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Chiral Oxazaborolidine−Aluminum Bromide Complexes Are Unusually Powerful and Effective Catalysts for Enantioselective Diels−Alder Reactions

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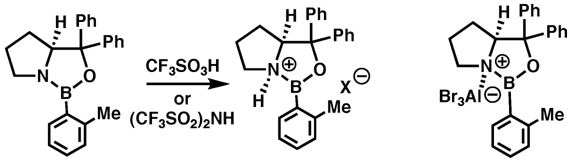
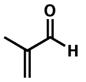
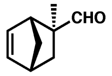
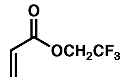
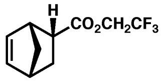
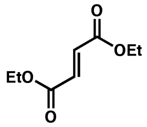
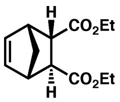
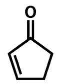
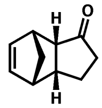
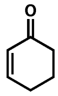
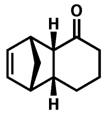
The oxazaborolidine **1** is a valuable chiral catalyst for the borane-mediated enantioselective reduction of achiral unsymmetrical ketones.[1] Protonation of **1** with triflic acid generates a chiral oxazaborolidinium cation **2**, which is an extraordinarily useful broad-spectrum catalyst for numerous Diels−Alder reactions.[2] It has been applied to the synthesis of many complex molecules.[2e−j] Because the oxazaborolidine **1** is quite a weak base, its full protonation can only be achieved using a very strong acid such as triflic acid or triflimide.



1 **2** **3**

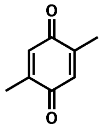
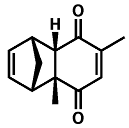
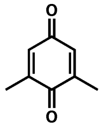
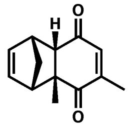
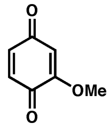
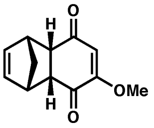
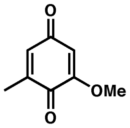
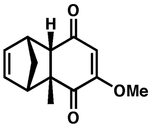
Even methanesulfonic and *p*-toluenesulfonic acids are not efficient proton donors with **1**. In early studies, it was observed that various Lewis acids did not appear to coordinate to **1** sufficiently to generate useful catalysts for Diels−Alder reactions. For instance, with BF_3 or CH_3AlCl_2 in CH_2Cl_2 solution, no useful catalysis was observed. Recently, we decided to reinvestigate Lewis acid activation despite the unpromising results obtained earlier. Using the very strong Lewis acid $AlBr_3$, it was found that complete complexation to form **3** occurred with 1 equiv each of **1** and $AlBr_3$ (by ^{1}H NMR analysis), despite the fact that $AlBr_3$ is sterically bulkier than BF_3. The ^{1}H NMR spectrum of **3** in CD_2Cl_2 showed downfield shifts for the pyrrolidine protons and the *o*-tolyl methyl comparable to those observed for N-protonation by triflic acid.[3] We were surprised not only by the clean formation of **3** from **1** but also by its strength and effectiveness as a Diels−Alder catalyst. Excellent Diels−Alder conversions were routinely observed with only 4 mol % of **3** and various dienes and dienophiles. The results of experiments with cyclopentadiene as the test diene and various dienophiles with 4 mol % of **3** as catalyst are summarized in Tables 1 and 2.

Table 1. Enantioselective Diels−Alder Reactions of Cyclopentadiene with Diverse Dienophiles in the Presence of 4 mol % of Catalyst **3** in CH_2Cl_2

dienophile	product	temp. (°C); time (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 equiv of cyclopentadiene. [b] The reaction was carried out at 2.0 M concentration with respect to dienophile and with 5 equiv of cyclopentadiene.

Table 2. Enantioselective Diels−Alder Reactions of Cyclopentadiene with Various Quinones in the Presence of 4 mol % of Catalyst **3** in CH_2Cl_2

quinone	product[a]	temp. (°C); time (h)	yield %; ee
		−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 dienophile and with 5 equiv of cyclopentadiene. [b] Toluene was used as solvent.

Taken together with previous studies on catalyst **2**,[2a−d] the data shown in Tables 1 and 2 indicate clearly that catalyst **3** is considerably more efficient than **2** (10−20 mol % generally required for optimum results). Because of this fact, in most cases, only 4 mol % of catalyst **3** produces excellent results in terms of both reaction yield and enantioselectivity. The use of catalyst **3** is especially advantageous for larger scale synthesis not only because of the low catalyst requirements but also because the chiral ligand precursor is easily and efficiently recovered.[4−6]

The wide applicability of catalyst **3** is also underscored by the nine examples shown in Table 3 which involve a collection of

