Asymmetric 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides, Thiocarbonyl Ylides, and Nitrones

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Doctoral thesis
Abstract

This thesis describes the development of methods for the preparation of chiral non-racemic substituted pyrrolidines, tetrahydrothiophenes, and isoxazolidines. This has been accomplished by using asymmetric intermolecular 1,3-dipolar cycloaddition reactions of azomethine ylides, thiocarbonyl ylides and nitrones, respectively, with various dipolarophiles.

The asymmetry in these reactions was introduced using two different approaches: a diastereoselective approach (i.e. using dipolarophiles linked to chiral auxiliaries and/or using enantiomerically pure ylides) and an enantioselective approach (i.e. the reacting partners are achiral and the reaction is catalysed by an enantiomerically pure catalyst). Thus, using the former approach, 3,4-disubstituted pyrrolidines and tetrahydrothiophenes were obtained in high diastereofacial selectivities (up to 90:10 dr). Using the latter approach, bicyclic fused isoxazolidines were obtained in up to 93% ee.

Some of the cycloadducts obtained from these reactions were transformed into enantiopure known precursors of some biologically active compounds \{[(3R,4R)-4-(hydroxymethyl)pyrrolidin-3-ol and octahydrocyclopenta[c]pyrro-3a-ylmethylamine dihydrobromide\} and an active stereoisomer of a sex pheromone component of a pine sawfly [the acetate of (2S,3R,7R,9S)-3,7,9-trimethyl-2-tridecanol]. The synthetic utility of these 1,3-dipolar cycloaddition reactions was also demonstrated by the syntheses of some new enantiopure organocatalysts which were found to be useful in some 1,3-dipolar cycloaddition reactions of nitrones with \(\alpha,\beta\)-unsaturated aldehydes.
List of Publications


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<td>Bu</td>
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<tr>
<td>ee</td>
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<td>The enantiomer of compound X</td>
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<td>Ethyl</td>
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<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
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<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
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<tr>
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1. Introduction

1.1 The 1,3-dipolar cycloaddition reaction

The [3 + 2] 1,3-dipolar cycloaddition is a reaction where two organic compounds, a dipolarophile, 1, and a 1,3-dipole (or ylide), 2, combine to form a five membered heterocycle 3 (Figure 1.1). The reaction is related to the Diels-Alder reaction where a diene and a dienophile form a six membered ring. From simple starting materials, the 1,3-dipolar cycloaddition reaction can furnish very complex heterocycles, containing multiple stereogenic centres. Therefore this reaction is often used as a key step in the syntheses of many natural products and pharmaceuticals. After its discovery in 1888, with diazoacetate ester as the 1,3-dipole, various other 1,3-dipoles have been used in this type of reaction.\(^1\)

![Figure 1.1](image)

Figure 1.1.

The asymmetric variants of this reaction using either chiral auxiliaries or chiral catalysts are relatively new research fields and have attracted a continually growing interest. Although progress has been made in these fields, resulting in valuable tools for the syntheses of enantiomerically pure heterocycles, there are still some unexplored areas which need to be investigated, or already existing methods that need to be improved. This is the reason why I began to study asymmetric 1,3-dipolar cycloaddition reactions.

1.2 The 1,3-dipole/ylide

The 1,3-dipole, also known as an ylide, bears a positive and a negative charge distributed over three atoms and has \(4\pi\) electrons. The most common atoms incorporated in the 1,3-dipole are nitrogen, carbon, oxygen or sulfur. Representative examples of some 1,3-dipoles are shown in Figure 1.2, but other types of 1,3-dipoles also exist.\(^2\) These are divided into two groups, the allyl anion type which has a bent structure and the propargyl/allenyl anion type with a linear structure as shown in Figure 1.2.\(^3\) Each of these dipoles has four resonance structures as exemplified for the nitrone and the diazoalkane in Figure 1.2. The ylide can, depending on the nature of the 1,3-dipole exist in an equilibrium between an \(E\)-form and a \(Z\)-form. This can have consequences for the diastereoselectivity in reactions with dipolarophiles. This topic is brought up to discussion in section 1.4.

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Figure 1.2. Examples of 1,3-dipoles.

1.3 The dipolarophile

The dipolarophile in a 1,3-dipolar cycloaddition is a reactive alkene moiety containing 2\(\pi\) electrons. Thus, depending on which dipole that is present, \(\alpha,\beta\)-unsaturated aldehydes, ketones, and esters, allylic alcohols, allylic halides, vinylic ethers and alkynes are examples of dipolarophiles that react readily (dipolarophiles 4-7, Figure 1.3). It must be noted, however, that other 2\(\pi\)-moieties such as carbonyls and imines also can undergo cycloaddition with dipoles. The alkene moiety can be mono-, di-, tri- or even tetrasubstituted (only monosubstituted ones are shown here). However, mostly due to steric factors, tri- and tetrasubstituted ones often display very low reactivity in reactions with dipoles.

Figure 1.3. Examples of dipolarophiles in 1,3-dipolar cycloaddition reactions.
It must be pointed out that dipolarophiles incorporating two conjugated double bonds such as dipolarophile 4 can exist in two different main conformations, \(s\)-\textit{cis} and \(s\)-\textit{trans}, respectively (Figure 1.3), where the \(s\)-\textit{cis}/\(s\)-\textit{trans} descriptor refers to the single bond connecting the two double bonds. Such \(s\)-\textit{cis}/\(s\)-\textit{trans}-isomerism can have a major impact on the outcome of an asymmetric 1,3-dipolar cycloaddition reaction and is discussed more in section 1.6.

1.4 Mechanistic aspects

The 1,3-dipolar cycloaddition reaction of a 1,3-dipole with a dipolarophile involves the 4\(\pi\) electrons of the dipole/ylide and the 2\(\pi\) electrons of the dipolarophile. The reaction mostly proceeds in a concerted manner, which means that all bonds are created simultaneously, but not necessarily to the same extent at a certain time. Consequently, the stereochemistry of the dipolarophile is conserved in the final product. This is exemplified in Scheme 1.1 where \(trans\)-2-butene 8 reacts with the hypothetical dipole 2 furnishing exclusively \(trans\)-9. Starting from the cis isomer of 8 will thus yield the cis isomer of 9.

![Scheme 1.1.](image)

If, on the other hand, the reaction proceeds via a two step mechanism, the stereochemistry of the starting dipolarophile is not necessarily conserved throughout the whole reaction. This is exemplified in Scheme 1.2, where \(trans\)-2-butene 8 reacts with the dipole 2 in a two step fashion furnishing the diastereomer \(cis\)-9 via isomerisation of the starting dipolarophile.

![Scheme 1.2.](image)

Depending on the nature of the dipole and the dipolarophile, the 1,3-dipolar cycloaddition reaction is controlled either by a LUMO(dipolarophile)-HOMO(dipole)- or a LUMO(dipole)-HOMO(dipolarophile) interaction but in
some cases a combination of both interactions is involved. An example of a LUMO(dipolarophile)-HOMO(dipole) controlled reaction is depicted in Scheme 1.3. The approach of the dipole (e.g. 10) to the dipolarophile (e.g. 11) can occur in an endo or exo mode resulting in two diastereomeric endo/exo cycloadducts, endo-12 and exo-12, respectively. An overview over both these approaches is depicted in Scheme 1.3 where the endo approach is stabilised by small secondary π-orbital interactions, contributing to the endo/exo selectivity of the reaction. However, other factors such as steric ones can have a major influence on this endo/exo selectivity and can often override this stabilising effect.

\[ \text{Scheme 1.3. Example of an endo- and an exo approach of a LUMO(dipolarophile)-HOMO(dipole) controlled reaction. Primary orbital interactions are indicated with double headed arrows and secondary orbital interactions with dotted lines.} \]

Moreover, depending on the substitution pattern of the ylide, this can exist in an equilibrium between a Z-form and an E-form. Reaction of each of these isomers with a dipolarophile, gives rise to diastereomeric cycloadducts, provided that the approach of these (endo or exo) is the same. This is exemplified in Scheme 1.4 where ylides Z-13 and E-13 react with the dipolarophile 4 via an exo approach furnishing diastereomeric cycloadducts trans-14 and cis-14 respectively. The cis/trans nomenclature for the description of the stereochemistry of the cycloadducts is thus often used instead of the exo/endo one to avoid confusion when ylides existing as an equilibrating mixture of Z/E isomers are used.

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Scheme 1.4. Reaction of two Z/E isomers of ylide 13 with dipolarophile 4 via an exo-approach.

In addition to the issues concerning diastereoselectivity discussed above, regioselectivity related ones can also arise. Thus, when both the ylide and the dipolarophile are nonsymmetric, regioisomeric adducts can be formed. This is exemplified in Scheme 1.5, where the hypothetical ylide 2 reacts in two different modes with dipolarophile 4, giving rise to the regioisomeric cycloadducts 15a and 15b. Nitrones are examples of nonsymmetric ylides, which upon reaction with nonsymmetric dipolarophiles sometimes furnish two regioisomeric cycloadducts. Depending on electronic factors and the substitution pattern of the ylide and the dipolarophile, both modes of addition of the ylide to the dipolarophile can occur.4

Scheme 1.5. Two alternative approaches of a hypothetical ylide 2 to dipolarophile 4 giving rise to regioisomers 15a and 15b.

1.5 Enantiomerically pure compounds

Many of the organic compounds present in our environment are chiral, that is, their respective mirror images are not identical. A compound and its nonsuperimposable mirror image are called a pair of enantiomers. Almost all the chemical and physical properties of enantiomers are the same. However, when put in a chiral non-racemic environment, such as in biological tissues, the effects of the enantiomers may differ considerably. Many examples of differences in biological activity of enantiomers have been found and the most well known one is probably that of the sedative drug neurosedyn (thalidomide in the US). Thus, the (R)-enantiomer is an efficient sedative, while the (S)-enantiomer (Figure 1.4) is a potent human teratogen (causing fetal abnormalities).

![Figure 1.4. The two enantiomers of thalidomide.](image)

The knowledge that enantiomers can have different effects has given rise to a demand to find methods to obtain the chiral drugs in enantiomerically pure forms. This can be accomplished using different approaches:

1) Resolution of a racemic mixture, that is, separation of two enantiomers through enzymatic or chemical methods.

2) Diastereoselective synthesis using chiral auxiliaries derived from enantiomerically pure starting materials.

3) Enantioselective synthesis from achiral starting materials mediated by a chiral non-racemic catalyst.

The two latter approaches will be considered in this thesis.

1.6 Diastereoselective 1,3-dipolar cycloaddition reactions using chiral auxiliaries, principle and origin of $\pi$-facial selectivity

Dipolarophiles of type 16 (Figure 1.5) exist, as mentioned in section 1.3, in an equilibrium between two different main conformations, $s$-cis and $s$-trans, respectively. Furthermore, the alkene moiety of dipolarophiles has two faces, a $si$-face and a $re$-face respectively, onto which dipoles can be added. This is exemplified in Figure 1.5 by the acrylic acid 16, which upon reaction in the $s$-cis or $s$-trans conformation with a dipole from the $si$-face (attack from the top face and bottom face respectively) gives the same $\pi$-facial selectivity furnishing the
same compound 17. Thus, in order to favour approach of the dipole to only one face (i.e. the *si-* or the *re-*face) of the dipolarophile, both the geometry of the dipolarophile and the mode of addition of the dipole must be controlled. This is the principle in asymmetric synthesis and can be accomplished by introducing chiral auxiliaries (described below) or chiral catalysts (described in section 1.8).

![Figure 1.5. Approach of a dipole to the *si-*face of acrylic acid 16 adopting either an *s-cis* or an *s-trans* conformation.](image)

When an achiral compound, for example acrylic acid 16 (Scheme 1.6), is linked to an enantiomerically pure auxiliary exemplified by 18, one obtains a new enantiomerically pure derivative, the dipolarophile 19, which is expected to react in a diastereoselective manner (i.e. diastereomers are formed in unequal amounts) with a reagent such as the hypothetical cyclic dipole 20. Because one of the two faces of the alkene moiety in the dipolarophile 19 is sterically shielded (i.e. the bottom face) from attack, whereas the other one is not, the attack of the dipole occurs mainly from the top face leading to a diastereoselective reaction (Scheme 1.6). Thus, this reaction pathway leads to the major diastereomeric cycloadduct 21 whereas attack from the bottom face leads to the minor one 22. This preference for one of the π-faces of the chiral dipolarophile is often referred to as diastereofacial selectivity or π-facial selectivity and should not be confused with the endo/exo diastereoselectivity described in section 1.4. It must be remembered that dipolarophiles of type 19 exist in an equilibrium between an *s-cis* and an *s-trans* conformation (*s-cis* the reactive conformer here) as described above. Attack onto the *s-trans* conformer of 19 by the dipole 20 from the least sterically hindered side would lead to the opposite diastereofacial selectivity (i.e. preference for diastereomer 22).
Scheme 1.6. Example of a general diastereofacial selective 1,3-dipolar cycloaddition reaction using a chiral auxiliary.

Because diastereomers often have different properties such as polarity and melting point, various standard techniques can be applied to separate these. After separation of the major and the minor diastereomer (i.e. 21 and 22 respectively), the chiral auxiliary of the individual major diastereomer can be removed, furnishing the desired enantiomerically pure compound 23 and the recovered chiral auxiliary 18. Because commercially available chiral auxiliaries are often expensive, mild and efficient methods are needed in order to attach the chiral auxiliary to the substrate and to remove it from the product. Of course it is essential that no epimerisation of the newly created stereocentre(s) occurs in the product in the removal step.

