Enantioselective Synthesis Based on Catalysis by Chiral Oxazaborolidinium Cations

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Outline

1. Introduction

During the 1980s, proline-derived chiral oxazaborolidines of general structure **1** (**Figure 1**) were introduced as catalysts for enantioselective reduction of prochiral ketones. This process, sometimes referred to as the CBS (Corey-Bakshi-Shibata) reduction,[1] has subsequently been applied to a wide range of ketonic substrates. A useful feature of the CBS reduction methodology is the availability of a well-defined stereochemical model for reduction (**2** in Figure 1). The application of this methodology for the asymmetric synthesis of a wealth of natural products and non-natural molecules has been reviewed previously.[2]

The chiral oxazaborolidines represented by **1** can also be used to generate a new class of powerful Lewis acids by activation with a strong protic or Lewis acid.[3] Such activated cationic oxazaborolidines are extremely effective catalysts for a wide range of asymmetric transformations. In this review, we provide an overview of the formation and utility of cationic oxazaborolidines as chiral catalysts and their application to the asymmetric synthesis of a wide variety of complex natural products and non-natural structures, especially by Diels-Alder addition.

2. Proton-Activation of Oxazaborolidines

Although various Lewis acids (e.g. BF_3, $SnCl_4$, $ZnCl_4$, $AlCl_3$) were found not to be useful for the coordinative activation of **1**, the strong protic acid, triflic acid (TfOH), turned out to be a powerful activator of **1a**: ^{1}H NMR measurement of a 1:1 mixture of **1a** and TfOH in $CDCl_3$ at -80 °C revealed the presence of two protonated species **3** and **4**, in a ratio of ca. 1.5:1 at about 0.05M concentration (**Scheme 1**).[4] Complete protonation required a very strong protic acid; acids such as methanesulfonic or benzenesulfonic acids were too weak. The Lewis acidity of **4**, expected to be high from the fact that a very strong protic acid is required to produce it from **1a**, was fully confirmed by subsequent studies. The equilibrium between **3** and **4** is facile (although slow on ^{1}H NMR timescale at -80 °C) and so the mixture is equivalent to the cation **4**.

2.1. Diels-Alder Reactions of α,β-Enals

The protonated oxazaborolidine **4** was first found to be an extremely powerful catalyst for the Diels-Alder reaction of 2-methacrolein or 2-bromoacrolein with a variety of dienes of quite different reactivity as shown in **Table 1**.[4] Optimization of the catalyst structure in terms of yield and enantioselectivity of this reaction revealed an *o*-tolyl group on boron to be the substituent of choice.[4] The C-aryl substituent 3,5-dimethylphenyl (*m*-xylyl or mexyl) was somewhat superior to phenyl (see Table 1), likely because of its greater basicity as a neighboring π-rich aromatic group.[4]

The highly enantioselective formation of the Diels-Alder adducts shown in Table 1 is considered to result from the preferred pre-transition-state assembly **6** (Figure 2), for which there is considerable precedent in our previous work.[5-7] The complex of the catalyst with 2-substituted acrolein has been proposed to involve an electrostatic interaction between the formyl hydrogen and the oxygen on boron that is synergistic with the coordination of formyl oxygen to boron. In the pre-transition-state assembly **6** the formyl carbon, rendered more positive due to the carbonyl coordination to boron, lies at Van der Waals contact distance (3.5 Å) above an *ortho*-carbon of the nearby mexyl group. This attractive interaction of the coordinated C=O and the neighboring π-rich benzenoid ring

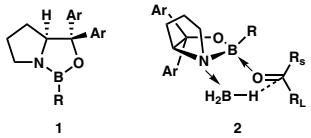
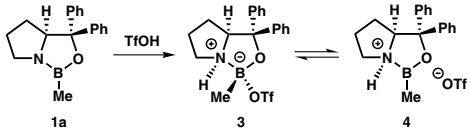
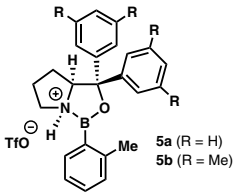


Figure 1. Chiral Oxazaborolidine **1** and the Stereochemical Model for CBS-Reduction. *(Ref. 2)*

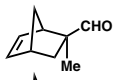
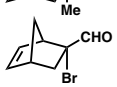
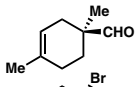
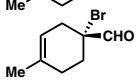
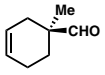
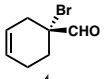
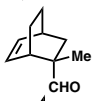
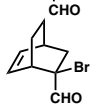


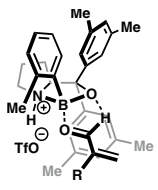
Scheme 1. Protonation of Oxazaborolidine **1a** with Triflic Acid. *(Ref. 4)*

Table 1. Diels-Alder Reactions of 1,3-Dienes with 2-Methacrolein or 2-Bromoacrolein Catalyzed by Proton-Activated Oxazaborolidines **5a** or **5b**. *(Ref. 4)*



5a (R = H)
5b (R = Me)

Product	Catalyst (mol %)	Temp (°C) Time (h)	Yield (%) (*exo*/*endo*)	*ee* (%)
	**5a** (6)	-95, 1	99 (91:9)	91
	5b (6)	-95, 1	97 (91:9)	96
	**5a** (6)	-95, 1	99 (91:9)	92
	5b (6)	-95, 1	99 (91:9)	96
	**5b** (6)	-78, 13	96	97
	**5a** (6)	-95, 1	98	97
	5b (6)	-95, 1	98	97
	**5b** (20)	-78, 24	85	94
	**5a** (6)	-95, 2	95	96
	5b (6)	-95, 2	97	96
	**5a** (20)	-78, 24	91 (5:95)	92
	5b (20)	-78, 24	58 (6:94)	92
	**5a** (6)	-95, 2	81 (6:94)	92
	5b (6)	-95, 2	85 (7:93)	92



6

Figure 2. Pre-transition-state Assembly for Enantioselective Diels-Alder Reactions of 2-Substituted α,β-Enals. *(Ref. 4)*

is maintained in the transition state even as the diene addition takes place to the α,β-bond of the enal. That π-π attractive interaction screens the rear face of the complexed *s-trans* α,β-enal and directs addition to the front face of the dienophile as shown in **6**. The mechanistic model exemplified by **6** is a reliable predictor of the absolute stereochemical course of Diels-Alder reactions of α,β-enals under catalysis by cationic oxazaborolidines.

