Chiral Tetraaza Ligands in Asymmetric Catalysis: Recent Progress

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Abstract: Nitrogen-containing ligands have become very popular in asymmetric catalysis, due to their robustness and availability in comparison to phosphines. Nitrogen-containing ligands are used in homogeneous catalysis, but they are suitable for heterogeneous processes, too. In this article we focus on chiral ligands with four nitrogen atoms and summarize recent progress achieved with these compounds in asymmetric catalysis.

Keywords: asymmetric catalysis; heterogeneous catalysts; homogeneous catalysts; immobilization; N-ligands; tetraaza ligands

1 Introduction

In 1994 Togni and Venanzi[1] reported very promising results with nitrogen donor ligands in asymmetric catalysis. Six years later, Fache et al.[2] published a precise review on the current state of the investigations in this area. Our purpose is not to repeat the topics of this comprehensive article, instead we shall concentrate our attention on the progress accumulated since then in catalytic asymmetric transformations using tetraaza ligands.

Nitrogen-containing ligands have several distinct advantages. First, they are largely available in enantiomerically pure form, both in the chiral pool (quinine, cinchonine, sparteine and strychnine) or as cheap industrial chemical intermediates. In addition, the production of chiral amines by resolution of the racemates[3] is probably one of the easiest and best documented methods of the separation of enantiomers.

On the other hand, chirality on the nitrogen atom is difficult to obtain. Contrary to the phosphines, the chiral nitrogen atoms epimerize instantaneously at room temperature. The formation of a stable chiral center on a nitrogen atom is, however, possible by using bicyclic structures.

The second advantage of the nitrogen-containing ligands lies in the chemistry of the nitrogen functional group itself. The chemistry of these is not always easy, but it has received such abundant attention that there exists, in most cases, numerous synthetic solutions to each possible transformation of these compounds. As a result, these synthetic possibilities allow tailor-made modifications for the preparation of ligands with specific physicochemical properties. Particularly, the interactions with the transition metals may be widely varied by preparing X-type ligands (amides, sulfonamides), L-type ligands (amines) or π-type ligands (imines).

Nitrogen-containing ligands are being used more and more in asymmetric catalysis. They turn out to be suitable for any type of catalysis and especially for heterogeneous catalysis,[4,5] which is one of their main advantages over phosphines. In addition, nitrogen-containing ligands may be used in asymmetric catalysis with transition metals, which are less expensive than noble metals.[6]

2 Reduction of C=C Bonds

The reduction of double bonds with homogeneous catalysts has emerged in the past few decades as an indispensable tool in laboratory-scale synthesis, as well as in the manufacturing of fine chemicals.[7] Historically, this field has been dominated by heterogeneous cata-

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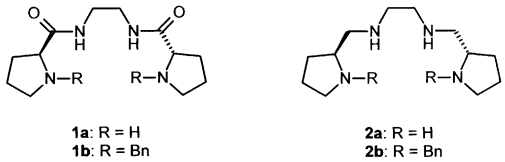
lysts, but the homogeneous ones offer advantages over the heterogeneous counterparts, for example, superior chemo-, regio-, and stereoselectivity.

The most frequently used metals for this transformation are Rh(I) and Ru(II) in combination with phosphines, but in the last few years many researchers have tried to extend the spectrum from the late transition-metal complexes to the early transition-metal complexes.

Although the phosphines have shown to be the best catalysts for this transformation (Noyori's BINAP, almost 100% ee),[8] since the beginning of the 1990s more and more articles dealing with nitrogen-containing ligands have appeared in the literature, especially for hydride transfer reduction.

2.1 Homogeneous Systems

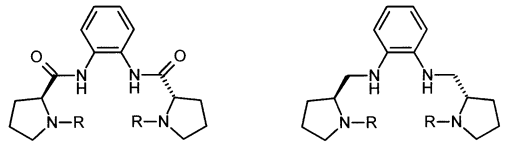
Starting from the readily available L-proline, Iglesias et al.[9] reported the preparation of the C_2-symmetric



1a: R = H
1b: R = Bn

2a: R = H
2b: R = Bn

Scheme 1.



3a: R = H
3b: R = Bn

4a: R = H
4b: R = Bn

Scheme 2.

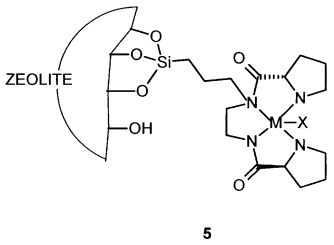
ligands **1** and **2** (Scheme 1), and their Rh(I) and Ir(I) complexes. These complexes were tested on the asymmetric hydrogenation of diethyl 2-methylbut-2-enedioate, showing that ligands of the type **1** gave only poor enantioselectivities (4–5% ee) but good chemical yields (~80%), whereas with the tetramine ligands **2** chemical yields over 80% and enantioselectivities of approximately 20% ee were achieved. The reason for this behavior could be the different coordination ability of both ligands. A five-membered ring is common for both, but with *N,O*-coordination for the former and with *N,N*-coordination for the latter.

One year later, Iglesias's group[10] synthesized four new ligands (**3** and **4**) with rigidity in the backbone (Scheme 2) as an alternative to the more flexible family of ligands **1** and **2**.

The catalytic activity of the Ir and Rh complexes of **3** and **4**, was also investigated on the hydrogenation of prochiral olefins. In all cases, the yields of the reactions were quantitative and the enantiomeric excess fluctuated between 9–30%.

The Ir complexes have shown higher rates (TOF) and enantioselectivities than the Rh complexes. The change of substituents at the pyrrolidine nitrogen plays a significant role in the optical induction. It increases while moving from hydrogen (16% ee) to benzyl group (30% ee), indicating that an enhanced steric demand around the metal center gives a decisive effect for higher enantioselectivity.

Cu and Mn complexes of **3** and **4** were also synthesized,[11] and evaluated in the enantioselective cyclopropanation of olefins and in the selective oxidation of sulfides to sulfoxides and sulfones, respectively. The results for both reactions were moderate, but they showed the possibility of using this type of ligands to catalyze important processes in organic chemistry.



