Scope and Limitations of Chiral *B*-[3,5-Bis(trifluoromethyl)phenyl]oxazaborolidine Catalyst for Use in the Mukaiyama Aldol Reaction

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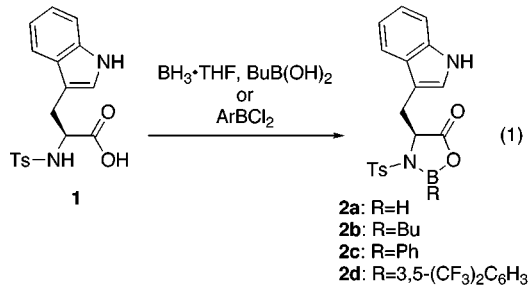
A new chiral oxazaborolidine catalyst was prepared in situ from 3,5-bis(trifluoromethyl)phenylboron dichloride and *N*-(*p*-toluenesulfonyl)-(*S*)-tryptophan. This catalyst is much more active than Corey's original catalyst for the Mukaiyama aldol reaction of aldehydes with silyl enol ethers. The observed *syn* selectivities and *re*-face attack of silyl enol ethers on carbonyl carbon of aldehydes imply that the extended-transition state model is applicable.

Introduction

Ever since we[1] and Helmchen's group[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, Corey's tryptophan-derived chiral oxazaborolidines **2a** and **2b** are highly effective for not only the Mukaiyama aldol reaction of aldehydes with silyl enol ethers[5d] but also the Diels−Alder reaction of α-substituted α,*β*-enals with dienes (eq 1).[5a−c,e] However, more than 20 mol % of **2b** is required



for the former reaction. Other chiral oxazaborolidines that have been developed for the enantioselective aldol reaction of aldehydes with relatively more reactive ketene silyl acetals also require large amounts (more than 20 mol %) 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 using 3,5-bis(trifluoromethyl)phenylboronic acid (**3**) in-

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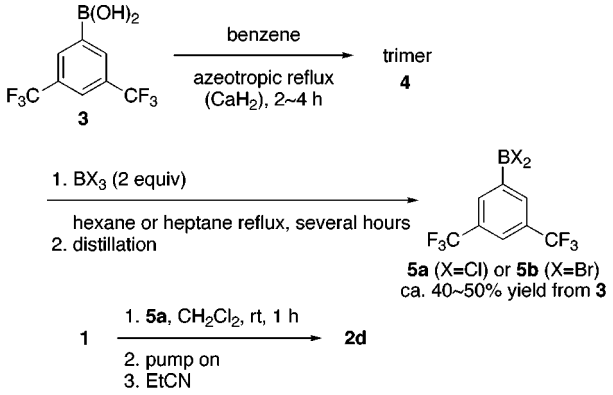
Scheme 1. Synthesis of 3,5-Bis(trifluoromethyl)phenylboron Dichloride (5) and Preparation of Catalyst 2d



stead of borane·THF.[10,11] The utility of **3** in 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 a designer chiral Lewis acid catalyst modified using arylboron dichlorides bearing electron-withdrawing substituents as Lewis acid components.[12]

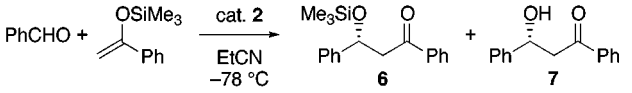
Results and Discussion

A new chiral oxazaborolidine catalyst **2d** was prepared by treating *N*-(*p*-toluenesulfonyl)-(*S*)-tryptophan (**1**) with an equimolar amount of 3,5-bis(trifluoromethyl)phenylboron dichloride (**5a**) in dichloromethane and subsequent removal of the resulting HCl and the solvent in vacuo (Scheme 1). Moisture-sensitive boron dichloride **5a** and boron dibromide **5b** were synthesized by dehydration of **3** to trimeric anhydride **4** and subsequent halogenation of **4** with 2 equiv of boron trichloride and boron tribromide, respectively. 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 in place of *N*-sulfonylamino acids has been easily prepared by adding an equimolar amount of the corresponding arylboronic acid at room temperature.[10]

According to Corey,[5d] terminal trimethylsilyloxy (vinylidene) olefins appear to be the most favorable substrates for enantioselective Mukaiyama aldol coupling catalyzed by **2b**, compared to more highly substituted olefins such as RCH=C(OSiMe$_3$)R′ or R$_2$C=C(OSiMe$_3$)-R′. In fact, 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 a solvent in the presence of **2** as a catalyst. Following Corey's procedure using 10 mol % of **2b**, we obtained the trimethylsilyl ether of aldol **6** and the free aldol **7** in respective yields of only 38% and 15%. However, when the *B*-phenyl analogue **2c** was used as a catalyst, the chemical yield was dramatically improved. Furthermore, when the *B*-3,5-bis(trifluoromethyl)phenyl analogue **2d** was used, catalytic activity and enantioselectivity were increased to a turnover of 25 and 91−93% ee, respectively. The absolute configuration of the aldol adducts indicated in Table 1 was uniformly *R*.

