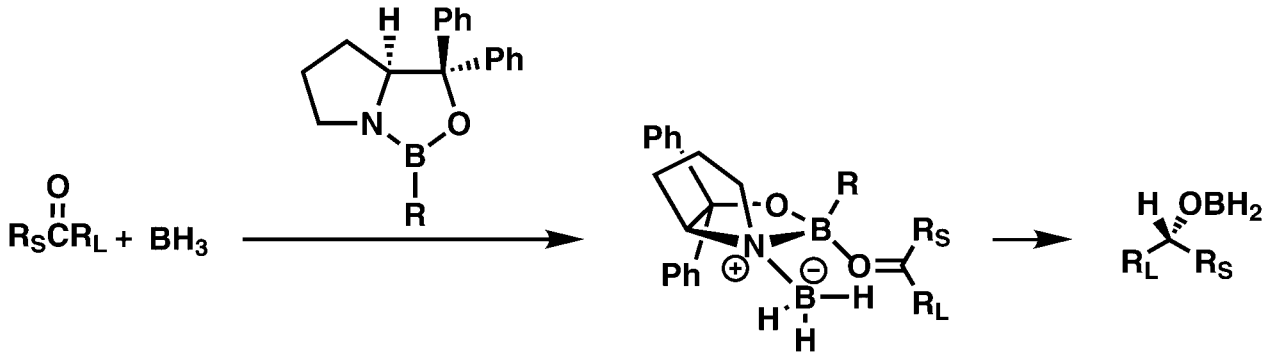
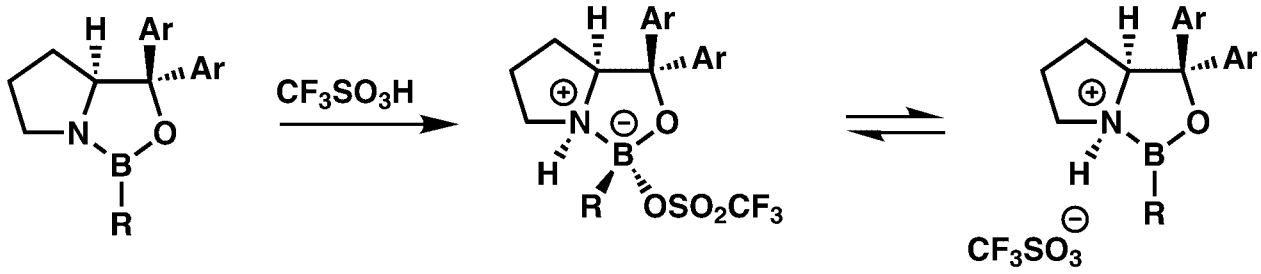
Enantioselective Diels-Alder-Reactions

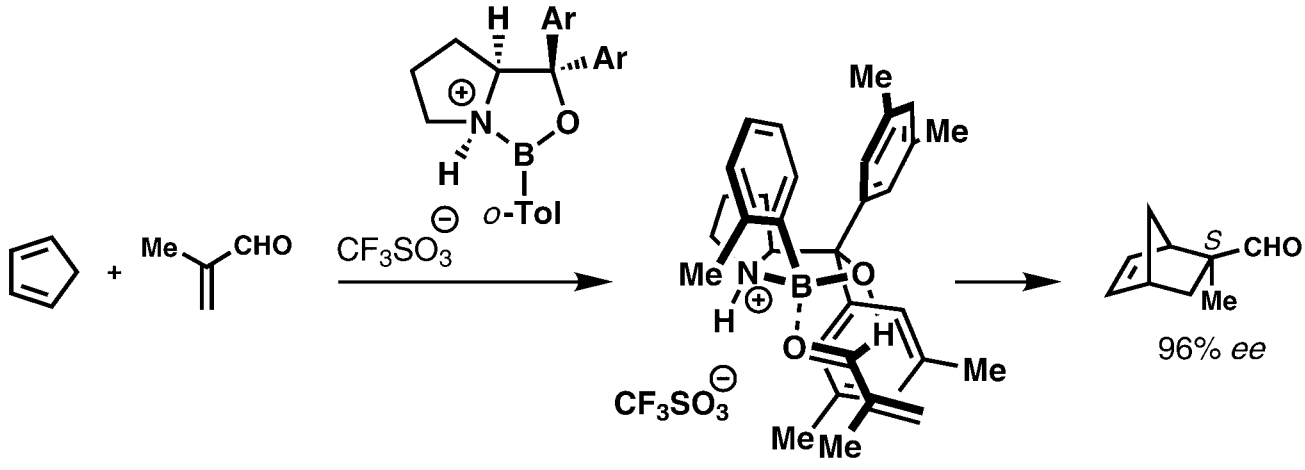
Oxazaborolidines are excellent catalysts for the highly enantioselective reduction of ketones:



The oxazaborolidines are converted by protonation into potent cationic chiral Lewis acids:



These chiral cationic Lewis acids are extraordinarily effective catalysts for enantioselective Diels–Alder reactions, for example:



96% *ee*

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Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications

E. J. Corey*

Dedicated to the Memory of Kurt Alder

One hundred years after the birth of Kurt Alder and seventy-five years after the discovery of his famous reaction, one of the most important and fascinating transformations in chemistry, research on that process continues to surprise, excite, delight, and inform the chemical community. This article is based on presentations given first at the University of Cologne, Germany (Kurt Alder lecture, 1992), then at the Roger Adams Award Symposium (1993), and later at the Bürgenstock Conference of 2001, and describes research by our group on the development and understanding of enantioselective versions of the Diels–Alder reactions. The elements of this review include 1) development of new chiral Lewis acid catalysts for highly enantioselective (>25:1) [4+2] cycloadditions; 2) the fine mechanistic details and pre-transition-state assemblies of these reactions; 3) the fundamental understanding of catalytic activity and enantioselectivity for highly enantioselective Diels–Alder processes; and 4) applications to the synthesis of complex molecules. The range and power of the Diels–Alder reaction have steadily increased over seven decades. The end of this remarkable development is not in sight, a high compliment to this field of Science and to its great inventor.

Keywords: asymmetric catalysis · chiral ligands · cycloaddition · Lewis acids · transition states

1. Introduction

This year marks the centennial of the birth of Kurt Alder (1902–1958), one of the twentieth century's great organic chemists. His discovery with Otto Diels[1] and the subsequent development of the Diels–Alder reaction were transforming events in chemistry, as recognized by the award of the Nobel Prize in Chemistry in 1950 to this teacher–student pair. The impact of the Diels–Alder reaction on synthetic chemistry was so great just 15 years after its discovery that Alder wrote in a long review in 1943, "Any attempt at a systematic treatment of the diene synthesis (as he modestly called his reaction) must be strictly limited in its scope."[2] Yet, the true power and effectiveness of the Diels–Alder reaction only began to be realized in the 1950s and 1960s with the elegant applications of the process to the total synthesis of many complex natural products.[3] The development continued with no let up in pace. Many different versions of the Diels–Alder reaction were elaborated, including intramolecular [4+2] cycloadditions, hetero Diels–Alder reactions, pressure-accelerated Diels–Alder reactions, and Lewis acid accelerated Diels–Alder reactions.[4] If one chemical reaction had to be selected from all those in the repertoire of synthetic organic chemists as the most useful and powerful synthetic construction, it was clear by 1970 that the Diels–Alder reaction would be the logical choice. Its application not only leads to a strong increase in molecular complexity (molecular size, topology, stereochemistry, functionality, and appendages), but also can result in structures that lend themselves to additional amplification of complexity by the use of other powerful synthetic reactions. Yet, further advances in scope and utility of this Grand Old Reaction of synthesis were to come. This article summarizes a program of research that has been carried out in our laboratories at Harvard University over the past three decades with the objective of extending the reach of the Diels–Alder reaction to new domains, especially in terms of control of absolute stereochemistry, and to a much deeper understanding of the fine mechanistic details and pathways of Lewis acid accelerated Diels–Alder additions. It must be emphasized at the outset that many other research groups have been active in the field of stereocontrol and enantioselective synthesis during this period. Also, the science of organic synthesis has benefited greatly from the development of new reagents and catalysts for other types of enantiose-

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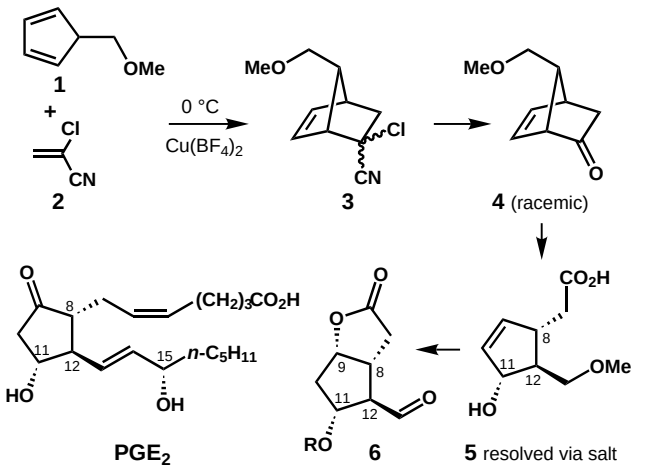
lective reactions, currently one of the most dynamic aspects of chemistry.[5–6]

2. Early Studies

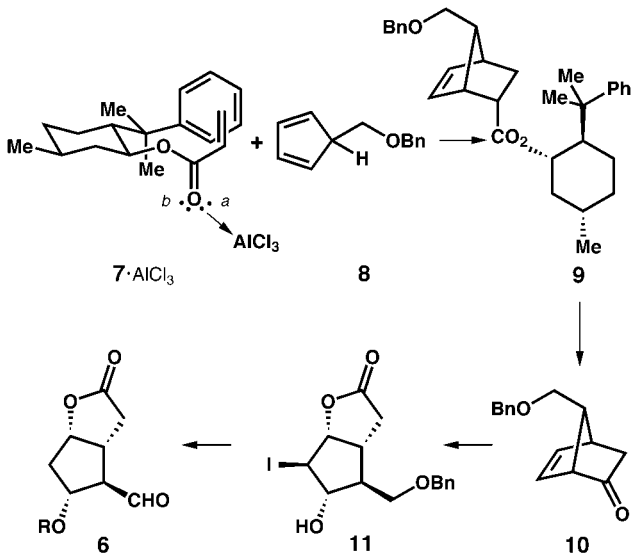
Three decades ago, a general synthesis of prostaglandins was demonstrated which provided access to biologically important prostaglandins (PGs) of all three known families from a common intermediate; for example, PGE_2 (a member of the second family) from lactone aldehyde **6** in Scheme 1.[7–9] The



Scheme 1. Synopsis of a general route for the synthesis of members of each of the three prostaglandin families from a common synthetic intermediate.

first step of the synthetic sequence was the cupric fluoroborate catalyzed Diels–Alder reaction of diene **1** with 2-chloroacrylonitrile (**2**) to form a mixture of the two diastereomeric α-chloronitriles **3**, base treatment of which afforded the racemic bicyclic ketone **4** efficiently. This example constituted the first use of a reactive Cu^{II} salt as a Lewis acid for accelerating the Diels–Alder addition, a demonstration of 2-chloroacrylonitrile as a ketene equivalent, and the first example of a catalytic Diels–Alder reaction in the synthesis of complex natural products. Baeyer–Villiger oxidation of the ketone **4** followed by lactone hydrolysis and resolution of the resulting racemic acid with ephedrine provided the chiral hydroxy acid **5**. Lactone aldehyde **6** was readily obtained from **5** and was transformed into the various PGs of the first, second, and third families. This synthesis proved to be so effective that it was used in many laboratories to prepare many PGs and PG analogues. However, it was apparent to us that the process could, in principle, be improved by eliminating the resolution step and the associated loss of material. This realization and subsequent research led to the development of the first highly enantioselective version of the Diels–Alder reaction.

