CHAPTER I

ASYMMETRIC DIELS-ALDER REACTIONS

1.1 Introduction

Since its discovery in 1928 the Diels-Alder reaction has become one of the most powerful tools in organic synthesis. Together with the Robinson annulation it has become the standard methodology to generate six membered carbon ring systems. To a large extent the great importance of this reaction derives from its very broad scope and the ability to generate two carbon-carbon σ-bonds and up to four contiguous stereogenic centers in one synthetic operation. In an asymmetric cycloaddition reaction there are at least four elements which govern the stereochemical course of the reaction. These elements are: cis-addition, endo addition, and diastereoselectivities of both the chiral diene and dienophile. There are several possibilities to achieve π-face differentiation in diastereoselective and enantioselective Diels-Alder reactions. These include the (temporary) attachment of a chiral auxiliary to the diene or dienophile or, more elegantly, the employment of a chiral catalyst. The chiral directing group should meet a number of criteria:

1) provide a wide range of Diels-Alder adducts in high chemical yield with virtually complete and predictable π-face stereodifferentiation.
2) both enantiomers or alternative topological counterparts should be readily available.
3) be capable of efficient attachment and nondestructive removal from the adduct with complete retention of the induced configuration.
4) permit facile purification of the major cycloadduct to almost 100% d.e.
5) impose crystallinity on intermediates and products.

In the following sections a review concerning asymmetric Diels-Alder reactions with chiral dienophiles, chiral dienes and chiral Lewis acids will be given. No efforts will be made to give a complete review since the main purpose of this chapter is to demonstrate the wide variety of these reactions.
1.2 Chiral dienophiles

The asymmetric Diels-Alder chemistry\(^4\) started with the pioneering work of Korolev and Mur,\(^5\) and Walborsky \textit{et al.}\(^6\) Cyclization of (-)-dimenthy1 fumarate (1.1) with butadiene (1.2), followed by hydrolysis to remove the chiral auxiliary, led to (-)-4-cyclohexene-1,2-dicarboxylic acid (1.3) with an enantiomeric excess of 5.4\%\(^7\).

\[
\begin{array}{c}
\text{1.1} \\
\text{1.2} \\
\text{1.3} \\
5.4\%\text{ e.e}
\end{array}
\]

\textit{Scheme 1.1}

For the Diels-Alder reaction depicted in Scheme 1.1 it was reported that the absolute configuration of the adducts was independent of the solvent. On the other hand Sauer and Kredel\(^8\) observed that in the reaction of acrylate esters 1.4 with cyclopentadiene the absolute configuration of the preferred diastereoisomer changed by modifying the solvent. Chiral acrylates 1.4 react with cyclopentadiene to give, after reduction with LiAlH\(_4\), in high yield the chiral endo and exo alcohols 1.5 and 1.6. However, the diastereoselectivities obtained in these cycloaddition reactions are low.

\[
\begin{array}{c}
\text{1.4} \\
\text{1.5} \\
\text{1.6}
\end{array}
\]

\textit{Scheme 1.2}

The diastereoface differentiation in the uncatalyzed thermal Diels-Alder reaction was considerably improved by Helmchen and Schmierer\(^9\) using chiral methyl fumarates. The chiral auxiliaries are readily accessible in enantiomerically pure form starting from (+)-camphor. The presence of the N-phenylcarbamoyl group results in an effective shielding of the fumarate and a high diastereoface differentiation.\(^10\) For example, the reaction of 1.7 with anthracene (1.8) leads to the cycloaddition product.
with 60% diastereomeric excess. The chiral auxiliary was removed by means of reduction with LiAlH₄ to afford 11S,12S diol 1.9.

\[ \text{Scheme 1.3} \]

Tolbert and Ali studied the cooperativity in asymmetric induction of the uncatalyzed Diels-Alder reaction. The enantiomeric ratio produced with a dienophile containing two independent chiral moieties, e.g. dibornyl fumarate, can be predicted on the basis of the asymmetric induction when a single chiral moiety is available. When the diene has two-fold symmetry the bischiral ratio is the square of the monochiral ratio.

