% aldehydes with a branched-

Scheme 174



264 Pydiphos



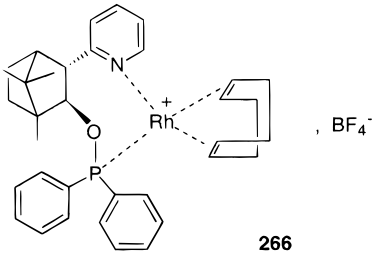
265 Pydiphos P-oxide

to-linear ratio of 95/5. The corresponding P-oxide enhanced the reaction rate (97% yield in 5 h) and kept the same regioselectivity, but in both cases enantioselectivity was less than 1%. Five other functionalized olefins were examined, but asymmetric induction was extremely low. At 80 °C and 80 bar of CO/H_2 (1:1), enantiomeric excesses of 10% were obtained for the hydroformylation of phenyl vinyl ether with **264** and of 1-phenyl-1-(2-pyridyl)-ethene with **265**.

In further studies,[494] the preformed PydiphosRh(CO)Cl and PydiphosPt($SnCl_3$)Cl complexes were used for the hydroformylation of styrene and gave, respectively, 28% and 31% ee with good branched regioselectivities (90%; 70%) but low activities (less than 30% conversion and 15% aldehyde yield).

The same group used, as a chiral ligand, a pyridylphosphine derived from (+)-camphor.[495] The corresponding cationic rhodium complex **266** (Scheme 175) showed good catalytic activity in the hydro-

Scheme 175



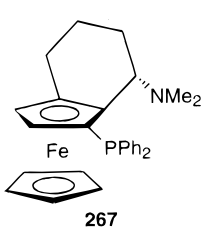
266

formylation of some vinyl−aromatic substrates, reaching conversions of more than 93% and aldehyde yields up to 70% with a substrate-to-catalyst ratio of 300:1. After 24 h at 80 °C and under a 1:1 mixture of CO/H_2, the reaction mixture was treated with $KMnO_4$. The corresponding carboxylic acids were obtained with variable branched-to-linear ratios (54/46 to 80/20). Low enantioselectivities (less than 12%) were achieved, except for 2-vinylnaphthalene, which gave the (*S*) acid with an enantiomeric excess of 45%.

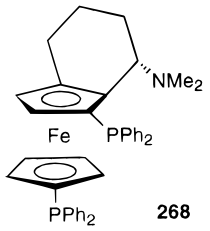
Very recently, Kollár et al.[496] studied the catalytic properties of platinum and rhodium complexes containing the amino−phosphino−ferrocenyl ligands **267** and **268** (Scheme 176).

A substrate-to-catalyst ratio of 1:4000 was used for the hydroformylation of styrene with 80 bar of CO/H_2 (1:1) at 60−100 °C. The rhodium complexes gave better chemo- and regioselectivities (99% yield of aldehydes with more than 89% of the branched isomer) but no significant enantioselectivity (ee < 2%). The best value reported, 21% ee, was obtained

Scheme 176



267

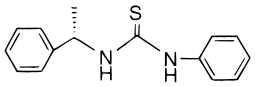


268

when $PtCl_2$(**267**) was used in the presence of $SnCl_2$ and bdpp ((2*S*,3*S*)-2,4-bis(diphenylphosphino)pentane). Bidentate chiral P,N-ligands derived from quinolines have also been tested by Faraone et al.[497] for the hydroformylation of olefins with rhodium.

Lately, various sulfur-containing rhodium(I) complexes have been used in the asymmetric hydroformylation of styrene by Claver et al.[498] Even if good results have been obtained in combination with chiral diphosphine ligands,[499] moderate enantioselectivities are reported when only dithioethers are employed as chiral ligands.[500] A new series of N,S-ligands has been recently developed in our laboratory: various chiral thioureas, C_2-symmetric or dissymmetric, have been synthesized and combined to $[Rh(cod)_2]BF_4$ before their use as catalysts during the hydroformylation of styrene.[501] (Scheme 177).

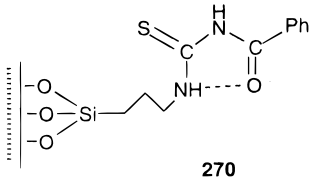
Scheme 177



269

Even if good chemo- and regioselectivities are observed, conversions remain low. The enantioselectivities reach 41% with the best result achieved by means of *N*-phenyl-*N*′-(*S*)−(1-phenylethyl)thiourea **269**. Such ligands are also interesting since they can be heterogenized, as suggested by the anchoring of rhodium(I) onto thiourea-functionalized silica xerogels such as **270** (Scheme 178), which was recently

Scheme 178



270

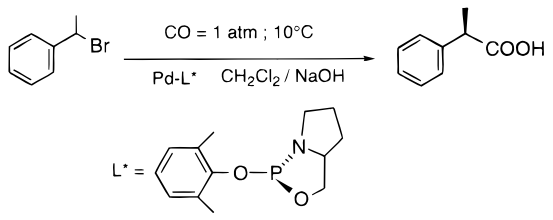
tested in the hydroformylation of styrene, giving recyclable catalysts.[502,503]

VIII.7. Carbonylation

Carbonylation reactions were reviewed in 1995,[480,481] so we will describe only recent developments in asymmetric carbonylation. A recent study reported good regioselectivities and enantiomeric excesses up to 99% with some chiral diphosphine−$PdCl_2$−$CuCl_2$ systems for the methoxycarbonylation of styrene (80 °C; 50 bar CO).[504] Among the few examples reported with nitrogen-containing chiral inducers, we can recall the first use of oxazaphospholane ligands under

phase transfer conditions carried out by Arzoumanian et al.[505] They performed the carbonylation of α-methylbenzylbromide (Scheme 179) by palladium

Scheme 179

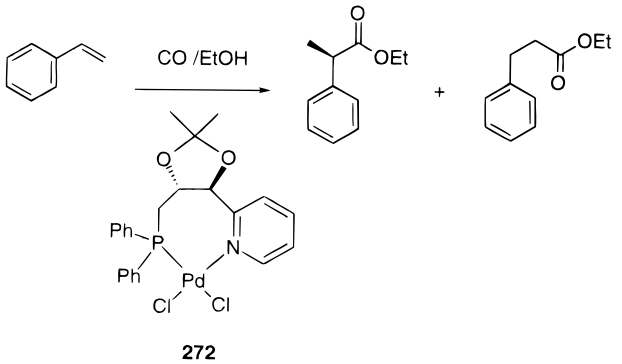


271

complexes in a biphasic NaOH(aq)/CH_2Cl_2 mixture with hexadecyltrimethylammonium bromide as a phase transfer agent, under ambient conditions. By adding an excess of chiral ligands such as 2-substituted-3,1,2-oxazaphospholanes, moderate yields and various enantioselectivities were reached, the best being 64% ee with ligand **271**. Even if the nitrogen atom is not coordinated to the metal center, it plays a crucial role in asymmetry since it is part of the chiral structure. This reaction is in fact an enantiomer discriminating carbonylation, which limits the chemical yield to 50%.

The use of nitrogen-containing ligands for asymmetric carbonylation was introduced by Alper and Hamel[506] in 1990. They used poly-L-leucine as a chiral inducer for the carbonylation of 2-buten-1-ol, which afforded 61% ee of (*R*)-α-methyl-γ-butyrolactone in the presence of $PdCl_2$, $CuCl_2$, HCl, CO, and O_2. As for more recent results, asymmetric induction has been achieved by means of P,N-ligands in hydroesterification reactions. Marchetti et al.[493b] reported the hydrocarboxyethoxylation of styrene in the presence of Pydiphos **264**. With a substrate-to-catalyst ratio of 300:1 and CO pressures of 105−120 bar at 100 °C, only the branched ester was formed even if the yields varied from 4% to 77% (Scheme 180). The best ee

Scheme 180

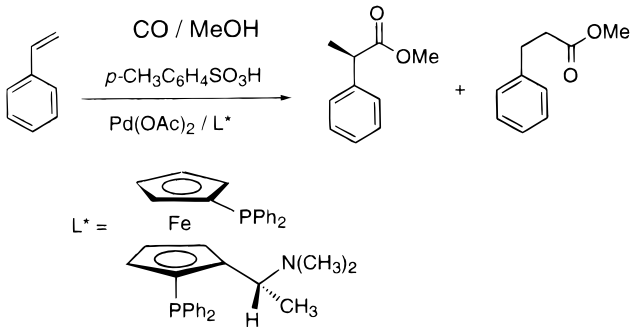


272

(20%) was obtained with the preformed palladium complex Pydiphos$PdCl_2$ (**272**), while the in situ system was almost unreactive (5% conversion; 2% ee).

Ferrocene-containing chiral aminophosphine ligands have been used by Inoue et al.[507] with a palladium precursor for the asymmetric methoxycarbonylation of styrene (Scheme 181). The catalytic system formed with ligand **273** was not very active (17% yield for a metal-to-substrate ratio of 1:50) and only moderately

Scheme 181

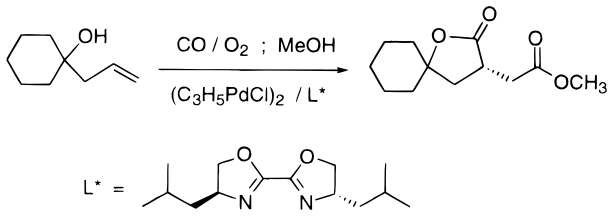


273

regioselective (44% of branched ester) but remarkably enantioselective: 86% optical yield was achieved.

The asymmetric intra- and intermolecular bis(alkoxycarbonylation) reactions of homoallylic alcohols catalyzed by palladium using chiral bis(oxazoline) ligands have been reported by Ukaji et al.[508] The reactions were carried out in the presence of copper(I) triflate (5% mol) under atmospheric pressure of carbon monoxide and oxygen at 25 °C with [Pd(η^3-C_3H_5)Cl]$_2$ (2% mol) and bis(oxazoline) ligand (8% mol). Optically active γ-butyrolactones were formed with various enantiomeric excesses. The best ee 65%, was obtained with ligand **274** (Scheme 182). It is

Scheme 182



274

noteworthy that the same reaction carried out in the presence of (+)-DIOP or (+)-BINAP ligands gave the corresponding lactone in less than 10% optical yield.

