A New and Extremely Active Corey's Chiral Oxazaborolidine Catalyst

Kazuaki Ishihara, Shoichi Kondo, Hisashi Yamamoto*

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan, CREST, Japan Science and Technology Corporation (JST), and Research Center for Advanced Waste and Emission Management (ResCWE), Furo-cho, Chikusa, Nagoya 464-8603, Japan

Fax +81-52-789-3222; E-mail: j45988a@nucc.cc.nagoya-u.ac.jp

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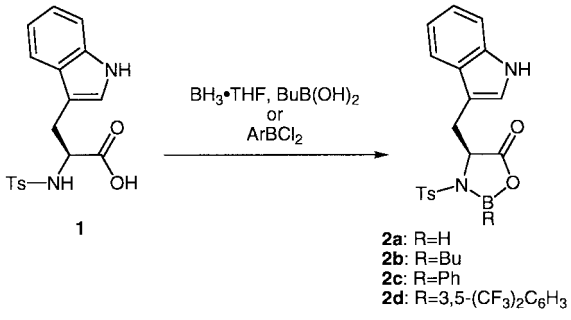
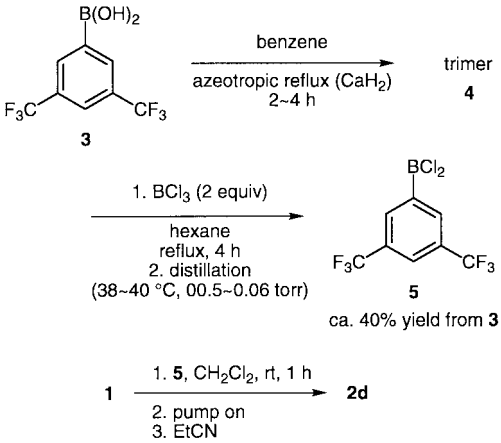
Abstract: A new chiral oxazaborolidine catalyst has been prepared *in situ* from 3,5-bis(trifluoromethyl)phenylboron dichloride and *N*-(*p*-toluenesulfonyl)-(*S*)-tryptophan. This catalyst is much more active than Corey's original catalyst for Mukaiyama aldol reaction of aldehydes with silyl enol ethers.

Key words: Mukaiyama aldol, enantioselective, arylboron dichloride, chiral oxazaborolidine, Lewis acid

Since our group[1] and Helmchen's[2a] independently announced a new class of chiral acyloxyboranes (CAB)[3] derived from *N*-sulfonylamino acids and borane•THF, chiral 1,3,2-oxazaborolidines, their utility as chiral Lewis acid catalysts in enantioselective synthesis has been convincingly demonstrated.[4-9] In particular, Coreyís tryptophan-derived chiral oxazaborolidines **2a** and **2b** are highly effective for not only Mukaiyama aldol reaction of aldehydes with silyl enol ethers[5d] but also Diels–Alder reaction of α-substituted α,β-enals with dienes (eq 1).[5a–c,e] More than 20 mol% of **2b** is required for the former reaction, however. Other chiral oxazaborolidines developed for the enantioselective aldol reaction of aldehydes with relatively more reactive ketene silyl acetals also require more than 20 mol% amounts to give aldol adducts in good yield.[6,7] We recently succeeded in enhancing the catalytic activities of CAB derived from 2,6-di(isopropoxy)benzoyltartaric acid and borane•THF and Brønsted acid-assisted chiral Lewis acid (BLA) derived from chiral tetrol and borane•THF by a modified method using 3,5-bis(trifluoromethyl)phenylboronic acid (**3**) instead of borane•THF.[10,11] The utility of **3** for the design of more active boron catalysts encouraged us to seek a new and extremely active Corey's catalyst **2d**. This paper describes a successful example of designer chiral Lewis acid catalyst modified using arylboron dichlorides bearing electron-withdrawing substituents as Lewis acid components.



A new chiral oxazaborolidine catalyst **2d** was prepared simply by treating of *N*-(*p*-toluenesulfonyl)-(*S*)-tryptophan (**1**) with an equimolar amount of 3,5-bis(trifluoromethyl)phenylboron dichloride (**5**) in dichloromethane and subsequent removal of produced HCl and the solvent *in vacuo* (Scheme 1).[12] Moisture sensitive boron dichloride **5** was synthesized by dehydration of **3** to trimeric anhydride **4** and subsequent chlorination of **4** with 2 equivalents of boron trichloride.[13] The preparation of oxazaborolidines from arylboron dichlorides was previously reported by Reilly and Oh[9a] and Harada *et al.*[9b–i] Although *B*-butyloxazaborolidine **2b** has been prepared from **1** and butylboronic acid by dehydration,[5] *B*-aryloxazaborolidine could not be prepared from arylboronic acid as observed by Nevalainen *et al.*[6p] and Harada *et al.*[9c] In contrast, CAB derived from 2,6-di(isopropoxy)benzoyltartaric acid has been easily prepared by adding an equimolar amount of the corresponding arylboronic acid at room temperature.[10]



