**Review Article**

**Chiral Lewis Acid Catalysts in Diels-Alder Cycloadditions:  
Mechanistic Aspects and Synthetic Applications of Recent Systems**

**Luiz C. Dias**

*Instituto de Química, Universidade Estadual de Campinas - UNICAMP, C.P. 6154, 13083-970 Campinas - SP, Brazil; e-mail: ldias@iqm.unicamp.br*

Received: December 9, 1996

Este artigo resume os avanços mais recentes na utilização de ácidos de Lewis quirais como catalisadores na reação de cicloadição de Diels-Alder. Catalisadores quirais de alumínio, boro, titânio, cobre, lanânídeos, magnésio e metais de transição são criticamente revisados. Estudos estruturais dos complexos formados entre ácidos de Lewis e compostos carbonílicos assim como aplicações sintéticas dos sistemas mais recentes são especificamente discutidos.

This review summarizes the recent progress which has been made in the use of chiral Lewis Acid catalysts in Diels-Alder cycloaddition reactions. Chiral catalysts containing aluminum, boron, titanium, copper, lanthanides, magnesium and transition-metals are critically reviewed. Structural studies on Lewis acid carbonyl complexes and synthetic applications of recent systems are specifically discussed.

**Keywords:** asymmetric Diels-Alder cycloaddition reaction, chiral Lewis acids, asymmetric catalysis, dienophile-Lewis acid complex

**Introduction**

Nature is asymmetric and molecular asymmetry in particular plays a crucial role in science and technology.

A variety of significant biological functions emerge through molecular recognition, and this requires strict matching of chirality, since most of the receptor sites in living organisms recognize and discriminate between stereo- and geometric isomers of drug molecules.

If single enantiomers are more selective, this could lead to a greater demand for enantiomerically pure intermediates and enantioselective technologies on the chiral drug world markets.

Enantioselective synthesis of chiral organic compounds is an important task for synthetic chemists, and the design of catalytic, asymmetric reactions that proceed with high enantioselectivity is an important goal in chemical synthesis.

The strategy is to employ a reagent that under normal circumstances does not react with the substrate, but undergoes a selective reaction under the influence of catalytic amounts of a chiral compound. Much effort has been devoted to the development of catalytic asymmetric reactions in which a large quantity of a chiral product can be prepared with only a small amount of a readily available and recoverable chiral auxiliary. Asymmetric catalysis using chiral Lewis acids, provides a general, powerful tool in this context.

Since the early 1970s, a large number of research groups have become interested in discovering new and practical techniques for the control of absolute stereochemistry and there has been remarkable progress in the field of catalytic asymmetric synthesis employing chiral Lewis acids.

This review covers recent progress in chiral Lewis acids catalyzed Diels-Alder reactions.

**Catalysis of the Diels-Alder Reaction**

**Introduction**

The Diels-Alder reaction is one of the most powerful methods of C-C bond construction in synthetic organic chemistry. It enables, in a one-step inter- or intramolecular reaction, the rapid preparation of cyclic compounds having a six-membered ring. The Diels-Alder reaction has several attractive features that have resulted in...
its use in innumerable syntheses of natural products: the high regio- and stereoselectivity typically displayed by this reaction, the ease of its execution, and the feature that during the course of the [4+2] cycloadDITION up to four new stereocenters may be created simultaneously \(^ {13}\). It may be classified into one of three types of \(\pi 2s + \pi 4s\) cycloaddition reactions: the normal HOMO diene-controlled reaction using an electron rich-diene and electron-deficient dienophile, the neutral Diels-Alder reaction, and the inverse electron demand or LUMO diene-controlled Diels-Alder reaction. If a concerted reaction is assumed, both a cis addition (suprafacial mode) and a preferred endo orientation (Alder rule) can be expected. However, significant exceptions to the Alder rule have been observed and several examples appear in this review. For example, unsaturated aldehydes with an \(\alpha\)-substituent are used extensively in asymmetric Diels-Alder reactions and consistently favor the exo adduct, with a few exceptions \(^ {66, 71, 72}\).

There are three basic strategies for the control of absolute configuration of the desired product in Diels-Alder reactions: the use of a chirally modified diene, a chirally modified dienophile or a chiral catalyst. In the past few years, a number of chiral auxiliaries and catalysts for asymmetric Diels-Alder reactions have been developed \(^ {10, 14}\). One of the requirements for the design of enantioselective Diels-Alder catalysts is a chiral Lewis Acid-C=O complex. This coordination of Lewis acids to the dienophile serves as the activation process and provides a chiral environment that affects facial selectivity. The understanding of enantioselectivity requires a knowledge of the detailed structure and concentration of each dienophile-Lewis acid complex present in equilibrium and the relative rates for the reaction of each with the diene. Even if the catalyst has a single fixed geometry in the complex with the \(\alpha, \beta\)-unsaturated carbonyl compound, the proportion of \(s\)-cis and \(s\)-trans \(\alpha, \beta\)-unsaturated complexes must be controlled, since these will lead to enantiomeric products.

**General considerations**

The complexation of the carbonyl oxygen with a Lewis acid reduces the electron density of the double bond and lowers the LUMO energy (\(\pi^*\) C=\(\pi\)=C=O orbital) of the carbonyl substrate. This complexation leads to the lowering of the activation energy and to the enhancement of the endo selectivity and regioselectivity commonly observed upon catalysis. This is due to the fact that coordination of Lewis acid to the carbonyl oxygen increases the magnitude of the coefficients at the carbonyl and at the \(\beta\)-carbon in the \(\pi^*\) C=\(\pi\)=C=O orbital, increasing secondary orbital interactions and rendering the molecule more susceptible to nucleophilic attack (Fig. 1) \(^ {15, 16, 17}\).

![Figure 1](image1.png)

**Figure 1.**

Clearly the conformational preferences of the Lewis acid carbonyl complex are ultimately responsible for determining the stereochemical course of Lewis acid mediated reactions \(^ {18, 19}\).

Three factors influence the reactivity and conformation of Lewis acid carbonyl complexes:

1) The mode of coordination:

![Figure 2](image2.png)

**Figure 2.**

A well-defined Lewis acid-C=O complex is needed: \(\eta_1\) (\(\sigma\) bonding) vs. \(\eta_2\) (\(\pi\) bonding) complexation (Fig. 2).

Some representative \(\eta_1\) (\(\sigma\)-type) and \(\eta_2\) (\(\pi\)-type) complexes and their X-ray structures were published by Schreiber in 1990 \(^ {18a}\). Examples of \(\eta_2\) (\(\pi\)-type) complexes involve electron-rich transition metals and electron deficient carbonyl compounds (Fig. 3). For the most part, main group, early transition metal, and lanthanide-based Lewis acids are believed to coordinate in a \(\sigma\)-fashion. It is interesting that cationic Re complexes exhibit \(\eta_1\) complexation with ketones and \(\eta_2\) complexation with aldehydes (Fig. 3).

![Figure 3](image3.png)

**Figure 3.**
2) The exact location of the Lewis acid with respect to its carbonyl ligand:

The geometry of η1 complexes (anti or syn coordination) should be well-defined (Fig. 4).

![Diagram of Lewis acid complexes](image)

Figure 4.

In aldehydes, complexation with BF₃ occurs anti to the alkyl substituent and the B-O-C-C fragment lies essentially in a common plane, as shown by X-ray crystallography of the complex between benzaldehyde and boron trifluoride. It is also noteworthy that NOE measurements are consistent with anti complexation based on a NOE interaction between Fluorine and the aldehyde proton even in solution (Fig. 4). Irradiation of the fluorine signal at 150.5 ppm upfield from CFCl₃ led to a 5% enhancement of the aldehyde proton absorption, whereas the aromatic protons remained unaffected (Fig. 4). In the acetaldehyde-BF₃ complex, MNDO calculations showed that the anti complex is 1.8 Kcal/mol lower in energy than the corresponding syn complex.

Very recently, Fu and coworkers provided structural data that suggests that π interaction of the type illustrated in Fig. 5 can define the formation of a complex formed between a carbonyl compound and a Lewis acid. The authors provided crystallographic evidence for σ and π donation simultaneously by a lone pair and by the π system of a carbonyl group to a divalent boron Lewis acid. This donation of electron density can organize the resulting complex without the need for a two-point binding between the carbonyl compound and the Lewis acid (Fig. 5).

It is not clear if stereoelectronic effects in Lewis acid-C=O complexes play a significant role or not. If we consider "S" as the most electronegative ligand in the Lewis acid, the interaction between the HOMO (oxygen lone pair) and LUMO (σ* M-S) will stabilize the illustrated conformation, although there is no evidence for this orienting effect in the X-ray structure reported by Reetz for the complex formed between benzaldehyde and BF₃ (Fig. 6).

This type of stabilization cannot be ruled out although the energy of the HOMO (oxygen lone pair) is considerably lowered because of the positive charge on oxygen, and the energy of the LUMO (σ* M-S) is increased because of the negative charge on M.

Very recently, Corey published three very interesting papers describing experimental X-ray crystallographic evidences for formyl CH--O and formyl CH--F hydrogen bonds (Fig. 7).

![Diagram of formyl hydrogen bonds](image)

Figure 7.

In these papers, Corey describes the use of formyl CH--O hydrogen bond as an additional factor which contributes to the high degree of enantioselectivity that is observed in several enantioselective Lewis acid catalyzed Diels-Alder cycloadditions (Fig. 7). In the last paper of this series, Corey describes applications of this new kind of hydrogen bond in determining transition-state geometry in chiral Lewis-acid catalyzed aldol, carboxylic alkylation and Diels-Alder reactions. The preference for this coplanar/eclipsed conformer derives from an attractive interaction between the formyl proton (acidified by coordination of oxygen to the boron) and the coplanar fluorine (more
electron rich because of the negative charge on boron\(^{18b-d}\). It has been suggested that this formyl CH—O hydrogen bond is an important factor that controls the crystal structures of simple bis-formamides\(^{21b}\).

Calculations of the energies and geometries of complexes of some aldehydes and ketones with Lewis acids have been performed and the effect of BH\(_3\) and BF\(_3\) coordination upon the rotational barriers about the C-C bond adjacent to the carbonyl group in these aldehydes was minimal, while the effect upon the conformational preferences of acetone was pronounced\(^{24}\). It is important to note that theory predicts a small rotational barrier about B-O bond.

In esters, complexation of the Lewis acid occurs anti to the R'OH moiety, as demonstrated by X-ray diffraction (Fig. 8)\(^{21a,22}\).

![Figure 8](image)

The (Z)-ester conformation is stabilized by a HOMO(oxygen lone pair)-LUMO(\(\sigma^*\)C-O) interaction (Fig. 9). In the (E) conformation this lone pair is aligned to overlap with \(\sigma^*\)C-R. Since \(\sigma^*\)C-O is a better acceptor than \(\sigma^*\)C-R (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction. Coordination of Lewis acid to the carbonyl oxygen decreases the LUMO energy and increases the HOMO-LUMO interaction. Such stabilization of the (Z)-ester conformation should be expected to increase in Lewis acid-substrate complex (Fig. 9).

![Figure 9](image)

In amides, Lewis acid complexation is oriented anti to R\(_2\)N moiety, because allylic strain strongly disfavors Lewis acid complexation syn to the R\(_2\)N moiety (Fig. 10)\(^{18a}\).

In 1994, Wiberg, Marquez and Castegon published an interesting paper on the availability of lone pairs on oxy-

![Figure 10](image)

Figure 10.

gen\(^{25}\). The authors studied properties related to the lone pairs such as: the electrostatic potential, the Laplacians of the charge density, the geometry of hydrogen bonding with water and with hydrogen fluoride, and the geometry of interaction with a proton (Fig. 11).

![Figure 11](image)

Figure 11.

This study, based on \(ab\) \(initio\) wave functions, showed considerable variation in the angle between the lone pair on oxygen and the axis of the carbon-oxygen double bond in aldehydes, ketones and carboxylic acid derivatives. The "size" of the lone pair also varies, and unsymmetrical ketones offer up an unsymmetrical pair of orbitals for interactions with reagents. This suggests that the geometries for hydrogen bonding found in X-ray crystallographic studies may be a result of crystal forces\(^{25}\).

3) The Lewis acid effect on the s-cis vs. s-trans equilibrium in \(\alpha,\beta\)-unsaturated carbonyl compounds\(^{18,19,26-32}\).

As was mentioned earlier, the conformation of the dienophile is also an important issue. The s-cis vs. s-trans conformation depends on the geometry of the Lewis acid-dienophile complex and both issues determine face selection. The observed enantioselectivity is a consequence of the effective steric shielding of one face of the coordinated \(\alpha,\beta\)-enal in the more reactive complex (Fig. 12)\(^{18,19,26-32}\). It is worthy of mention that the relative proportion of each one of these conformations in the equilibrium depends on the nature of X, R\(_1\), R\(_2\) and R\(_3\) (Fig. 12).