\[ \text{Figure 1.1} \]

Acrylate ester 1.10, prepared from (-)-8-phenylmenthol, has proven to be superior in the chiral directing capacity compared to the corresponding menthyl ester. The higher stereocontrol in this case has been attributed to the shielding of the Cα re face of the acrylate dienophile moiety by the phenyl ring of the auxiliary. Consequently, the diene addition is more facile to the si face of the acrylate. Later, several other auxiliary alcohols, which take advantage of the shielding effect of the phenyl ring, were designed.

Excellent diastereofacial selectivity (>100:1) was also achieved by Masamune et al. in the uncatalyzed addition reaction of 1.11 and cyclopentadiene. In this case the high selection is attributed to the strong hydrogen bonding between the hydroxyl and ketone functions in 1.11 which results in the formation of a five-membered chelate. Due to the diminished flexibility the two diastereotopic faces of the enone system become highly distinguishable.
Very early it was found that Lewis acids exert a strong catalytic effect in Diels-Alder reactions. The acceleration of the [4+2] cycloadditions results from a lowering in energy of the dienophile LUMO. In general there is also an increase in stereoselectivity and an enhancement of the regioselectivity.

Walborsky et al. observed that the addition of Lewis acids to the reaction mixture of 1.1 and butadiene (1.2) (Scheme 1.1) raised the diastereoselectivity to 27-78% depending on the reaction conditions. By complexation of the Lewis acid with the carbonyl oxygen of the dienophile the s-trans conformation becomes the energetically most favourable one. Lewis acid complexation results in an increased π-bond order of the enone single bond and thereby a more rigid complex is formed with less conformational freedom. When diester 1.1 is allowed to react with anthracene, under Lewis acid catalysis, complete asymmetric induction can be achieved. Also, in the reaction of dienophile 1.7 with anthracene (1.8) (see Scheme 1.3) the results were considerably improved by the addition of Lewis acid. Complete diastereoselectivity (d.e. > 99%, 100% yield) was obtained with 2 equivalents of AlCl₃ at -30°C in CH₂Cl₂.

Another interesting example is the Lewis acid catalyzed asymmetric Diels-Alder reaction between acrylamides 1.12, derived from (2R,5R)-2,5-disubstituted pyrrolidines and cyclopentadiene (1.13). The cycloadduct 1.14 was obtained with excellent diastereoface selectivity. With AlCl₃ as the Lewis acid endo-1.14 was prepared with 98% d.e. (endo/exo 95:5).

Scheme 1.4
Because of these outstanding results several of the Lewis acid catalyzed Diels-Alder reactions have been explored in the synthesis of natural products or analogues.\textsuperscript{21,22} The asymmetric Diels-Alder reactions with chiral butenolides are described in Chapter II.

1.3 Chiral dienes

An alternative approach to face selectivity in Diels-Alder reactions is the introduction of a stereogenic center within the diene or the attachment of a chiral auxiliary to the diene. Some pertinent examples of this class of asymmetric Diels-Alder reactions are reported in the following section. The first reports concerning chiral dienes were from David \textit{et al.}\textsuperscript{23} The addition of \textit{n}-butyl glyoxylate to carbohydrate derivative 1.15 afforded all four possible adducts 1.16a-1.16d. However, after the cycloaddition the number of dihydropyran can be reduced to two (1.16a and 1.16b) by epimerization of the created acetal center under anhydrous acidic conditions. The pure cycloadducts have been converted into optically active disaccharides.\textsuperscript{24} To obtain more insight in the steric course of these reactions, compounds 1.17-1.19 were also prepared and similarly subjected to cycloaddition.\textsuperscript{25,26} In each case a strong preference was observed for one of the \textit{\pi}-faces of the butadienyl ether, but no great preference for the endo addition was observed. A major drawback of the synthesis described above is that the corresponding cis-diienes are inert towards glyoxylic esters. The more active dienophile diethyl mesoxalate reacts with the cis and trans isomer of 1.15.\textsuperscript{27}

