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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

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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, lantanídeos, 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[1].

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[1,2].

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[3,4]. Asymmetric catalysis using chiral Lewis acids, provides a general, powerful tool in this context[5,6].

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[7,8].

This review covers recent progress in chiral Lewis acids catalyzed Diels-Alder reactions[9,10].

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[11,12]. 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

* This review is dedicated to Prof. José Tércio Barbosa Ferreira (*in Memoriam*) and to the Brazilian Chemical Society (SBQ).

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 α-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 α,β-unsaturated carbonyl compound, the proportion of *s-cis* and *s-trans* α,β-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 (π^* C=C-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 β-carbon in the π^* C=C-C=O orbital, increasing secondary orbital interactions and rendering the molecule more susceptible to nucleophilic attack (Fig. 1)[15,16,17].

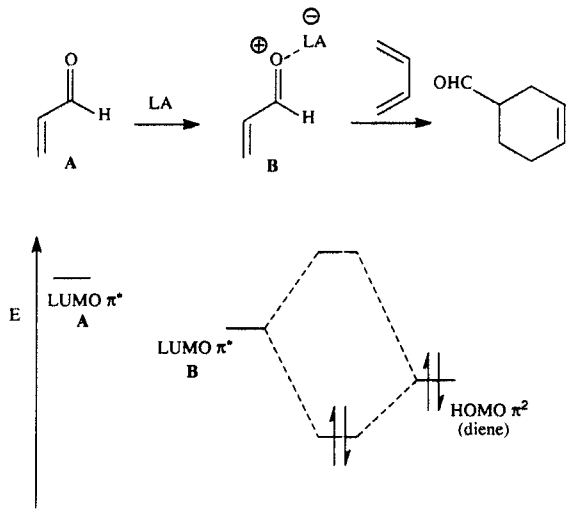


Figure 1.

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.

A well-defined Lewis acid-C=O complex is needed: η_1 (σ bonding) *vs.* η_2 (π bonding) complexation (Fig. 2).

Some representative η_1 (σ-type) and η_2 (π-type) complexes and their X-ray structures were published by Schreiber in 1990[18a]. Examples of η_2 (π-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 σ-fashion. It is interesting that cationic Re complexes exhibit η_1 complexation with ketones and η_2 complexation with aldehydes (Fig. 3).

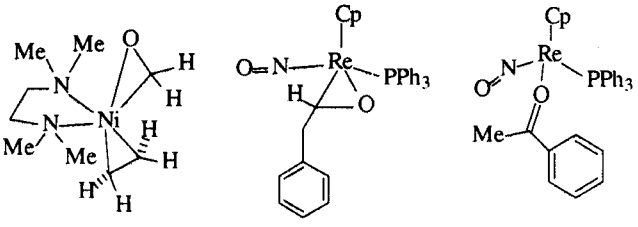


Figure 3.

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

The geometry of η_1 complexes (*anti* or *syn* coordination) should be well-defined (Fig. 4).

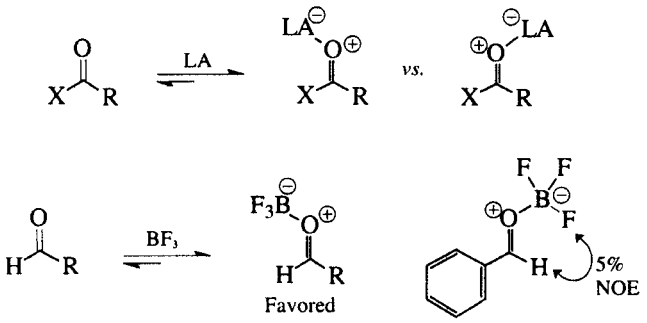


Figure 4.

In aldehydes, complexation with BF_3 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[20]. 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 $CFCl_3$ led to a 5% enhancement of the aldehyde proton absorption, whereas the aromatic protons remained unaffected (Fig. 4)[20]. In the acetaldehyde-BF_3 complex, MNDO calculations showed that the *anti* complex is 1.8 Kcal/mol lower in energy than the corresponding *syn* complex[20].

Very recently, Fu and coworkers provided structural data that suggests that π interaction of the type illustrated in Fig. 5 can define the conformation of a complex formed between a carbonyl compound and a Lewis acid [22b]. 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)[22b].

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 BF_3 (Fig. 6)[20,23].

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.

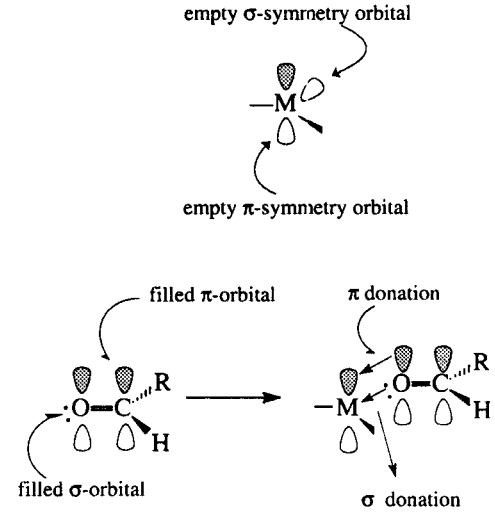


Figure 5.

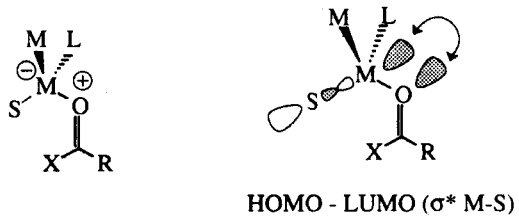


Figure 6.

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)[18b-d].

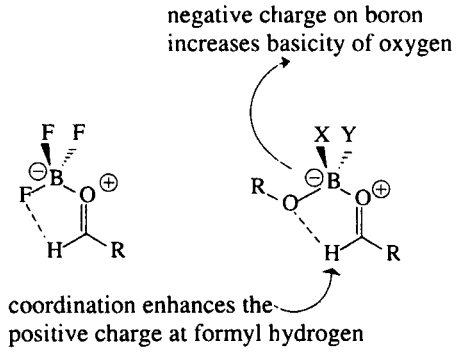


Figure 7.

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. carbonyl allylation and Diels-Alder reactions[18d]. 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'O- moiety, as demonstrated by X-ray diffraction (Fig. 8)[21a,22].

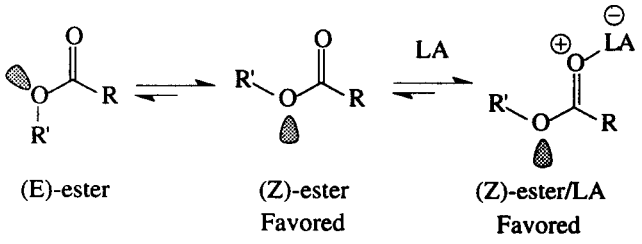


Figure 8.

The (Z)-ester conformation is stabilized by a HOMO(oxygen lone pair)-LUMO(σ*C-O) interaction (Fig. 9). In the (E) conformation this lone pair is aligned to overlap with σ*C-R. Since σ*C-O is a better acceptor than σ*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).

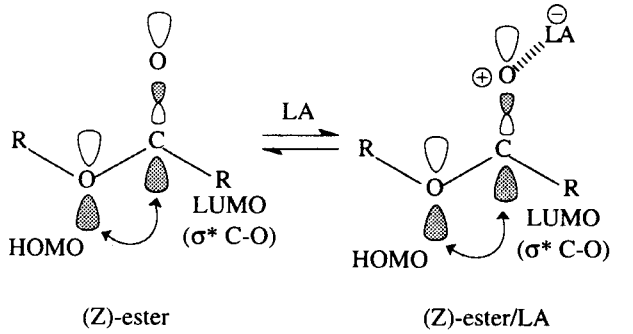


Figure 9.

In amides, Lewis acid complexation is oriented *anti* to R_2N moiety, because allylic strain strongly disfavors Lewis acid complexation *syn* to the R_2N moiety (Fig. 10)[18a].

In 1994, Wiberg, Marquez and Castejon published an interesting paper on the availability of lone pairs on oxygen[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).

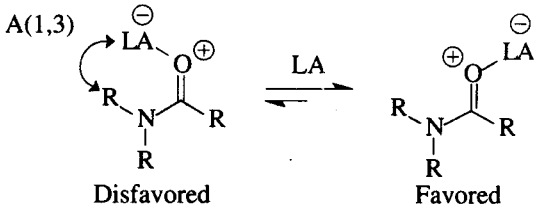


Figure 10.

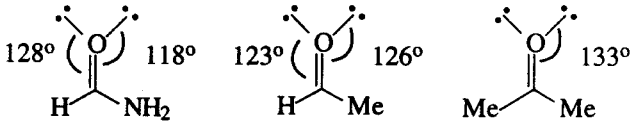


Figure 11.

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 α,β-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 α,β-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 α,β-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-bromoacrolein[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

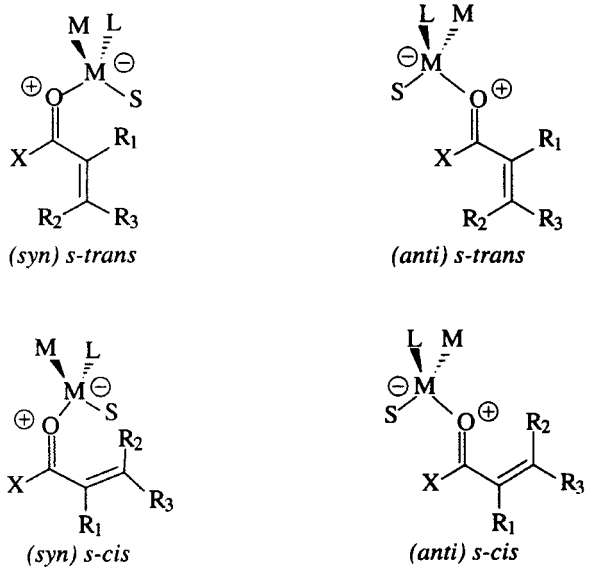
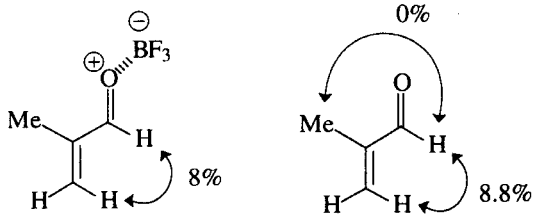


Figure 12.

process[28b]. 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 BF_3-catalyzed reaction, in which the *endo-s-trans* is the most stable transition state[28b]. 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 BF_3 and 2-methylacrolein[29]. From ^{1}H-NMR in CD_2Cl_2 solution and NOE studies (NOE enhancements indicated) even in solution, the same *s-trans* structure of this complex predominates (Fig. 13).



- *s-trans geometry* - *s-trans* geometry

- BF_3 coordinated *syn* to the formyl proton

Figure 13.

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 CD_2Cl_2 solution at 200 K[30]. 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 $SnCl_4$ or BF_3[19]. The same trend was observed for uncomplexed 2-heptenal (Fig. 14).

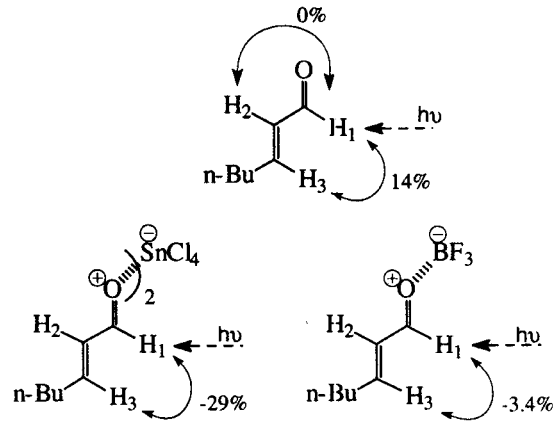


Figure 14.

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 $SnCl_4$ complexes prefer the *s-trans* form and the eclipsed conformation C illustrated in Fig. 15, when R = Me[31]. When R = Et, a more bulky group, the conformation D (*s-trans* form) is favored (Fig. 15).

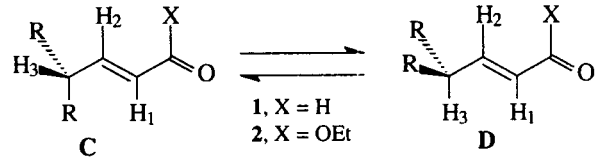


Figure 15.

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 $SnCl_4$ (Fig. 16).

The predominant conformation for the $SnCl_4$ complexed α,β-unsaturated ester 3, is the *s-trans* form E, with a rotational barrier around the Csp^2-Csp^2 single bond of about 12.5 Kcal/mol (Fig. 17).

A different situation is observed with $SnCl_4$-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

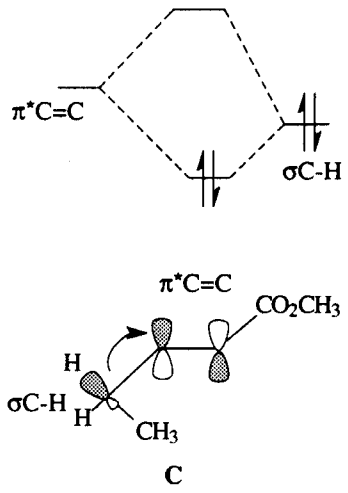
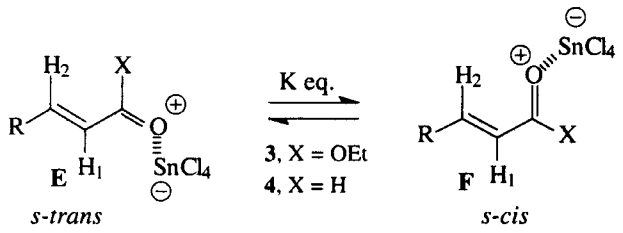


Figure 16.



^{1}H-NMR spectra at -40 °C showed approximately 97:3 ratio (*s-trans/ s-cis*) for X = OEt

Figure 17.

reactive conformation, as proposed by Corey and by Marshall[32,33].

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 *s-trans* conformation with coordination of the Lewis acid *anti* to the methoxy group favored by steric and electronic effects. For non-complexed acrylates, the *s-cis* conformation is preferred[26-32].

In 1994, Yamamoto and coworkers published an extensive study on *s-cis/s-trans* preference of acyclic α,β-unsaturated esters[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 *s-cis* conformation has a slight preference over the *s-trans* conformation, and that the populations of *s-cis* and *s-trans* conformers of methyl cinnamate in the gas phase at 4 K are nearly 1:1.

In an earlier work by Lewis *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 α,β-unsaturated carbonyl complexes. The crystal structure shows that the ligand lies *anti* to the ethoxy group and adopts an *s-trans* conformation with tin coordinated *syn* to the double bond (Fig. 18)[35].

In a very interesting example, there is experimental evidence that supports an *s-cis* conformation for a complex between an acrylate with a lactate moiety and $TiCl_4$ (Fig. 18)[35]. The authors were able to obtain crystals of this complex and determine its structure. The enoate group adopts an *s-cis* conformation in a chelated seven-membered cyclic structure, in which titanium is coordinated to two ester carbonyls. The Lewis acid is *anti* to the acrylate double bond and the enoate adopts an *s-cis* geometry (Fig. 18)[36,37].

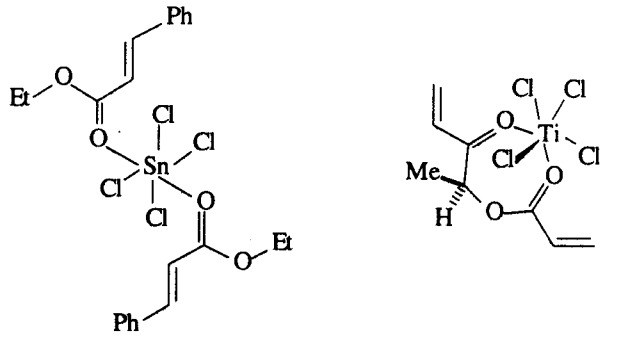


Figure 18.

In conclusion, α,β-unsaturated ester-Lewis acid complexes prefer the *s-trans* conformation not only in the ground state but also in the transition state except for the complexes of certain chiral acrylates in which a bidentate Lewis acid coordinates to a carbonyl oxygen of the enoate and an oxygen atom of a chiral auxiliary[38,39].

Regarding the use of acyl-1,3-oxazolidin-2-ones, it has been assumed that the uncomplexed carbonyl moiety would exist in the *s-cis* conformation avoiding nonbonding interactions present between the olefin and the ring atoms in its *s-trans* conformation[40]. Support for this assumption follows from conformational studies on α,β-unsaturated amides in which it was concluded that the *s-cis* conformer is strongly favored[40]. However, the *s-cis* form becomes unfavored in the α-methyl substituted amides. Although the complexed *s-cis* form should be more stable for imide dienophiles, some authors sometimes use the *s-trans* form of the complexed carbonyl moiety to explain the observed selectivity[18,48,94,96]. The situation becomes more complex because a bidentate ligand like acyl-1,3-oxazolidin-2-ones can occupy 1-free coordination site (1-point substrate binding) or 2-free coordination sites (2-point substrate binding) in the metal[41]. Depending on the metal used, several complexes (G-J) might be present in equilibrium (Fig. 19). The participation of each one of these complexes might depend on the nature of the Lewis acid and its ligands, the nature of the metal (propensity for 1 or 2-point binding) and also depend on steric and electronic interactions in the transition state. Although there is more experimental evidence favor-

ing the participation of the complexed *s-cis* form G, conformations H and I have also been used to explain the observed enantioselectivities in some Diels-Alder reactions (Fig. 19)[41,48,94,96].

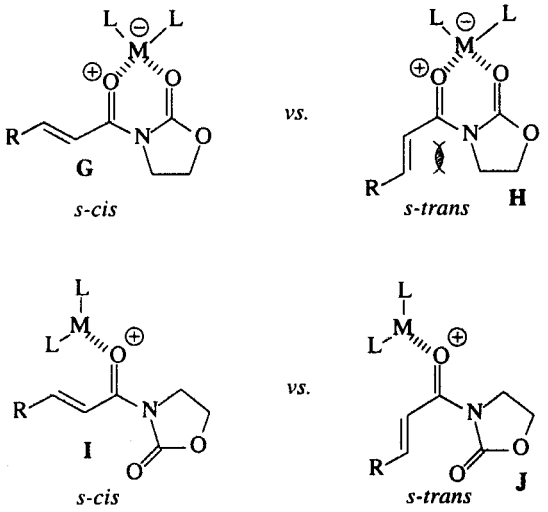


Figure 19.