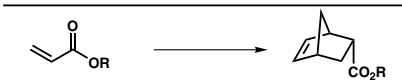
2.2. Diels-Alder Reactions of Other α,β-Unsaturated Carbonyl Compounds

The application of proton-activated oxazaborolidines **5a-b** was found not to be limited to α,β-enals as dienophiles and extended to a variety of α,β-unsaturated carbonyl compounds including α,β-unsaturated esters, lactones, ketones and especially quinones.[8] Our initial studies demonstrated that acrylate and crotonate esters are satisfactory dienophiles when cyclopentadiene was used as the diene (**Table 2**). However, due to the lower reactivity of crotonates relative to the corresponding acrylates, it is advantageous to use more reactive trifluoroethyl ester rather than methyl and ethyl ester.

The dienophile face selectivity for Diels-Alder addition to acrylate and crotonate esters was found to be opposite to that for α,β-enals. A likely reason for this divergent behavior emerged from X-ray crystallographic studies of BF_3-complexes of α,β-unsaturated esters and enones. As summarized in **Figure 3**, one of the fluorines on boron and the α-C-H of the unsaturated carbonyl compounds is in close proximity and within Van der Waals contact distance (2.67 Å).

These data suggest the possibility that the face selectivity observed for α,β-unsaturated esters and enones that possess an α-C-H group may be due to a pre-transition-state assembly of type **7** (**Figure 4**), which clearly would lead to opposite face-selectivity than the corresponding formyl C-H···catalyst interaction as in **6**.

Table 2. Diels-Alder Reactions of Acrylates and Crotonates with Cyclopentadiene Catalyzed by **5a-b**. *(Ref. 8)*

Dienophile R	Cat (mol %)	Temp (°C) Time (h)	Yield (%) (*endo*/*exo*)	*ee* (%)
				
H	**5a** (20)	-35, 1.5	99 (95:5)	98
Et	**5b** (20)	-20, 16	96 (97:3)	>99
				
Et	**5b** (13)	+4, 72	46 (91:9)	>98
CH_2CF_3	**5a** (20)	-20, 16	93 (95:5)	>98

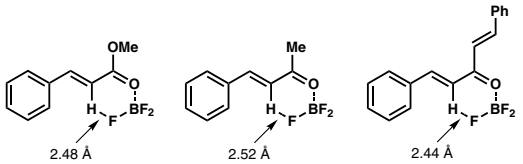


Figure 3. α-C-H to Fluorine Distances in BF_3 Complexes of α,β-Unsaturated Carbonyl Compounds as Determined by X-Ray Crystallography. *(Ref. 8)*

The generality of the catalytic enantioselective Diels-Alder reaction mediated by **5a** and **5b** and the α-CH···catalyst binding mode of reaction are further supported by the results summarized in **Figure 5**, which shows the products derived from cyclopentadiene and a variety of α,β-unsaturated carbonyl compounds. The utility of cyclic α,β-enones and quinone monoketals in the catalytic Diels-Alder processes is noteworthy, not only because of the good yields and enantioselectivities, but also because other chiral Lewis acids are ineffective for these substrate classes.

One limitation of the triflic acid-activated oxazaborolidines stems from their instability at temperatures above 4 °C, which significantly limits the scope of the Diels-Alder reactions within reactive dienes and/or dienophiles. Consequently, triflimide, $(CF_3SO_2)_2NH$ (known to be comparable in acid strength[9] to triflic acid), was investigated as activating agent. Fortunately, protonated triflimide catalysts were found to be sufficiently stable to be useful at 25-40 °C.[10] The development of triflimide-activated catalysts **8a-b** (**Figure 6**) has broadened the scope of the Diels-Alder reaction to include many less reactive partners and to allow shorter reaction times.

An instructive comparison of triflic acid- and triflimide-activated catalysts is shown in **Table 3**. The order of reactivity of α,β-unsaturated esters as dienophiles with **5a** or **8a** is acrylate > crotonate > cinnamate and for a given acid the trifluoroacetate ester is markedly more reactive then the methyl or ethyl ester.

The power of triflimide-activated catalysts **8a-b** in promoting asymmetric Diels-Alder reactions with less reactive dienes was further exemplified by using diethyl fumarate and trifluoroethyl acrylate as dienophiles (**Figure 7**).

The development of triflimide-activated catalysts has enabled the formation of cycloaddition products derived from less reactive 2,3-dimethylbutadiene (**Figure 8**). Even though products were obtained with somewhat reduced enantioselectivity, this is a real advance in extending the scope of the asymmetric Diels-Alder reaction toward less reactive dienophiles.

The effective range of the catalysts **5** or **8** also extends to heterodienes such as those in the furan series.[11] The use of furans as dienes for Diels-Alder reactions had been restricted due to their low reactivity and the reversibility of addition which has resulted in poor conversions and/or undesirable side reactions. Excellent results were obtained for the Diels-Alder reactions of a number of furan derivatives with trifluoroethyl acrylate using proton-activated catalysts **5a** and **8a**, as summarized in **Figure 9**.[11]

2.3. Diels-Alder Reactions of Quinones

Compared to other α,β-unsaturated carbonyl compounds, quinones are even better partners in these catalytic Diels-Alder

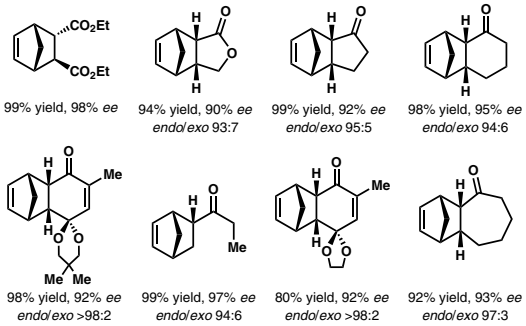


Figure 5. Examples of Diels-Alder Adducts from Reactions which Proceed Through α-CH•••Catalyst Binding. *(Ref. 8)*

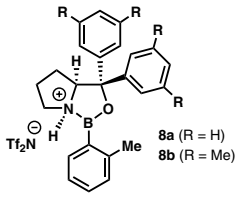
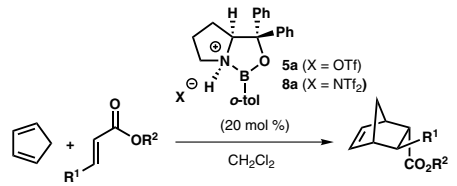


Figure 6. Triflimide-Activated Oxazaborolidines **8a** and **8b.** *(Ref. 10)*

Table 3. Comparison of Triflic Acid and Triflimide-Activated Catalysts in Diels-Alder Reactions. *(Ref. 10)*



R^1	R^2	Cat	Temp (°C) Time (h)	Yield (%) (*endo*/*exo*)	*ee* (%)
Me	Et	**5a**	4, 72	46 (91:9)	>98 (*endo*)
Me	Et	**8a**	20, 16	94 (89:11)	97 (*endo*)
Ph	CF_3CH_2	**5a**	4, 72	27 (85:15)	95 (*endo*), 94 (*exo*)
Ph	CF_3CH_2	**8a**	20, 16	79 (83:17)	93 (*endo*), 96 (*exo*)
Ph	CF_3CH_2	$EtAlCl_2$	20, 16	86 (88:12)	-

