Synthesis, structure and catalytic activity of chiral nitrogen-containing ligands.

Dissertation
zur Erlangung des Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat.)
der Naturwissenschaftlichen Fakultät IV
– Chemie und Pharmazie –
der Universität Regensburg

vorgelegt von

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2002

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eingereicht am: 19.12.2002
Prüfung am: 07.02.2003

Teilergebnisse aus dieser Arbeit wurden mit Genehmigung der Naturwissenschaftlichen Fakultät, vertreten durch den Betreuer der Arbeit, in folgenden Beiträgen vorab veröffentlicht:

Publikationen:

- Hechavarría Fonseca M., Eibler E., Zabel M., König B., *Inorg. Chim. Acta* **2002**, *in press*.

Tagungsbeiträge:

- Hechavarría Fonseca M., König B., 9th Meeting on Stereochemistry, 15.06-18.06-2001, Prague, Czech Republic: *"Synthesis and characterisation of a new chiral ligand and its transition metal complex for application in chiral recognition and asymmetric catalysis"*.
- Hechavarría Fonseca M., König B., 13th International Symposium on Homogeneous Catalysis, 03.09-07.09.2002, Tarragona, Spain: *"Synthesis of new Schiff bases as ligands for asymmetric catalysis"*.
- Hechavarría Fonseca M., König B., ORCHEM 2002, 12.09-14.09.2002, Bad Nauheim, Germany: *„Neue chirale Tetraazaliganden für die asymmetrische Katalyse"*.
- Hechavarría Fonseca M., König B., Summer School Medicinal Chemistry, 15.09-18.09.2002, Regensburg, Germany: *"Synthesis of new Schiff bases as ligands for asymmetric catalysis"*.

Die vorliegende Arbeit wurde von April 1999 bis September 1999 am Institut für Organische Chemie der Technischen Universität „Carolo-Wilhelmina“ zu Braunschweig und von Oktober 1999 bis August 2002 am Institut für Organische Chemie der Universität Regensburg unter der Leitung von Prof. Dr. Burkhard König angefertig.

Meinem Lehrer, Herrn Prof. Dr. B. König, danke ich herzlich für die Überlassung des interessanten Themas, die Möglichkeit zur Durchführung dieser Arbeit, die anregenden fachlichen Diskussionen und seine stetige Unterstützung.

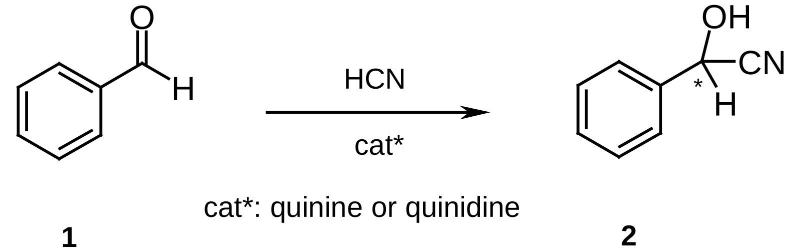
to my family

Content

1 Introduction

It is difficult to locate in the literature the initial reports on enantioselective reactions. After *Pasteur's* discoveries in 1858, many people tried to prepare optically active compounds from inactive precursors, though without doing much distinction between racemic or prochiral starting materials.[1]

In a pioneering investigation in 1908, *Bredig* prepared mandelonitrile **1** from benzaldehyde and HCN in the presence of an alkaloid (quinine or quinidine) as a catalyst[2] (*Scheme 1*).



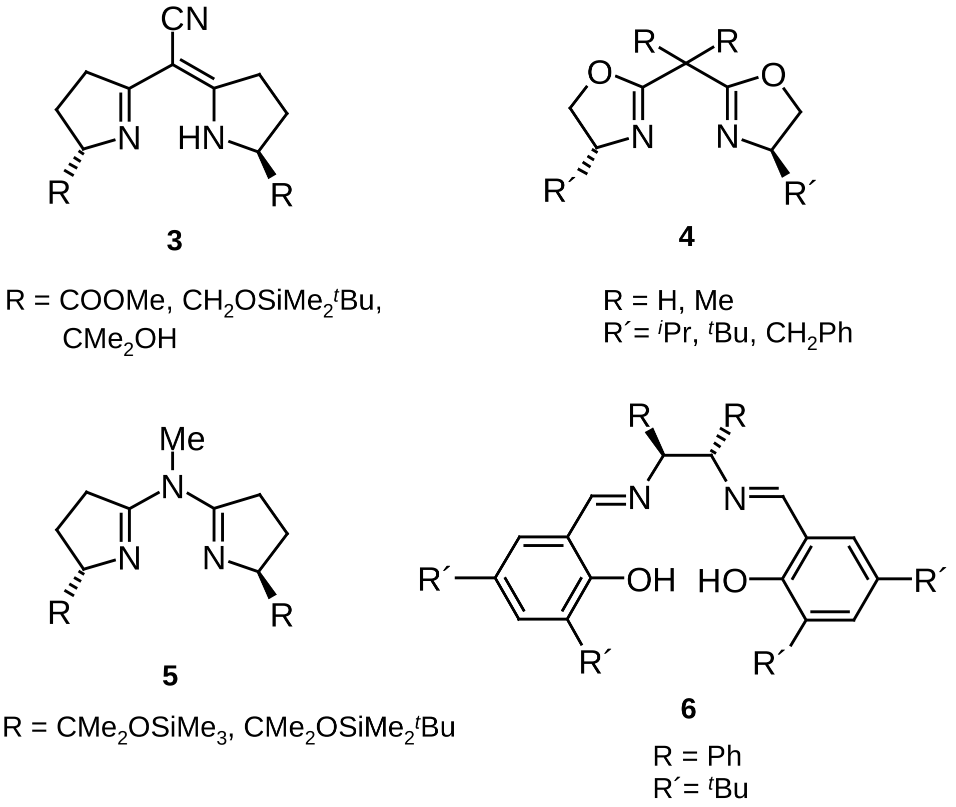
Scheme 1. Early example of asymmetric catalysis.

The enantioselectivities were less than 10 %, but this investigation itself was very important, because it represented the first example of the use of nitrogen-containing ligands on catalysis.

The decade 1980-1990 was a very successful period for asymmetric catalysis. *Pfaltz et al.* developed enantioselective reduction of *α*, *β*-unsaturated esters by sodium borohydride in ethanol in the presence of semicorrin **3**-$CoCl_2$ catalyst (*Scheme 2*) with enantioselectivities reaching 96 % *ee*.[3]

Using OsO_4 in catalytic amounts in the presence of a chiral amine in an organic solvent and water, and with a tertiary amine *N*-oxide as a secondary oxidant, *Sharpless et al.*[4] achieved the asymmetric dihydroxylation of isolated carbon-carbon double bonds. The enantioselectivities are highest with *trans*-stilbene (85 % *ee*) or *trans*-1-phenylpropene (65 % *ee*), and lowest for monosubstituted alkenes, such as styrene (56 % *ee*).

Cyclopropanation of alkenes[5, 6a-b, 7] was significantly improved by the use of a new generation of chiral copper complexes of ligands **3**-**5** (*Scheme 2*)[8]. *Doyle et al.*[9] also reported this asymmetric reaction with chiral complexes of Rh(II), achieving enantioselectivities as high as 89-90 % in many cases.



3

R = COOMe, $CH_2OSiMe_2{}^tBu$, CMe_2OH

4

R = H, Me
R´= ^iPr, ^tBu, CH_2Ph

5

R = CMe_2OSiMe_3, $CMe_2OSiMe_2{}^tBu$

6

R = Ph
R´= ^tBu

Scheme 2. Some nitrogen containing ligands prepared during 1980-1990.

In 1990, chiral salen-Mn complexes of **6** (*Scheme 2*) were successfully used by *Jacobsen*[10] and *Katsuki*[11] for catalytic epoxidation of alkenes, achieving enantioselectivities of 90 %. The structure of the catalysts, as well as the synthetic methods, were continually developed, especially by *Jacobsen* and co-workers, who used cheap oxidants such as sodium hypochlorite.

In 1994 *Togni* and *Venanzi*[12] reported very promising results with nitrogen donor ligands in asymmetric catalysis. Six years later, *Fache et al.*[13] 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, but we shall concentrate our attention on the progress accumulated since then in catalytic asymmetric transformations using tetra-aza 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[14] 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 epimerise 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 specifical physicochemical properties. Particularly, the interactions with the transition metals may be widely varied by preparing X-type ligands (amides, sulphonamides), 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,[15, 16] 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.[17]

1.1 Reduction of C=C Bonds

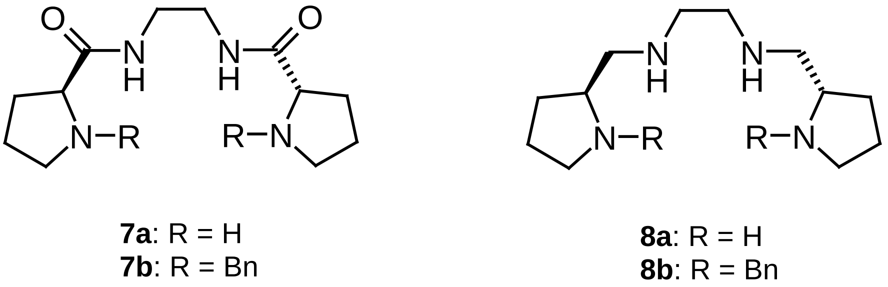
The reduction of double bonds with homogeneous catalysts has emerged in the past few decades as an indispensable tool in laboratory-scale synthesis, as well as in the manufacturing of fine chemicals.[18] Historically, this field has been dominated by heterogeneous catalysts, but the homogeneous ones offer identifiable advantages against 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 few last years many investigations 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*),[19] since the beginning of the 1990´s more and more articles dealing with nitrogen-containing ligands appeared in the literature, especially for hydride transfer reduction.

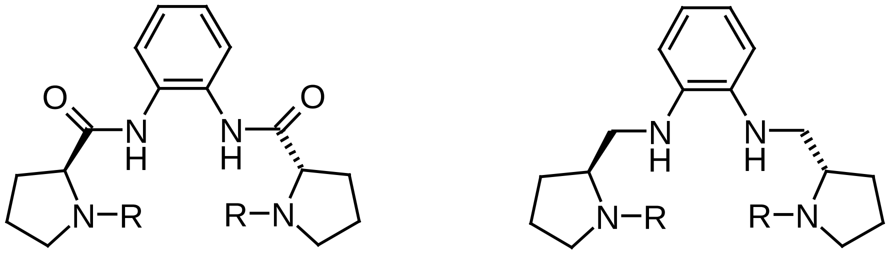
1.1.1 Homogeneous system

Starting from the readily available L-proline, *Iglesias et al.*[14] reported the preparation of the C_2-symmetric ligands **7** and **8** (*Scheme 3*), 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 **7** gave only poor enantioselectivities (4-5 % *ee*) but good chemical yields (~80 %), whereas with the tetramine ligands **8** chemical yields over 80 % and enantioselectivities of approximately 20 % *ee* were achieved. The reason for this behaviour 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.



Scheme 3. Ligands derived from L-proline.

One year later, *Iglesias´s* group[20] synthesised four new ligands (**9-10**) with rigidity in the backbone (*Scheme 4*) as an alternative to the more flexible family of ligands **7-8**.



9a: R = H
9b: R = Bn

10a: R = H
10b: R = Bn

Scheme 4. Analogues with rigidity in the backbone.

The catalytic activity of the Ir and Rh complexes of **9** and **10,** was also investigated on the hydrogenation of prochiral olefins. In all cases, the yields of the reactions were quantitative and the enantiomeric excesses fluctuated between 9-30 %.

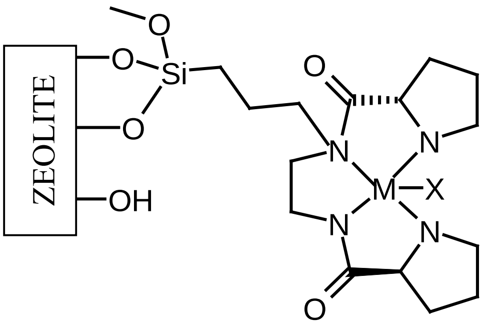
The Ir-complexes have shown higher rates (TOF) and enantioselectivities than the Rh-complexes. The change of substituents at the pyrrolidine nitrogen plays a significant role in the optical induction. It increases while moving from hydrogen (16 % *ee*) to benzyl group (30 % *ee*), indicating that an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

Cu and Mn complexes of **9** and **10** were also synthesised[21], 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 catalyse important processes in organic chemistry.

1.1.2 Heterogeneous system

Furthermore, *Iglesias et al*. also reported[22] the heterogenisation of the catalysts **7** and **8**. 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 5*).

The heterogenised complexes are still more stable than their homogeneous counterpart and they can be used several times without decreasing the 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.



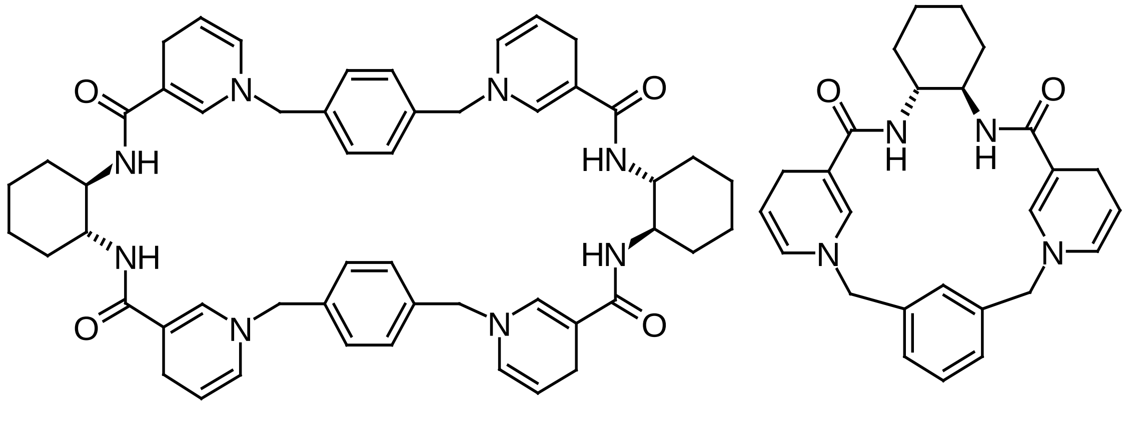
11

Scheme 5. Heterogenisation of ligand on inorganic support.

1.2 Reduction of C=O Bonds

Nicotinamide adenine dinucleotide (NAD^+/NADH) is a coenzyme which takes part in many biological oxidation-reduction reactions,[23] such as the conversion of ketons 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 a NADH model reported by *Ohno et al.*,[24] there has been a large number of different approaches to NADH mimicking.[25] 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[26] 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[27] are incorporated in model $\mathbf{1H_4}$ and two units in compound[28] $\mathbf{2H_2}$ (*Scheme 6*). Both compounds were used to test their ability to reduce prochiral carbonyl substrates stereoselectively.[29]



$\mathbf{1H_4}$ $\mathbf{2H_2}$

Scheme 6. Supramolecular designed NADH models.

When $\mathbf{1H_4}$ was used for the reduction of different ketons in the presence of Mg, low to moderate enantioselectivities were achieved. These results depend on the concentration of Mg, the reaction temperature and the used substrate. The best results (81 % *ee*) were obtained with methyl benzoylformate as substrate, 1.25 equivalents of Mg and at a temperature of –30 °C. A less selective process dominates at higher temperatures and Mg 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 when using $\mathbf{1H_4}$. It is also remarkable in this case, that the stereoselectivity was not affected by an increase in Mg 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.

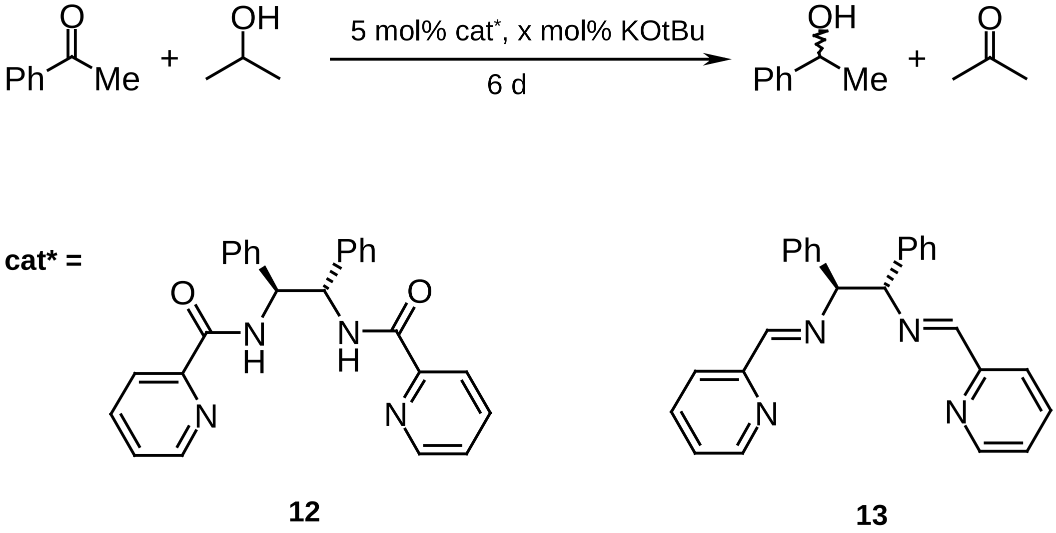
1.3 Hydrogen Transfer Reduction

For hydrogen transfer reactions the source of hydrogen is not molecular hydrogen. Instead, cyclohexene, cyclohexadiene, alcohols (methanol, benzylalcohol, 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 of the most appropriate hydrogen donor. Unlike asymmetric hydrogenation, where chiral phosphine ligands show an excellent performance, transfer hydrogenation uses frequently nitrogen-containing chiral ligands.

For a detailed review on hydrogen transfer reactions see *Gladiali et al.*[30, 31]

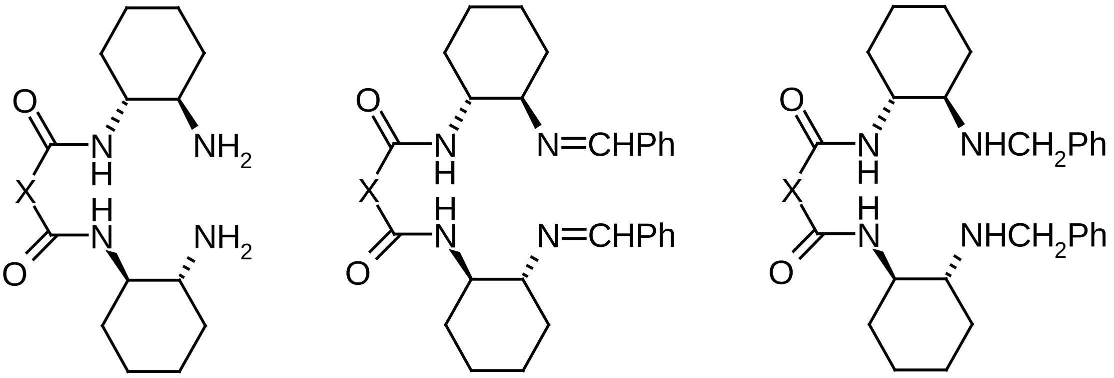
1.3.1 Homogeneous systems

Lemaire et al.[32] performed the hydrogen transfer reduction of acetophenone (*Scheme 7*) with two new tetra-aza ligands, the amide **12** and the imine **13**, complexed with Co, Ir and Rh. The results were disappointing despite which metal was used: only low conversion and 22 % of enantiomeric excess were obtained with the diamide **12**-Rh complex.



Scheme 7. Some catalysts for the hydride transfer reduction.

Other amide ligands (**14-16**, *Scheme 8*) complexed with Ru were synthesised for this catalytic transformation by *Marson* and *Schwarz*.[33] Acetophenone was used as substrate, joined with other *para*-substituted (F, Cl, OMe) phenyl-methyl ketons.



14 **15** **16**

a: X = -, **b:** X = $(CH_3)_2C$, **c:** X = CH_2CH_2

Scheme 8. Amide ligands.

The oxamide ligand **14a**, possessing terminal NH_2 groups, afforded enantioselectivities between 39-48 % and chemical yields around 30 %. Compared with NH_2 as a terminal group, a *N*-benzyl group (**16**) generally provided higher yields (64-71 %), but lower enantioselectivities (15 %). When the terminal group was an imine (**15**), very low or no enantiomeric excesses were detected.

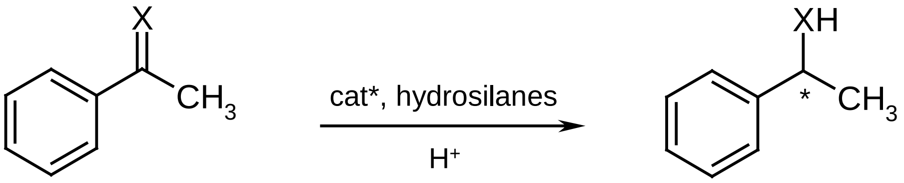
By analysis of the linker, an oxamide (**a**) afforded the best yields, but poor *ee*'s. In contrast, a malonamide spacer (**b**) gave lower yields but substantially higher *ee*'s and a succinimide linker (**c**) was unsuccessful.

In addition, a remarkable change in the configuration of the major enantiomer was observed for both active ligands (**14** and **16**) when the substituent in the ketone was changed.

1.4 Asymmetric Hydrosilylation

The asymmetric catalytic reduction of ketons 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 9*).[34]

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.

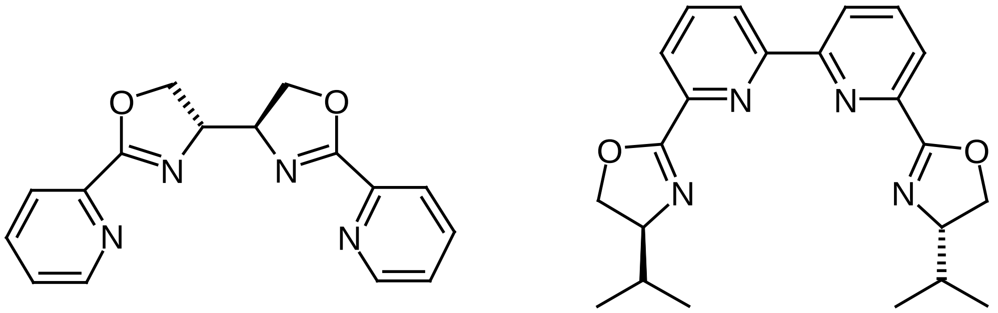


17 **18**

X = O, NR
(**R** = H or alkyl)

Scheme 9. Asymmetric hydrosilylation.

C$_2$-symmetric bioxazoles are capable of catalysing asymmetric reactions[35] (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 **19** was reported[36] as the first ligand with such structure change (*Scheme 10*). An encouraging result was obtained by testing **19** on the Rh-catalysed 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]



19 **20**

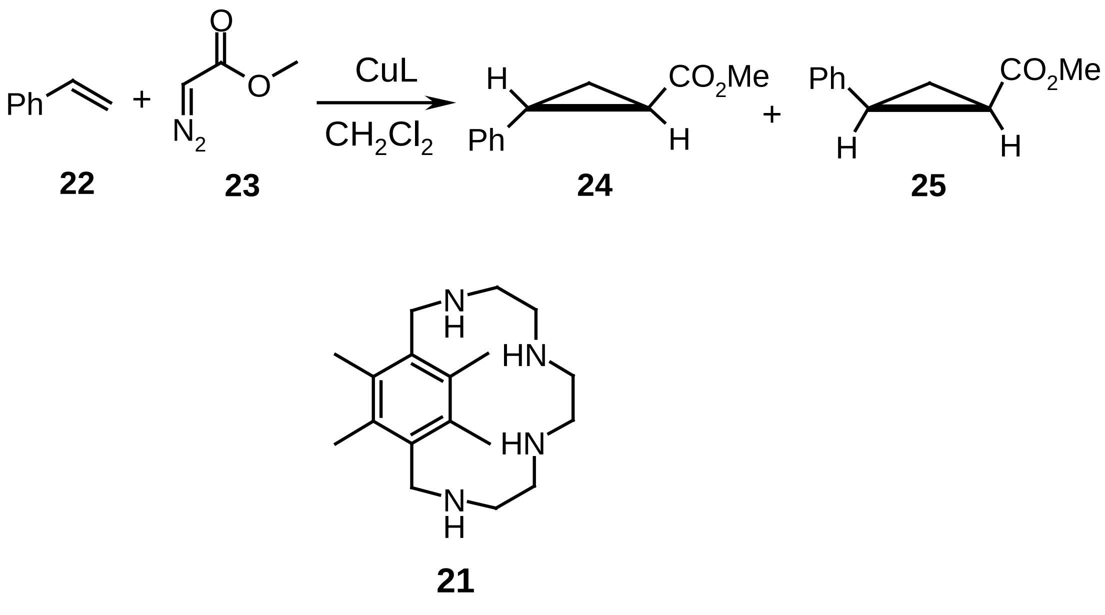
Scheme 10. C$_2$-symmetric ligands for hydrosilylation.

The tetradentate bis-(oxazolinyl)bipyridine (*bipymox*) **20** was synthesised in order to compare its catalytic properties with respect to bi- and tridentate oxazolinylpyridine ligands.[37] When **20** was complexed with $RhCl_3$, and particularly in the presence of 2 more equivalents of the ligand and $AgBF_4$, the asymmetric hydrosilylation of acetophenone was promoted with enantioselectivities up to 90 % for the (*S)*-isomer. This result is similar to that obtained with other ligands of this type.

1.5 Cyclopropanation

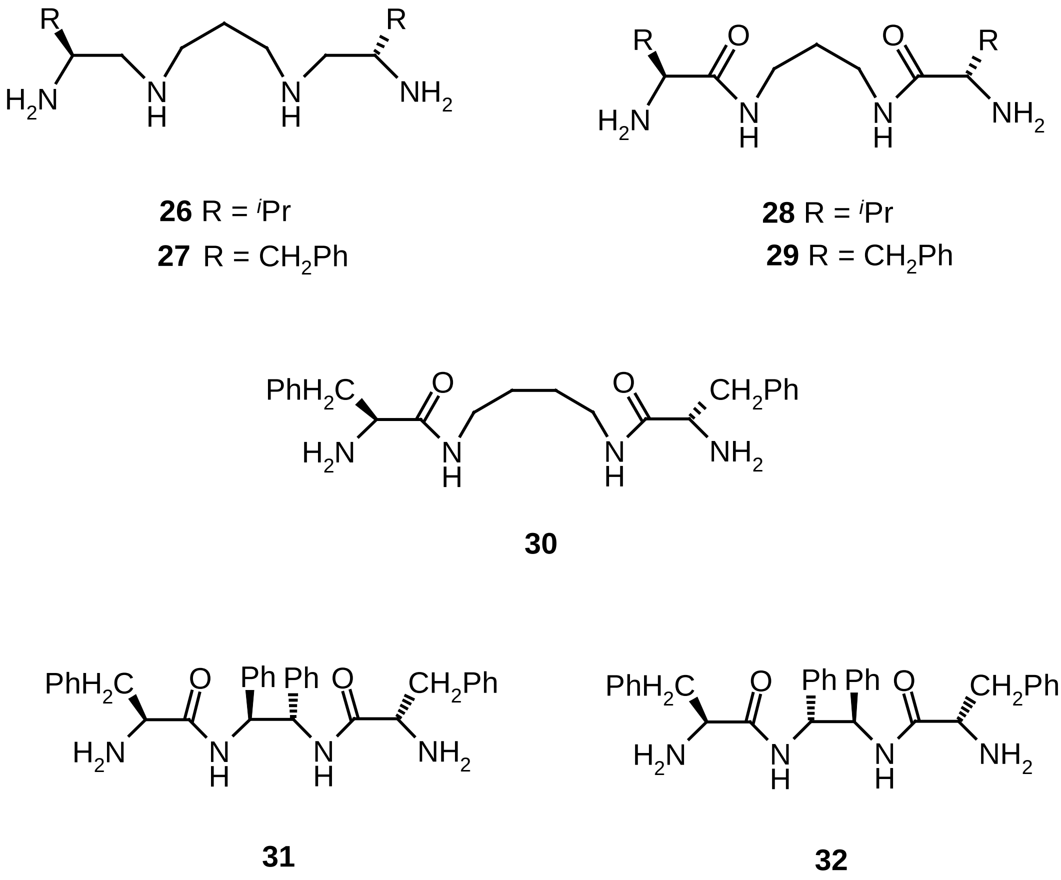
The benchmark cyclopropanation of styrene **22** with ethyl diazoacetate **23** is widely used to screen new catalysts. *Luis*, *Mayoral* and co-workers[38] tested the tetraaza-paracyclophane **21** in this reaction (*Scheme 11*), since ligands of this type have shown to stabilize Cu(I) with respect to its disproportionation into Cu(II) and Cu(0).[39]

Using this *in situ* prepared Cu(I)-complex only low yields and regioselectivities of the cyclopropane products **24** and **25** were obtained.



Scheme 11. Tetraaza-paracyclophane as catalyst for the cyclopropanation of styrene.

In order to study the ligand´s topology on the catalyst activity, several open-chain tetra-amines (**26-27**) and tetra-amides (**28-32**) (*Scheme 12*) were tested.



Scheme 12. Tetra-amine and tetra-amide ligands.

When the amines **26** and **27**, 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 **28** and **29**, 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 behaviour, but a clear reduction in the period of induction, was obtained with ligand **30**, which has a longer bridge.

The two diastereomeric ligands **31** and **32**, were also tested and showed very different actions. Whereas the reaction with **31** is very fast, use of **32** leads to an extremely long period of induction. In both cases no enantioselectivity was obtained.

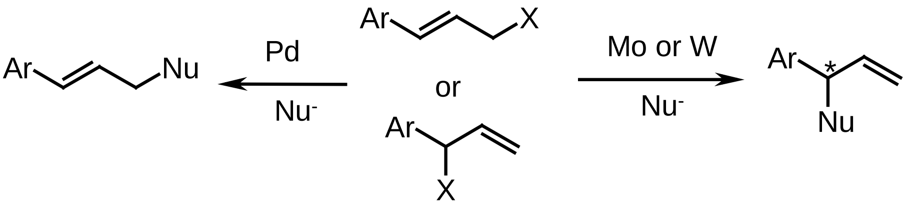
The ligands **28** and **29** were easily supported by anchoring on a functionalised polymer.[40] The resulting supported Cu(II) complexes show higher activities than their homogeneous counterparts, but a lowering of enantioselectivity.

1.6 Asymmetric Allylic Alkylation (AAA)

Since the first example[41] 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 the 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.[42]

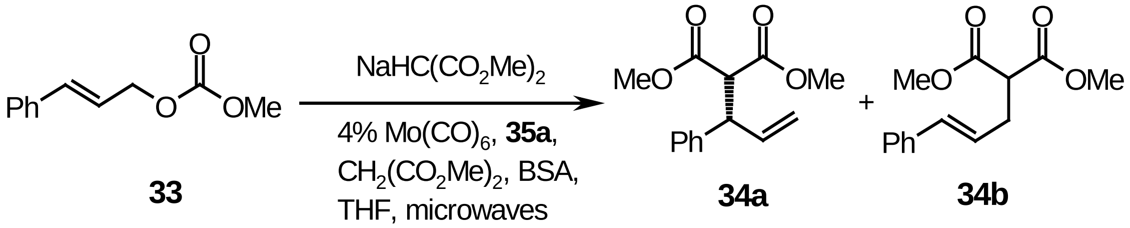
Although these transformations require rather sophisticated conditions, depending mainly on the nature of the catalytic species, they allow control of regio-, diastero-, and even enantioselectivity. Among the metals capable of effecting this reaction are Pd,[43] Mo,[44] W,[45] Ir,[46] Rh[47] and Ru.[48]

Interestingly, with aryl-substituted allyl systems, Pd-catalysed reactions normally provide products from attack at the less substituted terminus. On the other hand, Mo and W favour attack at the more substituted terminus.[30a] (*Scheme 13*).

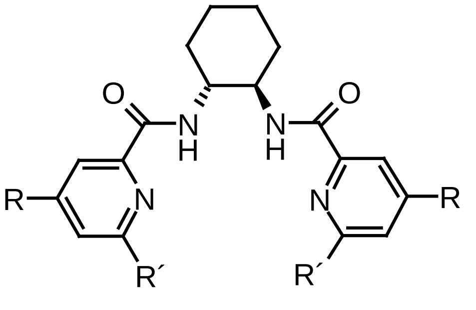


Scheme 13. Different paths for the AAA catalysed by Pd, Mo and W.

Moberg et al. reported[30c] the use of microwave irradiation for the asymmetric allylic alkylation of cinnamate **33** with dimethyl sodiomalonate (*Scheme 14*) in the presence of the inexpensive Mo(CO)$_6$ as precatalyst and ligand **35a** (*Scheme 15*). After 5 min at 250 W an 87 % yield of **34a** (98 % *ee R*) and **34b** in a 19:1 ratio was obtained.



Scheme 14. Asymmetric allylic alkylation of cinnamate.



35

35a R = R´= H

35b R = H, R´= Me

35c R = ^{t}Bu, R´= H

35d R = NO$_2$, R´= H

35e R = OMe, R´= H

Scheme 15. New substituted ligands for the AAA.

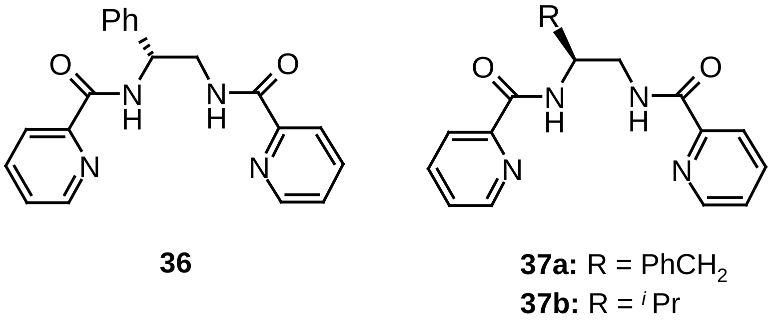
In order to study the influence of the steric and electronic properties of the ligand on the catalytic behaviour of the Mo-complexes, *Moberg´s* group prepared[30d] the ligands **35b-e**.

Replacing **35a** with **35b**, carrying a methyl group in 6-position of the pyridine ring, lower catalytic activity (79 % *ee* for **34a**) and only 30 % yield after 5 min at 200 W were observed. On the other hand, **35c** with a *tert*-butyl group in 4-position, showed the same enantiomeric excess as **35a**, but the yield was still low (46 %).

By introduction of a nitro group also in 4-position (**35d**), low reactivity (7 % after 5 min and 32 % after 8 min) but high enantioselectivity (97 % *ee R*) were achieved. In this case a prolonged heating did not result in a considerable increment of the conversion. The best results were achieved with the ligand **35e**, where along with a high enantioselectivity (>99 % *ee R*) and regioselectivity (41:1), a very good yield (>95 %) was possible to obtain.

The higher regioselectivity exhibited by ligand **35e** is in accordance with the statement by *Trost*[49] that σ-donating ligands enhance the attack at the more substituted position. The mechanism of Mo-catalysed allylations has not yet been clearly established. Nevertheless, from these results, it is concluded that sterical 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.[50] 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 (**36-37a, b**) without *trans*-1,2-diaminocyclohexane as the chiral scaffold (*Scheme 16*).

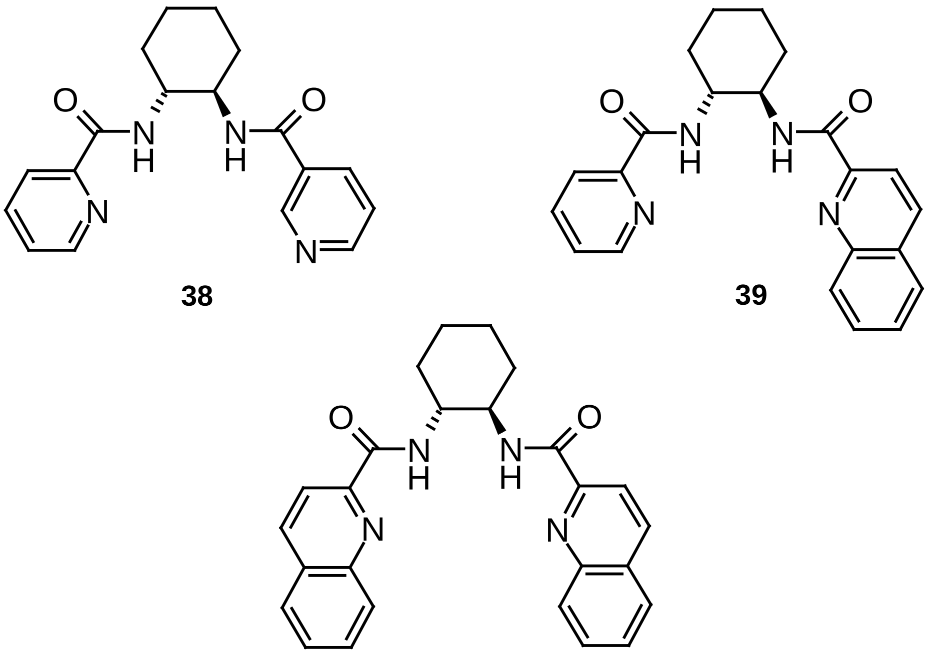


Scheme 16. Ligands for AAA with only a chiral center.

When the asymmetric reaction, illustrated in *scheme 14*, was realised with **36**, yields around 70 %, as well as fairly regio- and enantioselectivity in favour of the branched product **34a** (>8:1, ~90 % *ee R*) were achieved. This is not limited to only one substrate. By changing the cynnamyl-carbonates, similar results were attained. This observation confirms the hypothesis that one chiral center in the scaffold is sufficient to induce high levels of enantioselectivity.

To enhance the validity of this argument, the ligands **37a-b** were synthesised. The benzyl substituted ligand **37a** exhibited lower enantioselectivity (74-89 %) than **36**, but the isopropyl ligand **37b** gave much more improved results that are in the same range as those reported by *Trost* (98 % *ee*, 32:1 regioselectivity).

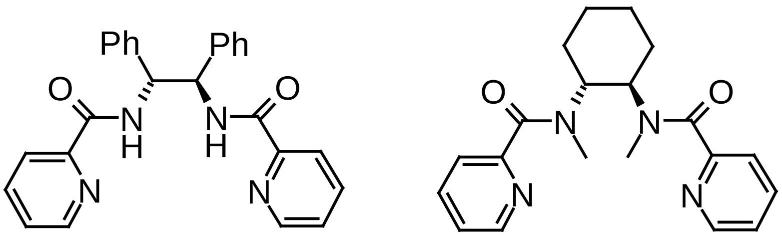
The binding mode of these tetra-aza ligands to molybdenum during the catalytic cycle is not clearly understood. Regarding to this, *Trost* and co-workers[51] investigated a series of ligands[52] (*Scheme 17*) with few, but important, modifications of their structure. The effectiveness of these new ligands was compared with that of **35a** as a standard ligand.
In initial studies, one of the picolinamide units on **35a** was replaced with a nicotinamide group (Compound **38**). The enantio- and regioselectivity[53] (99 % *ee R*, 46:1) were slightly better than with the standard ligand **35a** (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 **38**. Removal of both pyridine nitrogen atoms (bidentate ligand) led to a very poor ligand in terms of rate and selectivity (35 % yield, 24 % *ee*). Attending to this facts, *Trost* came to the conclusion that at least one picolinamide unit must be available to participate in the binding with Mo.



38 **39** **40**

Scheme 17. Rational designed ligands.

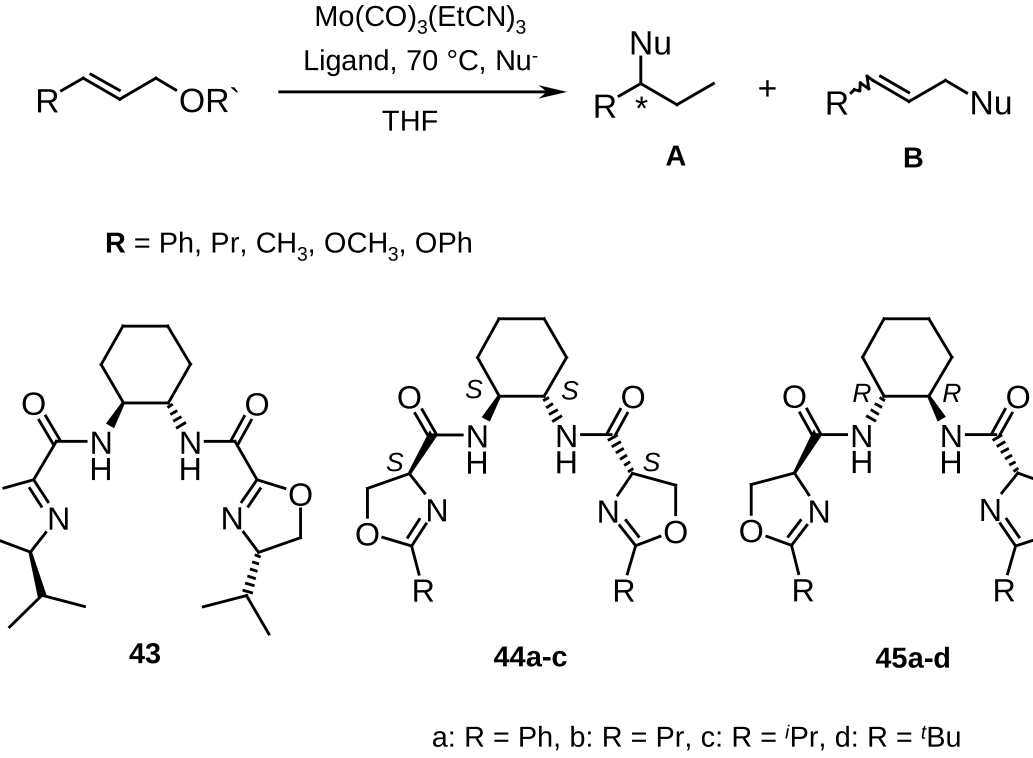
The steric factors also play a role in the effectiveness of a ligand. When a picolinamide unit of **35a** was changed by one (Compound **39**) or two (Compound **40**) quinoline analogues, much lower reaction rates were observed. Ligand **39** was acting highly enantioselective (98 % *ee*, *R*), while with **40** only traces of the products were detected.
Another ligand **41** (*Scheme 18*) with stilbenediamine as the chiral backbone showed a similar behaviour (95 % yield, 99 % *ee*, *R*) to the model ligand **35a**, but a decrease in the branched/linear ratio (19:1).



41 **42**

Scheme 18. New ligands to study the influence of the chiral backbone and the amine in the catalytic reaction.

The importance of the secondary amide was investigated by using ligand **42** (*Scheme 18*). This catalyst was 200-fold less active than **35a** 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 **35a** 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 synthesised. *Pfaltz*[54, 55] applied the already active bisoxazolines **43-45** to this Mo-catalysed transformation with various substrates (*Scheme 19*).



*Scheme 19. Pfaltz´*s bisoxazolines for the AAA.

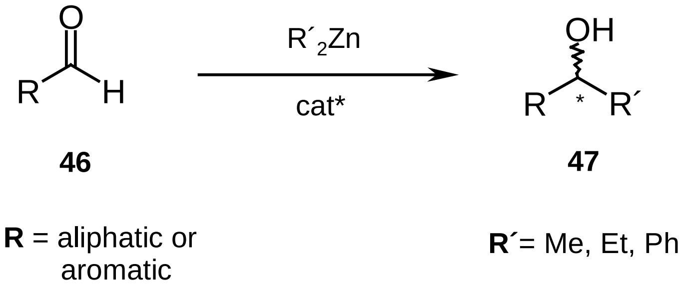
The bisoxazolines **43** and **44b** induced similar levels of enantioselectivity (~98 % *ee*) to the bispyridine ligand **35a** for the 3-phenylallyl derivative, however the branched/linear ratios were lower (14:1 *vs.* 49:1) and the reactions slower (24 h *vs.* 3 h)

In the case of the methyl substrate, the ligands **45b-c** gave the same regioselectivities (8:1 ratio of A:B) as **35a** with almost identical enantioselectivity (~98 % *ee*). The diasteromeric ligands **44b-c** and **45b-c** induced the opposite configuration of the product, implying that the enantioselectivity is largely controlled by the *trans*-diaminocyclohexane unit.

