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Abstract

This thesis deals with the development of synthetic methodologies for the preparation of enantio- and diastereomERICALLY enriched nitrogen-containing heterocycles.

Asymmetric Lewis acid mediated Diels-Alder reactions with 2H-azirines as dienophiles have been studied. Diastereoselective reactions with enantiomerically pure auxiliary-derived 2H-azirines afforded substituted bi- and tri-cyclic aza-heterocycles comprising a fused tetrahydropyridine–aziridine moiety in high yields and selectivities. It was found that the 8-phenylmenthol auxiliary was superior to Oppolzer’s bornane-2,10-sultam in these reactions. The influence of various Lewis acids on the reaction outcome was probed and their presence was crucial for successful reactions. The novel enantioselective aza-Diels-Alder reaction of benzyl-2H-azirine-3-carboxylate was investigated with a range of chiral Lewis acids and provided the corresponding cycloadducts in moderate to low yields and selectivities. The 2H-azirines were synthesized from the corresponding acrylates via the vinyl azides. An improved and general procedure for thermolysis of vinyl azides into 2H-azirines was developed.

Lewis acid mediated radical cyclizations of substituted N-chloro-4-pentenyl- and 4-hexenylamines gave the corresponding pyrrolidines in high yields and in moderate to high diastereoselectivities. The reactivity and stereoselectivity were found to be strongly influenced by the substituents on the alkenylamine. On the other hand, no apparent correlation between the different Lewis acids applied and the obtained selectivities was observed. The relative stereochemistry of the cyclic products could be predicted using the Beckwith-Houk stereochemical model. The pyrrolidines were rearranged via aziridinium ions, which were ring-opened to the corresponding piperidines. The efforts to develop enantioselective radical cyclizations of cationic aminyl radicals proved unsuccessful. Reaction conditions and chiral Lewis acids were varied, yet, racemic product mixtures were obtained. The N-chloro-N-alkenylamines were synthesized in good yields.

Keywords: diastereoselective, enantioselective, alkaloid, Lewis acid, chiral ligand, hetero-Diels-Alder reaction, 2H-azirine, aziridine, tetrahydropyridine, chiral auxiliary, vinyl azide, radical cyclization, cationic aminyl radical, pyrrolidine, piperidine, aziridinium ion, N-chloro-N-alkenylamine.

# Table of Contents

**Abstract**

**Table of Contents**

**Abbreviations**

**List of Publications**

## 1 Introduction

1.1 Aim of the Studies

## 2 Aza-Diels-Alder Reactions with 2H-Azirines as Dienophiles \(^1, \text{II, III}\)

2.1 Introduction

2.1.1 Stereocontrol in Diels-Alder Reactions

2.1.2 The Hetero-Diels-Alder Reaction

2.2 2H-Azirines

2.2.1 Introduction

2.2.2 2H-Azirines as Dienophiles

2.3 Diastereoselective Lewis Acid Mediated Diels-Alder Reactions - The Chiral Auxiliary Approach

2.3.1 A Comparative Study of 8-Phenylmenthol- and Oppolzer’s Sultam-derived Azirines in the Diels-Alder Reaction

2.3.2 Scope and Limitations - Dienes

2.3.3 Ring-opening of the Tricyclic [3.2.1.0] Aziridine Cycloadducts

2.3.3.1 Determination of the Absolute Configuration

2.3.4 Rationalization of the Stereochemical Outcome of the 8-Phenylmenthol-system

2.3.5 Rationalization of the Stereochemical Outcome of the Oppolzer’s Sultam-system

2.3.6 Conclusions

2.4 Enantioselective Lewis Acid Mediated Diels-Alder Reactions with Benzyl-2H-azirine-3-carboxylate

2.4.1 Chiral Lewis Acids

2.4.2 Conclusions

2.5 Synthesis of 2H-Azirines

2.5.1 Improved Procedure for Cyclization of Vinyl Azides into 3-Substituted 2H-Azirines

2.6 Concluding Remarks
3 Lewis Acid Mediated Stereoselective Cationic Aminyl Radical Cyclizations IV, V

3.1 Introduction

3.1.1 Regioselectivity in the Cyclization of 4-Pentenyl Aminyl Radicals and 5-Hexenyl Radicals

3.2 Diastereoselective Radical Cyclizations

3.2.1 Prediction of Stereochemical Outcome
3.2.2 Cyclizations – Terminal Olefins
3.2.3 Cyclizations – Disubstituted Olefins
3.2.4 Determination of the Diastereomeric Ratios
3.2.5 Rearrangement of Pyrrolidines into Piperidines
3.2.6 Synthesis of N-Chloro-N-Alkenylamines
3.2.7 Conclusions

3.3 Enantioselective Radical Cyclizations

3.3.1 Substrates and Chiral Lewis Acids
3.3.2 Conclusions

3.4 Concluding Remarks

References

Acknowledgements

Appendix A
### Abbreviations

<table>
<thead>
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<th>Abbreviation</th>
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<td>Δ</td>
<td>heat</td>
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<tr>
<td>BINOL</td>
<td>1,1′-bi(2-naphtol)</td>
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<td>D-A</td>
<td>Diels-Alder</td>
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<tr>
<td>DMPU</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
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List of Publications

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

I. Stereoselective aza-Diels-Alder reactions with 2H-azirines furnishing highly functionalized tetrahydropyridines
Ása Sjöholm Timén, Andreas Fischer and Peter Somfai

II. Investigation of Lewis Acid Catalyzed Asymmetric Aza-Diels-Alder Reactions of 2H-Azirines
Ása Sjöholm Timén, Andreas Fischer and Peter Somfai
Submitted.

III. Improved procedure for cyclization of vinyl azides into 3-substituted-2H-azirines
Ása Sjöholm Timén, Erik Risberg and Peter Somfai

IV. Probing the diastereoselectivity in the cyclization of cationic aminyl radicals
Martin Hemmerling, Ása Sjöholm and Peter Somfai

V. Investigation of the Lewis acid mediated stereoselective cyclization of cationic aminyl radicals leading to substituted pyrrolidines
Ása Sjöholm, Martin Hemmerling, Nicolas Pradeille and Peter Somfai

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1 Introduction

Synthetic organic chemistry deals with the creation of carbon-containing molecules which may find use in diverse areas such as medicine, agriculture, polymer- and petroleum-industry.

An enormous development in the field of organic synthesis has occurred since the early 19th century when the first synthesis of an organic molecule, urea, was reported. Already today there is an immense number of reactions that can be used for the synthesis of compounds with different levels of structural complexity. However, in order to meet the demands for cost-efficient and environmentally benign processes for the preparation of effective products, further improvements of existing methods as well as development of new synthetic methodology are still needed. The ideal synthetic pathway includes atom-efficient, high yielding, stereoselective, simple, non-toxic, and inexpensive reaction steps.

Alkaloids are an important group of naturally occurring compounds, which often comprise one or more nitrogen-containing cyclic moieties. Since this type of compounds often show interesting biological activities and also possess intriguing structures (Figure 1.1), they have for a long time attracted attention as synthetic targets from organic chemists.  

![Figure 1.1 Examples of heterocyclic alkaloids with biological activity and interesting structures.](image)

The majority of the alkaloids are, as many organic compounds, chiral. This is also true for biological receptors, which therefore, can distinguish between two stereoisomers of a substrate. The two enantiomers, as well as the racemate, may as a result, show different levels of activity or even different behavior, such as taste and smell but also pharmacological properties. One example is the two isomers of propranolol of which the (S)-enantiomer shows cardiac activity (as a β-blocker) and the (R)-enantiomer acts as a contraceptive (Figure 1.2). It is thus important to be able to obtain stereochemically pure compounds. The methods available for this purpose can be divided into three categories; resolution, use of the chiral pool, and asymmetric synthesis.
1.1 Aim of the Studies

The main focus of this thesis is the development of two synthetic methodologies, which generate nitrogen-containing heterocycles in a stereoselective fashion. During the course of our investigations, diastereoselective reactions as well as enantioselective reactions have been studied.

In the first method, discussed in Chapter 2, the heterocyclic products are formed via a Lewis acid mediated asymmetric [4+2] cycloaddition, the Diels-Alder reaction. Substituted 2H-azirines are used as dienophiles, which facilitate a convenient incorporation of a nitrogen atom into the fused cyclic structure (Scheme 1.1). Two ways to control the absolute stereochemistry of the cycloaddition adducts are presented: the use of chiral auxiliary-derived azirine-3-carboxylates in combination with Lewis acids, or by the application of chiral Lewis acids.

![Diels-Alder reaction with 2H-azirines as dienophiles.](image)

In addition, the synthesis of auxiliary-derived azirines, including an improved general method for thermal cyclization of vinyl azides into 2H-azirines, is also described in Chapter 2.
The second method, described in Chapter 3, involves intramolecular addition of cationic nitrogen-centered radicals onto double bonds, to give the kinetically favored pyrrolidines 3, which can be rearranged into the corresponding piperidines 4 (Scheme 1.2). These five- and six-membered aza-heterocycles are ubiquitous structural segments in natural as well as synthetic compounds. The investigation of the diastereoselective radical cyclizations of 2-substituted N-chloro-4-pentenyl and 4-hexenylamines is presented, as well as the corresponding enantioselective cyclizations of the 2,2-dimethyl-substituted N-chloro-4-pentenyl amines. In addition, the synthesis of the different N-chloroamines 2 is described in this part of the thesis.

Scheme 1.2 Lewis acid mediated radical cyclizations of cationic aminyl radicals and rearrangement of the formed pyrrolidines into the corresponding piperidines.
2 Aza-Diels-Alder Reactions with 2H-Azirines as Dienophiles I, II, III

2.1 Introduction

The Diels-Alder reaction, often cited as the most powerful reaction for the construction of six-membered rings,\textsuperscript{5-7} was discovered by Professor Otto Diels and his student Kurt Alder in 1928. They recognized that two sequential [4+2] cycloadditions of a conjugated diene, cyclopentadiene (5) to a dienophile, quinone (6) took place (Scheme 2.1). This discovery was later acknowledged by the award of the Nobel Prize in 1950.

\begin{center}
\begin{tikzpicture}
  \node (5) at (0,0) {5};
  \node (6) at (2,0) {6};
  \draw[->] (5) -- (6) node [midway, above] {D-A reaction};
  \draw[->] (6) -- (5) node [midway, below] {endo-addition};
\end{tikzpicture}
\end{center}

\textit{Scheme 2.1} The discovery of the Diels-Alder reaction.

The usefulness of this reaction arises from its versatility and high regio- and often stereoselectivity. It is the formation of two new $\sigma$-bonds at the expense of two $\pi$-bonds, and the formation of up to four contiguous stereogenic centers in one single transformation, which account for the high efficiency of the reaction. Not only does the Diels-Alder reaction create complex molecules in an atom-efficient way, but it also leads to compounds with amendable structural motifs. These qualities have made the Diels-Alder reaction a frequently employed reaction step in the total synthesis of various natural products.\textsuperscript{6}
2.1.1 Stereocontrol in Diels-Alder Reactions

Up to eight isomers can be formed in a [4+2] cycloaddition between unsymmetrical substrates (Scheme 2.2). Nevertheless, this reaction is known to give products with well defined and predictable relative stereochemistry. The regioselectivity is mainly governed by the substituents and is often enhanced by coordination to a Lewis acid.\textsuperscript{8}

The relative stereochemistry of the product is determined by the approach of the dienophile, \textit{exo} or \textit{endo}, to the diene (Scheme 2.2). Alder’s \textit{endo} rule predicts a preference for \textit{endo} approach, based on the maximum orbital overlap, although this rule seems to be strictly applicable only to cyclic substrates.\textsuperscript{9} Substituents, Lewis acid complexation and hetero atoms present in the \(\pi\)-system also influence the \textit{endo}/\textit{exo} selectivity.