![Figure 1.3](image-url)
Water soluble trans-butadienyl ethers were synthesized by using free glucose as the hydrophilic part. With dienophiles like acrylaldehyde, methyl acrylate and methacroleine complete endo selectivity was obtained. Fraser-Reid et al. developed another class of carbohydrate derived chiral dienes, in which the carbohydrate is not only a chiral auxiliary, but also forms a part of the diene itself. The α-face of compound 1.20 is rendered completely inaccessible by the O-isopropylidene ring and therefore the addition of a dienophile will be from the β-face. Reaction with maleic anhydride (1.21) afforded the endo adduct 1.22 as the single enantiomer. Diels-Alder reactions of analogous, six membered dienopyranosides 1.23 (\(R = H, OCH_3\)), were investigated by Giuliano and Buzby.

![Figure 1.4](image)

Reaction of 1.23 (\(R = H\)) with maleic anhydride (1.21) or maleimide gave a 1:1 mixture of two products. However, treatment of diene (\(R = OMe\)) 1.23 with maleimide gave a single crystalline product which resulted from the endo addition of maleimide to the β-face of 1.23 (\(R = OMe\)). Dienes of type 1.24, derived from glucose, were examined by Lipshutz et al. Maleic anhydride and dimethyl acetylenedicarboxylate each afforded a single cycloadduct, with complete endo selectivity. Also in the case of the diazodienes diethyl azodicarboxylate and N-phenyl-1,2,4-triazoline-3,5-dione only one product was formed in good yield (80% and 90%, respectively). In the group of Seebach diene 1.25 was developed, which can be obtained from L-serine via a multistep synthesis. The t-butyl substituent shields very effectively one side of this compound. Reaction with maleic anhydride 1.21 afforded the exo-cycloadduct 1.26 with 95% d.e.
Trost et al.\textsuperscript{34} have observed that the boron trifluoride catalyzed addition of 1.27 to acrolein gave 80\% (3R,4S,6R)-1.28 and 20\% of the (3S,4R,6S)-isomer. The related diene 1.29 reacted with juglone to provide 1.30 with complete asymmetric induction.\textsuperscript{35}

The absolute configuration of the products has been rationalized in terms of a $\pi$-stacking model. The aromatic ring serves as a steric steering group which directs the incoming dienophile to one of the enantiotopic faces of the diene. An alternative approach to $\pi$-face selectivity in Diels-Alder reactions is to incorporate a stereogenic center within the diene at the allylic position (1.31-1.33).\textsuperscript{36,37,38,39}

Two examples of conformational locked 1(E)-substituted 1,3-dienes containing a stereogenic center at the allylic position are the compounds 1.31 and 1.32. In the cycloaddition reaction of 1.31 with N-phenylmaleimide very high diastereoselectivities were obtained (upto 100\%). These high selectivities were also obtained in the reaction of N-phenylmaleimide and compound 1.32, which possesses a chiral sulfoxide functionality as directing group.
Complete π-face selectivity was attained in the Diels-Alder reaction of 1.33 with N-phenylmaleimide to produce the cycloadduct 1.34 as the exclusive diastereoisomer. The high stereoselectivity and regioselectivity of the intermolecular Diels-Alder reaction may be attributed to the presence of the Z-alkoxy substituent, which forces the reaction to proceed from the conformer with the Me-group perpendicular to the plane of the π-system and the large trimethylsilyloxy group pointing away from the MOM protecting group. This conformation results in the effective shielding of one of the π-faces of the diene.  