The systematic variation of the substituents in the oxazoline ring permits the optimisation of the enantioselectivity as well as the regioselectivity. While the *n*-propyl-substituted derivatives **44b** and **45b** produced comparable results to the *Trost´*s bispyridine ligand **35a**, only the racemic product with a low branched/linear ratio was obtained with the *tert*-butyl-substituted ligand **45d**.

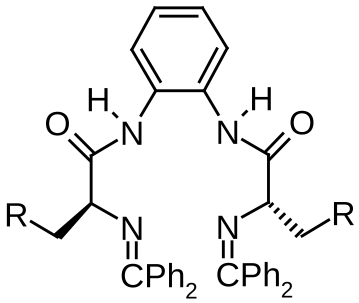
1.7 Dialkylzinc Addition

The first tetradentate ligand used in the addition of organozinc reagents to aldehydes (*Scheme 20*) was reported by *Dangel* and *Polt*.[56] 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-epoxid).[57]



Scheme 20. Addition of alkylzinc to aldehydes.

It was demonstrated by NMR studies that this ligand **48a** (*Scheme 21*) 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 up to 80 % and enantioselectivities between 86 and 96 % *ee* were achieved.



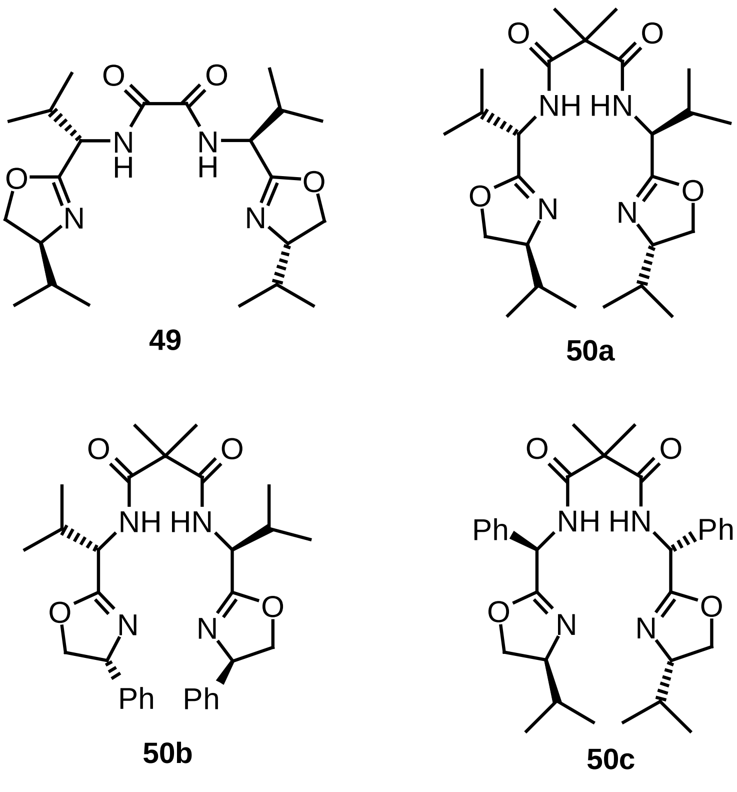
48 a: R = Ph
b: R = Me
c: R = ^{i}Pr

Scheme 21. First tetradentate ligands used for organozinc addition to aldehydes.

For further studies, another two ligands (**50b-c**) were synthesised 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 behaviour was observed for aliphatic aldehydes.

Novel C_2-symmetric tetradentate bisoxazoline ligands (*Scheme 22*) for the titanium-catalysed diethylzinc addition to aldehydes were reported by *Adolfsson* and *Pastor*.[58]



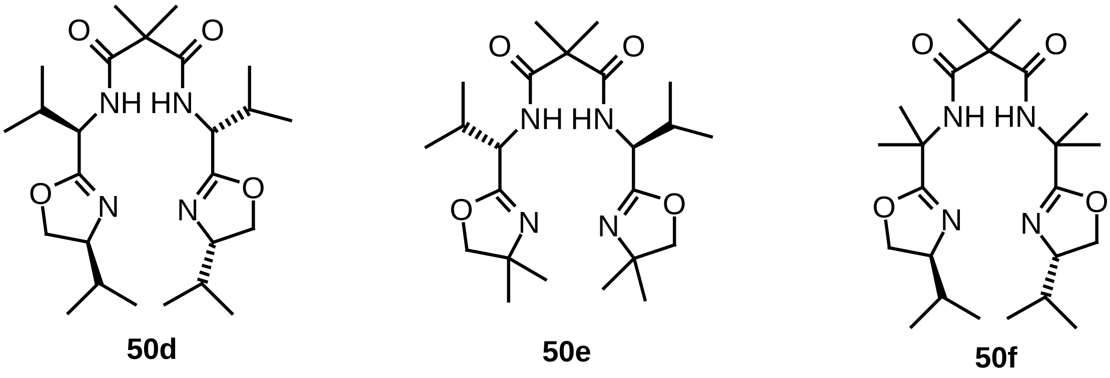
49 **50a**

50b **50c**

Scheme 22. Tetradentate bis-oxazoline ligands.

When ligand **49** 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 **50a**, a good conversion to the product (87 %) and increased enantiomeric excess (78 % *ee S*) were detected. Similar behaviour was observed by test of the ligands **50b** and **50c**. Surprisingly, although the absolute configuration of the chiral centers in the oxazoline parts of the ligand **50b** with respect to **50a** were interconverted, both gave the *S*- enantiomer.

Ligands **50d-f** (*Scheme 23*) were also synthesised, in order to study the influence of the stereochemistry in the oxazoline rings and/or at the stereocenters next to the amide functions in the catalytic reaction.

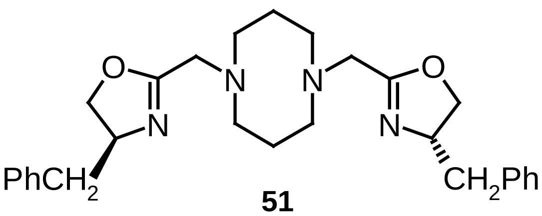


Scheme 23. Bisoxazoline ligands with changes in the stereochemistry.

The *R*-enantiomer of the alcohol was obtained in good yield and enantioselectivity (93 %, 73 % *ee*) when the ligand **50d** (diastereomer of **50a**) was tested. With the catalyst **50e,** with no chirality on the oxazoline rings, very good results (83 % yield, 89 % *ee S*) were obtained. In contrast, for **50f** 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 pyridinyl oxazoline have been found to catalyse the hydrosilylation of ketons in high yields with up to 95 % *ee*.[59] Combining this efficient backbone with 1,5-diazacyclooctane, a new chiral tetradentate ligand **51** (*Scheme 24*) was reported by *Shang* and co-workers.[60] A moderate enantioselectivity (42 % *ee*) was observed using 5 mol % of the ligand in the addition of diethylzinc to benzaldehyde.

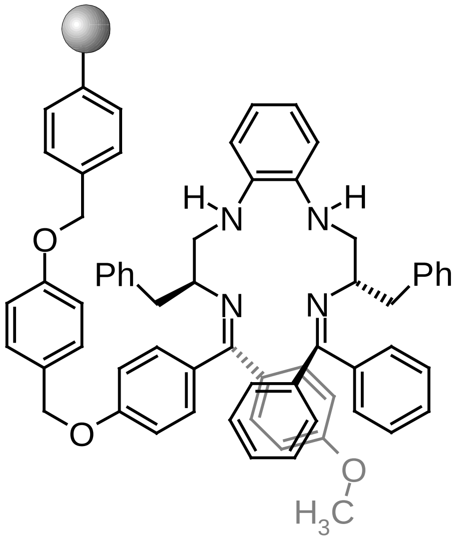


51

Scheme 24. New tetra-aza-ligand for the diethylzinc addition to benzaldehyde.

1.7.1 Immobilisation of catalyst for diethylzinc addition

The catalyst **48a** was transformed in a heterogeneous compound **52** (*Scheme 25*) by using the *Wang*[61] and the *Merrifield* resins.[62] The Et_2Zn 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 *ee*´s were considerably lower.



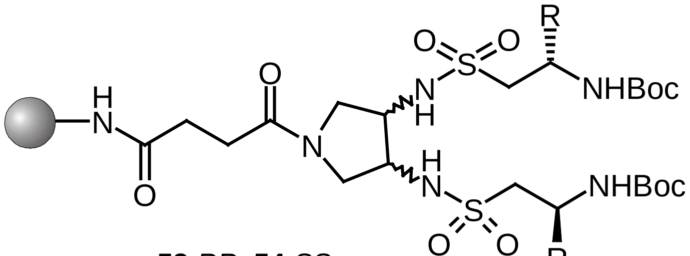
52

Scheme 25. Heterogeneous catalyst for the addition of Et_2Zn to benzaldehyde.

Combinatorial chemistry is extremely attractive as a method for finding and optimising ligands for catalysis,[63] because it offers the possibilities to generate and screen a number of compounds as well as optimise the conditions for studying these compounds (*e.g.* reaction conditions) in an iterative manner.

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 unfavourable 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[64] reported the synthesis of a library of peptidosulphonamide tweezers **53a-e** and **54a-e** (*Scheme 26*) 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.

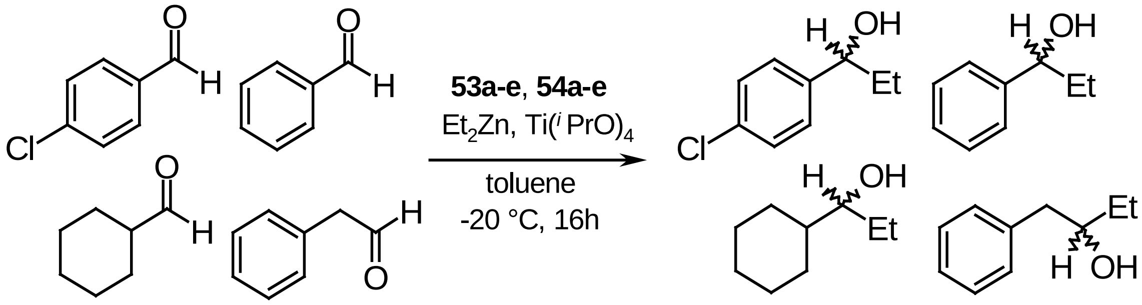


53 *RR*, **54** *SS*

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

Scheme 26. Peptidosulphonamide tweezers on the solid phase.

Instead of screening each resin-bound peptidosulphonamide tweezer with one substrate, the authors decided to use a mixture of aldehydes for the titanium mediated asymmetric addition of diethylzinc (*Scheme 27*).



Scheme 27. Combinatorial screening in the addition of diethylzinc to aldehydes.

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 *ee*'s and conversions were obtained. But this chirality is not sufficient for a high enantioselectivity since taurine containing pyrrolidine tweezers **53a** and **54a** 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 peptidosulphonamide **53e** and **54e** (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.

The best results were observed with the aromatic substrates using the leucine-derived peptidosulphonamide tweezers **53d** and **54d**.

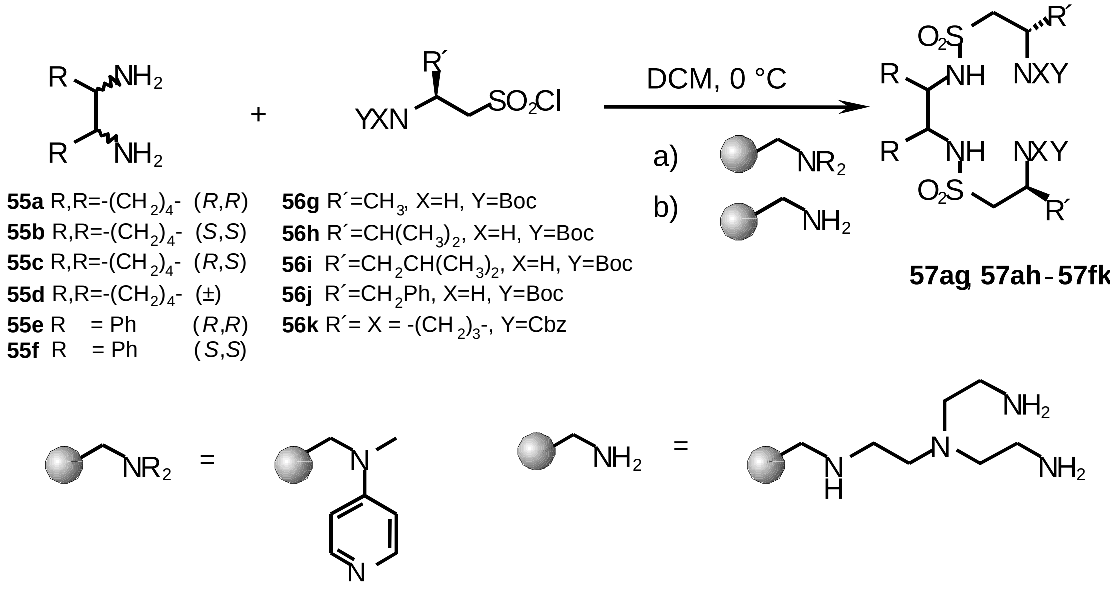
The homogeneous analogue of **53d** was synthesised and tested in the catalytic transformation. With this tweezer the *ee* values increased notably (56-66 %) as compared to the resin-bound ligand (32 %) confirming the earlier assumption.

Gennari and collaborators[65] have developed a new family of chiral ligands **55** (*Scheme 28*) based on a modular building block strategy and on the use of disulphonamide as a metal chelating unit.

For the diamine part of the library, they used two vicinal scaffolds: 1,2-diaminocyclohexane (**55a-d**) and 1,2-diphenylethylenediamine (**55e-f**), for which effective use in the fields of asymmetric synthesis and molecular recognition is well documented.

The sulphonyl chloride derived from L-alanine **56g**, L-valine **56h**, L-leucine **56i**, L-phenylalanine **56j** and L-proline **56k** were used.

To avoid the problems associated with workup and purification of the resulting products, solid phase extraction (SPE) techniques[66] were applied to the synthesis.



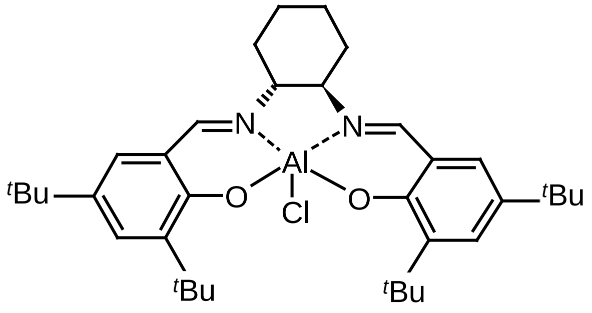
Scheme 28. New family of chiral ligands via parallel synthesis.

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 **57bj** (i.e., 1*S*,2*S*-diaminocyclohexane **55b** as diamine scaffold and the sulphonyl chloride **56j** derived from L-phenylalanine).[67] (2) The influence of the different *β*-aminosulphonyl side chains in controlling the enantioselectivity is as follows: R′= CH_2Ph (**56j**) > CH_3 (**56g**) > ^{i}Bu (**56i**) > ^{i}Pr (**56h**) >> $(CH_2)_3$ (**56k**). (3) The influence of the different scaffolds in controlling the enantioselectivity is as follows: *trans*-(1*S*,2*S*)-diaminocyclohexane (**55b**) > *cis*- diaminocyclohexane (**55c**) ~ (±)-racemic-1,2-diaminocyclohexane (**55d**) > (1*R*,2*R*)- diphenylethylenediamine (**55e**) ~ (1*S*,2*S*)-diphenylethylenediamine (**55f**) > *trans*-(1*R*,2*R*)-diaminocyclohexane (**55a**). (4) With the *cis* and the racemic scaffolds, moderated enantiomeric ratios were obtained in favour of the (*R*)-alcohol (~60 % ee). (5) With the (*R*,*R*)- diphenylethylenediamine scaffold, one single reasonable high enantiomeric ratio was obtained (ligand **57ej**, 78 % *ee* for the *R*-alcohol).

1.8 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.[68]

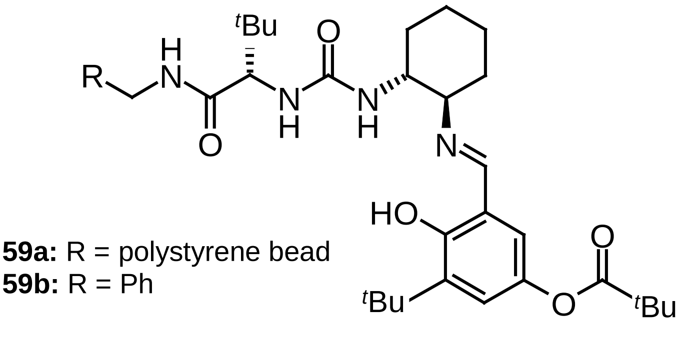
After the success accumulated by *Sigman* and *Jacobsen*[69] with the first example of a metal-catalysed enantioselective *Strecker*-type reaction, using a chiral Al(III)-salen complex **58** (*Scheme 29*), more efforts were made by this group to design new and effective catalysts for this transformation, with the help of combinatorial methods.



58

Scheme 29. Al(III)-salen complex for the *Strecker* synthesis.

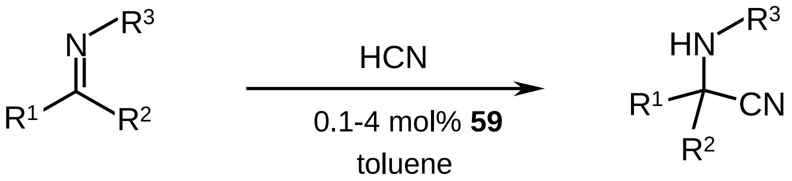
In this context, the non-metal *Schiff* base catalysts **59a-b** (*Scheme 30*) were reported[70-71] as remarkably general catalysts for the hydrocyanation of aldiimines and ketoimines,[72] producing *Strecker* adducts in >90 % *ee* for most substrates examined (*Scheme 31*).



59a: R = polystyrene bead
59b: R = Ph

Scheme 30. Structure of catalysts **59**.

The preparation of the catalyst was very easy, either in solution or on the solid phase. The use of the resin-bound catalyst **59a** allows *Strecker* product purification by simple filtration and solvent removal, and the catalyst can be reused indefinitely, without loss of either activity or enantioselectivity.



60 **61**

R^1 = more than 50 aromatic and aliphatic
R^2 = H or Me
R^3 = benzyl or allyl

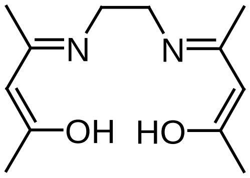
Scheme 31. Asymmetric *Strecker*-type synthesis.

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 **59** have been shown to be essential for both reactivity and enantioselectivity and thus appear to function cooperatively.

2 Synthesis of chiral ligands

2.1 Considerations

Since *Combes*[73] discovered the first salen ligand **62** (*Scheme 32*), these derivatives and their metal complexes have been recognised as an important class of catalysts, particularly in the case of achiral salen complexes in oxidation reactions.

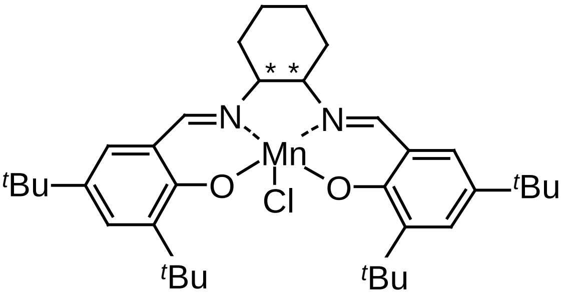


62

Scheme 32. First salen ligand discovered in 1889.

The development of chiral salen metal complexes and catalysts in the last decade has however stimulated a very rapid growth in the chemistry and application of these species. The variety of asymmetric reactions in which particular chiral metal salen complexes are proving useful grows steadily, and there is no evidence of this growth waning.[74]

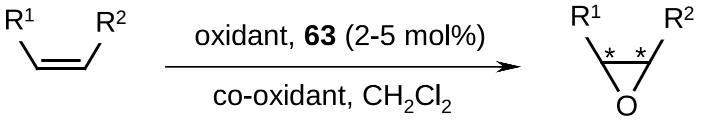
A prominent example is the *Jacobsen*´s Mn(III)-salen complex **63** (*Scheme 33*) which is currently the most efficient catalyst available for enantioselective epoxidation of unfunctionalised olefins.[75]



63

Scheme 33. *Jacobsen*´s catalyst.

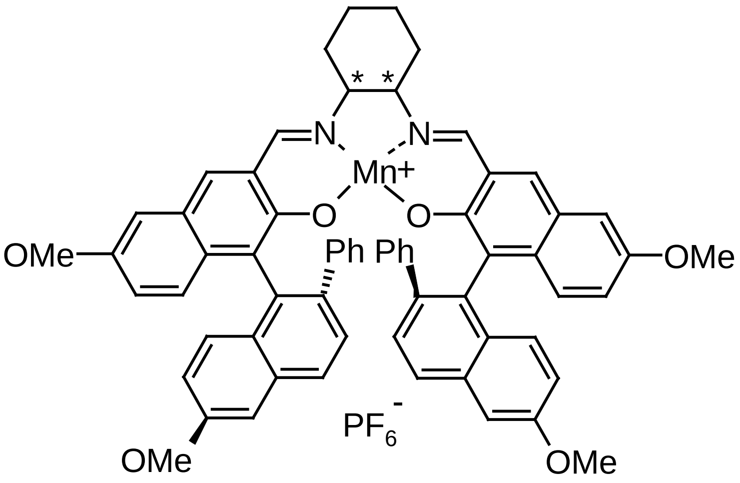
Through use of this catalyst in the asymmetric reaction shown in the *scheme 34*, yields up to 97 % and asymmetric induction as high as 98 % enantiomeric excess depending on the substrate were obtained.



Scheme 34. Asymmetric epoxidation of unfunctionalised olefins.

The source of oxygen used can be either an aqueous oxidant such as sodium hypochlorite or an organic peracid, for example *m*-chloroperbenzoic acid. The presence of a *N*-oxide as additive (*e.g*. *N*-methylmorpholine *N*-oxide or 4-phenylpyridine *N*-oxide) accelerates the catalysis rate, and influences positively the yield and the enantioselectivity of the epoxidation.

The catalytic activity of the salen ligands is not only limited to the epoxidation reaction. Many efforts have been made to extend the use of these ligands to other important transformations. *Jacobsen*´s group has successfully reported the hydrolytic kinetic resolution of racemic epoxides,[76] the asymmetric nucleophilic ring-opening of *meso*-epoxides using benzoic acid[77] (both in the presence of Co(III)-salen complexes), as well as the Cr(III)-salen catalysed epoxide ring-opening under solvent free conditions in the presence of azidotrimethylsilanolate[78] and the hetero-*Diels-Alder* reaction.[79]



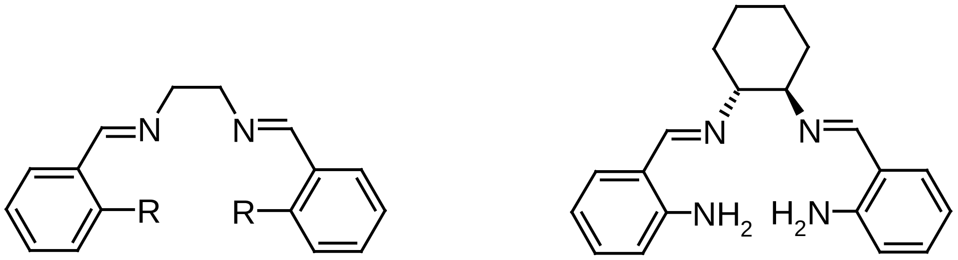
64

Scheme 35. Katsuki's salen complex.

Katsuki et al. published another set of salen complexes **64** shortly before *Jacobsen* (*Scheme 35*), which has as the main difference in the design, aryl groups in place of the bulky *tert*-butyl groups at the C-3 position.[80]

In the reaction of *scheme 34* using complex **64**, *Katsuki's* group has achieved lower enantioselectivities than *Jacobsen*, but other asymmetric reactions *e.g.* oxidation of sulfides[81], hydroxylation[82], kinetic resolution of racemic allenes[83] and cyclopropanation[84] were successfully catalysed for this system, not only with Mn as the metal, but also using complexes of Co and Cr.

In 1934 *Pfeiffer* and co-workers reported the formation of achiral *Schiff* bases **65a-b** by the condensation of diamines with aldehydes and their complexation with various metals.[85] Three decades later, *Uhlemann and Plath*[86] developed the synthesis of a new chiral *Schiff* base **66a** derived from *o*-nitrobenzaldehyde and 1*R*, 2*R*-diaminocyclohexane **67**.



65a: R = OH
65b: R = NH_2

66a

Scheme 36. Achiral and chiral *Schiff* bases.

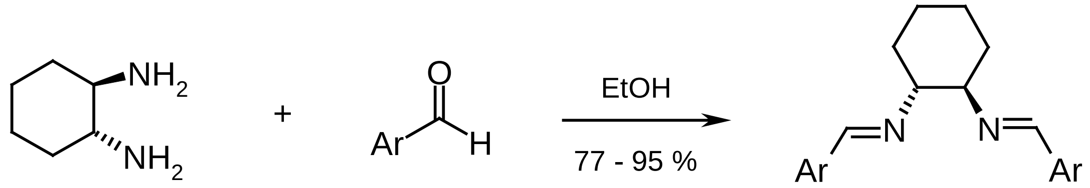
These nitrogen-containing ligands **65a-b** and **66a** have been widely used as chelating ligands for metal cations,[87] such as Ni(II), Cu(II), Co(III), Fe(III) and many others, but examples for asymmetric transformations catalysed by such complexes are still rare.

According to the structural analogy of ligand **66a** with the active salen ligands (both have a chiral diimine core accompanied of two donor heteroatoms) and to the fact that no application in catalysis for this kind of ligands is known, we decided to synthesise a sequence of new tetradentate ligands of general formula **66** (see *scheme 37* and *Table 1*), with the aim to prove their complexation abilities and their catalytic properties in standard asymmetric reactions.

2.2 Synthesis of imines

Perhaps the most common method for preparing imines is the reaction of aldehydes and ketons with amines. This reaction was first discovered by *Schiff*[88] and imines are normally referred to as *Schiff* bases.

The reaction is generally carried out by refluxing the carbonyl compound and the amine in an absolute solvent (*e.g.* ethanol).[89] As products, the imine and water emerged, the latter should be eliminated by azeotropic distillation or by adding $MgSO_4$ to prevent the hydrolysis of the formed *Schiff* base. This hydrolytic susceptibility of the imines is a limiting factor for this type of ligands because it often hinders further derivatisation or purification using aqueous solvents.[90]



***R*,*R*-67** **68a-d** **66a-d**

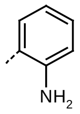
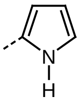
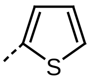
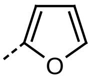
Scheme 37. Synthesis of the imine ligands.

For the synthesis of the proposed ligands the procedure reported by *Weber*[91] was used. In our case the enantiomeric pure 1*R*, 2*R*-(*trans*)-cyclohexanediamine **67** and the respective aromatic aldehydes (see *scheme 37* and *table1*) reacted in a 1:2 ratio in EtOH and the tetradentate ligands were achieved in good yields. For ligand **66d** the complete condensation was only obtained after addition of a 2 M NaOH solution.

In the ^{1}H NMR spectra of all four ligands the presence of a singlet at $\delta = 8$ is characteristic, which integrates two protons corresponding to the azomethine protons.

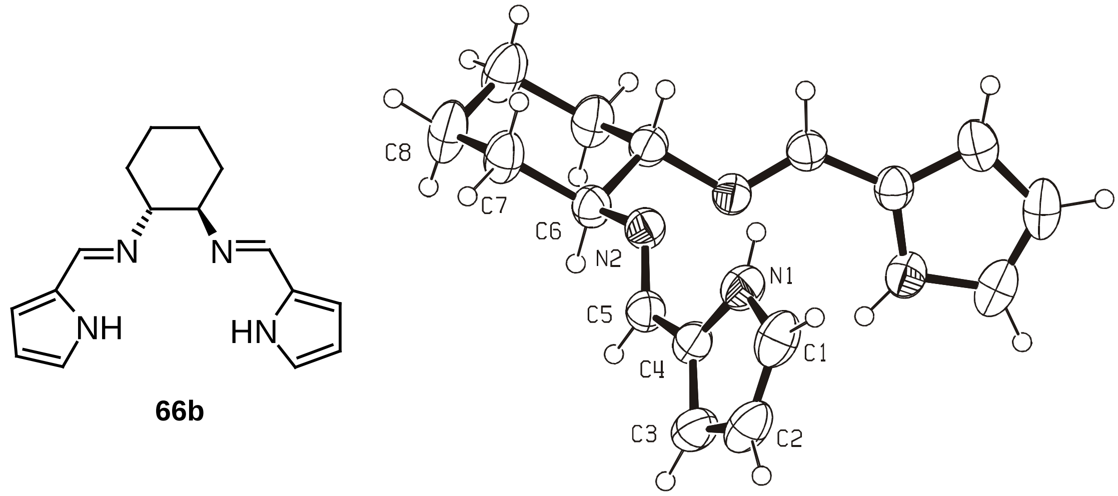
The tetraaza ligands **66a**[86] and **66b**[91], as well as their Ni(II)[92] and Cu(II)[93] complexes, were already reported. A detailed study of the circular dichroism (CD) and electronic absorption spectra of these complexes was also described by these authors. The signs of the Cotton effects could be correlated with the absolute configuration of a proposed flattened tetrahedral array of the donor atoms around the metal ion. This configuration was produced stereospecifically by the conformational preference of the central (*gauche*) chelate ring which results from the steric requirements of the ligands.

Table 1. Starting materials and yields for the synthesis of *Schiff* bases.[94]

entry	aldehyde	Ar	product	yield [%]
1	**68a**		**66a**	77 (80)[a]
2	**68b**		**66b**	90[b]
3	**68c**		**66c**	95
4	**68d**		**66d**	85

[a] The yield reported in ref. 86 is given in parenthesis. [b] The yield is not reported in ref. 91.

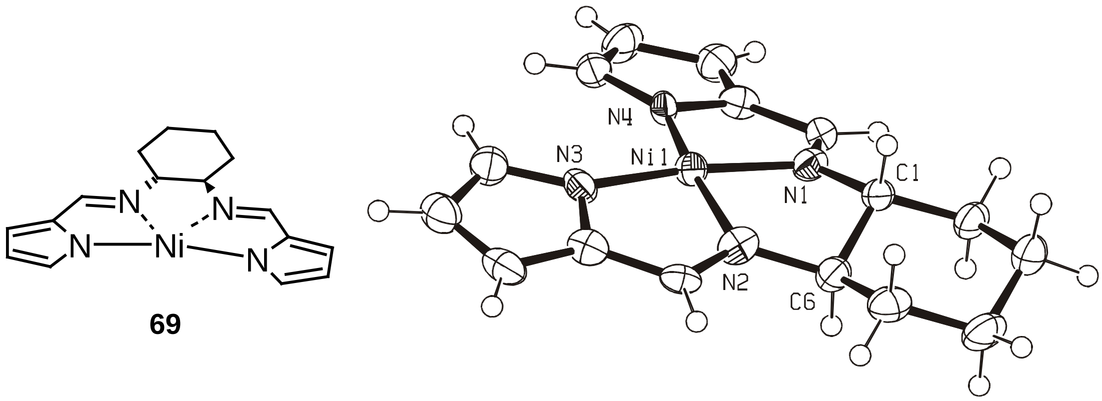
The slow evaporation of the solvent in a solution of ligand **66b** in chloroform provided X-Ray quality crystals. The structure of the ligand in the *scheme 38* shows that both pyrrol cores are oriented in different directions in the crystal.



66b

Scheme 38. ORTEP[95] representation of the derivative **66b**[96] with important atoms labelled.

The crystal structure of the neutral Ni complex **69** (*Scheme 39*) was also possible to determine. Here it is important to note the unusual presence of four molecules with independent symmetry in an unit cell, but there is a reasonable explanation for this. Each atom, except for the cyclohexane units, can be described in a centrosymmetrical space group. Due to the isomerical purity of the sample, the cyclohexanes are breaking the centrosymmetry and the only viable description results in an acentric space group. The residual parameters (*R*-values, Goodness-of-fit, see table 2 of x-ray appendix) clearly indicate the significance of this acentric model.

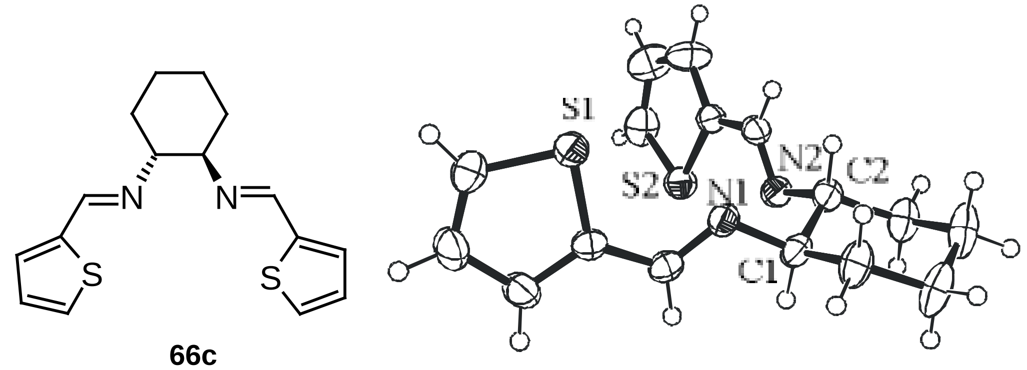


69

Scheme 39. ORTEP representation of the neutral Ni complex of **66b** with important atoms labelled.

From the ORTEP representation of the complex **69** on *scheme 39* the accommodation of the Ni cation in the middle of the cavity formed by the four nitrogen donor atoms can be observed, giving the complex a square planar coordination.

The X-ray structure analysis of **66c** (*Scheme 40*) confirms the proposed connectivity and stereochemistry. In the crystal, both thiophene moieties point in different directions. All bond length and angles are as expected.



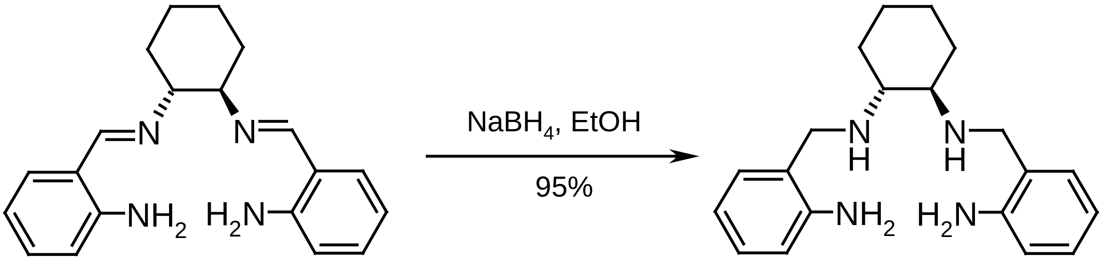
66c

Scheme 40. ORTEP representation of the ligand **66c** with important atoms labelled.[94]

All diimine ligands obtained are stable in air, they can be stored for a long time, but they are, as expected, sensitive to hydrolysis. Thus, we decided to synthesise a water robust ligand. For this, the compound **66a** was reduced with $NaBH_4$ in EtOH at 50 ºC to get compound **70** in 95 % yield (*Scheme 41*).[94] When this reaction was attempted at a lower temperature in the same solvent, only a slow and incomplete conversion of the substrate was obtained.

When the reduction was carried out with MeOH as solvent, no tetramine formation was observed. According to the NMR spectrum, only a decomposition product was possible to assign, which did not have the signals corresponding to the cyclohexane unit.

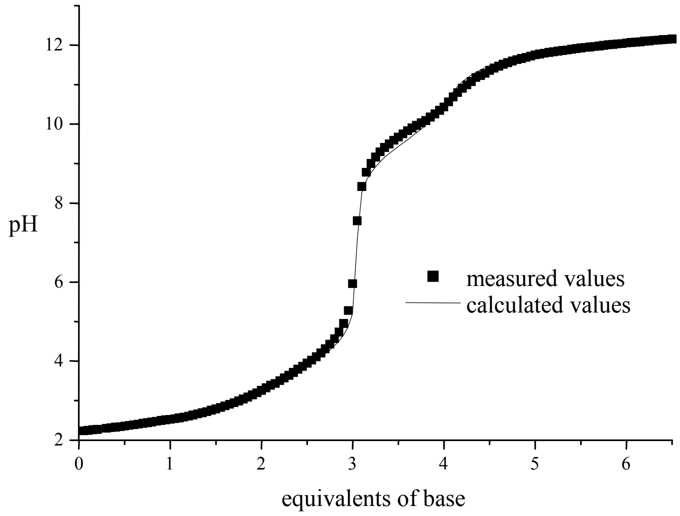
Reductions using hydrogen (50 bar) and Pd/C were also unsuccessful with similar results.



66a **70**

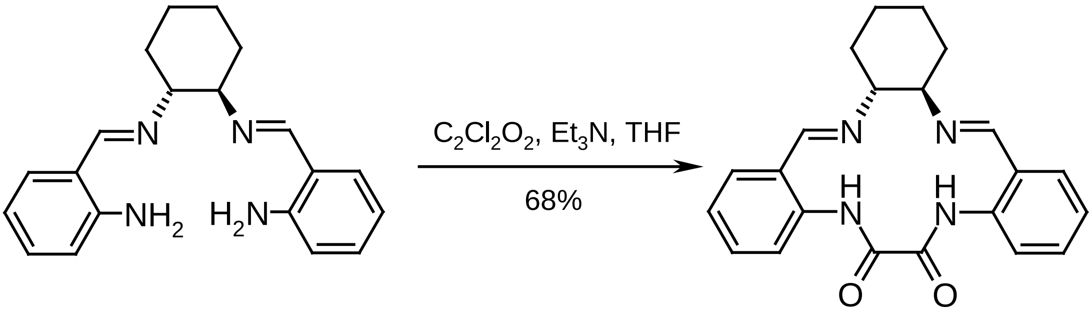
Scheme 41. Synthesis of a hydrolysis stable chiral ligand.

Two different pK_a values of 3.9 and 9.5 were determined for **70** in water by potentiometric titration, which are assigned to the aniline and secondary amino groups, respectively.[97]



Scheme 42. Potentiometric titration curve for ligand **70**.

The ligand **71** was synthesised from **66a** by reaction with oxalylchloride in THF in the presence of Et_3N as catalyst, according to the procedure reported in the literature.[98] After flash chromatography of the raw product in $CHCl_3$, the cyclic compound was obtained in 68 % yield as colourless crystals.



66a **71**

Scheme 43. Synthesis of a cyclic tetraaza ligand.

The ^{1}H NMR spectrum of **71** did show a signal at δ = 14.22 equivalent to two protons and corresponding to the substituted amine, which indicates a successful reaction. Additional evidence to the structure elucidation is the carbonyl signal in ^{13}C-NMR at δ = 159.7.

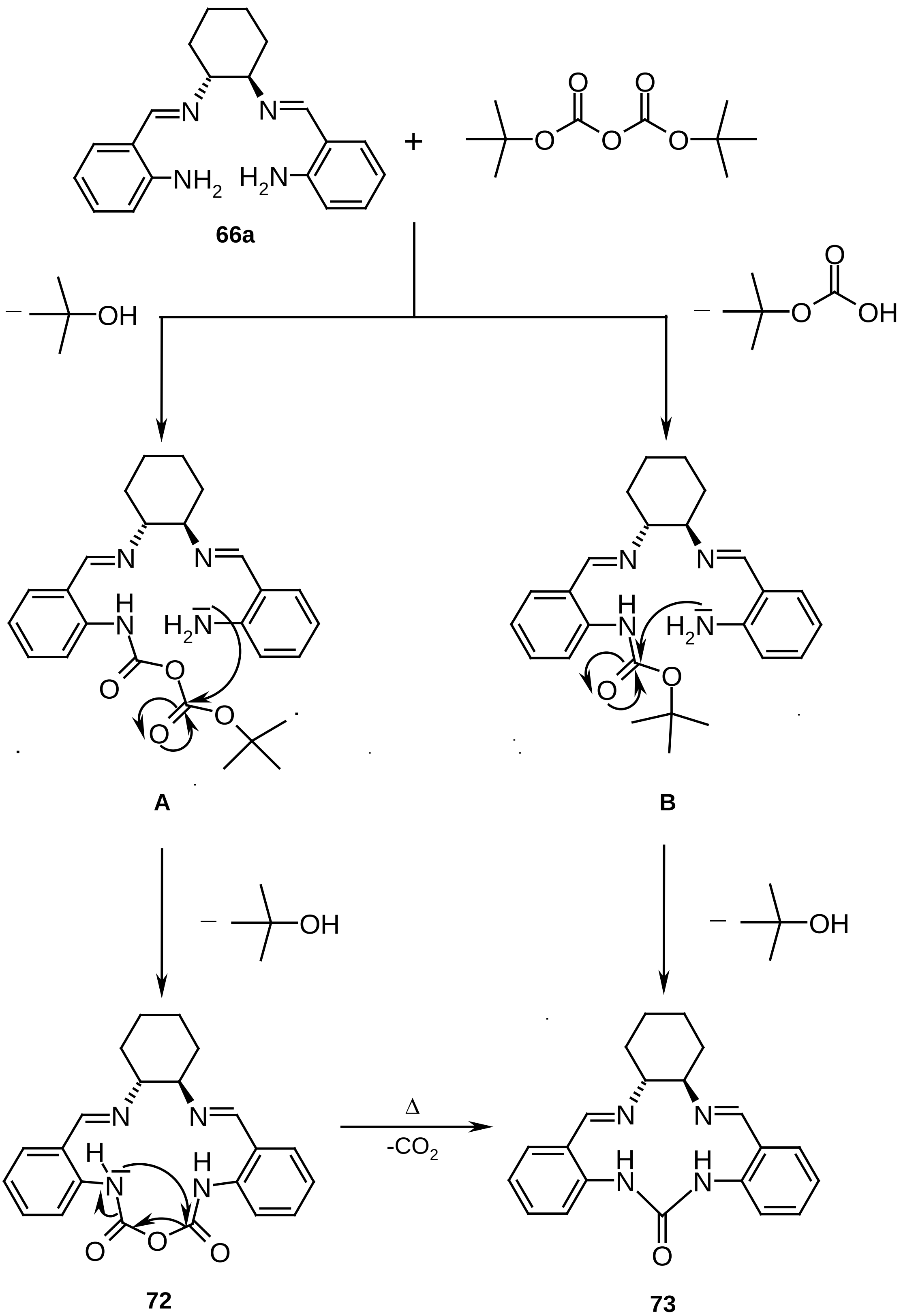
The synthesis of the ligand **73** from **66a** was attempted by reaction with Boc_2O in CH_2Cl_2 using DMAP as catalyst. Such reactions have been carried out with similar substrates giving yields of 87-96 %.[99]

According to the mechanism showed in *scheme 44*, an intermediate isocyanate **B** should be formed in the first step of the reaction, by nucleophilic attack of an aminic nitrogen on a carbonyl group of the Boc_2O and cleavage of a *tert*-butoxycarbonyl group. By subsequent nucleophilic addition of the second arylamine to the isocyanate and cleavage of *tert*-butanol the urea derivative **73** should be obtained.

After performing the reaction and successive chromatographic separations, a colourless product was obtained. This product, however, contains in its ^{13}C NMR spectrum two signals for carbonyl groups at δ = 151.3 and δ = 151.7, while only one was expected. On the other hand, the ^{1}H NMR shows the presence of two signals at δ = 9.68 and δ = 9.71, as expected, which can be attributed to the protons in the substituted amine. It was then thought that instead of the desired reaction taking place, another reaction yielding **72** as product occurred. This is also confirmed by mass spectrometry, which showed a molecular peak of m/z = 391.3.

Returning to the mechanism in *scheme 44*, when the isocyanate was formed in the first step, instead of a *tert*-butoxycarbonyl group, a *tert*-butoxy group was cleaved leading to an intermediate **A** with two carbonyl groups, which could be attacked by the second amine. The nucleophilic addition then takes place at the Boc-group giving the unexpected product **72**.

