$C_2$- and $C_3$-Symmetric Ligands via Ring-Opening of Aziridines: Applications in Asymmetric Catalysis

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Abstract

This thesis deals with the design and synthesis of chiral enantiopure nitrogen-containing ligands and the use of these ligands in asymmetric catalysis.

A modular synthetic approach to enantiopure nitrogen-containing ligands was developed. The synthetic method is based on the ring-opening of activated chiral aziridines by nitrogen nucleophiles. The aziridines are conveniently prepared from amino alcohols. The structure of the aziridine and of the nucleophile can be extensively varied and libraries of ligands are easily prepared. The use of primary amines affords $C_2$-symmetric bis(sulfonamides), whereas the use of ammonia affords $C_3$-symmetric tris(sulfonamides) that can be elaborated into the corresponding tetra-amines.

The $C_2$- and $C_3$-symmetric ligands were used in the asymmetric titanium-mediated addition of diethylzinc to benzaldehyde resulting in modest enantioselectivity, 76% ee. A thorough investigation of the reaction conditions revealed that the amount of Ti(OiPr)$_4$ has a decisive effect on the reaction rate and the stereochemical outcome of the reaction. The reaction time decreased from about 90 hours to 15 minutes and the enantioselectivity changed from 26% of the (R)-enantiomer to 72% of the (S)-enantiomer when the Ti(OiPr)$_4$:benzaldehyde ratio was increased from 0.125:1 to 1.48:1. Moreover, the titanium-mediated addition of diethylzinc to benzaldehyde was studied in the presence of chiral additives. The bis(sulfonamides) were also used in the cyclopropanation of cinnamyl alcohol. However, only low enantioselectivity was observed, 27% ee.

The $C_3$-symmetric tetra-amines were reacted to form azaphosphatranes. These weak acids were only partially deprotonated by the strong base KOTBu to form the corresponding proazaphosphatranes. The unexpectedly strong basicity of the proazaphosphatranes was believed to be due to steric effects as suggested by DFT calculations. The tetra-amines and the sulfonamides were used for the preparation of metal complexes of Lewis acidic metals such as titanium(IV) and zirconium(IV).

Keywords: asymmetric catalysis, aziridine, benzaldehyde, diethylzinc, enantioselective, ligand, proazaphosphatrane, ring-opening, sulfonamide, symmetry, titanium, zirconium

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Abbreviations

BINOL  1,1’-bi(2-naphthol)
DAIB  (-)-3-exo-(dimethylamino)isoborneol
DBNE  (1S,2R)-(-)-2-(N,N-dibutylamino)-1-phenylpropan-1-ol
DFT  density functional theory
DIOP  2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DNs  o,p-dinitrobenzenesulfonyl
dpp  diphenylphosphinyl
dr  diastereomeric ratio
MeO-MOP  2-(diphenylphosphino)-2’-methoxy-1,1’-binaphthyl
MS  molecular sieves
nd  not determined
oNs  o-nitrobenzenesulfonyl
pNs  p-nitrobenzenesulfonyl
PhI=NTs  [N-(p-toluenesulfonyl)imino]phenyliodinane
Re  rectus, right, a stereochemical descriptor
salen  [N,N'-ethylenebis(salicylidenaminato)-]
Ses  2-(trimethylsilyl)ethanesulfonyl
Si  sinister, left, a stereochemical descriptor
TADDOL  \( \alpha,\alpha',\alpha''\)-tetraaryl-1,3-dioxolane-4,5-dimethanol
tren  tri(a2-aminoethyl)amine
VAPOL  vaulted biphenantrol
List of publications

This thesis is based on the following papers, referred to in the text by their Roman numerals I-IV.

I. Sulfonamide Ligands from Chiral Aziridines – Application to the Titanium-Mediated Addition of Diethylzinc to Benzaldehyde
   Fredrik Lake and Christina Moberg

II. Ti-Mediated Addition of Diethylzinc to Benzaldehyde. The Effect of Chiral Additives
    Fredrik Lake and Christina Moberg

III. C3-Symmetric Azaphosphatranes
     Fredrik Lake, Lars Hagberg, Mats Svensson and Christina Moberg

IV. New Chiral Al(III), Ti(IV), and Zr(IV) Azatranes
    Massimiliano Forcato, Fredrik Lake, Patrick Renner, Lutz Gade, Giulia Licini, and Christina Moberg
    *Manuscript*

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1. Asymmetric Catalysis – Introduction

There is an ever increasing demand for enantiomerically pure compounds, especially from the pharmaceutical industry, which must comply with stricter regulations imposed by the authorities. The world-wide sale of single-enantiomer drugs in 2001 amounts to $147 billion, or approximately 36% of the total market of pharmaceutical products.¹ To meet this demand, a number of successful methods have evolved which transform simpler chiral or achiral compounds into enantiomerically enriched products. There are two distinct routes for obtaining enantiomerically pure compounds. Either is a racemate resolved into the two enantiomers or a stereoselective synthesis is performed, starting from enantiopure or achiral materials.

Resolution of a racemate is normally achieved by the addition of a chiral resolving agent that transforms the enantiomers into two diastereomers, which can be separated by techniques such as crystallisation or chromatography. The disadvantages are that suitable functionality must be present in the molecules that are to be separated, that an enantiopure resolving agent must be readily accessible and that the maximum yield is 50%, unless the undesired enantiomer can be recycled. A related strategy is the kinetic resolution of a racemate, which is based on the relative reaction rate of the enantiomers in the presence a chiral modifier, often an enzyme. The disadvantage of a low yield (maximum 50%) can be overcome by the introduction of a simultaneous racemisation process of the starting material. Resolution was the first method to evolve for the preparation of enantiopure substances and it is still commonly used in industry. The attractiveness of the method increases if the resolution is performed at the beginning of a synthetic sequence.

Stereoselective synthesis can be performed under substrate control, with chiral auxiliaries, under reagent control or with chiral catalysts. Chiral substrate control is based on the principle that the presence of a chiral element in a substrate makes the remaining groups or faces diastereotopic. High diastereoselectivities are possible and cyclic control often affords higher selectivities than acyclic control. However, substrate control is limited to the enantiopure starting materials that are easily available. Many of these are derived from natural sources, the chiral pool, e.g. amino acids, carbohydrates, terpenes and hydroxy acids. Another disadvantage is that many of these substances, e.g. terpenes and carbohydrates, contain too few or too many functional groups to be of general use. An achiral starting material can be converted into a chiral intermediate by using a stoichiometric amount of a chiral auxiliary. High diastereoselectivities are possible, but the use of a chiral auxiliary requires additional synthetic steps for its attachment and subsequent removal. A chiral reagent is also needed in a

stoichiometric amount although no additional steps are required for its attachment and removal. Reagent control is based on the differentiation of enantiotopic groups or faces in the achiral substrate, but there are only a limited number of reagents available. The most refined way of achieving asymmetric induction is the use of a chiral catalyst,\(^2\) which can either be a chiral ligand coordinating a metal ion, or a biocatalyst such as an enzyme or a catalytic antibody, even though low molecular weight organic molecules are gaining in importance as catalysts.\(^3\) This thesis deals mainly with catalysts comprising a chiral ligand and a metal. The advantage of using a chiral catalyst is that only a catalytic amount of an enantiopure substance is needed for the synthesis of a stoichiometric amount of a chiral material and this makes it the most atom efficient of the methods available. Only the ligand and the metal, present in a catalytic amount, needs to be separated from the product, provided that the process is highly selective. This is an advantage compared to the use of resolution techniques, chiral auxiliaries or chiral reagents for which larger amounts of material must be separated from the product.

The first asymmetric catalyst comprising a metal and a chiral ligand was reported by Nozaki et al. in 1966.\(^4\) Although the chiral Schiff base copper(II)-catalyst 1 (Figure 1) afforded low enantioselectivity in the asymmetric cyclopropanation of styrene, \(\text{ee} < 10\%\), the stage was set for further development in the area. The first highly enantioselective process was the homogeneous hydrogenation of olefins reported by Kagan in 1971.\(^5\) In 1968 Horner\(^6\) and Knowles\(^7\) had independently shown that rhodium(I), coordinated to monodentate chiral phosphines, catalysed the enantioselective hydrogenation of olefins, albeit with low enantioselection, \(\text{ee} \leq 15\%\). However, the use of Kagan’s \(\text{C}_2\)-symmetric bidentate DIOP-ligand 2 (Figure 1) afforded enantioselectivities up to 72%. An enormous expansion has since been witnessed in the field of asymmetric catalysis and numerous successful catalytic systems have been developed. This was recognised by awarding the Nobel Prize in Chemistry for 2001 to William S. Knowles and Ryoji Noyori for their work on asymmetric hydrogenation, and to K. Barry Sharpless for his work on asymmetric oxidation. An illustrative example of the development of stereoselective synthesis during the last 35 years is Corey’s work on prostaglandin \(\text{F}_2\alpha\) 3 (Figure 1).\(^8\) The first reported synthesis of this prostaglandin afforded the racemic product but later syntheses gave enantiopure material by the use of resolution, chiral auxiliary methodology and, ultimately, asymmetric catalysis.

1.1 Ligand Design

Despite the plethora of chiral ligands that are available, there is still a need for new ligands in order to improve the catalytic properties of transition metal complexes in terms of substrate generality, turnover number, turnover frequency, yield and enantioselection. The design of chiral ligands for use in asymmetric catalysis is a complex task and is often pursued on a trial-and-error basis, due to lack of mechanistic insight. A number of factors that affect the electronic and steric properties of a ligand must be considered, e.g. the type of donor atom or atoms, the hapticity and the bite or cone angle of the ligand as well as the chelate ring size.

Kagan’s DIOP ligand 2 (Figure 1) is an example of a bidentate ligand containing soft phosphorus donor atoms which forms a seven-membered chelate upon coordination to a suitable metal such as rhodium. Most of the ligands used in asymmetric catalysis are polydentate, although some examples of monodentate ligands are known, for example Hayashi’s monophosphine MeO-MOP 4 (Figure 2), which is a successful ligand for palladium-catalysed hydrosilylation. The steric and electronic requirements of mono- and bidentate ligands are discussed

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in terms of cone\(^1\) and bite angles\(^2\), respectively. A bidentate ligand containing one soft (phosphorus) and one relatively hard donor atom (imine nitrogen) is the phosphinoxazoline ligand 5, which, for example, is able to electronically govern the attack of a nucleophile on a Pd-allyl complex.\(^3\) Two further examples of successful ligands are the tetradentate salen ligand 6\(^4\) and the bidentate ligand TADDOL 7.\(^5\) The hard oxygen donor atoms of 7 form a seven-membered chelate with the hard titanium ion. Both ligands have found numerous applications in asymmetric catalysis, e.g. epoxidation and epoxide ring-opening reactions (salen) and cycloaddition and nucleophilic addition reactions (TADDOL). An interesting concept is represented by ligand 8 which forms a bifunctional catalyst upon coordination to aluminium.\(^6\) The oxygen atoms of the phosphine oxides serve as Lewis bases and activate the nucleophile, and the aluminium atom serves as a Lewis acid and activates the electrophile. High asymmetric induction has been observed in the cyanosilylation of aldehydes.

A factor that is occasionally important to consider is the symmetry of the ligand. \(C_2\)-Symmetric ligands have met with great success in asymmetric catalysis, e.g. ligands 2 and 6-8.\(^7\) In contrast, there are much fewer reports on successful \(C_3\)-symmetric ligands in asymmetric catalysis.\(^8\) Although a symmetric ligand is no guarantee of high enantioselection, there are circumstances where a symmetric ligand is likely to reduce the number of possible diastereomeric intermediates or transition states in a catalytic process, and thereby increase the probability of a highly selective process. Thus, a bidentate \(C_2\)-symmetric ligand in a tetrahedral or square planar geometry (9) (Figure 3) renders the two remaining coordination sites equivalent (homotopic), whereas the same ligand in an octahedral geometry (10) affords two pairs of homotopic sites, which are mutually non-equivalent (diastereotopic, the coordination of a second equivalent of the ligand leaves the two remaining sites homotopic). A tridentate \(C_2\)-symmetric ligand in a square planar geometry affords two diastereotopic coordination sites (11), whereas three homotopic sites are found in a facially coordinated octahedral complex (12). Moreover, two homotopic sites are also found for tridentate \(C_2\)-symmetric ligands in trigonal bipyramidal complexes (13). Thus, a bidentate \(C_2\)-symmetric ligand may have favourable properties in a tetrahedral or square planar geometry whereas a \(C_2\)- and a \(C_3\)-symmetric tridentate ligand may have advantageous properties in a trigonal bipyramidal and an octahedral geometry, respectively. A trigonal bipyramidal complex containing a \(C_3\)-symmetric tetradentate ligand (14)

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has only one free coordination site and the three-fold symmetry gives rise to three identical rotamers.

Some examples of successful $C_3$-symmetric ligands are 15-17 (Figure 4). Trialkanolamines such as 15 have been employed in the titanium and zirconium catalysed oxidation of sulfides to sulfoxides, and in the zirconium catalysed addition of azide and halide to meso-epoxides. The phosphine 16 has been applied in asymmetric hydrogenations of olefins (95% ee), and tris(oxazoline) 17 has been in used in asymmetric copper(I) catalysed cyclopropanation of styrene affording the corresponding cyclopropanes with 70% ee.

More practical requirements for an optimal ligand are that it should be easily available in few high-yielding synthetic steps in both enantiomeric forms, be stable towards air and moisture, be recyclable, be easily derivatized and, from an atom economical standpoint, have a low molecular weight.

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1.3 Scope of the Study

Earlier work by our group shows that \( C_2 \)- and \( C_3 \)-symmetric tri- and tetradeutate ligands can be obtained via ring-opening of chiral sulfonyl-activated aziridines, and that the \( C_2 \)-symmetric bis(sulfonamides) afford moderate enantioselection in the alkylation of benzaldehyde. This thesis deals with the extension of this work and the use of these ligands in new applications. The syntheses of chiral aziridines starting from amino alcohols and the ring-opening of the aziridines with a wide range of amines are described. The resulting sulfonamides can be deprotected and elaborated further into primary or secondary amines. The use of \( C_2 \)-symmetric bis(sulfonamides) as promoters of the asymmetric alkylation of benzaldehyde and the asymmetric cyclopropanation of cinnamyl alcohol is presented, as well as a careful optimisation study of the reaction conditions of the alkylation reaction. The \( C_3 \)-symmetric tetradeutate ligands could be reacted with phosphorus compounds in oxidation state three, and the surprisingly high basicity of the resulting compounds was rationalised with the assistance of DFT calculations. The synthesis of titanium(IV) and zirconium(IV) complexes with the \( C_3 \)-symmetric tetradeutate ligands is described.
2. C$_2$- and C$_3$-Symmetric Ligands Obtained via Ring-Opening of Aziridines

2.1 Introduction

Chiral nonracemic aziridines form an important class of compounds in organic chemistry. Aziridine rings exist in many biologically active substances and can also serve as ligands and chiral auxiliaries in stereoselective synthesis. However, the main characteristic of these three-membered heterocycles is their propensity to undergo ring-opening reactions with a wide range of nucleophiles, due to relief of ring strain. The ring-opening reactions are often highly regio- and stereoselective, which makes them useful in organic synthesis. For example, chiral $\alpha$-amino acids and vicinal diamines can be synthesised via ring-opening of aziridines.

2.1.1 Synthesis of chiral aziridines

In contrast to the situation as regards epoxides, there is no general and reliable method for the enantioselective catalytic aziridination of achiral starting materials. Instead, the majority of enantiopure aziridines are synthesised from other chiral compounds. Substances derived from the chiral pool, e.g. amino acids and hydroxy acids, are common starting materials. More indirect approaches involve diastereoselective aziridination of alkenes or imines attached to chiral auxiliaries, e.g. camphor, oxazolidinones, and sulfoxides, or enantioselective

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24 For a review over synthetic applications of chiral aziridines, see: McCoull, W.; Davies, F. A. Synthesis, 2000, 1347-1365.


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26 For a more detailed discussion, see chapter 2.2.


synthesis of aziridines starting from chiral epoxides, diols, and amino alcohols. These intermediates can be obtained via asymmetric catalytic transformations of alkenes, i.e. epoxidation, dihydroxylation or aminohydroxylation.

The methods of catalytic asymmetric aziridination that are available today can be divided into three categories. The first method to evolve was the addition of a nitrene to a prochiral alkene, which was described by Evans and co-workers in 1991, affording aziridines with moderate ee’s (61%). The copper complex of bis(oxazoline) catalysed reaction was improved later by Evans, resulting in aziridines with up to 97% ee, but only cinnamate esters afforded excellent ee-values (Scheme 1). Jacobsen and co-workers reported on the asymmetric copper catalysed aziridination using a chiral salen ligand (Scheme 2). An excellent ee-value (>98%) was reported for one substrate but also in this case the reaction was highly substrate dependent.
In a reaction complementary to that of a nitrene and a prochiral alkene, a carbene and a prochiral imine can be reacted in the presence of a chiral catalyst to give a chiral aziridine. This was first described by Jacobsen and co-workers using a bis(oxazoline) ligand, but it met with only moderate success (67% ee). Aggarwal and co-workers developed the successful sulfur ylide mediated addition of \textit{in situ} generated diazo compounds to prochiral imines (Scheme 3, promoter 20). Aziridines were obtained with excellent ee’s and, importantly, the group on the aziridine nitrogen atom could easily be varied.\footnote{Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. \textit{Angew. Chem., Int. Ed. Engl.} \textbf{1995}, \textit{34}, 676-678.}


\begin{equation}
\begin{array}{c}
\text{Ph} \equiv \text{N} \equiv \text{CHPh}_2 + \text{N}_2 \equiv \text{N} \equiv \text{Ph} \text{CO}_2\text{Et} \rightarrow \text{Ph} \equiv \text{N} \equiv \text{CHPh}_2 \text{CO}_2\text{Et} \text{Lewis acid (10 mol%)}
\end{array}
\end{equation}

\text{97% ee, 77% yield, dr >50:1}

\begin{equation}
\begin{array}{c}
\text{Ph} \equiv \text{N} \equiv \text{CHPh}_2 + \text{N}_2 \equiv \text{N} \equiv \text{Ph} \text{CO}_2\text{Et} \rightarrow \text{Ph} \equiv \text{N} \equiv \text{CHPh}_2 \text{CO}_2\text{Et} \text{Lewis acid (10 mol%)}
\end{array}
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\text{97% ee, 77% yield, dr >50:1}

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\end{array}
\end{equation}

\text{97% ee, 77% yield, dr >50:1}

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\begin{array}{c}
\text{Ph} \equiv \text{N} \equiv \text{CHPh}_2 + \text{N}_2 \equiv \text{N} \equiv \text{Ph} \text{CO}_2\text{Et} \rightarrow \text{Ph} \equiv \text{N} \equiv \text{CHPh}_2 \text{CO}_2\text{Et} \text{Lewis acid (10 mol%)}
\end{array}
\end{equation}

\text{97% ee, 77% yield, dr >50:1}
2.1.2 Ring-opening of aziridines

As mentioned earlier, the popularity of aziridines as intermediates in organic chemistry stems from their selective ring-opening reactions with a broad range of nucleophiles. However, the aziridine ring needs to be activated in order for an efficient reaction to occur, and aziridines are, therefore, classified as nonactivated or activated aziridines. Nonactivated aziridines have a hydrogen atom or an alkyl or aryl group attached to the aziridine nitrogen atom and ring-opening is often assisted either by the use of a Brönstedt or a Lewis acid, or via quaternisation. Activated aziridines have an electron-withdrawing substituent that can stabilize the developing negative charge on the nitrogen atom. Common examples are sulfonyl groups, such as the tosyl group, or carbonyl-containing groups such as N-acyl or carbamoyl. The disadvantage with carbonyl derivatives is the fact that they may be attacked by the nucleophile, while the disadvantage with sulfonyl groups is related to the difficulties associated with the subsequent deprotection. This thesis deals mainly with sulfonyl-activated aziridines.