This enantioselective synthesis of PGs via the key prostaglandin intermediate **6** (Scheme 2) used the dextrorotatory acrylate ester of 8-phenylmenthol (**7**) as a chiral ketene equivalent for the $AlCl_3$-catalyzed Diels–Alder reaction with



Scheme 2. Enantioselective synthesis of **6** by using 8-phenylmenthol as a chiral controller.

the achiral diene **8**.[10, 11] Cycloaddition occurred smoothly at $-55\,^{\circ}C$ in CH_2Cl_2 for 1 hour to give the *endo* adduct **9** in 89% yield with 97:3 diastereoselectivity. An oxidative C–C cleavage protocol converted **9** into the bicyclo[2.2.1]heptenone **10** with recovery of the 8-phenylmenthol controller. Ketone **10** was transformed by known procedures into the iodolactone **11** (100% *ee* after one recrystallization) and thence into the lactone aldehyde **6**.[7, 8]

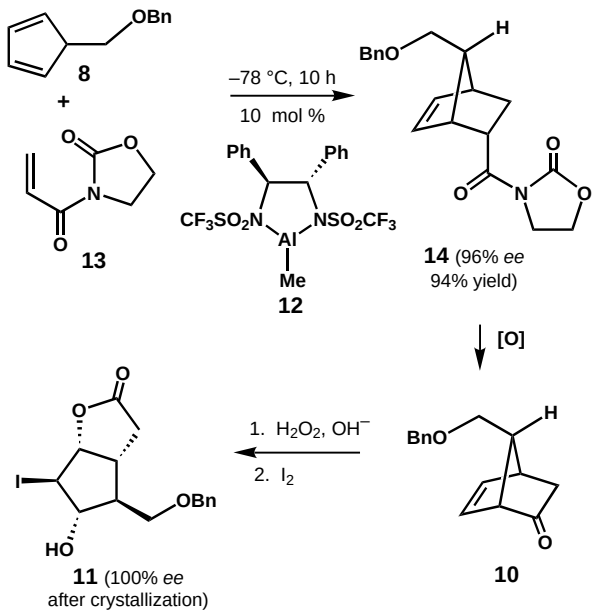
Elias J. Corey, born in 1928 in Methuen, 30 miles north of Boston, studied chemistry from 1945–1950 at the Massachusetts Institute of Technology, where he gained his doctorate for work on synthetic penicillins under the supervision of John C. Sheehan. In January 1951 he joined the University of Illinois at Urbana-Champaign as an Instructor in Chemistry and was promoted in 1956 to full Professor. Since 1959 he has been at Harvard University. For as long as he can remember he has enjoyed study, adventure, and discovery.

The mechanistic insights which guided the selection of the 8-phenylmenthol as chiral controller and the development of this enantioselective route to PGs can be summarized as follows. The activation of the acrylate dienophile **7** by $AlCl_3$ was expected to occur by coordination to the sterically more accessible lone pair *a* on the carbonyl oxygen atom (Scheme 2). In that complex the antiperiplanar (*s-trans*) arrangement of the vinyl and carbonyl subunits of the acrylate is clearly much more stable than the synperiplanar (*s-cis*) form because of strong steric repulsion in the latter. In the complex $\mathbf{7}\cdot AlCl_3$, the phenyl group is situated so as to allow an attractive interaction between the cationic acrylyl group and the π-basic benzenoid ring, which is well positioned with the electron-deficient carbonyl carbon atom lying just over the *ortho* carbon atom of the phenyl substituent at the optimum π–π spacing of approximately 3.5 Å. Thus, the phenyl group of the controller can block the [4+2] cycloaddition of **8** to the rear face α,β-acrylyl olefin (i.e. the *Si* face of C_α) and thereby favor the formation of **9** by forcing the diene to add to the front face (*Re* face of C_α).[12] As expected on the basis of this argument, the stereoselectivity of the reaction of diene **8** with menthyl acrylate is relatively poor under the same conditions employed for the formation of adduct **9**. One more important point must be made here in regard to the transition state for the proposed reaction pathway. In that transition state, that is, as the diene **8** is adding to the α,β-double bond of $\mathbf{7}\cdot AlCl_3$, the carbonyl carbon atom of the acrylate remains highly electron-deficient and hence a strong attractive interaction is maintained between the neighboring π-electron-rich phenyl group and that carbonyl carbon atom. Thus, the phenyl group of the controller directly favors the transition state that leads to the dominant Diels–Alder product **9**.[13]

3. Enantioselective Diels–Alder Reactions with Chiral Diazaaluminolidines as Catalysts

The idea that π-electron-rich aromatic groups could be used both to stabilize specific transition-state geometries and to provide stereoselectivity through facial screening served as a promising heuristic for the development of enantioselective catalysts for Diels–Alder reactions. Guided in part by this idea, a new type of catalytic enantioselective Diels–Alder reaction was discovered, one example of which is shown in Scheme 3. The bistrifluoromethanesulfonamide of (*S*,*S*)-1,2-diphenyl-1,2-diaminoethane reacts with trimethylaluminum in 1,2-dichloroethane to form the diazaaluminolidine catalytic system **12**. The reaction of **8** with 3-acryloyl-1,3-oxazolidin-2-one (**13**) in the presence of **12** (10 mol%) produces efficiently the chiral Diels–Alder adduct **14** (96% *ee*) shown in Scheme 3.[14–16] The bistriflamide ligand is readily recovered for reuse and consequently only 10 mol% of the inexpensive trimethylaluminum is consumed in this process, which provides an excellent route to PGs via the usual intermediates **10** and **11**.

The fine mechanistic details of the Diels–Alder reaction **8** + **13** → **14** are of great interest because of its high efficiency and novelty. In the solid state, the diazaaluminolidine exists as a dimer whose structure was determined by X-ray crystallography to be that shown in Figure 1 A.[17] The ^1H, ^{13}C and ^{19}F NMR spectra of this diazaaluminolidine show that it also exists as a dimer in CH_2Cl_2 solution.[17] However, in the presence of one or more equivalents of 3-acryloyl-1,3-oxazolidin-2-one, the Diels–Alder catalyst forms a 1:1 complex whose preferred geometry was revealed by low-temperature ^1H and ^{13}C NMR spectroscopic analysis (including NOE) to be that shown in Figure 1 B. It is of interest that this geometry of the 1:1 complex places the metal-complexed carbonyl group and an aromatic ring in proximity and leads to the possible transition-state assembly shown in Figure 2 A,



Scheme 3. Catalytic enantioselective Diels–Alder reaction for the general synthesis of prostaglandins.

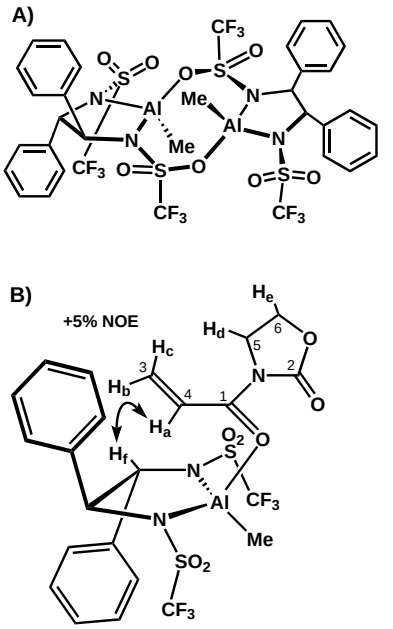


Figure 1. A) X-ray solid-state and solution structure of catalyst **12**. B) Complex of **12** with **13** as revealed by low-temperature ^1H NMR spectroscopic analysis.

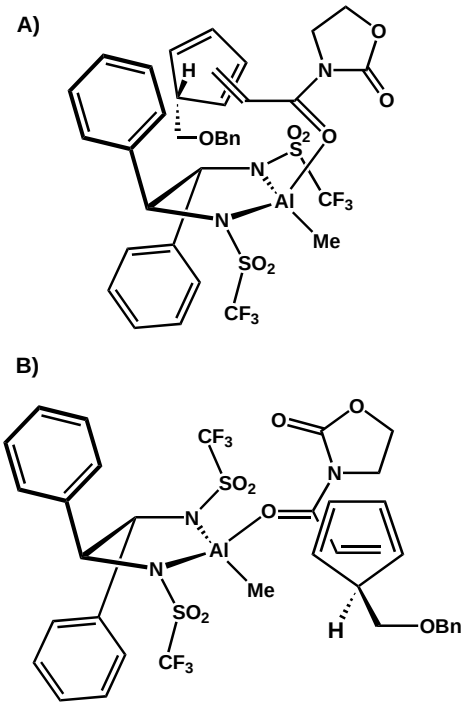
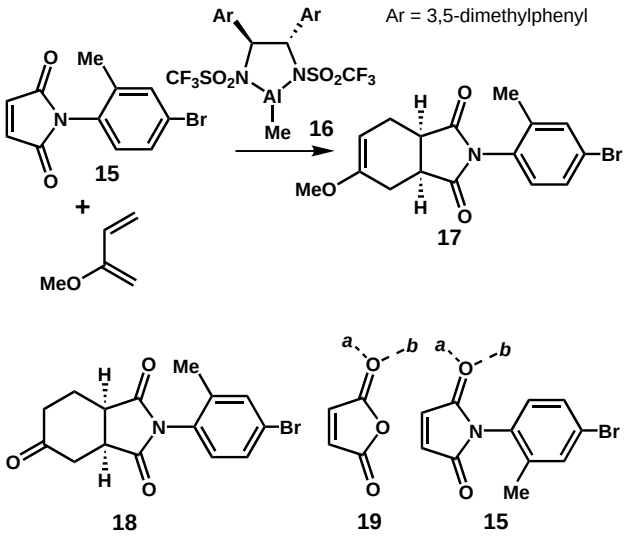


Figure 2. A) Favored pre-transition-state assembly for the formation of **14**. B) Less favored alternative.

which is consistent with the observed enantioselectivity.[17] An alternative transition-state assembly, which cannot be excluded, is shown in Figure 2B. Despite the NMR spectroscopic evidence indicating the geometry of Figure 2A to be favored, it is entirely possible that the main reaction course involves a minor component of the system such as that in Figure 2B. This sort of issue invariably recurs in the analysis of mechanistic pathways for enantioselective reactions, and, indeed, is a central problem in the design of new enantioselective catalysts and reagents. It is one of the most interesting problems in the field of mechanistic chemistry. Further evidence in favor of the transition-state assembly in Figure 2A is the fact that the replacement of the two phenyl groups of the catalyst by cyclohexyl groups results in a catalytic reaction that is not enantioselective. Furthermore, replacement of the two phenyl groups by the more electron-rich 3,5-dimethylphenyl group leads to a catalyst that gives rise to even higher enantioselectivities in various Diels–Alder reactions such as those with *N*-arylmaleimides as dienophiles.

The Diels–Alder reaction of 2-methoxybutadiene with the *N*-arylmaleimide **15** in the presence of catalyst **16** (20 mol%) in toluene at $-78\,^{\circ}C$ affords the adduct **17** in 96% yield with >97% *ee* (Scheme 4), the absolute configuration of which was shown by acidic hydrolysis to the crystalline ketone **18** and X-ray diffraction analysis.[18] *Ortho* substitution on the *N*-aryl group in the maleimide is essential for optimal enantioselectivity, which suggests that steric shielding to prevent complexing of the catalyst to lone pair *b* is crucial. In contrast, the use of maleic anhydride (**19**) instead of **15** in the reaction led to the formation of an adduct with a very low *ee* value (<20%), possibly because of coordination of catalyst **16** with



Scheme 4. Enantioselective synthesis of **17** and **18** through catalyst coordination to electron pair a of **15**.