It was thought that on heating **72**, it would release CO_2, thus leading to **73**. A DSC (see appendix 7.4) was performed on **72**. A sample of 7.041 mg of **72** was heated from 25 to 300 °C under N_2 at a rate of 10 °C/min. The reaction set in at 259.1 °C and the sample lost 0.818 mg in weight, which corresponds to the loss of CO_2 (theoretically 0.794 mg). A proposed reaction mechanism is shown in *scheme 44*. However, the temperature at which this reaction makes is of limited synthetic interest.



Scheme 44. Mechanism of the nucleophilic substitution with Boc$_2$O.

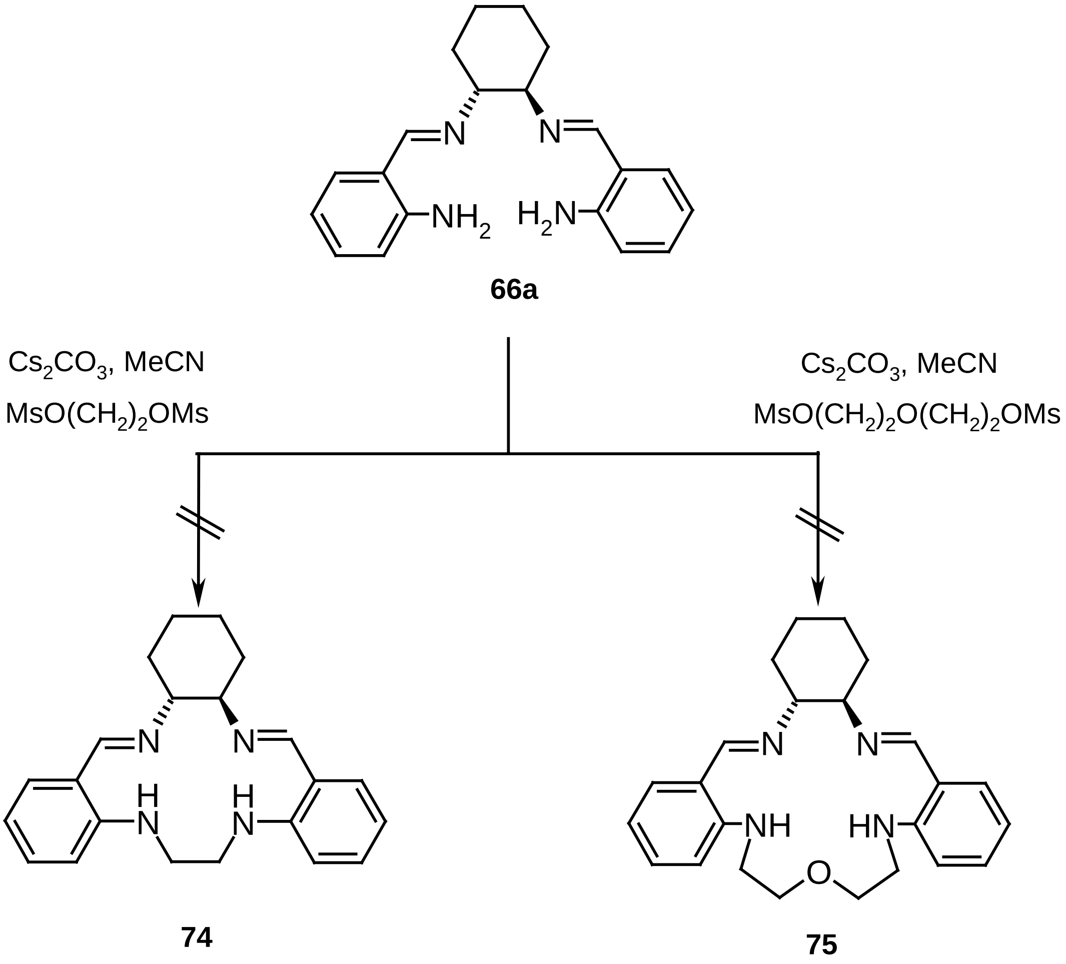
The synthesis of **73** thus never succeeded. Possible ways of obtaining this compound, could be to react the tetraaza ligand **66a** with urea while heating,[100] with phosgene in benzene,[101] with diphosgene in dioxane,[102] with carbon dioxide in the presence of a strong base or with methyl chloroformate and Et_3N in CH_2Cl_2.[103] However, no further efforts were made to obtain **73**.

The synthesis of the ligands **74** and **75** were attempted starting from **66a** (see *scheme 45*), by reaction with ethylene glycol dimesylate or diethylene glycol dimesylate, respectively, and Cs_2CO_3 in MeCN, as reported for the synthesis of several macrocyclic structures.[104]

Although the reaction mixtures were refluxed for a long time (~12 hours) and consequently stirred for one week, no product formation was observed.

Biernat and *Luboch* have reported,[105] that diamines may be directly alkylated under these conditions, but using this method, low yields are usually obtained.

A better alternative for the synthesis of cyclic tetraaza ligands could be the generation of the tosylamide derivative starting from the diamine. This tosyl derivative reacts smoothly with the dimesylates after deprotonation with Cs_2CO_3, to achieve the cyclic nitrogen-containing ligands as tosyl derivative.[106, 107] The free ligand could be obtained by removal of the tosyl groups with 48 % HBr and an excess of phenol.[103]

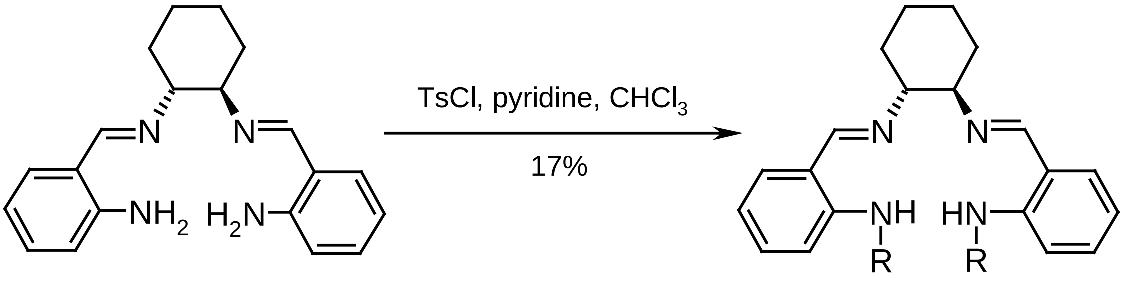


Scheme 45. Attempts to synthesise other macrocyclic structures.

2.3 Derivatisation of Imines

The tosylated derivative **76a** was synthesised using **66a** as substrate by reaction with TsCl in pyridine (*Scheme 46*). After chromatographic separation of the reaction mixture, sulphonamide **76a** in combination with *N*-tosyl-*o*-aminobenzaldehyde as by-product were obtained. This by-product originates from the hydrolysis of the carbon-nitrogen double bond.[108] The separation of both compounds was complicated by the fact that their R_f-values are almost the same.

The sulphonamide **76a** could be finally isolated by dissolving this mixture in AcOEt and adding hexane until a precipitate was observed. Yellow crystals were obtained in only 17 % yield, what shows that this synthetic route was ineffective.



66a

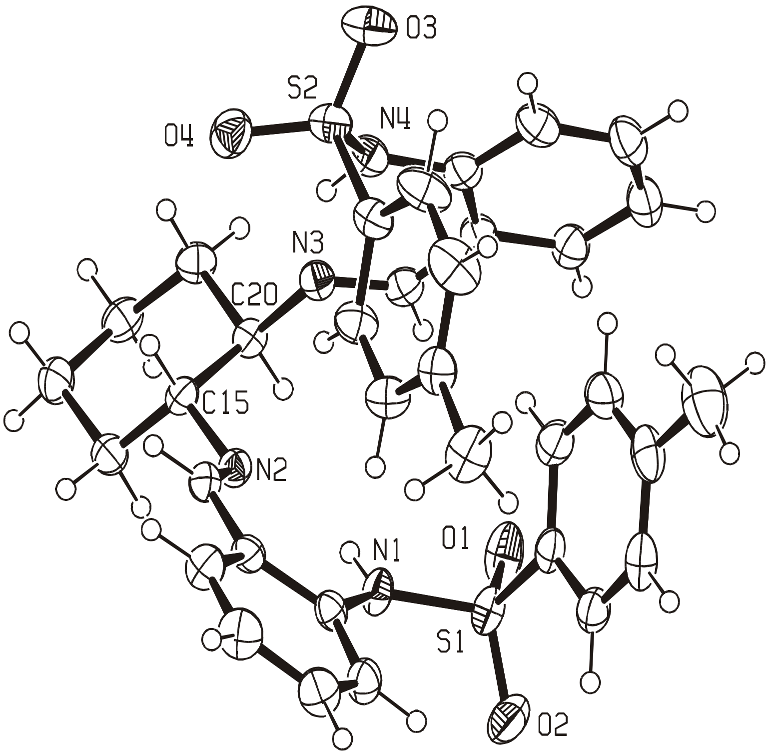
76a: R = Ts

Scheme 46. Synthesis of a sulphonamide derivative.

Crystals of compound **76a** for X-Ray analysis were obtained by evaporation of the mixture of solvents (hexane/AcOEt). The packing scheme and spatial molecular arrangement are controlled by weak interactions, in which the tosyl groups are involved. In the *scheme 47* a face to face π-stacking which exists between both terminal tosyl rings can be observed. Likewise, edge to face interactions can be found between the tosyl and the benzylidene rings.

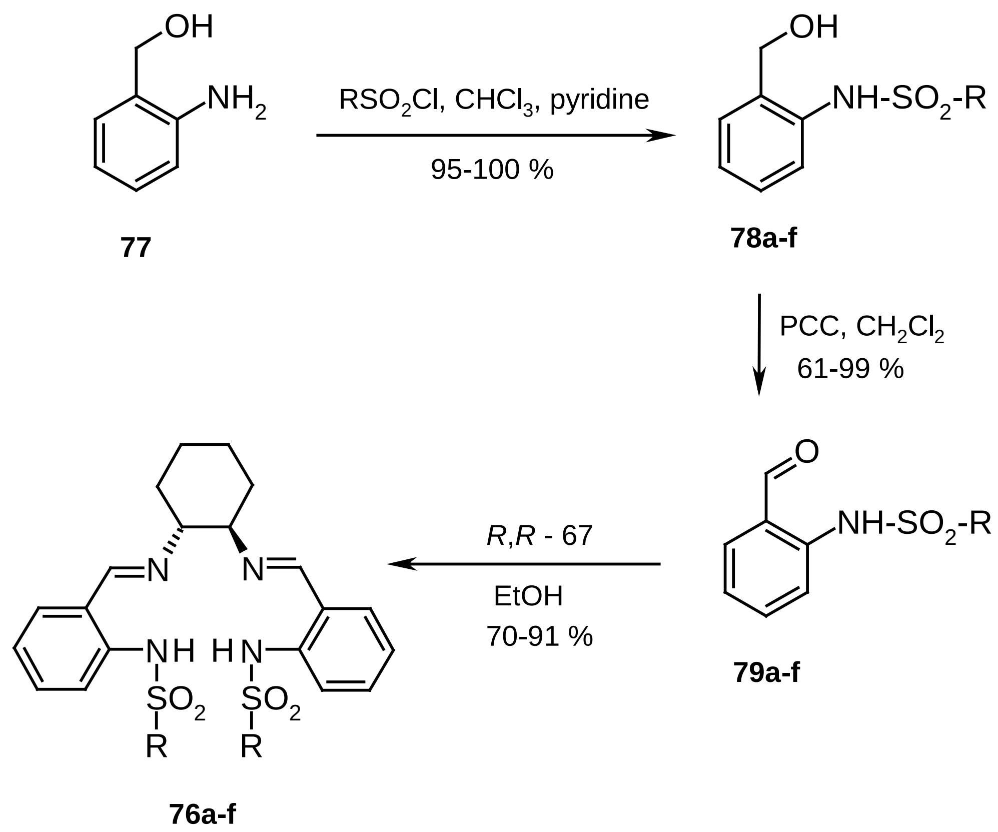
This spatial arrangement of **76a** suggests that, with a simple torsion around the azomethine groups and the subsequent repulsion of the tosyl groups, this ligand could provide a single pseudo-planar N_4 compartment, where a metal center can be accommodated.

The X-Ray structures of the Ni(II) and Cu(II) complexes of this ligand have been reported in the literature.[109] Both metal ions assume a tetrahedrally distorted square planar coordination geometry, involving the four nitrogen atoms of the dianionic ligand.[110]



Scheme 47. ORTEP representation of the ligand **76a** with all atoms labelled.

An alternative way to obtain the sulphonamide **76a** is the direct condensation of the chiral 1*R*, 2*R*-*trans*-cyclohexanediamine and the *N*-tosyl-aldehyde[111] in ethanol. By using this method a better yield (66 %) of the ligand was achieved.



R = a: *p*-MeC_6H_4 , **b:** C_6H_5, **c:** *p*-$MeOC_6H_4$, **d:***p*-$NO_2C_6H_4$,
e: *p*-ClC_6H_4, **f:** 2,4,6-$Cl_3C_6H_2$

Scheme 48. Alternative synthetic route to the sulphonamide ligands.

A third attempt to obtain **76a-f** is shown in *scheme 48*. The commercially available *o*-amino-benzylalcohol (**77**) is used as starting material. It reacts[112] with different sulphonyl chlorides in the presence of pyridine to give the *N*-protected alcohols **78a-f** in almost quantitative yields (see *table 2*). In the ^1H NMR spectra of the six derivatives a broad singlet at about $\delta = 8$ is observed, corresponding to the sulphonamide proton, which confirms the successful substitution.

Table 2. Yields obtained for the substituted benzylalcohols **78**, aldehydes **79** and *Schiff* bases **76** from *scheme 48*.

R	**78** [%]	**79** [%]	**76** [%]
a: *p*-MeC_6H_4	98	74	85
b: C_6H_5	95	61	74
c: *p*-$MeOC_6H_4$	100	90	78
d: *p*-$NO_2C_6H_4$	100	95	91
e: *p*-ClC_6H_4	100	99	69
f: 2,4,6-$Cl_3C_6H_2$	100	90	71

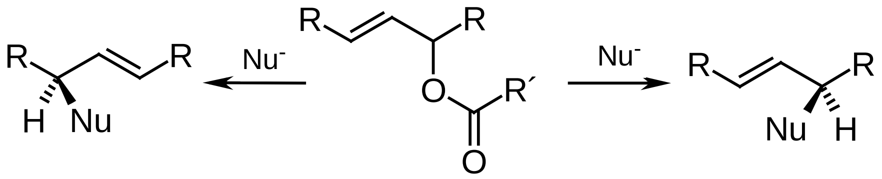
With the use of PCC,[113] the alcohols are oxidised to the corresponding aldehydes **79a-f**, in very good yields. The presence of the aldehyde was proven again in ^1H NMR by the appearance of a new singlet at approximately $\delta = 10$, which is characteristic for this functional group.

The *Schiff* bases with general structure **76** were synthesised in good yields, in the same way as described before (see section 2.2).

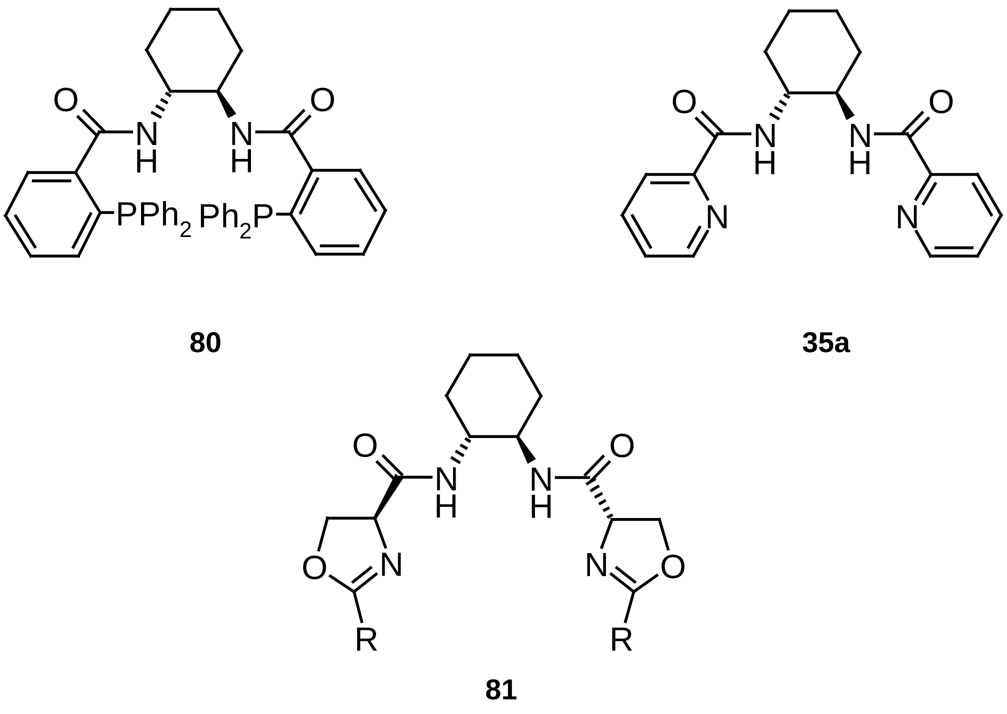
This synthetic route gives the sulphonamides **76a-f** in only three steps and provides superior yields than those reported by *Katsuki* and co-workers for the synthesis of the analogue achiral *Schiff* base.[114]

2.4 Amide ligand and derivatives

Amide ligands are effective catalysts for a great number of asymmetric transformations. With the aim to study the asymmetric induction in the AAA, *Trost´s* group described the synthesis of ligand **80** (see *scheme 50*) and its derivatives.[115] Using this compound, high enantioselectivity (92 %) was obtained for the reaction illustrated in *scheme 49*, when R = Me. But the results were not satisfactory when R = Ph, which demonstrates that the catalyst imposes a size restriction on the substrate.



Scheme 49. Asymmetric allylic alkylation reaction.



80

35a

81

R = Ph, Pr, ^{i}Pr, ^{t}Bu

Scheme 50. Bis-amide ligands

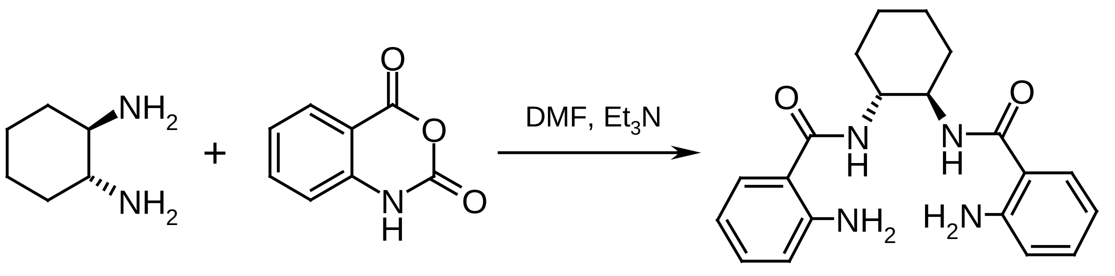
As already discussed in the introduction of this work, ligand **35a** (*Trost's* ligand) constitutes the most selective catalyst for the AAA with many different substrates and making use of Pd, Mo and W.

The bis-dihydrooxazoles of type **81** were reported by *Pfaltz*[116] to catalyse reactions, such as asymmetric epoxidation[117] or the enantioselective *Michael* addition.[118] But the very good results achieved by *Trost*'s group with ligand **35a** encouraged the authors to test the bis-dihydroozaxoles in the AAA. Although the ligand **35a** was generally superior, the bis-dihydroozaxoles gave improved regio- and enantioselectivity with certain substrates. An attractive feature of these type of ligands is the option to finetune their structure by variation of the substituents at the dihydrooxazole rings.

According to the reactivity shown for the above mentioned ligands, we decided to synthesise similar compounds (**83** and **84a-d**), that contain the chirale bis-amide unit combined with free or substituted amines.

This kind of diamide is generally synthesised starting from the activated carboxylic acid[119, 120] and reaction with the chiral diamine. An effective one step alternative was published for the synthesis of **35a** without previous derivatisation.[121]

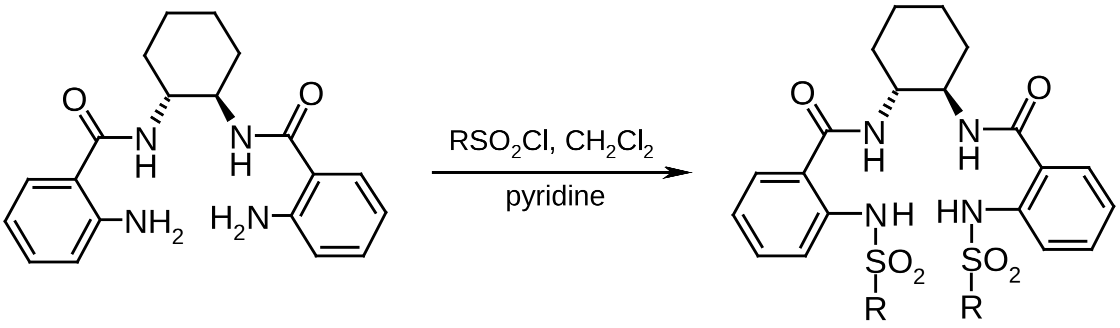
On the other hand, a detailed, easy and particularly short synthesis for **83** and **84a** was published by *Somanathan* and co-workers.[122] To get **83**, they used isatoic anhydride **82** and the 1*R*, 2*R*-*trans*-cyclohexanediamine (**67**) in a 2:1 ratio (*Scheme 51*) as starting materials. The diamine was first dissolved in DMF and treated with Et_3N, followed by slow addition of a solution of the anhydride in the same solvent. After 26 h stirring at 50-60 °C, the ligand **83** was obtained with a yield of 60 %. The structure was confirmed by NMR, mass spectrometry and elemental analysis.



R,R-67 **82** **83**

Scheme 51. Diamide synthesis starting from isatoic anhydride.

With use of the ligand **83**, it was possible to obtain sulphonamide derivatives by reaction with the appropriate sulphonyl chlorides. The compounds **84a-d** (represented in *scheme 52*) were obtained with very similar yields in all cases (~60 %).



83 **84a-d**

R = **a**: CH_3, **b**: *p*-MeC_6H_4, **c**: *p*-$NO_2C_6H_4$, **d**: *p*-ClC_6H_4

Scheme 52. Sulphonamide derivatives of **83**.

Although the synthesis of the ligands **83** and **84a** were reported by *Somanathan´s* group, no application of these compounds in catalytic asymmetric transformations have, to the best of our knowledge, taken place up to now.

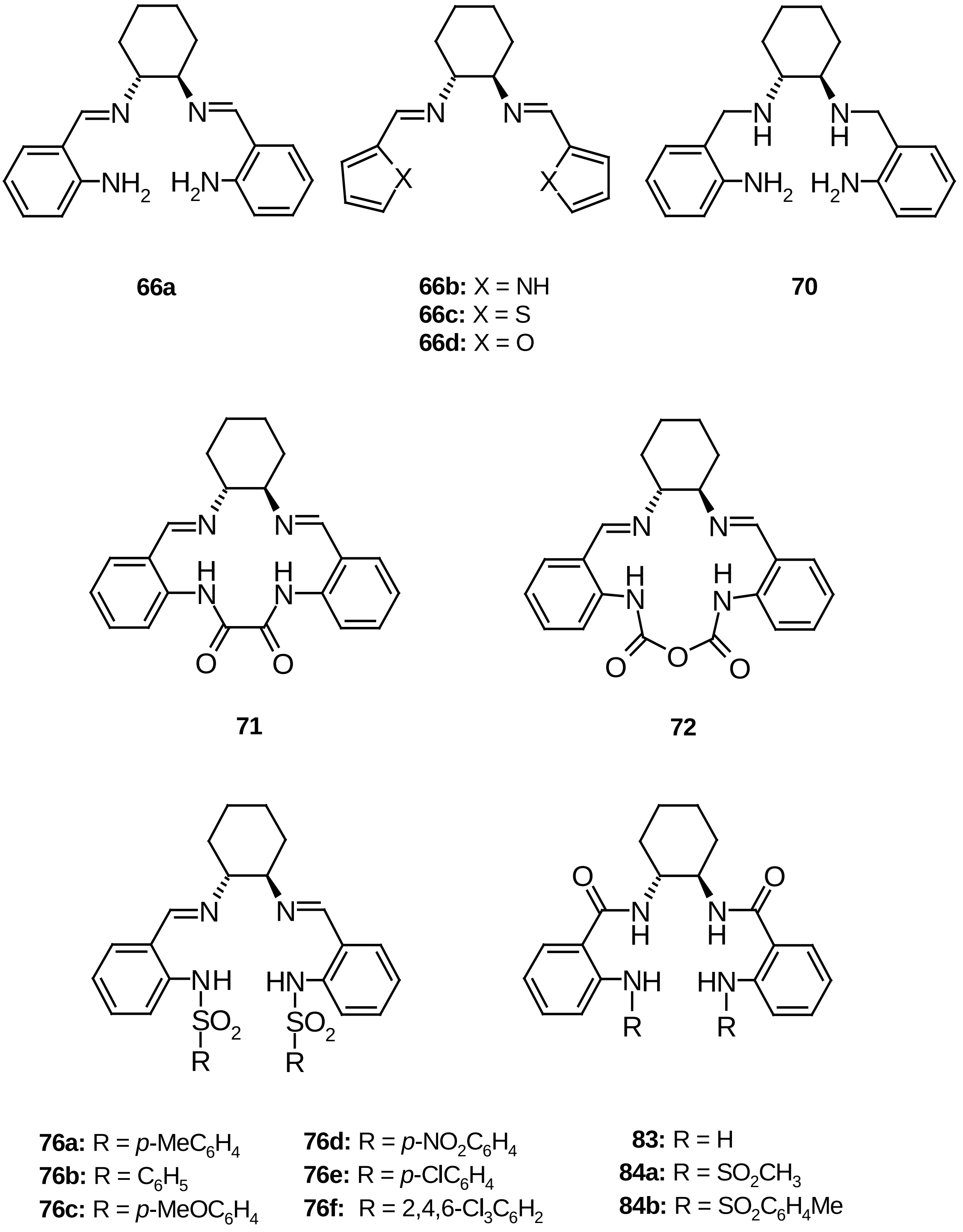
3 Enantioselective Catalysis

3.1 General Considerations

During this work chiral diaminocyclohexane-based tetradentate ligands (see *scheme 53*) were synthesised in a few steps with very good yields, in order to test their activity as catalysts for asymmetric reactions.

Standard asymmetric reactions were used as catalytic transformations, such as the addition of diethylzinc to aldehydes, the epoxidation of styrene in the presence of Mn(III), the Cu(I) catalysed cyclopropanation of the same alkene, the *Lewis* acid catalysed *Mukaiyama* aldol reaction, the *Michael* addition to chalcone using Co(II)[123] and the hydrogen transfer reduction of acetophenone.[124]

The results obtained will be presented and discussed in comparison to known mechanisms described for similar systems.



66a

66b: X = NH
66c: X = S
66d: X = O

70

71

72

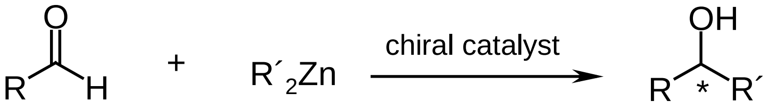
76a: R = p-MeC_6H_4
76b: R = C_6H_5
76c: R = p-$MeOC_6H_4$
76d: R = p-$NO_2C_6H_4$
76e: R = p-ClC_6H_4
76f: R = 2,4,6-$Cl_3C_6H_2$

83: R = H
84a: R = SO_2CH_3
84b: R = $SO_2C_6H_4Me$

Scheme 53. Ligands synthesised for enantioselective catalysis.

3.2 Addition of diethylzinc to aldehydes

The enantioselective addition of organozinc reagents to aldehydes catalysed by chiral ligands (see *scheme 54*) has received widespread attention because it is an efficient method for generating optically active secondary alcohols.[125, 126]



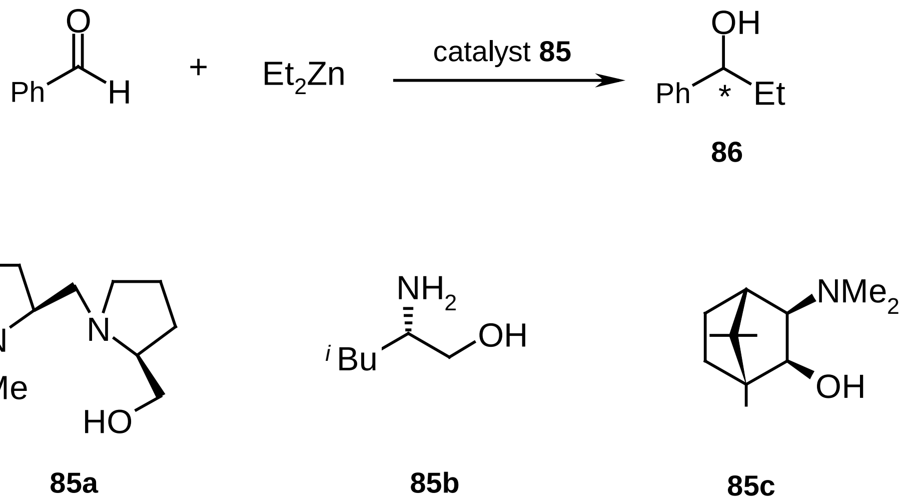
Scheme 54. General addition of organozinc reagents to aldehydes

These optically active alcohols obtained using chiral non racemic auxiliaries are part of many naturally occurring compounds, biologically active molecules and materials, such as liquid crystals. They are also important as synthetic intermediates for the preparation of various functionalities such as halides, amines, esters, ethers, etc.[127]

Organozinc reagents have been known for more than 150 years. In fact, *Frankland* discovered the first organometallic compound, diethylzinc.[128] Due to their moderate reactivity in comparison with the more reactive organomagnesium and organolithium reagents, the use of these reagents was limited to the *Simmons-Smith* reaction, the *Reformatsky* reaction and the polymerisation of oxirane.[129] The principal disadvantage of the alkylation of aldehydes with dialkylzincs lies in the slow course of the reaction at room temperature and the formation of by-products at higher temperatures.[130]

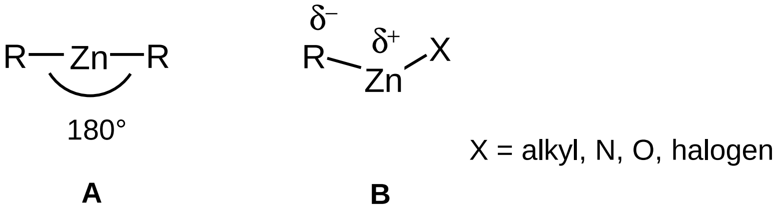
The first nucleophilic addition of diethylzinc to benzaldehyde (see *scheme 55*) was reported by *Mukaiyama et al.* in the presence of *β*-amino alcohol **85a** derived from (*S*)-proline.[131] Although no asymmetric induction was observed, the 1-phenylpropanol **86** was obtained in 76 % yield.

In 1984 *Oguni* and *Omi* described the first asymmetric alkylation with diethylzinc through use of a primary *β*-amino alcohol, (*S*)-leucinol **85b**, giving the secondary alcohol **86** with optical purity of 49 %.[132]



Scheme 55. Addition of diethyl zinc to benzaldehyde catalysed by aminoalcohols.

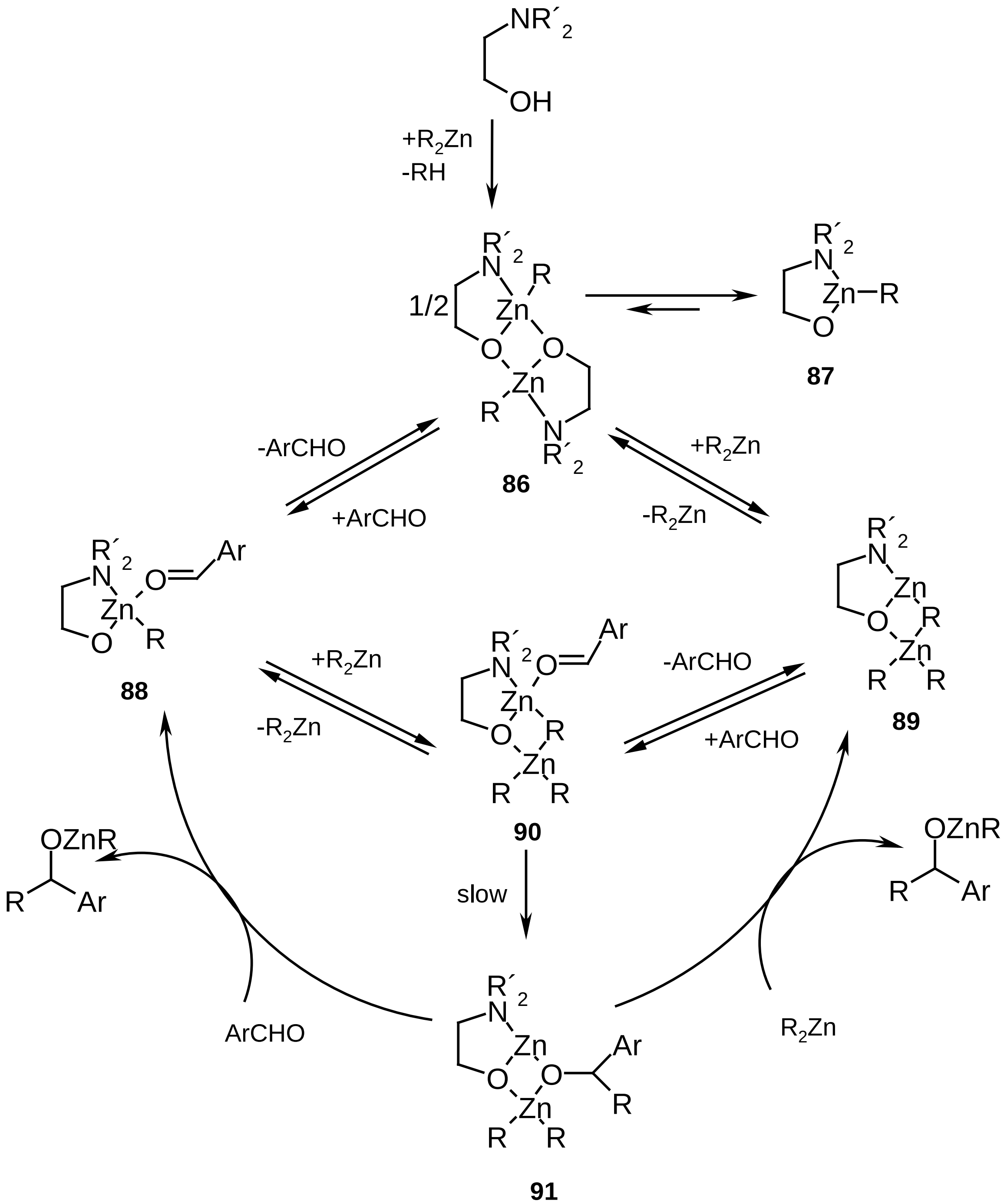
The reason for the high reactivity of organozinc reagents in the presence of auxiliaries such as amino alcohols, is discussed with help of the structures **A** and **B** on *scheme 56*. Monomeric dialkylzincs with sp-hybridised linear geometry at Zn (**A**) are inert to carbonyl compounds because the alkyl-metal bonds are rather nonpolar.[133] However, the bond polarity can be enhanced by creating a bent geometry in which the Zn atom uses molecular orbitals of a higher p character. In particular, coordinatively unsaturated bent compounds with an electronegative substituent X (structure **B**) bearing the high donor ability of the alkyl group R and an acceptor character at the zinc center.[121] In this way, the nucleophilicity of the alkyl group increases and the addition becomes possible.



Scheme 56. Structure of the monomeric dialkylzinc and of the bent complex with an electronegative substituent.

Noyori and co-workers reported the first highly enantioselective catalytic addition of diethylzinc to benzaldehyde using 2 mol % of (-)-3-exo-(dimethylamino)isoborneol [(-)-DAIB, **85c**] as ligand (see *scheme 55*). After 6 hours the (*S*)-1-phenylpropanol was obtained in nearly quantitative yield and an excellent enantiomeric excess of 99 % *ee*.[134] The catalyst is also effective for other aromatic aldehydes but the enantioselectivity of the addition to heptanal is only moderate (61 % *ee*).

Noyori has proposed a mechanism (see *scheme 57*) for the addition of dialkylzinc to aldehydes[121] supported by different methods, such as X-Ray, NMR, molecular weight and kinetic measurements, as well as molecular orbital and density functional calculations.[135]



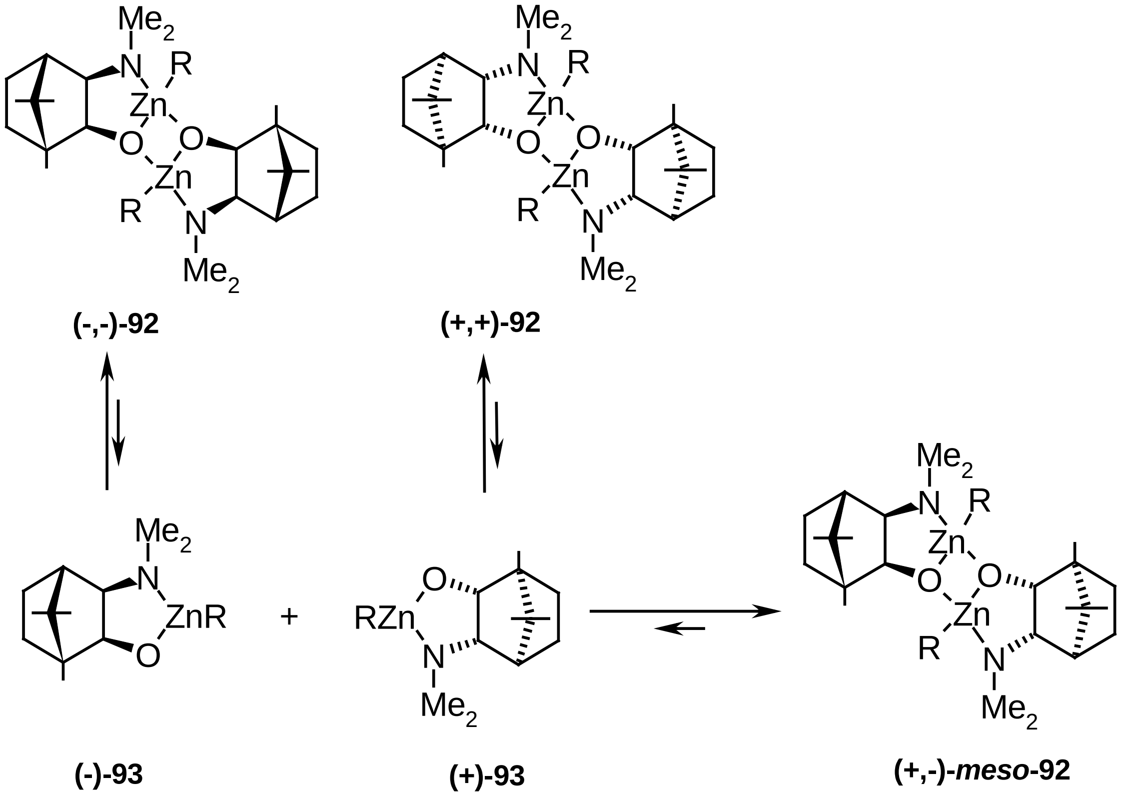
Scheme 57. Mechanism proposed by *Noyori* for the addition of dialkylzinc compounds to aromatic aldehydes in the presence of amino alcohols.

By reaction of equimolar amounts of amino alcohol and dialkylzinc, an alkane is eliminated to produce an alkylzinc alkoxide with a five-membered chelate ring. In accordance with molecular weight measurements, this complex exists in aromatic hydrocarbons[136] as dimer **86** in equilibrium with the monomer **87**. When **86** and an equivalent amount of benzaldehyde are mixed, the dimeric structure of **86** is ruptured, probably via a dissociative mechanism, to produce an equilibrating mixture of **86** and **88**. The complex **88** possesses an aldehyde and alkyl group in the same coordination sphere and is incapable of undergoing intramolecular alkyl transfer reaction. The addition of an equimolar amount of dialkylzinc to **88** results in formation of the dinuclear mixed-ligand complex **90**.

The dimer **86** is also cleaved by addition of one equivalent of dialkylzinc to reversibly produce **89**. This new dinuclear complex accepts a benzaldehyde at its vacant coordination site to form **90**. The species **86-90** exist as a rapidly equilibrating mixture. Each species is also convertible with other possible structural isomers by intra- or intermolecular processes. In fact, it was observed by NMR spectroscopy that the Zn-R groups in this mixture (**86-90**) are indistinguishable.

The dinuclear complex **90** undergoes intramolecular alkyl transfer to produce the alkoxide-bridged dinuclear Zn product **91**.[137] Upon addition of benzaldehyde or dialkylzinc, **91** decomposes to the primary product and **88** or **89** respectively.

For the enantioselective alkylation *Noyori* has observed a nonlinear relationship between the enantiomeric purity of the catalyst and the purity of the product.[138] When the alkylation of benzaldehyde with diethyl zinc was conducted in the presence of 8 mol % of **(-)-85c** (optical purity = 15 % *ee*) (see *scheme 55*), the (*S*)-1-phenylpropanol **86** was obtained with in 95 % *ee*. This important phenomenon of the amplification of the chirality (see *scheme 58*) is explained by the fact that the minor isomer of the chiral catalyst **(+)-93** forms a heterodimeric *meso*-type complex **(+,-)-*meso*-92** with the major isomer **(-)-93** by non-self-recognition. This *meso*-complex is relatively stable and does not catalyse the alkylation. On the other hand, the major isomer of the chiral catalyst **(-)-93**, as well as the minor isomer **(+)-93**, form by self-recognition a less stable homodimeric complex **(-,-)-92** or **(+,+)-92** which dissociates more easily to catalyse the alkylation reation.

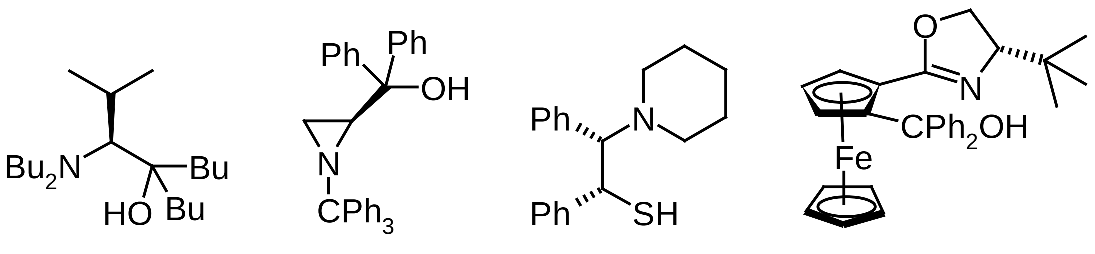


Scheme 58. Explanation of the amplification of the chirality observed by *Noyori* in the enantioselective alkylation of aldehydes with alkylzinc catalysed by amino alcohols.

A great variety of other chiral ligands has been successfully used for the alkylation of aldehydes with organozincs. Starting from L-valine, *Luche* and co-workers synthesised the optically active β-amino alcohol **94** (see *scheme 59*), which possesses flexible butyl groups on both the nitrogen and the hydroxyl carbon.[139a] In the presence of 10 mol % of this ligand, diethylzinc can be added to certain aliphatic and aromatic aldehydes to give the (*R*)-alcohols with 82-97 % *ee*.[137b] Ligands with similar structure, but containing rigid diphenyl substituents on the hydroxyl carbon, showed much lower enantioselectivities (2-75 % *ee*).

Zwanenburg et al. reported an effective chiral aziridino alcohol **95** (see *scheme 59*).[140] This compound catalysed the reaction of aromatic, β-branched aliphatic and cyclic aliphatic aldehydes with diethylzinc with 95-99 % *ee*.

Amino alcohols are not the only class of compounds that have been used as catalysts for the alkylation of aldehydes with organozincs. *Kellogg* and co-workers prepared chiral amino thiols and disulfides from ephedrine for the aforementioned asymmetric reaction.[141] The amino thiol **96** (see *scheme 59*) showed very high enantioselectivities (98-100 % *ee*), especially for the reaction of aromatic aldehydes with diethylzinc.[142]



94 **95** **96** **97**

Scheme 59. Successful ligands for the addition of dialkylzincs to aldehydes.