Mono-substituted aziridines are generally attacked at the sterically least hindered carbon atom in the aziridine ring, the exception being phenyl- and vinyl-substituted aziridines. Here, the nucleophile preferably attacks the benzyl or allylic position, but the regioselectivity of the attack is sometimes poor. The outcome of a nucleophilic attack on a 2,3-disubstituted aziridine is less predictable, but the nucleophilic attack occurs stereospecifically through an SN2 mechanism. There are examples, where a functional group in a side chain is capable of directing the attack of the nucleophile, and conditions for regioreversal have been found. The literature describes the use of many nucleophiles in the ring-opening of sulfonyl-activated aziridines, e.g. chiral enolates to give γ-amino amides, lithium acetylides to give α-amino acids, copper catalysed addition of lithiated aromatics to give β-arylalkyl amines, TMSN₃ and TMSCN to give vicinal diamines and β-amino acids, respectively, primary and secondary amines to give vicinal diamine derivatives, alkoxides to give amino ethers, and hydride in the total synthesis of diterpenoids. Lewis acids have been employed in the ring-opening reactions with alcohols [Sn(OTf)₂ and BF₃•OEt₂] and amines [Yb(OTf)₃ and InBr₃] as nucleophiles. Tributylphosphine has also...
been used as a catalyst for the ring-opening of aziridines using different heteroa-

tom nucleophiles. Jacobsen and co-workers have developed a chromium-
catalysed system, which performs asymmetric ring-opening of meso aziridines,

using azide as the nucleophile, and produces diamine derivatives with up to 94% ee.

2.2 Synthesis of chiral N-sulfonyl aziridines

2.2.1 Introduction

Amino alcohols are convenient starting materials for the synthesis of chiral

aziridines. Some of them are commercially available but there are also numerous

procedures for their preparation, e.g. through reduction of the corresponding

amino acids. The synthesis of N-sulfonyl activated aziridines from amino alco-
hols requires the transformation of the hydroxy group into a good leaving group.
The most frequently used methods are the Mitsunobu reaction and the use of

sulfonyl chlorides.

2.2.2 Results and discussion

(S)-N-Triflic-2-isopropylaziridine 22 has previously been synthesised in our

group starting from (S)-valinol 23 in a one-pot procedure, which probably pro-
duces via intermediate 24 (Scheme 5). Reaction of (S)-valinol 23 with 2.2

equivalents of triflic anhydride in the presence of two equivalents of triethyl-
amine afforded aziridine 22 in 90% yield and in acceptable purity (about 90%)
after aqueous basic work-up.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{OH} \quad \text{2.2 Tf}_2\text{O} \quad \text{2 NEt}_3 \\
\text{R} & \quad \text{HN} \quad \text{OTf} \\
\text{Basic work up} \\
23 & \quad \text{R} = \text{iPr} \\
27 & \quad \text{R} = \text{Me} \\
28 & \quad \text{R} = \text{Bn} \\
22 & \quad \text{R} = \text{iPr} \\
29 & \quad \text{R} = \text{Me} \\
30 & \quad \text{R} = \text{Bn}
\end{align*}
\]

Scheme 5

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57 See for example: (a) Sutton, P. W.; Bradley, A.; Farràs, J.; Romaine, P.; Urpi, F.; Vilarrasa, J. Tetra-
hedron 2000, 56, 7947-7958. (b) Berry, M. B.; Craig, D. Synlett 1992, 41-44.
The methodology described above has now been extended to other amino alcohols. Thus, aziridines 25 and 26 were prepared starting from (S)-alaninol 27 and (S)-phenylalaninol 28, respectively (Scheme 5). Aziridines 25 and 26 were found to polymerise upon evaporation of the solvent. Therefore, the subsequent ring-opening step was performed in situ. Aziridine 22 can be isolated but should be used directly after its preparation since it decomposes slowly at room temperature.

Aziridine 31 was previously synthesised in our group in a two-step procedure starting from (S)-alaninol 27 (Scheme 6). The bis(sulfonated) intermediate 32 was isolated and treated with excess NaNH to give aziridine 31 in a combined yield of 29% for the two steps.

Synthetic pathways to aziridines 31 and 33 have now been developed, commencing from either the amino acids or the amino alcohols (Scheme 6). Aziridines 31 and 33 were prepared via one-pot procedures, starting from their respective amino alcohols. Aziridine 31 was obtained in 74% yield by treating (S)-alaninol with 1.15 equivalents of TsCl followed by 1.05 equivalents of MsCl in the presence of four equivalents of triethylamine. Analogously, aziridine 33 was prepared in 92% yield. The yield of 33 was moderate (61%) when MsCl was replaced by TsCl. However, Kim et al. recently reported on the one-pot synthesis of 31 and 33 in 73 and 82% yield, respectively, starting from their respective amino alcohol using two equivalents of TsCl. It was also possible to synthesise aziridines 31 and 33 starting from (S)-alanine and (S)-valine, respectively, according to a procedure developed by Craig and Berry. N-Tosylation of (S)-alanine 34 followed by LiAlH₄ reduction of the carboxylic acid group in 36 to the corresponding alcohol gave 38 in 84% yield for the two steps. Analogously, the isopropyl analogue 39 was prepared in 94% yield, starting from (S)-valine 35. Tosylation of the hydroxy group of 39 followed by base-mediated ring closure gave aziridine 33 in 91% yield. An acceptable yield of 31, 63%, was obtained when 38 was subjected to the same conditions on a small scale (1.3 mmol), but when the reaction was run on a 75 mmol scale only low yields of 31 were obtained. Instead, ring-closure was achieved under Mitsunobu conditions, producing 31 in 74% yield when performed on a mmol scale, and 65% yield when performed on a larger scale (60 mmol). Once again, ring closure to form aziridine 31 proved more difficult than ring closure to aziridine 33. (S)-Valinol (23) was prepared in about 60% yield by the reduction of (S)-valine using either LiAlH₄ or BH₃, whereas only traces of (S)-alaninol (27) were isolated after

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60 Aziridines 31 and 33 were recently synthesised via this route in the improved yields of 88 and 90%, respectively. See: Argouarch, G.; Gibson, C. L.; Stones, G.; Sherrington, D. C. Tetrahedron Lett. 2002, 43, 3795-3798.
reduction of (S)-alanine with borane in THF. The reduction of the N-tosylated amino acids (36, 37) was preferred to the reduction of the non-derivatised amino acids. The lower yields associated with the non-derivatised amino acid reductions were probably due to difficulties in isolating the amino alcohols during work-up.

\[ \text{Scheme 6. (a) 2 TsCl, pyridine; 47%. (b) 1.5 NaH, THF; 62%. (c) i: 1.15 TsCl, 4 NEt_3, CH_2Cl_2, ii: 1.05 MsCl; 31 74%, 33 92%. (d) 1.04 TsCl, 1 NaOH, 1 NEt_3, water/acetone; 36 88%, 37 95%. (e) 3.1 LiAlH_4, THF/Et_2O; 38 95%, 39 99%. (f) 1.9 DEAD, 1.1 PPh_3, THF; 31 74%, 1.2 TsCl, 3 NEt_3, DMAP; 33 91%. (g) 2.4 NaBH_4, 2 I_2, THF (for 23 also 2 LiAlH_4, Et_2O); 27 nd, 23 60%.} \]
2.3 Synthesis of $C_2$-symmetric bis(sulfonamides)

2.3.1 Introduction

$C_2$-symmetric bis(sulfonamides) are useful ligands in asymmetric catalysis (see Chapter 3). They are usually prepared by allowing chiral diamines to react with achiral sulfonfonyl chlorides or other suitable sulfonic acid derivatives. The use of chiral amines and chiral sulfonyl chlorides affords diastereomeric ligands. In order to optimise the properties of a certain ligand in a catalytic application, it is desirable to have access to synthetic methods that allow easy and extensive variation of the ligand structure. Previous work from our group show that $C_2$-symmetric bis(sulfonamide) ligands and $C_3$-symmetric tetra-amines can be synthesised via ring-opening of activated aziridines with primary amines and ammonia, respectively. The work presented below shows that this approach permits a wide structural variation of the resulting ligands since the structure of the two building blocks can easily be varied in a number of ways. For example, the amino group can be either a mono- or a diamine, and amines containing additional functional groups can be applied. Also, in the aziridine, the 2-substituent and the activating group attached to the nitrogen atom can easily be varied (vide supra). This modular approach gives access to a large number of bis(sulfonamide) ligands that can be tested in various catalytic applications.

2.3.2 Results and discussion

Several examples in the literature show that primary amines afford bis(sulfonamides) upon reaction with $N$-$p$-toluenesulfonyl- ($Ts$) and $N$-$p$-nitrobenzenesulfonylaziridines ($pNs$) in MeOH, CH$_3$CN and toluene. Surprisingly, a report states that benzylamine affords bis(sulfonamides) when reacting with $N$-tosylaziridines in MeOH, but that the reaction stops at the mono(sulfonamide) adduct when CH$_3$CN is used as solvent. Previous results

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from our group show that aziridine 22 yields bis(sulfonamides) upon reaction with benzylamine, 2-(aminomethyl)pyridine, and 2-aminophenol in MeOH. This study has now been extended to include other amines and aziridines.

The bis(sulfonamide) 40 was prepared by treatment of (R)-1-phenylethylamine with three equivalents of aziridine 22 (Scheme 7). A survey of different solvents showed that the highest yield (83%) was obtained when the reaction was performed in dichloromethane (Table 1, entry 1). The other three solvent combinations all afforded 40 in lower yields (Table 1, entries 2-4). In the alcoholic solvents, small amounts of a by-product resulting from ring-opening of 22 by the solvent were observed. The reaction forming the intermediate mono(adduct) was very fast and the primary amine was consumed within 30 minutes. However, the reaction of complete transformation of the mono(adduct) into the bis(adduct) 40 was slower in dichloromethane (40 hours) than in the other three solvent systems where the reaction required about 16 hours for completion. Reacting the aziridine 22 with (S)-1-phenylethylamine gave the diastereomer 41 in 76% yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>40 Yield [%][a]</th>
<th>Reaction time [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>83</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>63</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>58</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>tBuOH/iPrOH 7/3</td>
<td>64</td>
<td>16</td>
</tr>
</tbody>
</table>

[a] Isolated yields.

Next, more bulky primary amines were tested as nucleophiles in the reaction with 22. The bis(sulfonamides) 42 and 43 were prepared by reacting aziridine 22 with 1-methyl-1-phenylethylamine and 1,1-diphenylmethylamine with 65 and 82% yield, respectively (Scheme 7).

![Scheme 7](image)

70 An excess of 22 was used, since it was difficult to separate the bisadduct from the undesired monoadduct in the ring-opening reactions. Aziridine 22 was also difficult to purify due to its instability and the crude material was used instead. The purity of aziridine 22 was 90±5% as estimated by ¹H NMR and GCMS.
When 9-(aminomethyl)anthracene was used as the nucleophile, 39% of the bis(adduct) 44 was formed along with 23% of the mono(adduct) 45 (Scheme 8). No bis(adducts) were formed with the bulky amines tert-butylamine and tritylamine, and only the mono(adducts) 46 and 47, respectively, were isolated. This was in line with earlier reports on stericly demanding amines or aziridines producing the mono(adduct) only.56a,72-73 However, a large excess of less bulky amines also produced the mono(adduct) as the major product.74 Thus, reacting aziridine 22 with 9.5 equivalents of benzylamine produced mono(adduct) 48 in 75% yield together with 7% of the bis(adduct) 49.75

Next, the study was extended to include other aziridines as electrophiles in the ring-opening reaction. Benzylamine was reacted with aziridines 25 and 33 to give bis(sulfonamides) 50 and 51, respectively (Scheme 9). The methyl-substituted aziridine 25 was found to be more reactive than the isopropyl analogue 22, and 25 was used in situ to give 50 in 20% yield (based on the starting amount of (S)-alamino). The N-tosyl aziridine 33 is less reactive than the N-triflic analogue 22 and heating in MeOH at 50 °C for 27 hours was required for the formation of 51.75 Maligres et al. reported that N-p-nosyl aziridines reacted 50-60 times faster with primary amines than the corresponding N-tosyl aziridines,73 the rate difference probably being even larger when N-triflic aziridines are used. (S)-N-Triflic-2-benzylaziridine 26 was reacted with (R)-phenylethylamine to give bis(sulfonamide) 52.


It was reported from one study that the mono(adduct) was formed in high yield when benzylamine (1 equiv.) was treated with 2-methyl-N-p-nosylaziridine (1 equiv.) in THF: Maligres, P. E.; See, M.; Askin, D.; Reider, P. J. Tetrahedron Lett. 1997, 38, 5253-5256.76 Solomon, M. E.; Lynch, C. L.; Rich, D. H. Tetrahedron Lett. 1995, 36, 4955-4958.

76 The bis(adduct) 49 can be synthesised in 75% yield by using a slight excess of aziridine 22. See also footnote 58.
When amino alcohols were used as nucleophiles, the resulting ligands were obtained in somewhat lower yields. (−)-Norephedrine and 2-hydroxybenzylamine\textsuperscript{76} gave compounds 53 and 54, respectively, both in 41% yield, whereas 2-methoxybenzylamine gave compound 55 in 65% yield (Scheme 10).

Chiral ligands containing elements of planar chirality could be prepared from 54 and 55 via elaboration of their respective prostereogenic arene moieties. Reacting 55 with tricarbonyl(naphthalene)chromium in dibutylether at 125 °C for 5h produced a 1:1 mixture of diastereomers 56 and 57 together with some unreacted starting material (Scheme 11). The selectivity was somewhat higher when the reaction was performed in diethyl ether. Thus, 56 and 57 were produced as a 1:1.3 mixture of diastereomers in 67% total yield by reacting 55 with tricarbonyl(naphthalene)chromium\textsuperscript{77} in diethylether at 90 °C for 5h (Scheme 11). The diastereomers were separated by flash chromatography, but their instability hampered their characterisation.

\textsuperscript{76} 2-Hydroxybenzylamine was prepared by LiAlH\textsubscript{4} reduction of 2-hydroxybenzonitrile in 35% yield by a procedure similar to the one used by: Freudenreich, C.; Samama, J.-P.; Biellmann, J.-F. J. Am. Chem. Soc. 1984, 106, 3344-3353.

The scope of the aziridine ring-opening reactions with nitrogen nucleophiles was extended to the synthesis of tetradeutate ligands commencing from $C_2$-symmetric diamines (Scheme 12). Compounds 58 and 59 were prepared in 84 and 79% yield, respectively, starting from $(R,R)$- and $(S,S)$-1,2-diphenyl-1,2-diaminoethane. In order to reduce the risk of formation of tertiary amines, only a slight excess of aziridine 22 was used. Similarly, the two enantiomers of 1,2-diaminocyclohexane gave the diastereomeric compounds 60 and 61 in 64 and 67% yield, respectively. Aromatic amines proved to be capable of ring-opening aziridine 22. The axially chiral bis(sulfonamides) 62 and 63 were prepared from the corresponding chiral binaphthyl diamines in 58 and 61% yield. No tertiary amines were observed in the ring-opening reactions to form compounds 58-63, probably due to sterical effects.
2.4 Ring-opening of aziridines using ammonia as the nucleophile

2.4.1 Synthesis of C₃-symmetric tris(sulfonamides)

Previous work from our group shows that C₃-symmetric tris(sulfonamides) 64-67 can be prepared by treating the appropriate aziridine with 0.33 equivalents of ammonia (Scheme 13). The reactions were carried out in methanol at about 50 °C for four to five days. Some of the yields for these tris(sulfonamide) ligands have now been improved slightly by using an exact ratio of 1:3 between ammonia and the corresponding aziridine (Table 2). The ammonia concentration is conveniently determined by titration. The series of C₃-symmetric tris(sulfonamides) has also been extended to include compound 68 which was prepared in 70% yield.

![Scheme 13](image)

**Table 2. Aziridine ring-opening with ammonia in methanol.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Aziridine</th>
<th>Tris(sulfonamide)</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iPr</td>
<td>Tf</td>
<td>22</td>
<td>64</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>iPr</td>
<td>Ms</td>
<td>69</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>iPr</td>
<td>p-Ns</td>
<td>70</td>
<td>66</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Ts</td>
<td>31</td>
<td>67</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>iPr</td>
<td>Ts</td>
<td>33</td>
<td>68</td>
<td>70</td>
</tr>
</tbody>
</table>

[a] Isolated yields.

Microwave-induced heating has been proved to be successful in several organic reactions, including asymmetric catalysis. Microwave heating has now been applied to the synthesis of the C₃-symmetric tris(sulfonamide) 68, resulting in an improved yield and a considerably shorter reaction time (from 4 days to 45 minutes, *vide infra*). The usefulness of microwave heating has been demonstrated in a recent study by Licini et al., in the synthesis of the corresponding C₃-symmetric trialkanolamine ligands (15, Figure 4) from ammonia and chiral epoxides.  

---

75 A 2.0 M solution of ammonia in methanol was used (Aldrich). Titration was performed by using HCl with methyl red as an indicator.


An aziridine to ammonia ratio of 3:1:1 was initially used in the microwave-assisted ring-opening of aziridine 33. Heating at 160 °C for 30 minutes produced the tris(adduct) 68 in 60% yield along with the C2-symmetric bis(adduct) 71 and the mono(adduct) 72 in 16 and 20% yield, respectively (Scheme 14 and Table 3, entry 1). An increase of the reaction time to 75 minutes did not improve the yield of 68. However, 68 was obtained in 77% yield along with 13% of unreacted aziridine 33 when the aziridine to ammonia ratio was increased successively to 4:1 (entries 3 and 4). An increase of the reaction time from 45 to 75 minutes produced 68 in an improved yield of 85%. This yield could be improved slightly if the aziridine to ammonia ratio was increased further to 4.5:1 (88% yield, entry 6).