Even if nitrogen-containing ligands can lead to good chemoselectivities and branched-to-linear regioselectivities for hydroformylation reactions, the enantiomeric excesses obtained until now remain lower than those achieved with chiral phosphine−phosphite ligands.[488] Phosphorus-containing ligands such as diphosphines can also be good asymmetric inductors for carbonylation reactions,[504] but chiral P,N-ligands proved to be valuable asymmetry inducers. Nitrogen-containing ligands are, in addition, able to give very active carbonylation catalysts when associated to the right metal precursor. A remarkable example is the carbonylation of propyne to methyl metacrylate (MMA) under mild conditions (60 °C, 60 bar CO): the Pd(II) catalyst formed with 2-pyridyl diphenylphosphine is highly efficient (selectivity toward MMA of 99.95% with a TON up to 40 000 mol/mol·Pd/h), while the catalyst obtained with triphenylphosphine as the ligand is significantly less active.[509] Another aspect that makes N-ligands attractive is that they can lead to "green" carbonylation processes such as the production of methyl meth-

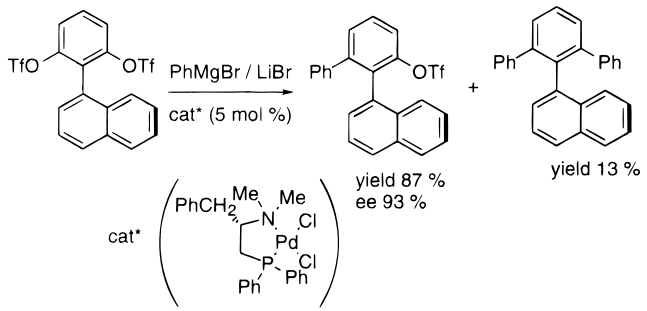
acrylate by the methoxycarbonylation of propyne[510] under mild, noncorrosive conditions (50 °C, 10 bar of CO) or the reductive carbonylation of aromatic dinitro compounds, avoiding the usual "phosgene route".[511]

VIII.8. Grignard Cross-Coupling

Nickel and palladium complexes catalyze the reaction of organometallic reagents (mostly secondary alkyl Grignard reagents, in the asymmetric version of the reaction) with alkenyl or aryl halides to give cross-coupling products. This Grignard cross-coupling, also called the Kumada−Corriu reaction, is one of the first uses of nitrogen-containing ligands for asymmetric catalysis. Indeed, good results were previously obtained by Kumada[512] using P,N-ligands derived from amino acids and by Kellogg using P,N,S-[513] or N,S-chelates.[514]

Nowadays, the enantioselective cross-coupling reaction is essentially developed for the obtention of optically active biaryls used as chiral auxiliaries for a variety of synthetic asymmetric reactions. Two different approaches have been investigated. On one hand, Hayashi et al.[515] proposed their asymmetric synthesis to proceed by palladium-catalyzed enantioposition-selective cross-coupling of one of both enantiotopic triflate groups on achiral biaryl ditriflates (Scheme 183).

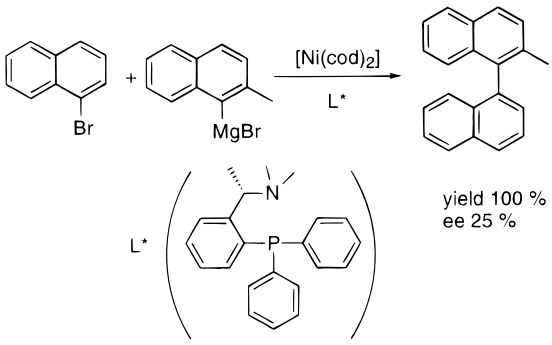
Scheme 183



A variety of chiral phosphine−palladium and aminophosphine−palladium complexes were tested for this transformation. As already reported by Kumada,[516] who pioneered the study of this coupling reaction, P,N-chelating systems proved to be more efficient than non-nitrogen-containing ligands. It was found that the enantioselectivity of the asymmetric coupling depicted in Scheme 183 was dependent on the yield of the diphenylation product. The authors indeed demonstrated that a kinetic resolution occurred during the second cross-coupling reaction. Interestingly, the biaryl compound prepared here was further transformed into the corresponding new chiral monodentate phosphine ligand. It was found to be effective for the palladium-catalyzed asymmetric hydrosilylation of styrene to yield 1-phenylethanol with 91% ee.

On the other hand, Yamagishi[517] studied the cross-coupling reaction of arylhalides and aryl Grignard reagents to prepare biaryls by the asymmetric formation of the $C_1-C_{1'}$ bond. They extended their reaction to the preparation of various biaryl compounds using nickel diaminophosphine catalysts. The results obtained for the asymmetric version of this transformation remained modest, however, because only 25% ee could be reached in the nickel-catalyzed cross-coupling reaction between 1-naphthyl bromide and 2-methyl-1-naphthylmagnesium bromide (Scheme 184).

Scheme 184

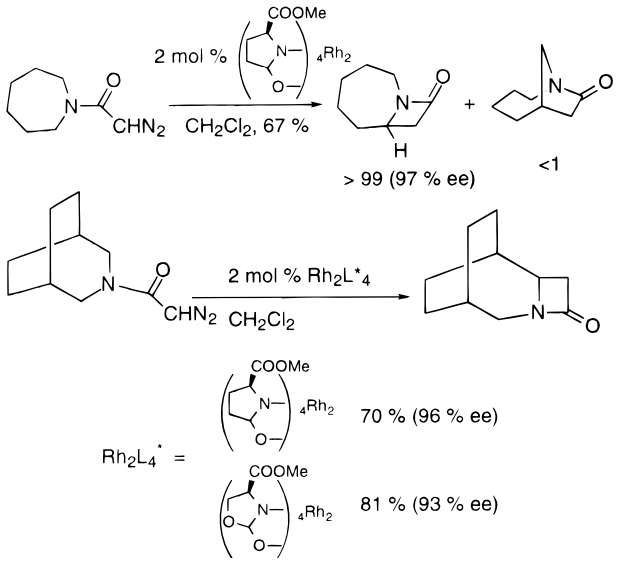


However, considering not only the huge success of biaryl structures as backbones for the preparation of new chiral liganding compounds, but also the difficulty of their synthesis, further attempts to perform this Grignard cross-coupling reaction in an asymmetric manner will probably be published soon.

VIII.9. Carbene Insertion into C−H Bonds

The intramolecular carbenoid C−H insertion is particularly useful for the synthesis of four-membered rings and proceeds with excellent control of relative and absolute stereochemistry. Doyle and Kalinin[518] studied a new route to β-lactams via intramolecular C−H insertion reactions of diazoacetyl−azacycloalkanes catalyzed by chiral dirhodium(II) carboxamidates. They thus investigated diazoacetamides derived from representative cyclic amines for the preferred production of β-lactams (Scheme 185).

Scheme 185

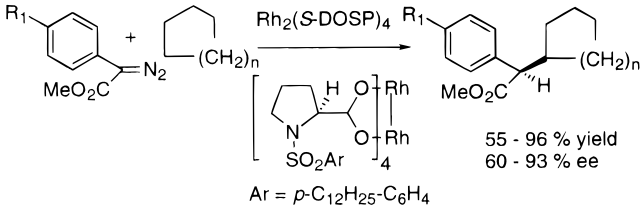


These reactions have been run with very high regio- and enantiocontrol. The application of such

cyclizations in natural product synthesis was demonstrated by Doyle[519] with the construction of chiral lignan lactones such as (−)-Hinokinin. Numerous examples were discussed further by Taber and Stiriba[520] in which this rhodium-mediated intramolecular C−H insertion allowed the direct construction of carbon−carbon bonds for the synthesis of various natural products.

The pendant reaction, namely, the intermolecular carbenoid C−H insertion, was often considered as a rather inefficient and unselective process, however. Davies and Hansen[521] nevertheless reported the decomposition of aryldiazoacetates by $Rh_2(S\text{-DOSP})_4$ to result in intermolecular C−H insertions with excellent yields and with high levels of asymmetric induction (Scheme 186). It must be noticed here that

Scheme 186

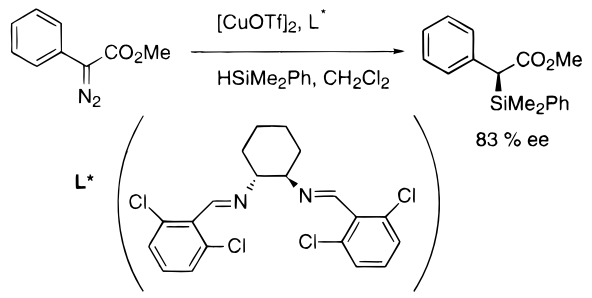


they used an N-containing, but not complexing, ligand.

The efficiency of this system contrasts with previously reported results in which more traditional carbenoid precursors were used. For example, no dimeric carbene products were formed in the reaction described in Scheme 186. The rhodium-catalyzed decomposition of methyl diazoacetoacetate was not effective, whereas the use of benzyl carbenoid precursors resulted in high asymmetric C−H insertion. These observations were in accordance with results reported for the asymmetric cyclopropanation by $Rh_2(S\text{-DOSP})_4$. This method has been successfully transposed to the C−H insertion of aryldiazoacetates to tetrahydrofuran (up to 76% ee).

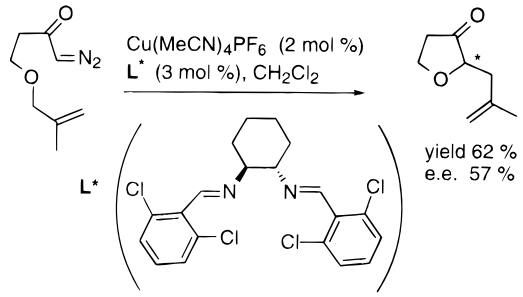
Jacobsen and Panek recently studied[522] a similar transformation in which the asymmetric carbenoid insertion occurred at the silicon−hydrogen bond of silanes. An efficient catalytic system for this reaction was obtained using a copper(I) catalyst associated with a chiral C_2-symmetric Schiff base (Scheme 187).

Scheme 187



Another type of C−H insertion reaction of carbenes has been reported, namely, the rearrangement of ylide-type intermediates. The reactions of ylides, generated by catalytic diazo decomposition in the presence of Lewis bases, were generally believed to occur from the free ylide rather than from the metal-associated ylide. As a consequence, few investigations of ylide formation employing a chiral catalyst were performed. However, the rearrangement of oxonium ylides generated from metal carbenoids constitutes a versatile approach to the synthesis of cyclic ethers. We shall now report some examples of such reactions in which catalytic systems were used with N-containing chiral ligands leading to asymmetric inductions. Clark et al.[523] studied the asymmetric version of this reaction by using chiral copper complexes as catalysts for the carbenoid generation in order to enantioselectively prepare substituted cyclic ethers from achiral α-diazo ketones (Scheme 188).

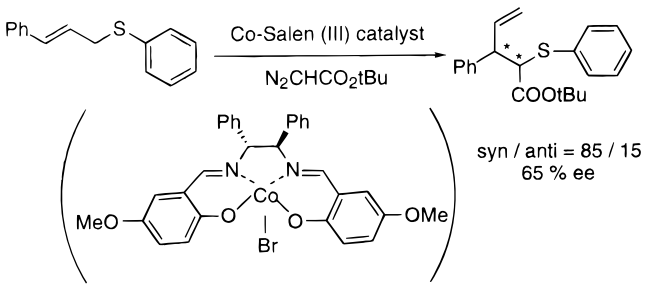
Scheme 188



These authors studied the asymmetric cyclization of various α-diazo ketones to give tetrahydrofuran-2-ones. Copper complexes of a wide variety of diimine ligands (bearing different aryl groups) were tested, and the best results are indicated in Scheme 188. The proposed mechanistic pathway is as follows: the chiral carbenoid formed is subsequently attacked by the oxygen of the ether group to give a metal-bound ylide with the creation of two stereogenic centers dictating the stereochemical outcome of the reaction. Rearrangement then occurs with efficient transfer of chirality to afford the desired cyclic ether, before or after loss of the metal. The preparation of five- and six-membered cyclic ethers is thus possible from achiral diazo ketones, with reasonable yields and enantioselectivities, using chiral copper complexes as catalysts.

Fukuda and Katsuki[524] further studied the catalytic enantioselective [2,3]-sigmatropic rearrangement of the S-ylide derived from allyl,aryl sulfides and α-diazoacetates using an optically active (salen)-cobalt(III) complex as catalyst (Scheme 189).

Scheme 189

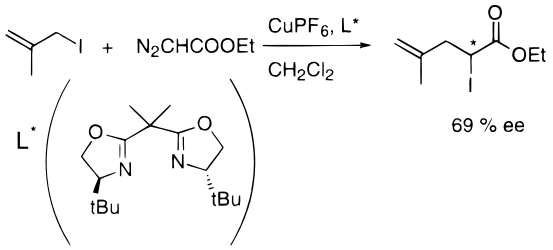


Regardless of the structure of the chosen chiral ligand, they always obtained a similar diastereoisomer ratio (anti/syn isomers ca. 85/15). The best

enantioselectivity observed reached 64% ee with the ligand depicted in Scheme 189. The mechanism of the transformation was not discussed in this case.

