A New Powerful and Practical BLA Catalyst for Highly Enantioselective Diels−Alder Reaction: An Extreme Acceleration of Reaction Rate by Brønsted Acid

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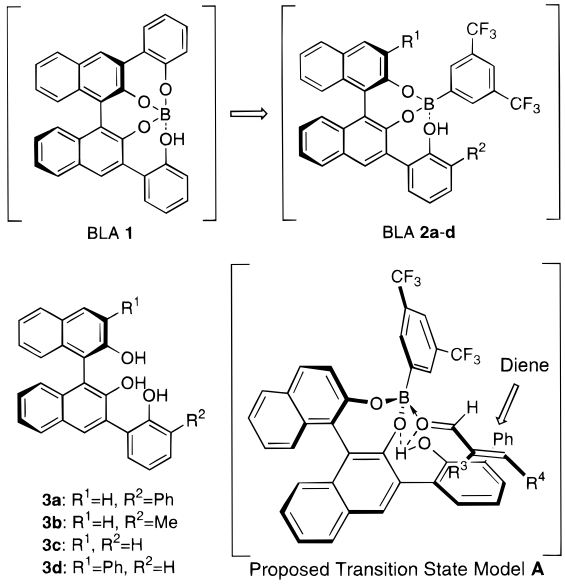
Spectacular advances have been achieved in recent years in enantioselective Diels−Alder reactions catalyzed by chiral Lewis acids.[1,2] One of our recent contributions was the introduction of a new class of chiral catalyst **1** which was presumed to be a Brønsted acid-assisted chiral Lewis acid (BLA).[2d,3] This is one of the best catalysts for the enantioselective and exo-selective cycloaddition of α-substituted α,*β*-enals with highly reactive dienes such as cyclopentadiene.[2d] With BLA **1** as well as most chiral Lewis acids, however, the corresponding reactions of α-unsubstituted α,*β*-enals like acrolein and crotonaldehyde exhibit low enantioselectivity and/or reactivity. Lack of an α-substituent on the dienophile decreases the enantioselectivity, and the existence of a *β*-substituent strikingly decreases the selectivity and reactivity. The scope of dienophiles which are applicable for less reactive dienes is quite limited. Our previous contribution was the development of helical titanium catalysts which were effective for enantioselective cycloaddition of both α-substituted and α-unsubstituted dienophiles.[2c] Unfortunately, their catalytic activities are moderate even for methacrolein because of too much streic hindrance from bulky ligand substituents. Thus, we initiated a study aimed at the design and synthesis of a more practical BLA which has greater catalytic acitivity. We report here a new type of BLA, **2a**, which was prepared from chiral triol **3a** and 3,5-bis(trifluoromethyl)-benzeneboronic acid (**4**). **2a** was extremely effective in enantioselective cycloaddition of both α-substituted and α-unsubstituted α,*β*-enals with various dienes.

Boronic acid **4** was chosen as the Lewis acidic metal component of the new BLA. We have found that this air-stable boronic acid has enough Lewis acidity to promote some reactions.[4] Chiral ligands for **4** require inclusion of a biphenol moiety to form a bidentate complex with the boron atom and a phenol moiety which functions as a Brønsted acid. Thus, several chiral triol ligands **3a**−**d** were designed based on the terphenol structure and synthesized from (*R*)-binaphthol using the Pd(0)-catalyzed-coupling reaction as a key step.[2d,5]

BLA **2a**−**d** were prepared *in situ* as follows. Method A: A mixture of chiral triol **3a** (1.2 equiv) and a solution of monomeric boronic acid **4** (1 equiv) in dichloromethane−THF[6] was stirred at ambient temperature for 2 h. The resulting



colorless solution was transferred into a Schlenk tube containing dichloromethane and powdered MS 4A (250 mg/0.05 mmol of **4**, activated[7]), and the mixture was stirred at ambient temperature for another 12 h. Then the solvents were evaporated, and the resulting solid was heated to 100 °C (oil bath) for 2 h under vacuum to dry the catalyst. After cooling to ambient temperature, the Schlenk tube was charged with dichloromethane to afford an active catalyst solution including MS 4A. Method B (a simplification of method A): A mixture of chiral triols **3a**−**d** (1.2 equiv), commercial boronic acid **4** (1 equiv),[6] THF (150 *μ*L/0.05 mmol of **4**, without drying),[8] powdered MS 4A (250 mg/0.05 mmol of **4**, nonactivated), and dichloromethane was stirred at ambient temperature for 12 h. The active catalyst solution was then prepared by treatment similar to method A.

