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Short communication

Effect of conformational control of chiral oxazaborolidine by π–π stacking interaction of a pentafluorophenyl group toward asymmetric borane reduction

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Abstract

A pentafluorophenyl group can act as a stereo-controlling group in oxazaborolidine-catalyzed asymmetric borane reduction through intramolecular π–π stacking interaction with a phenyl group. The intramolecular π–π interaction in oxazaborolidine bearing pentafluorophenyl group is confirmed by calculations and ^{1}H NMR study. The interaction affects the enantioselectivity of the asymmetric reduction of acetophenone while the extent is small.

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

1. Introduction

Aromatic–aromatic π–π stacking interaction is important phenomena for the host–guest chemistry and organic reactions [1]. Among them, a pentafluorophenyl (C_6F_5) group is a noteworthy group [2], because the π–π stacking interaction between C_6F_5 and non-fluorinated aryl groups regulates their arrangement in a face-to-face orientation rather than slipped parallel (or T-shaped) one [3] as usually seen between non-fluorinated aryl groups (Fig. 1) [1,4]. Despite many examples on the X-ray analyses of the crystal structures [5], only a few examples for utilization of the π–π stacking interaction of the C_6F_5 group in organic reactions are reported [6]. In particular, to our knowledge, there have been no reports on the utility of the interaction in an asymmetric catalysis. One of the reasons for the difficulty in using the C_6F_5 group as a stereo-controlling group is that the intermolecular interaction between the C_6F_5 and non-fluorinated aryl groups is too small to affect the organic reaction in polar organic solvents [5c,6b,7,8]. However, the intramolecular interaction might be effective even in organic solvents [8].

By the concept, we previously synthesized a novel chiral amino alcohol, (1*R*,2*S*)-2-amino-1-(pentafluorophenyl)-2-phenylethanol (**1a**), bearing both of the C_6F_5 and Ph groups [9]. In general, chiral amino alcohols have been often used as the ligand of catalyst of enantioselective borane reduction of ketones after conversion to oxazaborolidines [10]. In the reduction, oxazaborolidine **2b** derived from (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**1b**) is known to catalyze highly enantioselective borane reduction of ketones, in which Quallich et al. pointed out that the high enantioselectivity may come from the effective shielding of one face of the oxazaborolidine by the intramolecular interaction of two phenyl groups (Fig. 1) [11]. Therefore, shielding of one face of the oxazaborolidine is one of the most important requirements to achieve high enatioselectivity in the asymmetric borane reduction, that is, BH_3 needs to coordinate with N atom of **2** from one direction which gives α-BH_3 adduct to achieve the high enantioselectivity (Scheme 1) [10a].

We here demonstrated that the intramolecular face-to-face like interaction affected on the enantioselectivity by the difference in the conformations between **2a** and **2b** (Fig. 1), which are estimated by calculation and ^{1}H NMR studies. These results exemplified the possibility of the C_6F_5 group as the stereo-controlling group in organic solvents.

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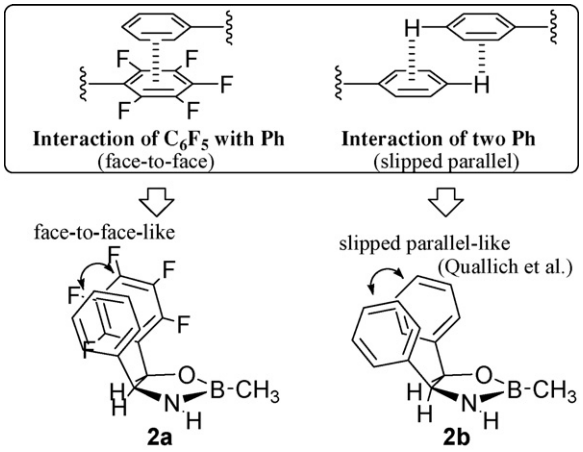
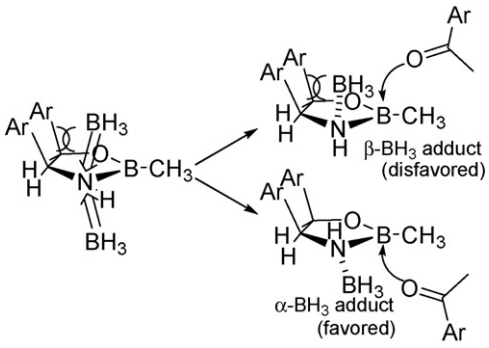


Fig. 1. Intramolecular π–π stacking interaction.