Table 1. Enantioselective Mukaiyama Aldol Reaction of Benzaldehyde with Trimethylsilyl Enol Ether Derived from Acetophenone Catalyzed by 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 to a mixed solution of **2** and benzaldehyde in propionitrile. [b] Isolated yield. [c] Determined by HPLC. [d] Data from reference 5d. The data after treatment of products with 1 M HCl are indicated.

Next, the reaction of several aldehydes with trisubstituted (*E*)-trimethylsilyl enol ethers was conducted at −78 °C in propionitrile in the presence of 10 mol % of **2d** as a catalyst. 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 to a solution of **2d** in propionitrile at −78 °C according to Corey's procedure (method A).[5d] The reaction proceeded quantitatively to give only the aldol products in a 78:22 *syn*−*anti* ratio, and the optical yield of the *syn* isomer **8** was 89% ee. In contrast, the reaction of isobutyraldehyde with the same silyl enol ether did not proceed well, probably due to the decomposition of isobutyraldehyde in the presence of the strong Lewis acid **2d** before addition of the trimethylsilyl enol ether. Nevertheless, the aldol adducts were obtained with 96% ee. On the other hand, the sequential addition of silyl enol ethers and aldehydes to a solution of catalyst **2d** (method B) gave the aldol adducts in higher yield, but the enantioselectivity was relatively low. Unfortunately, catalyst **2d** was less effective for the enantioselective reaction with silyl enol ethers derived from cyclopentanone and cycloheptanone. High enantioselectivity was also observed in the reaction with acyclic (*E*)-silyl enol ether derived from 3-pentanone. The use of 3,5-bis-(trifluoromethyl)phenylboron dibromide **5b** in place of **5a** in the in situ preparation of **2d** slightly diminished the enantioselectivity (method A′).

Similar experiments were examined for the reaction of aldehydes with (*Z*)-silyl enol ethers (Table 3). As expected, the reaction of aliphatic aldehydes with (*Z*)-trimethylsilyl enol ethers using method A did not proceed well, probably for the same reason as above. Fortunately, the reaction proceeded cleanly by adding trimethylsilyl

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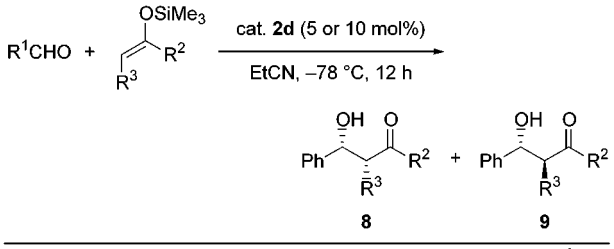
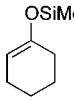
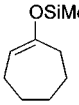
(12) Part of this work has been published as a preliminary communication: Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **1999**, 1283.

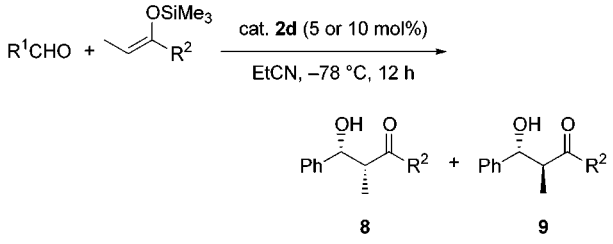
Table 2. Mukaiyama Aldol Reaction of Aldehydes with (*E*)-Silyl Enol Ethers



R[1]	silyl enol ether	method[a]	yield (%)[b]	8:9[c]	ee (%)[d] 8	ee (%)[d] 9
Ph		A	74	88:12	33	12
Ph		B	>99	80:20	9	2
Ph		A	>99	78:22	89	5
Ph		A′	>99	70:30	79	4
i-Pr		A[e]	36	77:23	96	96
Ph		A	85	66:34	29	14
Ph		B	>99	68:32	4	0
Pr		B	>99	48:52	95	93

[a] Method A: A solution of silyl enol ether (0.96 mmol) in propionitrile (0.32 mL) was added over 2 min to a mixed solution of **2d** (0.08 mmol) and an aldehyde (0.8 mmol) in propionitrile (0.65 mL). Method A′: Catalyst **2d**, prepared in situ from **1** and **5b** in place of **5a**, was used under the conditions in Method A. Method B: A solution of aldehyde (0.8 mmol) in propionitrile (0.32 mL) was added over 10 min to a mixed solution of the silyl enol ether (0.96 mmol) and **2d** (0.08 mmol) in propionitrile (0.65 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC. [e] 5 mol % of **2d** was used. [f] *E*:*Z* = 70:30.

