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Stereoselective Synthesis of Tetrasubstituted Alkenylboronates via 1,1-Organodiboronates

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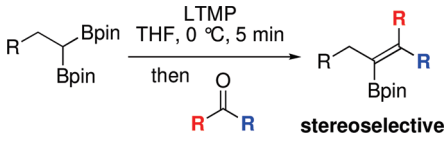
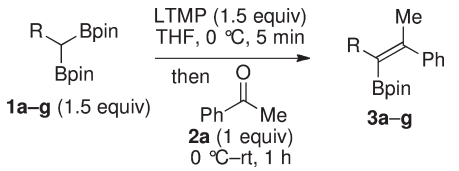
Received February 23, 2010



The stereoselective synthesis of tetrasubstituted alkenylboronates was established via the lithiation/nucleophilic addition reaction of 1,1-organodiboronates to carbonyl compounds. The present approach enables the facile and practical synthesis of tetrasubstituted olefins, which are useful synthetic intermediates for further functionalizations.

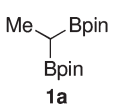
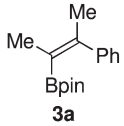
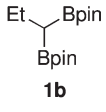
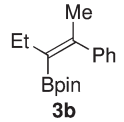
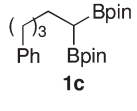
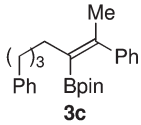
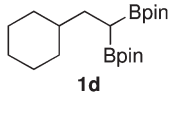
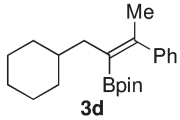
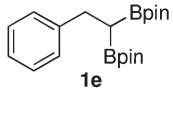
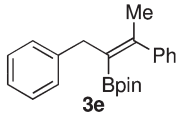
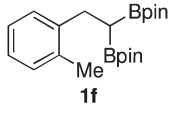
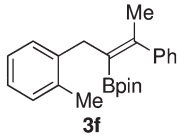
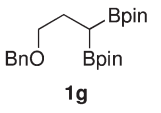
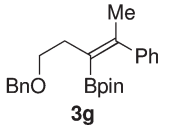
The development of a practical and stereoselective synthesis of multisubstituted olefins is a promising study in material and pharmaceutical chemistry. There are numerous reports on the synthesis of multisubstituted olefins that can readily undergo further functionalizations.[1] However, it is difficult to achieve the stereoselective synthesis of tetrasubstituted alkenylboronates via the well-known reactions even though further C−C bond formation could yield synthetically important tetrasubstituted olefins.[2,3] In this paper, we present a practical and facile synthesis of tetrasubstituted alkenylboronates via the nucleophilic addition of 1,1-organodiboronates to carbonyl compounds (Scheme 1, Bpin = pinacolboryl).

SCHEME 1. Addition of 1a−g to Acetophenone 2a



We previously reported the easy access to air-stable 1,1-organodiboronates via Rh-catalyzed sequential hydroboration of 1-alkynes.[4] The deprotonation reaction of the α-C−H bond adjacent to the boronate moieties of **1a** was examined using lithium 2,2,6,6-tetramethylpiperazide (LTMP).

TABLE 1. Variety of 1,1-Organodiboronates

entry	1,1-diboronate	product	% yield (*E*/*Z*)[a]
1	 **1a**	 **3a**	94 (>99/1)
2	 **1b**	 **3b**	94 (>99/1)
3	 **1c**	 **3c**	83 (>99/1)
4	 **1d**	 **3d**	74 (>99/1)
5	 **1e**	 **3e**	98 (>99/1)
6	 **1f**	 **3f**	75 (>99/1)
7	 **1g**	 **3g**	34 (>99/1)

[a] *E*/*Z* ratio was determined by NMR. The minor product was not observed. The geometry was confirmed by NOESY analyses and the conversion to literature known compounds.

The subsequent nucleophilic addition to acetophenone (**2a**) afforded (*E*)-tetrasubstituted alkenylboronate **3a** in high yield (entry 1, Table 1).[5] A precedent reported the lithiation of bisborylmethane and the subsequent nucleophilic addition, which led to ketones or aldehydes via successive oxidation. However, there have been no reports for the isolation of

(1) (a) Denmark, S. E.; Amburgey, J. *J. Am. Chem. Soc.* **1993**, *115*, 10386–10387. (b) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331–6332. (c) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959–7970. (d) Shi, Y.; Peterson, S. M.; Haberaecker, W. W., III; Blum, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 2168–2169. (e) Konno, T.; Kinugawa, R.; Morigaki, A.; Ishihara, T. *J. Org. Chem.* **2009**, *74*, 8456–8459.