It is generally accepted that Lewis acid complexation of \(\alpha,\beta\)-unsaturated carbonyl compounds dramatically stabilizes the s-trans conformation relative to the s-cis by either electronic or steric effects\(^{26}\). A recent conformational study by Houk showed that acrolein adopts the s-cis conformation upon Diels-Alder reaction with a diene, thus overriding the ground-state preference for the s-trans conformation\(^{27,28}\). If the s-cis form is available in the equilibrium for reaction, it may be the more reactive conformation. A similar trend has been suggested by Corey for catalyzed Diels-Alder reactions of 2-bromocroelene\(^{15b,64}\).

The Diels-Alder reaction between butadiene and methyl acrylate has been studied at several \(ab\) \(initio\) levels considering both the non-catalyzed and the BF\(_3\)-catalyzed
In the non-catalyzed reaction, the s-cis transition states are more stable than the corresponding s-trans transition states, and the exo approaches are preferred over the endo. This situation is reversed in the case of the BF₃-catalyzed reaction, in which the endo-s-trans is the most stable transition state. The comparison of these calculations with those carried out for the reaction between methyl acrylate and cyclopentadiene show that both the Lewis acid and the steric interactions of the methylene group of the cyclopentadiene influence these selectivities.

Corey isolated a 1:1 crystalline complex of BF₃ and 2-methylacrolein. From ¹H-NMR in CD₂Cl₂ solution and NOE studies (NOE enhancements indicated) even in solution, the same s-trans structure of this complex predominates.

For the uncomplexed 2-methylacrolein the s-trans form is about 2.2 kcal/mol more stable than the s-cis form, as revealed by NOE studies in CD₂Cl₂ solution at 200 K. The s-trans form of the uncomplexed α,β-enal is known to be more stable for α-bromoacrolein (ΔE = 0.5 kcal/mol) whereas for α-chloroacrolein the s-cis form is somewhat more stable (ΔE = 0.6 kcal/mol). There is no experimental evidence to support a preference for s-cis or s-trans forms of the Lewis acid-complexed α-haloacroleins. It appears that electronic or steric interactions in the transition state might favor the s-cis or s-trans complexed form, depending on the catalytic system used.

Denmark and Almstead have demonstrated by 1D-NOE experiments at -95 °C that the s-trans conformation is the predominant form for the complex of 2-heptenal and SnCl₄ or BF₃. The same trend was observed for uncomplexed 2-heptenal (Fig. 14).

Gung and Yanik, using a variable temperature NMR technique, showed that the α,β-unsaturated aldehydes 1, the α,β-unsaturated esters 2 and their SnCl₄ complexes prefer the s-trans form and the eclipsed conformation C illustrated in Fig. 15, when R = Me. When R = Et, a more bulky group, the conformation D (s-trans form) is favored.

This effect was attributed to a stabilizing interaction between the σ C-H bond and the π* C=C orbital and was increased in the presence of SnCl₄ (Fig. 16).

The predominant conformation for the SnCl₄ complexed α,β-unsaturated ester 3, is the s-trans form E, with a rotational barrier around the Csp²-Csp² single bond of about 12.5 Kcal/mol (Fig. 17).

A different situation is observed with SnCl₄-complexed α,β-unsaturated aldehydes 4, that show a rapid equilibrium between the s-trans form E and s-cis form F at or above -50 °C.

Although the s-trans form C is preferred in solution for α,β-unsaturated aldehydes, experimental observation led to the conclusion that the s-cis form F must be the more
ethoxy group and adopts an \textit{s-trans} conformation with tin coordinated \textit{syn} to the double bond (Fig. 18)\textsuperscript{35}.

In a very interesting example, there is experimental evidence that supports an \textit{s-cis} conformation for a complex between an acrylate with a lactate moiety and TiCl\textsubscript{4} (Fig. 18)\textsuperscript{35}. The authors were able to obtain crystals of this complex and determine its structure. The enolate group adopts an \textit{s-cis} conformation in a chelated seven-membered cyclic structure, in which titanium is coordinated to two ester carbonyls. The Lewis acid is \textit{anti} to the acrylate double bond and the enolate adopts an \textit{s-cis} geometry (Fig. 18)\textsuperscript{36,37}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure16.png}
\caption{Figure 16.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure18.png}
\caption{Figure 18.}
\end{figure}

\textsuperscript{1}H-NMR spectra at -40 °C showed approximately 97:3 ratio (\textit{s-trans}/\textit{s-cis}) for X = OEt reactive conformation, as proposed by Corey and by Marshall\textsuperscript{32,33}.

\textit{Ab initio} calculations have been performed on the conformations of acrylate derivatives and their complexes with Lewis acids. These calculations confirm that the acrylate-Lewis acid complexes prefer the \textit{s-trans} conformation with coordination of the Lewis acid \textit{anti} to the methoxy group favored by steric and electronic effects. For non-complexed acrylates, the \textit{s-cis} conformation is preferred\textsuperscript{26-32}.

In 1994, Yamamoto and coworkers published an extensive study on \textit{s-cis/s-trans} preference of acyclic \(\alpha,\beta\)-unsaturated esters\textsuperscript{34}. These authors studied the reactions of these enoates to elucidate the preference in the transition state. They also used supersonic jet spectroscopy, NOE experiments, and X-ray analysis to clarify the preference in the ground state. They observed that for uncomplexed methyl cinnamate in solution the \textit{s-cis} conformation has a slight preference over the \textit{s-trans} conformation, and that the populations of \textit{s-cis} and \textit{s-trans} conformers of methyl cinnamate in the gas phase at 4 K are nearly 1:1.

In an earlier work by Lewis \textit{et al.}, the octahedral complex formed between ethyl cinnamate and tin (IV) chloride (2:1) is particularly relevant to the discussion of conformational preferences of \(\alpha,\beta\)-unsaturated carbonyl complexes. The crystal structure shows that the ligand lies \textit{anti} to the
ing the participation of the complexed s-cis form G, con
formations H and I have also been used to explain the
observed enantioselectivities in some Diels-Alder reac-
tions (Fig. 19)\textsuperscript{41,48,94,96}.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{diagram19.png}
\caption{Figure 19.}
\end{figure}

Although in almost every case the s-trans geometry is
preferred, many examples of proposed s-cis geometry are
presented in this review. It appears that the dienophile
genometry is very case-dependent in present literature.

At this point we should emphasize that a critical ele-
ment in the rational design of chiral Lewis acids for effect-
ing stereoselective cycloaddition reactions to achiral
\(\alpha,\beta\)-unsaturated carbonyl compounds is an understand-
ing of the geometry of the reactive intermediates. The s-cis/s-
trans preference in the transition state is proposed based on
the product stereochemistry. Although some X-ray struc-
tures of acrylates and spectroscopy data have been re-
ported, the dynamics of s-cis/s-trans isomerization still
need to be better studied. It is of great importance to eval-
uate how the equilibrium structures may change in
going from the ground state to the transition state and
designing models to test the kinetic competence of various
alternative structures. It is also important to point out the
need for caution in basing predictions of reactive geo-
metries on X-ray and spectroscopic data, because the ther-
modinamically favored geometry of a molecule or complex
is not necessarily the same as the reactive geometry (cf.
the Curtin-Hammett principle)\textsuperscript{42,43}.

\textbf{Chiral aluminum Lewis acids}

One of the earliest examples of an asymmetric Diels-
Alder reaction was published in 1979 by Koga and cowork-
ers and involved a chiral aluminum catalyst\textsuperscript{44,18c,d}.

Catalytic amounts (16 mol\%) of menthloxyaluminum
dichloride prepared in situ from menthol 5 and ethylalu-
minum dichloride in toluene at -78 °C promoted the reac-
tion of cyclopentadiene and methacrolein affording the
exo-adduct 6 in 69\% yield and 72\% ee (Fig. 20).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{diagram20.png}
\caption{Figure 20.}
\end{figure}

Later, the same authors reinvestigated this reaction and
corrected the results for the cycloadduct 6 (56\% yield,
57\%ee). They proposed an interpretation of the stereo-
chemical relationship between the chiral auxiliary and the
Diels-Alder adduct, based on the observed absolute con-
figuration (Fig. 21)\textsuperscript{95,18c,d}.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{diagram21.png}
\caption{Figure 21.}
\end{figure}

Corey developed an asymmetric Diels-Alder approach
to prostaglandin synthesis based on a chiral aluminum cata-
lyst\textsuperscript{46}. The reaction of 5-(benzoyloxyethyl)-1,3-cyc-
lopentadiene and 3-acryloyl-1,3-oxazolidin-2-one 7a,
when catalyzed by the (S,S)-diazaaluminolide 8 (ca.
10mol\%) at -78 °C, produced after 18h the adduct 9 in 94\% yields and with 97:3 enantioselectivity (Fig. 22, Table 1)\textsuperscript{46}.

This protocol was used as the initial step in a catalytic enantioselective synthesis of a key intermediate for the
synthesis of prostanoids (Fig. 23)\textsuperscript{47}.

The structure of the chiral Diels-Alder catalyst in the
crystalline state was determined by an X-ray diffraction
study and revealed a dimeric structure with diazaalumino-
lide subunits\textsuperscript{48}. The authors suggested that the dienophile
is mono-coordinated to aluminum and adopts the s-trans
conformation in the 1:1 complex at the acryloyl oxygen
(single point binding), as depicted in Fig. 24 based on \(\text{H}-
and \^{13}\text{C}-\text{NMR data.}

Especially noteworthy is a 5\% NOE enhancement be-
tween the benzylic proton Hb and the olefinic proton Ha of
the acryloyl subunit. These data are consistent with the assigned geometry shown in Fig. 24 for the 1:1 complex of 7 and 8, which presumably is the reactive species in the catalyzed Diels-Alder process. This also suggests that the transition state assembly for the formation of Diels-Alder adduct 9 is that shown in Fig. 24. One of the phenyl groups blocks the access to the front face of the dienophile, and cyclopentadiene approaches from the back side in an endo transition state, consistent with the absolute configuration of the reaction product.

Diels-Alder reactions between cyclopentadiene and various dienophiles (mainly methacrolein) at -78 °C were catalyzed by various chiral dialkoxyaluminum catalysts 10, prepared from the corresponding diols and EtAlCl₂ (Fig. 25).  

Catalyst 10 proved to be the best of a series of examples in terms of ease of preparation, yields, and enantioselectivity.

In another example, the asymmetric Diels-Alder reaction of cyclopentadiene and methyl acrylate has been effected with high enantioselectivity under the influence of catalytic amounts of the chiral organoaluminum reagent (R)-12, prepared from trimethylaluminum and (R)-(+) 3,3''-bis-(triphenylsilyl)-1,1'-bi-2-naphthol in CH₂Cl₂ (Fig. 26).  

Treatment of methyl acrylate (1.0 equivalent) and cyclopentadiene (2.0 equivalents) with 10 mol% of (R)-12 (Ar = Ph) in CH₂Cl₂ at 0 °C for 9 h produced Diels-Alder adducts 13 and 14 in 82% yield; the endo:exo ratio of the cycloadducts was 96:4 by GLC analysis with 67% ee (endo...
isomer). The optical yields appeared to be increased by lowering the reaction temperature and by the use of nonpolar solvents such as toluene, but with a concomitant decrease in chemical yields (Fig. 26)\textsuperscript{50}.

\[
\begin{align*}
\text{CH}_2\text{Cl}_2 \text{ or toluene} & \quad \text{CHO} \\
1.0 \text{ equiv.} & \quad 1.2 \text{ equiv.}
\end{align*}
\]

\[
\begin{align*}
10 \text{ mol } \% & \quad 98 \% \text{ exo/endo, } 97.8 \% \text{ ee, } 100 \% \text{ yield} \\
0.5 \text{ mol } \% & \quad 97 \% \text{ exo/endo, } 97.7 \% \text{ ee, } 100 \% \text{ yield} \\
10 \text{ mol } \% & \quad 93 \% \text{ exo/endo, } 5 \% \text{ ee, } 84 \% \text{ yield} \\
10 \text{ mol } \% & \quad 97 \% \text{ exo/endo, } 23 \% \text{ ee, } 99 \% \text{ yield}
\end{align*}
\]

This approach is also applicable to the asymmetric Diels-Alder reaction of methyl propiolate and cyclopentadiene with catalytic (R)-12, giving the cycloadduct 15 in 55% ee (Fig. 27)\textsuperscript{50}.

\[
\begin{align*}
\text{CH}_2\text{Cl}_2 & \quad \text{CHO} \\
81 \% \text{ conversion} & \quad 81 \% \text{ conversion}
\end{align*}
\]

\[
\begin{align*}
\text{exo/endo} & \quad 90:10, 31 \% \text{ ee}
\end{align*}
\]

Recently, Wulff et al. reported aluminum/biaryl complexes as Diels-Alder catalysts\textsuperscript{51}. The authors examined catalysts generated from the vaulted biaryls 16, 17 and 18 and diethylaluminum chloride for reactions of methacrolein and cyclopentadiene (Fig. 28)\textsuperscript{51,52}.