Scheme 1. Direction of coordination of BH_3 toward N atom.

2. Results and discussion

To begin with, we evaluated the ability of the intramolecular π–π stacking interaction between the C_6F_5 and Ph groups in oxazaborolidine **2a** by using *ab initio* calculations at the MP2(full)/6-31G** level [12]. The structural optimization for both **2a** and **2b** showed that the dihedral angles of C^{Ar1}–C^1–C^2–C^{Ar2} (21.2°) and H^a–C^1–C^2–H^b (21.3°) in **2a** were found to be smaller than those of C^{Ar1}–C^1–C^2–C^{Ar2} (26.5°) and H^a–C^1–C^2–H^b (24.9°) in **2b** (Fig. 2). The smaller angle of C^{Ar1}–C^1–C^2–C^{Ar2} in **2a** would be attributed to the face-to-face π–π interaction between the C_6F_5 and Ph groups. Furthermore, the π–π interaction brings with distortion of the ring of **2a** because the dihedral angle of H^a–C^1–C^2–H^b in **2a** is smaller than that (24.8°) in non-substituted oxazaborolidine **2c**. As the result, upside of the N atom in **2a** is more shielded by the same direction of the aryl groups as compared to that in **2b**.

These structural predictions by calculation were confirmed by ^{1}H NMR analysis of **2a** and **2b** (Table 1). The observed coupling constants J_{H^a,H^b} for **2b** were unchanged in the range between 0 and 50 °C in d_8-THF, while that for **2a** was larger than that for **2b**, and decreased from 9.6 to 9.0 Hz with increasing the temperature from 0 to 50 °C. The decrease in J_{H^a,H^b} value means that the dihedral angle of H^a–C^1–C^2–H^b becomes wider. Thus, the π–π interaction brings the Ph group close to the C_6F_5 group, leading to narrow dihedral angle with distortion of the ring at 0 °C as predicted by above calculations; however, raising the temperature would cancel the π–π interaction, leading to wide dihedral angle. Interestingly, such a change in dihedral angle of **2a** was not observed in d_8-toluene in a similar temperature variation, suggesting that the intramolecular π–π interaction would be cancelled with the aromatic solvent.

Temperature-dependent conformational change should influence the enantioselectivity of the asymmetric borane reduction catalyzed by **2a**, because the closely arranged aryl groups by the π–π interaction would inhibit BH_3 approaching to N atom from the direction which gives a disfavored β-BH_3 adduct (Fig. 3).

The asymmetric borane reductions of acetophenone (**3**) in THF were performed by using 10 mol% of (4*S*,5*R*)-**2a** or **2b** in a range between −40 and 50 °C (Table 2 and Fig. 4a) [13]. The enantioselectivities of (*R*)-alcohol **4** in the reaction with **2b**

