Asymmetric Hetero Diels–Alder Reaction Catalyzed by Stable and Easily Prepared CAB Catalysts

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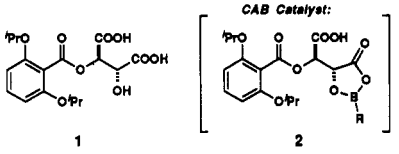
Summary: A stable chiral (acyloxy)borane (CAB) complex is prepared in situ by mixing tartaric acid derivative and arylboric acid at room temperature. A solution of the catalyst is effective to catalyze hetero Diels–Alder reaction to produce dihydropyrone derivatives of high optical purities.

We recently described a new method for catalytic enantioselective Diels–Alder reactions based on chiral (acyloxy)borane (CAB) catalyst using tartaric acid[1] or amino acid as a chiral controller unit.[2] Recent applications from this laboratory, which include Aldol synthesis,[3] and Sakurai–Hosomi reaction[4] broaden the versatility of this catalyst. Excellent enantioselectivities and wide applicability thus contribute to the outstanding utility of the CAB system. This paper reports several new developments in this area and further uses.

In contrast to **2**, R = H, which is both air and moisture sensitive, the B-alkylated catalyst **2**, R = Ph or alkyl, is stable and can be stored in closed containers at room temperature. This catalyst is easily prepared from phenyl- or alkylboric acid and **1**; reactions of the ester **1** and phenylboric acid in propionitrile at room temperature smoothly produced the reactive catalyst. Its molecular weight, found cryoscopically in benzene, corresponds closely with the value calculated for a monomeric species **2**, R = Ph. The product showed a new carbonyl absorption at 1821 cm^{-1}, characteristic of the five-membered-ring carbonyl compound and different from that of the six-membered-ring structure.[5]



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A solution of the catalyst **2**, R = Ph, is sufficiently reactive and catalyzes the Diels–Alder, aldol, and Sakurai–Hosomi reactions. Although the asymmetric inductions achieved by these complexes are slightly less efficient than that of the corresponding hydride-type catalyst,[6] the catalysts were shown to be an excellent system for hetero Diels–Alder reaction[7,8] which is the subject of the present paper.

Table I. CAB-Mediated Asymmetric Hetero Diels–Alder Reaction[a]

entry	aldehyde	diene	catalyst R of boric acid	product yield,[b] %	product % ee (confign)[c]
1	PhCHO	**3a**	(BH_3)[d]	11	52 (*R*)
2			Bu	67	73 (*R*)
3			Ph	63	75 (*R*)
4			2,4,6-Me_3Ph	47	95 (*R*)
5			2,4,6-$^iPr_3$Ph	55	95 (*R*)
6			*o*-MeOPh	80	79 (*R*)
7			*o*-^{i}PrOPh	63[e]	84 (*R*)
9		**3b**	Bu	56 (12)	93 (2*R*,3*R*)
10			Ph	65 (29)	87 (2*R*,3*R*)
11			2,4,6-Me_3Ph	<5	
12			*o*-MeOPh	95 (5)	97 (2*R*,3*R*)
13	(*E*)-PhCH=CHCHO	**3a**	*o*-MeOPh	40	79 (*R*)
14			*o*-^{i}PrOPh	63[e]	86 (*R*)
15		**3b**	*o*-MeOPh	86 (6)	97[f] (2*S*,3*R*)
16	CH_3CH=CHCHO	**3b**	*o*-MeOPh	79 (<1)[e]	92

[a] Unless otherwise noted, the reaction was carried out in freshly distilled propionitrile using 20 mol % of catalyst and 1.2 equiv of the diene per aldehyde at −78 °C for 4–9 h. [b] Isolated yield by column chromatography; for the cis/trans mixture, the yield of the major cis isomer is designated, parentheses indicate yield of the trans isomer. [c] Unless otherwise specified, the ee values were determined by HPLC using chiral column (Chiralcel OD using hexane–^{i}PrOH (50:1)). The absolute configuration was determined by comparison of the sign of optical rotation; see ref 7. [d] In this case a solution of BH_3 in tetrahydrofuran (1.05 M) was used and the catalyst complex was prepared at 0 °C for 15 min. [e] The reaction was carried out at −78 °C for 20 h. [f] The optical yield was substantiated by HPCL analysis of the (*S*)-(−)-MTPA ester of the alcohol, which was derived from the adduct by 1,4-reduction with L-Selectride followed by reduction of the resulting saturated ketone with $NaBH_4$.