In order to control the absolute stereochemistry, discrimination between the two \(\pi\)-faces is needed. This can be achieved by substrate-control, including the use of a chiral auxiliary, and by the use of chiral catalysts. Although many fruitful examples of asymmetric Diels-Alder reactions with chiral auxiliaries have been reported, the two additional steps required in order to attach and remove the auxiliary and the need for equimolar amounts of the enantiomerically pure entity, are the drawbacks. A more appealing approach for asymmetric synthesis is, therefore, the use of chiral catalysts.
2.1.2 The Hetero-Diels-Alder Reaction

The Diels-Alder reaction is equally powerful for the construction of six-membered heterocycles.\(^{10}\) Any of the atoms in the dienophile and the diene may be exchanged for a heteroatom such as nitrogen, oxygen or sulfur which imply an enormous diversity in the structural types of substrates and, hence, the formed cycloadducts. The first reported imine dienophile was mentioned by Alder already 60 years ago. However, unactivated imines are generally not reactive enough to be used as dienophiles in aza-Diels-Alder reactions. This can be circumvented by having one, or preferably two, electron-withdrawing substituents on the imine group. The most commonly used activators for acyclic imines are carbonyl and sulfonyle groups.\(^{11,12}\) Alternatively, a Lewis acid or a protic acid can be used to activate the imine. Theoretical studies indicate that the mechanism of the hetero-Diels-Alder reaction may change from a concerted non-synchronous to a stepwise mechanism (a tandem Mannich-Michael reaction for imine dienophiles) depending on the substituents.\(^{13}\) Lewis acid activation can have the same influence on the mechanism, which has been shown for an oxo-Diels-Alder reaction.\(^{14}\) When ZnCl\(_2\) was used as catalyst the products were formed via a concerted reaction, whereas in the presence of BF\(_3\)·OEt\(_2\) the reaction proceeded by a stepwise mechanism. Carbonyl-containing compounds have been extensively, and successfully, used together with Lewis acids in catalytic enantioselective transformations.\(^{13,15}\) However, the development of catalytic enantioselective aza-Diels-Alder reactions with imines as dienophiles has only recently been explored, with varying results.\(^{11,13}\) One reason for this may be that imines and amines have some properties differing from those of the carbonyl compounds, properties which have to be considered in order to obtain high selectivities and yields. The nitrogen atom in amines is more Lewis basic than the oxygen atom in carbonyl compounds. This leads to a stronger coordination to the chiral Lewis acid, thus, deactivating or inhibiting the catalyst. Imines also exist as E- and Z-isomers which increases the number of TS-structures and, consequently, the number of possible products in the Diels-Alder reaction. The sometimes low stability of the imine dienophiles and the presence of an acidic α-proton, leading to formation of enamines, may also have contributed to make the aza-Diels-Alder reaction less frequently used than the corresponding reaction with carbonyl compounds.
2.2 2H-Azirines

2.2.1 Introduction

2H-Azirines are three-membered unsaturated nitrogen-containing heterocycles with a carbon-nitrogen double bond (Figure 2.1). The bond lengths and angles have been determined by X-ray crystallography and it was found that the C(2)-N bond is longer and the C-C bond shorter than those in simple aliphatic imines.\textsuperscript{16,17}

![Figure 2.1 Structure of the 2H-azirine.](image)

Typical bond angles are N=C-C, 72°, C-C-N, 48°, and C-N=C, 60°. The small ring size and, hence, the large deviation from normal bond angles impart a substantial strain, which has been estimated by molecular orbital calculations to be 44-48 kcal/mol.\textsuperscript{18} This ring strain, the reactive π-bond and the nitrogen lone pair electrons make the 2H-azirines highly reactive and allow for their participation in a variety of reactions. The majority of these, such as nucleophilic addition, hydrogenation and cycloaddition reactions take place at the activated π-bond. There are also reports of photolytic and thermal ring cleavage of the C(2)-N bond, leading to transient vinyl nitrenes.\textsuperscript{16,19} Although 2H-azirines are less basic than aliphatic imines they can still act as nucleophilic reagents and react with, for instance, acylating agents.\textsuperscript{20} This versatility makes azirines valuable synthetic intermediates for the preparation of various amines such as aziridines and more complex heterocycles. However, the high reactivity may cause stability problems, especially with activating groups such as carbonyl, carboxylic ester, amide, phosphate, and acylsulfonamide groups attached to the 3-position.
Surprisingly, despite their high reactivity, $2H$-azirines occur naturally. The first azirine-containing natural product to be isolated was the antibiotic azirinomycin (7), which was obtained from *Streptomyces aureus* (Figure 2.2). Both enantiomers of dysidazirine (8 and 9) and (S)-(+)‐antazirine (10) have been isolated from a marine sponge, *Dysidea fragilis*. However, only (R)-(−)-dysidazirine shows biological activity.\(^\text{22}\)

![Figure 2.2 Naturally occurring $2H$-azirines](image)

### 2.2.2 $2H$-Azirines as Dienophiles

$2H$-azirines are inherently more reactive than acyclic imines and there are literature examples of unactivated azirines which participate in Diels–Alder reactions, albeit with reactive dienes such as tetraphenylcyclopentadienone.\(^\text{23}\) With an activating substituent in the 3-position, [4+2] cycloadditions take place also with less reactive dienes, including cyclopentadiene, 1,3-cyclohexadiene, and 2,3-dimethylbutadiene.\(^\text{24,25}\) Somfai *et al.* showed that it is possible to use Lewis acids to activate the azirines towards cycloaddition with various dienes. This eliminates the need for specific substituents and increases the versatility of the reaction.\(^\text{26,27}\)

The $2H$-azirine-3-carboxylates are less basic and more reactive than their acyclic counterparts, they have a well defined conformation around the double bond, and no acidic $\alpha$-proton.\(^\text{2}\) These inherent characteristics appear to make the $2H$-azirine-3-carboxylates the ideal dienophiles for catalytic enantioselective reactions.

The formed cycloaddition products contain a fused tetrahydropyridine–aziridine moiety, which has a large potential for further synthetic manipulations (Scheme 2.3).

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\(^\text{2}\) The $1H$-azirine, which is the possible enamine product, is highly unstable and about 33-37 kcal/mol higher in energy than the $2H$-azirine.
The double bond created in the Diels-Alder reaction can be dihydroxylated, the carboxylic ester reduced to the corresponding alcohol, and the aziridine-ring opened to form a product with a [3.2.1] ring system (from the tricyclic Diels-Alder products, Chapter 2.3.3). The formed aziridines, when substituted with carboxylic acid derivatives, can also be considered as both α- and β-amino acid derivatives and may, therefore, be valuable for the synthesis of unnatural amino acids.

Many biologically active compounds, synthetic as well as naturally occurring, contain the β-amino alcohol functionality. The α-glucosidase inhibitor nojirimycin (11), which belongs to a group of aza-sugars is one example (Figure 2.3). Analogous compounds containing an aziridine ring have also been synthesized, some of which exhibit an inactivating effect on glycosylhydrolases.

Figure 2.3 Nojirimycin (11) and an aziridine analogue 12 are examples of biologically active aza-sugars.
Moreover, enantiomerically pure hydroxymethyl-substituted aziridines have been applied successfully as ligands in reactions such as diethylzinc additions to aldehydes and imines.\textsuperscript{31} Also chiral bicyclic aza-cycloadducts have found use as efficient ligands in various metal-catalyzed asymmetric transformations (Figure 2.4), including transfer hydrogenations, allylic oxidations, rearrangement of epoxides, and diethylzinc additions to imines.\textsuperscript{32}

![Figure 2.4 An example of chiral bicyclic amines used as ligands in metal-catalyzed transformations.](image.png)

### 2.3 Diastereoselective Lewis Acid Mediated Diels-Alder Reactions - The Chiral Auxiliary Approach

Most Diels-Alder reactions with 2\textit{H}-azirines as dienophiles give exclusively the \textit{endo} cycloaddition products (with respect to the three-membered ring). One exception is the reaction with furan (as diene).\textsuperscript{33} Calculations indicate that there is a strong preference for an \textit{exo} orientation of the nitrogen lone pair in imines.\textsuperscript{34} This has been explained by repulsion between the \(\pi\)-system of the diene and the nitrogen lone pair. Accordingly, the three-membered ring of the azirine would be situated in an \textit{endo} fashion with an \textit{exo}-oriented lone pair. For formaldimine and butadiene an energy difference of 4.9 kcal/mol was found between the two diastereomeric transition structures, favoring the \textit{exo} lone pair.

Despite the many examples of excellent regio- and diastereoselective [4+2] cycloadditions of azirines, only few attempts to control the absolute stereochemistry have been published.\textsuperscript{24,35,36} For these systems, the inherent chiral information in auxiliaries and azirine ring governed the stereochemical outcome. Davies and co-workers reported on the asymmetric synthesis of 2-aryl-2\textit{H}-azirine-3-phosphonates 13 (Figure 2.5), which underwent highly stereoselective Diels-Alder reactions with 2,3-dimethylbutadiene, \textit{trans}-1,3-pentadiene, and Danishefsky’s diene.\textsuperscript{24} Although only one stereoisomer was isolated in each case, the need for a sterically demanding substituent on the azirine ring is a drawback, as it is difficult to remove this group after the reaction. Gilchrist \textit{et al.} investigated the two isobornyl-derived azirines 14\textit{a} and 14\textit{b} as well as the (S)-phenylethylamide-substituted azirine 15 in Diels-Alder reactions (Figure 2.5). The stereoselectivity of the cycloaddition was low, with 14\textit{b} affording products with slightly higher de, than 14\textit{a}.\textsuperscript{36} No selectivity was observed in the Diels-Alder reactions with azirine 15.\textsuperscript{35}
Nevertheless, there are numerous examples of the successful use of chiral auxiliaries in Diels-Alder reactions, although not as many for the aza-cycloadditions.\textsuperscript{11,13,37} The selectivity is often increased upon coordination of a Lewis acid to either the dienophile, the diene or to both. However, many azirines, particularly the ester-substituted ones, are extremely susceptible to acid-catalyzed decomposition and this limits their use together with Lewis acids. Chiral auxiliaries are often attached to the substrates via an ester or amide linkage, which activates but also destabilizes the azirines, and thus complicates the use of Lewis acids. However, previous work in our laboratory has shown that it is possible to enhance the reactivity of unactivated, as well as activated azirines, by coordination to Lewis acids without serious decomposition of the azirines (Chapter 2.2.2). With this in mind, we decided to investigate the combination of chiral auxiliary-derivatized 2H-azirines and Lewis acids in Diels-Alder reactions.

### 2.3.1 A Comparative Study of 8-Phenylmenthol- and Oppolzer’s Sultam-derived Azirines in the Diels-Alder Reaction

Among the many different auxiliaries used in Diels-Alder reactions, cyclohexyl-based secondary alcohols \textsuperscript{16} and \textsuperscript{17} and camphor derivatives such as \textsuperscript{19} repeatedly have given useful levels of stereochemical induction (Figure 2.6).\textsuperscript{8,37-39}
However, the readily available (−)-menthol (16) does itself rarely induce high selectivities. Therefore, analogues have been developed. One such analogue is Corey’s 8-phenylmenthol (17). Its synthesis and use in natural product synthesis was first described in 1975, and it has since then found use in a variety of reactions.38

Oppolzer and co-workers have developed a class of auxiliaries based on the bornane-2,10-sultam skeleton 19.39 The α,β-unsaturated N-acylsultams, such as acryloyl sultam 20, undergo highly stereoselective [4+2] cycloadditions to both cyclic and acyclic conjugated dienes in the presence of EtAlCl₂ and TiCl₄.39 The two auxiliaries 17 and 19 were, due to their well known performance, selected for our study.

The earlier mentioned poor results obtained in the Diels-Alder reactions of dienophiles 14a, 14b and 15, were assumed to be due to the low barrier of rotation between the two azirine conformers. This hypothesis was based on the theoretical study of 2H-azirine-3-carboxylic acid, which showed the two minimized conformers to be almost equal in energy, with a barrier of interconversion through rotation of only 1.9 kcal/mol (Figure 2.7).41

![Figure 2.7 Two energy minimized conformers of 2H-azirine-3-carboxylic acid.](image)

This finding led us to explore chelating Lewis acids, capable of complexation to both the azirine-nitrogen atom and the carbonyl-oxygen atom, in order to circumvent the problem with the rotation around the azirine-carbonyl single bond. Magnesium, zinc and lanthanide halides are mild Lewis acids known to form chelates and, therefore, MgBr₂·OEt₂, ZnCl₂·OEt₂ and YtCl₃ were selected for initial studies.42 The two azirines 21a and 21b were reacted with 1-methoxy-1,3-butadiene (22) in dichloromethane under thermal conditions as well as in the presence of two equivalents of a Lewis acid (Scheme 2.4).
Scheme 2.4 Diels-Alder reaction of 2H-azirines 21a and 21b with 1-methoxy-1,3-butadiene (22).

The reactions performed without Lewis acid at room temperature gave no or low diastereoselectivity (entries 1 and 2, Table 2.1). These results are in line with those previously obtained with other auxiliaries reported by Gilchrist. Upon addition of MgBr₂·OEt₂ to azirine 21a, a remarkable increase in selectivity occurred, and 23a and 24a were obtained as a 94:6 mixture (entry 3). For the sultam-derived azirine 21b, the influence of the MgBr₂·OEt₂ was not of the same magnitude, giving 23b and 24b in 40% de (entry 4).

Table 2.1 Lewis acid mediated Diels-Alder reactions of 21a and 21b with 22.

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<td>23a, 24a</td>
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<td>–78 to –20</td>
<td>43e</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>21b</td>
<td>23a, 24b</td>
<td>YbCl₃</td>
<td>–78 to –60</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>21a</td>
<td>23a, 24a</td>
<td>Mg(OTf)₂</td>
<td>–78</td>
<td>84d</td>
<td>8g</td>
</tr>
<tr>
<td>10</td>
<td>21a</td>
<td>23a, 24a</td>
<td>Mg(ClO₄)₂</td>
<td>–78</td>
<td>73d</td>
<td>2g</td>
</tr>
<tr>
<td>11</td>
<td>21a</td>
<td>23a, 24a</td>
<td>MgI₂·(OEt₂)ₓ</td>
<td>–78</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a) Reaction conditions; 0.05 M of azirine in CH₂Cl₂, 2 equiv of Lewis acid, and 2 equiv of diene 22 at the specified temperature. b) The absolute configuration has not been determined for 23b and 24b. c) Determined by ¹H NMR. d) Based on unreacted azirine. e) After chromatography. f) Opposite major diastereomer compared to entries 2, 4, and 8. g) Opposite major diastereomer compared to entries 1, 3, 5, and 7.

