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Enantioselective Catalysis Based on Cationic Oxazaborolidines

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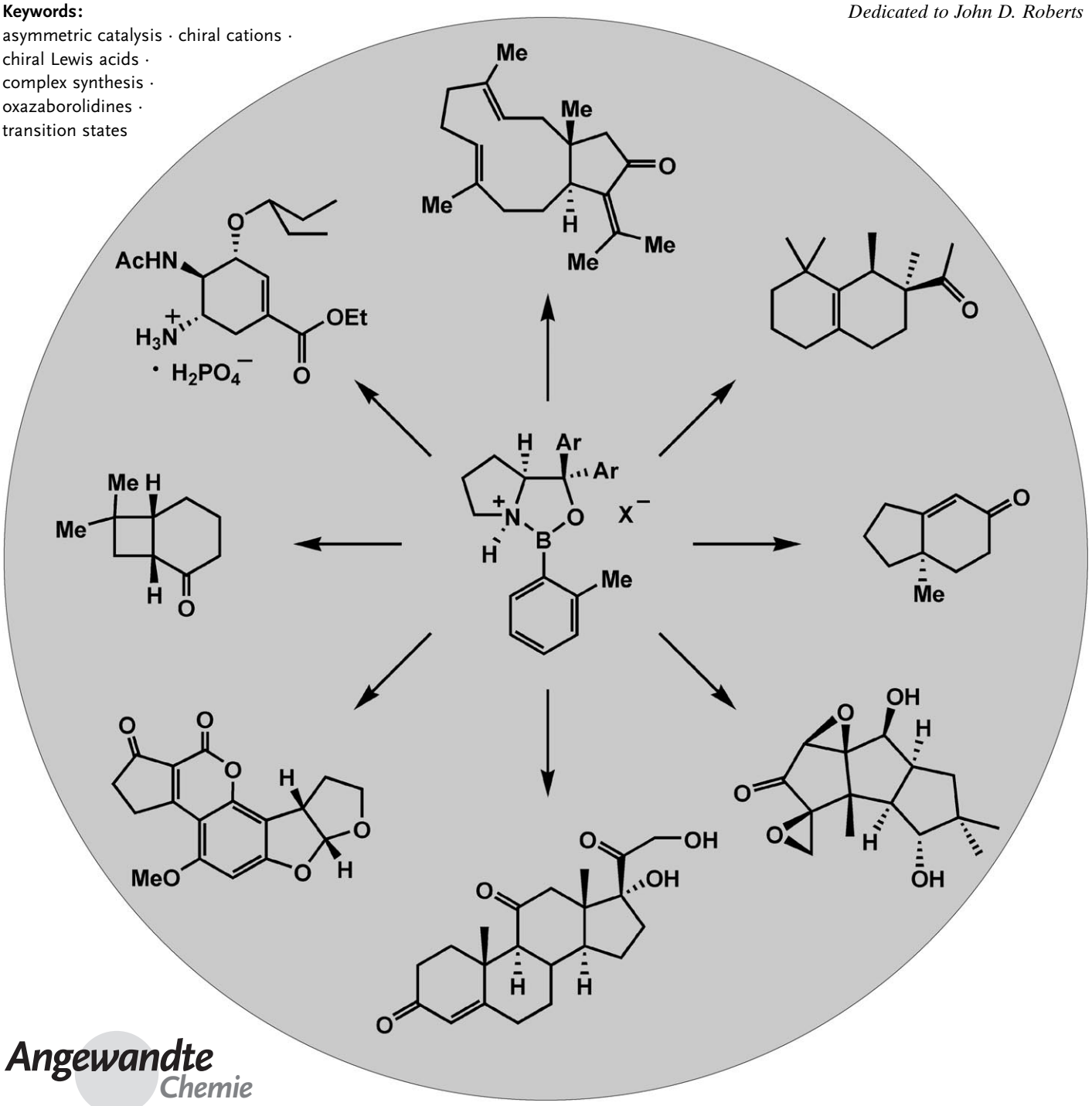
asymmetric catalysis · chiral cations · chiral Lewis acids · complex synthesis · oxazaborolidines · transition states

Dedicated to John D. Roberts

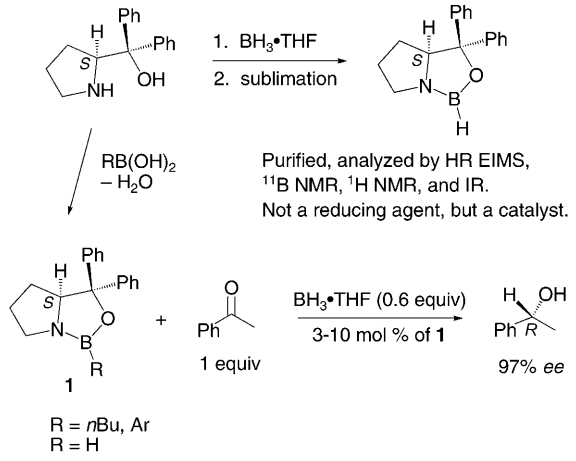


Over the past several decades a revolution has occurred in chemistry that has essentially been unnoticed by those outside the field, even in other sciences. In brief, this includes the following: 1) our understanding of how chemical reactions occur, 2) our ability to invent new reactions, 3) our ability to utilize reactions that construct a vast assortment of useful or complicated molecules, and 4) our ability to apply chemical principles and knowledge to understand biological and medical problems. Within synthetic chemistry, a new science has been set in place beside the old, especially in terms of the control of absolute and relative stereochemistry and the creation of new types of useful catalysts that function in ways that were hitherto unimaginable. This Review deals with one aspect of such catalysis which has emerged only in the past six years: the generation and application of super-Lewis acidic chiral oxazaborolidinium ions for enantioselective catalysis. Progress in this area has encompassed the formation of such catalysts, the detailed pathways of the reactions that they control and accelerate, the reactions that they can promote, and the ways in which they can be applied to advantage.

From the Contents

1. Introduction

Research from our laboratory over a span of three decades on the development of enantioselective Diels–Alder reactions was reviewed in this journal in 2002 on the occasion of the centennial of the birth of Kurt Alder.[1,2] Since that time, there have been several significant developments in this area.[2f–h] The focus of this Review is one of these, the use of chiral cations derived from oxazaborolidines by various activation procedures. An early step in the unfolding of this approach was the successful use of proline-derived oxazaborolidines of general type **1** (Scheme 1) as catalysts for the enantioselective reduction of prochiral ketones.[3] Of equal importance was the development of mechanistic insights into the detailed pathway that such reactions entail.



Scheme 1. Formation of (*S*)-proline-derived oxazaborolidines of type **1** and their use as catalysts for the reduction of acetophenone by BH_3·THF as the stoichiometric reductant.

The formation of the oxazaborolidine catalyst system and the application to the enantioselective reduction of a typical ketonic substrate, acetophenone, are illustrated in Scheme 1. The scope of this reduction is very broad. The main limitations arise from the presence of Lewis-basic groups in a ketonic reactant that can preferentially coordinate with BH_3. Countless successful applications of this method for the enantioselective synthesis of chiral secondary alcohols from ketones have been described. The process is commonly referred to as the Corey–Bakshi–Shibata (CBS) reduction.[4]

The most logical pathway for the oxazaborolidine-catalyzed reduction of ketones by borane is summarized in Scheme 2. Coordination to BH_3, the first step, leads to a *cis*-fused catalyst–BH_3 complex **2**. The *cis*-fused geometry, which is much more stable than the corresponding *trans* arrangement, has been demonstrated by an X-ray single crystal structure determination for **2**, R = Me.[4,5] Borane coordination in **2** enhances the Lewis acidity of the ring borane to a level that leads to facile complexation with ketonic oxygen, forming in the case of acetophenone the more stable complex **3** (by coordination at lone pair *b*). The size of the phenyl substituents on the oxazaborolidine ring restricts rotation

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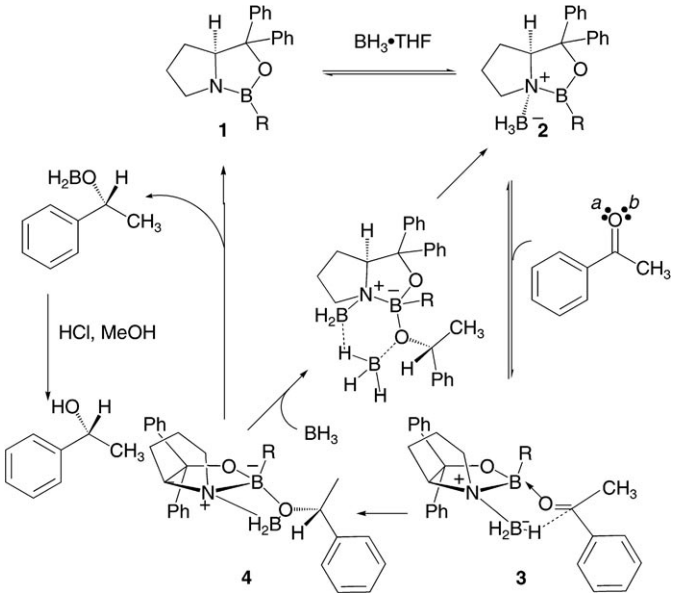
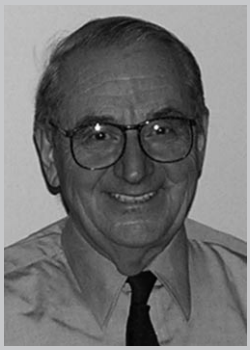


Scheme 2. Proposed pathway for the catalytic enantioselective reduction of prochiral ketones such as acetophenone by chiral oxazaborolidines of type **1**.

about the B–OCR_2 bond of **3** such that intramolecular hydride transfer from boron to carbon produces **4** with high π-facial selectivity. The ketone reduction eventually produces a dialkoxyborane with regeneration of catalyst **1**. Thus, the (*S*)-proline-derived catalyst **1** selectively promotes the formation of (*R*)-1-phenylethanol from acetophenone and BH_3·THF. The mechanistic pathway shown in Scheme 2 appears to be general and highly favored. As a consequence, it is possible to predict with confidence the absolute stereochemical course of reductions catalyzed by oxazaborolidines

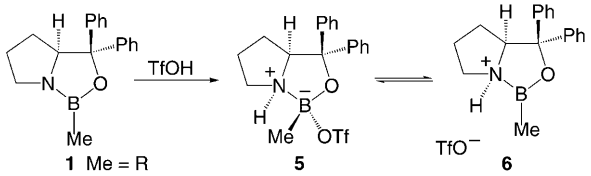
2. Proton Activation of Oxazaborolidines: Diels–Alder Reactions of α,β-Enals

A priori, it seemed reasonable that the type of catalysis which is postulated in Scheme 2 could be applied to the development of enantioselective processes other than reductions and, specifically, many reactions that are subject to acceleration by strong Lewis acids. We were especially interested in the possibility of achieving enantioselective versions of the most powerful synthetic constructions, such as the Diels–Alder reaction and other cycloaddition processes.[1,5]



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. In 2007, he published with Barbara Czakó and László Kürti the interdisciplinary textbook Molecules and Medicine.