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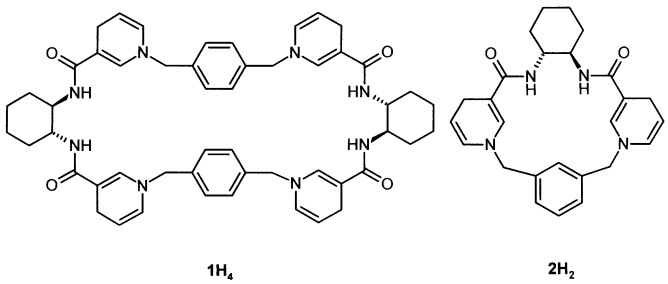
Scheme 3.



Scheme 4.

2.2 Heterogeneous Systems

Furthermore, Iglesias et al. reported[12] the heterogenization of the catalysts **1** and **2**. The strategy used preserved as much as possible the coordination sphere of the metal. This is achieved by anchoring the homogeneous catalyst to an inorganic support (USY or MCM-41 zeolite) *via* covalent bonds between the solid support (silanol groups −Si−OH) and the ligand (or complex) that has the appropriate groups [−Si(OEt)$_3$] at a position remote from the metal center (Scheme 3).

The heterogenized complexes are still more stable than their homogeneous counterparts and they can be used several times without decreasing activity. Nevertheless, the enantioselectivity achieved with the heterogeneous systems remains close to that obtained with the homogeneous ones. It is interesting to note that, for homogeneous catalysts, an induction period (5 – 30 min) was observed, while for heterogeneous catalysts this period was not detected, probably as a consequence of the strong capability of zeolites to adsorb H_2 on their surfaces, which increases the local concentration of hydrogen and accelerates the rate of the reaction.

3 Reduction of C=O Bonds

Nicotinamide adenine dinucleotide (NAD^+/NADH) is a coenzyme which takes part in many biological oxidation-reduction reactions,[13] such as the conversion of ketones and aldehydes to alcohols and *vice versa*. The enzymatic reduction of a prochiral ketone carried out by NADH proceeds *via* a selective transfer of one of the two diastereotopic hydrogens in the dihydropyridine ring of NADH. The hydrogen is transferred stereoselectively to the ketone, generating a chiral alcohol. Since the first asymmetric reduction using an NADH model reported by Ohno et al.,[14] there has been a large number of different approaches to NADH mimicking.[15] The general concept is to start with nicotinamide and then modify it, for example, by introducing various chiral auxiliaries in the amide or methyl groups at C-2 and C-4 in the dihydropyridine ring.

Gran and co-workers[16] reported NADH models designed by a supramolecular approach, where the substrate that will be reduced is bound into a hydrophobic pocket of the model. Four nicotinamide units[17] are incorporated in model $\mathbf{1H_4}$ and two units in compound[18] $\mathbf{2H_2}$ (Scheme 4). Both compounds were used to test their ability to reduce prochiral carbonyl substrates stereoselectively.[19]

When $\mathbf{1H_4}$ was used for the reduction of different ketones in the presence of magnesium ions, low to moderate enantioselectivities were achieved. These results depend on the concentration of magnesium ions, the reaction temperature and the used substrate. The best results (81% ee) were obtained with methyl benzoylformate as substrate, 1.25 equivalents of magnesium ions and at a temperature of $-30\,^{\circ}C$. A less selective process dominates at higher temperatures and magnesium ion concentrations.

It seems as if the role of the metal ion is not only to act as a Lewis acid, but also to form a ternary complex holding the reagent and the substrate together.

The reductions with compound $\mathbf{2H_2}$ were more selective (96% ee) than those using $\mathbf{1H_4}$. It is also remarkable in this case that the stereoselectivity was not affected by an increase in magnesium ion concentration or by lowering of the temperature.

The reason for these differences could be that a fast, less selective, bimolecular reaction does not take place in the case of the smaller macrocycle. Another explanation might be that the macrocyclic framework of $\mathbf{2H_2}$ is more rigid than the one of $\mathbf{1H_4}$, which suggests that coordination of more than one metal ion to $\mathbf{2H_2}$ does not cause a conformational change, thus leading to a less selective reaction.

4 Hydrogen Transfer Reduction

For hydrogen transfer reactions the source of hydrogen is not molecular hydrogen. Instead, cyclohexene, cyclohexadiene, alcohols (methanol, benzyl alcohol, 2-propanol) and formic acid have been successfully used as hydrogen donors. This method avoids all the risks associated with molecular hydrogen and allows the modulation of the rate and chemoselectivity of the reaction by choosing the most appropriate hydrogen donor. Unlike asymmetric hydrogenation, where chiral

phosphine ligands show an excellent performance, transfer hydrogenation frequently uses nitrogen-containing chiral ligands.

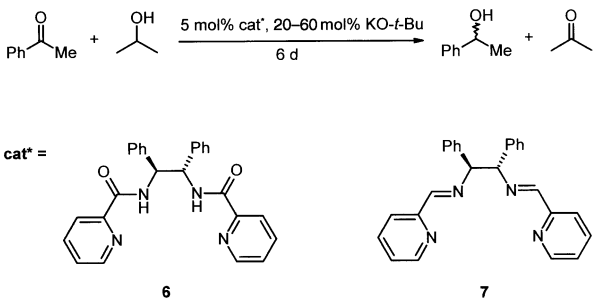
4.1 Homogeneous Systems

Lemaire et al.[20] performed the hydrogen transfer reduction of acetophenone (Scheme 5) with two new tetraaza ligands, the amide **6** and the imine **7**, complexed with Co, Ir and Rh. The results were disappointing irrespective of which metal was used: only low conversion and 22% enantiomeric excess were obtained with the diamide **6**-Rh complex.

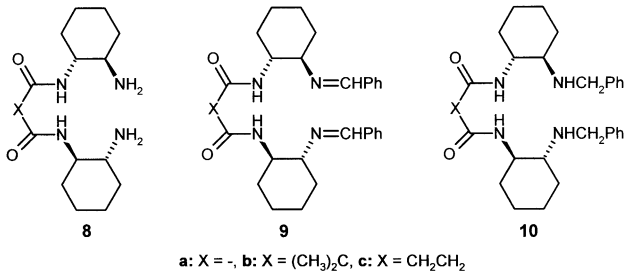
Other amide ligands (**8 – 10**, Scheme 6) complexed with Ru were synthesized for this catalytic transformation by Marson and Schwarz.[21] Acetophenone was used as substrate, together with other *para*-substituted (F, Cl, OMe) phenyl methyl ketones.