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 geometry is very case-dependent in present literature.

At this point we should emphasize that a critical element in the rational design of chiral Lewis acids for effecting stereoselective cycloaddition reactions to achiral α,β-unsaturated carbonyl compounds is an understanding 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 structures of acrylates and spectroscopy data have been reported, the dynamics of *s-cis/s-trans* isomerization still need to be better studied. It is of great importance to evaluate 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 geometries on X-ray and spectroscopic data, because the thermodinamically favored geometry of a molecule or complex is not necessarilly the same as the reactive geometry (cf. the Curtin-Hammett principle)[42,43].

Chiral aluminum Lewis acids

One of the earliest examples of an asymmetric Diels-Alder reaction was published in 1979 by Koga and coworkers and involved a chiral aluminum catalyst[44,18c,d].

Catalytic amounts (16 mol%) of menthyloxyaluminum dichloride prepared *in situ* from menthol **5** and ethylaluminum dichloride in toluene at -78 °C promoted the reaction of cyclopentadiene and methacrolein affording the *exo*-adduct **6** in 69% yield and 72% ee (Fig. 20).

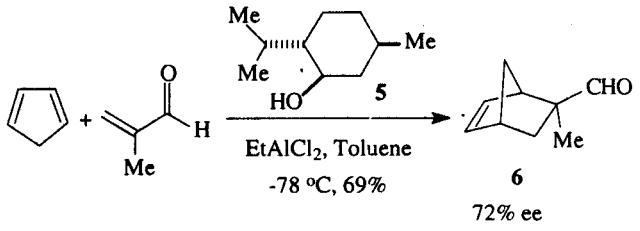


Figure 20.

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 stereochemical relationship between the chiral auxiliary and the Diels-Alder adduct, based on the observed absolute configuration (Fig. 21)[45,18c,d].

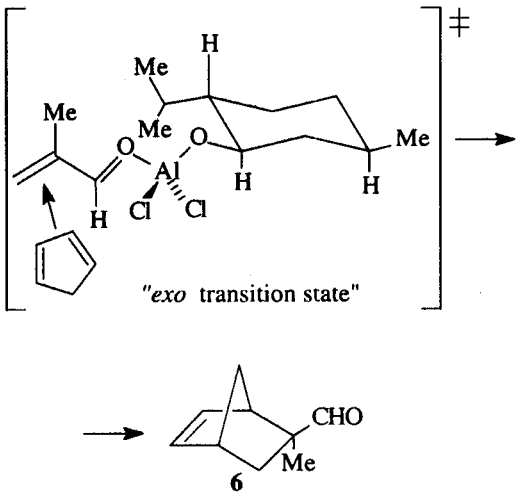


Figure 21.

Corey developed an asymmetric Diels-Alder approach to prostaglandin synthesis based on a chiral aluminum catalyst[46]. The reaction of 5-(benzyloxymethyl)-1,3-cyclopentadiene 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% yield and with 97:3 enantioselectivity (Fig. 22, Table 1)[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)[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 diazaaluminolide subunits[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 ^{1}H- and ^{13}C-NMR data.

Especially noteworthy is a 5% NOE enhancement between the benzylic proton Hb and the olefinic proton Ha of

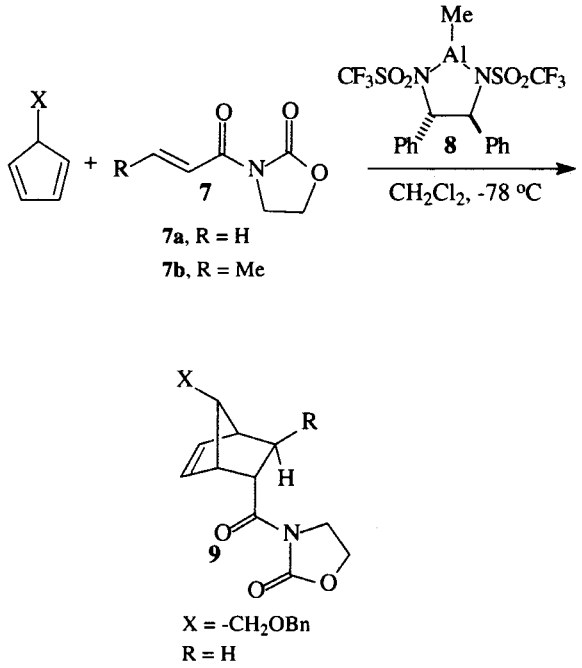


Figure 22.

Table 1.

X	R	mol% cat.	*endo:exo*	%ee	yield (%)
H	H	10	> 50:1	91	92
H	Me	20	96:4	94	88
CH_2OBn	H	10	—	94	94

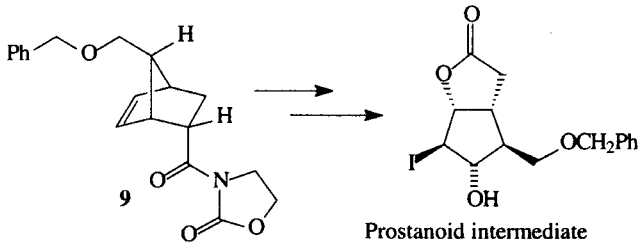


Figure 23.

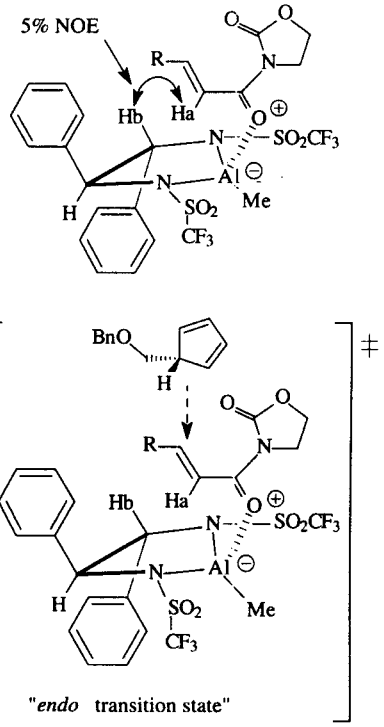


Figure 24.

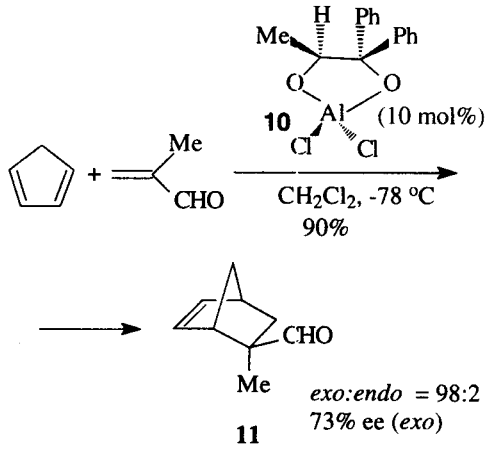


Figure 25.

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 $EtAlCl_2$ (Fig. 25)[49].

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-(triphenylsylil)-1,1'-bi-2-naphthol in CH_2Cl_2 (Fig. 26)[50].

Treatment of methyl acrylate (1.0 equivalent) and cyclopentadiene (2.0 equivalents) with 10 mol% of (R)-**12** (Ar = Ph) in CH_2Cl_2 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)[50].

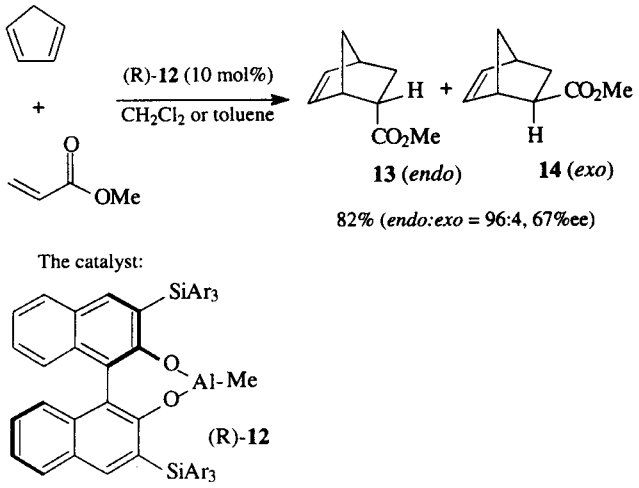


Figure 26.

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)[50].

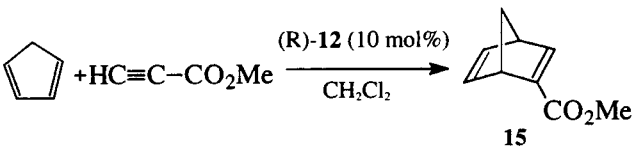


Figure 27.

Recently, Wulff *et al.* reported aluminum/biaryl complexes as Diels-Alder catalysts[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)[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.

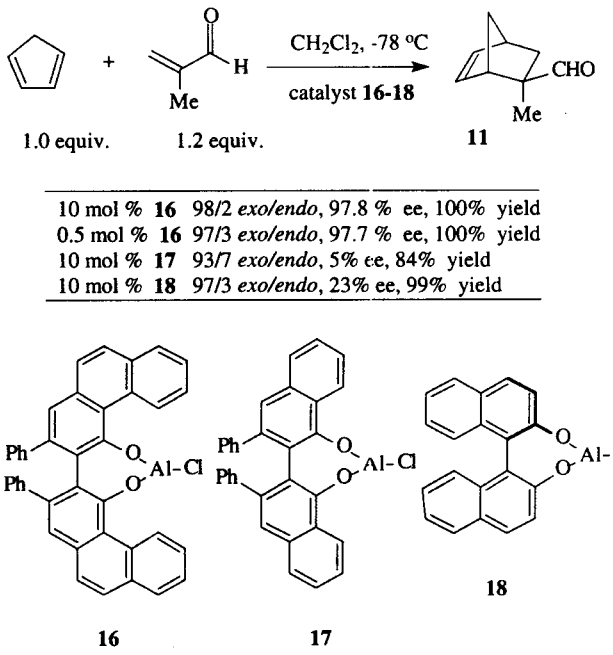


Figure 28.

In 1994, Cativiela and coworkers reported an asymmetric Diels-Alder reaction catalyzed by menthoxy-aluminum derivatives supported on silica-gel and alumina (Fig. 29)[53].

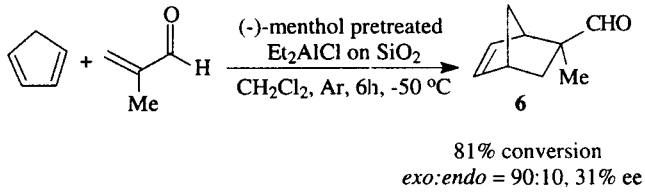


Figure 29.

The solids obtained by treatment of alumina or silica gel with Et_2AlCl are efficient catalysts for Diels-Alder reactions. A similar methodology has been used to support menthoxyaluminum 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[53].

Another highly enantioselective Diels-Alder reaction was reported by Corey *et al.* in 1994 based on a chiral aluminum catalyst[54]. Addition of 2-methoxybutadiene **19** to N-tolyl-maleimide **20** (R = o-tolyl) in the presence of catalyst **21** (Ar = 3,5-dimethylphenyl, 20 mol%, -78 °C, toluene) afforded adduct **22** (R = o-tolyl) in 98% yield and 93% ee (one recrystallization from i-PrOH-hexanes fur-

nished the enantiomerically pure compound) (Fig. 30)[54]. When R = o-*t*-butylphenyl in maleimide **27**, the corresponding adduct **22** (R = o-t-butylphenyl) is obtained in 95% ee.

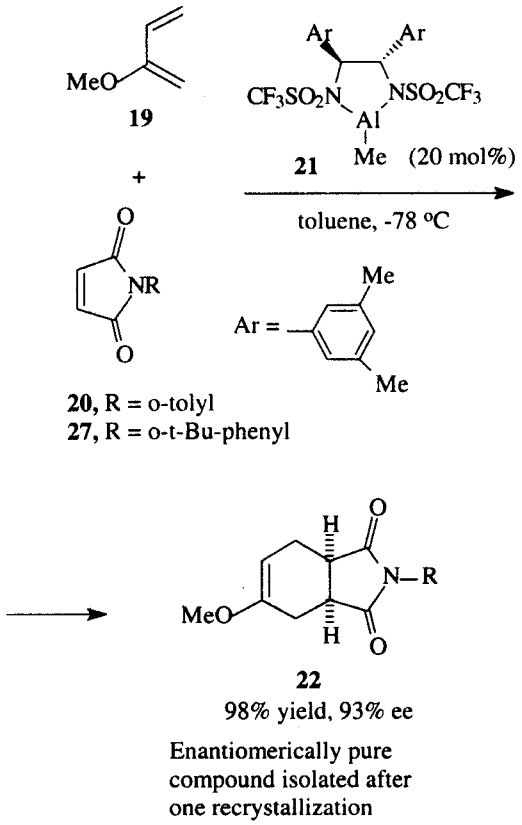


Figure 30.

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[54]. 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-arylmaleimides **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_2Cl_2 solution is evident from ^{1}H-NMR and NOE experiments (Fig. 32).

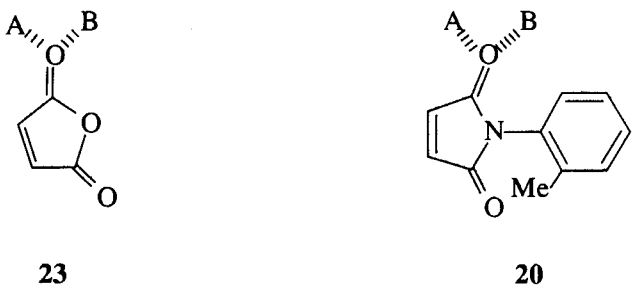
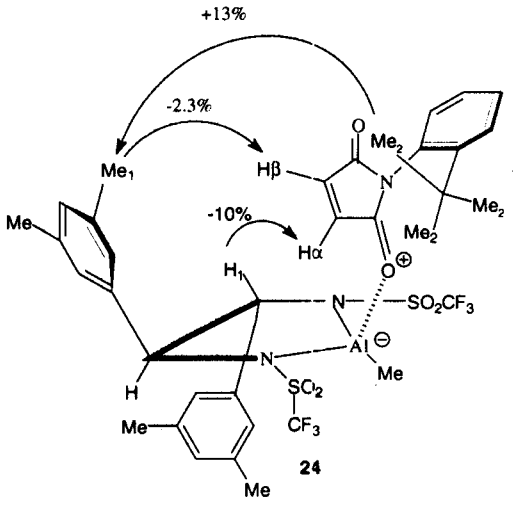


Figure 31.



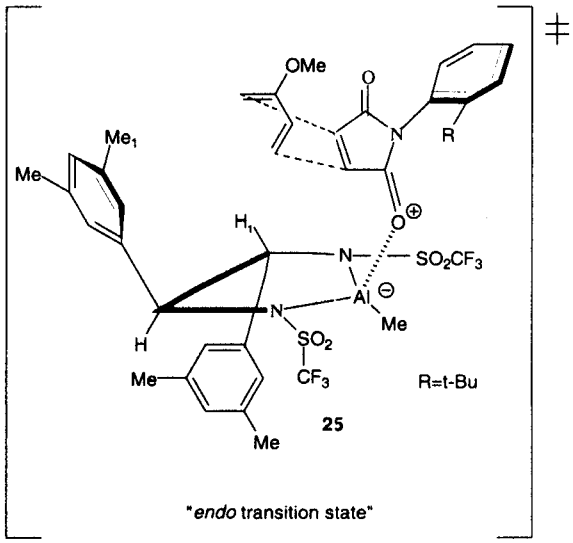


Figure 32.

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]

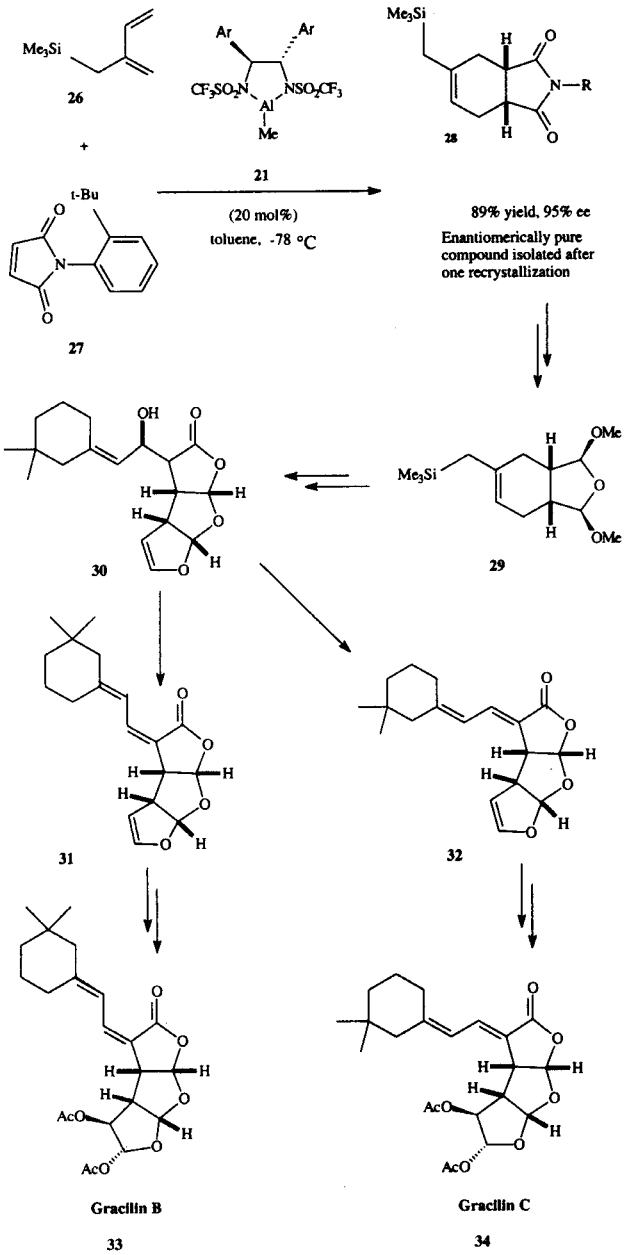


Figure 33.

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-((trimethylsilyl)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 transformations[55,56].