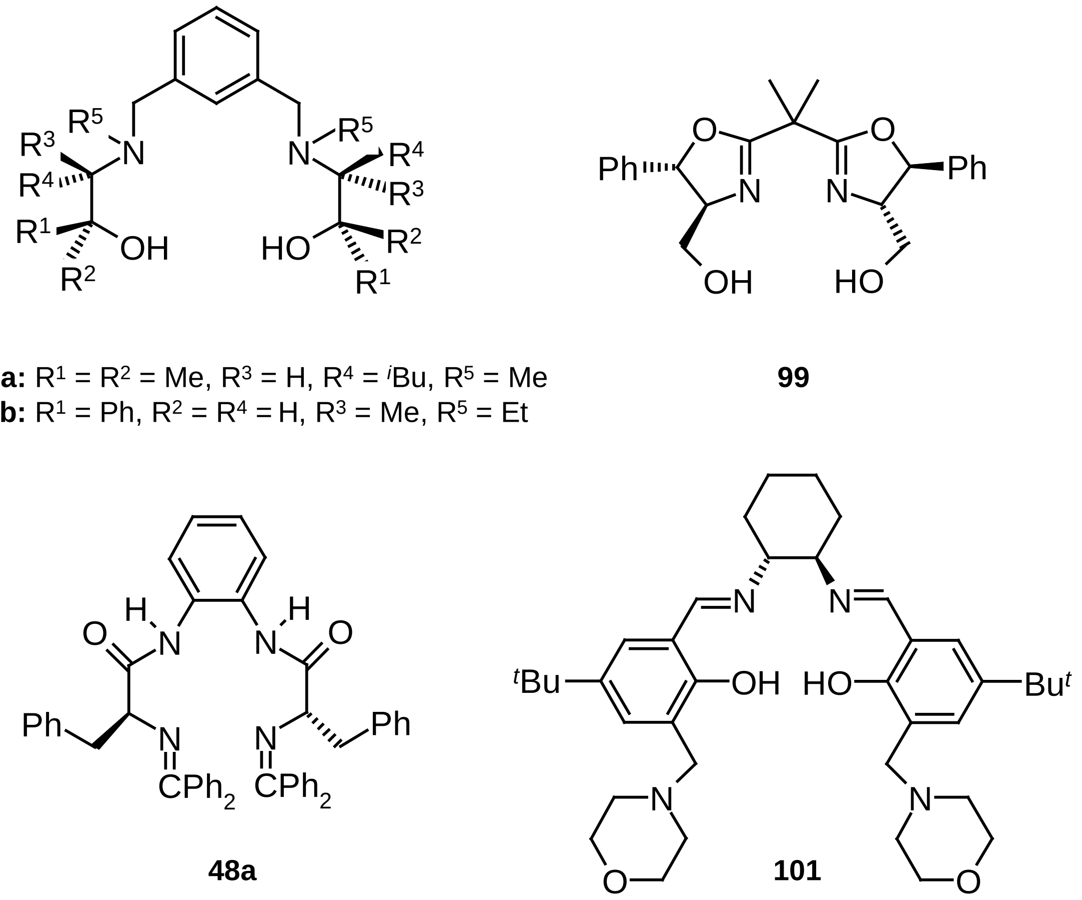
A number of ferrocene-based chiral ligands have been attracted the attention for asymmetric catalysis because of their planar chirality (in substituted ferrocene), their unique bulky structure and their chemical inertness. *Bolm et al.* described the application of the ferrocene ligand **97** (see *scheme 59*) containing a chiral oxazoline unit, to catalyse the reaction of diethylzinc with aromatic, aliphatic and *α*, *β*-unsaturated aldehydes with 83-94 % yield and 78-95 % *ee* at 0 °C in toluene.[143]

On the other hand, ligands containing two amino alcohol units (**98a-b** in *scheme 60*) have been prepared by *Pedrosa* and co-workers.[144] For the catalytic reaction of several aromatic aldehydes these ligands showed high enantioselectivities (90-98 % *ee*).

Chiral oxazolines have been used for the asymmetric organozinc addition. *Reiser* and co-workers reported the activity of the bis(oxazoline) **99** (see *scheme 60*) in the addition of diethylzinc to aromatic and aliphatic aldehydes. High enantioselectivities (83-95 % *ee*) have been achieved, especially with aromatic aldehydes. In the case of aliphatic aldehydes, both yield and enantioselectivity could be considerably increased in the presence of catalytic amounts of *n*-BuLi as additive.[145]

Dangel and *Polt* published the first tetra-aza ligand **48a** (see *scheme 60*) used in the asymmetric addition of alkylzincs to aromatic and aliphatic aldehydes.[56] In the explanation of the reaction mechanism was assumed that two Zn atoms are involved in alkyl transfer, the “inner” Zn is surrounded by electron-donating nitrogens, while the "outer" Zn is only "solvated" by exchangeable oxygens[146]. The yields and enantioselectivities obtained have been discussed earlier in section 1.7.

One year later, *Kozlowski* and *DiMauro* reported a set of modular bifunctional salen catalysts which contains *Lewis* acid and *Lewis* base activating groups (*e.g.* **101** in *scheme 60*). With the use of the Zn complex of **101**, high levels of conversion (78-99 %) and enantiomeric excess (69-91 % *ee*) were obtained for aromatic as well as aliphatic aldehydes.[147]



98a: $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = {}^iBu$, $R^5 = Me$
98b: $R^1 = Ph$, $R^2 = R^4 = H$, $R^3 = Me$, $R^5 = Et$

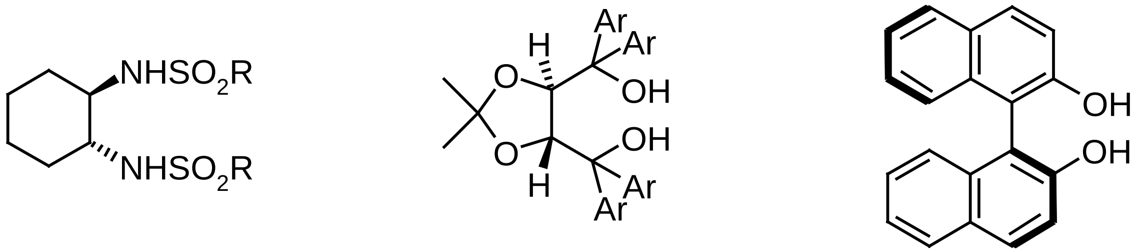
99

48a

101

Scheme 60. Ligands forming tetracoordinated complexes with Zn.

Ohno and *Kobayashi* developed the initial studies of the asymmetric addition reactions using bis(sulphonamide)-based ligands (*e.g.* **102a-c**, see *scheme 61*).[148] They found that the addition of diethylzinc to benzaldehyde with the ligands **102** as catalysts was rather slow, even at room temperature, and produced the chiral secondary alcohols in 57 % yield with only 54 % ee.



102a: R = CF_3
102b: R = *p*-MeC_6H_4
102c: R = 1-naphthyl

103a: Ar = Ph
103b: Ar = 2-naphthyl

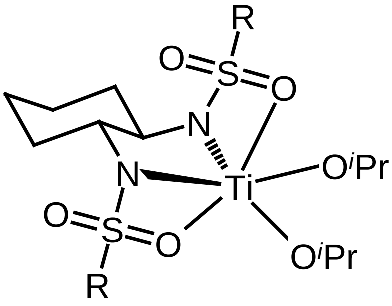
(*S*)-104

Scheme 61. Ligands used in the presence of titaniumtetraisopropoxide.

On the other hand, when the asymmetric reaction was carried out in the presence of $Ti(O^iPr)_4$ yields superior to 85 %, with very good enantioselectivities (98 % *ee*), were obtained.[148b]

Subsequently, *Knochel* and co-workers explored the scope of this process and found that a wide variety of functionalised secondary alcohols could be obtained with high enantioselectivity.[149] In these studies, the catalytic active species were generated *in situ* from the ligand, dialkylzinc reagents and titanium tetraisopropoxide.

X-Ray investigations developed by *Walsh* and co-workers established the structure of the bis(sulfonamido)-titanium complexes.[150] The titanium center coordinates two sulphonyl oxygens and the sulfonamido nitrogens, creating a rigid asymmetric environment (see *scheme 62*), which may be important in the transfer of asymmetry in the transition state of the asymmetric addition reaction.[151]



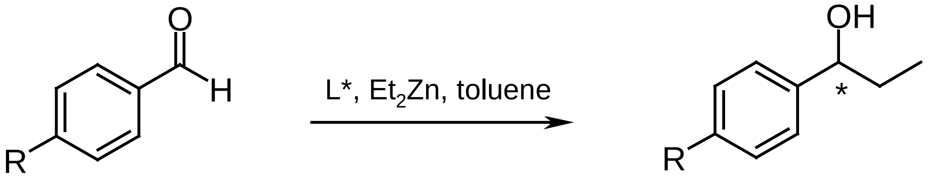
Ti-**102**, **R** = *p*-$MeOC_6H_4$

Scheme 62. Structure of the titanium complex (Ti-**102**) established by X-Ray.

All of the ligands discussed so far for the catalytic dialkylzinc addition contain nitrogen atoms. Compounds without nitrogen have also been widely used in many other asymmetric transformations (*e.g.* TADDOLs **103a-b** and BINOL **104**, see *scheme 61*).
Seebach and co-workers have extensively studied the asymmetric organozinc addition using the titanium complexes of the TADDOLs **103a-b**. In the presence of 20 mol % of these titanium complexes, with an excess amount of $Ti(O^iPr)_4$ and at temperatures from –76 to –20 °C, additions of dialkylzinc reagents to aromatic and aliphatic aldehydes were highly enantioselective (82-99 % *ee*). The sterically bulkier complex derived from **103b** was a more effective catalyst than **103a**, especially for aliphatic, olefinic and acetylenic aldehydes.[152]
BINOL ligands are axially chiral diols that have found application in asymmetric catalysis, among other things.[153] In 1997, the groups of *Nakai*[154] and *Chan*[155] independently reported the use of titanium complexes of ligand **104** (see *scheme 61*) for the asymmetric diethylzinc addition to aldehydes. It was found that the ratio of ligand and $Ti(O^iPr)_4$ in the chosen solvent had great effect on the enantioselectivity. The best results (up to 92 % *ee* for aliphatic, aromatic and *α*, *β*-unsaturated aldehydes) were obtained by a ratio of 1:7 **[(*S*)-104**: $Ti(O^iPr)_4$] in CH_2Cl_2 and 1:12 in toluene.

3.3 Results of the catalysis

The synthesised ligands were first screened in the asymmetric addition of diethylzinc to benzaldehyde **105a** to obtain the chiral 1-phenylpropanol **106a** (see *scheme 63*).

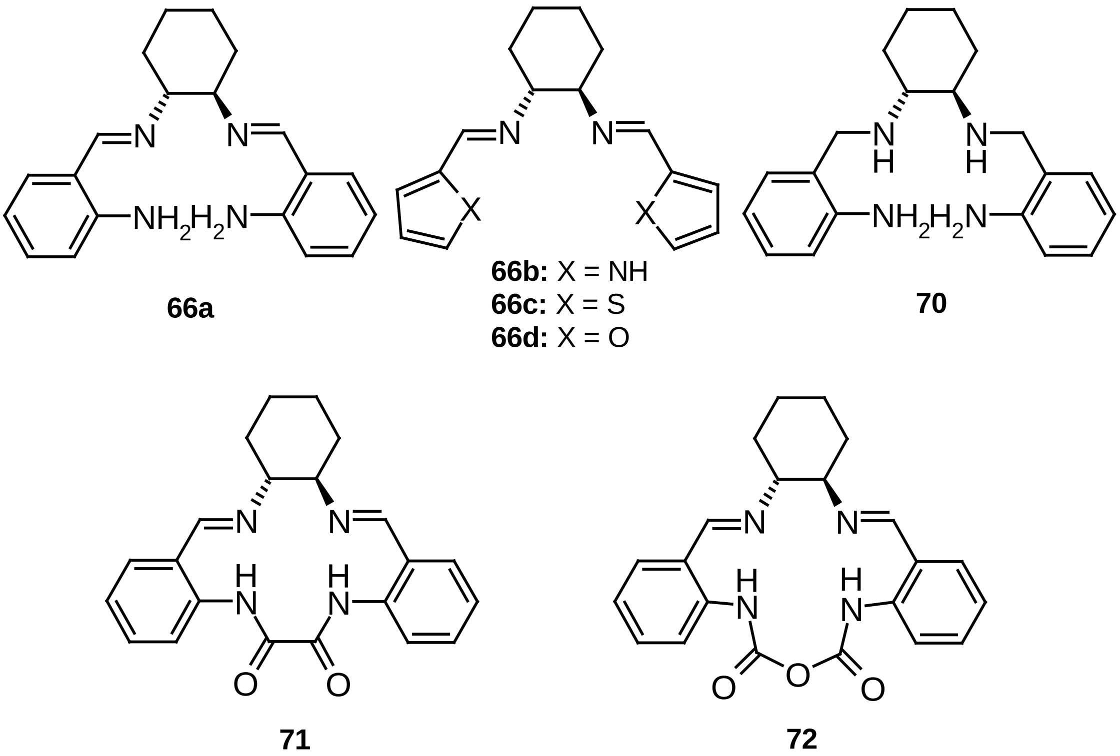


105a: R = H
105b: R = Cl
105c: R = MeO

106a: R = H
106b: R = Cl
106c: R = MeO

Scheme 63. Addition of diethylzinc to aromatic aldehydes.

The catalytic reactions were carried out according to the method reported by *DiMauro* and *Kozlowski*,[144] by using 5 mol % of the corresponding ligand. The reaction time for the preliminary catalysts was 24 hours in all cases. *Table 3* shows the results obtained with ligands **66a-d**, **70**, **71** and **72**, which are represented in *scheme 64*.



Scheme 64. First ligands screened on the addition of diethylzinc to benzaldehyde.

Table 3. Results obtained using the diimine ligands **66a-d** and **70-72** in the asymmetric diethylzinc addition to benzaldehyde **105a**.

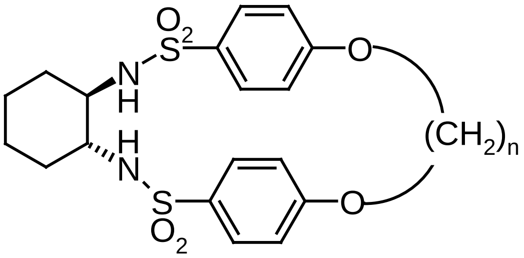
entry	catalyst	yield [%]	*ee* [%]	configuration
1	**66a**	32	3	(*R*)
2	**66b**	12	3	(*S*)
3	**66c**	32	6	(*S*)
4	**66d**	30	5	(*S*)
5	**70**	19	3	(*R*)
6	**71**	51[a]	*racemic*	-
7	**72**	88 [a]	6	(*S*)

[a] yield determined by GC.

After testing the acyclic ligands (entries 1-5, *table 3*), it was only possible to obtain low yields (12-32 %) of the secondary alcohol **106a** (see *scheme 63*) and very modest enantioselectivities. Although these ligands are *Lewis* bases (possess nitrogen, sulphur or oxygen as electron donor atoms), which permit the activation of diethylzinc by formation of zincates, presumably the reached nucleophilicity was not high enough for the efficient alkyl group transfer to the aldehyde and consequently for the enhancement of the enantiomeric purity of the alcohols.

With the cyclic diimine ligands **71** and **72** better yields in 1-phenylpropanol **106a** (51 and 88 %, entries 6-7, *table 3*) were obtained than with the acyclic ones, but no or very low enantioselectivities were observed. The cause of this behaviour could be the small size of the disposable cavity, which is not large enough to accommodate the Zn atom to form the intermediate zincate essential for the intramolecular alkyl transfer reaction.

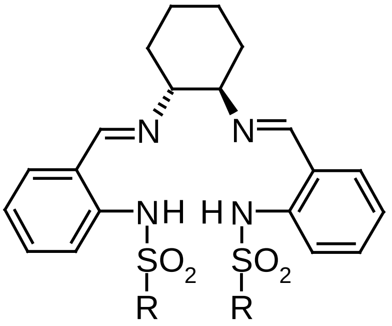
This hypothesis is in accordance with the results reported by *Walsh* and co-workers.[156] They synthesised a set of macrocyclic bis(sulphonamide) ligands **107** (see *scheme 65*), where the aryl groups are joined with carbon-based tethers of variable length. When the tether was short (n = 6, 9, 10 and 12), the resultant catalysts exhibited low enantioselectivities (10-38 %), but when the length of the tether was extended (n = 18, 22), the catalytic activity increased, and approached that of the acyclic ligands (**102a-c**, see *scheme 61*).



107: n = 6, 9, 10, 12, 18, 22

Scheme 65. Macrocyclic bis(sulphonamide) ligands **107** for the addition of diethylzinc to benzaldehyde.

Different sulphonamide derivatives (**76a-f**, see *scheme 66*) were synthesised analogous to the catalysts **102a-c** (see *scheme 61*), which have been successfully used in the asymmetric alkylation with organozinc reagents. *Table 4* summarises the yields of the (*R*)-1-phenylpropanol **106a** and enantioselectivities (70 and 74 % *ee*, respectively) reached with the *p*-toluenesulphonamide and the benzenesulphonamide derivatives (**76a** and **76b**, entries 1-2) at room temperature and after 24 hours. A lower yield, but also good enantioselectivity, was obtained with the *p*-methoxy-benzenesulphonamide substituted ligand **76c**.



76a: R = *p*-MeC_6H_4
76b: R = C_6H_5
76c: R = *p*-$MeOC_6H_4$
76d: R = *p*-$NO_2C_6H_4$
76e: R = *p*-ClC_6H_4
76f: R = 2,4,6-$Cl_3C_6H_2$

Scheme 66. Sulphonamides used as catalyst in the asymmetric alkylation reaction.

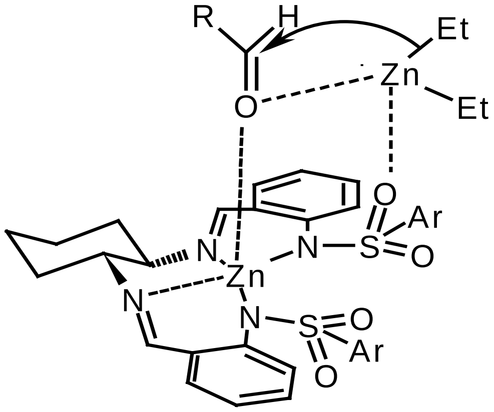
Table 4. Results obtained using the diimine-sulphonamide ligands **76a-f** (see *scheme 66*) in the asymmetric diethylzinc addition to benzaldehyde **105a**.

entry	catalyst	yield [%]	*ee* [%]	configuration
1	**76a**	100	70	(*R*)
2	**76b**	100	74	(*R*)
3	**76c**	74	70	(*R*)
4	**76d**	43	38	(*R*)
5	**76e**	47	55	(*R*)
6	**76f**	34[a]	21	(*R*)

[a] yield determined by GC.

Due to the strongly electron-withdrawing nature of the sulphonyl group, the sulphonamide protons are acidic, having pK_a´s similar to phenol ($pK_a \sim 10$).[157]

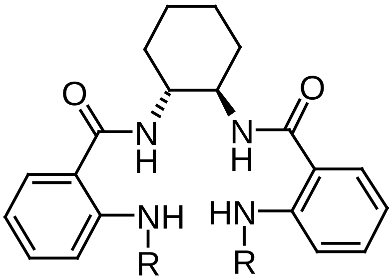
Dangel and *Polt* have proposed a mechanism for the asymmetric addition of diethylzinc with tetra-aza ligands, in which has been assumed that two Zn atoms are involved in the alkyl transfer: the “inner” Zn atom and the “outer” Zn atom (previously mentioned in section 3.2).[56] When diethylzinc was added to the ligand, a tetracoordinate sulfonamido-Zn complex with a strong *Lewis* acidity was formed (see *scheme 67*). By coordination to this *Lewis* acidic Zn atom, the aldehyde (electrophile) was activated. Its electrophilicity is enhanced to be favourable attacked by the diethylzinc.[158] On the other hand, the “outer” zinc is “solvated” by exchangeable oxygens. This increases its nucleophilicity and favours the alkyl transfer.



Scheme 67. Possible mechanism for the addition of diethylzinc to aldehydes.

On the other hand, and not clear on this model is the behaviour of the sulphonamides with electron-withdrawing substituents (**76d-f**, entries 4-6, *table 4*). They have shown lower reactivities and enantioselectivities for the catalytic reaction.

In *table 5* the results obtained with the synthesised amide ligands (see *scheme 68*) can be seen. When 5 mol % of the diamide **83**, as well as its derivatives **84a-b** were used, only yields of about 50 % have been achieved. The enantioselectivities obtained with the free diamide-diamine ligand **83** and its dimesyl-derivative **84a** are low, but very similar (25 and 28 %, respectively), while with the bulkier ditosyl-derivative **84b** only a very slight asymmetric induction could be measured. It is interesting to mention the change in the stereochemistry of the preferred product from *R* to *S* when the steric hindered chiral ligand **84b** was used.



83: R = H
84a: R = Ms
84b: R = Ts

Scheme 68. Bis-amide ligands for the asymmetric addition of diethylzinc to benzaldehyde.

Table 5. Results obtained using ligand **83** and its sulphonamide derivatives **84a-b** (see *scheme 68*) in the asymmetric diethylzinc addition to benzaldehyde **105a**.

entry	catalyst	yield [%]	*ee* [%]	configuration
1	**83**	55	25	(*R*)
2	**84a**	47	28	(*R*)
3	**84b**	50	5	(*S*)

After the preliminary screening of the majority of the synthesised ligands, only the sulphonamide-derivatives **76a** and **76b** (see *scheme 66*) have shown to promote the asymmetric alkylation of benzaldehyde with diethylzinc in excellent yields and with good enantioselectivities.

From the numerous studies made on chiral sulphonamides of 1*R*, 2*R*-(*trans*)-diamine-cyclohexane **102a-c** (*scheme 61*), it is known that these ligands can act as efficient catalysts in variable quantities. A reduction in the amount of chiral ligand from 2.00 to 0.05 mol % has no effect on the yield and enantioselectivity of the *sec*-alcohol.[159]

Based on this, the ligand **76a** was selected with the aim to determine the optimal amount of this ligand needed for the addition of diethylzinc to benzaldehyde **105a** (see *scheme 63*). From the experiments listed in *table 6*, it can be seen that after 48 hours and using 1.0 and 2.5 mol % of the catalyst, low yields, as well as low enantiomeric excesses, were obtained (entries 1-2). Quantitative yield and good enantioselectivity were achieved when 5 mol % were used. Further increases in the amount of the catalyst (7.0 and 10.0 mol %) did not improve the progress of the catalysis. Thus, for the future catalytic alkylations it was decided to utilise the optimised quantity of 5 mol % of catalyst.

Table 6. Results of the test searching for the optimal quantity of the catalyst **76a** to use in the asymmetric alkylation with diethyzinc.

entry	catalyst (mol %)	yield [%][a]	*ee* [%]
1	1.0	29	30
2	2.5	29	56
3	5.0	100	70
4	7.0	100	70
5	10.0	100	70

[a] isolated yield after 48 hours.

Encouraged by the results obtained with the sulphonamide derivatives **76a-b** in the addition of diethylzinc to benzaldehyde **105a**, and having optimised the reaction conditions (amount of the catalyst, equivalents of diethylzinc) it was decided to extend this asymmetric alkylation to other aldehydes. The *p*-chlorobenzaldehyde **105b** and *p*-methoxybenzaldehyde **105c** (see *scheme 63*) and furfural **108** (heteroaromatic aldehyde, see *scheme 69*) were then selected as substrates.

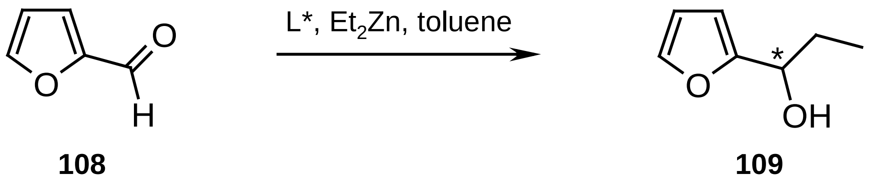
The reactions were run under the same conditions described at the beginning of the section 3.3, but at two different temperatures (0 and 25 °C). The results are reported in *table 7*.

As expected, the yields obtained with both ligands and for all aldehydes used were higher at room temperature (entries 6, 8, 10, 12, 14, 16) than at 0 °C (entries 5, 7, 9, 11, 13, 15), but they were much lower than those obtained with benzaldehyde (entries 1-4). The presence of an electron donor substituent (OMe) on the *para* position of aldehyde **105c** contributes to an increase in the yield of the secondary alcohol **106c**, while the electron acceptor substituent (Cl, aldehyde **105b**) in the same position causes the opposite effect.

Table 7. Addition of diethylzinc to *p*-substituted benzaldehydes **105b-c** and heteroaromatic aldehyde **108** using the diimine-sulphonamides **76a** and **76b**.[160]

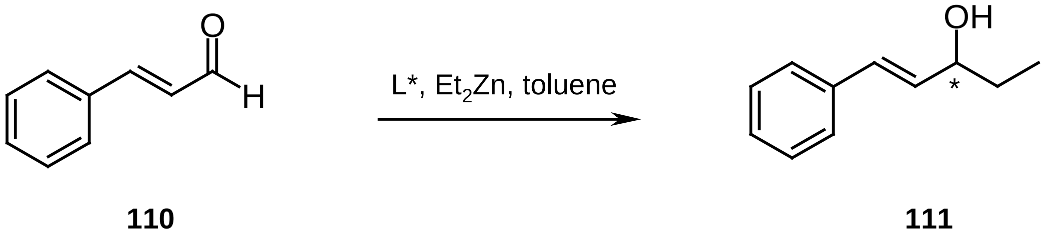
entry	Aldehyde R	ligand	temp (°C)	yield [%]	*ee* [%]	config.
1	H	**76a**	0	89	71	(*R*)
2	H	**76a**	25	100	70	(*R*)
3	H	**76b**	0	93	75	(*R*)
4	H	**76b**	25	100	74	(*R*)
5	Cl	**76a**	0	21	64	(*R*)
6	Cl	**76a**	25	60	71	(*R*)
7	Cl	**76b**	0	23	69	(*R*)
8	Cl	**76b**	25	65	74	(*R*)
9	OMe	**76a**	0	53	45	(*R*)
10	OMe	**76a**	25	70	62	(*R*)
11	OMe	**76b**	0	51	57	(*R*)
12	OMe	**76b**	25	76	56	(*R*)
13	Furfural	**76a**	0	49	70	(*R*)
14	Furfural	**76a**	25	61	28	(*R*)
15	Furfural	**76b**	0	21	69	(*R*)
16	Furfural	**76b**	25	44	37	(*R*)

Unexpectedly, the enantioselectivities achieved for both *para*-substituted aromatic secondary alcohols (**106b** and **106c**, see *scheme 63*) were superior when the reactions were carried out at room temperature (entries 6, 8, 10). For the heteroaromatic aldehyde furfural (**108**, see *scheme 69*) the opposite behaviour was observed, *i.e.* at 0 °C better enantiomeric excesses (70 and 69 % *ee*, entries 13 and 15) than at room temperature were obtained.



Scheme 69. Addition of diethylzinc to furan-2-carboxaldehyde **108**.

Under the asymmetric catalysis conditions mentioned above, the *α*, *β*-unsaturated cinnamaldehyde **109** (see *scheme 70*) reacts exclusively by 1, 2-addition in the presence of diethylzinc. No formation of the 1, 4-addition product was detected. From *table 8*, it can be seen that low yields (8-20 %), but moderate enantioselectivities (31-44 % *ee*), were obtained with both ligands.



Scheme 70. Enantioselective addition of diethylzinc to *α*, *β*-unsaturated aldehyde **110**.

Table 8. Results of the asymmetric 1,2-addition of diethylzinc to cinnamaldehyde **110** with the diimine-sulphonamide ligands **76a** and **76b**.[161]

entry	aldehyde	ligand	temp (°C)	yield [%][a]	*ee* [%]
1	**110**	**76a**	0	8	38
2	**110**	**76a**	25	19	31
3	**110**	**76b**	0	12	44
4	**110**	**76b**	25	20	33

[a] isolated yield

The attempts to alkylate heptanal with diethylzinc in presence of the chiral sulphonamides **76a** and **76b** were unsuccessful. No conversion could be detected after four days reaction, neither at 0 °C nor at room temperature.

When the ligands **76a** and **76b** catalysed the addition of diethylzinc to *para*-substituted benzaldehydes, an anomalous behaviour on the enantioselectivity of the achieved secondary alcohol was observed. The enantioselectivities were higher at room temperature than at 0 °C. Therefore, an additional set of catalyse was performed with both ligands at 50 °C to investigate the influence of higher temperature on the progress of the reaction.[162] Using benzaldehyde **105a** as substrate, quantitative yields of 1-phenylpropanol **106a** were achieved after five hours. In comparison with the enantioselectivities reached at room temperature, only a slight diminution (approximately 8 %) had taken place when the temperature was increased (see details in *table 9*).

Table 9. Influence of the increase of temperature on the yield and enantioselectivity of the addition of diethylzinc to benzaldehyde.

entry	ligand	temp (°C)	yield [%]	*ee* [%]
1	**76a**	50	100	62
2	**76a**	25	100	70
3	**76b**	50	100	67
4	**76b**	25	100	74

In section 3.2 the course of the asymmetric diethylzinc addition to aldehydes using bis(sulphonamide)-based ligands **102a-c** as catalysts was discussed. The catalytic reaction was rather slow even at room temperature, and produced the chiral secondary alcohols in moderate yields and enantioselectivities. But when this reaction was carried out in the presence of $Ti(O^iPr)_4$, very good yields and enantioselectivities were obtained.[148b]

Inspired by these observations, it was decided to test the activity of the ligand **76a** in the diethylzinc addition to benzaldehyde in the presence of $Ti(O^iPr)_4$.

A mixture of ligand (5 mol %) and $Ti(O^iPr)_4$ (1.4 equivalents) dissolved in toluene was stirred for one hour under reflux to form the titanium complex. After cooling to room temperature, diethylzinc (2.5 equivalents) and benzaldehyde were added. After workup of the reaction, the 1-phenylpropanol **106a** was obtained in 73 % yield, but with only 5 % *ee* (entry 1, *table 10*).

This result can be explained according to the observations made by *Kobayashi et al.* on the asymmetric alkylation reaction with C_2-symmetric bis(sulphonamides) (*e.g.* **102a**, see *scheme 61*). When the reaction was performed at temperatures higher than 0 °C, competition between chiral and achiral catalytic processes had taken place, with preference for the latter. Under these conditions the reactivity of $Ti(O^iPr)_4$ was higher than the reactivity of the chiral titanate complexes, what lead to a considerable decrease in the enantioselectivity of the alkylation.[148b] With the aim to inhibit this process, further attempts to catalyse the asymmetric reaction under addition of $Ti(O^iPr)_4$ were developed at –30 °C (entries 2-3, *table 10*).

Table 10. Addition of diethylzinc to benzaldehyde in the presence of titaniumtetraisopropoxide and ligand **76a**.

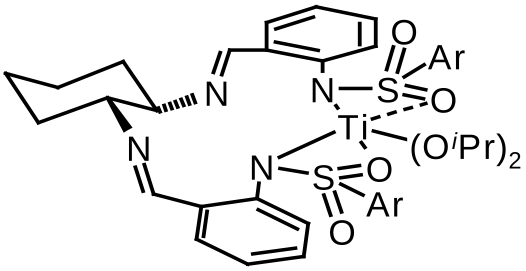
entry	eq. $Ti(O^iPr)_4$	temp (°C)	yield [%][a]	*ee* [%]
1	1.4	25	73	5
2	0.6	-30	36	6
3	1.2	-30	48	3

[a] yields determined by GC.

Kobayashi also demonstrated that when the reaction was carried out with a quantity of $Ti(O^iPr)_4$ lower than 0.3 equivalents (in relation to the aldehyde), prolonged reaction time was still necessary at room temperature for completion of the reaction. On the other hand, an excess of titanium (1.2 equivalents) accelerated the progress of the reaction and did not cause a decrease in the enantioselectivity. When an excess of titanium was combined with an excess of dialkylzinc, the best results were obtained.[148b]

From *table 10* it can be seen that when using an excess of $Ti(O^iPr)_4$ (entry 3), an increase in the yield of the secondary alcohol was observed, in comparison to the yield obtained with 0.6 equivalents of the metal alkoxide (entry 2). But in both cases no improvement on the enantioselectivities was possible, even at low temperature.

Contrary to what was expected with use of $Ti(O^iPr)_4$, only a drastic decrease on the yields and enantioselectivities was obtained.



Ti-**76**

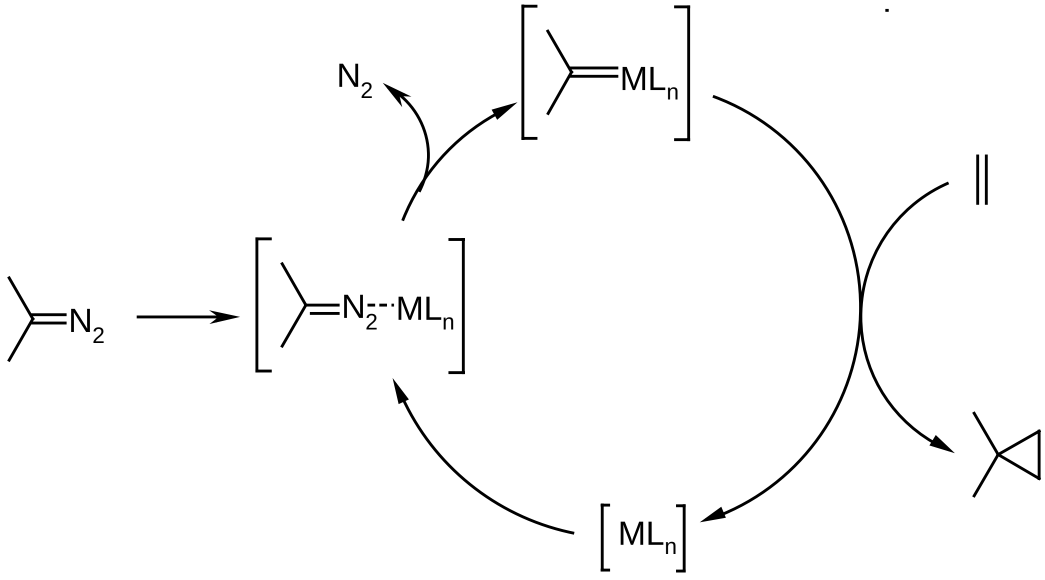
Scheme 71. Possible intermediate for the addition of diethylzinc to benzaldehyde with ligand **76** in the presence of Ti(O^{i}Pr)$_4$.

The only obvious explanation for this behaviour is the formation of a complex between titanium and the chiral sulphonamide **76a**, analogous to the structurally characterised complex Ti-**102** (see *scheme 62*, section 3.2). With the addition of Ti(O^{i}Pr)$_4$, the sulphonamide should be deprotonated to give the complex presented in *scheme 71*, where titanium coordinates the sulfonamido nitrogens and two sulphonyl oxygens. As can be seen, the nitrogen donor atoms attached to the chiral centers do not participate in the chelation, therefore only an achiral complex can be obtained, with a subsequent lack of enantiomeric control in the catalytic reaction.

3.4 Cyclopropanation

Cyclopropanes are versatile intermediates in organic synthesis that can be converted to a variety of useful products by cleavage of the strained three-membered ring.[163] Great efforts have been made to develop efficient stereoselective methods for the synthesis of cyclopropanes[164] because numerous natural and synthetic cyclopropanes have shown interesting physiological activities.[165] In particular, the cyclopropanation of olefins with diazo compounds has received considerable attention and, during the last two decades, efficient homogeneous metal catalysts have been found, which have strongly enhanced the scope of this reaction.[166]

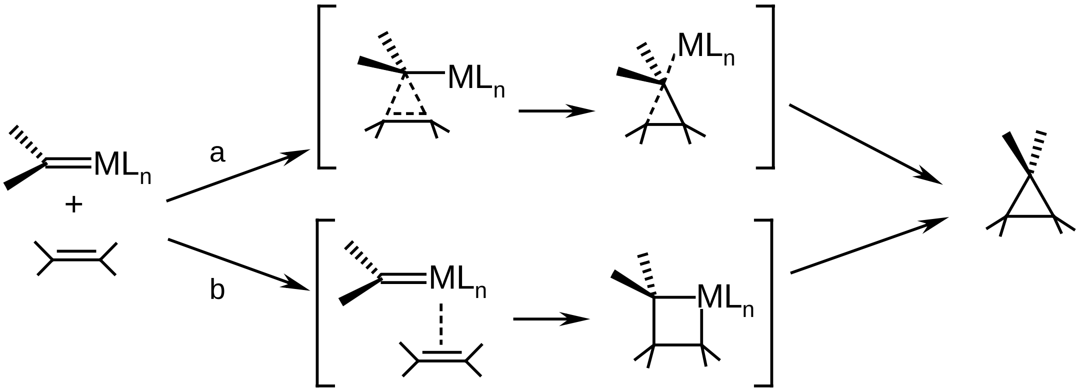
Among the many different transition metal compounds that are known to catalyse the extrusion of dinitrogen from diazo compounds, the most general and widely used catalysts are Cu and dinuclear Rh(II) complexes. Palladium complexes, for example, are efficient catalysts for the cyclopropanation of electron-deficient carbon-carbon double bonds with diazoalkanes, in contrast to Cu and Rh catalysts which are better suited for reactions with electron-rich olefins.[167] Attempts to develop chiral Pd catalysts for enantioselective cyclopropanation have not been successful so far,[168] but promising results have been obtained by using Co[169] and Ru[170] complexes.



Scheme 72. Catalytic cycle for the cyclopropanation.

The mechanism of transition metal-catalysed dinitrogen extrusion from diazo compounds is not known in detail, but there is a general agreement that metal-carbene complexes are formed in this process.[165] In the last years, Ru- and Os-carbene complexes have been isolated from stoichiometric reactions with diazoacetates and demonstrated to be active catalysts for cyclopropanation.[171] For the Cu-catalysis it is assumed that the reaction takes place by an analogous mechanism via short-lived Cu-carbene intermediates.

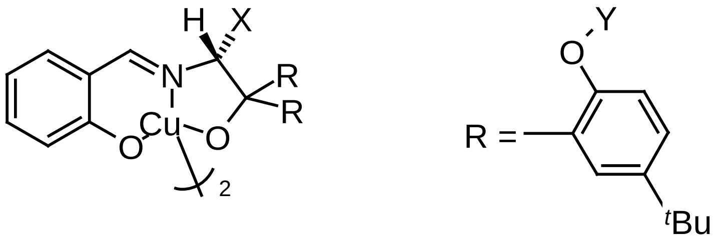
In *scheme 72* the catalytic cycle for the cyclopropanation can be seen. In the first step, the metal-carbene intermediate is formed by reaction among the chiral metal complex and the diazo compound. This step is not of primary concern for the enantioselective reaction. In the second step, the metal-carbene complex reacts with the substrate, this being the enantioselective step.



Scheme 73. Pathways for the formation of cyclopropane rings.

The cyclopropanation is initiated by the interaction of the electrophilic metal-carbene species with the π-system of the olefin (see *scheme 73*). For the formation of the cycloprane ring two different mechanisms have been proposed: a concerted pathway (**a**) or a two-step process via a metallacyclobutane (**b**). The pathway (**a)** resembles the mode of addition of free carbenes to C=C double bonds. The principal bonding interaction in this case initially develops between the electrophilic carbenoid C-atom and the π-system of the alkene. The second pathway (**b**) begins with coordination of the olefin to the metal center leading to a metallacyclobutane as the central intermediate which then undergoes reductive elimination to cyclopropane.

Inspired by the pioneering work of *Nozaki* and co-workers,[172] numerous research groups initiated the search for more efficient catalysts for enantioselective cyclopropanation. The most spectacular advances were made by *Aratani* and collaborators. After extensive evaluation of many different salicylaldiimine ligands, they found a practically useful catalyst (**112a-b**, see *scheme 74*), which gave moderate to high enantioselectivities in the cyclopropanation of olefins with alkyl diazoacetates.[173]



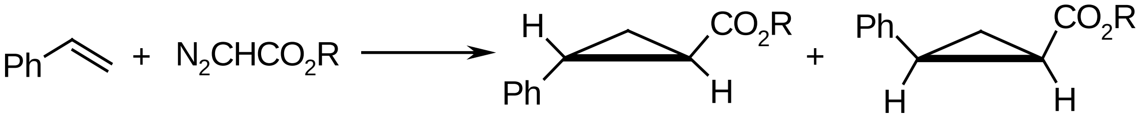
112a: $X = CH_3$, $Y = C_8H_{17}$
112b: $X = CH_2Ph$, $Y = C_4H_9$

Scheme 74. Aratani's salicylaldiimine-Cu-complexes for the enantioselective cyclopropanation.

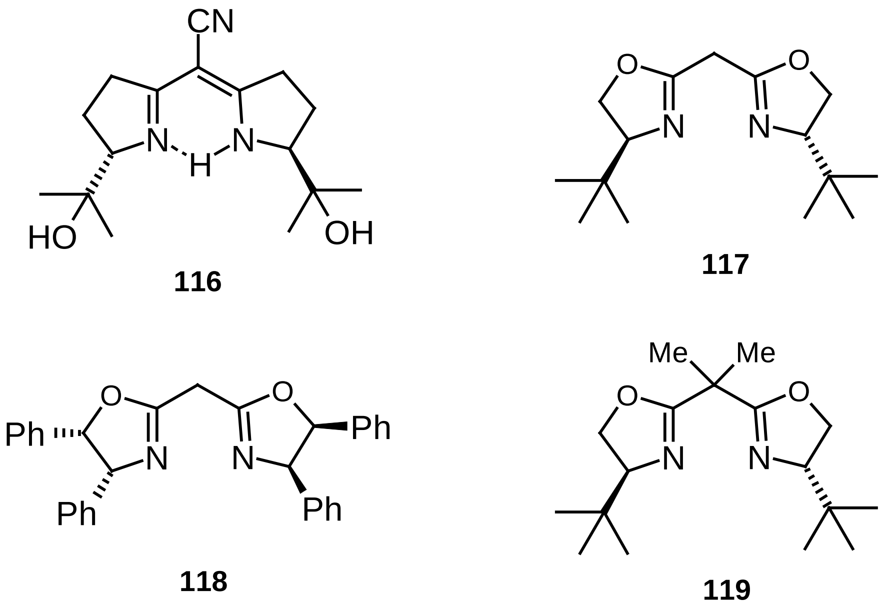
In this way, esters of chrysanthemic acid and permethrinic acid, which are important precursors for the synthesis of pyrethroid insecticides, can be prepared in >90 % *ee*.