The oxamide ligand **8a**, possessing terminal NH_2 groups, afforded enantioselectivities between 39 – 48% and chemical yields of around 30%. Compared with NH_2 as a terminal group, an *N*-benzyl group (**10**) generally provided higher yields (64 – 71%), but lower enantioselectivities (15%). When the terminal group was an imine (**9**), very low or no enantiomeric excesses were detected.

By analysis of the linker, an oxamide (**a**) afforded the best yields, but poor enantioselectivities. In contrast, a malonamide spacer (**b**) gave lower yields but substantially higher enantioselectivities and a succinimide linker (**c**) was unsuccessful.



Scheme 5.



Scheme 6.

In addition, a remarkable change in the configuration of the major enantiomer was observed for both active ligands (**8** and **10**) when the substituent in the ketone was changed.

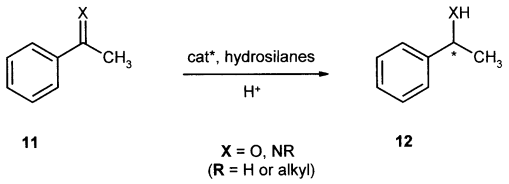
5 Asymmetric Hydrosilylation

The asymmetric catalytic reduction of ketones and imines with certain organohydrosilanes and a transition-metal catalyst is called hydrosilylation, and is recognized as a versatile method providing optically active secondary alcohols and primary or secondary amines (Scheme 7).[22]

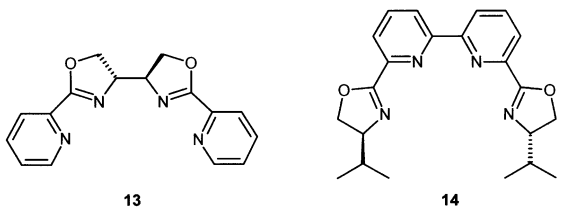
The hydrosilylation is important as a preparative method, but its manipulative feasibility makes this reaction a powerful tool as a test reaction for asymmetric catalysis, so that the potential of newly designed chiral ligands and catalysts can be continuously scrutinized.

C_2-Symmetric bioxazoles are capable of catalyzing asymmetric reactions[23] (cyclopropanation, hydrogen transfer reaction, allylic alkylation and hydrosilylation) in the presence of Co, Ir, Pd and Rh. Nevertheless, up to now none of the known bioxazoles possess chirality in their backbone. Compound **13** was reported[24] as the first ligand with such a structure change (Scheme 8). An encouraging result was obtained by testing **13** on the Rh-catalyzed asymmetric hydrosilylation. The *R*-isomer of the alcohol was achieved in 50% ee and 75% yield. This result is comparable with those obtained for bioxazoles.[24]

The tetradentate bis(oxazolinyl)bipyridine (*bipymox*) **14** was synthesized in order to compare its catalytic properties with respect to bi- and tridentate oxazolinylpyridine ligands.[25] When **14** was complexed with $RhCl_3$, and particularly in the presence of 2 additional equivalents of the ligand and $AgBF_4$, the asymmetric hydrosilylation of acetophenone was promoted with enantio-



Scheme 7.



Scheme 8.

selectivities of up to 90% for the (*S*)-isomer. This result is similar to that obtained with other ligands of this type.

6 Cyclopropanation

The benchmark cyclopropanation of styrene **16** with ethyl diazoacetate **17** is widely used to screen new catalysts. Luis, Mayoral and co-workers[26] tested the tetraazaparacyclophane **15** in this reaction (Scheme 9), since ligands of this type have been shown to stabilize Cu(I) with respect to its disproportionation into Cu(II) and Cu(0).[27]

Using this *in situ* prepared Cu(I)-complex only low yields and regioselectivities of the cyclopropane products **18** and **19** were obtained.

In order to study the effect of the ligand's topology on the catalyst activity, several open-chain tetraamines (**20, 21**) and amides (**22 – 26**) (Scheme 10) were tested.

When the amines **20** and **21**, both with bulky substituents, were used in the cyclopropanation, no asymmetric induction was observed. The reaction time was very long and the yields were low.

In the case of the ligands **22** and **23**, it has been shown that the presence of carbonyl groups leads to a decrease in the induction period, a slight decrease in the *trans*/*cis* ratio and small but measurable enantioselectivities of the products.

Similar behavior, but a clear reduction in the period of induction, was obtained with ligand **24**, which has a longer bridge.

The two diastereomeric ligands **25** and **26**, were also tested and showed very different actions. Whereas the reaction with **25** is very fast, use of **26** leads to an extremely long period of induction. In both cases no enantioselectivity was obtained.

The ligands **22** and **23** were easily immobilized by anchoring on a functionalized polymer.[28] The resulting polymer-supported Cu(II) complexes show higher activities than their homogeneous counterparts, but a lower enantioselectivity.

7 Asymmetric Allylic Alkylation (AAA)

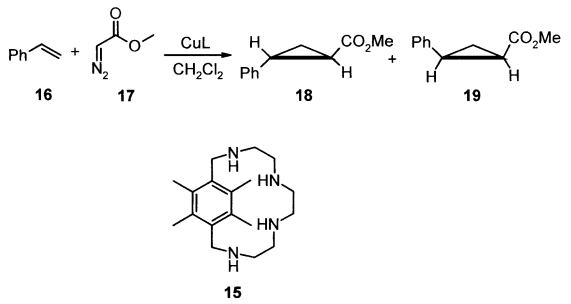
Since the first example[29] of inducing asymmetry at the allylic fragment with a palladium catalyst in 1977, the asymmetric allylic alkylation reaction (AAA) has undergone a revolutionary development in recent years to establish its synthetic viability. The major benefit of this transformation is the diversity of bond types that can potentially be formed. In addition to the formation of C–H and C–O bonds, also C–N, C–S, C–P, and most importantly C–C bonds, can be formed.[30]

Although these transformations require rather sophisticated conditions, depending mainly on the nature of the catalytic species, they allow control of regio-, diastero-, and even enantioselectivity. Among the metals capable of effecting this reaction are Pd,[31] Mo,[32] W,[33] Ir,[34] Rh[35] and Ru.[36]