**Table 3.** Microwave-assisted ring-opening of aziridine 33 with ammonia at 160 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time [min]</th>
<th>33:NH3</th>
<th>68 [%][a]</th>
<th>71 [%][a]</th>
<th>72 [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>3.1:1</td>
<td>60</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>3.1:1</td>
<td>61</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>3.5:1</td>
<td>68</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>4:1</td>
<td>77[bd]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>4:1</td>
<td>85</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>4.5:1</td>
<td>88[c]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] Isolated yields. [b] 13% of 33 was recovered. [c] 12% of 33 was recovered.
2.4.2 Synthesis of C₁- and C₂-symmetric sulfonamides, using ammonia as the nucleophile

Enantiopure vicinal diamine derivatives can be prepared via ring-opening of chiral aziridines by using large excesses of ammonia. Indeed, compound 72 was prepared in 71% yield by treating aziridine 33 with 16 equivalents of ammonia in methanol (Scheme 15). An alternative route is the reaction between an azide and an aziridine, followed by reduction of the azide group to the corresponding primary amine.

\[
\begin{align*}
\text{Scheme 15} & \quad \text{N}\hspace{0.5cm} \text{Ts} & \quad 16 \text{NH}_3 & \quad \text{MeOH} & \quad \text{H}_2\text{N} & \quad \text{NHTs} \\
33 & \quad 72 & \quad 71\%
\end{align*}
\]

Conditions for the preparation of C₂-symmetric secondary amines (e.g. bis(adduct) 73) starting from ammonia are delicate to find since the bis(adduct) may react further with any remaining aziridine to form the C₃-symmetric tris(adduct) 64 (Scheme 16). An excess of ammonia favours the formation of the primary amine 74, as seen above, and an excess of the aziridine favours the C₃-symmetric tertiary amine. However, the treatment of aziridine 22 with 0.65 equivalents of ammonia yielded the bis(adduct) 73 in 31% yield along with 21% of the mono(adduct) 74 and 8% of the tris(adduct) 64. Hydrogenolysis of 43 using H₂ and Pd/C, hydrolysis of 42 using TFA, or reaction of 74 with one equivalent of 22 may be more high-yielding approaches to 73.

\[
\begin{align*}
\text{Scheme 16} & \quad \text{N}\hspace{0.5cm} \text{Tf} & \quad 0.65 \text{NH}_3 & \quad \text{MeOH} & \quad \text{HN} & \quad \text{NHTf} & \quad \text{H}_2\text{N} & \quad \text{NHTf} & \quad \text{N}\hspace{0.5cm} \text{Tf} \\
22 & \quad 73 & \quad 31\% & \quad 74 & \quad 21\% & \quad 64 & \quad 8\%
\end{align*}
\]

---

2.5 Synthesis of \( C_3 \)-symmetric primary and secondary tetra-amines

The \( C_3 \)-symmetric tetra-amine 75 was previously prepared in our group in 85\% yield starting from 66 (Scheme 17). The \( N-p \)-nosyl protected amine was methylated and the \( p \)-nosyl group was removed using mercaptoacetic acid/NaOH in DMF, via a nucleophilic aromatic substitution mechanism.

\[ \text{Scheme 17. (a) } \text{Mel, K}_2\text{CO}_3, \text{DMF, quant. } ii: \text{HSCH}_2\text{COOH, LiOH, DMF, 41-63\%. (b) HSCH}_2\text{COOH, NaOH, DMF, 0\%.} \]

However, the high yield of the deprotection step was difficult to reproduce and 75 was obtained in yields in the region of 0-45\%. The use of Fukuyama’s original deprotection protocol of mercaptoacetic acid/LiOH in DMF improved the yield and 75 was isolated in yields of 41-63\% (albeit once in 82\% yield). Attempts using PhSH/K\( _2\)CO\(_3\) in DMF for up to 48h produced only partially deprotected material. The use of Na/N\( H_3\) at \(-78^\circ\text{C}\) gave 75 in less than 40\% yield and the material contained impurities that were difficult to remove. Employing Mg in MeOH/THF under ultrasonication gave a complex mixture.

Previous work in the group had also failed to produce the primary amine 76 from 66. The difficulties associated with the deprotection of the \( p \)-nosyl group to form primary and secondary \( C_3 \)-symmetric tetra-amines prompted the search for a more easily removable nitrogen-protection group, but still one that would facilitate the aziridine ring-opening using ammonia.

Other analogues of the \( p \)-Ns group, e.g. the \( o \)-Ns (\( o \)-nitrobenzenesulfonyl) and the DNs (\( o,p \)-dinitrobenzenesulfonyl) groups, were not tested even though they are supposedly easier to remove (especially the DNs group), and additional protocols for their deprotection are available. Another option is the Ses group.

---

87 The findings are in accordance with the results reported by Andersson and Alonso regarding deprotection of sulfonyl aziridines: Alonso, D. A.; Andersson, P. G. J. Org. Chem. 1998, 63, 9455-9461.
88 Maligres found that the \( p \)-Ns group could be removed by using PhSH/K\( _2\)CO\(_3\) in CH\(_3\)CN/DMF at 50 \(^\circ\text{C}\) to yield the primary amine, see footnote 73.
89 For the DNs group, see: (a) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. Tetrahedron Lett. 1997, 38, 5831-5834. For the deprotection of the \( o \)-Ns group by 2-mercaptoethanol/DBU in
[2-(trimethylsilyl)ethanesulfonyl] which is removed through treatment with fluoride,\textsuperscript{49} and the Dpp group (diphenylphosphinyl), which can be removed using MeOH/BF$_3$•OEt$_2$.\textsuperscript{90} The Dpp-aziridines are easily prepared in one-pot procedures from chiral amino alcohols and undergo ring-opening with both heteroatom-centered and carbon-centered nucleophiles. The Boc group (tert-butoxy carbonyl) is easily removed under acidic conditions and should be an attractive alternative. However, the preparation of N-Boc activated aziridines from amino alcohols is known to be problematic sometimes, due to the interference of the Boc-group during ring-closure.\textsuperscript{91} Indeed, ring-closure of 77, prepared from (S)-valinol,\textsuperscript{91} under Mitsunobu conditions did not produce the desired aziridine, and treatment of 77 with MsCl in the presence of excess NEt$_3$ only yielded the O-mesylated derivative 78 (Scheme 18). Treatment of three equivalents of 78 with ammonia did not yield the C$_3$-symmetric Boc-protected amine 79.

![Scheme 18](image)

Scheme 18. (a) 1.1 (Boc)$_2$O, NEt$_3$, DMAP, CH$_2$Cl$_2$, 40%. (b) 1.1 MsCl, 2 NEt$_3$, CH$_2$Cl$_2$, 65%. (c) 0.33 NH$_3$, 3.6 NEt$_3$, MeOH, 0%.

Considering the numerous methods available for the deprotection of the Ts-group and the fact that the Ts-protected amines 67 and 68 were accessible in good yields, we proceeded with the search for deprotection conditions which would produce both primary and secondary C$_3$-symmetric amines from their corresponding Ts-protected analogues.

Attempts to methylate 67 and 68 utilizing the conditions that were successful with the p-Ns analogue 66 (MeI, K$_2$CO$_3$, DMF) produced methylated 80 and 81, accompanied with small amounts of partially methylated material (Scheme 19). Use of the stronger base NaH gave fully methylated material in 91 and 90% yield, respectively, after purification. However, the purity of the crude products was excellent and the crude material would be used directly in the subsequent deprotection step. Detosylation of 81 was attempted using the mild conditions Mg in methanol under ultrasonication.\textsuperscript{92} Disappointingly, no deprotected material was observed and some of the starting material was recovered. Deprotection of


using Na/NH₃ at –78 °C for 2h gave 75 in 36% yield. The yield was improved to 52% when the reaction temperature was increased to –33 °C. When 81 was subjected to Na/naphthalene in DME, the ¹H NMR spectrum of the resulting crude product had no signals in the aromatic region but several by-products besides the desired amine 75 were observed. Heating 81 with HBr/AcOH (45% w/v) at 50 °C for 24 h did not produce amine 75, maybe because the reaction temperature was too low. However, refluxing (150 °C) 81 in an aqueous solution of HBr (48%) for 24 h gave 75 in isolated yields between 49 and 72% (Scheme 19). The conditions worked well also for the methyl analogue 80, producing 82 in yields of 43-64%. The primary amines 83 and 76 could be prepared in acceptable yields of 38 and 57%, respectively, by using the same conditions.

2.6 Summary

A modular approach to chiral sulfonamides was developed. Mono-, bis- and tris(sulfonamides) can be prepared in moderate to good yields (about 50-80%) starting from chiral sulfonyl activated aziridines and primary amines or ammonia. The aziridines are conveniently prepared in a one-pot procedure starting from 1,2-amino alcohols. The aziridines react with a wide range of nucleophiles such as primary amines, primary diamines, amino alcohols and aromatic amines. However, no bis(sulfonamides) are observed when bulky primary amines are used as nucleophiles and only the corresponding mono(sulfonamides) are obtained. The use of ammonia as nucleophile affords C₃-symmetric tris(sulfonamides). The reaction rate of the aziridine ring-opening reaction with ammonia can be increased by microwave heating. The tosyl group of the tris(sulfonamides) can be removed by using HBr (48%, aqueous solution) to form primary and secondary amines.

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3. Applications of Bis(sulfonamides) in Asymmetric Catalysis

Chiral enantiopure bis(sulfonamides) have found widespread use in asymmetric catalysis. For example, they have been successfully applied in the aluminium catalysed Diels-Alder reaction and ketene aldehyde cycloadditions to afford six- and four-membered rings with excellent enantioselectivities, and high enantioselectivities have also been observed in the magnesium bis(sulfonamide) catalysed amination of enolates. Bis(sulfonamides) are also known to promote the alkylation of aldehydes and the Simmons-Smith cyclopropanation of allylic alcohols. Moreover, stoichiometric amounts of boron bis(sulfonamides) have been used for the alkylation of aldehydes, for the Ireland-Claisen rearrangements and for the aldol reactions. This chapter describes the use of the bis(sulfonamides) that are presented in Chapter 2 as promoters of the titanium-mediated addition of diethylzinc to benzaldehyde and the cyclopropanation of cinnamyl alcohol.

3.1 Addition of diethylzinc to benzaldehyde

3.1.1 Introduction

Chiral secondary alcohols are integral parts of biologically active compounds and are versatile intermediates for further transformation. The two most obvious ways of synthesising such alcohols from achiral starting materials involve the enantioselective reduction of the corresponding ketone or the addition of an organometallic reagent to the corresponding aldehyde. The advantage of adding an organometallic reagent is that a carbon-carbon bond is formed and that the carbon skeleton thus is extended during the process.

The first highly enantioselective addition of an organometallic reagent to an aldehyde was reported by Mukaiyama et al. in 1979. Butyllithium and diethylmagnesium were added to benzaldehyde under the influence of the

---

lithium salt of the proline-derived amino alcohol 84, resulting in secondary alcohols with ee’s of 92-95%. The disadvantage of using lithium and magnesium reagents was their propensity to add to aldehydes in the absence of a ligand even at low temperatures. Even though the coordination of donor atoms like nitrogen and oxygen to an organometallic species normally increased their nucleophilicity, the rate acceleration was often too low to compete with the non-stereoselective pathway, and an excess of the ligand was needed to achieve acceptable enantioselection.103 To circumvent this problem the attention was turned to organozinc reagents. Frankland was the first to describe organozinc reagents as early as in 1848104 but they were considered as alternatives to lithium and magnesium reagents only after Mukaiyama et al.102 discovered that β-amino alcohols catalyzed their addition to aldehydes. The advantage of using alkylzinc reagents was that they did not add to aldehydes at room temperature in the absence of coordinating molecules. An excess of the deprotonated amino alcohol 84 failed to induce any chirality and it was not until 1984 that the first enantioselective addition of diethylzinc to benzaldehyde 85 was reported by Oguni and Omi (Scheme 20).105 The secondary alcohol 86 was obtained with 49% ee in the presence of 2 mol% (S)-leucinol 87.

The success of (S)-leucinol as a promoter for alkylation of aldehydes was soon followed by other reports on β-amino alcohols showing the excellent enantioselectivity of the alkylation reaction. Noyori and co-workers106 applied the DAIB ligand 88, which worked well with aromatic aldehydes, and Soai et al. introduced the norephedrine-derived ligand DBNE 89, which gave secondary alcohols with excellent ee’s when aliphatic aldehydes were used as substrates (Scheme 21).107 Noyori and co-workers107 also demonstrated that DAIB exhibited a positive non-linear effect when applied in the alkylation reaction. When DAIB (8 mol%) with 15% ee was used as a catalyst, the secondary alcohol 86 was obtained with 95% ee.

104 For a cover assay on zinc alkyls and the beginnings of main group organometallic chemistry, see: Seyferth, D. Organometallics 2001, 20, 2940-2955.
Monomeric dialkylzinc compounds have a linear geometry around the zinc atom and this makes the zinc-alkyl bond non-polar and the alkylzinc reagent unreactive toward aldehydes. When an amino alcohol is treated with an alkylzinc reagent, the nitrogen and oxygen donor atoms coordinate to the zinc atom forming a bifunctional catalyst 90 that is unable to act as an alkyl donor (Scheme 22). The zinc atom in the five-membered chelate in 90 serves as a Lewis acid and coordinates the aldehyde via the oxygen non-bonding orbital and the carbonyl carbon atom is activated for nucleophilic attack. The electrons in one of the lone pairs on the oxygen atom in 90 coordinate to the zinc atom in the zinc reagent and this Lewis basic coordination changes the geometry of the zinc reagent from linear to bent, and the carbon-zinc bond in Me2Zn is elongated resulting in an increased nucleophilicity. The geminal methyl groups in the ligand backbone direct the aldehyde to an endo coordination. Theoretical work on the mechanism and on possible transition state structures indicates that the aldehyde coordinates to the zinc atom in an anti-trans fashion 91, i.e. the two terminal cycles in the zinc-containing tricyclic system formed (the ligand backbone excluded) have a anti relationship and the aldehyde coordinates to the zinc atom with the lone pair trans to the phenyl ring of benzaldehyde (Scheme 22). The alkyl group is then transferred to the Si face of the aldehyde producing the product alkoxide. The product alkoxide is removed from the catalyst as an alkylzinc alkoxide and the formation of a stable tetramer is the driving force for the reconstitution of the catalyst, which is believed to be monomeric.

Several hundreds of efficient catalytic systems for the enantioselective addition of zinc reagents to aldehydes are now known, and the diversity of the structures which have been evaluated as ligands in the alkylation reaction is impressive, e.g. pyridyl alcohols, amino thiols, amines, diols, and bis-(sulfonamides). Two distinct alternatives exist for the addition of diethylzinc to aldehydes; the addition can be performed either in the presence or in the absence of Ti(OiPr)₄. An amino alcohol serves as a Lewis base which activates the zinc reagent and forms a Lewis acidic zinc species, e.g. 90, which activates the aldehyde. A bis(sulfonamide) or a diol in the presence of Ti(OiPr)₄ forms a Lewis acidic ligand-titanium complex which activates the aldehyde. The excess of Ti(OiPr)₄ which is normally used probably assists the alkyl transfer to the aldehyde. Examples of structures that are successful ligands, either in the presence or in the absence of Ti(OiPr)₄, are given in Table 4 and Figure 5. A comparison is made between the ligands on the basis of reaction time, reaction temperature, catalyst loading, and enantioselectivity of the benzaldehyde substrate. Furthermore, the number of aromatic, α,β-unsaturated, and aliphatic aldehydes which afford the corresponding secondary alcohol with 90% ee or more are listed in order to give a picture of the substrate generality. The alkylation reaction is in general much faster and is performed at lower temperatures in the presence of Ti(OiPr)₄. Aromatic aldehydes afford higher enantioselectivity than aliphatic aldehydes, as seen in Table 4. Diols 95 and 96 stand out as two of the most general promoters for the alkylation of a broad range of aldehydes, e.g. substituted benzaldehydes, linear and branched aliphatic aldehydes, and α,β-unsaturated aldehydes (entries 4 and 5). Bis(sulfonamide) 99 (vide infra) is an attractive alternative due to its straightforward preparation and it shows a remarkable catalytic activity at very low catalyst loading (entry 8). The substrate to catalyst ratio can be as high as 2000 while still maintaining an excellent enantioselectivity. The extensive work by Knochel et al. show the generality of 99 as a promoter for the alkylation of aldehydes. The substrate tolerance is as impressive as that of 95 and 96, and a number of aldehydes and functionalized organozinc reagents can be employed (vide infra).

113 For a detailed discussion on Knochel’s work, see Chapter 3.1.2.
Table 4. Comparison between different catalytic systems for the enantioselective addition of diethylzinc to aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lig.</th>
<th>Ti(OiPr)$_4$ (equiv.)</th>
<th>ee$^{[a]}$ [%]</th>
<th>Time$^{[a]}$ [h]</th>
<th>Temp. [°C]</th>
<th>S/C$^{[b]}$</th>
<th>Arom.$^{[b]}$</th>
<th>α,β-unsat.$^{[c]}$</th>
<th>Aliph.$^{[d]}$</th>
<th>Ref.</th>
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</tbody>
</table>

$^{[a]}$ For the benzaldehyde substrate. $^{[b]}$ The number of aromatic aldehydes which afford the corresponding product with ee $\geq$ 90%. $^{[c]}$ The same criterion as under b but for α,β-unsaturated aldehydes. $^{[d]}$ The same criterion as under b but for aliphatic aldehydes. $^{[e]}$ Only the aldehydes reported in the original papers are listed. Knochel’s work on 99 include over 50 aldehyde-organozinc combinations.

3.1.2. Bis(sulfonamides) as ligands for alkylation of aldehydes

The work on bis(sulfonamides) as ligands in the asymmetric addition of diethylzinc to aldehydes was pioneered by Yoshioka and co-workers in 1989. They sought a promoter class that contained stronger electron-withdrawing elements than those present in the amino alcohols, in order to achieve a rate acceleration of the catalytic reaction. They identified the sulfonyl group as a suitable candidate in this respect and prepared several ligands by reacting (R,R)-1,2-diaminocyclohexane with various sulfonyl chlorides. However, the bis(sulfonamides) produced the secondary alcohol (Scheme 20) with moderate enantioselection (36-83% ee) and only a weak rate acceleration was observed, even when bis(sulfonamide) was employed.

A suitable metal partner was sought to increase the rate and various Lewis acidic metal alkoxides

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Figure 5. Examples of ligands for the enantioselective alkylation of aldehydes.

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were screened in the reaction between Et₂Zn and benzaldehyde. Ti(OiPr)₄ stood out among the metal alkoxides tested, and at 2 mol% it was able to catalyze the alkylation of benzaldehyde in 80% yield in 12h at room temperature. The combination of bis(sulfonamide) 99 (4 mol%) and Ti(OiPr)₄ (4.8 mol%) was highly successful and alcohol 86 was produced with 98% ee after 2h at 0 °C. It was possible to use as little as 0.05 mol% of ligand 99 in combination with 120 mol% of Ti(OiPr)₄ and still obtain an excellent enantiomeric excess (98% ee). However, the introduction of Ti(OiPr)₄ complicated the alkylation reaction since Ti(OiPr)₄ alone catalysed the reaction in an non-selective fashion, and it was surprising to note that alcohol 86 could be obtained with high enantiomeric excess despite the use of a large excess of Ti(OiPr)₄. The role of the excess of Ti(OiPr)₄ was attributed to replacing the product alkoxide in the titanium-bis(sulfonamide) complex and thus reconstituting the active catalyst.