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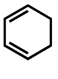
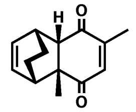
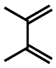
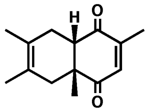
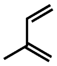
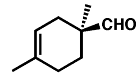
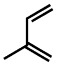
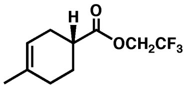
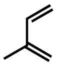
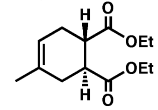
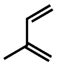
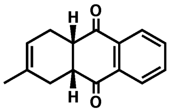
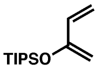
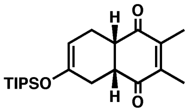
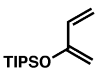
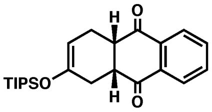
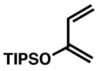
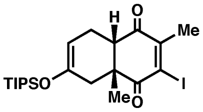
Table 3. Enantioselective Diels−Alder Reactions of an Assortment of Dienes and Dienophiles in the Presence of 4 mol % of Catalyst **3**

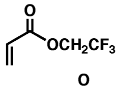
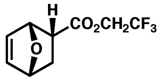
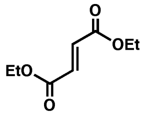
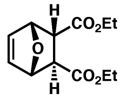
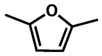
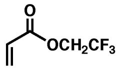
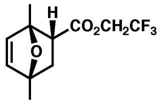
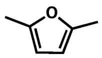
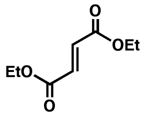
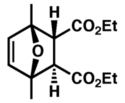
diene	product	temp. (°C); time (h)	yield %; ee
		−78; 16[a]	95; 99
		−78; 16[a]	97; 96
		−78; 16[b]	99; 97
		−20; 16[c]	98; 91
		−20; 48[d]	71; 97
		−78; 16[a]	99; 84
		−78; 1[e]	99; 99
		−78, 16[e]	99; 96
		−78, 12[f]	99; 99

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

different 1,3-dienes and dienophiles. In each case, including the first entry with the less reactive diene 1,3-cyclohexadiene, the reaction proceeds well with just 4 mol % of catalyst **3**. In the examples listed in Table 3, as well as those of Tables 1 and 2, the absolute configuration of the chiral Diels−Alder adduct obtained with the (*S*)-catalyst **3** corresponded to that resulting from the use of the triflic acid-activated catalyst **2**, as determined by comparison of optical rotation and HPLC or GC analysis using a chiral column.[6]

We have also briefly examined the catalytic enantioselective Diels−Alder reaction with two furans as diene component and trifluoroethyl acrylate and ethyl fumarate as dienophile partner with the results that are outlined in Table 4.[6] Furans are of special interest as Diels−Alder reactants since the products can be used to prepare chiral cyclohexane derivatives in which most or even all of the ring members are functionalized or chiral. The furan adducts are also useful since they can be deoxygenated by treatment with excess zinc dust and 3 equiv of TMSBr in CH_3CN to form the corresponding 1,3-cyclohexadiene; for example, the adduct in entry 3 of Table 4 is transformed into trifluoroethyl (1*R*)-2,5-dimethylcyclohexa-2,4-diene-1-carboxylate at 0 °C for 1 hr (76%).

Table 4. Enantioselective Diels−Alder Reactions with Furans in CH_2Cl_2 with **3** as Catalyst

furan	dienophile	product[a]	temp. (°C); time (h)	yield %; ee (endo:exo)
			−78, 8	99; 99 (88:12)
			−40, 16[b]	71; 99
			−78; 12	99; 94 (90:10)
			−40; 24[b]	72[c]; 91

[a] The reaction was carried out at 2.0−2.5 M concentration with respect to dienophile in CH_2Cl_2 with 5 equiv of furan in the presence of 4 mol % of catalyst. [b] 8 mol % of catalyst was used. [c] Yield based on conversion to the hydrogenated product.

We were not able to find Lewis acids other than $AlBr_3$ which were capable of activating **1** to generate useful catalysts for Diels−Alder reactions. It is perhaps surprising that $AlCl_3$ and $GaCl_3$ were much inferior to $AlBr_3$ as activators of **1**. Although activation was observed with BCl_3, the reaction rates and yields were diminished relative to $AlBr_3$. The greater turnover efficiency of catalyst **3** relative to **2** may be the result of greater steric screening of the catalytic boron site by the adjacent $AlBr_3$ subunit and diminished product inhibition. Weaker Lewis acids were totally unpromising as activators of **1**. In conclusion, our work indicates that the $AlBr_3$-derived catalyst **3** is both special and highly useful as a chiral catalyst.

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Supporting Information Available: Experimental procedures and characterization data for all reactions and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) For example, the *o*-tolyl methyl peak was shifted downfield from (δ) 2.63 in **1** to 2.81 in **3**, and the pyrrolidine methine proton was shifted from 4.54 in **1** to 5.26 in **3** (all at 23 °C).

(4) Catalyst **3** was generated by addition of 0.8 equiv of $AlBr_3$ in CH_2Br_2 solution (Aldrich Co.) to the oxazaborolidine **1**.

(5) In large-scale experiments, the chiral ligand diphenylpyrrolidinomethanol is easily recovered in pure condition for reuse upon workup, being soluble in aqueous acid and easily extracted from the basified aqueous solution. This ligand is used industrially and produced on large scale.

(6) Enantioselectivities were determined by either HPLC or gas chromatography using chiral columns; for experimental details, see Supporting Information.

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