Doyle[525] recently presented results indicating that metal-associated ylides were the primary product-forming intermediates in [2,3]-sigmatropic rearrangements. They focused on halonium ylides whose "free" ylides were achiral. They treated allyl iodide with ethyl diazoacetate in the presence of chiral copper(I) catalysts (Scheme 190) and obtained the expected

Scheme 190



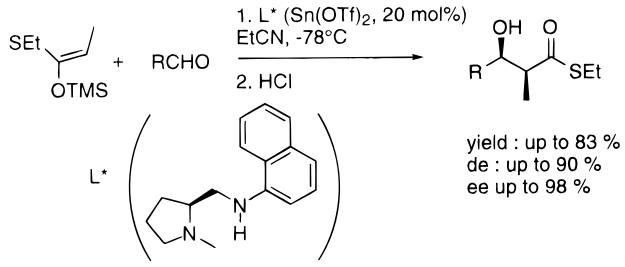
ylide rearrangement product in up to 69% ee. This catalyst-dependent selectivity necessarily implicates a metal-associated ylide in the product-forming step.

VIII.10. Addition to C═O Bonds

VIII.10.1. Aldol Reactions

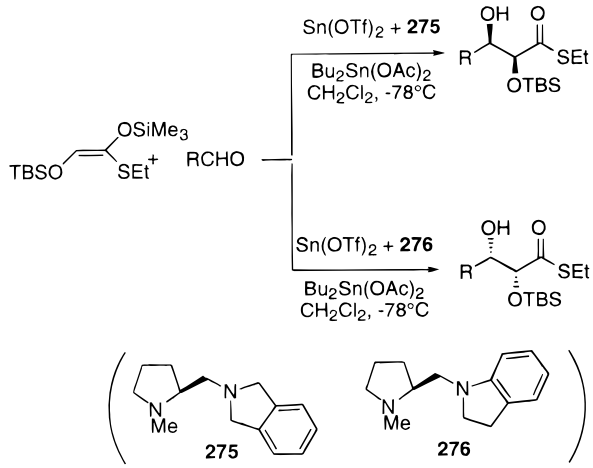
The aldol reaction is one of the most efficient methods for extending the carbon framework of an organic synthon. This transformation has been performed in both a catalytic and enantioselective manner through the use of chiral Lewis acids under mild reaction conditions.[526,527] Since the discovery of the catalytic asymmetric aldol reaction with enolsilanes by Mukaiyama et al., numerous extensions of this type of reaction have been reported.[528] Indeed, most of the successful asymmetric aldol reactions have been performed with catalysts containing oxygen chelates. In particular, different types of BINOL-based titanium(IV) complexes proved to be highly efficient catalysts.[529,530] Interesting results, concerning N-containing ligands and regarding activity and enantiomeric excesses, have also been reported by Mukaiyama et al.[531] for the transformation of thioketals with aldehydes in the presence of catalytic amounts of Sn(II)−chiral diamine complexes (Scheme 191).

Scheme 191



Furthermore, this group was interested in preparing both pure enantiomers of an organic synthon using similar types of chiral sources. Usually such reactions have to be performed with both enantiomers of the chiral inductors, which are often difficult to obtain (for example, alkaloids, amino acids, and sugars). Kobayashi et al.,[532] therefore, used N-containing chiral ligands prepared from L-proline and tetrahydroisoquinoline (compounds **275** and **276** in Scheme 192) for the asymmetric aldol reactions of

Scheme 192

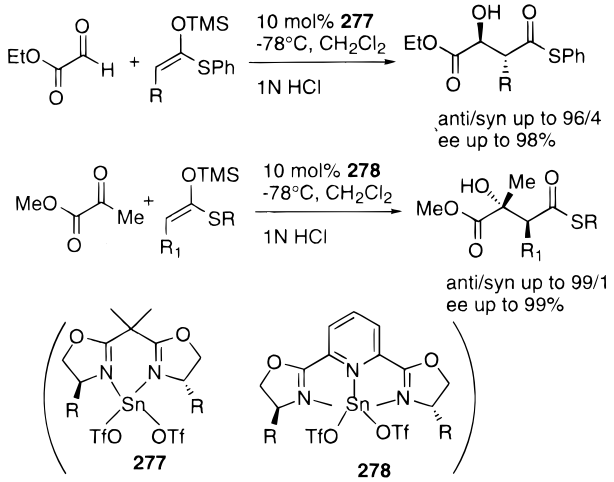


silyl enol ethers with aldehydes catalyzed by tin(II).

They tested a variety of aldehydes (aliphatic, allylic, aromatic, and heterocyclic) and could obtain both *syn*-enantiomers (up to syn/anti > 99/1 in each case) after the aldol reaction, with high enantioselectivity (up to 99% ee), by slightly modifying the structure of the chiral inductor.[533] In the example in Scheme 192, diamines **275** and **276** were prepared from L-proline, the only difference between them being the fusion point of the benzene ring connected to the pyrrolidine moiety. The two opposite stereoselectivities were assumed to be due to conformational differences in the chiral Lewis acids used.

Evans et al.[534] described the efficiency of the Lewis acidic complexes **277** and **278**, derived from $Sn(OTf)_2$ and bidentate bis(oxazoline) or tridentate pyridyl−bis(oxazoline), for the *anti*-aldol enantioselective addition of enolsilanes to glyoxylate and pyruvate esters (Scheme 193).

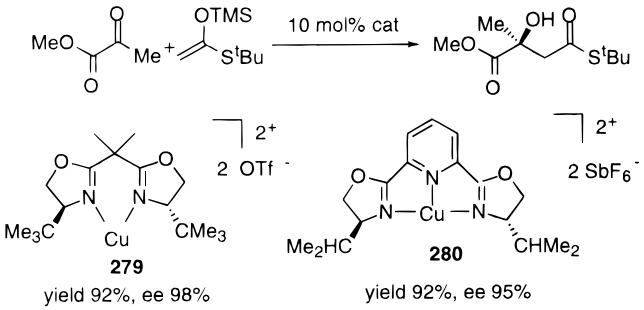
Scheme 193



The same group reported results in the development of chiral Cu(II)-based Lewis acids for catalyzing

aldol reactions with substrates that can participate in the catalyst chelation. They thus performed the catalytic enantioselective addition of enolsilanes to pyruvate esters (Scheme 194) to obtain functionalized

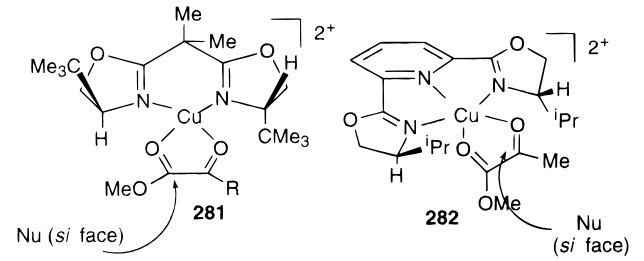
Scheme 194



succinate derivatives, useful synthons in natural product synthesis.[535]

The authors studied the scope of the reaction by varying either the ester or the acyl substituent on the pyruvate derivative and also by significantly modifying the structure of the enolsilane, without observing any loss of enantioselectivity. Through the use of substituted silylketene acetals, the reaction provided succinate derivatives with high *syn*-diastereoselectivity. The sense of induction was explained by invoking a square-planar Cu(II)box intermediate (**281** in Scheme 195) and a five-coordinate square-

Scheme 195



pyramidal complex (**282** in Scheme 195) in the case of catalyst **280**. The *si* face in both substrate−catalyst complexes is vulnerable to nucleophilic attack.

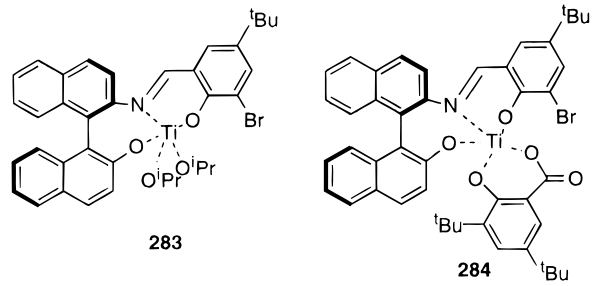
Evans et al. recently published articles summarizing the scope and mechanism of the catalytic enantioselective aldol addition of enolsilanes to (benzyloxy)-acetaldehyde[536] and to pyruvate esters[537] by using these C_2-symmetric oxazoline copper(II) complexes as chiral Lewis acids.

Yamamoto et al.[538] tested the same catalytic system (i.e., structures **279** and **280** described in Scheme 194) for the aldol reaction of the tributyltin enolate of cyclohexanone with benzaldehyde. Once again, the syn aldol adduct was preferentially formed but in this case the diastereo- and enantioselectivities were significantly lower (in both cases, only 28% de was obtained and negligible ee when using system **279**; conversely, ee reaches 84% with **280** as catalyst).

Chiral bis(oxazolinyl)zinc complexes have been reported by Cozzi et al.[539] to catalyze the allylation of aldehydes in good yield (up to 80%) when allyl tributyltin is used as the nucleophile. The enantiomeric excess remained modest however (only up to 46%).

The asymmetric catalytic version of the Mukaiyama aldol reaction has also been reported with complexes derived from Ti(IV) leading to high levels of enantioselectivity for the reaction of *O*-trimethylsilyl, *O*-methyl, and *O*-ethyl ketene acetals with aldehydes. For this particular type of catalysts, the best results have been obtained with alcoholates and phenolates as ligands.[540] Nevertheless, structures possessing both an oxygen and a nitrogen atom as binding sites were recently proved to belong to the most efficient and selective class of ligands. Thus, the complex (**283** in Scheme 196) was prepared from $Ti(OiPr)_4$ and

Scheme 196

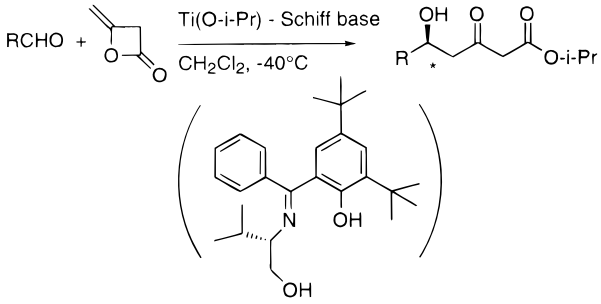


tridentate ligands derived from 2-amino-2′-hydroxy-1,1′-binaphthyl and led to mixtures of the β-hydroxy ester product and the silylated aldol counterpart with moderate enantioselectivities (respectively, 78% and 64% ee). The authors also prepared a Ti(IV) complex bearing a salicylate ligand (structure **284**) to facilitate the regeneration of the catalyst. This catalytic system proved to be general in its scope and afforded excellent levels of enantioinduction for both aliphatic and aromatic aldehydes.

The same authors developed a simplified procedure for preparing catalyst **284** in situ. They applied their new method to an elegant and efficient seven-step synthesis of (*R*)-(−)-epinephrine from commercially available veratraldehyde in an overall yield of 45%.[541] They also recently described[542] the synthetic interest of their strategy when applied to the enantioselective total synthesis of Macrolactin A.