Table 3. Mukaiyama Aldol Reaction of Aldehydes with (*Z*)-Silyl Enol Ethers



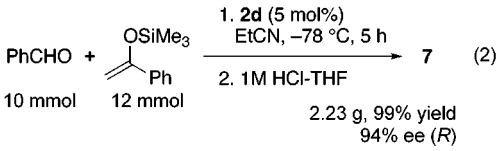
R[1]	silyl enol ether R[2] (*Z*:*E*)	method[a]	yield (%)[b]	8:9[c]	ee (%)[d] 8	ee (%)[d] 9
Pr	Ph (>99:1)	A	23	>99:1	96	–
Pr	Ph (>99:1)	B	>99	>99:1	>99	–
Pr	Et (97:3)	B	>99	62:38	92	77
i-Pr	Ph (>99:1)	B	>99	97:3	98	–
i-Pr	Et (97:3)	B[e]	94	83:17	92	91
(*E*)-MeCH=CH	Ph (>99:1)	B	85	95:5	97	–
PhC≡C	Ph (>99:1)	B	92	89:11	90	58

[a] See footnote *a* in Table 2. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC. [e] 5 mol % of **2d** was used.

enol ether followed by butyraldehyde to give only the *syn* aldol adduct with more than 99% ee.[7a]

The *syn* preference and the absolute preference for carbonyl *re*-face attack observed in the reactions of aldehydes with (*E*)- and (*Z*)-trimethylsilyl enol ethers suggests that the reaction occurs via an extended-transition state assembly (Figure 1).[5,10] *Anti* preference has been observed in the reaction of aldehydes with (*E*)-ketene trimethylsilyl acetals catalyzed by other chiral oxazaborolidines.[6,7a,b] Thus, we were able to expand the scope of the substrates that could be used in the enantioselective Mukaiyama-aldol reaction by developing *B*-3,5-bis(trifluoromethyl)phenyloxazaborolidine **2d**.

In summary, these results demonstrate that the introduction of an electron-withdrawing substituent such as 3,5-bis(trifluoromethyl)phenyl group to the B atom of chiral boron catalysts is an effective method for enhancing their catalytic activity. The present method is especially attractive for large-scale synthesis (eq 2).



Experimental Section

Preparation of Silyl Enol Ethers. 1-Phenyl-1-(trimethylsilyloxy)ethylene, 1-(trimethylsilyloxy)cyclopentene, and 1-(trimethylsilyloxy)cyclohexene were purchased from Aldrich. (*Z*)-3-Trimethylsilyloxy-2-pentene was prepared by heating 3-pentanone and chlorotrimethylsilane in dichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[13a] Other silyl enol ethers were prepared by quenching the corresponding lithium enolates, derived from ketones with lithium *N*,*N*-diisopropylamide (LDA) in THF, with chlorotrimethylsilane.[13b]

Preparation of 3,5-Bis(trifluoromethyl)phenylboron Dihalide (5). After a suspension of 3,5-bis(trifluoromethyl)-phenylboronic acid (**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 2−5 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. Each of 1 M solution of boron trichloride (30 mL, 30 mmol) in hexane and a 1 M solution of boron tribromide (30 mL, 30 mmol) in heptane was added to **4** at room temperature under argon. After the two reaction mixtures were heated at reflux for 4 h (oil bath: 100−105 °C) and 56 h (oil bath: 105−110 °C), respectively, solvents were removed by distillation. Dihaloboron compounds **5a** and **5b** were isolated as colorless oils by distillation under reduced pressure from the residues, respectively, in ca. 40−50% yield.

3: Purchased from Lancaster Synthesis Ltd.; ^{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).

5a: 38−40 °C (0.05−0.06 Torr); ^{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; ^{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 −64.3.