The vaulted 2,2'-binaphthol 17 provides a catalyst that is unselective relative to that derived from the vaulted 3,3'-biphenantrol 16. Using catalyst 16, high inductions were observed with slow addition of dienophile to give exo-Diels-Alder adducts 11 in up to 97.8% ee with 200 turnovers in 4 h at -80 °C. This is one of the highest inductions ever reported for the Diels-Alder reaction with a chiral catalyst and one of the lowest catalyst loadings ever reported for any asymmetric Diels-Alder reaction with any catalyst. The use of aromatic rings to construct the walls of the “chiral pocket” not only gives a deeper pocket when the walls are extended but at the same time gives a high definition to the asymmetry of possible approaches to the active site. This system allows for the creation of a “chiral pocket” that wraps around the reaction center.

In 1994, Cativiela and coworkers reported an asymmetric Diels-Alder reaction catalyzed by methoxy-aluminum derivatives supported on silica-gel and alumina (Fig. 29)\textsuperscript{53}.

The solids obtained by treatment of alumina or silica gel with Et\textsubscript{2}AlCl are efficient catalysts for Diels-Alder reactions. A similar methodology has been used to support methoxyaluminum derivatives. The introduction of (-)-menthol reduces the catalytic activity, but these solids are able to promote reaction between methacrolein and cyclopentadiene, leading to a moderate asymmetric induction. Both reaction rate and enantioselectivity are greatly influenced by the amount of (-)-menthol used to prepare the catalyst. So, solids obtained from equimolecular amounts of (-)-menthol and diethyl aluminum chloride lead to higher percentages of enantiomeric excess, but they have lower catalytic activity. Silica-supported catalysts are more active than alumina-supported ones\textsuperscript{53}.

Another highly enantioselective Diels-Alder reaction was reported by Corey et al. in 1994 based on a chiral aluminum catalyst\textsuperscript{54}. Addition of 2-methoxybutadiene 19 to N-tolyl-maleimide 20 (R = o-toly) in the presence of catalyst 21 (Ar = 3,5-dimethylphenyl, 20 mol%, -78 °C, toluene) afforded adduct 22 (R = o-toly) in 98% yield and 93% ee (one recrystallization from i-PrOH-hexamnes furr-
nished the enantiomerically pure compound (Fig. 30). When R = o-t-butylphenyl in maleimide 27, the corresponding adduct 22 (R = o-t-butylphenyl) is obtained in 95% ee.

\[
\text{MeO} + \begin{array}{c}
\text{CF}_3\text{SO}_2\text{N} \quad \text{Al} \\
\text{NSO}_2\text{CF}_3
\end{array} \quad (20 \text{ mol\%}) \\
\text{toluene, } -78 \degree \text{C}
\]

\[
\text{20, } R = \text{o-tolyl} \\
\text{27, } R = \text{o-t-Bu-phenyl}
\]

\[\text{22} \quad 98\% \text{ yield, } 93\% \text{ ee}
\]

Enantiomerically pure compound isolated after one recrystallization

Figure 30.

This reaction is an example involving C2σ-symmetric Z-dienophile in which enantioselectivity requires dissymmetry in the diene moiety.

The meta-methyl substituents in catalyst 21 (Ar = 3,5-dimethylphenyl) are crucial for the high enantioselectivity, as is shown by the fact that with catalyst 8 (Ar=phenyl) the corresponding adduct is obtained in only 58% ee. In contrast, Diels-Alder reactions of 2-methoxybutadiene 19 with maleic anhydride and catalyst 21 produces completely racemic product. This fact can be understood if the coordination of catalyst 21 to maleic anhydride occurs at the lone pair B in 23. In this case the dienophilic double bond will be far from the catalyst. In the case of N-aryl maleimides 20 and 27, coordination of catalyst 21 (Ar = 3,5-dimethylphenyl) to lone pair B is blocked by the bulk of the aryl group and coordination occurs at the lone pair A (Fig. 31).

X-ray studies demonstrated the dimeric nature of catalyst 21. The structure of a 1:1 diazaaluminolide:N(o-t-butylphenyl)maleimide complex, formed in CD$_2$Cl$_2$ solution is evident from $^1$H-NMR and NOE experiments (Fig. 32).

The NOE enhancements illustrated in 24 provides strong evidence for the participation of the transition state assembly 25 (Fig. 32). The data clearly indicate the proximity of H1 to Hα, Me1 to Hβ, and Me2 of t-butyl to Me1. Inspection of molecular models suggests that there may be van der Waals attraction between the aromatic methyl substituents in the catalyst part of 24 and the t-Bu of the
N-arylmaleimide partner that can favor organization of the complex as shown in Fig. 32. The aromatic (Ar = 3,5-dimethylphenyl) group of the catalyst blocks the front face of the dienophile and the diene would have to approach from the back face of the dienophile in the electronically matched orientation illustrated in 25 (Fig. 32). As an application of this methodology Corey et al. reported the first synthesis of the biosynthetically and structurally unusual marine natural products gracilins B 33 and C 34 from a common intermediate (Fig. 33).55

The correct chirality and all the carbon atoms of the trioxacyclic ring system of the gracilins were established in the initial Diels-Alder reaction of 2-((trimethyl-silyl)methyl)-butadiene 26 with N-(o-tert-butylphenyl)maleimide 27 in the presence of 20 mol% of catalyst 21 in toluene at -78 °C for 12 h, producing adduct 28 in 89% yield and 95% ee. After recrystallization from hexanes, enantiomerically pure 28 was converted to gracilins B 33 and C 34 after a number of other noteworthy transformations55,56.

**Chiral boron Lewis acids**

Chiral oxazaborolidines

Itosu and collaborators developed 1,3,2-oxazaborolidines as a new generation of homochiral reduction catalysts57. In the past 15 years oxazaborolidine chemistry has become a powerful tool for the enantioselective reduction of unsymmetrical ketones and has been used in countless catalytic asymmetric transformations58.

The first application of chiral oxazaborolidines in Diels-Alder reactions was reported by Yamamoto et al. and also by Helmchen et al., who prepared boron-unsubstituted oxazaborolides from N-sulfonamides of β-aminoacids and borane59,60.

According to Yamamoto, the reaction of methacrolein and 2,3-dimethyl-1,3-butadiene in the presence of 10 mol% of the (S)-ethylglycine derived 2,4,6-trisopropyl benzene-sulfonamide (S)-35 as catalyst, afforded 36 in 73% yield and 74% ee (Fig. 34).59

![Figure 34](image)

The cycloaddition reaction between (E)-crotonaldehyde and cyclopentadiene in the presence of catalytic amounts of (S)-35 afforded the corresponding Diels-Alder adduct in 52% yield, with a 93:7 endo/exo ratio and 54% ee.

Helmchen and colleagues showed that the utilization of the oxazaborolidine derived from (S)-valine, (S)-37 (20 mol% catalyst), in the reaction of (E)-crotonaldehyde and cyclopentadiene afforded the Diels-Alder adduct 38 in 58% yield (72% ee, endo/exo = 97:3) (Fig. 35).60,61

**Figure 33.**

[Chemical structures and reactions shown in the figure]

[Chemical structures and reactions shown in the figure]
Interestingly, maximum enantioselectivity (methacrolein, 86% ee; crotonaldehyde, 81% ee) was achieved in donor solvents (THF or acetonitrile)\(^6\).

Asymmetric Diels-Alder reactions of cyclopentadiene with methacrolein catalyzed by chiral oxazaborolines 39 derived from N-tosyl-L-α-amino acids afforded cycloadducts in quantitative yields\(^6\). Variation of the position of an electron donating atom in the α-side chain of the oxazaborolide (R group) showed that enantioselectivity is controlled by the presence of electron donor atoms in positions 2 and 4 (Fig. 36)\(^6\).

The cycloaddition reactions with the more electron-deficient α-bromoacrolein in the presence of catalyst 39 were investigated for R = PhCH\(_2\) (Fig. 37) and the desired product 41 was obtained in 99% yield (95:5 \textit{exo:endo} ratio, 55% ee). However, higher enantioselectivity was observed with electron donating substituents in the α-side chain of the catalyst (R = p-MeOPhCH\(_2\) = 96:4 \textit{exo:endo}, 72% ee; R = p-PhCH\(_2\)OPhCH\(_2\) = 96:4, 81% ee).

These results were explained by the proposed transition state model illustrated in Fig. 38 (R = PhCH\(_2\)OCH\(_2\)). A strong donor-acceptor interaction is possible between the oxygen atom of the substituent benzyloxymethyl in position 2 and the carbonyl carbon of the complexed dienophile. A π-stacking interaction between the aromatic ring and the olefinic double bond of the dienophile is also possible. Both of these electronic attractive interactions block one of the dienophile faces allowing approach of the cyclopentadiene from the opposite face of the benzylloxymethyl group\(^6\).

Remarkable enantioselectivities were observed by Corey and coworkers using the (S)-tryptophan derived oxazaborolidine catalyst (S)-40. The authors showed that (S)-40 catalyzes the reaction between cyclopentadiene and α-bromo- or α-chloroacrolein to afford the 2-(R)-2-\textit{exo}-formyl Diels-Alder adduct 41 with at least 200:1 enantioselectivity (Fig. 39)\(^6\).

Isoprene and α-bromoacrolein underwent Diels-Alder addition under catalysis by 5 mol% of (S)-40, (R = H), to form 42 in 76% yield and 96:4 enantioselectivity (Fig. 40).

The important intermediate for prostaglandin synthesis, 43, was prepared by reaction of the enantiomer (R)-40 (R=n-Bu or H, 5 mol%), α-bromoacrolein and 5-(benzyloxymethyl)-cyclopentadiene (2.5 equiv.) at -78 °C for 8h.
in CH₂Cl₂. This reaction afforded the adduct 43 with 95:5 (exo/endo CHO) diastereoselectivity and greater than 96:4 enantioselectivity in 83% yield (Fig. 41)⁶⁴,⁶⁵.

Corey’s mechanistic rationale for the source of asymmetric induction is represented by the transition state assembly illustrated in Fig. 42 in which an attractive donor-acceptor interaction favors coordination of the dienophile at the face of boron that is cis to the 3-indolyl methyl substituent⁶⁵,¹⁸,c,d.

In this complex, the π-basic indole and π-acidic dienophile can assume a parallel orientation at the ideal separation of 3 Å for donor-acceptor interaction (better overlap for the s-cis geometry). The amino acid moiety directs the steric bulk of the sulfonfyl group to the opposite face of the ring and this group controls the coordination site and thus defines the configuration of the boron stereogenic center. That the aldehyde is complexed to the face of boron that is proximate to the indole ring is indicated by the bright orange-red color of the complex at 210 K that corresponds to a broad absorption band in the 400-600 nm region, indicative of a charge-transfer complex between the α,β-enedal and the indole ring. This interaction could be responsible for the high ee’s observed with this catalyst, when compared to those used by Helmchen and Yamamoto⁵⁹-⁶¹. A key factor in this approach is that the dienophile prefers the s-cis conformation over the s-trans due to the interactions between α-bromine substituent and the indole ring.

A very interesting synthetic application of this methodology was used by Marshall and coworkers in the synthesis of the spirotetratone subunit of Kijanolide, the aglycon of the antitumor antibiotic Kijaniyminc (Fig. 43)⁶⁶. Cycladdition of diene 44 to α-bromoaacrolein in the presence of stoichiometric amounts of the Corey oxazaborolidine (S)-

Figure 43.
40 (R = H) in CH₂Cl₂ at -78 °C led to the isolation of the adduct 46 in 88% yield and 72% ee for the endo adduct (Fig. 43).

The authors reported that the best conditions for this reaction require a full equivalent of the Lewis acid and the endo-product is formed exclusively, in contrast to the major exo-product in the catalytic reaction of cyclopentadiene and α-bromoacrolein according to Corey and Loh⁴⁴,⁶⁵.

The adduct 45 was converted to spirotetrotonate 49 through a sequence involving Pummerer rearrangement of the derived sulfoxide 46, oxidation of the resulting aldehyde 47, and Dieckmann cyclization of the diester 48 followed by in situ quenching with MOMCl (Fig. 44)⁶⁶.