The catalytic enantioselective reaction of diketene with aldehydes has been efficiently performed by Oguni et al.[543] with chiral Schiff base−titanium alkoxide complexes (Scheme 197). They obtained the

Scheme 197

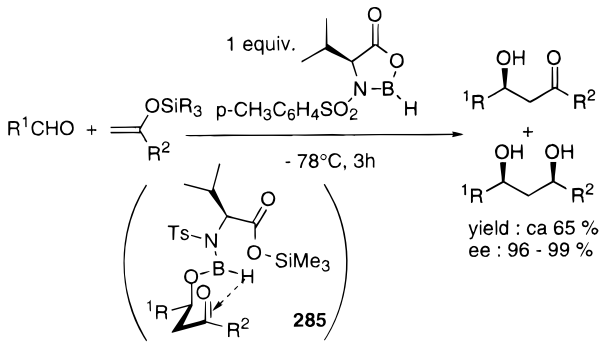


corresponding 5-hydroxy-3-oxoesters with high enantioselectivities (up to 92% ee).

The direct enantioselective (noncatalytic) synthesis of *syn*-1,3-diols by the reaction of aldehydes with enol

silyl ethers has, furthermore, been described in the presence of a chiral borane complex[544] (Scheme 198).

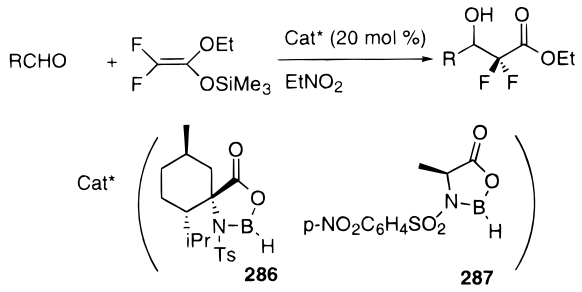
Scheme 198



The *syn*-1,3-diols prepared in this reaction were almost enantiomerically pure, which was not the case for the *β*-hydroxy ketones formed as byproducts. The authors suggested here that the selective reduction of the reaction intermediates occurred by an intramolecular hydride transfer (as for **285**, Scheme 198) after the enantioselective aldol addition. This reaction is interesting because two asymmetric transformations are successfully accomplished by only one promoter.

Iseki et al.[545] similarly studied the asymmetric addition of aldehydes to a difluoroketene silyl acetate in the presence of a substoichiometric amount of chiral Lewis acid (structure **286** and **287** in Scheme 199). They obtained the corresponding α,α-difluoro-

Scheme 199

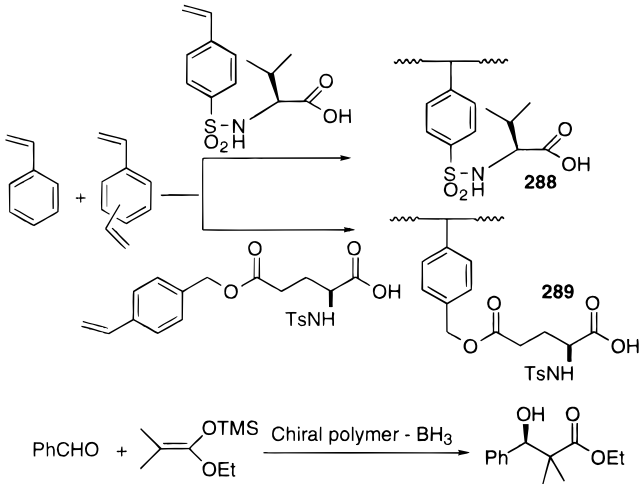


β-hydroxy esters with high enantioselectivities (up to 98% ee).

Asymmetric aldol reactions can be performed with very high enantioselectivities using O,O,N-ligands or N-ligands. Many of the proposed catalysts suffer from relatively low turnovers, however. In some cases, stoichiometric amounts of the metallic complexes have to be used. Several attempts to heterogenize these catalytic systems have consequently been made in order to facilitate the separation and recycling of the expensive catalyst. Most results are obtained with oxygen-containing ligands, but oxygen/nitrogen chelates were also successfully immobilized. For example, Kiyooka et al. reported the preparation and use of polymer-supported chiral borane (with pendant α-amino acid moieties, Scheme 200) for the aldol reaction of benzaldehyde with silyl ketene acetal.[546]

The presence of stoichiometric amounts of chiral borane promoters was necessary to enhance the reaction rate. The polymer could be reused several

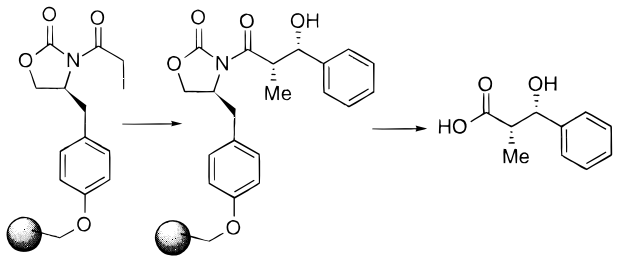
Scheme 200



times without loss of activity. Up to 90% ee could be obtained by using polymer **288** at low temperature, but the conversion remained low. By increasing the temperature, the isolated yield could be improved but the selectivity of the reaction decreased (using polymer **289**, 40% yield, 67% ee). To explain this behavior, the authors proposed that different polymer conformations were more or less adequate for the enantiodetermining process.

Combinatorial chemistry has strongly renewed interest in solid support synthesis. Heterogeneous catalytic reactions could be obtained by immobilizing the substrate, allowing an easy separation of the catalyst and the substrate. Very recently, using this concept of asymmetric heterogeneous catalysis, another group[547] reported the use of a resin-bound Evans's auxiliary in solid-phase aldol reactions (Scheme 201).

Scheme 201

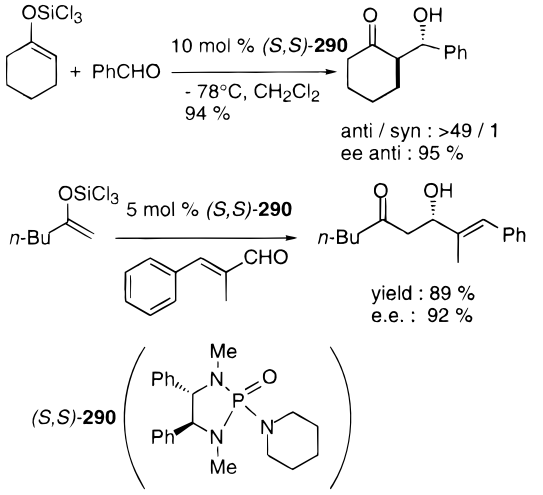


The formation of the corresponding resin−enolate was achieved using an excess of dibutylboron triflate, which was eliminated before the reaction with benzaldehyde. The cleavage of the aldol product was successfully performed with lithium hydroxide and led to a single syn diastereoisomer (de greater than 98%, high enantioselectivity of the resin) with 63% yield from the resin-bound auxiliary, based on the initial loading of the chiral auxiliary on the resin. Of course, such a strategy cannot be considered a catalytic transformation, but the recycling of the chiral polymer remains economically worthwhile.

Denmark and co-workers[548] reported that trichlorosilyl enolates of methyl ketones undergo aldol addition in the presence of a catalytic amount of the

stilbene diamine-derived phosphoramide (Scheme 202, structure **290**) to produce β-hydroxy ketones

Scheme 202



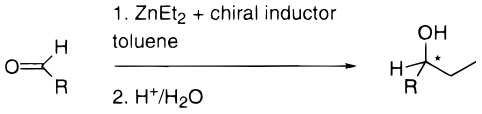
with very good enantioselectivities.

In this example, the nitrogen atom acts as the chiral part of the ligand but it also increases the basicity of the phosphinoxide, this last effect being crucial for the activity of the catalyst.

VIII.10.2. Nucleophilic Addition of Dialkylzinc Reagents

The addition of diethylzinc to aldehydes in the presence of catalytic amounts of chiral ligands is an efficient system for asymmetric carbon−carbon bond formation leading to the synthesis of secondary alcohols. This reaction will be only briefly described here because it is not the purpose of our review to describe transformations with stoichiometric quantities of metal. These types of additions, using catalytic amounts of chiral ligands, have, however, been widely studied and have led to interesting organic synthons, i.e., secondary alcohols, with high enantiopurity. The general procedure for this reaction is presented in Scheme 203, in which commercially available dieth-

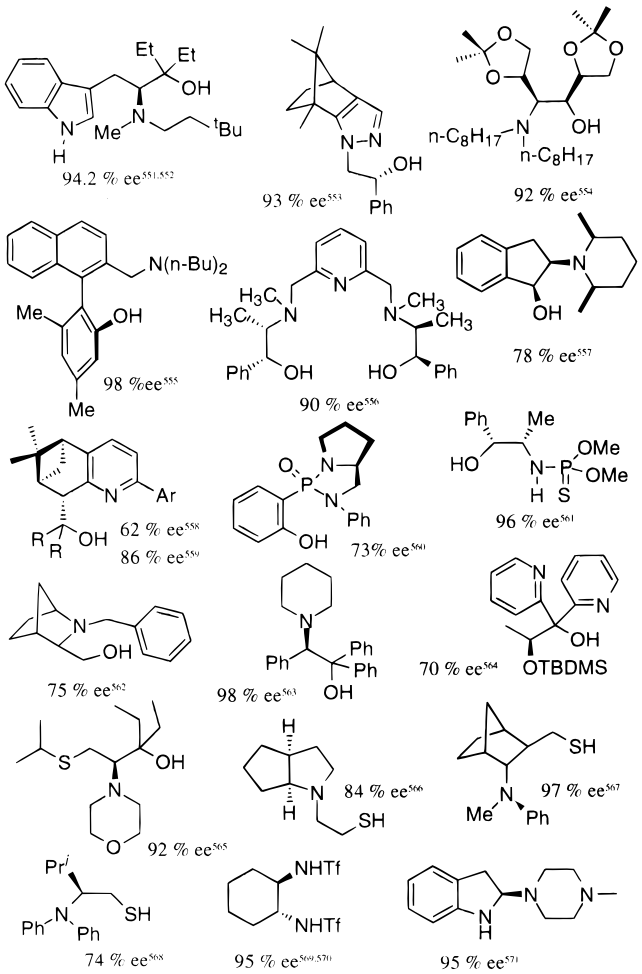
Scheme 203



ylzinc is usually used in important quantities and generally in a molar ratio of three compared to the substrate. This species acts both as an organometallic reagent and as a Lewis acid catalyst. The transformation of benzaldehyde is generally used as a model, because the typical side reaction of aldocrotonization cannot occur with this substrate.

This transformation has been exhaustively reviewed by Soai[549] and Noyori.[550] The asymmetric induction has mostly been achieved with chiral β-amino alcohols, leading to high enantiomeric excesses, particularly for the transformation of aromatic aldehydes. In Scheme 204, several chiral N,O-chelates and their efficiency (in terms of enantioselectivity) are reported for the addition of diethylzinc to benzaldehyde.

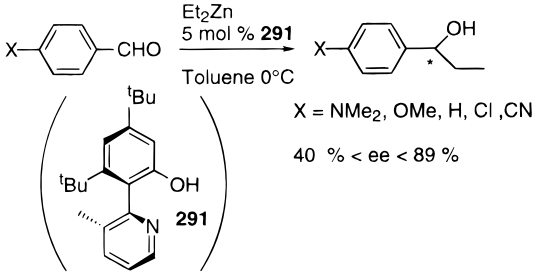
Scheme 204



Several N,S- or N,N-ligands[572] have even been reported to perform the diethylzinc addition with significant selectivities (Scheme 204). N,O-Containing ligands, especially chiral β-amino alcohol derivatives, are, however, by far the most successfully used for the asymmetric additions of organozinc reagents to benzaldehyde. Goldfuss and Houk[573] recently proposed PM3 transition state models obtained by semiempirical calculations to explain the general trends observed in this particular transformation by varying the structure of the chiral β-amino alcohol ligands used.

