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Highly Enantioselective [4 + 2] Cycloaddition Reactions Catalyzed by a Chiral *N*-Methyl-oxazaborolidinium Cation

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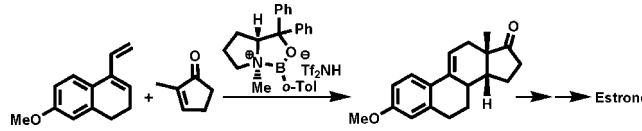
ABSTRACT



The reaction of lithium aryl borohydrides with salts of *β*-amino alcohols provides a new route for the synthesis of oxazaborolidines. This method also leads to the first synthesis of hitherto elusive *N*-methyl oxazaborolidine cations, specifically the cationic proline derivative 3. Compound 3 is a strong chiral Lewis acid which is very effective for catalysis of [4 + 2]-cycloaddition reactions in good yield and with high enantioselectivity. Several diverse examples illustrate the scope of these catalytic reactions.

Oxazaborolidines derived from (*S*)- or (*R*)-proline, of general formula **1**, have proved to be exceptionally useful reagents in catalytic enantioselective synthesis. They have been applied successfully to the highly selective reduction of many prochiral ketones in conjunction with various H-containing boranes.[1,2] In addition, cationic reagents of formula **2**, generated by the attachment of an electrophilic group to nitrogen, are very effective and potent chiral Lewis acids that promote Diels−Alder reactions,[3] [2 + 2]-cycloadditions[4] and [3 + 2]-cycloadditions,[5] and Mukaiyama−Michael reactions.[6] These cationic catalysts can be generated by the protonation of nitrogen using a very strong protic acid (CF_3SO_3H or $(CF_3SO_2)_2NH$), *but not by weaker acids*. Lewis acid activation of **1** by $AlBr_3$ also leads to valuable electrophilic chiral catalysts of type **2** (Figure 1).[3j] Surprisingly, other strong Lewis acids did *not* give useful catalysts when combined with **1**.

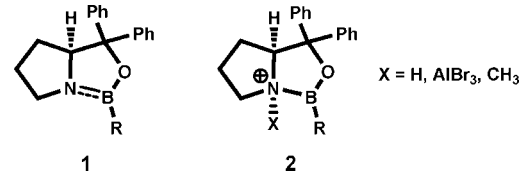


Figure 1. Oxazaborolidine catalysts **1** and **2**.

In addition, attempts during the early phase of the work in these laboratories to generate cationic catalysts of type **2**, X = CH_3, did *not* meet with success because of the very

(1) For a review, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

(2) For a recent application, see: (a) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347. See also: (b) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708–13713.

(3) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808–3809. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992–9993. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390. (d) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800–4802. (e) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979–3982. (f) Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 740–742. (g) Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 1346–1352. (h) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310–6311. (i) Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 11958–11959. (j) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498–1499.

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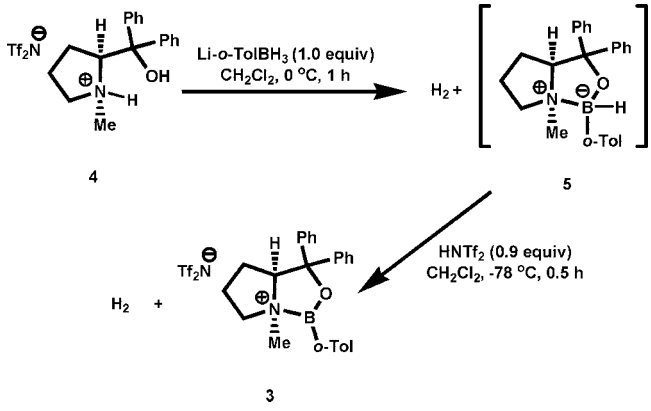
low nucleophilicity of oxazaborolidines. Specifically, attempts to methylate **1** using $MeOSO_2CF_3$ and Me_3O^+ BF_4^- did not lead to the formation of **2**, X= CH_3. Further, this cation was not produced when *N*-methyl-1,1-diphenylpyrrolidinomethanol or the corresponding bistrimethylsilyl ether were treated with $PhBBr_2$ or $PhB(OSO_2CF_3)_2$.

In this account, we report the first successful synthesis of **2**, X = CH_3, and the application of this cationic catalyst to enantioselective [4 + 2]-cycloaddition reactions. In addition, we provide a comparison of this catalyst with **2**, X = H, and **2**, X = $AlBr_3$ in a number of test cases.