19 at lone pair *b* or, alternatively, because of a blend of pathways that involves both *a* and *b* coordination.

Low-temperature 2D ^{1}H NMR spectroscopic analysis of the 1:1 complex of the dienophile *N*-(2-*tert*-butylphenyl)maleimide and **16** in CD_2Cl_2 solution at $-73\,^{\circ}C$ revealed the NOE enhancements that are summarized in Figure 3 and led

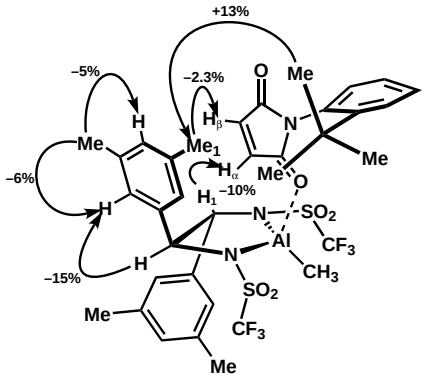


Figure 3. Observed NOE enhancements in the 1:1 complex of **16** with *N*-(2-*tert*-butylphenyl)maleimide.

to the implication of the structure shown in the Diels–Alder pathway.[18] That structure allows optimal $\pi-\pi$ interaction between the Al-coordinated carbonyl group and C2 of the nearby 3,5-dimethylphenyl group. Figure 4A shows the pre-transition-state assembly that leads from this complex as pictured in Figure 3 to the experimentally observed product (e.g. **17**, Scheme 4). Shown in Figure 4B is an alternative pre-transition-state assembly that might also produce a compound such as **17**, but involves severe repulsions and is, therefore, unlikely to be significant.[18]

The utility of the enantioselective Diels–Alder reactions of achiral *N*-arylmaleimides with the chiral catalyst **16** has been demonstrated by an enantioselective total synthesis of gracilins B and C, a pair of structurally novel marine natural products (Scheme 5).[19] The key step is the initial Diels–

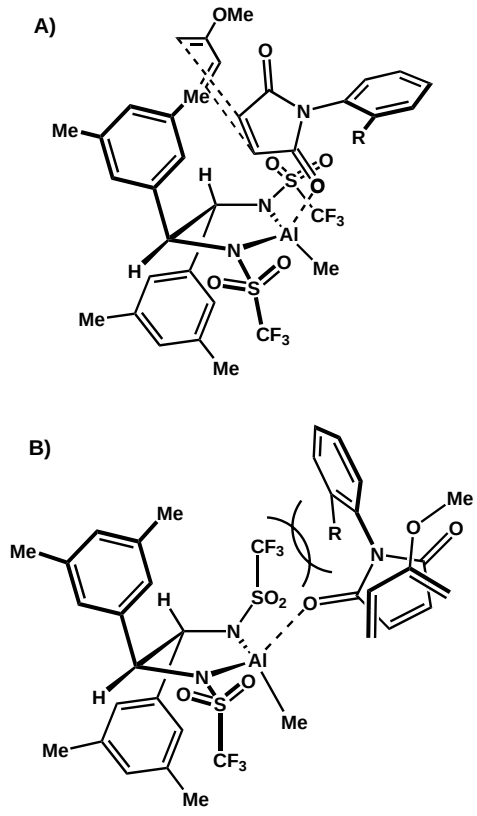
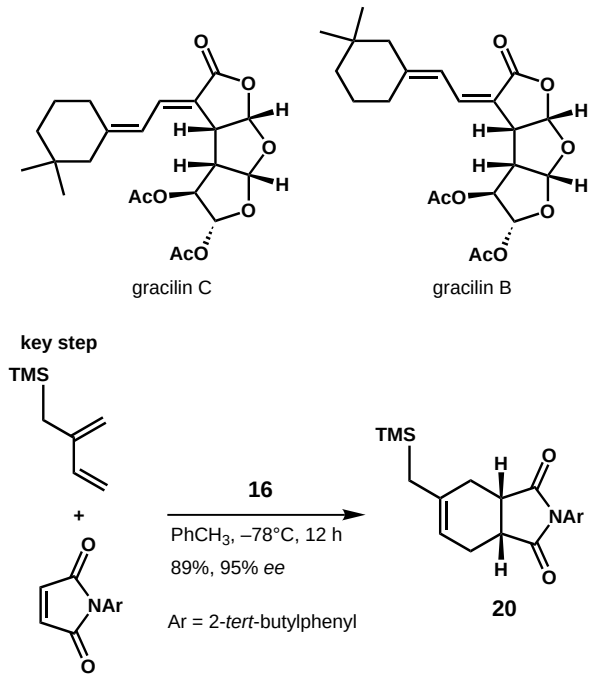


Figure 4. A) Favored and B) disfavored pre-transition-state assemblies for the reaction of 2-methoxybutadiene with **15** and catalyst **16** to form **17**.

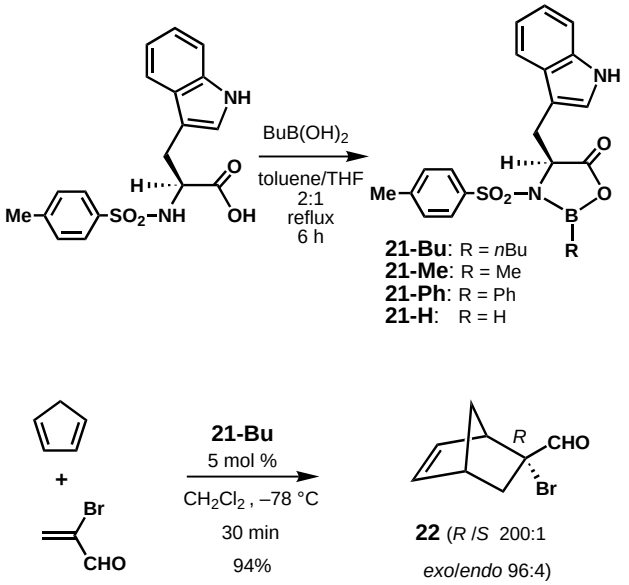


Scheme 5. Establishment of a structural platform (**20**) for the synthesis of gracilins B and C by catalytic enantioselective Diels–Alder reaction. TMS = trimethylsilyl.

Alder reaction using catalyst **16**, which directs the reaction of 2-trimethylsilylmethylbutadiene and *N*-(2-*tert*-butylphenyl)-maleimide to form the chiral adduct **20** (89% yield, 95% *ee*). In the synthesis, the maleimide carbon atoms of **20** become the central tetrahydrofuran subunit of gracilins B and C, and the cyclohexene moiety provides the carbon atoms for the two five-membered rings fused to it. As with the PG syntheses outlined in Schemes 1–3, the six-membered ring formed in the key Diels–Alder step does not remain as such in the final target structure. This is an interesting and now not uncommon "strategic look-ahead" feature of retrosynthetically planned syntheses of complex structures that depends on the remarkable power of the Diels–Alder reaction to create versatile intermediates that can be radically modified en route to the final target.

4. Oxazaborolidines as Chiral Catalysts

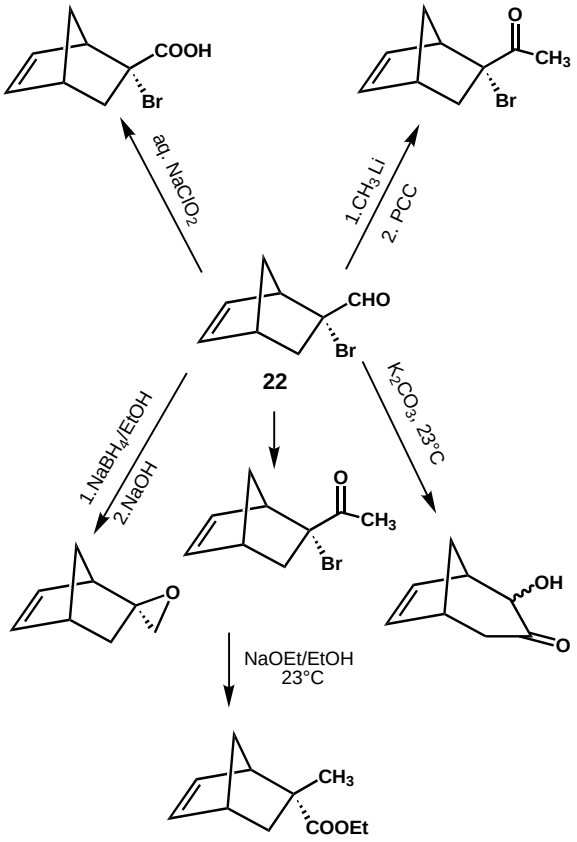
The use of chiral oxazaborolidines as catalysts for the enantioselective reduction of ketones by various boranes has proven to be a valuable synthetic method.[20] The oxazaborolidine system also appeared to have considerable potential for application to other reactions. Our experience with the role of neighboring π-electron-rich aromatic groups to channel Diels–Alder reactions along a specific stereochemical pathway led to a study of *N*-arylsulfonyl tryptophan derivatives as ligands for enantioselective Diels–Alder reactions because of the high π-electron-donating character of the indole ring. (*S*)-*N*-*p*-Toluenesulfonyltryptophan could be converted into the *B*-*n*-butyloxazaborolidine **21-Bu** (Scheme 6).[21] The *B*-methyl (**21-Me**) and *B*-phenyl (**21-Ph**) analogues can be prepared similarly. Furthermore, oxazaborolidine **21-H** · THF is available by reaction of *N*-*p*-toluenesulfonyltryptophan with a solution of BH_3 in THF followed by removal of solvent in vacuo. Just 5 mol% of catalyst **21-Bu** suffices for the acceleration and control of the reaction of cyclopentadiene and 2-bromoacrolein at –78 °C in CH_2Cl_2 to form enantioselectively (ca. 200:1) the 2*R* adduct **22** in high



Scheme 6. Generation of oxazaborolidines from (*S*)-*N*-*p*-toluenesulfonyltryptophan and application to a highly enantioselective Diels–Alder reaction.

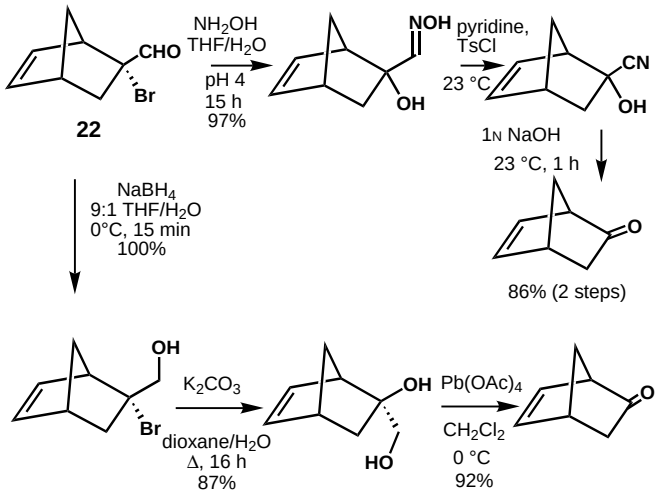
yield.[21] Equally good results are obtained with 2-chloroacrolein. The reaction of 2-methyl- or 2-ethylacrolein with cyclopentadiene affords the 2*R* adduct with 98:2 selectivity. In each of these reactions, the adduct with the *exo* orientation of the formyl group is obtained with high selectivity, for steric reasons. In contrast, the corresponding reaction of cyclopentadiene with acrolein forms the *endo* formyl adduct with opposite and low enantiofacial selectivity (30:70) with respect to the enal under the same conditions.[21] The mechanistic reasons for this difference are discussed below.