Chiral boron Lewis acids

Chiral oxazaborolidines

Itsuno and collaborators developed 1,3,2-oxazaborolidines as a new generation of homochiral reduction catalysts[57]. 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 transformations[58].

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 oxazaborolidines from N-sulfonamides of β-aminoacids and borane[59,60].

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-triisopropyl benzenesulfonamide (S)-**35** as catalyst, afforded **36** in 73% yield and 74% ee (Fig. 34)[59].

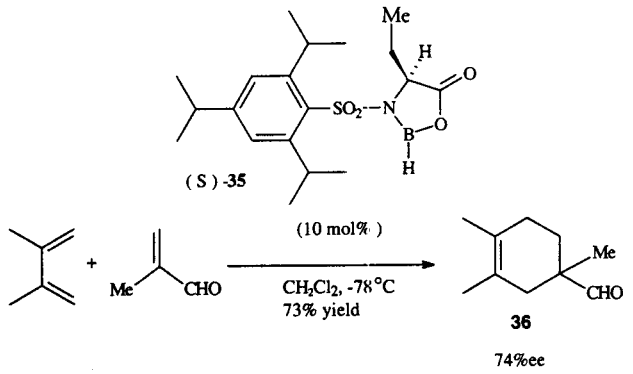


Figure 34.

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].

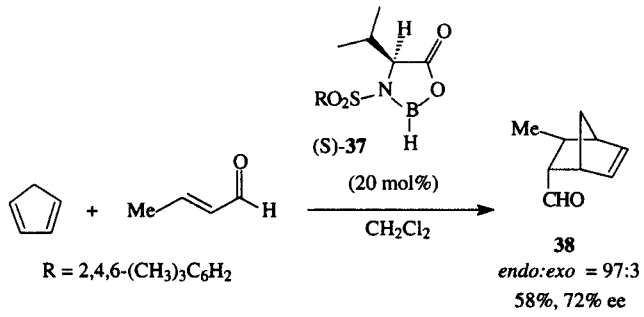


Figure 35.

Interestingly, maximum enantioselectivity (methacrolein, 86% ee; crotonaldehyde, 81% ee) was achieved in donor solvents (THF or acetonitrile)[62].

Asymmetric Diels-Alder reactions of cyclopentadiene with methacrolein catalyzed by chiral oxazaborolidines **39** derived from N-tosyl-L-α-amino acids afforded cycloadducts in quantitative yields[63]. Variation of the position of an electron donating atom in the α-side chain of the oxazaborolidine (R group) showed that enantioselectivity is controlled by the presence of electron donor atoms in positions 2 and 4 (Fig. 36)[63,18c,d].

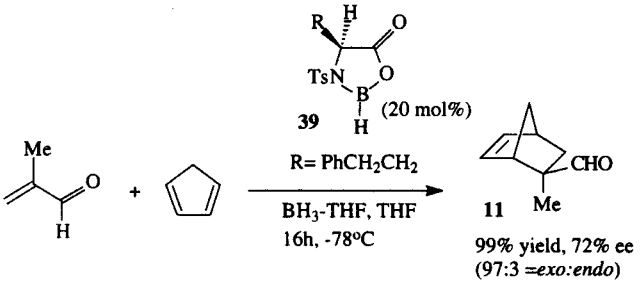


Figure 36.

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 *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 *exo:endo*, 72% ee; R = p-$PhCH_2OPhCH_2$ = 96:4, 81% ee).

These results were explained by the proposed transition state model illustrated in Fig. 38 (**39**, R = $PhCH_2OCH_2$). 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

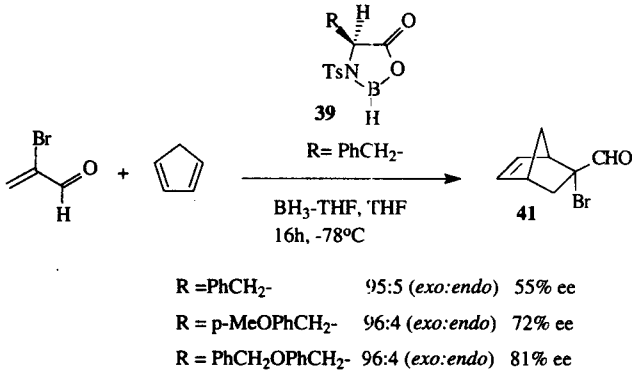


Figure 37.

block one of the dienophile faces allowing approach of the cyclopentadiene from the opposite face of the benzyloxymethyl group[63,18c,d].

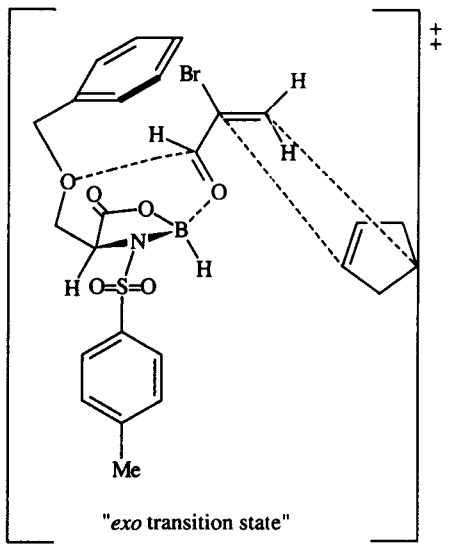


Figure 38.

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-*exo*-formyl Diels-Alder adduct **41** with at least 200:1 enantioselectivity (Fig. 39)[64,65,18c,d].

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

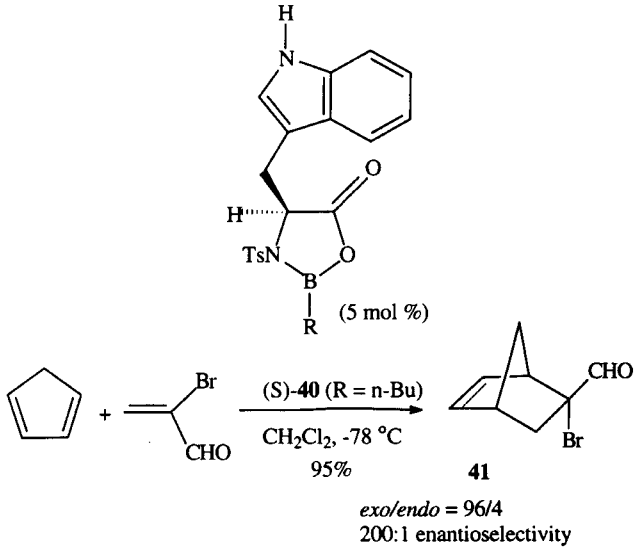


Figure 39.

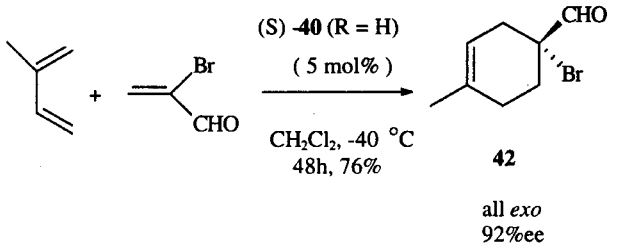


Figure 40.

in CH_2Cl_2. 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].

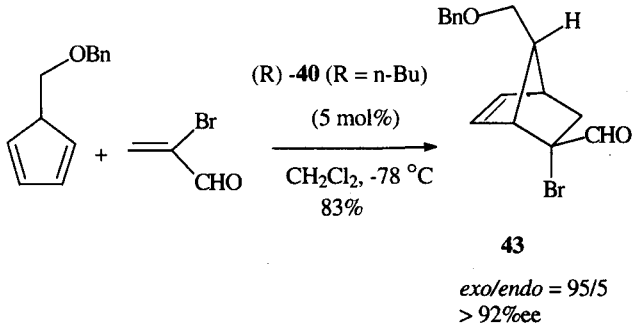
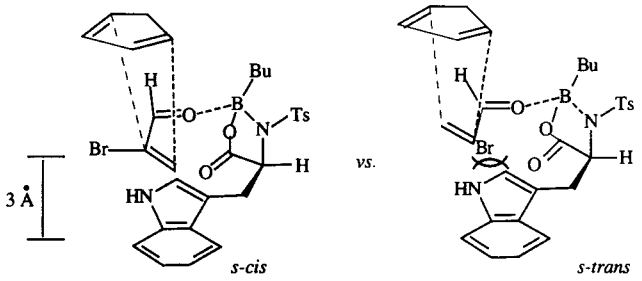


Figure 41.

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 substituent[65,18c,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



- *s-cis vs. s-trans* bulk of Br key
- Free catalyst is flexible; complexed catalyst is conformationally rigid as shown by NOE interactions
- Rapid equilibrium between free and complexed catalyst

Figure 42.

for the *s-cis* geometry). The amino acid moiety directs the steric bulk of the sulfonyl 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-enal 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 Yamamoto[59-61]. 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 spirotetronate subunit of Kijanolide, the aglycon of the antitumor antibiotic Kijanimycin (Fig. 43)[66]. Cycloaddition of diene **44** to α-bromoacrolein in the presence of stoichiometric amounts of the Corey oxazaborolidine (S)-

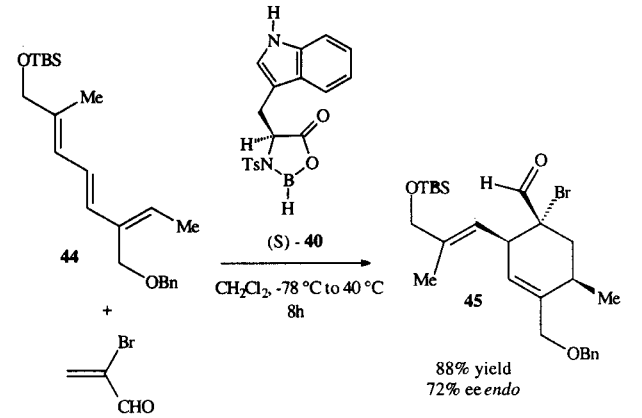


Figure 43.

40 (R = H) in CH_2Cl_2 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 Loh[64,65].

The adduct **45** was converted to spirotetronate **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].

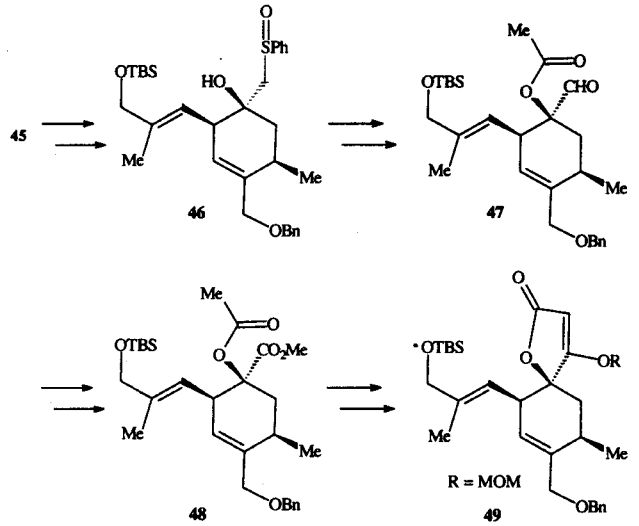
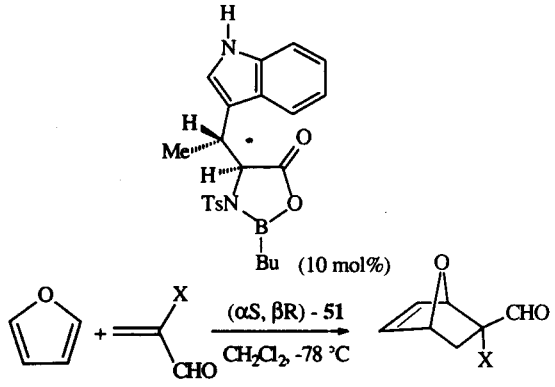


Figure 44.

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 derivatives[67]. 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 enantioselectivity[67]. 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 enantiomerically pure 7-oxabicyclo-[2.2.1]-hepten-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



50 X = Br, 92% ee (*exo:endo* = 99/1)
52 X = Cl, 90% ee (*exo:endo* = 99/1)

Figure 45.

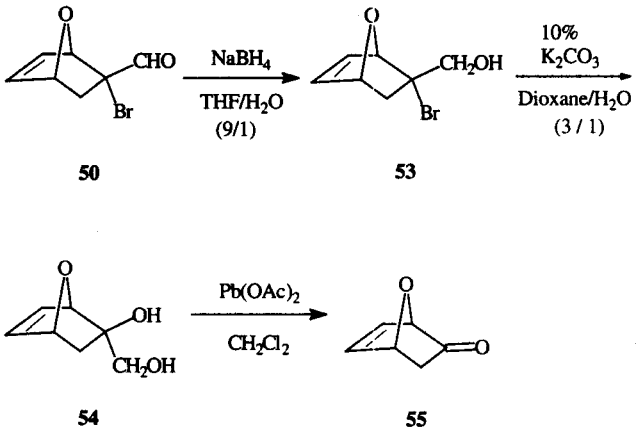


Figure 46.

(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 methacrolein in the presence of 25 mol% of catalyst (αS,βR)-**51** in toluene:CH_2Cl_2 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* hidrindenone **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 CH_2Cl_2 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**.

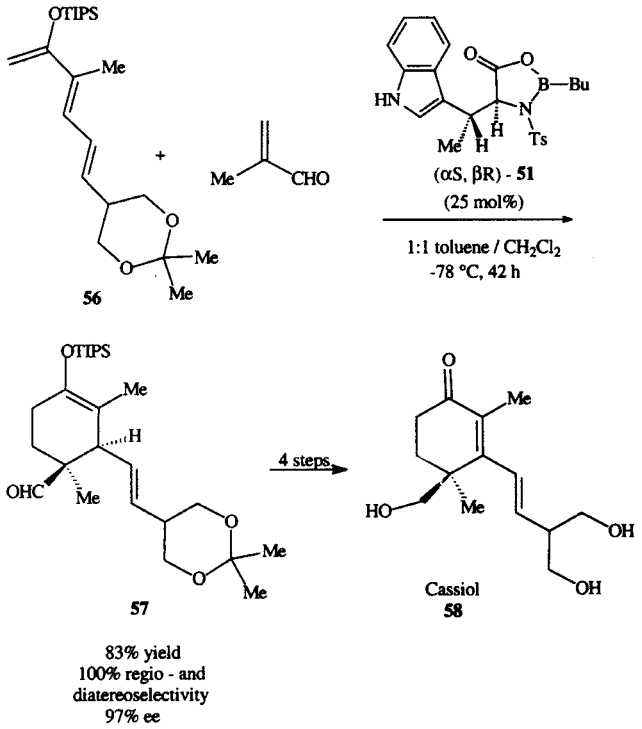


Figure 47.

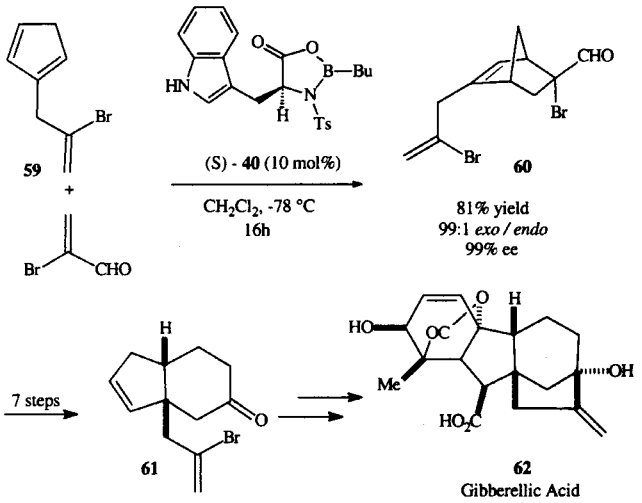


Figure 48.

It is interesting that with both catalysts (S)-**40** and (αS,βR)-**51**, studies with various dienophiles and cyclopentadiene reveal that enantioselectivities are very similar (α-bromo: 200:1; α-chloro: 200:1; α-methyl and α-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[71,72,18c,d]. The authors reported that the use of a stable 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 α,β-unsaturated aldehydes (Fig. 49).

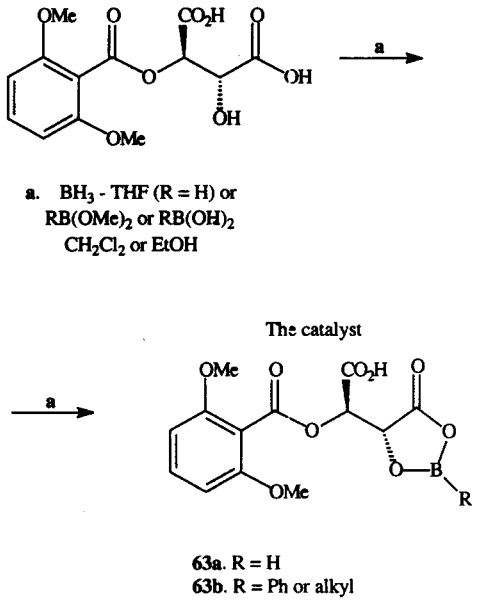


Figure 49.

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_2Cl_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).

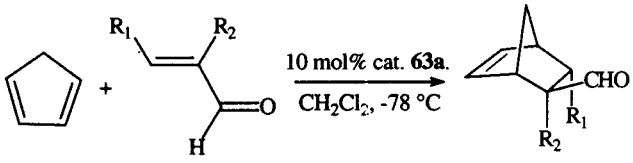


Figure 50.

Table 2.

R1	R2	Time (h)	yield (%)	*exo:endo*	ee %
H	Me	6	85	89:11	96
H	H	14.5	90	12:88	84 (R)
Me	H	10	53	10:90	2
Me	Me	9.5	91	97:3	90
H	Br	10	100	94:6	95

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 CH_2Cl_2 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-decatrienal **64**, catalyzed by a chiral acyloxyborane complex **63a**, in high stereo and enantioselectivity[71,72]. Addition of diene **64** to a solution of CAB catalyst (10 mol%) prepared from mono-(2,6-dimethoxybenzoyl) tartaric acid and borane, in CH_2Cl_2 at -40 °C provided an isomeric mixture of adducts in 84% yield (*endo:exo* ratio = 99:1), *endo* ee = 92% (Fig. 51).