The major advance in chiral catalyst design was the contribution of chiral semicorrin ligands (*e.g.* **116**, see *scheme 76*) for Cu made by *Pfaltz*.[174] With these ligands greater enantiocontrol (91-97 % *ee* for ***trans*-115**) for cyclopropanation of styrene was obtained (see *scheme 75*) than with *Aratani*'s ligands (69-81 % *ee* for ***trans*-115**), but their effectiveness was low with di- or trisubstituted alkenes, presumably for steric reasons.[175]

In the course of these investigations, Cu(I) was found to be the catalytically active species. This oxidation state can be reached by direct reduction of the Cu(II)-complex with the diazo compound, or by treatment of this complex with phenylhydrazine.[176]



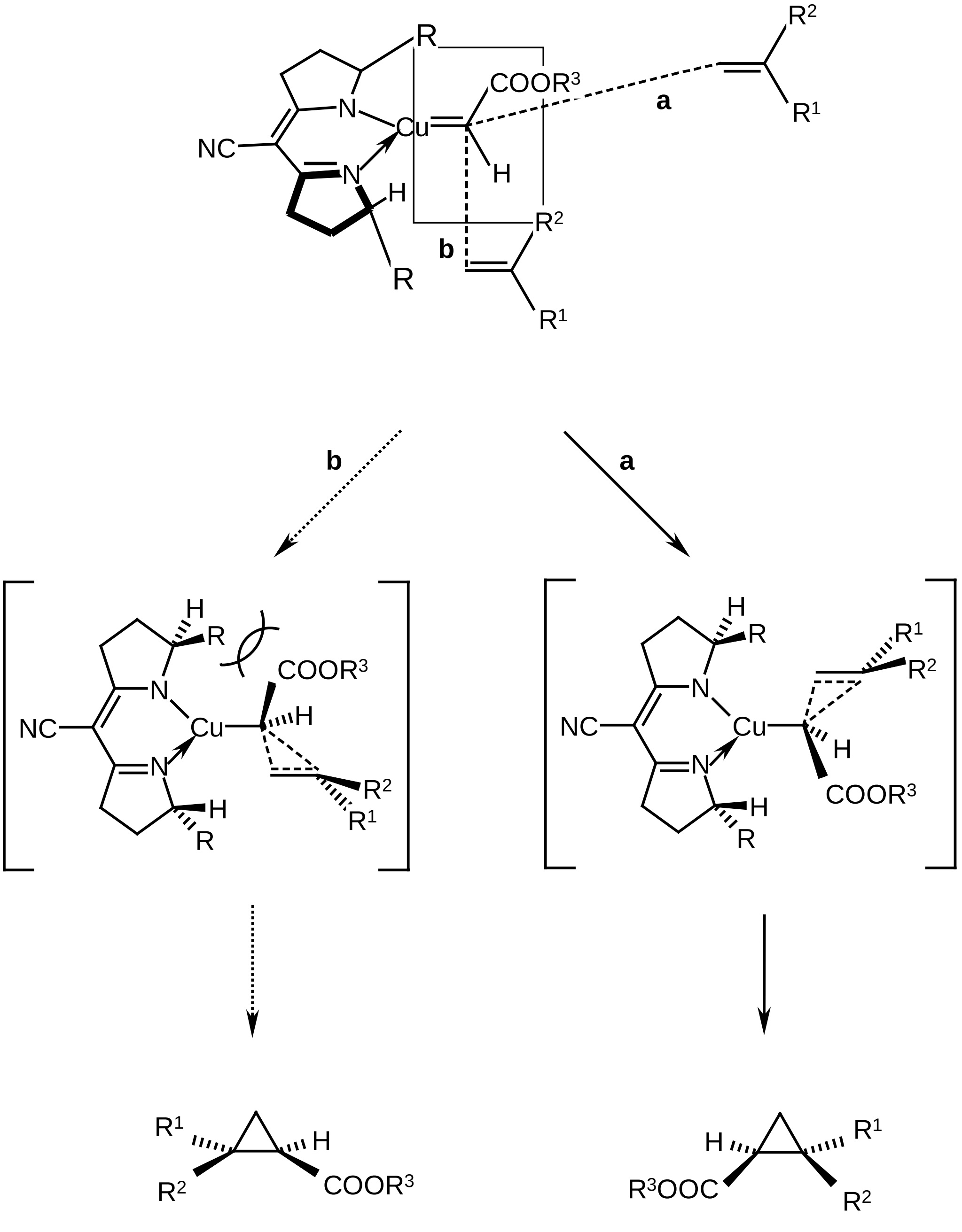
Scheme 75. Cyclopropanation of styrene with ethyl diazoacetate.



Scheme 76. Effective catalysts for the cyclopropanation.

In accordance with the advantages obtained by semicorrin ligands with Cu *Masamune*,[177] *Evans*[178] and *Pfaltz*[179] reported independently the application of bis-oxazoline ligands (**117-119**, *scheme 76*) to the cyclopropanation of olefins. *Evans* described the direct access to the (bis-oxazoline)-Cu(I) catalyst by *in situ* mixing of the ligand with stoichiometric amounts of CuOTf.

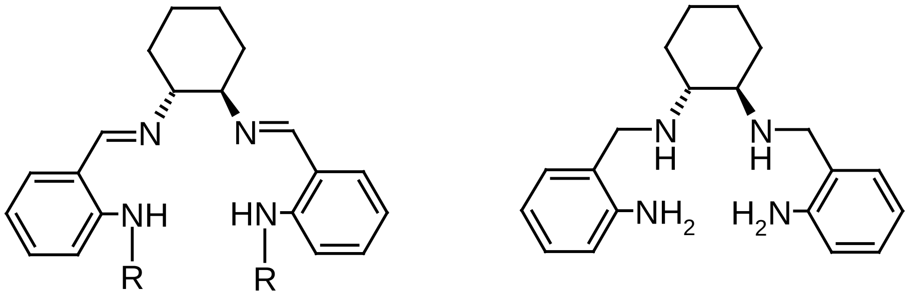
Scheme 77 shows the mechanism postulated by *Pfaltz* for the cyclopropanation of terminal olefins using semicorrins (*e.g.* **116**, see *scheme 76*) as catalysts.[173b] This mechanism is also applicable to other C_2-symmetric ligands. The plane defined by the trigonal carbene atom is assumed to be perpendicular to the ligand plane. This geometry is expected to be favored over a planar geometry, for steric and also electronic reasons. The olefin approaches the metal-carbene either from the front- or the back-side along pathway **b** or **a**. The principal bonding interaction initially develops between the electrophilic carbenoid C-atom and the terminal olefinic C-atom which is sterically more accessible and more nucleophilic than the substituted end of the C=C double bond. As a result of this interaction the two trigonal centers become pyramidal. Depending on the direction of attack, the carboxyl group at the carbenoid center either moves forward or backward relative to the plane bisecting the semicorrin ligand (pathways **a** and **b**). In the latter case (**b**), a repulsive steric interaction builds up between the ester group and the adjacent substituent at the stereogenic center of the semicorrin. Accordingly, pathway **a** is expected to be favored over pathway **b**. This fact is also supported by experimental data.



Scheme 77. Mechanism proposed by *Pfaltz* for the enantioselective cyclopropanation catalysed by Cu-semicorrin complex.

3.4.1 Results of the cyclopropanation of styrene

Following the procedure of *Masamune et al.*[174] the Cu(II)-complexes of ligands **66a**, **70** and **76a** (see *scheme 78*) were generated *in situ* by reaction between $Cu(OTf)_2$ and the respective ligand. In all cases dark violet complexes were formed. Unfortunately attempts to reduce these complexes to the active Cu(I) species under addition of phenylhydrazine failed.



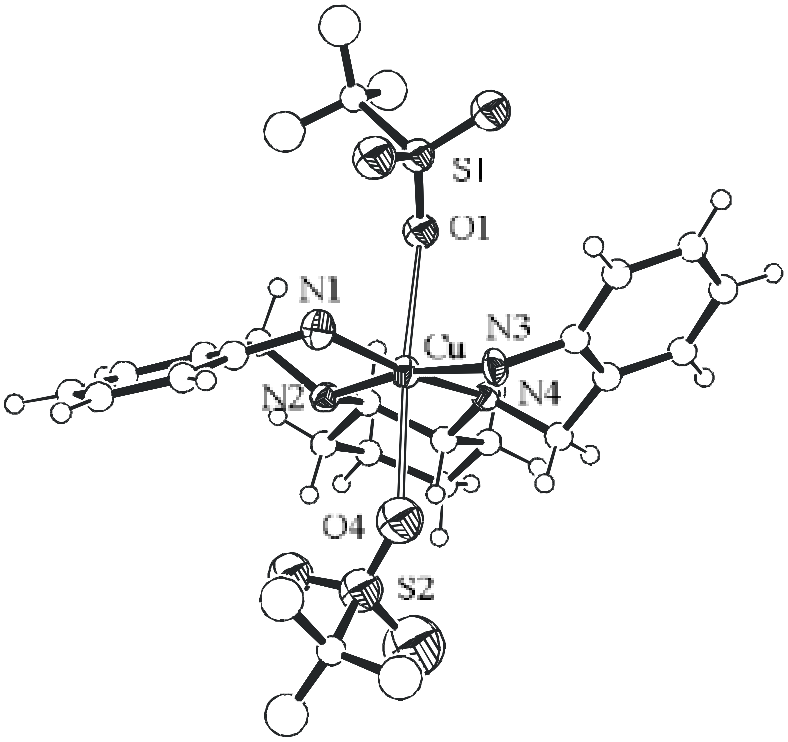
66a: R = H
76a: R = Ts

70

Scheme 78. Ligands used for the cyclopropanation of styrene.

X-Ray quality crystals of the Cu(II) complex of ligand **70** were obtained, and its structure shows the copper ion in a distorted *trans*-octahedral coordination sphere. The four coordination sites of the equatorial plane are occupied by nitrogen atoms with similar Cu-N bond lengths (see *scheme 79*). Only the Cu(1)-N(3) bond length is somewhat longer. The two triflate ligands coordinate via their oxygen atoms to the copper ion with similar Cu-O bond length of approximately 2.5 Å.

As already commented on section 2.3, the X-Ray structure of the Cu(II)-complex of **76a** have been reported in the literature.[109] The metal ion assumes a tetrahedrally distorted square planar coordination geometry, involving the four nitrogen atoms of the dianionic ligand.[110]



Scheme 79. ORTEP representation of the structure of the Cu(II)-complex of ligand **70** with important atoms labelled. The thermal ellipsoids are drawn at the 50% probability level except for the carbon atoms that are circles of arbitrary radius.

As an alternative to getting the active Cu(I) complexes of the selected ligands, the method reported by *Brunner* and collaborators[180] was used. The complexes were obtained directly *in situ* by treatment of the respective ligands (**66a**, **70** and **76a**) with Cu(I)-trifluoromethanesulfonate-toluene complex [Cu(OTf)$(C_7H_8)_{0.5}$]. The asymmetric cyclopropanation of styrene was then carried out according to the general procedure (*GP-8*, see experimental part).

The results obtained for the asymmetric reaction are summarised in *Table 11*. The use of 5 mol % of ligand and the same quantity of the triflate salt gave the best conversions and a significant diastereoselectivity of the catalytic reaction (entry 1).

Table 11. Asymmetric cyclopropanation of styrene catalysed by Cu(I).

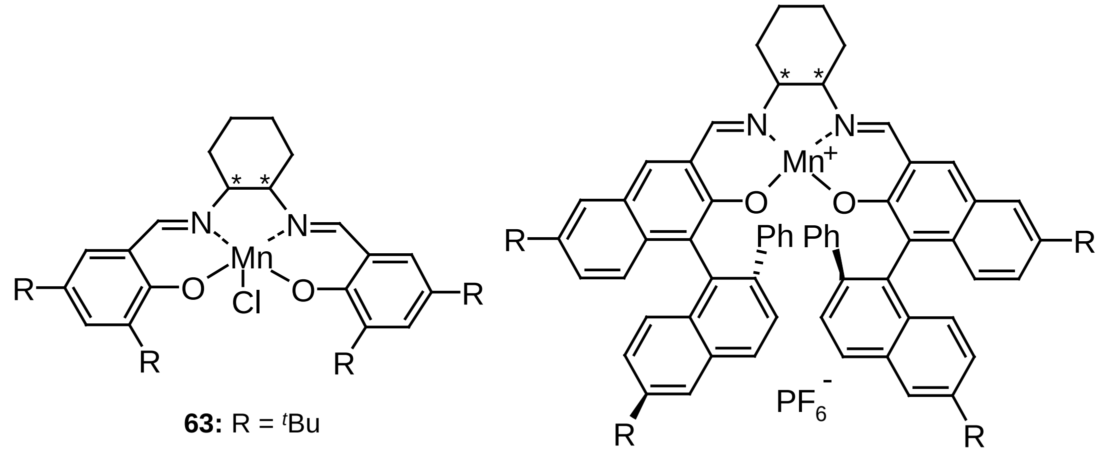
entry	ligand	mol %	yield[a] [%]	*cis*:*trans*	*cis* [% *ee*]	*trans* [% *ee*]
1	**66a**	5.0	52	30:70	8	2
2	**66a**	2.5	40	46:54	2	1
3	**70**	2.5	42	55:45	2	2
4	**76a**	2.5	30	47:53	*racemic*	*racemic*

[a] isolated product after column chromatography

Moreover, very low asymmetric induction (1-8 % *ee*, entries 1-3) or only the racemic mixture (entry 4) were possible to obtain with these ligands. A rational explanation for this observation might be the proven tetracoordination of the Cu metal ion by the four nitrogen atoms of each ligand, which hampers the substrate coordination necessary to achieve selectivity.

3.5 Epoxidation

Jacobsen and *Katsuki* have made great contributions to the asymmetric epoxidation of unfunctionalised olefins using optically active Mn-salen catalysts. Systematic variations of the steric and electronic environment of the complexes has led to the discovery of catalysts that are particularly effective for the epoxidation of mono-, *cis*-di-, tri- and tetrasubstituted olefins. High enantioselectivities could be achieved with this ample variety of substrates.[80] Two of the most effective ligands in terms of enantioselectivity are shown in *scheme 80*.

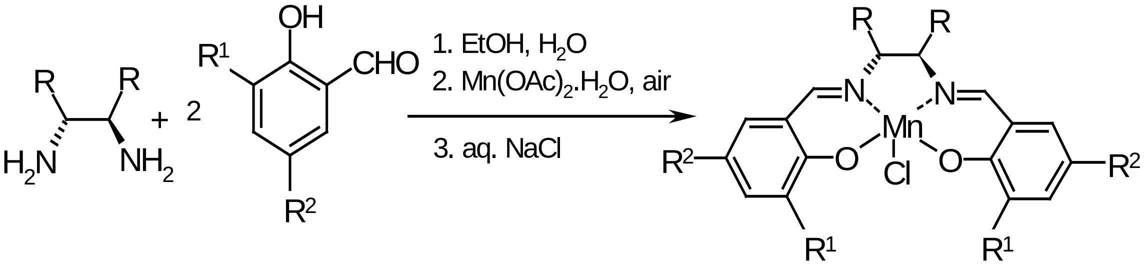


63: R = ^{t}Bu

64: R = OMe

Scheme 80. Mn-salen complexes used by *Jacobsen* and *Katsuki* for the epoxidation of olefins.

The Mn-salen complexes can be easily prepared from $Mn(OAc)_2.H_2O$, the chiral diamine **120**, and the appropriate salicylaldehyde **121** (see *scheme 81*).[181] This fact has enormously facilitated the catalyst exploration by synthesis of several hundred of optically active Mn-complexes.



120 **121** **122**

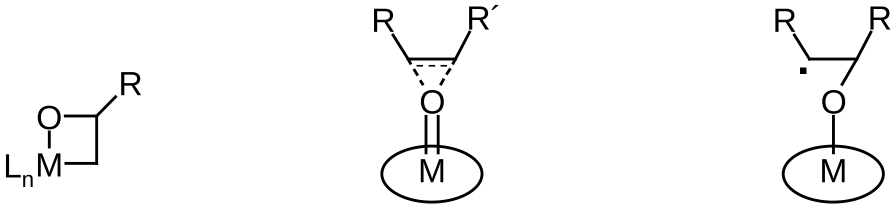
Scheme 81. Synthetic route to Mn-salen complexes.

Besides iodosylbenzene, aqueous sodium hypochlorite,[182] hydrogen peroxide,[183] molecular oxygen[184] and peracids[185] can also be used as a terminal oxidant. However, some oxidants require an appropiate additive. In the case of hydrogen peroxide, the co-existence of *N*-alkylimidazole is indispensable.[180] *Mukaiyama* and co-workers have reported that molecular oxygen can also be used as a terminal oxidant in combination with pivalaldehyde.[181] As already mentioned in the introduction, the epoxidation with *m*-CPBA can be carried out in the presence of *N*-methylmorpholine *N*-oxide.[182a-b] The role of the additive is to supress the undesired epoxidation with free *m*-CPBA.

For the Mn-salen catalysed epoxidation various solvents such as acetonitrile, dichloromethane, ethyl acetate and ether can be used at different temperatures (25 to –40 °C). However, the reaction is very slow at temperatures as low as –78 °C,[186] except when using *m*-CPBA as oxidant. In general, enantioselectivity is enhanced as the reaction temperature becomes lower.

For the mechanism of oxygen-atom transfer from high-valent metal oxo complexes have been considered fundamentally by two different proposals. The first invokes substrate attack at both the metal and oxo centers to generate an oxametallacycle intermediate **123** (see *scheme 82*). Such a mechanism was first advanced by *Sharpless* in 1977 in the context of chromyl chloride oxidations.[187] Although analogous proposals have been made for olefin epoxidation reactions catalysed by porphyrins and salen-complexes,[188] substancial evidence has been accumulated that indicates that oxametallacycle intermediates do not participate in these reactions.[189]

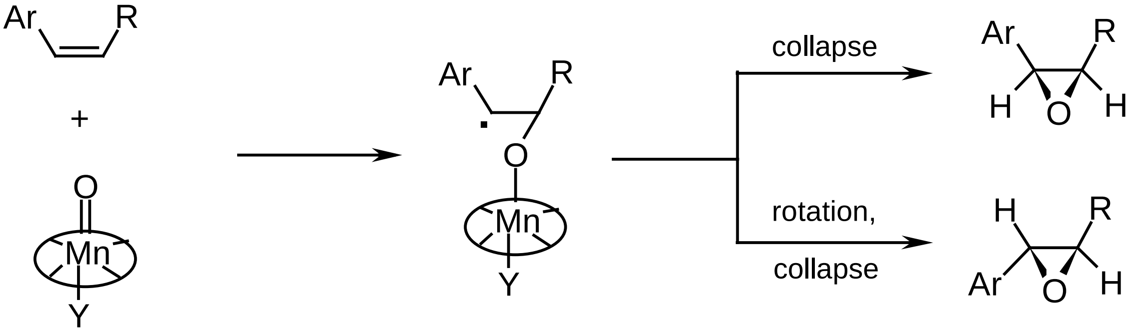
The second and more accepted mechanism for oxo-transfer involves direct substrate attack at the oxo ligand with concerted or sequential C-O bond formation (intermediates **124** and **125**, *scheme 82*).



123 **124** **125**

Scheme 82. Intermediates for the proposed mechanisms of the Mn-salen epoxidation.

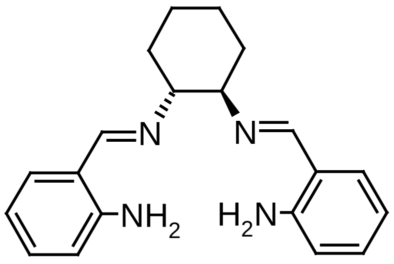
Compelling evidence for stepwise C-O bond formation in Mn-salen catalysed epoxidation is found in the formation of both *cis*- and *trans*-epoxides as primary products from acyclic *cis*-olefins.[190] The extent of the *trans*-epoxide formation depends strongly on the nature of the substrate. Whereas simple alkyl-substituted *cis*-olefins are epoxidised stereoespecifically, aryl-substituted *cis*-olefines produce mixtures of *cis*- and *trans*-epoxides with the *cis*-isomers being formed selectively. Epoxidation of conjugated dienes and enynes also lead to *cis*/*trans* mixtures, with the *trans*-epoxide predominating. These observations may be interpreted according to a stepwise mechanism (see *scheme 83*) in which a discrete radical intermediate undergoes competitive collapse to *cis*-epoxide and rotation/collapse to *trans*-epoxide.[191]



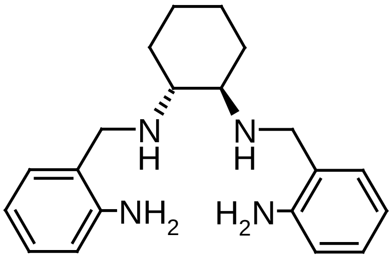
Scheme 83. Stepwise mechanism proposed by *Jacobsen* for the epoxidation with Mn-salen.

3.5.1 Results of the epoxidation of styrene

Numerous attempts to isolate the Mn(III)-complexes of ligands **66a** and **70** (see *scheme 84*) by coordination with $MnCl_2$, or with $Mn(AcO)_2$ followed by oxidation on air, failed. Although a dark brown solid[192] was obtained in both cases, only the peaks corresponding to the Mn-free-compounds were observed in mass spectroscopy.



66a

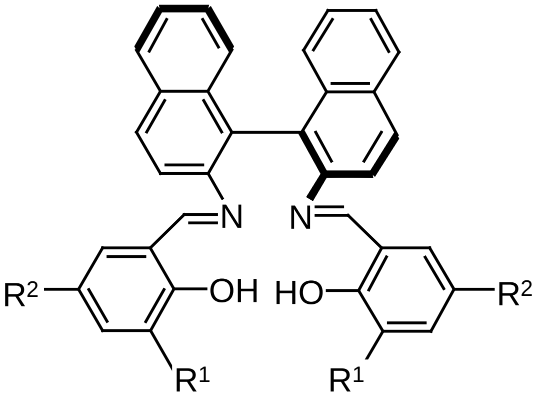


70

Scheme 84. Ligands tested for the epoxidation of styrene.

On the other hand, it is known that $Mn(AcO)_3.2H_2O$ catalysed the aerobic epoxidation of unfunctionalised olefins.[193] *Che* and co-workers have reported the effective epoxidation of alkenes with PhIO in the presence of the *in situ* $Mn(AcO)_3$ + (S)-H_2L **126** systems[194] (see *scheme 85*).

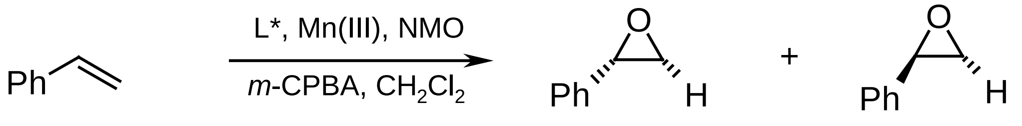
Therefore it was decided to make the catalytic epoxidation of styrene **113** with the *in situ* generated Mn(III)-complex of ligands **66a** and **70**, obtained by reaction of the respective ligand with this commercially available Mn salt.



126: R^1 = H, Cl, alkyl
R^2 = Cl, NO_2, Me

Scheme 85. Ligands used for the epoxidation of alkenes with PhIO, by *in situ* complexation with $Mn(AcO)_3$.

Following the procedure developed by *Zheng*,[195] styrene **113** was epoxidised with *m*-CPBA and NMO, in the presence of $Mn(AcO)_3$ and ligands **66a** and **70** (*scheme 86*). After 24 h styrene epoxide **127** was isolated as a racemic mixture and in 55 % yield in the case of the first ligand, and in 60 % yield and 12 % *ee* of the *trans*-epoxide with ligand **70**.



113 ***cis*-127** ***trans*-127**

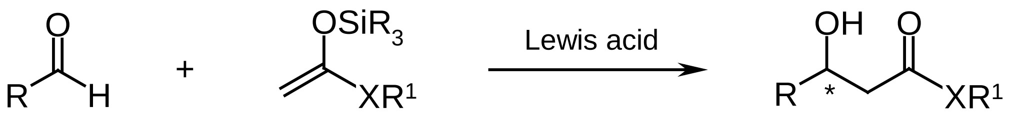
Scheme 86. Epoxidation of styrene

Activity and selectivity of the catalyst must be rated poorly for the reaction if compared to superior reported systems. The epoxidation of other olefins such as indene, *trans*-stilbene and cyclohexene was attempted with the latter catalyst, but without success.

3.6 *Mukaiyama* Aldol Reaction

The aldol addition is one of the most important methods for stereoselective construction of carbon-carbon bonds. New and powerful variants of these classical reactions have been developed in recent years.[196] Two classes were mainly used for asymmetric induction in these reactions: the use of asymmetric modified enolates or electrophiles[197] and the use of chiral *Lewis* acids.[198]

The chiral enolate or electrophile approach is much more general and gives high stereoselectivities due to the highly ordered nature of transition structures (closed transition models). The chiral center has to be removed after the complete aldol addition. To avoid this additional reaction step, a strategy is employed whereby chiral enolates can be reacted with achiral carbonyl compounds in the presence of chiral auxiliaries. Unfortunately, stoichiometric amounts of the chiral information are necessary. Up to now, and apart from enzymatic transformations, the *Mukaiyama* reaction has opened an enantioselective and catalytic approach using chiral *Lewis* acids.[199]

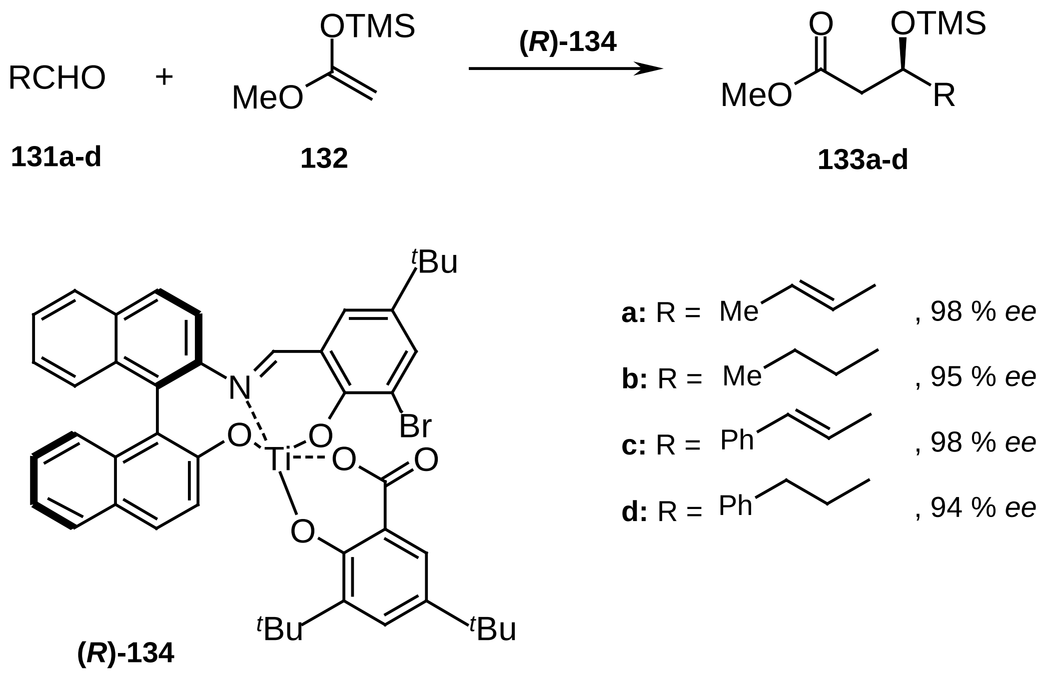


128 **129** **130**

Scheme 87. Mukaiyama aldol reaction.

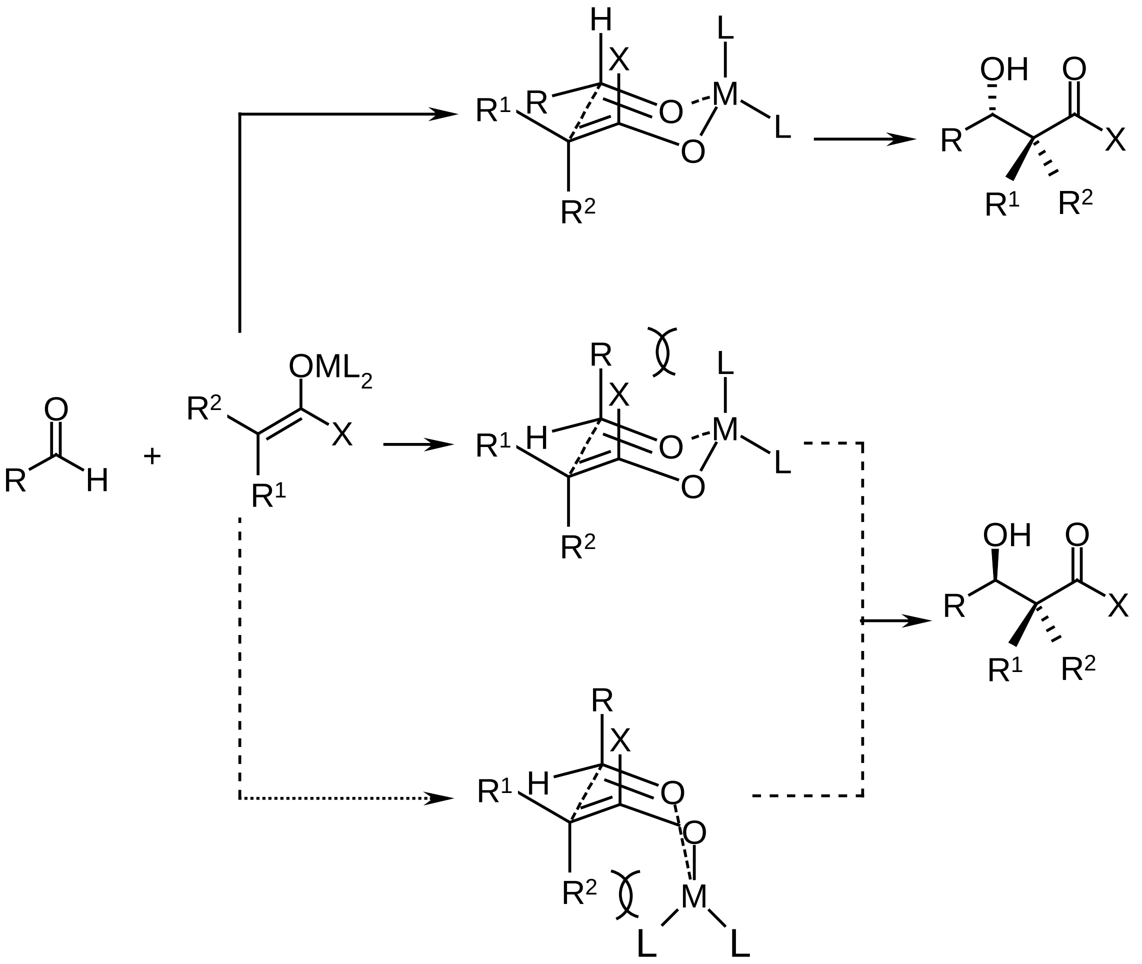
Mukaiyama and co-workers discovered the *Lewis* acid-mediated addition of enol silanes to aldehydes and acetals (see *scheme 87*).[200] This development proved to be a key lead for the subsequent evolution of this C-C forming reaction into a catalytic Si atom-transfer process. Typical enol silanes derived from esters, thioesters and ketons are unreactive to aldehydes at ambient temperatures. However, stoichiometric quantities of *Lewis* acids such as $TiCl_4$, $SnCl_4$, $AlCl_3$, BCl_3, $BF_3.OEt_2$ and $ZnCl_2$ were found to promote aldehyde addition to give *β*-hydroxycarbonyl adducts. Innumerable electrophilic promoters and catalysts have been investigated for this reaction including Sn(IV), Sn(II), Mg(II), Zn(II), Bi(III), Ln(III), Pd(II), Ti(IV), Zr(IV), Ru(II), Rh(II), Fe(II), Al(III), Cu(II), Au(I), R_3SiX, Ar_3C^+, acridinium salts, and clay.[201] Additionally, the aldol reaction of silyl enol ethers has also been conducted using Lewis bases as catalysts or promoters. These include fluoride,[202] for which naked enolates are proposed as the reactive species, and more recently, phosphoramide bases.[203]

Carreira and co-workers have found the most prominent metal complex catalyst for the *Mukaiyama* aldol addition, the Ti(IV)-*Schiff* base **134** represented in *scheme 88*.[204] This catalyst has shown a high activity and tolerance of a wide array of nucleophiles and electrophiles. Under optimised conditions, the simple methyl acetate-derived enol silane **132** adds to aldehydes **131a-d** in the presence of as little as 0.5 mol % of **134** at 0 °C to give adducts **133a-d** in high yields and up to 98 % *ee* (see *scheme 88*).



Scheme 88. Highly active Ti(IV)-based catalyst for the *Mukaiyama* aldol reaction.

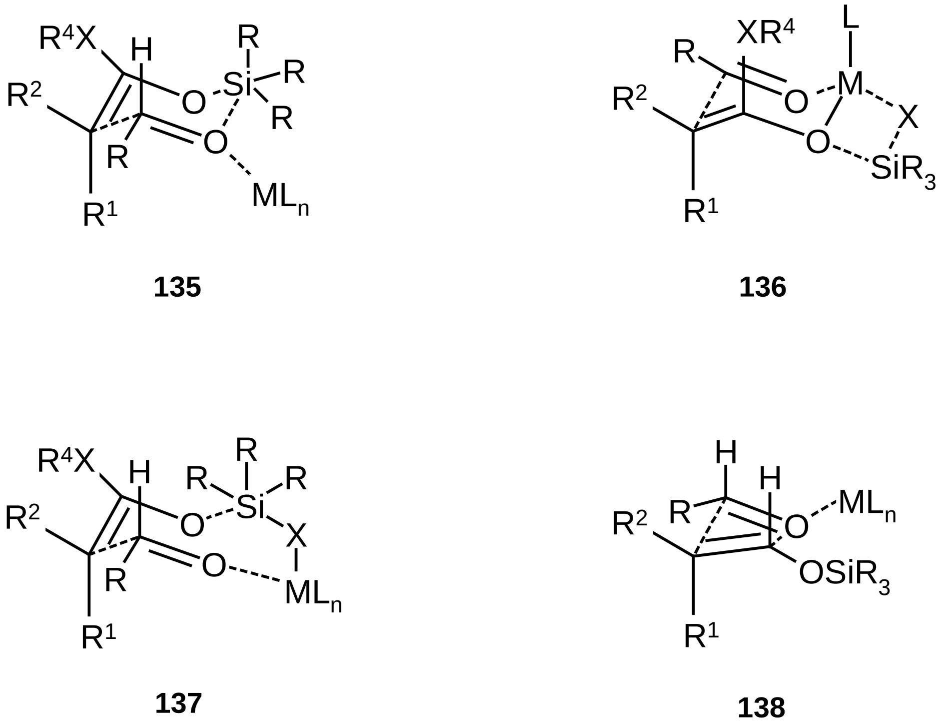
Studying the *Mukaiyama* aldol reactions, *Heathcock* proposed that the observed stereochemical outcome of the products in the Lewis-acid mediated addition of silyl ketene acetals to aldehydes was consistent with extended, open transition-state structures.[205] This analysis has gained wide acceptance as a result of its predictive power. Alternative models involving cyclic, closed structures have also been postulated. In particular, the latter has been employed with increasing regularity in the analysis of catalytic, enantioselective aldol reactions.[200b, 206] For a detailed analysis of the open structures see reference 199. In this chapter will be described only the closed transition structures. These structures are best understood within the *Zimmerman-Traxler* paradigm (*scheme 89*).



Scheme 89. Zimmerman-Traxler transition states for aldol additions reactions.

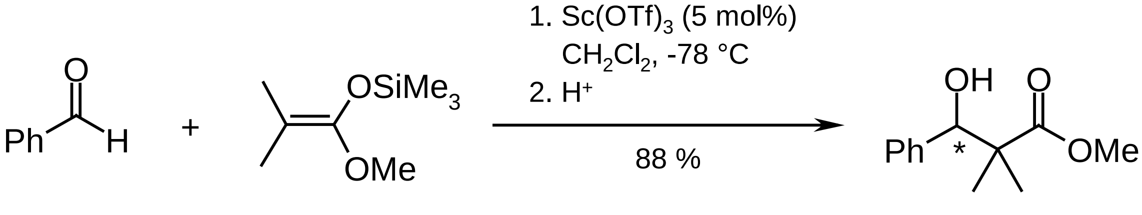
Superposition of this construction on the *Felkin-Anh* model for carbonyl addition reactions allows for the construction of transition-state models, which are impressive in their ability to account for many of the stereochemical features of aldol additions.[207] Moreover, consideration of dipole effects along with remote non-bonding interactions in the transition-state have imparted additional sophistication to the analysis of this reaction and provide a bedrock of information that may be integrated into the further development and refinement of the corresponding catalytic processes.[208] One of the most powerful features of the *Zimmerman-Traxler* model in its application to diastereoselective additions of chiral enolates to aldehydes is the correlation of enolate geometry (*Z- versus E-*) with simple diastereoselectivity in the products (*syn versus anti*).

The closed transition-state structures that have been proposed for the *Lewis* acid-mediated addition of enol silanes to aldehydes are of two general specifications (*scheme 90*). The first includes models in which the metal complex plays an integral role in the closed structure through its incorporation into the cyclic array (**136** and **137** in *scheme 90*). The second includes models in which the metal is exocyclic to the ring (**135** and **138** in *scheme 90*). These include six-membered rings **135**,[209] fused bicyclic 4- to 6-membered rings **136**,[210] eight-membered rings **137**,[198, 208d] and 4-membered rings **138**.[211] All of these models share a common mechanistic feature: the intact enol silane is the reactive nucleophilic species in the addition to aldehydes.



Scheme 90. Proposed closed transition-state structures for the *Mukaiyama* aldol addition of enol silanes.

Kobayashi and co-workers found that lanthanide trifluoromethanesulfonates [lanthanide triflats, $Ln(OTf)_3$] are excellent catalysts for aldol and *Michael* addition reactions. The reactions proceed smoothly in the presence of only a catalytic amount of $Ln(OTf)_3$ and the catalyst can be easily recovered and reused.[212] Both reactions were especially effective using $Sc(OTf)_3$.[213] Different silyl enolates reacted with aldehydes, acetals and *α*, *β*-unsaturated ketons in the presence of this catalyst to give the addition products in good yields (for an example see scheme *91*).



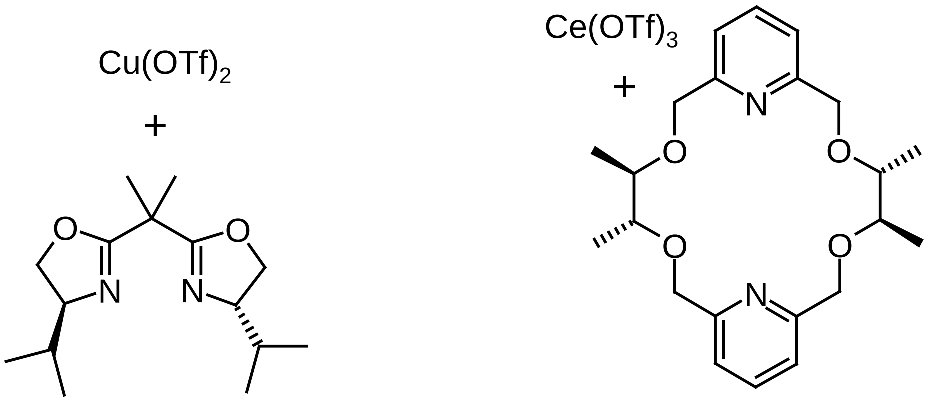
105a **139** **140**

Scheme 91. Sc(OTf)3 catalysed aldol reaction.

This reaction was not limited to anhydrous conditions. *Kobayashi et al.* also reported the efficient synthesis of aldol products in aqueous media using a wide variety of *Lewis* acids.[214] Asymmetric variants of the aldol reaction were also carried out by combination of the *Lewis* acid with chiral ligands.[215]

When Cu(OTf)2 (20 mol %) and the bis(oxazoline) **141** (24 mol %, see *scheme 92*) were used as catalyst for the *Mukaiyama* aldol reaction in aqueous ethanol, good yields and enantioselectivities were obtained even for simple aldehydes such as benzaldehyde.[212a, 216]

Recently, *Kobayashi* and his group developed the first asymmetric aldol reaction in aqueous media[212c] with Ln(OTf)3 using the chiral crown ether **142** (see *scheme 92*).[217] It was demonstrated that the cation size of rare earth metal triflates, including Ln(OTf)3, strongly affected the diastereo- and enantioselectivities of the aldol adduct. For the larger cations such as La, Ce, Pr and Nd, both diastereo- and enantioselectivities were high, while the smaller cations such as Sc and Yb showed no enantioselection.

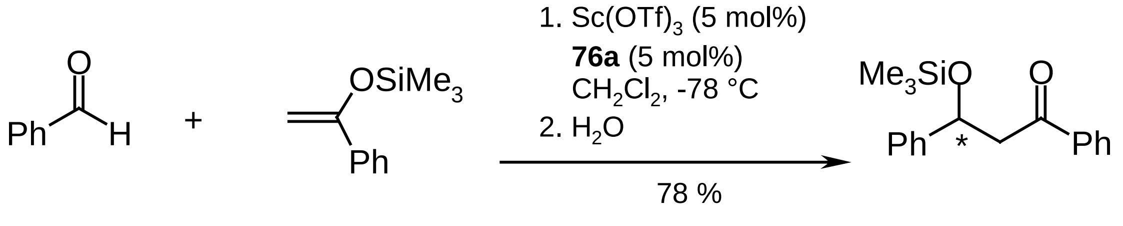


141 **142**

Scheme 92. Chiral ligands combined with *Lewis* acid for the asymmetric aldol addition.

3.6.1 Results of the *Mukaiyama* Aldol reaction.

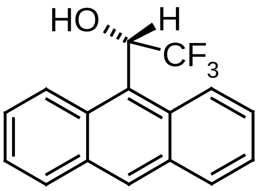
Ligand **76a** was selected to be used in the *Mukaiyama* aldol reaction of benzaldehyde **105a** with the silyl enol ether **143**. A variant of the method reported by *Kobayashi* and co-workers[211] was employed. Equimolar amounts (5 mol %) of the chiral ligand and of Sc(OTf)$_3$ were used as catalyst (see *scheme 93*). The reaction time was 8 h at –78 °C. After this time the mixture was warmed to room temperature, and 1 N HCl solution was added to obtain the *β*-hydroxy ketone **144**.



105a **143** **145**

Scheme 93. *Mukaiyama* aldol reaction catalysed by chiral ligand **76a** and Sc(OTf)$_3$.

When the reaction mixture was quenched with water, the compound **144** was not obtained, but its trimethyl silyl ether **145** (see *scheme 93*) was achieved in 78 % yield. This product was characterised and its optical purity was investigated by utilisation of (S)-(+)-1-(9-anthryl)-2,2,2-trifluorethanol **146** (*Pirkle* alcohol,[218] *scheme 94*).

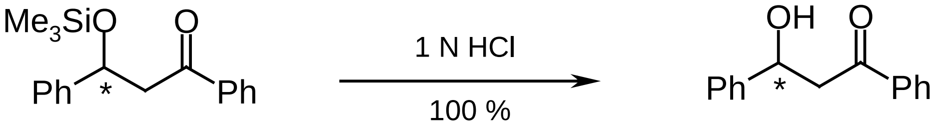


(*S*)-146

Scheme 94. (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluorethanol (*Pirkle* alcohol).

After recording the ^{1}H NMR spectrum of **145**, all signals were assigned, and attention was especially concentrated on the singlet at $\delta = -0.04$, corresponding to the trimethyl silyl ether group. After addition of four, and later other four, equivalents of the *Pirkle* alcohol, the separation of the enantiomers was clearly observed. Two singlets with the same intensity appeared at $\delta = -0.025$ and $\delta = -0.033$ instead of the lone one mentioned above ($\delta = -0.04$). This means that no enantioselectivity was induced with the catalytic system used. Only the racemic mixture was obtained.

Thereafter, the *β*-hydroxyketone **144** (see *schema 95*) was obtained quantitatively by acid hydrolysis of **145**.



145 **144**

Scheme 95. Acid hydrolysis to obtain the *β*-hydroxyketone **144**.

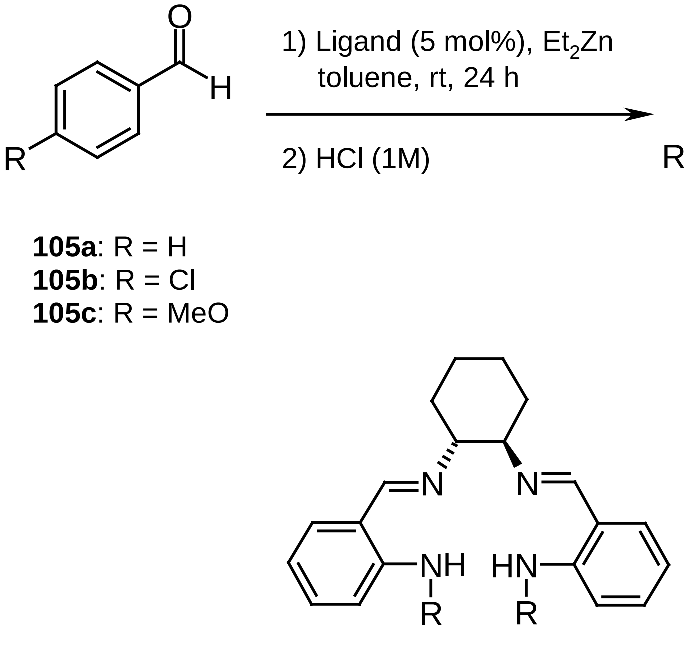
4 Summary

The synthesis of different nitrogen-containing ligands was developed during this work (**66a-d**, **70-72**, **76a-f**, **83** and **84a-d**, see *scheme 53*, section 3.1). The presence of the chiral (1*R*, 2*R*)-*trans*-cyclohexanediamine unit is the common structural element of all synthesised ligands. The synthetic methods selected allow to obtain the ligands in very good yields and in one to three steps.