* The absolute configuration has not been determined for 23b and 24b.
The same trend was observed for the reactions mediated by ZnCl$_2$·OEt$_2$, in which 23a and 24a were obtained in 80% de, in favor of 23a, and cycloadducts 23b and 24b in 27% de (entries 5 and 6). However, for the latter case the opposite diastereomer was obtained as the major product compared to that reported in entries 2, 4, and 8. YbCl$_3$ did not bring about any useful levels of stereo-differentiation for either azirine (entries 7 and 8). Interestingly, when applying Mg(OTf)$_2$, Mg(ClO$_4$)$_2$, and MgI$_2$·(OEt$_2$)$_x$ as alternative magnesium sources, no positive effect on the stereoselectivity nor on the reaction rate of the formation of 23a and 24a was found (entries 9-11). A similar observation regarding the activating effect of various magnesium salts was reported for the asymmetric reduction of imines in the presence of a Lewis acid.$^{43}$

It is clear from the results above, that MgBr$_2$·OEt$_2$ and ZnCl$_2$·OEt$_2$ have a large influence on the stereochemical outcome of the cycloaddition reaction using 8-phenylmenthol-derived azirine 21a as dienophile. These results support the hypothesis that a hindered rotation of the azirine moiety, due to bidentate coordination of the Lewis acids to the azirine nitrogen and the carbonyl oxygen, would result in improved stereoselectivity. This hypothesis is further corroborated by the increased reaction rate observed in the presence of the Lewis acids. One example is the cycloaddition of azirine 21a, which without Lewis acid required more than 24 h at room temperature to reach full conversion, while less than 10 min at -100 °C was sufficient in the presence of ZnCl$_2$·OEt$_2$. This effect could be ascribed to the lowering of the LUMO of the azirine, and thus, an increased reactivity towards cycloaddition.

This comparative study between the two chiral auxiliaries 17 and 19 clearly showed the 8-phenylmenthyl-2H-azirine-3-carboxylate (21a) to be the most promising substrate and this compound was selected for further studies.
2.3.2 **Scope and Limitations - Dienes**

In order to evaluate the synthetic scope of this reaction and to confirm the stereo-discriminating abilities of the chiral auxiliary 17, azirine 21a was reacted with an additional set of dienes, comprising Danishefsky’s diene (25), cyclohexadiene (28a), 2-(trimethylsilyloxy)-1,3-cyclohexadiene (28b), furan (31), and cyclopentadiene (5) (Scheme 2.5).

![Diels-Alder reactions](image.png)

**Scheme 2.5** Diels-Alder reactions of 2H-azirine 21a with diene 25, 28a, 28b, 31, and 5.

The Diels-Alder reactions of 21a gave with all the dienes, except furan, cycloaddition products in good to excellent selectivities in the presence of either MgBr₂·OEt₂ and/or ZnCl₂·OEt₂ (Table 2.2). Also in these reactions a considerable increase in the π-facial selectivity was observed when Lewis acids were employed in the reaction (compare entry 1 with 2 and 3; 4 with 6; 7 with 8; and 12 with 13 and 14). The reactions run in the absence of Lewis acid were first performed at approximately −78 °C, in order to estimate the rate of the background reaction at the temperature at which the Lewis acid mediated reactions were to take place. For most dienes, the uncatalyzed reaction was so slow at −78 °C that the temperature had to be increased. The thermal reaction with diene 25 gave a mixture of the cycloaddition products in 30% de and in 90% yield with no need for further purification (entry 1). In the presence of MgBr₂·OEt₂ the selectivity was increased to give a 98:2 mixture favoring 26, although, in lower yield (entry 2).
Table 2.2 Diels-Alder reactions of 2H-azirine 21a with diene 25, 28a, 28b, 31, and 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>LA</th>
<th>T (°C)</th>
<th>Products</th>
<th>Yield (%)</th>
<th>de(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>-</td>
<td>-75 to -40</td>
<td>26, 27</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>MgBr(_2)-OEt(_2)</td>
<td>-100</td>
<td>26, 27</td>
<td>56(^c)</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>ZnCl(_2)-OEt(_2)</td>
<td>-100 to -90</td>
<td>26, 27</td>
<td>31(^c)</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>28a</td>
<td>-</td>
<td>rt</td>
<td>29a, 30a</td>
<td>100(^d)</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>28a</td>
<td>MgBr(_2)-OEt(_2)</td>
<td>-77</td>
<td>29a, 30a</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>28a</td>
<td>ZnCl(_2)-OEt(_2)</td>
<td>-78</td>
<td>29a, 30a</td>
<td>99</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>28b</td>
<td>-</td>
<td>-75 to -40</td>
<td>29b, 30b</td>
<td>80(^c)</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>28b</td>
<td>MgBr(_2)-OEt(_2)</td>
<td>-75</td>
<td>29b, 30b</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>28b</td>
<td>ZnCl(_2)-OEt(_2)</td>
<td>-77</td>
<td>29b, 30b</td>
<td>99</td>
<td>34</td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>-</td>
<td>-75</td>
<td>32a, 33a</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>31</td>
<td>MgBr(_2)-OEt(_2)</td>
<td>-78</td>
<td>32a, 33a</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>-</td>
<td>-78 to -40</td>
<td>32b, 33b</td>
<td>99</td>
<td>8</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>MgBr(_2)-OEt(_2)</td>
<td>-100</td>
<td>32b, 33b</td>
<td>88(^c)(^e)</td>
<td>85</td>
</tr>
<tr>
<td>14</td>
<td>5</td>
<td>ZnCl(_2)-OEt(_2)</td>
<td>-100</td>
<td>32b, 33b</td>
<td>99</td>
<td>58</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>MgI(_2)(OEt(_2))(_x)</td>
<td>-78 to -40</td>
<td>-</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>16</td>
<td>5</td>
<td>MgBr(_2)</td>
<td>-100 to -72</td>
<td>32b, 33b</td>
<td>100(^e)</td>
<td>10</td>
</tr>
<tr>
<td>17</td>
<td>5</td>
<td>MgCl(_2)</td>
<td>-78 to -40</td>
<td>32b, 33b</td>
<td>100(^e)</td>
<td>15</td>
</tr>
<tr>
<td>18</td>
<td>5</td>
<td>Mg(OTf)(_2)</td>
<td>-100 to -72</td>
<td>32b, 33b</td>
<td>100</td>
<td>17(^g)</td>
</tr>
<tr>
<td>19</td>
<td>5</td>
<td>YbCl(_3)</td>
<td>-73</td>
<td>32b, 33b</td>
<td>100(^e)</td>
<td>31</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>SnCl(_4)</td>
<td>-90 to -60</td>
<td>32b, 33b</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>5</td>
<td>Ti(OiPr)(_4)</td>
<td>-71</td>
<td>32b, 33b</td>
<td>60</td>
<td>16</td>
</tr>
<tr>
<td>22</td>
<td>5</td>
<td>ZnCl(_2)-OEt(_2)(^h)</td>
<td>-77</td>
<td>32b, 33b</td>
<td>54(^c)</td>
<td>19</td>
</tr>
<tr>
<td>23</td>
<td>5</td>
<td>BF(_3)-Et(_2)O</td>
<td>-77</td>
<td>32b, 33b</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions; 0.05 M of azirine 21a in CH\(_2\)Cl\(_2\), 2 equiv of Lewis acid, and 2 equiv of diene at the specified temperature. \(^b\) Determined by \(^1\)H NMR. \(^c\) After chromatography. \(^d\) Based on unreacted azirine. \(^e\) Including ring opened aziridine. \(^f\) Only ring opened aziridine was obtained. \(^g\) Opposite major diastereomer compared to entries 12-17, 19, and 21. \(^h\) 0.1 Equivalents.

The selectivity and yield also dropped slightly for the reaction mediated by ZnCl\(_2\)-OEt\(_2\) (entry 3). The low yields might be explained by the acid-sensitivity of the diene, as well as of the formed product. Hydrolysis of the TMSO-group in the cycloadduct prior to chromatography may improve the yields, albeit of the corresponding \(\alpha,\beta\)-unsaturated ketone. For cyclohexadiene, ZnCl\(_2\)-OEt\(_2\) proved to be a valuable complement to MgBr\(_2\)-OEt\(_2\), promoting the formation of a 90:10 mixture of diastereomers 29a and 30a in 99% yield (entry 6). No product was isolated from the reaction mediated by MgBr\(_2\)-OEt\(_2\), although TLC indicated formation of a minor
amount of product during the course of the reaction. On the other hand, the TMSO-
substituted cyclohexadiene gave excellent result in the presence of MgBr₂·OEt₂, 97% de in quantitative yield (entry 8), whereas ZnCl₂·OEt₂ exhibited no influence on the stereoselectivity (compare entry 7 with 9). For both Lewis acids, a significant increase in the reaction rate was observed, from days for the thermal reaction to less than 30 min, thus, indicating a coordination to the azirine also for ZnCl₂·OEt₂. Furan was the only diene of those investigated, which did not afford any desired product (entries 10 and 11). In the MgBr₂·OEt₂ mediated reaction the azirine was completely consumed after 55 min. The cycloaddition products formed from furan and its derivatives under thermal reaction conditions are, according to the literature, highly susceptible to hydrolysis and alcoholysis. This might explain the absence of product, especially in the Lewis acid activated reaction.

The reaction between azirine \(21a\) and cyclopentadiene (5) was effectively accelerated by the use of MgBr₂·OEt₂ or ZnCl₂·OEt₂, which both gave the cycloadduct in good yield in less than 10 min. However, MgBr₂·OEt₂ was also in this case superior to ZnCl₂·OEt₂ concerning the induction of stereoselectivity, affording the cycloadducts \(32b\) and \(33b\) as a 93:7 mixture (entries 13 and 14).

Among the other magnesium-based Lewis acids explored, MgI₂·(OEt)ₓ was the only one which facilitated the cycloaddition reaction with cyclopentadiene in useful diastereoselectivity, giving a 89:11 mixture of products (entry 15). The isolated compounds were, however, not \(32b\) and \(33b\) as expected, but the corresponding ring-opened 2-aza-bicyclo[3.2.1]octene structures (Chapter 2.3.3). MgBr₂, MgCl₂, and Mg(OTf)₂ did not considerably improve the reaction rate, nor the selectivity (entries 16-18). In fact, in the presence of the latter, 17% de was obtained in favor of the opposite diastereomer which also was the case in the reaction using diene 22 (entry 9, Table 2.1). No plausible explanation has been found for these results. YbCl₃ proved to be unsatisfactory also in the Diels-Alder reaction with cyclopentadiene (entry 19), and so was SnCl₄, which did not afford any desired product. Computational studies performed in the group indicated that SnCl₄ may efficiently coordinate to azirines, and this was also supported by NMR experiments. However, these experiments were performed on 3-phenyl-2H-azirine which is more stable than azirine \(21a\).

It is worth noting that the Lewis acids which are the most successful in promoting the Diels-Alder reactions of azirine \(21a\), are etherate complexes. This becomes strikingly clear when comparing the results obtained with MgBr₂·OEt₂ and MgBr₂ (entries 13 and 16). No unambiguous explanation has been found yet, although the differences in solubility might be one reason. It is known that the etherate complexes of zinc and magnesium halides are more potent Lewis acids in CH₂Cl₂ than their uncomplexed counter parts, presumably due to increased solubility. Yet, the MgBr₂·OEt₂ was not entirely soluble at the reported reaction conditions (Table 2.1 and Table 2.2).
The basicity of the formed aziridines exceeds that of the corresponding 2H-azirines. This leads to inhibition or deactivation of the Lewis acid, and stoichiometric amounts of the acid are required. It was found, however, that 0.1 equivalents of ZnCl₂·OEt₂ was sufficient to catalyze the Diels-Alder reaction of azirine 21a with diene 5, with full conversion of the azirine after 4.5 h at −77 °C, although, with low selectivity (entry 22). The shorter reaction time (compared to days for the uncatalyzed reaction) indicates a catalytic effect. There is no information regarding the structure of the reacting species that is whether it is monomeric or oligomeric. Although a catalytic amount of Lewis acid is sufficient for promoting the reaction, the presence of two equivalents of ZnCl₂·OEt₂ gives higher stereoselectivity (compare entry 14 with 22).

2.3.3 Ring-opening of the Tricyclic [3.2.1.0] Aziridine Cycloadducts

The strained aziridine ring, (in the tri-cyclic cycloaddition products 32b and 33b) formed in the reaction between azirine 21a and diene 5, was found to undergo stereoselective ring-opening readily (Scheme 2.6).

All magnesium halides and YbCl₃ promoted the formation of the substituted 4-halo-2-aza-bicyclo[3.2.1]octene structure 34. With MgI₂·(OEt₂)ₓ as catalyst, the ring-opened diastereomers were exclusively formed (see entry 15, Table 2.2). A minor amount of 34c was also detected in the mixture of products obtained from the reaction mediated by SnCl₄. To ascertain that the diastereomeric ratio was maintained throughout the transformation, a mixture of 32b and 33b was stirred with MgBr₂·OEt₂, and the reaction was monitored by HPLC.* It was found that no epimerization occurred during the reaction. A few Lewis acids which were selected in an attempt to limit this undesired ring-opening reaction were, in addition to the previously discussed Mg(OTf)₂ and YbCl₃, Yb(OTf)₃ and Ti(OiPr)₄ (entry 21, Table 2.2). None of these displayed the same ability to influence the stereoselectivity as MgBr₂·OEt₂ and MgI₂·(OEt₂)ₓ did. Despite the modest diastereoselectivity, ZnCl₂·OEt₂ is the Lewis acid of choice for the Diels-Alder reaction of cyclopentadiene and alkyl-2H-azirine-3-

* A ZORBAX Rx-SIL column was used in these analyses.
carboxylates, as no ring-opening reaction occurs in the presence of this Lewis acid. The two 8-phenylmenthol-derived diastereomers 32b and 33b are also easily separated by standard column chromatography.