1.7 Doubly diastereoselective 1,3-dipolar cycloaddition reactions using chiral auxiliaries, matched versus mismatched case

This approach is similar to the one described in section 1.6 with the exception that both reacting partners are chiral and non-racemic. Compared with the singly diastereoselective reactions described in section 1.6, one expects a doubly diastereoselective reaction to proceed in higher diastereofacial selectivity,
provided that a matched pair of enantiomers are reacted with each other. In contrast, a reaction between a mismatched couple of reactants will proceed with lower diastereofacial selectivity. Thus, it is important to choose the appropriate absolute configuration of the substrate and the reactant. Figure 1.6 gives you an example of both a matched and a mismatched case in which the same dipolarophile as in Scheme 1.6 (i.e. 19), in an exo-mode, reacts with the chiral dipole 24 (matched case) and the enantiomer ent-24 (mismatched case) respectively. Thus, in the matched case in Figure 1.6, attack of the dipole 24 from the bottom face, results in unfavourable interactions between the two substituents of the dipole and the dipolarophile. Therefore attack occurs preferentially from the top face, where such interactions are absent. In the mismatched case, however, attack of the enantiomer ent-24 from both sides of the π-bond of the dipolarophile 19, results in unfavourable interactions. Thus, compared with the matched case, a lower degree of discrimination between the two π-faces of the dipolarophile by the dipole is expected.

![Matched case and Mismatched case](image)

**Figure 1.6.** Example of a general doubly diastereoselective 1,3-dipolar cycloaddition reaction including a matched case and a mismatched case respectively.

1.8 Enantioselective 1,3-dipolar cycloaddition reactions using chiral catalysts, principle and origin of π-facial selectivity

Enantioselective 1,3-dipolar cycloaddition reactions have become a rapidly growing field of research in organic chemistry. The reason for this is that this approach allows the chirality in the product to be introduced in the presence of only a catalytic amount of a chiral non-racemic derivative (i.e. a catalyst). Moreover, in contrast to the diastereoselective reactions involving attachment and removal of a chiral auxiliary, no such additional synthetic steps are necessarily required.
When a catalyst is coordinating to the dipole or the dipolarophile, the frontier molecular orbitals (FMO) of the dipole and/or the dipolarophile may change resulting in either an increase or a decrease in the energy gap ($\Delta E$) between the LUMO and the HOMO of the dipole and dipolarophile, respectively, or vice versa.\(^5\) A lowered energy gap will result in a faster reaction compared with the uncatalysed one. An example of a LUMO(dipolarophile)-HOMO(dipole) controlled reaction is illustrated in Figure 1.7. Thus, when the catalyst (e.g. a Lewis acid) coordinates to the carbonyl oxygen of the dipolarophile (e.g. 4) the LUMO energy of the dipolarophile decreases, which leads to a smaller energy gap between the LUMO of the dipolarophile and the HOMO of the dipole resulting in an increased reaction rate compared with the uncatalysed reaction, that is, $\Delta E^* < \Delta E$. It must be noted that coordination of the catalyst to the dipole also results in a faster reaction provided that the reaction is HOMO(dipolarophile)-LUMO(dipole) controlled. After dissociation of the catalyst from the product it is ready for another catalytic cycle (Figure 1.7).

![Figure 1.7](image_url)

**Figure 1.7.** The change in the LUMO (and the HOMO) energy of the dipolarophile 4 when a catalyst is coordinating to the carbonyl oxygen of the former, resulting in an increased reaction rate upon reaction with dipole 2, compared with the uncatalysed reaction.

It is obvious that if the catalyst is chiral and non-racemic, one \( \pi \)-face of the dipolarophile may be more shielded than the other one resulting in a discrimination of one of the \( \pi \)-faces by the dipole (Figure 1.8). Thus an enantioselective reaction is expected to occur giving rise to unequal amounts of two enantiomeric products. As pointed out in section 1.3 and 1.6, dipolarophiles of the types shown in Figure 1.8, can exist in both an \( s\text{-}cis \) and an \( s\text{-}trans \) conformation and this isomerism can have a major influence on the \( \pi \)-facial selectivity.

The catalyst is frequently a chiral non-racemic Lewis acid but can also be a non-metal containing organic compound. The catalyst attaches to the dipole or the dipolarophile either through chelation or through covalent bonds. Furthermore, depending on the nature of the dipolarophile (and the dipole) chelation of a Lewis acid to the dipolarophile (and the dipole) can occur through single or multiple points of attachments. Examples of mono- and bidentate binding of a chiral Lewis acid to a dipolarophile are depicted in Figure 1.8. This includes also an example of attachment of a non-metal containing catalyst to a dipolarophile (case C). Compared to case A, in which the dipolarophile contains only one Lewis basic site, B describes a case, where the dipolarophile contains two Lewis basic oxygens, which are expected to contribute to the formation of a more stable chelated complex with the Lewis acid. Thus, in order to favour binding of a catalyst to the dipolarophile rather than to the dipole, a dipolarophile containing at least two Lewis basic sites can be used.

Figure 1.8. Examples of different modes of attachment of a chiral catalyst to a dipolarophile. A: Monodentate chelation of a chiral Lewis acid. B: Bidentate chelation of a chiral Lewis acid. C: Covalently bonded non-metal containing catalyst. Due to steric shielding arising from the substituent of the chiral catalysts, attack of a dipole occurs from the bottom face (i.e. the \textit{re}-face).
2. 1,3-Dipolar cycloaddition reactions of azomethine ylides

2.1 General aspects

Azomethine ylides have the general structure 29 as depicted in Scheme 2.1 and belong to the allyl anion type having four resonance structures as described in section 1.2 (only one shown in Scheme 2.1). They are in general very reactive short-lived species, and thus they have to be prepared from a stable precursor in situ. Examples of ways to generate such species are acid catalysed decomposition of \( N \)-alkyl-\( N \)-methoxymethyl-\( N \)-(trimethylsilyl)methylamines 26, photolysis of aziridines 27 and proton abstraction from imine derivatives 28 (Scheme 2.1).[^6]

![Scheme 2.1. Examples of generation of azomethine ylides 29 from stable precursors. Reaction with an electron-deficient dipolarophile (i.e. 30) furnishes a pyrrolidine derivative 31.](image)

In the presence of a dipolarophile such as an \( \alpha,\beta \)-unsaturated acyl derivative (i.e. 30, Scheme 2.1) reaction readily occurs, furnishing a substituted pyrrolidine 31 containing up to four new stereogenic centres. The reactions of azomethine ylides with dipolarophiles are in general HOMO(dipole)-LUMO(dipolarophile) controlled.

2.2 Diastereoselective reactions using chiral auxiliaries

Since Padwa and co-workers performed the first diastereofacial selective 1,3-dipolar cycloaddition reaction in 1985 using a chiral non-racemic azomethine ylide,[^7] a number of other chiral azomethine ylides have been found to undergo


cycloaddition with dipolarophiles in varying degree of \( \pi \)-facial selectivity.\(^8\) The chiral ylides can be prepared from amines such as phenylethylamine, phenylglycinol and ephedrine, which are all commercially available in both enantiomeric forms. When using such types of ylides (i.e. 33), one disadvantage is that the original chiral centre in the starting amine (i.e. 32) is normally destroyed upon removal of the \( N \)-substituent of the cycloadduct (Scheme 2.2). Thus, the chiral amine, amine 32 is, via 33, 34, transformed into achiral 36 (and pyrrolidine derivative 35). Therefore, such reactions should not be considered as chiral auxiliary induced asymmetric cycloadditions. It must be noted, however, that there are successful examples where chiral auxiliaries have been attached to azomethine ylides and removed from the cycloadducts in a non-destructive manner.\(^8\)

![Scheme 2.2. Example of a general diastereofacial selective reaction using a chiral ylide.](image)

A number of asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides, where the chirality instead resides in the dipolarophile are described in the literature.\(^8,9\) Such chiral non-racemic dipolarophiles can be obtained via linkage of an enantiomerically pure chiral auxiliary to an achiral dipolarophile (Scheme 2.3). Thus, chiral dipolarophiles such as \( N \)-enoylderivatives (e.g. 41 and 42) are conveniently prepared from the corresponding acid chloride 38 (usually obtained from the acid 37 after treatment with \( \text{SOCl}_2 \)) and chiral auxiliaries such as camphorsultam 39\(^10\) and oxazolidinone derivatives 40\(^11\) after deprotonation of these with a base such as \( \text{MeMgBr} \) (Scheme 2.3).

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Scheme 2.3. Attachment of two different chiral auxiliaries to acyl chloride 38.

(1S)-(−)-Camphorsultam 39 (and the enantiomer) and oxazolidinone derivatives 40 are examples of commercially available chiral auxiliaries, which have frequently been used in various asymmetric reactions. A number of other chiral auxiliaries derived from the chiral pool are also available. For the former auxiliaries, mild and efficient methods are available for their removal from the product. Typical reagents for this include LiAlH₄, LiOH, alkoxides and Grignard reagents. This furnishes the corresponding primary alcohol, acid, ester and tertiary alcohol respectively, along with the recovered chiral auxiliary. When reacted with cyclic achiral or chiral azomethine ylides, dipolarophiles attached to camphorsultam give high asymmetric induction. High diastereofacial selectivities have also been reported when azomethine ylides attached to camphorsultam were reacted with various achiral dipolarophiles. Camphorsultam has also been used as a chiral auxiliary in other types of 1,3-dipolar cycloadditions.

Compared with camphorsultam, chiral non-racemic oxazolidinones have not been as extensively used as chiral auxiliaries in 1,3-dipolar cycloaddition reactions, but there are some examples in the literature involving achiral azomethine ylides\textsuperscript{17,18} and other types of 1,3-dipoles.\textsuperscript{19}

When the work described in paper I was started, no general and efficient 1,3-dipolar cycloaddition approach for the preparation of enantiopure trans-3,4-disubstituted pyrrolidines existed.\textsuperscript{20} Therefore, the potential of using the above mentioned chiral auxiliaries as well as other auxiliaries in such reactions was investigated (Scheme 2.4).

![Scheme 2.4. 1,3-Dipolar cycloaddition reaction of azomethine ylide 43\# with dipolarophile 44 attached to various chiral auxiliaries a-e.](image)

Thus, a number of well known chiral auxiliaries a-e were screened in the reaction of the azomethine ylide 43\# with cinnamoyl derivative 44. Various oxazolidinones (a, b, d), camphorsultam (c), and a sugarderivative (e) (Scheme 2.4) were used as chiral auxiliaries (H-Xc). Trifluoroacetic acid (TFA) catalysed azomethine ylide generation\textsuperscript{21} from compound 43 in the presence of one of the

\begin{thebibliography}{99}
\bibitem{20} At the time of manuscript preparation, a work similar to this was published where some oxazolidinone derived dipolarophiles had been screened in the above reaction with similar results, see ref. 17.
\end{thebibliography}
dipolarophiles 44 (a-e) gave in general a high yield of the separable diastereomeric cycloadducts 45 and 46. However, the diastereofacial selectivity obtained was low to moderate using any of these auxiliaries a-e (Table 2.1). The best result was obtained when camphorsultam c was used as the auxiliary (dr up to 74:26, entry 6). The solvent and the temperature had a certain effect on the diastereofacial selectivity (Table 2.1).

X-ray crystallography established the absolute configuration of the major diastereomer 45b as 3S,4R. Transformation of this compound to the corresponding ethyl ester (–)-3S,4R-47 (Scheme 2.4) allowed the assignment of the same 3S,4R absolute configuration of the other major diastereomeric cycloadducts 45a, 45c and 45d after transformation of the latter to the same ester (–)-3S,4R-47. However, auxiliary e gave a small preference for the 3R,4S diastereomer 46e.

Table 2.1. 1,3-Dipolar cycloaddition of ylide 43# with dipolarophile 44 attached to various chiral auxiliaries a-e, resulting in the diastereomeric cycloadducts 45 and 46.

<table>
<thead>
<tr>
<th>Entry</th>
<th>HXc</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>Dr 45:46</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>CH₂Cl₂</td>
<td>−78</td>
<td>10</td>
<td>58:42</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>quant.</td>
<td>57:43</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>Toluene</td>
<td>+20</td>
<td>quant.</td>
<td>70:30</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>CH₂Cl₂</td>
<td>−20</td>
<td>55</td>
<td>59:41</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>CH₂Cl₂</td>
<td>+20</td>
<td>quant.</td>
<td>64:36</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>CH₂Cl₂</td>
<td>+40</td>
<td>quant.</td>
<td>74:26</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>Toluene</td>
<td>+20</td>
<td>quant.</td>
<td>66:34</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>CH₂Cl₂</td>
<td>−20</td>
<td>quant.</td>
<td>54:46</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>Toluene</td>
<td>+20</td>
<td>quant.</td>
<td>63:37</td>
</tr>
<tr>
<td>10</td>
<td>j</td>
<td>CH₂Cl₂</td>
<td>−20</td>
<td>quant.</td>
<td>48:52</td>
</tr>
</tbody>
</table>
Remarkably, reaction of 43# with both dipolarophile 44a and 44b having opposite absolute configurations at the oxazolidinone moiety, gave diastereomer 45 with the 3S,4R configuration as the major adduct. This means that the reaction pathways for these reactions probably proceed through different intermediates, where the two dipolarophiles 44a and 44b adopt two different major conformations in the reaction with the dipole 43#.

It is known that N-enoyl-oxazolidinones, in the absence of Lewis acids, prefer a low energy s-cis conformation (conformers A and D, Figure 2.1). The s-trans conformers B and C are both significantly destabilised due to unfavourable interactions between the alkene- and the oxazolidinone moiety. Among the two lowest energy conformers A and D, the one having the two carbonyl oxygens trans-disposed (Z-conformer D, Figure 2.1) is the most stable one. This is due to an unfavourable dipole alignment in the U-conformer A. Thus, it is possible that the dipolarophile 44b mainly reacts via the lowest energy s-cis Z-conformer whereas 44a mainly reacts via the s-cis U-conformer A with ylide 43#. Attack of the ylide 43# from the least sterically hindered side of the \( \pi \)-bond of both of these will furnish the same 3S,4R stereoisomer 45 which also was that sense of \( \pi \)-facial selectivity experimentally observed.

