ChemInform Abstract: Asymmetric Diels-Alder Reactions Catalyzed by a Triflic Acid Activated Chiral Oxazaborolidine.

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · APRIL 2002

Impact Factor: 12.11 · DOI: 10.1021/ja025848x · Source: PubMed

3 AUTHORS, INCLUDING:

Takanori Shibata
Waseda University
18 PUBLICATIONS **192** CITATIONS

SEE PROFILE

J|A|C|S
COMMUNICATIONS

Published on Web 03/20/2002

Asymmetric Diels−Alder Reactions Catalyzed by a Triflic Acid Activated Chiral Oxazaborolidine

E. J. Corey,* Takanori Shibata, and Thomas W. Lee

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received February 7, 2002

Chiral oxazaborolidines **1** are very useful catalysts (e.g. with R = H, Me, *n*-Bu, or Ar) for the enantioselective reduction of ketones with BH_3·THF or catecholborane as stoichiometric reductants, a reaction that is of interest because of its wide scope and the extraordinary predictive power of the underlying mechanistic pathway.[1,2] We describe herein a new type of catalytic enantioselective Diels−Alder reaction that was inspired by this process and which employs a proline-derived oxazaborolidine of type **1** as precatalyst and triflic acid as activator to generate a potent cationic Lewis acid. In essence, a very strong protic acid is used to create a very strong Lewis acid, the reverse of the formation of a proton superacid from a Lewis acid, for example $HF + BF_3 \rightarrow H^+ BF_4^-$.

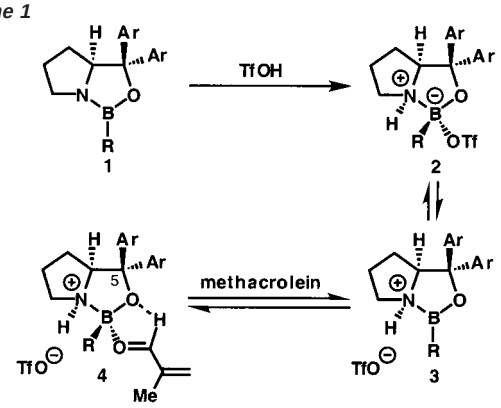
The reaction of the oxazaborolidine **1**, R = Me and Ar = C_6H_5, with anhydrous triflic acid (ratio 1:1) in CH_2Cl_2 (or CD_2Cl_2) results in the formation of an equilibrium mixture of two *N*-protonated species (**2** and **3** in Scheme 1) as indicated by low-temperature (−80 °C) ^{1}H NMR analysis.[3] No appreciable amount of triflic acid appears to be present with these 1:1 mixtures of **1** and triflic acid. The ratio of **2** to **3** in CD_2Cl_2 at −80 °C is approximately 1.5:1. The interconversion of **2** and **3** is slow on the ^{1}H NMR time scale, but becomes rapid at 0 °C, the coalescence temperature, T_C. The protonation of oxazaborolidine **1** by triflic acid is supported by downfield shifting (up to 0.5 ppm) of peaks corresponding to the methylene and methine hydrogens adjacent to nitrogen, and the appearance of $^+$N−H signals between 6.3 and 6.8 ppm. The species **2** and **3** are stable in CH_2Cl_2 in the temperature range 0 to −80 °C. Addition of 1 equiv of DMF results in a **3**·DMF complex, suggested by the upfield shifting of the B-Me peak from 0.4 to 0.0 ppm.

The Lewis acidity of the cationic Lewis acid **3** was expected to be high because of its cationic character[4,5] and because its formation requires the very strong triflic acid (methanesulfonic acid generates relatively weak catalytic activity from **1**). These findings place **3** and triflic acid near one another on an effective acidity scale. In fact, our results on catalysis of Diels−Alder reactions show that triflic acid and **3** lead to similar reaction rates at −94 °C.

