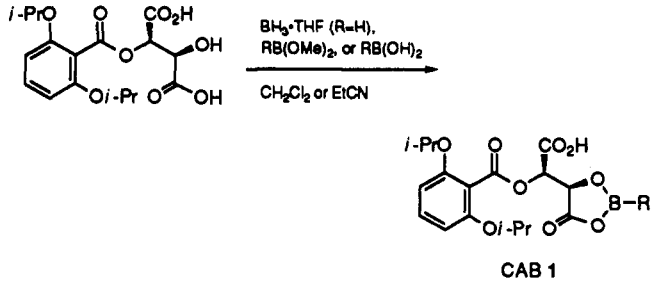
Enantioselective Diels–Alder Reaction of α-Bromo α,β-Enals with Dienes under Catalysis by CAB

Kazuaki Ishihara, Qingzhi Gao, and Hisashi Yamamoto*

School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-01, Japan

Received June 28, 1993

The power of organic synthesis has been expanded in recent years by advances in catalytic enantioselective reactions mediated by chiral Lewis acids.[1] One of the most effective syntheses is the tartaric acid-derived chiral (acyloxy)borane (CAB) 1, which has been shown to be an outstanding catalyst for enantioselective Diels–Alder,[2] hetero-Diels–Alder,[3] Mukaiyama aldol-type,[4] and Sakurai–Hosomi allylation[5] reactions. This note describes further application of the CAB to asymmetric Diels–Alder reaction of α-bromo α,β-enals with dienes.[6]



CAB 1

α-Bromo α,β-enals are useful dienophiles in the Diels–Alder process because of the exceptional synthetic versatility of the resulting adducts, for instance, the important intermediate for prostaglandin synthesis.[6,7] In the presence of 10 mol % of 1, R = H, α-bromoacrolein and cyclopentadiene in dichloromethane underwent smooth Diels–Alder reaction to give the (*S*)-bromo aldehyde in a quantitative yield, 95% ee and 94:6 (exo/endo CHO) diastereoselectivity; chiral ligand was efficiently recovered for reuse. Similar results were obtained for the catalyst 1, R = *o*-$PhOC_6H_4$, in propionitrile: a quantitative yield, 98% ee (*S*-enantiomer major), 94:6 (exo/endo CHO) diastereoselectivity. Chemical yield and enantioselectivity of the former reaction in the presence of 1 (R = H) were diminished when propionitrile was used in place of dichloromethane. However, propionitrile as a polar solvent is needed for the reaction in the presence of CAB 1 prepared by mixing a 1:1 molar ratio of tartaric acid derivative and alkylboric acid because of the solubility of the catalyst. The extent of asymmetric induction is largely dependent on the structure of boric acid; thus, bulky phenyl boric acid (R = *o*-$PhOC_6H_4$ vs *t*-BuC≡C) resulted in excellent asymmetric induction (98% ee and 86% ee, respectively). These results are in agreement with our previous observation.[3] Except for the problem of solubility, overall, dichloromethane is better than propionitrile as a solvent of Lewis acid-catalyzed Diels–Alder reaction. 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 cyclopentadiene from the *re* face of the *s*-trans conformer[8] should agree well with the results of previously reported CAB-catalyzed reactions.[2–5]

In order to explore the generality and scope of asymmetric reaction described above, Diels–Alder reactions of α-bromo α,β-enals with dienes in the presence of 10 mol % of CAB 1 (R = H) were examined. The results, together with those above, are summarized in Table I. This process is quite general, proceeds with high enantio- and exoselectivities, and is applicable to various dienes and β-substituted α-bromo α,β-enals.

In conclusion, tartaric acid-derived CAB catalyst has been supported by experiments which demonstrate a very powerful and practical chiral Lewis acid for catalytic enantioselective synthesis.

Experimental Section

General Methods. ^1H NMR spectra were measured at ambient temperature. Data are recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (hertz), integration, and assignment. ^{13}C NMR spectra are recorded in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard (deuteriochloroform at 77.07 ppm). High performance liquid chromatography (HPLC) was done using 4.6 mm × 25 cm Daicel chiral AD. All experiments were carried out under an atomosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E (Merck Art. 9385). Microanalyses were accomplished at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University.