Molecular modelling (CS Chem3D Pro\textsuperscript{TM} 4.0) indicated that the energy difference between the U- and the Z-conformer of dipolarophiles 44a and 44b was 3.5 and 5.5 kcal/mol respectively (Figure 2.2, this figure was incorrectly depicted in paper I). Thus, due to this energy difference for the two dipolarophiles it is possible that 44a reacts mainly via the high energy U-conformation, whereas 44b reacts mainly via the low energy Z-conformation (Figure 2.2). There are also examples in the literature in which N-enoylderivatives attached to auxiliary b (Scheme 2.5) react, in the absence of bidentate chelating Lewis acids, with the same sense of \( \pi \)-facial selectivity as 44b with reagents other than 1,3-dipoles.\textsuperscript{23}

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\[\text{Figure 2.1.}\]


[23] See e.g. Schneider, C.; Reese, O. Synthesis 2000, 1689-1694.
Figure 2.2. Proposed reaction pathways via two different conformers of 44a and 44b. It is assumed that $\Delta G^*_{U}$ and $\Delta G^*_{Z}$ are approximately equal for both reactions of ylide 43# with 44a and 44b and that $\Delta G^*_{U} < \Delta G^*_{Z}$ for the individual reactions.

The sense of $\pi$-facial selectivity observed when reacting ylide 43# with the camphorsultam derived dipolarophile 44c can be explained by the model depicted in Figure 2.3. It has been proposed that $N$-enoyl camphorsultams, in the absence of Lewis acids, react with 1,3-dipoles such as nitrile oxides in an $s$-cis conformation, where the sulfone oxygens of the sultam moiety and the carbonyl oxygen are trans-located in relation to the C-N amide bond. Attack of the dipole then occurs on the opposite side to that occupied by the axially oriented sulfone oxygen (O$\alpha$) due to unfavourable interactions between the incoming dipole and the axially oriented sulfone oxygen (O$\alpha$, Figure 2.3). Thus, in accordance with the experimentally observed $\pi$-facial selectivity in the reaction of 44c with ylide 43#, the major pathway is probably the one depicted in Figure 2.3.

Figure 2.3. Proposed major reaction pathway when reacting ylide 43# with dipolarophile 44c.

2.3 Doubly diastereoselective reactions using chiral auxiliaries

Although there are successful examples of 1,3-dipolar cycloadditions of chiral azomethine ylides with achiral dipolarophiles resulting in high π-facial selectivities, improvement in the selectivity can often be achieved if both the azomethine ylide and the dipolarophile are chiral and non-racemic. The singly diastereoselective 1,3-dipolar cycloaddition reactions described in section 2.2 proceeded in low to moderate diastereofacial selectivities. Therefore it was tempting to apply a doubly diastereoselective approach in this reaction.

Paper II describes the efforts to increase the diastereofacial selectivity in the reaction depicted in Scheme 2.4 by using the phenylethylamine derived chiral non-racemic azomethine ylides (Scheme 2.5). Doubly diastereoselective reactions with a broader set of chiral dipolarophiles are included in paper III and IV.


Scheme 2.5. 1,3-Dipolar cycloadditions of either the achiral ylide 43# or the chiral ones, 48# and 49#, with dipolarophile 44 attached to various chiral auxiliaries a-c.

Table 2.2. Singly and doubly diastereoselective 1,3-Dipolar cycloadditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>HXc</th>
<th>Solvent</th>
<th>Ylide</th>
<th>Products major (minor)</th>
<th>Dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Toluene</td>
<td>43#</td>
<td>45 (46)</td>
<td>70:30</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>Toluene</td>
<td>48#</td>
<td>50 (51)</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Toluene</td>
<td>49#</td>
<td>52 (53)</td>
<td>66:34</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>CH$_2$Cl$_2$</td>
<td>43#</td>
<td>45 (46)</td>
<td>64:36</td>
</tr>
<tr>
<td>5</td>
<td>b</td>
<td>CH$_2$Cl$_2$</td>
<td>48#</td>
<td>50 (51)</td>
<td>75:25</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>CH$_2$Cl$_2$</td>
<td>49#</td>
<td>52 (53)</td>
<td>57:43</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>CH$_2$Cl$_2$</td>
<td>43#</td>
<td>45 (46)</td>
<td>74:26</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>CH$_2$Cl$_2$</td>
<td>48#</td>
<td>50 (51)</td>
<td>78:22</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>CH$_2$Cl$_2$</td>
<td>49#</td>
<td>52 (53)</td>
<td>71:29</td>
</tr>
</tbody>
</table>
Table 2.2 shows that the diastereofacial selectivity is mainly controlled by the chiral dipolarophiles rather than by the chiral azomethine ylides. The mismatched cases (i.e. reactions with the ylide 49#) gave slightly lower diastereofacial selectivities compared to the reactions involving the achiral azomethine ylide 43#. In the matched cases (i.e. reactions with the ylide 48#), the highest diastereofacial selectivities were obtained.

The doubly diastereoselective reactions of the chiral ylides 48# and 49# with the dipolarophile 54 were also investigated (Scheme 2.6). Although being a more electron-rich dipolarophile compared with the cinnamoyl derivatives 44 and thus, it should be less reactive than the latter ones, I hoped that this vinyl ether containing dipolarophile (i.e. 54) should be reactive enough in reactions with the ylides 48# and 49# to provide a pyrrolidine containing an oxygen-functionality in position 4 of the pyrrolidine ring.

![Scheme 2.6. 1,3-Dipolar cycloaddition of either the chiral ylide 48# or 49# with dipolarophile 54.](image)

**Table 2.3.** Diastereofacial selectivity as a function of solvent polarity [$E_r(30)$] in the reaction of either the ylide 48# (matched case) or 49# (mismatched case) with dipolarophile 54.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>$E_r(30)$ [kcal mol$^{-1}$]</th>
<th>Dr matched (mismatched)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heptane</td>
<td>31.1</td>
<td>63:37 (65:35)</td>
</tr>
<tr>
<td>2</td>
<td>Cyclohexane</td>
<td>30.9</td>
<td>64:36 (62:38)</td>
</tr>
<tr>
<td>3</td>
<td>CCl$_4$</td>
<td>32.4</td>
<td>61:39 (50:50)</td>
</tr>
<tr>
<td>4</td>
<td>1,4-Dioxane</td>
<td>36.0</td>
<td>79:21 (61:39)</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>33.9</td>
<td>70:30 (52:48)</td>
</tr>
<tr>
<td>6</td>
<td>Diethyl ether</td>
<td>34.5</td>
<td>70:30 (54:46)</td>
</tr>
<tr>
<td>7</td>
<td>CHCl$_3$</td>
<td>39.1</td>
<td>74:26 (69:31)</td>
</tr>
<tr>
<td>8</td>
<td>EtOAc</td>
<td>38.1</td>
<td>78:22 (58:42)</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>37.4</td>
<td>75:25 (58:42)</td>
</tr>
<tr>
<td>10</td>
<td>CH$_2$Cl$_2$</td>
<td>40.7</td>
<td>83:17 (71:29)</td>
</tr>
<tr>
<td>11</td>
<td>Acetone</td>
<td>42.2</td>
<td>85:15 (73:27)</td>
</tr>
<tr>
<td>12</td>
<td>CH$_3$CN</td>
<td>45.6</td>
<td>88:12 (75:25)</td>
</tr>
<tr>
<td>13</td>
<td>DMF</td>
<td>43.2</td>
<td>87:13 (71:29)</td>
</tr>
<tr>
<td>14</td>
<td>DMSO</td>
<td>45.1</td>
<td>86:14 (76:24)</td>
</tr>
</tbody>
</table>
Indeed, under optimised conditions, reaction of ylide 48# with dipolarophile 54 (Scheme 2.6) furnished cycloadduct 55 in up to 88:12 dr and in a good yield in most cases (up to 93% combined isolated yield of 55 and 56). The π-facial selectivity of this reaction was found to be strongly dependent on the solvent polarity because, when screening various solvents, selectivities in the matched cases (i.e. reactions with the ylide 48#) were in the range of 1.6:1 to 7:1 dr (Table 2.3). In general, the mismatched cases (i.e. reactions with the ylide 49#) gave slightly lower diastereofacial selectivities.

![Diagram of the reaction of ylide 48# with dipolarophile 54](image)

Figure 2.4. Log (dr) as a function of solvent polarity $E_{T}(30)$ in the reaction of the ylide 48# with dipolarophile 54.
A linear relationship between the logarithm of the diastereomeric ratio [log (dr)] and the solvent polarity as expressed by the $E_T(30)$ parameter was observed (Figure 2.4). Such linear relationships have been observed by others in Diels-Alder reactions with camphorsultam derivatives as chiral auxiliaries.

When reacted with acyclic dipolarophiles, the influence from the chiral azomethine ylides on the $\pi$-facial selectivity, is obviously small (Table 2.2). However, these ylides are derived from one of the enantiomers of phenylethylamine which is a cheap, commercially available starting material. Thus, in order to prepare enantiomerically pure trans-3,4-disubstituted pyrrolidines, the doubly diastereoselective approach presented above should be useful for obtaining maximum diastereofacial selectivity.

Based on the results discussed above and with the moderate diastereofacial selectivities obtained in mind, I hoped that the chiral azomethine ylides 48# and 49# would react with cyclic dipolarophiles in higher diastereofacial selectivities. Because, there were no examples in the literature of 1,3-dipolar cycloaddition reactions of azomethine ylides with monocyclic five- and six-membered $\alpha,\beta$-unsaturated acyl derivatives attached to chiral auxiliaries, this was investigated.

The camphorsultam auxiliary, which when attached to acyclic dipolarophiles, had so far given the highest diastereofacial selectivities, was attached to cyclopent-1-enecarboxylic acid chloride and 2,5-dihydrothiophene-1-carboxylic acid chloride. This furnished dipolarophiles 59 and 60, respectively (Scheme 2.7). When these were reacted with either the chiral azomethine ylide 48# or the enantiomer 49#, a major influence from the chiral ylides was observed (Figure 2.5).


Scheme 2.7. 1,3-Dipolar cycloaddition of either the achiral azomethine ylide 43# or the chiral ones 48# and 49#, with the cyclic dipolarophiles 59 or 60.

Figure 2.5. Diastereomeric ratio (dr) as a function of solvent and ylide used (43#, 48# or 49#) in the reaction with dipolarophile 59. Bars down mean an excess of the cycloadduct 61 or 65. Bars up mean an excess of the cycloadduct 62, 64 or 66.

For example, when the ylide 48# was reacted with dipolarophile 59 in CH₂Cl₂, cycloadduct 65 was obtained in 82:18 dr (65:66). When the enantiomer 49# was reacted with the same dipolarophile under the same conditions, the π-facial selectivity was reversed (dr 32:68, 63:64). The solvent also had a great influence on the diastereofacial selectivity in all individual reactions involving the chiral ylides 48# and 49# (Figure 2.5). However, reactions with the achiral ylide 43# gave a low selectivity in all solvents investigated. The sulphur-containing dipolarophile 60 reacted with the ylides 49# in approximately the same diastereofacial selectivity as that observed for dipolarophile 59, to give a mixture of the major cycloadduct 68 and the minor one 67 in a good yield.
The diastereomeric cycloadducts 61/62, 63/64, 65/66 and 67/68 could be separated, either by column chromatography or by recrystallisation to give the individual, pure diastereomers. One of these (compound 64) was transformed to an enantiopure known precursor of an antibacterial compound (section 2.5). This allowed the assignment of the absolute configurations of the newly created stereocentres of compound 64 by optical rotation measurements. The configurations of the other major and minor diastereomeric cycloadducts could then be established by the optical rotation values of suitable compounds obtained after some transformations.

In contrast to their reactions with acyclic dipolarophiles, the chirality of the ylides 48# and 49# obviously had a relatively high effect on the diastereofacial selectivity when these were reacted with chiral cyclic dipolarophiles 59 and 60. For comparison, I also wanted to investigate whether such a high influence also could be obtained when those chiral ylides were reacted with achiral cyclic dipolarophiles. Thus, when reacted with either compound 69 or 70 in CH₂Cl₂, ylide 49# furnished two diastereomeric cycloadducts (71 and 72) or (73 and 74), respectively, both in a 64:36 diastereomeric ratio (Scheme 2.8). Although only a moderate selectivity was achieved, the diastereomeric cycloadducts 71/72 and 73/74 were obtained in excellent yields and were readily separated by column chromatography. Therefore, the singly diastereoselective approach depicted in Scheme 2.8, should be useful for the preparation of enantiopure bicyclic fused pyrrolidines.

Scheme 2.8. Reaction of the chiral azomethine ylide 49# with two different achiral cyclic dipolarophiles 69 and 70.
2.4 Enantioselective reactions using chiral catalysts

Examples of enantioselective metal-catalysed 1,3-dipolar cycloaddition reactions of azomethine ylides with dipolarophiles are few and all of these employ azomethine ylides of type 75 (Scheme 2.9) which are stabilised by an adjacent electron acceptor. The Lewis acid catalysed reactions of such stabilised azomethine ylides generally proceed via an intermediate in which the ylide coordinates to the catalyst in a bidentate fashion (Scheme 2.9). Cycloaddition with an electron-deficient dipolarophile of type 76 furnishes a highly functionalised pyrrolidine 77.

![Scheme 2.9. Coordination of a chiral Lewis acid to a stabilised azomethine ylide 75 and subsequent cycloaddition with an electron-deficient dipolarophile 76.](image)

The first reported enantioselective reaction of this type involved chiral non-racemic ephedrine ligands in conjunction with MnBr₂ or CoCl₂ as catalysts in the reaction of α-amino ester derived azomethine ylides with methyl acrylate.30 Thus, up to 96% ee was obtained for the cycloadducts. Other catalysts such as chiral phosphane ligands in conjunction with Ag(I) salts have also been used in such types of reactions.31,32 Very recently, Zinc(II)-bisoxazolines were used as efficient catalysts in the same type of reaction, which furnished highly substituted proline derivatives in good diastereo- and enantioselectivities.33

It was tempting to investigate whether such an enantioselective approach also could be employed in reactions with non-stabilised azomethine ylides (Scheme 2.10). Because reactions of most non-stabilised azomethine ylides with electron-deficient dipolarophiles are HOMO(dipole)-LUMO(dipolarophile) controlled, coordination of a Lewis acid to the dipolarophile might result in an increased reaction rate, whereas coordination to the azomethine ylide might result in a decreased one. Thus, in order to obtain a catalytic process, the Lewis acid should coordinate to the dipolarophile rather than to the ylide. A bidentate chelation of the Lewis acid to the dipolarophile is expected to give a stronger complex than a monodentate binding.34 This can be accomplished by using dipolarophiles containing two Lewis basic carbonyl oxygens, that is, using dipolarophile 79 instead of 78 (Scheme 2.10). The key issue was, whether a bidentate binding to

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the dipolarophile was enough favoured over binding to the ylide 43#. Chiral non-racemic bis-oxazolines and bis-oxazolinylpyridines (e.g. 81 and 82) are well known chiral ligands, which in conjunction with various metals form chiral Lewis acids suitable for use in enantioselective transformations,\textsuperscript{35} such as Diels-Alder reactions,\textsuperscript{36} cyclopropanation reactions,\textsuperscript{37} 1,3-dipolar cycloaddition reactions of nitrones\textsuperscript{34} and stabilised azomethine ylides as have been described above.\textsuperscript{33}

Scheme 2.10. Attempt to introduce chiral catalysts 81 and 82 in the reaction of the unstabilised azomethine ylide 43# with either dipolarophile 78 or 79.

