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Broad-Spectrum Enantioselective Diels−Alder Catalysis by Chiral, Cationic Oxazaborolidines

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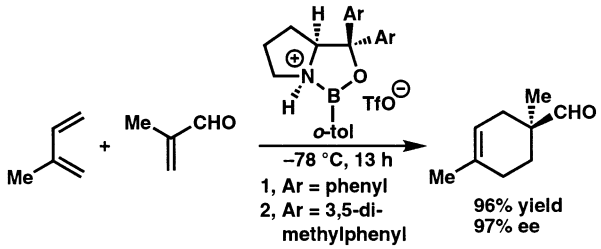
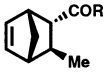
The cationic chiral Lewis acids **1** and **2**, generated from the corresponding oxazaborolidines by protonation by trifluoromethanesulfonic (triflic) acid are excellent catalysts for enantioselective reaction of 2-substituted acroleins with a variety of dienes, for example:[1]



The unusually high catalytic activity of **1** and **2** is consistent with their cationic nature[1,2] and the fact that a very strong acid (triflic but not methanesulfonic acid)[1] is required for their efficient generation. The excellent enantioselectivity and absolute stereochemical course can be understood in terms of the pretransition state assembly shown in **3**, for which there is ample precedent.[3,4] The ease of preparation, potency, and economy of catalysts **1** and **2**, their obvious utility in the Diels−Alder reactions of dienes with 2-substituted acroleins, and the evident transparency of mechanism[1] all motivated the present study which was carried out to probe the reaction with a range of other types of dienophiles. Previous research on many other chiral catalysts for enantioselective Diels−Alder reactions has repeatedly shown that the realization of high ee values for certain dienophiles generally does not carry over to other types and also that most of these chiral Lewis acids are generally not powerful enough to function successfully in cases for which the intrinsic reactivity (i.e., for the uncatalyzed reaction) is marginal or low.[5] It is most encouraging that the range of applicability of catalysts **1** and **2** in enantioselective Diels−Alder reactions exceeds that of any previously described.[5]

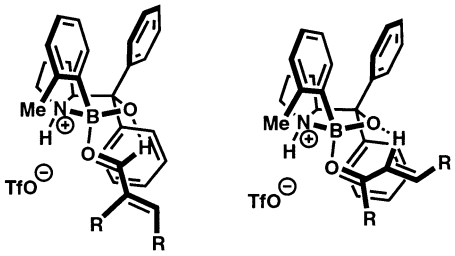
As set forth in Table 1 acrylate and crotonate esters are useful substrates in enantioselective Diels−Alder reactions with cyclopentadiene as test diene, even though the corresponding aldehydes afford adducts with only mediocre enantioselectivity.[6,7] As expected, ethyl crotonate is considerably less reactive than ethyl acrylate. Nonetheless enantioselectivities are high in both systems. Trifluoroethyl crotonate is more reactive than ethyl crotonate and affords both excellent yield and enantioselectivity. Clearly the electrophilicity of the dienophile−Lewis acid complex is greater for the trifluoroethyl ester than for ethyl because of the electron-withdrawing (inductive) effect of CF_3 relative to that of CH_3. There seems to be a limit to the range of application of this phenomenon with esters since hexafluoroisopropyl crotonate appears to be less reactive than either the ethyl or trifluoroethyl ester, presumably because it is not sufficiently basic to form a productive complex with **1** or **2**. Remarkably, as shown in Table 1, acrylic acid reacts with cyclopentadiene in the presence of **1** to afford the *endo* Diels−Alder adduct in excellent yield and enantioselectivity. This appears to be the first highly enantioselective Diels−Alder reaction with a free carboxylic acid as the dienophile component. In addition, ethyl vinyl ketone and ethyl *E*-1-propenyl ketone underwent Diels−Alder addition, the former in excellent yield and enantioselectivity. The result with ethyl vinyl ketone is noteworthy since this appears to be the only known case of this type to proceed with such high efficiency.[8,9]

Table 1. Diels−Alder Reactions of Cyclopentadiene with Representative Acyclic Dienophiles Catalyzed by Chiral Lewis Acid **1** or **2** in CH_2Cl_2

Dienophile R	Cat. (mol%)	Condt. (°C, h)	Product % yield[a] (*endo*:*exo*)[b]	%ee[c]
				
H	2 (6)	−95, 2	90 (92:8)	69[d]
Et	2 (20)	−20, 2	99 (94:6)	97
OH	1 (20)	−35, 1.5	99 (95:5)	98
OEt	1 (20)	−20, 16	94 (97:3)	98
OEt	2 (20)	−20, 16	96 (97:3)	>99
				
H	1 (20)	−95, 1.5	36 (84:16)	63[d]
Et	1 (20)	−20, 2	97 (69:31)	65
OEt	2 (13)	+4, 72	46 (91:9)	>98
OCH_2CF_3	1 (20)	−20, 16	93 (95:5)	>98

[a] Isolated yield. [b] Endo−exo ratios were determined by ^{1}H NMR or GC analysis or both. [c] Enantioselectivities were determined by ^{1}H NMR MTPA analysis or GC analysis. [d] Opposite enantiomer obtained.