Knochel developed the scope of the asymmetric alkylation reaction by introducing functionalized dialkylzinc reagents. These reagents were prepared from the corresponding alkyl iodides via a copper-catalysed iodine-zinc exchange reaction. The asymmetric alkylation reaction catalyzed by 99 and Ti(OiPr)₄ tolerated the presence of functional groups like esters and chlorides, if the ester group or the chlorine atom was separated by at least four carbon atoms from the zinc atom, and alcohols with excellent ee’s were obtained (Scheme 23). The methodology was also extended to include β-stannylated saturated and α,β-unsaturated aldehydes as well as β-silylated α,β-unsaturated aldehydes and acetylenic aldehydes. The products obtained, when these aldehydes were used as substrates in the alkylation reaction could be modified further in a number of ways.

\[
\begin{align*}
R(CH_2)_n & \quad \text{Et}_2\text{Zn (150 mol%) Cul (0.3 mol%)} \\
\text{CuI (0.3 mol%)} & \quad \text{Et}_2\text{Zn (250 mol%)} \\
\text{Ti(OiPr)₄ (200 mol%)} & \quad \text{R}^*\text{CHO, 99 (8 mol%) OH} \\
\text{R(CH}_2)_n & \quad \text{R}^*\text{(CH}_2)_n\text{R} \\
\text{Scheme 23. R = CH}_3, \text{ Cl, OCOR'} & \quad 90-97\% \text{ ee}
\end{align*}
\]

---

An alternative and milder path to functionalized organozinc reagents commences with alkenes. The one-pot procedure involves hydroboration of the alkene to the corresponding borane, which readily undergoes a boron-zinc exchange with diethylzinc to form the organozinc reagent (Scheme 24). The functional group tolerance is impressive: ester groups, silyl ethers, acrylates, alkyl iodides and alkyl bromides are tolerated in the alkylation reaction, if they are separated by at least three carbon atoms from the zinc atom. The drawback of these zinc reagents is that an excess (two-three equivalents) is needed for a high chemical yield and high enantioselectivity. Moreover, only one of the alkyl groups bound to zinc is transferred to the aldehyde in the alkylation reaction. The problems can be avoided by treating the organozinc reagent with (Me₃SiCH₂)₂Zn forming a new organozinc reagent in which the Me₃SiCH₂ moiety behaves as a nontransferable group. These mixed organozinc reagents can be used in smaller amounts but at the expense of the reaction rate, and a smaller excess of Ti(OiPr)₄ must be used to suppress the background reaction. The combination of functionalised organozinc reagents, bis(sulfonamide) 99, and Ti(OiPr)₄ can be successfully employed in the syntheses of complex structures.

\[
\text{FG-R} \xrightarrow{1. \text{BHEt}_2} (\text{FG-R''}_2Zn) \xrightarrow{2. 2 \text{Et}_2Zn} \text{R''CHO} \quad (\text{FG-R'})_2\text{ZnTi(OiPr)}_4
\]

Scheme 24. FG: Ester, silyl ether, acrylate, iodide, bromide.


3.1.3. The present study – Optimisation of the reaction conditions

Earlier work in our group dealing with bis(sulfonamide) 49 as a ligand for the enantioselective addition of diethylzinc to benzaldehyde, had shown that the enantiomeric excess of 1-phenylpropanol (86) was highly dependent upon the reaction conditions (Scheme 25). The amount of Ti(OiPr)$_4$ was an important factor and a ratio of benzaldehyde:49:Ti(OiPr)$_4$:Et$_2$Zn of 1:0.125:1.48:1.2 in the presence of activated 4Å molecular sieves had proven to be optimal, giving 86 with 78% ee. A precatalyst, prepared by heating 49 and Ti(OiPr)$_4$ in a 1:1 ratio in the presence of molecular sieves, had been used in the catalytic reactions.

Further optimisation of the reaction conditions has now been performed and the ligands which are described in Chapter 2 have been evaluated as promoters in the alkylation reaction under the newly optimised conditions. The effect of the amount of Ti(OiPr)$_4$ was studied in order to give a clear picture of how it influences the catalytic reaction as well as the competing achiral background reaction. The experiments were performed in the presence of 0.125 equivalents of ligand 49, 1.2 equivalents of Et$_2$Zn, and activated 4Å molecular sieves, but without heating 49 with an equimolar amount of Ti(OiPr)$_4$ to form a precatalyst. In the absence of Ti(OiPr)$_4$ a slow and unselective reaction occurred, which probably proceeded via a zinc-bis(sulfonamide) complex, and 86 was obtained with 21% ee (Table 5, entry 1). This was in line with results obtained with ligand 99 and derivatives thereof, which gave 86 with modest ee’s in the absence of Ti(OiPr)$_4$. The (R)-enantiomer of the product dominated when ligand 49 and Ti(OiPr)$_4$ were present in equimolar amounts during the catalytic reaction, but the ee was still low (26%) and the reaction was very slow (entry 2). However, increasing the amount of Ti(OiPr)$_4$ successively from 0.34 equivalents to 1.68 equivalents changed the enantioselectivity in a remarkable fashion and increased the reaction rate. It was surprising to note that the enantiomer obtained as the major product, when an excess of Ti(OiPr)$_4$ was used, was opposite to the major enantiomer obtained, when equimolar amounts of Ti(OiPr)$_4$ and ligand 49 were used (compare entries 2 and 3). Further increases of the amount of Ti(OiPr)$_4$ led to increased enantioselectivity and a maximum of the ee (59%, entry 6) was reached at around 1.5 equivalents of Ti(OiPr)$_4$. Seebach and co-workers observed...
a similar phenomenon to an even larger extent with the TADDOL ligand 7 (Figure 2), and with 4-methoxybenzaldehyde as the substrate. The (R)-
enantiomer of the product was obtained with 98% ee when two equivalents of
the catalyst (TiL₂) was used in the absence of Ti(OiPr)₄, whereas the (S)-
enantiomer was obtained with 94% ee when 0.1 equivalents of the same catalyst
was used in the presence of 1.2 equivalents of Ti(OiPr)₄. The precatalyst in the
latter case probably formed a Ti(OiPr)₂L species in the presence of Ti(OiPr)₄.

Table 5. The influence of the amount of Ti(OiPr)₄ on the enantioselectivity
and the reaction rate in the addition of diethylzinc to benzaldehyde.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ti(OiPr)₄ (equiv.)</th>
<th>Time [h][b]</th>
<th>Conv. [%][b]</th>
<th>ee [%][c]</th>
</tr>
</thead>
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<tr>
<td>1</td>
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<td>50</td>
<td>24</td>
<td>15 (S)</td>
</tr>
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<td>26 (R)</td>
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<tr>
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<td></td>
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<td>4</td>
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<td>22 (S)</td>
</tr>
<tr>
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<td>77</td>
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<td>0.05</td>
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<td></td>
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</tr>
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<td>1</td>
<td>100</td>
</tr>
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<td></td>
<td></td>
<td>1</td>
<td>29</td>
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</table>

[a] The reactions were performed in the presence of 1.2 equiv. of Et₂Zn and
activated 4 Å MS (250 mg/mmol 85), but without using a precatalyst. [b]
Reaction time at –35 °C. [c] Determined by GC.

The reaction rate was increased considerably also when the amount of Ti(OiPr)₄
was increased. Thus, 87% conversion was reached after four hours when 0.34
equivalents of Ti(OiPr)₄ were used, whereas full conversion was reached after 15
minutes when 0.68 equivalents of Ti(OiPr)₄ were employed (Table 5, entries 3
and 4). As mentioned earlier, the alkylation of aldehydes was complicated by
the introduction of the Lewis acidic Ti(OiPr)₄, since the titanium can catalyze the
reaction in a non-selective way. However, the background reaction was too
slow to compete with the ligand-catalyzed pathway and should not influence the

stereochemical outcome of the reaction. Full conversion was reached within 15 minutes in the presence of ligand 49 and 1.48 equivalents of Ti(OiPr)\textsubscript{4}, whereas no product was detected after 15 minutes in the absence of 49 when the same amount of Ti(OiPr)\textsubscript{4} was employed (entries 6 and 9). The rate of the background reaction was also influenced by the amount of Ti(OiPr)\textsubscript{4} and 29% conversion was reached after 1h when 1.48 equivalents of the titanium alcoholate was used, whereas only 17% conversion was reached after the same time when 0.68 equivalents was used (entries 8 and 9).

The alkylation reaction catalyzed by bis(sulfonamides) such as 49 is ligand accelerated, probably due to the presence of the strongly electron-withdrawing sulfonyl groups. Seebach et al. suggest that the role of the excess of Ti(OiPr)\textsubscript{4} is to replace the product alkoxide on the catalyst by isopropoxide and thus reconstitute the catalyst. The presence of Ti(OiPr)\textsubscript{4} has a decisive effect on the enantioselectivity when a TADDOL-titanium complex containing enantiopure 1-phenylpropoxides coordinating to titanium is used as a catalyst. An excess of Ti(OiPr)\textsubscript{4} (1.2 equivalents) affords the secondary alcohol (86) with much higher ee than is observed in the absence of Ti(OiPr)\textsubscript{4}. A large excess of Ti(OiPr)\textsubscript{4} (1.2-1.8 equivalents) is commonly employed in the bis(sulfonamide) catalyzed addition of alkylzinc reagents to aldehydes. For example, bis(sulfonamide) 97 (Figure 5) gives 86 with 4% ee in the presence of 0.20 equivalents of Ti(OiPr)\textsubscript{4} (an equimolar amount), whereas the use of 1.4 equivalents gives 99% ee.

Activated 4 Å molecular sieves are sometimes employed in asymmetric catalysis, especially when d\textsuperscript{6} early transition metals such as titanium are used as the metal source. The roles of the sieves are different in different reactions; the sieves may serve to trap water, or as sources of limited amounts of water. The structure and the water content of molecular sieves can have a decisive effect on the outcome and reproducibility of a catalytic reaction. Molecular sieves can also assist complex formation between ligand and metal. The presence of water can largely influence the enantioselectivity in titanium bis(sulfonamide) mediated alkylation reactions.

\begin{thebibliography}{99}
\bibitem{Hanson} Hanson, R. M.; Sharpless, K. B. \textit{J. Org. Chem.} \textbf{1986}, \textit{51}, 1922-1925.
\end{thebibliography}
The influence of activated 4 Å molecular sieves on the outcome of the alkylation reaction was examined using bis(sulfonamide) 49 and 1.2 equivalents of Et₂Zn without forming a precatalyst. The alcohol 86 was obtained with 59% ee both in the presence and in the absence of activated 4 Å molecular sieves, and the reaction rate was unchanged (Table 6, entries 1 and 2). The background reaction was also unaffected by the presence of molecular sieves (compare entries 3 and 4). The use of non-activated 4 Å molecular sieves attenuated the reaction rate considerably, yet the enantioselectivity was improved slightly compared to the effect of activated 4 Å molecular sieves (entries 5 and 6).

<table>
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<tr>
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<td>250[d]</td>
<td>26</td>
<td>30</td>
<td>53 (S)</td>
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</table>

[a] The reactions were performed using 1.2 equiv. of Et₂Zn and without the use of a precatalyst. [b] Reaction time at –35 °C. [c] Determined by GC. [d] Non-activated 4Å MS.

Heating bis(sulfonamide) 49 and Ti(OiPr)₄ in toluene at 60 °C did not produce a titanium bis(sulfonamide) complex according to ¹H and ¹³C NMR spectroscopy. The acidic sulfonamide protons were still visible in the ¹H NMR spectrum and the addition of activated 4 Å molecular sieves did not assist the ligand exchange. Similar observations were made by Walsh and co-workers with derivatives of 99, and they suggested that Et₂Zn is needed to deprotonate the bis(sulfonamide) for ligand exchange to occur (vide infra). In order to promote titanium bis(sulfonamide) complex formation before the addition of the aldehyde, we mixed ligand 49, Ti(OiPr)₄, and Et₂Zn at –78 °C, allowed the mixture slowly to reach room temperature and kept that temperature for 140 minutes before the aldehyde was added. Improved enantioselectivity was observed under these conditions, the enantiomeric excess of 86 increasing from 59 to 72% (Table 7, entries 1 and 2). Keeping the mixture for an extended time at room temperature did not improve the enantioselectivity (entry 3). Varying the Ti(OiPr)₄:Et₂Zn ratio afforded a slower and less selective catalytic reaction (entries 4 and 5).

The influence of complex formation on the enantioselectivity and the reaction rate in the addition of diethylzinc to benzaldehyde was studied using the optimised conditions, i.e. a benzaldehyde:Ti(OiPr)₄:Et₂Zn ratio of 1:1.48:1.2 in the absence of 4 Å MS and keeping the reaction mixture at room temperature before adding the aldehyde. The enantioselectivity was almost unaffected when the amount of 49 was reduced from 12.5 mol% to 6 mol%, but the reaction rate decreased and 97% conversion was achieved after 1 h (Table 8, entries 1 and 2). Almost identical results were obtained when 4 mol% of ligand 49 was used (entry 3), whereas at 2 mol% the enantioselectivity increased with the conversion to reach 67% after 3 hours (entry 4). Competition from the non-selective background reaction was probably responsible for the lower enantioselectivity when 2 mol% of 49 was employed. Interestingly, the enantioselectivity increased with the conversion when 6 mol% or less of ligand 16 was used. The chiral alkoxide formed in the reaction probably coordinate to the catalytically active species and influence the enantioselectivity. Variation in the enantioselectivity with the conversion had also been observed with derivatives of ligand 99 in the alkylation of benzaldehyde.\(^{141}\)


<table>
<thead>
<tr>
<th>Entry</th>
<th>49 (equiv.)</th>
<th>Ti(OiPr)₄ (equiv.)</th>
<th>Et₂Zn (equiv.)</th>
<th>Kept at rt [^{[a]}]</th>
<th>Time [^{[b]}]</th>
<th>Conv. ([^%)][^{[c]}]</th>
<th>ee ([^%)][^{[c]}]</th>
</tr>
</thead>
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<td>1.48</td>
<td>1.2</td>
<td>No</td>
<td>0.25</td>
<td>100</td>
<td>59 ((S))</td>
</tr>
<tr>
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<td>0.125</td>
<td>1.48</td>
<td>1.2</td>
<td>Yes</td>
<td>0.25</td>
<td>97</td>
<td>72 ((S))</td>
</tr>
<tr>
<td>3</td>
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<td>1.48</td>
<td>1.2</td>
<td>Yes</td>
<td>3.25</td>
<td>90</td>
<td>63 ((S))</td>
</tr>
<tr>
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<td>1.48</td>
<td>3.0</td>
<td>Yes</td>
<td>1.2</td>
<td>96</td>
<td>16 ((S))</td>
</tr>
<tr>
<td>5</td>
<td>0.125</td>
<td>0.68</td>
<td>3.0</td>
<td>Yes</td>
<td>1.2</td>
<td>94</td>
<td>10 ((S))</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Ligand 49, Ti(OiPr)₄, and Et₂Zn were mixed at –78 °C, allowed to reach rt during 75 min and kept at rt for 140 min before benzaldehyde was added at –78 °C. \[^{[b]}\] Reaction time at –35 °C. \[^{[c]}\] Determined by GC. \[^{[d]}\] The reaction mixture was held at rt for 11 h before the aldehyde was added.
Table 8. The influence of the amount of ligand 49 on the reaction rate and the enantioselectivity in the addition of diethylzinc to benzaldehyde.\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>49 (equiv.)</th>
<th>Time [h]\textsuperscript{[b]}</th>
<th>Conv. [%]\textsuperscript{[c]}</th>
<th>ee [%]\textsuperscript{[c]}</th>
</tr>
</thead>
<tbody>
<tr>
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<td>72 (S)</td>
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<tr>
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<td>86</td>
<td>67 (S)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>97</td>
<td>71 (S)</td>
</tr>
<tr>
<td>3</td>
<td>0.04</td>
<td>0.25</td>
<td>81</td>
<td>66 (S)</td>
</tr>
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<td>70 (S)</td>
</tr>
<tr>
<td>4</td>
<td>0.02</td>
<td>0.25</td>
<td>53</td>
<td>57 (S)</td>
</tr>
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<td></td>
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<td>95</td>
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<td>3</td>
<td>96</td>
<td>67 (S)</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} The reactions were performed at a benzaldehyde:Ti(OiPr)\textsubscript{4}:Et\textsubscript{2}Zn ratio of 1:1.48:1.2 in the absence of 4 Å MS. The mixture was kept at rt before the aldehyde was added. \textsuperscript{[b]} Reaction time at –35 °C. \textsuperscript{[c]} Measured by GC.

3.1.4. Evaluation of sulfonamides as promoters for the addition of diethylzinc to benzaldehyde.

The ligands which are described in Chapter 2 were assessed in the enantioselective addition of diethylzinc to benzaldehyde in order to examine how the structural differences in the ligands affect the outcome of the catalytic reaction. The conditions that had been found to be optimal for bis(sulfonamide) 49 were employed, i.e. a ligand:benzaldehyde:Ti(OiPr)\textsubscript{4}:Et\textsubscript{2}Zn ratio of 0.06:1:1.48:1.2 in the absence of 4 Å molecular sieves (Scheme 26). We assumed that 6 mol% of the ligand would be sufficient to suppress the non-selective background reaction. Mono(sulfonamide) 48 (Scheme 26) afforded low enantioselectivity (3% ee) in the alkylation reaction and only 6% of the aldehyde was consumed after 15 minutes (Table 9, entry 1). The ligand catalyzed pathway could probably not compete with the achiral background reaction. The alkylation reaction was much faster in the presence of bis(sulfonamide) 73, the conversion then being 44% after 15 minutes (entry 2). Interestingly, the enantioselectivity varied with the conversion and the ee of 86 was 10% at full conversion. As seen in the optimisation study above, replacement of the hydrogen atom by a benzyl group at the secondary amine moiety afforded a ligand which accelerated the reaction even further, and the enantioselectivity was substantially improved giving 86 with 71% ee (entry 3). Lowering of the reaction temperature from –35 °C to –78 °C did not improve the selectivity and the ee of 86 was 50% after 3h, whereas the conversion was 10% (entry 4). Full conversion was achieved after an additional 90 minutes at –55 °C and the enantiomeric excess of 86 increased to 69% (entry 4). The introduction of a bulkier group in the ligand, as in 40 (Scheme 26) and 41, slightly improved both the reaction rate and the enantioselectivity (entries 5 and 6). However, either configuration of this
additional stereocentre improved the enantioselectivity in favour of the (S)-enantiomer. The reaction was exceptionally fast in the presence of ligands 40 and 41 and full conversion was reached within 15 minutes. The enantioselectivity was not improved when ligands 42 and 43, having additional steric bulk at the benzylic position, were used in the alkylation reaction (entries 7 and 9). A slower and less selective reaction took place when the reaction solvent was changed from toluene to THF, in which ligand 42 was completely soluble (entry 8). Ligand 43 displayed as strong ligand-acceleration effect, as did ligands 40 and 41, and the benzaldehyde was completely consumed within 15 minutes. The enantiomeric excess of 86 increased with increased conversion when ligand 42 and anthracene derivative 44 were applied in the catalytic reaction.