Recently, Corey showed that an oxazaborolidine (αS, βR,)-51 derived from N-tosyl-(αS,βR)-β-methyl-tryptophan, catalyzes Diels-Alder reaction of α-bromoacrolein and furan with 96:4 enantioselectivity, leading to an efficient synthesis of numerous chiral 7-oxabicyclo[2.2.1]heptene derivatives⁶⁷. The reaction of 5 equivalents of furan with α-bromo acrolein in the presence of 10 mol% of (αS,βR)-51 in dichloromethane at -78 °C was complete in 5 h and gave the Diels-Alder adduct 50, in 98% yield and 96:4 enantioselectivity⁶⁷. The adduct 52 (X = Cl), was also obtained in 98% yield under these conditions with an enantiomeric ratio of 95:5 (Fig. 45).

Interestingly, the analogous catalyst (S)-40 (R = n-Bu) lacking the β-methyl group (derived from S-tryptophan), was not as effective in catalyzing the formation of 50 and 52 and considerably lower reaction rates and yields were observed. The Diels-Alder adduct 50, was converted to the enantio-omically pure 7-oxabicyclo[2.2.1]-hept-5-en-2-one 55, a valuable intermediate for the synthesis of many natural products, in 78% overall yield (Fig. 46)⁶⁷-⁶⁹.

In a more recent work, Corey et al. have shown some applications of chiral oxazaborolidines (αS, βR)-51 and (S)-40 in the total synthesis of two unusual structures, Cassiol 58 and Gibberellic acid 62 (Figs. 47 and 48, respectively)⁷⁰. Cassiol is a rare compound obtained from the extracts of Chinese cinnamon stem bark that possesses potent anti-ulcer activity. A short synthesis of Cassiol 58 was developed and the key intermediate 57 was prepared by a catalytic asymmetric Diels-Alder reaction using the chiral oxazaborolidine (αS,βR)-51 (Fig. 47). Cycloaddition of E,E-triene 56 and macrolein in the presence of 25 mol% of catalyst (αS,βR)-51 in toluene:CH₂Cl₂ at -78 °C for 42 h afforded adduct 57 in 83% yield and 97% ee with complete position and diastereoselectivity.

The first catalytic enantioselective total synthesis of the plant growth regulator Gibberellic acid 62 was accomplished via cis hidrinendenone 61, prepared from the key intermediate 60 (Fig. 48)⁷⁰. Diels-Alder reaction of 2-(2-bromoallyl)-1,3-cyclopentadiene 59 and 1.05 equivalents of α-bromoacrolein in the presence of 10 mol% of catalyst (S)-40 at -78 °C in CH₂Cl₂ for 16 h afforded the Diels-Alder adduct 60 in 81% yield and 99% ee (exo/endo ratio = 99:1). After a number of steps adduct 60 was converted to Gibberellic acid 62.
chiral (acyloxy)borane complex 63a prepared in situ by mixing a tartaric acid derivative and borane at room temperature catalyzes the reaction of simple achiral \(\alpha,\beta\)-unsaturated aldehydes (Fig. 49).

\[
\begin{align*}
\text{a. } \text{BH}_3 \cdot \text{THF} (R = H) \text{ or} \\
\text{RB(OMe)}_2 \text{ or RB(OH)}_2 \\
\text{CH}_2\text{Cl}_2 \text{ or EtOH}
\end{align*}
\]

The catalyst

\[
\begin{align*}
63\text{a. } R &= H \\
63\text{b. } R &= \text{Ph or alkyl}
\end{align*}
\]

Figure 49.

In contrast to 63a (R = H) which is both air and moisture sensitive, the Boron-alkylated catalyst 63b (R = Ph or alkyl) is stable and can be stored in closed containers at room temperature (Fig. 49).

The reaction of methacrolein and cyclopentadiene in the presence of catalytic amounts of CAB catalyst 63a in CH\(_2\)Cl\(_2\) at -78 °C afforded the desired Diels-Alder adduct in 85% yield (exo/endo = 89/11) and was shown to be 96% ee (major exo isomer) with \(R\) configuration (Fig. 50, Table 2).

It is interesting that with both catalysts (S)-40 and (\(\alpha\)S,\(\beta\)R)-51, studies with various dienophiles and cyclopentadiene reveal that enantioselectivities are very similar (\(\alpha\)-bromo: 200:1; \(\alpha\)-chloro: 200:1; \(\alpha\)-methyl and \(\alpha\)-ethyl: 96:4). The corresponding reaction with acrolein exhibited low enantioselectivity (30:70) and the opposite face selectivity predominates.

Chiral (Acyloxy)-Borane (CAB) catalysts

A highly selective asymmetric Diels-Alder reaction was reported in 1989 by Yamamoto and coworkers\(^{71,72,15,31}\). The authors reported that the use of a stable

Table 2.

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>exo:endo</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>6</td>
<td>85</td>
<td>89:11</td>
<td>96</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>14.5</td>
<td>90</td>
<td>12:88</td>
<td>84 (R)</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>10</td>
<td>53</td>
<td>10:90</td>
<td>2</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>9.5</td>
<td>91</td>
<td>97:3</td>
<td>90</td>
</tr>
<tr>
<td>H</td>
<td>Br</td>
<td>10</td>
<td>100</td>
<td>94:6</td>
<td>95</td>
</tr>
</tbody>
</table>

The use of unnatural tartaric acid as chiral ligand resulted in the formation of the S isomer (84% yield, exo/endo
= 90/10; 96% ee). One of the many attractive aspects of this method is that both enantiomers of tartaric acid can be easily obtained at low cost.

In the presence of 10 mol% of catalyst 63a (R=H), α-bromoacrolein and cyclopentadiene in CH₂Cl₂ solution underwent smooth Diels-Alder reaction to give the (S)-bromo aldehyde adduct in quantitative yield with 95% ee and 94/6 (exo/endo CHO) diastereoselectivity (Fig. 50, Table 2). This process is general and is applicable to various dienes and aldehydes proceeding with high enantioselectivity. A particularly interesting feature of the process can be seen from the data in Fig. 50. The α-substituent on the dienophile increases the enantioselectivity (acrolein vs. methacrolein), while β-substitution dramatically decreases the selectivity (crotonaldehyde).

Yamamoto et al. also described the asymmetric intramolecular Diels-Alder reaction of 2-methyl-(E,E)-2,7,9-decatetraene 64, catalyzed by a chiral acyloxyborane complex 63a, in high stereo and enantioselectivity. Addition of diene 64 to a solution of CAB catalyst (10 mol%) prepared from mono-(2.6-dimethoxybenzoyl) tartaric acid and borane, in CH₂Cl₂ at -40 °C provided an isomeric mixture of adduct in 84% yield (endo:exo ratio = 99:1), endo ee = 92% (Fig. 51).

![Figure 51](image)

The absolute (S) configuration of the formylated carbon and the stereochemistry at the ring junction of the adduct were determined based on X-ray analysis of the corresponding p-bromobenzoate ester. The same reaction without the α-substituent afforded the adduct in 74% yield but lower enantioselectivity (endo:exo = 99:1, endo ee = 46%).

In 1993, Yamamoto and colleagues published further applications of CAB catalysts to asymmetric Diels-Alder reactions of α-bromo-α,β-enals with dienes (Fig. 52) and.

It is interesting to note that the use of α-bromo-crotonaldehyde in this reaction with cyclopentadiene lead to an excellent enantioselectivity (98%ee) when compared to crotonaldehyde (2%ee) (Figs. 50 and 52). Similar results were obtained for the same reactions using the catalyst 63b (R = o-Ph-OC₆H₄), in propionitrile: 99% yield, 98% ee (S-enantiomer major), 94/6 (exo/endo CHO) diastereoselectivity. Considering the product configuration, the aryl group in the CAB catalyst 63a (from natural tartaric acid) blocks the bottom si-face of the complexed aldehyde and the selective approach of the diene from the re-face of the s-trans conformer should be favorable in a transition state assembly analogous to that illustrated in Fig. 53.

![Figure 53](image)

In an attempt to obtain mechanistic information about this reaction, Yamamoto et al. studied the solution conformation of the CAB-complexed methacrolein and crotonaldehyde using NOE difference measurements (Fig. 54).

Uncomplexed methacrolein and CAB catalyst must reside primarily in the s-trans conformation as shown by NOE
difference spectra. Irradiation of Ha resulted in ~6.3% NOE at the Hc signal and no NOE at either Hb or Hd signals.

For crotonaldehyde, the results in Fig. 54 indicate that uncomplexed crotonaldehyde is primarily in the s-trans conformation; the CAB-crotonaldehyde complex (R = n-C4H9C≡C-; R = H) is primarily in the s-trans conformation; the CAB-crotonaldehyde complex (R = 3,5-(CF3)2C6H3, R = o-PhOC6H4) is in the s-cis conformation.

<table>
<thead>
<tr>
<th>Complex</th>
<th>NOE (saturate / observe, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=H</td>
<td>Ha/Hb Ha/Hc Ha/Hd Ha/Ha</td>
</tr>
<tr>
<td>R=o-PhOC6H4</td>
<td>0  -10 0  6.3</td>
</tr>
<tr>
<td>Methacrolein</td>
<td>0  -22 0  -33</td>
</tr>
</tbody>
</table>

* uncomplexed methacrolein in s-trans conformation
* NOE data give no information about transition state conformation

<table>
<thead>
<tr>
<th>Complex</th>
<th>NOE (saturate / observed, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hc/2Hm</td>
<td>Ha/Hc Hd/2Hm Hd/Hp</td>
</tr>
<tr>
<td>Methacrolein</td>
<td>-32  -12  -25  -29</td>
</tr>
</tbody>
</table>

* Noe data lends support to π-stacking array
* No chemical shift information given

Figure 54.

It has been established by the use of NOE difference measurements that the effective shielding of the si-face of the CAB coordinated α,β-enal arises from π-stacking of the 2,6-diisopropoxybenzene ring and the olefin subunit of α,β-enal. Strong NOEs were obtained between protons of the aromatic ring (Hm and Hp) and protons of the olefin subunit of α,β-enal for the 63a (R = H) α,β-enal complex in CD2Cl2 solution at -95 °C. The results obtained with NOE experiments were unambiguous in the establishment of the preferred conformation in the ground state of CAB-α,β-enal complexes (Fig. 55).

Figure 55.

The authors also studied the influence of the boron substituent (R group) on absolute stereoinduction in the Diels-Alder reaction and observed that sterically bulky aryl substituents resulted in a turnover of the absolute stereochemistry for α-unsubstituted α,β-enals like acrolein and crotonaldehyde (s-cis conformation favored). On the other hand, the stereochemistry of the reaction of an α-substituted α,β-enal like methacrolein was quite independent of the steric features of the boron substituent (s-trans conformation favored) (Fig. 56).
In addition, the same authors reported that a solution of the CAB catalyst 63 is effective in catalyzing hetero Diels-Alder reactions to produce dihydropyrene derivatives 67 of high optical purities. The hetero-Diels-Alder reaction of aldehydes with Danishefsky diene 66 was promoted by 20 mol% of CAB catalyst in propionitrile solution at -78 °C for several hours (Fig. 57). After usual workup, the crude product was treated with trifluoroacetic acid in CH₂Cl₂ to afford dihydropyrene 67 in good yields.

![Diagram](image)

**Figure 58.**

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>yield (%)</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Ph</td>
<td>80</td>
<td>79(R)</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>Me</td>
<td>p-MeC₆H₄</td>
<td>&gt;99</td>
<td>97</td>
</tr>
<tr>
<td>Me</td>
<td>(E)-PhCH=CH</td>
<td>40</td>
<td>79</td>
</tr>
<tr>
<td>Me</td>
<td>(E)-MeCH=CH</td>
<td>79</td>
<td>92</td>
</tr>
<tr>
<td>Me</td>
<td>84</td>
<td>(&gt;99% cis)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 57.**

The proposed transition state assembly is illustrated in Fig. 58 (from natural tartaric acid). CAB catalysts effectively cover the **si**-face of carbonyl when coordinated and the selective approach of nucleophiles from the **re**-face leads to the observed product configuration.

Other chiral boron Lewis acids

In 1990 Kaufmann and Boese described the utilization of a chiral catalyst 69 prepared from (S)-(-)-1,1'-bi-2-naphthol 68 and mono-bromoborane dimethylsulfide in Diels-Alder reactions between methacrolein and cyclopentadiene (Fig. 59). Whereas the uncatalyzed reaction provided only 15% yield (exo:endo = 86:14) after 42 h even at 20 °C, conducting the reaction in CH₂Cl₂ at -78°C in the presence of 3 mol% of 69 led to the isolation of the cycloadducts in 85% yield (exo:endo ratio = 97:3; exo ee = 90%) (Fig. 59).