In principle, coordination of a Lewis acid with **1** could produce an analog of the borane complex **2** (Scheme 2) in which the boron member of the oxazaborolidine ring might be strongly Lewis acidic and chiral. Following up on this possibility, experiments were conducted to determine whether complexes at the nitrogen of **1** (R = Me) with various Lewis acids could promote enantioselective Diels–Alder addition of cyclopentadiene to reactive dienophiles such as 2-methylacrolein. However, initial studies involving BF_3, $SnCl_4$, $ZnCl_2$, and $AlCl_3$ were not promising. Attention was then directed toward the use of protic acids to effect the activation of **1**. The most successful results were obtained by the use of triflic acid (TfOH) as activator.[6] ^{1}H NMR measurements of a 1:1 mixture of **1** (R = Me) and TfOH in $CDCl_3$ at −80 °C revealed the presence of two protonated species, **5** and **6**, in a ratio of ca. 1.5:1 at about 0.05 M concentration (Scheme 3). Methanesulfonic acid and weaker



Scheme 3. Generation of an equilibrium mixture of tetracoordinate (**5**) and tricoordinate (**6**) oxazaborolidinium species by protonation of **1** with triflic acid.

acids did not lead to complete protonation of **1**, R = Me. The Lewis acidity of **6** is high, as might be expected from the fact that a very strong protic acid, triflic acid, was required to produce it from **1**. The equilibrium between **5** and **6** is facile (although slow on the ^{1}H NMR timescale at 80 °C) and, as a result, the mixture behaves as if it were **6** and powerfully catalyzes the Diels–Alder reaction between cyclopentadiene and 2-methylacrolein. Studies to optimize the yield and enantioselectivity of this reaction with respect to the substituent on boron and other reaction parameters (see Table 1) showed that an *o*-tolyl substituent on boron gave the best results.[6] The C-aryl substituent 3,5-dimethylphenyl (*m*-xylyl or mexyl) was somewhat superior to phenyl, likely because of its greater basicity as a neighboring π-rich aromatic group.[1,5,7] The highly enantioselective formation of adduct **7** from cyclopentadiene and 2-methylacrolein is that expected from the preferred pre-transition-state assembly **8** (Figure 1), for which there is considerable precedent in our previous work.[1,7] The complex of the catalyst with 2-methylacrolein is pro-

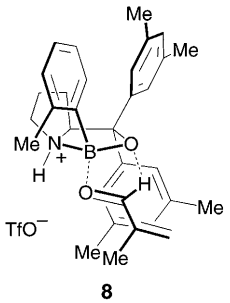
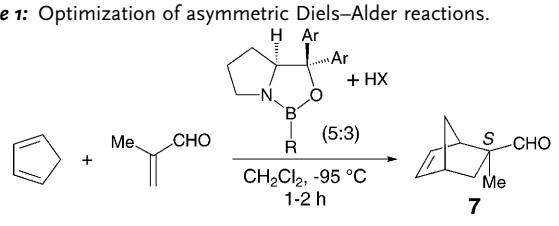


Figure 1. Model for the reactive complex of an oxazaborolidinium cation and the dienophile α-methylacrolein.

Table 1: Optimization of asymmetric Diels–Alder reactions.



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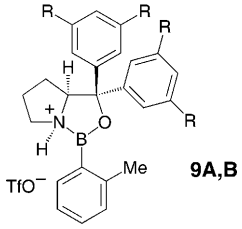
Entry	R	Ar	HX (6 mol%)	Yield [%] (*exo*/*endo*)	*ee* [%]
1	Me	Ph	TfOH	98 (92:8)	20
2	Bu	Ph	TfOH	98 (93:7)	6
3	Ph	Ph	TfOH	91 (83:17)	75
4	4-MeO-C_6H_4	Ph	TfOH	96 (89:11)	76
5	4-Me-C_6H_4	Ph	TfOH	95 (88:12)	77
6	2-Me-C_6H_4	Ph	TfOH	91 (89:11)	90
7	2-Et-C_6H_4	Ph	TfOH	73 (89:11)	78
8	2-*i*Pr-C_6H_4	Ph	TfOH	NR (–)	–
9	2-biphenyl	Ph	TfOH	91 (92:8)	56
10	2,6-Me_2-C_6H_3	Ph	TfOH	NR (–)	–
11	1-naphthyl	Ph	TfOH	93 (80:20)	81
12	2-Me-C_6H_4	Ph	NfOH	95 (88:12)	91
13	2-Me-C_6H_4	Ph	MsOH	30 (87:13)	90
14	2-Me-C_6H_4	Ph	none	NR (–)	–
15	2-Me-C_6H_4	2-naphthyl	TfOH	92 (92:8)	91
16	2-Me-C_6H_4	3,5-Me_2-C_6H_3	TfOH	99 (89:11)	96

posed to involve an electrostatic interaction between the formyl hydrogen and the oxygen on boron that is synergistic with formyl-oxygen to boron coordination.[1,7] In **8** the formyl carbon, made more positive by coordination to boron, lies at Van der Waals contact distance (3.5 Å) above C(2), an *ortho* carbon, of the nearby mexyl group, and the attractive interactions between them is maintained in the transition state even as the diene is adding to the α,β-π 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 **8**. The mechanistic model exemplified by **8** is a reliable predictor of the absolute stereochemical course of Diels–Alder reactions of α,β-enals under catalysis by cationic oxazaborolidines. The enantioselectivity of these Diels–Alder reactions is generally greater at lower temperatures. This is a consequence of the high level of organization of assemblies such as **8**, a sizeable negative entropy of activation ($\Delta S^{\ddagger}$) for this favored pathway, and a lower $\Delta G^{\ddagger}$ and reaction barrier at lower temperature, as a result of the relationship: $\Delta G^{\ddagger} = \Delta H - T\Delta S^{\ddagger}$.

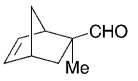
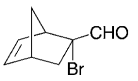
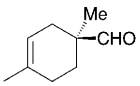
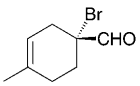
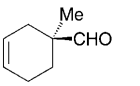
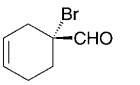
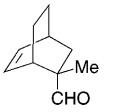
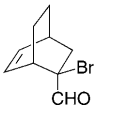
3. Diels–Alder Reaction of Other α,β-Unsaturated Carbonyl Compounds

The high enantioselectivity of the Diels–Alder reaction of the 2-substituted α,β-enals 2-methylacrolein and 2-bromoacrolein with protonated oxazaborolidine catalysts has been demonstrated with a variety of dienes of quite different reactivity, as shown by the results that are summarized in Table 2 for two different catalysts, **9A** and **9B**.[6] Proton-

Table 2: Diels–Alder reactions of 1,3-dienes with 2-methacrolein or 2-bromoacrolein (in CH_2Cl_2) catalyzed by chiral Lewis acid **9A** (R = H) or **9B** (R = Me).



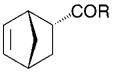
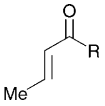
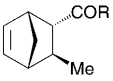
9A,B

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

activated oxazaborolidines **9A** and **9B** are effective catalysts for Diels–Alder reactions of a variety of α,β-unsaturated carbonyl compounds beyond α,β-enals—including α,β-unsaturated esters, lactones, ketones, and, especially, quinones.[8] The results of the initial survey of the addition of cyclopentadiene to several simple acyclic α,β-unsaturated carbonyl compounds using catalyst **9A** or **9B** are shown in Table 3.[8] Acrylate and crotonate esters are satisfactory dienophiles. However, because the latter are less reactive than the corresponding acrylates, it is advantageous to use the more rapidly reacting trifluoroethyl ester rather than methyl and ethyl ester.

We determined experimentally that the dienophile face selectivity for Diels–Alder addition to acrylate and crotonate esters is opposite to that for the α,β-enals described above (Table 2). The most likely reason for this different behavior emerged from X-ray crystallographic studies of solid complexes of α,β-unsaturated esters and enones with BF_3, which revealed proximity within the Van der Waals contact distance (2.67 Å) of one of the fluorines on boron and the α-C-H proton, as shown below for the crystalline complexes **10**, **11**,

Table 3: Diels–Alder reactions of cyclopentadiene with representative acyclic dienophiles catalyzed by chiral Lewis acid **9A** or **9B** in CH_2Cl_2.

Dienophile R	**9** (mol%)	*T* [°C], *t* [h]	Product yield [%] (*endo*/*exo*)	*ee* [%]
				
Et	**9B** (20)	−20, 2	99 (94:6)	97
OH	**9A** (20)	−35, 1.5	99 (95:5)	98
OEt	**9A** (20)	−20, 16	94 (97:3)	98
OEt	**9B** (20)	−20, 16	96 (97:3)	>99
				
Et	**9A** (20)	−20, 2	97 (69:31)	65
OEt	**9B** (13)	+4, 72	46 (91:9)	>98
OCH_2CF_3	**9A** (20)	−20, 16	93 (95:5)	>98

and **12** (Figure 2). These data suggest the possibility that the face selectivity observed for α,β-unsaturated enones and esters that possess an α-C-H group may be due to a pre-

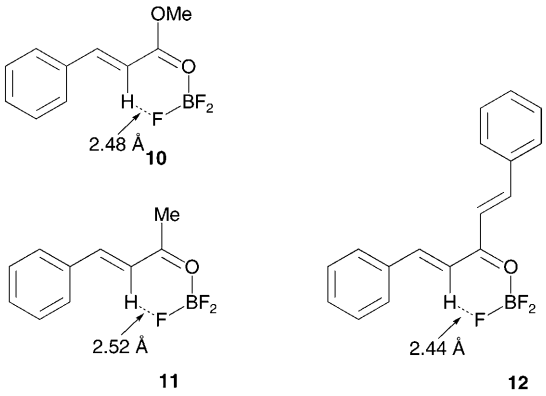


Figure 2. α-C-H to fluorine distances in BF_3 complexes of α,β-unsaturated carbonyl compounds as determined by X-ray crystallography.

transition-state assembly of type **13** (Figure 3) which clearly would lead to opposite face-selectivity than that corresponding to formyl C-H/ligand interaction, as shown to the left of Figure 3 for comparison.