Zhang et al.[574] observed that the selectivity of the addition of diethylzinc to *para*-substituted benzaldehyde in the presence of a chiral pyridyl phenol (**291** in Scheme 205) depended on the electronic nature of

Scheme 205



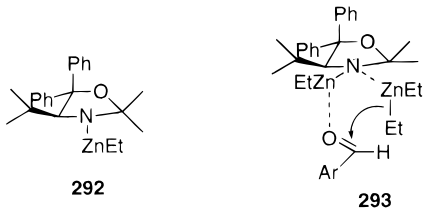
the aryl aldehyde in a linear free energy relationship

and increased with the electron-withdrawing effect of the X-substituent.

The superiority of N,O-ligands over their N,N-counterparts has been also demonstrated by the work of Vyskocil et al.[575] The *N*,*N*-dimethylated analogue of NOBIN (2-hydroxy-2′-amino-1,1′-binaphthyl), in conjunction with n-Buli, led to 88% ee for the addition of diethylzinc to benzaldehyde, a much higher ee value than those obtained by BINAM and its derivatives, which do not exceed 35%.

Prasad and Joshi[576] prepared and used chiral zinc amides as catalysts to perform the asymmetric addition of diethylzinc to aldehydes. It is now well-documented that the catalytic process involves a chiral zinc alkoxide with a tricoordinated center. The authors therefore prepared the more reactive zinc amide with dicoordinated zinc (**292** in Scheme 206),

Scheme 206

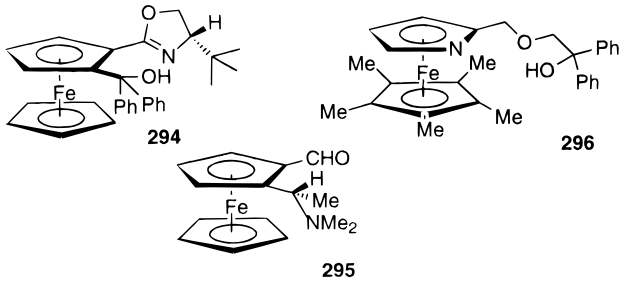


which, as a better Lewis acid, proved to be an efficient catalyst in the enantioselective addition of diethylzinc to benzaldehyde (>99% ee).

They explained this enhanced enantioselectivity by an activation of the aldehyde by zinc amide followed by the transfer of an ethyl group from diethylzinc, as for **293** in Scheme 206.

Other types of chiral ligands have been developed to perform the addition of diethylzinc on benzaldehyde, namely, ferrocene derivatives. Bolm et al.[577,578] reported the preparation and use of a new ferrocenyl oxazoline derivative (**294** in Scheme 207), with both

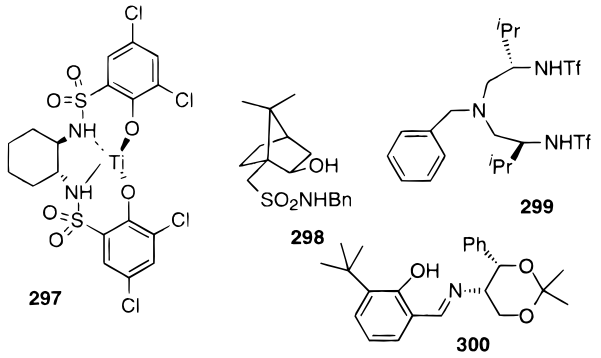
Scheme 207



planar and central chirality, that acted as a chelating ligand in zinc catalysis with benzaldehyde (93% ee). Interestingly, high ee values were also obtained for the transformation of aliphatic aldehydes. Similarly, Fukuzawa and Kato[579] reported chiral 2-(1-dimethylaminoethyl)ferrocene carbaldehyde (structure **295** in Scheme 207) to be an effective catalyst for the asymmetric addition of diethylzinc to either aromatic, linear, or branched aliphatic aldehydes (up to 93% ee). Chiral ferrocenyl amino alcohols possessing either OH or NR_2 functionality α to the ferrocenyl ring were prepared and tested by Nicolosi and Howell,[580] but they led to moderate enantioselectivities. Fu et al.[581] prepared 2-substituted heterocycles that are chiral by virtue of π-complexation to a metal (**296**). They served as effective chiral ligands, catalyzing the enantioselective addition of diethyl zinc to benzaldehyde with 90% ee in 88% yield.

The addition of diethyl zinc to aldehydes has been widely studied. It seems that dimeric complexes containing the chiral ligands act both as Lewis acids for the carbonyl activation and as the origin from which the nucleophilic group is transferred. Therefore, several groups have used different chiral Lewis acids for the carbonyl activation, such as titanate complexes with a chiral tetradentate ligand. For example, Zhang et al.[582] described the use of catalyst **297** (Scheme 208) for the transformation of benzal-

Scheme 208

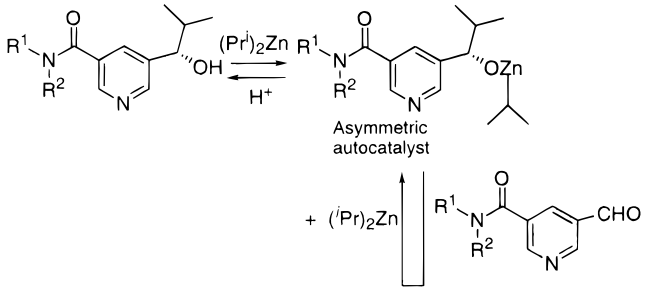


dehyde in 99% yield and 99% ee. Pritchett et al.[583,584] reported an improved procedure for the asymmetric transfer of alkyl groups from zinc to aldehydes utilizing these bis(sulfonamide) ligands and leading to alcohol products, sometimes with high enantioselectivities. Very recently, Gennari et al.[585] studied this family of chiral ligands via parallel synthesis and high-throughput screening for the construction of a disulfonamides library. Ramon and Yus[586] prepared chiral bidentate ligands (derived from (+)-10-camphorsulfonyl chloride) and titanium alkoxide (**298** in Scheme 208) and exhaustively studied the influence of temperature, titanium alkoxide stoichiometry, additives, and aldehyde and ligand structures on enantioselectivity in the addition of diethylzinc on aldehydes. Enantiomeric excess values of up to 72% were obtained with structure **298**. Moberg's group[587] modified chiral aziridines to obtain bis(ethylsulfonamide)amines (**299**) for the catalytic titanium-mediated addition of diethylzinc to benzaldehyde. They thus obtained 1-phenylpropanol in up to 78% ee. Other examples of chiral N-containing ligands for the enantioselective addition of diethylzinc were reported by Yamashita.[588] His group used chiral imines prepared from amino−dimethyl−phenyl−dioxane (**300**) for the transformation of aryl aldehydes in up to 85% ee. Analogous chiral imines have been successfully used as ligands in titanium-mediated diethylzinc additions to benzaldehyde (ee up to 92%) by Fleischer and Braun.[589]

Very interestingly, this reaction has also been performed as an asymmetric, autocatalytic reaction. The product itself is a catalyst, and it catalyzes its own asymmetric synthesis.[590] Soai et al.[591] reported the successful utilization of zinc alkoxides of chiral

5-carbamoyl-3-pyridyl alkanols (Scheme 209) as asym-

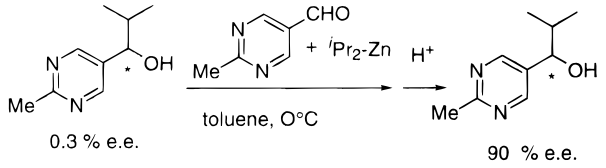
Scheme 209



metric autocatalysts for such a reaction.

The same group later reported[592,593] that a trace amount of 2-methylpyrimidyl alkanol with only a slight ee (0.2−0.3%) was automultiplied with dramatic amplification of ee (up to about 90%) in one-pot asymmetric autocatalytic reaction using diisopropylzinc and 2-methylpyrimidine-5-carbaldehyde (Scheme 210). Recently, they reported even more

Scheme 210

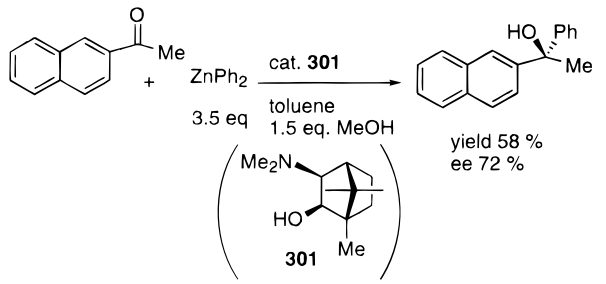


efficient asymmetric autocatalysis with (2-alkynyl-5-pyrimidyl)alkanols.[594]

Noyori et al.[595] recently performed computer simulations to explain the unusual nonlinear phenomena observed during the asymmetric reaction of dimethylzinc and benzaldehyde in the presence of (2*S*)-3-*exo*-(dimethylamino)isoborneol. This study indicates that the degree of nonlinear effects in asymmetric catalysis is affected by the enantiomeric excess of the catalyst, by the concentrations of the catalyst, reagent, and substrate, as well as by the extent of conversion.

Dosa and Fu[596] reported a method for the catalytic asymmetric addition of an organometallic reagent to a ketone. They indeed found DAIB (3-*exo*-(dimethylamino)isoborneol (**301** in Scheme 211) to serve as an

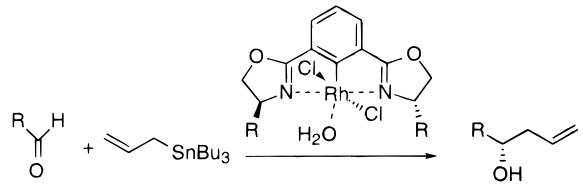
Scheme 211



efficient catalyst for the enantioselective addition of diphenylzinc to aryl−alkyl or dialkyl ketones.

Among various carbon−carbon bond forming reactions, asymmetric allylation of carbonyl compounds is also a valuable means of constructing chiral functionalized structures. Nakamura's group[597] has prepared a highly reactive allylating agent synthesized by treatment of allylzinc bromide with a lithiated bis(oxazoline). By addition to an alkyl alkynyl ketone, the desired allylation product was obtained with excellent enantioselectivity (>99%). Nishiyama et al.[598] reported the formation of an air-stable and water-tolerant complex by the reaction of (Phebox)-$SnMe_3$ (Phebox = 2,6-bis(oxazolinyl)benzene) and [(*c*-octene)RhCl]$_2$. The Phebox ligand chelates via a central carbon−metal covalent bond and both nitrogen atoms of the oxazoline rings (Scheme 212). This

Scheme 212



complex was then tested in the catalytic enantioselective allylation of aldehydes with allyltributylstannane.

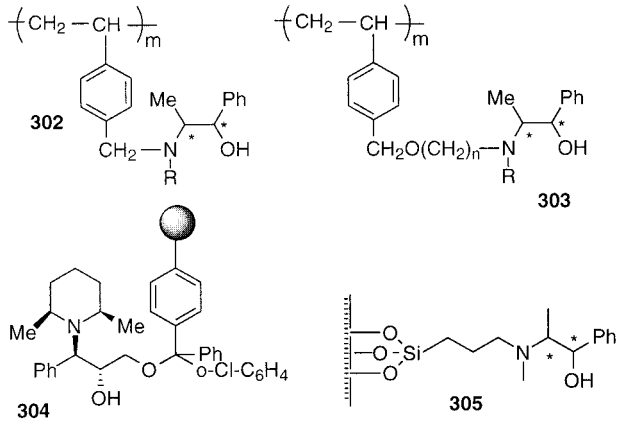
The best enantioselectivity (61%) was achieved by using the Bn−Phebox derived complex. Interestingly, the catalyst could be recovered from the reaction mixture by silica gel chromatography and reused with almost the same catalytic activity and enantioselectivity.