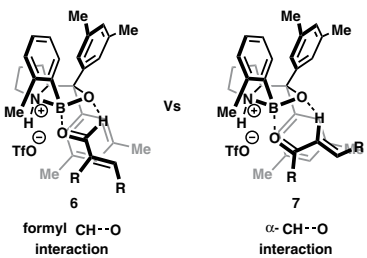


Figure 4. Difference in Stereochemical Model for the Diels-Alder Reaction of α,β-Enals and Other α,β-Unsaturated Carbonyl Compounds with Catalyst **5b.** *(Ref. 8)*

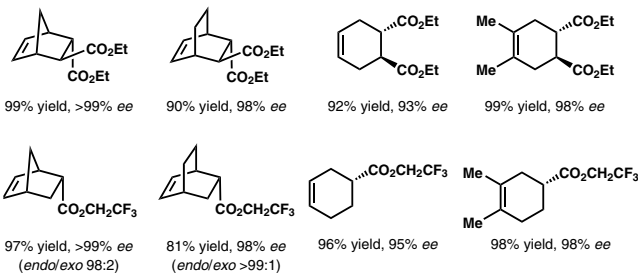


Figure 7. Assorted Examples of Diels-Alder Products Derived from Diethyl Fumarate and Trifluoroethyl Acrylate Using Triflimide-Activated Catalysts **8a** or **8b.** *(Ref. 10)*

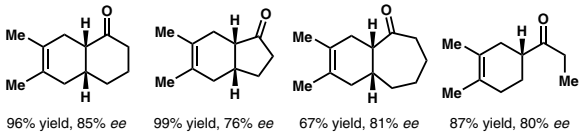


Figure 8. Diels-Alder Products Derived from α,β-Enones and 2,3-Dimethylbutadiene Catalyzed by Triflimide-Activated Catalysts **8a** or **8b**. *(Ref. 10)*

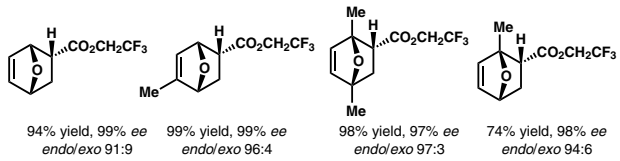


Figure 9. Products of Diels-Alder Reactions between Trifluoroethyl Acrylate and Furans Using Catalyst **5a** or **8a.** *(Ref. 11)*

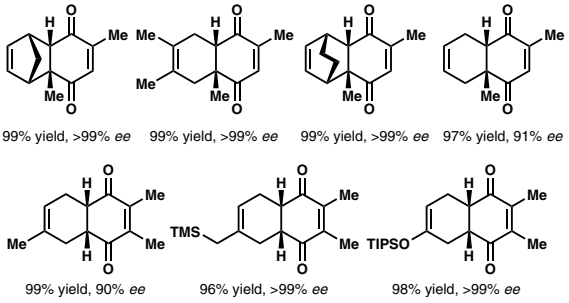
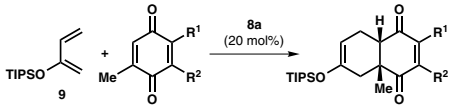
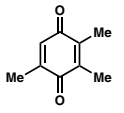
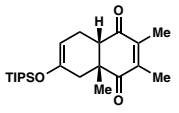
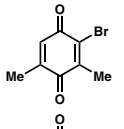
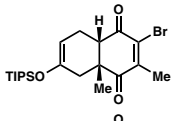
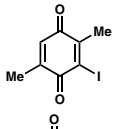
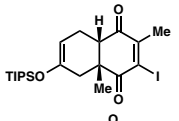
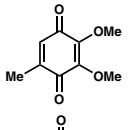
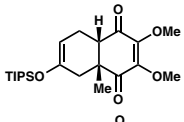
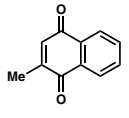
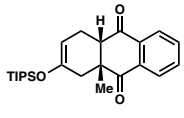


Figure 10. Diels-Alder Products Derived from 2,5- and 2,3-Dimethyl 1,4-Benzoquinones with Various Dienes Obtained Using Triflimide-Activated Catalysts **8a.** *(Ref. 10)*

Table 4. Enantioselective Diels-Alder Reactions of Trisubstituted 1,4-Benzoquinones with 2-Triisopropylsilyloxybutadiene Catalyzed by **8a.** *(Ref. 16)*



Quinone	Product	Temp (°C) Time (h)	Yield (%), *ee* (%)
		-78, 12	98, 99
		-78, 3	96, 97
		-78, 16	99, >99
		-50, 48	85, 95
		-60, 36	96, 91

reactions with various dienes. In general, quinones are highly reactive substrates and so the scope of the reaction is broad and the yields and enantioselectivities are excellent. These factors are quite significant, since the quinone-Diels-Alder subtype is a very powerful construction that is highly useful for the synthesis of many natural products and other complex molecules. Despite their synthetic value, enantioselective quinone-Diels-Alder reactions were elusive until it was discovered[12-15] that the use of Mikami's BINOL-$Cl_2Ti(O\textit{i}\text{-}Pr)_2$ catalyst can give adducts with good enantioselectivity. The scope of this catalysis, however, was restricted to a very limited set of reactants such as naphthoquinone and quinone monoketals. As shown in Figure 5, the triflic acid-activated catalyst **5a** is an efficient and very general catalyst for Diels-Alder reactions of quinone monoketals as dienophiles.

Because of the synthetic importance for the asymmetric Diels-Alder reactions of quinones, the scope of this process was evaluated in detail. The triflimide activated catalyst **8a** was found to be an excellent catalyst for Diels-Alder reactions of 2,3- and 2,5-dimethyl-1,4-benzoquinones with a variety of dienes as depicted in **Figure 10**.[10] Diels-Alder reactions between unsymmetrical dienes and 2,5-dimethyl-1,4-benzoquinones, which involve regioselectivity as well as enantioselectivity issues, were also tested using catalyst **8a**. Although the position selectivity was found to be rather nominal, both regioisomers were formed in excellent enantioselectivities.[10]

The high yields and enantioselectivities of these reactions extend to a wide range of other quinones, including mono-, di- and trisubstituted quinones.[16] Catalyst **8a** was once again found to be the most efficient. The results obtained for the unsymmetrical test diene 2-triisopropylsilyloxybutadiene (**9**) and five different trisubstituted quinones are displayed in **Table 4**. Excellent yields, enantioselectivities and position selectivities were realized.