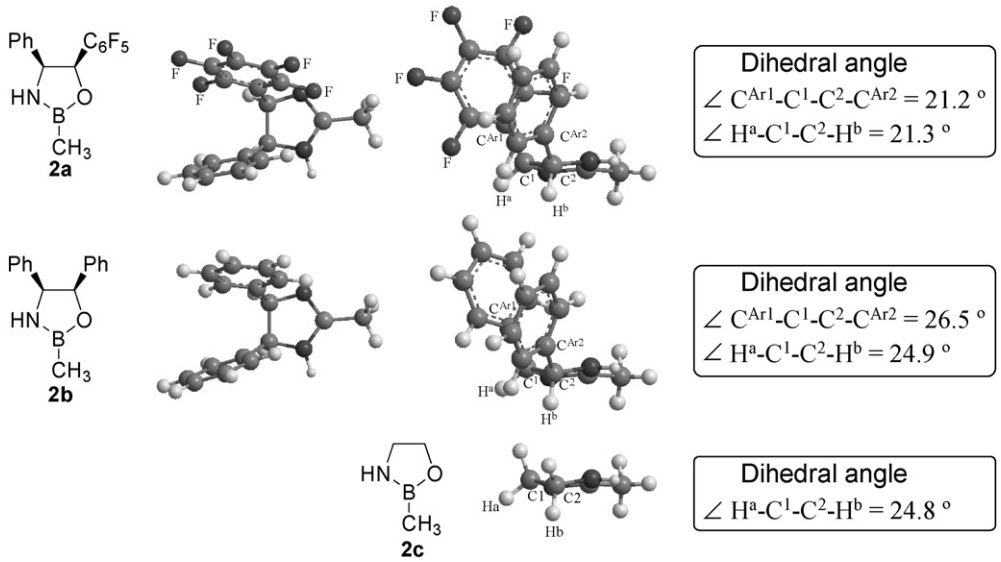


Fig. 2. *Ab initio* calculations of oxazaborolidine **2**.

Table 1
Coupling constants between H^a and H^b

Solvent	**2a**		**2b**	
	Temperature (°C)	*J* (Hz)	Temperature (°C)	*J* (Hz)
d_8-THF	50	9.0	50	8.6
	0	9.6	0	8.6
d_8-Toluene	50	9.0	50	8.6
	0	9.0	0	8.6

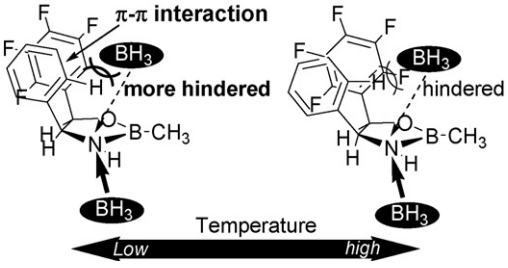
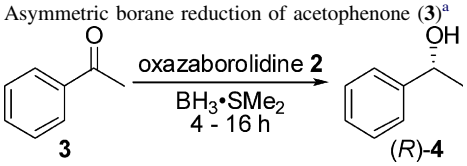


Fig. 3. Effect of temperature-dependent conformational change for coordination of BH_3.

decreased from 94 to 89% ee with decreasing the reaction temperature from 50 to −20 °C (Table 2, entries 12–15) and further lowering the temperature to −40 °C drastically decreased to 54% ee (entry 16). The temperature effect is known as a common phenomenon in the oxazabororidine-catalyzed borane reductions [14], and explained by the competitive non-catalyzed free BH_3 reduction in a slowered catalytic cycle with decreasing the reaction temperature. On the contrary, in the reaction with **2a**, the enantioselectivities of (*R*)-alcohol **4** gradually increased from 86 to 92% ee with decreasing the reaction temperature until 0 °C (entries 1–3), although the enantioselectiveies decreased below −20 °C similarly (entries 4 and 5). The increase of the enantioselectivity in the range of 50–0 °C is consistent with the conformational change by the π–π interaction [15].

The phenomenon becomes more remarkable by the reaction using stoichiometric amount of **2a** and **2b** to avoid the competitive achiral BH_3 reduction (Table 2 and Fig. 4b). The enantioselectivities in the reaction with **2a** increased from 92 to 99% ee with decreasing the reaction temperature (entries 6–8) in contrast to the constant selectivities [14g] (97% ee) in the reactions with **2b** (entries 17–19). Furthermore, no change in the enantioselectivities was observed in the reaction with

Table 2
Asymmetric borane reduction of acetophenone (**3**)[a]