The activity of the ligands was investigated in the following asymmetric reactions:

(1) Addition of diethylzinc to aldehydes

All ligands were tested in the asymmetric alkylation of benzaldehyde **105a** with diethylzinc (see *scheme 96*).



105a: R = H
105b: R = Cl
105c: R = MeO

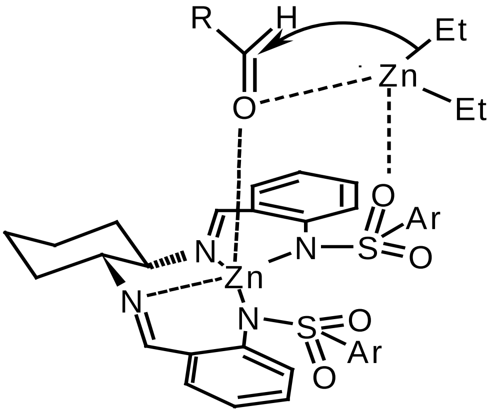
106a: R = H
106b: R = Cl
106c: R = MeO

76a: R = $SO_2C_6H_4CH_3$
76b: R = $SO_2C_6H_5$

Scheme 96. Addition of diethylzinc to aldehydes and the most successful ligands for this reaction.

The chiral sulphonamides **76a-f** showed a great activation of the asymmetric reaction, reaching in the case of **76a** and **76b** quantitative yields of the chiral alcohol **106a** and very good enantioselectivities (70 and 74 % *ee*).

A possible mechanism for the catalysis with these ligands was postulated on the basis of reports found in the literature for tetra-aza ligands (see *scheme 97*).



Scheme 97. Suggested mechanism of the addition of diethylzinc with sulphonamides **76**.

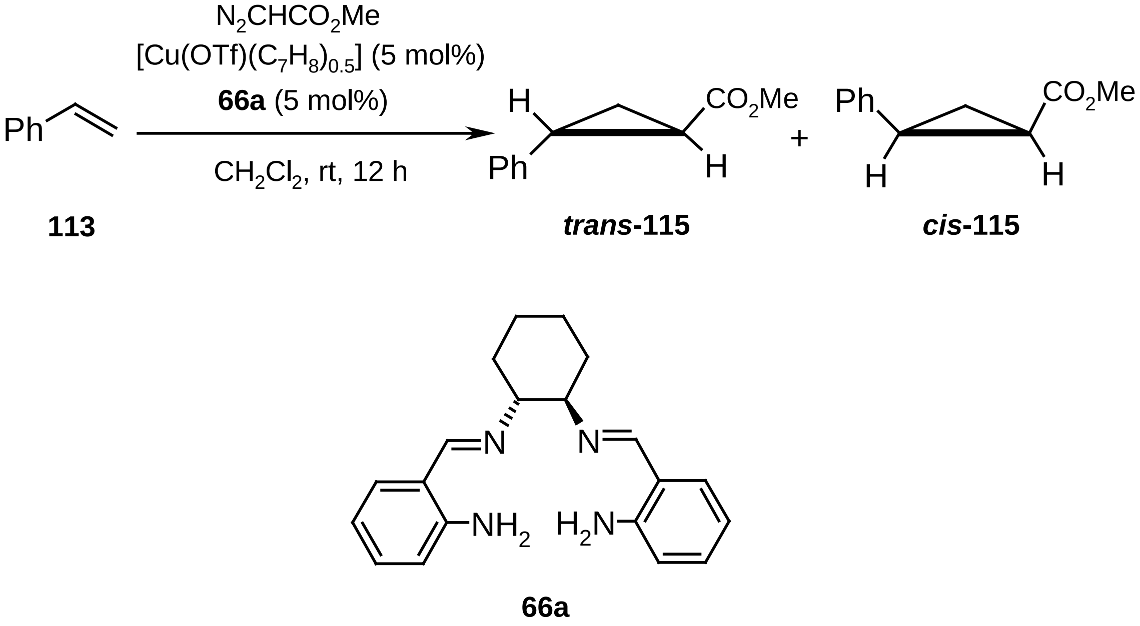
The addition of diethylzinc to *p*-substituted benzaldehydes (**105b-c**), to heteroaromatic (**108**) and to unsaturated aldehydes (**110**) was also carried on in the presence of **76a** and **76b** at two different temperatures. Attempts of alkylation of heptanal using these ligands were unsuccessful.

For these best ligands, the asymmetric alkylation of benzaldehyde was carried out at three different temperatures (0, 25 and 50 °C), whereby increased the yield and the rate of reaction, but decreased the enantioselectivities.

Contrary to the expected, the asymmetric alkylation using $Ti(O^iPr)_4$ as additive for a bimetallic catalysis gave only very small enantiomeric excess.

(2) Cyclopropanation with Cu(I)

The ligands **66a**, **70** and **76a** were selected to be tested in the asymmetric cyclopropanation of styrene with diazoacetate. Cu(I) complexes of these ligands were generated *in situ* with $[Cu(OTf)(C_7H_8)_{0.5}]$.



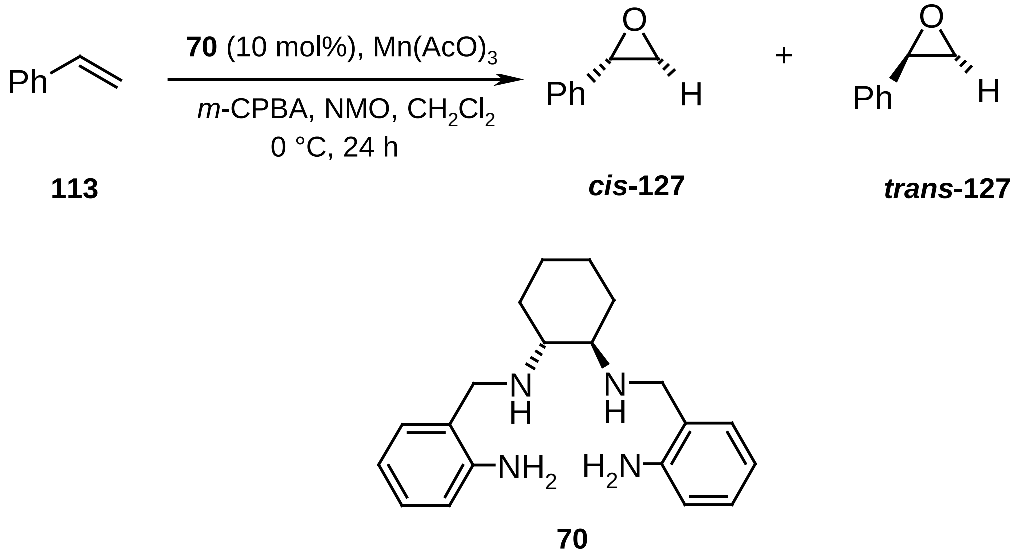
Schema 98. Cyclopropanation of styrene with methyl diazoacetate.

A considerable diastereoselectivity (*cis*:*trans*, 30:70) was obtained with 5 mol % of ligand **66a**. For all ligands used very low enantioselectivities were achieved.

(3) Epoxidation

The ligands **66a** and **70** were tested in the asymmetric epoxidation of styrene. Efforts to synthesise the Mn(III)-complexes of both ligands were unsuccessful. *In situ* catalysis in the presence of the ligands and $Mn(OAc)_3$ were developed.

With ligand **70** the phenyloxirane was obtained in 60 % yield and 12 % *ee*.

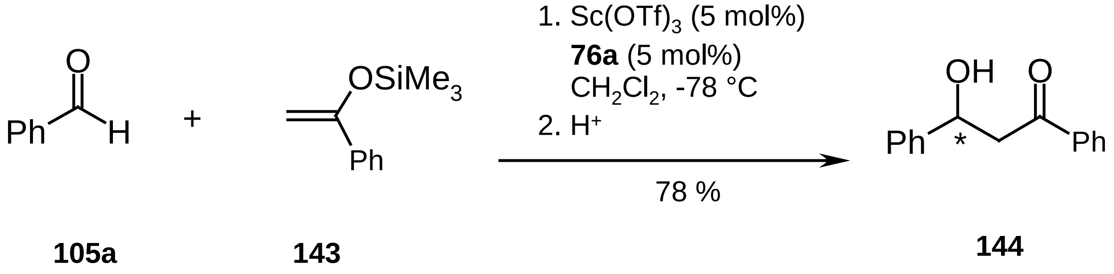


Scheme 99. Epoxidation of styrene in the presence of Mn(AcO)$_3$.

(4) *Mukaiyama* Aldol reaction

The aldol reaction of benzaldehyde **105a** with the silyl enol ether **143** was performed using Sc(OTf)$_3$ as *Lewis* acid and **76a** as chiral ligand.

The keto alcohol **144** was obtained in 78 % yield as racemic mixture.



Scheme 100. Mukaiyama aldol reaction

5 Experimental Part

5.1 Instruments and general techniques

Melting points (mp) were determined with a Büchi SMP 20 and are uncorrected.

IR-spectra: were recorded with a Bio-Rad FTS 3000 MX FT-IR.

^{1}H NMR: Bruker ARX 400 (400 MHz), Bruker AC 250 (250 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 7.26 ppm), dimethylsulfoxide (DMSO-d_6, 2.49 ppm) and tetramethylsilane (TMS, 0 ppm). The spectra were analysed by first order, the coupling constants are in Hertz (Hz). Characterisation of the signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = double doublet, dt = double triplet, dq = double quartet, ddd = double double doublet. Integration is determined as the relative number of atoms.

^{13}C NMR: Bruker ARX 400 (100.1 MHz), Bruker AC 250 (62.9 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 77 ppm), dimethylsulfoxide (DMSO-d_6, 36.9 ppm) and tetramethylsilane (TMS, 0 ppm). ^{13}C NMR resonance assignment were aided by the use of the DEPT 135 technique to determine the number of hydrogen atom attached to each carbon atom as is declared as: + = primary or tertiary (positive DEPT signal intensity, - = secondary (negative DEPT signal) and quat = quaternary (no DEPT signal intensity.

X-Ray: Data collections were performed at 173(± 1) K with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) on a STOE-IPDS diffractometer (University of Regensburg). The structures of the compounds were solved by direct methods SIR-97[219] and refined by full-matrix least-squares method on F^2 using SHELXL-97.[220]

Optical rotation was measured on a Perkin Elmer Polarimeter 241 with sodium lamp at 589 nm in the specified solvent.

MS-spectra: Varian CH-5 (EI), Finnigan MAT SSQ 7000 (ESI).

Elemental Analysis: Microanalytical Laboratory of the University of Regensburg.

Gas chromatography was performed on a Carlo Erba 8160, Fisons 8130, Fisons 9100 and HP 5890 II. The detailed conditions have been described separately for the corresponding substances.
The determination of yields by gas chromatography, for the addition of diethylzinc to benzaldehyde **105a**, were performed in the presence of acetophenone as internal standard on a Chromatograph Fisons 9100, Detector FID 230 °C, Inject Split 230 °C, Column Zebron ZB-1n, 15 m, 0.25 mm, 0.25 µm, Oven Temperature 100 °C, Carrier gas He_2, Column Head Pressure 3 bar. Retention times: 5.38 min (acetophenone), 8.02 min (1-phenyl-1-propanol **106a**).

Thin layer chromatography (TLC) was performed on alumina plates coated with silica gel (Merck silica gel 60 F 254, layer thickness 0.2 mm). Visualisation was accomplished by UV-light (wavelength $\lambda = 254$ nm) and vanillin/sulfuric acid solution in EtOH.

Column chromatography was performed on silica gel (70-230 mesh) from Merck.

Potentiometric titrations were performed with a computer controlled pH-meter (pH 3000, WTW) and dosimat (Dosimat 665, Metrohm). For all titrations 0.1 M perchloric acid and 0.1 M tetraethylammonium hydroxide (TEAOH) in water containing tetraethylammonium perchlorate to maintain an ionic strength of $I = 0.1$ were used. TEAOH solutions were calibrated with mono sodium phthalate. A titration of perchloric acid with TEAOH solution was used for calibration and to determine $\log K_w$. All measurements were performed at 25 C.

Solvents were distilled and dried according to standard laboratory methods.[221]

Chemicals were purchased from commercial suppliers and only in few cases, where distillation was necessary (for example, aldehydes), direct used.

All reactions with oxygen or moisture sensitive reactants were performed under nitrogen atmosphere.

5.2 Synthesis of compounds

(1*R*, 2*R*)-*trans*-cyclohexanediamine[222] and *o*-aminobenzaldehyde[223] were synthesised according to procedures of the literature. The optical purity measured $[\alpha]_D^{25}$= -25° for the chiral diamine coincided with the value reported in the literature[224] $[\alpha]_D^{25}$= -25.5° (c = 5, HCl 1 M).

5.2.1 General procedures

General Procedure for the synthesis of imines (*GP-1*): (1*R*, 2*R*)-*trans*-cyclohexanediamine (**67**) and the corresponding aldehyde were dissolved in dry EtOH in a molar ratio of 1:2, respectively. The resulting mixture was stirred under nitrogen atmosphere either at room temperature or refluxed for the time stated and the solvent was evaporated in vacuum. The crude *Schiff* base was recrystallised in the indicated solvent.

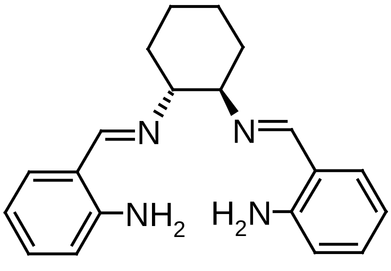
General procedure for the synthesis of substituted amino alcohols 78 (*GP-2*): A solution of *o*-aminobenzyl alcohol (**77**) and pyridine in dry $CHCl_3$ was treated drop wise with a solution of the appropriate sulphonyl chloride in $CHCl_3$ at room temperature. The reaction mixture was stirred magnetically 3 h. After evaporation of the reaction mixture to dryness, the resulting residue was taken up in ethyl acetate and saturated aqueous ammonium chloride. The organic phase was separated, dried with Na_2SO_4, filtered and evaporated.

General procedure for the oxidation of substituted amino alcohols to aldehydes 79 (*GP-3*): To a stirred suspension of PCC in CH_2Cl_2 was added drop wise a solution of the substituted amino alcohol **78** in the same solvent. The mixture was stirred for 3 h at room temperature. The liquid was decanted from the solid which was washed several times with Et_2O. The combined organic layer was passed through a short pad of silica gel and evaporated to give the product. The product was recrystallised from the specified solvent.

General Procedure for the synthesis of protected amides (*GP-4*): To a suspension of *N*,*N*′-Bis-(2-aminobenzoyl)-1*R*, 2*R*-diaminocyclohexane (**83**) in CH_2Cl_2, pyridine was added, and then the appropriate sulphonyl chloride in small portions. After stirring for 18 h the reaction mixture was washed with HCl (5 %), the organic layer was separated and dried with Na_2SO_4. Evaporation of the solvent afforded substituted products **84**.

General Procedure for the synthesis of metal complexes *(GP-5)*: To a methanol or ethanol solution of the ligand an equimolar amount of the metal salt was added. The mixture was refluxed for 1 h, the solvent was evaporated, the solid residue was dried and the complex was recrystallised.

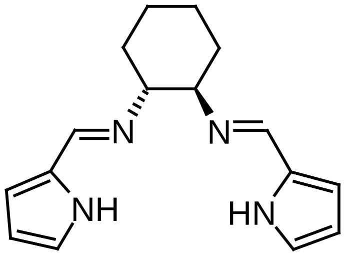
5.2.2 Preparation of compounds



66a

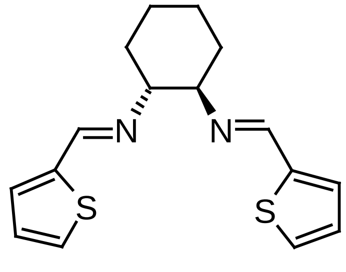
***N*,*N*′-Bis-(2-amino-benzylidene)-cyclohexane-1*R*, 2*R*-diamine (66a):** According to *GP-1*, the *Schiff* base was obtained by reaction of 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (1.96 g, 17.2 mmol) and aldehyde **68a** (4.10 g, 33.7 mmol) in 20 ml of EtOH. The mixture was refluxed for 30 min and the resulting white precipitate was recrystallised from EtOH (15 ml) to yield **66a** (4.25 g, 13.28 mmol, 77 %), as a white solid. mp = 183 °C. - IR (KBr): $\nu = 3471$, 3248, 2937, 2914, 2850, 2360, 1626, 1581, 1489, 1456, 1390, 1324, 1152, 1089, 1029, 980, 943, 751 cm^{-1}. - ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.40$-1.95 (m, 8H), 3.20-3.24 (m, 2H), 6.28 (s, 4H), 6.59 (m, 4H), 7.06 (m, 4H), 8.24 (s, 2H, 2 HC=N). - ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 24.5$ (-), 33.5 (-), 74.5 (+), 115.4 (+), 115.9 (+), 117.9 (C_{quat}), 130.4 (+), 133.3 (+), 148.4 (C_{quat}), 163.1 (+). - MS (CI-

MS/DCI), m/z (%): 320 (50) [M$^{+•}$], 200 (14) [M$^{+•}$ – N=CPhNH$_2$], 120 (100) [N=CPhNH$_2$].- Calculated for $C_{20}H_{24}N_4$: C 74.97, H 7.55, N 17.48. Found: C 74.47, H 7.40, N 17.15.



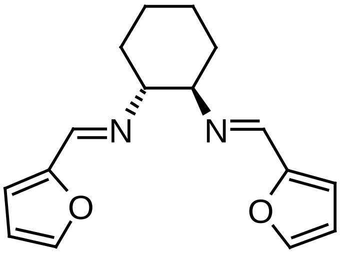
66b

N,N´-Bis-(1H-pyrrol-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (66b): 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (0.8 g, 7 mmol) and 2-pyrrolcarboxaldehyde (**68b**) (1.34 g, 14.04 mmol) were allowed to react according to *GP-1* in 10 ml of EtOH. The mixture was stirred 3 h at room temperature. The crude product was recrystallised from MeOH (8 ml) to yield **66b** (1.69 g, 6.3 mmol, 90 %) as a white solid. mp = 178 °C. - IR (KBr): ν = 3232, 3111, 2944, 2910, 2852, 2280, 1633, 1558, 1446, 1420, 1379, 1360, 1318, 1136, 1088, 1031, 831, 732 cm^{-1}. - ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.38-1.46 (m, 2H), 1.5-1.67 (m, 2H), 1.81-1.84 (m, 4H), 3.15-3.19 (m, 2H), 4.62 (bs, 2H), 6.11 (dd, 2H, J = 3.5, 2.6 Hz), 6.40 (dd, 2H, J = 3.5, 1.4 Hz), 6.83 (dd, 2H, J = 2.6, 1.4 Hz), 7.94 (s, 2H, 2 HC=N). - ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 24.3 (-), 33.4 (-), 73.2 (+), 109.4 (+), 116.2 (+), 122.7 (+), 128.9 (C$_{quat}$), 152.6 (+). - MS (CI-MS/DCI), m/z (%): 268 (56) [M$^{+•}$], 176 (32) [M$^{+•}$– N=CH-pyrrole], 94 (100) [N=C-pyrrole]. - Elemental Analysis: Calculated for $C_{16}H_{20}N_4$, C 71.61, H 7.51, N 20.88. Found C 72.00, H 7.70, N 20.90.



66c

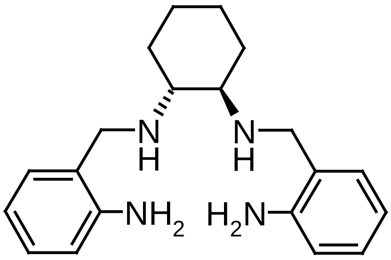
N,N´-Bis-(thiophene-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (66c): 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (0.60 g, 5.30 mmol) and 2-thiophenecarboxaldehyde (**68c**) (1 ml, 10.50 mmol) in 10 ml of EtOH were stirred for 4 h at room temperature and worked up according to *GP-1*. The crude product was recrystallised from EtOH/ Et_2O (1:1, 7 ml) to give **66c** (1.5 g, 5 mmol, 95 %) as a white solid. X-ray quality crystals were obtained by slow evaporation of an ethanol solution of this ligand. mp = 137 °C. - IR (KBr): ν = 3452, 3243, 2927, 2837, 1792, 1728, 1627, 1427, 1378, 1345, 1289, 1213, 1133, 1080, 1036, 856, 826, 758, 730, 715 cm^{-1}. - ^1H NMR (250 MHz, $CDCl_3$): δ = 1.40-1.48 (m, 2H), 1.78-1.86 (m, 6H), 3.30-3.33 (m, 2H), 6.95 (dd, 2H, *J* = 5.0, 3.6 Hz), 7.13 (dd, 2H, *J* = 3.6, 1.2 Hz), 7.27 (dd, 2H, *J* = 5.0, 1.2 Hz), 8.26 (d, *J* = 0.5 Hz, 2H, HC=N).- ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.4 (-), 32.8 (-), 73.3 (+), 127.1 (+), 128.2 (+), 130.1 (+), 142.4 (C_{quat}), 154.3 (+). - MS (EI), m/z (%): 302 (12) [$M^{+\bullet}$], 193 (100) [$M^{+\bullet}$ -N=CH-thiophene], 112 (74) [N=CH-thiophene]. - Calculated for $C_{16}H_{18}N_2S_2$: C 63.54, H 6.00, N 9.26. Found: C 63.17, H 6.00, N 9.17.



66d

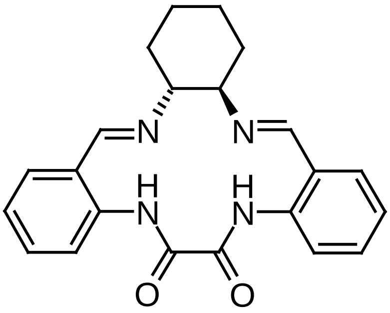
N,N´ -Bis- (furan-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (66d): 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (1 g, 8.9 mmol) and furancarboxaldehyde (**68d**) (1.5 ml, 17.9 mmol) in 20 ml of EtOH were refluxed for 3 h in the presence of 5 ml 2 M NaOH. The red solution was evaporated and the crude product was crystallised from Et_2O (25 ml) to yield **66d** (2.05 g, 7.59 mmol, 85%) as a red-brown solid. mp = 93 °C. - IR (KBr): ν = 3412, 3094, 2931, 2857, 1646, 1634, 1481, 1449, 1274, 1193, 1012, 933, 881, 765, 742 cm^{-1}. - ^1H NMR (250 MHz, $CDCl_3$): δ = 1.37-1.43 (m, 2H), 1.68-1.79 (m, 6H), 3.27-3.31 (m, 2H), 6.35 (dd, 2H, *J* = 3.5, 1.7 Hz), 6.60 (dd, 2H, *J* = 3.5, 0.6 Hz), 7.39 (d, 2H, *J* = 1.7 Hz), 7.93 (s, 2H, HC=N). - ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.9

(-), 32.6 (-), 73.5 (+), 111.2 (+), 114.4 (+), 144.4 (+), 149.8 (+), 150.7 (C_{quat}). - MS (CI-MS/DCI), m/z (%): 270 (19) [$M^{+\bullet}$], 177 (51) [$M^{+\bullet}$-N=CH furan], 96 (100) [N=CH furan].



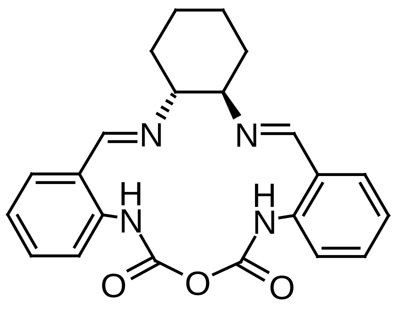
70

N,N′ -Bis- (2-ethyl-phenylamine)- cyclohexane-1*R*, 2*R*-diamine (70): The *Schiff* base **66a** (2.0 g, 6.25 mmol) dissolved in dry ethanol was heated to 50 °C, then $NaBH_4$ (0.95 g, 25 mmol) was added in portions. After the addition was completed, the reaction mixture was refluxed for 1 h under N_2. The product was precipitated with water, the solid was filtered off and washed with cold water. Yield: 1.93 g, 6 mmol, 95 %. mp = 101 °C. - IR (KBr): ν = 3394, 3364, 3311, 3288, 3025, 2938, 2914, 2852, 1618, 1587, 1494, 1458, 1425, 754, 727 cm^{-1}. - ^1H NMR (250 MHz, $CDCl_3$): δ = 1.05-1.30 (m, 4H), 1.54-1.75 (m, 4H), 2.17-2.26 (m, 4H), 3.58 (d, 2H, *J* = 12.3 Hz, CH_2), 3.88 (d, 2H, *J* = 12.3 Hz, CH_2), 4.43 (bs, 4H), 6.58-6.7 (m, 4H), 6.98-7.1 (m, 4H). - ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.9 (-), 31.4 (-), 49.8 (-), 61.1 (+), 115.7 (+), 117.8 (+), 124.7 (C_{quat}), 128.2 (+), 129.7 (+), 146.5 (C_{quat}). - MS (CI-MS/DCI; plasma gas), m/z (%): 325.3 (100) [MH^+].- Calculated for $C_{20}H_{28}N_4$: C 74.03, H 8.70, N 17.27. Found: C 73.32, H 8.63, N 17.01.



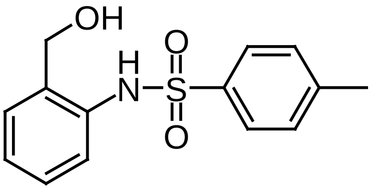
71

7,10-Cyclooxalamide-N,N´-bis-(phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (71): *Schiff* base **66a** (400 mg, 1.25 mmol) and dry Et$_3$N (0.35 ml, 2.51 mmol) were solved in 20 ml dry THF under nitrogen with stirring. A solution of oxalylchloride (0.15 ml, 1.77 mmol) in 25 ml dry THF was added with syringe pump over a period of 2.5 h. The reaction mixture was then stirred for 19 h at room temperature. The mixture was concentrated to half volume and colourless precipitates of the product were filtered off. Flash chromatography of the raw product in CHCl$_3$ afforded the cyclic compound **71** (318 mg, 0.85 mmol, 68 %). mp = 223-225 °C (decomposes at this temperature). - IR (KBr): ν = 3440, 2963, 2925, 2854, 2359, 1683, 1635, 1577, 1506, 1440, 1290, 1261, 1159, 1093, 1025, 939, 859, 802, 753 cm^{-1}. - ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.53-2.13 (m, 8H), 3.79 (s, 2H), 7.00 (dd, 2H, J = 7.6 Hz), 7.18 (d, 2H, J = 7.6 Hz), 7.40 (dd, 2H, J = 7.9, 7.6 Hz), 8.52 (s, 2H, HC=N), 8.87 (d, 2H, J = 7.9 Hz), 14.22 (s, 2H, PhNH). - ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 24.38 (-), 33.1 (-), 73.59 (+), 119.95 (+), 122.75 (C$_{quat}$), 123.52 (+), 130.75 (+), 132.85 (+), 138.57 (C$_{quat}$), 159.74 (C$_{quat}$), 163.24 (+). - MS (PI-EIMS) m/z (%): 374.2 (8) [M$^{+\bullet}$], 228.2 (22) [M$^{+\bullet}$ – N=CH-Ph-NHCO], 147.1 (100) [N=CH-Ph-NHCO].



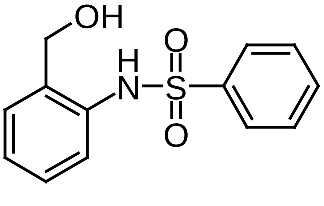
72

7,10-Cyclodicarbonic-diamide-N,N´-bis-(phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (72): Boc$_2$O (657 mg, 3.01 mmol), DMAP (41 mg, 0.34 mmol) and *Schiff* base **66a** (500 mg, 1.56 mmol) were dissolved in 10 ml dry CH$_2$Cl$_2$ under nitrogen with stirring. The reaction mixture was stirred for 30 minutes at room temperature and then at 40 °C for 6 h. Evaporation of the solvent and crystallisation of the residue from 50 ml EtOH afforded **72** as raw product. After two chromatographic columns (in AcOEt) a colourless product (230 mg, 0.59 mmol, 38 %) was obtained. mp = 253-255 °C (decomposes at this temperature). – IR (KBr): ν = 3413, 3208, 3062, 2923, 2856, 1679, 1608, 1498, 1463, 1385, 1296, 1270, 1227, 1157, 1139, 938, 794, 754 cm^{-1}. - ^{1}H NMR (250 MHz, DMSO-d$_6$): δ = 1.31-1.45 (m, 3H), 1.73-1.77 (m, 3H), 1.90-1.95 (m, 1H), 2.63-2.67 (m, 1H), 3.62-3.71 (m, 1H), 5.04-5.09 (m, 1H), 5.96 (s, 1H, HC=N), 6.51 (s, 1H, HC=N), 6.79-7.16 (m, 4H), 7.20-7.23 (m, 3H), 7.29-7.32 (m, 1H), 9.68 (s, 1H, PhNH), 9.71 (s, 1H, PhNH).- ^{13}C NMR (62.9 MHz, DMSO-d$_6$): δ = 24.93 (-), 25.58 (-), 30.72 (-), 31.96 (-), 53.96 (+), 63.76 (+), 81.24 (+), 87.63 (+), 113.29 (+), 113.34 (+), 118.03 (C$_{quat}$), 118.21 (C$_{quat}$), 120.87 (+), 120.92 (+), 127.28 (+), 127.43 (+), 129.27 (+), 129.46 (+), 136.47 (C$_{quat}$), 136.53 (C$_{quat}$), 151.33 (C$_{quat}$), 151.67 (C$_{quat}$). - MS (CI-MS) m/z (%): 391.3 (100) [MH$^{+\bullet}$], 244.2 (73), [MH$^{+\bullet}$ – N=CH-Ph-NHCO].



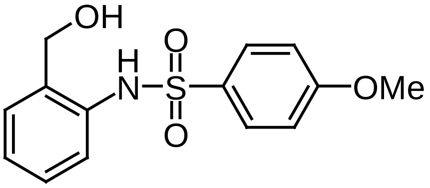
78a

N-(2-hydroxymethyl-phenyl)-4-methyl-benzenesulphonamide (78a): *o*-Aminobenzyl alcohol (**77**) (2 g, 16.24 mmol) in 60 ml CHCl$_3$, pyridine (1.56 ml) and 4-toluenesulphonyl chloride (3.43 g, 18 mmol) in 17 ml CHCl$_3$ reacted as described in *GP-2*. Ethyl acetate (50 ml) and saturated ammonium chloride solution (40 ml) were used. A white solid (4.41 g, 15.9 mmol, 98 %) was achieved. - ^{1}H NMR (250 MHz , CDCl$_3$): δ = 2.38 (s, 3H, CH$_3$), 4.39 (s, 2H, CH$_2$), 7.06-7.09 (m, 2H), 7.19-7.28 (m, 3H), 7.42 (d, 1H, *J* = 7.9 Hz), 7.64 (dd, 2H, *J* = 4.7, 1.8 Hz).



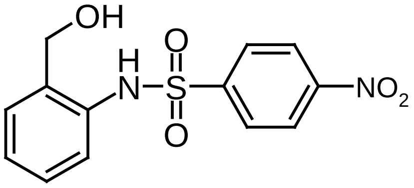
78b

N-(2-hydroxymethyl-phenyl)-benzenesulphonamide (78b): *o*-Aminobenzyl alcohol (**77**) (4 g, 32.5 mmol) benzenesulphonyl chloride (4.61 ml, 36 mmol) and pyridine (3.12 ml) in $CHCl_3$ (120 + 35 ml) were allowed to react according to *GP-2*. The residue was taken up in ethyl acetate (100 ml) and ammonium chloride (80 ml). The product **78b** was obtained as white solid (8.15 g, 31 mmol, 95 %). - ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 4.3$ (s, 2H, CH_2), 7.06 (dd, 2H, J = 5.4 Hz), 7.18-7.24 (m, 1H), 7.35-7.44 (m, 3H), 7.48-7.52 (m, 1H), 7.71-7.75 (m, 2H), 8.34 (bs, 1H, NH).



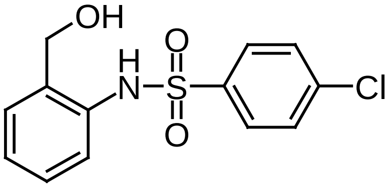
78c

N-(2-hydroxymethyl-phenyl)-4-methoxy-benzenesulphonamide (78c): *o*-Aminobenzyl alcohol (**77**) (4 g, 32.48 mmol), 4-methoxybenzenesulphonyl chloride (7.44 g, 36 mmol), pyridine (3.12 ml), and $CHCl_3$ (120 + 34 ml) reacted according to *GP-2*. To taken up the residue ethyl acetate (50 ml) and ammonium chloride solution (40 ml) were used. The reaction yield a light yellow solid (8.6 g, 31.05 mmol, 100 %) as product. - ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.82$ (s, 3H, OCH_3), 4.40 (d, 2H, J = 4.1 Hz, CH_2), 6.86-6.89 (m, 2H), 7.07-7.1 (m, 2H), 7.19-7.28 (m, 1H), 7.41 (d, 1H, J = 7.9 Hz), 7.66-7.70 (m, 2H), 7.88 (bs , 1H, NH).



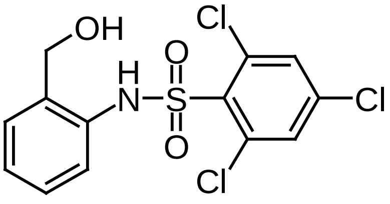
78d

N-(2-hydroxymethyl-phenyl)-4-nitro-benzenesulphonamide (78d): *o*-Aminobenzyl alcohol (**77**) (1 g, 8.12 mmol in 30 ml $CHCl_3$), pyridine (0.78 ml) and 4-nitrobenzenesulphonyl chloride (1.96 g, 8.85 mmol, in 9 ml $CHCl_3$) were permitted to react as shown in *GP-2*. After treatment with ethyl acetate (30 ml) and ammonium chloride solution (20 ml) a yellow solid of **78d** was obtained (2.5 g, 8.12 mmol, 100 %). - ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.48$ (bs, OH), 4.31 (s, 2H, CH_2), 7.09 (m, 2H), 7.19-7.24 (m, 1H), 7.37 (d, 1H, J = 7.9 Hz), 7.89-7.94 (m, 2H), 8.21-8.26 (m, 2H), 8.8 (bs, 1H, NH).



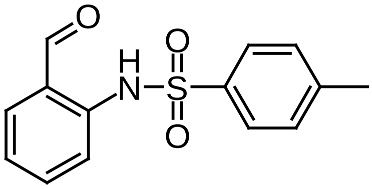
78e

N-(2-hydroxymethyl-phenyl)-4-chlor-benzenesulphonamide (78e): *o*-Aminobenzyl alcohol (**77**) (1 g, 8.12 mmol in 30 ml $CHCl_3$), pyridine (0.78 ml) and 4-chlorbenzenesulphonyl chloride (1.87 g, 8.85 mmol in 9 ml $CHCl_3$) were stirred by *GP-2*. After extraction with ethyl acetate (30 ml) and ammonium chloride solution (20 ml) a white solid was obtained (2.41 g, 8.1 mmol, 100 %). - ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.12$ (s, OH), 4.34 (s, 2H, CH_2), 7.06-7.1 (m, 2H), 7.18-7.25 (m, 1H), 7.35-7.4 (m, 3H), 7.64-7.7 (m, 2H), 8.44 (bs, 1H, NH).



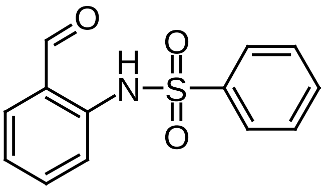
78f

N-(2-hydroxymethyl-phenyl)-2,4,6-trichlor-benzenesulphonamide (78f): *o*-Aminobenzyl alcohol **77** (180 mg, 1.46 mmol in 8 ml $CHCl_3$), pyridine (0.14 ml) and 2,4,6-trichlorbenzenesulphonyl chloride (450 mg, 1.61 mmol in 8 ml $CHCl_3$) were allowed to react according to *GP-2*. Thereby changes the colour of the mixture from yellow to red. Product **78f** was achieved in quantitative yield (536 mg, 1.46 mmol, 100%) and was used in the oxidation without characterisation.



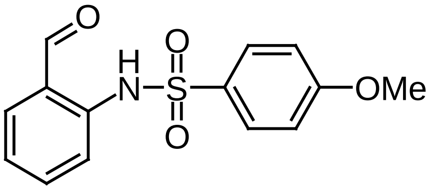
79a

N-(2-formyl-phenyl)-4-methyl-benzenesulphonamide (79a): A suspension of PCC (5.13 g, 23.8 mmol) in CH_2Cl_2 (80 ml) and a solution of alcohol **78a** (4.4 g, 15.86 mmol) in the same solvent (160 ml) reacted as described in *GP-3*. The raw product was crystallised from $CHCl_3$/ EtOH (1:5, 24 ml) to yield **79a** as white solid (3.21 g, 11.66 mmol, 74 %). - ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.37$ (s, 3H), 7.13-7.25 (m, 3H), 7.47-7.79 (m, 5H), 9.83 (s, 1H, CHO), 10.79 (bs, 1H, NH).



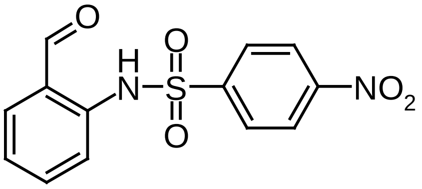
79b

N-(2-formyl-phenyl)-benzenesulphonamide (79b): A suspension of PCC (5 g, 23.25 mmol) in CH_2Cl_2 (75 ml) and the protected alcohol **78b** (4.07 g, 15.5 mmol) in CH_2Cl_2 (155 ml) reacted according to *GP-3*. After recrystallisation with $CHCl_3$/EtOH (1:5, 12 ml) a white solid (2.48 g, 9.5 mmol, 61 %) was afforded. - ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.17$ (ddd, 1H, $J = 7.5$, 6.7, 0.77 Hz), 7.42-7.59 (m, 5H), 7.66 (dd, 1H, $J = 1.6$ Hz), 7.89 (dd, 2H, $J = 6.7$, 1.6 Hz), 9.83 (s, 1H, CHO), 10.82 (bs, 1H, NH).



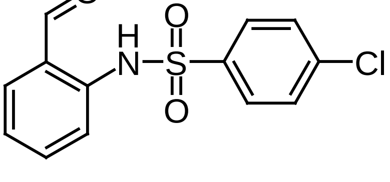
79c

N-(2-formyl-phenyl)-4-methoxy-benzenesulphonamide (79c): The alcohol **78c** (8.6 g, 29.3 mmol) in 320 ml CH_2Cl_2, PCC (10 g, 46.57 mmol) in 160 ml CH_2Cl_2 were stirred according to *GP-3* to get the aldehyde **79c** as a white solid (7.69 g, 26.43 mmol, 90 %). - ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.81 (s, 3H), 6.88-6.91 (m, 2H), 7.16-7.19 (m, 1H), 7.47-7.85 (m, 5H), 9.82 (s, 1H, CHO), 10.75 (bs, 1H, NH). - ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 55.56 (+), 114.25 (+), 117.68 (+), 121.81 (C_{quart}), 122.85 (+), 129.40 (+), 130.78 (C_{quart}), 135.76 (+), 136.10 (+), 139.93 (C_{quart}), 163.23 (C_{quart}), 194.98 (+).



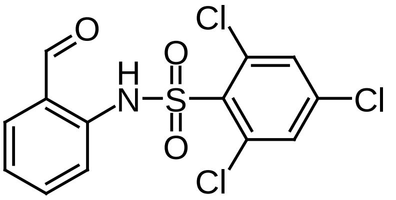
79d

N-(2-formyl-phenyl)-4-nitro-benzenesulphonamide (79d): To a suspension of PCC (2.82 g, 13.09 mmol) in 40 ml CH_2Cl_2 was added a solution of the protected alcohol **78d** (2.69 g, 8.72 mmol in 80 ml CH_2Cl_2) in agreement with *GP-3*. After recrystallisation with $CHCl_3$/ EtOH (1:7, 16 ml) a yellow solid (2.54 g, 8.29 mmol, 95 %) was obtained. - ^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.08 (d, 1H, *J* = 7.96 Hz), 7.39 (t, 1H, *J* = 7.5 Hz), 7.58 (ddd, 1H, *J* = 7.5, 1.6 Hz), 7.81 (dd, 1H, *J* = 7.5, 1.6 Hz), 7.94 (ddd, 2H, *J* = 6.9, 4.4, 2.4 Hz), 8.36 (ddd, 2H, *J* = 6.9, 4.4, 2.4 Hz), 10.06 (s, 1H, CHO), 10.84 (bs, 1H, NH). - ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 124.12 (+), 124.72 (+), 126.48 (+), 128.54(+), 129.06 (C_{quart}), 130.63 (+), 135.27 (+), 137.82 (C_{quart}), 143.9 (C_{quart}), 150.04 (C_{quart}), 191.69 (+). - MS (PI-EIMS), m/z (%): 306 (8) [$M^{+\bullet}$], 120.1 (100) [M-SO_2 $C_6H_4NO_2$]$^+$, 92.1 (50) [Ph-NH]$^+$.



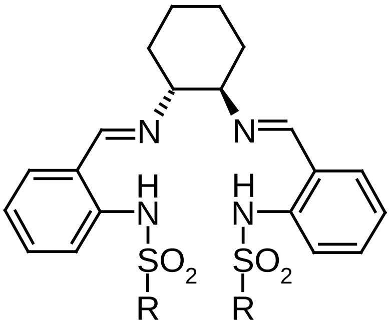
79e

N-(2-formyl-phenyl)-4-chlor-benzenesulphonamide (79e): To a stirred suspension of PCC (2.77 g, 12.86 mmol) in 40 ml CH_2Cl_2 was added with drop funnel a solution of alcohol **78e** (2.55 g, 8.57 mmol) in 80 ml of CH_2Cl_2 following the *GP-3*. After working up the aldehyde (2.52 g, 8.53 mmol, 99 %) was obtained. - ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.17-7.24 (m, 1H), 7.42 (dt, 2H, *J* = 6.7, 4.5 Hz), 7.50-7.70 (m, 3H), 7.82 (dt, 2H, *J* = 6.7, 4.4 Hz), 9.83 (s, 1H, CHO), 10.82 (bs, 1H, NH). - ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 117.99 (+), 122.10 (C_{quart}), 123.5 (+), 128.7(+), 129.51 (+), 135.97 (+), 136.28 (+), 137.84 (C_{quart}), 139.5 (C_{quart}), 139.86 (C_{quart}), 195.14 (+). - MS (PI-EIMS), m/z (%): 295.0 (7.5) [$M^{+\bullet}$], 120.1 (100) [$M-SO_2PhCl]^+$, 92.1 (32) [$Ph-NH]^+$.



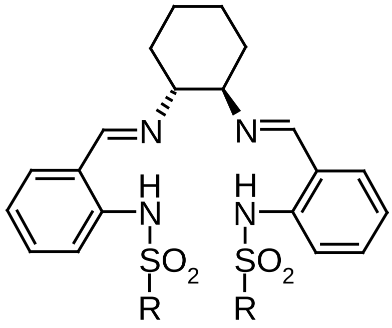
79f

N-(2-formyl-phenyl)-2,4,6-trichlor-benzenesulphonamide (79f): The alcohol **78f** (536 mg, 1.46 mmol in CH_2Cl_2 (70 ml) was dropped to a suspension of PCC (472 mg, 2.19 mmol) in 50 ml CH_2Cl_2. The reaction proceed according to *GP-3*. After chromatographic column the product was obtained as yellow solid (479 mg, 1.31 mmol, 90 %). - ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.20 (ddd, 1H, *J* = 7.5, 6.4 Hz), 7.44 (s, 2H), 7.55 (ddd, 1H, *J* = 7.5, 6.4, 1.5 Hz), 7.64-7.69 (m, 2H), 9.89 (s, 1H, CHO), 11.56 (bs, 1H, NH). - ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 116.22 (+), 121.46 (C_{quart}), 123.19 (+), 131.38(+), 132.99 (C_{quart}), 136.16 (+), 136.42 (+), 136.60 (C_{quart}), 138.95 (C_{quart}), 139.05 (C_{quart}), 194.74 (+).