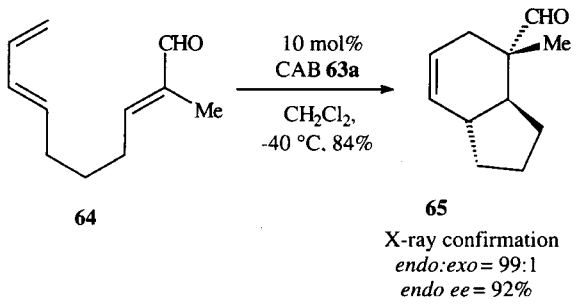


Figure 51.

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)[73,18c,d].

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-OC_6H_4), in propionitrile: 99% yield, 98% ee (S-enantiomer major), 94/6 (*exo/endo* CHO) diastereoselectivity. Considering the product configuration, the aryl

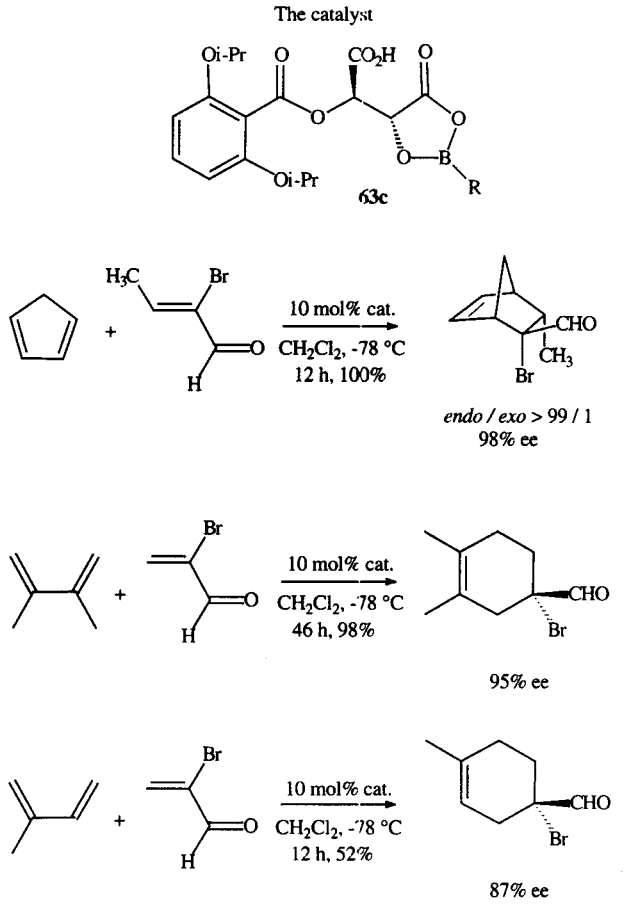


Figure 52.

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.

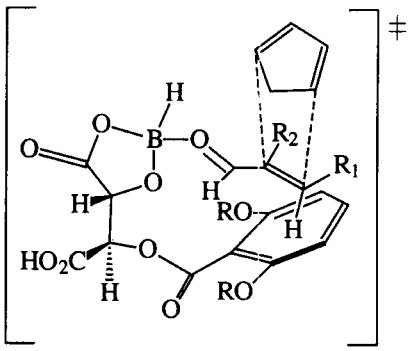


Figure 53.

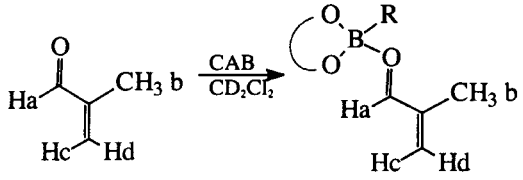
In an attempt to obtain mechanistic information about this reaction, Yamamoto *et al.* studied the solution conformation of the CAB-complexed methacrolein and crotonaldehyde using NOE difference measurements (Fig. 54)[73,74,18c,d].

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-$C_4H_9C{\equiv}C$-, R = H) is primarily in the *s-trans* conformation; the CAB-crotonaldehyde complex (R = 3,5-$(CF_3)_2C_6H_3$, R = o-$PhOC_6H_4$) is in the *s-cis* conformation[71-75].

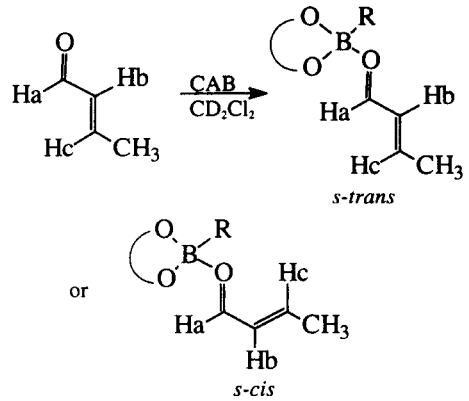
Methacrolein



Complex	NOE (saturate / observe, %) Ha/Hb	Ha/Hc	Ha/Hd	Hc/Ha
R=H	0	-10	0	6.3
R=o-$PhOC_6H_4$	0	-22	0	-33
Methacrolein	0	6.3	0	18

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

Crotonaldehyde

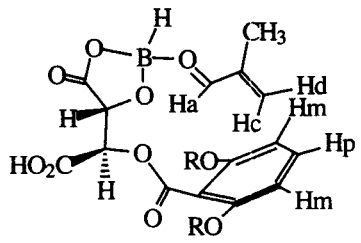


Complex	NOE (saturate / observe, %) Ha/Hb	Ha/Hc	Hb/Ha	Hc/Ha
R=H	0	18	-	-
R=o-$PhOC_6H_4$	-14	0	-18	-
R=3,5-$(CF_3)_2C_6H_3$	-32	0	-48	-
Methacrolein	0	6.3	0	18

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 CD_2Cl_2 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).

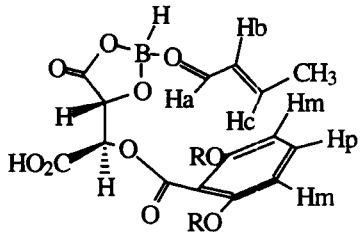
Methacrolein



B

NOE (saturate / observed, %) Hc/2Hm	Hc/Hp	Hd/2Hm	Hd/Hp
-32	-12	-25	-29

Crotonaldehyde



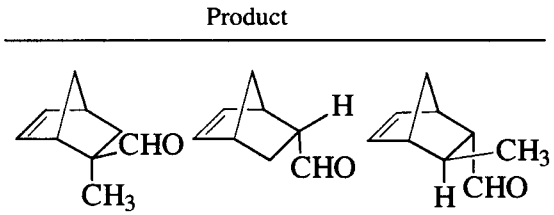
B

NOE (saturate / observed, %) Hb/2Hm	Hb/Hp	Hc/2Hm	Hc/Hp
-8	-6	2	-32

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

Figure 55.

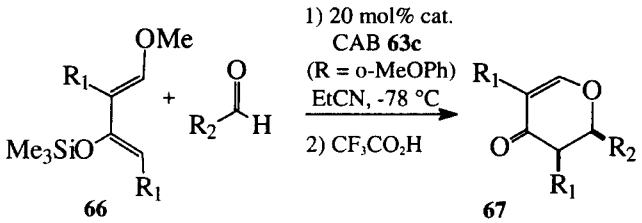
The authors also studied the influence of the boron substituent (R group) on absolute stereoinduction in the Diels-Alder reaction and observed that sterically bulky aryl substituents resulted in a turnover of the absolute stereochemistry for α-unsubstituted α,β-enals like acrolein and crotonaldehyde (*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).



63 (R group)	Product %ee	%ee	%ee
PhC≡C-	62(R)	48(R)	40(R)
H	87(R)	47(R)	2(S)
O-PhOC$_6$H$_4$	93(R)	57(S)	67(S)

Figure 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 dihydropyrone derivatives **67** of high optical purities[76,77]. 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 CH_2Cl_2 to afford dihydropyrone **67** in good yields[76,77].



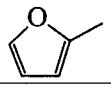
R_1	R_2	yield(%)	ee%
H	Ph	80	79(R)
Me	Ph	95	97
Me	p.MeC$_6$H$_4$	>99	97
Me	(E)-PhCH=CH	40	79
Me	(E)-MeCH=CH	79	92
Me		84	98 (>99% cis)

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)[78]. Whereas the uncatalyzed reaction provided only 15% yield (*exo:endo* = 86:14) after 42 h even at 20 °C, conducting the reaction in CH_2Cl_2 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).

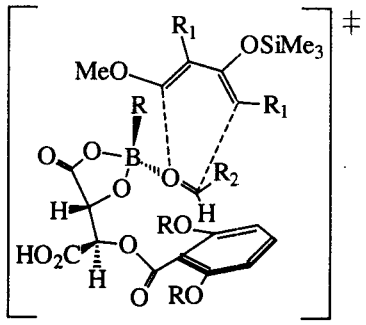


Figure 58.

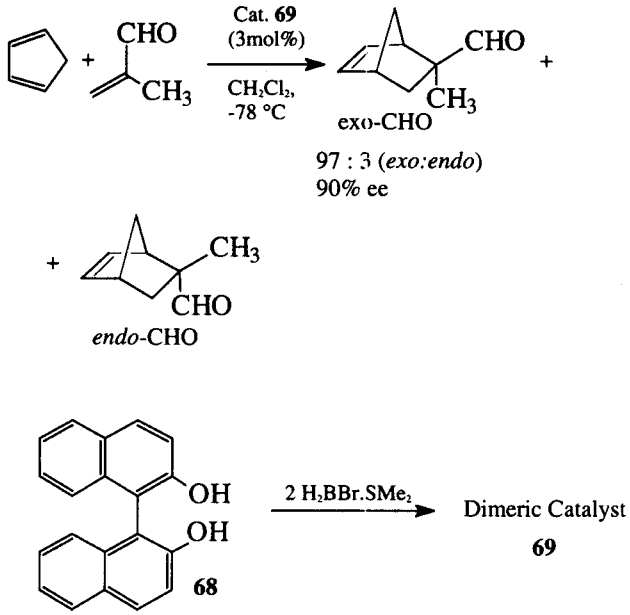
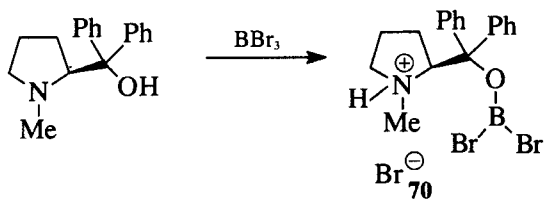


Figure 59.

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[79a]. 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[79b]. The structures of these complexes were determined by ^1H, ^{11}B and ^{13}C 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-



Dienophile	Diene	Yield (%)	*exo:endo*	% ee
Me, CHO		84	>99:1	97
Et, CHO		87	>99:1	73

Figure 60.

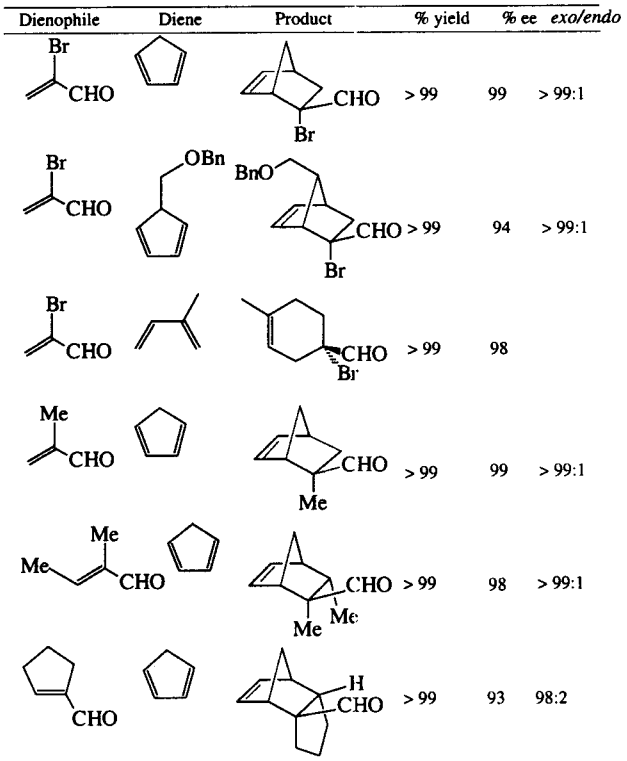
pending on the aminoalcohol used, with prolinol affording the highest ee (97%)[79b].

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 α-substituted α,β-enals and dienes (Fig. 61)[80,18c,d]. The catalyst (R)-**71** was prepared by reaction of (R)-3,3'-bis-(2-hydroxyphenyl)-2,2'-dihydroxy-1,1'-bin aphthyl with $B(OMe)_3$ in CH_2Cl_2 at reflux with removal of MeOH. BLA was found to be a good catalyst for the enantioselective reactions of α-substituted α,β-enals, but α-unsubstituted α,β-enals like acrolein and crotonaldehyde exhibit low enantioselectivity. High enantioselectivities and *exo* selectivity were obtained for Diels-Alder additions of α-substituted α,β-enals with dienes in the presence of catalyst **71** as illustrated in Fig. 61.

To rationalize the highly stereoselective course of this 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 α,β-enal is proposed (Fig. 62)[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 π-basicity of the phenoxyl group. This hydrogen bonding leads to a parallel orientation between the π-basic phenoxyl moiety and the π-acidic dienophile at the ideal separation (3Å) for donor-acceptor interaction. In this conformation, the Cα-*si* 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 α-substituted α,β-enals with various dienes[81,18c,d]. The



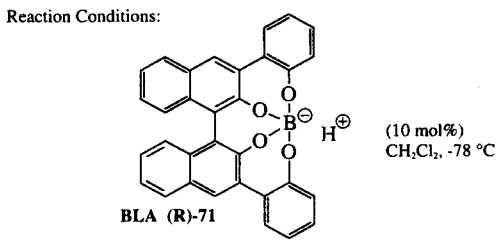
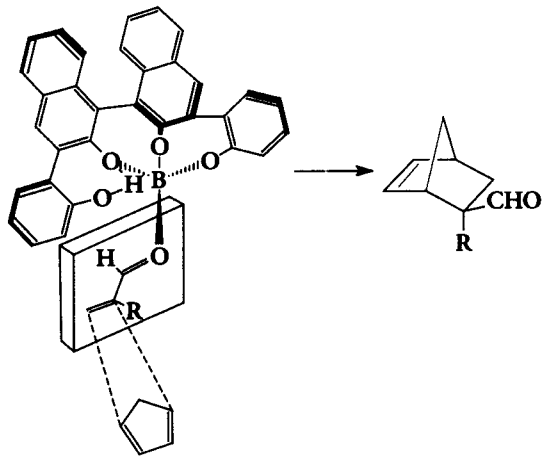


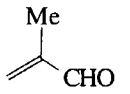
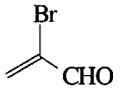
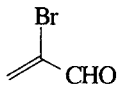
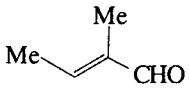
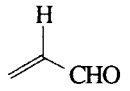
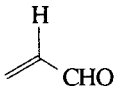
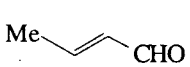
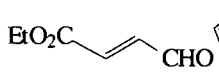
Figure 61.



Non-helical arrangement of the aryl groups.

Figure 62.

cycloaddition reactions between various α,β-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).

Dienophile	Diene	*exo/endo*	%ee (conf.)
			99 (S)
		90 / 10	> 99 (R)
		10 / 90	95
		98 / 2	96
		3 / 97	95 (S)
		0 / 100	96 (S)
		10 / 90	95 (S)
		2 / 98	95 (R)

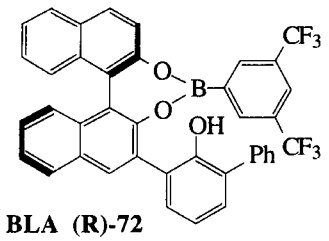


Figure 63.

This (R)-BINOL-based Diels-Alder system **72** produces adducts of opposite absolute configuration in comparison with (R)-BINOL-based **71**. It should be noted that BLA (R)-**72** is an excellent catalyst for less reactive dienophiles but also for less reactive dienes such as acyclic dienes and cyclohexadiene. As an extension of this methodology, the intramolecular Diels-Alder cycloaddition of the α-unsubstituted trienal **73** was undertaken and *endo* adduct **74** was obtained in 95% yield and 80% ee[81] (Fig. 64).

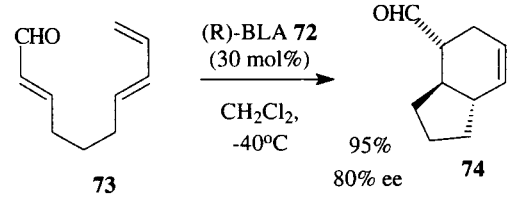


Figure 64.

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[71,72] (Fig. 51). These results can be explained by invoking the transition state model illustrated in Fig. 65.

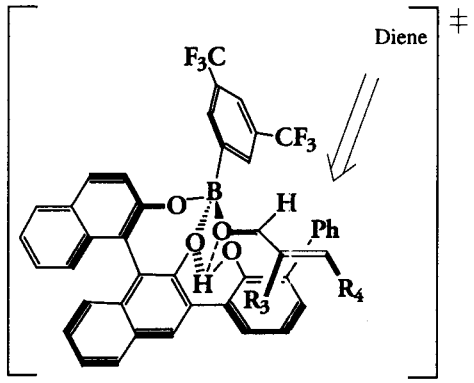
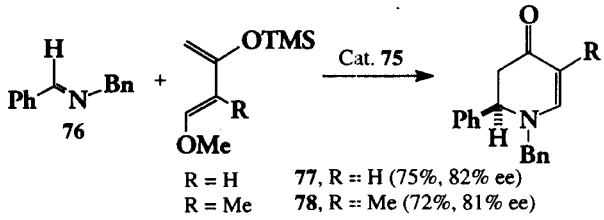


Figure 65.

Although not catalytic, a successful asymmetric aza-Diels-Alder reaction of an imine mediated by *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_2Cl_2 at ambient temperature for 1 h) was described in 1992 by Yamamoto and Hattori[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).



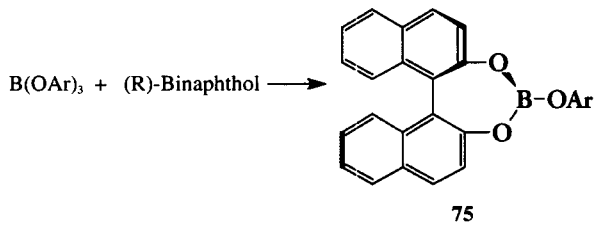


Figure 66.