New chiral (acyloxy)borane complex **2** was easily prepared in situ by mixing a 1:1 molar ratio of tartaric acid derivative **1** and phenylboric acid in dry propionitrile at room temperature for 0.5 h. The hetero Diels–Alder reaction of aldehydes with Danishefsky diene **3** was promoted by 20 mol % of this catalyst solution at −78 °C for several hours. After usual workup, the crude adduct was treated with trifluoroacetic acid in CH_2Cl_2 to afford dihydropyrone **4**. Product diastereomer and enantiomer ratios were determined by analytical HPLC, and absolute

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(2) (a) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (b) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197. Recently, the similar catalyst was reported to be useful in organic synthesis, see: (c) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276. (d) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (e) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365.

(3) (a) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (b) Furuta, K.; Maruyama, T.; Yamamoto, H. *Synlett* **1991**, 439. (c) As an interesting report using boron catalyst, see: Hawking, J. M.; Loren Stefan, *J. Am. Chem. Soc.* **1991**, *113*, 7794.

(4) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561.

(5) Five-membered-ring carbonyl compound derived from lactic acid and phenylboric acid, 1811 cm^{-1}; six-membered-ring structure derived from β-hydroxybutyric acid and phenylboric acid, 1773 cm^{-1}. Carbonyl peak of 1817 cm^{-1} was observed for the cyclic product derived from the cyclohexanol *C*-1-mono-ester of **1** and phenylboric acid.

(6) With the catalyst generated from **1** and phenylboric acid, the following preliminary results are obtained: Diels–Alder with methacrolein and cyclopentadiene at −78 °C for 5 h: >95% yield and 79% ee. Aldol synthesis with benzaldehyde and silyl enol ether of acetophenone at −78 °C for 5 h: 94% yield and 78% ee. Sakurai–Hosomi reaction with benzaldehyde and 2-methyl-1-(trimethylsilyl)-2-propene at −40 °C for 5 h: 94% yield and 75% ee. Full details of these results will be reported in due course.

(7) Our recent asymmetric hetero Diels–Alder reaction, see: Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. Maruoka, K.; Nonoshita, K.; Yamamoto, H. *Synth. Commun.* **1988**, *18*, 1453.

(8) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

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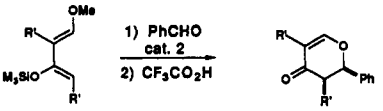

3 a: R' = H
b: R' = Me

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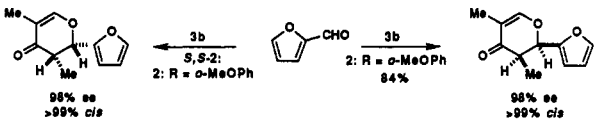
configurations were determined by comparison of the specific rotation values with those of the literature.[7] Some of the results are summarized in Table I.