In experiments requiring dry solvents, propionitrile and dichloromethane were freshly distilled from calcium hydride and ether and tetrahydrofuran (THF) were freshly distilled from sodium metal using benzophenone ketyl as indicator. Benzene and toluene were dried over sodium metal. Methylene chloride and dimethylformamide (DMF) were stored over 4A molecular sieves. Pyridine and triethylamine were stored over potassium hydroxide pellets. BH_3·THF is obtained from Toso-Akzo Chem. Co. Ltd., Japan. Other simple chemicals were purchased and used as such.

(2*R*,3*R*)-2-*O*-(2,6-Diisopropoxybenzoyl)tartaric Acid. To a slightly suspended solution of 2,6-diisopropoxybenzoic acid (4.77 g, 20 mmol) and dibenzyl tartrate (6.61 g, 20 mmol) in dry benzene (100 mL) was added trifluoroacetic anhydride (3.1 mL, 22 mmol) dropwise over a period of 20 min at room temperature. After being stirred for 30 min, the pale yellow solution was poured into saturated $NaHCO_3$ and extracted with ether repeatedly. The combined organic layer was dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography on silica gel using a mixture of hexane, ether, and

(1) For a review of chiral Lewis acids, see: (a) Narasaka, K. *Synthesis* **1991**, 1. (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(2) (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254. (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.

(3) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951.

(4) (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) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* In press.

(5) (a) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561. (b) Marshell, J. A.; Tang, Y. *Ibid.* **1992**, 653. (c) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* In press.

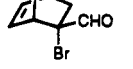
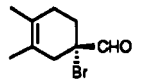
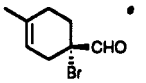
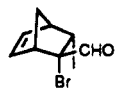
(6) (a) Corey, E. J.; Loh, T. P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (b) Ishihara, K.; Yamamoto, H. Unpublished results.

(7) Corey, E. J.; Cywin, C. L. *J. Org. Chem.* **1992**, *57*, 7372.

(8) In separate chemical and physical studies on the machanism of CAB-catalyzed Diels–Alder reaction (Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.*, in press), it has been clearly shown that methacrolein appears to favor *s*-trans conformation in the transition-state assembly of catalytic Diels–Alder reaction using CAB.

0022-3263/93/1958-6917$04.00/0

Table I. Asymmetric Diels–Alder Reaction of α-Bromo α,β-Enals with Dienes

entry	α,β-enal	diene	CAB, R	solvent [temp (°C), time (h)]	product[b]	yield (%)[c] [exo/endo][d]	ee (%) [confign]
1			H	CH_2Cl_2 [−78, 10]		100 [94/6]	95 [*S*]
2				C_2H_5CN [−78, 10]		73 [93/7]	87 [*S*]
3			*o*-$PhOC_6H_4$	C_2H_5CN [−78, 10]		100 [94/6]	98 [*S*]
4			*t*-BuC≡C	C_2H_5CN [−78, 6]		100 [96/4]	86 [*S*]
5			H	CH_2Cl_2 [−78, 46]		80	95
6				CH_2Cl_2 [−40, 12]		52	87 [*S*]
7				CH_2Cl_2 [−78, 12]		100 [>99/1]	98

[a] Unless otherwise noted, the reaction was carried out in freshly distilled dichloromethane or propionitrile using 10 mol % of catalyst 1 and 4 equiv of diene per aldehyde. [b] The figure given for product shows the major diastereomer. [c] Isolated yield by column chromatography for the exo/endo mixture. [d] The values correspond to the major diastereomers. [e] Complete position selectivity was given. [f] *Z* isomer (*Z*/*E* = >99/1) was used.