As has been described in Section 1.2, Lewis acids are able to promote the Diels-Alder reaction by lowering the LUMO of the dienophile and to increase the regioselectivity. During the last 5 years there has been a growing interest in the design of chiral Lewis acids and their application in the asymmetric Diels-Alder reaction. A complexation of a chiral Lewis acid with one of the reaction components would yield an asymmetric reagent with a potential for guiding a selective approach of the remaining cycloaddition component. The advantage of using these chiral catalysts is that the processes for the introduction and removal of the chiral auxiliary (either of the diene or dienophile) can be omitted and that stoichiometric amounts of the chiral auxiliary would no longer be necessary. The chiral Lewis acids can roughly be divided in three main groups: Lewis acids based on aluminum, titanium, and boron. Their achiral equivalents have shown to be excellent catalysts in Diels-Alder reactions with a
The first asymmetric Diels-Alder reaction catalyzed by chiral Lewis acids and with considerable asymmetric induction (72% o.p.) was reported by Koga et al.\(^1\) The best results were obtained in the reaction of methacrolein (1.35) and cyclopentadiene (1.13) with menthylalkylaluminum dichloride as the chiral catalyst.

![Scheme 1.6](image)

The application of this type of chiral Lewis acids, with only one coordination to the dienophile, has been very limited. With methyl acrylate the endo adduct of cyclopentadiene is obtained with very low enantiomeric excesses (6-9% e.e.). It was postulated that the low chiral induction in the case of these conformationally mobile catalysts was due to the possible rotation around the two Al-O bonds in the Lewis acid dienophile complex (Figure 1.7) and around the O-menthyl bond.\(^4\) In any reasonable conformation of the complexed s-trans dienophile the chiral moiety is probably at too a great distance to effect a significant induction.

![Figure 1.7](image)

Much higher selectivities were obtained by Chapuis and Jurczak\(^4\) with the bidentate ligands 1.37 (R' = Me) and 1.39 (R' = Me). The advantage of these compounds over e.g. methyl acrylate is their potential rigidity. Chelation of a Lewis acid would prevent the rotation around the C(O)-N bond. The reaction of 1.39 (R = H, R' = H) with cyclopentadiene (1.13) was further improved by Corey et al.\(^4\) In the presence of 10...
mol% of (S,S)-1.41 as a catalyst, 1.40 was obtained in 95% e.e. (endo/exo > 50:1). For 1.37 (R = Me) adduct 1.38 was obtained in 96% e.e.

For 1.37 (R = Me) adduct 1.38 was obtained in 96% e.e.

\[
\begin{align*}
\text{C}_{6}H_{5} & \quad \text{C}_{6}H_{5} \\
\text{CF}_{3}\text{SO}_{2}N & \quad \text{NSO}_{2}\text{CF}_{3} \\
\text{CH}_{3} & \quad 1.41 \\
\end{align*}
\]

Scheme 1.7

1.4.2 Chiral Lewis acids based on titanium

In 1986 Narasaka reported a highly enantioselective Diels-Alder reaction between achiral dienes and dienophiles using a chiral titanium (IV) alkoxide.\(^{49}\) In the reaction of cyclopentadiene (1.13) with crotonoyl-1,3-oxazolidin-2-one (1.42), catalyzed by 1 and 2 equivalents, respectively, of 1.44, the endo adduct 1.43 was obtained in 75% and 92% e.e.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{P-O-P-O,} & \quad \text{Cl} \\
\text{Xo.Ti-Cl} & \quad 1.44 \\
\end{align*}
\]

\[
\begin{align*}
\text{He} & \quad \text{O} \\
\text{C} & \quad \text{O} \\
\text{O} & \quad \text{Cl} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{Cl} \\
\text{Cl} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Scheme 1.8