With the aim of developing a general method for the enantioselective preparation of trans-3,4-disubstituted pyrrolidines, the chiral non-racemic bis-oxazoline 81 and bis-oxazolinylpyridine 82 were tested as catalysts in the reaction of the unstabilised azomethine ylide 43# with two different dipolarophiles 78 and 79 (Scheme 2.10). Because, in the absence of a Lewis acid, the azomethine ylide 43# reacts very fast with electron-deficient dipolarophiles, a stoichiometric amount of chiral Lewis acid was used. Thus, to a pre-formed complex between one of the dipolarophiles 78 or 79 and one of the catalysts 81 or 82 was added ylide precursor 43. Acid catalysed (TFA) generation of the corresponding ylide followed by cycloaddition resulted in the formation of cycloadduct 80, unfortunately in a very low ee (up to 8% ee using catalyst 82 and dipolarophile 78).

On addition of the ylide precursor 43, the initially formed complex between the catalyst and the dipolarophile was probably decomposed, which could explain the disappointing results obtained. Thus the ylide precursor 43 is probably a stronger Lewis base than the carbonyl oxygens of the dipolarophiles 78 and 79. Support for this idea was also obtained by some \textsuperscript{13}C NMR studies of the initially formed complex and its decomposition when the ylide precursor was added. Therefore, further studies of this catalytic approach were abandoned.

2.5 Applications

Many natural alkaloids contain a pyrrolidine ring. Examples are numerous of the successful syntheses of such naturally occurring alkaloids and their analogues in which an asymmetric 1,3-dipolar cycloaddition of an azomethine ylide with a dipolarophile has played a key role in the synthetic sequence. Some recent examples are the total synthesis of the antitumor antibiotic (−)-quinocarcin, a precursor to the alkaloid (+)-conessine (used in the treatment of dysentery), (+)- and (−)-spirotryprostatin B, (−)-2α-tropanol, (−)-cucurbitine, (−)-horsfiline, and the analgesic alkaloid epibatidine (Figure 2.6). Asymmetric 1,3-dipolar cycloadditions of azomethine ylides have also been utilised as key steps in the total syntheses of many unnatural bioactive substances, for example some cocaine antagonists, antibacterial compounds and glucosidase inhibitors.

3,4-Disubstituted pyrrolidines (section 2.2 and 2.3) have found applications as receptor antagonists.

Figure 2.6. Examples of alkaloids synthesised via an asymmetric 1,3-dipolar cycloaddition of an azomethine ylide as a key step. The pyrrolidine unit obtained in this step is marked in red.

Having demonstrated that enantiopure 3,4-disubstituted pyrrolidines could be obtained via singly and doubly diastereoselective 1,3-dipolar cycloaddition reactions (section 2.2 and 2.3), I also wanted to find synthetic applications of such reactions. Hence, these were utilised as key steps in the syntheses of two bioactive substances containing a pyrrolidine ring. First a short synthesis of a known\textsuperscript{47,48} enantiomerically pure glycosidase inhibitor (compound 84, Scheme 2.11) was accomplished. Thus, starting from the chiral ylide precursor 49 and dipolarophile ent-54, compound ent-55 was obtained via a doubly diastereoselective 1,3-dipolar cycloaddition (section 2.3) in 75% yield and >99:1 dr, after removal of the minor diastereomer ent-56 by column chromatography (Scheme 2.11). This compound was treated with LiAlH\textsubscript{4} to give alcohol 83 in 88% yield, along with recovered camphorsultam (90% yield). Reductive removal of the benzylic groups of 83 using Pd/C under an atmosphere of hydrogen furnished the enantiomerically pure compound 84 in 99% yield (65% overall yield from ent-54). The enantiomer ent-84 was also synthesised starting from the antipodes of the dipole precursor 49 (i.e. 48) and the dipolarophile ent-54 (i.e. 54). The new synthetic pathway for the synthesis of 84 described here is shorter and more high yielding compared with the already existing one.\textsuperscript{47}

![Scheme 2.11. Synthesis of a known inhibitor of glycosidase 84.](image_url)

Enantiomerically pure derivatives of azabicyclo[3.3.0]octanes (i.e. 87 and its enantiomer, Scheme 2.12) exhibit antibacterial activity against both Gram-positive and Gram-negative organisms.\textsuperscript{49} Such compounds can be prepared via a 1,3-dipolar cycloaddition of an achiral azomethine ylide with an achiral dipolarophile followed by resolution of the racemic cycloadducts in a later step.\textsuperscript{49} An alternative route to obtain these compounds is via an asymmetric 1,3-dipolar cycloaddition with the aid of chiral auxiliaries. This approach has the advantage that the chirality is introduced in an early step.

Thus, using the doubly diastereoselective approach described in section 2.3 and some other transformations, I prepared the enantiomerically pure known azabicyclo[3.3.0]octane 87 according to Scheme 2.12.

![Scheme 2.12. Preparation of a precursor to an antibacterial compound. (a) Ti(OEt)$_4$, EtOH, reflux, 90%. (b) NH$_2$Li, THF, reflux, 77%. (c) LiAlH$_4$, THF. (d) H$_2$, Pd/C. (e) HBr, 80% yield from 86.](image)

Hence, compound 64, which was obtained via an asymmetric 1,3-dipolar cycloaddition in 59% yield and >99:1 dr after removal of the minor diastereomer (section 2.3), was subjected to Ti(OEt)$_4$ catalysed ethanolysis. This afforded ester 85 in 90% yield, which upon treatment with lithium amide in excess furnished the primary amide 86 (77%). Reduction of this using LiAlH$_4$ followed by removal of the phenylethyl group using Pd/C under hydrogen gave the corresponding diamine which was treated with aqueous HBr to give the enantiomerically pure target salt 87, in 80% overall yield from amide 86. Compound 87 was identical in all respects with the one previously prepared.

Because as will be described in section 4.3, substituted pyrrolidines are frequently employed as organocatalysts in various enantioselective transformations, I hoped that the bicyclic compounds 71-74 (Scheme 2.8), due to their rigid structure, could act as efficient potential organocatalysts after some transformations. To be able to screen a variety of differently substituted derivatives of such catalysts, functional group transformations have to be performed with the cycloadducts 71-74. These contain a carbonyl group, which can act as an electrophilic site to which various nucleophiles can be added. Moreover, compounds 73 and 74 both incorporate sulfide moieties, which can be transformed into other functional groups. Thus, addition of Grignard reagents to cycloadducts 71-74 will furnish tertiary alcohols. After some additional transformations, potential catalysts capable of forming hydrogen bonds can be obtained. The resulting alcohols can be protected as ethers resulting in catalysts possessing other properties. Furthermore, the sulphur-containing compounds 73 and 74 can be oxidised to the corresponding sulfones. This will lead to the incorporation of a more polar and sterically restricted moiety which may play an important role for the efficiency of the catalyst. Thus, various substituted derivatives of cycloadducts 71-74 have been synthesised and their potential as catalysts in enantioselective transformations has been evaluated.

To be able to build up a library of structurally different potential catalysts, large amounts of the starting fused bicyclic pyrrolidines were needed. These could be obtained via doubly diastereoselective 1,3-dipolar cycloadditions as described in section 2.3. However, as already described (section 2.3), the chirality of the ylide was more important than that of the cyclic dipolarophile for obtaining a high π-facial selectivity. Therefore, I decided to prepare the desired bicyclic adducts from the chiral azomethine ylide 48# and achiral cyclic dipolarophiles via singly diastereoselective reactions. As will be presented in section 4.3, out of the bicyclic fused pyrrolidines tested, the ones containing a sulfone moiety were found to be the most efficient catalysts. Therefore, only the syntheses of these are presented in Scheme 2.13.

Scheme 2.13. Preparation of some potential organocatalysts: a) PhMgBr or p-MeO(C₆H₄)MgBr, THF, 62%. b) NaH, MeI, THF, 88%. c) (i) 1-chloroethylchloroformate, 1,8-bisdimethylaminonaphthalene, CICH₂CH₂Cl, reflux. (ii) MeOH, reflux, 65-96% overall.
Thus, a 1,3-dipolar cycloaddition of the chiral azomethine ylide derived from 48 with the achiral dipolarophile 88 gave a 60:40 diastereomeric mixture of cycloadducts 89 and 90. Column chromatography afforded the individual pure diastereomers in >99:1 dr. Grignard addition to the major diastereomer 89 using either PhMgBr or p-MeO(C₆H₄)MgBr yielded the corresponding tertiary alcohols 91 and 92, respectively. The phenylethyl groups of these were removed by treatment with a dealkylation reagent⁵¹ to give the pyrrolidinium salts 93 and 94. Attempts to remove the phenylethyl group by using other reagents such as Pd/C under hydrogen failed. Only desulfurised byproducts along with the recovered starting material were obtained. The same transformations were made starting from the minor cycloadduct 90 to give compounds ent-93 and ent-94. Compound 96 was obtained from the minor cycloadduct 90 via a Grignard reaction and transformation of the resulting alcohol 95 to the corresponding methyl ether, followed by removal of the phenylethyl group. It must be noted that compounds 93, 94 and 96 and the corresponding enantiomers of these could also be prepared via a 1,3-dipolar cycloaddition reaction of 2,5-dihydrothiophene-3-carboxylic acid methyl ester 70 with ylide 48# (Scheme 2.8). However, using 70 as the dipolarophile required one extra step in the synthetic sequence (i.e. oxidation of the sulphur moiety). Therefore, the methyl sulfolenecarboxylate 88 was chosen as the dipolarophile.

The catalytic efficiency of the metal-free, new, potential organocatalysts depicted in Scheme 2.13 in 1,3-dipolar cycloaddition reactions of nitrones with some dipolarophiles are presented in section 4.3.

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3. 1,3-Dipolar cycloaddition reactions of thiocarbonyl ylides

3.1 General aspects

As depicted in Scheme 3.1, thiocarbonyl ylides have the general structure 100. They belong to the allyl anion type having four resonance structures as described in section 1.2 (only one shown in Scheme 3.1). Thiocarbonyl ylides are often reactive, short-lived species and thus have to be prepared in situ from a precursor. Examples of generation of these are decomposition of 2,5-dihydro-1,3,4-thiadiazoles 97, CsF catalysed elimination of Me₃SiCl from compound 98 and deprotonation of sulfenium salts 99 (Scheme 3.1). Other methods also exist. The resulting ylide 100 readily undergoes 1,3-dipolar cycloaddition reactions, mainly with electron-deficient dipolarophiles (i.e. 101), to give tetrahydrothiophenes 102. Depending on the substitution pattern of the dipolarophile and the ylide, up to four new stereogenic centres can be created in one single step.

![Scheme 3.1. Examples of generation of thiocarbonyl ylides 100. In the presence of an electron-deficient dipolarophile 101, these undergo cycloaddition to give tetrahydrothiophene derivatives 102.](image)

3.2 Diastereoselective reactions using chiral auxiliaries

With the exception of a few 1,3-dipolar cycloaddition reactions of a masked thiocarbonyl ylide (i.e. a thioisomünchnone) with some chiral non-racemic nitroalkenes resulting in dihydrothiophenes after rearrangement, there are,

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except for the two works included in this thesis. To my knowledge no reported asymmetric 1,3-dipolar cycloaddition reactions of thiocarbonyl ylides with dipolarophiles.

Having demonstrated that enantiomerically pure trans-3,4-disubstituted pyrrolidines can be obtained via 1,3-dipolar cycloaddition reactions with the aid of chiral auxiliaries (section 2.2 and 2.3), it was interesting to investigate if a similar approach could be used for the syntheses of enantiomerically pure trans-3,4-disubstituted tetrahydrothiophenes.

When the same ylide was allowed to react with some chiral dipolarophiles attached to camphorsultam (103, 54 and 44c, Scheme 3.2), the major diastereomeric tetrahydrothiophenes 104, 106 and 108 were formed together with the separable minor diastereomers 105, 107 and 109, respectively, in high diastereofacial selectivities (dr ~90:10) and good yields (89-95% yield). Thus, the first asymmetric 1,3-dipolar cycloaddition of a thiocarbonyl ylide with chiral dipolarophiles resulting in trans-3,4-disubstituted tetrahydrothiophenes had been developed. It is worth noting, that when some chiral oxazolidinones were screened as chiral auxiliaries in the same reaction, considerably lower diastereofacial selectivities were obtained.

In order to secure the absolute configurations of the newly created stereocentres in the tetrahydrothiophene rings, the major cycloadducts 104, 106 and 108 were transformed into enantiomerically pure compounds 112, 113 and 115 of known absolute configurations (Scheme 3.3). The signs of optical rotation of these were compared with the ones in the literature.

Scheme 3.2. 1,3-Dipolar cycloaddition of thiocarbonyl ylide 98# with dipolarophile 103, 54 or 44c.