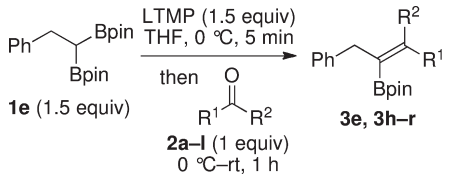
(2) For recent examples, see: (a) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670–14671. (b) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506–12507. (c) Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc.* **2007**, *129*, 12634–12635. (d) Takimoto, M.; Hou, Z. *J. Am. Chem. Soc.* **2009**, *131*, 18266–18268.

(3) (a) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709. (b) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, *2*, 1041–1044. For other olefination reactions, see: (c) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1045. (d) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784. (e) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96–105.

DOI: 10.1021/jo1003407 Published on Web 04/15/2010

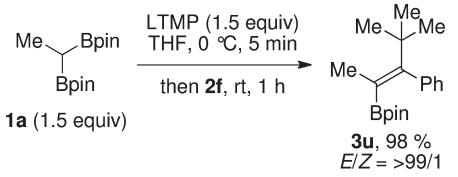
the corresponding alkenyl boronates that are derived from ketones.[6] The reaction of 1,1-organodiboronates **1b**−**1f** and ketone **2a** gave the corresponding (*E*)-products **3b**−**3f** in high to excellent yields (entries 2−6). The benzyloxy group diminished the yield of product **3g** albeit with almost perfect stereoselectivity (entry 7).

SCHEME 2. Addition of 1e to Ketones 2a−l



Various types of carbonyl compounds were used for the synthesis of multisubstituted alkenylboronates (Scheme 2, Table 2). The reactions of symmetrical ketones such as benzophenone (**2b**) and cyclohexanone (**2c**) afforded the corresponding products **3h** and **3i**, respectively, in almost quantitative yields (entries 1 and 2). The reaction of aromatic ketones **2d**−**j** gave the products **3j**−**p** in good to excellent yields with almost perfect stereoselectivities (entries 3−9). The electronic effect of aryl ketones bearing an electron-withdrawing or electron-donating substituent did not change the stereoselectivity (entries 8 and 9). Aliphatic ketones such as 3-methylbutan-2-one (**2k**) and 1-cyclohexylethanone (**2l**) afforded the corresponding products **3q** and **3r**, respectively, in high to excellent yields with almost perfect stereoselectivities (entries 10 and 11). The reaction of **1a** with **2f** afforded **3u** in excellent yield and stereoselectivity (Scheme 3). Therefore, the aryl group of ketones could regulate the stereoselectivity in every case.

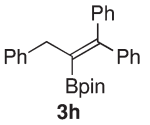
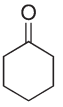
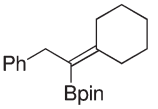
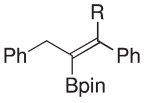
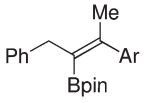
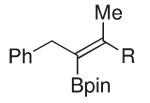
SCHEME 3. Addition of 1a to 2f



To verify the configuration of the isolated alkene products, we converted some of them into known compounds.[7,8] The Suzuki−Miyaura cross-coupling reaction of **3a** using a catalytic amount of $[Pd(Pt\text{-}Bu_3)_2]$ with iodobenzene gave the literature known compound **4a**, the geometry of whose olefinic moiety is (*Z*); therefore, the geometry of alkenylboronate **3a** should be (*E*) (Scheme 4). The use of **3e** gave the literature known compound **4e**, the geometry of whose olefinic moiety is (*Z*); therefore, the geometry of alkenylboronate **3e** should be (*E*). The cross-coupling reaction of **3k** gave the literature known compound **4k** (Scheme 5). Moreover, the X-ray diffraction analysis of **3l** clearly shows that (*E*)-product was obtained (see, Supporting Information). Therefore, the stereochemistry of these products could be confirmed.

The coordinating group in ketones on the boronate moiety changed the stereoselectivities of products (Scheme 6). The reaction of 2-methoxyacetophenone **2m** gave the corresponding product **3s**, whose major stereoisomer had an opposite geometry compared with those of products **3e** and **3j**−**p** as shown in Table 2. The strongly coordinative dimethylamino group of **2n** obviously controlled the stereoselectivity to give the corresponding (*E*)-product **3t** in moderate yield (entry 2). These results indicate that the

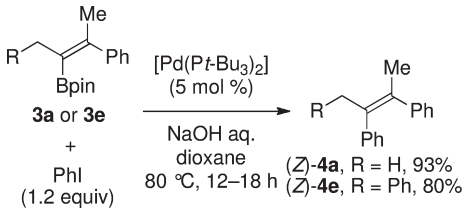
TABLE 2. Variety of Ketones

entry	ketone	product	yield (*E*/*Z*)[a]
1	 **2b**	 **3h**	98
2	 **2c**	 **3i**	98
			