The heterogenization of the ligands active for the addition of alkylzinc derivatives to aldehydes has been extensively studied. This is partly due to the fact that chiral amino−alcohol derivatives are numerous and easily available. These compounds, as we have seen, are highly effective for this transformation and, furthermore, are easily modified for heterogenization. Indeed, there are many examples of heterogeneous catalytic systems for this reaction, compared to other methods of asymmetric carbon−carbon bond formation.

Several articles present variations of the alkylation of aldehydes in which the catalytic system, mostly including N,O-containing ligands, is heterogenized in order to be easily recovered and reused.

Soai and co-workers[599] successfully performed the enantioselective addition of dialkylzincs to *N*-diphenylphosphinylimine in the presence of a chiral amino alcohol supported on polystyrene resin with high enantiomeric excess (up to 91%). Systems such as structures **302** and **303** (Scheme 213) have been examined concerning the influence on the enantioselectivity of the carbon-chain spacer between the chiral function and the polymer resin. Temperature and solvent dependency were also considered. When reused, these structures led to comparable selectivities but loss of activity was observed. Pericàs et al.[600] conducted similar studies in which they anchored enantiomerically pure epoxides to Merrifield resins with different degrees of cross-linking and functionalization. They then introduced secondary amines to yield chiral resin ethers similar to those prepared by Soai's group. They examined the catalytic behavior of these chiral resin ethers in the addition of diethylzinc to benzaldehyde. They concluded that the

Scheme 213



lower the functionalization/reticulation of the ligands, the higher the induced enantioselectivity, in accordance with the monomeric nature of the catalytically active species in this reaction. The best results for a heterogeneous ligand in this transformation (about 92% ee) were obtained by this group by modifying a 2-chlorotrityl chloride resin (Barlos) using the same methodology (structure **304** in Scheme 213).

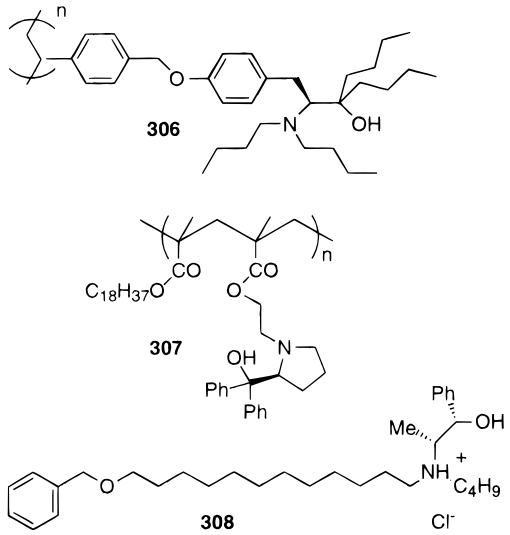
Halm and Kurth[601] modified bis(sulfonamides), already described as efficient homogeneous catalysts, to obtain a monomeric chiral auxiliary containing two polymerizable units (i.e., divinyl functions). Subsequent copolymerization with styrene afforded a resin with cross-link functionalization that can be considered as a solid-phase pseudo-C_2-symmetric catalyst. Tested for the enantioselective alkylation of aldehydes with diethylzinc, this catalyst led to high enantiomeric excesses. Loss of activity was observed when the catalyst was recycled, however.

Aside from organic polymers, inorganic materials are an interesting class of support for the heterogenization of homogeneous catalysts. Laspéras et al.[602] reported the immobilization of chiral ephedrine by covalent linkage to new mesoporous templated silicas of the MCM-41 family (structure **305** in Scheme 213). Up to 40% ee could be obtained in the enantioselective addition of diethylzinc to benzaldehyde with this chiral inorganic−organic material compared to 67% with the homogeneous ephedrine catalyst. The lower rates and enantioselectivities observed in heterogeneous compared to homogeneous catalysis were ascribed to a possible participation of the uncovered surface in the racemic alkyl transfer or to a restricted accessibility to the catalytic sites in heterogeneous catalysis. No studies concerning the reuse of the catalytic system are described.

Interestingly, the group of Kragl et al. studied the possibility of binding the chiral ligands involved in the catalytic process to soluble polymers, which allows these ligands to be used in a membrane reactor. Polymers have thus been prepared from structure **306**[603] and also from α,α-diphenyl-L-prolinol[604] to obtain material **307** in Scheme 214.

The soluble catalyst **307** possesses a molecular weight of 96 000 g·mol^{-1} so that it can be retained by an ultrafiltration membrane within the reaction vessel. The enantiomeric excess achieved for the

Scheme 214

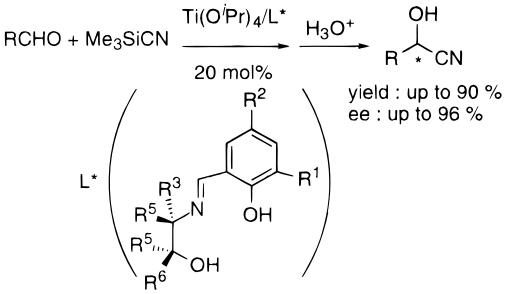


addition of diethylzinc to benzaldehyde with catalyst **307** is only 80%, however, compared to 97% with the uncoupled ligand. This low value is not sufficient for preparative use, but the main advantage of this approach is the increase of the total turnover number for the chiral ligand. Hailes and Madden[605] reported the use of a new homopolymer-recoverable salt catalyst in the asymmetric alkylation of aromatic aldehydes with diethylzinc. They described the synthesis of benzyloxyalkyl norephedrine salts (Scheme 214, structure **308**), easily recycled because of their limited solubility in water and mixed water systems. Promising enantiomeric excesses (up to 80%) could be obtained with this reusable salt catalyst that is deprotonated in situ.

VIII.10.3. Trimethylsilylcyanation

Enantiomerically pure cyanohydrins are versatile synthons for the preparation of various useful synthetic intermediates. The enantioselective addition of trimethylsilylcyanide to aldehydes catalyzed by chiral metal complexes is therefore a powerful method for the obtention of such compounds. Important research carried out with chiral Schiff base−titanium alkoxide complexes has led to high enantiomeric excesses (Scheme 215).

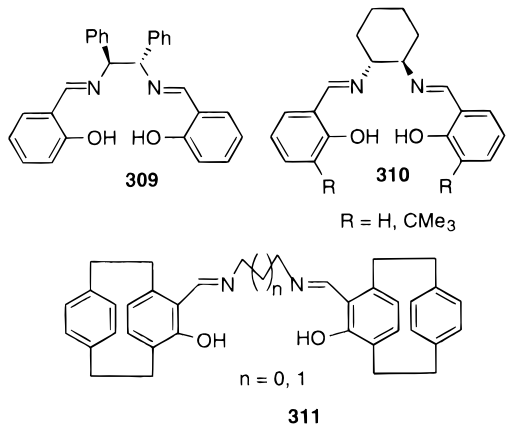
Scheme 215



Oguni et al.[606] intensively studied this reaction by adding trimethylsilylcyanide to a variety of aliphatic or aromatic aldehydes in the presence of a catalyst prepared in situ from titanium tetraisopropoxide and a chiral Schiff base (as proposed in Scheme 215 with

R groups being alkyl or phenyl substituents). The best ligand (R^1 = *t*-Bu, R^3 = *i*-Pr, others are hydrogen) led to 91% ee in the silylcyanation of 4-methoxybenzaldehyde and to 96% ee for the transformation of *trans*-2-methyl-2-butenal. Yaozhong et al.[607] observed higher enantioselectivities with similar systems when the molar ratio of the Schiff base to Ti(O-*i*Pr)$_4$ was 2:1. They, furthermore, found chiral salen−titanium complexes to be effective catalysts for the enantioselective trimethylsilylcyanation of benzaldehyde.[608,609] They assumed that the use of tetradentate chelates (**309** in Scheme 216) of bis-

Scheme 216

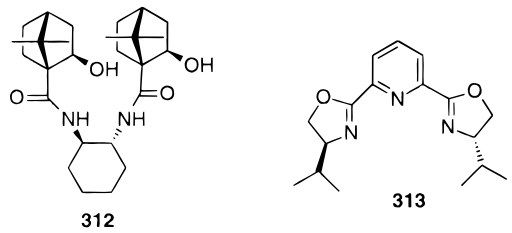


Schiff bases would avoid the formation of multinuclear aggregates (possible with bidentate ligands) and simplify the dynamic reaction equilibria. They indeed obtained good enantioselectivities (up to 87% ee), and activities remained good when smaller amounts of catalyst were used (5 mol %, ligand/metal = 1.1/1).

Belokon and his group worked on the modification of the basic structure of these salen derivatives[610,611] and tested them in the asymmetric trimethylsilylcyanation of various aliphatic, aromatic, and α,β-unsaturated aldehydes.

They prepared the (salen)Ti(IV) catalysts **310** (Scheme 216) derived from chiral 1,2-diaminocyclohexane. These metallic complexes were quite promising and led to a maximum of 81% ee when a sterically hindered structure was used (R = CMe_3). All the coordination sites in the complex were occupied by strong ligands (the tetradentate ligand or alkoxide molecules). The authors therefore suggested that the mechanism should proceed through a preliminary interaction of trimethylsilylcyanide with the complex, resulting in the coordination of the CN function at the apical position of the complex. Its nucleophilic delivery, from the chiral complex to the carbonyl group of the aldehyde, would then be the determining step governing the enantioselection. They, furthermore, described[612] the preparation and the characterization of the titanium complex $TiCl_2L$ (where L = (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)cyclohexane-1,2-diamine), the geometry of which was proven by X-ray structure analysis. This compound was shown to be an efficient catalyst for the asymmetric addition of Me_3SiCN to benzaldehyde to produce (*S*)-2-phenyl-2-trimethylsilyloxyacetonitrile in 86% ee. Later, they again modified the structure of the chiral N-containing inductor[613] (structures **311** in Scheme 216) and prepared ligands in which the only elements of chirality were two disubstituted [2.2]-paracyclophane moieties. One ligand (for which *n* = 0) proved to be effective (84% ee) for the enantioselective trimethylsilylcyanation of benzaldehyde. Interestingly, the catalyst was recovered from the reaction mixture by precipitation with hexane and reused at least 5 times without loss of activity. On the contrary, when the link between both ethylendiamine moieties was a propylene spacer (*n* = 1), major losses of enantioselectivity and especially of activity were observed. The authors also modified ligand **310** (Scheme 216) by disubstitution with [2,2]-paracyclophane moieties but selectivity was not improved. Uang et al.[614] prepared dihydroxy-*trans*-1,2 diamide (structure **312** in Scheme 217), which

Scheme 217



also proved to be a useful chiral ligand for asymmetric induction in conjunction with titanium tetraisopropoxide. They indeed obtained up to 98% ee for the enantioselective addition of trimethylsilyl cyanide to various aldehydes. They considered their method to be advantageous because of the good stability of the ligands.

Chiral Ti(IV) complexes have been mostly investigated as catalysts for the enantioselective synthesis of cyanohydrins with numerous ligands.[615] For instance, Cole et al.[616] proposed a new method, inspired from combinatorial and related strategies, for the development of such catalysts. They synthesized and collectively screened diverse peptide-based structures which induced enantiocontrol for the titanium-catalyzed addition of trimethylsilylcyanide to epoxides. Stepwise modification of the ligand structures afforded high enantioselectivities (up to 86%).

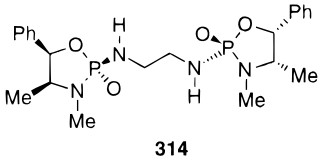
Metals other than titanium have also been involved in the enantioselective catalytic trimethylsilylcyanation of aldehydes.