![Diagram](image)

**Figure 59.**

In another good example, the asymmetric Diels-Alder reaction of α,β-unsaturated aldehydes with cyclopentadiene is catalyzed by a chiral boron reagent generated in situ from boron tribromide and a chiral prolinol derivative, affording the corresponding adducts in good yields and good enantioselectivity. The authors presume that the active catalyst is the HBr salt 70 (Fig. 60).

Later, Agarwal et al. prepared several complexes (including 70) containing a Lewis acid and a Bronsted acid by the reaction of an aminoalcohol and a trihaloborane. The structures of these complexes were determined by ¹H, ¹¹B and ¹³C analysis and shown to be acyclic 70 rather than cyclic. Diels-Alder cycloaddition between methacrolein and cyclopentadiene in the presence of these catalysts afforded high exo selectivity and enantioselectivity de-
pending on the aminoalcohol used, with prolinol affording the highest ee (97%)\textsuperscript{79b}.

In a recent paper, Yamamoto and Ishihara described the application of a Bronsted acid-assisted chiral Lewis acid (BLA) to the catalytic asymmetric Diels-Alder reaction between $\alpha$-substituted $\alpha,\beta$-enals and dienes (Fig. 61)\textsuperscript{80,18c,d}. The catalyst (R)-71 was prepared by reaction of (R)-3,3'-bis-(2-hydroxyphenyl)-2,2'-dihydroxy-1,1'-binaphthyl with B(OMe)\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2} at reflux with removal of MeOH. BLA was found to be a good catalyst for the enantioselective reactions of $\alpha$-substituted $\alpha,\beta$-enals, but $\alpha$-unsubstituted $\alpha,\beta$-enals like acrolein and crotonaldehyde exhibit low enantioselectivity. High enantioselectivities and exo selectivity were obtained for Diels-Alder additions of $\alpha$-substituted $\alpha,\beta$-enals with dienes in the presence of catalyst 71 as illustrated in Fig. 61.

To rationalize the highly stereoselective course of the reaction and the mechanism of catalysis, the authors proposed the transition state assembly illustrated in Fig. 62. An attractive donor-acceptor interaction from coordination of the dienophile at the face of boron that is cis to the 2-hydroxyphenyl substituent, and a high $s$-trans preference for the conformation of $\alpha,\beta$-enal is proposed (Fig. 62)\textsuperscript{80,18c,d}.

It is possible that hydrogen bonding of the 2-hydroxyphenyl group with an oxygen of the adjacent boron-oxygen bond in the complex increases the Lewis acidity of the boron center and the $\pi$-basicity of the phenoxyl group. This hydrogen bonding leads to a parallel orientation between the $\pi$-basic phenoxyl moiety and the $\pi$-acidic dienophile at the ideal separation (3Å) for donor-acceptor interaction. In this conformation, the $C\alpha$-$s$ face of the dienophile is open to approach by the diene.

In 1996, Yamamoto and coworkers described further improvements on the BLA catalyzed Diels-Alder reaction of $\alpha$-substituted $\alpha,\beta$-enals with various dienes\textsuperscript{81,18c,d}. The cycloaddition reactions between various $\alpha,\beta$-enals and dienes in the presence of catalyst (R)-72 are given in Fig. 63. The adducts are formed in good yields and high enantioselectivities in each case (Fig. 63).
This result can be compared with the CAB-catalyzed reaction, which afforded the adduct 74 in 74% yield and 46% ee, with endo:exo ratio = 99:1\textsuperscript{71,72} (Fig. 51). These results can be explained by invoking the transition state model illustrated in Fig. 65.

![Diagram](image)

**Figure 65.**

Although not catalytic, a successful asymmetricaza-Diels-Alder reaction of an imine mediated by \textit{in situ} generated chiral boron complex of type 75 (conveniently prepared by mixing a 1:1 molar ratio of optically active binaphthol and triphenyl borate in CH\textsubscript{2}Cl\textsubscript{2} at ambient temperature for 1 h) was described in 1992 by Yamamoto and Hattori\textsuperscript{82}. The aza-Diels-Alder reaction of an aldimine with Danishefsky diene was promoted by this complex in solution in the presence of 4 Å molecular sieves at -78 °C for several hours (Fig. 66).

![Diagram](image)

**Figure 66.**

The usefulness of this methodology was displayed in the asymmetric synthesis of (-)-anabasine \textsuperscript{82}, an alkaloid derived from nicotinic acid (Fig. 67)\textsuperscript{82}.

A mixture of 3-pyridylaldimine 79 and Danishefsky diene was treated at -78 °C with the chiral boron complex derived from (S)-Binaphthol to obtain dihydropyrididine 80 in 68% yield and 90% ee. This compound was converted to (-)-anabasine 82 in 3 steps.
The enone unit is in s-trans conformation; the carbonyl group is parallel to the naphthalene ring within van der Waals radii ~3.17 Å. Electrostatic and dipole-induced-dipole attraction between the Lewis acid activated carboxyloxy group and the electron rich arene favors this conformation, where the edge of the naphthalene blocks the bottom face of the dienophile leaving the top face open to approach by dienes (Fig. 69).

Spectroscopic evidence (selective shielding of dienophile protons by the arene) is consistent with X-ray structure. A more recent report from the same group showed that the catalyst with the more polarizable arene (1-naphthyl) affords higher enantioselectivity than the catalyst with the less polarizable arene (phenyl). This demonstrates that increasing the polarizability of the arene group shifts the enolate over the ring and gives higher enantioselectivity.  

Itsuno and his co-workers described the use of polymer-supported chiral Lewis acids as asymmetric catalysts for Diels-Alder reactions of methacrolein with cyclopentadiene (Fig. 70). These catalysts were prepared from monobromoborane or borane with cross-linked polymers having a chiral moi-

Racemic 83 was prepared by hydroboration of the cyclohexene precursor, followed by resolution via its crystalline complex with menthone. Crystal structure of the (+/-)-83-methyl crotonate complex showed that:

- Boron and naphthalene are equatorial on the chair cyclohexane;
- Boron complexes the carbonyl oxygen anti to the C-O bond of the ester;

<table>
<thead>
<tr>
<th>R</th>
<th>n</th>
<th>yield (%)</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Me</td>
<td>1</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>1</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>H</td>
<td>2</td>
<td>83</td>
<td>88</td>
</tr>
</tbody>
</table>
ety such as aminooalcohol, diol or N-sulfonyl aminoacid. By using this polymeric catalyst, the Diels-Alder adduct was obtained in 93% yield with 99:1 exo:endo selectivity and 65% ee (exo isomer), the same enantioselectivity as the non-polymeric case. More recently, Itsuno reported that a new polymeric catalyst having oxyethylene crosslinkages exhibit better performance in promoting enantioselective Diels-Alder reactions. The use of insoluble polymeric catalysts facilitates the separation of the solid catalyst and the chiral polymer is recovered quantitatively by simple filtration and can be reused several times without any loss of enantioselectivity.

Bidentate chiral Lewis acids derived from 1,8-naphthalenediylbis(dichloroborane) have been found to be active catalysts for the asymmetric Diels-Alder reactions using chiral ligands derived from aminoacids and diols (Fig. 71).

![Diagram](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Ligand: Diboran</th>
<th>exo:endo</th>
<th>%ee</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>1.0</td>
<td>92:8</td>
<td>44(0)</td>
<td>84</td>
</tr>
<tr>
<td>Me</td>
<td>1.0</td>
<td>63:37</td>
<td>100(0)</td>
<td>46</td>
</tr>
<tr>
<td>H</td>
<td>1.0 TsHN</td>
<td>6:94</td>
<td>62(0)</td>
<td>53</td>
</tr>
<tr>
<td>Br</td>
<td>1.0</td>
<td>86:14</td>
<td>36(0)</td>
<td>81</td>
</tr>
<tr>
<td>Br</td>
<td>2.0</td>
<td>80:20</td>
<td>28(0)</td>
<td>81</td>
</tr>
<tr>
<td>Br</td>
<td>2.0 PhO</td>
<td>80:20</td>
<td></td>
<td>83</td>
</tr>
</tbody>
</table>

Figure 71.

The goal is to enforce a highly rigid transition state assembly via a bidentate Lewis acid, and a range of enantioselectivities has been achieved with cyclopentadiene and various α,β-unsaturated aldehydes. An interesting NMR solution investigation shows evidence for simultaneous coordination of 2,2-dimethyl-pyranone by 1,8-naphthalenediylbis(dichloroborane) (Fig. 72).

The proposed model to account for facial selectivity is illustrated in Fig. 72.

This model has similarities to the Corey oxazaborolidine transition state assembly. The front face of the enal is blocked by the tryptophan ring due to a π-interaction between the indole moiety and the dienophile and also between the toluenesulfonamide and the naphthalene system. The proposed transition state also is consistent with bridging chlorides to stabilize the electron deficient boron.

Asymmetric hetero Diels-Alder reactions of glyoxylate with acid-labile Danshifsky diene are catalyzed in high enantio- and cis(endo)-diastereoselectivity by a chiral aminoacid derived boron complex (Fig. 74). This reaction is promoted by a catalytic amount (10 mol%) of complex 85 at -78 °C to give the endo isomer 88 in 69% isolated yield after acid treatment (CF3CO2H). The same reaction with diene 87 leads also to endo-diastereoselectivity (86% yield, 74% cis) and good enantioselectivity (80% ee).

The exo-mode of cycloaddition would be disfavored by interaction between R2 and Bln*. Because of dipolar repulsion between the two carbonyl groups, the glyoxylate
should possess the \textit{s-trans} conformation (Fig. 75). The boron catalyst 85 should be complexed to glyoxylate in an \textit{anti} (monodentate) fashion and the Diels-Alder reaction should proceed with \textit{endo} orientation. The reaction occurs via the favorable transition state assembly for one directional diene approach from the site proximal to the sulfonyleamino group.

![Figure 74.](image)

**Figure 74.**

The chiral tartrate-derived dioxaborolidine 90 has been used to effect enantioselective Diels-Alder reactions of \(\alpha\)-bromoacrolein and cyclopentadiene\(^{89}\). In the presence of 20 mol\% of catalyst 90, the (2R)-bromoaldehyde is obtained in 96\% yield, 85:15 (R:S) enantioselectivity and 96:4 (\textit{exo:endo}) diastereoselectivity (Fig. 76).

The proposed transition state is illustrated in Fig. 77. The two tartrate ester units prefer to occupy the axial position with respect to the dioxaborolidine unit. The sta-bilized dipole-dipole interaction between the carbonyl carbon (\(\delta^+\) \(\alpha\)-bromoacrolein) and the proximate ester carbonyl oxygen together with the attractive interaction of \(\pi\)-basic benzyl ring and the \(\pi\)-acidic dienophile in the \textit{s-cis} conformation locks the dienophile in a fixed orientation. Approach of the diene from the less sterically hindered side (opposite to the aryl ring) afforded the cycloadduct in good enantioselectivity.

An extremely useful enantioselective Diels-Alder reaction was reported recently by Corey \textit{et al.} that described the utilization of a super-reactive cationic oxazaborinane catalyst 91 (Fig. 78)\(^{90,18c,d}\). This strong chiral Lewis acid promotes Diels-Alder reaction between reactive and unreactive dienes and dienophiles. With tetrabromoborate as counterion, good enantioselectivities were achieved in the reaction of cyclopentadiene with several \(\alpha,\beta\)-enals. With tetraks-[3,5-bis(trifluoromethyl)]borate as counterion, the reaction of isoprene and \(\alpha\)-bromoacrolein at -94 °C gave the desired cycloadduct in 90\% yield and 96\% ee.

The proposed \textit{exo} transition state (for cyclopentadiene) is illustrated in Fig. 79 and shows that one of the -NCH\(_2\)Ar blocks the lower face of the \textit{s-trans}-coordinated dienophile (Fig. 79)\(^{90,18c,d}\). It should be noted that the authors proposed an \textit{s-trans} geometry for the complex \(\alpha\)-substituted unsaturated aldehyde/Lewis acid, contrary to previous observations that this aldehyde reacts in the \textit{s-cis} form.
Dias prepared in situ from TiCl₄(OPr)₂ and a chiral 1,4 diol derived from (+)-tartaric acid. Carrying out the reaction in a mixture of toluene/petroleum ether in the presence of 4 Å molecular sieves (4 Å MS), the cycloadduct 93 having an octa-hydronaphthalene skeleton was obtained in 70% yield as a single endo isomer in more than 95% ee (Fig. 80).

Figure 80.