The products in each case are as expected from the pre-transition-state assembly shown in **Figure 11** with the help of the following additional information: (a) the diene attaches to the less substituted double bond; (b) C-1 of triisopropylsilyloxybutadiene is more nucleophilic than C-4 and its bonding to quinone is stronger than that of C-4 in the transition state (concerted, asynchronous pathway); (c) C-1 of diene attaches preferentially to the carbon of the quinone which is β to the catalyst coordinated carbonyl group; and (d) an *endo*, suprafacial addition occurs at sterically unshielded face of the α,β-double bond to form the Diels-Alder adduct.[16]

Similar levels with respect to yield and enantioselectivity were observed for the Diels-Alder reactions of di- and monosubstituted quinones with 2-triisopropylsilyloxybutadiene as exemplified in **Table 5** and **Table 6**, respectively. In these cases also, one positional isomer predominates even when more than one is theoretically possible.

Based on the observation of the results summarized in Figure 10 and Tables 4-6, the following set of selection rules for the prediction of structure and absolute configuration of the products

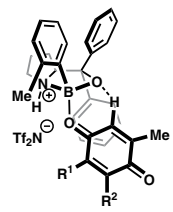


Figure 11. Pre-transition-state Assembly for Enantioselective Diels-Alder Reactions of 1,4-Benzoquinones. *(Ref. 16)*

obtained in Diels-Alder reactions of quinones using catalyst **8a** was proposed:

(1) For a quinone carbonyl flanked by C_α-H and C_α-R, the major product will result from catalyst coordination preferentially at the oxygen lone pair on the C-H side *a* rather than the C-R side *b* because *a* is sterically more accessible than *b* (see **Figure 12a**).

(2) Catalyst coordination at the more basic of the two 1,4-quinone oxygens will predominate, and this mode will lead to the preferred Diels–Alder adduct (see **Figure 12b**).

(3) If a double bond of the quinone in 1,3-diene addition bears two hydrogens, it will be more reactive than that bearing substituent(s), especially one or two π-electron donor groups.

(4) For monosubstituted 1,4-quinones (or *p*-benzoquinone itself), the major product pathway will involve coordination of catalyst at C=O *syn* to the HC=CH subunit that undergoes [4+2]-cycloaddition (see **Figure 12c**).

(5) C(1) of 2-triisopropylsilyloxy-1,3-butadiene (**9**), the more nucleophilic end of the diene, will attach to the carbon β to the carbonyl group that coordinates with the catalyst, i.e., the more electrophilic carbon.

(6) The preferred three-dimensional transition state corresponds to the *endo* arrangement of diene and catalyst-coordinated quinone.

2.4. Enantioselective [3+2]-Cycloaddition: Synthesis of Aflatoxin B_2

The very positive results obtained with the chiral oxazaborolidinium cations **8a-b** as catalysts for enantioselective Diels–Alder reactions encouraged the study of their application to [3+2]-cycloaddition processes. The possibility of such reactions was successfully investigated in the context of developing a simple enantioselective route to the microbial toxin aflatoxin B_2 (**10**). As outlined in **Scheme 2**, addition of 2,3-dihydrofuran (just over 1 equiv) to a solution of triflimide catalyst *ent*-**8a** and 2-methoxy-1,4-benzoquinone in a mixture of CH_2Cl_2 and CH_3CN at -78 °C and subsequent reaction at -78 °C to 23 °C gave the [3+2] cycloadduct **11** in 65% yield.[17] This was converted in several steps to the isomeric phenol **12**, which upon condensation with 2-ethoxycarbonyl-3-bromo-2-cyclopentenone gave aflatoxin B_2 (**10**), as shown in Scheme 2. This is by far the simplest known enantioselective route to **10**.

Strong evidence that the [3+2] cycloaddition reaction that produced adduct **11** is actually a two step process was obtained from a simple experiment in which a reactive intermediate was trapped. When the [3+2]-cycloaddition was carried out with a ten-fold excess of 2,3-dihydrofuran over 2-methoxybenzoquinone, the formation of cycloadduct **11** was suppressed and a new product was formed in an approximately equal amount. The structure of the product was shown unequivocally to be **13** (**Scheme 3**) by X-ray crystallographic analysis. Since it is likely that **13** arose by trapping of the intermediate **15**, a reaction pathway for the formation of **13** that involved **15** as an intermediate was proposed. It is reasonable that both the 1:1 cycloadduct **11** and the 2:1 adduct **13** are formed via the pre-transition-state assembly **14** and intermediate **15**.[17] This [3+2] cycloaddition reaction, even though limited in scope, could be extended to a few different quinones, and adducts were obtained with high enantioselectivity.[17]

2.5. Asymmetric Michael Addition to α,β-Unsaturated Enones

The reaction of α,β-enones with silyl enol ethers of esters using proton-activated chiral oxazaborolidines follows a Michael addition

Table 5. Enantioselective Diels-Alder Reactions of 2,3- or 2,6-Disubstituted 1,4-Benzoquinones with 2-Triisopropylsilyloxybutadiene Catalyzed by **8a**. *(Ref. 16)*

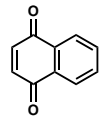
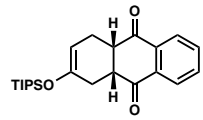
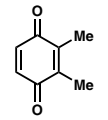
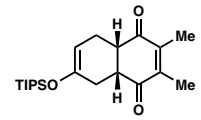
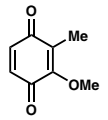
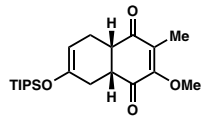
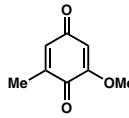
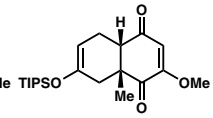
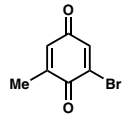
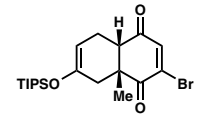
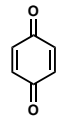
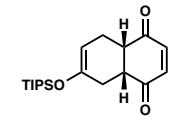
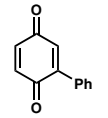
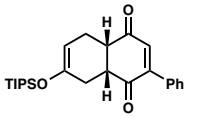
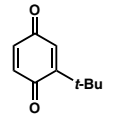
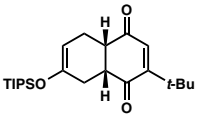
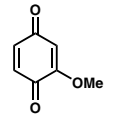
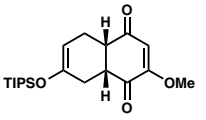
Quinone	Product	Temp (°C) Time (h)	Yield (%), *ee* (%)
		-78, 2	98, 97
		-95, 2	98, >99
		-78, 12	84, 90
		-50, 96	98, 92
		-78, 4	95, 91