Later it was found that these high e.e.'s could also be obtained by the use of a catalytic amount of the chiral titanium (IV) complex 1.44.\(^{50}\) In the presence of 4Å molecular sieves and with 10 mol% of 1.44, adduct 1.43 was obtained in 91% e.e. (endo/exo 92:8). Also the solvent has a remarkable effect on the enantioselectivity of this reaction. The optically purity of the adduct was greatly increased in the order of benzene, toluene, xylenes and mesitylenes. The additional alkyl groups of the benzene ring of the solvent prevent \(\pi\)-stacking and therefore the interaction between the solvent
and the Ti-complex with the dienophile are minimized. The same increase in optical purity could be effected by the addition of an apolar, non-coordinating solvent. When the Diels-Alder reaction of 1.42 with isoprene was performed in toluene the e.e. is 60%, whereas in toluene-petroleum ether (1:1) the e.e. increased to 94%.\textsuperscript{51,52}

Chapuis and Jurczak\textsuperscript{47} also investigated chiral Ti(IV) catalysis using 3-crotonoyl- (1.37) and 3-acryloyl-4,4-dimethyl-1,3-oxazolidin-2-one (1.39). The best results were obtained with 1.37, TiCl\textsubscript{4} and chiral ligand 1.45 in a 1:1:1 ratio. With cyclopentadiene the addition product 1.38 was obtained in 99% yield (endo/exo 94:6) with an e.e. of >98%.

\[ \text{Figure 1.8} \]

1.4.3 Chiral Lewis acids based on boron

Chiral Lewis acids based on boron were examined by Kelly \textit{et al.}\textsuperscript{53} High asymmetric induction was found in the reaction of juglone (1.46) and 1-methoxy-1,3-cyclohexadiene (1.47), which was catalyzed by a chiral Lewis acid prepared \textit{in situ} from borohydride and (S)-3,3'-diphenyl-1,1'-bis-β-naphthol (1.48). To obtain the high e.e. (>98%), 2 equivalents of this chiral Lewis acid are needed.

\[ \text{Scheme 1.9} \]

Also the chiral Lewis acids based on derivatives of tartaric acid show very high
In the reaction of methacrolein (1.35) with cyclopentadiene (1.13) (see Scheme 1.10) the exo aldehyde 1.36 was formed in 96% e.e. (endo/exo 10:90).

\[
\begin{align*}
\text{HOOC} & \quad \text{COOH} \\
& \quad \text{CHO} \quad \text{CHO} \quad \text{OH} \\
1.50 & \quad + \quad \text{BH}_3 \cdot \text{THF} \quad \text{CH}_2\text{Cl}_2, \text{0}^\circ \text{C} \quad \xrightarrow[]{} \quad \text{BLn}^* \\
& \quad + \\
& \quad 10 \text{ mol}\% \text{ BLn}^* \quad \text{CH}_2\text{Cl}_2, \text{-78}^\circ \text{C} \quad \text{85}\% \\
\end{align*}
\]

Scheme 1.10

1.4.4 Miscellaneous

The iron (III) complex of the bis(dihydrooxazolyl)propane 1.52 catalyzes the Diels-Alder reaction of cyclopentadiene (1.13) with the bidentate dienophile 3-acryloyl-1,3-oxazolidin-2-one (1.39). Corey et al.\textsuperscript{57} reported that treatment of 1.52 with FeCl\textsubscript{2} and iodine resulted in formation of an active complex, presumably [1.52-FeCl\textsubscript{2}I], which catalyzes the formation of the endo cycloaddition product with high selectivity. The use of 10 mol\% of the complex at -50 °C results in an e.e. of 86% (endo/exo 99:1).