After a number of steps, the cycloadduct 93 was converted to the compound 94, a valuable synthetic intermediate for the synthesis of compactin 95 and analogues (Fig. 81).

Figure 81.

A similar approach was used by Corey in 1991 in a report using a modified version of the Narasaka catalyst. The titanium (IV) complex 96 was prepared by reaction of the corresponding diol with Ti(OPr)₄ followed by reaction with 1 equivalent of SiCl₄ in toluene at 23 °C. The reaction of cyclopentadiene and 3-(2-propenyl)-2-oxazolidinone 7a in toluene at -40 °C for 12 h in the

---

**Diene** | **Product** | **Yield (%)** | **%ee**
--- | --- | --- | ---
\[ \begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*} \] | \[ \begin{align*}
\text{CHO} & \quad 99 \quad 94 \\
\text{Br} & \quad 99 \quad 96 \\
\end{align*} \] | \[ \begin{align*}
\text{CHO} & \quad 99 \quad 98 \\
\text{Me} & \quad 91:9 \\
\end{align*} \]

---

**The catalyst:**

\[ \text{Ar}_2 \text{B} = \text{B[C}_6\text{H}_3\text{-3,5-(CF}_3)_2 \text{]} \]

---

**Diene** | **Product** | **Yield (%)** | **%ee**
--- | --- | --- | ---
\[ \begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*} \] | \[ \begin{align*}
\text{CHO} & \quad 99 \quad 93 \\
\text{Br} & \quad 4:96 \\
\end{align*} \]

---

**Chiral titanium Lewis acids**

A highly efficient chiral titanium catalyst for Diels-Alder cycloadditions has been developed by Narasaka. The hydranaphthalene moieties of mevinic acids were synthesized enantioselectively by using the asymmetric intramolecular Diels-Alder reaction catalyzed by a chiral titanium reagent (Ti-TADDOL catalyst). This reaction proceeds in a highly enantioselective manner by the use of a catalytic amount (30 mol%) of the chiral titanium reagent.
presence of 20 mol% of catalyst afforded the Diels-Alder
cycloadduct 97a (R = H) in 80% yield, with 95:5 endo:exo
selectivity and 97:3 enantioselectivity (Fig. 82, Table 4).

![Figure 82](image-url)

Table 4.

<table>
<thead>
<tr>
<th>R</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>yield (%)</th>
<th>endo:exo % ee (endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>-40</td>
<td>12</td>
<td>80</td>
<td>95:5  94</td>
</tr>
<tr>
<td>Me</td>
<td>-10</td>
<td>8</td>
<td>92</td>
<td>93:7  93</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>-30</td>
<td>8</td>
<td>90</td>
<td>81:19  91</td>
</tr>
</tbody>
</table>

The sense of the asymmetric induction for the above
reactions can be explained by the proposed transition state
assembly illustrated in Fig. 83.

![Figure 83](image-url)

Although there is no mechanistic work on this model,
the authors proposed that the dienophile is complexed to
the metal in the s-trans geometry such that the α,β-unsatu-
rated carbonyl moiety and the proximate ring are in parallel
planes with an optimum spacing (ca. 3Å) for a π-stacking
interaction.

In 1995, DiMare and Seebach independently reported
related studies describing the stereochemical outcome of
Diels-Alder reactions in which Ti-TADDOLates are used
as Lewis acids, and about proposals of a model for the
underlying mechanism. The DiMare group has done
and VT-NMR experiments of complexes formed from
Ti-TADDOLates and unsaturated N-acyloxazolidinones to
obtain information about the species involved in this reaction.
The Seebach group studied the influence of the mode of catalyst preparation, amount of the catalyst, presence of molecular sieves, concentration of the reactants, temperature, solvent, and TADDOL structure on the same reaction.

The catalytic activity of the titanium complexes of
cis-N-sulfonyl-2-amino-1-indanols (98, Fig. 84) in Diels
Alder reactions was reported by Corey and coworkers in 1993. Catalyst preparation involves the complexation of the corresponding aminoalcohol with Ti(O'Pr)₄ followed by removal of iPrOH and reaction with SiCl₄ to give the mixed Cl-O'Pr titanium catalyst. Cycloaddition reaction between α-bromoacrolein and cyclopentadiene in the presence of 10 mol% of this catalyst afforded the (R)-bromoal-
dehyde 41 in 94% yield, 93% ee and 67:1 (exo:endo) diastereoselectivity (Fig. 84). The reaction between iso-
prene and α-bromoacrolein gave the aldehyde 42 in quan-
titative yield and 90% ee (Fig. 84).

![Figure 84](image-url)

The authors proposed that this reaction occurs via the
transition state assembly illustrated in Fig. 85, in which the
aldehyde adopts the s-cis conformation and assumes a
parallel orientation to the indane ring system.

In a recent paper, Keck and coworkers reported a formal
hetero Diels-Alder reaction using catalysts generated from
(R) or (S)-BINOL and Ti(O'Pr)₄, which leads to dihydropyr-
rones with good to excellent enantiomeric excess (Fig. 86, Table 5).

The adduct 99 derived from α-(benzylxyloxy)-acetalde-
hyde (entry 2, 97% ee) is known to be an important inter-
mediate en route to compactin 95 (Fig. 81) and mevilonin 118 (Figs. 81 and 94). Compound 99 can be converted easily to the subunit 100 (Fig. 87).

Wada and coworkers described a catalyzed asymmetric intermolecular hetero Diels-Alder reaction involving (E)-

In the same report, the cycloadduct derived from protected 3-hydroxypropanal has been shown to be a useful intermediate for the construction of the sub-units found in the complex natural products swinholide and scytophycin C.

Wada and coworkers described a catalyzed asymmetric intermolecular hetero Diels-Alder reaction involving (E)-
clopentadiene and \(\alpha,\beta\)-unsaturated aldehydes in the presence of different chiral Lewis acid catalysts.

Asymmetric Diels-Alder reaction of methacrolein with alkoxydienes 106 catalyzed by the binaphthol-derived chiral titanium (BINOL-Ti) complex 107 afforded the endo-cycloadducts 108 with good enantioselectivities. The authors propose a transition state where the aldehyde adopts the \(s\)-trans conformation with an \(anti\) complex being formed between aldehyde and titanium catalyst (Fig. 90, Table 8).

The reaction of 5-hydroxynaphthoquinone (juglone) 109 with butadienyl acetate catalyzed by the BINOL-Ti complex 107 freed from MS (Molecular Sieves) proceeds in 96% ee affording the \(endo\) adduct 110 which is very useful as an intermediate for the synthesis of antra-cyclines and tetra-cycline antibiotics (Fig. 91).

![Figure 89.](image)

**Table 7.**

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>X</th>
<th>aldehyde</th>
<th>(endo:exo)</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>-78</td>
<td>(\text{Si(o-tolyl)}_3)</td>
<td>acrolein</td>
<td>85:15</td>
<td>96</td>
</tr>
<tr>
<td>-78</td>
<td>(\text{Si(t-BuPh}_2)</td>
<td>acrolein</td>
<td>93:7</td>
<td>92</td>
</tr>
<tr>
<td>-40</td>
<td>(\text{Si(t-BuPh}_2)</td>
<td>methacrolein</td>
<td>4:96</td>
<td>62</td>
</tr>
<tr>
<td>-78</td>
<td>(\text{Si(o-tolyl)}_3)</td>
<td>methacrolein</td>
<td>1:99</td>
<td>94</td>
</tr>
</tbody>
</table>

![Figure 90.](image)

![Figure 91.](image)

The same BINOL-Ti MS-free was used in the condensation of methyl glyoxylate with methoxybutadienes. This cycloaddition reaction proceeds smoothly to give the 2,6-\(cis\)-(\(endo\)) adduct 112 with high enantioselectivity (Fig. 92, Table 9).

Of the two possible transition states leading to the \(cis\)-product, the \(syn\)-\(endo\) transition state A should be less favorable because of the steric repulsion in the sterically demanding titanium complex. Anti (monodentate) com-

![Figure 92.](image)

**Table 8.**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>(endo:exo)</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>93:7</td>
<td>85</td>
</tr>
<tr>
<td>Me(_2)NCO</td>
<td>H</td>
<td>99:1</td>
<td>87</td>
</tr>
<tr>
<td>Ac</td>
<td>H</td>
<td>99:1</td>
<td>94</td>
</tr>
<tr>
<td>Ac</td>
<td>Me</td>
<td>89:11</td>
<td>80</td>
</tr>
</tbody>
</table>
plexation between titanium catalyst and aldehyde makes the hetero Diels-Alder proceed through the anti-endo orientation A (Fig. 93).

![syn-endo A](image)

![anti-endo B](image)

Figure 93.

The glyoxylate adducts are useful intermediates for the synthesis of monosaccharides and also the lactone portion in mevilonin or compactin (Fig. 81), coenzyme A reductase inhibitors as illustrated in Fig. 94.39

![Figure 94](image)

Table 9.

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>-112:113</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>88:12</td>
<td>96</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>98:2</td>
<td>93</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>98:2</td>
<td>95</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>92:8</td>
<td>71</td>
</tr>
</tbody>
</table>

A very interesting phenomenon in these catalytic reactions is that MS-free complex 107 exhibits not only a linear relationship between the ee's of BINOL-Ti 107 and the Diels-Alder products but also a positive non linear effect (asymmetric amplification), depending simply on the mixing of (R)-107 with (S)-107 or (+/-)-107.

Narasaka and Yamamoto used a catalytic asymmetric Diels-Alder reaction of a 3-borylpropenoic acid derivative in the first asymmetric total synthesis of (+)-Paniculide 122, a highly oxygenated sesquiterpene (Fig. 95).104,105

![Figure 95](image)

Reaction of (E)-3-[(5,5-dimethyl)-1,2,3-dioxaborin-an-2-yl)-propenoyl]-1,3-oxazolidin-2-one 119 with 1-acetoxy-3-methyl-1,3-butadiene using a catalytic amount of the chiral titanium reagent 92 in toluene-petroleum ether and 4 Å MS afforded the adduct 120 in 82% yield and 94% ee.104

Selective oxidation of the boryl group with m-CPBA in CH2Cl2 in the presence of Li2CO3 at 0 °C afforded the alcohol 121 in good yield. This alcohol was transformed to (+)-Paniculide 122 after a sequence of transformations.

The cycloaddition reaction between oxazolidinone-based dienophiles and cyclopentadiene is efficiently catalyzed by the chiral metalocene complex [[(S)-1,2-ethylenebis(η⁵-tetrahydroindenyl)] Zr(OTf)2 123 as well as its titanium analog (Fig. 96, Table 1).106

The level of asymmetric induction (70-95% ee) is good in polar solvents like nitromethane and 2-nitropropane and poor in solvents like CH2Cl2, but the endo selectivity is higher in CH2Cl2.
Bosnich and Odenkirk used a stable, chiral diaquo titanocene complex 124 as a catalyst of Diels-Alder reactions between α,β-unsaturated aldehydes and cyclopentadiene in CH₂Cl₂ at -78 °C (Fig. 97)¹⁰⁷,¹⁰⁸. The exo:endoratio is high for α-substituted aldehydes, but the enantioselectivities are only moderate (26-75% ee).

In 1995, Mikami and coworkers reported the use of binaphthol (BINOL) catalysts in (hetero) Diels-Alder reactions of 1-methoxy-butadienes with methacrolein, α-bromoacrolein and glyoxylates (Fig. 98)¹⁰⁹. They showed that for methacrolein and glyoxylates, but not for α-bromoacrolein, the BINOL-catalyst (X = Br) is more effective than the analogous de-brominated catalyst (X = H) in terms of yields and enantioselectivity¹¹⁰.

The initial results with the phenyl-substituted ligand 125a (R = Ph) were not encouraging. In contrast to Corey's observation that this ligand performs very well in the analogous Fe(III)-catalyzed reactions, combination of ligand 125a (R = Ph) and Cu(OTf)₂ (10 mol%) in CH₂Cl₂ led only to 30% ee (95:5, endo:endoor 79). Changing the R group in catalyst 125 from Ph (125a) to t-Bu (125c), led to an increase in endo enantioselectivity (> 98% ee) (Fig. 99)¹¹².
The cycloaddition reaction with the crotonate derivative 7b in the presence of catalyst 125c (R' = t-Bu) afforded the corresponding endo-product in 97% ee at -15 °C while the more reactive thiazolidine-2-thione analog 126b gave the endo-product in 94% ee at -45 °C (Fig. 100)\textsuperscript{112}.