The generality of the catalytic enantioselective Diels–Alder reaction mediated by **9A** and **9B** and the α-CH···ligand binding mode of reaction are further supported by the examples given in Table 4, which involve cyclopentadiene as a test diene and a variety of α,β-unsaturated carbonyl compounds.[8] Whereas the absolute configuration of the product from an α,β-enal, shown in the first entry of Table 4, corresponds to the formyl CH···O bonding model, all the other products are those expected of the α-CH···O bonding as in **13**. 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

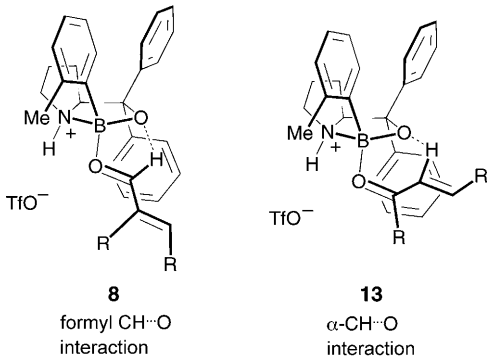
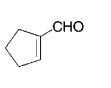
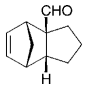
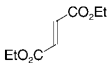
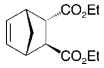
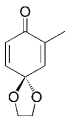
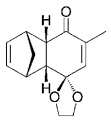
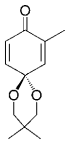
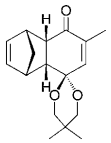


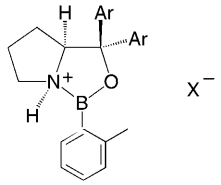
Figure 3. Differing models of complexation of α,β-enals and other α,β-unsaturated carbonyl compounds with catalyst **6**.

Table 4: Diels–Alder reactions of cyclopentadiene with various dienophiles catalyzed by chiral Lewis acid **9A** or **9B** in CH_2Cl_2.

Dienophile	Product		Cat. (mol%)	*T* [°C], *t* [h]	Yield [%] (*endo*/*exo*)	*ee* [%]
			**9A** (20)	−95, 1	95 (8:92)	94
			**9A** (20)	−35, 1.5	99	98
			**9A** (20)	−20, 36	99 (91:9)	88
			9B (20)	−20, 64	94 (93:7)	90
		*n*=1	**9B** (20)	−20, 14	99 (95:5)	92
		n=2	**9A** (20)	−20, 16	97 (91:9)	93
		n=2	**9B** (20)	−20, 15	98 (94:6)	95
		n=3	**9B** (20)	−20, 22	92 (97:3)	93
			**9A** (20)	−20, 1	33 (>98:2)	84
			9A (10)	−78, 1	80 (>98:2)	92
			9B (20)	−78, 1	91 (>98:2)	71
			**9A** (10)	−78, 1	98 (>98:2)	92

because other chiral Lewis acids are ineffective for these substrate classes.

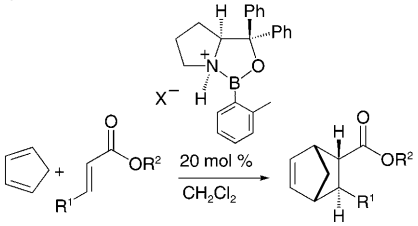
Another reagent which can be used for proton activation of oxazaborolidines of type **1** (Scheme 1) is triflimide, $(CF_3SO_2)_2NH$, which is known to be at least comparable in acid strength to triflic acid.[9–11] Triflimide activation of **1** affords a more stable catalyst than that generated with triflic acid. Whereas the oxazaborolidinium triflates **9A** and **9B** generally must be used at 4°C or below because of instability at higher temperatures, the corresponding triflimides **14A** and **14B** (Figure 4) are sufficiently stable to be useful at 25–40°C. This is an important advantage since it broadens the range of Diels–Alder reactions which may be carried out successfully to include many less reactive partners and shortens the time required for good conversion. An instructive comparison of triflate- and triflimide-activated catalysts is shown in Table 5.[10] We have determined that the order of



9A Ar = C_6H_5, X = CF_3SO_3
9B Ar = 3,5-dimethylphenyl, X = CF_3SO_3
14A Ar = C_6H_5, X = $(CF_3SO_2)_2N$
14B Ar = 3,5-dimethylphenyl, X = $(CF_3SO_2)_2N$

Figure 4. Catalysts formed by protonation of oxazaborolidines with triflic acid or triflimide.

Table 5: Comparison of triflate **9A** and triflimide **14A** as catalysts.



R^1	R^2	X	Conc.	*T* [°C], *t* [h]	Yield, *ee* [%] (*endo*/*exo*)
Me	Et	TfO	0.25	4, 72	46, >98 (*endo*) (91:9)
Me	Et	Tf_2N	0.25	20, 16	94, 97 (*endo*) (89:11)
Ph	CF_3CH_2	TfO	1.0	4, 72	27, 95 (*endo*) (85:15), 94 (*exo*)
Ph	CF_3CH_2	Tf_2N	1.0	20, 16	79, 93 (*endo*) (83:17), 96 (*exo*)
Ph[a]	CF_3CH_2	–	0.25	20, 16	86, 0 (*endo*) (88:12), 0 (*exo*)

[a] $EtAlCl_2$ (20 mol%) was used as a Lewis acid catalyst.

reactivity of α,β-unsaturated esters as dienophiles with **9A** or **14A** is acrylate > crotonate > cinnamate and for a given acid the trifluoroacetate ester is markedly more reactive than the methyl or ethyl ester.

The experimental data presented in Table 6 using ethyl fumarate as the dienophile show that the enantioselective Diels–Alder reaction with catalysts **14A** and **14B** proceeds well even with less reactive dienes such as butadiene.[10] Similarly, a range of dienes of different reactivity can be induced to add enantioselectively to trifuoroethyl acrylate (Table 7).

Diels–Alder reactions of cyclic α,β-enones such as 2-cyclopentenone and 2-cyclohexenone with less reactive dienes also proceed with considerably better yield and enantioselectivity using oxazaborolidinium triflimides as compared to oxazaborolidinium triflates.[10]

Table 6: Diels–Alder reactions of diethyl fumarate, 20 mol% **14A** or **14B** as catalyst, and less reactive dienes.

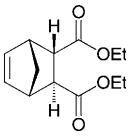
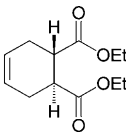
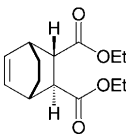
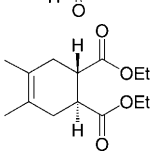
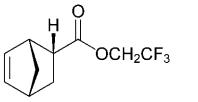
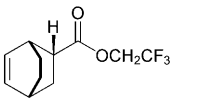
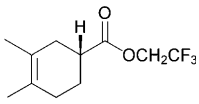
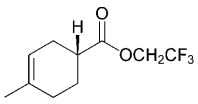
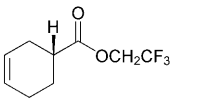
Diene	Product	Cat.	Solvent	*T* [°C], *t* [h]	Yield, *ee* [%]
		**14A**	$PhCH_3$	−60, 2	99, >99
		**14B** **14B**	CH_2Cl_2 $PhCH_3/CH_2Cl_2$	20, 40 20, 16	79, 88 92, 93
		**14B** **14A**	CH_2Cl_2 $PhCH_3$	20, 40 20, 40	80, 96 90, 98
		**14B**	$PhCH_3$	20, 16	99, 98

Table 7: Diels–Alder reactions of trifluoroethyl acrylate, 20 mol% **14A** or **14B**, and less reactive dienes.

Diene	Product	Cat.	Solvens	*T* [°C], *t* [h]	Yield, *ee* [%] (*endo*:*exo*)
		**14A**	$PhCH_3$	−60, 2	97, >99 (98:2)
		**14A**	$PhCH_3$	20, 40	81, 98 (>99:1)
		**14A**	$PhCH_3$	20, 16	98, 98
		**14A**	$PhCH_3$	0, 8	99, 98
		**14A** **14B**	$PhCH_3$ neat	20, 40 20, 24	78, 88 96, 95

4. Diels–Alder Reaction of Quinones

Compared to other α,β-unsaturated carbonyl compounds, quinones are even better partners in Diels–Alder reactions with various dienes.[10] 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 natural products and other complex molecules. Some results with 2,5- and 2,3-dimethylbenzoquinone and a

Table 8: Diels–Alder reaction of 2,5- and 2,3-dimethylbenzoquinone with various dienes using catalyst **14A**.

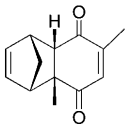
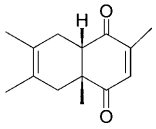
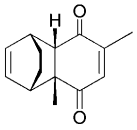
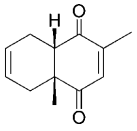
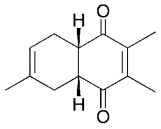
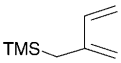
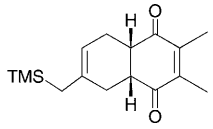
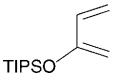
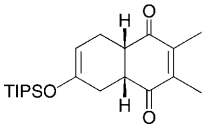
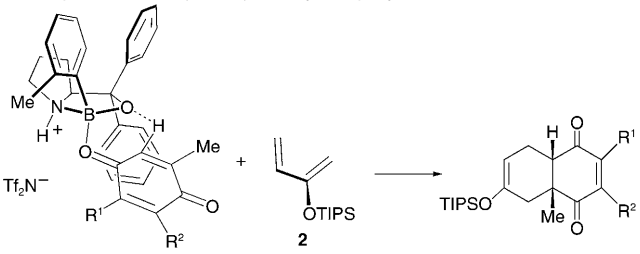
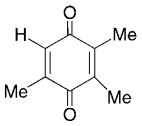
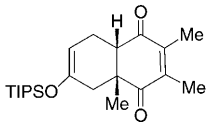
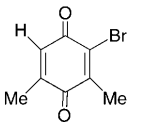
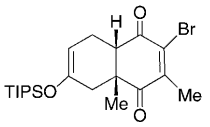
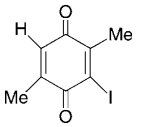
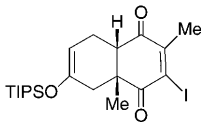
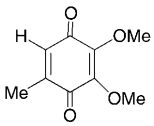
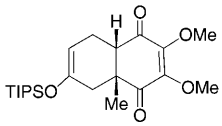
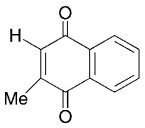
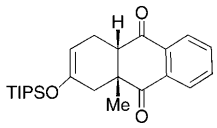
Diene	Product	Solvent	*T* [°C], *t* [h]	Yield, *ee* [%]
		CH_2Cl_2	−95, 2	99, >99
		CH_2Cl_2	−95, 2	99, >99
		CH_2Cl_2	−78, 16	99, >99
		CH_2Cl_2	−78, 48	97, 91
		$PhCH_3$ $PhCH_3$ CH_2Cl_2	−20, 0.5 −78, 0.5 −95, 2	95, 70 94, 88 99, 90
		$PhCH_3$	−78, 0.5	96, >99
		$PhCH_3$ CH_2Cl_2	−92, 2 −95, 2	80, >99 98, >99

Table 9: Enantioselective Diels–Alder reactions of trisubstituted 1,4-benzoquinones catalyzed by **14A** (0.2 equiv).



