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Synthesis of novel oxazaborolidines *B*-C_6F_5 and their effectiveness as asymmetric catalysts

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Abstract

Novel oxazaborolidines *B*-C_6F_5 were synthesized by modified protocol from $C_6F_5B(OMe)_2$ (in place of usual $C_6F_5B(OH)_2$) and the corresponding amino alcohols, aiming to know the π–π stacking and electron-withdrawing effects of C_6F_5 group in asymmetric reduction of ketones. Although the results were not simply explained by the expected effects, significant difference was observed in the enantioselectivity between the catalysts with *B*-C_6H_5 and *B*-C_6F_5.

Keywords: Pentafluorophenyl group; Oxazaborolidine; π–π stacking; Asymmetric borane reduction

1. Introduction

Oxazaborolidines are useful chiral catalysts for asymmetric borane reduction, Diels–Alder reactions, and aldol reactions [1]. The substituent on B atom of the oxazaborolidine plays a significant role in governing the selectivity and stability of the catalyst system [2]. The most commonly used substituent on the B atom is the electron-donating Me group (oxazaborolidine *B*-Me) [1,3], although an electron-deficient substituent (i.e. –C_6H_4-*p*-F) has also attracted much attention among researchers [2a,4]. We have focused on the use of a pentafluorophenyl group as an electron-deficient substituent, because the pentafluorophenyl group has been shown to have interesting properties, including (1) a stronger electron-withdrawing effect relative to that of a phenyl group [5], (2) a different substituent effect due to its greater bulkiness compared to a phenyl group [6], and (3) formation of a face-to-face π–π stacking structure with any aromatic group [7]. Among these properties, the strong electron-withdrawing effect is particularly interesting, as it should cause a decrease in the electron density of the B atom in oxazaborolidine *B*-C_6F_5. Hence, we synthesized novel chiral oxazaborolidines *B*-C_6F_5 **1a** and **1b** (Fig. 1), and investigated their catalytic ability in asymmetric borane reduction of acetophenone and pentafluoroacetophenone.

2. Results and discussion

Oxazaborolidines are usually synthesized from an amino alcohol and an aryl (or alkyl) boronic acid in toluene under azeotropic conditions to remove water generated in the reaction. Preparation of electron-deficient *B*-Ar oxazaborolidines (such as Ar = 4-F-C_6H_4, 3-NO_2-C_6H_4) in a similar manner has been reported [2a]. However, the reaction of pentafluorophenylboronic acid (**2**) with an amino alcohol such as (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**3a**) or (*S*)-α,α-dipheny-2-pyrrolidinemethanol (**3b**) did not proceed under typical conditions (Scheme 1). Interestingly, boronic acid **2** reacted with 1,2-diphenyl-1,2-ethandiol (**4**) using the same protocol to give boronate **5** quantitatively (Scheme 2). The difference between the reaction using amino alcohol **3** and that using diol **4** seems to be related to the presence of an amino group. Therefore, we hypothesized that the reaction of **2** with **3** was disturbed by hydrogen-bonding between the amino group of **3** and a proton of **2** [8]. We attempted to avoid this problem by replacing the boronic acid with $C_6F_5B(OMe)_2$ (**6**) [9], which was generated *in situ* by treatment of trimethyl boronate with C_6F_5MgBr at −78 °C for 1 h (Scheme 3). The resulting crude **6**

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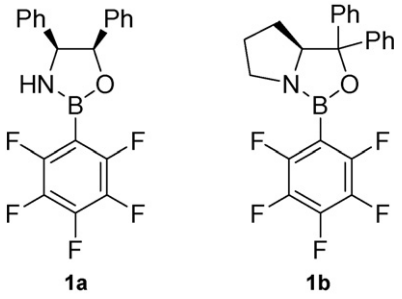
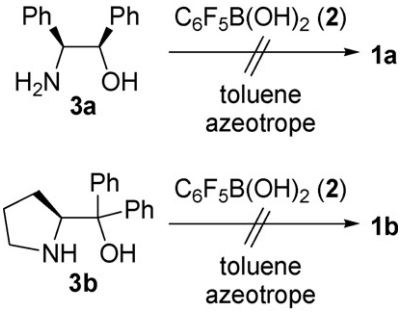


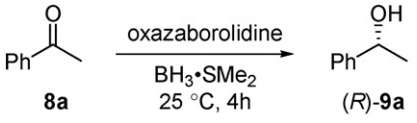
Fig. 1. Chiral oxazaborolidine *B*-C_6F_5.