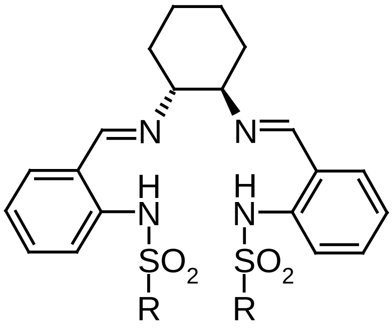
76a: R = p-MeC$_6$H$_4$

N,N´-Bis-(4-methyl-benzenesulfonamid-phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (76a): Aldehyde **79a** (1.57 g (5.72 mmol) and 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (326 mg, 2.86 mmol) were solved in 15 ml dry EtOH. The reaction was stirred 1 h under reflux according to *GP-1*. Yellow crystals of the *Schiff* base **76a** (1.54 g, 2.45 mmol, 85 %) were achieved after recrystallisation from EtOH (10 ml). mp = 273-274 °C. - IR (KBr): ν = 3649, 3443, 2925, 2860, 2361, 1630, 1599, 1578, 1497, 1449, 1411, 1338, 1288, 1157, 1089, 928, 811, 757 cm^{-1}. - ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.48-1.59 (m, 2H), 1.72-1.96 (m, 6H), 2.06 (s, 6H), 3.54-3.58 (m, 2H), 6.62 (d, 4H, *J* = 8.2 Hz), 6.91 (ddd, 2H, *J* = 7.7, 0.91 Hz), 7.16-7.27 (m, 4H), 7.43 (d, 4H, *J* = 8.2 Hz), 7.48 (d, 2H, *J* = 7.7 Hz), 8.46 (s, 2H, N=CH), 13.20 (s, 2H, NH). - ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 21.25 (+), 24.29 (-), 33.58 (-), 73.44 (+), 116.93 (+), 120.39 (C$_{quart}$), 122.29 (+), 127.08 (+), 129.27 (+), 131.27 (+), 133.71 (+), 136.45 (C$_{quart}$), 139.38 (C$_{quart}$), 143.1 (C$_{quart}$), 164.1 (+).- MS (ESI), m/z (%): 629.1 (100) [MH$^+$]. - Elemental Analysis, Calculated for C$_{34}$H$_{36}$N$_4$O$_4$S$_2$: C 64.95, H 5.78, N 8.92. Found C 64.65, H 5.79, N 8.86.



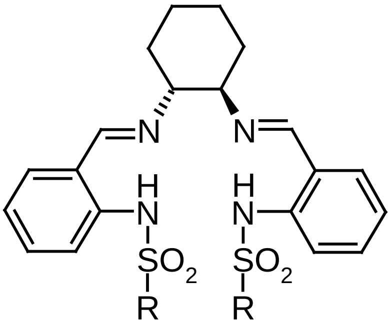
76b: R = C_6H_5

N,N´-Bis-(benzenesulfonamid-phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (76b): The aldehyde **79b** (997 mg, 3.8 mmol) and 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (218 mg, 1.9 mmol) were solved in dry EtOH (7 ml), and the reaction mixture was refluxed for 1 h under nitrogen as indicated in *GP-1*. After work up and recrystallisation from EtOH (5 ml), yellow crystals (850 mg, 1.41 mmol, 74%) were obtained. mp = 185-186 ºC. - IR (KBr): ν = 3441, 3060, 2933, 2858, 1634, 1579, 1500, 1444, 1421, 1199, 1157, 1089, 931, 862, 752, 713 cm^{-1} - ^1H NMR (250 MHz, $CDCl_3$): δ = 1.51-1.59 (m, 2H), 1.78-1.93 (m, 6H), 3.51-3.55 (m, 2H), 6.88-7.05 (m, 6H), 7.16-7.29 (m, 6H), 7.45 (d, 2H, *J* = 8.0 Hz), 7.62 (dd, 4H, *J* = 8.0 Hz), 8.44 (s, 2H, N=CH), 13.3 (s, 2H, NH-SO_2). - ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.25 (-), 33.46 (-), 73.33 (+), 116.99 (+), 120.35 (C_{quart}), 122.43 (+), 127.01 (+), 128.75 (+), 131.41 (+), 132.52 (+), 133.65 (+), 139.24 (C_{quart}), 139.56 (C_{quart}), 164.12 (+). - MS (ESI), m/z (%): 601.2 (100) [MH^+], 358.1 (11) [M-($HCPhNHSO_2Ph$)]. - Elemental Analysis: Calculated for $C_{32}H_{32}N_4O_4S_2$, C 63.98, H 5.37, N 9.33, S 10.67. Found C 64.19, H 5.65, N 9.53, S 10.66.



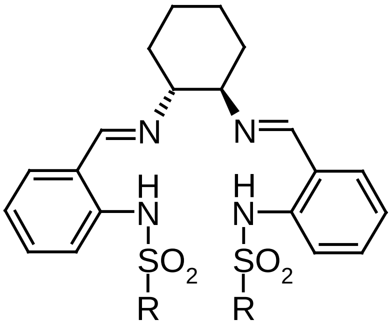
76c: R = *p*-MeOC_6H_4

N,N´-Bis-(4-methoxy-benzenesulfonamid-phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (76c): Aldehyde **79c** (2 g, 6.87 mmol) and 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (0.39 g, 3.43 mmol) in EtOH (25 ml) reacted as described in *GP-1* for 1 h. A yellow powder (3.55 g, 5.37 mmol, 78 %) was obtained after recrystallisation with EtOH (16 ml). mp = 200-202 °C. - IR (KBr): ν = 3574, 2929, 2856, 2360, 2341, 1627, 1595, 1577, 1497, 1338, 1261, 1154, 1093, 925 cm^{-1}. - ^1H NMR (400 MHz, $CDCl_3$): δ = 1.53-1.64 (m, 2H), 1.78-1.96 (m, 6H), 3.48 (s, 6H), 3.62-3.64 (m, 2H), 6.19 (dd, 4H, *J* = 7.0, 2.0 Hz), 6.97 (dd, 2H, *J* = 7.5, 6.7 Hz), 7.22-7.3 (m, 2H), 7.33 (dd, 2H, *J* = 7.5 Hz), 7.43 (dd, 4H, *J* = 6.7, 2.0 Hz), 7.52 (d, 2H, *J* = 8.2 Hz), 8.55 (s, 2H, N=CH), 13.22 (s, 2H, NH-SO_2). - ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.26 (-), 33.67 (-), 55.24 (+), 73.43 (+), 113.68 (+), 116.75 (+), 120.3 (C_{quart}), 122.2 (+), 129.22 (+), 130.61 (C_{quart}), 131.22 (+), 133.7 (+), 139.4 (C_{quart}), 162.48 (C_{quart}), 163.92 (+). - MS (ESI), m/z (%): 661.2 (100) [MH^+]. - Elemental Analysis, Calculated for $C_{34}H_{36}N_4O_6S_2$: C 61.80, H 5.49, N 8.48. Found C 61.73, H 5.45, N 8.43.



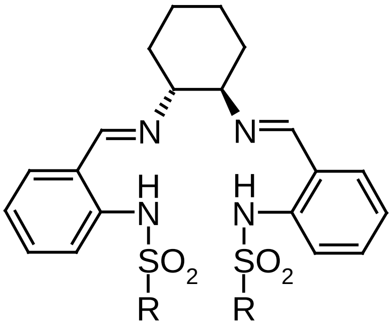
76d: R = *p*-$NO_2C_6H_4$

N,N´-Bis-(4-nitro-benzenesulfonamid-phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (76d): 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (415 mg, 3.64 mmol) and the aldehyde **79d** (2.23 g, 7.28 mmol) in dry EtOH (20 ml) were refluxed for 3 h following the *GP-1*. The product was obtained as yellow solid (2.29 g, 3.31 mmol, 91 %). mp = 118-120 °C. – IR (KBr): ν = 3576, 3448, 3103, 2933, 2861, 1630, 1606, 1578, 1531, 1499, 1347, 1311, 1088, 1043, 760, 733 cm^{-1}. - ^1H NMR (250 MHz, $CDCl_3$): δ = 1.53-1.98 (m, 8H), 3.57-3.61 (m, 2H), 7.01 (dt, 2H, *J* = 8.0, 1.1 Hz), 7.29-7.34 (m, 4H), 7.50 (d, 2H, *J* = 8.0 Hz), 7.72 (s, 8H), 8.5 (s, 2H, N=CH), 13.62 (s, 2H, NH-SO_2). - ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.17 (-), 33.58 (-), 73.15 (+), 116.96 (+), 120.21 (C_{quart}), 123.22 (+), 123.88 (+), 128.17 (+), 132.07 (+), 133.82 (+), 138.75 (C_{quart}), 145.22 (C_{quart}), 149.68 (C_{quart}), 164.33 (+). - MS (ESI), m/z (%): 691.2 (100) [MH^+], 429.1 (50) [$M-2xSO_2C_6H_4NO_2$]$^+$.



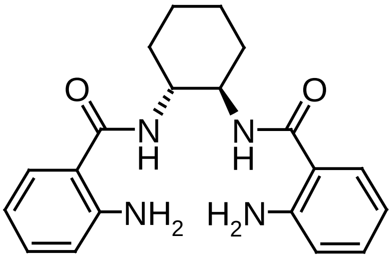
76e: R = *p*-ClC_6H_4

N,N´-Bis-(4-chlor-benzenesulfonamid-phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (76e): A mixture of 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (260 mg, 2.28 mmol) and the aldehyde **79e** (1.35 g, 4.57 mmol) in EtOH (14 ml) was stirred at reflux for 1 h according to *GP-1*. A yellow powder (1.06 g, 1.58 mmol, 69 %) was achieved after recrystallisation with the same solvent (12 ml). mp = 177-178 °C. - IR (KBr): ν = 3466, 2939, 2860, 1630, 1579, 1500, 1475, 1427, 1394, 1337, 1282, 1201, 1157, 1089, 933, 831, 767, 613 cm^{-1}. - ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.55-1.60 (m, 2H), 1.76-1.94 (m, 6H), 3.55-3.59 (m, 2H), 6.77 (dt, 4H, *J* = 6.6, 4.4 Hz), 6.97 (ddd, 2H, *J* = 7.5, 6.6, 0.9 Hz), 7.23-7.31 (m, 4H), 7.41-7.5 (m, 6H), 8.48 (s, 2H, N=CH), 13.33 (s, 2H, NH-SO_2-). - ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.21 (-), 33.56 (-), 73.29 (+), 116.84 (+), 120.25 (C_{quart}), 122.7 (+), 128.37 (+), 128.92 (+), 131.61 (+), 133.72 (+), 137.76 (C_{quart}), 138.94 (C_{quart}), 138.97 (C_{quart}), 164.11 (+). - MS (ESI, -pESI), m/z (%): 667.3 (100) [$M-H^+$]$^-$. - Elemental Analysis, Calculated for $C_{32}H_{30}N_4Cl_2O_4S_2$: C 57.40, H 4.52, N 8.37. Found C 57.45, H 4.41, N 8.35.



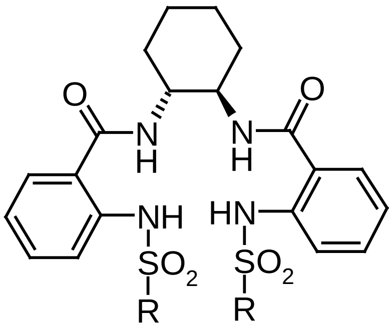
76f: R = 2,4,6-$Cl_3C_6H_2$

N,N´-Bis-(2,4,6-trichlor-benzenesulfonamid-phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamine (76f): According to *GP-1*, a mixture of 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (29 mg, 0.25 mmol) and the aldehyde **79f** (186 mg, 0.51 mmol) in EtOH (5 ml) was refluxed 1 h. Yellow crystals of **76f** (147 mg, 0.18 mmol, 71 %) were attained after recrystallisation with the same solvent (4 ml). mp = 132-134 °C. - IR (KBr): ν = 3446, 3067, 2931, 2858, 1633, 1562, 1537, 1498, 1412, 1367, 1290, 1177, 1140, 1040, 934, 864, 834, 797, 756, 661, 617, 574 cm^{-1}. - ^1H NMR (250 MHz, $CDCl_3$): δ = 1.43-1.97 (m, 8H), 3.41-3.48 (m, 2H), 6.96-7.02 (dt, 2H, *J* = 7.6 Hz), 7.19-7.25 (dt, 2H, *J* = 7.6 Hz), 7.33-7.40 (m, 8H), 8.42 (s, 2H, N=CH), 14.15 (s, 2H, NH-SO_2). - ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.17 (-), 33.05 (-), 73.16 (+), 115.55 (+), 119.71 (C_{quart}), 122.29 (+), 131.27 (+), 131.83 (+), 133.88 (+), 133.93 (C_{quart}), 136.32 (C_{quart}), 138.3 (C_{quart}), 139.04 (C_{quart}), 164.18 (+). - MS (ESI), m/z (%): 807.1 (100) $[MH]^+$, 462.0 (78) $[M-HCPhNHSO_2PhCl_3]^+$, 391.3 (25) $[M-HCPhNHSO_2PhCl_5]^+$. - Elemental Analysis, Calculated for $C_{32}H_{26}N_4Cl_6O_4S_2$: C 47.60, H 3.25, N 6.94. Found C 47.32, H 3.41, N 6.78.



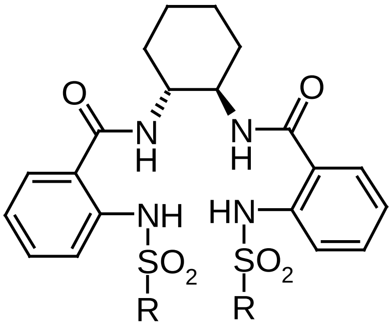
83

N,N´-Bis-(2-aminobenzoyl)-1*R*, 2*R*-diaminocyclohexane (83): To a mixture of 1*R*, 2*R*-(*trans*)-cyclohexanediamine (**67**) (2 g, 17.5 mmol) and Et_3N (9.75 ml) in 50 ml dry DMF was added with syringe pump, a solution of isatoic anhydride **82** (5.7 g, 35 mmol) in 35 ml dry DMF. During the addition and in the following 26 h the temperature was maintained between 50-60 °C. The reaction mixture was poured into 400 ml cold water and was extracted with CH_2Cl_2 (3 x 100 ml). The organic layer was washed with $NaHCO_3$-solution (10 %) and dried with Na_2SO_4. Evaporation of the solvent afforded compound **83** as white solid (3.59 g, 10.2 mmol, 58 %). mp = 234-235 °C. - IR (KBr): ν = 3416, 3284, 3064, 2937, 2857, 1620, 1585, 1531, 1448, 1366, 1319, 1259, 1155, 1097, 1033, 858, 813, 791, 747, 684 cm^{-1}. - ^1H NMR (250 MHz, DMSO-d_6): δ = 1.15-1.48 (m, 4H), 1.69-1.72 (m, 2H), 1.87-1.92 (m, 2H), 3.81-3.84 (m, 2H), 6.25 (bs, 4H, NH_2), 6.43 (dt, 2H, J = 7.8 Hz), 6.63 (dd, 2H, J = 8.2 Hz), 7.04 (t, 2H, J = 8.2, 1.2 Hz), 7.34 (dd, 2H, J = 7.8, 1.2 Hz), 7.96 (d, 2H, CO-NH). - ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.64 (-), 31.70 (-), 52.37 (+), 114.52 (+), 115.17 (C_{quart}), 116.11 (+), 128.17 (+), 131.47 (+), 149.33 (C_{quart}), 168.85 (C=O). - MS (ESI), m/z (%): 353.0 (100) [MH^+]. - Elemental Analysis, Calculated for $C_{20}H_{24}N_4O_2$: C 68.16, H 6.86, N 15.90. Found C 67.88, H 6.56, N 15.48.



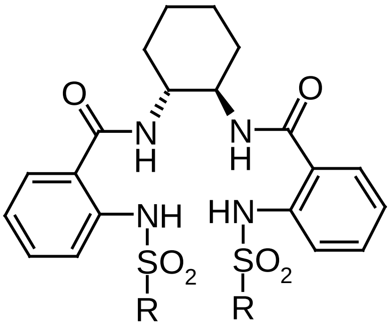
84a: R = CH_3

N,N´-Bis-[(2-N´´-methanesulphonylamino)benzoyl)]- 1*R*, 2*R*-diaminocyclohexane (84a): The diamide **83** (800 mg, 2.27 mmol) was suspended in 30 ml CH_2Cl_2, pyridine (0.18 ml) and methane sulphonyl chloride (0.41 ml, 5.27 mmol) were added. The mixture was stirring and working out according to *GP-4.* After recrystallisation with $CHCl_3$/ EtOH (1:3) the compound **84a** (792 mg, 1.56 mmol, 69 %) was obtained as white solid. mp = 115-117 °C. - IR (KBr): ν = 3477, 3344, 3175, 3011, 2933, 2860, 2360, 1637, 1598, 1539, 1493, 1396, 1330, 1262, 1154, 1109, 974, 756 cm^{-1}. - ^{1}H NMR (250 MHz, DMSO-d$_6$): δ = 1.28-1.31 (m, 2H), 1.52-1.55 (m, 2H), 1.73-1.76 (m, 2H), 1.86-1.91 (m, 2H), 2.94 (s, 6H), 4.00 (bs, 2H), 7.14 (dd, 2H, *J* = 7.8, 5.7 Hz), 7.44 (t, 4H, *J* = 5.7 Hz), 7.71 (d, 2H, *J* = 7.8 Hz), 8.72 (d, 2H, CO-NH), 10.97 (s, 2H, HN-SO_2CH_3). - ^{13}C NMR (101 MHz, DMSO-d$_6$): δ = 24.55 (-), 31.27 (-), 39.53 (+), 52.24 (+), 118.75 (+), 120.49 (C$_{quart}$), 122.81 (+), 128.57 (+), 132.44 (+), 138.57 (C$_{quart}$), 167.68 (C=O). – MS (ESI, -pESI), m/z (%): 507.1 (100) [M-H$^+$]$^-$. Elemental Analysis, Calculated for $C_{22}H_{28}N_4O_6S_2$: C 51.95, H 5.55, N 11.02. Found C 52.18, H 6.03, N 10.72.



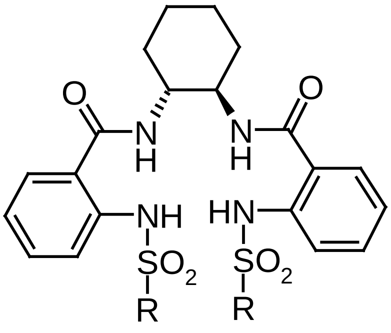
84b: R = *p*-MeC$_6$H$_4$

N,N´-Bis-[(2-N´´-4-methylbenzenesulphonylamino)benzoyl)]- 1*R*, 2*R*-diaminocyclohexane (84b): Compound **83** (800 mg, 2.27 mmol) in 30 ml CH_2Cl_2, pyridine (0.18 ml) and 4-toluenesulphonyl chloride (1 g, 5.27 mmol) were allowed to react as described in *GP-4*. The raw product was recrystalised from $CHCl_3$/ EtOH (1:5) to yield 66 % (984 mg, 1.49 mmol) of **84b** as white solid. mp = 252-253 °C. - IR (KBr): ν = 3402, 3368, 2937, 2858, 2392, 1634, 1595, 1534, 1495, 1446, 1333, 1269, 1158, 1093, 935, 752, 562 cm^{-1}. - ^{1}H NMR (250 MHz, DMSO-d$_6$): δ = 1.28-1.31 (m, 2H), 1.45-1.49 (m, 2H), 1.74-1.82 (m, 4H), 2.21 (s, 6H), 3.95 (bs, 2H), 7.02-7.09 (m, 2H), 7.14 (d, 4H, *J* = 8.1 Hz), 7.39 (t, 4H, *J* = 5.0, 2.5 Hz), 7.53 (d, 4H, *J* = 8.1 Hz), 7.63 (d, 2H, *J* = 8.1 Hz), 8.64-8.67 (d, 2H, CO-NH), 11.57 (s, 2H, HN-Ts). - ^{13}C NMR (62.9 MHz, DMSO-d$_6$): δ = 20.87 (+), 24.53 (-), 31.19 (-), 52.17 (+), 118.79 (+), 120.38 (C$_{quart}$), 123.08 (+), 126.64 (+), 128.55 (+), 129.74 (+), 132.37 (+), 135.84 (C_{quart}), 138.30 (C_{quart}), 143.66 (C_{quart}), 167.66 (C=O). - MS (ESI, -pESI), m/z (%): 659.2 (100) $[M-H^+]^-$



84c: R = *p*-$NO_2C_6H_4$

N,N´-Bis-[(2-N´´-4-nitrobenzenesulphonylamino)benzoyl)]- 1*R*, 2*R*-diaminocyclohexane (84c): Compound **83** (800 mg, 2.27 mmol) in 30 ml CH_2Cl_2, pyridine (0.18 ml) and 4-nitrobenzenesulphonyl chloride (1.17 g, 5.27 mmol) reacted following *GP-4*. From recrystallisation with $CHCl_3$/ EtOH (1:7) were obtained yellow crystals (1.02 g, 1.41 mmol, 62 %). mp = 248-250 °C. - IR (KBr): ν = 3406, 3374, 3103, 2938, 2861, 1630, 1596, 1534, 1493, 1449, 1373, 1348, 1201, 1165, 1092, 1012, 944, 855, 752, 685, 601, 555 cm^{-1}. - ^1H NMR (250 MHz, DMSO-d_6): δ = 1.25-1.41 (m, 4H), 1.71-1.74 (m, 4H), 3.85 (bs, 2H), 7.08-7.15 (m, 2H), 7.37-7.46 (m, 4H), 7.54 (d, 2H, *J* = 7.5 Hz), 7.91 (d, 4H, *J* = 8.8 Hz), 8.25 (dd, 4H, *J* = 8.8, 7.5 Hz), 8.6 (d, 2H, CO-NH), 11.6 (s, 2H, HN-SO_2). - ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.48 (-), 30.96 (-), 52.28 (+), 120.06 (+), 121.96 (C_{quart}), 124.09 (+), 124.67 (+), 128.29 (+), 128.65 (+), 132.45 (+), 137.03 (C_{quart}), 144.02 (C_{quart}), 149.91 (C_{quart}), 167.45 (C=O). - MS (ESI, -pESI), m/z (%): 721.2 (100) $[M-H^+]^-$. Elemental Analysis, Calculated for $C_{32}H_{30}N_6O_{10}S_2$: C 53.18, H 4.18, N 11.63. Found C 52.90, H 4.07, N 11.56.



84d: R = *p*-ClC_6H_4

N,N´-Bis-[(2-N´´-4-chlorbenzenesulphonylamino)benzoyl)]- 1*R*, 2*R*-diaminocyclohexane (84d): Compound **83** (800 mg, 2.27 mmol) in 30 ml CH_2Cl_2, pyridine (0.18 ml) and 4-chlorbenzenesulphonyl chloride (1.11 g, 5.27 mmol) reacted as shown by *GP-4*. The protected compound **84d** was afforded as white powder (1.07 g, 1.52 mmol, 67 %) after recrystallisation with petrolether/Et_2O (1:1). mp = 217-218 °C. - IR (KBr): ν = 3378, 3175, 3011, 2938, 2858, 1634, 1585, 1534, 1495, 1448, 1392, 1334, 1276, 1204, 1162, 1091, 1012, 940, 827, 754, 705, 611 cm^{-1}. - ^1H NMR (250 MHz, DMSO-d_6): δ = 1.27-1.48 (m, 4H), 1.76-1.8 (m, 4H), 3.90 (bs, 2H), 7.07-7.13 (m, 2H), 7.37-7.48 (m, 8H), 7.58-7.67 (m, 6H), 8.65 (d, 2H, CO-NH), 11.54 (s, 2H, HN). - ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.52 (-), 31.08 (-), 52.24 (+), 119.57 (+), 121.2 (C_{quart}), 123.64 (+), 128.53 (+), 128.6 (+), 129.48 (+), 132.42 (+), 137.49 (C_{quart}), 137.66 (C_{quart}), 138.23 (C_{quart}), 167.54 (C=O). - MS (ESI, -pESI), m/z (%): 699.2 (100) $[M-H^+]^-$. - Elemental Analysis, Calculated for $C_{32}H_{30}N_4Cl_2O_6S_2$: C 54.78, H 4.31, N 7.99. Found C 54.70, H 4.27, N 7.86.

5.2.3 Preparation of some metal complexes

70-Cu(II)-OTf: Ligand **70** (300 mg, 0.9 mmol) and $Cu(OTf)_2$ (330 mg, 0.9 mmol) were reacted in ethanol (7ml) according to *GP-5*, and recrystallised from the same solvent (7 ml) to yield 611 mg (96%) of the complex as violet solid. X-ray quality crystals were obtained by slow evaporation of an ethanol solution of this complex. mp = 235 °C. - IR (KBr): ν = 3455, 3292, 3246, 3120, 2943, 2860, 1621, 1582, 1503, 1460, 1285, 1232, 1090, 1027, 956, 925, 761, 636 cm^{-1}. - MS (ESI), *m*/*z* (%): 536.1 (100) $[M-TfO^-]^+$. -

Calculated for $C_{22}H_{22}CuF_6N_4O_6S_2$ C 38.85; H 3.26; N 8.24. Found: C 38.04; H 3.75; N 8.01.

70-Zn(II): Ligand **70** (100 mg, 0.3 mmol) and $Zn(OAc)_2 \cdot 2H_2O$ (68 mg, 0.3 mmol) were reacted in methanol (5ml) according to *GP-5*, and recrystallised from EtOH (3 ml) to yield 107 mg (92%) of the neutral complex as light yellow solid. mp = 270 °C. - MS (ESI), *m*/*z* (%): 387.2 (100) $[M-H^+]^+$.

70-Ni(II): Ligand **70** (100 mg, 0.3 mmol) and $Ni(OAc)_2 \cdot 4H_2O$ (77 mg, 0.3 mmol) were reacted in methanol (7ml) according to *GP-5*, and recrystallised from EtOH (5 ml) to yield 103 mg (90%) of the neutral complex as dark green solid. mp = 272 °C. - MS (ESI), *m*/*z* (%): 381.2 (100) $[M-H^+]^+$.

70-Cu(II): Ligand **70** (100 mg, 0.3 mmol) and $Cu(OAc)_2 \cdot H_2O$ (62 mg, 0.3 mmol) were reacted in methanol (5ml) according to *GP-5*, and recrystallised from EtOH (3 ml) to yield 110 mg (95%) of the neutral complex as violet solid. mp = 98 °C. - MS (ESI), *m*/*z* (%): 386.2 (100) $[M-H^+]^+$.

5.3 Catalysis

General remarks

The catalytic reactions (addition of diethylzinc to aldehydes, cyclopropanation and *Mukaiyama* aldol reaction) were carried out in Schlenk flasks under nitrogen atmosphere and using dry solvents. The other catalyse did not need absolute conditions. The enantio- and/or the diastereosectivity of the products was determined by GC, HPLC or ^{1}H NMR. For the enantiomeric separation investigations by NMR, the (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluorethanol **146** (*Pirkle* alcohol) was used.

To test the reproducibility of the results obtained, each catalysis was performed at least twice under exactly the same conditions.

5.3.1 General procedures

General Procedure for the addition of diethylzinc to aldehydes (*GP-6*): The ligand was solved in dry toluene (6 ml) under nitrogen, diethylzinc (1.1 M solution in toluene, 0.1 ml, 0.11 mmol) was added, and the mixture was allowed to stir for 1 h at room temperature, then cooled to 0 °C or maintained at room temperature. The rest of diethylzinc (2.17 ml, 2.39 mmol) was dropped slowly. After five minutes the aldehyde (1mmol) was added. The reaction was stirred until no more aldehyde was observed (TLC), then quenched with 2 M HCl (6 ml). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by short path distillation or by flash chromatography to give the alcohol.

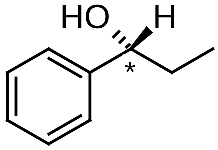
General Procedure for the epoxidation of styrene with m-CPBA (*GP-7*): A solution of styrene (312 mg, 3 mmol), NMO (2.03 g, 15 mmol), ligand (0.3 mmol, 10 mol %) and $Mn(AcO)_3$ (40.2 mg, 0.15 mmol, 5 mol %) in 10 ml CH_2Cl_2 was cooled to 0 °C. Solid *m*-CPBA (1.035 g, 6 mmol) was added in four portions over 2 min. The reaction mixture was stirred for 24 h at this temperature, 10 ml of 1 M NaOH were added and the organic phase was separated and washed with brine (2 x 10 ml). The combined aqueous phase were extracted with CH_2Cl_2 (2 x 10 ml), and the combined organic phases were dried with Na_2SO_4 and concentrated to approximately 2 ml. This residue was chromatographed on silica gel (hexane/ethyl acetate 19:1).

General Procedure for the cyclopropanation of styrene with diazoacetate (*GP-8*): The ligand (0.1 or 0.05 mmol) and copper(I) trifluoromethanesulfonate-toluene complex (0.1 or 0.05 mmol) were dissolved in dry CH_2Cl_2 (6 ml) under nitrogen atmosphere. The mixture was stirred 1 h, then styrene (0.23 ml, 2.0 mmol) was added. Finally methyl diazoacetate (1 ml, 8 % in CH_2Cl_2) diluted in 6 ml dry CH_2Cl_2 was added drop wise over 8 h with syringe pump into the reaction mixture. After complete addition this mixture was stirred for additional 3 h, the solvent was removed by evaporation and the residue was chromatographed on silica gel (hexane/ethyl acetate 10:1).

General Procedure for the *Mukaiyama* aldol reaction (*GP-9*)[225]: To a suspension of Sc(OTf)$_3$ (25 mg, 50 µmol, 5 mol %) and ligand (5 mol %) in CH_2Cl_2 (2.5 ml) was added benzaldehyde (102 µl, 1 mmol) and drop wise the silylenolate (308 µl, 1.5 mmol) in CH_2Cl_2 (4 ml) at –78 ºC. The reaction was stirred at this temperature for 8 h. After the reaction was completed, water was added to quench. The product was extracted with CH_2Cl_2 and the combined organic layer was dried with Na_2SO_4. After filtration and evaporation, the crude product was chromatographed (hexane/ethyl acetate 10:1) on silica gel to yield the pure aldol product.

General Procedure for the *Michael* addition to chalcone (*GP-10*)[226]: A glass flask with a magnetic stirring bar was charged in air with Co(OAc)$_2$.4H_2O (7.5 mg, 30 µmol, 4 mol %), ligand (45 µmol, 6 mol %) and ethanol (3 ml). After stirring for 30 minutes at room temperature, the solution was filtered and treated sequentially with chalcone (156 mg, 0.75 mmol), diethylmalonate (0.3 ml, 1.98 mmol) and DIPEA (0.15 ml, 0.9 mmol). The reaction mixture was stirred for 15 h. After evaporation of the solvent, the residue was purified by column chromatography (hexane/ethyl acetate 19:1) to afford the product.

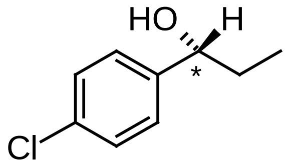
5.3.2 Test of the ligands



106a

1-Phenyl-1-propanol (106a): Ligand **76a** (31.4 mg, 0.05 mmol, 5 mol %), diethylzinc (2.5 eq., 1.1 M in toluene) and freshly distilled benzaldehyde **105a** reacted as described in *GP-6*. The reaction time was 48 h at room temperature. After purification by short path distillation, 136 mg (1 mmol, 100 %) of the wished product are obtained as colourless oil.

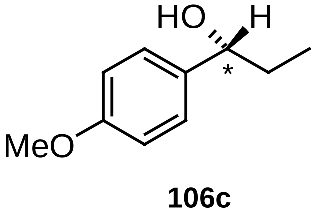
R*f* = 0.32 (hexane/ethyl acetate 5:1). - $[\alpha]_D^{25}$= +30.6 (*c* = 1.11, $CHCl_3$) for the (*R*)-enantiomer.[227] - ^1H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, 3H, *J* = 7.5 Hz, CH_3), 1.74-1.83 (m, 2H, *J* = 13.6, 7.5, 7.0 Hz, CH_2), 2.46 (s, OH), 4.59 (t, 1H, *J* = 7.0 Hz, CH), 7.29-7.37 (m, 5H, ArH). –GC Analysis: Chromatograph HP 5890 II, Detector FID 300 °C, Inject Split 260 °C, Column Restek Rt βDEX cst, 30 m, 0.32 mm, 0.25 μm, Oven Temperature 85 °C, Carrier gas H_2, Column Head Pressure 3 bar. Retention times: 24.36 min (*R*), 26.45 min (*S*), 70 % *ee* (*R*)-enantiomer.



106b

1-(4-Chlorphenyl)-1-propanol (106b): Ligand **76a** (31.4 mg, 0.05 mmol, 5 mol %), diethylzinc (2.5 eq., 1.1M in toluene) and 4-chlorbenzaldehyde (140.6 mg, 1 mmol) in 6 ml toluene were stirred according to the *GP-6* until the aldehyde was consumed (TLC-controlled). The reaction time was 48 h at room temperature. The product was purified by flash chromatographic column (hexane/ethyl acetate 8:1) to yield 103 mg (0.6 mmol, 60 %) of the chiral alcohol as colourless oil.

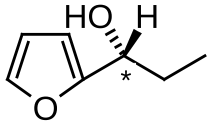
R*f* = 0.32 (hexane/ethyl acetate 5:1). $[\alpha]_D^{25}$= +31.7 (*c* = 1.0, C_6H_6) for the (*R*)-enantiomer.[228] - ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, 3H, *J* = 7.4 Hz, CH_3), 1.64-1.86 (m, 3H, CH_2 and OH), 4.58 (t, 1H, *J* = 6.5 Hz), 7.25-7.33 (m, 5H, ArH). - GC Analysis: Chromatograph HP 5890 II, Detector FID 300 °C, Inject Split 250 °C, Column Restek Rt βDEX cst, 30 m, 0.32 mm, 0.25 μm, Oven Temperature 110 °C, Carrier gas H_2, Column Head Pressure 1.5 bar. Retention times: 29.27 min (*R*), 32.08 min (*S*), 71 % *ee* (*R*)-enantiomer.



106c

1-(4-Methoxyphenyl)-1-propanol (106c): Ligand **76a** (31.4 mg, 0.05 mmol, 5 mol %), diethylzinc (2.5 eq., 1.1M in toluene) and freshly distilled 4-methoxybenzaldehyde (121 µl, 1 mmol) in 6 ml toluene were stirred according to the *GP-6* until all aldehyde was consumed (TLC-controlled). The reaction time was 48 h at room temperature. The raw product was purified by flash chromatographic column (hexane/ethyl acetate 10:1) to yield 116.2 mg (0.7 mmol, 70 %) of the chiral alcohol as colourless oil.

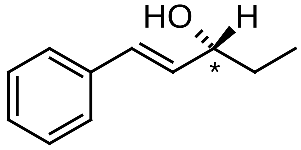
R_f = 0.26 (hexane/ethyl acetate 5:1). - $[\alpha]_D^{25}$ = +23.0 (*c* = 1.01, C_6H_6) for the (*R*)-enantiomer. - ^1H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, 3H, *J* = 7.4 Hz, CH_3), 1.65-1.89 (m, 3H, CH_2 and OH), 3.80 (s, 3H, OCH_3), 4.54 (t, 1H, *J* = 6.6 Hz), 6.85-6.90 (m, 2H, ArH), 7.24-7.28 (m, 2H, ArH). - GC Analysis: Chromatograph HP 5890 II, Detector FID 300 °C, Inject Split 250 °C, Column Restek Rt βDEX cst, 30 m, 0.32 mm, 0.25 µm, Oven Temperature 110 °C, Carrier gas H_2, Column Head Pressure 1.5 bar. Retention times: 27.49 min (*R*), 30.08 min (*S*), 62 % *ee* (*R*)-enantiomer.



109

1-(2-Furyl)-1-propanol (109): Ligand **76a** (31.4 mg, 0.05 mmol, 5 mol %), diethyl zinc (2.5 eq., 1.1M in toluene) and freshly distilled fural-2-carboxaldehyde (83 µl, 1 mmol) in 6 ml toluene were permitted to react according to the *GP-6* until the aldehyde was consumed (TLC-controlled). The reaction time was 48 h at room temperature. The product was purified by flash chromatographic column (hexane/ethyl acetate 8:1) to yield 77 mg (0.61 mmol, 61 %) of the product as colourless oil.

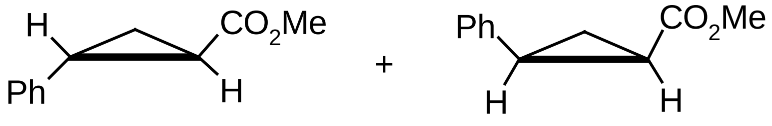
R_f = 0.29 (hexane/ethylacetate 5:1). - $[\alpha]_D^{25}$ = +24.6 (*c* = 1.18, $CHCl_3$) for the (*R*)-enantiomer.[229] - ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, 3H, *J* = 7.4 Hz, CH_3), 1.69-1.99 (m, 3H, CH_2 and OH), 4.55 (t, 1H, *J* = 6.7 Hz), 6.19 (d, 1H, *J* = 3.2 Hz, ArH), 6.28 (dd, 1H, *J* = 3.2, 1.8 Hz, ArH,), 7.32 (dd, 1H, *J* = 1.8 Hz, ArH). - GC Analysis: Chromatograph HP 5890 II, Detector FID 300 °C, Inject Split 250 °C, Column Restek Rt βDEX cst, 30 m, 0.32 mm, 0.25 µm, Oven Temperature (Program) 125 °C (45 min) and 12 °C/min until 180 °C (15 min), Carrier gas H_2, Column Head Pressure 1.5 bar. Retention times: 23.73 min (*R*), 24.95 min (*S*). 28 % *ee* (*R*)-enantiomer.



111

1-Phenyl-1-penten-3-ol (111): Ligand **76a** (31.4 mg, 0.05 mmol, 5 mol %), diethyl zinc (2.5 eq., 1.1 M in toluene) and freshly distilled cinnamaldehyde (126 µl, 1 mmol) in 6 ml toluene were stirred according to the *GP-6* until the aldehyde was consumed (TLC-controlled). The reaction time was 56 h at room temperature. The raw product was purified by flash chromatographic column (hexane/ethyl acetate 10:1) to yield 30.8 mg (0.19 mmol, 19 %) of the unsaturated alcohol as colourless oil.

R_f = 0.36 (hexane/ethylacetate 5:1). - $[\alpha]_D^{25}$ = +4.41 (*c* = 1.36, $CHCl_3$) for the (*R*)-enantiomer. - ^1H NMR (250 MHz, $CDCl_3$): δ = 0.98 (t, 3H, *J* = 7.4 Hz, CH_3), 1.56-1.74 (m, 3H, CH_2 and OH), 4.18-4.25 (m, 1H, CH), 6.18-6.26 (dd, 1H, *J* = 15.9, 6.7 Hz, HC=CH-CHOH), 6.58 (d, 1H, *J* = 15.9 Hz, Ar-HC=CH,), 7.24-7.40 (m, 5H, ArH). - HPLC Analysis: HP 1090 M, Column: LAB ID 61, Daicel Chiralcel OD-H, 260 mm, 4.60 mm, 5µm, Temperature of the column 25 °C, Inj. 7 µl/ 0.5 ml/min, Detector: Programmable Fluorescence Detector HP 1046 A. Solvent 90 % hexane + 10 % 2-propanol, isocratic. Retention times: 18.98 min (*R*), 11.44 min (*S*). 31 % *ee* (*R*)-enantiomer.

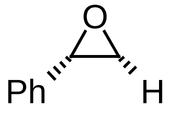


***trans*-115** ***cis*-115**

2-Phenyl-cyclopropanecarboxylic acid methyl ester (115): The ligand **66a** (32 mg, 0.1 mmol, 5 mol %) and copper(I) trifluoromethanesulfonate-toluene complex

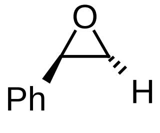
(51.7 mg, 0.1 mmol, 5 mol %) were dissolved in dry CH_2Cl_2 (6 ml) under nitrogen atmosphere. The mixture was stirred 1 h, then styrene (0.23 ml, 2.0 mmol) was added. Finally methyl diazoacetate (1 ml, 8 % in CH_2Cl_2) diluted in 6 ml dry CH_2Cl_2 was added drop wise over 8 h by syringe pump into the reaction mixture. After complete addition this was stirred for additional 3 h, the solvent was removed by evaporation and the residue was chromatographed on silica gel (hexane/ethylacetat 10:1) to obtain the mixture of cyclopropanes as a colourless oil.

R_f = 0.28 (*trans*) and 0.35 (*cis*). - ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 (ddd, 1H, J = 8.4, 6.5, 4.5 Hz, CHCH_2CH, *trans*-isomer), 1.35 (ddd, 1H, J = 8.7, 7.9, 5.1 Hz, CHCH_2CH, *cis*-isomer), 1.60 (ddd, 1H, J = 9.2, 5.3, 4.5 Hz, CHCH_2CH, *trans*-isomer), 1.71 (ddd, 1H, J = 7.5, 5.6, 5.1 Hz, CHCH_2CH, *cis*-isomer), 1.91 (ddd, 1H, J = 8.4, 5.3, 4.2 Hz, C*H*Ph, *trans*-isomer), 2.12 (ddd, 1H, J = 9.2, 7.9, 5.6 Hz, C*H*Ph, *cis*-isomer), 2.53 (ddd, 1H, J = 9.2, 6.5, 4.2 Hz, C*H*CO, *trans*-isomer), 2.58 (ddd, 1H, J = 9.2, 8.7, 7.5 Hz, C*H*CO, *cis*-isomer), 3.43 (s, 3H, OCH_3, *cis*-isomer), 3.72 (s, 3H, OCH_3, *trans*-isomer), 7.08-7.10 (m, 2H, Ph-H), 7.11-7.31 (m, 8H, Ph-H). The optical purity of the product was determined by chiral gas chromatography using the following conditions: Chromatograph Fisons 8130, Detector FID 230 °C, Inject Split 250 °C, Column CP-Chirasil-Dex CB, 25 m, 0.25 mm, 0.25 µm, Oven Temperature 115 °C, Carrier gas He_2, Column Head Pressure 1.18 bar. Retention times: 16.41 min (*cis*-1*S*,2*R*), 17.89 min (*cis*-1*R*,2*S*), 18.81 min (*trans*-1*R*,2*R*), 19.48 min (*trans*-1*S*,2*S*).



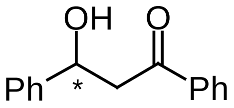
cis-127

+

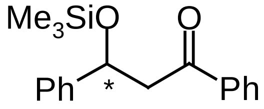


trans-127

2-Phenyl-oxirane (127): A solution of styrene (312 mg, 3 mmol), NMO (2.03 g, 15 mmol), ligand **70** (97.2 mg, 0.3 mmol, 10 mol %) and $Mn(AcO)_3$ (40.2 mg, 0.15 mmol, 5 mol %) in 10 ml CH_2Cl_2 was cooled to 0 °C. Solid *m*-CPBA (1.035 g, 6 mmol) was added in four portions over 2 min. The reaction mixture was stirred for 24 h at this temperature, 10 ml of 1 M NaOH were added and the organic phase was separated and washed with brine (2 x 10 ml). The combined aqueous phase were extracted with CH_2Cl_2 (2 x 10 ml), and the combined organic phases were dried with Na_2SO_4 and concentrated to approximately 2 ml. This residue was chromatographed on SiO_2 (hexane/ethylacetate 19:1) to give the epoxide (216 mg, 1.8 mmol, 60 %). - ^{1}H NMR (250 MHz, $CDCl_3$)[230]: $\delta = 2.6$ (dd, 1H, $J = 5.4, 2.6$ Hz), 3.0 (dd, 1H, $J = 4.0, 5.4$ Hz), 3.7 (dd, 1H, $J = 2.6, 4.0$ Hz), 7.17 (m, 5H). Conditions for determination of enantiomeric excess by gas chromatography: HP 5890 II, Detector FID 300 °C, Inject Split 260 °C, Column Restek Rt βDEX cst, 30 m, 0.32 mm, 0.25 µm, Oven Temperature, Carrier gas He_2, Column Head Pressure 1.18 bar. Retention times: 43.11 min (*cis*), 46.46 min (*trans*), 12 % *ee* for ***trans*-127**.