Thus, hydrolysis of compounds 104 and 108 furnished the acids 110 and 111, respectively, along with recovered camphorsultam, whereas reduction of 106 using LiAlH₄ gave the alcohol 114 (Scheme 3.3). Desulfurisation of these tetrahydrothiophene derivatives using Ra-Ni in refluxing ethanol gave the enantiomerically pure compounds 112, [α]D₂⁵ = −38.1 (lit.⁵⁶ for ent-112 [α]D₂³ = +40.65), 113 [α]D₂⁵ = −55.9 (lit.⁵⁷ [α]D₂⁰ = −41.7) and 115 [α]D₂⁵ = −63.1, (lit.⁵⁶ for ent-115 [α]D²¹.₅⁵ = +53.1). Thus, the major cycloadducts 104, 106 and 108 have the absolute configurations as depicted in Scheme 3.2. The sense of π-facial selectivity is thus the same as that observed when azomethine ylides were reacted with the same dipolarophiles as above (section 2.2 and 2.3). The reaction pathway probably proceeds in the same manner as that depicted in Figure 2.3.

3.3 Applications

Because the asymmetric 1,3-dipolar cycloaddition chemistry of thiocarbonyl ylides is an almost unexplored area, there are only examples of some non-asymmetric cycloadditions, which have served as key steps for the construction of racemic tetrahydrothiophenes. One example is the total synthesis of biotin in racemic form. This vitamin has been obtained via two different approaches, both involving an intermolecular 1,3-dipolar cycloaddition reaction of a thiocarbonyl ylide as the key step (Scheme 3.4).⁵⁸,⁵⁹ Other 1,3-dipolar cycloadditions of thiocarbonyl ylides with various dipolarophiles resulting in racemic heterocycles have been described elsewhere.⁶⁰ It must be noted that enantiopure biotin has been obtained via asymmetric intramolecular 1,3-dipolar cycloadditions of a nitrone and an azide respectively, both derived from L-cysteine.⁶¹

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Scheme 3.4. Two different approaches for the synthesis of (+/−)-biotin via intermolecular 1,3 dipolar cycloaddition reactions of thiocarbonyl ylides.

Having established an efficient approach for the syntheses of enantiopure trans-3,4-disubstituted tetrahydrothiophenes, I was especially delighted to find, that dipolarophile 54, although being relatively electron-rich, was reactive enough to undergo cycloaddition with ylide 98# (Scheme 3.2). The reason for my delight was that the resulting major cycloadduct 106 incorporated a 3-methylalkan-2-ol unit (Figure 3.1), a frequently observed structural motif in many natural products. Although various approaches already existed for the construction of this moiety, the cycloaddition approach described in Scheme 3.2 would furnish, in one single step, an enantiopure derivative of the threo-unit of this in high yield.

Figure 3.1. The 3-methylalkan-2-ol unit.


One example of a compound containing a chiral non-racemic threo-3-methylalkan-2-ol unit is the active sex pheromone component of *Macrodiprion nemoralis* 116 (Scheme 3.5). For identification purposes, this compound and each of its 15 stereoisomers have recently been synthesised by me. One key step employed in the total syntheses of the threo-isomers was the coupling of an alkyllithium (e.g. 117) with an enantiopure lactone (e.g. 118) followed by a Huang-Minlon reduction and a Mitsunobo inversion of the secondary alcohol (Scheme 3.5). However, because this sequence was not very efficient, an alternate pathway to obtain the threo-isomers in an improved overall yield was desirable.

**Scheme 3.5.** Retrosynthetic analysis of the active sex pheromone component of *Macrodiprion nemoralis* 116, and previous approach to obtain this from the building blocks 117 and 118.

From the retrosynthetic analysis (Scheme 3.5), bond breaking of the target molecule 116 as indicated furnishes three synthons 119-121, one of which can be referred to as a threo-3-methylalkan-2-ol unit (i.e. 121). This synthon is equivalent to the building block 124, which can easily be obtained via an asymmetric 1,3-dipolar cycloaddition followed by further transformations (section 3.2). Synthon 119 is equivalent to the corresponding alkyl halide 122 and the dianionic synthon 120 corresponds to 1,3-dithiane, 123. Thus, two sequential alkylations of 1,3-dithiane with the two building blocks 122 and 124 followed by a few synthetic steps would furnish the target molecule 116.

Outlined below is the total synthesis of the active sex pheromone component of *Macrodiprion nemoralis*, (2S,3R,7R,9S)-3,7,9-trimethyl-2-tridecyl acetate 116 (Scheme 3.6). As described in section 3.2, an asymmetric 1,3-dipolar cycloaddition reaction of the thiocarbonyl ylide 98 with dipolarophile 54 furnishes the major diastereomeric tetrahydrothiophene 106 and the minor one 107. After separation of these and reductive removal of the chiral auxiliary of the major diastereomer 106, one obtains compound 114 (Scheme 3.2 and 3.3). The building block ent-114 was prepared using the same sequence but starting from the antipode of 54.

This was transformed to the corresponding bromide 126 using PPh₃ and Br₂ (Scheme 3.6). The same functional group transformation was performed with enantiomerically pure alcohol 125 which was obtained via two sequential asymmetric alkylations as previously described. The resulting bromide 127 was coupled with 1,3-dithiane, 123, after deprotonation of the latter using butyllithium (BuLi). This furnished compound 128 in 95% yield. Deprotonation of this using BuLi followed by the addition of DMPU as a cosolvent and the bromide 126 yielded the dialkylated dithiane 129 in 83% yield. In order to obtain a satisfactory yield in this step it was necessary to perform the reaction using an excess of compound 128. Unreacted 128 could then be recovered almost quantitatively in the purification step. Treatment of 129 with Ra-Ni in refluxing ethanol accomplished the simultaneous reduction of the dithiane and the tetrahydrothiophene unit as well as the removal of the benzyl group. Thus, after treatment with AcCl, the target pheromone 116 was obtained in 83% yield. Unfortunately, according to GC- and ¹³C NMR analyses performed, a certain degree of epimerisation at the C-2 and C-3 stereogenic centres had occurred during the desulfurisation-debenzylation reaction.

Scheme 3.6. Total synthesis of the active sex pheromone component of Macrodiprion nemoralis 116.
(a) (i) BuLi, THF, −20 °C. (ii) add 127, −78 °C. (iii) −78 °C → R.T, 95% yield. (b) (i) BuLi, THF, −78 °C. (ii) −78 °C → −20 °C. (iii) −78 °C, DMPU, add 126. (iv) −78 °C → −30 °C, 83% yield. (c) Ra-Ni, EtOH, H₂, 22 °C, 72% yield. (d) AcCl, CH₂Cl₂, 100% yield.
However, it was found that the undesired epimerisation could be suppressed if the reaction, at room temperature, was performed in the presence of hydrogen gas with Ra-Ni as the catalyst. Thus, 116 was now obtained in 72% yield in >99% stereoisomeric purity after esterification. It is well known that secondary alcohols often suffer from epimerisation when subjected to Ra-Ni, and that this can be circumvented if a hydrogen source is added to the reaction mixture. The epimerisation is proposed to occur through a reversible oxidation-reduction mechanism of the secondary alcohol. However, in this case epimerisation also occurred at the C-3 stereogenic centre. When a stereoisomerically pure sample of the alcohol of 116 was subjected to Ra-Ni in refluxing ethanol, epimerisation was observed only at the C-2 stereogenic centre. Therefore, the observed C-3 epimerisation for the 129 \rightarrow 116 transformation probably originates from the desulfurisation reaction of the tetrahydrothiophene unit.

The new approach shown above, in which a 1,3-dipolar cycloaddition reaction was used as one key step for the synthesis of the the active sex pheromone component of *Macrodiprion nemoralis*, proved to be more efficient than the approach previously published. It could probably also be used for the syntheses of other natural products containing this threo-3-methylalkan-2-ol unit.


[65] See e.g. (a) refs. 64e, 64f, (b) Nakamura, K.; Ushio, K.; Oka, S.; Ohno, A.; Yasui, S. *Tetrahedron Letters* 1984, 25, 3979-3982.

4. 1,3-Dipolar cycloaddition reactions of nitronesVII.VIII

4.1 General aspects

Nitrones have been used in numerous studies of asymmetric 1,3-dipolar cycloadditions. In general, nitrones are relatively stable species and do not need to be prepared in situ. The most convenient approach for the generation of these is condensation between secondary hydroxylamines and an aldehyde or a ketone, but other methods also exist such as oxidation of tertiary hydroxylamines or alkylation of oximes with alkyl halides (Scheme 4.1).67

![Scheme 4.1](image)

Scheme 4.1. Examples of generation of nitrones and subsequent 1,3-dipolar cycloaddition with dipolarophile. The resulting isoxazolidine can be ring opened to give an amino alcohol.

The resulting nitrone exists as an equilibrium mixture of the Z- and the E-form with the Z-configuration being, in general, the most stable form.68 Jørgensen et al. have carried out some analyses on C-N-diphenylnitrone and found that the Z-isomer is the most stable one by 11 kcal/mol.69 The activation energy for the conversion of the Z- to the E-form is calculated to be 33 kcal/mol and therefore, the conversion will be very slow at ambient temperature. The configuration of aliphatic aldonitrones (i.e. R₂ or R₃ = H in 133) has not been extensively investigated but there are some examples where they prefer the Z-configuration.70 However, some nitrones have been isolated in good yields in their E-forms.71 Depending on which form of the nitrone that reacts with a

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dipolarophile (i.e. 134) and the mode of approach of this (endo/exo), either the endo- or the exo-diastereomer of an isoxazolidine 135 is formed containing up to three new stereogenic centres (Scheme 4.1).

Isoxazolidines can easily be ring opened by treatment with various reagents such as palladium or Raney nickel, both in the presence of hydrogen, Na(Hg) or Zn/AcOH to give aminoalcohols of the type 136. Such aminoalcohols are valuable building blocks for the preparation of biologically important compounds. The reactions of nitrones with electron-deficient dipolarophiles are in general dominated by HOMO(dipole)-LUMO(dipolarophile) interactions, whereas reactions with electron-rich dipolarophiles are dominated by LUMO(dipole)-HOMO(dipolarophile) interactions. 74

4.2 Diastereoselective reactions using chiral auxiliaries

Because no diastereoselective 1,3-dipolar cycloadditions of nitrones using chiral auxiliaries have been investigated by me, such reactions are not discussed in this thesis. Instead, the readers are referred to the literature describing this topic.8,9

4.3 Enantioselective reactions using chiral catalysts

The enantioselective variant of the 1,3-dipolar cycloaddition chemistry of nitrones has until recently been an unexplored area. The first enantioselective reaction was reported in 1994, when some chiral oxazaborolidines were found to catalyse the reactions of some nitrones with electron-rich dipolarophiles. 75 Since then, numerous other chiral catalysts have been used in this type of reaction. 76

The 1,3-dipolar cycloaddition of a nitrone with a dipolarophile is either referred to as a normal electron-demand reaction or an inverse electron-demand reaction.76 The former reaction is dominated by a HOMO(dipole)-LUMO(dipolarophile) interaction, whereas the latter is dominated by a LUMO(dipole)-HOMO(dipolarophile) interaction. Thus, the activation energy for a normal electron-demand reaction is lowered when a Lewis acid is coordinating to the dipolarophile, whereas coordination to the nitrone in an inverse electron-demanding reaction gives the same effect. In order to favour a coordination of the catalyst to the dipolarophile rather than to the nitrone, a dipolarophile containing two Lewis basic sites can be used (see section 1.8 and 2.4). Therefore, in normal electron-demand reactions, dipolarophiles of type 138 (Scheme 4.2) containing two carbonyl oxygens are often used. These can, in combination with a Lewis acid, chelate in a bidentate fashion to the metal.

Chiral non-racemic ligands of type $140$ in combination with Mg(II)- or Zn(II) salts have been found to catalyse reactions of such dipolarphiles with various nitrones $137$ to give either the exo- or the endo-isomer of $139$ as the predominant cycloadduct in better than 80% ee.\(^7\) Depending on the R-groups of ligand $141$, and the inorganic salt used, that is, Yb(OTf)$_3$ or Ni(ClO$_4$)$_2$, good to excellent enantioselectivity of the endo-adduct $139$ is obtained.\(^7\) Jørgensen et al. found that catalysts derived from chiral non-racemic diols, that is, ligands of type $142$, and Ti(IV) salts catalysed the reactions of nitrones $137$ with dipolarophiles $138$ in good enantioselectivities (up to 62% ee).\(^7\) Since then numerous variants of this type of reaction resulting in improvement in enantioselectivity as well as diastereoselectivity have been reported.\(^8\) Some catalysts of this type anchored to a solid support have also been used in the above reaction with similar results as for the related catalysts in solution.\(^8\) Pd(II) complexes have also been employed as catalysts in reactions of electron-deficient dipolarophiles with nitrones. The BINAP ligand $143$ in combination with various Pd(II) salts catalyse the reaction depicted in Scheme 4.2 (upper half) and give high enantiomeric excesses for both the exo- and the endo-adduct $139$.\(^8\) Depending on which salt and which additive that are used, the analogous BINOL ligand $144$ ($R_1 = H$) in combination with either Sc(OTf)$_3$ or Yb(OTf)$_3$ give either the (+) - or the (–)-enantiomer of endo-$139$ in excellent diastereoselectivity and enantioselectivity.\(^8\) Good results have also been obtained when $R_1$ in $144$ is exchanged for various chiral non-racemic bis-oxazolines.\(^8\) Recently, very promising results have been obtained in


Ni(II) catalysed reactions using chiral ligand 145. In the presence of this, the reactions of various nitrones 137 with dipolarophiles of type 138 give endo-139 in excellent diastereo- and enantioselectivity.85

The reactions presented so far have involved electron-deficient dipolarophiles of type 138 in which the catalyst coordinates to the dipolarophile in a bidentate fashion. A monodentate binding of the catalyst to the dipolarophile will enable one to perform reactions using dipolarophiles containing only one Lewis basic site. Thus, the two extra steps involving the attachment of the oxazolidinone auxiliary to 138 and its removal from the product will not be needed. Indeed, this can be accomplished by careful choice of Lewis acid and chiral ligand. Kündig et al. reported that ruthenium and iron salts in combination with chiral non-racemic diols are efficient catalysts for the enantioselective 1,3-dipolar cycloadditions of various nitrones with α,β-unsaturated aldehydes furnishing isoxazolidines in excellent enantioselectivities.86 Chiral non-racemic cobalt(III) complexes have also proven to be efficient catalysts in this type of reaction.87

\[ \text{Scheme 4.2. Various ligands 140-146 used in conjunction with Lewis acids in enantioselective 1,3-}
\]
dipolar cycloaddition reactions of nitrones with either electron-deficient dipolarophiles (upper half)
or electron-rich dipolarophiles (lower half).