The usefulness of this methodology was displayed in the asymmetric synthesis of (-)-anabasine **82**, an alkaloid derived from nicotinic acid (Fig. 67)[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 dihydropyridone **80** in 68% yield and 90% ee. This compound was converted to (-)-anabasine **82** in 3 steps.

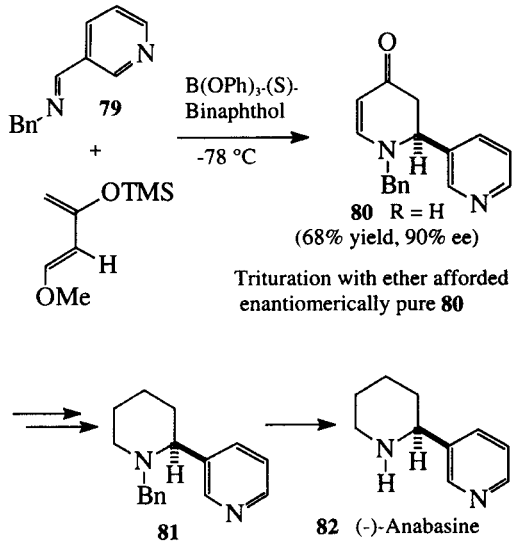


Figure 67.

Hawkins reported the utilization of aromatic alkyldichloroboranes **83** as catalysts in Diels-Alder reactions between cyclopentadiene and cyclohexadiene with α,β-unsaturated esters, giving the corresponding cycloadducts in high yields and enantioselectivity (Fig. 68, Table 3)[83].

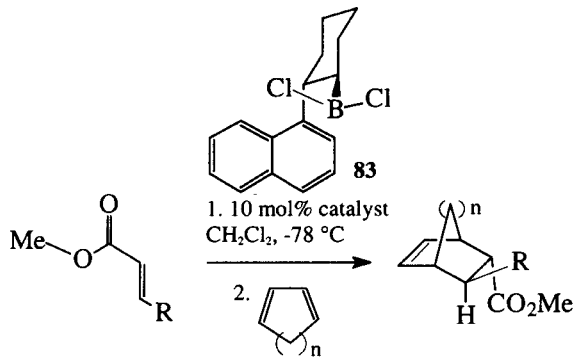


Figure 68.

Table 3.

R	n	yield (%)	ee%
H	1	97	97
Me	1	91	93
CO_2Me	1	92	90
H	2	83	88

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;

-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 carboalkoxy 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).

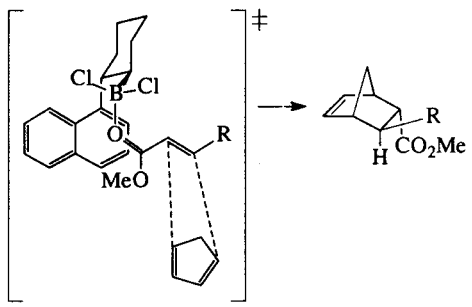


Figure 69.

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 enoate over the ring and gives higher enantioselectivity[84].

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)[85].

These catalysts were prepared from monobromoborane or borane with cross-linked polymers having a chiral moi-

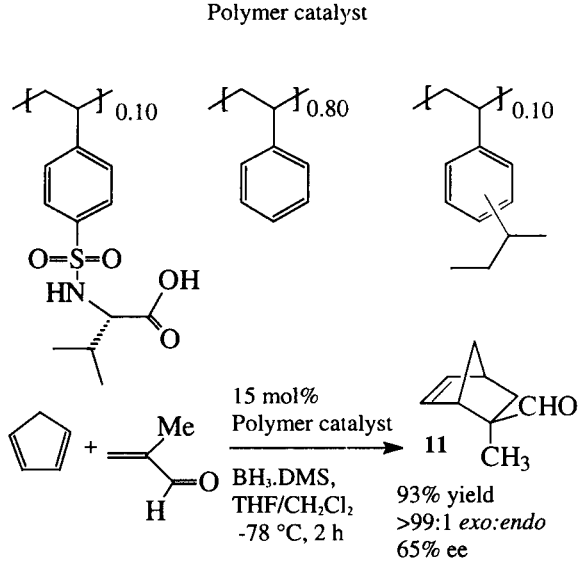
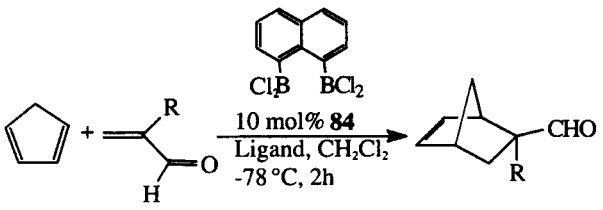


Figure 70.

ety such as aminoalcohol, 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[60,85,88]. More recently, Itsuno reported that a new polymeric catalyst having oxyethylene cross-linkages exhibit better performance in promoting enantioselective Diels-Alder reactions[85c]. 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) **84** have been found to be active catalysts for the asymmetric Diels-Alder reactions using chiral ligands derived from aminoacids and diols (Fig. 71)[86,87].



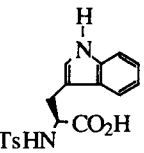
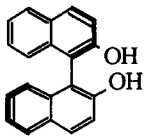
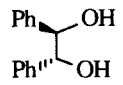
R	Ligand: Diborane	Ligand	*exo:endo*	%ee	% yield
Br	1.0		92:8	44(exo)	84
Me	1.0		63:37	100(endo)	46
H	1.0		6:94	62(endo)	53
Br	1.0		86:14	36(exo)	81
Br	2.0		80:20	28(exo)	81
Br	2.0		80:20	---	83

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-naphthalenediyl-bis-(dichloroborane) (Fig. 72).

The proposed model to account for facial selection is illustrated in Fig. 73[86,87].

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.

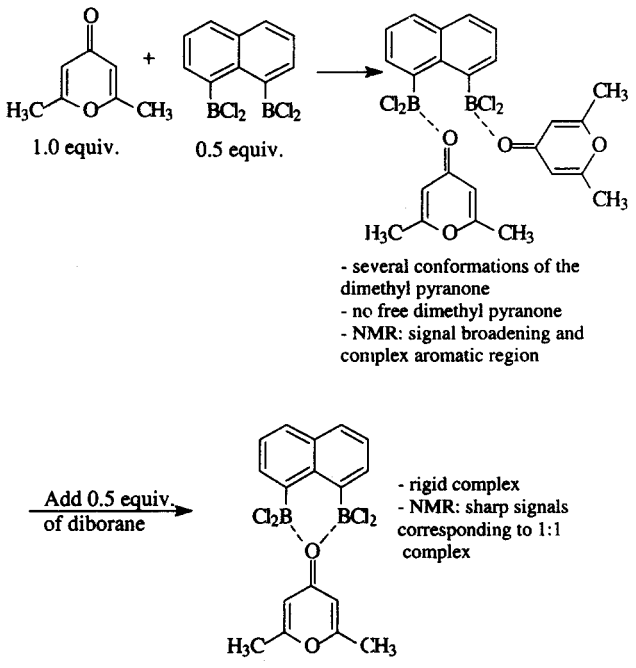
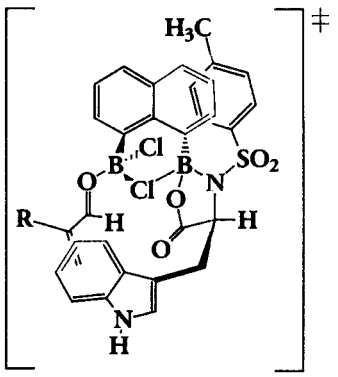


Figure 72.



Front face of the enal blocked by the tryptophan ring.

Figure 73.

Asymmetric hetero Diels-Alder reactions of glyoxylate with acid-labile Danishefsky diene are catalyzed in high enantio- and cis(*endo*)-diastereoselectivity by a chiral aminoalcohol derived boron complex (Fig. 74)[88].

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 (CF_3CO_2H). 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 R_2 and Bln*. Because of dipolar repulsion between the two carbonyl groups, the glyoxylate

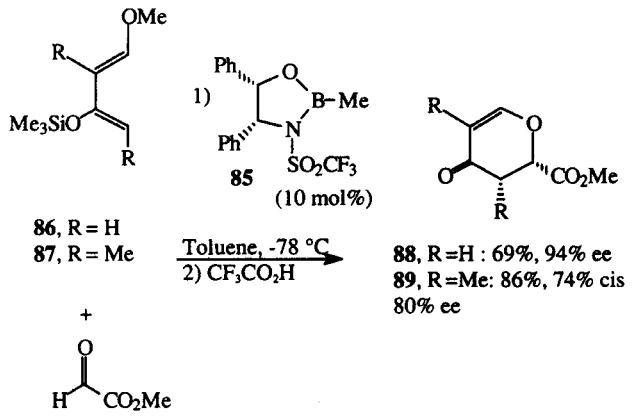


Figure 74.

should posses the *s-trans* conformation (Fig. 75). The boron catalyst **85** should be complexed to glyoxylate in an *anti* (monodentate) fashion and the Diels-Alder reaction should proceed with *endo* orientation. The reaction occurs via the favorable transition state assembly for one directional diene-approach from the site proximal to the sulfonylamino group.

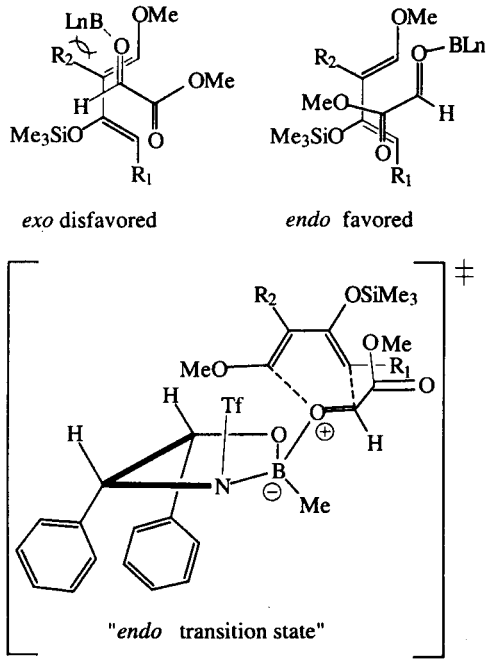


Figure 75.

The chiral tartrate-derived dioxaborolidine **90** has been used to effect enantioselective Diels-Alder reactions of α-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 (*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-

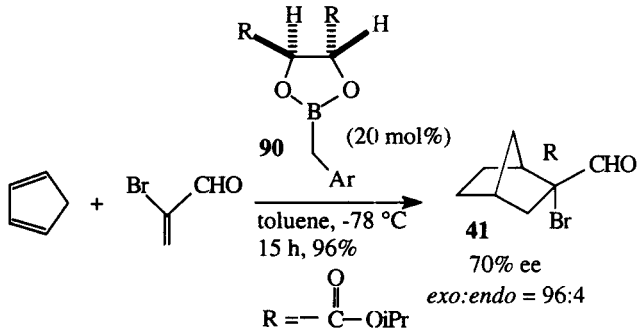


Figure 76.

bilized dipole-dipole interaction between the carbonyl carbon (δ+ α-bromoacrolein) and the proximate ester carbonyl oxygen together with the attractive interaction of π-basic benzyl ring and the π-acidic dienophile in the *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

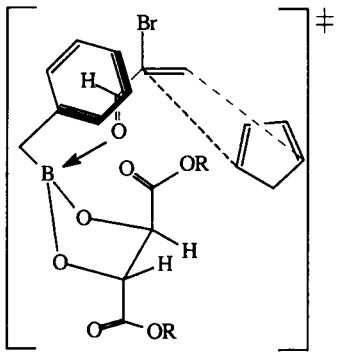
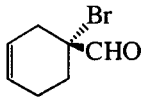
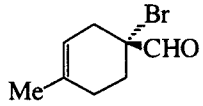
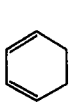
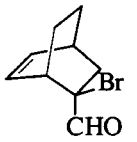
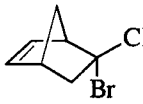


Figure 77.

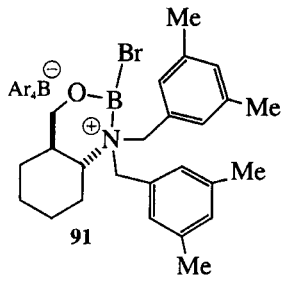
enantioselectivity.

An extremely useful enantioselective Diels-Alder reaction was reported recently by Corey *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 α,β-enals. With tetrakis-[3,5-bis(trifluoromethyl)]borate as counterion, the reaction of isoprene and α-bromoacrolein at -94 °C gave the desired cycloadduct in 90% yield and 96% ee.

The proposed *exo* transition state (for cyclopentadiene) is illustrated in Fig. 79 and shows that one of the -NCH_2Ar blocks the lower face of the *s-trans*-coordinated dienophile (Fig. 79)[90,18c,d]. It should be noted that the authors proposed an *s-trans* geometry for the complex α-substituted unsaturated aldehyde/Lewis acid, contrary to previous observations that this aldehyde reacts in the *s-cis* form.

Diene	Product	Yield(%)	%ee
		99	94
		99	96
		99 *exo:endo* 4:96	93
		99 *exo:endo* 91:9	98

The catalyst:



91

$Ar_4B^{\ominus}$ = $B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4^{\ominus}$

Figure 78.

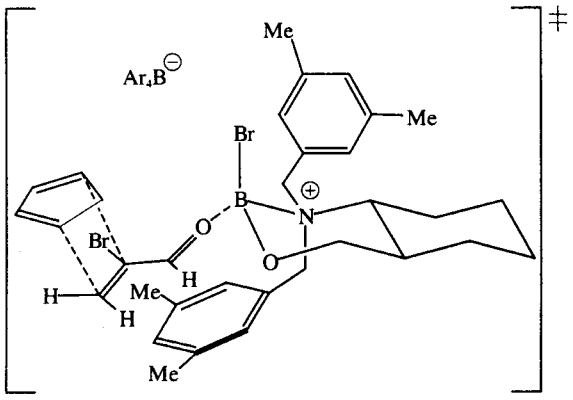


Figure 79.

Chiral titanium Lewis acids[18,91]

A highly efficient chiral titanium catalyst for Diels-Alder cycloadditions has been developed by Narasaka[92,93]. The hydronaphthalene moieties of mevinic acids were synthesized enantioselectively by using the asymmetric intramolecular Diels-Alder reaction catalyzed by a chiral titanium reagent (Ti-TADDOL catalyst)[91-95]. This reaction proceeds in a highly enantioselective manner by the use of a catalytic amount (30 mol%) of the chiral titanium reagent **92** prepared *in situ* from $TiCl_2(O^iPr)_2$ and a chiral 1,4 diol derived from (+)-tartaric acid[96B]. 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)[94,95].

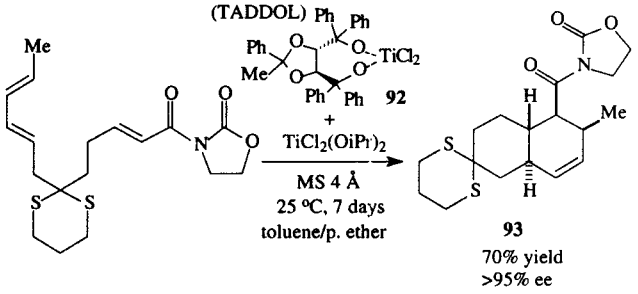


Figure 80.

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 [91-95] (Fig. 81).

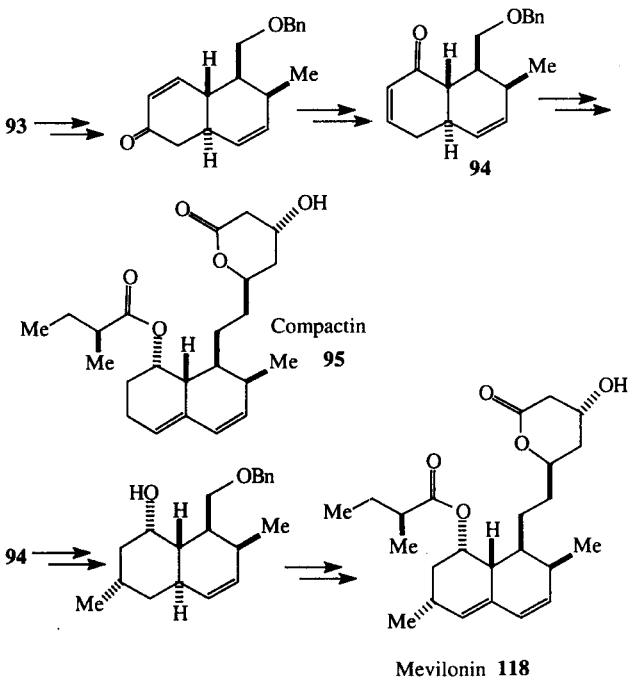


Figure 81.

A similar approach was used by Corey in 1991 in a report using a modified version of the Narasaka catalyst[96,97]. The titanium (IV) complex **96** was prepared by reaction of the corresponding diol with $Ti(O^iPr)_4$ followed by reaction with 1 equivalent of $SiCl_4$ in toluene at 23 °C[97]. The reaction of cyclopentadiene and 3-(2-propenoyl)-2-oxazolidinone **7a** in toluene at -40 °C for 12 h in the

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).

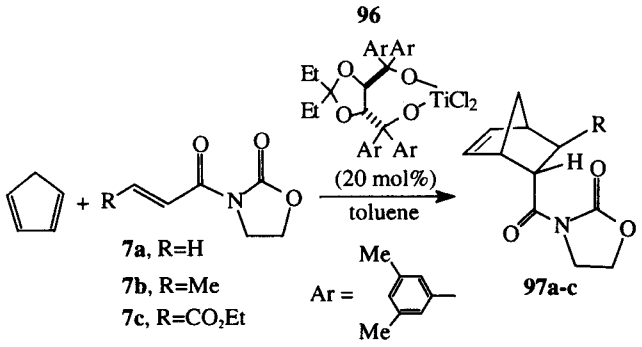


Figure 82.

Table 4.