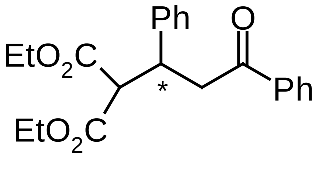
144



145

1,3-Diphenyl-3-trimethylsilanyloxy-propan-1-one (145): $Sc(OTf)_3$ (25 mg, 0.05 mmol, 5 mol %) and ligand **76a** (31.42 mg, 0.05 mmol, 5 mol %) were suspended in CH_2Cl_2 (2.5 ml) and stirred for 1 h. The mixture was cooled to –78 °C and benzaldehyde (102 µl, 1 mmol) was added. A solution of silyl enol ether (308 µl, 1.5 mmol) in 4 ml CH_2Cl_2 was added to the mixture with the syringe pump. The reaction was stirred at this temperature for 8 h, then it was warmed up to room temperature and the work out was done according to *GP-8*. The product was purified by flash chromatographic column (hexane/ethyl acetate 19:1) to yield **145** as white solid (233 mg, 0.78 mmol, 78 %). $R_f = 0.72$ (hexane/ethylacetate 4:1). - ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.00$ (s, 9H, $OSiMe_3$), 3.04 (dd, 1H, CH_2, $J = 15.5, 8.8, 3.8$ Hz), 3.60 (dd, 1H, CH_2, $J = 15.5, 8.8$ Hz), 5.38 (dd, 1H, CH, $J = 8.8, 3.8$ Hz), 7.24-7.61 (m, 8H, ArH), 7.96-8.01 (m, 2H, ArH). - MS (PI-EIMS), m/z (%): 298.3 (19) [M^+], 283.3 (12) [$M-CH_3$]$^{\cdot}$, 208.3 (53) [$M-Me_3SiOH$], 179.3 (100) [$PhCO_2SiMe_2$]$^+$, 105.2 (32) [PhCO]$^+$, 73.1 (90) [$SiMe_3$]$^+$.

3-Hydroxy-1,3-diphenyl-propan-1-one (144): Compound **145** (174 mg, 0.58 mmol) was solved in 4 ml HCl (1 M):THF (1:1) and the solution was stirred 30 min at room temperature. The mixture was diluted with water (10 ml), the product was extracted with Et_2O (3 x 10 ml) and the organic phase was washed with $NaHCO_3$ saturated solution (2 x 10 ml) and brine (1 x 10 ml) and dried with Na_2SO_4. The solvent was evaporated to get **144** as white solid (131 mg, 0.579 mmol, 99 %). $R_f = 0.33$ (hexane/ethylacetate 4:1). - ^1H NMR (250 MHz, $CDCl_3$): $\delta = 3.39$ (d, 2H, CH_2, $J = 6.0$ z), 3.63 (d, 1H, OH), 5.32-5.38 (m, 1H, CH), 7.30-7.50 (m, 7H, ArH), 7.56-7.62 (m, 1H, ArH), 7.94-7.98 (m, 2H, ArH).



147

Diethyl 2-(3-oxo-1, 3-diphenylpropyl)propanedioate (147): $Co(AcO)_2.4H_2O$ (7.5 mg, 30 µmol, 4 mol %), the protected diamide **84a** (15.84 mg, 45 µmol, 6 mol %) and ethanol (3 ml) were allowed to react according to *GP-9*. After stirring for 30 minutes at room temperature, the pink solution was filtered and treated sequentially with chalcone (156 mg, 0.75 mmol), diethylmalonate (0.3 ml, 1.98 mmol) and DIPEA (0.15 ml, 0.9 mmol). The reaction mixture was stirred for 15 h, the solvent was evaporated and the residue was chromatographed (hexane/ ethylacetate 19:1) to afford the product **147** (32 mg, 0.08 mmol, 11 %). - $R_f = 0.27$ (hexane/ethylacetate 10:1). - ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (t, 3H, $J = 7.1$ Hz, CH_3), 1.19 (t, 3H, $J = 7.1$ Hz, CH_3), 3.40 (dd, 1H, $J = 16.7$, 9.0 Hz, CO-CH_2), 3.50 (dd, 1H, $J = 16.7$, 4.8 Hz, CO-CH_2), 3.77 (d, 1H, $J = 9.0$ Hz, Ph-CH), 3.91 (q, 2H, $J = 7.1$ Hz, CH_2), 4.12-4.22 (m, 3H, CH_2 and $CH(CO)_2$), 7.20-7.22 (m, 5H, ArH), 7.33-7.50 (m, 3H, ArH), 7.82-7.85 (m, 2H, ArH).

6 Literature and Notes

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7 Appendix

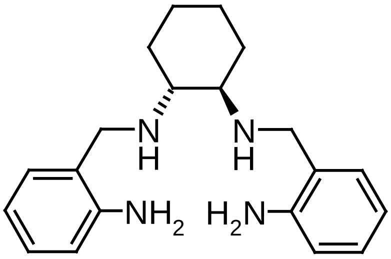
7.1 Abbreviations

AcOEt	Ethylacetat
Ar	Aryl
Boc	*tert*-Butoxycarbonyl
DIPEA	Diisopropylethylamine
DMAP	Dimethylaminopyridin
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DSC	Differential scanning calorimetry
eq.	equivalents
Et	Ethyl
EtOH	Ethanol
GC	Gas chromatography
h	hours
HPLC	High performance liquid chromatography
^{i}Pr	*iso*-Propyl
IR	Infrared spectroscopy
m-CPBA	*m*-Chlorpenbenzoic acid
Me	methyl
MeO	metoxy
MeOH	Methanol
min.	minutes
Ms	methanesulfonyl
OTf	Trifluormethanesulfonyl
PCC	Pyridiniumchlorchromat
Ph	Phenyl
R_f	Retention factor
rt	room temperature
^{t}Bu	*tert*-Butyl
THF	Tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl

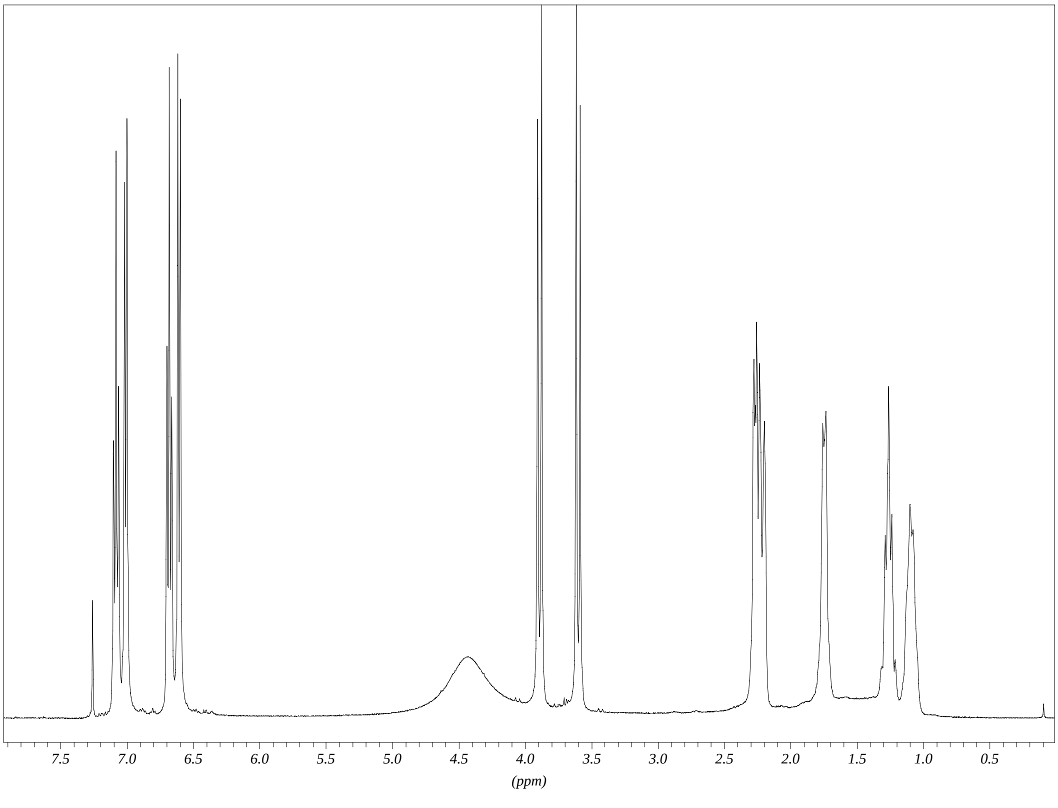
7.2 NMR Appendix

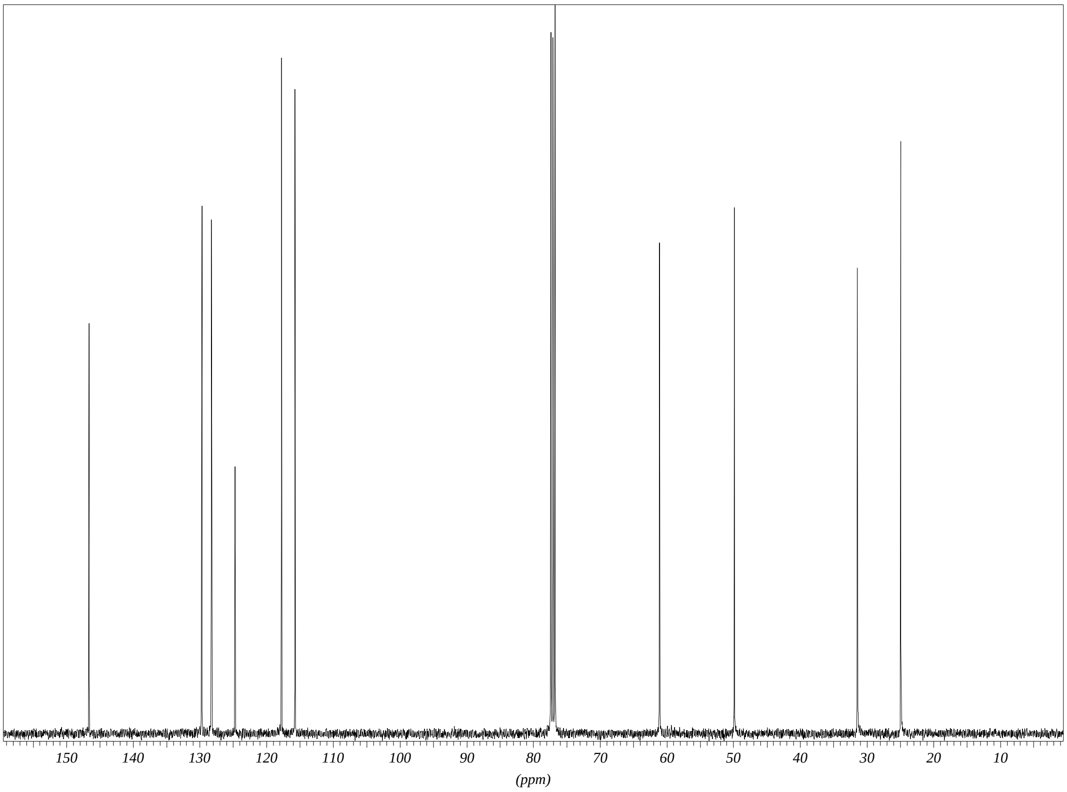
Sequence of the presented spectra: ^{1}H-, ^{13}C- and DEPT-spectra.

N,N´ -Bis- (2-ethyl-phenylamine)- cyclohexane-1*R*, 2*R*-diamine (70)



70

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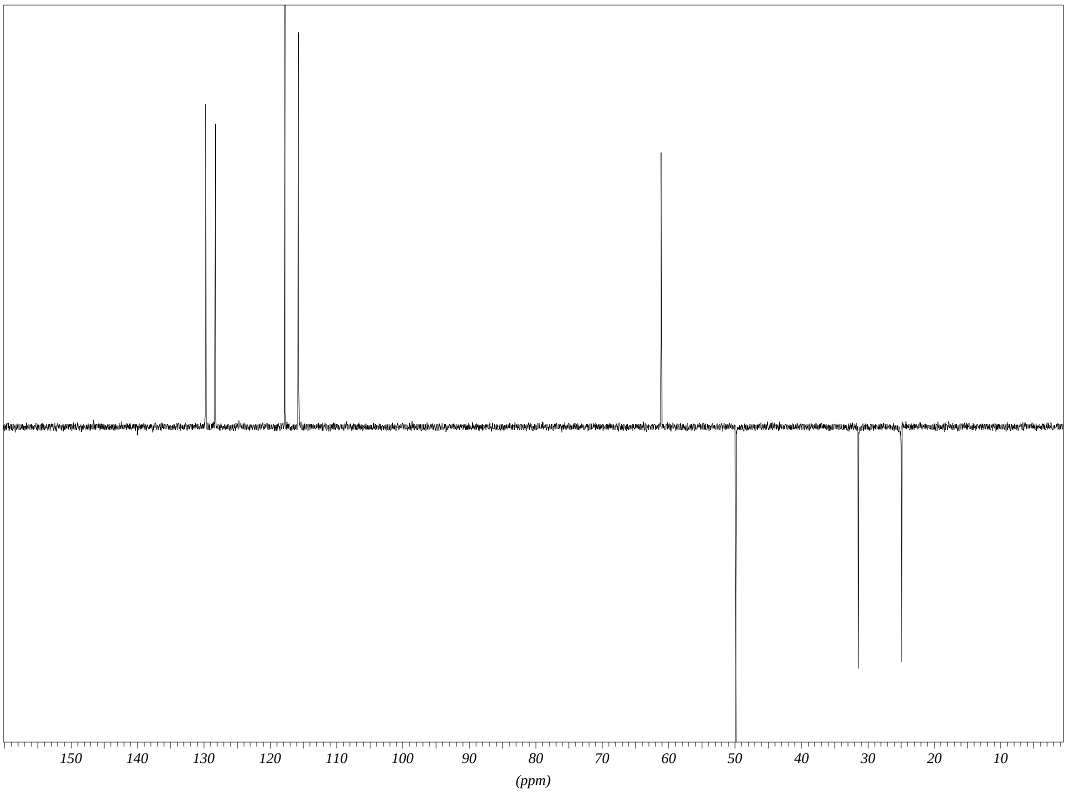
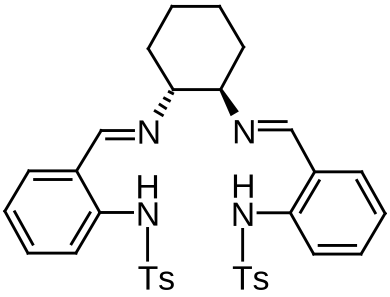
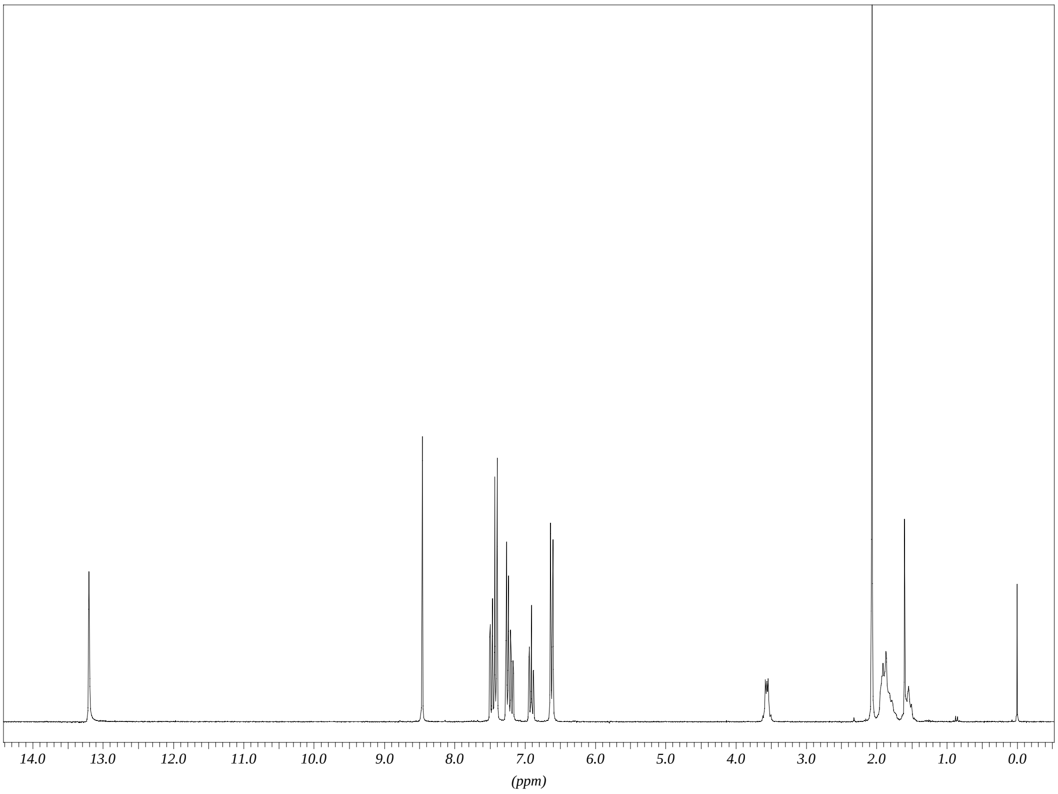
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

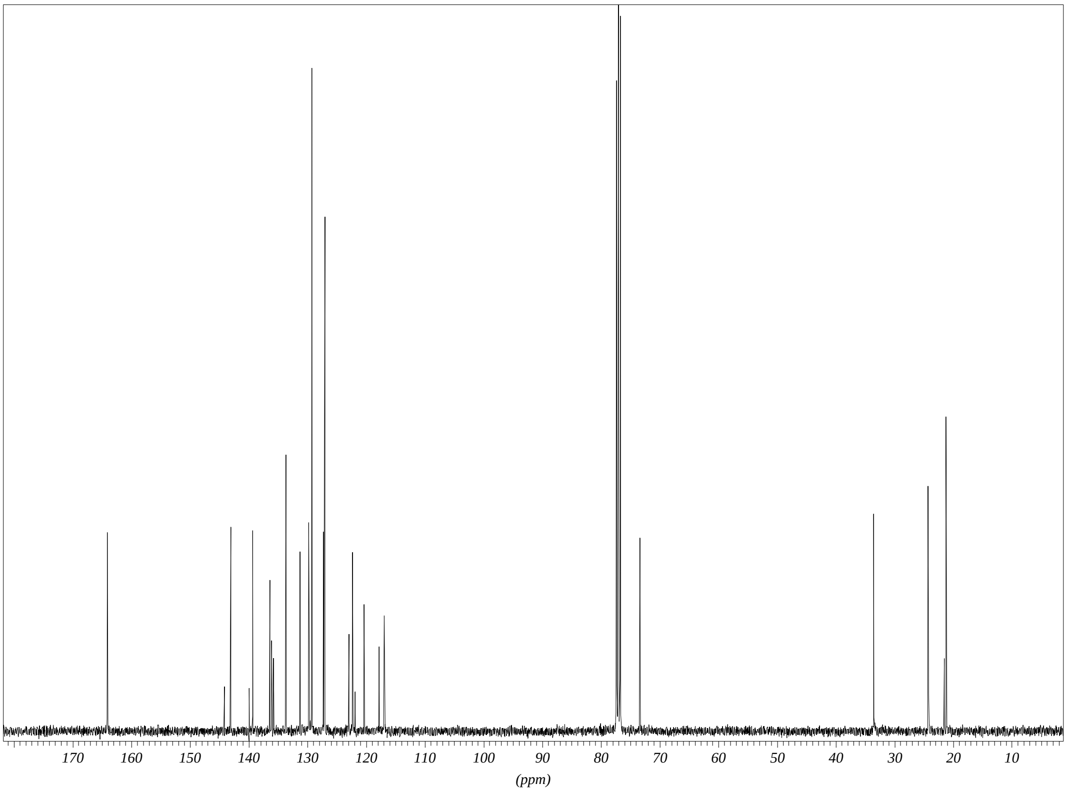

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

N,N´-Bis-(4-methyl-benzenesulfonamid-phenyl-2-ylmethylene)-cyclohexane-1*R*, 2*R*-diamin (76a)



76a

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130
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70
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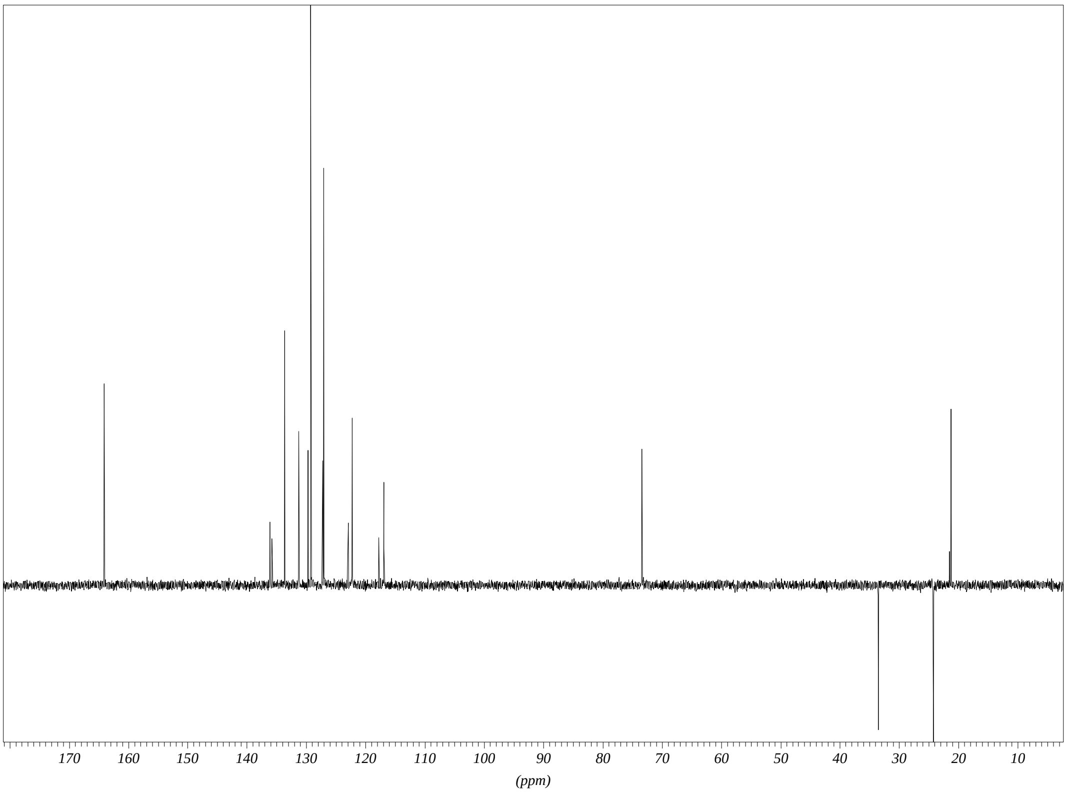
30
20
10
(ppm)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80
70
60
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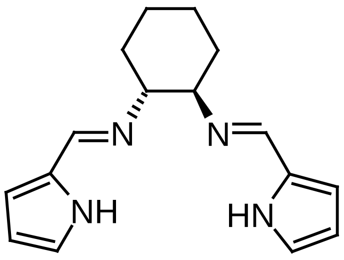
40
30
20
10
(ppm)

7.3 X-Ray-Appendix



66b

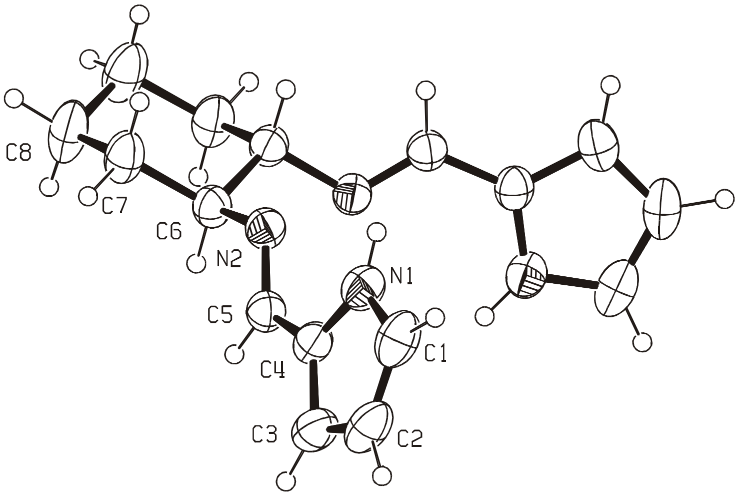
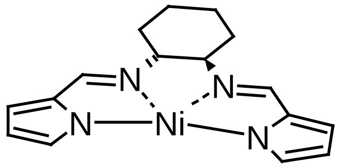


Table 1. Crystal data and structure refinement for **66b**.

Identification code	00178	
Empirical formula	$C_{16}H_{20}N_4 . H_2O$	
Formula weight	286.38	
Temperature	297(1) K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic, P 2(1)	
Unit cell dimensions	a = 5.5671(4) Å	α = 90°
	b = 8.8420(6) Å	β = 90°
	c = 16.5505(15) Å	γ = 90°
Volume	814.69(11) $Å^3$	
Z, calculated density	2, 1.167 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	308	
Crystal size	0.78 x 0.40 x 0.32 mm	
θ-range for data collection	2.46 to 27.94°	
Index ranges	-7<=h<=7, -11<=k<=11, -21<=l<=21	
Reflections collected/ unique	14155 / 1951 [R_{int} = 0.0392]	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	1951 / 0 / 102	
Goodness-of-fit on F^2	0.946	
Final R indices [I>2σ(I)]	R_1 = 0.0346, wR_2 = 0.0896	
R indices (all data)	R_1 = 0.0411, wR_2 = 0.0921	
Absolute structure parameter	1.4(17)	
Largest diff. peak and hole	0.224 and -0.112 e. $Å^{-3}$	



69

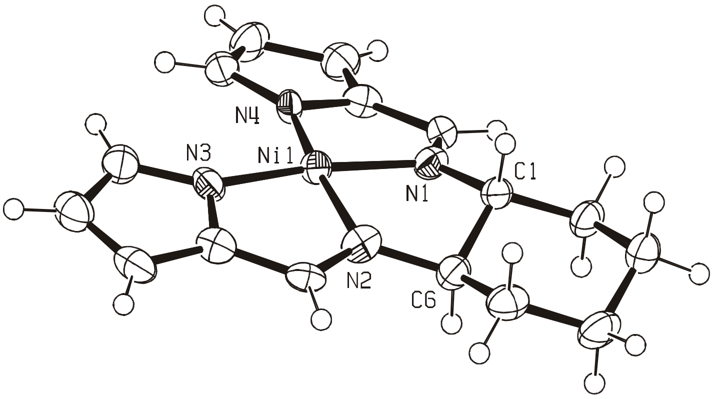


Table 2. Crystal data and structure refinement for complex **69**.

Identification code	A020	
Empirical formula	$C_{16}H_{18}N_4Ni$	
Formula weight	325.03	
Temperature	173(1) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P 2(1)	
Unit cell dimensions	a = 17.3130(13)Å	α = 90º
	b = 8.5882(4) Å	β = 111.754(8)
	c = 21.3267(15) Å	γ = 90º
Volume	2945.2(4) $Å^3$	
Z, calculated density	8, 1.466 Mg/m^3	
Absorption coefficient	1.316 mm^{-1}	
F(000)	1360	
Crystal size	0.48 x 0.28 x 0.08 mm	
θ-range for data collection	1.98 to 25.73º	
Index ranges	-21<=h<=21, -10<=k<=10, -26<=l<=25	
Reflections collected/ unique	24877 / 10805 [R_{int} = 0.0542]	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	10805 / 1 / 757	
Goodness-of-fit on F^2	0.848	
Final R indices [I>2σ(I)]	R_1 = 0.0369, wR_2 = 0.0815	
R indices (all data)	R_1 = 0.0611, wR_2 = 0.0874	
Absolute structure parameter	0.01(2)	
Largest diff. peak and hole	0.869 and -0.547 e.$Å^{-3}$	

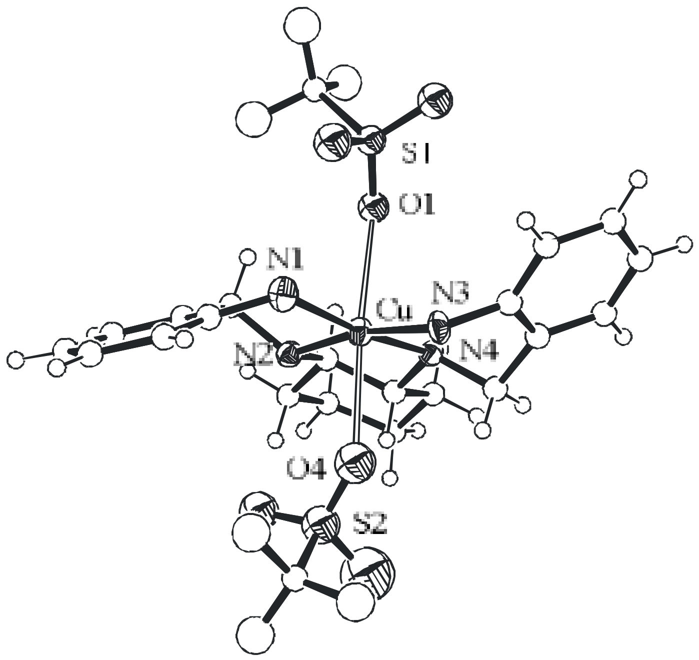
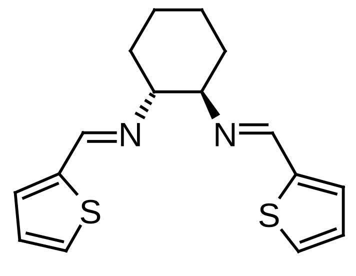


Table 3. Crystal data and structure refinement for **70**-Cu(II)OTf complex.

Identification code	A087	
Empirical formula	$C_{22}H_{22}CuF_6N_4O_6S_2$	
Formula weight	680.13	
Temperature	173(1) K	
Wavelength	0.71073 Å	
Crystal system, space group	Hexagonal, P 6(5)	
Unit cell dimensions	a = 22.2112(9) Å	α = 90º
	b = 22.2112(9) Å	β = 90º
	c = 9.9262(4) Å	γ = 120º
Volume	4240.9(3) $Å^3$	
Z, calculated density	6, 1.598 Mg/m^3	
Absorption coefficient	1.004 mm^{-1}	
F(000)	2070	
Crystal size	0.14 x 0.10 x 0.06 mm	
θ-range for data collection	2.75 to 25.92º	
Index ranges	-27<=h<=27, -27<=k<=27, -12<=l<=12	
Reflections collected/ unique	43595 / 5478 [R_{int} = 0.1130]	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	5478 / 1 / 370	
Goodness-of-fit on F^2	0.874	
Final R indices [I>2σ(I)]	R_1 = 0.0538, wR_2 = 0.1027	
R indices (all data)	R_1 = 0.0851, wR_2 = 0.1109	
Absolute structure parameter	0.00(2)	
Largest diff. peak and hole	1.413 and -0.667 e. $Å^{-3}$	



66c

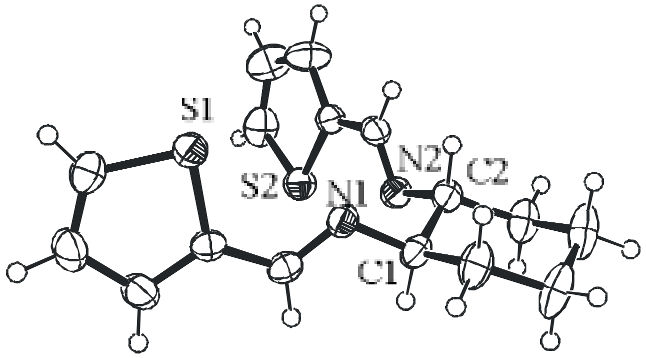
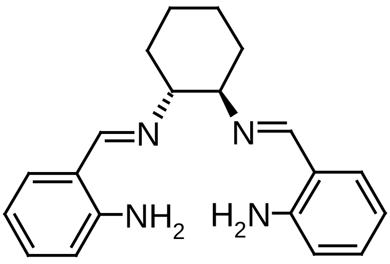


Table 4. Crystal data and structure refinement for ligand **66c**.

Identification code	00179	
Empirical formula	$C_{16}H_{18}N_2S_2$	
Formula weight	302.46	
Temperature	173(1) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P 2(1)	
Unit cell dimensions	*a* = 8.7560(8) Å	α = 90°
	b = 9.2982(10) Å	β = 113.806(9)°
	c = 10.7734(9) Å	γ = 90°
Volume	802.49(14) $Å^3$	
Z, calculated density	2, 1.252 Mg/m^3	
Absorption coefficient	0.324 mm^{-1}	
F(000)	320	
Crystal size	0.66 x 0.20 x 0.12 mm	
θ-range for data collection	2.54 to 27.98°	
Index ranges	-11<=h<=11, -12<=k<=12, -14<=l<=14	
Reflections collected/ unique	13731 / 3774 [R_{int} = 0.0641]	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	3774 / 1 / 181	
Goodness-of-fit on F^2	1.012	
Final R indices [I>2σ(I)]	R_1 = 0.0337, wR_2 = 0.0819	
R indices (all data)	R_1 = 0.0388, wR_2 = 0.0836	
Absolute structure parameter	-0.04(6)	
Largest diff. peak and hole	0.283 and -0.165 e. $Å^{-3}$	



66a

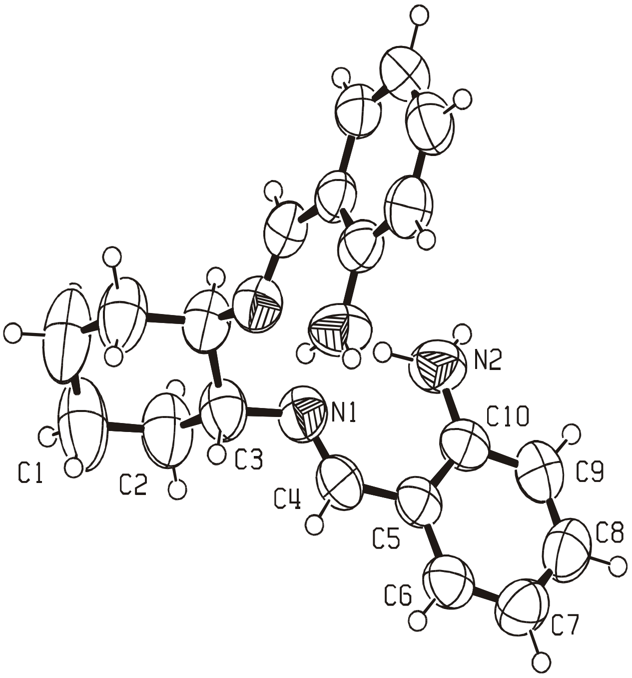
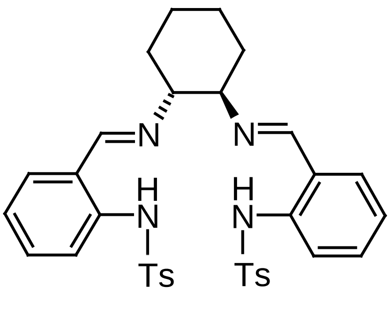


Table 5. Crystal data and structure refinement for ligand **66a**.

Identification code	A089	
Empirical formula	$C_{20}H_{24}N_4$	
Formula weight	320.43	
Temperature	293(2) K	
Wavelength	1.54180 Å	
Crystal system, space group	Orthorhombic, P 2(1)	
Unit cell dimensions	a = 5.6277(2) Å	α = 90°
	b = 8.6752(4) Å	β = 90°
	c = 18.6223(16)Å	γ = 90°
Volume	909.17(9) $Å^3$	
Z, calculated density	2, 1.171 Mg/m^3	
Absorption coefficient	0.551 mm^{-1}	
F(000)	344	
Crystal size	0.40 x 0.28 x 0.12 mm	
θ-range for data collection	4.75 to 64.90°	
Index ranges	-6<=h<=6, -10<=k<=10, -21<=l<=21	
Reflections collected/ unique	6088 / 1553 [R_{int} = 0.0645]	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	1553 / 0 / 118	
Goodness-of-fit on F^2	1.102	
Final R indices [I>2σ(I)]	R_1 = 0.0342, wR_2 = 0.0906	
R indices (all data)	R_1 = 0.0352, wR_2 = 0.0920	
Absolute structure parameter	0.0(6)	
Largest diff. peak and hole	0.116 and -0.099 e. $Å^{-3}$	



76a

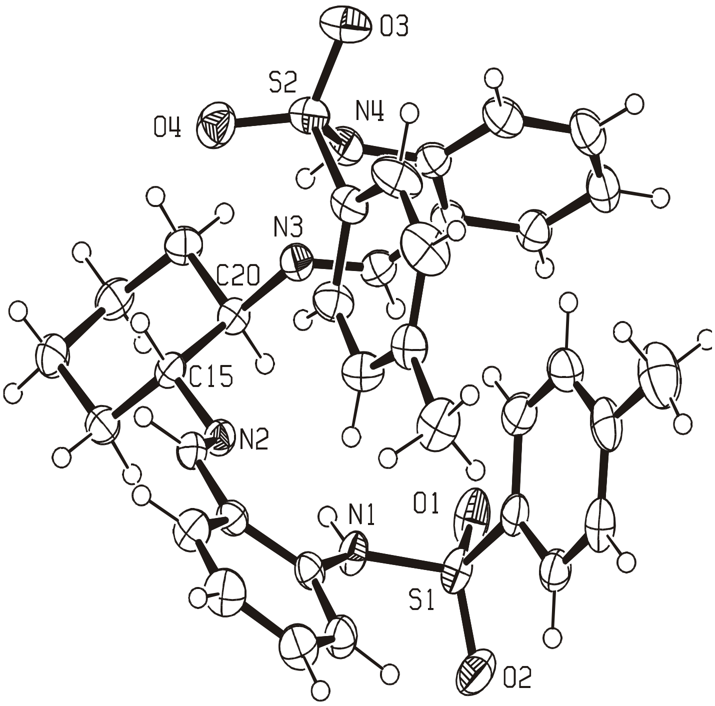
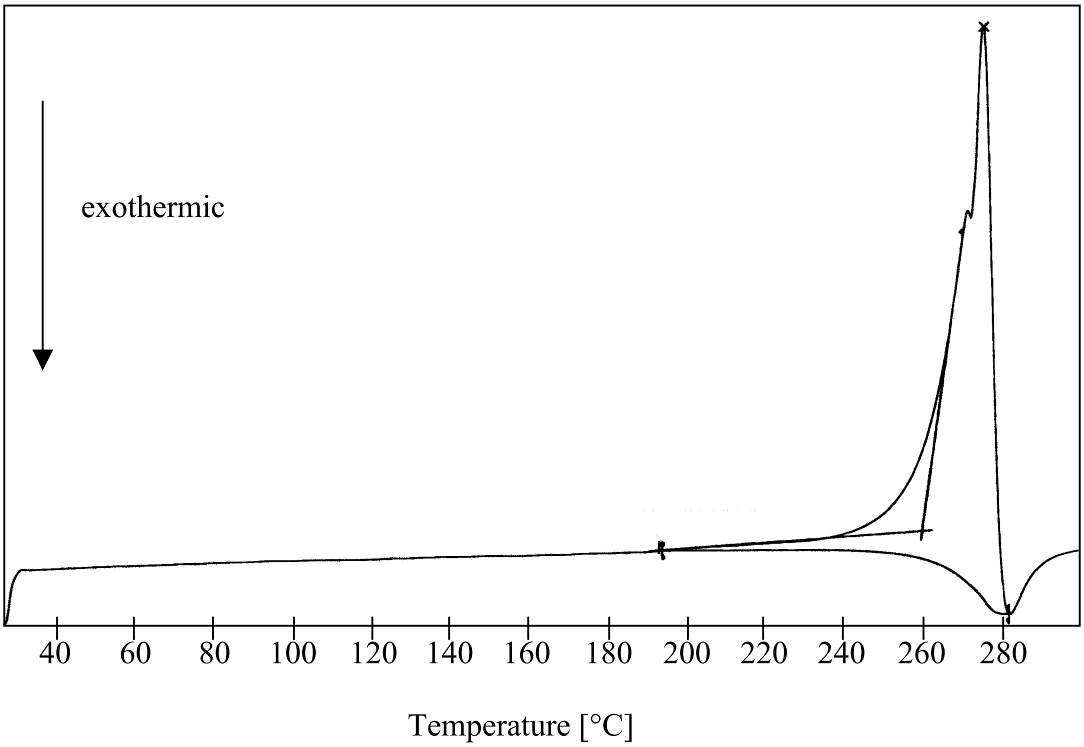


Table 6. Crystal data and structure refinement for ligand **76a**.

Identification code	A097	
Empirical formula	$2(C_{34}H_{36}N_4S_2O_4)$	
Formula weight	2526.32	
Temperature	173(1) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P 2(1)	
Unit cell dimensions	*a* = 11.5046(7) Å	α = 90°
	b = 15.0938(6) Å	β = 91.576(8)°
	c = 18.8714(12) Å	γ = 90°
Volume	3275.7(3) $Å^3$	
Z, calculated density	1, 1.280 Mg/m^3	
Absorption coefficient	0.206 mm^{-1}	
F(000)	1333	
Crystal size	0.50 x 0.12 x 0.08 mm	
θ-range for data collection	1.77 to 25.89°	
Index ranges	-14<=h<=14, -18<=k<=18, -23<=l<=23	
Reflections collected/ unique	46771 / 12643 [R_{int} = 0.0531]	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	12643 / 1 / 835	
Goodness-of-fit on F^2	0.855	
Final R indices [I>2σ(I)]	R_1 = 0.0331, wR_2 = 0.0612	
R indices (all data)	R_1 = 0.0527, wR_2 = 0.0653	
Absolute structure parameter	0.00(3)	
Largest diff. peak and hole	0.232 and -0.178 e. $Å^{-3}$	

7.4 Differential Scanning Calorimetry for ligand 72.



Curriculum Vitae

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09.1991-06.1996	Chemistry Studies, University of Santiago de Cuba and University of Havana. (Diploma).
09.1996-07.1998	Master work in Organic Chemistry, University of Havana. “Synthesis and biological activity of steroidal polyhydroxyketones”
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Acknowledgements

I would like to thank my Ph.D. tutor Prof. Dr. Burkhard König, who gave me the opportunity to perform my Ph.D. in Germany. He offered me an interesting research project and supported its development.

I thank Dr. T. Burgemeister, F. Kastner, A Schramm and G. Stülher for recording NMR spectra, Dr. K. K. Mayer, J. Keirmaier and W. Söllner for recording mass spectra, G. Wandinger for the elemental analyses and especially Dr. M. Zabel for the x-ray structure analyses.

For the numerous GC-measurements and HPLC determinations I thank Dr. E. Eibler and Dr. R. Vasold, and for the optical rotation measurements I thank N. Kastner-Pustet.

I am grateful to Dr. Claudius Böhm and Dr. Thomas Zwack for their helpful suggestions at the beginning of the catalysis experiments, and to Thomas Hjelmgaard for the contribution to some synthesis. I want to thank Frauke Henning for the test of ligands in the asymmetric hydrogen transfer reduction.

For the thoroughly correction of this thesis I would like to thank Dr. Annette Raach, Therese Clarke, Stefan Miltschitzky, Michael Kruppa, Thomas Suhs and Jens Paetzold.

For the financial support of this work I want to thank the DAAD.

I thank Elisabeth Liebl, Dr. Werner Braig, Dr. Christa Braig, Prof. Dr. Theodor Troll, Doris Kaps, Helga Leffler-Schuster, Ernst Lautenschlager and Andreas for their support.

I am grateful to Roland Reichenbach-Klinke, Michael Subat, Michael Klein, Hans Gallmeier, Christoph Bonauer, Valery Kozhevnikov, Christian Mandl, Katherina Cernovska, Thomas Walenzyck, Tom Fricke, Thorsten Graf, Martin Rödel, Mario Pelka

Daniela Fischer, Mirjam Sax and Mike Kercher for the contribution to my Ph.D. work with chemical advices and moral support.

I thank Dr. Wolfgang Pitsch for his support during all the time of my Ph.D. work, for the many suggestions and discussions, for the correction of my thesis and for the help to solve any problems with my computer.

I would like to thank all my friends, who either in the proximity or in the distance, stay always with me and give me the force to continue.