5b: 48−50 °C (0.015 Torr); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.83 (s, 1H), 8.27 (s, 2H); ^{11}B NMR (C_6D_6, 96 MHz) δ 56.6; ^{13}C NMR (C_6D_6, 75.5 MHz) δ 123.0 (q, J = 273.2 Hz, 2C), 127.3 (s, 1C), 131.1 (q, J = 33.6 Hz, 2C), 135.0−135.8 (m, 1C), 136.2 (s, 2C); ^{19}F NMR (C_6D_6, 282 MHz) δ −64.0.

Preparation of Chiral Oxazaborolidine Catalyst 2d. To a suspension of **1**[5a] (32.3 mg, 0.09 mmol) in dichloromethane (0.75 mL) was added **5a** (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.

2d: ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 2.37 (s, 3H), 3.56 (dd, J = 2.6, 15.0 Hz, 1H), 3.83 (dd, J = 4.5, 15.0 Hz, 1H), 4.56−4.59 (m, 1H), 7.08−7.30 (m, 4H), 7.26 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 7.5 Hz, 1H), 7.95 (s, 1H), 8.04 (s,

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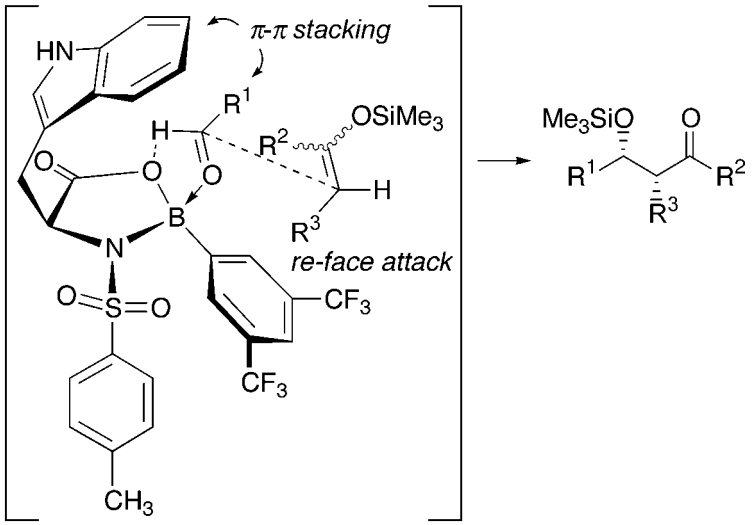

Figure 1. Proposed extended-transition state assembly.

2H), 8.22 (brs, 1H); ^{11}B NMR (CD_2Cl_2, 96 MHz) δ 33.8; ^{19}F NMR (C_6D_6, 282 MHz) δ −64.2.

Representative Procedure for the Mukaiyama Aldol Reaction Catalyzed by 2d (Method A, Table 1). To **2d** (0.075 mmol, 6 mol %) prepared by the preceding procedure 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 1-phenyl-1-(trimethylsiloxy)ethylene (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 12 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 aqueous 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 (hexanes−ethyl acetate = 4:1) afforded 282 mg (>99% yield) of the known aldol product **7**. ^{1}H NMR, ^{13}C NMR, and IR spectroscopic data are in agreement with those reported in the literature.[10b] The enantiomeric ratio and the absolute configuration were determined by HPLC analysis (Daicel OD-H column with hexane−*i*-PrOH = 20:1, flow rate = 1.0 mL/min):[16c] t_R = 21.2 ((*S*), minor enantiomer), 24.4 ((*R*), major enantiomer) min.

For the determination of the *syn*/*anti* ratios, enantiomeric ratios, and absolute configurations of other aldol adducts **8** synthesized by the similar procedure A or B (Tables 2 and 3), see Supporting Information.

Large Scale Enantioselective Syntheis of (*R*)-7. To a suspension of **1**[5a] (215.0 mg, 0.60 mmol) in dichloromethane (2.0 mL) was added **5a** (147.4 mg, 0.50 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. To **2d** (0.50 mmol, 5 mol %) prepared by the preceding procedure was added propionitrile (5 mL) at room temperature. After being cooled to −78 °C, benzaldehyde (1.01 mL, 10 mmol) was added, and a solution of 1-phenyl-1-(trimethylsiloxy)ethylene (2.46 mL, 12 mmol) in propionitrile (5 mL) was subsequently added dropwise over 1 h. The reaction mixture was stirred at −78 °C for 5 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 (5 mL) and 1 M aqueous HCl (5 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 (hexanes−ethyl acetate = 4:1) afforded 2.23 g (99% yield) of the known aldol product **7** [94% ee (*R*)].

Supporting Information Available: Characterization data of aldols **8** (Tables 2 and 3) and HPLC traces of the optical and diastereomeric purity. This material is available free of charge via the Internet at http://pubs.acs.org.

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