Entry	**2**	Equiv.	Solvent	Temperature (°C)	ee (%)	Conv. (%)
1	**2a**	0.1	THF	50	86	100[b]
2	**2a**	0.1	THF	30	88	100[b]
3	**2a**	0.1	THF	0	92	97[b]
4	**2a**	0.1	THF	−20	90	97[c]
5	**2a**	0.1	THF	−40	60	24[c]
6	**2a**	1	THF	50	92	100[b]
7	**2a**	1	THF	30	94	100[b]
8	**2a**	1	THF	0	99	100[b]
9	**2a**	1	Toluene	50	87	100[b]
10	**2a**	1	Toluene	30	87	100[b]
11	**2a**	1	Toluene	0	87	100[b]
12	**2b**	0.1	THF	50	94	100[b]
13	**2b**	0.1	THF	30	94	100[b]
14	**2b**	0.1	THF	0	91	93[b]
15	**2b**	0.1	THF	−20	89	94[c]
16	**2b**	0.1	THF	−40	54	38[c]
17	**2b**	1	THF	50	97	100[b]
18	**2b**	1	THF	30	97	100[b]
19	**2b**	1	THF	0	97	100[b]

[a] Solution of **3** in solvent was added dropwise by syringe pump (20 μL/min) to the BH_3 solution.
[b] Stirred for 4 h.
[c] Stirred for 16 h.

toluene in the range of 50–0 °C, even if **2a** was used (entries 9–11). The tendency of change of enantioselectivities in all results is completely compatible with the conformational prediction by calculation and ^{1}H NMR observation (Table 1), suggesting that ability in asymmetric induction can be controlled by intramolecular π–π interaction between the C_6F_5 and Ph groups.

The intermolecular π–π interaction between the C_6F_5 and aromatic groups has been known to be not enough strong in organic solvent. However, we here demonstrated the possibility that the intramolecular π–π stacking interaction between the neighborhood aryl groups could control the conformation of the catalyst even in organic solvent, influencing the enantioselectivity of the asymmetric catalysis while it is weak. These results opened the utility of the C_6F_5 group for a new entry of the stereo-controlling group.

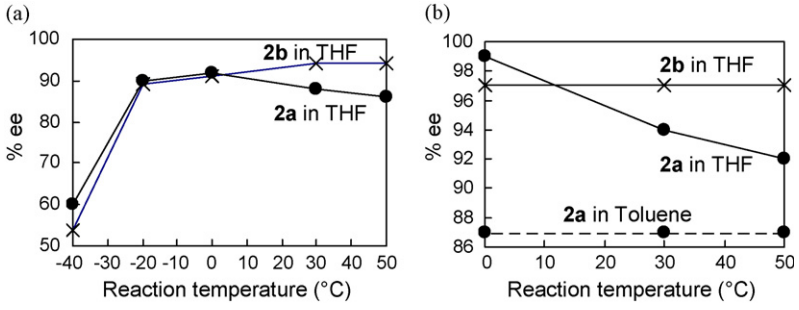


Fig. 4. Temperature effect of % ee on the asymmetric borane reduction using **2**. (a) Catalytic amount of **2** and (b) stoichiometric amount of **2**.

3. Experimental

3.1. General experimental procedures

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dehydrated toluene and THF were purchased from Kanto Chemical Co. and then were stored in Schlenk tubes under an argon atmosphere. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Preparative column chromatography was carried out by using silica gel (Fuji Silysia BW-127 ZH, 100–270 mesh). ^{1}H NMR and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, and 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 $BF_3{\cdot}Et_2O$.

3.2. (4S,5R)-2-Methyl-5-(pentafluorophenyl)-4-phenyl-1,3,2-oxazaborolidine (**2a**)

A 20 mL of dry Schlenk tube was charged with (1*R*,2*S*)-2-amino-1-(pentafluorophenyl)-2-phenylethanol (**1a**) (15 mg, 0.050 mmol) and toluene (1.0 mL) under an argon atmosphere. The suspended solution was heated at 50 °C to afford a colorless solution, followed by cooling down to room temperature. To the solution was added trimethylboroxine (4.6 μL, 0.033 mmol). After being stirred for 12 h at room temperature, the solvent was distilled until 0.5 mL remained. To the reaction mixture was added toluene (0.5 mL) and then the solution was re-distilled until 0.5 mL remained. After repeating the cycle of toluene addition–distillation three times, the remaining toluene was removed in vacuo to give (4*S*,5*R*)-2-methyl-5-(pentafluorophenyl)-4-phenyl-1,3,2-oxazaborolidine (**2a**) as a white solid. The oxazaborolidine **2a** was used for asymmetric borane reduction of acetophenone **3** without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.45 (s, 3H), 3.74 (br, 1H), 5.21 (d, J = 9.3 Hz, 1H), 6.08 (d, J = 9.3 Hz, 1H), 7.09–7.20 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$ (except for C_6F_5)) δ 62.9, 76.9, 125.8, 127.9, 128.2, 140.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −164.5 to −164.3 (m, 2F), −156.5 (t, J = 21 Hz, 1F), −142.1 (br, 2F); ^{11}B NMR (192 MHz, $CDCl_3$) δ 35.7.