For studies of the catalytic, enantioselective cycloaddition using **2a**−**d**, methacrolein and cyclopentadiene were selected as the representative substrates. The results are summarized in Table 1. In the presence of 5 mol % of **2a**−**d** prepared by method A or B, the reaction proceeded smoothly and was sterically controlled to form (*S*)-exo-adduct enantioselectively. On the contrary, the reactions using chiral Lewis acids prepared from (*R*)-diols which do not contain a Brønsted acid component were relatively slow under the same conditions, and low conversion and a reduced level of absolute induction were observed (entries 7 and 8). It should be noted that the Brønsted acid in the BLA catalysts clearly accelerates the cycloaddition.

The substituents R^1 and R^2 of triol ligands **3** appear significant in determining which is the preferable hydroxy group in **3** serving as Brønsted acid. The best enantioselectivity and highest reactivity were obtained in the reaction using **2a** (entries 1 and 2), while a dramatic decrease of rate and selectivity was observed with **2b**−**d** (entries 4−6). Although the formation of two bidentate complexes between **3** and **4** is possible, R^2 sterically prevents a coordination between the hydroxy group adjacent to R^2 and the boron atom.

The most striking feature in the present process is the role of water, THF, and molecular sieves in preparation of the catalyst. The enantioselectivity was diminished to less than 80% ee in the reaction using **2a** prepared *in situ* in the presence of activated

(1) For a recent review, see: Ishihara, K.; Yamamoto, H. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: London, 1995; Vol. 1, p 29.

(2) For some leading articles on enantioselective Lewis acid catalyzed Diels−Alder reaction of α,*β*-unsaturated aldehydes with dienes, see: (a) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481. (b) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (c) Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938. (d) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (e) Kündig, E. P.; Bourdin, B.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1856. (f) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

(3) (a) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (b) Aggarwal, V. K.; Anderson, E.; Giles, R.; Zaparucha, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1301.

(4) For references on chiral Lewis acid using **4**, see: (a) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483. (b) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.

(5) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

(6) Boronic acid **4**, which is commercially available from Lancaster Synthesis, Ltd., contains varying amounts of cyclic trimeric anhydrides (boroxines). A 0.043 M solution of monomeric **4** was prepared by addition of water (54 *μ*L, 3 mmol), dry THF (3 mL), and dichloromethane (20 mL) to a commerical **4** (1 mmol, >90% trimer).

(7) MS 4A was activated by heating at 200 °C under vacuum for 12 h.

(8) THF (no stabilizer) was purchased from Wako Pure Chemical Industries, Ltd.

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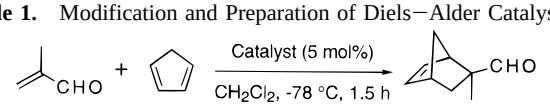
Table 1. Modification and Preparation of Diels−Alder Catalysts



entry	chiral ligand	method[a]	yield[b] (%)	% ee[c] (config)[e]
1	(*R*)-**3a**	A	96	99 (*S*)
2		B	94	98 (*S*)
3		A[d]	95	48 (*S*)
4	(*R*)-**3b**	B	89	50 (*S*)
5	(*R*)-**3c**	B	97	77 (*S*)
6	(*R*)-**3d**	B	63	60 (*S*)
7	(*R*)-**3a** (MeO)[e]	B	9	45 (*S*)
8	(*R*)-binaphthol	B	22	46 (*S*)

[a] See text. [b] Isolated yield. [c] The ee of major isomer and the absolute configuration of its carbonyl α-carbon are indicated. For determination methods, see supporting information. [d] No THF was added. [e] (*R*)-3-(2-Methoxyphenyl)-2,2′-hydroxy-1,1′-binaphthyl was used.

MS 4A under anhydrous conditions. Preparation of a sufficient amount of **2a** is assumed to be difficult under these conditions since the trimer of **4** is easily generated by dehydration and the trimer is not readily dissociated by the addition of **3a**. In fact, **4** usually exists as a mixture of monomer, dimer, and trimer.[6] To prevent trimerization of **4** in preparation of the catalyst, **3a** and **4** were mixed under aqueous conditions and then dried (methods A and B) since the presence of water or THF deactivates **2a**; in this manner 99% ee was obtained (entry 1). Significant was that use of the solution obtained by filtering the MS 4A off of **2a** after preparation by method B provided the same high level of enantioselectivity. Although molecular sieves are essential for dehydration, they may facilitate the aryloxy-ligand exchange reaction in the *in situ* preparation step of **2a**. However, using **2a** prepared without addition of THF gave low enantiomeric excess (48%, entry 3); this would be attributable to the stability of monomeric **4** by coordination of THF.[9]

From the results of this study, BLA **2a** was thus determined to be the optimum catalyst, and representative results in the cycloadditions between various α,*β*-enals and dienes are given in Table 2. The adducts were formed in high yield with excellent enantioselectivity in each case.[10] In particular, the additions of the less reactive *β*-substituted α,*β*-enals with cyclopentadiene gave very good results. Also, **2a** was an excellent catalyst for not only less reactive dienophiles but also less reactive dienes such as acyclic dienes and cyclohexadiene. On the whole, method A was superior to method B both in catalytic activity and in enantioselectivity for the cycloaddtion (e.g., (*E*)-2-pentenal in Table 2).