The catalytic Diels–Alder process outlined in Scheme 6 is synthetically very useful. The small amount of the diastereomeric *endo* aldehyde that contaminates **22** is easily removed by stirring at room temperature with the equivalent amount of aqueous silver nitrate because it is much more reactive than **22** (owing to the *exo* orientation of the bromine atom) and affords water-soluble products. The bromoaldehyde **22** is a very versatile intermediate as it can be converted into a wide variety of useful products (Scheme 7).



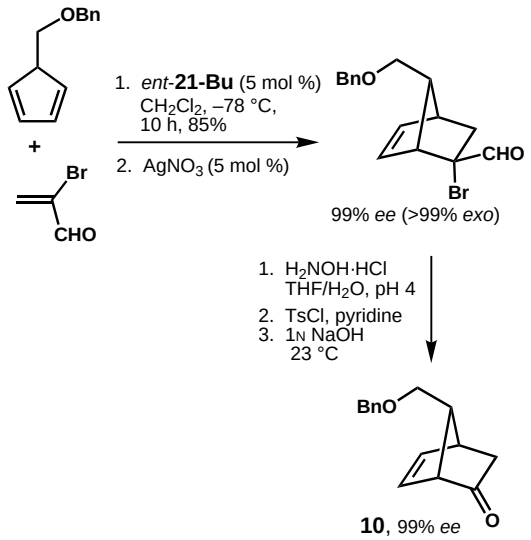
Scheme 7. Some transformations of Diels–Alder adduct **22**. PCC = pyridinium chlorochromate.

Two very efficient methods have been developed for the transformation of **22** into bicyclo[2.2.1]hepten-2-one with high (>99%) enantiomeric purity (Scheme 8). Catalyst **21-Bu** (Scheme 6) is also useful for the promotion of highly enantioselective Diels–Alder reactions of 2-chloro- or 2-bromoacrolein with furan, 2-methylbutadiene, or 2-triisopropylsilyloxybutadiene.[21–24] The application of catalyst *ent*-**21-Bu** to the catalytic enantioselective synthesis of prostaglandins is



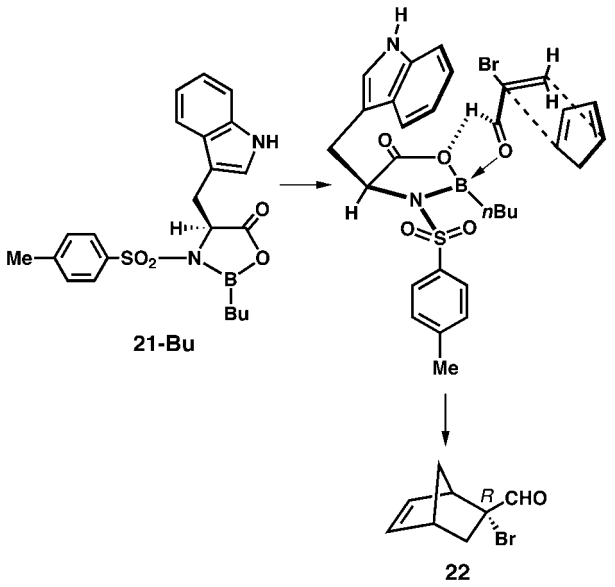
Scheme 8. Efficient syntheses of chiral bicyclo[2.2.1]hepten-2-one. Ts = *p*-toluenesulfonyl.

summarized in Scheme 9.[24] Because of the simplicity and efficiency of this approach it is well suited for large-scale production. The catalyst precursor, (*R*)-*N*-*p*-tosyltryptophan, is cheap and easily recovered for reuse.



Scheme 9. Catalytic enantioselective synthesis of the key prostaglandin intermediate **10**.

The concept that led to the discovery of the enantioselective Diels–Alder catalyst **21** can be summarized as follows: If the dienophilic α,β-enal coordinates to the face of the boron atom in **21** that is *cis* to the 3-indolylmethyl substituent, the π-basic indole unit can stabilize the π-acidic coordinated dienophile through internal π-complexation (Scheme 10). In the complex, the indole and α,β-enal moieties can assume a parallel orientation at the ideal separation (ca. 3.5 Å) for π-interaction. Steric screening by the indole ring would serve to block one face of the α,β-enal from attack by the diene. The pre-transition-state assembly for the reaction of the *s-cis*-α,β-enal complex with cyclopentadiene successfully predicts the correct absolute configuration of the product **22**.



Scheme 10. Proposed pre-transition-state assembly for the enantioselective addition of 2-bromoacrolein and cyclopentadiene catalyzed by **21-Bu**.

Some support for this model is provided by the following experimental results:[24] 1) Addition of 2-bromoacrolein to catalyst **21-Bu** in CH_2Cl_2 at $-78\,^{\circ}C$ results in an immediate orange-red coloration (similar to that of the indole-1,3,5-trinitrobenzene mixture in CH_2Cl_2), thus indicating a π-acceptor/donor interaction. 2) Catalysts in which the 3-indolylmethyl group of **21-Bu** is replaced by phenyl or isopropyl groups are effective in catalyzing the Diels–Alder reaction, but are only weakly enantioselective and actually favor the *enantiomer* of **22**. 3) The catalyst **23-Bu** (Figure 5), which is

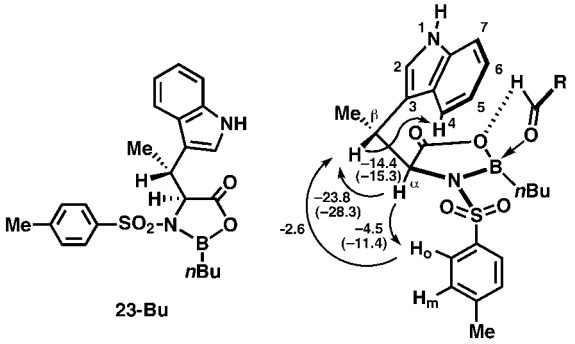


Figure 5. NOE data on the complex of catalyst **23-Bu** with 2-methylacrolein.

analogous to **21-Bu** and is obtained from *N*-tosyl-($\alpha S,\beta R$)-β-methyltryptophan is as effective as **21-Bu** in accelerating and controlling the formation of adduct **22**, as expected for the transition-state assembly shown in Scheme 10. It is even somewhat more enantioselective than **21-Bu** as a catalyst for the reaction of cyclopentadiene and 2-methylacrolein. The geometry of the complex of **23-Bu** with 2-methylacrolein has been probed by NMR spectroscopic studies, especially low-temperature ^{1}H 2D NOESY measurements.[24] The NMR spectral data demonstrate that the catalyst–aldehyde complex is conformationally fairly rigid and that the preferred molecular geometry approximates that depicted in Figure 5 (ca. 55° $HC_\alpha C_\beta H$ dihedral angle). The aldehyde complexation is rapidly reversible on the NMR timescale at 210 K, as indicated by the chemical shifts for the aldehyde moiety (e.g. as compared to the static methylacrolein–BF_3 complex) and its sharp spectrum. The fact that 2-methylacrolein is complexed to the face of the boron atom that is proximate to the indole ring is indicated by the bright orange-red color of the complex at 210 K, which fades upon warming to 250 K and reappears on cooling. This color, which corresponds to a broad absorption band in the 400—600-nm region, indicates π-complexation between the π-donor indole ring and the coordinated aldehyde, consistent with the sort of arrangement shown in Figure 5 and with approximately 3.5-Å spacing between donor and acceptor elements. Further evidence for the proximity of the coordinated aldehyde and indole subunits in the complex derives from the fact that the ^{1}H NMR peak assigned to the CH_3 group of 2-methylacrolein in the 1:1 mixture with **23-Bu** moves *upfield* with decreasing temperature (from $\delta = 1.79$ at 262 K to $\delta = 1.46$ at 188 K in CD_2Cl_2) in contrast to the *downfield* shift of the signal for the CH_3 group in a 1:1 mixture of 2-methylacrolein and BF_3 with decreasing temperature.

Since the NMR spectral data indicate that the association of α,β-enal and catalyst is rapidly reversible on the NMR timescale, it is clear that complexes of both *s-cis* and *s-trans* forms of the α,β-enal are in rapid equilibrium, and that enantioselectivity arises from a faster reaction of the *s-cis* complex **24a** than of the *s-trans* complex **24b** (Figure 6). One

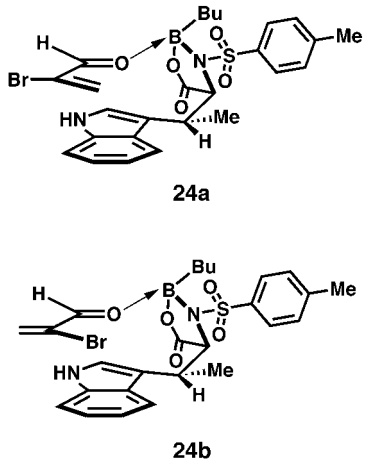


Figure 6. *s-cis* (**24a**) and s-*trans* (**24b**) Complexes of 2-bromoacrolein with Diels–Alder catalyst **23-Bu**.

apparent reason for a preferred pathway via **24a** is that the transition state for the addition of cyclopentadiene involves less steric repulsion than that from **24b**. Specifically, the $sp^2 \rightarrow sp^3$ transformation of the α and β carbon atoms in the transition state from **24b** entails serious repulsion between the α-bromine substituent and the indole ring, which maintains proximity because of the attraction with the electron-deficient formyl carbon atom in the transition state. The transition state from **24a** is free from this repulsion of the bromine atom. The nearest indole atom neighbor of the formyl carbon atom in

complex **24a** or **24b** is the nitrogen atom, a geometry which corresponds electronically (in the HOMO – LUMO sense) to that observed in the crystalline indole – 1,3,5-trinitrobenzene complex,[25] and which is therefore ideal for maintaining proximity between the formyl and indole subunits. In summary, the *s-cis* complex **24a** and the *s-trans* complex **24b** expose opposite faces of the dienophile to attack by the diene, and the enantioselectivity of the reaction is a consequence of the considerable difference in transition-state energies, with that corresponding to reaction from the *s-cis* complex **24a** being the lower. It is of considerable interest in connection with these ideas that, as we have shown for the solid state (by X-ray diffraction analysis) and for solution in CH_2Cl_2 (by low-temperature ^{13}C and ^1H NMR spectroscopic studies), the only observed form of the BF_3 – 2-methylacrolein complex is that with *s-trans* geometry.[26] The fact that the **21-Bu**- or **23-Bu**-catalyzed reaction of cyclopentadiene and acrolein is not very enantioselective is consistent with this analysis for **24a** and **24b** pathways of Figure 6.

Another insight into the fine details of the enantioselective Diels – Alder reactions of α,β-enals with dienes in the presence of the chiral catalysts **21** and **23** emerged from the X-ray crystallographic studies of BF_3 complexes with various formyl compounds, including 2-methylacrolein (see above).[27] These investigations revealed a new kind of hydrogen bond, exemplified generally by structures **25** and **26** (Figure 7).[27b]

25 **26**

Figure 7. Examples of formyl C–H···F and C–H···O hydrogen bonds.