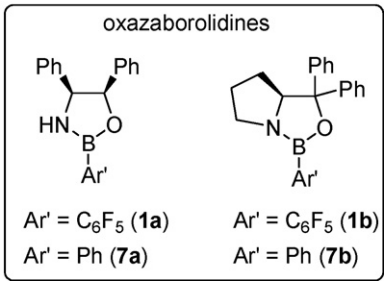


Scheme 1. Reaction of $C_6F_5B(OH)_2$ with amino alcohols.

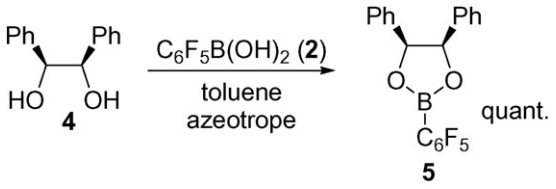
was treated with **3a** in benzene [10] under azeotropic conditions for 3 h. After addition of dry Et_2O, the remaining Mg salt was removed through glass wool under an argon atmosphere, giving oxazaborolidine *B*-C_6F_5 **1a**. Oxazaborolidine *B*-C_6F_5 **1b** was synthesized from **3b** in a similar manner. Further purification of oxazaborolidines **1a** and **1b** was unsuccessful. Based on their ^{1}H NMR spectra, however, the compounds were judged to be sufficiently pure for use in subsequent catalytic reactions [11].

Table 1
Asymmetric borane reduction of **8a**

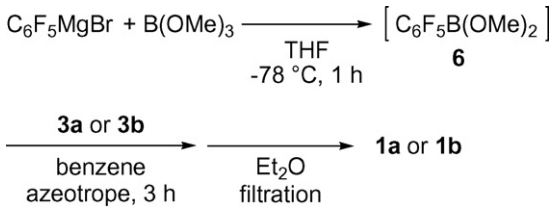




Entry	Oxazaborolidine	% ee (conv.) of (*R*)-**9a**
1	Ar′ = C_6F_5 (**1a**)	17% ee (100%)
2	Ar′ = Ph (**7a**)	83% ee (100%)
3	Ar′ = C_6F_5 (**1b**)	88% ee (100%)
4	Ar′ = Ph (**7b**)	>99% ee (100%)



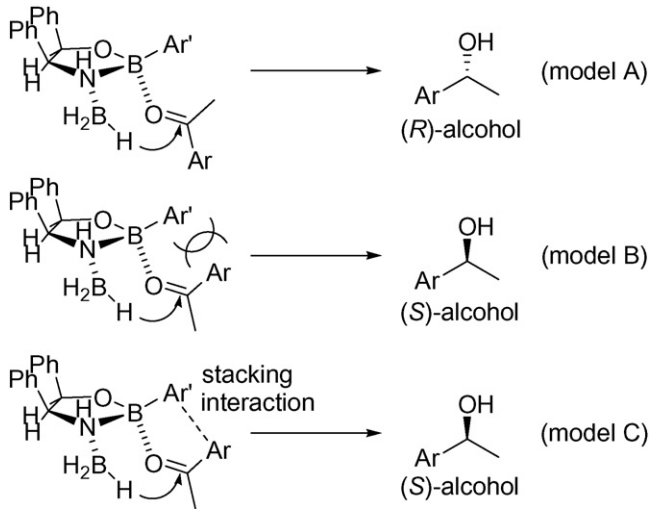
Scheme 2. Reaction of $C_6F_5B(OH)_2$ with diol.



Scheme 3. Synthesis of oxazaborolidines *B*-C_6F_5.