![Figure 101.](image)

**Table 12.**

<table>
<thead>
<tr>
<th>7b-d</th>
<th>endo:exo</th>
<th>endo ee %</th>
<th>T (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b, R = Me</td>
<td>96:4</td>
<td>97</td>
<td>-15</td>
</tr>
<tr>
<td>c, R = CO₂Et</td>
<td>94:6</td>
<td>95</td>
<td>-55</td>
</tr>
<tr>
<td>d, R = Ph</td>
<td>90:10</td>
<td>90</td>
<td>25</td>
</tr>
</tbody>
</table>

![Figure 102.](image)

**Table 13.**

<table>
<thead>
<tr>
<th>126</th>
<th>endo:exo</th>
<th>endo ee %</th>
<th>T (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b, R = Me</td>
<td>96:4</td>
<td>94</td>
<td>-45</td>
</tr>
<tr>
<td>c, R = CO₂Et</td>
<td>84:16</td>
<td>96</td>
<td>-55</td>
</tr>
<tr>
<td>d, R = Ph</td>
<td>92:8</td>
<td>97</td>
<td>-35</td>
</tr>
</tbody>
</table>

It is interesting to note that with the cinnamate derivatives 7d and 126d, the opposite trend is observed and the sulfur derived dienophile exhibits the highest endo enantioselection (97% ee at -35 °C).

The Cu(II)-catalyzed reaction of the mixed fumarate dienophiles 7c and 126c affords the best endo:exo diastereoselection for the acrylimide 97c (94:6), although the endo enantioselectivity is the same in both cases\textsuperscript{112,114}.

Copper(II) as a Lewis acid is a moderately oxophilic metal with a high propensity for 4-coordinancy. A bidentate ligand can occupy 2 free coordination sites and 2-point substrate binding is possible (Fig. 101)\textsuperscript{113}.

To rationalize the observed enantioselectivity the authors proposed the transition state illustrated in Fig. 102. These selectivities might be explained assuming the expected square planar coordination geometry of metal-s-cis dienophile complex, with approach of the diene from the Cα-re-face of dienophile, opposite to the bulky t-butyl group\textsuperscript{112,114}.

In an elegant study, the authors proposed double stereodifferentiating experiments using the enantiomeric chiral imides (R)- and (S)-128, under identical conditions, to probe the nature of the proposed catalyst-substrate complex (Fig. 103). In the stereochemically matched case with dienophile (R)-128 (copper center square planar and dienophile s-cis), the reaction afforded adduct 129 in 87% yield and 99:1 endo(1):endo(2) diastereoselectivity (Figs. 103 and 104)\textsuperscript{112,114}.

![Figure 103.](image)
In the mismatched case (copper center square planar and dienophile s-cis), the catalyzed reaction with (S)-127 gave only 10% yield of 130 with 68:32 endo(1):endo(2) diastereoselectivity, demonstrating that the catalyst dominates the sense of induction (Figs. 103 and 104).

Figure 104.

Evans and coworkers also reported the utilization of Cu(OTf)₂-bis(imine) complex as an effective catalyst for the Diels-Alder reaction. The 2,6-dichlorophenyl-substituted ligand 131, the most effective catalyst, can be readily prepared from enantiomerically pure trans-1,2-cyclohexanediimine and 2,6-dichloro-benzaldehyde (Fig. 105, Table 14). As can be seen from the data, the acrylate, crotonate and cinnamate imides afford good endo enantioselection but poor endo/exo diastereoselectivity.

Figure 105.

The best results were obtained with the more reactive sulfur dienophile derivatives 126b-d, which afforded much higher endo/exo diastereoselectivity (> 90:10) and good endo enantioselection. These results are rationalized by an enhancement in two-point binding promoted by the higher affinity of the C=S ligand for the copper center. It is believed that low diastereoselectivity may be due to the intervention of one-point catalyst binding.

The proposed model to explain the sense of asymmetric induction in these reactions involves a square-planar bis-(imine)-Cu(OTf)₂ catalyst-substrate complex, with approach of the diene from the less-hindered Cα-Si face of the s-cis dienophile (Fig. 106). This proposed model is supported by double stereodifferentiating experiments using chiral oxazolidine-thiones.

Figure 106.

In 1995, Evans and coworkers described very interesting counterion effects in the utilization of Cu(II) complexes of tridentate bis-(oxazolyl)-pyridine (pybox) ligands [Cu(II)-(pybox)X₂] 132a-d in reactions with α-substituted acroleins (Fig. 107, Table 15).
Table 15.

<table>
<thead>
<tr>
<th>Triflate catalyst 132a</th>
<th>Time (h)</th>
<th>T (°C)</th>
<th>endo:exo</th>
<th>Major isomer ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R = H)</td>
<td>116</td>
<td>-20</td>
<td>97:3</td>
<td>85%</td>
</tr>
<tr>
<td>(R = Br)</td>
<td>60</td>
<td>-40</td>
<td>3:97</td>
<td>87%</td>
</tr>
<tr>
<td>(R = Me)</td>
<td>120</td>
<td>-20</td>
<td>4:96</td>
<td>85%</td>
</tr>
</tbody>
</table>

SbF₆⁻ catalyst 136d

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>T (°C)</th>
<th>endo:exo</th>
<th>Major isomer ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R = H)</td>
<td>18</td>
<td>-20</td>
<td>94:6</td>
</tr>
<tr>
<td>(R = Br)</td>
<td>12</td>
<td>-78</td>
<td>2:98</td>
</tr>
<tr>
<td>(R = Me)</td>
<td>8</td>
<td>-40</td>
<td>3:97</td>
</tr>
</tbody>
</table>

The catalyst 132d with non-coordinating counterion SbF₆⁻ is ca. 20 fold more reactive than the OTf⁻ catalyst 132a. The cationic (pybox)Cu(SbF₆)₂ complex showed the best results in terms of reaction rates and enantioselectivities when compared with the triflate catalysts (Fig. 107). With the non-coordinating counterion SbF₆⁻ the intervention of a square planar catalyst-substrate complex such as 133 is consistent with the observed sense of asymmetric induction (Fig. 108).

- A tridentate ligand can occupy 3 free coordination sites
- 1 point substrate binding possible

Figure 108.

At this point, the authors reinvestigated the bis-(oxazoline)-copper(II) complexes 125c in reactions of acrylimides 7 and several dienes and observed that the cationic Cu(II) complex 125c (X=SbF₆⁻) always afford higher asymmetric induction than the analogous triflate complex 125c (X=OTf⁻) (Fig. 109)¹¹⁶a.

The same authors proposed that the lower enantioselectivity observed with the triflate-based catalyst might be due to the intervention of a competing cycloaddition from a less highly organized one-point binding catalyst-dienophile complex such as 134 (Fig. 110).

In a more recent paper, Evans et al. reported a systematic comparison of the cationic Lewis acidic Cu(II) and Zn(II) catalysts derived from bis-(oxazoline), box, and pyridyl-bis-(oxazoline), pybox. They concluded that the cationic Cu(II)-box complexes are superior to their Zn(II) counterparts as chiral Lewis acid catalysts for the imide Diels-Alder reactions¹¹⁶b.

A similar counterion effect was observed by Davies and coworkers at Merck in 1996¹¹⁷. Chiral bis-oxazolines 135 were used in Cu(SbF₆)₂ catalyzed asymmetric reactions of the two-point binding acrylimides 7a and cyclopentadienes at -75 °C and high enantioselectivities (up to 95% ee) and good endo diastereoselectivities (39:1) were obtained (Fig. 111).

The Cu(OTf)₂ (135a) catalyzed process afforded the desired product in 92% ee and 130:1 endo:exo diastereoselection at -65 °C. Using the Cu(SbF₆)₂ catalyst 135b, this adduct was obtained in 95% ee and 39:1 endo:exo diastereoselectivity¹¹⁷.
dimethyl moiety in ligand 135 (Φ = 104.7°) to a cyclopropyl in ligand 136a (Φ = 110.6°) lead to an increase in enantioselectivity from 82.5 to 96.3% ee at -50 °C, with a 44:1 endo:exo ratio. The same reaction with ligand 136a at -70 °C afforded the adduct 97a in 98.4% ee and 96:1 endo:exo diastereoselectivity.

In 1996, Ghosh and coworkers disclosed their results using a bis-(oxazoline) chiral catalyst analogous to that used by the Merck group. The Ghosh group reported highly enantioselective cycloadditions between cyclopentadiene and various bidentate dienophiles in the presence of copper(II)-bis-(oxazoline) catalyst 137 derived from cis-1-amino-2-indanol (Fig. 113, Table 17).

The observed enantioselectivities can be rationalized based on the transition state models proposed by Corey and Evans in which Cu(II) assumes a square planar complex with the bis-(oxazoline) ligand 137 and the s-cis-dienophile.

In 1995, Jorgensen and Johanssen disclosed their results on asymmetric hetero Diels-Alder and Ene reactions catalyzed by chiral copper(II) bis-(oxazoline) complexes. The reactions of ethyl and isopropyl glyoxylate with less reactive dienes afforded the hetero Diels-Alder and Ene products in good yields and moderate enantioselectivity. The reaction of 1,3-butadiene with isopropyl glyoxylate in the presence of Cu(II)-catalyst 125c (X=OTf) afforded adduct (S)-138 in 55% yield and 87% ee (Fig. 114).

The authors observed that the absolute stereochemistry of this reaction is dependent on catalyst applied; the bis-(oxazoline) ligand 125c with a tert-butyl substituent gives the opposite stereochemistry when compared with the bis-(oxazoline) ligand 125a with a phenyl substituent. This difference has been attributed to a square planar complex with 125c, and a tetrahedral arrangement at the metal in...
ligand 125a\textsuperscript{121a}. The same authors published a very interesting paper on solvent effects in asymmetric Hetero Diels-Alder and Ene reactions using Cu(II)-bis(oxazoline) catalysts\textsuperscript{121b}. The use of polar solvents such nitroalkanes that could stabilize the dissociating ions leads to a significant improvement of the catalytic properties of a Cu(II)-bis(oxazoline) catalyst in hetero Diels-Alder reactions of alkylglyoxylates with dienes. This methodology has been used for the synthesis of a synthon for sesquiterpene lactones\textsuperscript{121b}.

More recently, the Evans group reported a highly enantioselective Diels-Alder reaction between acryloyl oxazolidinone 7 with furan\textsuperscript{122,123}. This reaction, catalyzed by cationic bis(4-tert-butyl)oxazoline\textsuperscript{b}Cu(II) complex 125c with hexafluoracetone (SbF6\textsuperscript{b}) counterion at -78 °C, afforded the cycloadduct 139 in 97% yield with an endo:exo ratio of 80:20 and the endo isomer was obtained in 97% ee (Fig. 115)\textsuperscript{122a,96b}.

The synthetic utility of this reaction is demonstrated by the conversion of 139 to ent-shikimic acid 140, synthesized in 7 steps and 37% overall yield from imide 7 (Fig. 116).

The same cationic Cu(II)-bis(oxazoline) complex 125c (SbF6\textsuperscript{b} counterion) effectively catalyze the intramolecular Diels-Alder reaction of several trienimides with excellent enantioselectivity\textsuperscript{122b}. In the presence of 5mol% of catalyst 125c, phenyl-substituted trienimide 141 afforded adduct 142 in 86% yield and 92% ee after 5 h at ambient temperature (Fig. 117).

This methodology is applied in the synthesis of the marine toxin (-)-isopulo'upone 146 (Fig. 118). Treatment of trienimide 143 with 5 mol% of catalyst 125c in CH2Cl2 at ambient temperature provided cycloadduct 144 in 81% yield and 96% ee (>99:1 endo:exo). This bicyclic compound was transformed to the marine natural product (-)-isopulo'upone 146 after 6 steps (Fig. 118).
The relative stereochemical assignments were confirmed by an X-ray structure and the absolute stereochemistry can be explained by the proposed four-coordinate square planar Cu(II)-bis(oxazoline)-substrate complex (Fig. 102)\textsuperscript{112-114}.

**Chiral lanthanide(III) Lewis acids.**

Recently, some highly efficient asymmetric Diels-Alder reactions catalyzed by chiral lanthanide(III) triflates have been reported\textsuperscript{124,125}.