Table 9. Bis(sulfonamide)-mediated addition of diethylzinc to benzaldehyde.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time [h][b]</th>
<th>Conv. [%][c]</th>
<th>ee [%][c]</th>
<th>Yield [%][d]</th>
<th>Conv. [%][e]</th>
</tr>
</thead>
<tbody>
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<td>19</td>
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<td>6</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>0.25</td>
<td>44</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>100</td>
<td>10 (S)</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
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<td>86</td>
<td>67 (S)</td>
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<td></td>
</tr>
<tr>
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<td></td>
<td></td>
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<td>97</td>
<td>71 (S)</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>3[f]</td>
<td>10</td>
<td>50 (S)</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td>4.5[g]</td>
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<td>69 (S)</td>
<td>-</td>
</tr>
<tr>
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<td>0.25</td>
<td>97</td>
<td>75 (S)</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>0.25</td>
<td>99</td>
<td>76 (S)</td>
<td>93</td>
<td>99</td>
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<tr>
<td>7</td>
<td>42</td>
<td>0.25</td>
<td>42</td>
<td>48 (S)</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>56 (S)</td>
<td>91</td>
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<tr>
<td>8[h]</td>
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<td>12 (S)</td>
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<td>14</td>
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<td>96</td>
<td>69 (S)</td>
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<td>96</td>
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<td>10</td>
<td>44</td>
<td>0.25</td>
<td>73</td>
<td>56 (S)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2.33</td>
<td>98</td>
<td>63 (S)</td>
<td>98</td>
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</tbody>
</table>

[a] A ligand:benzaldehyde:Ti(OiPr)₄:Et₂Zn ratio of 0.06:1:1.48:1.2 was used. The reaction mixture was kept at rt before the benzaldehyde was added. [b] Reaction time at −35 °C. [c] Determined by GC. [d] Determined by GC using an external standard. [e] Conversion after 15 min at −35 °C. [f] Reaction time at −78 °C. [g] 3 h at −78 °C followed by 1.5 h at −55 °C. [h] THF was used as solvent.
The (S)-alaninol-derived ligand 50 was inferior to its (S)-valinol analogue 49 as a promotor for the addition of diethylzinc to benzaldehyde (Scheme 27). Only 11\% conversion was reached after 15 minutes and the enantiomeric excess was 19\% at full conversion with the (S)-enantiomer dominating (Table 10, entry 1). The use of ligand 51, containing the less electron-withdrawing tosyl groups rather than the trifluoromethanesulfonyl groups as in ligand 49, interestingly favoured the formation of the (R)-enantiomer of 86 with 50\% ee in the alkylation reaction.\textsuperscript{142} The presence of the tosyl groups in ligand 51 slowed down the catalytic reaction compared to the use of ligand 49, and only 18\% conversion was reached after 15 minutes (entry 2). The hydroxy-containing ligands 53 and 54 resulted in low enantioselectivity in the catalytic reaction (entries 3 and 4). The hydroxy groups were probably coordinated to the titanium in the catalytic species and the increased sterical congestion might be responsible for the low selectivity. Walsh and co-workers as well as Seebach and co-workers observed decreased enantioselectivity with sterically encumbered derivatives of 99 and 96, respectively.\textsuperscript{143,134} whereas the tetradentate ligand 97 afforded excellent enantioselectivity.\textsuperscript{119} The use of the O-methylated ligand 55 afforded a more rapid and selective alkylation reaction than was observed with the hydroxy analogue 54, giving 86 with 61\% ee (entry 5). Whereas the enantioselectivity increased with the conversion when ligands 50 and 51 were employed in the alkylation reaction, use of ligand 53 caused a decrease in the selectivity with conversion. The diastereomeric ligands 56 and 57 showed a behaviour similar to that of ligand 55 in the catalytic reaction (entries 6 and 7). The unstable ligands 56 and

\textsuperscript{142} This is in accordance with the results obtained by Lin et al. who reported that the tosyl-derivative of 73 favoured the (R)-enantiomer of 86. See footnote 85.

might have decomposed to ligand 55, alternatively, the planarly chiral arene moiety was situated too far from the catalytic centre to affect the enantioselectivity. Ligands 50 and 54 afforded higher enantioselectivities, 67 and 60% respectively, under the conditions used in the previous investigation in our group, i.e., forming a precatalyst by heating equimolar amounts of ligand and Ti(OiPr)₄, using activated 4 Å molecular sieves in the catalytic reaction but without keeping the mixture at room temperature before addition of the aldehyde. The results indicated that optimal conditions probably must be found for each particular ligand.

Table 10. Bis(sulfonamide)-mediated addition of diethylzinc to benzaldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time [h]</th>
<th>Conv. [%]</th>
<th>ee [%]</th>
<th>Yield [%]</th>
<th>Conv. [%]</th>
</tr>
</thead>
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<td>7 (S)</td>
<td>1.5</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>89</td>
<td>23 (S)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.3</td>
<td>100</td>
<td>19 (S)</td>
<td>97</td>
<td>11</td>
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<tr>
<td>2</td>
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<td>0.25</td>
<td>18</td>
<td>31 (R)</td>
<td>1</td>
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<td></td>
<td></td>
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<td>50 (R)</td>
<td>99</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
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<td>29 (S)</td>
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<td>61 (S)</td>
<td>90</td>
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<td>57</td>
<td>1.67</td>
<td>94</td>
<td>65 (S)</td>
<td>78</td>
<td>76</td>
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</table>

[a] A ligand:benzaldehyde:Ti(OiPr)₄:Et₂Zn ratio of 0.06:1:1.48:1.2 was used. The reaction mixture was kept at rt before the benzaldehyde was added. [b] Reaction time at –35 °C. [c] Determined by GC. [d] Determined by GC using an external standard. [e] Conversion after 15 min at –35 °C. [f] 5 mol% of the ligand was used.
The tetradeionate ligands 58 and 59 (Scheme 28) both favoured the formation of the (R)-enantiomer of 86 with 59 and 12% ee, respectively, when they were applied in the catalytic reaction (Table 11, entries 1 and 2). The diastereomeric ligands promoted the alkylation at a similar rate and the conversion was 29 and 27%, respectively, after 15 minutes. A decrease in enantioselectivity with conversion was observed in the alkylation reaction in the presence of ligand 58 whereas a linear relationship was observed with ligand 59. The 1,2-diaminocyclohexane derivatives 60 and 61 did not mediate the addition of diethylzinc to benzaldehyde to any appreciable extent and only racemic products were obtained (entries 3 and 4). The low reaction rate indicated that a substantial amount of the secondary alcohol was formed via the Ti(OiPr)₄-catalyzed pathway. The poor solubility of ligands 60 and 61 in toluene was not responsible for the lack of enantioselectivity, since similar results were obtained when the reactions were performed in THF, where the ligands were completely soluble. The axially chiral ligands 62 and 63 afforded low enantioselectivity in the catalytic reaction and 86 was obtained in 9 and 5% ee, respectively, with the (R)-enantiomer dominating (entries 5 and 6). The rate acceleration observed in the presence of ligands 62 and 63 should ensure that the background reaction did not influence the enantioselectivity. C₃-symmetric tris(sulfonamide) ligands 64 and 68 exhibited low enantioselectivity when they were applied in the alkylation reaction. Interestingly, the two (S)-valinol-derived ligands afforded the product 86 with opposite configuration (entries 7 and 8). Ligand 68, containing tosyl groups as electron-withdrawing elements, promoted the formation of the (R)-enantiomer of 86, whereas the triflate analogue 64 afforded the (S)-enantiomer even though the (R)-enantiomer dominated at low conversion. This was in line with the results obtained for tosyl-derivative 51, which favoured the formation of the (R)-enantiomer, whereas the triflate analogue 49 favoured the formation of the (S)-enantiomer.
Table 11. Sulfonamide-mediated addition of diethylzinc to benzaldehyde.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time [h](^{[b]})</th>
<th>Conv. [%](^{[c]})</th>
<th>ee [%](^{[c]})</th>
<th>Yield [%](^{[d]})</th>
<th>Conv. [%](^{[e]})</th>
</tr>
</thead>
<tbody>
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<td>80 (R)</td>
<td>1.67</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.67</td>
<td>73</td>
<td>65 (R)</td>
<td>5</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>59(^{[f]})</td>
<td>5.25</td>
<td>87</td>
<td>12 (R)</td>
<td>87</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>60(^{[i]})</td>
<td>18.25</td>
<td>93</td>
<td>0</td>
<td>89</td>
<td>5</td>
</tr>
<tr>
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<td>0</td>
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<td>4</td>
</tr>
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<td>5</td>
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<td>9 (R)</td>
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<td>3.33</td>
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<td>5 (R)</td>
<td>84</td>
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<tr>
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<td>68</td>
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<td>25 (R)</td>
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<td></td>
<td>18</td>
<td>96</td>
<td>31 (R)</td>
<td>91</td>
<td>20</td>
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</table>

\(^{[a]}\) A ligand:benzaldehyde:Ti(OiPr)\(_2\):Et\(_2\)Zn ratio of 0.06:1:1.48:1.2 was used. The reaction mixture was kept at rt before the benzaldehyde was added. \(^{[b]}\) Reaction time at –35 °C. \(^{[c]}\) Determined by GC. \(^{[d]}\) Determined by GC using an external standard. \(^{[e]}\) Conversion after 15 min at –35 °C. \(^{[f]}\) 5 mol% of the ligand was used. \(^{[i]}\) Similar results were obtained in THF. \(^{[h]}\) A mixture of THF:toluene 1:7 was used to solubilize the ligand.

\begin{center}
\textbf{Scheme 28}
\end{center}
With a few exceptions, benzaldehyde and similar aromatic aldehydes are the substrates which afford the highest enantioselectivities in the asymmetric alkylation of aldehydes. The large difference between the small hydrogen atom and the relatively large phenyl ring, and the absence of acidic α-protons make benzaldehyde a perfect substrate for the addition of an alkyl group, even though the synthetic utility is limited. In general it is difficult to obtain excellent enantioselectivities with aliphatic aldehydes, but higher ee’s are often obtained if the aliphatic aldehydes contain a substituent at the α-position. Addition of diethylzinc to cyclohexanecarboxaldehyde in the presence of ligand under the optimised conditions (see above) affords alcohol with low enantiomeric excess, 25% ee (Scheme 29). The reaction time is markedly longer than for benzaldehyde, and 90% conversion is achieved after 36 hours.

\[
\text{Scheme 29}
\]

3.1.5. Proposal of a catalytic cycle

Some features of the intermediates involved in the bis(sulfonamide)-mediated enantioselective alkylation of aldehydes are known, even though suggestions regarding possible transition state structures are rare. The X-ray structure of the zinc-bis(sulfonamide) complex obtained by mixing Et₂Zn with the bis(n-butanesulfonamide) derivative is known (Scheme 30). It shows that the zinc atom is bound to both of the sulfonamide nitrogen atoms, preserving the C₂-symmetry. Sulfonamide protons are acidic with pKₐ-values of about 7-10, and bis(sulfonamides) are easily deprotonated by Et₂Zn. Work by Walsh and co-workers shows that mixing ligand with excess Ti(OiPr)₄ does not lead to the formation of a titanium complex, Instead, mixing with Ti(OiPr)₂(NMe₂)₂ results in the formation of the bis(sulfonamide) titanium complex (Scheme 30). The X-ray structure shows that titanium has a distorted octahedral geometry and that one oxygen atom of each sulfonyl group is coordinated to the titanium centre, maintaining a rigid C₂-symmetric structure of the complex. Furthermore, the use of a ligand

The Ti(OiPr)$_4$:Et$_2$Zn mixture gives the same results in the alkylation reaction as is observed when the titanium complex 107 is employed under the same conditions. The results indicate that Et$_2$Zn serves to deprotonate 106 and that the bis(sulfonamide) zinc complex reacts with Ti(OiPr)$_4$ in situ to form 107. However, the driving force of this reaction remains unclear. The absence of non-linear effects when ligand 106 is employed in the catalytic reaction suggests that the catalytically active species is monomeric. The enantioselection observed in the alkylation reaction with titanium complexes containing two bis(sulfonamide) ligands, (TiL)$_2$, are inferior to the enantioselection observed when complexes containing one sulfonamide ligand is used, indicating that the active species has the stoichiometry of Ti(OiPr)$_2$L. It is of importance that a C$_2$-symmetric trans-conformation of the aryl groups in the catalyst 107 is maintained during the reaction. Catalysts, in which a short tether forces the aryl groups (108, n=6) into a syn-conformation, are inferior to catalysts, in which a longer tether (108, n=22) allows a trans-conformation to be maintained during the reaction (Scheme 30).

It is not known whether the ethyl group is transferred from zinc or from titanium, and whether the transfer occurs inter- or intramolecularly. $^1$H NMR studies on a mixture of Et$_2$Zn and Ti(OiPr)$_4$ reveal a concentration-dependent equilibrium where no monomeric Et$_2$Zn is present but signals from at least two ethyl groups are observed. These studies, by Yoshioka and co-workers, on ligand 99 (Figure 5) led to the proposal of the species TiL(Et)(OiPr) as a crucial intermediate, from which transfer of the ethyl group occurred faster than in any other ethyl-containing species. Paquette and Zhou also proposed that the ethyl group is transferred intramolecularly from titanium to the aldehyde. However, it seems unlikely that the strong Ti-O bond is replaced by the weaker Ti-C bond, even though the Ti-C bond is stronger than the corresponding Zn-C bond. Moreover, an intramolecular transfer would probably result in an unfavourable angle of approach of the ethyl group. A bimetallic complex comprising Et$_2$Zn,
titanium and the ligand, and from which the ethyl group is transferred intramolecularly from zinc, seems more probable, as suggested by the groups of Knochel\textsuperscript{127}, Seebach\textsuperscript{134} and Zhang\textsuperscript{119}.

A mechanistic scenario is presented below, based on our findings with bis(sulfonamide) 49 and the observations reported in the literature on similar systems. Treatment of 49 with Et\textsubscript{2}Zn results in gas evolution (ethane) and the probable formation of intermediate 109, where the tertiary nitrogen atom probably is coordinated to the zinc atom (Scheme 31). The intermediate 109 catalyzes the addition of diethylzinc to benzaldehyde in a slow and unselective process, and only 58\% conversion is achieved in four days (21\% ee). These results indicate that 109 is not the catalytically active species when the reaction is performed in the presence of Ti(OiPr)\textsubscript{4}. Instead, the zinc complex 109 probably reacts with Ti(OiPr)\textsubscript{4} forming a titanium complex of the type Ti[bis(sulfonamide)](OiPr)\textsubscript{2}, which presumably is the active species in the catalytic reaction. The X-ray structure of the aluminium complex of ligand 49 shows that the tertiary nitrogen atom coordinates to aluminium, and a similar coordination can be expected in the titanium complexes.\textsuperscript{149} A distorted trigonal bipyramidal (110) or an octahedral geometry is possible, by analogy with a similar achiral bis(sulfonamide) ligand.\textsuperscript{150} Two complexes are possible for the octahedral coordination of ligand 49. Either a facial or a meridional coordination of the bis(sulfonamide) is possible, resulting in the complexes 111 or 112, respectively. It is difficult to predict the exact structures and the relative stability of the octahedral complexes and whether or not there is an interaction between the sulfonyl oxygen atoms and the titanium centre. The sulfonamide nitrogen atoms can be expected to have a planar geometry\textsuperscript{140} and each isopropyl group in the ligand should force the sulfonamide group into a trans relationship. This should destabilise the facially coordinated structure 111 since the two sterically demanding sulfonamide groups would then be in close proximity. We did not succeed to obtain spectroscopic evidence for any of the intermediates.

Benzaldehyde is a weak ligand which prefers to coordinate to titanium trans to the strong isopropoxide ligand in 112, resulting in complex 113 (Scheme 32). A coordination such as that seen in complex 114 might also be possible if the benzyl group is residing below the plane. A recent proposal by Corey and co-workers suggests that hydrogen bonding between an aldehyde proton and an alkoxide ligand bound to titanium can be invoked to explain the stereochemical outcome of asymmetric transformations. Such an interaction is improbable in our system since a hydrogen bond between the aldehyde proton and the oxygen atom of the equatorial isopropoxide group in 113 will bring the sulfonamide, which is sitting above the plane, and the benzaldehyde moieties too close to each other. A hydrogen bond to the highly electron deficient sulfonamide nitrogen is unlikely even though, according to the proposed model, the aldehyde proton should be situated in a nearly optimal position. Our model then predicts that the ethyl group attacks the aldehyde from the Si face at the same time as the isopropoxide ligand trans to the aldehyde leaves the catalyst (see 115), probably forming iPrOZnEt. This model predicts the formation of the observed (S)-alcohol (116). A possible mode of activation of the diethylzinc is seen in structure 115, where the equatorial titanium isopropoxide oxygen coordinates to the zinc atom of diethylzinc or, alternatively, an intermolecular ethyl transfer from an ethylzinc species like 117 can be envisaged. Both scenarios would probably ensure that the aldehyde is attacked at a favourable angle.

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153 A hydrogen bond to the oxygen atom of the isopropoxide sitting in the equatorial position should result in an attack on the Re face, which would give the (R)-alcohol.

The excess of Ti(OiPr)₄ will replace the alkoxide residue from the intermediate 116 (Scheme 32) and reconstitute the intermediate 112 (Scheme 31). The non-linearity between the conversion and the enantiomeric excess that is observed with some of our ligands in the alkylation reaction indicates that the catalyst is not intact during these catalytic process. It is possible that structure 116 serves as a catalyst of the alkylation reaction and that the chiral alkoxide residue coordinates to the titanium in 116 in a favourable or unfavourable way, causing an increase or a decrease, respectively, in the enantiomeric excess.