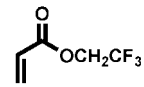
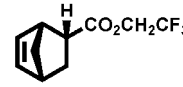
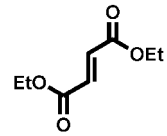
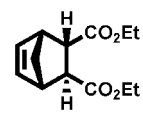
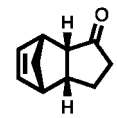
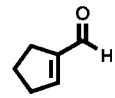
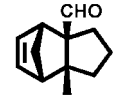
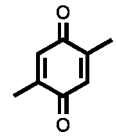
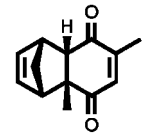
Specifically, we have prepared the cationic methyl-coordinated catalyst **3** in situ from the *N*-methyl-1,1-diphenylpyrrolidinomethanol triflimide salt (**4**) by the two-step sequence: (1) reaction of **4** with 1 equiv of lithium *o*-tolyl-borohydride[7] in CH_2Cl_2 at 0 °C for 1 h and (2) treatment of the resulting cyclic borohydride **5** with 0.9 equiv of $(CF_3SO_2)_2NH$ at −78 °C for 0.5 h (Scheme 1). Confirmation of the structure of **3** was obtained by ^1H and ^{11}B NMR analysis[8] and by its catalytic action as a chiral Lewis acid which generally parallels that of the cationic complexes **2**, X = H or X = $AlBr_3$. Clearly, the formation of the highly reactive **3** from the stable dipolar ion **5** is driven by the formation of the very stable molecule H_2 byproduct. We have not attempted to isolate the highly electrophilic, reactive, and moisture sensitive catalyst **3**. In all our work, it was generated and used in situ in CH_2Cl_2 or toluene.

Scheme 1. Preparation of Catalyst **3**



The effectiveness of catalyst **3** was evaluated using the reaction of cyclopentadiene with a variety of dienophiles that had been found in previous research to produce Diels−Alder adducts in high yield and enantiomeric purity with catalysts **2**, X = H, and **2**, X = $AlBr_3$. In each of the five test reactions, closely comparable results were obtained (see Table 1), and the same enantiomer predominated.

Table 1. Enantioselective Diels−Alder Reaction of Cyclopentadiene and Various Dienophiles Using Catalyst **3**

dienophile	product[a]	temp (°C) time (h)	% yield;ee (endo:exo)
	 **6**	-78; 1.5	99; 97 (97:3)
	 **7**	-60; 8	99; 96
	 **8**	-50; 8	99; 92 (96:4)
	 **9**	-78; 1.5	96; 90 (10:90)
		-78; 1[b]	97; 98

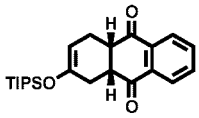
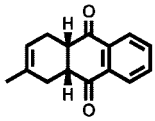
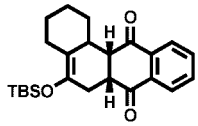
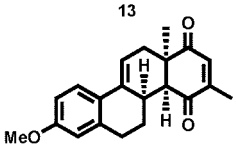
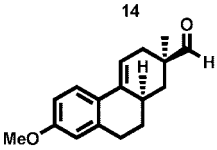
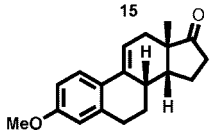
[a] Each reaction was carried out at 0.25 M in CH_2Cl_2 with respect to the dienophile, and 10 mol % of catalyst **3**. [b] Reaction carried out at 0.20 M.

We then carried out a study to compare directly catalyst **3** with catalyst **2**, X = $AlBr_3$. The results of these experiments with various dienes and dienophiles are summarized in Table 2. It can be seen from these data that catalyst **3** was generally at least equally effective as **2**, X= $AlBr_3$, and in two of the six examples considerably more so. These studies show that catalyst **3** is worth considering as an alternative to **2**, X = H, or **2**, X = $AlBr_3$, and may be more useful in those cases where the proton or $AlBr_3$-activated oxazaborolidine is not satisfactory.

The absolute configuration of the Diels−Alder adducts **11**, **12**, and **15**,[2b] obtained with (*S*)-catalyst **3**, corresponds to those resulting from the use of the triflimide activated catalyst **2**, X = H, as determined by comparison of optical rotation and HPLC analysis using a chiral column.[3d] The absolute configuration of **13** was determined by crystallization from *i*-PrOH and X-ray diffraction analysis.[9] The absolute configuration of **14** was assigned by analogy with the other cases.