dichloromethane (6:1.5:2.5) as eluent to give 6.73 g (65%) of dibenzyl mono(2,6-diisopropoxybenzoyl)tartrate as a colorless semisolid. This tartrate was dissolved in ethyl acetate (50 mL) and to the solution was added 0.67 g of 10% Pd/C powder under an argon atmosphere. The argon was then replaced by hydrogen and the reaction mixture was stirred at atmospheric pressure and room temperature for 15 h. The mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo to afford 4.66 g (100%) of mono(2,6-diisopropoxybenzoyl)tartric acid as a colorless solid. mp 81 °C; $[\alpha]_D$ −28.5° (*c* 1.1, EtOH); IR (KBr) 2982, 1744, 1547, 1466, 1255, 1113, 1070 cm^{-1}; ^1H NMR ($CDCl_3$–DMSO-d_6, 200 MHz) δ 1.25 (d, 6H, $2CH_3$, *J* = 6 Hz), 1.26 (d, 6H, $2CH_3$, *J* = 6 Hz), 4.49 (quint, 2H, C*H*$(CH_3)_2$, *J* = 6 Hz), 4.73 (d, 1H, HOC*H*CO_2, *J* = 1.4 Hz), 5.70 (d, 1H, CO_2CHCO_2, *J* = 1.4 Hz), 6.46 (d, 2H, *m*-C_6H_3, *J* = 8 Hz), 7.17 (t, 1H, *p*-C_6H_3, *J* = 8 Hz). Anal. Calcd for $C_{17}H_{22}O_4$: C, 55.13; H, 5.94. Found: C, 54.95; H, 6.24.

(*o*-Phenoxyphenyl)boric Acid. To a solution of diphenyl ether (2.6 g, 15 mmol) in 30 mL of THF was added BuLi (10 mL, 16 mmol, 1.6 *M* in hexane) at 0 °C. To this yellow solution was added $B(OMe)_3$ (1.82 mL, 16 mmol) at the same temperature and the colorless suspended solution was stirred at room temperature for 1 h. Then the mixture was poured into diluted HCl (20 mL of 1 N HCl and 80 mL of water) and extracted with ether repeatedly. The combined ether layer was dried over Na_2SO_4 and evaporated, and the residue was purified by column chromatography on silica gel using EtOAc–hexane = 1/3 as eluant. Recrystallization from ether/hexane afforded the corresponding boric acid as a white solid (29% yield): mp 138–139 °C; IR ($CHCl_3$) 3550, 1447, 1348, 1323, 1225, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.7–5.8 (2H, br, OH), 6.71 (1H, d, *J* = 8 Hz, CHCO), 7.04–7.43 (8H, m), 7.91 (1H, dd, *J* = 2, 7 Hz, CHCB). Anal. Calcd for $C_{12}H_{11}O_3B$: C, 67.40; H, 5.10. Found: C, 67.35; H, 5.14.

(3,3-Dimethyl-1-butynyl)dimethoxyborane.[9] To a solution of 3,3-dimethyl-1-butyne (3.7 mL, 30 mmol) in 25 mL was slowly added BuLi (18.8 mL, 30 mmol, 1.6 M in hexane) at −78 °C. After 30 min of stirring at −78 °C, the generated lithium acetylide solution was slowly added to a solution of methyl borate (3.5 mL, 30 mmol) in 25 mL of Et_2O at −78 °C by a double-ended needle. Toward the end of the addition, the precipitate which had formed became quite voluminous, somewhat hampering the stirring. The reaction was maintained at −78 °C for 40 min after which anhydrous HCl in EtOAc (2.27 M, 14 mL, 32 mmol) was added. The cooling bath was removed and the reaction mixture allowed to warm to room temperature. After removal of the precipitated LiCl by filtration and removal of the volatiles under reduced pressure, the slightly pale yellow liquid was distilled to give the desired product (1.5 g, 32% yield): bp 55–60 °C/21 Torr; ^1H NMR ($CDCl_3$) δ 1.26 (s, 9H, *t*-Bu), 3.62 (s, 6H, 2OMe).

α-Bromoacrolein. Following a literature procedure,[10] acrolein was converted into α-bromoacrolein as a colorless oil (bp 38 °C/22 Torr) in two steps: IR (film) 1701, 1599, 1203, 945, 916, 540 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.90 (d, *J* = 3.4 Hz, 1H, C*H*H), 6.91 (d, *J* = 3.4 Hz, 1H, CH*H*), 9.26 (s, 1H, CHO).

(*Z*)-α-Bromocrotonaldehyde. Following a literature procedure,[11] (*E*)-crotonaldehyde was converted into (*Z*)-α-bromocrotoaldehyde as a colorless oil (bp 68 °C/25 Torr): IR (film) 1699, 1624, 1165, 642, 517 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (d, *J* = 6.9 Hz, 3H, CH_3), 7.26 (q, *J* = 6.9 Hz, 1H, MeC*H*), 9.23 (s, 1H, CHO).