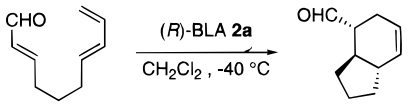
The high enantioselectivity and stereochemical results attained in these reactions can be understood in terms of the transition-state model **A**. This model is consistent with the observed absolute stereochemical selectivity and is analogous to that proposed for the BLA **1**.[2d,3]

Table 2. Enantioselective Diels−Alder Reaction Catalyzed by **2a**[a]

dienophile	diene[b]	**2a** (mol %) [method][c]	yield (%)[d] [exo:endo][e]	ee (%)[e] [config][e]
CH_2═CBrCHO	CP	5 [B][f]	>99 [90:10]	>99 [*R*]
	CP	1 [B][f]	97 [88:12]	97 [*R*]
	CH	10 [B][g]	65 [10:90]	95
	DMB	10 [B][h]	95	91
	IP	10 [B]	95	>99 [*R*]
(*E*)-MeCH═CMeCHO	CP	20 [A][i]	90 [98:2]	96
CH_2═CHCHO	CP	5 [A]	84 [3:97]	95 [*S*]
	CH	10 [B]	>99 [0:100]	96 [*S*]
	DMB	10 [B]	97	>99
	IP	10 [A]	95	99
(*E*)-MeCH═CHCHO	CP	20 [A]	94 [10:90]	95 [*S*]
(E)-EtCH═CHCHO	CP	20 [A][j]	73 [9:91]	98
	CP	20 [B][k]	57 [18:82]	75
(*E*)-PhCH═CHCHO	CP	20 [A][l]	94 [26:74]	80
(*E*)-EtO_2CCH═CHCHO	CP	5 [A]	91 [2:98]	95 [*R*]

[a] Unless otherwise noted, reactions were conducted in dichloromethane using aldehyde (1 equiv, 0.25 M) and diene (4 equiv) in the presence of **2a** at −78 °C for 1−24 h. [b] CP: cyclopentadiene; CH: 1,3-cyclohexadiene; DMB: 2,3-dimethylbutadiene; IP: isoprene. [c] See text. [d] Isolated yield for the exo/endo mixture. [e] The ee of major isomer and the absolute configuration of its carbonyl α-carbon are indicated. For determination methods, see supporting information. [f] Aldehyde (0.5 M) in dichloromethane. [g] 50 mg of MS 4A per 0.05 mmol of **4** used. [h] MS 4A was removed after preparation of **2a**. [i] −78 °C, 50 h. [j] −78 °C, 72 h. [k] −40 °C, 38 h. [l] −40 °C, 60 h.

We demonstrate the extension to the intramolecular cycloaddtion of an α-unsubstituted trienal. The reaction of (*E*,*E*)-2,7,9-decatrienal in the presence of **2a** (30 mol %, method A) provided only endo adduct in 95% yield with 80% ee (*R*). This result was much better than that (74% yield, 46% ee, exo:endo = 1:99) previously given by CAB-catalyzed reaction.[11]



In conclusion, this paper describes a rational basis for the design of BLA complexes which possess sufficient Lewis acidity to catalyze a wide range of synthetically useful Diels−Alder reactions. In particular, the importance of the acceleration effect of BLA in the enantioselective Diels−Alder reaction catalyzed by Lewis acid has been documented.[12]

Supporting Information Available: Experimental procedures and spectral data for all new compounds (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) Actually, more than 98% of **4** existed as a monomer in dichloromethane−THF (20:3) with the addition of 2 equiv of water while ca. 20% of **4** existed as a dimer or trimer in dichloromethane alone.

(10) **3a** was readily and efficiently recoverable and could be reused. A reaction mixture was treated with aqueous 2 N NaOH, and products were extracted with pentane. Acidification of the aqueous layer and extraction with dichloromethane afforded **3a** (>90%).

(11) Furuta, K.; Kanematsu, A.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 7231.

(12) Part of this work was financially supported by a Grant-in-Aid for Scientific Study from the Ministry of Education, Science and Culture of the Japanese Government. H.K. also acknowldeges a JSPS Fellowship for Japanese Junior Scientists.