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{N} & \quad \text{N} \\
1.39 & \quad + \quad \text{CpRu(Ph,P)}(\text{CH}==\text{CH})\text{PF}_6 \quad \text{CH}_2\text{Cl}_2/\text{nitropropane} \quad \text{-50}^\circ \text{C} \quad \xrightarrow[]{} \quad \text{1.40 86}\% \text{ e.e.} \quad \text{endo/exo 99 : 1} \\
\end{align*}
\]

Scheme 1.11

The hetero Diels-Alder reaction between Danishefsky's diene (1.53) and benzaldehyde (1.54) is catalyzed by a cationic ruthenium complex, CpRu(Ph\textsubscript{2}P)(CH\textsubscript{2}==CH\textsubscript{2})PF\textsubscript{6}. When the phosphorous ligand is replaced by chiral diphosphines such as CHIRAPHOS and DIOP, the asymmetric inductions are 25% and 16% respectively.\textsuperscript{58}
1.5 Aims of this study and survey of the contents

At the beginning of the research described in this thesis the catalytic asymmetric Diels-Alder reaction had scarcely been investigated. No good catalytic processes with high enantiomeric excess were known at that time. At the same time the Diels-Alder reactions with chiral dienophiles needed further improvement as the number of diastereoselective cycloaddition reactions was limited to a few cases only. In most cases no complete diastereoselectivity was obtained. Besides, most chiral auxiliaries which were used were rather expensive or had to be synthesized by a multistep syntheses. The inherent problem of the chiral dienophiles used sofar was their conformational freedom leading to low selectivities, although the results were considerably improved by means of Lewis acid complexation. The disadvantage of Lewis acids is that they also catalyze the polymerization of dienes. Therefore, in most catalyzed reactions the dienes are limited to the most simple and cheap ones like butadiene or cyclopentadiene.

The general purposes of our research was: (i) to synthesize a chiral dienophile which would meet all the criteria described in Section 1.1, i.e. both enantiomers should be available, the absolute configuration of the Diels-Alder adducts should be predictable and the starting material should be a crystalline compound; (ii) to synthesize a number of substituted chiral dienophiles; (iii) to study these dienophiles in the thermal Diels-Alder reaction. Furthermore these dienophiles should have low conformational freedom, resulting in a high diastereoselectivity, and no Lewis acid catalysis should be needed in the cycloaddition reactions with these dienophiles.

- In Chapter 1 a brief review is given of diastereoselective and enantioselective Diels-Alder reactions with chiral dienophiles, chiral dienes and Diels-Alder reactions catalyzed by chiral Lewis acids.
- The synthesis of enantiomerically pure 5-alkoxy-2(5H)-furanones is described in Chapter 2. The chiral dienophile was modified by introducing substituents to the C,C double bond of the furanone ring. These new chiral dienophiles were studied in thermal Diels-Alder reactions to investigate the π-face selectivity. Furthermore, it was demonstrated that alkyl substituents on the 3- or 4-position of the furanone ring have a dramatic effect on the reactivity of these systems in the [4+2] cycloadditions.

- In Chapter 3 an alternative route for the Diels-Alder products of 4-alkyl-5-menthyloxy-2(5H)-furanones is described. By alkylation of the products obtained from the diastereoselective Diels-Alder reaction of 5-menthyloxy-2(5H)-furanone, enantiomerically pure products with a quaternary stereogenic carbon were obtained in high yield.

- The Diels-Alder reactions of 5-menthyloxy-2(5H)-furanone with relatively simple dienes, as described in Chapter 2, were extended to the synthesis of polycyclic compounds like decalones and hydroindanones. Up to four new stereogenic centers with absolute stereocontrol and well defined absolute configuration could be introduced.

- Based on the results obtained in the previous chapter, in Chapter 5 several attempts are described for the synthesis of warburganal, a natural insect antifeedant. A new route to an important intermediate for the synthesis of drimane related sesquiterpenes has been developed.

- In the last chapter the development of an activated 5-menthyloxy-2(5H)-furanone is described. The reactivity is increased by the introduction of a sulfonyl group at the 4-position of the furanone. Several examples are given which show the increased reactivity compared to the unsubstituted 5-menthyloxy-2(5H)-furanone described in Chapter 2. The thesis is concluded with a survey in English and in Dutch.

1.6 References


For other acrylamides see:
22. For a review about Diels-Alder reactions in natural product synthesis see:
43. For a review see: Narasaka, K. *Synthesis* 1991, 1.