Quinone	Product	*T* [°C], *t* [h]	Yield, *ee* [%]
		−78, 12	98, 99
		−78, 3	96, 97
		−78, 16	99, >99
		−50, 48	85, 95
		−60, 36	96, 91

variety of dienes are outlined in Table 8.[10] The high yields and enantioselectivities of these reactions encouraged us to examine a range of other quinones, including tri-, di-, and monosubstituted quinones. The results for the unsymmetrical diene 2-triisopropylsilyloxybutadiene and five different trisubstituted quinones are displayed in Table 9 and, again, are outstanding in terms of yield and enantioselectivity.[12] In addition, the reactions with two unsymmetrical components exhibit excellent position selectivity. The products in each case are as expected from the pre-transition-state assembly shown in Table 9 with the help of the following additional information: 1) the diene attaches to the less substituted double bond; 2) C(1) of triisopropylsilyloxybutadiene is more nucleophilic than C(4) and its bonding to the quinone is stronger than that of C(4) in the transition state (concerted, asynchronous pathway); 3) C(1) attaches preferentially to the carbon of the quinone which is β to the catalyst-coordinated carbonyl group; and 4) an *endo*, suprafacial addition occurs at the sterically unshielded face of the α,β-double bond to form the Diels–Alder adduct.[12]

Highly efficient and enantioselective Diels–Alder reactions of 2-triisopropylsilyloxybutadiene with a series of di- and mono-substituted quinones are exemplified in Tables 10 and 11.[12] Here also, one position isomer predominates when more than one is theoretically possible.

As a result of observations reported in Tables 8–11, we derived the following selection rules for Diels–Alder reactions of quinones using catalyst **14A** to serve as guides for the prediction of reaction products:[12]

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 5).
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 6).
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), espe-

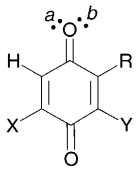


Figure 5.

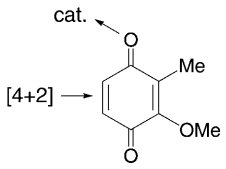
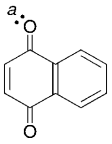
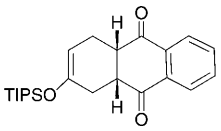
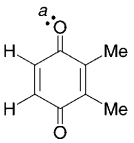
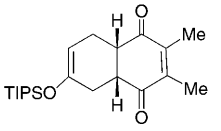
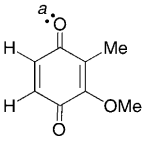
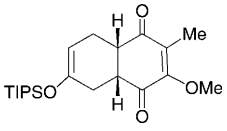
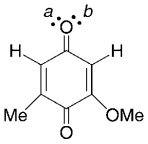
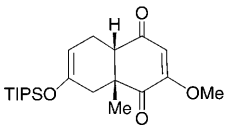
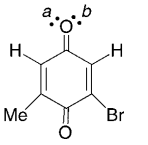
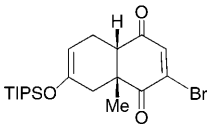


Figure 6.

Table 10: Enantioselective Diels–Alder reactions of 2,3- or 2,6-disubstituted 1,4-benzoquinones and 2-triisopropylsilyloxy-1,3-butadiene catalyzed by **14A** (0.2 equiv).

Quinone	Product	*T* [°C], *t* [h]	Yield, *ee* [%]
		−78, 2	98, 97
		−95, 2	98, >99
		−78, 12	84, 90
		−50, 96	98, 92
		−78, 4	95, 91

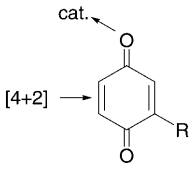


Figure 7.

cially one or two π-electron donor groups.

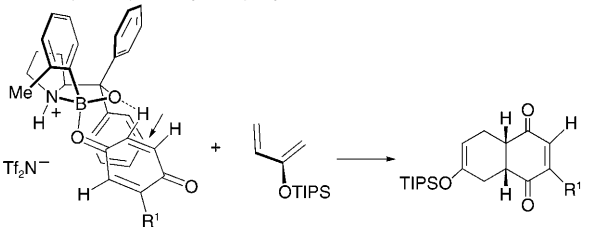
4) For monosubstituted 1,4-quinones (or *p*-benzoquinone itself), the major product pathway will involve coordination of catalyst at C=O *syn* to the HC=CH subunit that undergoes [4+2]-cycloaddition (see Figure 7).
5) C(1) of 2-triisopropylsilyloxy-1,3-butadiene (**2**), the more nucleophilic end of 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.

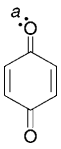
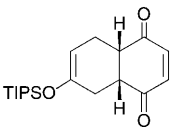
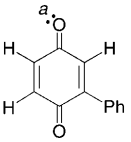
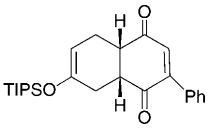
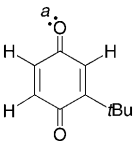
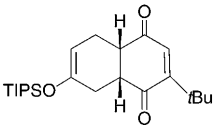
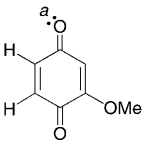
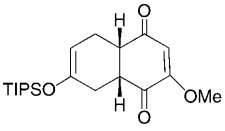
5. Diels–Alder Reactions of $AlBr_3$-activated Oxazaborolidines

The discovery of the high efficiency and utility of proton-activated oxazaborolidines prompted the reinvestigation of our initial approach to the activation of oxazaborolidines by Lewis acids. The original negative findings for BF_3, $SnCl_4$, $ZnCl_2$, $MeAlCl_2$ were confirmed. Despite the ineffectiveness of these Lewis acids, we then examined the use of the soluble and very strong Lewis acids BBr_3 and $AlBr_3$ (the latter as a commercially available 1.0 M solution in CH_2Br_2). 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.[13] 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 **9A** and **14A** and fully consistent with the analogous structure **15** (Figure 8).[13] A comparison of the Diels–Alder reactions catalyzed by **15** with those catalyzed by the proton-activated oxazaborolidines **9A** and **14A** revealed generally similar results in terms of reaction yield and enantioselectivity. One advantage of the $AlBr_3$-activated **15** was that the reaction proceeded well with only 4 mol% of catalyst, as compared to ca. 10 mol% for **9A** and **14A** in most instances (possibly the result of less serious product inhibition of the catalytic process). The results for the reactions of cyclopentadiene with a variety of dienophiles are shown in Table 12.[13]

Excellent results were also obtained for catalyst **15** in Diels–Alder reactions of quinones with cyclopentadiene (Table 13) and also various other dienes (Table 14).[13]

Table 11: Enantioselective Diels–Alder Reactions of unsubstituted or monosubstituted 1,4-benzoquinones and 2-triisopropylsilyloxy-1,3-butadiene catalyzed by **14A** (0.2 equiv).



Quinone	Product	*T* [°C], *t* [h]	Yield [%], *ee*
		−78, 6	85, 88
		−78, 24	87, 94
		−78, 12	92, 91
		−78, 16	95, 91

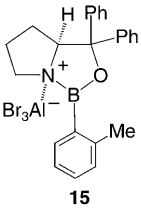
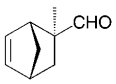
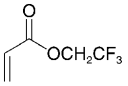
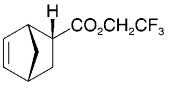
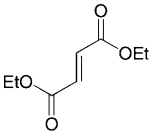
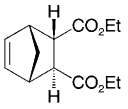
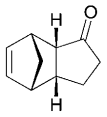
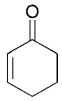
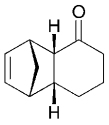


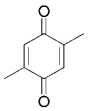
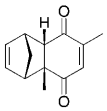
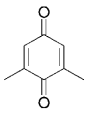
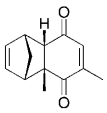
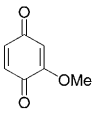
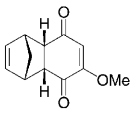
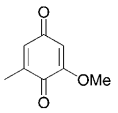
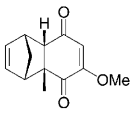
Figure 8. Oxazaborolidine–$AlBr_3$ complex.

Table 12: Enantioselective Diels–Alder reactions of cyclopentadiene with diverse dienophiles in the presence of 4 mol% catalyst **15** in CH_2Cl_2.

Dienophile	Product	*T* [°C], *t* [h]	Yield, *ee* [%] (*endo*/*exo*)
		−78, 2[a]	99, 93 (8:92)
		−78, 8[a]	98, 99 (97:3)
		−78, 6[b]	95, 98
		−40, 1[b]	95, 92 (97:3)
		−20, 6[b]	99, 95 (94:6)

[a] Reaction was carried out at 0.5 M concentration with respect to dienophile and with 5 equivalents of cyclopentadiene. [b] The reaction was carried out at 2.0 M concentration with respect to the dienophile and with 5 equivalents of cyclopentadiene.

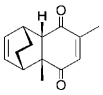
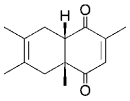
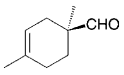
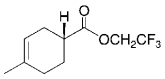
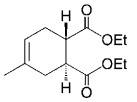
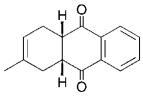
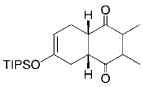
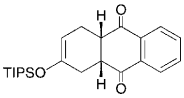
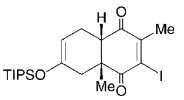
Table 13: Enantioselective Diels–Alder reactions of cyclopentadiene with various quinones in the presence of 4 mol% catalyst **15** in CH_2Cl_2.[a]

Quinone	Product	*T* [°C], *t* [h]	Yield, *ee* [%] (*endo*/*exo*)
		−78, 0.5	99, 99
		−78, 2	99, 97
		−78, 12[b]	97, 72
		−78, 12	99, 88

[a] Each reaction was carried out at 0.2 M with respect to the dienophile with 5 equivalents of cyclopentadiene. [b] Toluene was used as solvent.

The data summarized in Tables 12–14 and the need to use only 4 mol% of catalyst clearly indicate the value of $AlBr_3$ activation which is convenient and reproducible using a solution of $AlBr_3$ in CH_2Br_2. We also expect that the scope of the reaction will extend far beyond the substrates listed here, for instance to the use of less reactive and heterodienes, such as furan.[13]

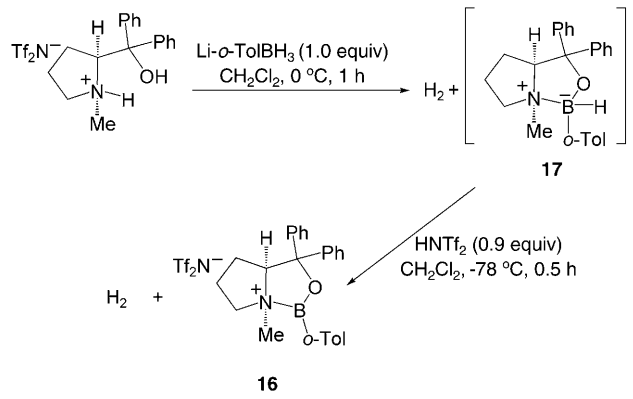
Table 14: Enantioselective Diels–Alder reactions of an assortment of dienes and dienophiles in the presence of 4 mol% catalyst **15**.