2.3.3.1 Determination of the Absolute Configuration by X-Ray Crystallography

Compound 34a was found to be a solid, and after recrystallization, the absolute configuration was determined by X-ray crystallography (Figure 2.8).

![Figure 2.8 X-Ray structure of compound 34a.](image)

The absolute configuration of the major isomers obtained in the Diels-Alder reactions, 23a, 26, 29a, and 29b, were assigned by analogy with 32b by comparison of the NMR-spectra. The relative stereochemistry of the cycloaddition products was determined by 2D-NMR experiments, such as NOESY, COSY, HMQC, and HMBC.

2.3.4 Rationalization of the Stereochemical Outcome of the 8-Phenylmenthol-system

The established absolute configurations of the major products are in agreement with what can be expected from the accepted model of the 8-phenylmenthol auxiliary (Figure 2.9).⁵

![Figure 2.9 The presumed TS-structure of the [4+2] cycloaddition of azirine 21a with cyclopentadiene.](image)
It is believed that the carbonyl group in the ester linkage is aligned with the axial C(1) hydrogen atom (in the cyclohexyl group) in order to minimize the sterical interactions. With a syn periplanar O=C–C=N conformation, one face of the azirine ring is shielded by the phenyl group, which is oriented parallel to the ester-azirine π-system. In the presence of a chelating Lewis acid, the azirine moiety is locked in an s-cis conformation, thus, leading to an approach of the diene to the Si-face of the azirine.

In an attempt to confirm the structure of the proposed chelating model, the monodentate Lewis acid BF₃·OEt₂ was applied. No desired product was obtained even though all the azirine was consumed (entry 23, Table 2.2). According to NMR-spectroscopy, only degradation products were present.

Low temperature NMR-studies of azirine 21a (Figure 2.10) with ZnCl₂·OEt₂ showed a downfield shift of the imine carbon and an upfield shift of the carbonyl carbon (compare entry 1 with entries 2 and 3, Table 2.3). Also the C(O) (C(5) in Figure 2.10) undergoes a downfield shift in the presence of the Lewis acid. These findings do not contradict the suggested bidentate coordination.

![Figure 2.10 8-Phenylmenthyl-2H-azirine-3-carboxylate (21a).](image)

**Table 2.3** Influence of ZnCl₂·OEt₂ on the $^{13}$C NMR-shifts of 2H-azirine 21a in CD₂Cl₂.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>LA</th>
<th>Equiv</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>164.43</td>
<td>156.17</td>
<td>76.07</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>164.99</td>
<td>153.64</td>
<td>77.30</td>
<td>ZnCl₂·OEt₂</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>165.15</td>
<td>151.24</td>
<td>77.53</td>
<td>ZnCl₂·OEt₂</td>
<td>2</td>
</tr>
</tbody>
</table>

$^a$) Measured on a 500 MHz instrument. The chemical shifts are reported in ppm.
2.3.5 Rationalization of the Stereocchemical Outcome of the Oppolzer’s Sultam-system

The poor results obtained in the cycloaddition reactions with azirine 21b were initially somewhat surprising, given the many successful examples in the literature of similar systems. However, a closer look reveals a few important differences compared to, for instance, the acryloyl sultam 20, such as the methine group of the azirine and the presence of an additional Lewis basic atom. The excellent stereoselectivities obtained with acryloyl sultam 20 in cycloaddition reactions (Chapter 2.3.1), have been explained by the coordination of a Lewis acid to both the carbonyl oxygen and to the sulfonyl group, which effectively activates and rigidifies the TS-structure (A, Figure 2.11).39,48 The carbon-carbon double bond adopts an s-cis conformation to minimize steric interactions with H(3) on the bicyclic skeleton, which leads to attack of the diene from the least hindered Cα-si face. In the absence of Lewis acid the s-cis anti conformation C minimizes the unfavorable dipole and steric interactions.49 For the corresponding azirine, the reasoning is not as straightforward. It is not obvious to which of the Lewis basic atoms (sulfonyl oxygen, carbonyl oxygen, or azirine nitrogen) the metals coordinate. Both magnesium and zinc complexes are frequently used together with oxygen- and nitrogen-coordinating ligands, and in fact, Kobayashi and co-workers have showed that ZnCl2 does not discriminate between aldimines and aldehydes.50 If the Lewis acid coordinates to the azirine and the carbonyl group, the s-cis anti conformation D can be expected in order to minimize the electrostatic interactions. However, if the Lewis acid coordinates to the sulfonyl group instead of to the azirine nitrogen, thus leading to free rotation around the azirine–carbonyl single bond, the two conformers E and F have to be considered.

Figure 2.11 Possible conformations of conjugated N-acyl sultams.
Structure G is a plausible conformation in the thermal reaction. Thus, the results obtained for this substrate, i.e. with different major diastereomer formed in the presence of ZnCl₂·OEt₂, compared to that formed in the thermal reaction or using MgBr₂·OEt₂, could possibly be rationalized by an azirine–zinc–carbonyl complexation with a si-approach of the diene (D). For the MgBr₂·OEt₂ mediated reaction and the thermal reaction, an approach of the diene to the re-face of the azirine TS-structures E and G would lead to the opposite diastereomer. However, the low selectivities observed in the reactions with azirine 21b (Table 2.1) reflect the small differences in energy between the structures in the above selectivity model.

**2.3.6 Conclusions**

The chiral auxiliary approach, with 8-phenylmenthol-derived 2H-azirines, provided a variety of bi- and tri-cyclic nitrogen-containing heterocycles in high regio-, relative-, and absolute stereoselectivity and in good to excellent yields. The presence of a Lewis acid was essential for successful reactions. The absolute stereochemistry of 34a was determined by X-ray crystallography, while that of the others was assigned by analogy. The stereochemical outcome could be rationalized by the established model of the 8-phenylmenthol auxiliary.

**2.4 Enantioselective Lewis Acid Mediated Diels-Alder Reactions with Benzyl-2H-azirine-3-carboxylate**

As a continuation of our studies on the Lewis acid mediated Diels-Alder reactions with auxiliary-derivatized azirines, we decided to investigate the corresponding enantioselective reaction with benzyl-2H-azirine-3-carboxylate (35a) (Scheme 2.7). The azirine was reacted with cyclopentadiene (5) in the presence of one or 0.3 equivalents of a chiral catalyst, which afforded the cycloadducts 36.

\[
\text{BnO} \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CH}_2\text{Cl}_2
\end{array} \quad \begin{array}{c}
\text{LA-Ligand}^* \\
\text{CH}_2\text{Cl}_2
\end{array} \quad \text{36}
\]

Scheme 2.7 The enantioselective Diels-Alder reaction of benzyl-2H-azirine-3-carboxylate (35a).

---

* In the above reasoning, no consideration has been taken to the fact that the reacting species may not be monomers.

† The absolute configuration of the enantiomers has not been determined.
2.4.1 Chiral Lewis Acids

A wide range of chiral ligands in combination with various Lewis acidic metal ions are known from the literature to catalyze the Diels-Alder reaction successfully. Some of these ligands, the BINOL, the TADDOL, the bisoxazolines and the CBS-oxazaborolidine, and the 1,2-disulfonamides, were chosen for our study along with the bis(sulfonamide)amine (Figure 2.12). Lewis acids that were known to form complexes with the selected ligands were screened at first. One important parameter regarding the choice of catalysts was that the complexes had to be formed in the absence of external nucleophilic bases or metals, unless separable before the Diels-Alder reaction. This was to eliminate the risk for addition of the possible nucleophiles to the activated azirine and aziridine, as well as unselective cycloadditions promoted by the potentially Lewis acidic counter ions.

![Chiral ligands applied in the enantioselective Diels-Alder reaction of azirine 35a.](image)

The reaction proceeded smoothly under thermal conditions (i.e. without chiral catalyst), and clean conversion of azirine 35a into 36 was obtained in less than 15 min at room temperature. Although a lower reaction rate was observed at lower temperatures (−78 °C and −40 °C) the cycloadducts were, nevertheless, detected after 15 min. After 1.5 h at −40 °C, the Diels-Alder products were the predominant compounds in the reaction mixture. This reaction gave 36 in 75% yield after chromatography (entry 1, Table 2.4). Interestingly, the reactions were significantly slower in the presence of most of the chiral catalysts, with those formed from 39, 40, and 42 being the exceptions. The reaction mediated by the BINOL-AlMe complex required 24 h at −35 °C and afforded the cycloadducts in 51% ee and in 41% yield

* (−)-Menthol, (1R,2S)-5-nor-8-phenylmenthol, (4’R)-2-(4’5’-dihydro-4’-phenyl-2’-oxazoly)-6-(hydroxymethyl)pyridine, (R,R)-1,2-diphenylethylene-1,2-diamine, and (R,R)-cyclohexane-1,2-bis(trifluorosulfonamide) were also part of the screening but gave no stereo-discrimination.

† The catalysts were formed according to, or in analogy with, literature procedures and were used immediately after preparation.
after purification (entry 2). The same reaction conducted with 0.3 equivalents of catalyst gave 36 in 16% ee (entry 3). This result could be ascribed to the uncatalyzed formation of the cycloadducts, thus, leading to lower enantioselectivity. The yield was not determined since the key issue was the stereoselectivity of the reaction. Many of the chiral Lewis acid combinations that were examined did either induce no stereoselectivity, or caused degradation of the substrate and/or the product. The latter was the case for the BINOL-AlCl complex (entry 4), which was investigated with the aim to increase the rate of the reaction. Zinc, which may coordinate four ligands, and proved to work well in the diastereoselective Diels-Alder reaction (Chapter 2.3.1 and 2.3.2) was applied in the form of Et₂Zn together with 37. Despite the possibility of bidentate coordination of the catalyst to the substrate only 5% ee and 11% yield were obtained in this reaction (entry 5). The TADDOL-AlMe complex gave, after approximately 24 h, the cycloadducts 36 in 27% yield and 35% ee. Also the TADDOL-ligand was used together with AlMe₂Cl, and the same result was obtained as with BINOL, i.e. no Diels-Alder product was isolated.

![Table 2.4 The influence of chiral Lewis acids on the Diels-Alder reaction of 2H-azirine 35a with 5.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>LA</th>
<th>Ligand</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-40</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>AlMe₃</td>
<td>37</td>
<td>-35</td>
<td>41</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>AlMe₃&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(R)-37</td>
<td>-50 to -35</td>
<td>nd</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>Me₂AlCl</td>
<td>37</td>
<td>-40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Et₂Zn</td>
<td>37</td>
<td>-30</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>AlMe₃</td>
<td>38</td>
<td>-40</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>FeCl₃</td>
<td>39</td>
<td>-40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Mg(ClO₄)₂</td>
<td>39</td>
<td>-40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Mg(ClO₄)₂&lt;sup&gt;e&lt;/sup&gt;</td>
<td>39</td>
<td>-40</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>Mg(ClO₄)₂&lt;sup&gt;e&lt;/sup&gt;</td>
<td>39</td>
<td>-60</td>
<td>25</td>
<td>52</td>
</tr>
<tr>
<td>11</td>
<td>Mg(ClO₄)₂&lt;sup&gt;e&lt;/sup&gt;</td>
<td>40</td>
<td>-40</td>
<td>nd</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>41</td>
<td>41</td>
<td>-40</td>
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<td>AlMe₃</td>
<td>42</td>
<td>-60</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>ZnEt₂</td>
<td>42</td>
<td>-40</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
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<td>-40</td>
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<td>5</td>
</tr>
<tr>
<td>16</td>
<td>AlMe₃</td>
<td>44</td>
<td>-60</td>
<td>20</td>
<td>19</td>
</tr>
</tbody>
</table>

<sup>a</sup>) The azirine 35a (0.1 mmol) in CH₂Cl₂ and the diene were added to the catalyst (0.1 mmol) in CH₂Cl₂ at the specified temperature. <sup>b</sup>) After chromatography. <sup>c</sup>) Determined by chiral HPLC, column: Chiralcel, OD-H. <sup>d</sup>) 0.3 Equiv of catalyst. <sup>e</sup>) In the presence of 4Å molecular sieves.
The bisoxazoline ligand 39 has been applied frequently and successfully in [4+2] cycloadditions, most commonly together with Cu(II) or Zn(II) salts such as Cu(OTf)$_2$, Cu(SbF$_6$)$_2$ or Zn(OTf)$_2$. A complex with FeCl$_3$ was reported to give high asymmetric induction in the Diels-Alder reaction of an activated N-aryl imine with Danishefsky’s diene. However, this bisoxazoline catalyst was not equally efficient in the same reaction with azirine 35a (entry 7). In this case no desired product was isolated. The result obtained with the corresponding magnesium complex, formed from Mg(ClO$_4$)$_2$, was just as discouraging (entry 8). Despite complete consumption of the azirine, only unidentified byproducts were obtained. Nevertheless, upon addition of powdered 4Å molecular sieves, the cycloadducts 36 were obtained in 32% ee and in 22% yield (entry 9). This reaction was also significantly accelerated in the presence of the catalyst, with no remaining azirine after 40 min. When the same reaction was conducted at –60 °C, an increase in the enantioselectivity to 52% ee was achieved. Remarkable effects of molecular sieves on the stereochemical outcome have previously been observed in asymmetric catalytic Diels-Alder reactions, as well as in 1,3-dipolar cycloadditions. Different theories of the origin of this effect have been suggested, such as participation of the molecular sieves in the active catalyst complex, as well as the removal of water from the reaction mixture. The presence of water has been suggested to induce formation of the opposite stereoisomer in the magnesium-catalyzed Diels-Alder reaction, presumably, due to formation of an octahedral complex with two molecules of water acting as ligands. Although the presence of molecular sieves did not improve the selectivity for the reaction catalyzed by the phenyl-substituted bisoxazoline 40, the reaction time was considerably shortened (entry 11). In this case all azirine was consumed after less than 10 min. The triflic acid salt of CBS-oxazaborolidine 41 and its analogues have been reported to catalyze the Diels-Alder reaction of α,β-unsaturated aldehydes. These cationic catalysts were, however, considered to be too strongly acidic to be applied with the unstable ester azirine 35a, and 41 was therefore employed. The complete lack of stereoinduction and the higher yield of 67%, indicated that no coordination to the azirine took place (entry 12). The two 1,2-diphenyl-bissulfonamides 42 and 43 were used together with AlMe$_3$ and afforded the cycloaddition products in low yields and selectivities (entries 13 and 15). Ligand 42 was also applied as a complex with Zn (from Et$_2$Zn), and although a shorter reaction time was observed (10 min compared to one day for the corresponding aluminum complex) the formation of 36 proceeded without significant selectivity (entry 14). The cycloadducts were obtained in 20% yield.