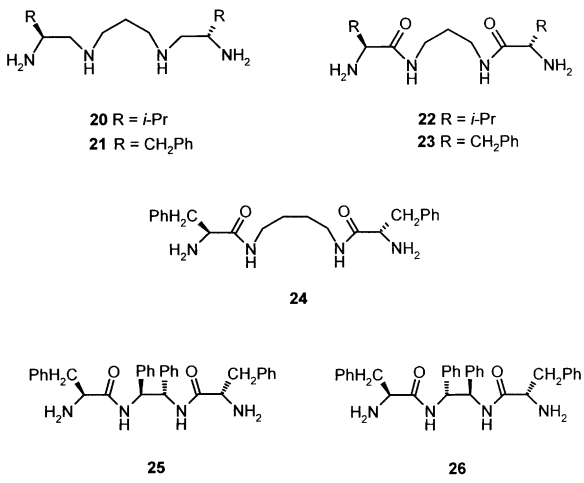
Interestingly, with aryl-substituted allyl systems, Pd-catalyzed reactions normally provide products from attack at the less substituted terminus. On the other hand, Mo and W favor attack at the more substituted terminus.[32a] (Scheme 11).

Moberg et al. reported[32c] the use of microwave irradiation for the asymmetric allylic alkylation of cinnamate **27** with sodium dimethyl malonate (Scheme 12) in the presence of the inexpensive $Mo(CO)_6$ as pre-catalyst and ligand **29a** (Scheme 13). After 5 min at 250 W an 87% yield of **28a** (98% ee *R*) and **28b** in a 19 : 1 ratio was obtained.

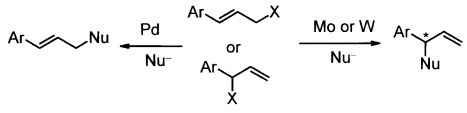
In order to study the influence of the steric and electronic properties of the ligand on the catalytic behavior of the Mo complexes, Moberg's group prepared[32d] the ligands **29b – e**.



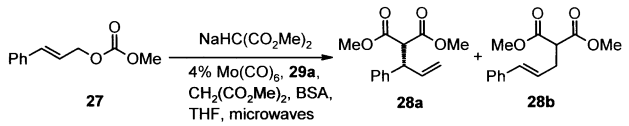
Scheme 9.



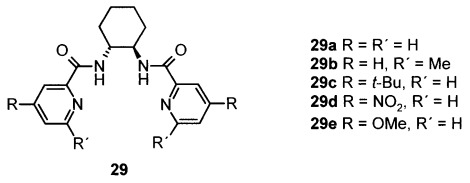
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

Replacing **29a** with **29b**, carrying a methyl group in the 6-position of the pyridine ring, lower catalytic activity (79% ee for **28a**) and only 30% yield after 5 min at 200 W were observed. On the other hand, **29c**, with a *tert*-butyl group in the 4-position, showed the same enantiomeric excess as **29a**, but the yield was still low (46%).

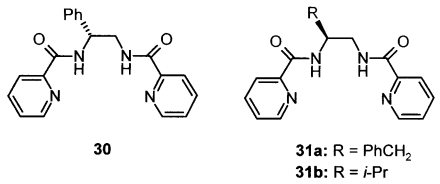
By introduction of a nitro group in the 4-position (**29d**), low reactivity (7% after 5 min and 32% after 8 min) but high enantioselectivity (97% ee *R*) was achieved. In this case a prolonged heating did not result in a considerable increased conversion. The best results were achieved with the ligand **29e**, which gave high enantioselectivity ($>99\%$ ee *R*) and regioselectivity (41:1), and a very good yield ($>95\%$).

The higher regioselectivity exhibited by ligand **29e** is in accordance with the statement by Trost[37] that σ-donating ligands enhance the attack at the more substituted position.

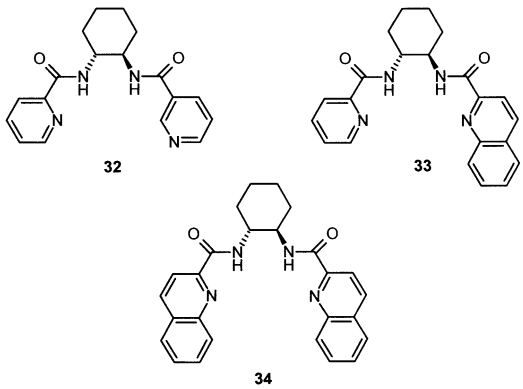
The mechanism of Mo-catalyzed allylations has not yet been clearly established. Nevertheless, from these results, it is concluded that steric hindrance close to the coordination site is indeed deleterious for the selectivity, as well as for the reactivity of the catalytic process.

The importance of one or two chiral centers and of the C_2-symmetry of the most used ligands in asymmetric allylic alkylation was investigated by Kočovský and co-workers.[38] They assumed that one chiral center might be sufficient to determine the sense of wrapping of the metal by the ligand, thereby creating a similar chiral environment. For this, they designed, among others, three new ligands (**30, 31a, b**) without *trans*-1,2-cyclohexanediamine as the chiral scaffold (Scheme 14).

When the asymmetric reaction, illustrated in Scheme 12, was catalyzed with **30**, yields around 70%, as well as fair regio- and enantioselectivity in favor of the branched product **28a** ($>8:1$, $\sim 90\%$ ee *R*) were achieved. This is not limited to only one substrate. By changing the cinammyl carbonates, similar results were attained. This observation confirms the hypothesis that



Scheme 14.



Scheme 15.

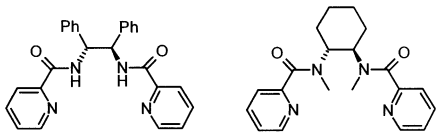
one chiral center in the scaffold is sufficient to induce high levels of enantioselectivity.

To enhance the validity of this argument, the ligands **31a, b** were synthesized. The benzyl substituted ligand **31a** exhibited lower enantioselectivity (74–89%) than **30**, but the isopropyl ligand **31b** gave much more improved results that are in the same range as those reported by Trost (98% ee, 32:1 regioselectivity).

The binding mode of these tetraaza ligands to molybdenum during the catalytic cycle is not clearly understood. Regarding to this, Trost and co-workers[39] investigated a series of ligands[40] (Scheme 15) with few, but important, modifications of their structure. The effectiveness of these new ligands was compared with that of **29a** as a standard ligand.