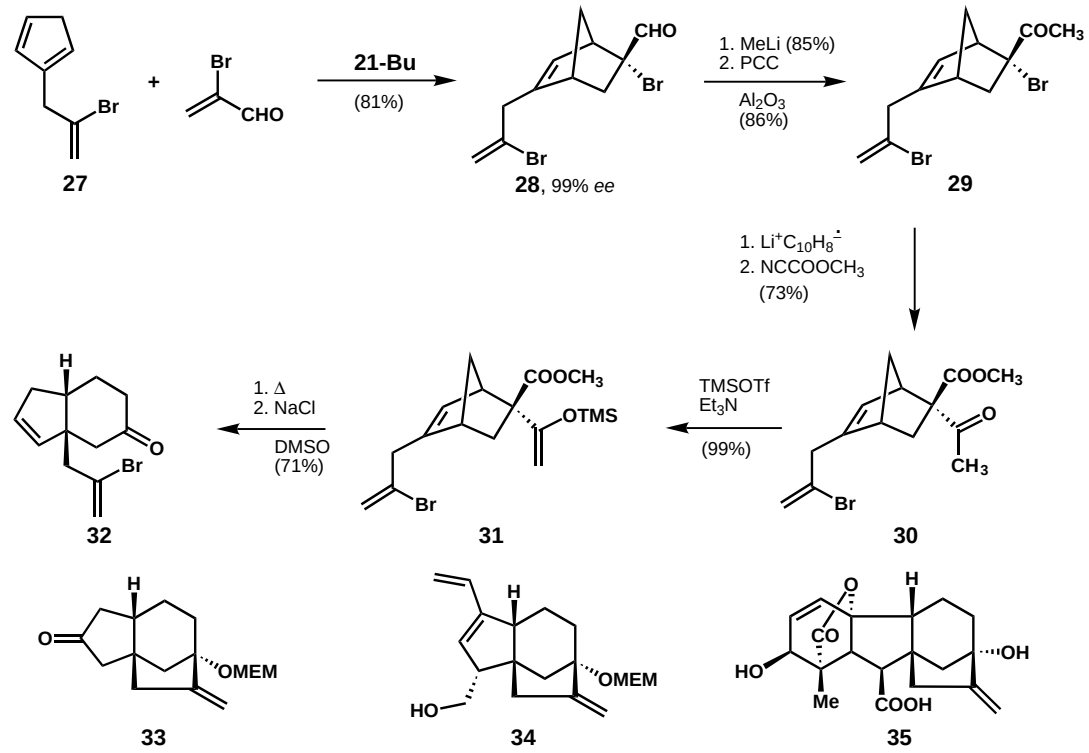
Specifically, the X-ray crystal structures of BF_3 complexes with benzaldehyde, 2-methylacrolein, 2,3-methylenedioxybenzaldehyde, and *N*,*N*-dimethylformamide show a preference for a geometry in which the formyl group and one B–F bond are coplanar (eclipsed) as shown in **25**. The H···F distances in these complexes are 2.35 – 2.36 Å, which is smaller than the sum of the van der Waals radii of the H and F atoms (2.67 Å).[28] The formyl C–H···O hydrogen bonding indicated in **26** has been observed in several different X-ray crystal structures, including that of the complex of catecholboron bromide with *N*,*N*-dimethylformamide.[27b] The formyl C–H···O distances in such complexes range from 2.41 – 2.59 Å and are well below the sum of the van der Waals radii of 2.72 Å.[28] These formyl C–H···F and C–H···O bonds can be thought of as induced or cooperative hydrogen bonds, since coordination of a formyl group at the boron atom simultaneously causes the formyl proton to become more positive and an electronegative atom bonded to the boron atom to become more negative.[29, 30] The formyl C–H···X hydrogen bond appears to be an important organizing factor in many types of Lewis acid catalyzed enantioselective reactions.[29, 30] The pre-transition-state assemblies for oxazaborolidine-catalyzed Diels – Alder reactions of 2-bromoacrolein, which are depicted in Scheme 10 and Figure 5, incorporate the formyl C–H···O hydrogen bond as a key organizing factor in addition to the factors discussed above. The application of the formyl C–H···O hydrogen-bonding idea to the formulation of 3D transition-state structures has led to a clearer understanding of the fundamental reasons for the enantioselectivity of many different catalytic reactions,[30] a fact that adds confidence in its validity and predictive value.

5. Applications of Chiral Oxazaborolidines to Multistep Syntheses

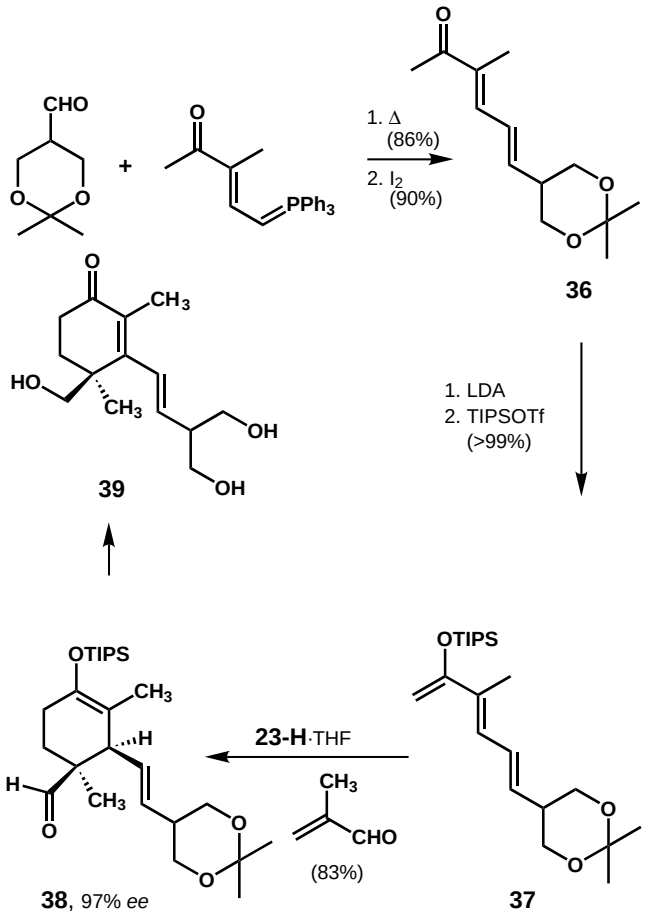
The utility of oxazaborolidine catalysts **21** and **23** in synthesis has been demonstrated by various applications to target-oriented syntheses, three of which are summarized herein. A very effective enantioselective synthesis of the plant hormone gibberellic acid (**35**) is outlined in Scheme 11. The Diels – Alder reaction of diene **27** and 2-bromoacrolein in the presence of catalyst **21-Bu** at $-78\,^\circ C$ provided adduct **28** with 99 % *ee*.[23] α-Bromoaldehyde **28** was converted into the corresponding α-bromo methyl ketone **29**, which underwent reductive methoxycarbonylation to form the *exo* methyl ester **30**. The keto ester **30** was transformed into the enol trimethylsilyl ether **31**. Thermolysis of **31** led to Cope rearrangement to form a β-keto ester, which gave the hydrindanone **32** upon demethoxycarbonylation by heating with NaCl in dimethyl sulfoxide. The transformation of **32** via tricyclic ketone **33** and tricyclic diene **34** to gibberellic acid (**35**) followed the route developed earlier.[31–33]

The key steps in a short enantioselective total synthesis of cassiol (**39**), a scarce and potent antiulcer agent, are depicted in Scheme 12.[23] The diene **37** was produced from the corresponding dienone **36**, which was prepared by the Wittig coupling shown. Diels – Alder reaction of **37** with 2-methylacrolein in the presence of **23-H** · THF as catalyst gave adduct **38** with 97 % *ee* in CH_2Cl_2 at $-78\,^\circ C$. Cassiol (**39**) was accessed from **38** by a simple four-step sequence. The process outlined in Scheme 12 can be used to prepare gram quantities of cassiol conveniently with ordinary laboratory glassware. As predicted from the mechanistic model for the Diels – Alder reaction (Scheme 10), the use of catalyst **21-Bu** produces the adduct with poorer enantioselectivity owing to repulsions between the B–Bu substituent and the terminal substituent on the 1,3-diene subunit. Further, the catalyst **21-H** leads to a somewhat lower *ee* value than does **23-H** (94 vs 97 % *ee*).[23] Finally, the use of the *tert*-butyldimethylsilyloxy analogue of the triisopropylsiloxy triene **37** in the Diels – Alder reaction leads to considerably lower enantioselectivity.[23]

The successful enantioselective synthesis of cassiol (**39**) encouraged us to undertake the more challenging synthesis of eunicenone A (**51**) which is outlined in Scheme 13.[34] The 1,4-disubstituted diene **44** was prepared by starting with geranylgeranylacetylene (**40**). This preparation employed a new silyllithium reagent, 2-anisyldimethylsilyllithium, which was generated from disilane **43**. As in the case of the synthesis of cassiol (Scheme 12), it was necessary to employ the catalyst **23-H** to obtain high enantioselectivity in the Diels – Alder



Scheme 11. Enantioselective total synthesis of gibberellic acid (**35**). DMSO = dimethyl sulfoxide; MEM = methoxyethoxymethyl.

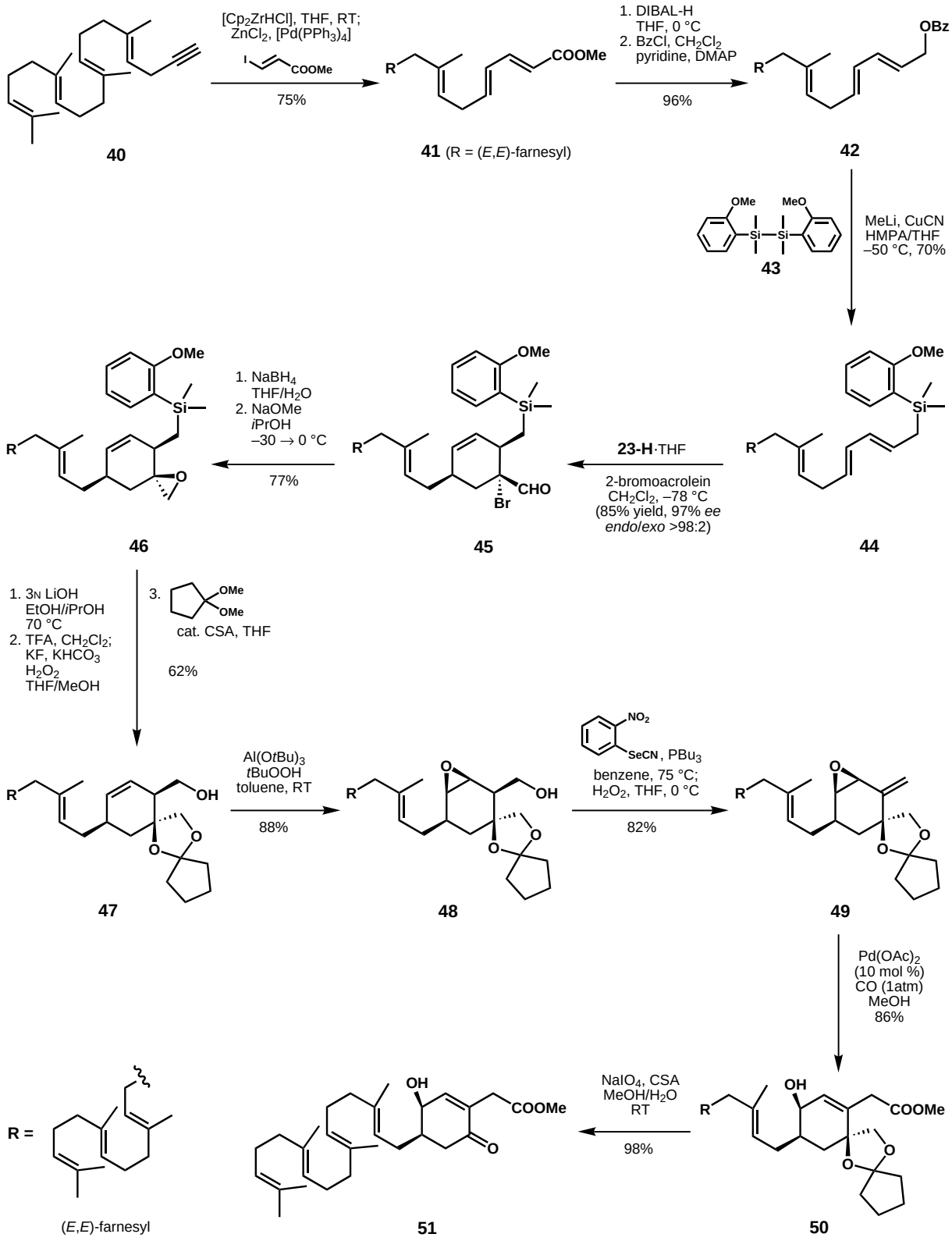


Scheme 12. Enantioselective total synthesis of cassiol (**39**). TIPS = triisopropylsilyl.