Dienophile	Product	*T* [°C], *t* [h]	Yield, *ee* [%] (*endo*/*exo*)
		−78, 16[a]	95, 99
		−78, 16[a]	97, 96
		−78, 16[b]	99, 97
		−20, 16[c]	98, 91
		−20, 48[d]	71, 97
		−78, 16[a]	99, 84
		−78, 1[e]	99, 99
		−78, 16[e]	99, 96
		−78, 12[f]	99, 99

[a] The reaction was carried out at 0.2 M initial concentration (C_0) with respect to the dienophile in CH_2Cl_2 with 5 equivalents of diene. [b] C_0 0.5 M with respect to dienophile in CH_2Cl_2. [c] C_0 1.0 M with respect to the dienophile in CH_2Cl_2. [d] The reaction was carried out neat with 3 equivalents of diene. [e] C_0 0.3 M with respect to the dienophile in PhMe with 1.5 equivalents of the diene. [f] 2 equivalents of diene used.

6. Enantioselective Catalysis by a Lewis-Acidic *N*-Methyl-oxazaborolidinium Cation

Another type of chiral Lewis acid with the oxazaborolidine core is the *N*-methylated oxazaborolidinium cation **16** (see Scheme 4). The most obvious method to form this cation—direct methylation of the corresponding oxazaborolidine **1**—has not been workable, probably because of the very low basicity of **1**. Even the most powerful available methylating agents, $MeOSO_2CF_3$ and $Me_3O^+BF_4^-$, did not convert **1** to **16**. The successful generation of **16** was achieved by the two-step, one-flask sequence shown in Scheme 4.[14] The salt generated from (*S*)-1,1-diphenylpyrrolidinemethanol and triflimide in CH_2Cl_2 was treated with 1 equivalent of lithium *o*-tolylborohydride and the resulting cyclic dipolar ion **17** was treated with slightly under 1 equivalent of triflimide to give cation **16**.[14] This synthesis is interesting because it is so different from the methods that start with preformed oxazaborolidine which have been used for catalysts **9A** and **14A** or **15**. The formation of the boron-containing ring and

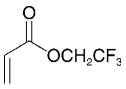
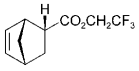
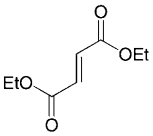
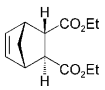
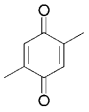
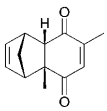


Scheme 4. Synthesis of catalyst **16**.

the strongly Lewis-acidic catalyst **16** are clearly driven by the great stability of the co-product H_2 and its evolution as a gas from the reaction mixture.

The *N*-methyl-oxazaborolidinium cation **16** functions very well as a chiral Lewis acid as shown by the test reactions with cyclopentadiene that are summarized in Table 15.[14]

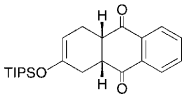
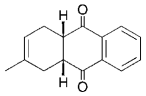
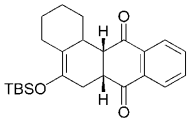
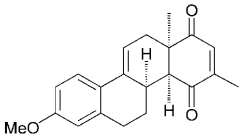
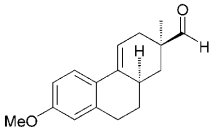
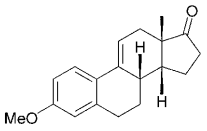
Table 15: Enantioselective Diels–Alder reactions of cyclopentadiene and various dienophiles using catalyst **16**.

Dienophile	Product	*T* [°C], *t* [h]	Yield, *ee* [%] (*endo*/*exo*)
		−78, 1.5	99, 97 (97:3)
		−60, 8	99, 96
		−50, 8	99, 92 (96:4)
		−78, 1.5	96, 90 (10:90)
		−78, 1[b]	97, 98

[a] Each reaction was carried out at 0.25 M in CH_2Cl_2 with respect to the dienophile, and 10 mol% of catalyst **16**. [b] Reaction carried out at 0.20 M.

We have compared catalyst **16** with the $AlBr_3$-activated oxazaborolidine **15** in the Diels–Alder reaction with a variety of dienes and dienophiles. The results are outlined in Table 16. Although higher levels of the *N*-methyl catalyst **16** are required in order to attain a convenient rate of reaction as compared to the *N*-$AlBr_3$ catalyst (10 mol% vs 4 mol%), the yields and enantioselectivities are similar. Catalysts **9A**, **14A**, and **16** produce the same enantiomeric products from a wide range of substrates and appear to function by the same basic mechanism.

Table 16: Comparative studies of [4+2]-cycloaddition reactions catalyzed by **16** and **15**.

Product	Cat. **16**		Cat. **15**	
	T [°C], *t* [h]	Yield, *ee* [%] (*endo*/*exo*)	*T* [°C], *t* [h]	Yield, *ee* [%] (*endo*/*exo*)
	−78, 4[a]	95, 96	−78, 16[b]	99, 96
	−78, 16[c]	97, 84	−78, 16[b]	99, 84
	−78, 4[a]	83, 96	−78, 2[a]	90, 12
	−78, 2.5[a]	87, 98	−78, 2[a]	87, 84
	−78, 2.5[a]	90, 98	−78, 0.5[a]	95, 98
	23, 24[a,d]	98, 82 (99)[e]	−20, 48[a]	50, 75

[a] Catalyst loading at 20 mol%. [b] Catalyst loading at 4 mol%. [c] Catalyst loading at 10 mol%. [d] Prepared using the *R* enantiomer. [e] After a single recrystallization.

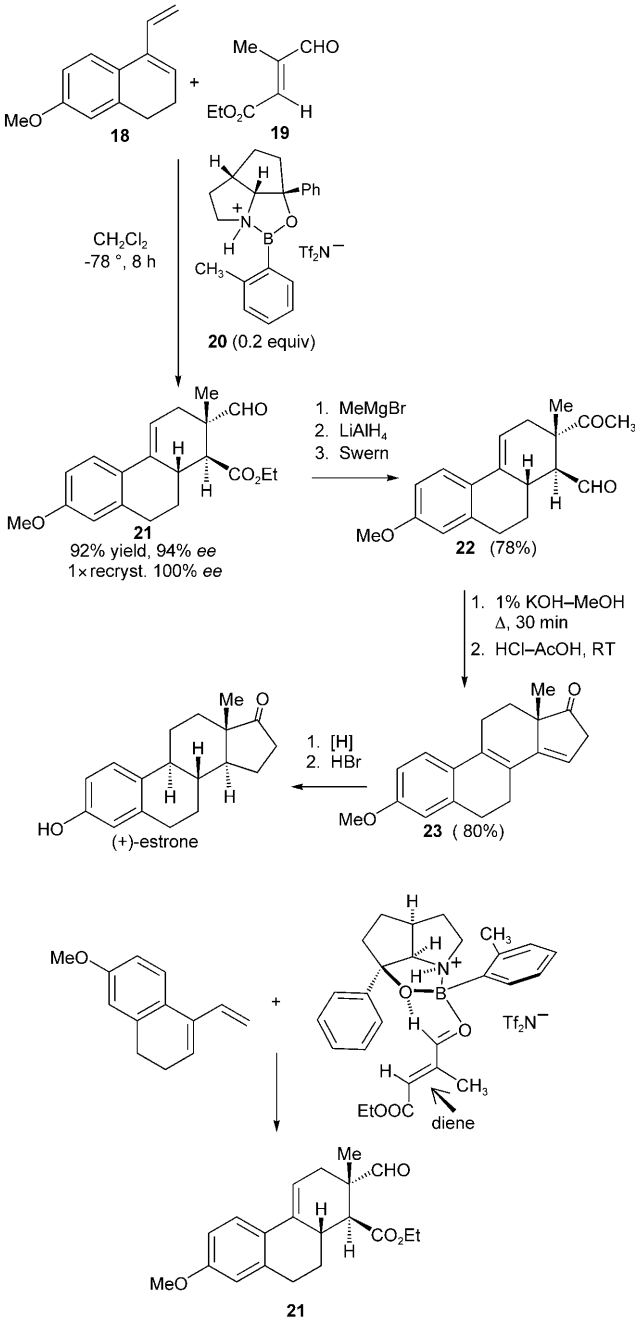
7. Application of Chiral Cationic Oxazaborolidinium Catalysts to Enantioselective Synthesis

Cationic chiral oxazaborolidines have been shown to be extremely useful and versatile catalysts for the synthesis of many biologically interesting complex molecules. This utility has been demonstrated by applications which will be outlined in this section. The new catalysts enhance the power of synthesis not only because they allow enantioselective syntheses which have not previously been possible, but also because the mechanistic model is powerfully predictive. This makes it possible to design enantioselective syntheses retrosynthetically with added confidence and also to select at the outset the appropriate enantiomer of the oxazaborolidine.

7.1. New Synthesis of Estrone

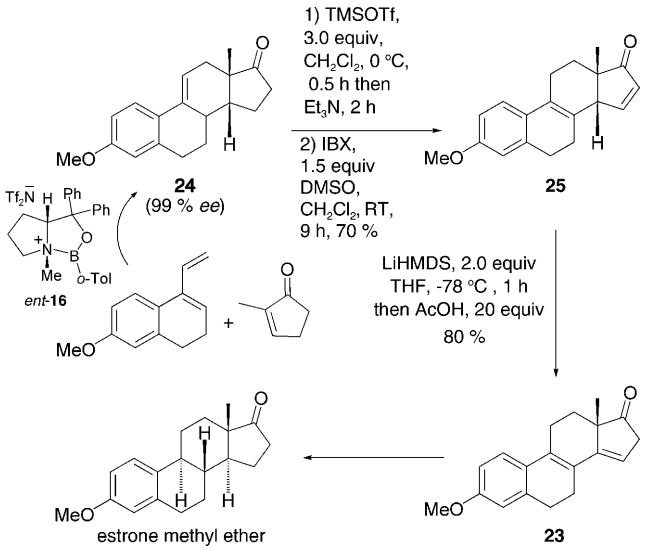
Two different enantioselective routes for the synthesis of estrone have been developed in our laboratories which take advantage of cationic oxazaborolidine-catalyzed Diels–Alder reactions to establish diastereomer-controlling stereocenters in the very first step. In the earlier of these,[15] outlined in

Scheme 5, Dane's diene **18**,[16] and dienophile **19** underwent Diels–Alder reaction in the presence of catalyst **20** to form the adduct **21** in 92% yield and 94% *ee* (enhanced to 100% *ee* by



Scheme 5. Enantioselective synthesis of (+)-estrone from Dane's diene (**18**).

a single recrystallization). The catalyst **20**, which is readily available by enantioselective synthesis,[15] behaves similarly to the enantiomer (*ent*-**9A**) of the (*S*)-proline-derived catalyst **9A**, as expected from the mechanistic model. In our experience, catalysts *ent*-**9A** and **20** may be used interchangeably. The tricyclic adduct was transformed in three high-yielding steps to the keto aldehyde **22** which underwent addition/isomerization to form the tetracyclic dienone **23**. (+)-Estrone is available from **23** by a one-flask procedure[17] in high yield. The second route to (+)-estrone, which is shorter still, is summarized in Scheme 6. Reaction of Dane's



Scheme 6. A second synthesis of estrone. IBX = 2-iodoxybenzoic acid; DMSO = dimethylsulfoxide; HMDS = hexamethyldisilazane.