In initial studies, one of the picolinamide units on **29a** was replaced with a nicotinamide group (compound **32**). The enantio- and regioselectivity[41] (99% ee *R*, 46:1) were slightly better than with the standard ligand **29a** (97% ee *R*, 35:1) but the yield of the reaction was lower (93% *vs.* 95% yield). In order to discriminate the binding capacity of the nitrogen atom of the nicotinamide group, a simple benzamide ligand (tridentate ligand) was tested. The reaction gave the same results as the reaction with **32**. Removal of both pyridine nitrogen atoms (bidentate ligand) led to a very poor ligand in terms of rate and selectivity (35% yield, 24% ee). Reviewing these facts, Trost came to the conclusion that at least one picolinamide unit must be available to participate in the binding with Mo.

The steric factors also play a role in the effectiveness of a ligand. When a picolinamide unit of **29a** was



Scheme 16.

changed by one (compound **33**) or two (compound **34**) quinoline analogues, much lower reaction rates were observed. Ligand **33** was acting highly enantioselective (98% ee, *R*), while with **34** only traces of the products were detected.

Another ligand **35** (Scheme 16) with stilbenediamine as the chiral backbone showed a similar behavior (95% yield, 99% ee *R*) as the model ligand **29a**, but a decrease in the branched/linear ratio (19:1) was noted.

The importance of the secondary amide was investigated by using ligand **36** (Scheme 16). This catalyst was 200-fold less active than **29a** and gave poor enantioselectivities. This observation confirmed the suspicion that the secondary amide ligands were deprotonated under the basic conditions of the AAA reaction. This was supported by deprotonating the ligand with trityllithium and then forming the active catalyst.

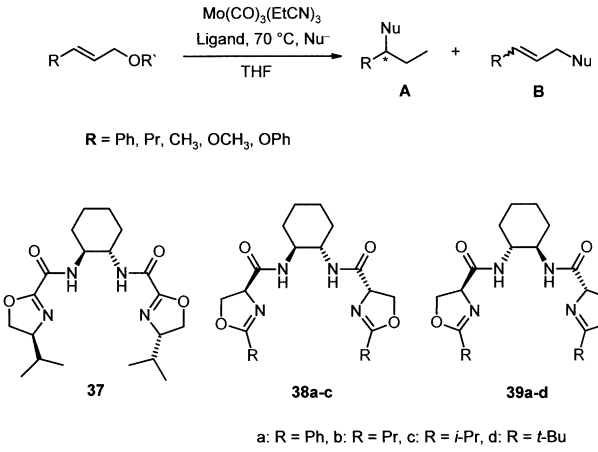
In summary, these studies provide the first picture of the type of coordination existing between ligands and metal for the AAA. Contrary to the initial hypothesis of the authors, a bidentate coordination of the two pyridine nitrogen atoms is clearly not involved. The efficiency of the tridentate ligands indicates that only one pyridyl nitrogen atom of ligand **29a** participates in the coordination. Furthermore, either the dianion or the monoanion of the two secondary amides appears to be involved.

After the success with Trost's ligand in the AAA, other ligands containing its modular system were synthesized. Pfaltz[42,43] applied the already active bisoxazolines **37 – 39** to this Mo-catalyzed transformation with various substrates (Scheme 17).

The bisoxazolines **37** and **38b** induced similar levels of enantioselectivity (~98% ee) than the bispyridine ligand **29a** for the 3-phenylallyl derivative, however the branched/linear ratios were lower (14:1 *vs.* 49:1) and the reactions slower (24 h *vs.* 3 h).

In the case of the methyl substrate, the ligands **39b, c** gave the same regioselectivities (8:1 ratio of A:B) as **29a** with almost identical enantioselectivity (~98% ee). The diastereomeric ligands **38b, c** and **39b, c** induced the opposite configuration of the product, implying that the enantioselectivity is largely controlled by the *trans*-cyclohexanediamine unit.

The systematic variation of the substituents in the oxazoline ring permits the optimization of the enantioselectivity as well as the regioselectivity. While the *n*-propyl-substituted derivatives **38b** and **39b** produced



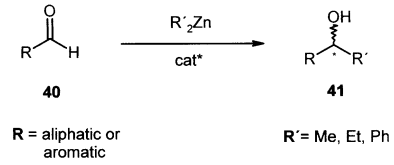
Scheme 17.

comparable results to the Trost's bispyridine ligand **29a**, only the racemic product with a low branched/linear ratio was obtained with the *tert*-butyl-substituted ligand **39d**.

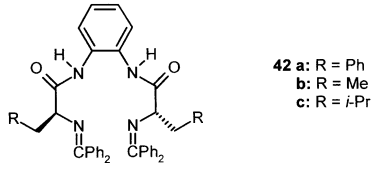
8 Dialkylzinc Addition

The first tetradentate ligand used in the addition of organozinc reagents to aldehydes (Scheme 18) was reported by Dangel and Polt.[44] This ligand was screened at the beginning for epoxidation of olefins with unsuccessful results on the catalytic activity (only 4% ee for *trans*-β-methylstyrene epoxide).[45]

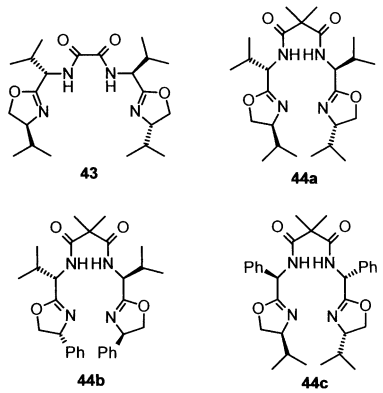
It was demonstrated by NMR studies that this ligand **42a** (Scheme 19) formed a tetradentate complex with zinc. When 3 – 5 mol % of this complex were used for the asymmetric addition of alkylzinc (dimethyl- or diethylzinc) to aliphatic or aromatic aldehydes (benzaldehyde, 2-furaldehyde, 3-phenylpropanal and nonanal), yields of up to 80% and enantioselectivities between 86 and 96% ee were achieved.



Scheme 18.



Scheme 19.



Scheme 20.