3.1.6. The effect of chiral additives on the enantioselectivity of the addition of diethylzinc to benzaldehyde

Even though the exact structure of the catalytically active species is unknown in the bis(sulfonamide) mediated addition of diethylzinc to benzaldehyde, it can be stated that a neutral bis(sulfonamido) titanium(IV) complex would require the coordination of two anionic ligands. The ligands are probably two isopropanoxide molecules, even though the presence of an ethyl group on titanium has been suggested (vide supra). The structure of the alkoxides that coordinate titanium can have a decisive effect on the outcome of the asymmetric alkylation reaction. A study by Knochel and co-workers shows that the ee of the product alcohol is increased from 0 to 93% when the Ti(OiPr)₄ is replaced by the bulkier Ti(OtBu)₄. However, the task of finding the optimal size of the titanium alkoxide employed is delicate. Another study by Knochel and co-workers reveals that an equimolar mixture of Ti(OiPr)₄ and Ti(OtBu)₄ affords optimal enantioselectivity, whereas Yus and co-workers report that the use of Ti(OiPr)₄ affords higher enantioselectivity than the use of Ti(OtBu)₄ or Ti(OEt)₄. Moreover,

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moderate enantioselectivities are observed when achiral bis(sulfonamides) are used as ligands in combination with titanium bound to (S)-1-phenylpropanol (86). Our observation of non-linearity between the ee and the conversion in the asymmetric alkylation reaction (vide supra) indicates that the enantioselectivity can be affected by the presence of chiral coordinating alkoxides. This observation suggests that it might be possible to improve the enantioselectivity of the bis(sulfonamide) 49 in the alkylation reaction by the use of chiral coordinating groups as additives in the reaction. Thus, chiral amines, chiral amino alcohols and chiral alcohols have now been used in the presence of bis(sulfonamide) 49 and Ti(OiPr)₄.

A ligand 49: additive: Ti(OiPr)₄ ratio of 1:1:1 (12.5 mol% of each) was used in the alkylation reaction as it was believed to favour the formation of a titanium complex containing one molecule of ligand 49 and one molecule of the additive, but other combinations might have been formed. The mixture was heated in toluene at 60 °C for 90-160 minutes, after which Et₂Zn (1.2 equivalents) and benzaldehyde were added at –78 °C. The reactions were quenched after about 90 hours at –35 °C. The ee-values of the catalytic reactions in the presence of chiral mono- and diamines and amino alcohols are reported in Figure 6. The conversion was >87% with all of the additives except the amino alcohols. The reaction in the absence of any additive gave 86 in 26% ee in favour of the (R)-enantiomer (Figure 6, 1). The two enantiomers of 1-phenylethylamine both favored the (S)-enantiomer of 86, but the ee’s were very low (Figure 6, 2 and 3). The two enantiomers of 1,2-diaminocyclohexane also afforded the (S)-enantiomer, but again the ee’s observed were low (4 and 5). The highest enantioselectivity, 49% (S), was observed when (1R,2R)-1,2-diphenyl-1,2-ethanediamine (118) was used as an additive, whereas its enantiomer favoured the formation of the (R)-enantiomer with 16% ee (7 and 8). The axially chiral diamine (R)-1,1’-binaphthyl-2,2’-diamine, (−)-sparteine and the two amino

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159 No imines were detected in the reactions even though similar conditions had been used to favour their formation: (a) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. J. Org. Chem. 1990, 55, 2552-2554. (b) Bhattacharyya, S.; Chatterjee, A.; Williamson, S. C. Synlett, 1995, 1079-1080.
alcohols (R)-2-phenylglycinol and (S)-phenylalaninol, all afforded low enantioselectivities in the alkylation reaction (9-12.)

Figure 6. The effects on the enantioselectivity caused by amines and amino alcohols when used as additives in the addition of diethylzinc to benzaldehyde. [a] 1: No additive. 2: (R)-1-Phenylethylamine. 3: (S)-1-Phenylethylamine. 4: (1R,2R)-1,2-Diaminocyclohexane. 5: (1S,2S)-1,2-Diaminocyclohexane. 6: cis-1,2-Diaminocyclohexane. 7: (1R,2R)-1,2-Diphenyl-1,2-ethanediamine. 8: (1S,2S)-1,2-Diphenyl-1,2-ethanediamine. 9: (R)-1,1’-Binaphthyl-2,2’-diamine. 10: (−)-Sparteine. 11: (R)-2-Phenylglycinol. 12: (S)-Phenylalaninol. [a] A stock-solution of the ligand mixture was prepared by heating 49 and Ti(OiPr)4 in toluene at 40 °C for 11 h, followed by 60 °C for 4 h and removal of the 4 Å MS. A sample of the stock-solution (12.5 mol%) was heated with the appropriate additive in toluene at 60 °C for 90-160 min. The mixture was cooled to −78 °C and Et2Zn (1.2 equiv.) and benzaldehyde were added. The mixture was stirred at −35 °C for about 90 h.

The results obtained with mono- and bidentate alcohols as additives under the conditions described above are summarised in Figure 7. The conversion is >90% with a few exceptions. It is interesting to note that all monodentate alcohols favour the formation of the (R)-enantiomer of 86, whereas the bidentate alcohols all favour the (S)-enantiomer, with one exception, (R)-BINOL. Two equivalents of the monodentate alcohol L-menthol also favour the (R)-enantiomer (entry 4). (−)-TADDOL affords the highest enantioselectivity, 46% ee, of the alcohols tested. Studies on BINOL/Ti(OiPr)4 as a system for alkylation of aldehydes show that (S)-BINOL favours the (S)-enantiomer of 86 with 92% ee in the presence of a small excess of Ti(OiPr)4, a result which partially explains the enantioselectivity observed for the BINOL additives.


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160 The (−)-TADDOL ligand (=L) and Ti(OiPr)4, afford the following results in the absence of any additive: TiL(OiPr)2 (1.2 equiv.) 90% (S), TiL(OiPr)2 (0.2 equiv.) and Ti(OiPr)4 (1.2 equiv.) 98% (S), TiL2 (1.0 equiv.) 90% (R). See footnote 134.

Figure 7. The effect of mono- and bidentate alcohols as additives on the enantioselectivity in the addition of diethylzinc to benzaldehyde. 1: No additive. 2: D-Menthol. 3: L-Menthol. 4: 2 equiv. L-Menthol. 5: (1S,2S,5S)-(−)-Myrtanol. 6: Methyl (S)-(−)-mandelate. 7: cis-1,2-Cyclohexanediol. 8: Dimethyl L-tartrate. 9: (−)-TADDOL. 10: (2R,5R)-2,5-Hexanediol. 11: (2S,5S)-2,5-Hexanediol. 12: (1S,2S)-1,2-di-α-Tolylethane-1,2-diol. 13: (R)-(−)-BINOL. 14: (S)-(−)-BINOL.

The results obtained with enantiomeric pairs of additives indicate the presence of diastereomeric complexes in the alkylation reactions. If titanium complexes containing only one additive and no ligand dominate the stereochemical outcome of the alkylation reaction, then (1R,2R)-1,2-diaminocyclohexane, for example, would favour the formation of the opposite enantiomer to that obtained with (1S,2S)-1,2-diaminocyclohexane, but with the same ee. Of course, many combinations of Ti(OiPr)$_4$, ligand 49 and the additive are possible and the enantioselectivity, the relative concentration and the reaction rate of each species must be considered.

Attempts to improve the enantioselectivity of the catalytic reaction in the presence of diamine 118 (Scheme 33) were made by optimising the reaction conditions. However, a marked decrease in the enantioselectivity was observed when the amount of Ti(OiPr)$_4$ was increased from 0.125 to 1.35 equivalents, probably due to competition from the background reaction (Table 12, entries 1 and 2). It was surprising to note that full conversion was not achieved, despite the extended reaction time and the large excess of Ti(OiPr)$_4$ (entry 2). Keeping the reaction mixture at room temperature before the aldehyde was added slightly improved the enantioselectivity (entry 3). An increase of the amount of Et$_2$Zn under the same conditions did not improve the enantioselectivity (entry 4). The
use of diamine 118 and Ti(OiPr)$_4$ in a 1:1 ratio in the absence of 49, afforded the (S)-enantiomer with low ee (3%) in a slow reaction (entry 5), whereas 118 in the absence of 49 and of Ti(OiPr)$_4$ favoured the (R)-enantiomer, albeit in an even slower process (entry 6).

Table 12. The influence of diamine 118 on the enantioselectivity in the addition of Et$_2$Zn to benzaldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>49 (equiv.)</th>
<th>118 (equiv.)</th>
<th>Ti(OiPr)$_4$ (equiv.)</th>
<th>Et$_2$Zn (equiv.)</th>
<th>Kept at rt $^a$</th>
<th>Time $^b$ (h)</th>
<th>Conv. $^c$ [%]</th>
<th>ee [%] $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td>1.2</td>
<td>No</td>
<td>90</td>
<td>96</td>
<td>49 (S)</td>
</tr>
<tr>
<td>2</td>
<td>0.125</td>
<td>0.125</td>
<td>1.35</td>
<td>1.2</td>
<td>No</td>
<td>91</td>
<td>90</td>
<td>3 (S)</td>
</tr>
<tr>
<td>3</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td>1.2</td>
<td>Yes</td>
<td>94</td>
<td>85</td>
<td>53 (S)</td>
</tr>
<tr>
<td>4</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td>3.0</td>
<td>Yes</td>
<td>95</td>
<td>98</td>
<td>45 (S)</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>0.125</td>
<td>0.125</td>
<td>1.2</td>
<td>No</td>
<td>91</td>
<td>64</td>
<td>3 (S)</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>0.125</td>
<td>-</td>
<td>1.2</td>
<td>No</td>
<td>111</td>
<td>47</td>
<td>61 (R)</td>
</tr>
</tbody>
</table>

$^a$ The reaction mixture was kept at rt before the aldehyde was added. $^b$ Reaction time at –35 °C. $^c$ Determined by GC.
3.2. Bis(sulfonamides) as promoters of asymmetric cyclopropanation

The cyclopropyl subunit is an integral part of many natural and non-natural products. The two most successful methods of achieving catalytic asymmetric cyclopropanation are the classical Simmons-Smith reaction and the decomposition of diazo compounds in the presence of copper or rhodium. The drawback of using diazo compounds is that only those stabilised by carbonyl moieties can be used, which limits the scope to carbonyl-substituted cyclopropanes. This thesis deals with the asymmetric Simmons-Smith reaction only.

In 1958 Simmons and Smith discovered that alkenes were transformed into the corresponding cyclopropanes in the presence of CH$_2$I$_2$ and Zn-Cu. It was soon realised that the Simmons-Smith reagent, IZnCH$_2$I, was more reactive towards allylic alcohols and ethers than towards simple alkenes. Furukawa et al. introduced Et$_2$Zn and CH$_2$I$_2$ as means of generating a homogeneous zinc carbenoid reagent, EtZnCH$_2$I. Early attempts to achieve asymmetric induction in the cyclopropanation reaction in the presence of (S)-leucine failed. The first catalytic asymmetric Simmons-Smith reaction was described by Takahashi et al. in 1992. Bis(sulfonamide) mediated the cyclopropanation of cinnamyl alcohol, affording the corresponding cyclopropane with 76% ee (Scheme 34). The reaction was extended to include a number of allylic alcohols even though the presence of a free hydroxy group was essential for high enantioselectivity. Lower enantioselectivity was observed in the reaction of when combinations of Ti(OiPr)$_4$ and various bis(sulfonamides) were used, although TiCl$_4$ and Ti(OiPr)$_4$ catalysed the cyclopropanation. Imai et al. improved the enantioselectivity of the cyclopropanation reaction to 85% ee, by applying bis(sulfonamide). Denmark et al. performed extensive studies on both the reaction conditions and the promoter structure, and bis(sulfonamide) was identified as the optimal promoter of the cyclopropanation of cinnamyl.

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Denmark et al. identified three experimental features as crucial for a highly enantioselective reaction to occur: firstly, the preformation of the ethylzinc alkoxide of the alcohol substrate via deprotonation of the allylic alcohol by Et₂Zn, secondly, the preformation of the zinc-promoter complex via deprotonation of the bis(sulfonamide) by Et₂Zn, and finally, the use of in situ generated ZnI₂ (from Et₂Zn and I₂). It was suggested, based on spectroscopic studies and reaction investigations, that the presence of ZnI₂ favoured the formation of the more reactive cyclopropanation reagent IZnCH₂I via a Schlenk equilibrium. The enantioselectivity of 121 was improved from 80 to 89% ee under the optimised conditions, and a number of allylic alcohols afforded excellent ee’s, 80-89% ee, but the reaction protocol was rather laborious. An X-ray structure of the zinc-bis(sulfonamide) complex of the bis(n-butanesulfonamide) derivative of 123 (Scheme 30, structure 105) was obtained and a transition state model was proposed. A related approach to catalytic asymmetric cyclopropanation was presented by Charette and Brochu who reported on the successful cyclopropanation of cinnamyl alcohol in the presence of one equivalent of (ICH₂)₂Zn and a chiral Lewis acid. The titanium-TADDOLate mediated the cyclopropanation of cinnamyl alcohol, affording the product 121 with 92% ee. However, the use of bis(sulfonamides) in combination with zinc, titanium, boron or aluminium afforded lower enantioselectivities, 0-44% ee.

We decided to test some of the sulfonamides described in Chapter 2 as promoters of the cyclopropanation of cinnamyl alcohol 120 (Scheme 35). The simpler protocol developed by Takahashi et al. was used for the initial screening, i.e. adding CH₂I₂ (three equivalents) to a solution of the bis(sulfonamide) (0.1 moles) in diethyl ether.

Scheme 34

We decided to test some of the sulfonamides described in Chapter 2 as promoters of the cyclopropanation of cinnamyl alcohol 120 (Scheme 35). The simpler protocol developed by Takahashi et al. was used for the initial screening, i.e. adding CH₂I₂ (three equivalents) to a solution of the bis(sulfonamide) (0.1 moles) in diethyl ether.

equivalent), cinnamyl alcohol and Et₂Zn (two equivalents) in CH₂Cl₂ at –23 °C (Method A). However, the stoichiometry of the reagents used was unclear, but deprotonation of the bis(sulfonamide) and the alcohol with Et₂Zn probably occurred. The remaining Et₂Zn presumably reacted with CH₂I₂ to form (ICH₂)₂Zn (0.9 equivalents), leaving an excess of CH₂I₂. Charette and Brochu showed that ROZnEt did not form ROZnCH₂I or the corresponding cyclopropyl adduct in the presence of CH₂I₂. However, cyclopropanation of cinnamyl alcohol (120) under these conditions afforded the product 121 in 85% yield after 48 hours in the absence of any chiral promoter (Table 13, entry 1). This fact complicated the development of a highly enantioselective reaction and a strong ligand-acceleration was needed. Indeed, the starting material was completely consumed within 19 hours in the presence of the bis(sulfonamide) 49 (entry 2), and the rate acceleration was high enough to ensure that most of the product was formed via the ligand-accelerated pathway. Disappointingly, the enantioselectivity was only 3%. The use of the tetradentate ligand 58 caused a slightly slower reaction, and only the racemic product was obtained. The use of mono(sulfonamide) 48 gave an even slower reaction and a very low enantioselectivity was observed (3%, entry 4). Somewhat improved enantioselectivity was observed with the hydroxy-containing bis(sulfonamide) 53, which afforded the product with 12% ee (entry 5). Ligand 53 promoted the cyclopropanation reaction at a higher rate than the ligands 48 and 49. The use of the bis(sulfonamide) 49 under the conditions developed by Denmark et al. (Method B, vide supra) afforded a substantial rate acceleration and full conversion was reached within 90 minutes (entry 6). However, the enantioselectivity of the reaction was still very low (3% ee). Slightly improved enantioselectivity, 17% ee, was observed in the presence of bis(sulfonamide) 53, and an increase of the ligand loading from 10 to 20 mol% improved the enantiomeric excess of 121 to 27% ee (entries 7 and 8).

Table 13. Sulfonamide-mediated cyclopropanation of cinnamyl alcohol.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>A</td>
<td>1.8:1</td>
<td>48</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>49 (0.10)</td>
<td>A</td>
<td>1:0</td>
<td>19[^f]</td>
<td>3 (S,S)</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>58 (0.10)</td>
<td>A</td>
<td>30:1</td>
<td>48</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>48 (0.10)</td>
<td>A</td>
<td>8.4:1</td>
<td>48</td>
<td>3 (S,S)</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>53 (0.10)</td>
<td>A</td>
<td>1:0</td>
<td>24</td>
<td>12 (R,R)</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>49 (0.10)</td>
<td>B</td>
<td>-</td>
<td>1.5[^g]</td>
<td>3 (R,R)</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>53 (0.10)</td>
<td>B</td>
<td>-</td>
<td>1.5[^g]</td>
<td>17 (R,R)</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>53 (0.20)</td>
<td>B</td>
<td>-</td>
<td>1.0[^g]</td>
<td>27 (R,R)</td>
<td>80</td>
</tr>
</tbody>
</table>

[a] See Supplementary material. [b] The ratio between 121 and 120 after 24 h measured by GCMS. [c] Reaction time at –23 °C. [d] Measured by HPLC. [e] Isolated yield. [f] Not optimised. [g] Unoptimised reaction time at 0 °C.
3.3 Aluminium bis(sulfonamide) complexes as catalysts of [2+2]-
cycloadditions

Tamai et al. were the first to report on the catalytic asymmetric cycloaddition of
ketenes to aldehydes, giving β-lactones with moderate ee’s.\textsuperscript{195} The reaction was
recently improved by Nelson et al. who successfully applied our
bis(sulfonamide) 49 in the aluminium-catalysed ketene-aldehyde cycloaddition
reaction, affording β-lactones with high enantiomeric excess, ee 89-95%
(Scheme 36).\textsuperscript{177} The ketene was generated \textit{in situ} from acetyl bromide and
di(isopropyl)ethylamine, and the reaction tolerated a wide range of aldehydes,
e.g. conjugated ynamides and straight-chain, β-branched and alkoxy-substituted
aldehydes. The scope of the reaction was extended to include propionyl bromide
and other acid bromides as ketene precursors.\textsuperscript{178} The success of catalyst 125 in
the cycloaddition reaction was attributed to a ligand-defined geometric distortion
which markedly enhanced the Lewis acidity of 125.\textsuperscript{149} An X-ray structure of 125
showed a tetra-coordinated complex which adopted a trigonal monopyramidal
geometry with the methyl group and the sulfonamide nitrogens defining the
equatorial plane. It was suggested that the ligand-imposed coordination geometry
was responsible for the Lewis acidity observed, by providing an empty orbital
ideally disposed to accepting a Lewis basic ligand, despite the electron-rich
nature of the tetra-coordinated aluminium atom.\textsuperscript{149} The synthetic potential of
enantiopure β-lactones as versatile intermediates was shown in their elaboration

\textsuperscript{175} (a) Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano, S. \textit{J. Chem. Soc., Chem. Comm.}
\textsuperscript{177} (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. \textit{J. Am. Chem. Soc.} 1999, 121, 9742-9743. (b) For a High-
into propionate aldol adducts, allenes, β-amino acids, dihydropyrones, β-peptides and carboxylic acids.