3.3. Typical procedure of asymmetric reduction of acetophenone (**3**)

To a solution of oxazaborolidine **2a** which was synthesized as above mentioned in THF (1.0 mL) was added borane dimethylsulfide complex (28 μL, 0.30 mmol). After being stirred at 0 °C for 10 min, the solution of acetophenone (**3**) (58 μL, 0.50 mmol) in THF (1 mL) was added via syringe pump over 1.5 h, and then the reaction mixture was stirred at 0 °C for 4 h. To the mixture was added methanol (1 mL) and then the solvent was removed under reduced pressure. The residue was analyzed by chiral HPLC after purification through a short column chromatography (SiO_2, hexane/EtOAc (3:1)). The conditions of HPLC are as follows: column; Daicel CHIRALCEL OB-H, ϕ 4.6 mm × 25 cm, hexane/*i*-PrOH (9:1), 0.4 mL min^{-1}, UV 254 nm, retention time (t_R); (*S*)-**4**: 17.5 min (4%), (*R*)-**4**: 22.9 min (96%). $[\alpha]_D^{24} = +52.8$ (*ca.* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (t, J = 6.3 Hz, 3H), 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 cm^{-1}.

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References

[1] (a) C.A. Hunter, K.R. Lawson, J. Perkins, C.J. Urch, J. Chem. Soc., Perkin Trans. 2 (2001) 651–669;
(b) E.A. Meyer, R.K. Castellano, F. Diederich, Angew. Chem. Int. Ed. 42 (2003) 1210–1250.
[2] K. Uneyama, Organofluorine Chemistry, Blackwell, Oxford, 2006, pp. 37–45.
[3] S. Tsuzuki, K. Honda, T. Uchimaru, M. Mikami, K. Tanabe, J. Am. Chem. Soc. 124 (2002) 104–112.
[4] S. Pérez-Casas, J. Hernández-Trujillo, M. Costas, J. Phys. Chem. B 107 (2003) 4167–4174.
[5] More recent examples:
(a) S. Bacchi, M. Benaglia, F. Cozzi, F. Demartin, G. Filippini, A. Gavezzotti, Chem. Eur. J. 12 (2006) 3538–3546;
(b) I.Y. Bagryanskayaa, Y.V. Gatilova, E. Lorkb, R. Mewsb, A.V. Zibarev, J. Fluorine Chem. 127 (2006) 746–754;
(c) T. Korenaga, Y. Kawauchi, T. Kosaki, T. Ema, T. Sakai, Bull. Chem. Soc. Jpn. 78 (2005) 2175–2179;
(d) C.E. Smith, P.S. Smith, R.Ll. Thomas, E.G. Robins, J.C. Collings, C. Dai, A.J. Scott, S. Borwick, A.S. Batsanov, S.W. Watt, S.J. Clark, C. Viney, J.A.K. Howard, W. Clegg, T.B. Marder, J. Mater. Chem. 14 (2004) 413–420;
(e) S.W. Watt, C. Dai, A.J. Scott, J.M. Burke, R.L. Thomas, J.C. Collings, C. Viney, W. Clegg, T.B. Marder, Angew. Chem. Int. Ed. 43 (2004) 3061–3063;
(f) T. Shima, E.B. Bauer, F. Hampel, J.A. Gladysz, Dalton Trans. (2004) 1012–1028;
(g) J. Ruiz, C. Vicente, V. Rodríguez, N. Cutillas, G. López, C.R. Arellano, J. Organomet. Chem. 689 (2004) 1872–1875;
(h) C. Knapp, E. Lork, R. Mews, A.V. Zibarev, Eur. J. Inorg. Chem. 12 (2004) 2446–2451.
[6] (a) G.W. Coates, A.R. Dunn, L.M. Henling, J.W. Ziller, E.B. Lobkovsky, R.H. Grubbs, J. Am. Chem. Soc. 120 (1998) 3641–3649;
(b) M.J. Marsella, Z.-Q. Wang, R.J. Reid, K. Yoon, Org. Lett. 3 (2001) 885–887;
(c) M. Morimoto, S. Kobatake, M. Irie, Chem. Rec. 4 (2004) 23–38;
(d) Y. El-Azizi, A. Schmitzer, S.K. Collins, Angew. Chem. Int. Ed. 45 (2006) 968–973.
[7] S.L. Cockroft, C.A. Hunter, K.R. Lawson, J. Perkins, C.J. Urch, J. Am. Chem. Soc. 127 (2005) 8594–8595.
[8] In Ref. [6b], "ArH–ArF interactions in the solution state are typically observed in organic solvents only when ArH and ArF species are present