For further studies, another two ligands (**44b, c**) were synthesized with different steric bulk of amino acid residues (L-Ala and L-Val, respectively).

As expected, the decreased bulk of the amino acid residue (L-Ala) on the catalyst caused a decrease in selectivity for both aromatic and aliphatic aldehydes. With increased steric demand (L-Val), enhanced stereoselection was observed with benzaldehyde, but the opposite behavior was observed for aliphatic aldehydes.

Novel C_2-symmetric tetradentate bis-oxazoline ligands (Scheme 20) for the titanium-catalyzed diethylzinc addition to aldehydes were reported by Adolfsson and Pastor.[46]

When ligand **43** was used with a catalytic amount of titanium isopropoxide, a high yield of 1-phenyl-1-propanol (90%) was achieved, but very poor enantioselectivity (only 4% of the *S*-isomer). Using the malonic acid-derived ligand **44a**, a good conversion to the product (87%) and increased enantiomeric excess (78% ee *S*) were detected. Similar behavior was observed by test of the ligands **44b** and **44c**. Surprisingly, although the absolute configuration of the chiral centers in the oxazoline parts of the ligand **44b** with respect to **44a** were interconverted, both gave the *S*- enantiomer.

Ligands **44d – f** (Scheme 21) were synthesized in order to study the influence of the stereochemistry of the oxazoline rings and/or at the stereocenters next to the amide functions in the catalytic reaction.

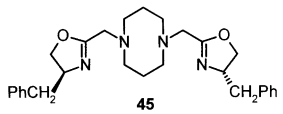
The *R*-enantiomer of the alcohol was obtained in good yield and enantioselectivity (93%, 73% ee) when the ligand **44d** (diastereomer of **44a**) was tested. With the catalyst **44e**, with no chirality on the oxazoline rings, very good results (83% yield, 89% ee *S*) were obtained. In contrast, for **44f** a huge drop in conversion and enantioselectivity (18%, 25% ee *S*) was observed. From these results the following conclusions have been derived. A stereocenter close to the amide functions is necessary for a good conversion, and even more for a high enantioselectivity. In addition, their stereochemistry determines the configuration of the resulting product. The stereochemistry of the substituents in the oxazoline ring does not play a role in the progress of the asymmetric catalysis, at least not in the specifically reported cases.

Oxazoline moieties have shown to be a very useful backbone for the synthesis of chiral ligands for asymmetric catalysis. For example, Rh complexes of pyridinyloxazoline have been found to catalyze the hydrosilylation of ketones in high yields with up to 95% ee.[47] Combining this efficient backbone with 1,5-diazacyclooctane, a new chiral tetradentate ligand **45** (Scheme 22) was reported by Shang and co-workers.[48] A moderate enantioselectivity (42% ee) was observed using 5 mol % of the ligand in the addition of diethylzinc to benzaldehyde.

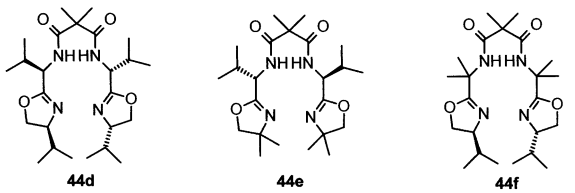
Recently we have reported the catalytic activity of two tetradentate ligands (**46**[49] and **47**, Scheme 23) in the addition of diethylzinc to benzaldehyde. By use of 5 mol % of the ligands only low yields of the secondary alcohol and very small enantioselectivities (3% ee) were obtained.[50]

Their catalytic activities were formally tested in the Cu(I) cyclopropanation of styrene and in the Mn(III) epoxidation of this olefin. For the first reaction, a significant diastereoselectivity was obtained using ligand **46**, but the enantioselectivity was poor with both ligands. On the other hand, a good yield on epoxide (60%) but only enantioselectivity of 12% ee were obtained with ligand **47**.

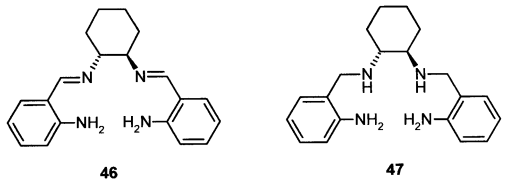
Several sulfonamides **48a – f** (Scheme 24) derived from ligand **46** were synthesized and screened as catalyst for the asymmetric alkylation with diethylzinc.[51] Lemaire and co-workers published recently the synthesis of



Scheme 22.



Scheme 21.



Scheme 23.

two of these sulfonamide ligands (**48a** and **48 g**) using a different pathway, and their coordination ability with various metal ions.[52]

When benzaldehyde was used as substrate quantitative yields of 1-phenylpropanol and good asymmetric induction (70 and 74% ee, respectively) were obtained with ligands **48a** and **48b**. A lower yield, but still good enantioselectivity was obtained with the *p*-methoxybenzenesulfonamide-substituted ligand **48c**. Ligands **48d – f** gave less satisfying results.

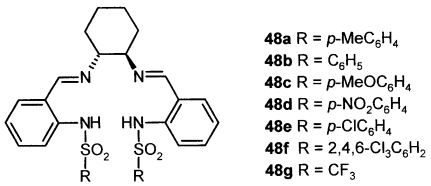
Encouraged by these results the asymmetric alkylation was extended to other aldehydes: *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde and furfural. The yields obtained with both ligands (**48a** and **48b**) and for all aldehydes used were higher at room temperature than at 0 °C, but they were much lower than those obtained with benzaldehyde (see ref.[51]). The presence of an electron-donor substituent (OMe) on the *para* position of the aldehyde contributes to an increase in the yield of the secondary alcohol, while the electron-acceptor substituent (Cl) in the same position causes the opposite effect.

When the temperature of the asymmetric alkylation of benzaldehyde using the above-mentioned ligands was increased to 50 °C, quantitative yields of 1-phenylpropanol were achieved after five hours and only a slight decrease of the enantioselectivity was observed.

With the aim to increase the enantioselectivity of the catalytic reaction, Ti(O-*i*-Pr)$_4$ was added. In this case the yields as well as enantioselectivities of 1-phenylpropanol dropped off drastically under these conditions.