When instead electron-rich dipolarophiles such as vinyl ethers are employed in the reactions with nitrones (i.e. inverse electron-demand reactions), coordination of the catalyst to the nitrone is in general responsible for the rate acceleration. Ligands 140 and 141 in combination with either Cu(II) or Zn(II) salts form catalysts, which have been used in reactions of various nitrones 137 with vinyl ethers 147 to give isoxazolidines endo-148 and exo-148, both in high enantiomeric purities (Scheme 4.2). When aluminium complexes of BINOL ligands of type 144 are used in the same reaction, exo-148 is obtained in high diastereo- and enantioselectivity (up to 97% ee). Reactions with cyclic nitrones also give good results using the same catalysts. When vinyl ethers of type 147 react with nitrones 137 and when immobilised or polymerised aluminium complexes of ligands of type 144 are used as catalysts, the results are comparable to those obtained for similar experiments in homogenous solutions. C₂-symmetrical ligands of type 142 as well as other C₂ symmetrical diols and amines in the presence of Ti(IV) salts have been used with moderate success in the same type of reaction. As mentioned in the beginning of this section, oxazaborolidines (i.e. 146) catalyse the reactions of nitrones with electron-rich dipolarophiles. By varying the R-substituents of catalyst 146 and using it in reactions of some nitrones with electron-rich dipolarophiles, good enantiomeric purity is obtained for exo-148. Various other B(III) catalysts derived from C₂-symmetric diols and amines have also been used but with moderate success. Low enantioselectivities are obtained if Pd(II) complexes of ligand 143 or a Ti(IV) complex of chiral non-racemic cyclacene are used as catalysts in reactions of nitrones 137 with electronrich dipolarophiles 147.

As demonstrated by Ukaji and Inomata et al, enantioselective 1,3-dipolar cycloaddition reactions of nitrones can also be conducted with allylic alcohols as dipolarophiles. By employing enantiomerically pure disopropyl tartrate in the presence of Zn(II), reactions of nitrones with allyl alcohols proceed to give the corresponding cycloadducts in high diastereo- and enantioselectivities.

All of the enantioselective reactions described so far have involved catalysts composed of enantiomerically pure ligands coordinated to various metal-salts. Those catalysts often have to be used under dry conditions under an inert atmosphere. A more easily managed, metal-free catalyst gives operational and economical advantages over the ones containing metals. Therefore, organocatalysis has become a very active research field at present. Organocatalysts are often low molecular weight compounds readily available from inexpensive starting materials. They can in general be reused in a convenient manner. Because organocatalysts do not contain any heavy metals, they are, in general, more environmentally friendly than most chiral Lewis acid catalysts. Moreover, organocatalysed reactions can often be conducted under air and even in wet solvents.

A milestone in the field of organocatalysis is the development of the enantioselective Robinson annulation of triketones of type 149 catalysed by proline (Scheme 4.3). Thus, in the presence of this naturally occurring amino acid (i.e. 150), such triketones undergo Robinson annulation to give chiral non-racemic bicycles 151, which, after dehydration, furnish compounds of type 152.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{O} & \quad \text{N} \\
\text{CO} & \quad \text{H} \\
\text{R}^2 & \quad \text{R}^1 \\
\text{H} & \quad \text{2O} \\
\text{R}^1 & \quad \text{O} \\
\text{R}^2 & \quad \text{n}
\end{align*}
\]

Scheme 4.3. Asymmetric Robinson annulation of trikone 149 mediated by proline catalyst 150.

This approach has opened a new route for enantioselective syntheses of steroids and other natural products such as taxol. The mechanism of this reaction has been a subject of debate and has recently been proposed to occur through the transition state depicted in Scheme 4.3. Support for this proposal has been gained from kinetic studies. Thus enamine formation from proline and the carbonyl moiety of the triketone is followed by an intramolecular cyclisation. The reaction is facilitated by the simultaneous mediated proton transfer from the carboxylic acid moiety of the proline to the carbonyl oxygen of the ketone.

Since the discovery of the proline catalysed Robinson annulation reaction discussed above, organocatalysis has become a rapidly growing research area in organic chemistry. In the field of 1,3-dipolar cycloaddition reactions, MacMillan et al. have been the first to explore organocatalysis. They have developed a general protocol for the enantioselective syntheses of isoxazolidinones from nitrones of type 137 and α,β-unsaturated aldehydes 153 catalysed by the phenylalanine derived organocatalyst 154 (Scheme 4.4).

Thus, various nitrones of type 137 react with α,β-unsaturated aldehydes 153 in the presence of this catalyst to give endo-155 in high diastereo- and enantioselectivity. The rate acceleration caused by catalyst 154 is due to iminium ion formation from a condensation reaction between the catalyst and the aldehyde (Figure 4.1). Compared with the uncatalysed reaction, the formation of the iminium salt results in a lowering of the LUMO energy of the π-moiety of the dipolarophile. The major attack of the nitrones occurs on the least sterically hindered side of the π-bond as indicated in Figure 4.1. Hydrolysis in situ of the iminium species furnishes the aldehyde product and the catalyst 154, which then is ready for another catalytic cycle.

Scheme 4.4. The first reported organocatalytic 1,3-dipolar cycloaddition reaction.

Although, the general organocatalytic approach for the construction of enantiomerically pure isoxazolidines described above is available, cyclic dipolarophiles such as cyclpent-1-enecarbaldehyde, have not been used in this type of reaction.\textsuperscript{104} Therefore, I wanted to investigate the organocatalysed reactions of such types of dipolarophiles (i.e. 161 and 162, Scheme 4.5) with various nitrones 163a-g derived from both aliphatic and aromatic aldehydes (Scheme 4.5). The aim was to find efficient organocatalysts for this type of reaction in terms of yield, diastereo-, and enantioselectivity.

First, the reaction of aldehyde 161 with nitrone 163a was investigated. When these were mixed in CH\textsubscript{3}NO\textsubscript{2} at ambient temperature, no reaction occurred. At elevated temperatures, a mixture of two diastereomeric racemic cycloadducts was obtained, which after treatment with NaBH\textsubscript{4}, furnished the more readily separable reduced major cycloadduct 164a and the minor one 165a (Scheme 4.5). However, these were formed in low exo/endo selectivity along with two additional regioisomers, albeit in a good yield. Thus, because no reaction occurred at ambient temperature, this was a good starting point for the introduction of a catalyst in this reaction. Hence, in the presence of the HCl salt of the MacMillan catalyst 154 (Scheme 4.5) either in wet CH\textsubscript{3}NO\textsubscript{2} or DMF at ambient temperature, reaction took place. The reduced cycloadduct 164a was obtained in a good diastereoselectivity but was nearly racemic (~ 5\% ee) and the yield was low. This disappointing result was in sharp contrast to the results obtained when acyclic dipolarophiles were used in the same reaction.\textsuperscript{103} This encouraged me to investigate other types of organocatalysts for this reaction.

The bicyclic fused pyrrolidines ent-93, ent-94, and 96, prepared via an asymmetric 1,3-dipolar cycloaddition as described in section 2.5, have very rigid structures and are substituted with bulky aromatic rings. I reasoned that such ammonium salts might be suitable as catalysts in the reaction depicted in Scheme 4.5. The main point was whether or not the presence of such catalysts with increased bulk and rigidity would result in a higher reactivity and selectivity of the reaction.

\textsuperscript{104} After paper VII was published a work describing the use of chiral cobalt(III) complexes as catalysts in reactions of nitrones with cyclopent-1-enecarbaldehyde appeared: See ref. 87.
Scheme 4.5. 1,3-Dipolar cycloadditions of various nitrones 163a-g with either aldehyde 161 or 162 catalysed by some organocatalysts.

Gratifyingly, when compound ent-93, ent-94, or 96, was used as catalyst in the reaction depicted in Scheme 4.5, a reasonable overall yield of the reduced diastereomeric cycloadducts 164a and 165a was obtained in a moderate diastereoselectivity (Table 4.1, entries 1-4). Separation of the enantiomers of the major diastereomer 164a using chiral stationary phase capillary GC revealed that when either catalyst ent-93 or ent-94 was used, a good enantioselectivity had been obtained (up to 76% ee, entry 4). Other catalysts of this type, lacking the sulfone- and/or the tertiary alcohol functional group(s), were also investigated in the same reaction. However, when such catalysts were used, considerably lower enantioselectivities were obtained. Correct choice of solvent also turned out to be crucial for obtaining good enantioselectivity and for sufficient solubility of the catalysts. Among the solvents investigated, DMF was the solvent of choice.
Table 4.1. 1,3-Dipolar cycloaddition of nitrone 163a with aldehyde 161 catalysed by ammonium salt ent-93, ent-94 or 96. 

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>Dr (164a:165a)</th>
<th>%ee 164a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ent-93</td>
<td>72</td>
<td>+10</td>
<td>59</td>
<td>83:17</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>96</td>
<td>48</td>
<td>+10</td>
<td>39</td>
<td>89:11</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>ent-94</td>
<td>120</td>
<td>+10</td>
<td>61</td>
<td>80:20</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>96</td>
<td>-10</td>
<td>45</td>
<td>72:28</td>
<td>76</td>
</tr>
</tbody>
</table>

*The nitrone 163a (3.7 mmol) and the catalyst (0.48 mmol) were added to a solution of the aldehyde 161 (4.8 mmol) in DMF (15 ml) and water (86 µl). Work-up using EtOAc/H₂O followed by chromatography furnished two diastereomeric cycloadducts which immediately were subjected to NaBH₄ reduction. This furnished the two individual diastereomers 164a and 165a after a standard work-up procedure and separation by column chromatography. The yields are based on the overall isolated yield of 164a and 165a. The enantiomeric excess of 164a was determined of the corresponding trifluoroacetate of the former using a chiral β-Dex-325 GC capillary column.*

When the pyrrolidinium salt ent-94 was applied as the catalyst, the enantioselectivity obtained in the reaction of aldehyde 161 with nitrone 163a was good and the yield and diastereoselectivity were reasonable. However, it was tempting to investigate if the selectivity could be further improved by using other types of organocatalysts.
Proline and derivatives thereof have been used as organocatalysts in various types of enantioselective reactions\textsuperscript{100} such as Michael reactions of aliphatic aldehydes and ketones with nitroolefins\textsuperscript{105} and of nitroalkanes with $\alpha,\beta$-unsaturated enones,\textsuperscript{106} in Diels-Alder reactions of $\alpha,\beta$-unsaturated aldehydes with dienes,\textsuperscript{107} and in the newly discovered nucleophilic addition reaction of nitrones to ketones.\textsuperscript{108}

Hence, for use in 1,3-dipolar cycloadditions of nitrones, proline seemed to be a suitable starting material for the preparation of potential organocatalysts. Thus, pyrrolidinium salts \textsuperscript{156-158}\textsuperscript{109} containing a tertiary alcohol or ether moiety and bicyclic compounds \textsuperscript{159-160}\textsuperscript{110} (Scheme 4.5) were prepared according to literature procedures and explored as catalysts in the reaction of aldehyde \textsuperscript{161} with nitrone \textsuperscript{163a} (Table 4.2).

Reactions of aldehyde \textsuperscript{161} with nitrone \textsuperscript{163a} in the presence of each of the salts \textsuperscript{156-158} proceeded in appreciable conversion only when catalyst \textsuperscript{158} was used (Table 4.2, entries 1-3). At first these results seem puzzling. However, because catalysts \textsuperscript{156} and \textsuperscript{157} are amino alcohols they can probably form catalytically inactive species (i.e. protonated \textsuperscript{N,\textit{O}}-acets) with aldehyde \textsuperscript{161} as outlined in Scheme 4.6. The fairly efficient catalysts ent-\textsuperscript{93} and ent-\textsuperscript{94} (as HCl-salts) are also aminoalcohols. However, due to their rigid bicyclic structures, they are probably unable to form such inactive species. This explains why the latter catalysts work in this reaction whereas the catalysts \textsuperscript{156} and \textsuperscript{157} are inactive. The ether derivative \textsuperscript{158} cannot form such an inactive protonated \textsuperscript{N,\textit{O}}-acetal with aldehyde \textsuperscript{161}. Despite this, a very low yield of \textsuperscript{164a} was obtained when this was used as catalyst, albeit in a good enantioselectivity (Table 4.2, entry 3).

\begin{align*}
\text{Scheme 4.6.} & \text{ Formation of an unreactive protonated } N,\textit{O}-\text{acetal from aldehyde } \text{161} \text{ and either catalyst } 156 \text{ or 157.}
\end{align*}

\[\text{161} + \text{156 or 157} \rightarrow \text{unreactive}\]

Table 4.2. 1,3-Dipolar cycloaddition of aldehyde 161 with nitrone 163a catalysed by various ammonium salts 156-160 derived from proline.\(^a\)

![Image of chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>((HX))_n</th>
<th>Time</th>
<th>Temp. ((^\circ C))</th>
<th>Yield %(%)</th>
<th>Dr ((164a:165a))</th>
<th>%ee 164a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>156</td>
<td>HCl</td>
<td>72 h</td>
<td>+25</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>157</td>
<td>HCl</td>
<td>48 h</td>
<td>+25</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>158</td>
<td>HCl</td>
<td>96 h</td>
<td>+25</td>
<td>12</td>
<td>80:20</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>159</td>
<td>HCl</td>
<td>144 h</td>
<td>+10</td>
<td>26</td>
<td>95:5</td>
<td>85</td>
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<td>5</td>
<td>159</td>
<td>2 HCl</td>
<td>72 h</td>
<td>+10</td>
<td>50</td>
<td>93:7</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>159</td>
<td>HCl</td>
<td>144 h</td>
<td>+10</td>
<td>44</td>
<td>95:5</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>159</td>
<td>2 HCl</td>
<td>72 h</td>
<td>+10</td>
<td>49</td>
<td>97:3</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>159</td>
<td>2 HClO(_4)</td>
<td>120 h</td>
<td>+10</td>
<td>44</td>
<td>80:20</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>159</td>
<td>2 TFA</td>
<td>72 h</td>
<td>+10</td>
<td>31</td>
<td>84:16</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>160</td>
<td>2 HCl</td>
<td>120 h</td>
<td>−25</td>
<td>23</td>
<td>93:7</td>
<td>93</td>
</tr>
<tr>
<td>11(^b)</td>
<td>160</td>
<td>2 HCl</td>
<td>120 h</td>
<td>+10</td>
<td>21</td>
<td>97:3</td>
<td>91</td>
</tr>
<tr>
<td>12(^c)</td>
<td>160</td>
<td>2 HCl</td>
<td>144 h</td>
<td>+10</td>
<td>70</td>
<td>95:5</td>
<td>91</td>
</tr>
<tr>
<td>13(^d)</td>
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<td>2 HCl</td>
<td>120 h</td>
<td>+10</td>
<td>63</td>
<td>89:11</td>
<td>83</td>
</tr>
<tr>
<td>14(^d)</td>
<td>160</td>
<td>2 HCl</td>
<td>120 h</td>
<td>−25</td>
<td>17</td>
<td>28:72</td>
<td>91</td>
</tr>
</tbody>
</table>

\(^a\) The reactions were performed as described under Table 4.1. \(^b\) 1:1 ratio 161:163a, 1 mol\% catalyst. \(^c\) 1:2 ratio 161:163a. \(^d\) No water added.