R	T (°C)	Time (h)	yield (%)	*endo:exo*	% ee (*endo*)
H	-40	12	80	95:5	94
Me	-10	8	92	93:7	93
CO_2Et	-30	8	90	81:19	91

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

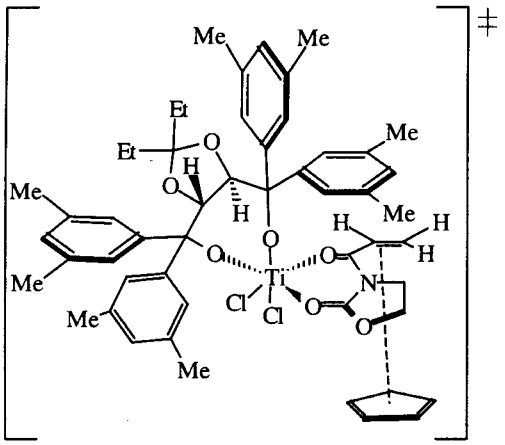


Figure 83.

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-unsaturated carbonyl moiety and the proximate ring are in parallel planes with an optimum spacing (*ca.* 3Å) for a π-stacking interaction[98].

In 1995, DiMare and Seebach independently reported realated 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 [97]. The DiMare group has done ^1H- and ^{13}C- VT-NMR experiments of complexes formed from Ti-TADDOLates and unsaturated N-acyloxazolidinones to obtain information about the species involved in this reaction[97a]. 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 [97b].

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[99]. Catalyst preparation involves the complexation of the corresponding aminoalcohol with $Ti(O^iPr)_4$ followed by removal of ^iPrOH and reaction with $SiCl_4$ to give the mixed Cl-O^{i}Pr titanium catalyst **98**. Cycloaddition reaction between α-bromoacrolein and cyclopentadiene in the presence of 10 mol% of this catalyst afforded the (R)-bromoaldehyde **41** in 94% yield, 93% ee and 67:1 (*exo:endo*) diastereoselectivity (Fig. 84). The reaction between isoprene and α-bromoacrolein gave the aldehyde **42** in quantitative yield and 90% ee (Fig. 84).

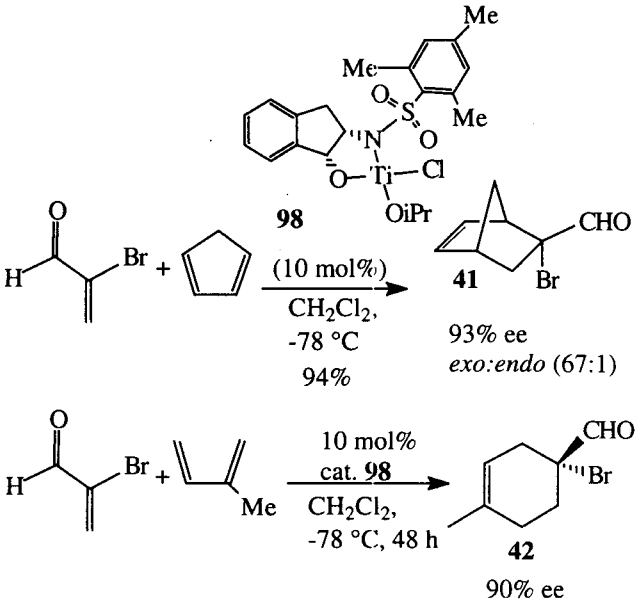


Figure 84.

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 $Ti(O^iPr)_4$, which leads to dihydropyrones with good to excellent enantiomeric excess (Fig. 86, Table 5)[100,101].

The adduct **99** derived from α-(benzyloxy)-acetaldehyde (entry 2, 97% ee) is known to be an important inter-

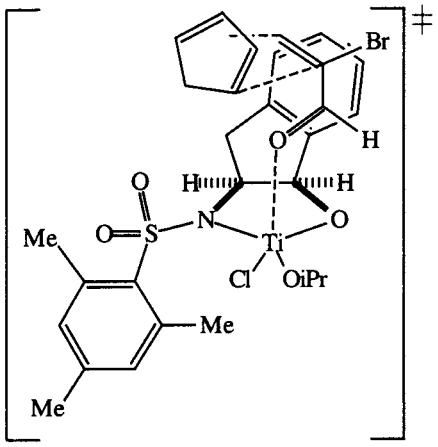


Figure 85.

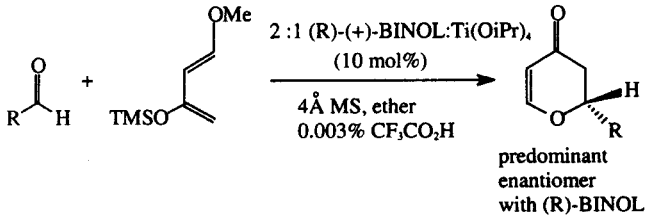


Figure 86.

Table 5.

R	T (°C)	Time (h)	yield (%)	% ee
1.TBSOCH$_2$CH$_2$-	-20	72	55	92
2.BnOCH$_2$-	-20	40	60	97
3.furyl-	-20	40	61	97
4.n-C$_8$H$_{17}$	-20	72	88	97

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).

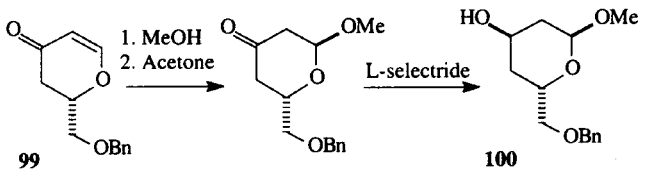


Figure 87.

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)-2-oxo-1-phenylsulfonyl-3-alkenes **101** and vinyl ethers **102** (Fig. 88, Table 6)[102].

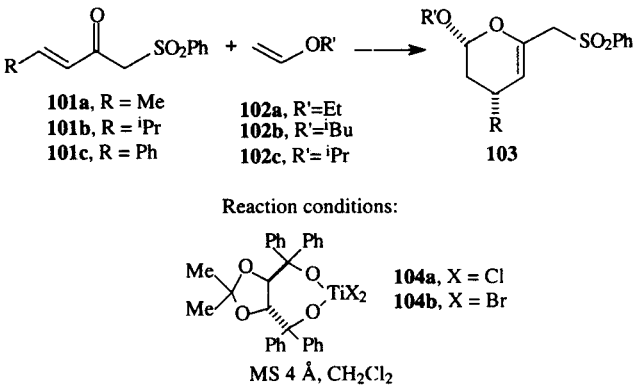


Figure 88.

Table 6.

Enone **101**	Vinyl ether **102**	catalyst **104** (mol%)	T (°C)	Ti me (h)	adduct **103** Yield(%)	%ee
a	b	b (10)	-50	6	(96)	74
a	c	b (10)	-78	20	(90)	97
a	c	b (5)	-78	24	(90)	95
b	c	b (10)	-78	24	(92)	95
c	c	b (10)	-78	24	(88)	74
a	a	a (50)	-30	17	(85)	62

Enones **101a-c** were allowed to react with excess amounts of vinyl ethers **102a-c** in the presence of catalytic amounts of chiral Lewis acids (Ti-Taddol catalyst) **104a,b** in CH_2Cl_2 solution at low temperatures leading to the desired *cis*-cycloadducts **103** in excellent yields and good enantioselectivities[102]. The titanium bromide catalyst (**104b**) was found to be more effective than the chloro analog **104a** improving both the catalytic cycle and reaction rate acceleration and the enantioselectivity was also enhanced with the increase of bulkiness of the alkoxyl substituent R' of dienophiles **102a-c**.

In 1993, Yamamoto and coworkers described a chiral helical titanium reagent as an excellent Lewis acid catalyst for asymmetric induction[103]. Asymmetric Diels-Alder reaction of cyclopentadiene and acrolein was effected in the presence of binaphthol derived catalyst **105** (10 mol%) producing the major *endo* adduct in 96% ee (Fig. 89, Table 7).

With different α,β-unsaturated aldehydes and dienes in the presence of 10 mol% of **105**, cycloadducts were produced with a high level of enantioselectivity. This catalyst efficiently blocks the *re* face of the α,β-unsaturated aldehyde upon coordination anti to the *s-trans* form. In the same paper, the authors made an interesting comparison of the optical purity in asymmetric Diels-Alder reaction of cy-

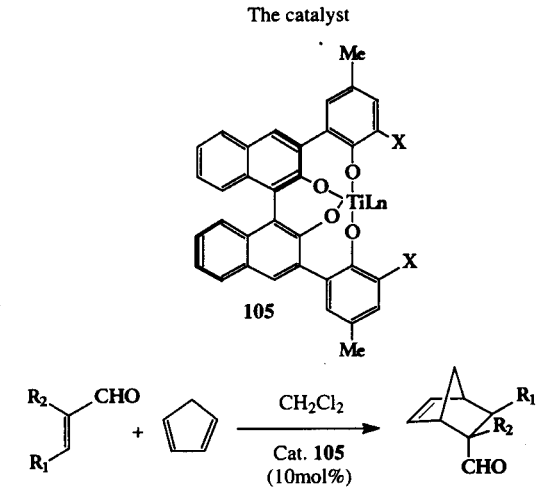


Figure 89.

Table 7.

T (°C)	X	aldehyde	*endo:exo*	% ee
-78	$Si(o\text{-}tolyl)_3$	acrolein	85:15	96
-78	$Si(t\text{-}BuPh_2)$	acrolein	93:7	92
-40	$Si(t\text{-}BuPh_2)$	methacrolein	4:96	62
-78	$Si(o\text{-}tolyl)_3$	methacrolein	1:99	94

clopentadiene and α,β-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[95]. 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

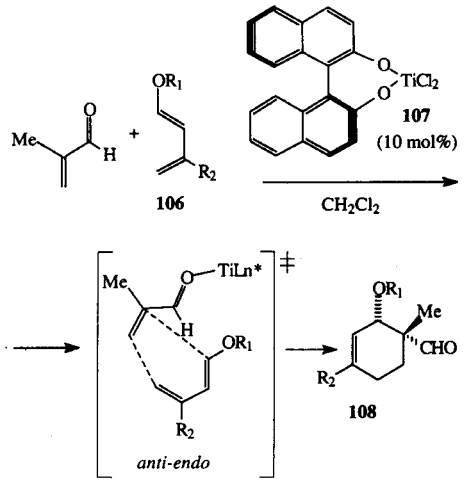


Figure 90.

Table 8.

R1	R2	*endo:exo*	%ee
Me	H	93:7	85
Me_2NCO	H	99:1	87
Ac	H	99:1	94
Ac	Me	89:11	80

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).

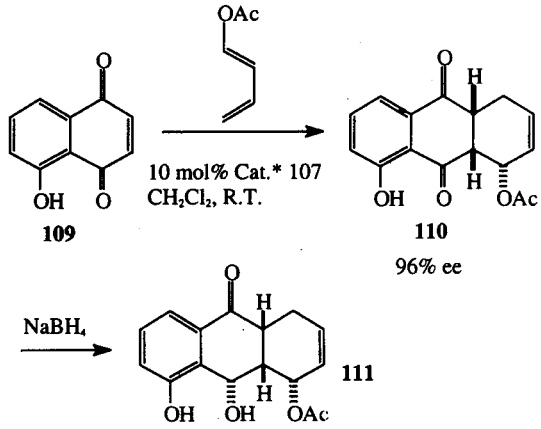


Figure 91.

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-

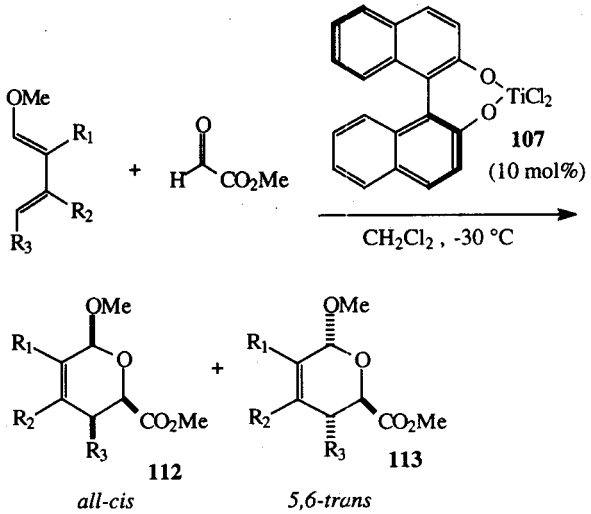


Figure 92.

Table 9.

R1	R2	R3	·112:113	% ee
H	H	H	88:12	96
H	H	Me	98:2	93
Me	H	Me	98:2	95
H	Me	H	92:8	71

plexation between titanium catalyst and aldehyde makes the hetero Diels-Alder proceed through the *anti-endo* orientation **B** (Fig. 93).

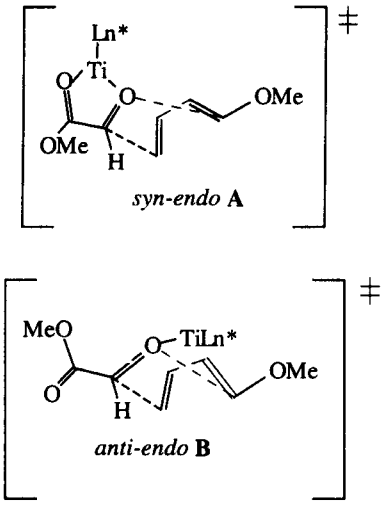


Figure 93.

The glyoxylate adducts are useful intermediates for the synthesis of monosaccarides and also the lactone portion in mevilonin or compactin (Fig. 81), coenzyme A reductase inhibitors as illustrated in Fig. 94[91].

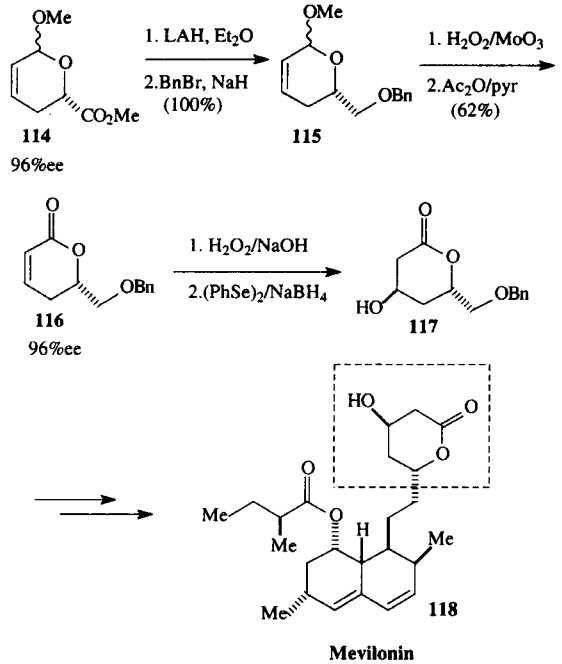


Figure 94.

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].

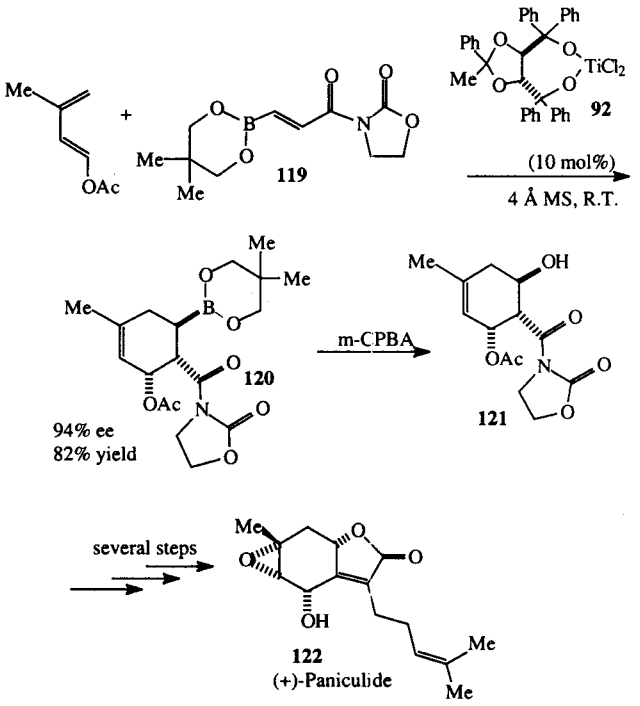


Figure 95.

Reaction of (E)-3-[((5,5-dimethyl)-1,2,3-dioxaborinan-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 CH_2Cl_2 in the presence of Li_2CO_3 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 metallocene complex [(S)-1,2-ethylene-bis(η^5-tetrahydroindenyl)] $Zr(OTf)_2$ **123** as well as its titanium analog (Fig. 96, Table 10)[106].

The level of asymmetric induction (70-95% ee) is good in polar solvents like nitromethane and 2-nitropropane and poor in solvents like CH_2Cl_2, but the *endo* selectivity is higher in CH_2Cl_2.

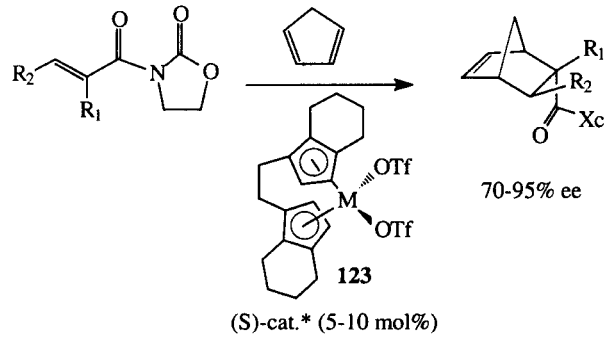
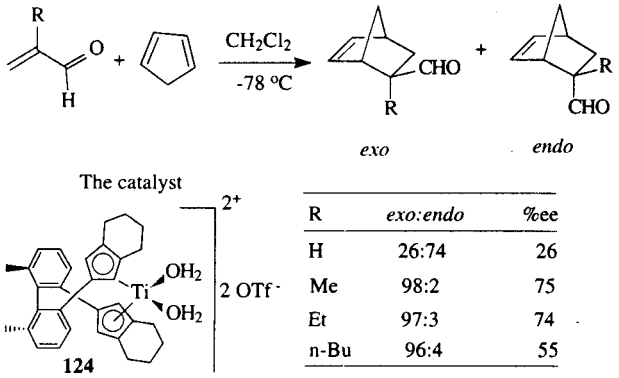


Figure 96.

Table 10.

cat. (mol%)	R1	R2	solvent	T (°C)	*endo:exo*	% ee
Ti(10)	H	H	CH_2Cl_2	0	9:1	0
Ti(10)	H	H	CH_3NO_2	0	7:1	88
Ti(5)	H	H	CH_3NO_2	-30	7:1	89
Zr(1)	H	H	CH_2Cl_2	-78	30:1	30
Zr(5)	H	H	$NO_2CH(CH_3)_2$	-78	6:1	92
Zr(5)	H	Me	$NO_2CH(CH_3)_2$	-78	15:1	95

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 CH_2Cl_2 at -78 °C (Fig. 97)[107,108]. The *exo:endo* ratio is high for α-substituted aldehydes, but the enantioselectivities are only moderate (26-75% ee).