Typical Procedure for an Asymmetric Diels–Alder Reaction of α-Bromo-α,β-enals with Dienes. Method A. To a solution of monoacylated tartaric acid (37 mg, 0.1 mmol) in dry dichloromethane (1 mL) or propionitrile (1 mL) was added BH_3·THF (88 μL, 0.1 mmol, 1.14 M in THF) at 0 °C under Ar. The reaction mixture was stirred for 1 h at that temperature, during which period the evolution of hydrogen gas ceased, and then the solution was cooled to −78 °C. To this were introduced α-bromo α,β-enal (1 mmol) and diene (3 mmol) successively. After several hours of stirring, the solution was poured into diluted hydrochloric acid and the product was extracted with ether. The solvent was distilled, and the residue was treated with saturated sodium bicarbonate. Usual workup followed by chromatographic separation gave Diels–Alder adducts.

Method B. Monoacylated tartric acid (37 mg, 0.1 mmol) and alkylboric acid or 1-alkynyldimethoxyborane (0.1 mmol) were dissolved in dry propionitrile (1 mL), the resulting solution was stirred at 25 °C for 30 min, and the reaction system was cooled to −78 °C. α-Bromo α,β-enal (1 mmol) and diene (3 mmol) were added successively and the reaction mixture was stirred for several hours at the low temperature. This cold solution was poured into water and the product was extracted with ether repeatedly. The combined ether layers were dried and concentrated and the residue was treated with saturated sodium bicarbonate. Usual workup was followed by column chromatography to give Diels–Alder adducts.

The absolute configurations were determined by comparison of optical rotation values with data in the literature; if necessary, the adducts were converted to known compounds. Product diastereomeric and enantiomeric ratios were determined by analytical HPLC and ^1H NMR spectroscopy of the adduct, the corresponding (+)/(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters,[12] or the corresponding (−)-(2*R*,4*R*)-2,4-pentanediol acetal.

The physical properties and analytical data of the Diels–Alder adducts are given below.

(1*S*,2*S*,4*S*)-2-Bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde: semi-solid; TLC, R_f = 0.68 (hexane–EtOAc, 4:1); IR

(9) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631.

(10) Chow, Y. L.; Bakker, B. H. *Can. J. Chem.* **1982**, *60*, 2268.
(11) Dowd, P.; Webber, W. *J. Org. Chem.* **1982**, *47*, 4774.
(12) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(film) 2978, 2826, 1725 (C=O), 1442, 1333, 1221, 1126, 1014, 723, 692, 476 cm^{-1}; ^1H NMR ($CDCl_3$, 200 Hz) δ 1.34 (d, J = 9.4 Hz, 1H, C(7)H), 1.40–1.60 (m, 2H, C(3)*H*H, C(7)*H*), 2.65 (dd, J = 3.5, 13.4 Hz, 1H, C(3)H*H*), 3.0 (brs, 1H, C(4)H), 3.3 (brs, 1H, C(1)H), 6.15 (dd, J = 3.0, 5.6 Hz, 1H, C(5)H), 6.48 (dd, J = 3.0, 5.6 Hz, 1H, C(6)H), 9.35 (endo) and 9.56 (exo) (s, 1H, CHO). Anal. Calcd for C_8H_9OBr: C, 47.76; H, 4.47. Found: C, 47.68; H, 4.63. The absolute configuration of the adduct was determined by conversion to the known norbornen-2-one[13] by a literature procedure.[6a] The ee was determined by ^1H NMR analysis of the Mosher ester derived from the Diels–Alder adduct. To the Diels-Alder adduct (10–20 mg) in 1.2 mL of THF and 0.2 mL of H_2O at room temperature was added sodium borohydride (1 equiv). After being stirred for 15 min, the solution was dried over $MgSO_4$, filtered, and washed with dichloromethane. The combined organic layers were concentrated *in vacuo*. The resulting alcohol was converted to the Mosher ester according to the usual procedure using (*R*)-(+)-MTPA. The following resonances were diagnostic. **Exo *R* isomer:** ^1H NMR ($CDCl_3$, 500 MHz) δ 4.60 (d, J = 11.8 Hz, 1H, C*H*HO), 4.65 (d, J = 11.8 Hz, 1H, CH*H*O). **Exo *S* isomer:** ^1H NMR ($CDCl_3$, 500 MHz) δ 4.51 (d, J = 12.2 Hz, 1H, C*H*HO), 4.73 (dd, J = 12.2 Hz, CH*H*O).