Iovel et al.[617] recently reported a new catalytic system prepared from $AlCl_3$−Pybox (Scheme 217, structure **313**) effective for the trimethylsilylcyanation of aldehydes. Mandelonitrile was synthesized in the presence of 20% $AlCl_3$−Pybox in 92% isolated yield and more than 90% ee.

The authors studied the $AlCl_3$−Pybox (1:1) system by means of ^{1}H NMR, and they concluded that the initial C_2-symmetrical structure in the N-containing ligand was lost via coordination to the aluminum center. This was confirmed by theoretical calculations indicating the formation of a monocoordination complex between pybox and $AlCl_3$ via the nitrogen atom of one of the oxazoline rings.

Furthermore, the asymmetric cyanosilylation of benzaldehydes has been successfully performed by the combined use of samarium(III) chloride and a chiral bis-phosphoramidate derived from ephedrine (**314** in Scheme 218).[618]

Scheme 218



314

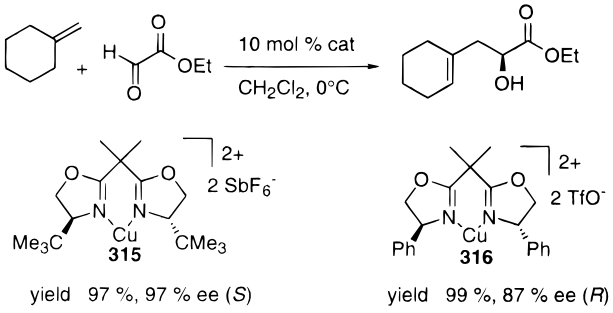
These reactions, performed at room temperature, led to promising ee values (up to 84% in the case of benzaldehyde) with very high turnovers (0.1 mol % of $SmCl_3$ and 0.3 mol % of chiral bis-phosphoramidate ligand). The authors reused the chiral ligand, after precipitation and filtration from the reaction mixture, with no loss of activity or selectivity.

Similarly, Aspinall et al.[619] reported the catalytic asymmetric cyanohydrin synthesis mediated by lanthanide(III) chloride Pybox complexes. They assumed that the strong donor pyridine and the potentially tridentate nature of the ligand should lead to stable complexes. Therefore, they optimized the silylcyanation of benzaldehyde with various $LnCl_3$(^{i}Pr-pybox) catalytic systems (Ln = Pr, Y, La, Eu, Yb) and different solvents to obtain up to 89% ee with $YbCl_3$ as catalyst (Yb has the smallest ionic radius). Interestingly, a reversal of enantioselectivity was observed by using $LaCl_3$.

VIII.10.4. Ene Reaction

In the course of their studies concerning the use of bidentate bis(oxazolines) as ligands for the copper-catalyzed Diels−Alder and aldol reactions, Evans et al.[620] further demonstrated that these chiral Cu(II)-based Lewis acids also catalyze the enantioselective addition of a variety of olefins to glyoxylate esters (Scheme 219).

Scheme 219



yield 97 %, 97 % ee (*S*) yield 99 %, 87 % ee (*R*)

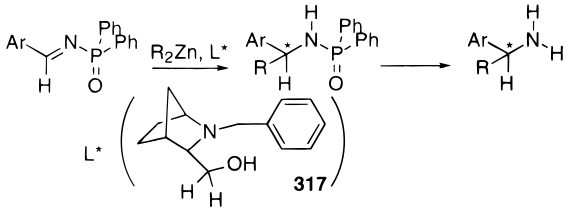
As can be seen in Scheme 219, either enantiomer of the α-hydroxyesters could be obtained from a single enantiomeric ligand series. The scope of the reaction between ethyl glyoxylate with other olefins has been investigated and has led to excellent enantioselectivities and yields, even by using functionalized 1,1- or 1,2-disubstituted olefins.

VIII.11. Addition of Carbon Nucleophiles to C═N Bonds

VIII.11.1. Addition of Organometallic Reagents to Imines

The asymmetric addition of organometallic reagents to carbonyl compounds is among the most common transformations leading to the formation of a carbon−carbon bond. In particular, the addition of diorganozinc reagents to prochiral aldehydes has been widely studied. Some researchers were therefore interested in testing the parent reaction, i.e., the addition of organometallic compounds to activated imines, to study the scope and limitations of this α-aminoalkylation reaction. Andersson[621] prepared a set of new β-amino alcohols (structure **317** in Scheme 220) containing the 2-azanorbornyl framework for the

Scheme 220

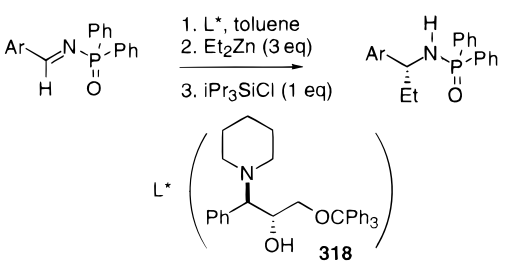


enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines. Imines are indeed considerably less reactive than aldehydes, and activation of the amino group is required to allow the reaction to proceed at a practical rate.

High enantioselectivities (up to 92% ee) were obtained by varying the substituents on the ligand, in both the catalytic and stoichiometric processes. One drawback of this system is that stoichiometric amounts of ligand were required to achieve good activities. However, 90% of the chelating agent could be recovered during the workup procedure of the reaction. Next, the addition products could be easily converted into the free amines, without racemization, by acidic hydrolysis.

Pericàs[622] recently proposed another strategy for activating the addition of dialkylzinc reagents to imines, namely. by using trialkylsilyl halides. The optimal structure for the ligand appeared to have both a bulky primary alcohol protecting group and a cyclic six-membered ring amine (structure **318**, in Scheme 221). These characteristics are identical to

Scheme 221

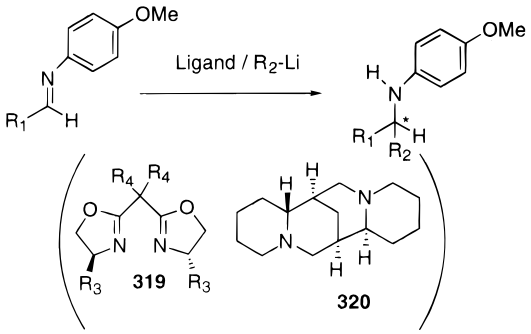


those recommended for chelates active in the enantioselective addition of diethylzinc to aldehydes, thus indicating close similarities of transition states in both processes.

The authors then tested a dual amino alcohol/Lewis acid activation: triisopropylsilyl chloride was the most efficient mediator in terms of rate enhancement and enantiomeric excess of the resulting phosphonamides (up to 91% ee).

Denmark reported the asymmetric addition of organolithium reagents to imines in the presence of bis(oxazoline)s (structure **319** in Scheme 222) or (−)-

Scheme 222



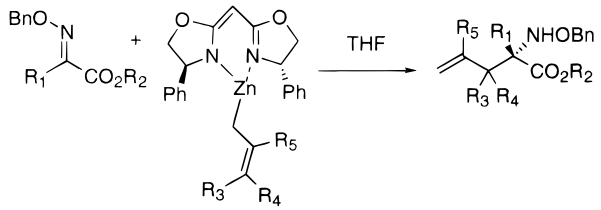
sparteine (structure **320**).[623]

This group demonstrated that these types of ligands could serve as promoters for the selective addition of organolithium reagents to aromatic, olefinic, and aliphatic aldimines, since ee values up to 98% could be reached. In those cases, the ligands were used in catalytic amounts, whereas the organolithium reagents were present in excess (in a molar ratio of at least two).

Denmark and Nicaise[624] recently reviewed the enantioselective conversion of prochiral azomethine functions to chiral amines by ligand-mediated addition of organometallic reagents.

There are few examples dealing with the enantioselective allylation of C=N double bonds. Hanessian and Yang[625] reported the allylation of α-ketoester *O*-benzyl oximes with the aid of chiral bis(oxazoline)s in the presence of allylzinc reagents (Scheme 223).

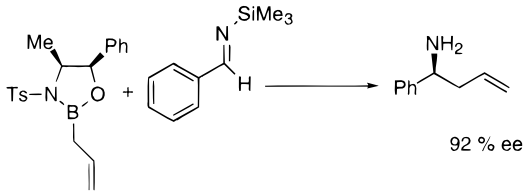
Scheme 223



Excellent enantioselectivities were obtained (up to 94% ee) using the phenyl-substituted bis(oxazoline) ligand depicted in Scheme 223. The allylation products could easily be transformed, by simple functional manipulations, into the corresponding, synthetically useful L-allylglycine and its substituted derivatives. Nakamura et al.[626] simultaneously reported the same system to react efficiently with cyclic aldimines, such as dihydroisoquinoline, to give the corresponding allylderivatives in 72% yield and 95% ee.

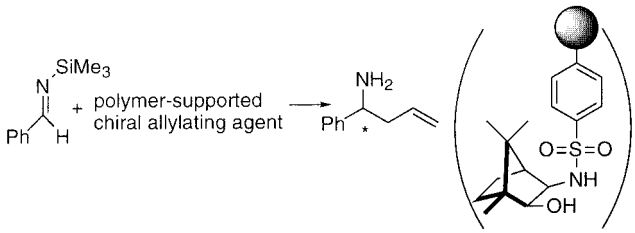
Itsuno[627] alternatively described the enantioselective allylboration of imines toward the formation of optically active homoallylamines. Substrates of choice included N-substituted imines such as oxime ethers, sulfenimines, and *N*-trimethylsilylimines because of the relatively high stability of their C=N function. The reaction of these compounds with a chiral modified monoallylborane led to the corresponding allylated amines in up to 80% ee. The best result (92% ee, Scheme 224) was obtained using a *β*-allyloxazaborolidine derived from (−)-norephedrine.

Scheme 224



Very interestingly, the same group[628] reported the first enantioselective allylation of similar substrates using polymer-supported chiral allylboron reagents. They thus prepared chiral polystyrenes possessing *N*-sulfonylamino alcohol moieties as pendant groups (Scheme 225). These chiral polymers were then

Scheme 225



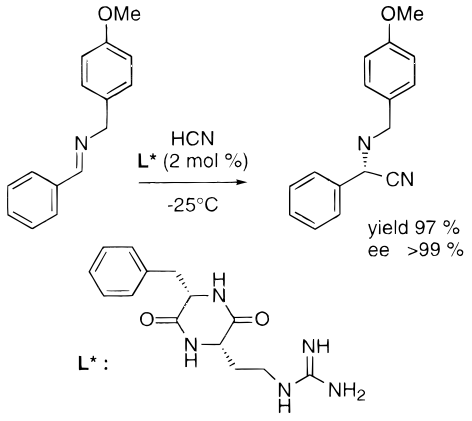
treated with triallylborane to afford polymeric allylating agents which were used for the enantioselective allylation of trimethylsilylimine.

The allylation of *N*-(trimethylsilyl)benzaldehyde imine with such systems occurred with nearly quantitative yield and high enantioselectivities (up to 90% ee). The reaction carried out with another polymeric chiral allylating agent, namely, the endo isomer, gave the same homoallylamine with reversed stereoselectivity. Interestingly, the enantioselectivities obtained from the heterogeneous systems were higher than those obtained from their homogeneous counterparts, probably due to microenvironmental effects originating from the cross-linked polymer. The recovery of the chiral polymer was described without examples of its reutilization, however. The development of new methods for the synthesis of versatile chiral amines is of undeniable interest. A catalytic version of the aforementioned method is still to be found.