reaction of the 1,4-disubstituted diene **44** with 2-bromoacrolein. With this catalyst, in CH_2Cl_2 solution at $-78\,^{\circ}C$, the desired adduct **45** was obtained regiospecifically (as a result of the strong electron-donating effect of the silyl substituent) in 85% yield and 97% *ee*. The α-bromoaldehyde **45** was converted into the epoxide **46** and thence into the hydroxy ketal **47** (Scheme 13). The use of the 2-anisyldimethylsilyl group in the synthesis was beneficial with regard to the yield and enantioselectivity of the Diels–Alder addition and also crucial in the conversion of **46** into **47** because it permitted hydroxydesilylation to be carried out under mild conditions which did not cause unwanted changes in other parts of the substrate.[34] The completion of the synthesis of **51** necessitated the selective epoxidation (**47**→**48**), dehydration (**48**→**49**), catalytic methoxycarbonylation (**49**→**50**) and hydrolytic glycol cleavage (**50**→**51**), all of which are of special note (Scheme 13).

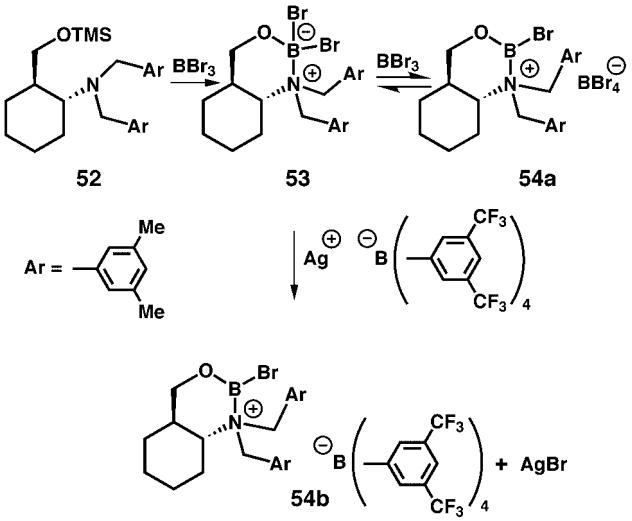
6. Enhancement of Acidity in Chiral Lewis Acids

Attachment of bidentate or higher coordination chiral ligands to a Lewis acidic metal normally reduces the Lewis acidity, since additional electron density generally is transferred from ligand to metal. The development of chirally coordinated Lewis acids of undiminished acidity requires an approach different from that described in the foregoing sections of this review. A successful method for the generation of chiral superreactive Lewis acids has recently been devised (Scheme 14).[35] A key element of this research was the idea that the cationic complex $\mathbf{54}^{+}BBr_4^{-}$ would be a very strong

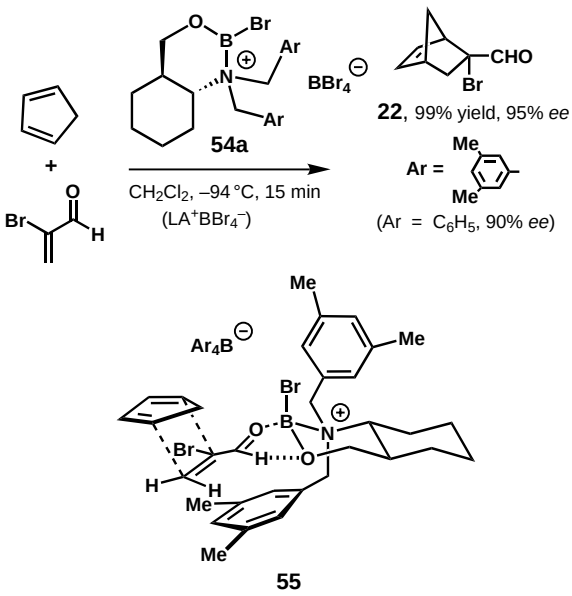


Scheme 13. Enantioselective total synthesis of eunicenone A (**51**). DIBAL-H = diisobutylaluminum hydride; Bz = benzoyl; DMAP = 4-dimethylaminopyridine; HMPA = hexamethyl phosphoramide; CSA = camphorsulfonic acid.

Lewis acid (in the order of acidity of BF_3), even though it carries a bidentate ligand. Reaction of the tertiary amine trimethylsilyl ether **52** with BBr_3 (1 – 1.6 equiv) in CH_2Cl_2 at $-78\,^{\circ}C$ gave bromotrimethylsilane and an equilibrating mixture of the two cyclic oxazaborinanes **53** and **54a**. Treatment of the mixture with a silver tetraarylboronate produced the corresponding tetraarylboronate **54b**. When **54a** or **54b** (10 mol %) is used, cyclopentadiene and a variety of α,β-enals



Scheme 14. Synthesis of cationic Lewis acid **54**.

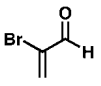
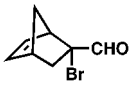
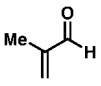
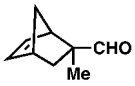
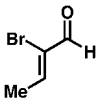
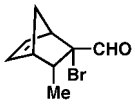
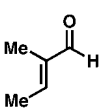
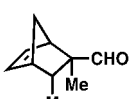
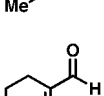
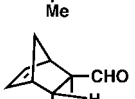


Scheme 15. Enantioselective Diels–Alder reaction of cyclopentadiene and 2-bromoacrolein to form **22**, possibly via pre-transition-state assembly **55**. LA = Lewis acid.[35]

react in CH_2Cl_2, even at $-94\,^{\circ}C$, to form Diels–Alder adducts in very good yield and enantioselectivity (Table 1).

The absolute stereochemical course of the reaction and a likely pre-transition-state assembly **55** are shown in Scheme 15. The conformation of the cationic moiety of **55** corresponds to that determined by X-ray crystallography for the internally hydrogen-bonded hydrobromide of the amino alcohol corresponding to **52** (Scheme 14).[35] The coordinated *s-trans* α,β-enal is oriented for optimal formyl C–H···O hydrogen bonding and π-electron interaction between the formyl carbon atom and the neighboring aromatic donor group. Approach of the diene to the sterically accessible face of the α,β-enal leads to the predominant enantiomer **22**. By the use of catalyst **54b** (but not **54a**) even relatively unreactive dienes such of 1,3-butadiene and 1,3-cyclohexadiene can be converted into Diels–Alder adducts with 2-bromoacrolein in high yield (99%) and with excellent enantioselectivity (93–98% *ee*).[35]

Table 1. Enantioselective Diels–Alder reaction of 1,3-cyclopentadiene with α,β-unsaturated aldehydes[a] catalyzed by **54**.[35]

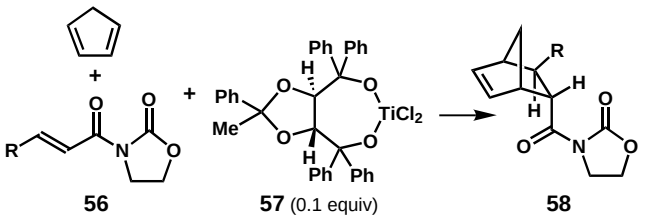
Dienophile	Catalyst	*exo*/*endo*	Yield [%]	*ee* [%] (Configuration)	Product
	**54a**	94:6	99	95 (2*R*)	
	54b	91:9	99	98 (2*R*)	
	**54a**	88:12	99	90 (2*S*)	
	54b	89:11	98	87 (2*S*)	
	**54a**	>98:2	99	91	
	54b	>98:2	99	96	
	**54a**	>98:2	88	89	
	54b	>98:2	97	89	
	**54a**	>98:2	99	96	
	54b	>98:2	97	82	

[a] Reaction conditions: CH_2Cl_2, $-94\,^{\circ}C$, 2 h.

7. Catalytic Enantioselective Diels–Alder Reactions with Bidentate Dienophiles

In principle, another strategy for increasing the reactivity of a catalyst dienophile complex to a degree that allows reaction with unreactive dienes is to replace a monodentate dienophile by a bidentate equivalent. This type of catalytic enantioselective Diels–Alder reaction was demonstrated by the pioneering research of Prof. K. Narasaka and co-workers.[36] A few examples of the Narasaka catalytic enantioselective Diels–Alder process are shown in Scheme 16. Unlike the

The mechanistic and stereochemical ideas that led to the development of the cationic catalyst **54** are valuable, not only because they lead to a rational comprehension of the reasons for enantioselectivity in catalytic Diels–Alder reactions, but also because their predictive power allows the design of new types of effective catalysts. For example, the idea of π-electron-rich aromatic rings for the selective stabilization of specific Diels–Alder transition states led to the selection of the 3,5-dimethylphenyl group for catalyst **54**. It was verified experimentally that **54** is, in fact, a considerably more selective catalyst than the phenyl analogue, in accordance with our guiding principles. One can safely state that at present the discovery of new catalysts is limited more by the time required for experimental testing and execution than by the design process itself. In this sense, the recent advances in catalytic enantioselective reactions are truly revolutionary. Kurt Alder could not possibly have imagined such a level of sophistication for his "diene synthesis."



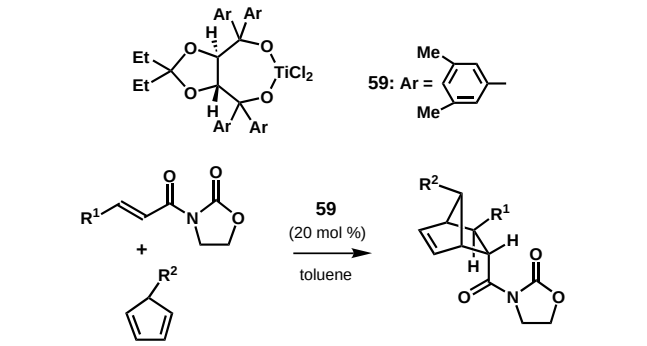
56a: R = H, (93% yield, 96:4 *endo* / *exo*, 64% *ee* (*endo*))
56b: R = Me, (87% yield, 92:8 *endo* / *exo*, 91% *ee* (*endo*))
56c: R = Ph, (72% yield, 88:12 *endo* / *exo*, 64% *ee* (*endo*))

Scheme 16. The catalytic Diels–Alder process of K. Narasaka et al.[36]

Diels–Alder reaction of *N*-acrylyloxazolidinones referred to in Scheme 3 and Figure 3, the Narasaka system involves bidentate coordination of the *N*-acrylyloxazolidinones **56** with catalyst **57** on the pathway to the adducts **58**.[36] Even though the Lewis acid catalyst **57** is not very strong, the bidentate nature of the coordinating dienophile **56** allows sufficient complexation and activation to afford reasonable rates of Diels–Alder reaction at -10 to $-50\,^{\circ}C$. The structure of the catalyst **57**, which is supported by ^1H NMR spectral data,[36] and the bidentate nature of the dienophile **56** strongly suggest that the catalytic process involves the addition of the diene to an octahedral complex of the two.