in high concentrations or held in close proximity by an appropriate scaffold." is described.

[9] T. Korenaga, H. Tanaka, T. Ema, T. Sakai, J. Fluorine Chem. 122 (2003) 201–205.

[10] Recent reviews:
(a) E.J. Corey, C.J. Helal, Angew. Chem. Int. Ed. 37 (1998) 1986–2012;
(b) V.A. Glushkov, A.G. Tolstikov, Russ. Chem. Rev. 73 (2004) 581–608.

[11] G.J. Quallich, T.M. Woodall, Tetrahedron Lett. 34 (1993) 4145–4148.

[12] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision B.04, Gaussian, Inc., Pittsburgh, PA, 2003.

[13] Synthesis of novel oxazaborolidine **2a** from **1a** and asymmetric borane reduction of **3** using **2a** were performed in a similar way of the case of **2b** in ref. [11].

[14] (a) J.M. Brunel, M. Maffei, G. Buono, Tetrahedron: Asymmetry 4 (1993) 2255–2260;
(b) G.B. Stone, Tetrahedron: Asymmetry 5 (1994) 465–472;
(c) Y.Z. Jiang, Y. Qin, A.Q. Mi, Chin. Chem. Lett. 6 (1995) 9–12;
(d) J. Zhao, X. Bao, X. Liu, B. Wan, X. Han, C. Yang, J. Hang, Y. Feng, B. Jiang, Tetrahedron: Asymmetry 11 (2000) 3351–3359;
(e) C.E. Garrett, K. Prasad, O. Repič, T.J. Blacklock, Tetrahedron: Asymmetry 13 (2002) 1347–1349;
(f) R.E. Huertas, J.A. Corella, J.A. Soderquist, Tetrahedron Lett. 44 (2003) 4435–4437;
(g) J. Xu, T. Wei, Q. Zhang, J. Org. Chem. 68 (2003) 10146–10151;
(h) J. Xu, T. Wei, S.-S. Lin, Q. Zhang, Helv. Chim. Acta 88 (2005) 180–186.

[15] The enantioselectivities in the reduction using **2a** is lower than that using **2b** at the temperature over 0 °C. Xu et al. showed that the stronger Lewis acidity of the boron atom of the oxazaboloridine decreased enantioselectivity in the oxazaborolidine-catalyzed BH_3 reduction because of slowing down of the catalytic cycle (J. Xu, T. Wei, Q. Zhang, J. Org. Chem. 69 (2004) 6860–6866.). In our calculations at the MP2-6/31G**, the Mulliken charge of **2a** (+0.8178) is larger than that of **2b** (+0.7959), which shows that the Lewis acidity of **2a** is stronger than that of **2b** because of strong electron-withdrawing effect of C_6F_5 group. From these considerations, the decrease of enantioselectivity with **2a** under the conditions with weaker π–π interaction at high temperature is reasonably understandable by actualized effect of the Lewis acidity as compared with the case using **2b**. The π–π interaction is expectable to increase the enantioselectivity although the higher Lewis acidity may reduce it.