VIII.11.2. Strecker Synthesis

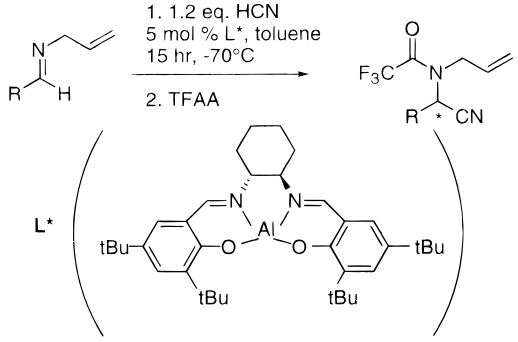
We shall now discuss the Strecker reaction, i.e., the addition of cyanide to imines, a straightforward strategy for the asymmetric synthesis of α-amino acid derivatives. Several enantioselective versions of the Strecker synthesis, in which optically active amines served as chiral auxiliaries, have been reported. Lipton et al.[629] improved this strategy by using a chiral catalyst (a cyclic dipeptide, Scheme 226) which permitted the conversion of imines to amino acids in high yields and high enantioselectivities.

Scheme 226



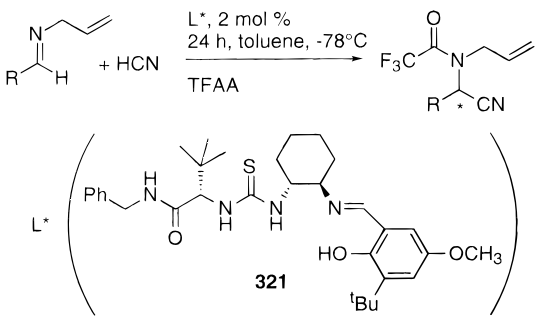
Jacobsen[630] recently described the first example of a metal-catalyzed enantioselective Strecker reaction, which occurred using a chiral (salen)Al(III) complex (Scheme 227).

Scheme 227



The addition of HCN to *N*-allylbenzaldimine afforded the expected product in 91% isolated yield and 95% ee. Various *N*-allyl imines were evaluated in this reaction to give the corresponding products in good yields and moderate to excellent enantioselectivities. To illustrate the applicability of the method, the authors successfully converted an imine with a low catalyst loading on a large scale. They simultaneously used and described a parallel library approach for the discovery and optimization of ligands (Schiff base catalysts) useful for the asymmetric Strecker reaction.[631] Structure **321** depicted in Scheme 228 led to

Scheme 228



78% isolated yield and 91% ee. This system exhibited promising enantioselectivity both on the solid phase and in solution.

IX. Conclusions

When we decided to write this review, we naturally believed that nitrogen-containing ligands had an increasing interest although lesser value compared to the ubiquitous phosphine ligands. After collecting and analyzing more than 600 recent articles, however, we have clearly shown that nitrogen-containing ligands have already overtaken phosphorus-containing ligands in many domains of asymmetric catalysis. The discovery of the value of chiral phosphines in asymmetric catalysis has had enormous conceptual and historical importance. Nevertheless, nitrogen-containing ligands now seem to be better equipped to meet the diverse requirement of practical asymmetric catalysis.

To summarize the wide scope of application of N-ligands, in Tables 1−5 we collected their main performances in asymmetric catalysis over the last five years. As it is very difficult to classify the different types of nitrogen-containing ligands, we chose a combination of both, the type of chemical functional groups and structural similarities of the ligand. The similarities include the use of an already known functional group, such as imine, in a particular new type of structure, such as bis(oxazoline), salen, etc. Classifying the reaction is, of course, much easier: we first considered the type of bond formed and then the type of substrate. In these tables we describe results obtained only in the last 5 years. However, most of the previously discovered nitrogen-containing ligands were still being studied. As a consequence, we believe that most of the existing catalytic systems using nitrogen-containing ligands are described in the present tables.

Table 1 shows the nitrogen-containing ligands tested for asymmetric C−H bond formation. Reduction with molecular hydrogen is one of the asymmetric reactions for which diphosphines are still the ligands of choice. Spectacular new results in terms of activity and enantioselectivity have indeed been reported in recent years with this type of ligands. Nevertheless, one of the best results published so far is the reduction of aromatic ketones with an association of BINAP and a diamine as ligand for the ruthenium-catalyzed reduction. Among the other types of reductions, semicorrin is the ligand most used with inorganic hydride, although amino sulfonamides appear to be the best ligands for hydride transfer reactions. Hydrosilylation has received less attention, but phosphine with oxazoline and bis(oxazoline) ligands are frequently used in this field.

Due to the easy oxidation of phosphine, it is not surprising that nitrogen-containing ligands and, to lesser extent, oxygen-containing ligands have provided the best selectivities and activities in asymmetric C−O bond formation. Table 2 shows the nitrogen-containing ligands tested for asymmetric C−O bond formation.

Epoxidation of C−C double bonds using salen-type ligands could be considered as one of the major successes of the past 10 years, although in the particular case of allylic alcohols, the titanium tartaric acid complex is still the best system. Salen-type ligands are even more valuable if the stereoselective

Table 1. Asymmetric C−H Bond Formation Using Nitrogen-Containing Ligands

type of N-ligands	reduction with hydrogen	reduction with inorganic hydride	hydride transfer	hydrosilylation
amino/imino phosphines	yes		yes	yes
diamines	yes		yes	
cinchona and derivatives	yes			
amino/imino alcohols/phenols		yes	yes	
salen and salen types		yes		
bis(oxazolines) and similar				yes
semicorrins		yes		
aromatic heterocycles/pyridines			yes	yes
sulfonamides			yes	
amides, ureas, thioureas	yes		yes	

Table 2. Asymmetric C−O Bond Formation Using Nitrogen-Containing Ligands

type of N-ligands	epoxidation	dihydroxylation	epoxide opening	allylic oxidation	Baeyer−Villiger-type reaction	Wacker	sulfoxide synthesis
cinchona and derivatives		yes					
amino/imino alcohols/phenols	yes				yes		yes
salen types	yes		yes	yes			yes
bis(oxazolines)	yes			yes		yes	
porphyrins	yes						

Table 3. Asymmetric C−N Bond Formation Using Nitrogen-Containing Ligands

type of N-ligands	hydroamination of C=C	α CO amination	hydroxyamination	aziridine synthesis	allylic amination
amino/imino phosphines	yes				yes
cinchona and derivatives			yes		
salens				yes	
sulfonamides		yes			

Table 4. Asymmetric C−C Bond Formation with Allylic and Vinylic Positions Using Nitrogen-Containing Ligands

type of N-ligands	allylic substitution	Heck reaction	cyclo-propanation	Diels−Alder reaction	Michael-type addition	Grignard cross coupling	hydro-formylation
amino/imino phosphines	yes	yes	yes	yes	yes	yes	yes
diamines	yes						
amino/imino alcohols/phenols					yes		
salens				yes			
bis(oxazolines)	yes		yes	yes	yes		
semicorrins			yes				
aromatic heterocycles	yes		yes	yes			
porphyrins			yes				
sulfonamides			yes	yes			
amides, ureas, thioureas	yes		yes	yes			

Table 5. Asymmetric C−C Bond Formation with Carbonyls and Imines as Substrates Using Nitrogen-Containing Ligands

type of N-ligands	aldol reaction	addition of alkyl zinc on aldehyde	cyanohydrine synthesis	addition of organometallic on imine group	Strecker
diamines	yes			yes	yes
amino/imino alcohols/phenols	yes	yes	yes	yes	yes
salens			yes		yes
bis(oxazolines)	yes		yes	yes	
sulfonamides	yes				
amides, ureas, thioureas			yes		

opening of the epoxide ring is taken into account. Compared to these last ligands the use of cinchona derivatives for the dihydroxylation of the C=C double bonds is of the same degree of fundamental and practical interest. Potential new types of oxidations, such as allylic oxidation, Baeyer−Villiger, and Wacker-type reactions, were recently described using one of the known classes of nitrogen-containing ligands.

Table 3 summarizes the use of nitrogen-containing ligands in asymmetric C−N bond formation. Asymmetric C−N bond formation is a more recent (and more difficult) objective of catalysis, so only a few significant results have been described untill now. Most of the approaches are more or less conceptually related to the best results obtained for asymmetric formation of C−O and C−C bonds.

Table 4 describes the results obtained with nitrogen-containing ligands for C−C bond formation onto an allylic or vinylic position. Numerous ligands were tested for asymmetric allylic substitution. The most general and useful system concerns the ligand developed by Trost. This ligand possesses two amides and two phosphine coordinating groups in a “chiral pocket”. The asymmetric version of the Heck reaction has only very recently been studied. Aside from the well-known diphosphines, only the association of

oxazoline and phosphine was successfully tested in recent years. Cyclopropanation has received much more attention. Depending on the type of catalyst and reaction, disulfonamides, pybox, amino alcohols, bis(oxazolines), and even substituted pyridines lead to good results in particular cases. Similarly, in case of the Diels−Alder reaction, several types of nitrogen-containing ligands were proven to be efficient for different types of substrates when associated with specific metal ions. Bis(oxazolines) seem to be the most used ligands. The asymmetric Michael-type additions catalyzed by metal complexes are generally performed in the presence of phosphines and amino phosphines. Nevertheless, promising new results with amino alcohols and bis(oxazolines) have just been published. Asymmetric cross-coupling was performed very early in the presence of nitrogen-containing ligands, but amino phosphine ligands still appear to be the best type of ligand for nickel- or palladium-catalyzed reactions. Asymmetric hydroformylation is currently performed with high ee and regioselectivity with phosphite ligands. Only a few recent results with aminophosphines and thioureas have been published.

Table 5 shows the type of nitrogen-containing ligands used in asymmetric C−C bond formation, with carbonyls or imines as the substrates. Aldol condensation is probably one of the most synthetically useful reactions. It is therefore understandable that many efforts are currently being made to control the stereoselectivity of the reaction. Aside from the important results obtained with binol-type ligands, other ligands such as diamines, bis(oxazolines), or imino phenols, associated with Lewis acids, also led to good results in terms of chemical yields and enantioselectivities. A plethoric number of amino alcohols are used for the addition of alkyl zinc reagents to aldehydes and more rarely to ketones. Chiral imino phenol as well as salen, diamide, and pybox-type ligands can be used with titanium salts for asymmetric cyanhydrin formation. The same types of ligands have been tested with substrates bearing an imine group and led to very important results for the asymmetric Strecker reaction.

These five tables show the increasing importance of nitrogen-containing ligands for asymmetric catalysis in many kinds of reactions. The diversity of the types of nitrogen-containing ligands allows an adaptation to different types of reactions and metals. On the other hand, we believe that many of the associations (i.e., reaction/metal/nitrogen-containing ligand) not yet tested possess potential applications. In other words, the missing associations in Tables 1−5 could be more important than the existing ones.

The other objective of this review was to collect information on the use of nitrogen-containing ligands to synthesize catalysts that are easy to separate and recycle. The heterogenization of nitrogen-containing ligands was performed for most of the more efficient catalytic systems. It is notewhorthy that the delay between the discovery of an efficient homogeneous catalytic system (ADmix for example) and the publication of results with the corresponding heterogeneous system is shorter than for phosphine ligands. The heterogeneization of nitrogen-containing ligands is already illustrated with inorganic and organic supports. In this last case the ligand can be included either in the main chain or in a pendant group.

The relatively easy chemistry of nitrogen-containing ligands could also be a crucial advantage for using new separation systems (biphasic, supported biphasic, melting salt, supercritical fluids, and use of membranes). Moreover, nitrogen-containing functionnal groups are much more appropiate in order to perform combinatorial strategy for research studies.

We stopped collecting references at the end of June 1999. The number of articles published on the subject through this period is very impresive, which makes this review actually unexhaustive. However, it clearly shows the importance and high potential of nitrogen-containing species as chiral inductors for asymmetric catalysis.

X. References

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