Scheme 1 Synthesis of 3,5-Bis(trifluoromethyl)phenylboron Dichloride (**5**) and Preparation of Catalyst **2d**

According to Corey's paper,[5d] terminal trimethylsilyloxy (vinylidene) olefins appear to be the most favorable substrates for the enantioselective Mukaiyama aldol coupling catalyzed by **2b** as compared to more highly substituted olefins like RCH=($OSiMe_3$)R' or R_2C=C($OSiMe_3$)R'. Actually, the reaction of trimethylsilyl enol ether derived from cyclopentanone with benzaldehyde afforded the aldol products in only 71% yield even in the presence of 40 mol% of **2b**.[5d]

Our initial studies, summarized in Table 1, were conducted with benzaldehyde and trimethylsilyl enol ether derived from acetophenone at –78 °C in propionitrile as solvent in the presence of **2** as catalyst (eq 2).[14] Following Corey's procedure using 10 mol% of **2b**, we obtained the trimethylsilyl ether of aldol **6** and the free aldol **7** in only 38% and 15% yields, respectively. However, when the *B*-phenyl analog **2c** was used as catalyst, the chemical yield was improved strikingly. Furthermore, when the *B*-3,5-bis(trifluoromethyl)phenyl analog **2d** was used, catalytic activity and enantioselectivity were increased to a turnover of 25 and 91~93% ee respectively. The absolute configuration of aldol adducts indicated in the Table was uniformly *R*.

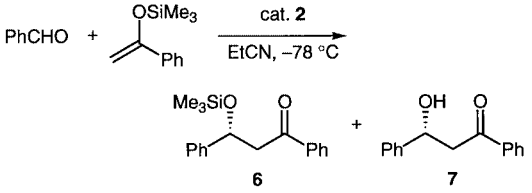


Table 1 Enantioselective Mukaiyama Aldol Reaction of Benzaldehyde with Trimethylsilyl Enol Ether Derived from Acetophenone Catalyzed by **2** (eq 2)[a]

catalyst (mol%)	time (h)	6 yield (%)[b]	6 ee (%)[c]	7 yield (%)[b]	7 ee (%)[c]
2b (20)	14	–[d]	–[d]	82[d]	89[d]
2b (10)	13	38	82	15	82
2c (10)	3	88	79	11	76
2d (10)	3	91	93	4	68
2d (6)	7	96	91	4	76
2d (4)	15	94	91	4	72

[a] The silyl enol ether was added into a mixed solution of **2** and benzaldehyde in propionitrile. [b] Isolated yield. [c] Determined by HPLC. See reference 14. [d] Data of reference 5d. The data after treatment of products with 1 *M* HCl is indicated.

Next, the reaction of several aldehydes with trisubstituted trimethylsilyl enol ethers was conducted at –78 °C in propionitrile in the presence of 10 mol% of **2d** as catalyst (eq 3).[14] The results of these experiments are summarized in Table 2. In the reaction of benzaldehyde with the trimethylsilyl enol ether of cyclohexanone, both substrates were sequentially added in a solution of **2d** in propionitrile at –78 °C according to Coreyís procedure.[5d] The reaction proceeded quantitatively to give only the aldol products in 78:22 diastereomeric ratio **8**:**9**, and the optical yield of **8** was 89% ee. The reaction of butyraldehyde with the (*Z*)-trimethylsilyl enol ether derived from propiophenone, however, did not proceed well, probably due to the decomposition of butyraldehyde in the presence of the strong Lewis acid **2d** before addition of the trimethylsilyl enol ether. Fortunately, the reaction proceeded cleanly by adding trimethylsilyl enol ether followed by butyraldehyde to afford only the *syn* aldol adduct with more than 99% ee.[7a] The *syn* selection observed in both reactions of aldehydes with (*E*)- and (*Z*)-trimethylsilyl enol ethers suggests that the reaction occurs *via* extended-transition state assemblies. It is noteworthy that the *anti* selection has been observed in the reaction of aldehydes with (*E*)-ketene trimethylsilyl acetals catalyzed by other chiral oxazaborolidines.[6,7] Thus, we were able to expand the scope of the substrates which were usable for the enantioselective Mukaiyama-aldol reaction by developing *B*-3,5-bis(trifluoromethyl)phenyloxazaborolidine **2d**.