---

* Only degradation products were observed also in the reaction with the bisoxazoline-copper complex formed from Cu(OTf)$_2$.

† Similar effects of molecular sieves on other types of reactions, such as palladium catalyzed oxidative cyclizations and diethylzinc additions to aldehydes, have been reported.

‡ In the absence of molecular sieves traces of product were obtained.
yield and 19% ee, in the presence of the catalyst formed from bis(sulfonamide)amine 44 and AlMe3 (entry 16).

The low yields obtained in the catalyzed reactions were partly due to decomposition during purification. Loss of material was observed during chromatography on silica as well as on aluminum oxide.

2.4.2 Conclusions

The inherent problem in the presented enantioselective Diels-Alder reaction seems to be the low rate of the reactions mediated by the chiral catalysts compared to the thermal (background) reaction. This makes it difficult to obtain a catalytic system, and in the presence of stoichiometric amounts of Lewis acidic catalysts the sensitive azirine decomposes over time. Efforts to investigate more powerful Lewis acids such as BBr3, Me2AlCl and FeCl3 together with ligands, only brought about formation of unidentified degradation products and resulted in black reaction mixtures. Thus, the efforts to increase the reaction rate in this way were unsuccessful. Since the uncatalyzed reaction affords the desired products in higher yield and, compared with most of the screened catalysts, in shorter time, it appears that the steric hindrance of the ligands contributes to the lower reaction rate. This is further supported by the increased reactivity obtained in the diastereoselective Diels-Alder reactions of the auxiliary-derivatized azirine 21a by the complexation of the Lewis acids (Chapter 2.3.1 and 2.3.2). Formation of aggregates of the catalysts and/or the catalyst-substrate complexes may also explain the low reactivity. The drastic effect of the molecular sieves on the yield and rate of the reactions indicate their participation in the catalytic system.

It is difficult, for these reasons, to formulate a rationale for the outcome of these reactions as there are many parameters which influence Lewis acid catalyzed reactions. However, it is clear that careful optimizations of ligands, Lewis acids (including counterions), concentrations, solvents, and additives are needed for this enantioselective approach towards the tricyclic aza-heterocycles 36 to become useful.

2.5 Synthesis of 2H-Azirines

There are a number of methods for the formation of azirines. A frequently used method is to employ vinyl azides, such as 49a, which undergo thermally or photolytically induced cyclization to the corresponding 2H-azirines (Scheme 2.8). The vinyl azides 49a, 49b, and 52a were prepared via their corresponding acrylates, by the use of modified literature procedures. Sulfonamide 45 was converted into the trimethylsilyl derivative 46 before treatment with acryloyl chloride in the presence of CuCl2. The direct conversion of 45 into 47b is supposedly accompanied by substantial amounts of the “dimeric” structure, incorporating two molecules of auxiliary linked together by 1-propanone, formed through a conjugate addition-
elimination reaction. A standard transformation converted the 8-phenylmenthol 17 into the corresponding acrylate 47a.

Scheme 2.8 Synthesis of 2H-azirines 21a, 21b, and 35a. Reagents and conditions: (a) TMSCl, Et3N, CH3CN, PhMe; (b) acryloyl chloride, CuCl2, PhMe; (c) Br2, CH2Cl2, 48a: 50 °C, 48b: rt, 51: rt a: 95%, b: 81%, 51:60 (d) NaN3, DMF, 49a: 20 min at 85 °C, 49b: 8 min at 60 °C, and 52a: 12 min at 65 °C, 49a: 65%, 49b: 56%;52a:70% (e) CH2Cl2, 150 °C, 20 min, 21a and 21b: >95%;35a: 85% (f) acryloyl chloride, Et3N, DMAP, CH2Cl2, 0 °C.63

The three acrylates 47a, 47b, and 50 were brominated before treatment with preheated NaN3 in DMF to form the vinyl azides 49a, 49b, and 52a. The outcome of this reaction was strongly dependent on time and temperature. Therefore, these parameters were optimized. The literature procedure for the formation of the vinyl azide 52a, that is, heating for eight minutes at 65 °C, worked well for this substrate, although a slightly extended reaction time (12 min) gave higher yields. For the somewhat more reactive sultam-derived 48b, full conversion was reached after eight minutes at 60 °C. The 8-phenylmenthol derivative 48a required the most forceful conditions, 20 min at 85 °C. At shorter reaction times or lower temperatures the corresponding vinyl bromides were obtained in varying amounts. A common literature procedure for the formation of azirine 35a includes heating of vinyl azide 52a in toluene to reflux for 10 h. This procedure was not successful in our hands due to severe byproduct formation. Therefore, the transformation of the obtained vinyl azides into the azirines was further examined.
2.5.1 Improved Procedure for Cyclization of Vinyl Azides into 3-Substituted 2H-Azirines

Three mechanisms for the thermally induced cyclization of vinyl azides have been proposed and debated (A-C, Scheme 2.9)\(^5\).\(^6\)

\[
\begin{align*}
A & \quad \text{elimination of molecular nitrogen from vinyl azide} \quad \text{Scheme 2.9} \\
B & \quad \text{concerted loss of molecular nitrogen and ring formation, with participation of the } \pi \text{-bond} \\
C & \quad \text{intraconmolecular } [3+2] \text{ cycloaddition of the azido group to the double bond} 
\end{align*}
\]

\(\text{Scheme 2.9 Plausible mechanisms for formation of 2H-azirines 56 from vinyl azides 53.}\)

Route A describes the elimination of molecular nitrogen from vinyl azide 53, to form a transient vinylnitrene 54, which may undergo ring closure to the azirine. There is no evidence as of yet for this intermediate in this reaction. The most supported mechanism is the one described by route B, in which a concerted loss of molecular nitrogen and ring formation, with participation of the \(\pi\)-bond, takes place. An intramolecular [3+2] cycloaddition of the azido group to the double bond, forming an intermediate triazole 55 from which molecular nitrogen is expelled, has also been suggested (route C).

While the initial formation of the azirine may or may not involve an intermediate vinylnitrene, this species can, however, be formed from the azirine and hence lead to undesired byproducts (Figure 2.13)\(^1\).\(^9\).\(^4\).\(^6\).

\[
\begin{align*}
\text{Figure 2.13 Equilibrium between 2H-azirine and vinylnitrene.}
\end{align*}
\]
Thermolysis of vinyl azides most often requires elevated temperatures and has commonly been performed in refluxing toluene but there are also examples when heptane and dioxane have been used.\textsuperscript{60,66} Despite boiling points between 98 and 110 °C for these solvents, the reported reaction times required for full conversion of the vinyl azides were up to 10 h. Depending on the properties of the desired product, these high-boiling solvents might be difficult to separate from the formed azirines. One way to circumvent this problem could be to perform the reactions at a lower temperature (60 °C),\textsuperscript{67} however, this is not applicable for all substrates and, in addition, significantly longer reaction times, typically one to seven days, are needed. Since azirines generally are thermally unstable, with some decomposition occurring even at ambient temperature,\textsuperscript{68} prolonged heating should be avoided.

A convenient improvement of the literature procedure for these cyclizations has emerged from earlier work in our research group.\textsuperscript{26,69} It was found that by conducting the thermolysis of the vinyl azides in a closed vessel, low-boiling solvents such as diethyl ether and pentane could be used also at elevated temperatures. However, this protocol (125 °C for 2 h), although successful for some substrates, was not generally applicable and for 2-azidoacrylic esters low yields and purities of the corresponding azirines were obtained. The activated azirine-3-carboxylic esters decompose more easily than the analogous aryl- or alkyl-azirines do, and their formation is often accompanied by substantial amounts of byproducts. It was hence crucial to find reaction conditions, which would allow the preparation of these azirines in high yields and purities, and for this reason an optimization study of the thermolysis of vinyl azides into 2H-azirines was undertaken.

Azidoacrylic ester 52a was chosen as the substrate (Scheme 2.10) and the effect of temperature, reaction time, solvent, and concentration on the thermolysis was studied. NMR measurements were used with 1,4-di-\textsuperscript{tert}-butylbenzene as a standard to determine the yield of the reactions.\textsuperscript{*}

* Determination of T1 for azirine 35a and 1,4-di-\textsuperscript{tert}-butylbenzene was undertaken in order to ensure complete relaxation and, hence, accurate measurements.
Scheme 2.10 Thermolysis of vinyl azides 52a-h.

In an attempt to find the optimal combination of temperature and time, vinyl azide 52a was cyclized at different temperatures in CH$_2$Cl$_2$. The best result was obtained at 150 °C after 20 min (entry 4, Table 2.5), which was the minimum time at this temperature for complete conversion of 52a. Lower temperatures gave lower yields despite prolonged reaction times (entries 1, 2 and 3). After 6 h at 100 °C, 13% of vinyl azide still remained and the yield of azirine 35a was 43%. It was also noted that for the reactions run at 100 °C and 125 °C the amount of product stayed constant after some time (2 h and 30 min respectively), despite continued heating and presence of vinyl azide. However, after 20 h at 100 °C no azirine (and no vinyl azide) remained. This could be explained by the formation of the corresponding vinylnitrene from the azirine. Once formed, this highly reactive species may react in a number of ways, thus shifting the azirine–vinylnitrene equilibrium. Although it may be reasonable to assume that a lower temperature favors azirine over vinylnitrene, the formation of byproducts is irreversible and consumes the vinylnitrene intermediate.

Table 2.5 Temperature dependence of the thermolysis of 52a$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Yield of 35a$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>360</td>
<td>43$^c$</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>1200</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>75</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>20</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$) Reaction conditions: 0.1 M of 52a in CH$_2$Cl$_2$. $^b$) Determined by $^1$H NMR. $^c$) With 13% of azide remaining.
The thermolysis of 2-azidoacrylic esters is strongly solvent dependent which is evident from the selected results presented in Table 2.6. When the reaction was performed in pentane (entry 1), no azirine was detected, however, 52% was obtained in toluene (entry 2). Diethyl ether, which previously had proven to work well for some substrates, was clearly not a choice for the synthesis of alkyl 2H-azirine-3-carboxylates (entry 3). On the other hand, azirine 35a was obtained in 85% in dichloromethane (entry 4) and a few other polar solvents such as chloroform, dichloroethane, and acetonitrile also showed promising results. The exception was THF, in which large amounts of byproducts were formed when conducting the cyclization. The vinyl azide 52a was insoluble in pentane and this may be a reason for the absence of product (vide infra). Lack of solubility is nevertheless not the reason for the poor results obtained in etheric solvents, and no likely explanation has been found. In accordance with the proposed mechanism for this transformation, the outcome of the reaction should not be governed by the solvent polarity. Since the best result was achieved in CH2Cl2, which has a low boiling point and is a suitable solvent for Lewis acid catalyzed Diels-Alder reactions, further thermolysis optimizations were performed using this solvent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield of 35a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pentane</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>Et2O</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CH2Cl2</td>
<td>85</td>
</tr>
</tbody>
</table>

Table 2.6 Solvent dependence of the thermolysis of 52a

The concentration dependence of the thermolysis was also studied (Table 2.7). In all cases the vinyl azide 52a was completely consumed. Despite this, at a concentration of 0.50 M, only traces of azirine 35a were found (entry 1) and 36% was obtained at 0.25 M (entry 2). It is apparent that a low concentration is essential for a successful reaction outcome and at 0.10 M of vinyl azide, azirine 35a was obtained in 85% (entry 3). A plausible explanation could once again be the presence of a vinylnitrene intermediate formed from the azirine. The extents of the competing intermolecular side reactions of this transient species most probably increase at the expense of the intramolecular cyclization back to the azirine at higher concentrations and, hence, the inferior yields. Furthermore, this could also explain the absence of product in the reactions with poor solubility of the vinyl azide and azirine (vide supra), since the substrate and product occur locally in exceptionally high concentrations.
Table 2.7 Concentration dependence of the thermolysis of 52a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration (M)</th>
<th>Yield of 35a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>0.10</td>
<td>85</td>
</tr>
</tbody>
</table>

a) Reaction conditions: The azirine 52a was heated in CH₂Cl₂ at 150 °C for 20 min. b) Determined by ¹H NMR.