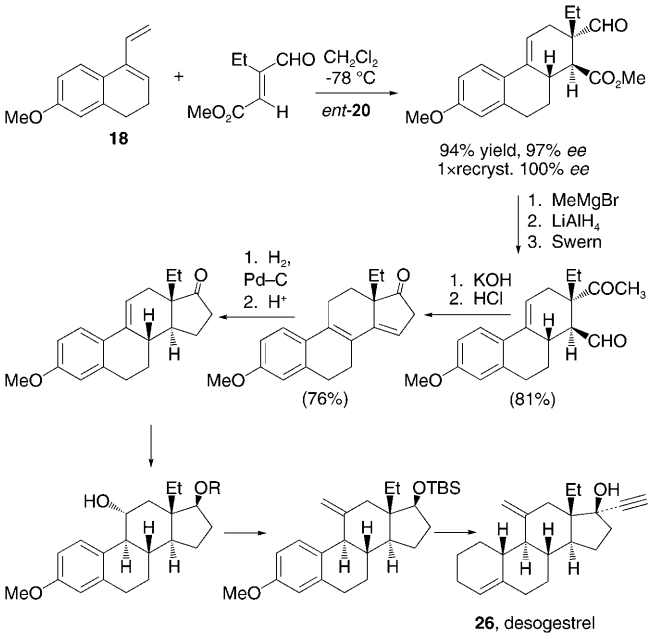
diene (**18**) with 2-methyl-2-cyclopentenone in the presence of the *N*-methyl-oxazaborolidinium cation *ent*-**16** provided the Diels–Alder adduct **24** in 82% yield and 98% *ee* (99% *ee* after a single recrystallization). Ketone **24** was transformed to the corresponding α,β-enone **25** and then isomerized to dienone **23**, the above described intermediate for the synthesis of (+)-estrone.

7.2. Enantioselective Synthesis of Desogestrel

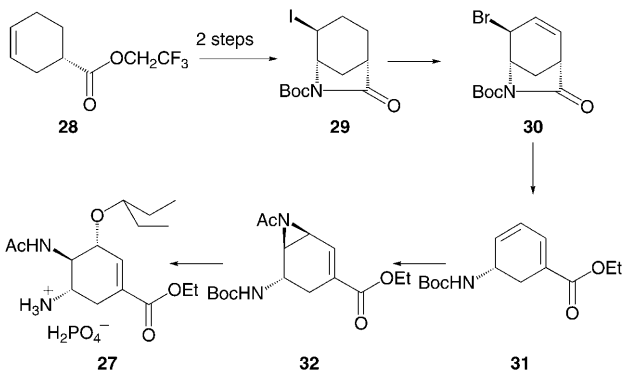
The third-generation oral contraceptive desogestrel **26** is currently produced industrially by total synthesis. A shorter, simpler route to **26** has been developed using as a first step a similar Diels–Alder reaction to that described in Section 7.1 for the synthesis of (+)-estrone (see Scheme 6). The overall process is summarized briefly in Scheme 7.[15]

7.3. Enantioselective Synthesis of the Oral Antiflu Agent Oseltamivir

The antiflu drug oseltamivir (Tamiflu) (**27**) is produced industrially starting with either shikimic or quinic acid by a lengthy route that involves potentially hazardous azide-containing reagents and intermediates.[18] A shorter and simpler route has been described that starts from the Diels–Alder adduct prepared from 1,3-butadiene and trifluoroethyl acrylate using as catalyst *ent*-**14A** (10 mol%, 23 °C, 97% yield, > 97% *ee*).[19] The pathway for this synthesis of **27** is summarized in Scheme 8. The chiral trifluoroethyl ester **28**



Scheme 7. Synthesis of desogestrel.

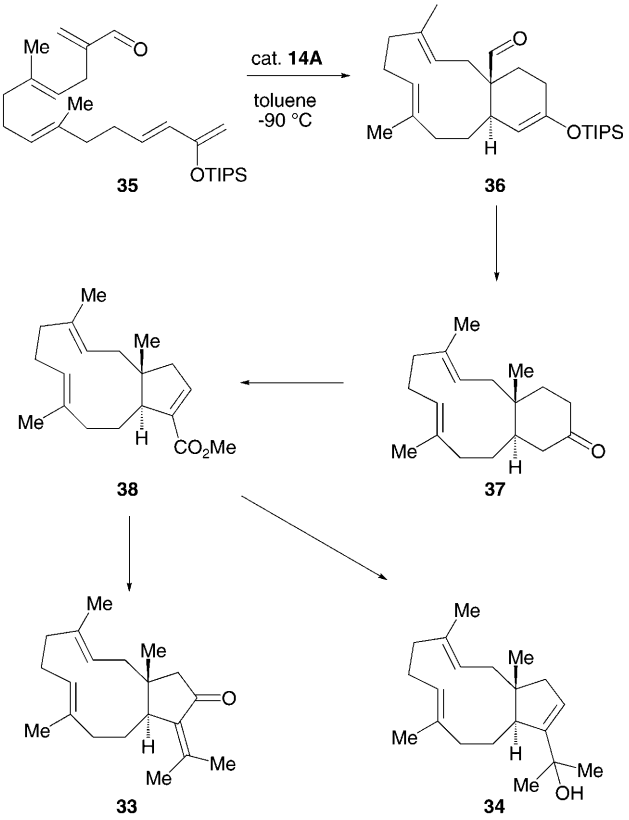


Scheme 8. Enantioselective synthesis of oseltamivir. Boc = *tert*-butoxycarbonyl.

was transformed into iodolactam **29**[19,20] which upon elimination of HI and allylic bromination gave the bromo lactam **30** in high yield, further converted with ethanolic base to diene ester **31**. Bromoamidation[19,21] of **31** and base treatment afforded aziridine ester **32** from which oseltamivir was obtained two steps in ca. 30% overall yield.

7.4. Synthesis of Dolabellanes and Intramolecular Diels–Alder Reactions

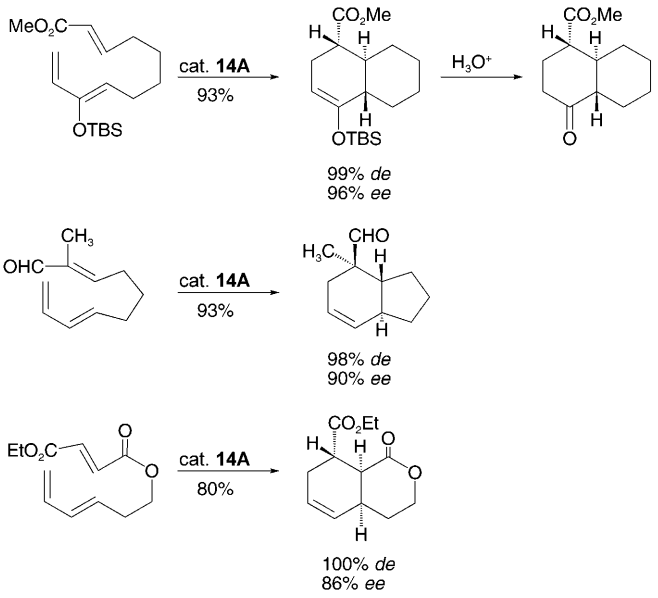
The intramolecular subtype of the Diels–Alder reaction is an exceedingly powerful synthetic method. Cationic chiral oxazaborolidines can serve as effective reagents for the catalysis and control of the absolute stereochemical course of these bicyclization reactions. One novel example is the application of catalyst **14A** to the synthesis of members of the dolabellane family of marine natural products including dolabellatrienone (**33**) and dolabellatriene (**34**) (Scheme 9).[22,23] The readily accessible penta-unsaturated



Scheme 9. Synthesis of dolabellatriene and other dolabellanes.

α,β-enal **35**, when added slowly to the solution of the triflimide of cation **14A** in toluene at −90 °C, underwent internal Diels–Alder reaction to form as major product the required bicyclic aldehyde **36** in 72% yield and 90% *ee* (Scheme 9). This bicyclization reaction is noteworthy for several reasons: 1) it is highly diastereo- and enantioselective; 2) it generates an 11-membered ring efficiently as well as a 6-membered ring; 3) there are few effective methods for forming 11-membered rings; and 4) the bicyclization reaction failed with numerous achiral strong Lewis acids, including Me_2AlCl, $MeAlCl_2$, $EtAlCl_2$, and $BF_3{\cdot}Et_2O$.[22] The synthetic route led to target structures **33** and **34** by straightforward ring contraction (6→5) and appendage/functional group introduction.[22]

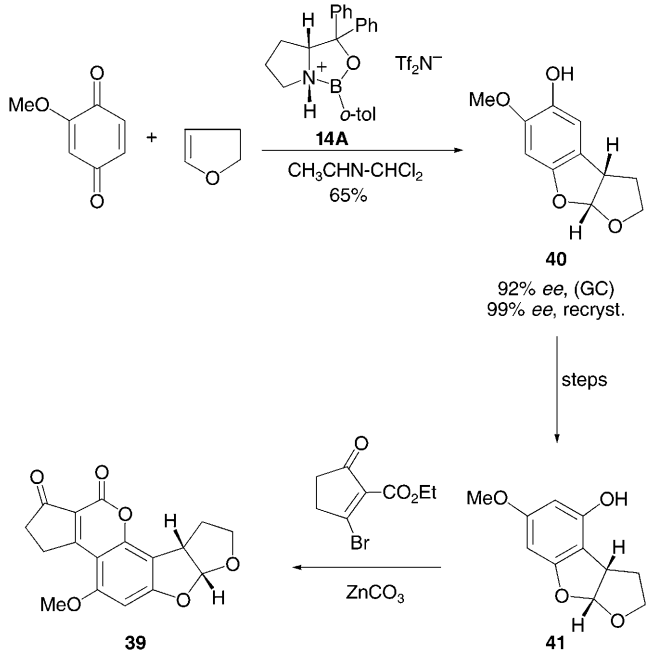
A variety of enantioselective Diels–Alder reactions were carried out using the triflimide catalyst **14A** in order to test the scope of this method.[24] Some representative reactions are shown in Scheme 10. There are numerous other applications of oxazaborolidinium cations to bicyclization reactions that are deserving of study.



Scheme 10. Three examples of intramolecular Diels–Alder reactions with the triflimide catalyst **14A**.