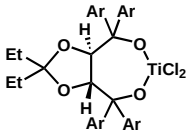
Since there are *ten* possible diastereomeric octahedral complexes, and twice as many if both *s-cis* and *s-trans* conformers of the dienophile are considered, it is quite remarkable that even modest enantioselectivity was observed. Because of the importance of understanding the mechanistic/structural basis for such enantioselectivity, and our interest in the theory of catalytic enantioselective Diels–Alder processes, we extended our investigations to the Narasaka system, with interesting results.[37] As is indicated in Table 2, the replacement of the phenyl group in the Narasaka catalyst by 3,5-dimethylphenyl, which is more π-basic, produced a superior catalyst, **59**, which afforded greatly improved enantioselectivities. The importance of π-basicity in the aryl substituent is further indicated by the results summarized in Table 3 with a series of catalysts in which the aryl group was varied.[37] The superiority of catalyst **59** (Ar = 3,5-dimethylphenyl) over **60** (Ar = 3,5-bis(trifluoromethyl)phenyl or 3,5-dichlorophenyl) provides convincing experimental evidence that the aryl group enhances enantioselectivity as a neighboring π-electron-rich substituent, which simultaneously serves a stabilizing and steric screening function in the transition state. One attractive formulation of the pre-transition-state assembly for the enantioselective pathway in the Narasaka system is depicted in Figure 8.[37]

Table 2. Improved catalyst **59** for the Narasaka Diels–Alder process.



R^1	R^1	T [°C]	t [h]	Yield [%]	*endo*/*exo*	*ee* [%] (*endo*)
H	H	−40	12	80	95:5	94
H	$BnOCH_2$	−30	12	83	>99:1	95
Me	H	−10	8	92	93:7	93
COOEt	H	−30	8	90	81:19	91

Table 3. Enantioselectivity of the reaction of *N*-acrylyloxazolidinone with cyclopentadiene as a function of the Ar group in catalyst **60**.



Ar	T [°C]	t [h]	Yield [%]	*endo*/*exo*	*ee* [%] (*endo*)
Ph[a]	−50	12	70	93:7	73
β-Naphth[a]	−50	36	86	93:7	68
6-MeO-β-Naphth[a]	−50	40	76	90:10	82
3,5-Me_2Ph (**59**)[a]	−40	12	80	95:5	94
3,5-$(CF_3)_2$Ph[b]	−50	20	81	92:8	68
3,5-Cl_2Ph[b]	−50	18	75	93:7	44

[a] Catalyst preparation: 1) diol + $Ti(OiPr)_4$; 2) $SiCl_4$. [b] Catalyst preparation: diol and $TiCl_4$ in diethyl ether, removal of solvent in vacuo, addition of toluene, and evaporation. Naphth = naphthalene.

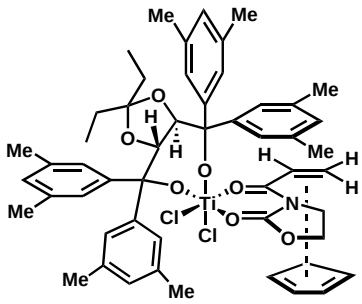


Figure 8. Possible pre-transition-state assembly for the $(RO)_2TiCl_2$-catalyzed Diels–Alder reaction in the Narasaka system.

Another effective catalyst for enantioselective Diels–Alder reactions has been developed for *N*-acrylyloxazolidinones as dienophiles. This catalyst is based on the readily available chiral bisoxazolines **61** and **62** (Figure 9).[38, 39] Metal complexes of these rigid ligands provide catalysts of well-

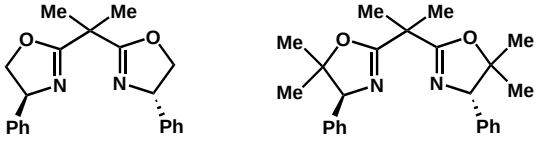
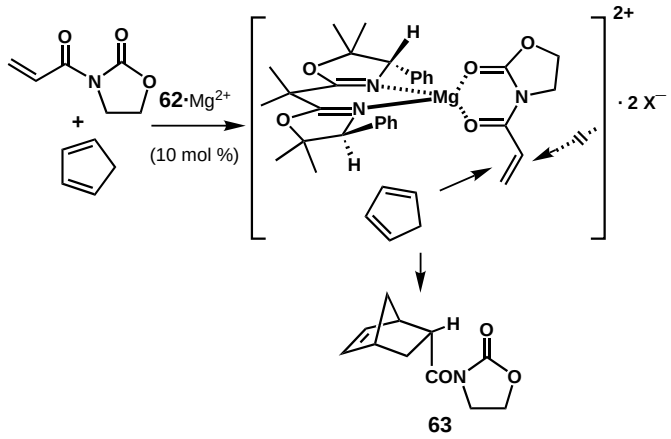


Figure 9. Chiral bisoxazoline ligands for enantioselective metal catalysis.

defined molecular geometry which are very promising for a number of important reactions. The complex of **62** with magnesium iodide or magnesium tetraphenylborate catalyzes the reaction of cyclopentadiene with *N*-acryloyloxazolidinone in CH_2Cl_2 at $-50\,^{\circ}C$ to form the adduct **63** (Scheme 17) with



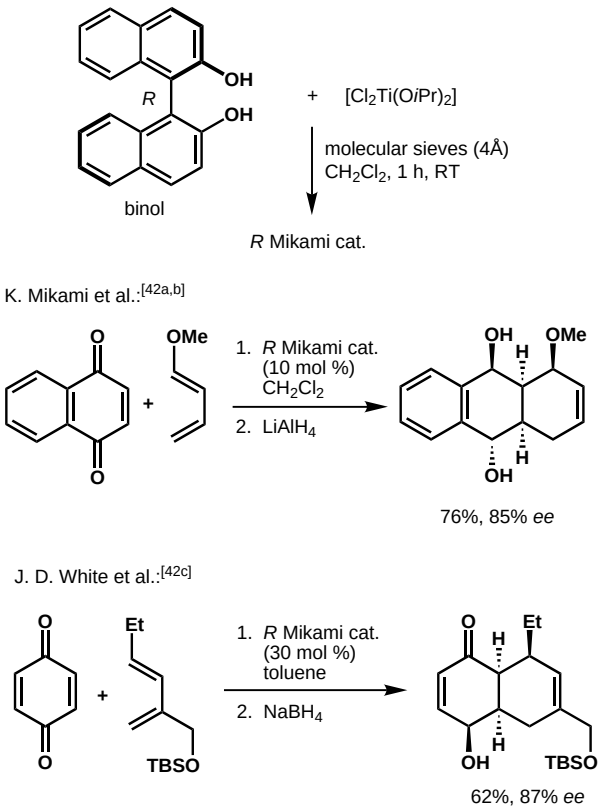
Scheme 17. An enantioselective Diels–Alder reaction catalyzed by the cationic magnesium complex of **62**.[39]

95.5:4.5 enantioselectivity and 98:2 *endo*/*exo* selectivity (84% yield).[39] The absolute stereochemistry of this reaction product agrees with the expectation of the favored pre-transition-state assembly shown in Scheme 17 in which tetrahedral magnesium binds and activates the bidentate dienophile and phenyl screening provides the basis for face-selective addition to the *s-cis* form of the dienophile.[39] The use of the complex of **62** with Cu^{II} to catalyze the same reaction leads to the selective formation of the *enantiomer* of **63**, as expected for a process via the square-planar complex of **61** · Cu^{II} with the dienophile.[40] The complex of **61** with ferric iodide is also an effective catalyst for the synthesis of **63** probably via the octahedral cationic complex [**61** · FeI_2 · *N*-acryloyloxazolidinone]$^+$.[38] An interesting feature of these three catalyst systems is that a cationic form of the metal complex is required to accelerate the reaction. Neutral species are clearly not sufficiently Lewis acidic because of the electron-donating nature of the bidentate bisoxazoline ligand. These findings emphasize the important influence of ligand and charge on catalytic effectiveness.

8. Enantioselective Diels–Alder Reactions with Quinone Monoketals

For more than six decades, the Diels–Alder reaction subtype with quinones as dienophiles has provided a powerful construction for functionalized *cis*-fused decalin systems. Many syntheses of complex natural products have been recorded in which the quinone Diels–Alder reaction has been used to set in place an initial arrangement of rings and stereocenters that paves the way for elaboration of the final target structure by a subsequent series of selective reactions. Examples include some of the most notable achievements in complicated synthetic chemistry, for instance: steroids, reserpine, ibogamine, dendrobine, gibberellic acid, trichodermol, and euonyminol.[41]

In each of these cases, the initial Diels–Alder reaction generated a racemic adduct from which the synthesis of chiral natural product was possible only with an intervening resolution step and the usual loss of material (>50%). For many years, no methods were available for conducting the key quinone Diels–Alder reactions for these syntheses so as to lead enantioselectively to chiral adducts. This gap in methodology is just starting to be filled.[42, 43] Some recent developments, which involve Mikami's catalyst (a red Ti^{IV}–binol complex of unknown structure), are summarized in Scheme 18.[42] The Mikami catalyst appears to be chloride-free and to involve μ-oxo bridges between at least two Ti units. The minimal structure would appear to be the μ_2-bridged possibility binol–Ti(μ_2O,μ_2O)Ti–binol.



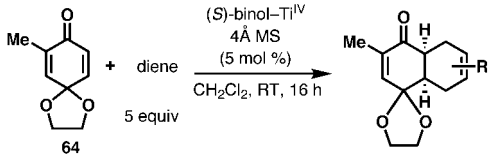
Scheme 18. Preparation of Mikami's catalyst and application to enantioselective quinone Diels–Alder reactions. TBS = *tert*-butyldimethylsilyl.

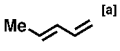
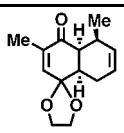
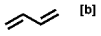
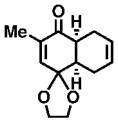
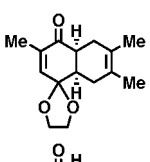
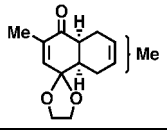
Recent investigations in our laboratories have focused on the use of 1,4-quinone monoketals (which are essentially 1,4-quinone equivalents) rather than the corresponding quinones, for reasons which include the following: 1) the monoketals are expected to be more Lewis basic; 2) the monoketals would provide adducts that do not undergo facile aromatization, in contrast to the 1,4-quinone adducts, which are known to aromatize readily and to be difficult to handle (unless at least one of the 6,6-fusion substituents is a non-hydrogen angular group); 3) the monoketals lead to adducts in which one of the two carbonyl groups of the 1,4-quinone is already protected, thus simplifying the task of further selective transformations;

and 4) the monoketals are accessible synthetically either from oxidative *p*-ketalization of phenols or from transketalization starting from 4,4-dimethoxy-2,5-cyclohexadienones.[44] The 4,4-dimethoxy-2,5-cyclohexadienones themselves did not serve as useful dienophiles. Much better results were obtained with ethylene monoketals (e.g. **64** (Table 4)) and 3,3-dimethyl-1,3-diol-derived (neopentyl) ketals (e.g. **65** (Table 5)) with the binol–Ti^{IV}-based catalyst in the presence of molecular sieves.[45] Very good yields, enantioselectivities, and *endo/exo* selectivities were obtained. The use of 4-Å molecular sieves that contain water was critical, in accordance with previous observations for catalytic ene reactions.[42, 46, 47] In the absence of molecular sieves or in the presence of molecular sieves that had been desiccated by heating to 150 °C under vacuum, the reactions were slower and less efficient. The results for ethylene ketal **64** are summarized in Table 4 for the *S* Mikami catalyst (5 mol %) in CH_2Cl_2 at 23 °C. Enantioselectivities (81–84 % *ee*) were somewhat lower for butadiene and 2,3-dimethylbutadiene than for (*E*)-1,3-pentadiene (98 %). Even better results were obtained with neopentyl monoketal **65** than for ethylene ketal **64** (Table 5).