Table 6. Enantioselective Diels-Alder Reactions of Unsubstituted or Monosubstituted 1,4-Benzoquinones with 2-Triisopropylsilyloxybutadiene Catalyzed by **8a**. *(Ref. 16)*

Quinone	Product	Temp (°C) Time (h)	Yield (%), *ee* (%)
		-78, 6	85, 88
		-78, 24	87, 94
		-78, 12	92, 91
		-78, 16	95, 91

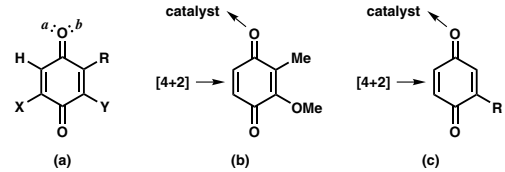
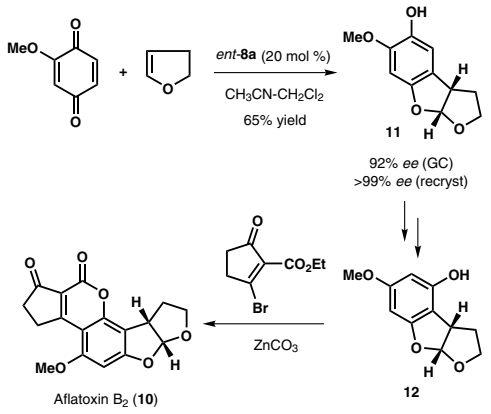
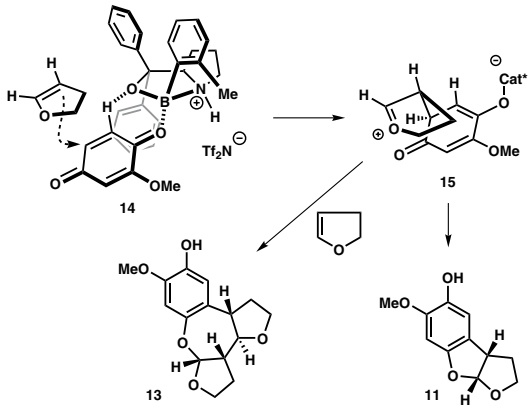


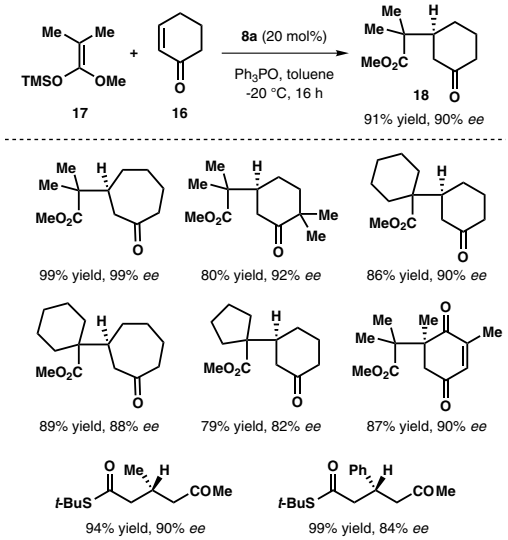
Figure 12. Catalyst Binding and Diene Approach to Quinones. *(Ref. 16)*



Scheme 2. Asymmetric [3+2]-Cycloaddition Reaction and its Application to the Enantioselective Synthesis of Aflatoxin B_2. *(Ref. 17)*



Scheme 3. Rational Pathway for the Formation of **11** and **13** via **15** with Catalyst **8a**. *(Ref. 17)*



Scheme 4. Catalytic Enantioselective Michael Addition: the Reaction and Substrate Scope. *(Ref. 18)*

pathway rather than the [2+2]-cycloaddition route (see Section 3.3). The Michael addition process is exemplified in **Scheme 4** using 2-cyclohexenone (**16**) and the trimethylsilyl enol ether of methyl isobutyrate (**17**) as substrates. The reaction proceeds efficiently (91% yield) and the product (**18**) is obtained with 90% *ee* when a catalytic amount of triphenylphosphine oxide is used as a trap for transiently formed Me_3Si^+ (or equivalent).[18] A fairly general substrate scope (see Scheme 4) for this reaction could be achieved under slightly modified reaction conditions and Michael adducts were obtained with high enantioselectivity.[18] As in the case of cycloaddition reactions, the absolute configuration of the Michael adduct can be predicted using an analogous stereochemical model (see Figure 4).

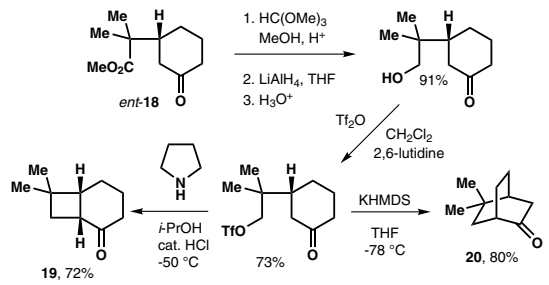
The Michael adduct *ent*-**18**, obtained using *ent*-**8a** as the catalyst, could be converted either to the fused-ring bicyclic product **19** or the bridged-ring isomer **20** as shown in **Scheme 5**.[18] The chiral bicyclo[4.2.0]octanone **19** is an intermediate for the enantioselective synthesis of the unique sesquiterpene β-caryophyllene.[19]

2.6. Enantioselective Cyanosilylation of Carbonyl Compounds

Considering the activation of aldehydes by protonated oxazaborolidines and the resulting highly enantioselective Diels-Alder reactions of enals (see Section 2.1), it is not surprising that these catalysts can be effective in promoting enantioselective nucleophilic addition to aldehydes.

Cyanosilylation was chosen as the model reaction and was indeed found to proceed highly enantioselectively with 10 mol % **8b** (Figure 6) when trimethylsilyl cyanide (TMSCN) was used as the reagent and catalytic amount (20 mol %) of triphenylphosphine oxide (Ph_3PO) as additive.[20] A variety of aromatic and aliphatic aldehydes underwent efficient cyanosilylation and the corresponding cyanohydrins were obtained after acidic work-up with >90% ee in all cases (**Table 7**). Data from a number of NMR and IR experiments suggested the possible formation of phosphine oxide bound isocyanide [Ph_3P(OTMS)(N=C:)] as the active nucleophile in this reaction.[20] The absolute configuration of these products is in agreement with the stereochemical model (**Figure 13a**).