(5) Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 11958–11959.
(6) Liu, D.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 8160–8161.
(7) The lithium *o*-tolylborohydride was prepared using a modification of H. C. Brown's procedure: Singaram, B.; Cole, T. E.; Brown, H. C. *Organometallics* **1984**, *3*, 774–777.
(8) For example, the *o*-tolyl methyl peak was shifted downfield to (δ) 2.78 in **3** from 2.63 in **1** which is comparable to **2**, X = $AlBr_3$ (2.81). The pyrrolidine methine proton was shifted to 4.95 in **3** from 4.54 in **1** which is comparable to **2**, X = $AlBr_3$ (5.26). The *N*-Me peak was shifted to 2.54 in **3** from 2.46 in **5**. The ^{11}B NMR shows a shift from (δ) +7.7 for **5** to +34 for **3**.
(9) See Supporting Information.

Table 2. Comparative Studies of [4 + 2]-Cycloaddition Reactions Catalyzed by **3** and **2**, X = $AlBr_3$

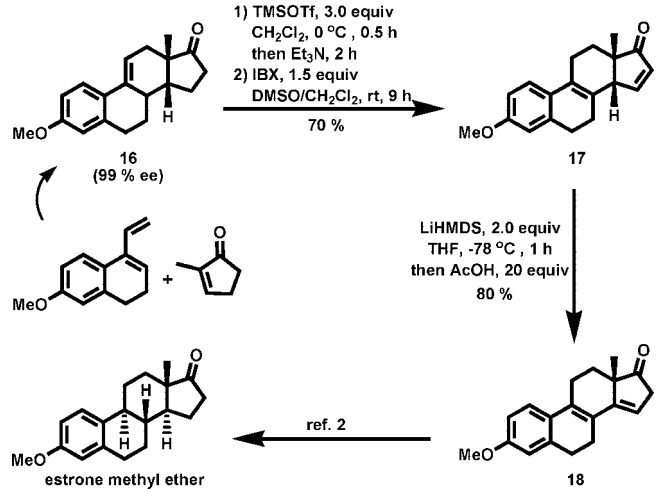
product	catalyst 3 temp (°C); time (h)	% yield; ee	catalyst 2, X = $AlBr_3$ temp (°C); time (h)	% yield; ee
 **11**	-78; 4[a]	95; 96	-78; 16[b]	99; 96
 **12**	-78; 16[c]	97; 84	-78; 16[b]	99; 84
 **13**	-78; 4[a]	83; 96	-78; 2[a]	90; 12
 **14**	-78; 2.5[a]	87; 98	-78; 2[a]	87; 84
 **15**	-78; 2.5[a]	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 of **3**. [e] After a single recrystallization.

The adduct **16**[10] (Table 2) was transformed into the estrone precursors **17** and **18** as shown in Scheme 2. We have recently described a one-flask process for the conversion of **18** into estrone methyl ether.[2] The sequence shown here

(10) For comparison, the triflimide cationic catalyst **2**, X = H, afforded **16** in 85% yield and 78% ee.

Scheme 2. Short Synthesis of Estrone Using Catalyst **3**



demonstrates another short and simple enantioselective route to estrone and illustrates one successful practical application of catalyst **3**.

The successful generation of **3**, after numerous failed attempts, opens the way for the synthesis and evaluation of numerous other chiral catalysts. Specifically, the reaction of the amino alcohol salt **4** and Li-*o*-tolBH_3 exemplifies a new method for the formation of oxazaborolidine and related BN heterocycles, which should be very useful for the synthesis of chiral Lewis acids. Studies of such structures and new applications of **3** and its analogues are underway. We believe that the catalyst **3** is well suited for both laboratory and larger-scale use. The chiral amino alcohol corresponding to **4** is readily recovered from Diels−Alder reactions for reuse.

Acknowledgment. E.C. is the recipient of a Pfizer postdoctoral fellowship and gratefully acknowledges Prof. Bakthan Singaram (UC Santa Cruz) for information on the preparation of lithium *o*-tolylborohydride (see Supporting Information).

Supporting Information Available: Spectroscopic and analytical data for all new compounds, as well as selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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