R	*exo:endo*	%ee
H	26:74	26
Me	98:2	75
Et	97:3	74
n-Bu	96:4	55

Figure 97.

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 enantioselectivity[110].

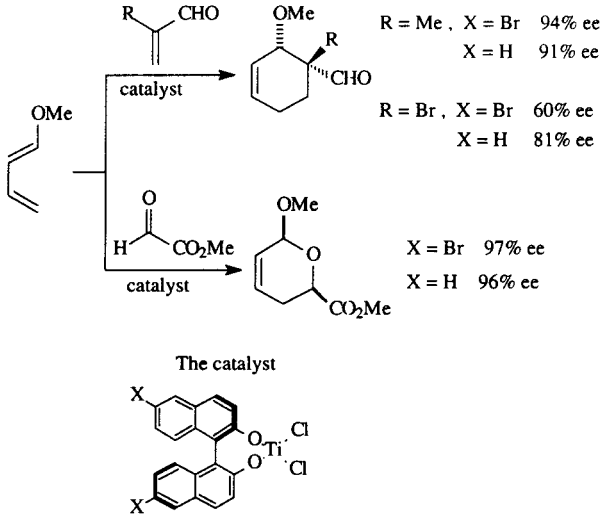


Figure 98.

Chiral copper(II) Lewis acids.

A remarkable selectivity was described by Evans and coworkers in 1993 demonstrating the utility of chiral Cu(II)-bis-(oxazoline) complexes **125** as Lewis acids in the catalysis of the Diels-Alder reactions of unsubstituted and β-substituted acrylimides with cyclopentadiene (Fig. 99, Table 11) [111-114].

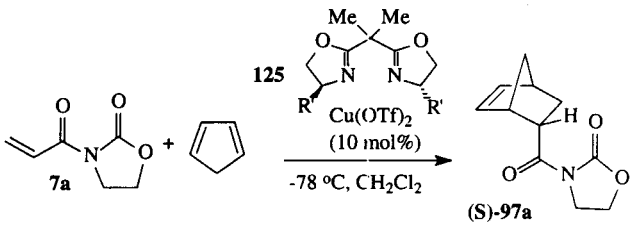


Figure 99.

Table 11.

ligand **125**	yield (%)	*endo:exo*	*endo* ee %
a, R' = Ph	92	95:5	30
b, R' = $CHMe_2$	93	96:4	58
c, R' = CMe_3	86	98:2	> 98

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 CH_2Cl_2 led only to 30% ee (95:5, *endo:exo*)[132]. 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)[112].

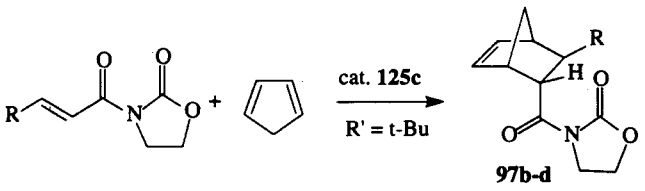


Table 12.

7b-d	*endo:exo*	*endo* ee %	T (°C)
b,R = Me	96:4	97	-15
c, R = CO_2Et	94:6	95	-55
d, R = Ph	90:10	90	25

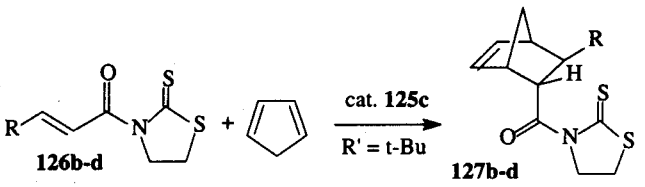


Table 13.

126	*endo:exo*	*endo* ee %	T (°C)
b, R = Me	96:4	94	-45
c, R = CO_2Et	84:16	96	-55
d, R = Ph	92:8	97	-35

Figure 100.

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[112,114].

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

To rationalize the observed enantioselection 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 com-

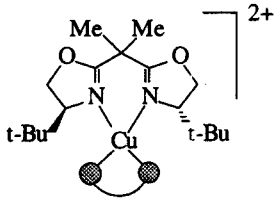


Figure 101.

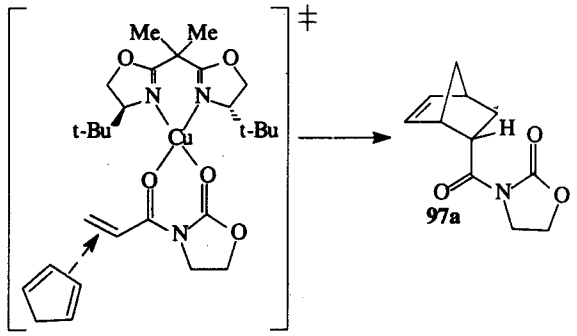


Figure 102.

plex, with approach of the diene from the Cα-*re*-face of dienophile, opposite to the bulky *t*-butyl group[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)[112,114].

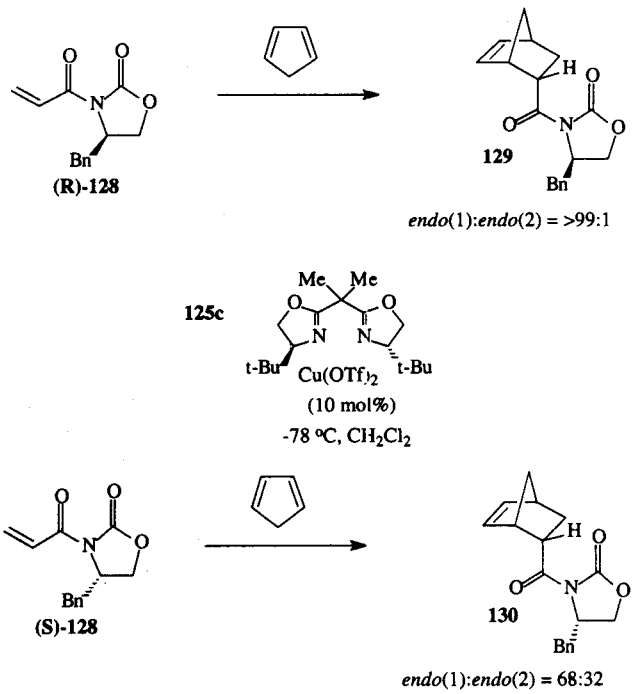


Figure 103.

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).

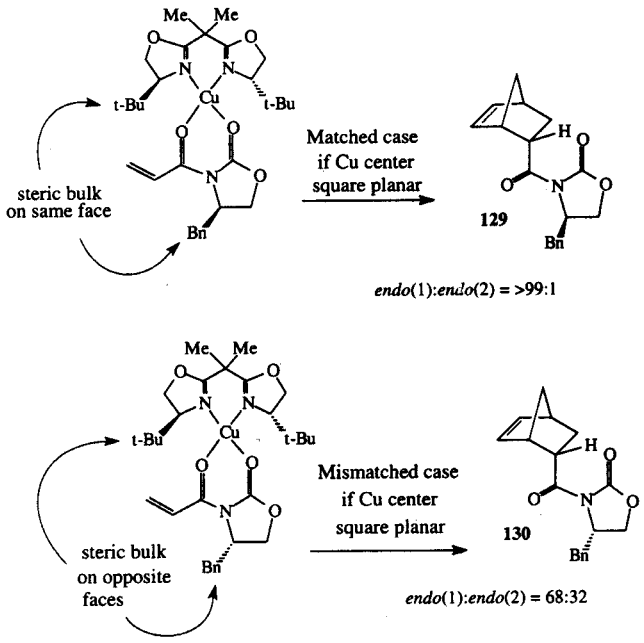


Figure 104.

Evans and coworkers also reported the utilization of $Cu(OTf)_2$-bis(imine) complex as an effective catalyst for the Diels-Alder reaction[114-115]. The 2,6-dichlorophenyl-substituted ligand **131**, the most effective catalyst, can be readily prepared from enantiomerically pure trans-1,2-cyclo-hexanediamine 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.

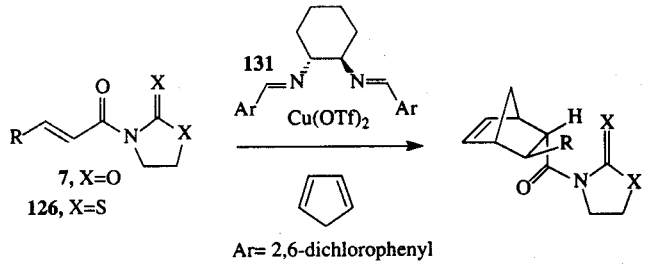


Figure 105.

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

Table 14.

	Dienophile b-d	Time (h)	T (°C)	*endo:exo*	*endo* ee (R) Product	yield (%)
7	b, R = Me	30	-10	65:35	83	90
X = 0	c, R = CO_2Et	24	-55	55:45	94	98
	d, R = Ph	84	25	60:40	85	83
126	b, R = Me	16	-30	93:7	91	86
X = S	c, R = CO_2Et	24	-55	90:10	88	99
	d, R = Ph	48	-20	92:8	92	84

affinity of the C=S ligand for the copper center[114]. 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[114].

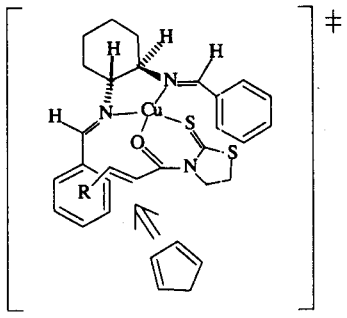


Figure 106.

In 1995, Evans and coworkers described very interesting counterion effects in the utilization of Cu(II) complexes of tridentate bis-(oxazolinyl)-pyridine (pybox) ligands [Cu(II)-(pybox)X_2] **132a-d** in reactions with α-substituted acroleins (Fig. 107, Table 15)[116].

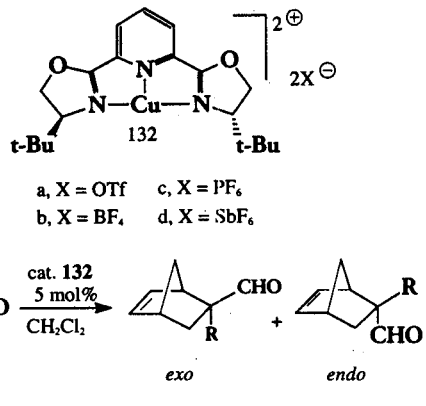


Figure 107.

Table 15.

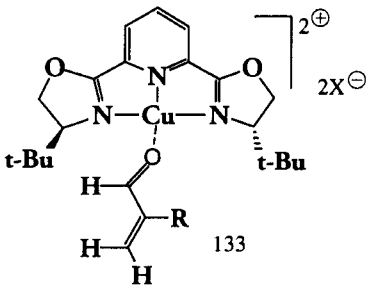
Triflate catalyst **132a**

	Time (h)	T (°C)	*endo:exo*	Major isomer ee
(R = H)	116	-20	97:3	85%
(R = Br)	60	-40	3:97	87%
(R = Me)	120	-20	4:96	85%

SbF_6^- catalyst **136d**

	Time (h)	T (°C)	*endo:exo*	Major isomer ee
(R = H)	18	-20	94:6	85%
(R = Br)	12	-78	2:98	96%
(R = Me)	8	-40	3:97	92%

The catalyst **132d** with non-coordinating counterion SbF_6^- is *ca.* 20 fold more reactive than the OTf^- catalyst **132a**. The cationic (pybox)$Cu(SbF_6)_2$ 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 SbF_6^- 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

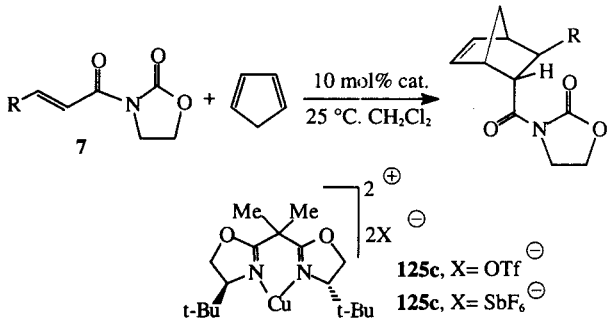
- 1 point substrate binding possible

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=SbF_6^-) 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



	counterion	time(h)	*endo* ee	yield (%)
R = Me +25 °C	X = OTf^-	8	94	95
	X = SbF_6^-	8	96	98
R = Ph +25 °C	X = OTf^-	24	99	85
	X = SbF_6^-	24	96	96
R = Cl +25 °C	X = OTf^-	24	53	10
	X = SbF_6^-	24	95	96

Figure 109.

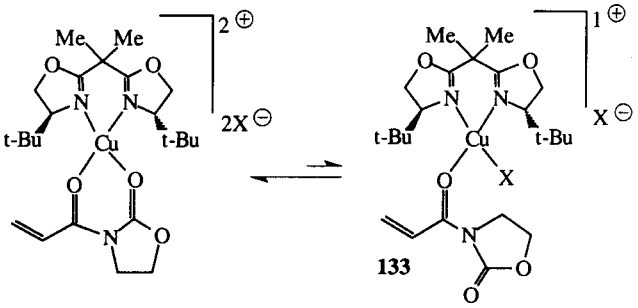
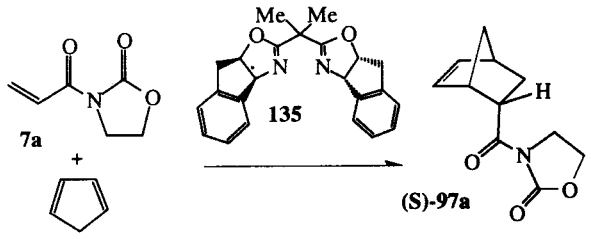


Figure 110.

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 reactions[116b].

A similar counterion effect was observed by Davies and coworkers at Merck in 1996[117]. Chiral bis-oxazolines **135** were used in $Cu(SbF_6)_2$ 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 $Cu(SbF_6)_2$ catalyst **135b**, this adduct was obtained in 95% ee and 39:1 *endo:exo* diastereoselectivity[117].



135a, $Cu(OTf)_2$ 92% ee (130:1, *endo:exo*)

135b, $Cu(SbF_6)_2$ 95% ee (39:1, *endo:exo*)

Figure 111.

Also in 1996, the Merck group published an interesting paper on the influence of ligand bite angle on spirobis-(oxazolines) in the enantioselectivity of copper(II)-catalyzed Diels-Alder reactions (Fig. 112)[118,119]. The spirobis-(oxazolines) **136a-d** were prepared by treatment of the corresponding unsubstituted bis-(oxazolines) with TMEDA, diisopropylamine and butyllithium at -65 °C, followed by alkylation with the appropriate diiodoalkane.

As can be seen from the data in Fig. 112, the larger the value of Φ in **136a-d-** and hence the ligand bite angle θ, the higher the observed enantioselectivity. Substitution of the 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[118,119].

In 1996, Ghosh and coworkers disclosed their results using a bis-(oxazoline) chiral catalyst analogous to that used by the Merck group[120]. 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).

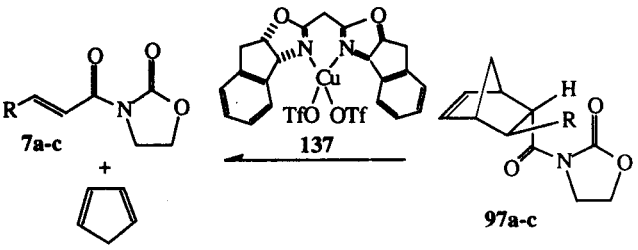
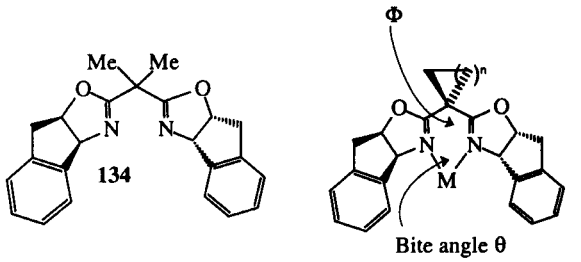


Figure 113.



136a, n = 1 **136c**, n = 3

136b, n = 2 **136d**, n = 4

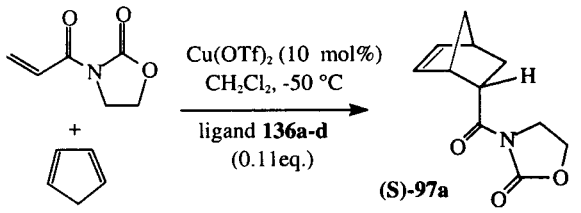


Figure 112.

Table 16.

Ligand	Φ (°)	% ee *endo* (S)	*endo:exo*
136a	110.6	96.3	44:1
136b	108.0	92.0	38:1
136c	105.8	89.5	37:1
136d	103.7	83.0	26:1
135	104.7	82.5	49:1

Table 17.

R	% ee	*endo:exo*
a, R = H	99	> 99:1
b, R = Me	84	90:10
c, R = CO_2Et	94	93:7

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[112,116,132].

In 1995, Jorgensen and Johannsen disclosed their results on asymmetric hetero Diels-Alder and Ene reactions catalyzed by chiral copper(II) bis-(oxazoline) complexes[121a]. 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)[121a].

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

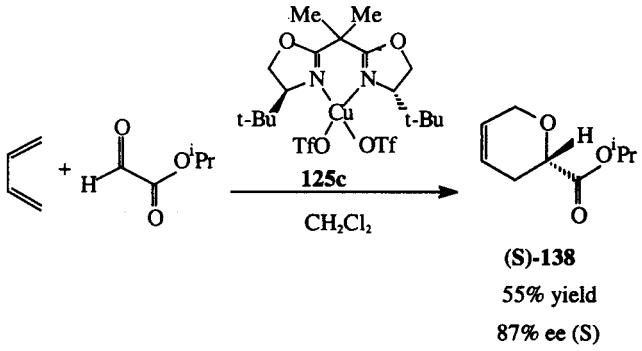


Figure 114.

ligand **125a**[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[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[121b].