The catalytic oxazaborolidine method has also been extended to include ketonic substrates.[21] Catalyst **5b** was found to be superior in this case and the products were obtained with the same face selectivity as for aldehydes. A pre-transition-state assembly (**Figure 13b**) analogous to the one for aldehyde cyanosilylation



Scheme 5. Synthesis of Chiral Fused or Bridged-ring Ketones from a Michael Adduct. *(Ref. 18)*

but involving α-C-H···O hydrogen bonding instead of formyl C-H···O hydrogen bonding could be invoked to explain the same face selectivity.[21]

3. Aluminum Bromide-Activated Oxazaborolidines

The discovery of the high efficiency and utility of proton-activated oxazaborolidines prompted the reinvestigation of the earliest approach to the activation of oxazaborolidines by Lewis acids. The original negative findings for BF_3, $SnCl_4$, $ZnCl_2$, $MeAlCl_2$ were confirmed. In contrast, the very strong Lewis acids BBr_3 and $AlBr_3$ (the latter is available from Aldrich as a 1.0M solution in CH_2Br_2) provided viable catalysts. It was found that activation by $AlBr_3$ afforded a complex that was comparably effective as TfOH- or Tf_2NH-activated oxazaboroline as a catalyst for enantioselective Diels–Alder reactions.[22] BBr_3-activation was definitely inferior to $AlBr_3$-activation, although better than that observed for the other Lewis acids mentioned above. The $AlBr_3$-activated oxazaborolidine is stable in the temperature range -78 °C to -20 °C in CH_2Cl_2 solution. The ^1H NMR spectrum is very similar to that for the proton-activated catalysts **5a** and **8a** and fully consistent with the analogous structure **21** (**Figure 14**).

3.1. Diels-Alder Reactions of Various Dienophiles

A comparison of the Diels–Alder reactions catalyzed by $AlBr_3$-activated oxazaborolidine **21** with those catalyzed by the proton-activated oxazaborolidines **5a** and **8a** revealed generally similar results in terms of reaction yield and enantioselectivity. One advantage of the $AlBr_3$-activated **21** was that the reaction proceeds well even with only 4 mol % of catalyst, as compared to ca. 10 mol % for **5a** and **8a** in most instances (possibly the result of less serious product inhibition of the catalytic process).[22] Catalyst **21** can be generated both conveniently and reproducibly using a solution of $AlBr_3$ in CH_2Br_2. The results for the reactions of a variety of dienophiles with cyclopentadiene, isoprene and less reactive heterodienes such as furans are shown in **Figure 15**.[22]

Excellent results were also obtained for catalyst **21** in Diels-Alder reactions of quinones with various dienes (**Figure 16**).[22]

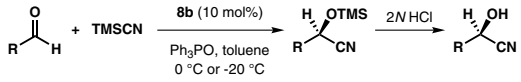
3.2. Diels-Alder Reactions of Maleimides

Maleimides are an interesting class of dienophiles that have been utilized successfully for diastereoselective Diels-Alder reactions with a number of chiral dienes.[23-24] However, despite the usefulness of the products obtained via Diels-Alder reactions using maleimide dienophile, the range of catalytic enantioselective versions of this reaction has been rather limited.[25-27] Very recently we have developed a catalytic asymmetric Diels-Alder reaction of maleimides using activated oxazaborolidines **8a** and **21**, which showed broad scope both in terms of dienes and maleimides.[28] *Endo*-adducts were obtained exclusively (*dr* >99:1) in very high yield and with excellent enantioselectivity as indicated by the examples in **Figure 17**.[28]

3.3. Enantioselective [2+2]-Cycloaddition Reactions

A process for enantioselective [3+2]-cycloaddition reactions involving the π-electron rich vinylic ether 2,3-dihydrofuran using as chiral catalyst the triflimide **8a** was described in Section 2.4. It was surmised that vinyl ethers might also participate in enantioselective [2+2]-cycloadditions using the same catalyst. Such a result was first realized with the test reaction of 2,3-dihydrofuran with trifluoroethyl acrylate in the presence of a catalytic amount of the $AlBr_3$-activated oxazaborolidine **21**, as outlined in **Scheme 6**.[29] The *exo*-cycloadduct **22** was produced with near perfect diastereo- and enantioselectivity in 87% yield.

Table 7. Oxazaborolidinium-Catalyzed Cyanosilylation of Aldehydes. *(Ref. 20)*



R	Time (h)	Yield (%)	*ee* (%)
phenyl	40	94	95
2-tolyl	72	95	91
4-anisyl	40	91	90
4-cyanophenyl	144	98	97
cyclohexyl	40	97	90
tert-butyl	40	96	91
n-hexyl	48	96	91

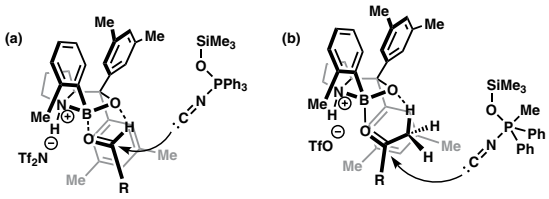


Figure 13. Pre-transition-state Assembly for Enantioselective Cyanosilylation of (a) Aldehydes and (b) Ketones. *(Ref. 21)*

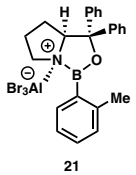


Figure 14. Oxazaborolidine–$AlBr_3$ Complex **21**. *(Ref. 22)*

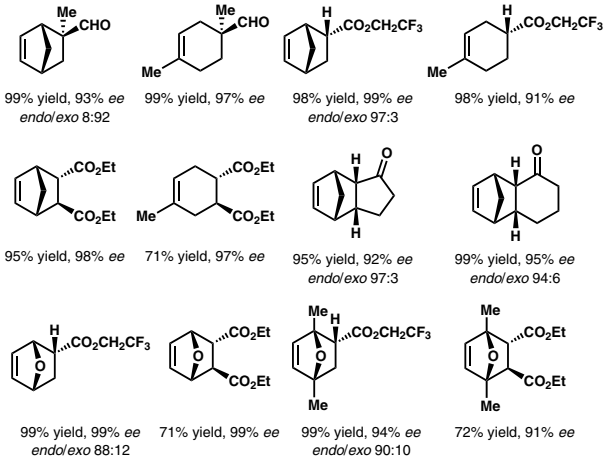


Figure 15. A Selection of Products Obtained by Enantioselective Diels-Alder Reactions in the Presence of $AlBr_3$-Activated Oxazaborolidine **21**. *(Ref. 22)*