Oxazaborolidine *B*-C_6F_5 **1a** and **1b** were used as a catalyst for asymmetric borane reduction of aryl ketones, acetophenone (**8a**) and pentafluoroacetophenone (**8b**). Asymmetric reduction of **8a** with 10 mol% of (4*S*,5*R*)-**1a** (or (*S*)-**1b**) and BH_3 was carried out, giving (*R*)-1-phenylethanol (**9a**) in quantitative yield with 17% ee (88% ee for (*S*)-**1b**) (Table 1, entries 1 and 2). The enantioselectivity was significantly lower than that obtained using oxazaborolidine *B*-Ph (4*S*,5*R*)-**7a** (Table 1, entry 1 vs. 2). The tendency was similar to that using oxazaborolidines (*S*)-**1b** and (*S*)-**7b** (Table 1, entry 3 vs. 4). One reason for the low enantioselectivity using (4*S*,5*R*)-**1a** and (*S*)-**1b** may be the increased Lewis acidity of the B atom in the oxazaborolidine due to the strong electron-withdrawing effect of the pentafluorophenyl group. The stronger Lewis acidity of the boron atom of the oxazaborolidine was reported to rather decrease the enantioselectivity in the reduction [2b]. In addition, the electron-withdrawing pentafluorophenyl group simultaneously reduces the basicity of amino group, which is disadvantageous in terms of coordination of BH_3. However, the π–π stacking interaction between the C_6F_5 group in **1a** (or **1b**) and the Ph in **8a** should also have an effect on enantioselectivity [12,13]. In general, ketonic substrates are preferentially attacked by hydride from the *Si*-face to give the (*R*)-alcohol, as the ketonic substrate binds with (4*S*,5*R*)-oxazaborolidine, minimizing the steric interaction between the *B*-Ar′ group and the ketonic Me group (Scheme 4, model A). Inherently, face-to-face alignment between the *B*-Ar′ group and the ketonic Ar group is sterically unfavorable (Scheme 4, model B). However, if a stacking interaction exists between the Ar′ and the Ar group, the transition state shown in model C is more favorable than model B (Scheme 4, model C). Thus, the reduced enantioselectivity, when **1a** or **1b** was used, may be attributed to the influence of transition states.

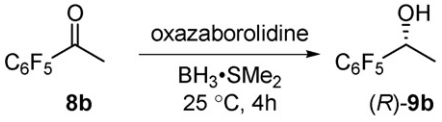
In order to confirm the presence or absence of a stacking interaction between C_6F_5 and C_6H_5, asymmetric reduction of pentafluoroacetophenone (**8b**) was carried out using **1** or **7** (Table 2). Reduction of **8b** using (4*S*,5*R*)-**1a** or (*S*)-**1b** is expected to give the (*R*)-alcohol with a higher % ee than that of **8a** using (4*S*,5*R*)-**7a** or (*S*)-**7b**, on the basis that enhanced

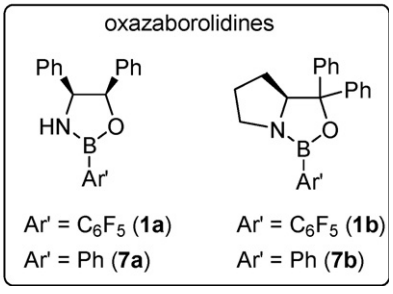


Scheme 4. Possible transition states of BH_3 reductions with oxazaborolidines.

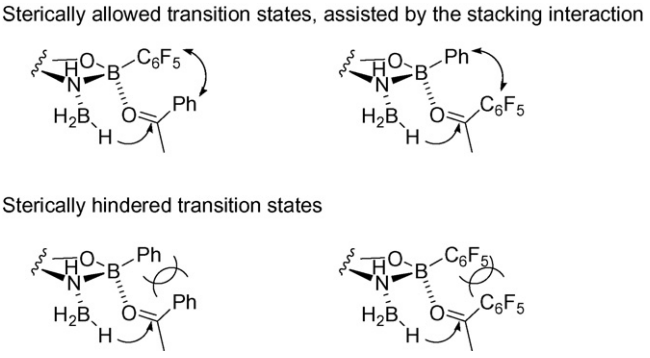
repulsion between the two C_6F_5 groups results in preferential formation of model A (Scheme 4, Scheme 5). However, the result obtained was contrary to our expectations, giving the (*R*)-alcohol with a much reduced ee of 7% for **1a** or 33% for **1b** (entry 1 (or 3) of Table 2 vs. entry 2 (or 4) of Table 1). For the reaction shown in entry 2 (or 4), Table 2, if there is a $C_6F_5\cdots$Ph interaction between **7a** (or **7b**) and **8b**, model C (Scheme 4) should be formed preferentially, giving the (*S*)-alcohol, or the (*R*)-alcohol with reduced % ee. However, the product was the (*R*)-alcohol, with a higher ee than that of entry 1 (Table 2, entry 2 (or 4) *vs*. entry 1 (or 3)). These results led us to conclude that the effect of the stacking interaction in organic solvent is sufficiently small, and that it has no effect on these reaction systems, as reported in our previous paper [14].