A chiral ytterbium triflate (20 mol%), prepared from ytterbium triflate, (R)-(+)-binaphthol and cis-1,2,6-trimethylpiperidine, catalyzes the reaction of crotonyl-1,2-oxazolin-2-one 7b with cyclopentadiene in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C to afford the cycloadduct 97b in 77% yield and up to 95% ee (endo/exo = 89:11), favoring the (2S,3R)-endo adduct (Fig. 119)\textsuperscript{126}.

\[ R \text{NO}_2 + \text{HC} = CHCH}_5 \xrightarrow{\text{MS 4 Å, CH}_2\text{Cl}_2, 0 °C} 97b, d \]
\[ 97b, R = \text{Me, 95% ee} \]
\[ 97d, R = \text{Ph, 83% ee} \]

**Figure 119.**

In 1994, Kobayashi and co-workers reported other lanthanide(III) triflates as catalysts\textsuperscript{128}. They observed that yields and selectivities diminished rapidly in accordance with the increase of the ionic radius as shown in Fig. 122, Table 18.

\[ \text{Me} = \text{C} = \text{CNO}_2 + \text{HC} = CHCH}_5 \xrightarrow{\text{MS 4 Å, CH}_2\text{Cl}_2, 0 °C} \]

**Figure 122.**

<table>
<thead>
<tr>
<th>Ln</th>
<th>yield (%)</th>
<th>endo/exo</th>
<th>2S,3R:2R,3S</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu</td>
<td>60</td>
<td>89:11</td>
<td>96.5:3.5</td>
<td>93</td>
</tr>
<tr>
<td>Yb</td>
<td>77</td>
<td>89:11</td>
<td>96.5:3.5</td>
<td>93</td>
</tr>
<tr>
<td>Tm</td>
<td>46</td>
<td>86:14</td>
<td>87.5:12.5</td>
<td>75</td>
</tr>
<tr>
<td>Er</td>
<td>24</td>
<td>83:17</td>
<td>84.5:15.5</td>
<td>69</td>
</tr>
<tr>
<td>Ho</td>
<td>12</td>
<td>73:27</td>
<td>62.5:37.5</td>
<td>25</td>
</tr>
<tr>
<td>Y</td>
<td>6</td>
<td>70:30</td>
<td>60.0:40.0</td>
<td>20</td>
</tr>
<tr>
<td>Gd</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Figure 120.**
The authors observed also that the selectivities lowered in accordance with the stirring time of the catalyst solution and temperature. These results were ascribed to the aging of the catalyst and it was found that the dienophile is effective in preventing the catalyst from aging. A particularly interesting feature of this process is that the enantioselectivities can be reversed by using achiral ligands as additives as shown in Fig. 123 (Table 19).

![Figure 123.](image)

Table 19.

<table>
<thead>
<tr>
<th>Additive</th>
<th>yield (%)</th>
<th>endo:exo</th>
<th>(2S,3R):(2R,3S)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>77</td>
<td>89:11</td>
<td>96:4</td>
<td>(93)</td>
</tr>
<tr>
<td>Me</td>
<td>80</td>
<td>88:12</td>
<td>22:78</td>
<td>(55)</td>
</tr>
<tr>
<td>Me</td>
<td>83</td>
<td>93:7</td>
<td>10:90</td>
<td>(81)</td>
</tr>
</tbody>
</table>

When 3-(2-butenyl)-1,3-oxazolidin-2-one was used as an additive, the endo-adduct (2S,3R) was obtained in 66% yield, endo:exo = 87:13, and 88% ee. With 3-acetyl-1,3-oxazolidin-2-one as an additive, the endo-adduct (2S,3R) was obtained in 77% yield, endo:exo = 89:11, and 93% ee. On the other hand, when acetylacetone derivatives were used, reversed enantioselectivities were observed and the endo adduct with the absolute configuration (2R,3S) was obtained in up to 83% yield, endo:exo = 93:7, and 81% ee (3-phenyl-acetylacetone as additive).

Another example of the application of a chiral Yb(OTf)₃-BINOL complex as catalyst was described by Markó in cycloaddition reactions between 3-carbomethoxy-2-pyrene 148 (3-CMP) with vinyl ethers and vinyl sulfides, affording bicyclic lactones 149 in good yields and good enantioselectivities. On heating, these lactones lose CO₂ to afford chiral cyclohexadienes 150. They observed that the vinyl sulfides always gave higher ee’s than the related vinyl ethers (Fig. 124).

![Figure 124.](image)

The utilization of TADDOL and (-)-menthol derivatives led to racemic Diels-Alder adducts.

**Chiral magnesium Lewis acids**

In 1992 Corey and Ishihara reported the utilization of the C2-symmetric chiral bis-(oxazoline) ligand 151. This ligand, synthesized from (S)-phenylglycine, is an effective catalyst for enantioselective Diels-Alder addition in combination with magnesium iodide (made from Mg + I₂ in ether at 25 °C) or magnesium tetraphenylborate (made from MgCl₂ + tetraphenylboral in CH₃CN at 50 °C) (Fig. 125).

![Figure 125.](image)

The catalyst 152 (0.1 equiv.) and 0.2 equiv. of AgSbF₆ (co-catalyst) converts cyclopentadiene and 3-acyloyloxazolidin-2-one 7 in CH₂Cl₂ at -80 °C over 16 h to the chiral adduct (R)-97 in 84% yield with 98:2 endo:exo selectivity and 91% ee. The observed enantioselection in this reaction is opposed to that observed with Cu(II) catalysts (Fig. 126).

The same reaction in the presence of 151-Mg(Ph₃B)₂ in 2:1 CH₂Cl₂/PrNO₂ at -50 °C over 18 h produced the cycloadduct with 90% enantioselectivity and 97:3 endo:exo selectivity. The authors proposed a 1:1:1 com-
plex of 151, Mg$_{2}^{2+}$ and the bidentate dienophile in a tetrahedral arrangement of donor groups about the metal and the s-cis conformation for the α,β-unsaturated system. In this complex, the back face of the double bond is blocked by phenyl and the diene approach is from the Cα-si face (Fig. 126).

![Figure 126.](image)

In 1995, Fujisawa and coworkers reported high enantioselectivity in the reaction between cyclopentadiene and 3-acryloyl-1,3-oxazolidin-2-one 7 using a chiral magnesium(II)-complex 154 of 2-(2-p-toluenesulfonylamino)-phenyl-4-phenyl-oxazoline 153 prepared from inexpensive D-phenylglycino119.

![Figure 127.](image)

Although the yields and enantioselectivities were good using stoichiometric amounts of this complex, the utilization of 20 mol% of catalyst afforded only 84% ee of the corresponding product in 78% yield.

In 1996, Desimoni and coworkers reported the first enantioselective synthesis of both (R)-97 and (S)-97 with the same bis-(oxazoline)-magnesium perchlorate chiral catalyst (Fig. 128)140.

The tetrahedral coordination of catalyst and dienophile gave the endo adduct (S)-97 (68-70% ee). The addition of two equivalents of water favors the octahedral coordination and the same catalyst gives the enantiomer (R)-97 (59-65% ee)140. It should be noted that the enantioselectivities in these reactions are low and cannot compete in terms of enantioselective efficiency with the Evans and Corey protocols116,136.

In 1996, Llera et al. disclosed their results on the use of chiral magnesium(II)-complexes prepared from hydroxysulfides and magnesium iodide41. The reaction between 3-acryloyl-1,3-oxazolidin-2-one 7 and cyclopentadiene in the presence of catalytic amounts of hydroxysulfoxide 155 and magnesium iodide afforded cycloadduct (S)-97 in 95% yield and 88% enantioselectivity (98:2, endo:exo diastereoselectivity) (Fig. 129).

![Figure 129.](image)

Chiral transition metal-based Lewis acids

In the presence of 5 mol% of the iron catalyst 156 and 2.5 mol% of 2,6-di-tert-butylpyridine, α-bromoacrolein reacted with 1,3-cyclohexadiene to give the cycloadduct in 88% yield and 99% ee with a 90:10 endo:exo ratio142 (Fig. 130).

The best results were obtained with the very reactive α-bromoacrolein and the use of various dienes led to useful levels of enantioselection.
Yamashita and Katsuki related the use of optically active oxo(salen) manganese(V) complexes 157 as chiral Lewis acid catalysts, although the enantioselectivities are low. Reaction between cyclopentadiene and α-bromoacrolein in the presence of 10 mol% of iodosylbenzene as co-oxidant afforded the exo-adduct with 68% ee\(^{143}\) (Fig. 131).

Carmona and Cativiela reported recently the first rhenium enantioselective catalyst for the Diels-Alder reaction between methacrolein and cyclopentadiene\(^{144}\). The best results in terms of rate and enantioselectivity were obtained using the SbF\(_5\) catalyst derivative 158 (Fig. 132).

**Conclusion**

Recent advances in the application of chiral Lewis acid catalysts of aluminum, boron, titanium, copper, magnesium and lanthanides have been reviewed. A number of chiral ligands systems such as aluminum/biaryl, oxazaborolidines, acyloxy-borane, BINOL-Ti, TADDOL-Ti derivatives and Cu(II)-bis-oxazolines have been shown to be especially effective. Some new ligands have been developed and some metals such as lanthanides have been shown to be promising in specific applications to date.

Concerning the asymmetric hetero Diels-Alder reactions, only a limited number of efficient methods are available. Research directed at the development of new methods for the highly stereoselective execution of asymmetric hetero Diels-Alder cycloadditions is needed.

The state of the art of organic synthesis is the enantioselective homogeneous catalysis involving substoichiometric amounts of optically active auxiliaries. Concerning the Diels-Alder cycloaddition, advances are expected in the use of less reactive dienes and dienophiles as well as in enantioselective variants of the intramolecular version. It is also expected to see more developments in the use of transition-metal complexes as chiral catalysts.

**Acknowledgments**

I am grateful to Dr. Adrian M. Pohlitz and Dr. Denise Curi from Universidade Estadual de Campinas (UNICAMP), and also to Professor David A. Evans and Jeffrey S. Johnson from Harvard University for helpful comments and useful suggestions during the preparation of this manuscript. Support has been provided by FAEP-UNICAMP and FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo).

**References**


13. (a) For an interesting publication describing some of the historical background of the discoveries of the diene synthesis and the orbital symmetry conservation rules, see: Berson, J.A. Tetrahedron 1992, 48, 3.


33. (a) Marshall, J.A.; Beaudoin, S. J. Org. Chem. 1994, 59, 7833; (b) see also Reference 29.
56. Recently, Jorgensen and coworkers reported a catalytic hetero-Diels-Alder reaction of (S)-binol-AlMe as a catalyst. The (R)-enantiomer was obtained as the major product with up to 97% ee (13 to 73% yield):
62. Traditionally, Lewis basic solvents are avoided in Lewis acid chemistry, CH2Cl2 and hydrocarbons being the standard solvents. However, the importance of donor solvents is quite apparent from a recent work: Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. Chem. Lett. 1990, 1455.
75. NOE data give no information about transition state configuration.
77. For a recent review about asymmetric hetero Diels-Alder reaction, see: Waldmann, H. Synthesis 1994, 535.
89. L-tartrate derived catalysts have been used to effect enantioselective Diels-Alder reaction between α-bromoacrolein and cyclopentadiene: Loh, T.-P.; Wang, R.-B.; Sim, K.-Y. Tetrahedron Lett. 1996, 37, 2989.
105. Recently, Tietze and coworkers reported \(^1\)H-NMR investigations of the temperature and pressure dependence on the equilibrium between the chiral Lewis acid and Ti(OiPr)\(_2\)Cl\(_2\). They observed that increasing temperature and pressure cause an increase of the amount of the Ti(OiPr)\(_2\)Cl\(_2\) in the equilibrium, decreasing the enantioselectivity of the cycloaddition reaction: Tietze, L.F.; Ott, C.; Frey, U. Liebigs Ann. 1996, 63.


115. In 1995, Feringa and coworkers described the utilization of a chiral bis-imine copper (II) complex as catalyst for the Diels-Alder reaction of 1-vinyl-2, 2, 6-trimethyl-cyclohexene and 3-[(E)-3-(methoxycarbonyl)-propenyl]-1, 3-oxazolidin-2-one under high pressure leading to a drimane sesquiterpene precursor in up to 64% ee: Knol, J.; Meetsma, A.; Feringa, B.L. Tetrahedron:Asymmetry 1995, 6, 1069.


125. Mikami recently reported the use of yttrium (bis-triflylamide) complexes as a new type of asymmetric catalyst for hetero Diels-Alder reactions with Danishefsky diene in the presence of water in up to 66% ee: Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H. Synlett 1995, 975.


132. For more results on this methodology, see: (a) Markó, I.E.; Evans, G.R.; Declerq, J.P.; Feneau-Dupont, J.; Tinant, B. Bull. Soc. Chim. Belg. 1994, 103, 29; (b)
137. For an example of the utilization of Mg(II)-complexes of conformationally constrained bis-(oxazoline) derived chiral catalysts, see Reference 111.
138. (a) In this work, the same reaction in the presence of an Fe(III)-containing catalyst afforded 87% yield of 97 with 99:1 endo:exo selectivity and 86% ee. (b) For one more example of a chiral Fe(III) catalyst, see: Khiar, N.; Fernández, I.; Alardia, F. Tetrahedron Lett. 1993, 34, 123.

FAPESP helped in meeting the publication costs of this article