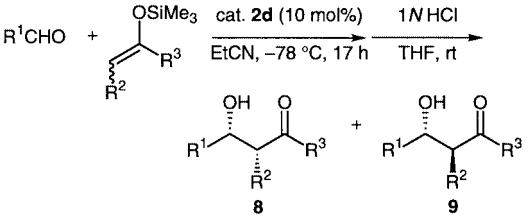
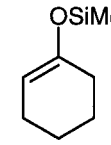
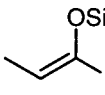


Table 2 Enantioselective Mukaiyama Aldol Reaction of Aldehydes with Trimethylsilyl Enol Ethers Catalyzed by **2d** (eq 3)[a]

R^1	silyl enol ether	yield (%),[b] 8:9[c]	ee (%) 8	ee (%) 9
Ph		99, 78:22	89[d]	5[d]
C_3H_7		>99,[f] >99: 1	>99[g,h]	–[g]
C_3H_7		23, >99: 1	96[g]	–[g]

[a] Unless otherwise noted, a solution of silyl enol ether (0.96 mmol) in propionitrile (0.32 mL) was added over 2 min into a mixed solution of **2d** (0.08 mmol) and an aldehyde (0.8 mmol) in propionitrile (0.65 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis (Daicel chiral OD-H column, flow rate=0.5 mL/min): t_R=14.3 (major-*syn*), 15.6 (minor-*syn*), 17.8 (minor-*anti*), 24.3 (major-*anti*) min. [e] >99% *Z*. [f] A solution of butyraldehyde (0.8 mmol) in propionitrile (0.32 mL) was added over 10 min into a mixed solution of the silyl enol ether (0.96 mmol) and **2d** (0.08 mmol) in propionitrile (0.65 mL). [g] Determined by HPLC analysis (Daicel OD-H column, flow rate=1.0 mL/min): t_R=5.96 (minor-*syn*), 6.46 (major-*syn*) min. [h] **8**: $[\alpha]_D^{27.7}$=+18.4 (*c*=1.09, benzene).

In summary, it has been demonstrated that the introduction of an electron-withdrawing substituent such as 3,5-bis(trifluoromethyl)phenyl group on the *B* atom of chiral boron catalysts is one of the most effective methods for enhancement of their catalytic activity.

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(12) Experimental procedure for the preparation of **2d**: To a solution of **1** (32.3 mg, 0.09 mmol) in dichloromethane (0.75 mL) was added **5** (22.1 mg, 0.075 mmol) at room temperature under argon. After being stirred for 1 h the mixture was concentrated *in vacuo* to give **2d** as a white solid, which was dissolved in propionitrile and used for Mukaiyama aldol reactions.
(13) Experimental procedure for the synthesis of **5**: After a solution of **3** (3.86 g, 15 mmol) in benzene (30 mL) was heated at reflux with removal of water (CaH_2 in a Soxhlet thimble) for 2~4 h (oil bath: 100~105 °C), the solution was cooled to room temperature and concentrated *in vacuo* to give trimeric anhydride **4** as white solid. **3**: ^{1}H NMR (C_6D_6, 300 MHz) δ 7.81 (s, 1H), 8.01 (s, 2H); **4**: ^{1}H NMR (C_6D_6, 300 MHz) δ 8.01 (s, 1H), 8.46 (s, 2H). A 1 M solution of boron trichloride (30 mL, 30 mmol) in hexane was added to **4** at room temperature under argon. After the reaction mixture was heated at reflux for 4 h (oil bath: 100–105 °C), hexane was removed by heating. Dichloroboron compound **5** was isolated as a colorless oil by distillation from the residue at 38~40 °C under 0.05~0.06 torr. **5**: ^{1}H NMR (C_6D_6, 300 MHz) δ 7.80 (s, 1H), 8.12 (s, 2H); ^{11}B NMR (C_6D_6, 96 MHz) δ 53.2 (δ 0.0 for BF_3•Et_2O); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 123.1 (q, *J*=272.8 Hz, 2C), 127.1 (s, 1C), 131.0 (q, *J*=33.5 Hz, 2C), 134.8-135.2 (m, 1C), 135.5 (s, 2C); ^{19}F NMR (C_6D_6, 282 MHz) δ 129.1 (δ 129.5 for $CF_3C_6H_5$).
(14) Experimental procedure for the reaction of benzaldehyde with 1-phenyl-1-(trimethylsiloxy)ethylene catalyzed by **2d** is representative. To **2d** (0.075 mmol, 6 mol%) prepared according to ref. 12 was added propionitrile (1 mL) at room temperature. After being cooled to –78 °C, benzaldehyde (127 μL, 1.25 mmol) was added, and a solution of the trimethylsilyl enol ether (308 μL, 1.5 mmol) in propionitrile (0.5 mL) was subsequently added dropwise over 2 min. The reaction mixture was stirred at –78 °C for 7 h and then quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with ether and then the combined organic phases were dried over $MgSO_4$ and evaporated. The residue was dissolved in THF (2 mL) and 1 M aq HCl (2 mL), and the resulting solution was allowed to stand for 30 min. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ether. The combined organic phases were dried over $MgSO_4$ and evaporated to an oily residue. Silica gel chromatography (hexane:EtOAc = 4:1) afforded 282 mg (>99% yield) of the known aldol product. HPLC analysis (Daicel OD-H column with hexane:*i*-PrOH = 20:1, flow rate=1.0 mL/min) indicated an enantiomeric excess of 90.4% (t_R major 19.6 min (*S*); minor 23.1 min (*R*)).

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