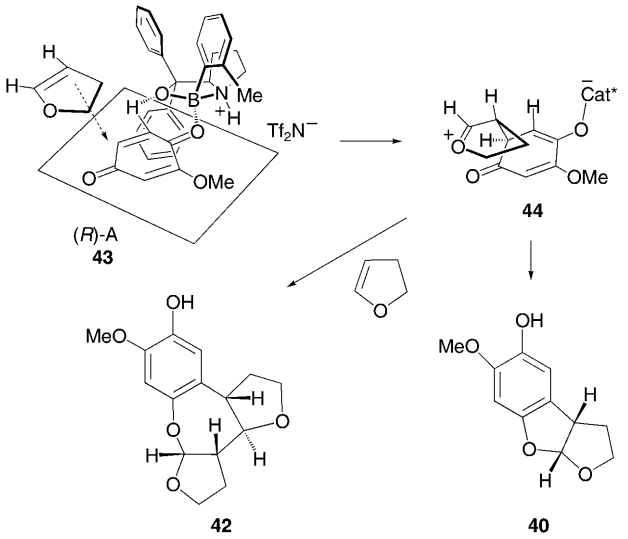
7.5. Synthesis of Aflatoxin B_2: Catalytic [3+2]-Cycloaddition

The very positive results obtained with the chiral oxazaborolidinium cations as catalysts for enantioselective Diels–Alder reactions encouraged the study of their application to [3+2] cycloaddition processes.[25] The possibility of such reactions was successfully investigated in the context of developing a simple enantioselective route to the microbial toxin aflatoxin B_2 (**39**).[26,27] The pathway of synthesis is outlined in Scheme 11. Addition of 2,3-dihydrofuran (just over 1 equiv) to a solution of triflimide catalyst **14A** 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 0 °C gave the [3+2] cycloadduct **40** in 65% yield. This was converted in several steps to the isomeric phenol **41** which upon condensation with 2-ethoxycarbonyl-3-bromo-2-cyclopentenone gave aflatoxin B_2 (**39**), as shown in Scheme 11. This is by far the simplest known enantioselective route to **39**.



Scheme 11. Enantioselective synthesis of aflatoxin B_2.

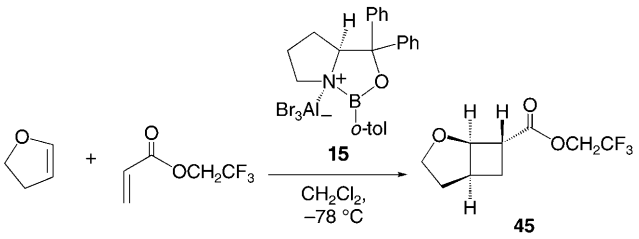
Strong evidence that the [3+2] cycloaddition reaction that produced adduct **40** is actually a two step process was obtained from a simple experiment in which a reactive intermediate was trapped. When the [3+2] cycloaddition was carried out with a ten-fold excess of 2,3-dihydrofuran over 2-methoxybenzoquinone, the formation of cycloadduct **40** was suppressed and a new product was formed in approximately equal amounts. The structure of the product was shown unequivocally to be **42** by X-ray crystallographic analysis (see Scheme 12). Since it is likely that **42** arose by trapping of the intermediate **44**, a reaction pathway for the formation of **42** that involved **44** as an intermediate was proposed. It is reasonable that both the 1:1 cycloadduct **40** and the 2:1 adduct **42** are formed via the pre-transition-state assembly **43** and intermediate **44**.[27]



Scheme 12. Reaction pathway for the formation of adducts **40** and **42** from 2,3-dihydrofuran, 2-methoxybenzoquinone, and catalyst **14A**.

7.6. Enantioselective [2+2]-Cycloaddition Reactions

The preceding section describes a process for enantioselective [3+2]-cycloaddition reactions involving the π-electron rich vinylic ether 2,3-dihydrofuran using as chiral catalyst the triflimide **14A**. 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 **15**, as outlined in Scheme 13.[29] The cycloadduct **45**, produced in 87% yield (with >99% diastereose-



Scheme 13. Formation of the bicyclic ester **45**.

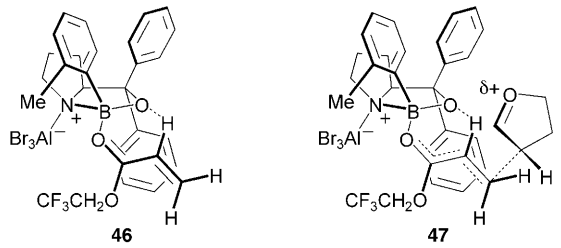
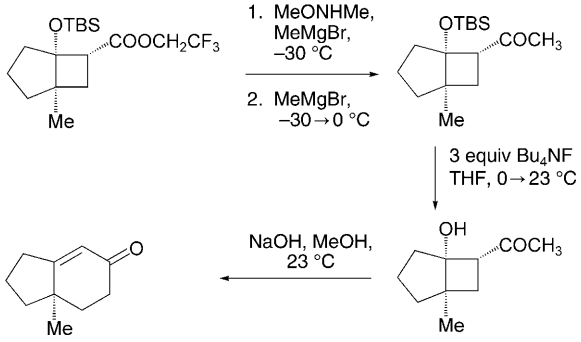


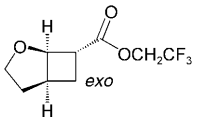
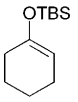
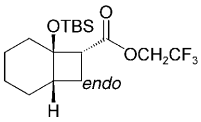
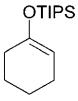
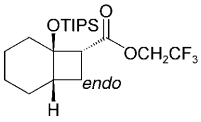
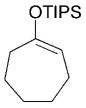
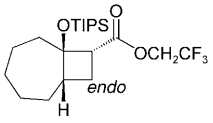
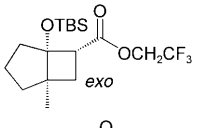
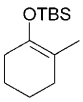
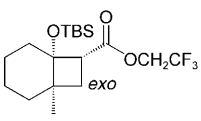
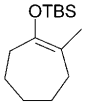
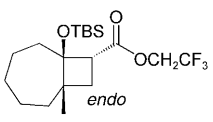
Figure 9. Intermediates in a [2+2]-cycloaddition reaction.



Scheme 14. Conversion of a chiral [2+2] cycloadduct to a chiral bicyclic α,β-enone.

lectivity and 99% enantioselectivity), was shown to have the absolute configuration shown by chemical correlation with a known chiral compound. Similar enantioselective [2+2]-cycloaddition reactions occur between trifluoroethyl acrylate and silyl enol ether derivatives of ketones. The results for a series of cyclic vinyloxysilanes and trifluoroethyl acrylate using $AlBr_3$-activated catalyst **15** are summarized in Table 17.[29,30] The structures and the absolute configurations of the adducts were established experimentally. It is noteworthy that the $AlBr_3$-activated catalyst **15** was found to be quite superior for those [2+2]-cycloaddition reactions to the triflimide-activated catalyst **14A**. Also of interest is the fact that the predominating geometry, specifically *endo* vs *exo* $COOCH_2CF_3$ substitution, varies with the vinyl ether substrate. It has been proposed that all the reactions summarized in Table 17 occur by non-concerted, two-step processes starting from complex **46** and proceeding via the pre-transition-state assembly **47** (Figure 9). Such a pathway can explain the divergent stereoselectivities shown in Table 17. The [2+2]-cycloadducts listed in Table 17 are useful as chiral synthetic intermediates. One such application is outlined in Scheme 14 which describes a pathway to chiral fused-ring, bicyclic α,β-enones.

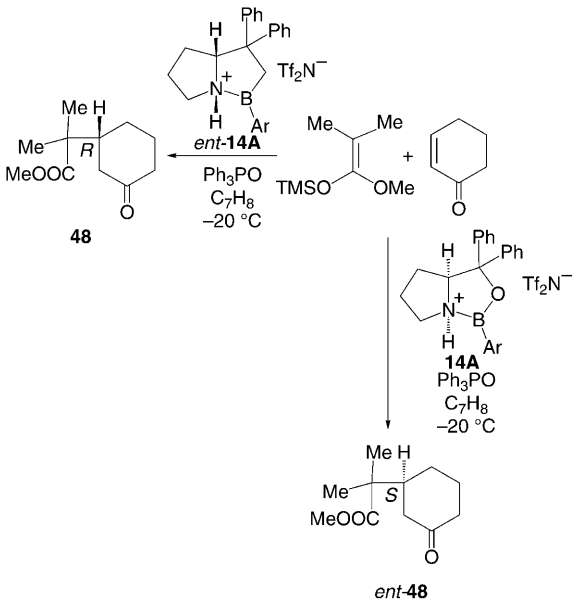
Table 17: Enantioselective [2+2]-cycloaddition of trifluoroethyl acrylate to enol ethers with 10 mol% of catalyst **15** in CH_2Cl_2 at −78 °C.

Enol ether	Product	*t* [h]	Yield [%]	*ee* [%]
		3	87 (1:>99)	99
		6	97 (82:18)	92
		12	99 (97:3)	92
		6	99 (99:1)	99
		0.5	99 (1:99)	98
		16	99 (10:90)	98
		4	91 (96:4)	98

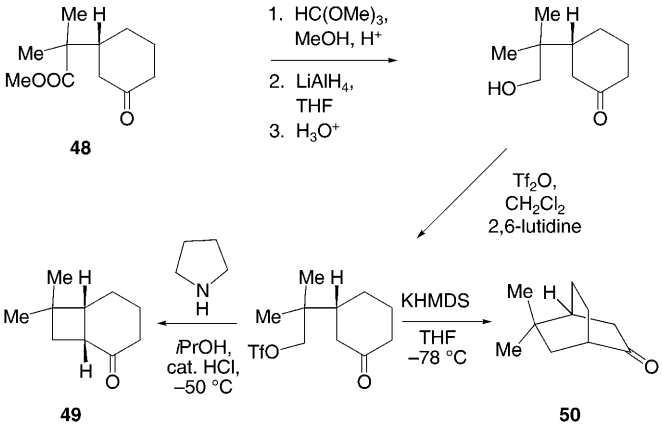
7.7. Enantioselective Michael Addition to α,β-Unsaturated Enones

The reaction of α,β-enones with silyl enol ethers of esters using proton-activated chiral oxazaborolidines follows a Michael addition pathway rather than the [2+2]-cycloaddition route described in the preceeding section. The Michael addition process is exemplified in Scheme 15 using 2-cyclohexanone and the trimethylsilyl enol ether of methyl isobutyrate as substrates.[31] The reaction shown in this Scheme proceeds efficiently (91% yield) and with a 20:1 enantioselectivity if a small amount of triphenylphosphine oxide is used as a trap for transiently formed Me_3Si^+ (or equivalent).[32] The Michael adduct **48** could be converted either to the fused-ring bicyclic product **49** or the bridged-ring isomer **50** as shown in Scheme 16.[31] The chiral [4.2.0]-bicyclooctanone **49** is an intermediate for the enantioselective synthesis of the unique sesquiterpene β-caryophyllene.[33]

The enantioselective oxazaborolidinium cation promoted Michael addition process has been shown to be applicable to a variety of α,β-unsaturated carbonyl compounds.[31]



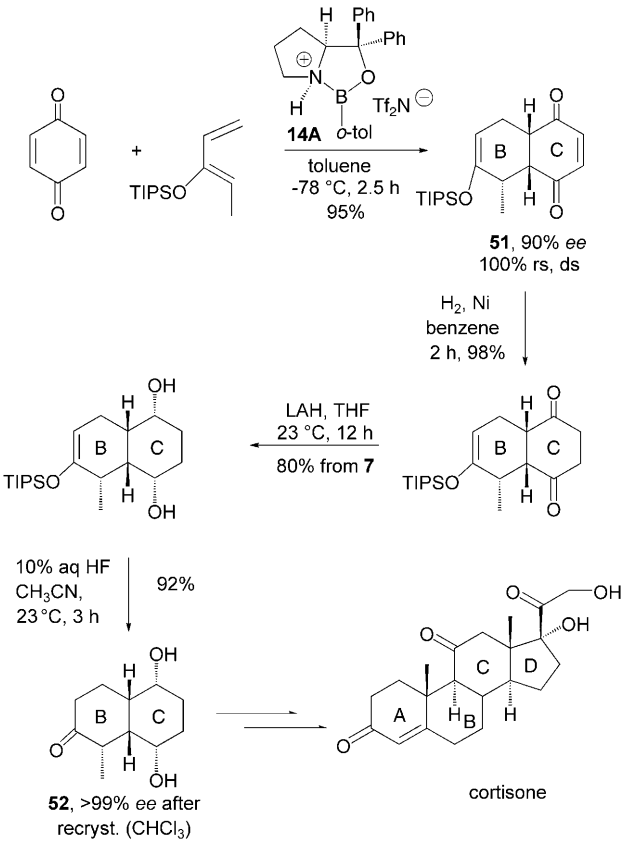
Scheme 15. Enantioselective Michael addition to 2-cyclohexenone.