3.4 Summary

The sulfonamides that are described in Chapter 2 have been evaluated as promoters of the titanium-mediated addition of diethylzinc to benzaldehyde and of the Simmons-Smith cyclopropanation of cinnamyl alcohol. The promoter structure was found to be important for both the enantioselection and the reaction rate of the addition of diethylzinc to benzaldehyde, although only moderate ee-values were observed. Highest enantioselectivity and reaction rate, 76% ee and full conversion within 15 minutes, was observed for bis(sulfonamides) substituted with bulky groups at the tertiary amino group. The reaction conditions have a large influence on the outcome of the reaction and a large excess of Ti(OiPr)₄ favours both the reaction rate and the enantioselcetion. The titanium-mediated addition of diethylzinc to benzaldehyde was also performed in the presence of bis(sulfonamide) together with various chiral additives such as amines and alcohols. However, the ee-values were only modest although large variations were observed. Only one of the tested bis(sulfonamides) induced chirality in the cyclopropanation of cinnamyl alcohol, 27% ee, but other sulfonamides should be tested. The versatility of the sulfonamides as ligands for asymmetric catalysis was shown by Nelson et al. in the keten aldehyde cycloaddition and the sulfonamides should be evaluated as promoters for other types of Lewis acid mediated processes such as Diels-Alder reactions.

4. Applications of $C_3$-Symmetric Ligands in Asymmetric Catalysis

We identified several areas where our $C_3$-symmetric tetra-amines could be successfully employed for asymmetric transformations. We expected that it would be possible to react the amines with phosphorus in the two oxidation states (III) and (V). Similar achiral compounds have found applications as Lewis and Brönstedt bases in organic synthesis. Furthermore, achiral tren analogues, tris(2-aminoethyl)amine, exhibit a rich coordination chemistry with a number of metal ions and we were aiming to explore this chemistry using our chiral tren-analogues, and to apply the resulting metal complexes in various catalytic applications.

4.1 $C_3$-symmetric proazaphosphatranes

The so-called azaphosphatranes, 126-128 and 134 (Figure 8), and the proazaphosphatranes, 129-133 make up an interesting class of compounds prepared from tetra-amines (Figure 8). The first examples of these compounds, 126 and 129, were prepared by Verkade and co-workers in 1989. The axial $N\rightarrow P$ transannular bond and the trigonal bipyramidal geometry around the pentacoordinated phosphorus atom are characteristic of the azaphosphatranes. The transannular bonding in the azaphosphatranes stabilises the protonated species and is responsible for the remarkable basicity and nucleophilicity observed in the proazaphosphatranes. The pK$_a$-values of the protonated azaphosphatranes 126, 127 and 128 in acetonitrile are 32.9, 33.6 and 33.5, respectively. This means that the proazaphosphatranes parallel the basicity of Schwesinger’s $P_2$ phosphazene bases, 135 (Figure 8, R = alkyl group). Proazaphosphatrane 129 is a stronger Lewis base than P(NMe$_2$)$_3$ due to the stabilising transannular bonding in the resulting Lewis acid/base adduct.
proazaphosphatranes 129-131 are applied as non-ionic Brönsted bases and Lewis bases in a number of transformations, e.g. as catalysts of the silylation of hindered alcohols, as promoters of the acylation of alcohols, as promoters of the nitroaldol reaction, as catalysts for the synthesis of β-hydroxy nitriles and as promoters for the allylation of aromatic aldehydes.

Both the Yamamoto and the Verkade groups recently described the syntheses of chiral proazaphosphatranes but no successful applications in asymmetric synthesis were reported. The seemingly more rigid proazaphosphatrane 133 was prepared in nine steps from (S)-proline, whereas proaza-phosphatrane 132 was prepared from (S)-phenylethylamine in four steps (Figure 8).

4.1.1 Results and discussion

It was surmised that a useful application of our C₃-symmetric tetra-amines would be found in the synthesis of chiral proazaphosphatranes, and that these compounds could serve as versatile Lewis or Brönstedt bases in asymmetric synthesis. Azaphosphatranes 136 and 137 were prepared analogously to 126 by the reaction of the tetra-amines 75 and 82, respectively, with one equivalent of PCl(NEt)₂ in CH₃CN (Scheme 37). The reaction with the isopropyl analogue 75 was followed by ¹H NMR spectroscopy of the product, which initially exhibited

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129, 130 and 131 were compared as promoters in some of the reactions and the yields of the resulting products in general descended in the order: 131 > 130 > 129. See reference 188.
a complex spectrum. However, the spectrum gradually became simpler as the C₃-symmetric azaphosphatrane 136 was formed, and complete formation was reached after about 12 hours. Steric effects probably had an important effect on the reaction rate of the ring closure to the azaphosphatrane; 126 needed only one hour, whereas 132H, 136 and 137 required about 12 hours for completion. A number of spectroscopic criteria indicated transannular bonding in 136 and 137; upfield ³¹P NMR chemical shifts of –6.5 and –7.9 ppm, respectively, as well as ¹JPH of 511 and 506 Hz, respectively, are known to be typical of pentacoordinated phosphorus. Furthermore, the presence of ³JPH of 12.4 and 12.3 Hz, respectively, of one of the diastereomeric protons, PNaxCHH, and the ²JPC observed between PNaxCH2 gave further support of transannulation in 136 and 137. Attempts to obtain crystals of 136 and 137 for determination of their solid state structures failed.

An upper limit of the pKₐ-value of 126 in DMSO was estimated to 26.8 and a strong base such as KOtBu (pKₐ of tBuOH in DMSO: 32.2) was needed for its deprotonation. However, the deprotonation of 136 to form the strong base 138 was problematic and the conditions successfully employed by Verkade and co-workers, i.e. two equivalents of KOtBu in CH₃CN, failed (Scheme 37). Attempts to deprotonate 136 under the conditions above, followed by treatment with BH₃, were unsuccessful, whereas in the presence of 18-crown-6, 25% of deprotonated 138 was observed by means of ¹H NMR spectroscopy. The best results were obtained when 2.2 equivalents of KOtBu in DMSO were used, affording 72% of 138 according to ¹H NMR. The use of 5.5 equivalents of KOtBu in DMSO did not improve the amount of azaphosphatrane 138 observed. It was not possible to separate the deprotonated base 138 from the remaining

201 A pKₐ-value of tBuOH of 28.6 in DMSO was used, see footnote 186a. However, in the referred work by Arnett a pKₐ-value of 29.4 is reported, see: Arnett, E. M.; Small, L. E. J. Am. Chem. Soc. 1977, 99, 808-816.
203 For the use of KOtBu/18c6, see: DiBiase, S. A.; Gokel, G. W. J. Org. Chem. 1978, 43, 447-452.
204 The ¹H NMR spectrum of 138 could partly be deduced from the spectrum of the mixture. The ¹JHH of the NCCH₂ groups decreased from 17.4 to 11.9 Hz and the corresponding protons underwent an upfield shift from 2.52 to 1.92 ppm. The ³¹P shift was 119.4. A similar ³¹P shift and decrease in ¹JHH was observed for 129, see footnote 184a.
205 It was of importance to use freshly dried DMSO and sublimated KOtBu, since lower amounts (40-60%) of 138 were obtained otherwise.
The use of stronger bases such as NaH, NaNH₂, MeLi or n-BuLi in THF afforded no deprotonated product. Alternative methods of synthesising 138 starting from 75 were unsuccessful. Treatment of 75 with three equivalents of BuLi followed by addition of PCl₃ did not produce 138, neither did the reaction between 75 and one equivalent of n-BuLi, followed by the addition of PCl(NEt₂)₂, P(NMe₂)₃ was not considered as an alternative, since Verkade and co-workers had shown that it reacted exceedingly slowly with tetra-arnines. Moreover, the methyl analogue 137 was difficult to deprotonate completely. As estimated by ¹H NMR, about 70% of 137 was deprotonated to form 139, when 137 was treated with KOtBu (2.6 equiv.) in CH₃CN. The use of five equivalents of KOtBu did not improve the degree of deprotonation and the use of one equivalent of n-BuLi in THF failed to deprotonate 137.

Our experimental results indicated that the proazaphosphatranes 138 and 139 are stronger bases than the achiral proazaphosphatrane 129 and the chiral proazaphosphatranes 132 and 133, since the conjugated acids of 129, 132 and 133 were completely deprotonated by an excess of KOtBu, whereas 136 and 137 were only partially deprotonated. In order to understand the difficulties associated with the deprotonation, DFT calculations were performed on the bases 138, 139, 129 and 133, and on their conjugated acids 136, 137, 126 and 134, respectively (Figure 8 and Scheme 37). The results showed that large structural changes occurred when the azaphosphatranes were deprotonated. One of the most notable changes was that the geometry around phosphorus changed from trigonal bipyramidal (NeqPNeq 119°) to approximately tetrahedral (NeqPNeq 104°). A similar but reversed change occurred for the axial nitrogen atom where the CH₂NaxCH₂ angle changed from 113° to 120° upon deprotonation. Another important feature was the increase of the PNax distances. The PNax bond lengths calculated for 126, 136 and 137 were 2.10, 2.04 and 2.06 Å, respectively, whereas the corresponding distances in the proazaphosphatranes 129, 138 and 139 were 3.49, 3.30 and 3.40 Å, respectively. The P-Nax distance in 129 was calculated to 3.36 Å: Nyulászi, L.; Veszprémi, T.; D’Sa, B. A.; Verkade, J. Inorg. Chem. 1996, 35, 6102-6107.

204 Extraction of the reaction mixture with n-pentane failed to separate the proazaphosphatrane 138 from 136 since the two compounds exhibited similar solubilities.
205 The amount of 139 decreased to 25-45% when CH₃CN and KOtBu were not freshly purified.
206 The Jₚ,H values of the NCH₃ groups decreased from 18.3 to 10.6 Hz and the corresponding protons underwent an upfield shift from 2.54 to 2.06 ppm. Compare footnote 204.
207 This distance was found to be 1.967 Å according to X-ray crystallography, see footnote 184a.
209 The P-Nax distance in 130 was determined to 3.293 Å by X-ray crystallography, see footnote 187.
slight deviations from sp$_2$-hybridisation were observed. The bond lengths and bond angles calculated in the azaphospha tranes and the proazaphosphatranes were found to be in agreement with those found in other calculations and with the available X-ray data. The structural changes that accompany the deprotonation of 134 to form 133 (Figure 8) were not as pronounced according to our calculations. The PN$_{ex}$ distance increased from 2.20 Å to merely 2.50 Å upon deprotonation. The phosphorus atom went from a planar to an approximately tetrahedral geometry, whereas the CH$_2$N$_{ex}$CH$_2$ angle was unaffected at 114°.

The calculations suggest that the conformational changes occurring upon deprotonation of the azaphosphatranes are responsible for the differences in acidity of these species. When the P-N$_{ex}$ distances increase during the deprotonation process, the methyl groups on the equatorial nitrogen atoms and the substituents on the neighbouring carbon atoms approach each other (Figure A). This gives rise to steric repulsion between these groups descending in the order 138>139>129 as reflected by the values calculated for the “twist” of the molecules. Thus, 136 is less prone to undergo deprotonation than 126 since the steric repulsion between the N-methyl and the isopropyl groups in 138 is much larger than the corresponding repulsion between the N-methyl groups and the hydrogen atoms in 129 (Figure A). The calculations show that the energy required to deprotonate 136 is 29.6 kJ/mol higher than that required to deprotonate 137, which in turn is 38.6 kJ/mol higher than that required for 126. Calculations on the chiral azaphosphatrane 134 and proazaphosphatrane 133

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212 Brandt, P.; Lake, F.; Moberg, C. Unpublished results.
show that deprotonation of 134 and 126 require similar energy.

Chiral nucleophilic catalysts for the acylation of secondary alcohols commonly contain nitrogen or phosphorus as their nucleophilic atom. Verkade and co-workers employed proazaphosphatrane 129 (Figure 8) as a nucleophilic catalyst for the silylation of deactivated and sterically hindered alcohols. We decided to test 139 as a nucleophilic silylation catalyst in a desymmetrization process (Scheme 38). Some preliminary attempts were made to protect one of the enantiotopic hydroxy groups of 1,2-cis-cyclohexanediol 140 selectively, as the corresponding silyl ether 141, by using the mixture of 139 and 137 that was obtained after the incomplete deprotonation attempt (Scheme 37). We used a protocol similar to that developed by Verkade and co-workers, i.e. 0.2 equivalents of 139 in the presence of 1.0 equivalents of TBDMSCI and 1.1 equivalents of NEt3. A survey of different solvents and reaction conditions revealed that the highest conversion of 140 to 141, 17\%, was obtained in THF or CH2Cl2 at room temperature. However, we were not able to determine the ee of 141. It should be noted that these experiments were performed before the calculations were made, and the calculations clearly show that NEt3 cannot function as a stoichiometric base, a fact that would explain the low conversion of 140 into 141 under the conditions employed.

Scheme 38

213 Brandt, P.; Lake, F.; Moberg, C. Unpublished results. The chiral 132 and 132H+ are expected to have acid-base properties similar to those of 129 and 126.


4.2 C₃-Symmetric phosphoramides

Chiral phosphoramides are useful Lewis bases in asymmetric synthesis. They are known to catalyse the asymmetric allylation of aldehydes, the asymmetric ring-opening of epoxides by chloride, and the asymmetric aldol reaction. Verkade and co-workers recently reported on the preparation of the C₃-symmetric phosphoramide. We surmised that a C₃-symmetric phosphoramide such as 143 could be prepared from the tetra-amine and that the resulting phosphoramide might be an even stronger Lewis base than those reported so far, due to donation of electron density from the ideally placed axial nitrogen atom. However, there is a risk that a successful catalytic cycle is hampered by the conformational changes that might occur when the geometry around the phosphorus atom changes from trigonal bipyramidal to tetrahedral (see discussion above on the structural changes that occur when 136 and 137 is deprotonated).

The reaction of 75 with three equivalents of n-BuLi, followed by the addition of POCl₃, produced oligomeric material only. Attempts with NEt₃ in 1,2-dichloroethane and slow addition of POCl₃ and 75 were more promising, although we were not able to obtain spectroscopic data, and work is still in progress within our group.

\[
\text{N-NHMe + POCl₃ → NEt₃ + \text{PN}}_3\text{N-NR}_3\text{O}_3\text{R}
\]

Scheme 39

\[
\text{R = (S)-Phenylethyl}
\]

223 A possible way of synthesising 138 might be to reduce 143. For the reduction of phosphine oxides, see: Naumann, K.; Zon, G.; Mislow, K. J. Am. Chem. Soc. 1969, 91, 7012-7023.
4.3 $C_3$-Symmetric titanium and zirconium complexes

The coordination chemistry of tren, tris(2-aminoethyl)amine (144 $R=H$, Figure 9), and its derivatives have been studied extensively. The alkyl-, trialkylsilyl-, and pentafluorophenyl derivatives of the tripodal tetra-amine ligand coordinate to a wide range of transition metals and main group elements. The ligands often coordinate to the metal in a tetradentate fashion, forming rigid trigonal bipyramidal complexes or, in the absence of an apical ligand, monopyramidal complexes (145). For example, complexes of the pentafluorophenyl derivative (144 $R=C_6F_5$) with tungsten and molybdenum as well as rhenium and vanadium in various oxidation states have been prepared. Moreover, the trialkylsilyl derivatives (144 $R=SiR_3$) have been shown to coordinate to titanium (III and IV), vanadium (III and IV), chromium (III), manganese(III) and iron(III), as well as molybdenum(IV) and cerium (III and IV).

There are only a few reports on chiral tren analogues. The amines 146229 and 147229 (Figure 10) are mentioned above in conjunction with the preparation of the proazaphosphatranes 132 and 133 (Figure 8). A more favourable transfer of chirality might be expected for metal complexes of tetra-amines substituted at the methylene positions rather than at the nitrogen atoms, due to formation of more rigid structures with the chirality residing in the chelate. Examples of chiral tridentate nitrogen-based ligands are 148229 and the macrocyclic ligand 149231 (Figure 10). The zirconium(IV) complex of 148 affords moderate to good

![Figure 9. The tetradentate ligand tren, 144, and its pyramidal coordination, 145.](image_url)

enantioselection in the stoichiometric and catalytic alkylation of aryl aldehydes, and the manganese complex of 149 exhibits modest enantioselection in the oxidation of styrene.

![Figure 10. Examples of $C_3$-symmetric tetra- and triamines.](image)

We aimed at coordinating our $C_3$-symmetric tetra-amines (75 and 82, Scheme 40) and tris(sulfonamides) (64 and 68, Scheme 41) to various Lewis acidic metals such as titanium(IV) and aluminium(III), and at using the complexes in Lewis acid catalysed asymmetric transformations. The achiral alkyl and trialkylsilyl analogues of 144 (Figure 9) had been complexed to titanium(IV), boron(III) and aluminium(III) as well as to zirconium(IV) and hafnium(IV), whereas reports on the corresponding metal complexes of tris(sulfonamides) are rare. The metal complexes of our chiral tris(sulfonamide) derivatives 64 and 68 (Scheme 41), containing the strongly electron-withdrawing sulfonyl groups, were expected to be stronger Lewis acids than the more electron-rich complexes of the $N$-methyl analogues 75 and 82 (Scheme 40). It might be necessary to transform the tetravalent metal complexes of the $N$-methyl ligands 75 and 82 to the corresponding cationic complexes to increase the Lewis acidity, although the aluminium complex of the achiral methyl analogue of 144 coordinates Lewis bases.

### 4.3.1 Results and discussion

We first pursued the synthesis of the titanium complexes from the $N$-methylated compounds. Attempts with Ti(NEt$_2$)$_4$ in a transamination process with 75 in THF at 60 °C only returned the starting material. We then turned our attention to the salt metathesis reaction of the lithium amides of 75 and 82 with TiCl$_4$(THF)$_2$.

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Ligands 75 and 82 were treated with three equivalents of n-BuLi in pentane at –50 °C, and the solutions were stirred at room temperature for two hours. TiCl4(THF)_2 was added to the lithium amides at –60 °C and the mixtures were stirred at room temperature for 48 hours, resulting in deep red solutions. The LiCl formed was removed by centrifugation and the titanium complexes 150 and 151 were isolated as highly moisture-sensitive red solids after evaporation of the solvent. Both compounds exhibited 1H and 13C NMR spectra consistent with the expected threefold symmetry. Numerous attempts were made to grow crystals of 150 and 151 from a number of solvent combinations, but the crystals obtained were too small to be suitable for X-ray crystallographic determination. We did not succeed to form the corresponding zirconium complex from the lithium amide of 75 and ZrCl4.