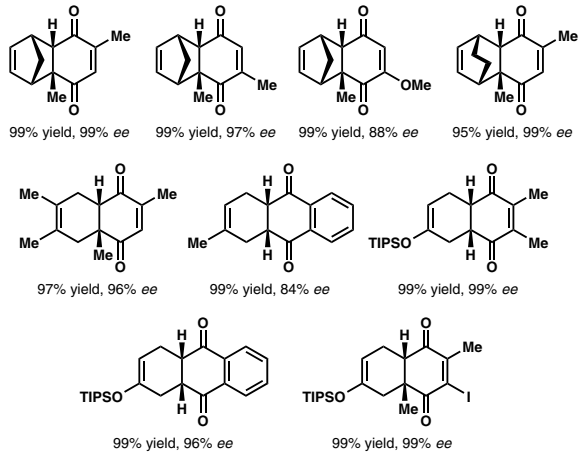


Figure 16. A Selection of Products Obtained via Diels-Alder Reactions of an Assortment of Quinones and Dienophiles Using **21** (4 mol %). *(Ref. 22)*

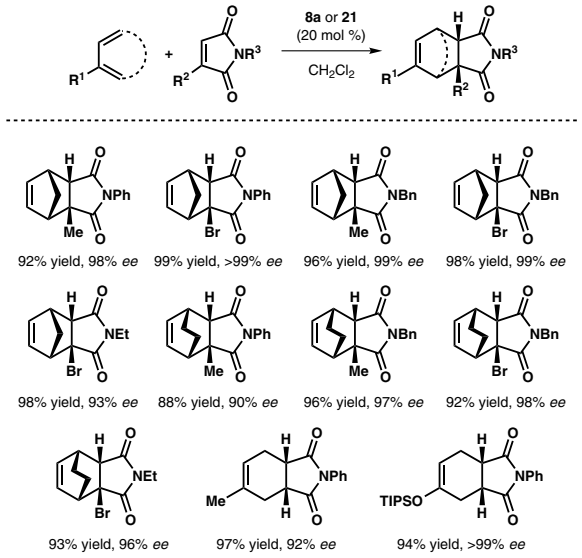
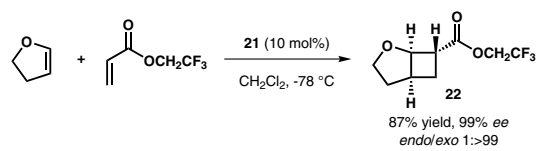


Figure 17. Diels-Alder Reaction of Maleimides as Dienophile: the Reaction and Substrate Scope. *(Ref. 28)*



Scheme 6. Asymmetric [2+2]-Cycloaddition Using Catalyst **21** for the Formation of Bicyclic Ester **22**. *(Ref. 29)*

Similar enantioselective [2+2]-cycloaddition reactions occur between trifluoroethyl acrylate and silyl enol ether derivatives of ketones as summarized in **Table 8**.[29]

It is noteworthy that the $AlBr_3$-activated catalyst **21** was found to be quite superior for [2+2]-cycloaddition reactions to the triflimide-activated catalyst **8a**. Also of interest is the fact that the predominating geometry, specifically *endo* vs *exo* $CO_2CH_2CF_3$ substitution, varies with the vinyl ether substrate.[29] It has been proposed that these reactions occur by non-concerted, two-step processes starting from complex **23** and proceeding via the pre-transition-state assembly **24** (**Scheme 7**), which explain the divergent stereoselectivities shown in Table 8.

4. Lewis-Acidic *N*-Methyl-oxazaborolidinium Cation

Another type of chiral Lewis acid with the oxazaborolidine core is the *N*-methylated oxazaborolidinium cation **25** (**Scheme 8**).[30] The cationic species **25** is an efficient chiral Lewis acid catalyst as shown by various Diels-Alder adducts summarized in Scheme 8.

A comparison of catalyst **25** with $AlBr_3$-activated oxazaborolidine **21** in the Diels-Alder reaction is outlined in **Table 9**.[30] Although higher levels of the *N*-methyl catalyst **25** are required in order to attain a convenient rate of reaction as compared to the $AlBr_3$-activated catalyst **21** (10 mol % vs 4 mol %), catalyst **25** afforded the adducts in similar or higher yield in most cases. Catalysts **5**, **8**, **21**, and **25** produce the same enantiomeric products from a wide range of substrates and appear to function by the same basic mechanism discussed above.

5. Application of Oxazaborolidinium Cations in Enantioselective Synthesis

Cationic chiral oxazaborolidines have been shown to be extremely useful and versatile catalysts for the synthesis of many biologically interesting complex molecules.[17,31-35] This utility has been demonstrated by applications some of which will be outlined in

Table 8. Enantioselective [2+2]-Cycloaddition Reactions of Trifluoroethyl Acrylate to Silyl Enol Ethers with 10 mol % Catalyst **21** in CH_2Cl_2 at –78 °C. *(Ref. 29)*

Enol ether	Product	Time (h)	Yield (%) (*endo*:*exo*)	*ee* (%)
OTBS	TBSO H $CO_2CH_2CF_3$ H *endo*	6	97 (82:18)	92
OTIPS	TIPSO H $CO_2CH_2CF_3$ H *endo*	12	99 (97:3)	92
OTIPS	TIPSO H $CO_2CH_2CF_3$ H *endo*	6	99 (99:1)	99
OTBS Me	TBSO H $CO_2CH_2CF_3$ Me *exo*	0.5	99 (1:99)	98
OTBS Me	TBSO H $CO_2CH_2CF_3$ Me *exo*	16	99 (10:90)	98
OTBS Me	TBSO H $CO_2CH_2CF_3$ Me *endo*	4	91 (96:4)	98

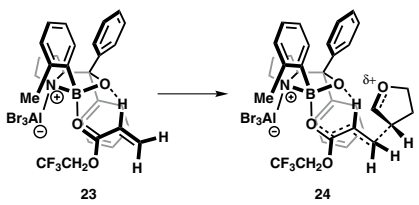
this section. The new catalysts enhance the power of synthesis not only because they enable enantioselective syntheses which have not previously been possible, but also because the mechanistic model is powerfully predictive and allows the selection of the appropriate enantiomer of the oxazaborolidine for a synthesis a priori.