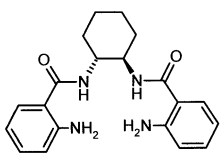
A particularly short synthesis for **49** and **50a** was published by Somanathan and co-workers.[53] We synthesized the analogues **50b – d** and tested the activity[54] of **49** and **50a, b** as catalysts for the asymmetric addition of diethylzinc to benzaldehyde.

When 5 mol % of the diamide **49**, as well as its derivatives **50a, b** were used, only yields of about 50%

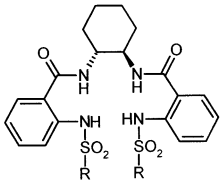


48a R = *p*-MeC$_6$H$_4$
48b R = C$_6$H$_5$
48c R = *p*-MeOC$_6$H$_4$
48d R = *p*-NO$_2$C$_6$H$_4$
48e R = *p*-ClC$_6$H$_4$
48f R = 2,4,6-Cl$_3$C$_6$H$_2$
48g R = CF$_3$

Scheme 24.



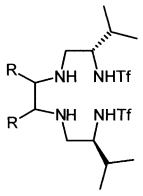
49



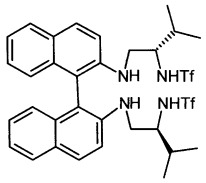
50

50a R = CH$_3$
50b R = *p*-MeC$_6$H$_4$
50c R = *p*-NO$_2$C$_6$H$_4$
50d R = *p*-ClC$_6$H$_4$

Scheme 25.



51a R = Ph (*R*,*R*)
51b R = Ph (*S*,*S*)
51c R = -(CH$_2$)$_4$- (*R*,*R*)
51d R = -(CH$_2$)$_4$- (*S*,*S*)



52a (*R*)-Binaphthyl
52b (*S*)-Binaphthyl

Scheme 26.

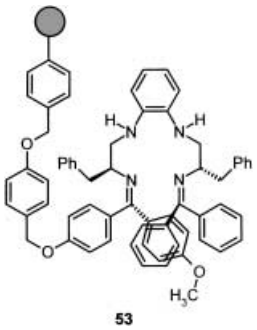
have been achieved. The enantioselectivities obtained with the free diamide-diamine ligand **49** and its dimesyl derivative **50a** are low (25 and 28%, respectively), while with the bulkier ditosyl derivative **50b** only a very slight asymmetric induction could be measured.[55]

By treatment of (*S*)-2-isopropyl-*N*-(trifluoromethylsulfonyl)aziridine with different chiral diamines, Moberg has obtained tetradentate ligands with C_2-symmetry (**51a – d**, Scheme 26) and with axial chirality (**52a, b**, Scheme 26).[56] Their catalytic activity was investigated in the addition of diethylzinc to benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$. Use of ligand **51a** resulted in quite high enantioselectivity at the beginning of the reaction (80% ee at 29% conversion), but the enantiomeric excess decreased as the reaction proceeded. The diastereomer **51b** gave a secondary alcohol with lower enantioselectivity (12% ee) but the same absolute configuration. Derivatives **51c, d** afforded racemic products and the binaphthyl ligands showed only a slight selectivity (9 and 5% ee, respectively). In these experiments it was demonstrated that the absolute configuration of the product is determined by the configuration of the part in the ligand originating from the aziridine.

8.1 Immobilization of Catalyst for Diethylzinc Addition

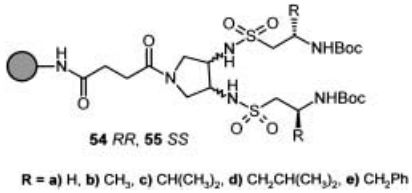
The catalyst **42a** was transformed into a heterogeneous compound **53**[44] (Scheme 27) by using the Wang[57] and the Merrifield resins.[58] The Et$_2$Zn-activated resin was then used multiple times in the asymmetric alkylation reaction without a decrease in either the yields or the enantioselectivities. In comparison with the soluble catalyst, only slight diminutions in the yields were noticed but the enantioselectivities were considerably lower.

Combinatorial chemistry is extremely attractive as a method for finding and optimizing ligands for catalysis,[59] because it offers the possibilities to generate and screen a number of compounds as well as optimize the conditions for studying these compounds (e.g., reaction conditions) in an iterative manner.



53

Scheme 27.



54 *RR*, 55 *SS*

R = a) H, b) CH_3, c) $CH(CH_3)_2$, d) $CH_2CH(CH_3)_2$, e) CH_2Ph

Scheme 28.

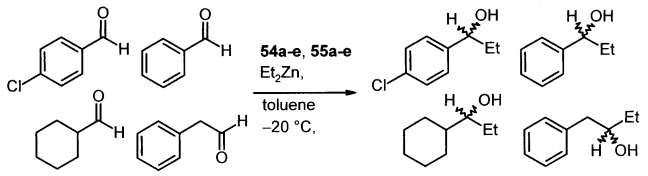
Although screening an immobilized solid phase catalyst ligand clearly has disadvantages compared to screening in solution, such as the heterogeneous nature of a solid phase bead causing unfavorable kinetics and possible interactions of the reactants with the solid phase, the very same heterogeneous nature of the bead has the advantages that catalyst and product can be easily separated and the catalyst can be recovered.

Liskamp and co-workers[60] reported the synthesis of a library of peptidosulfonamide tweezers **54a – e** and **55a – e** (Scheme 28) on the solid phase, the screening of the ligands and the resynthesis in solution of the best ligand in order to compare the catalytic activity.

Instead of screening each resin-bound peptidosulfonamide tweezer with one substrate, the authors decided to use a mixture of aldehydes for the titanium-mediated asymmetric addition of diethylzinc (Scheme 29).

It was observed that high conversion was paralleled by high enantioselectivity. The two aromatic aldehydes showed the highest conversions and enantioselectivities.

The influence of the configuration of the chiral centers in pyrrolidine was not very high, however, with the *RR*-pyrrolidine in general the highest enantioselectivities and conversions were obtained. But this chirality is not sufficient for a high enantioselectivity since taurine-containing pyrrolidine tweezers **54a** and **55a** did not show an appreciable enantioselectivity. The side chain could also have an influence on the enantioselectivity. According to the results obtained with the phenylalanine-derived peptidosulfonamide **54e** and **55e** (no increase in the ee), it is apparently clear that the size of this chain is not the only factor involved. Both parts are important for the steric progress of the reaction.