We then explored the possibility of forming titanium and zirconium complexes of the tris(sulfonamide) ligands 65 and 68 (Scheme 41). However, no titanium or zirconium complexes were formed under similar conditions to that described above, i.e. treating the tris(sulfonamide) ligand with three equivalents of n-BuLi in toluene, followed by the addition of TiCl4(THF)_2 or ZrCl4. The use of the weaker base NEt3 in CH2Cl2 in combination with TiCl4(THF)_2 or ZrCl4 was also unsuccessful. However, a clean and rapid formation of zirconium complex 152 took place when 64 was treated with an equimolar amount of Zr(NMe2)4 in toluene (Scheme 41).234 The Ts-analogue 68 required heating at 50 °C for formation of the zirconium complex 153. The reactivity observed in the transamination reactions of the sulfonamide derivatives seemed to parallel the acidity of the sulfonamide protons. A similar trend in reactivity was observed with the corresponding titanium and aluminium complexes prepared by Licini and co-workers. The reaction of 64 with AlMe3 or Ti(NEt2)4 to form 154 and 155 was much faster than the corresponding reaction of 67 with the same metal sources to form 156 and 157 (Scheme 41).
Attempts were made to employ the \( C_3 \)-symmetric metal complexes in Lewis acid catalysed transformations. The \textit{in situ} prepared complex of \( \text{TiCl}_4 \) and 67 was used in the addition of TMSN\(_3\) to cyclohexene oxide. Full conversion was achieved within 24 hours but only racemic material was observed. Moreover, Licini and co-workers applied the titanium complex 157 and the aluminium complexes 154 and 156 in the Diels-Alder reaction of cyclopentadiene with 3-(1-oxo-2-propenyl)-2-oxazolidinone. However, only racemic material was observed when catalytic amounts (0.1 equivalents) of the complexes were present, whereas the endo product was obtained with 20% ee when an excess (1.4 equivalents) of complex 154 was present.\footnote{Licini, G. et al. Unpublished results.} These disappointing results prompted us to search for \( C_3 \)-symmetric ligands which would induce higher selectivity. We assumed that the transfer of chirality from the methine substituent to the \( N \)-substituent in trigonal pyramidal complexes such as 152-157 would be hampered due to the flexible nature of the sulfonyl group. A phenyl derivative might serve this purpose better since a restricted rotation about the \( N\text{-C}_\text{aryl} \) bond would be expected. Work is in progress both in our group and in the Licini group to prepare \( N \)-aryl analogues such as the \( N \)-phenyl and the more electron-withdrawing \( N \)-pentafluorophenyl derivatives. Another plausible explanation of the low selectivity observed is that the cavity at the apical position is too small to allow complexation of a Lewis base. Moreover, the results obtained with complex 154 are in stark contrast to the results obtained for the aluminium complex of the \( C_2 \)-symmetric bis(sulfonamide), see complex 125 (Scheme 36).
4.4 Summary

Tetra-amines 75 and 82 were applied in the syntheses of C$_3$-symmetric azaphosphatranes 136 and 137 (Scheme 37). These weak acids were only partially deprotonated by the strong base KOTBu in DMSO, indicating that the pK$_a$-values of 136 and 137 in DMSO are about 32. The surprisingly strong basicity of the proazaphosphatranes 138 and 139 was believed to be due to steric effects, as suggested by DFT calculations. The conformational changes that occur upon deprotonation are responsible for the repulsion between the N-methyl groups and the neighbouring methine substituents.

Attempts to prepare C$_3$-symmetric phosphoramides are an ongoing research area in our group. These compounds are expected to be strong Lewis bases due to donation of electron density from the ideally placed apical nitrogen atom. Interesting applications might be the asymmetric allylation of aldehydes and the asymmetric ring-opening of meso-epoxides.

Titanium(IV) and zirconium(IV) complexes were prepared from our C$_3$-symmetric ligands. The N-methyl analogues required deprotonation by BuLi, followed by the addition of TiCl$_4$(THF)$_2$, whereas the N-sulfonyl derivatives reacted in transamination processes with M(NR$_2$)$_4$. The use of the complexes in various Lewis acid mediated applications has so far only resulted in low enantioselectivities. The preparation of more effective ligands is in progress.
5. Concluding remarks

A modular approach to chiral enantiopure nitrogen-containing ligands was developed. Mono-, bis- and tris(sulfonamides) were prepared by reacting sulfonyl-activated aziridines with a wide range of primary amines and ammonia. The sulfonamides can be elaborated further into their corresponding primary and secondary amines.

The bis(sulfonamides) are useful ligands in asymmetric catalysis, as shown by us and others. For example, they promote the addition of diethylzinc to benzaldehyde and the cyclopropanation of cinnamyl alcohol with moderate enantioselection.

The $C_3$-symmetric tetra-amines were reacted with phosphorus compounds in oxidation states III and V. The strong basicity of the resulting proazaphosphatranes was rationalised by the use of DFT-calculations.

Titanium(IV) and zirconium(IV) complexes were prepared from the $C_3$-symmetrical tetra-amines and tris(sulfonamides).

The use of the ligands in various Lewis acid mediated processes are in progress in the group.
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In memoriam Rune Lake.
Supplementary material

For general procedures, see paper I. NMR spectra were recorded in CDCl$_3$ unless otherwise stated.

**Bis(sulfonamide) 52**

Aziridine 26 was prepared from (S)-phenylalaninol according to the method described for aziridine 1a in paper I. The solvent was carefully evaporated after the work-up procedure until about 5 mL remained, and the resulting solution was used immediately in the subsequent ring-opening reaction. Complete evaporation of the solvent should be avoided due to the risk of polymerisation of the aziridine. GC-MS analysis showed that the purity of aziridine 26 was > 95%.

Bis(sulfonamide) 52 was prepared according to the method described for compounds 19-24 in paper I starting from (S)-phenylethylamine (0.81 mmol, 103 µL) and 26 (assumed to be about 1.8 mmol). Purification by MPLC (gradient 0-60% EtOAc in hexanes) gave a sticky semi-solid in 47% yield (0.38 mmol, 0.25 g). [α]$^D_{20}$ = -69.0 (c = 0.58, MeOH). $R_f = 0.45$ (20% EtOAc in hexanes). NMR spectra were recorded in CDCl$_3$.

1H NMR (500 MHz): δ 1.06 (d, $J$ = 6.8 Hz, 3H, CH$_3$), 2.36 (dd, $J$ = 13.9 and 9.9 Hz, 2H, NCH$_2$), 2.44 (dd, $J$ = 13.9 and 4.1 Hz, 2H, NCH$_2$), 2.63 (dd, $J$ = 13.8 and 8.1 Hz, 2H, C$_{benzylic}$H$_3$), 2.92 (dd, $J$ = 13.8 and 4.8 Hz, 2H, C$_{benzylic}$H$_3$), 3.83-3.87 (m, 2H, C$_H$NHTf), 4.10 (q, $J$ = 6.8 Hz, 1H, C$_{benzylic}$H), 4.95 (br s, 2H, NHTf), 7.06 (d, $J$ = 6.9 Hz, 4H, H$_{aromatic}$), 7.21-7.25 (m, 2H, H$_{aromatic}$), 7.27-7.31 (m, 7H, H$_{aromatic}$), 7.34-7.37 (m, 2H, H$_{aromatic}$); 13C NMR (125.8 MHz): δ 9.5, 40.3, 53.4, 54.3, 56.1, 119.4 (q, $J_{CF} = 327$ Hz), 127.3, 127.8, 128.6, 128.7, 128.9, 129.3, 136.0, 141.6.

**Tris(sulfonamide) 81**

A 100 mL flask was charged with NaH (35.8 mmol, 1.43 g, 60% dispersion in oil) and the NaH was washed with pentane (3×10 mL). DMF (20 mL) was added and the suspension was cooled to 0 °C. Compound 68 (5.44 mmol, 4.00 g) was dissolved in DMF (25+8 mL) in a 50 mL flask and the solution was added dropwise via a canula to the NaH suspension during 30 min. The suspension was stirred for 10 min at this temperature before the dropwise addition of methyl iodide (32.7 mmol, 2.03 mL, 6.00 equiv.) during 10 min. The suspension was stirred over-night in the warming cooling bath and then quenched by careful addition of water (40 mL). CH$_2$Cl$_2$ (50 mL) was added, the phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (4×50 mL). The combined organic phases were washed with brine, dried over MgSO$_4$, filtered, and concentrated to give a 94% yield of a white sticky solid (5.09 mmol, 3.95 g).
which was pure enough to use directly in the deprotection step. An analytical sample was obtained by recrystallisation from 80% EtOAc in hexanes which yielded colourless crystals in 90% yield (4.92 mmol, 3.83 g). M. p.: 172-174 °C. \([\alpha]^2_{20} = -32.1 \ (c = 0.70, \text{CH}_2\text{Cl}_2)\). \(R_I = 0.35 \ (40\% \text{ EtOAc in hexanes})\). \(^1\text{H} \text{ NMR} \ (500 \text{ MHz}): \delta \ 0.85 \ (d, \ J = 6.9 \text{ Hz}, 9\text{H}, \text{iPr CH}_3), 0.97 \ (d, \ J = 6.7 \text{ Hz}, 9\text{H}, \text{iPr CH}_3), 1.79 \ (\text{octett, } J = 6.6 \text{ Hz}, 3\text{H}, \text{CH(CH}_2)_3), 2.07 \ (dd, \ J = 13.6 \text{ and } 6.7 \text{ Hz}, 3\text{H}, \text{NCH}_2\text{H}), 2.41 \ (s, 9\text{H}, \text{p-tolCH}_3), 2.70 \ (s, 9\text{H}, \text{NCH}_3), 2.95 \ (dd, \ J = 13.6 \text{ and } 6.7 \text{ Hz}, 3\text{H}, \text{NCH}_2\text{H}), 3.75 \ (\text{app q, } J = 6.6 \text{ Hz}, 3\text{H}, \text{CHNSO}_2), 7.27 \ (d, \ J = 8.2 \text{ Hz}, 6\text{H}, \text{H aromatic}), 7.70 \ (d, \ J = 8.2 \text{ Hz}, 6\text{H}, \text{H aromatic}); \ ^{13}\text{C} \text{ NMR} \ (125.8 \text{ MHz}): \delta 19.8, 20.6, 21.7, 30.2, 55.2, 60.0, 127.5, 129.6, 137.3, 143.2; \text{Anal. Calcd for } \text{C}_{39}\text{H}_{60}\text{N}_4\text{O}_6\text{S}_3 \ (777.12): \text{C, 60.28; H, 7.78; N, 7.21. Found: C, 60.36; H, 7.81; N, 7.17.}

**Tris(sulfonamide) 80**

Compound 80 was prepared analogously to compound 81. Trissulfonamide 67 (2.32 mmol, 1.51 g) gave trimethylated 80 as a white solid in 99% crude yield (2.30 mmol, 1.59 g). The solid was pure enough to be used directly in the subsequent deprotection step. An analytical sample was obtained by flash chromatography (40% EtOAc in hexanes) which yielded a white solid in 91% yield (2.10 mmol, 1.45 g). M. p.: 57-59 °C. \([\alpha]^2_{20} = -55.3 \ (c = 0.90, \text{CHCl}_3)\). \(R_I = 0.35 \ (30\% \text{ EtOAc in hexanes})\). \(^1\text{H} \text{ NMR} \ (500 \text{ MHz}): \delta 0.84 \ (d, \ J = 6.6 \text{ Hz}, 9\text{H}, \text{CHC}_3), 2.37 \ (dd, \ J = 12.9 \text{ and } 8.4 \text{ Hz}, 3\text{H}, \text{NCH}_2\text{H}), 2.42 \ (s, 9\text{H}, \text{p-tolCH}_3), 2.51 \ (dd, \ J = 13.0 \text{ and } 5.8 \text{ Hz}, 3\text{H}, \text{NCH}_2\text{H}), 2.72 \ (s, 9\text{H}, \text{NCH}_3), 4.00 \ (\text{app sextt, } J = 6.7 \text{ Hz}, 3\text{H}, \text{CHNSO}_2), 7.30 \ (d, \ J = 8.1 \text{ Hz}, 6\text{H}, \text{H aromatic}), 7.67 \ (d, \ J = 8.2 \text{ Hz}, 6\text{H}, \text{H aromatic}); \ ^{13}\text{C} \text{ NMR} \ (125.8 \text{ MHz}): \delta 15.1, 21.7, 28.4, 51.0, 59.2, 127.2, 129.8, 137.1, 143.3; \text{Anal. Calcd for } \text{C}_{33}\text{H}_{48}\text{N}_4\text{O}_6\text{S}_3 \ (692.96): \text{C, 57.20; H, 6.98; N, 8.09. Found: C, 57.39; H, 7.10; N, 8.02.}

**Tetra-amine 75**

A 250 mL flask was charged with the tris(sulfonamide) 81 (8.58 mmol, 6.67 g), phenol (82.8 mmol, 7.80 g), and HBr (109 mL, 48% in water). The mixture was refluxed at 155 °C for 24 h. Water (150 mL) and NaOH (s) were carefully added to the cooled dark red mixture until pH ≈ 1. The aqueous phase was washed with EtOAc (7×80 mL), the pH of the aqueous phase was increased to > 13 with NaOH (s), and aqueous was extracted with CH$_2$Cl$_2$ (5×80 mL). The combined organic phases were dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo leaving a red oil which was purified by bulb-to-bulb distillation (150-155 °C/0.5 mmHg) giving a slightly yellow oil in 72% yield (6.17 mmol, 1.94 g). For spectral data see footnote 59.
Tetra-amine 82

Tetra-amine 82 was prepared analogously to compound 75. Tris(sulfonamide) 80 (6.26 mmol, 4.34 g) gave tetra-amine 82 in 60% yield (3.75 mmol, 0.87 g). Distillation (110 °C/0.05 mmHg) gave the product as a colourless oil which partially solidified upon standing. [α]D20 = 155 (c = 0.26, CHCl3). 1H NMR (500 MHz): δ 0.95 (d, J = 6.2 Hz, 9H, CH3), 1.15 (br s, 3H, NHMe), 2.19 (dd, J = 12.9 and 3.2 Hz, 3H, NCH2), 2.33 (dd, J = 12.9 and 10.0 Hz, 3H, NCH), 2.41 (s, 9H, NCH3), 2.58-2.62 (m, 3H, CH); 13C NMR (125.8 MHz): δ 19.5, 35.4, 53.4, 63.2. Anal. Calcd for C12H30N4 (230.39): C, 62.56; H, 13.12; N, 24.32. Found: C, 62.43; H, 12.95; N, 24.17.

Tetra-amine 76

Tetra-amine 76 was prepared analogously to compound 75. Tris(sulfonamide) 68 (2.04 mmol, 1.50 g) gave tetra-amine 76 in 57% yield (1.71 mmol, 0.32 g). Distillation (170-180 °C/0.1 mmHg) gave the product as a yellow viscous oil. [α]D20 = 179 (c = 0.72, MeOH). 1H NMR (400 MHz): δ 0.90 (d, J = 6.7 Hz, 9H, CH3), 1.50 (octett, J = 6.6 Hz, 3H, CH(CH3)2), 1.89 (br s, 6H, NH2), 2.26-2.29 (m, 6H, NCH2), 2.67-2.72 (m, 3H, NCH); 13C NMR (100.6 MHz): δ 18.4, 19.3, 32.3, 53.5, 59.6; Anal. Calcd for C15H36N4 (272.47): C, 66.12; H, 13.32; N, 20.56. Found: C, 65.93; H, 13.28; N, 20.42.

Tetra-amine 83

Tetra-amine 83 was prepared analogously to tetra-amine 75. Tris(sulfonamide) 67 (5.38 mmol, 3.50 g) gave tetra-amine 83 in 38% yield (2.04 mmol, 0.39 g). Distillation (105-110 °C/0.13 mmHg) gave the product as a clear oil which partly solidified upon standing. [α]D20 = 183 (c = 0.73, MeOH). 1H NMR (500 MHz): δ 0.98 (d, J = 6.3 Hz, 9H, CH3), 1.57 (br s, 6H, NH2), 2.14-2.24 (m, 6H, CH2), 3.04-3.09 (m, 3H, CH); 13C NMR (125.8 MHz): δ 24.4, 43.9, 64.1.

Mono(sulfonamide) 72α

Aziridine 33 (0.426 mmol, 102 mg) was added in two portions to a solution of ammonia in methanol (6.8 mmol, 3.4 mL, 2.0 M) under a nitrogen atmosphere. The mixture was heated at 50 °C for 41 h in a sealed flask. Flash chromatography (gradient 5-10% MeOH in CH2Cl2, 4 cm column) yielded 77 mg (0.30 mmol, 71%) of 72 as a white solid, Rf = 0.26 (5% MeOH in CH2Cl2).
For an experimental procedure, see Paper I. M. p.: 189-192 °C (slightly yellow solid). $[\alpha]_{D}^{20} = -23.3$ (c = 0.40, MeOH). $R_f = 0.10$ (100% EtOAc in hexanes). $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 0.83 (d, $J = 6.7$ Hz, 3H, CH$_3$), 0.84 (d, $J = 6.7$ Hz, 3H, CH$_3$), 1.63 (octett, $J = 6.4$ Hz, 1H, $C(\text{CH}_3)_2$), 2.63 (dd, $J = 12.3$ and 7.1 Hz, 1H, NCH$_2$H), 7.08 (br s, 3H, NHTf and NH$_2$); $^{13}$C NMR (125.8 MHz, DMSO-d$_6$): $\delta$ 18.4, 18.7, 31.0, 42.5, 58.1, 122.3 ($q$, $J_{CF} = 327$ Hz, CF$_3$).

**Typical procedure for the cyclopropanation of cinnamyl alcohol. Method A.**

Bis(sulfonamide) 49 (0.090 mmol, 48.8 mg) and cinnamyl alcohol (0.902 mmol, 121.0 mg) were dissolved in CH$_2$Cl$_2$ (9.0 mL) in a 25 mL flask under an argon atmosphere. Et$_2$Zn (1.80 mmol, 1.80 mL, 1.0 M in hexanes) was added dropwise (gas evolution) at –23 °C, followed by CH$_2$I$_2$ (2.70 mmol, 218 µL), also added dropwise. Aliquots were removed with a syringe and quenched with 2 M NaOH, the aqueous phase was extracted with CH$_2$Cl$_2$, the combined organic phases were dried with MgSO$_4$ and filtered, and the volatiles were removed in vacuo. The reaction mixture was quenched at –23 °C and was worked up as described above. The resulting oil was purified by flash chromatography (gradient 10-40% EtOAc in hexanes) giving 121 as a colourless oil in 69% yield (0.62 mmol, 93 mg). The ee was determined by HPLC (Chiralcel OD-H, 5% 2-propanol in hexane, 1.0 mL/min, $t_R$ for 2S,3S-isomer: 11.0 min, $t_R$ for: 2R,3R-isomer 13.6 min): 3% (2S,3S).

**Method B.**

Bis(sulfonamide) 53 (0.069 mmol, 40.2 mg) and cinnamyl alcohol 120 (0.343 mmol, 46.0 mg) were dissolved in CH$_2$Cl$_2$ (4.6 mL) in a 10 mL flask under an argon atmosphere (Flask A). Et$_2$Zn (0.41 mmol, 0.41 mL, 1.0 M in hexanes) was added dropwise (gas evolution) at 0 °C and the clear solution was stirred for 30 min. I$_2$ (0.686 mmol, 0.175 g) was dissolved in CH$_2$Cl$_2$ (8.0 mL) under an argon atmosphere (Flask B). Et$_2$Zn (0.69 mmol, 0.69 mL, 1.0 M in hexanes) was added dropwise and the milky suspension was stirred for 7 min., whereafter CH$_2$I$_2$ (0.69 mmol, 55 µL) was added dropwise. The content of Flask A was transferred via a canula to Flask B. The reaction mixture was quenched after 1 h and purified as described above. 80% yield (0.27 mmol, 41 mg), 27% ee (2R,3R).