The face selectivities of the enantioselective Diels−Alder reactions of α,β-unsaturated esters, α,β-enones, and acrylic acid which are summarized in Table 1 are opposite to those observed earlier for 2-substituted acroleins for which pretransition-state assembly **3** was advanced. In our view the most logical and likely pretransition-state assembly for the non-α,β-enal cases shown in Table 1 is that depicted in **4**. Complex **4** differs from **3** in the electron pair which is coordinated to the Lewis acidic center in the catalyst. To



3 **4**

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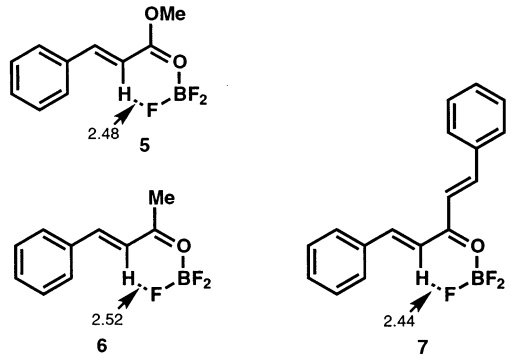
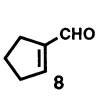
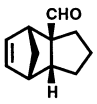
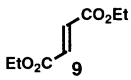
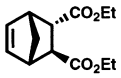
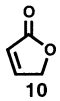
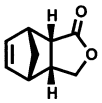
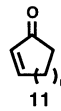
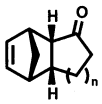
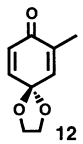
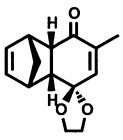
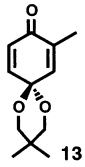
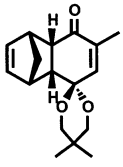
test this hypothesis stable crystalline complexes of BF_3 with methyl cinnamate, benzylidene acetone, and dibenzylidene acetone were prepared and subjected to X-ray single-crystal structure determination. The structures found for these complexes **5**, **6**, and **7**, respectively, involve coordination of BF_3 to a lone pair on the carbonyl group syn to an α,β-double bond, as proposed for complex **4**. In



addition the distances between the α-olefinic hydrogen and the nearest fluorine range between 2.44 and 2.52 Å, as shown. These distances are appreciably shorter than the sum of the van der Waals radii for H and F, 2.67 Å (H = 1.20 Å, F = 1.47 Å), which points to the likelihood of an attractive H−F interaction (coordinatively induced hydrogen bond). A similar H−O interaction may help organize the pretransition-state assemblies for the reactions shown in Table 1.[4]

Further confirmation of the unusually wide scope and promise of the enantioselective Diels−Alder reactions catalyzed by **1** and **2** is provided by the data displayed in Table 2. An outstanding result was obtained with the cyclic α,β-enal **8** which follows the expected pathway via a complex of type **3**. Diethyl fumarate (**9**) and 2-butenolide (**10**) both afforded the adducts shown in high yield and ee, the absolute stereochemical course indicating reaction via complexes of type **4**, as expected. Remarkably good results were obtained with the cyclic α,β-enones **11**, 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone, to give the products predicted from the complex **4** model. To the best of our knowledge, these are the first examples of chiral Lewis-acid-catalyzed Diels−Alder reactions with these fundamental cyclic α,β-enone structures.[10] Finally, the quinone monoketals **12** and **13** provide Diels−Alder adducts with good yields and enantioselectivities, thus demonstrating the effectiveness of catalysts **1** and **2** in promoting the hitherto difficult, but important, quinone Diels−Alder subtype.[11] The absolute stereochemical course of these reactions of quinone monoketals **12** and **13** can also be explained in terms of a favored reaction channel via a complex of type **4**.

Table 2. Diels−Alder Reactions of Cyclopentadiene with Various Dienophiles Catalyzed by Chiral Lewis Acid **1** or **2** in CH_2Cl_2

Dienophile	Product		Cat. (mol%)	Condt. (°C, h)	% yield[a] (*endo*:*exo*)[b]	%ee[c]
 8			1 (20)	−95, 1	95 (8:92)	94
 9			1 (20)	−35, 1.5	99	98
 10			1 (20) 2 (20)	−20, 36 −20, 64	99 (91:9) 94 (93:7)	88 90
 11		n=1 n=2 n=3	2 (20) 1 (20) 2 (20) 2 (20)	−20, 14 −20, 16 −20, 15 −20, 22	99 (95:5) 97 (91:9) 98 (94:6) 92 (97:3)	92 93 95 93
 12			1 (20) 1 (10) 2 (20)	−20, 1 −78, 1 −78, 1	33[d] (>98:2) 80 (>98:2) 91 (>98:2)	84 92 71
 13			1 (10)	−78, 1	98 (>98:2)	92

[a] Isolated yield. [b] Endo−exo ratios determined by ^{1}H NMR or GC analysis or both. [c] Enantioselectivities determined by ^{1}H NMR MTPA analysis or GC analysis. [d] Side products corresponding to further Diels−Alder reactions of desired product with cyclopentadiene obtained (ca. 43%).

In conclusion, the studies reported herein provide additional evidence of the utility of the recently introduced chiral Lewis acids **1** and **2** in enantioselective synthesis. We believe that the mechanistic models implied by complexes **3** (for 2-substituted α,β-enals) and **4** (for α,β-enones and esters) have useful predictive power. The application of **1** and **2** to other types of reactions will be reported in due course.

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Supporting Information Available: General procedure for the enantioselective reactions and product characterization for the cases reported in Tables 1 and 2 (PDF). X-ray crystallographic data for complexes **5**, **6**, and **7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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