Table 2
Asymmetric borane reduction of **8b**





Entry	Oxazaborolidine	% ee (conv.) of (*R*)-**9b**
1	Ar′ = C_6F_5 (**1a**)	7% ee (100%)
2	Ar′ = Ph (**7a**)	35% ee (100%)
3	Ar′ = C_6F_5 (**1b**)	33% ee (100%)
4	Ar′ = Ph (**7b**)	70% ee (100%)



Scheme 5. Transition states giving (*S*)-alcohol.

We developed the novel oxazaborolidines *B*-C_6F_5 **1a** and **1b** by modification of a conventional method and examined their effectiveness as asymmetric catalysts. The use of (4*S*,5*R*)-**1a** or (*S*)-**1b** as a catalyst had unexpected results; the role of the C_6F_5 group in this reaction system is not yet well understood. In order to investigate the utility of these catalysts, further systematic study, based on other reactions such as the asymmetric Diels–Alder and aldol reactions, is required.

3. General experimental procedures

All reactions were carried out under an argon atmosphere with dry solvents, unless otherwise noted. Dehydrated toluene, Et_2O and THF were purchased from Kanto Chemical Co. and then were stored in Schlenk tubes under an argon atmosphere. Reagents used were purchased and used without further purification. Preparative column chromatography was carried out by using silica gel (Fuji Silysia BW-127 ZH, 100-270 mesh). ^{1}H NMR spectra were measured at 300 MHz, and ^{13}C NMR spectra were measured at 151 MHz. The chemical shifts are given relative to tetramethylsilane (TMS). ^{19}F NMR spectra were measured at 282 MHz, and chemical shifts are given relative to CCl_3F using C_6F_6 as secondary reference (−162.9 ppm). ^{11}B NMR spectra were measured at 192 MHz, and chemical shifts are given relative to $BF_3{\cdot}Et_2O$.

*3.1. (4S,5R)-4,5-Diphenyl-2-pentafluorophenyl-1,3,2-oxazaborolidine (**1a**)*

A 20 mL of dry Schlenk tube was charged with Mg (26.7 mg, 1.1 mmol), THF (0.3 mL), bromopentafluorobenzene (30 μL, 0.24 mmol) and trace amount of I_2 under an argon atmosphere. Then, THF (1.0 mL) was added, followed by addition of bromopentafluorobenzene (95 μL, 0.76 mmol) dropwise over 15 min. After the mixture was added to 1.0 mL of THF solution of trimethyl borate (330 μL, 3.0 mmol) at −78 °C, the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure to give white solid of crude dimethyl pentafluorophenylboronate (**6**). After addition of (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**3a**) (210 mg, 1.0 mmol) and benzene (40 mL) to the crude **6**, the mixture was stirred for 3 h under conditions of azeotrope

with Dean-Stark trap containing molecular sieves 3A. The solvent was removed under the pressure of <1 mmHg at 30 °C for 1 h to give pale yellow solid. After addition of Et_2O to the solid, the white suspension was filtered through glass wool under argon atmosphere. The solvent was removed under the pressure of <1 mmHg at 40 °C for 1 h to give (4*S*,5*R*)-4,5-diphenyl-2-pentafluorophenyl-1,3,2-oxazaborolidine (**1a**). This oxazaborolidine **1a** was readily used for asymmetric borane reduction of ketones without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.53 (br, 1H), 5.21 (d, J = 6.6 Hz, 1H), 6.00 (d, J = 6.6 Hz, 1H), 6.92–7.15 (m, 10H); ^{13}C NMR (151 MHz, $CDCl_3$ (except for C_6F_5)) δ: 64.1, 84.6, 126.3, 127.1, 127.3, 127.4, 127.5, 127.8, 137.9, 139.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −162.8 to −162.7 (m, 2F), −151.1 (t, J = 21 Hz, 1F), −131.2 to −131.1 (m, 2F); ^{11}B NMR (192 MHz, $CDCl_3$) δ: 30.2.