Promising results were however obtained when either the ammonium salt 159 or 160 was used as catalysts. With catalyst 160 being the most efficient one, both a high diastereo- and enantioselectivity were obtained (Table 4.2, entries 4 and 6). Compared with the monohydrochloride salts, the dihydrochloride salts of 159 and 160 were more efficient catalysts in terms of both yield and enantioselectivity (compare entry 4 vs 5 and 6 vs 7). Because catalyst 160 was slightly more efficient compared to 159, further investigations were performed using the former.
First, the influence of the counterions of the diammonium salt 160 was investigated. Thus, whereas the dihydrochloride salt of 160 furnished isoxazolidine 164a in 92% ee, the corresponding TFA and HClO₄ salts gave much lower enantio- and diastereoselectivities (compare entry 7 with entries 8 and 9, Table 4.2). A low temperature or a low catalyst loading had no significant influence on the diastereo- and enantioselectivity (entries 10 and 11). However, the yields dropped significantly. When running the reaction under standard conditions, but using an excess of nitrone 163a, a good yield with preserved high enantioselectivity was obtained (Table 4.2, entry 12).

The effect of water in the reaction mixture was also investigated. Thus, when no water was added to the reaction mixture and depending on the reaction temperature, either the enantioselectivity or the diastereoselectivity changed significantly (entries 13-14).

Having established compound 160 (as the 2HCl-salt) as an efficient organocatalyst in the reaction of nitrone 163a with aldehyde 161 in terms of both diastereo- and enantioselectivity, the yields are still moderate. This is partly due to the formation of two diastereomeric byproducts, which have been identified as adducts 164b and 165b after reduction with NaBH₄ (Scheme 4.7). For example, in one experiment (Table 4.2, entry 10) 164b has been isolated as a major byproduct in 92% ee. This byproduct is formed through hydrolysis of the original added nitrone to the corresponding aldehyde and hydroxyl amine. This hydroxyl amine (i.e. N-methylhydroxylamine) then reacts with aldehyde 161 to give a new nitrone 163b, which in the presence of the catalyst (e.g. 160) and aldehyde 161, furnishes, after reduction, the cycloadduct 164b and its diastereomer 165b (Scheme 4.7).

With catalyst 160 in hand, I also wanted to investigate its catalytic performance in reactions of other types of nitrones with two different cyclic dipolarophiles 161 and 162. The results are summarised in Table 4.3.
Table 4.3. 1,3-Dipolar cycloadditions of various nitrones 163b-g (100 mol%) with either aldehyde 161 or 162 (100 mol%) in wet DMF in the presence of catalyst 160 (2HCl-salt, 10 mol%) resulting in cycloadducts (164 and 165) or (166d and 167d) after reduction with NaBH₄.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Nitrone</th>
<th>Time</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>Dr (164:165) or (166d:167d)</th>
<th>%ee 164 or 166d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>120 h</td>
<td>+10</td>
<td>68</td>
<td>98:2</td>
<td>76 (&gt;99)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>120 h</td>
<td>+10</td>
<td>63</td>
<td>99:1</td>
<td>84 (&gt;99)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>161</td>
<td>163b-g</td>
<td>120 h</td>
<td>−10</td>
<td>50</td>
<td>97:3</td>
<td>90 (&gt;99)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>161</td>
<td>163c</td>
<td>144 h</td>
<td>−25</td>
<td>76</td>
<td>&gt;99:1</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>161</td>
<td>163d</td>
<td>24 h</td>
<td>+20</td>
<td>58</td>
<td>&gt;99:1</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>161</td>
<td>163d</td>
<td>24 h</td>
<td>−20</td>
<td>48</td>
<td>&gt;99:1</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>161</td>
<td>163e</td>
<td>144 h</td>
<td>+20</td>
<td>51</td>
<td>98:2</td>
<td>53</td>
</tr>
<tr>
<td>8</td>
<td>161</td>
<td>163f</td>
<td>96 h</td>
<td>−20</td>
<td>56</td>
<td>&gt;99:1</td>
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<td>9</td>
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<td>56:44</td>
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<td></td>
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<td>24 h</td>
<td>+20</td>
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<td>48</td>
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<tr>
<td>11</td>
<td>162</td>
<td>163d</td>
<td>120 h</td>
<td>+20</td>
<td>38</td>
<td>&gt;99:1</td>
<td>37</td>
</tr>
</tbody>
</table>

<sup>a</sup>The reactions were performed following the same procedure as described under Table 4.1 but using a stoichiometric amount of nitrone and aldehyde and 10 mol% catalyst.<sup>b</sup> >99% ee after one recrystallisation from EtOAc/heptane. <sup>c</sup>The nitrone dissolved in DMF was slowly added (36 h) to a solution containing the aldehyde and the catalyst in wet DMF.
Table 4.3 shows that, when other nitrones than 163a were reacted with aldehyde 161, higher diastereoselectivities and lower enantioselectivities were in general obtained. One exception was the nitrone 163b, which upon reaction with 161 and after reduction, furnished cycloadduct 164b in both a high diastereomeric and enantioselectivity (entries 1-3). Fortunately, recrystallisation of 164b improved the enantiomeric excess to >99%. Reaction of nitrone 163g with aldehyde 161 furnished, after reduction, an inseparable diastereomeric mixture of the known cycloadducts 164g and 165g in low diastereoselectivity (Table 4.3, entry 9, yield and ee not determined). Initial attempts to react the more sterically demanding aldehyde 162 with nitrone 163a failed and only traces of the corresponding diastereomeric cycloadducts were obtained. However, reaction with the more reactive nitrone 163d furnished the reduced cycloadduct 166d in excellent diastereoselectivity, albeit in a moderate enantioselectivity and yield (entries 10 and 11, Table 4.3).

Among the results presented in Table 4.3 were some remarkable ones. First, comparing the reactions, where 164b was obtained as a byproduct as described in Scheme 4.7, with reactions under the same conditions between nitrone 163b and 161, the enantioselectivity obtained of 164b was significantly lower (compare entry 1, Table 4.3, 76% ee with entry 10, Table 4.2, where 164b was obtained as a byproduct in 92% ee). Moreover, a higher enantioselectivity was obtained if the concentration of the nitrone 163b was kept low (compare entries 1 and 2, Table 4.3). In some instances the reaction time also had a certain influence on the enantioselectivity (compare entries 10 and 11, Table 4.3).

These observations indicated that a competing reaction existed, which produced racemic cycloadducts. One would suspect that this reaction could be the uncatalysed reaction of one of the nitrones 163a-g with either aldehyde 161 or 162. However, as mentioned above, in the absence of a catalyst in the reaction of 163a with aldehyde 161 at ambient temperature, no reaction occurred. Moreover, the presence of a catalyst in the reaction described in entry 4 (Table 4.3) is a prerequisite to obtain any conversion. Therefore, another competing reaction is probably taking place. In Scheme 4.7, I described the mechanism for the formation of non-racemic byproduct 164b obtained in a sequence via hydrolysis of the original added nitrone 163a followed by the formation of nitrone 163b. In addition to this competing non-racemic pathway described in Scheme 4.7, I suspected that a racemic one, involving the same nitrone 163b, existed. The nitrone 163b is detected in various amounts in the reactions studied in Scheme 4.5, with the highest amounts in the reactions performed at ambient temperature. Would it be possible that this nitrone 163b also could act as a reactive dipolarophile in reactions with the other nitrones? Such a possible competing reaction is depicted in Scheme 4.8.
Thus, if the $\pi$-bond of the cyclopentenyl moiety of this nitrone 163b is sufficiently activated for attack by the original nitrone, cycloaddition will furnish a new nitrone 168, which upon hydrolysis *in situ* followed by reduction with NaBH$_4$ gives racemic cycloadduct 164 along with the corresponding hydroxylamine (Scheme 4.8). The existence of the proposed competing reaction depicted in Scheme 4.8 explains why a low concentration of the original added nitrone results in a higher enantioselectivity and why longer reaction times lead to a decrease in enantioselectivity.

To test the hypothesis, that such a competing reaction existed, nitrone 163b was dissolved in dry DMF and stirred for five weeks. This resulted, after hydrolysis and reduction, in the formation of a considerable amount of the racemic product 164b (~30% yield). Furthermore, when a diammoniumsalt (i.e. TMEDA 2HCl-salt) not able to form a catalytic active iminiumspecies was added, the reaction rate for this reaction increased slightly. Thus, these observations strongly support the existence of the competing reaction depicted in Scheme 4.8. Thus, the low enantioselectivity obtained in some of the reactions of the nitrones 163 with the aldehydes 161 and 162 can be partly due to this competing reaction. However, the enantioselectivity is evidently dependent also on the nature of the nitrone and aldehyde used.

In addition to the undesired competing reaction involving nitrone 163b as a spontaneously reactive dipolarophile, its formation from the original nitrone *via* hydrolysis, also led to the production of various amounts of non-racemic byproducts 164b and 165b (as exemplified in the reaction of nitrone 163a with aldehyde 161 in Scheme 4.7). Thus, the formation of such adducts provides one explanation for the moderate yields obtained in most instances involving the various nitrones 163a-g and the aldehydes 161 and 162 (Table 4.2 and 4.3).

The formation of the nitrone 163b from the original nitrone can be prevented by lowering the water concentration in the reaction mixture. However, as mentioned previously, in order to achieve high enantio- and diastereoselectivity, it is necessary to perform the reactions in wet solvents, and an alternative way to suppress the formation of nitrone 163b is needed. If the aldehyde from which the nitrone is derived is present as an additive in the reaction mixture, this aldehyde might trap any hydroxylamine liberated and thus, less amount of nitrone 163b will be formed.

This hypothesis was tested in a separate experiment. Thus, the reaction of nitrone 163c with aldehyde 161 was performed using the conditions in entry 4, Table 4.3, but in the presence of 10 equiv. of butyraldehyde as an additive.
However, while the enantioselectivity remained the same, the yield dropped significantly. Therefore, another method, which would reduce the amounts of hydrolysis products from the original added nitrone would be desirable. It must be noted that the yields were strongly dependent on the reaction time. The reactions in Scheme 4.5 were quenched after a satisfying conversion had been obtained but with a maximum reaction time of 144 hours. Thus, slightly better yields than those presented in Table 4.1, 4.2 and 4.3 could in most cases be achieved by using prolonged reaction times.

The reactions presented so far have been performed on a 4 mmol scale using 10–13 mol% of the catalyst. To constitute a useful method for the syntheses of fused non-racemic isoxazolidines, the reactions depicted in Scheme 4.5 ought also to be possible to perform on a larger scale and with a lower catalyst loading.

The aldehyde 161 and nitrone 163b were chosen as dipolarophile and dipole, respectively, in such a large scale reaction. Thus, using a stoichiometric amount of these on a 0.1 molar scale in the presence of 5 mol% of catalyst 160 (2HCl-salt) and allowing the reaction to go to completion at –8 °C, resulted in a 80% overall isolated yield of a mixture of the reduced cycloadducts 164b (85% ee, dr 94:6) and 165b after 11 days. One single recrystallisation of the crude mixture of these from EtOAc/heptane improved the ee and dr of 164b to over 99% and >99:1, respectively (56% overall yield). Thus, this result was comparable to that obtained when the reaction was performed on a smaller scale using a higher catalyst loading (Table 4.3, entry 3). However, the yield was improved.

In summary, when reacting the nitrones 163a-g with aldehyde 161 or 162 in the presence of catalyst 160 (2HCl-salt), the enantioselectivity is variable and depends on the nature of the nitrone and aldehyde used. When nitrone 163a is reacted with aldehyde 161, an enantiomeric excess of up to 93% is obtained. No matter which nitrone or aldehyde that is used, the diastereoselectivity is, in general, excellent. However, the yields are often moderate. It must be noted that the reactions were performed with a low loading of both the catalyst and the substrate. A high yield, diastereoselectivity, and enantioselectivity, were obtained when one reaction (i.e. reaction between 163b and 161) was scaled-up and performed using a prolonged reaction time and a low catalyst loading.

![Figure 4.2. NOE observed in the major and the minor cycloadducts 164a and 165a respectively.](image)

The relative configuration of the major and the minor cycloadducts 164a and 165a, respectively, was determined using NOE experiments. Thus, the minor diastereomer displayed a 2% NOE between the two methine protons as shown in Figure 4.2. This NOE was absent in the major diastereomer. Instead, a strong NOE was observed between the phenyl protons and the CH₂-OH protons. This assignment of relative configuration was also supported by the strong shielding
effect of the phenyl group resulting in a upfield shift of the CH$_2$-OH signals (3.27–3.42 ppm) of the major diastereomer relative to those of the minor diastereomer (3.56–3.75 ppm).