The new CAB catalyst disclosed herein exhibited the following characteristic features: (1) An extent of asymmetric induction is largely dependent on the structure of boric acid. In general, bulky phenylboric acid resulted in excellent asymmetric induction. Overly bulky substituents, however, led to the eminent loss of reactivity (entry 11), while the alkoxy substituents increased the reactivity of the catalyst without significant loss of selectivity. The catalyst derived from 2,4,6-trialkylphenylboric acid or *o*-alkoxyphenylboric acid thus reveals high reactivity and asymmetric induction with diene **3a** (entries 4 and 5) and **3b** (entries 12, 14, and 15), respectively. (2) Choice of alkoxyphenylboric acid is crucial for obtaining the high *diastereoselectivities* with diene **3b** (entries 12, 15, 16) which is in accord with our previous observation.[7] (3) Judging from the product configuration, CAB catalyst (from natural tartaric acid) should effectively cover the *si* face of carbonyl when coordinated, and the selective approach of nucleophiles from the *re* face should agree well with the results of previously reported CAB-catalyzed Aldol and Sakurai-Hosomi reactions.[3,4] (4) Since unnatural tartaric acid derivatives are equally accessible in optically pure form, the present method allows the synthesis of *both antipodal* products by choosing the handedness of the chiral auxiliary 1.

The power of the CAB catalytic reaction for the enantioselective route to carbon-branched pyranose derivatives is seen from the following example:[9]



We believe that the experimental results outlined above will stimulate further exciting advances for designer Lewis acid and offer essential information on the direction of future design of CAB catalyst.[10]

Acknowledgment. Support of this research by the Ministry of Education, Science and Culture of the Japanese Government and the Takeda Foundation are greatly appreciated.

(9) Danishefsky, S.; Maring, C. *J. Am. Chem. Soc.* **1985**, *107*, 7762.

(10) **General Procedure.** Ligand 1 (148 mg, 0.4 mmol) and phenylboric acid (48 mg, 0.40 mmol) were dissolved in dry propionitrile (2 mL), the resulting solution was stirred at 25 °C for 30 min, and the reaction system was cooled to -78 °C. Aldehyde (2.0 mmol) and then diene (2.4 mmol) were added successively and the reaction stirred a further 8 h at the same low temperature before being poured into 4 N HCl. The product was extracted with ether repeatedly, and the combined ether layers were dried and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), treated with trifluoroacetic acid (0.184 mL, 2.4 mmol), and stirred at 0 °C for 1 h. Usual workup, yielding crude adduct, was followed by column chromatography to give the pure pyrone.

The Total Synthesis of 15(*S*)-HPETE

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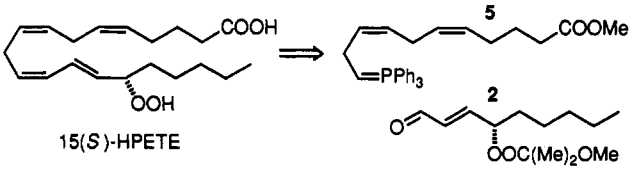
Summary: The total synthesis of 15(*S*)-HPETE in enantiomerically pure form is achieved through C=C bond formation in the presence of a masked hydroperoxide. Selective reduction of a peracid in the presence of a hydroperoxide affords a mild method for removal of an HPETE methyl ester.

The hydroperoxyeicosatetraenoic acids (HPETEs) are polyunsaturated hydroperoxides formed upon enzymatic peroxidation of arachidonic acid. These unstable natural products are the precursors of leukotrienes and lipoxins and may also contribute to carcinogenesis.[1] Despite the biomedical importance of HPETEs and other polyunsaturated hydroperoxides, there is as yet no broadly applicable method for their stereoselective synthesis in enantiomerically pure form. Lipoxygenase enzymes catalyze the stereoselective dioxygenation of specific polyunsaturated fats to the (*S*)-hydroperoxy-(*E,Z*)-diene unit found in HPETEs, but only a limited number of lipoxygenases

Scheme I



are readily available. The instability of the HPETEs and the apparent requirement for penultimate introduction of the labile hydroperoxide group have frustrated previous attempts at asymmetric chemical synthesis. For example, direct chemical dioxygenation of 1,4-dienes via autoxidation or singlet oxygenation produces a racemic mixture of hydroperoxide regioisomers while nucleophilic displacement of optically active sulfonates or phosphates with hydroperoxide nucleophiles proceeds with low stereospecificity.[2-4] Although the chromatographic resolution

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