The quinone monoketal Diels–Alder adducts are more useful in synthesis than the corresponding quinone adducts because they are more stable and already monoprotected so as to differentiate the two carbonyl functions. Thus, adduct **66** is simply and selectively converted into the *trans*-fused isomer **67** and into the bridged iodo ether **68**; these operations are not feasible for the quinone adduct corresponding to **66** (Scheme 19).[44] The advances described herein on the enantioselective Diels–Alder reactions of dienes with quinone monoketals by using the Mikami catalyst provide great incentive to develop other catalysts for these and related systems, for example simple α,β-enones, which present a unique standing challenge.

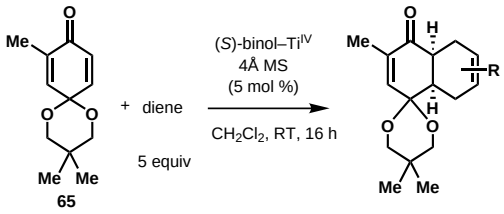
Table 4. Enantioselective Diels–Alder reactions of quinone monoketal **64** with various dienes.

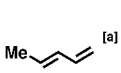
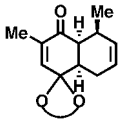
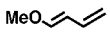
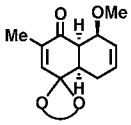
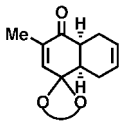
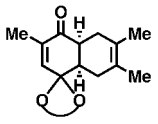
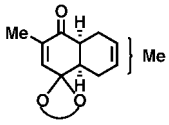


Diene	Product	Yield [%]	*ee* [%]
 [a]		97	98
 [b]		91	81
		88	84
		91	84, 72[c]

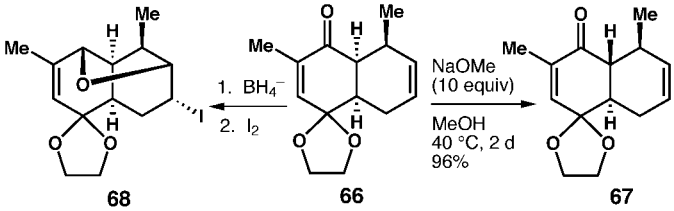
[a] *endo/exo* >98:2. [b] Reaction at −20 °C for 72 h. [c] Mixture of regioisomers (53:47).

Table 5. Enantioselective Diels–Alder reactions of quinone monoketal **65** with various dienes.



Diene	Product	Yield [%]	*ee* [%]
 [a]		90	99
		90	99
 [b]		95	95
		95	90
		91	96, 91[c]

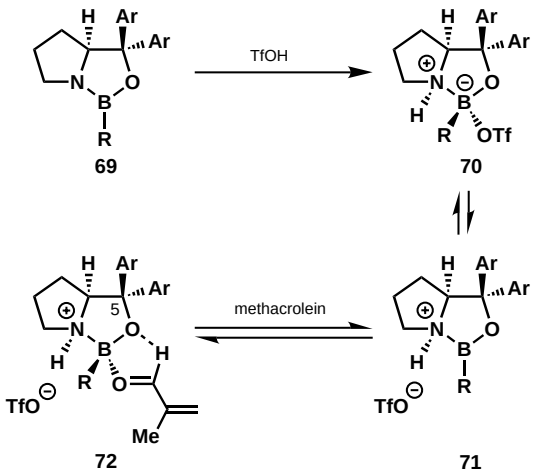
[a] *endo/exo* >99:1. [b] Reaction at −20 °C for 72 h. [c] Mixture of regioisomers (56:44).



Scheme 19. Some transformations of chiral quinone monoketal adduct **66**.

9. Asymmetric Diels–Alder Reactions Catalyzed by a Triflic Acid Activated Chiral Oxazaborolidine

Chiral oxazaborolidines **69** (Scheme 20) are very useful catalysts (e.g. with R = H, Me, *n*Bu, or Ar) for the enantioselective reduction of ketones by using $BH_3 \cdot THF$ or catecholborane as stoichiometric reductants, a reaction that is of interest because of its wide scope and the extraordinary



Scheme 20. Transformation of the chiral oxazaborolidine **69** to the chiral cationic Lewis acid **71**. TfOH = triflic acid = trifluoromethanesulfonic acid.

predictive power of the underlying mechanistic pathway.[20, 48] We have recently devised a new type of catalytic enantioselective Diels–Alder reaction, which was inspired by this process and which employs a proline-derived oxazaborolidine of type **69** as a precatalyst and triflic acid as an activator to generate a potent cationic Lewis acid.[49] In essence, a very strong protic acid is used to create a very strong Lewis acid, the reverse of the formation of a proton superacid from a Lewis acid, for example, $HF + BF_3 \rightarrow H^+BF_4^-$.

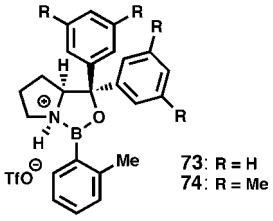
The reaction of the oxazaborolidine **69** (R = Me, Ar = C_6H_5) with anhydrous triflic acid (ratio 1:1) in CH_2Cl_2 (or CD_2Cl_2) results in the formation of an equilibrium mixture of two N-protonated species **70** and **71** (Scheme 20) as indicated by low-temperature (−80 °C) ^{1}H NMR spectroscopic analysis. No appreciable amount of triflic acid appears to be present with these 1:1 mixtures of **69** and triflic acid. The ratio **70**/**71** in CD_2Cl_2 at −80 °C is approximately 1.5:1. The interconversion of **70** and **71** is slow on the ^{1}H NMR timescale, but becomes rapid at 0 °C, the coalescence temperature.

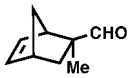
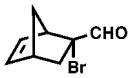
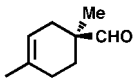
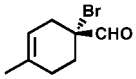
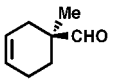
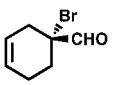
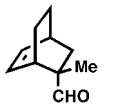
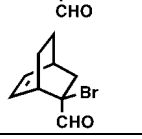
The Lewis acidity of **71** was expected to be high because of its cationic character[35] and because its formation requires the very strong triflic acid (methanesulfonic acid generates relatively weak catalytic activity from **69**). These findings place **71** and triflic acid near one another on an effective acidity scale. In fact, our results on catalysis of Diels–Alder reactions show that triflic acid and **71** lead to similar reaction rates at −94 °C.

The rationale for the application of **71** to the enantioselective catalysis of Diels–Alder reactions of α,β-unsaturated aldehydes is derived from previous research on Lewis superacids and catalytic enantioselective reaction pathways.[30, 35] Coordination of the α,β-enal (e.g. methacrolein) to **71** was expected to lead to an organized formyl C–H···O hydrogen-bonded complex **72** (Scheme 20).[30, 35] The electron-deficient α,β-enal subunit in complex **72** can attract the *cis* Ar group on C5 of the oxazaborolidine ring by a π–π donor–acceptor interaction (see below). This attractive interaction will persist in the Diels–Alder transition state since the formyl carbon atom maintains its strong positive charge all along the reaction pathway.

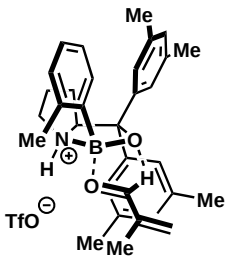
It was determined from studies to optimize the structure of the catalyst **71** that the best results were obtained for **73** (R = *o*-tolyl, Ar = phenyl) and **74** (R = *o*-tolyl, Ar = 3,5-dimethylphenyl) (Table 6). Most Diels–Alder reactions were fast, even at −95 °C in CH_2Cl_2 as solvent with 6 mol% of catalyst and 2-methyl- or 2-bromoacrolein as test dienophiles. As indicated in Table 6, very good yields and enantioselectivities were found with catalysts **73** or **74** in 14 cases, and even unreactive dienes such as 1,3-butadiene and 1,3-cyclohexadiene gave satisfactory results.

Table 6. Diels–Alder reactions of 1,3-dienes with 2-methacrolein or 2-bromoacrolein (CH_2Cl_2) catalyzed by **73** or **74**.



Diene	Product	Catalyst (mol%)	T [°C], t [h]	yield [%] (*exo*/*endo*)	*ee* [%]
		**73** (6) **74** (6)	−95, 1 −95, 1	99 (91:9) 97 (91:9)	91 96
		**73** (6) **74** (6)	−95, 1 −95, 1	99 (91:9) 97 (91:9)	92 96
		**74** (6)	−78, 13	96	97
		**73** (6) **74** (6)	−95, 1 −95, 1	98 98	97 97
		**74** (20)	−78, 24	85	94
		**73** (6) **74** (6)	−95, 2 −95, 2	95 97	96 96
		**73** (20) **74** (20)	−78, 24 −78, 24	91 (5:95) 58 (6:94)	92 92
		**73** (6) **74** (6)	−95, 2 −95, 2	81 (6:94) 85 (7:93)	92 92

The absolute stereochemical course of the Diels–Alder reactions represented in Table 6 can be understood in terms of the type of catalyst–aldehyde complex shown in **73** and the pre-transition-state assembly depicted in **75**. In **75** the formyl carbon atom is situated above C2 of the nearby 3,5-dimethylphenyl group, which effectively screens the rear face of the complexed *s*-



trans α,β-enal from attack by the diene component. Addition of the diene to the *Re* (front) face of the α,β double bond leads to the enantiomers shown in Table 6.

10. Conclusions

In recent years, the power of the Diels – Alder reaction has been greatly increased as a result of the development of catalytic enantioselective versions, as described herein. Yet, it is likely that there is much more to learn with regard to new catalysts, further extensions to the many types of Diels – Alder partners, and the determination of the fine mechanistic details of these highly intricate processes. The ultimate goal is clear: to control the enantioselectivity of any Diels – Alder reaction that generates a chiral product from achiral diene and dienophile precursors. The realization of all of these objectives would be a tremendous accomplishment and an eloquent testimony to the intellectual prowess of the community of synthetic chemists.

It is a great pleasure to thank the many wonderful coworkers who have accompanied me on the scientific journey that is retraced herein. Their names appear in the references cited. However, special mention needs be made to the following stalwart members of the Corey research family: Harry Ensley, Yi Bin Xiang, Stanislas Pikul, Sephar Sarshar, Michael Letavic, Teck-Peng Loh, Angel Guzman-Perez, Mihai Azimioara, Jeffrey Rohde, Yujiro Hayashi, Noboyuki Imai, Thomas Lee, Matthius Bruening, and Takanori Shibata. I am also grateful to Pfizer Inc. for generous financial support over the years.

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[2] K. Alder in *Newer Methods of Preparative Organic Chemistry*, Interscience, New York, **1948**.
[3] N. Anand, J. S. Bindra, S. Ranganathan, *Art in Organic Synthesis*, Holden-Day, San Francisco, **1970**.
[4] W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, **1990**.
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