The optimized reaction conditions, with 0.10 M of the substrate in CH₂Cl₂ at 150 °C for 20 min in a sealed tube, was applied to seven additional vinyl azides, 52b-52h, in order to investigate the generality of this method (Scheme 2.10 and Table 2.8). The 3-position of the substrate was substituted by a variety of functional groups such as; an unhindered ester group in 52a, a chiral sterically demanding ester substituent in 52b, a chiral sterically demanding acylsulfonamide in 52c, an alkyl group in 52d, a phenyl group in 52e, electron poor and rich aryl groups in 52f and g, and a naphthyl group in 52h. Pleasingly, all substrates gave the corresponding azirines in good to excellent yields.

Table 2.8 Thermolysis of vinyl azides 52a-52h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>3Nb</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td>3Nc</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>3Nd</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>3Ne</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>3Nf</td>
<td>&gt;95</td>
</tr>
<tr>
<td>7</td>
<td>3Ng</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>3Nh</td>
<td>82</td>
</tr>
</tbody>
</table>

a) Reaction conditions: The azirines were heated in CH₂Cl₂ at 150 °C for 20 min. b) Determined by ¹H NMR.
2.6 Concluding Remarks

Two approaches for novel asymmetric Diels-Alder reactions of 2H-azirines have been investigated. At this point, the catalytic enantioselective Diels-Alder reactions do not afford the cycloadducts in useful levels of enantiomeric excess or yields. However, further optimizations with more stable azirines may improve the results. The one issue which must be addressed in order to achieve a successful reaction is the low reactivity of the catalyst–azirine substrate compared to the uncatalyzed reaction.

The short and straightforward synthesis of the auxiliary-derived 2H-azirines and the high diastereoisomeric excess and yields of the cycloadducts make the chiral auxiliary approach a valuable method for formation of enantiomerically enriched alkaloids incorporating a fused tetrahydropyridine-aziridine moiety.
3 Lewis Acid Mediated Stereoselective Cationic Aminyl Radical Cyclizations IV, V

3.1 Introduction

Radical reactions represent a valuable complement to the more frequently used ionic reactions. Several features, such as high chemoselectivity, high functional group tolerance, mild reaction conditions, the rare need for protecting groups, stability towards moisture, and general applicability have given radical reactions increasing attention. These reactions are ideal for the construction of new bonds in sterically crowded structures, since there are no counter ions or aggregation spheres associated to the radical center, as there are in ionic reactions. The formation of heterocycles by radical cyclization is a well established methodology. It allows for the construction of monocyclic compounds as well as of two or more rings by cascade reactions. It has, therefore, found use in a number of natural product syntheses.

Contrary to many highly reactive ionic reagents, which can be stored for longer periods of time, radical species are generally transient and react readily by radical-radical combination or disproportionation (Scheme 3.1). Any molecule having a bond, which is easily cleaved homolytically and is not too sterically hindered, may react with a radical. The rate of a reaction between a radical and a non-radical is dependent on the structure of both reactants and may therefore vary considerably. This is a reason for the high chemoselectivity, which can be obtained in radical reactions. Electronically stabilized radicals, i.e. radicals with an adjacent heteroatom or conjugating group, may react at lower rates with non-radicals. This stabilization does not affect the rate of dimerization, which occurs at the diffusion controlled limit with essentially no enthalpy of activation.

\[ R^\prime + R^\prime \rightarrow R-R \text{ Combination} \]

\[ R^\prime + H \rightarrow R-H + \text{ Disproportionation} \]

Scheme 3.1

There are various ways to generate radicals. One of the most common methods is to use an initiator such as AIBN. The energy required for the bond dissociation can be provided by heat or by irradiation. Alternative methods include radical formation by oxidation or reduction using electrolytic methods or metal salts. Transition metals having two relatively stable adjacent oxidation states, such as copper and iron, can participate in electron transfer reactions.
Solvent effects on the rates of reactions between radicals and nonradical species are generally small. However, ethers, chloroform, carbon tetrachloride or solvents having benzylic protons such as toluene are likely to interfere in radical reactions and are not optimal solvents for reactions of slow or intermediate rates. Moisture is not an obstacle since the hydroxyl radical is a powerful hydrogen atom abstractor. Thus, water, alcohols and acetic acid can be used as solvent.

Triplet oxygen is a diradical and the presence of air in a reaction mixture can be deleterious. Radical reactions should therefore be conducted under inert atmosphere unless the desired reaction involves incorporation of oxygen.

Aminyl radicals are less reactive than alkyl radicals. This is evident by comparing rate constants for hydrogen abstraction from tributyltin hydride, \( k_{\text{H(alkyl)}} \approx 3 \times 10^6 \text{ M}^{-1}\text{s}^{-1} \) and \( k_{\text{H(aminyl)}} \approx 8 \times 10^4 \text{ M}^{-1}\text{s}^{-1} \).\(^{74}\) The reactivity pattern follows the strength of the bonds to hydrogen. Despite the higher electronegativity of nitrogen compared to carbon, the bonds to hydrogen are weaker. Alkyl radicals are nucleophilic in nature, which means that the unpaired electron is situated in a relatively high lying SOMO and therefore interacts primarily with the LUMO of the other reactant, for example an alkene. Despite their high reactivity, carbon-centered radicals do not add to simple alkyl substituted double bonds. However, the corresponding intramolecular additions take place readily (for certain ring sizes). For the weakly nucleophilic neutral aminyl radical, not even intramolecular cyclization occurs at a substantial rate. The proposed equilibrium between an unsubstituted alkenyl aminyl radical and the corresponding cyclized product favors the acyclic aminyl radical according to certain studies.\(^{75}\) However, the introduction of substituents on the alkyl chain seems to shift the equilibrium to the cyclic product.\(^{76-78}\) The corresponding protonated aminyl radicals are electrophilic and significantly more reactive than the aminyl radicals.\(^*\) For instance, in the well known Hoffman-Löffler-Freytag reaction a protonated aminyl radical \(58\) abstracts a favorably oriented hydrogen atom to afford a carbon-centered radical \(59\) (Scheme 3.2).

---

\(^*\) The rate constant for the reaction of dialkylaminium cation radicals with the electron rich hydrogen atom in triphenyltin hydride is \(2.4 \times 10^8 \text{ M}^{-1}\text{s}^{-1}\). This is considerably higher than the rate constant for the corresponding reaction with alkyl radicals, which is \(5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}\).\(^{79}\)
Scheme 3.2 Synthesis of pyrrolidines by the Hofmann-Löffler-Freytag reaction.

This radical may in turn abstract a chlorine atom to form the chloroalkylammonium compound 60, which under basic conditions cyclizes to the corresponding pyrrolidine 61. Yet, in the presence of a suitably situated double bond the rate of intramolecular cyclization exceeds that of hydrogen abstraction (Scheme 3.3). The cationic nitrogen-centered radical 63 thus adds to the double bond, which leads to the formation of an aza-heterocycle with a carbon-centered radical 64. This radical abstracts a chlorine atom from a chloroamine 62 to give the desired product 65 and a new nitrogen-centered radical 63, which can continue the radical chain.

Scheme 3.3 Intramolecular radical chain cyclization of cationic alkenylamines. $A= H^+$ or Lewis acid.

Complexation of an aminyl radical to a Lewis acid also creates a cationic electrophilic radical, although with a reactivity between that of the neutral and the protonated aminyl radicals.$^{71,80}$ Consequently, they readily add to double bonds (Scheme 3.3) but do not undergo Hoffman-Löffler-Freytag reactions (Scheme 3.2). The possible side reactions, such as intermolecular addition of either the nitrogen- or the formed carbon-centered radical to a double bond, normally do not occur. Entropy greatly favors cyclization relative to addition.
3.1.1 Regioselectivity in the Cyclization of 4-Pentenyl Aminyl Radicals and 5-Hexenyl Radicals

In cyclization reactions of 4-pentenyl aminyl radicals two cyclic products can be obtained, pyrrolidines from 5-exo addition and piperidines from 6-endo addition to the π-bond (Scheme 3.4).

![Scheme 3.4](image)

**Scheme 3.4** The formation of piperidines and pyrrolidines by 6-endo and 5-exo cyclization, respectively.

Both 5-exo-Trig and 6-endo-Trig cyclizations are favored according to Baldwins rules. However, theoretical as well as synthetic studies, mainly on the corresponding alkyl radical systems (5-hexenyl radicals), have shown that 5-exo cyclizations predominate. The regioselectivity can be ascribed to the stereoelectronic demands present in the interaction between the radical and the double bond. The energetically most favored transition structure for 5-exo cyclization is approximately 3 kcal/mol lower in energy than the analogous 6-endo transition structure. The C1-C6-C5 angle in the 5-hexenyl radical during exo cyclization is 106° while for endo cyclization the same angle is 94° (Figure 3.1). The former closely resembles the 104° seen in methyl radical addition to C(2) of propene. The distorted angle leads to less efficient overlap between the SOMO of the radical and LUMO of the alkene. As a comparison, the preferred attack of a methyl radical in the reaction with propylene occurs at the terminal carbon according to calculations. The energy difference between “endo” and “exo” attack for these compounds, which do not have any geometrical constraints due to formation of a cyclic structure, is 1.8 kcal/mol in favor of “endo” attack. On the contrary, the strain produced in the endo cyclizations more than overrides the general steric and electronic preference for attack at the terminal carbon atom and, thus, the exo-cyclization is preferred.

---

* Substituents on the internal carbon (C(5)) of the double bond or nuclear substitution in the connecting chain by for instance silicon leads to increased preference for 6-endo cyclization. Ring strain in polycyclic systems may have the same effect.
3.2 **Diastereoselective Radical Cyclizations**

The substituent effect on the stereochemical outcome of the cyclizations of 5-hexenylalkyl radicals has been thoroughly investigated.\(^{82}\) It was found that the stereochemistry of the products could be predicted by a transition state model formulated by Beckwith and Houk (Chapter 3.2.1).\(^{81,83}\) Despite fruitful applications of this stereoselective approach to form cyclic structures using carbon-centered radicals, only scattered examples of the analogous cyclization of aminyl radicals have been presented.\(^{77,84-87}\) One example is the cyclization of 1-substituted aminium cation radicals, which gave the corresponding products in low to moderate levels of diastereoselectivity.\(^{85}\) A natural product synthesis employing a 1-substituted aminyl radical, generated from the alkenylamine 66 via the chloroamine, gave in the presence of tributyltin hydride the ant venom alkaloid as a single diastereomer in 59% yield (Scheme 3.5).\(^{77}\)

![Figure 3.1](image-url)  
*Figure 3.1 The optimized 5-exo and 6-endo TS-structures of cyclization of the 5-hexenyl radical.\(^{81}\)*

\[\begin{align*}
\text{C}_7\text{H}_{15} & \overset{\text{NH}}{\text{C}_3\text{H}_7} \quad 1) \text{NCS} & \quad \text{C}_7\text{H}_{15} \overset{\text{N}}{\text{C}_4\text{H}_9} \quad + \text{Enantiomer} \\
2) \text{Bu}_3\text{SnH}, \text{AIBN} & \quad \text{Ant Venom Alkaloid} \\
\end{align*}\]

*Scheme 3.5 Diastereoselective synthesis of ant venom alkaloid.*
Another example is the total synthesis of an indolizidine alkaloid, gephyrotoxin-223AB, which was obtained together with its diastereomer as a 4.8:1 mixture after reduction of the corresponding cycloadducts with tributyltin hydride (Scheme 3.6). This naturally occurring alkaloid is found in the skin of poison-dart frogs.

**Scheme 3.6 Diastereoselective synthesis of Gephyrotoxin-223AB.**

Thus, the cyclization reactions of cationic aminyl radicals for formation of diastereomerically enriched nitrogen containing heterocycles have considerable potential. This prompted us to investigate the influence of the reaction conditions, the Lewis acid employed, and the substituents R<sup>1</sup>-R<sup>3</sup> on the diastereoselectivity of the cyclization of Lewis acid complexed cationic aminyl radicals (Scheme 3.7). The study was designed to determine if the Beckwith-Houk model could be applied also for the cyclization of nitrogen-centered radicals (Scheme 3.8).

**Scheme 3.7 The influence of R<sup>1</sup>-R<sup>3</sup>, the Lewis acid, and the reaction conditions on the diastereoselectivity.**

### 3.2.1 Prediction of Stereochemical Outcome

The Beckwith-Houk model is based on the resemblance between the radical TS-structure and cyclohexane, here exemplified with a cationic aminyl radical in Scheme 3.8. It was proposed that the 5-<i>exo</i> cyclization of 5-hexenyl radicals takes place via any of the four conformations **A-D**. The TS-structures **A** and **C** were termed “chair”, **B** and **D** “boat” all in line with the conformers of cyclohexane. As for cyclohexane, the two “chair” conformations are lower in energy than the two “boat” conformations.
However, the energy difference between the chair-like and the boat-like TS-structures of the 5-hexenyl radical was found to be only 1 kcal/mol, which should be compared to 7 kcal/mol for cyclohexane. The predictions of the stereochemical outcome of the cyclization is based on the sterical interactions of the substituents. In this example, the chair-like TS-structure $A$ with an equatorial substituent $R^2$ in the 2-position is energetically most favored. As previously noted, transition structure $B$ is only slightly higher in energy and will afford the opposite diastereomer compared to $A$. Depending on the size of $R^2$, it is also possible that structure $C$ has to be considered, which would result in lower selectivity. The doubly disfavored TS-structure $D$ is believed to be too high in energy to significantly contribute to product formation.