The same assignment of relative configuration of the major cycloadduct 164b and the minor one 165b was also supported by treatment of a mixture of these adducts with I$_2$ in the presence of NaHCO$_3$. Thus only the major adduct 164b, which has the hydroxyl group and the alkene moiety in close proximity, underwent an intramolecular iodoetherification, leaving the minor diastereomer unaffected (scheme 4.9). Thus, a single spirocyclic adduct, either with the structure 169 or 170 (position of the iodine not determined), was obtained.

![Scheme 4.9. Iodoetherification of a mixture of the two diastereomers 164b and 165b. Only the major diastereomer 164b reacts and forms a tricyclic spiroadduct.](image)

Although in low diastereoselectivity, the same relative exo-configuration of the major cycloadduct 164g was secured through comparison of the $^1$H NMR data of an inseparable mixture of 164g and 165g (obtained from 161 and 163g, Table 4.3, entry 9) with those in the literature of 165g.$^{87}$

It is reasonable to believe that all other major cycloadducts possess the same relative exo-configuration. Surprisingly, the exo-selectivity obtained in this work is opposite to that obtained when aldehyde 161 was reacted with C-N-diarylnitrones in the presence of chiral Lewis acid catalysts.$^{87}$

In reactions of the nitrones 163a-g with the activated iminiumspecies from aldehyde 161 and catalyst 160 (2HCl-salt), the origin of diastereoselectivity can be explained by the models depicted in Figure 4.3.

![Figure 4.3. Origin of diastereoselectivity when reacting nitrones 163a-g with the iminiumspecies from aldehyde 161 and catalyst 160 (2HCl-salt).](image)
Thus, either an exo-approach of the Z-forms of the nitrones or an endo-approach of the E-forms of those explains the observed diastereoselectivity (Figure 4.3). However, as mentioned in section 4.1, aldonitrones exist almost exclusively in their Z-forms with a large barrier of interconversion. Moreover, it has recently been reported that aldonitrones react with α,β-unsaturated aldehydes in their Z-forms under conditions similar to those used in this work. Thus, the most probable major reaction pathway is the one where the nitrones in their Z-forms react with the activated iminium species via an exo-approach.

In order to determine the absolute configurations of the major cycloadducts obtained in Scheme 4.5, one of those, 164a, was transformed via a few synthetic steps into the diol 172 (Scheme 4.10). The sign of optical rotation of this diol was compared with that of the enantiomer, ent-172, prepared from compound 173 with known absolute configuration. The latter compound was generously supplied by Dr. Kei Manabe. These two compounds, 172 and ent-172, displayed opposite signs of optical rotation and should therefore be enantiomers. It is reasonable to assume that the nitrones 163b-g react in the same fashion as nitrone 163a with aldehyde 161, and thus, the corresponding reduced cycloadducts should have the absolute configurations as depicted in Scheme 4.5.

![Scheme 4.10. Preparation of diols 172 and ent-172.](image)

With the knowledge of the absolute configurations of the reduced major cycloadducts 164, the origin of π-facial selectivity can be explained as outlined in Figure 4.4. Reaction between the catalyst 160 (2HCl-salt) and the aldehyde 161 gives a reactive iminium species, which either can adopt a Z- or an E-conformation. Moreover, the cyclopentenyl moiety of the aldehyde can either adopt an s-trans or an s-cis conformation, resulting in four possible reactive intermediates A-D (Figure 4.4). If only steric factors are considered, the major attack of the nitrones should occur on the least sterically hindered side of the π-bond of the cyclopentenyl moiety. Thus, intermediates A and D are unlikely to be

the major reactive intermediates because in order to explain the experimentally observed sense of π-facial selectivity, attack of the nitrones has to occur on the sterically hindered side of the π-bond. The two remaining possible intermediates B and C both fulfill the criterion of having the α-Si–β-Re face more exposed than the α-Re–β-Si face. Molecular mechanics calculations (CS Chem3D Pro™ 4.0) performed on simplified models of B and C (i.e. exchanging the piperidinium moiety for a trimethylammonium one), indicated that their low energy conformations had approximately the same energy. Due to the long distance between the piperidinium ring of the catalyst and the reacting π-bond, in intermediate B a low degree of discrimination between the two π-faces is expected. However, in C one of the π-faces is efficiently shielded by the piperidinium moiety. Thus, attack of the nitrones onto this intermediate will preferentially occur on the α-Si–β-Re face with a higher degree of discrimination than that expected for intermediate B. When only steric factors are considered, reaction involving the intermediate C best explains the observed sense of π-facial selectivity. However, electronic effects may also play a major role here. Therefore, B cannot be ruled out as the major reactive intermediate.

![Figure 4.4](image)

**Figure 4.4.** Reactive intermediates from aldehyde 161 and catalyst 160 (2HCl-salt). Attack on the α-Si–β-Re face by the nitrones 163a-g as indicated by arrows will furnish the major enantiomers of cycloadducts 164a-g.
4.4 Applications

Isoxazolidines are structural key moieties in many bioactive substances and herbicides. Because they are also easily ring opened to the corresponding aminoalcohols as described in section 4.1, they can serve as attractive building blocks for the construction of other natural products and bioactive substances. Isoxazolidines are also building blocks for the preparation of chiral ligands for use in enantioselective transformations. Because the total syntheses of various natural products and other bioactive substances via asymmetric 1,3-dipolar cycloaddition reactions of nitrones are numerous, only a few examples will be presented here (Figure 4.5).

Figure 4.5. Examples of alkaloids synthesised via an asymmetric 1,3-dipolar cycloaddition as a key step. The remaining original atoms, which formed the isoxazolidine ring are marked in red.

Substituted piperidines are naturally occurring compounds, which display various biological activities. An efficient approach for the syntheses of such compounds in enantiomerically pure forms is via 1,3-dipolar cycloaddition reactions of nitrones with dipolarophiles in which one or both of the reacting partners are chiral and non-racemic. Using this approach, (+)-azimic acid and the related alkaloid (+)-julifloridine (not shown) were recently obtained (Figure 4.5). Other examples include the total synthesis of the antimalarial 2-substituted piperidine (+)-febrifugine, the related alkaloid (+)-isofebrifugine (not shown), the spirocyclic piperidine derivative (−)-histrionicotoxin isolated from a “dart-poison” frog, and (+)-monomorine I.

Other types of alkaloids have also been successfully obtained via an asymmetric 1,3-dipolar cycloaddition reaction as a key step. For example (+)-sedridine and (−)-hygroline were synthesised starting from cyclic nitrones and chiral non-racemic vinyl sulfoxides and other chiral dipolarophiles (Figure 4.5). A doubly diastereoselective reaction of a chiral carbohydrate derived nitrone with vinylglycine derivatives furnished, after some additional transformations, (+)-acivicin, which has antitumor activity. A carbohydrate derived nitrone was also used in the synthesis of the antibacterial compound (+)-negamycin. Finally, the pharmacologically active alkaloids (−)-haemantidine, (+)-pretazettine and (+)-tazettine were synthesised from the precursor depicted in Figure 4.5, obtained via an asymmetric intramolecular 1,3-dipolar cycloaddition reaction followed by some additional synthetic steps.

A literature survey reveals that the various bicyclic fused isoxazolidines 164, obtained via the enantioselective 1,3-dipolar cycloadditions depicted in Scheme 4.5, are structurally similar to known bioactive substances and chiral ligands used in asymmetric synthesis. Hence, the amino acid moiety 175 (Figure 4.6) has been found to be an important structural feature in antiviral compounds effective against herpes simplex virus both in vitro and in vivo.\(^{123}\) This moiety is structurally related to the isoxazolidines 164 and therefore, such isoxazolidines could serve as potentially attractive building blocks for the syntheses of such types of amino acids.

![Figure 4.6](image_url)  
**Figure 4.6.** Structural similarities between amino alcohol 174, amino acid derivative 175 and compound 164.

Moreover, compound 164 is a possible building block for the syntheses of spirocyclic derivatives. Some spirocyclic compounds have found application as chiral ligands in asymmetric synthesis.\(^{124}\) For example amino alcohol 174 and derivatives of this have been used with success as chiral auxiliaries in asymmetric Diels-Alder reactions.\(^{125}\)

Encouraged by the good results reported with spirocyclic derivatives as chiral ligands in asymmetric synthesis, I wanted to synthesise an enantiopure spirocyclic aminoalcohol from cycloadduct 164 and explore its utility as a chiral ligand in various asymmetric transformations.\(^{126}\)

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\(^{126}\) Unpublished results.
In order to synthesise a spirocyclic ring system from isoxazolidines of type 164 (Figure 4.6) the exocyclic sidechains in the former must be connected (i.e. \( R^3 \) and the hydroxymethyl substituent). As was mentioned above, cycloadduct 164b, which could be obtained in a good yield on a large scale, and enantiomerically pure by recrystallisation, underwent iodoetherification in the presence of iodine and a base to give a single unidentified spirocyclic adduct (i.e. 169 or 170, the position of the iodine not determined, Schemes 4.9 and 4.11). I thought that further transformation of this could furnish the enantiopure spirocyclic amino alcohol 178 (Scheme 4.11).

![Scheme 4.11. Preparation of dispirocyclic compound 178.](image)

Hence, dehydrohalogenation of this iodoetherification product 169/170 by treatment with a base (DBU) furnished a single compound, which should have the structure as shown in 176 or 177 (position of double bond not determined). Catalytic hydrogenation of the \( \pi \)-bond of this followed by ring opening of the isoxazolidine ring using Zn (dust) in diluted AcOH gave the target dispirocyclic molecule 178 in \(~90\%\) overall yield from compound 164b. It must be noted that no purification procedure other than extraction was involved in the synthetic sequence from 164b to the target molecule 178. The direct transformation of compound 169/170 to 178 in one step was attempted by treatment with various reagents such as Zn/AcOH and super-hydride. However, all attempts failed and either hydrodehalogenation only or N-O cleavage only was observed. Surprisingly, when other reagents than Zn/AcOH were used, the reduction of the N-O bond proved to be very difficult.
Having established an efficient, short and high yielding synthesis of enantiopure dispirocyclic aminoalcohol 178, this compound was employed as a chiral ligand in enantioselective transformations.\textsuperscript{127} Because amino alcohols have been widely used as chiral ligands in reactions of organozinc with aromatic aldehydes,\textsuperscript{128} the efficiency of compound 178 as a ligand in this type of reaction was first investigated.

Thus, in the presence of 5 mol\% of this at –8 °C, the reaction of diethylzinc with benzaldehyde furnished 1-phenyl-1-propanol in nearly full conversion after 2 days (Scheme 4.12). However, the ee of the product was disappointingly low (22\% ee). Although this result does not encourage further investigation of ligand 178 as catalyst in this type of reaction, amino alcohol 178 is a possible potential efficient ligand in other types of asymmetric transformations. This is currently being investigated.

Scheme 4.12. Diethylzinc addition to benzaldehyde in the presence of chiral ligand 178.

\[\text{[127]} \quad \text{Unpublished results.}\]
\[\text{[128]} \quad \text{Soai, K.; Niwa, S. Chem. Rev. 1992, 92, 833-856.}\]
5. Conclusions and outlook

This thesis describes the use of either chiral auxiliaries or chiral catalysts in the syntheses of chiral non-racemic pyrrolidines, tetrahydrothiophenes, and isoxazolidines via 1,3-dipolar cycloadditions. With camphorsultam being the most efficient auxiliary, good asymmetric inductions have been achieved in the reactions of azomethine ylides and thiocarbonyl ylides. When a chiral non-racemic azomethine ylide was applied, significant improvement in $\pi$-facial selectivity was observed only when this ylide was reacted with cyclic dipolarophiles. Because the major and the minor diastereomeric pyrrolidine- and tetrahydrothiophene cycloadducts were separable either by column chromatography or by recrystallisation, diastereomerically pure 3,4-disubstituted pyrrolidines and tetrahydrothiophenes were obtained. Cleavage of the chiral auxiliaries furnished valuable enantiomerically pure building blocks.

The relatively new field of 1,3-dipolar cycloaddition reactions catalysed by metal-free chiral non-racemic organocatalysts, has also been investigated. Thus, various pyrrolidinium salts have been applied as catalysts in the reactions of some nitrones with 1-cycloalkene-1-carboxaldehydes. In some cases, these reactions furnish fused bicyclic isoxazolidines in high diastereoselectivities and enantioselectivities. One can forecast that this area of organocatalysis will be a fast growing one in the future.

When comparing the two approaches of asymmetric 1,3-dipolar cycloaddition reactions discussed in this thesis, that is, either by using chiral auxiliaries or chiral catalysts, one has to consider both the advantages and drawbacks of each of them. Whereas the former approach demands two extra synthetic steps, that is, attachment and removal of the auxiliary, the latter approach does not. Moreover, for the latter one, only a catalytic amount of a chiral material is, in most cases, needed to achieve an enantioselective process. The advantage of the first approach involving chiral auxiliaries is, that diastereomeric cycloadducts are obtained, which are, in general, easy to separate, furnishing, after auxiliary removal, an enantiopure product. However, when using the chiral catalyst approach, the cycloadducts are frequently obtained as mixtures of enantiomers, which are notoriously difficult to resolve. Normally complicated crystallisation schemes or multistep chromatography on chiral stationary phases are needed to affect resolution on a preparative scale. Thus, there is a demand to find catalysts that can furnish practically only the desired enantiomer. Although such catalysts exist for some types of cycloaddition reactions, they are often limited to certain kind of dipolarophiles and dipoles. Therefore, the development of more efficient catalysts can be expected to be a major area of research in the future.

Finally, this thesis has also included the synthetic applications of the asymmetric 1,3-dipolar cycloaddition reactions towards natural products and other bioactive substances. Also, potential catalysts have been obtained by using this approach. From simple starting materials and in one single step, it has been shown that 1,3-dipolar cycloadditions can furnish very complex cycloadducts containing several new stereogenic centres. Therefore, it comes as no surprise that such reactions often are key steps in the total syntheses of natural products.
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