3.2. (S)-1-(Pentafluorophenyl)tetrahydro-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole (1b)

(*S*)-1-(Pentafluorophenyl)tetrahydro-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (**1b**) was prepared from (*S*)-α,α-diphenyl-2-pyrrolidinemethanol following the procedure described for **1a**.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93–1.03 (m, 1H), 1.72–1.80 (m, 1H), 1.81–1.95 (m, 2H), 3.18–3.38 (m, 2H), 4.65 (dd, J = 5.9, 10.0 Hz, 1H), 7.03–7.43 (m, 8H), 7.42–7.57 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$ (except for C_6F_5)) δ: 26.3, 30.0, 43.0, 72.8, 87.6, 126.0, 126.3, 126.4, 127.0, 127.6, 128.0, 144.1, 147.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −163.1 to −162.9 (m, 2F), −152.3 (t, J = 21 Hz, 1F), −130.5 to −130.4 (m, 2F); ^{11}B NMR (192 MHz, $CDCl_3$) δ: 30.0.

3.3. Meso-2-(pentafluorophenyl)-4,5-diphenyl-1,3,2-dioxaborolane (5)

A 20 mL of dry Schlenk tube was charged with *meso*-1,2-diphenyl-1,2-ethanediol (**4**) (21 mg, 0.10 mmol), pentafluorophenylboronic acid (23 mg, 0.11 mmol) and toluene (2.0 mL) under an argon atmosphere. After being stirred at room temperature, the mixture was stirred for 4 h under conditions of azeotrope with Dean-Stark trap containing molecular sieves 3A. The solvent was removed under reduced pressure to give white solid. The resulting solid was purified by recrystallization from petroleum ether–CH_2Cl_2 to give *meso*-2-(pentafluorophenyl)-4,5-diphenyl-1,3,2-dioxaborolane (**5**) in quantitative yield (39 mg, 0.10 mmol).

mp 115–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.01 (s, 2H), 6.90–7.10 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$ (except for C_6F_5)) δ: 83.6, 126.3, 127.6, 127.8, 136.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −162.5 to −162.2 (m, 2F), −149.2 (t, J = 22 Hz, 1F), −129.4 to −129.1 (m, 2F); ^{11}B NMR (192 MHz, $CDCl_3$) δ: 30.9; IR (KBr) 698, 719, 754, 1209, 1255, 1340, 1367, 1412, 1485, 1651, 2950, 3040 cm^{-1}; anal. calcd. for $C_{20}H_{12}BF_5O_2$: C, 61.58; H, 3.10; found: C, 60.21; H, 3.37%.

3.4. Typical procedure of asymmetric reduction of ketone

To a THF (1.0 mL) solution of oxazaborolidine **1a** (0.1 mmol) prepared above was added borane dimethylsulfide complex (28 μL, 0.30 mmol). After being stirred at room temperature for 10 min, the solution of acetophenone (**8a**) (120 μL, 1.0 mmol) in THF (2.0 mL) was added via syringe pump over 1.5 h, and then the reaction solution was stirred at room temperature for 4 h. To the solution was added methanol (1 mL) and then the solvent was removed under reduced pressure. After purification through a short column chromatography (SiO_2, hexane/EtOAc (3:1)), the residue was analyzed by chiral HPLC; Daicel CHIRALCEL OB-H, Ø 4.6 mm × 25 cm, hexane/*i*-PrOH (9: 1), 0.4 mL min^{-1}, UV 254 nm, retention time (t_R); (*S*)-**8a**: 17.5 min (41.4%); (*R*)-**8a**: 22.9 min (58.6%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.51 (d, J = 6.3 Hz, 3H), 1.77 (br, 1H), 4.91 (q, J = 6.3 Hz, 1H), 7.25–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.0, 70.2, 125.3, 127.4, 128.5, 145.9; IR (CCl_4) 537, 903, 998, 1076, 1255, 1463, 1491, 2978 and 3350 cm^{-1}.

Acknowledgements

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