![Scheme 3.8](image)

*Scheme 3.8* The Beckwith-Houk model applied to cyclization of the cationic 4-pentenyl aminyl radical.

A large substituent e.g. $R^2$ is presumed to function as a conformational lock due to its resistance to occupy the axial position in structure $C$, thus leading to fewer possible transition state structures ($A$ and $B$). The diastereoselectivity obtained in this case is believed to be a good measure of the energy difference between $A$ and $B$. With a smaller substituent it would be expected that a larger proportion of the product is represented by the *trans*-substituted (in this example) pyrrolidine 69 formed via TS-structures $B$ and $C$. Consequently, the difference in observed *cis:trans* ratio in the reactions with a small and a large $R^2$ gives a rough estimate of product formation via TS-structure $C$.

* This implies that Curtin-Hammett conditions do not apply.
Although this model significantly simplifies the prediction of the relative stereochemistry of the products, the comparison to the chair and boat conformations of cyclohexane regarding the origin of the selectivity may not be valid. Instead, 1-butene provides a more convincing model. This is illustrated by the Newman projections of the hexenyl radical and 1-butene (Figure 3.2). 1-Butene adopts two low energy conformations \( G \) (skew) and \( H \) (gauche), of which \( H \) is disfavored by approximately 0.5-1 kcal/mol.\(^{82}\) The small energy difference between the chair-like (\( E \)) and the boat-like (\( F \)) structures may, thus, result from allylic interactions.

![Figure 3.2](image)

**Figure 3.2** The “chair” (\( E \)) and “boat” (\( F \)) TS-structures of the 5-hexenyl radical and two conformers \( G \) and \( H \) of 1-butene.

### 3.2.2 Cyclizations – Terminal Olefins

The reaction conditions used in early reports for the cyclization of cationic nitrogen-centered radicals generated from \( N \)-chloroamines involved \( H_2SO_4 \), \( CuCl–CuCl_2 \), \( FeCl_2–FeCl_3 \), or \( TiCl_3–TiCl_4 \) in water–acetic acid mixtures or in THF–water–acetic acid mixtures.\(^{71,90*}\) Our first objective was to optimize the reaction conditions regarding yield and stereoselectivity. The racemic \( N \)-chloroamine 67a, substituted with a \textit{tert}-butyl group (\( R_2 \)) on the alkyl chain and a butyl substituent (\( R_1 \)) at the nitrogen atom, was chosen as substrate (Scheme 3.9). The corresponding alkyl radical is known to cyclize especially rapidly due to substituent effects. The literature procedure with \( CuCl–CuCl_2 \) and \( FeCl_2–FeCl_3 \) afforded pyrrolidines 68a and 69a in moderate to good diastereomeric excesses and in good to excellent yields (entries 1 and 2, Table 3.1). The radical chain reaction initiated by \( TiCl_3 \) in a water–acetic acid mixture gave the products in significantly lower yield (entry 3), albeit in similar selectivity as was observed with the redox couples. It was believed that a lower

\(^{*}\) Alternative reaction conditions including Cu(I) salts in THF were published after our investigations were made.\(^{96,87}\)
reaction temperature would result in higher selectivity, however, for this to be possible the aqueous phase had to be exchanged for an organic solvent.

Scheme 3.9 Cyclization of N-chloro-N-alkenylamine 67 into pyrrolidines 68 and 69.

Previously reported synthetic studies have indicated that the cyclization induced by CuCl–CuCl₂ and FeCl₂–FeCl₃ occurs via a redox chain mechanism (Scheme 3.10), while a radical chain reaction is initiated by TiCl₃–TiCl₄ (see Scheme 3.3).⁷¹

Scheme 3.10 Redox chain radical cyclization of a cationic aminyl radical.

Consequently, copper and iron redox couples are less efficient in organic solvents due to their low solubility. Although the solubility of TiCl₃ is relatively low, this is not as crucial as for the redox couples since the titanium salt merely functions as an initiator, and, in an ideal case, is not needed to maintain the radical chain. Therefore, TiCl₃ was chosen for further investigations. Both yields and diastereoselectivities increased when the cyclizations were performed in dichloromethane (compare entries 3–5). However, only a minor temperature effect was observed on the selectivity when the temperature was lowered from –30 to –78 (compare entries 4 and 5).

Table 3.1 Cyclization of N-butyl-N-chloro(2-tert-butylpent-4-enyl)amine (67a) under different conditions (R¹ = Bu, R² = t-Bu, Scheme 3.8).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Solvent</th>
<th>Solvent ratio</th>
<th>T (°C)</th>
<th>Yielda (%)</th>
<th>68a:69ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl–CuCl₂</td>
<td>THF:H₂O:HOAc</td>
<td>1:2:2</td>
<td>–20</td>
<td>93</td>
<td>87:13</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₂–FeCl₃</td>
<td>THF:H₂O:HOAc</td>
<td>1:2:2</td>
<td>–20</td>
<td>83</td>
<td>78:22</td>
</tr>
<tr>
<td>3</td>
<td>TiCl₃–TiCl₄</td>
<td>H₂O:HOAc</td>
<td>1:1</td>
<td>–20</td>
<td>22</td>
<td>83:17</td>
</tr>
<tr>
<td>4</td>
<td>TiCl₃–TiCl₄</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>–30</td>
<td>59</td>
<td>88:12</td>
</tr>
<tr>
<td>5</td>
<td>TiCl₃–TiCl₄</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>–78</td>
<td>62</td>
<td>90:10</td>
</tr>
</tbody>
</table>

a) Isolated yields. b) Ratios determined by ¹H NMR.
Next, the influence of the Lewis acid on the reaction outcome was studied using N-chloroamine 67a (entries 1-12, Table 3.2). The cyclization reactions were initiated by 0.1 equivalents of TiCl$_3$ and performed at –78 °C in dichloromethane. No reaction took place in the absence of Lewis acid (entry 1). However, a significant increase in yield was achieved when TiCl$_4$ was substituted for Ti(O/Pr)Cl$_3$, BF$_3$-OEt$_2$, Cu(OTf)$_2$, AlMe$_3$, and MgBr$_2$-OEt$_2$ (compare entry 2 with 3, 4, 7, 10, and 12). The observed selectivities were within a narrow range when using these Lewis acids, from 88:12 for MgBr$_2$-OEt$_2$ to 93:7 for BF$_3$-OEt$_2$. Although it has been suggested that copper- and aluminum-based Lewis acids may coordinate to π-bonds, thus leading to more rigid transition states and higher stereoselectivity, no such effect was observed in this case.

The cycloadducts were attained in high selectivity also in the presence of Sn(OTf)$_2$, albeit in low yield (entry 6). Despite a large excess of the Lewis acid and prolonged reaction time, a substantial amount of starting material remained in this case. A similar result was obtained when Zn(OTf)$_2$ was applied (entry 8). Interestingly, when dichloromethane was exchanged for THF the selectivity dropped for the BF$_3$-OEt$_2$ mediated reaction (compare entry 4 with 5), and no product was formed in the presence of Zn(OTf)$_2$ (entry 9). The aluminum-based Lewis acid MAD (methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) did not promote the formation of 68a and 69a and the N-chloroamine was recovered (entry 11). The complete lack of reaction led us to believe that the interaction between the radical and the double bond was prevented by the too sterically demanding ligand. A mixture of the chlorinated and the corresponding brominated pyrrolidines was formed in good yield and diastereoselectivity in the presence of MgBr$_2$-OEt$_2$ (entry 12). Similar diastereoselectivity and yield, i.e. 89:11 and 92%, were obtained in the reaction promoted by triflic acid (entry 13). The protonated aminium radical cyclized rapidly.

The same general reaction conditions were applied when the effect of the N-substituent (R$_1$) was explored. The N-butyl group was substituted for a benzyl (in 67b), a $p$-methoxy benzyl (in 67c), or an $\alpha$-methoxyethyl group (in 67d), which resulted in somewhat lower levels of selectivity in all cases (entries 14-16). The additional site of coordination available in 67d did not improve the outcome of the reaction (compare entry 16 with 3).

* Diastereoselective radical cyclizations of N-chloro-N-pentenylamines catalyzed by various copper salts were recently reported by Göttlich and co-workers. The diastereoselectivity was greatly enhanced in the cyclizations of an 1-substituted N-chloro-N-pentenylamine in the presence of CuPF$_6$ and TMCDA (trans-$N,N',N',N'$-tetramethylcyclohexanediamine, 5 equiv). A single isomer was isolated in 52% yield. The selectivity dropped in the corresponding cyclization of a 2-substituted N-chloro-N-pentenylamine, with the best result obtained using CuPF$_6$ and TMEDA (10:1, 43% yield). The obtained selectivities were attributed to the bulky ligand sphere of the catalyst.
### Table 3.2 Cyclization of 67 into pyrrolidines 68 and 69.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>LA</th>
<th>Yield(^b) (%)</th>
<th>68:69(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>TiCl(_4)</td>
<td>62</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>Ti(O(_i)Pr)(_3)Cl(_3)</td>
<td>94</td>
<td>90:10</td>
</tr>
<tr>
<td>4</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>BF(_3)·OEt(_2)</td>
<td>95</td>
<td>93:7</td>
</tr>
<tr>
<td>5</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>BF(_3)·OEt(_2)</td>
<td>95(^d)</td>
<td>83:17</td>
</tr>
<tr>
<td>6</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>Sn(OTf)(_2)</td>
<td>38</td>
<td>93:7</td>
</tr>
<tr>
<td>7</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>Cu(OTf)(_2)</td>
<td>90</td>
<td>91:9</td>
</tr>
<tr>
<td>8</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>Zn(OTf)(_2)</td>
<td>50</td>
<td>89:11</td>
</tr>
<tr>
<td>9</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>Zn(OTf)(_2)</td>
<td>-(^d)</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>AlMe(_3)</td>
<td>100</td>
<td>90:10</td>
</tr>
<tr>
<td>11</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>MAD</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>MgBr(_2)·OEt(_2)</td>
<td>93</td>
<td>88:12</td>
</tr>
<tr>
<td>13</td>
<td>67a</td>
<td>Bu</td>
<td>t-Bu</td>
<td>TfOH</td>
<td>92</td>
<td>89:11</td>
</tr>
<tr>
<td>14</td>
<td>67b</td>
<td>Bn</td>
<td>t-Bu</td>
<td>BF(_3)·OEt(_2)</td>
<td>97</td>
<td>80:20</td>
</tr>
<tr>
<td>15</td>
<td>67c</td>
<td>p-MeOBn</td>
<td>t-Bu</td>
<td>BF(_3)·OEt(_2)</td>
<td>100</td>
<td>86:14</td>
</tr>
<tr>
<td>16</td>
<td>67d</td>
<td>C(_2)H(_4)OMe</td>
<td>t-Bu</td>
<td>Ti(O(_i)Pr)(_3)Cl(_3)</td>
<td>93</td>
<td>87:13</td>
</tr>
<tr>
<td>17</td>
<td>67e</td>
<td>Bu</td>
<td>Me</td>
<td>BF(_3)·OEt(_2)</td>
<td>100(^f)</td>
<td>80:20</td>
</tr>
<tr>
<td>18</td>
<td>67e</td>
<td>Bu</td>
<td>Me</td>
<td>Cu(OTf)(_2)</td>
<td>20(^f)</td>
<td>83:17</td>
</tr>
</tbody>
</table>

\(^a\) In deoxygenated CH\(_2\)Cl\(_2\), 0.1 equiv of TiCl\(_3\), 2 equiv of Lewis acid, –78 °C, and for 20 min to 9 h. \(^b\) Isolated yields. \(^c\) Ratios determined by \(^1\)H NMR. \(^d\) In deoxygenated THF. \(^e\) Conversion, based on \(^1\)H NMR.

When the sterically demanding and rigidifying tert-butyl substituent (R\(^2\)) was replaced by a methyl group, the diastereoselectivities dropped considerably, regardless of the Lewis acid applied. In the presence of BF\(_3\)·OEt\(_2\) the cis:trans ratio decreased from 93:7 for 68a:69a to 80:20 for 68e:69e (compare entries 4 and 17). A similar result was achieved when using Cu(OTf)\(_2\), although with only 20% conversion (entry 18).\(^*\) The reaction times were prolonged significantly in both cases, from less than 25 min for the tert-butyl-substituted 67a to seven hours for the methyl-substituted 67e in the BF\(_3\)·OEt\(_2\) promoted reaction.

No apparent correlation was found between the obtained stereoselectivities presented in Table 3.2 and the properties of the Lewis acids applied. As the result observed

\(^*\) Due to the volatility of the product, isolated yields could not be determined.
when using triflic acid was comparable to those obtained in the presence of Lewis acids, it seems plausible that it is primarily an activating and rate enhancing effect which is exerted by the Lewis acids. The Beckwith-Houk model appears valid also for the cyclization of nitrogen-centered radicals, as a clear effect of the properties of the 2-substituent on the diastereoselectivity was observed. The bulky tert-butyl group functions as a conformational lock in 67a by occupying the equatorial position, thus, leading to higher selectivities than those observed for the methyl-substituted 67e, just as predicted from the model (Chapter 3.2.1).