The rationale for the application of **3** to the enantioselective catalysis of Diels−Alder reactions of α,β-unsaturated aldehydes is derived from previous research on Lewis superacids and catalytic enantioselective reaction pathways.[4−6] Coordination of the α,β-enal to **3** was expected to lead to an organized formyl C−H···O hydrogen bonded complex (**4** in Scheme 1).[4,5] In that complex the electron-deficient α,β-enal subunit can attract the *cis* Ar group on C(5) of the oxazaborolidine ring by a π−π donor−acceptor interaction (see below).[4,5b,6] This attractive interaction will persist in the Diels−Alder transition state since the formyl carbon maintains its strong positive charge all along the reaction pathway.[4−6]

Optimization studies on the application of the cationic oxazaborolidine **3** as a catalyst for enantioselective Diels−Alder reaction to determine the most favorable reaction parameters were carried out with the results that are summarized in Table 1. As indicated earlier, triflic acid was more effective than the weaker methanesulfonic acid (entry 13) in generating an active Diels−Alder catalyst; the unprotonated oxazaborolidine **1** showed no catalytic activity (entry 14). The nature of the boron substituent was found to be important to enantioselectivity, since much lower enantioselection resulted from the use of **1**, R = Me or Bu, than from **1**, R = C_6H_5 (entries 1−3). The best B-aryl substituent found thus far is *o*-tolyl (entries 6 and 12−16). Ar = 3,5-dimethylphenyl as an aryl substituent in **1** gave better enantioselectivity relative to Ar = phenyl in some cases, which is consistent with results from previous studies and with the neighboring π-donor effect described above.[4,5b,6,7] Independent experiments varying the ratio of **1** to triflic acid pointed to 1.2:1 as the optimum.

Scheme 1



After determination of the most favorable parameters for Diels−Alder reactions catalyzed by the cationic Lewis acids **3**, the scope of this process for **6A** and **6B** was studied with the results shown in Table 2. Excellent yields and enantioselectivities were obtained with 2-methyl or 2-bromoacrolein and a variety of 1,3-dienes. The Diels−Alder reactions with reactive dienes such as cyclopentadiene are fast even at −95 °C, an indication of the very strong Lewis acidity of the *N*-protonated catalysts **6A** or **6B** (rates are somewhat faster with the former). Good yields and enantioselectivities were observed for the reactions of the relatively unreactive butadiene and 1,3-cyclohexadiene, confirming the potent Lewis acidity of **6A** and **6B** and suggesting the possibility that a wide range of dienes can be used in enantioselective Diels−Alder reactions with α,β-enals.

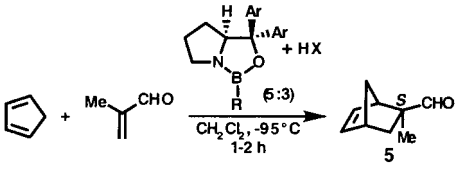
The absolute configurations of the Diels−Alder products shown in Table 2 have been assigned by measurement of optical rotation and comparison with known substances.[3,4] Catalysts **6A** and **6B** are the only ones known to effect highly enantioselective reaction between butadiene and 2-methylacrolein.[8,9]

The absolute stereochemical course of the Diels−Alder reactions represented in Table 2 can be understood in terms of the type of catalyst−aldehyde complex shown in **4** and the pre-transition-state

* Address correspondence to this author. E-mail: corey@chemistry.harvard.edu.

10.1021/ja025848x CCC: $22.00

Table 1. Optimization of Asymmetric Diels-Alder Reactions

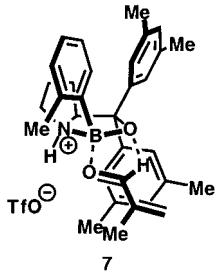


5

entry	R	Ar	HX (6 mol %)	% yield (*exo*:*endo*)[a]	% ee[b]
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-Ph	Ph	TfOH	96 (89:11)	76
5	4-Me-Ph	Ph	TfOH	95 (88:12)	77
6	2-Me-Ph	Ph	TfOH	91 (89:11)	90
7	2-Et-Ph	Ph	TfOH	73 (89:11)	78
8	2-*i*Pr-Ph	Ph	TfOH	NR (−)	−
9	2-biphenyl	Ph	TfOH	91 (92:8)	56
10	2,6-Me_2-Ph	Ph	TfOH	NR (−)	−
11	1-naphthyl	Ph	TfOH	93 (80:20)	81
12	2-Me-Ph	Ph	NfOH	95 (88:12)	91
13[c]	2-Me-Ph	Ph	MsOH	30 (87:13)	90
14[d]	2-Me-Ph	Ph	none	NR (−)	−
15	2-Me-Ph	2-naphthyl	TfOH	92 (92:8)	91
16	2-Me-Ph	3,5-Me_2-Ph	TfOH	99 (89:11)	96

[a] *Exo*:*endo* determined by ^{1}H NMR analysis. [b] Enantioselectivities determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester and ^{1}H NMR analysis. [c] −95 to −78 °C. [d] −95 to 0 °C.