Scheme 29.

The best results were observed with the aromatic substrates using the leucine-derived peptidosulfonamide tweezers **54d** and **55d**.

The homogeneous analogue of **54d** was synthesized and tested in the catalytic transformation. With this tweezer the ee values increased notably (56 – 66%) as compared to the resin-bound ligand (32%) confirming the earlier assumption.

Gennari and collaborators[60] have developed a new family of chiral ligands **58** (Scheme 30) based on a modular building block strategy and on the use of disulfonamide as a metal chelating unit.

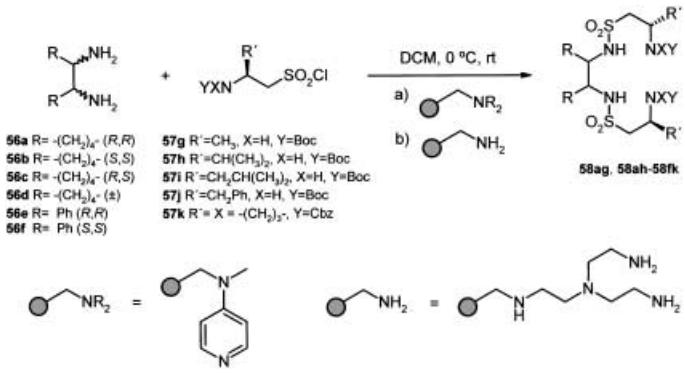
For the diamine part of the library, they used two vicinal scaffolds: 1,2-cyclohexanediamine (**56a – d**) and 1,2-diphenylethylenediamine (**56e – f**), for which effective use in the fields of asymmetric synthesis and molecular recognition is well documented.

The sulfonyl chloride derived from L-alanine **57 g**, L-valine **57 h**, L-leucine **57i**, L-phenylalanine **57j** and L-proline **57k** were used.

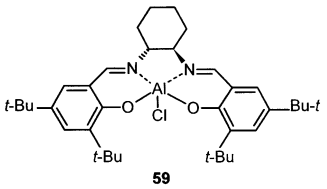
To avoid the problems associated with work-up and purification of the resulting products, solid phase extraction (SPE) techniques[62] were applied to the synthesis.

The obtained ligands were tested several times by the combinatorial approach used in the addition of diethylzinc to aldehydes. A number of interesting and somewhat unexpected results were revealed after screening:

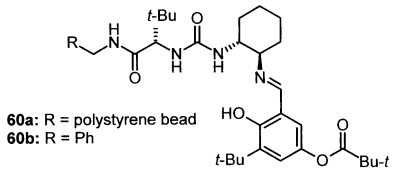
(1) The best ligand for this reaction is **58bj** (i.e., 1*S*,2*S*-cyclohexanediamine **56b** as diamine scaffold and the sulfonyl chloride **57j** derived from L-phenylalanine).[63]



Scheme 30.



Scheme 31.



Scheme 32.

(2) The influence of the different β-aminosulfonyl side chains in controlling the enantioselectivity is as follows: R'=CH_2Ph (**57j**) > CH_3 (**57 g**) > *i*-Bu (**57i**) > *i*-Pr (**57 h**) >> $(CH_2)_3$ (**57k**).
(3) The influence of the different scaffolds in controlling the enantioselectivity is as follows: *trans*-(1*S*,2*S*)-cyclohexanediamine (**56b**) > *cis*-cyclohexanediamine (**56c**) ~ (±)-racemic-1,2-cyclohexanediamine (**56d**) > (1*R*,2*R*)-diphenylethylenediamine (**56e**) ~ (1*S*,2*S*)-diphenylethylenediamine (**56f**) > *trans*-(1*R*,2*R*)-cyclohexanediamine (**56a**).
(4) With the *cis* and the racemic scaffolds, moderate enantiomeric ratios were obtained in favor of the (*R*)-alcohol (~60% ee).
(5) With the (*R*,*R*)- diphenylethylenediamine scaffold, one single reasonable high enantiomeric ratio was obtained (ligand **58ej**, 78% ee for the *R*-alcohol).

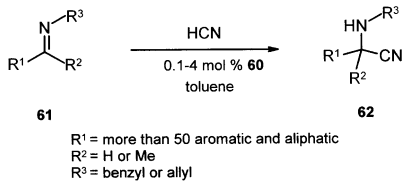
9 Asymmetric Strecker Reaction

The catalytic asymmetric Strecker-type reaction offers one of the most direct and viable methods for the asymmetric synthesis of α-amino acid derivatives.[64]

After the success accumulated by Sigman and Jacobsen[65] with the first example of a metal-catalyzed enantioselective Strecker-type reaction, using a chiral Al(III)-salen complex **59** (Scheme 31), more efforts were made by this group to design new and effective catalysts for this transformation, with the help of combinatorial methods.

In this context, the non-metal Schiff base catalysts **60a, b** (Scheme 32) were reported[66,67] as remarkably general catalysts for the hydrocyanation of aldiimines and ketoimines,[68] producing Strecker adducts in >90% ee for most substrates examined (Scheme 33).

The preparation of the catalyst was very easy, either in solution or on the solid phase. The use of the resin-bound catalyst **60a** allows Strecker product purification



Scheme 33.

by simple filtration and solvent removal, and the catalyst can be reused indefinitely, without loss of either activity or enantioselectivity.

Preliminary kinetic experiments indicate that the reaction follows Michaelis-Menten kinetics consistent with reversible binding of imine followed by rate-limiting addition of HCN. Consistent with the notion that these catalysts are enzyme-like, all structural components of **60** have been shown to be essential for both reactivity and enantioselectivity and thus appear to function cooperatively.

10 Conclusion

The presented examples from the recent literature illustrate the continuously growing importance and application of nitrogen-containing ligands in asymmetric catalysis. By increasing the number of coordination sites from two, as in many of the classical C_2-symmetric ligands, to tetradentate ligands, new reactions and/or better selectivities were observed in some cases. However, other examples, such as the Mo-catalyzed allylation, showed that only three out of four nitrogen coordination sites are necessary for catalyzing the reaction. So it is still difficult to derive general rules for the perfect ligand from the available data, but easy to predict that more chiral ligands with more that two nitrogen atoms will be used successfully in homogeneous and heterogeneous catalysis in the future.

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