### 3.2.3 Cyclizations – Disubstituted Olefins

The pure cis- and trans-N-chloro-N-alkenylamines 70a and b were cyclized in order to probe the effect of a terminal alkene substituent (Scheme 3.11). Surprisingly, a cis:trans ratio of 69:31 was obtained in the reaction of Z-isomer 70a in the presence of BF₃·OEt₂ (entry 1, Table 3.3), which should be compared to 93:7 for the monosubstituted 67a (entry 4, Table 3.2). The same considerable drop in selectivity was observed in the AlMe₃-mediated reaction (compare entries 2, Table 3.3 and 10, Table 3.2).

![Scheme 3.11 Cyclization of cis- and trans N-chloro-N-alkenylamines 70a and b.](image)

Interestingly, no significant difference in selectivity was observed between the cyclization of trans-70b and cis-70a using BF₃·OEt₂ (entries 1 and 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>LA</th>
<th>Yield (%)</th>
<th>71:72</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70a</td>
<td>H</td>
<td>Me</td>
<td>BF₃·OEt₂</td>
<td>100</td>
<td>69:31</td>
</tr>
<tr>
<td>2</td>
<td>70a</td>
<td>H</td>
<td>Me</td>
<td>AlMe₃</td>
<td>92</td>
<td>73:27</td>
</tr>
<tr>
<td>3</td>
<td>70b</td>
<td>Me</td>
<td>H</td>
<td>BF₃·OEt₂</td>
<td>93</td>
<td>66:34</td>
</tr>
</tbody>
</table>

a) In deoxygenated CH₂Cl₂, 0.1 equiv of TiCl₃, 2 equiv of Lewis acid, –78 °C, 30 min. b) Isolated yields. c) Ratios determined by GC-MS.

The presence of both a terminal Z-alkene substituent and a ring substituent usually increases the selectivity, as the boat-like–equatorial transition state should be higher in energy. Therefore, a more pronounced difference in selectivity between the
products formed from the Z- and E-substituted olefins was also expected. However, the anticipated increase in selectivity, which is commonly observed for disubstituted alkenes in the formation of five-membered rings in radical as well as non-radical cyclizations due to A\textsuperscript{1,3}-strain, was not observed.\textsuperscript{93}

3.2.4 Determination of the Diastereomeric Ratios

The diastereomeric ratios of the pyrrolidines in Scheme 3.13 were determined by \textsuperscript{1}H NMR spectroscopy of the corresponding piperidines \textsuperscript{77},\textsuperscript{*} which were formed by a stereospecific ring-expansion (\textit{vide infra}). However, this method was not applicable to pyrrolidines \textsuperscript{71} and \textsuperscript{72} due to the exocyclic stereogenic center formed in the cyclization, most likely with no selectivity. This stereogenic center was, therefore, removed by Bu\textsubscript{3}SnH reduction to give pyrrolidines \textsuperscript{75} and \textsuperscript{76} (Scheme 3.12).\textsuperscript{94} In order to avoid rearrangement of the pyrrolidines into the corresponding piperidines during the reaction, the reduction was performed in the presence of BF\textsubscript{3}·OEt\textsubscript{2}, which coordinated to the nitrogen atom (\textit{vide infra}). The \textit{cis:trans} ratios were then determined by GC-MS.

\begin{center}
\textbf{Scheme 3.12 Reduction of 2-chloromethyl-pyrrolidines.}
\end{center}

A comparison of the analytical results obtained by NMR spectroscopy of \textsuperscript{77}a and its diastereomer \textsuperscript{78}a to those obtained after reduction, i.e. of \textsuperscript{73} and \textsuperscript{74}, confirmed that no epimerization had occurred during the reduction or the rearrangement reactions. The observed \textit{cis:trans} ratios were 89:11 and 87:13 respectively, which is within experimental error.

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\textsuperscript{*} It is possible to determine the diastereomeric excesses of the pyrrolidines in C\textsubscript{6}D\textsubscript{6} by \textsuperscript{1}H NMR, as no rearrangement takes place in this solvent. However, the signals of the diastereomeric piperidine isomers \textsuperscript{77} were better resolved than those of the corresponding pyrrolidines.
3.2.5 Rearrangement of Pyrrolidines into Piperidines

2-Chloromethyl pyrrolidines, e.g. 68, rearrange readily to the corresponding piperidines 77 (Scheme 3.13). This well-known transformation proceeds via a cyclic aziridinium intermediate A, which is stereospecifically ring opened by the chloride ion to form a mixture of the pyrrolidine and the piperidine. The substitution pattern of the pyrrolidine as well as the reaction conditions such as solvent, temperature, and nucleophile determine the pyrrolidine:piperidine ratio. The thermodynamically more stable piperidines usually predominate.

Scheme 3.13 Rearrangement of pyrrolidines 68 into the corresponding piperidines 77.

Full conversion was obtained in chlorinated solvents such as chloroform at room temperature \( t_{1/2} \approx 1 \) h when pyrrolidines 68a, d, e and 69a, d, e were rearranged into piperidines 77a, d, e and 78a, d, e.

3.2.6 Synthesis of N-Chloro-N-Alkenylamines

The \( N \)-chloro-\( N \)-alkenylamines 67a-e, 70a and b were prepared from the commercially available tert-butylacetyl chloride (79) and ethyl propanoate (81) using standard transformations (Scheme 3.14 and Scheme 3.15). Good to excellent yields were obtained in all steps. Compounds 80, 82, 84, 85, 87, and 90 were synthesized according to previously published procedures.
Scheme 3.14 Synthetic route for the preparation of N-chloro-N-alkenyl amines 67a, b, c, d, e, and 70b. Reagents and conditions: (a) EtOH, Et₃N, CH₂Cl₂ 95%; (b) 82, 84: LDA, allylbromide, DMPU, THF, 82%, 83%: KHMDS, trans-crotylbromide, THF 56%; (c) LiAlH₄, Et₂O, 70-90%; (d) MsCl, DIPEA, CH₂Cl₂ 83-98%; (e) 91a: butylamine, 92%, 91b: benzylamine 96%, 91c: p-methoxybenzylamine 83%, 91d: methoxyethylamine 81%; (f) NCS, CH₂Cl₂ 80-98%.

* It was not possible to convert the carboxylic ester 82 (Scheme 3.14) into the corresponding Z-alkene ester due to lactone formation during the dihydroxylation step.

Scheme 3.15 Synthetic route for the preparation of N-chloro-N-alkenyl amine 70a. Reagents and conditions: (a) TBDMSCl, pyridine, TEA, CH₂Cl₂, 99%; (b) OsO₄, NMO, t-BuOH, THF, H₂O; (c) NaIO₄, NaHCO₃, THF, H₂O, 85%; (d) ethyl(triphenyl)phosphonium bromide, KHMDS, THF, 80%; (e) TBAF, THF, 86%; (f) MsCl, TEA, CH₂Cl₂, 88%; (g) butylamine, 98%; (h) NCS, CH₂Cl₂, 82%.
3.2.7 Conclusions

The diastereoselective Lewis acid mediated radical cyclizations of \( N \)-chloro-\( N \)-alkenylamines afforded trisubstituted pyrrolidines in good to excellent yields and in varying diastereomeric excesses. The presence of a Lewis acid or a protic acid was essential for successful reactions. However, no correlation between the applied Lewis acids and the obtained \textit{cis:trans} selectivities was found. It has been shown that the stereochemical outcome in these reactions can be predicted by applying the Beckwith–Houk stereochemical model, originally developed for cyclization of carbon-centered radicals. The formed pyrrolidines rearrange readily into the corresponding piperidines under mild conditions.
3.3 Enantioselective Radical Cyclizations

After the inspiring results obtained in the Lewis acid catalyzed diastereoselective radical cyclizations a logical continuation was to undertake the investigation of the corresponding enantioselective reactions. The use of chiral catalysts is the preferred approach toward enantiomerically enriched compounds. The ideal situation is when the absolute configuration of the formed stereogenic center is governed by the chiral catalyst, independent of any chirality present in the substrate. This methodology has, to the best of our knowledge, not been applied to cyclizations of aminyl radicals. However, the growing interest for the use of enantioselective addition and cyclization reactions of carbon-centered radicals is encouraging. 102

3.3.1 Substrates and Chiral Lewis Acids

Initially, chloroamine 100a was prepared and cyclized under achiral conditions with BF3·OEt2 as well as in the presence of chiral catalysts such as the complex formed from Cu(OTf)2 and tert-butyl bisoxazoline (Scheme 3.16). However, chloroamine 100a proved to be rather volatile and showed low reactivity at temperatures below zero, also in the presence of BF3·OEt2. The low reactivity of this substrate may be explained by the substituent effect and is in accordance with the observations made in the corresponding reactions of the methyl- and tert-butyl-substituted N-alkenylamine radicals (Chapter 3.2.2). The entropy change for ring closures is believed to be made more favorable by alkyl substitution, due to reduced mobility of the alkyl chains. The analysis of the obtained enantiomeric mixture of pyrrolidines 101a and ent-101a was also an obstacle, as chiral GC did not afford any separation.

N-chloro-N-alkenylamine 100b having a UV-absorbing phenyl group and being less volatile was thereafter prepared, cyclized and evaluated. Also this substrate gave cycloadducts which were inseparable on chiral GC but also on chiral HPLC. *

* Chiralcel OD–H and OJ columns were used on the HPLC and Chromtech Chiraldex G–TA on the GC.
Nevertheless, it was possible to use $^1$H NMR spectroscopy for analysis of the diastereomeric salts of pyrrolidines 101b and ent-101b, which were obtained by mixing the pyrrolidines with the enantiopure carboxylic acids 102 and 103 (Figure 3.3). This analytical method worked well for the pure cycloadducts, although, in the presence of chiral ligands the spectral analysis became more difficult and the complicated spectra did not provide conclusive results.

Figure 3.3 Enantiopure carboxylic acids used for the determination of ee by $^1$H NMR.

In collaboration with the group of Dr Göttlich, the gem-dimethyl-substituted chloroamine 104 was applied in catalytic radical cyclizations. These cyclizations were performed using catalytic amounts of Cu(I) or Mn(III) based metal salts, which can promote the cyclization reaction via a redox process, together with a chiral ligand (Figure 3.4). Titanium and aluminum based chiral Lewis acids were investigated in radical chain reactions with TiCl$_3$ as radical initiator (Figure 3.5).

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* The donation of the enantiopure carboxylic acids by Prof. Moberg is greatly appreciated.

† The donation of chloroamine 104 by Dr Göttlich is greatly appreciated.
In addition to varying the catalysts the influence of temperature, solvent and amount of ligand and metal was studied. Due to the basicity of the nitrogen atom, leading to a deactivating effect on catalysis (Chapter 2.1.2), the majority of these reactions were conducted at elevated temperatures to increase the turnover. The cycloadducts were obtained as mixtures of pyrrolidines $105a$ and $105b$ and piperidines $106a$ and $106b$. Catalysts A–D afforded the product mixtures in 47 to 82% yield, while no product was obtained using catalysts E–H. A minor amount of product was obtained in the presence of catalyst I. This latter reaction was performed at low temperature.

The enantiomeric excess of the cyclizations was determined by chiral GC of piperidines $106a$ and $106b$. The results were disappointing. In all reactions, independent of catalyst, ligand–metal ratio, amount of catalyst, solvent or temperature, 1:1 mixtures of the enantiomeric products were obtained. The reaction conditions did, however, affect the yield and ratio of the pyrrolidines and piperidines.

* The chiral column Hydrodex®-$\beta$-6-TBDM was used.
3.3.2 Conclusions

Attempts to perform enantiomeric radical cyclizations of achiral N-chloro-N-alkenylamines into pyrrolidines and piperidines were unsuccessful. The aim to find catalysts with the ability to override the inherent diastereoselectivity exerted by substituents present in the substrates seems remote, since no induction was observed in the reactions using achiral alkenylamines.

3.4 Concluding Remarks

Enantioselective radical cyclizations of N-chloro-N-alkenylamines are at the present stage not a possible route to enantiomerically enriched pyrrolidines or piperidines. One alternative may be the use of chiral auxiliaries, which have been successfully used in alkyl radical cyclizations.\textsuperscript{105} However, careful considerations of the attachment of the auxiliary will be required, as the reacting center needs to be in close proximity to the chirality-inducing group. The reactivity and characteristics of the nitrogen radical can also be expected to be affected if the auxiliary is attached to the nitrogen atom.

Substituted N-chloro-N-alkenylamines may be valuable substrates for formation of diastereomerically enriched pyrrolidines and piperidines. The predictability of the relative stereochemistry of the products is an advantage. The benefit with chloroamines as precursors for the aminyl radicals is the possibility for further functionalization of the formed cyclic products, which contain a C–Cl bond. On the other hand, this is also a drawback since it is difficult to control the rearrangement of the pyrrolidines into the piperidines.

Figure 3.5 Chiral catalysts used in the radical chain cyclizations.
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Appendix A

The following is a description of my contribution to publications I-V, as requested by KTH:

I. Performed all lab work and wrote the article.

II. Performed all lab work and wrote the manuscript.

III. I shared lab work and writing of the article with E. Risberg.

IV. I shared lab work with Dr. M. Hemmerling.

V. Performed the majority of the lab work and supervised the diploma worker N. Pradeille, who synthesized N-chloro-N-alkenylamine 70b. I wrote the article.