assembly depicted in **7**. In **7** the formyl carbon is situated above C(2) of the nearby 3,5-dimethylphenyl group, which effectively screens the rear face of the complexed *s-trans*-α,*β*-enal from attack by the diene component. Addition of the diene to the *re* (front) face of the α,*β*-double bond leads to the enantiomers shown in Table 2.[10]



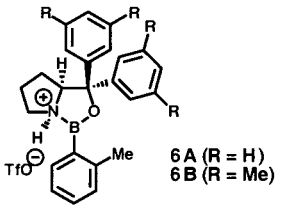
7

We believe that there are many potential uses for catalysts **6A** and **6B** (and their analogues) in catalytic enantioselective synthesis beyond those outlined herein. These powerful, new chiral Lewis superacids are easily generated from commercially available amino alcohols by condensation with an arylboroxine to give an oxazaborolidine and subsequent activation with triflic acid. Finally, it is likely that the use of triflic acid to generate strong chiral Lewis acids has great potential in enantioselective synthesis.

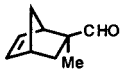
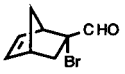
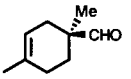
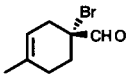
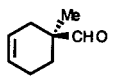
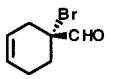
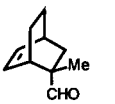
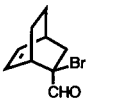
Acknowledgment. We are grateful to the Graduate School of Okaiyama University and to Boehringer Ingelheim for fellowships to T.S. and T.W.L., respectively.

Supporting Information Available: Experimental procedures for the preparation and use of catalysts **6** along with characterization data of Diels−Alder adducts and low-temperature NMR experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Table 2. Diels−Alder Reactions of 1,3-Dienes with 2-Methacrolein or 2-Bromoacrolein (CH_2Cl_2) Catalyzed by Chiral Lewis Acid **6A** or **6B**[3]



6 A (R = H)
6 B (R = Me)

Diene	Product	Cat.[a] (mol %)	Condt (°C, h)	% yield[b] (*exo*:*endo*)	%ee[c]
		A (6)	-95, 1	99 (91:9)	91
		B (6)	-95, 1	97 (91:9)	96
		A (6)	-95, 1	99 (91:9)	92
		B (6)	-95, 1	99 (91:9)	96
		B (6)	-78, 13	96	97
		A (6)	-95, 1	98	97
		B (6)	-95, 1	98	97
		B (20)	-78, 24	85	94
		A (6)	-95, 2	95	96
		B (6)	-95, 2	97	96
		A (20)	-78, 24	91 (5:95)	92
		B (20)	-78, 24	58 (6:94)	92
		A (6)	-95, 2	81 (6:94)	92
		B (6)	-95, 2	85 (7:93)	92

[a] Ratio of 1:TfOH = 1.2:1. [b] *Exo*:*endo* ratios were determined by ^{1}H NMR analysis. [c] Enantioselectivities were determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester, and ^{1}H NMR analysis, or conversion to the benzoate and HPLC analysis.

References

(1) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(2) For a review, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Intl. Ed. Engl.* **1998**, *37*, 1986.
(3) For details, see Supporting Information.
(4) Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502.
(5) For recent reviews of this subject see: (a) Corey, E. J.; Lee, T. W. *J. Chem. Soc., Chem. Commun.* **2001**, 1321. (b) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* In press [May issue, 2002].
(6) Corey, E. J. *Abstracts of the Thirty-third National Organic Chemistry Symposium*; American Chemical Society: Washington, DC, 1993; pp 30−46.
(7) (a) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938. (b) Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089. (c) Corey, E. J.; Matsumara, Y. *Tetrahedron Lett.* **1991**, *32*, 6289.
(8) The diarylprolinol from which catalysts **6A** and **6B** are made can be recovered for reuse (>95%) upon workup.
(9) Since triflic acid is a powerful catalyst for the Diels−Alder reactions reported herein, in CH_2Cl_2, even at −94 °C, the high enantioselectivities recorded in Table 2 argue against its presence in significant amount in the reaction mixtures.
(10) The formation of *exo*-formyl adducts from 2-methyl or 2-bromoacrolein and cyclopentadiene (Table 2) is characteristic of these reactants[4,5] and is likely due to less steric repulsion between the *syn*-7-H and *exo*-formyl group than for *exo*-bromine or -methyl in the transition states.

JA025848X