5.1. Enantioselective Synthesis of Complex Targets

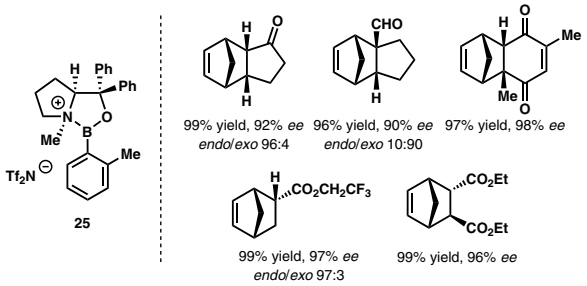
The application of the oxazaborolidinium-catalyzed asymmetric [3+2]-cycloaddition reaction in a short enantioselective synthesis of microbial toxin aflatoxin B_2 (**10**, Scheme 2)[17] was outlined above. Many other natural and non-natural complex molecules were synthesized using oxazaborolidinium-catalyzed Diels-Alder cycloaddition reactions. These include estrone,[30-31] desogestrel,[31] laurenditerpenol,[36] oseltamivir[35] and dolabellane-type marine natural products[33] as shown in **Figure 18**. Among these, particularly noteworthy is the enantioselective synthesis of oral antiflu drug oseltamivir (Tamiflu®, **29**), for which a short, scalable and simple route was developed starting with the Diels-Alder adduct prepared from 1,3-butadiene and trifluoroethyl acrylate.[35]

5.2. Conversion of Racemic Synthetic Routes into Enantioselective Pathway

The transformative role of chiral oxazaborolidinium cations can be gauged by the recent demonstration that several of the classic achievements of synthesis of racemic natural products from the period 1950 to 2000 can be elevated to the most modern enantioselective standards through their use.[32] These include Sarett's total synthesis of cortisone (**32**),[37] Kende's total synthesis of the alkaloid dendrobine (**33**),[38] Eschenmoser's photochemical route to vitamin B_{12},[39] Chu-Moyer/Danishefsky's synthesis of myrocin C (**38**),[40] Mehta's general approach to triquinanes[41] and several others. **Figure 19** illustrates some of these natural products.

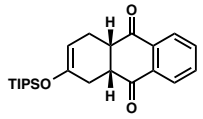
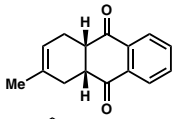
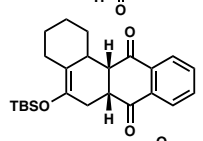
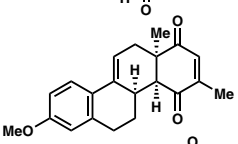
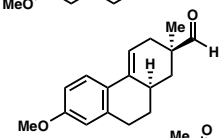
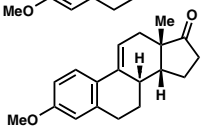


Scheme 7. Plausible Reaction Pathway for the [2+2]-Cycloaddition. *(Ref. 29)*



Scheme 8. *N*-Methyl-oxazaborolidinium Triflimide **25** and Some Diels-Alder Adducts Obtained by Using **25.** *(Ref. 30)*

Table 9. Comparative Studies of [4+2]-Cycloaddition Reactions Catalyzed by **21** and **25.** *(Ref. 30)*

Product	Cat	Temp (°C), Time (h)	Yield (%), *ee* (%)
	**21**	-78, 16	99, 96
	25	-78, 4	95, 96
	**21**	-78, 16	99, 84
	25	-78, 16	97, 84
	**21**	-78, 2	90, 12
	25	-78, 4	83, 96
	**21**	-78, 2	87, 84
	25	-78, 2.5	87, 98
	**21**	-78, 0.5	95, 98
	25	-78, 2.5	90, 98
	**21**	-20, 48	50, 75
	25	23, 24	98, 82

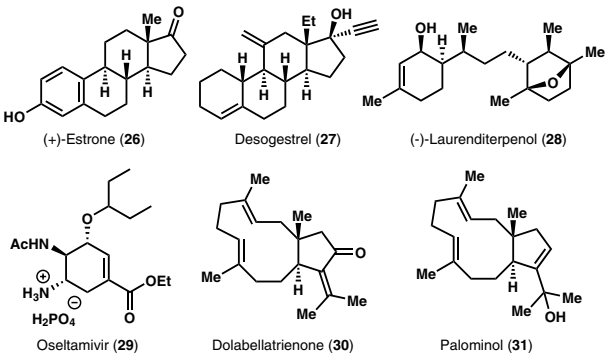


Figure 18. A selection of Complex Molecules Synthesized Using Enantioselective Diels-Alder Reactions. *(Ref. 31,33,35,36)*

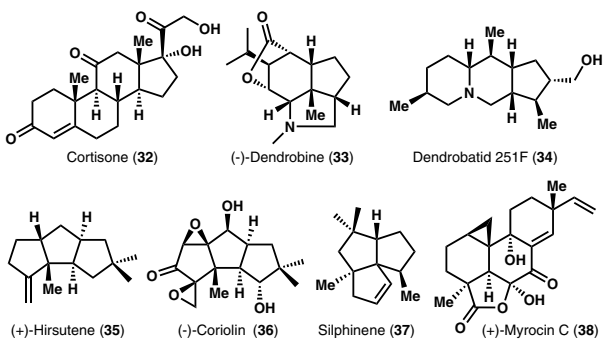


Figure 19. Examples of Natural Products Synthesized Enantioselectively Following their Classic Racemic Routes. *(Ref. 32)*

5.3. Other Applications

Besides the synthesis of natural and non-natural targets, protonated and $AlBr_3$-activated oxazaborolidine catalyzed Diels-Alder reactions have also been used for the stereoselective synthesis of woody fragrances like georgyone, arborone and their structural relatives.[34,42] In addition, very recently our lab has reported the enantioselective synthesis of chiral-bridged dienes, which, by coordination to Rh(I), can serve as excellent catalysts for the enantioselective conjugate addition of vinyl and aryl groups to α,β-unsaturated ketones.[43]

6. Conclusions

Chiral oxazaborolidines derived from 1,1-diphenylpyrrolidinomethanol can be activated by protonation (at N) using very strong proton acids [e.g., CF_3SO_3H or $(CF_3SO_2)_2NH$] or coordination with $AlBr_3$ (at N) to form very strong chiral Lewis acids. The efficiency of such Lewis acids as chiral catalysts for promoting different cycloadditions, Michael addition, cyanosilylation of carbonyl compounds is reviewed here. The application of these enantioselective reactions, especially the Diels-Alder reaction, for the synthesis of numerous complex natural products and non-natural compounds shows their utility. These reactions were developed only during the last decade and have not yet become standard tools of synthesis. However, the applicability of this class of chiral Lewis acids keeps increasing as evident from a number of reports by our group[43-46] as well as by other groups[47-52] which clearly indicate the potential for further development.

7. Acknowledgements

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Keywords: asymmetric catalysis; oxazaborolidine; chiral Lewis acid; Diels-Alder reaction; natural product.

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In 2010, Santanu returned to India and joined the Department of Organic Chemistry at the Indian Institute of Science, Bangalore as an Assistant Professor. His research interests revolve around developing new methods for asymmetric catalysis.

Elias J. Corey, born in 1928 in Methuen, 30 miles north of Boston, studied chemistry from 1945 to 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. He recently published with Barbara Czakó and László Kürti the interdisciplinary textbook *Molecules and Medicine*, voted by the American Association of Publishers as the best book in the Sciences for 2007.