Scheme 16. Synthesis of chiral fused or bridged-ring ketones from a Michael adduct.

7.8. Conversion of Classical Synthesis of Racemic Natural Products into Enantioselective Routes

The transformative role of chiral oxazaborolidinium cations can be gauged by the recent demonstration that several of the great achievements of synthesis of racemic natural products from the period 1950 to 2000 can be elevated to the most modern standards through their use.[34] Many of these synthesis commenced with a reaction of two achiral Diels–Alder components to form a racemic adduct. That initial construction, though providing a useful platform for further elaboration toward the target structure, necessitated some sort of resolution step in order to provide enantiomerically pure, as opposed to racemic, product. The use of chiral oxazaborolidinium catalysts to remedy this situation can be exemplified by the specific case of the total synthesis of cortisone/cortisol, in particular by the elegant synthesis of Louis Sarett and co-workers at Merck Co (USA).[35] The



Scheme 17. A summary of the modernized version of the Sarett–Merck total synthesis of cortisone/cortisol. LAH = lithium aluminum hydride.

modified version[34] of the Sarett–Merck synthesis is outlined in its early stages in Scheme 17. The Sarett–Merck synthesis was never commercialized, partly because optical resolution was difficult and could only be achieved at the (late) stage of an advanced tricyclic intermediate. Using the chiral catalyst **14A**, the chiral Diels–Alder adduct **51** was easily obtained in the required absolute configuration with 20:1 enantioselection. A simple recrystallization of intermediate **52** affords the enantiomerically pure compound.

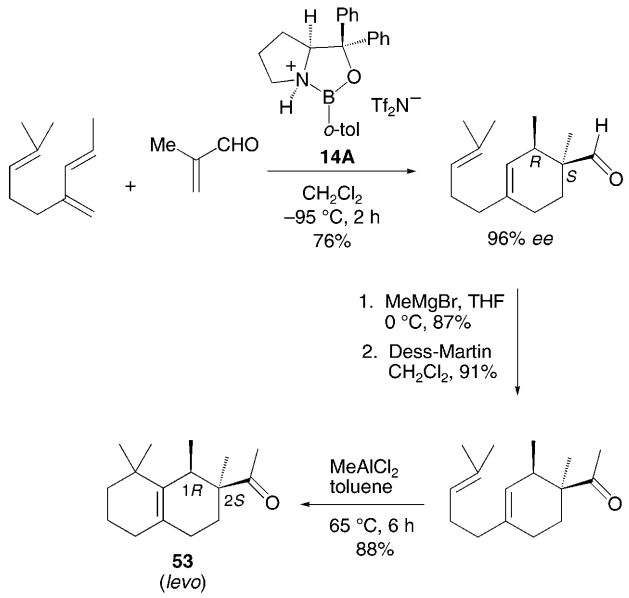
In a similar way we have demonstrated[34] modern enantioselective versions of Kende's total synthesis of the alkaloid dendrobine,[36] Eschenmoser's photochemical route to vitamin B_{12},[37] the Chu-Moyer/Danishefsky synthesis of mirocin C,[38] Mehta's general approach to triquinanes,[39] and several others.

7.9. Other Applications

The application of the chiral triflimide-activated catalyst **14A** allowed the first enantioselective synthesis of the woody odorants georgyone (**53**) and arborone (**54**) and permitted the assignment of absolute configuration (Figure 10).[40] The synthesis of georgyone (levorotatory form) is shown in Scheme 18. It is interesting that, although **53** possesses a pleasant and strong woody odor, the enantiomer has a sweaty, metallic odor. Arborone (**54**) also has very nice woody odor,

53 (*levo*) **54** (*dextro*)

Figure 10. Absolute configurations of woody odorants as determined by enantioselective synthesis.



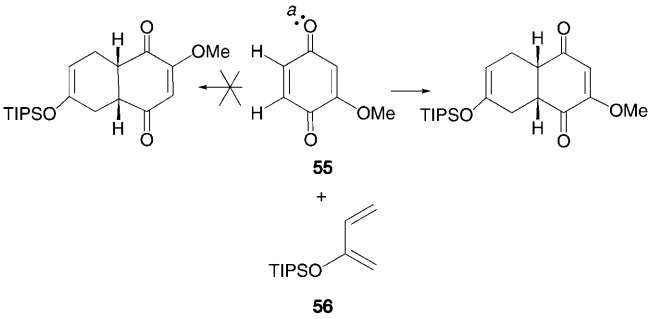
Scheme 18. Synthetic route to the woody odorant georgyone (**53**).

but its enantiomer is virtually odorless. These and other data provided new insights into the chemical nature of the binding site of the olfactory receptor for woody odorants.[40]

Chiral oxazaborolidinium cation **14A** has also been applied successfully to the enantioselective cyanosilylation of aldehydes[41] and methyl ketones.[42]

7.10. Some Mechanistic Aspects of the Enantioselective Catalysis of Diels–Alder Reactions by Chiral Oxazaborolidinium Ions

In Section 3 of this Review we noted that the face selectivity of oxazaborolidinium-catalyzed Diels–Alder reactions at the dienophile depends on the structural type of the dienophile. For 2-substituted α,β-enals, formyl CH···O hydrogen bonding in the catalyst–dienophile complex leads to a preferred pathway via **8**, whereas for α,β-unsaturated carbonyl compounds having an α-C–H bond (for instance esters, lactones, ketones, or quinones) α-CH···O hydrogen bonding favors reaction via complex **13** (see Figure 3). This mechanistic rational is in accord with all the results summarized herein, and it appears to be reliably predictive. With benzoquinones as dienophiles there are clearly other factors which determine the preferred pathway for reaction. For example, in the reaction of 2-methoxy-1,4-benzoquinone (**55**) and 2-triisopropylsilyloxy butadiene (**56**) these other factors include the following: 1) preferred reaction at the 5,6-double bond (clearly favorable because it leaves intact the highly stabilized β-methoxy-α,β-enone subunit) and 2) preferred coordination of the catalyst at lone pair *a* of the quinone, which happens to be on the more basic of the two carbonyl groups in **55** (see Scheme 19).[43] These and other data on



Scheme 19. Oxazaborolidinium-catalyzed Diels–Alder pathways from **55** and **56**.

regioselectivities of Diels–Alder with quinones and unsymmetrical dienes all point to a strong preference for the pathway that involves catalyst binding to the *more basic* of the two quinone carbonyl oxygens.

In contrast to the behavior and selectivities observed with quinones, the *less basic* trifluoroethyl acrylate is more reactive that the more basic methyl acrylate.[43]

We believe that the simplest explanation of this dichotomy is one based on the degree of synchronicity of the cycloaddition. In principle, there are two extremes of the possible spectrum of transition states (TS) for a Lewis acid-catalyzed Diels–Alder reaction. At one end of the spectrum (reaction A) lies the perfectly synchronous TS in which the two new C–C bonds for ring formation are formed to the same extent (structure **TS A**) (Figure 11). At the other end is the extreme (reaction B) in which one of the two bonds is formed to a considerable extent and the other has not yet started to develop (structure **TS B**; Figure 11).[43] In reaction B, electron delocalization of the unshared lone pair on Y is much diminished in going from the initial catalyst-coordinated dienophile to **TS B**, whereas in reaction A that delocalization is not significantly decreased. Thus, the syn-

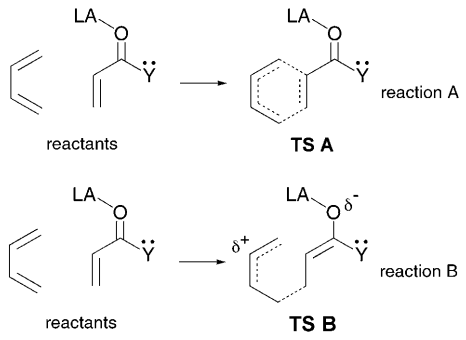


Figure 11. Range of transition states for catalyzed Diels–Alder reactions.

chronicity of the TS and also the rate of Diels–Alder reaction can be expected to depend on the nature of Y or, more generally, on the structure of the dienophile. If the TS leading to the quinone Diels–Alder product is synchronous (reaction type A), it is easy to rationalize the formation of this product since the strength of the bond between the coordinated oxygen and the catalyst will be undiminished in the TS. It would seem logical that transition states for Diels–Alder reactions of quinones would tend toward the synchronous end of the mechanistic spectrum because both terminal carbons of C=C undergoing addition are substituted by electron-withdrawing carbonyl groups (accounting for the high relative reactivity of quinones in these reactions). In addition, if one imagines an asynchronous TS for the reaction of 2-methoxy-1,4-benzoquinone (**55**) with 2-triisopropylsilyloxybutadiene (**56**, see Scheme 19), as shown in Figure 12, it is clear that the

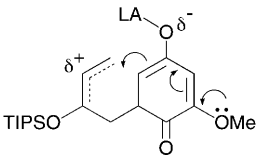


Figure 12.

effect of the methoxy group would be to favor ring closure, thus favoring a more synchronous pathway.[43] On the other hand, if the reactions of ethyl acrylate and trifluoroethyl acrylate are asynchronous (reaction B; Figure 11) and electron donation from Y is decreased in going from the coordinated transition state, the trifluoroethyl ester would be expected to react faster than the ethyl ester, as observed.[43]

8. Conclusions

Chiral oxazaborolidines derived from 1,1-diarylpyrrolidinomethanol can be activated by protonation (at N) using the strongest protic acids (e.g. CF_3SO_3H) or coordination with $AlBr_3$ (at N) to form very strong chiral Lewis acids. The resulting chiral boron electrophiles are powerful chiral catalysts that can effectively promote many [4+2], [3+2], and [2+2]-cycloaddition reactions with high enantioselectivity. Their great utility has been demonstrated by numerous applications including in multistep synthesis of complex chiral molecules.

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