More recently, the Evans group reported a highly enantioselective Diels-Alder reaction between acryloyl oxazolidinone **7** with furan[122,123]. This reaction, catalyzed by cationic bis(4-tert-butyloxazoline)Cu(II) complex **125c** with hexafluoroantimonate (SbF_6^-) 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)[122a,96b].

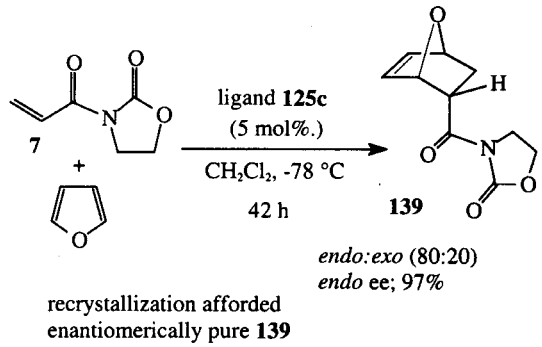


Figure 115.

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** (SbF_6^- counterion) effectivelly catalyze the intramolecular Diels-Alder reaction of several trienimides with excellent enantioselectivity[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).

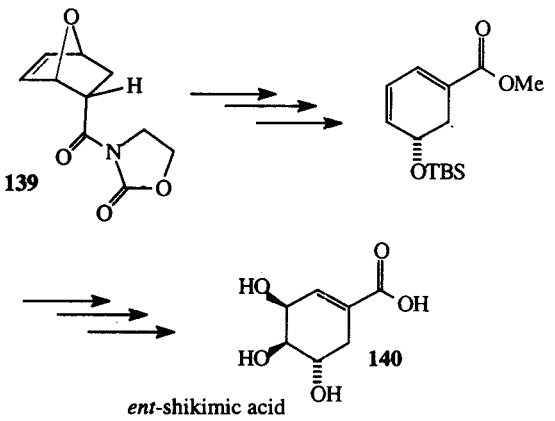


Figure 116.

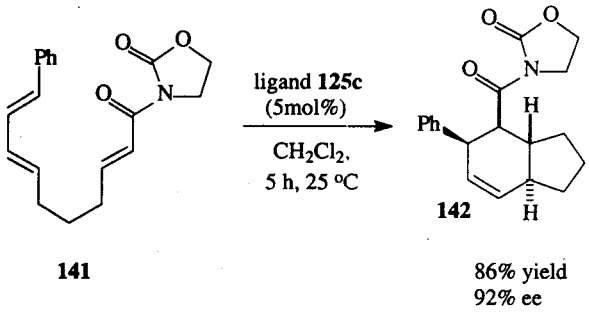


Figure 117.

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 CH_2Cl_2 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).

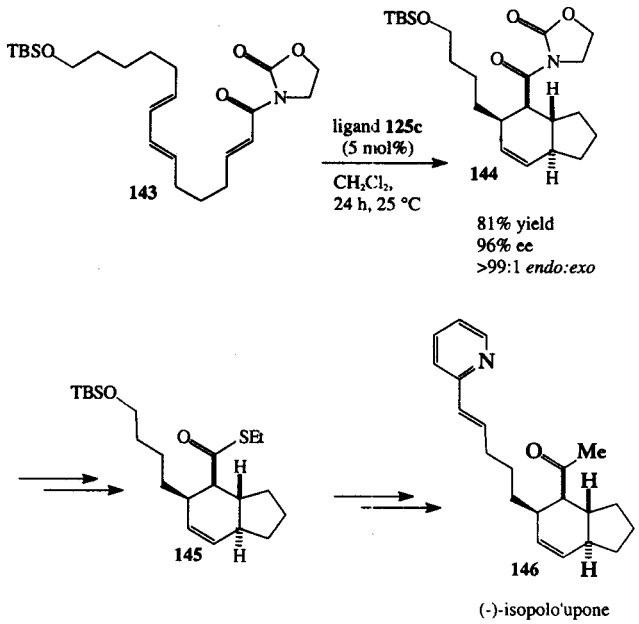


Figure 118.

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)[112-114].

Chiral lanthanide(III) Lewis acids.

Recently, some highly efficient asymmetric Diels-Alder reactions catalyzed by chiral lanthanide(III) triflates have been reported[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-oxazolidin-2-one **7b** with cyclopentadiene in CH_2Cl_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)[126].

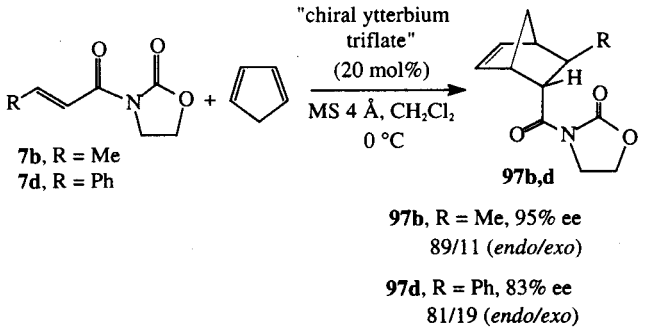


Figure 119.

In 1994, Kobayashi demonstrated that a chiral scandium catalyst is also effective in the enantioselective Diels-Alder reaction of acyl-1,3-oxazolidin-2-ones with dienes, and that the corresponding adducts were obtained in high yields and enantioselectivities (R = Ph, 97% ee, 90:10 *endo/exo*; R = Me, 96% ee, 86/14 *endo:exo*)[127]. The authors proposed structure **147** for the catalyst based on ^{13}C-NMR chemical shifts of the carbons of the N-methyl groups of *cis*-1,2,6-trimethylpiperidine (TMP) and IR data. ^{13}C-NMR spectroscopy of the catalyst (TMP + $Sc(OTf)_3$ + (R)-BINOL) indicated the existence of a hydrogen bond between the nitrogen of *cis*-1,2,6-trimethypiperidine and the binaphthol hydrogens (Fig. 120).

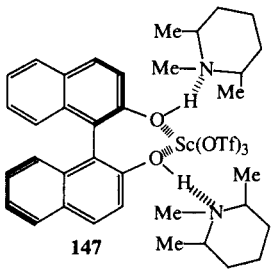


Figure 120.

The proposed transition state is illustrated in Fig. 119 and is rationalized by assuming an intermediate octahedral Sc(III)-dienophile complex. The Cα-*si* face of the dienophile is blocked by the bulky amine, and the diene approaches the dienophile from the Cα-*re* face, affording the observed product (Fig. 121).

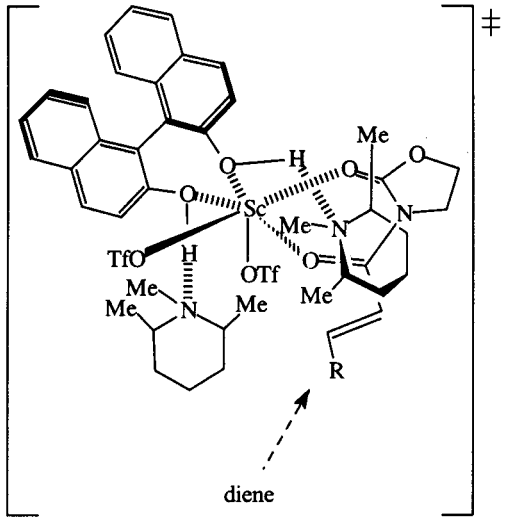


Figure 121.

Also in 1994, Kobayashi and co-workers reported other lanthanide(III) triflates as catalysts[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.

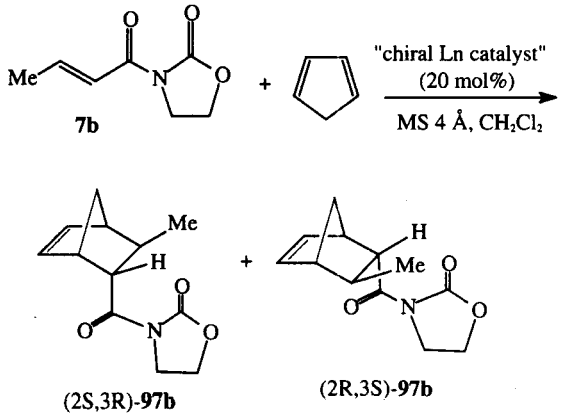


Figure 122.

Table 18.

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

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)[129,130].

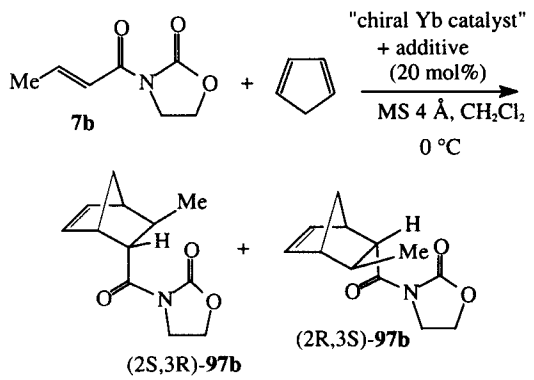
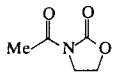
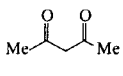
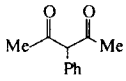


Figure 123.

Table 19.

Additive	yield (%)	*endo:exo*	(2S,3R):(2R,3S)	ee(%)
	77	89:11	96:4	(93)
	80	88:12	22:78	(55)
	83	93:7	10:90	(81)

When 3-(2-butenoyl)-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-pyrone **148** (3-CMP) with vinyl ethers and vinyl sulfides, affording bicyclic lactones **149** in good yields and good enantioselectivities[131]. On heating, these lactones lose CO_2 to afford chiral cyclohexadienes **150**. They observed that the vinyl sulfides always gave higher ee's than the related vinyl ethers (Fig. 124)[132].

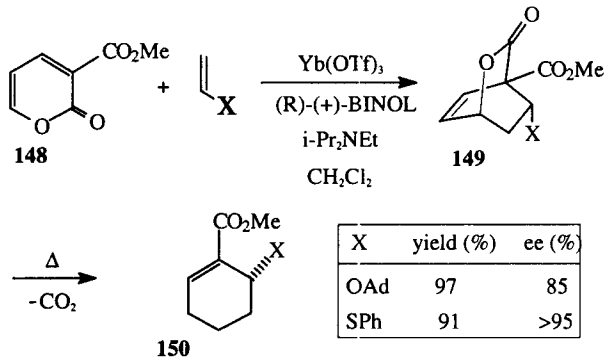


Figure 124.

The utilization of TADDOL and (-)-menthol derivatives led to racemic Diels-Alder adducts[133].

Chiral magnesium Lewis acids

In 1992 Corey and Ishihara reported the utilization of the C2-symmetric chiral bis-(oxazoline) ligand **151**[134-136]. This ligand, synthesized from (S)-phenylglycine, is an effective catalyst for enantioselective Diels-Alder addition in combination with magnesium iodide (made from Mg + I_2 in ether at 25 °C) or magnesium tetraphenylborate (made from $MgCl_2$ + tetraphenylboral in CH_3CN at 50 °C) (Fig. 125)[136-137].

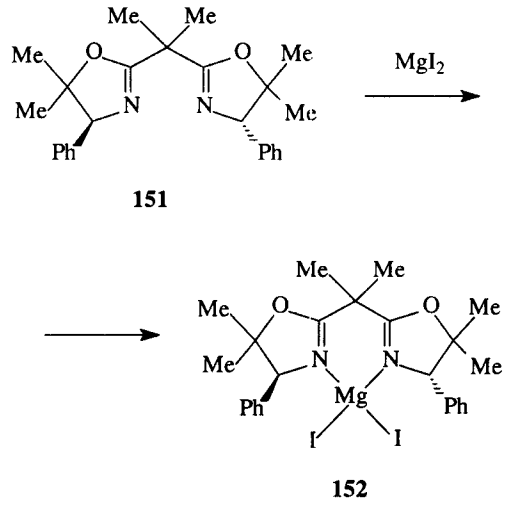


Figure 125.

The catalyst **152** (0.1 equiv.) and 0.2 equiv. of $AgSbF_6$ (co-catalyst) converts cyclopentadiene and 3-acryloyloxazolidin-2-one **7** in CH_2Cl_2 at -80 °C over 16 h to the chiral adduct (R)-**97** in 84% yield with 98:2 *endo:exo* selectivity and 91% ee[136]. The observed enantioselection in this reaction is opposed to that observed with Cu(II) catalysts (Fig. 126)[136-138].

The same reaction in the presence of **151**-Mg(Ph$_4$B)$_2$ in 2:1 CH_2Cl_2/^{i}PrNO$_2$ at -50 °C over 18 h produced the cycloadduct with 90% enantioselectivity and 97:3 *endo:exo* selectivity[138]. The authors proposed a 1:1:1 com-

plex of **151**, Mg^{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).

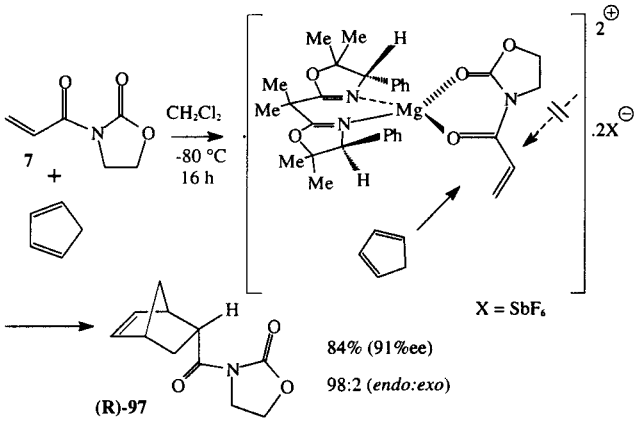


Figure 126.

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-phenylglycinol (Fig. 127)[139].

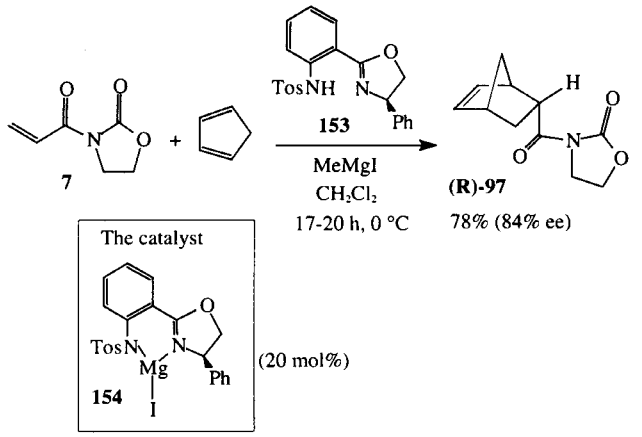


Figure 127.

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

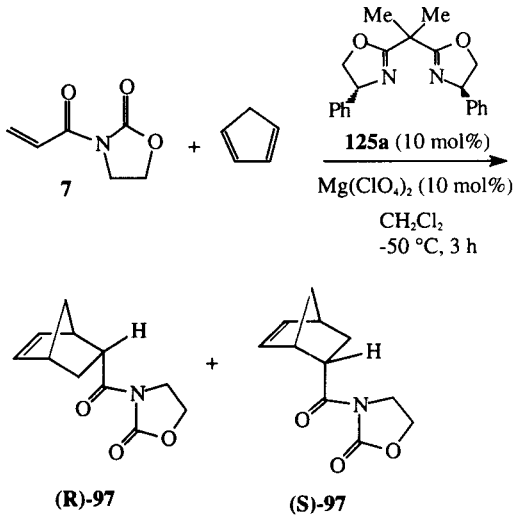


Figure 128.

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 protocols[116,136].

In 1996, Llera *et al.* disclosed their results on the use of chiral magnesium(II)-complexes prepared from hydroxysulfoxides and magnesium iodide[141]. 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).

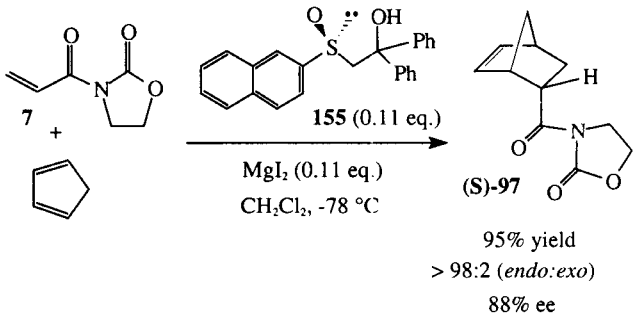
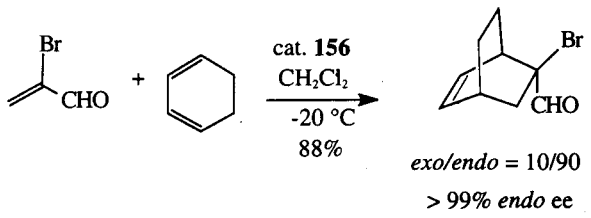


Figure 129.

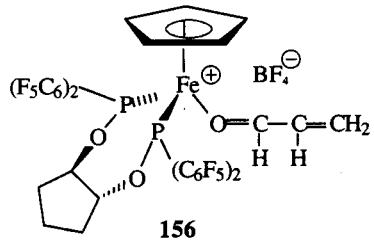
Chiral transition metal-based Lewis acids

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* ratio[142] (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.



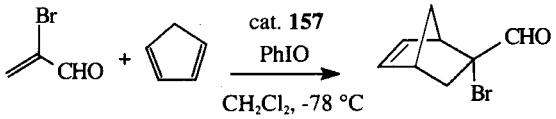
The catalyst:



156

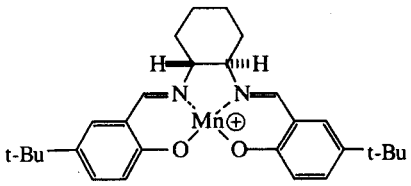
Figure 130.

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).



exo/endo = 98/2
68% *exo* ee
93% yield

The catalyst:



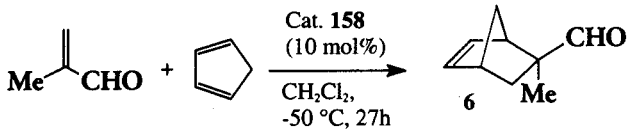
157 $PF_6^⊖$

Figure 131.

Carmona and Cativiela reported recently the first rhodium 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_6^- 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



71% ee (R)
73% yield
98:2 (*exo:endo*)

catalyst **158**:
$[(\eta_5\text{-}C_5Me_5)Rh(R\text{-}Prophos)(H_2O)](SbF_6)_2$

Figure 132.

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. Is is also expected to see more developments in the use of transition-metal complexes as chiral catalysts.

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