1-Bromo-3,4-dimethyl-3-cyclohexene-1-carboxaldehyde: liquid; TLC, R_f = 0.62 (hexane–EtOAc, 5:1); IR (film) 2952, 2923, 2855, 1727 (C=O), 1461, 1453, 1444, 1378 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.62 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.09–2.25 (m, 4H, $2CH_2$), 2.56 (d, J = 17.7 Hz, C*H*H), 2.74 (d, J = 17.7 Hz, CH*H*), 9.34 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 18.62, 18.97, 19.96, 31.27, 40.03, 67.76, 122.27, 125.47, 192.16. Anal. Calcd for $C_9H_{13}OBr$: C, 49.77; H, 5.99. Found: C, 49.76; H, 6.19. The ee was determined by ^1H NMR analysis of the Mosher ester derived from the Diels–Alder adduct by the same procedure using (*R*)-(+)-MTPA as above. The following resonances were diagnostic: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.57 (major enantiomer) and 1.59 (minor enantiomer) (s, 3H, CH_3), 4.53 (minor enantiomer) and 4.54 (major enantiomer) (s, 1H, C*H*HO).

(*S*)-1-Bromo-4-methyl-3-cyclohexene-1-carboxaldehyde: liquid; TLC, R_f = 0.60 (hexane–EtOAc, 5:1); IR (film) 2955, 2926, 2855, 1727 (C=O), 1440, 1432 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.68 (d, J = 1.3 Hz, 3H, CH_3), 2.10–2.29 (m, 4H, CH_2CH_2), 2.59–2.65 (m, 1H, MeCH=CHC*H*H), 2.77–2.82 (m, 1H, MeC=CHCH*H*), 5.32–5.34 (m, 1H, MeC=C*H*), 9.37 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 23.13, 28.54, 31.00, 34.48, 67.12, 117.10, 192.27. Anal. Calcd for $C_8H_{11}OBr$: C, 47.29; H, 5.42. Found: C, 47.31; H, 5.51. Absolute stereochemistry was assigned by analogy with cyclopentadiene.[6a] The ee was determined by HPLC analysis of the corresponding benzoyl ester using a Daicel AD column with 0.25% *i*-PrOH in hexane for elution; 1 mL/min; retention times 14.8 min for major enantiomer and 16.3 min for minor enantiomer.

(1*SR*,2*SR*,4*SR*)-2-Bromo-3-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde: TLC, R_f = 0.52 (hexane–EtOAc, 4:1); IR (film) 2968, 1725 (C=O), 1456, 1377, 1334, 1172, 1136, 1057, 1012, 893, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.98 (d, J = 7.0 Hz, 3H), 1.37 (d, J = 7.4 Hz, 1H), 1.58 (d, J = 7.4 Hz, 1H), 2.59 (dq, J = 3.2, 7.0 Hz, 1H), 2.81 (br, 1H), 3.30 (br, 1H), 6.17 (dd, J = 5.6, 3.0 Hz, 1H), 6.39 (dd, J = 3.2, 5.6 Hz, 1H), 9.51 (s, 1H). Anal. Calcd for $C_9H_{11}OBr$: C, 50.23; H, 5.12. Found: C, 50.40; H, 5.06. The ee was determined by ^1H NMR analysis of the acetal derived from the Diels–Alder adduct. A mixture of the Diels–Alder adduct (10–20 mg), (–)-(2*R*,4*R*)-2,4-pentanediol (1.5 equiv), triethyl orthoformate (1.1 equiv), and *p*-toluenesulfonic acid monohydrate (1–2 mg) in dry benzene (1 mL) was stirred at room temperature for several hours (TLC check). The following resonances were diagnostic: ^1H NMR ($CDCl_3$, 500 MHz) δ 4.68 (minor enantiomer) and 4.72 (major enantiomer) (s, 1H, CHO_2).

Acknowledgment. Financial support from the Ministry of Education, Science and Culture of the Japanese Government is gratefully acknowledged.

(13) Paquette, L. A.; Doecke, C. W.; Kearney, F. R.; Drake, A. F.; Hason, S. F. *J. Am. Chem. Soc.* **1980**, *102*, 7228.