3	**2d**	**3j**, R = Et	95 (>99/1)
4	**2e**	**3k**, R = Bn	98 (>99/1)
5	**2f**	**3l**, R = *tert*-Bu	93 (>99/1)
6	**2g**	**3m**, R = *i*-Pr	96 (>99/1)
7	**2h**	**3n**, R = *c*-Hex	98 (>99/1)
			
8	**2i**	**3o**, Ar = 4-MeOC$_6$H$_4$-	72 (>99/1)
9	**2j**	**3p**, Ar =4-CF$_3$-C$_6$H$_4$-	70 (>99/1)
			
10	**2k**	**3q**, R = *i*-Pr	91 (>99/1)
11	**2l**	**3r**, R = *c*-Hex	98 (>99/1)

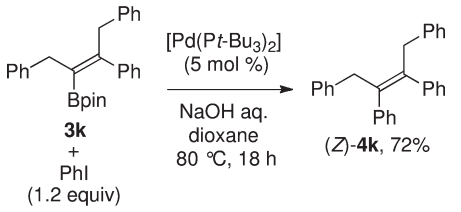
[a] *E*/*Z* ratio was determined by NMR analyses. The minor product was not observed. The geometry was confirmed by NOESY analyses, the conversion to literature known compounds, and X-ray diffraction analyses.

(4) Endo, K.; Hirokami, M.; Shibata, T. *Synlett* **2009**, 1131–1135.
(5) For the optimization of reaction conditions, see Supporting Information.
(6) The nucleophilic addition of lithium triborylmethide was reported: (a) Castle, R. B.; Matteson, D. S. *J. Organomet. Chem.* **1969**, *20*, 19–28. (b) Matteson, D. S.; Tripathy, P. B. *J. Organomet. Chem.* **1970**, *21*, 6–8. (c) Matteson, D. S.; Tripathy, P. B. *J. Organomet. Chem.* **1974**, *69*, 53–62. The nucleophilic addition of lithium bis(ethylenedioxyboryl)methide or bis(trimethylene-dioxyboryl)methide and subsequent oxidation was reported: (d) Matteson, D. S.; Moody, R. J.; Jesthi, P. K. *J. Am. Chem. Soc.* **1975**, *97*, 5608–5609. (e) Matteson, D. S.; Moody, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 3196–3197. (f) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20–28.
(7) For **4a**: (a) Anderson, P. G. *Tetrahedron Lett.* **1994**, *35*, 2609–2610. For **4e**: (b) Joo, W.-C.; Hong, J.-H.; Choi, S.-B.; Son, H.-E. *J. Organomet. Chem.* **1990**, *391*, 27–36. For **4k**: (c) Tolbert, L. M.; Ali, M. Z. *J. Org. Chem.* **1985**, *50*, 3288–3295.
(8) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440. $Pd/P(t\text{-}Bu)_3$ is an excellent catalyst for Suzuki−Miyaura cross-coupling reactions: (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

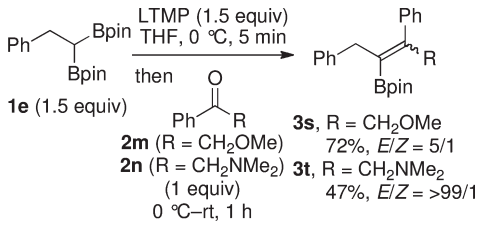
SCHEME 4. Suzuki−Miyaura Cross-Coupling of 3a and 3e



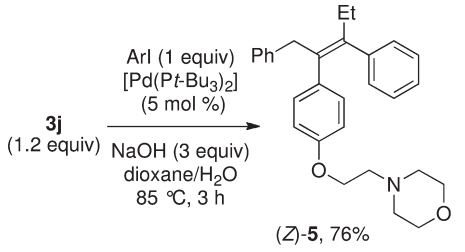
SCHEME 5. Suzuki−Miyaura Cross-Coupling of 3k



SCHEME 6. Addition of 1e to Ketones 2m and 2n



SCHEME 7. Synthesis of Tamoxifen Derivative (*Z*)-5



stereoselectivity of *syn*-elimination could be controlled by means of the coordination on boron.

Finally, we examined the two-step synthesis of tamoxifen derivative **5** from **1e** (Scheme 7). Although a biological activity of **5** higher than that of tamoxifen has been reported, the stereoselective synthesis of **5** had not been established previously.[9] A precedent for the stereoselective synthesis of tamoxifen derivatives was not suitable for the synthesis of tetrasubstituted olefins bearing asymmetrical alkyl groups. The cross-coupling reaction of **3j** and ArI afforded the desired product **5** in 76% yield as a sole stereoisomer. The present synthetic route could be complementary to the previous syntheses of various types of tamoxifen congeners bearing triaryl substituents.[2]

A plausible mechanism could be expressed as shown in Figure 1. Typical models for lithium alkoxide intermediates, **OLi-1** and **OLi-2**, are shown after nucleophilic addition of

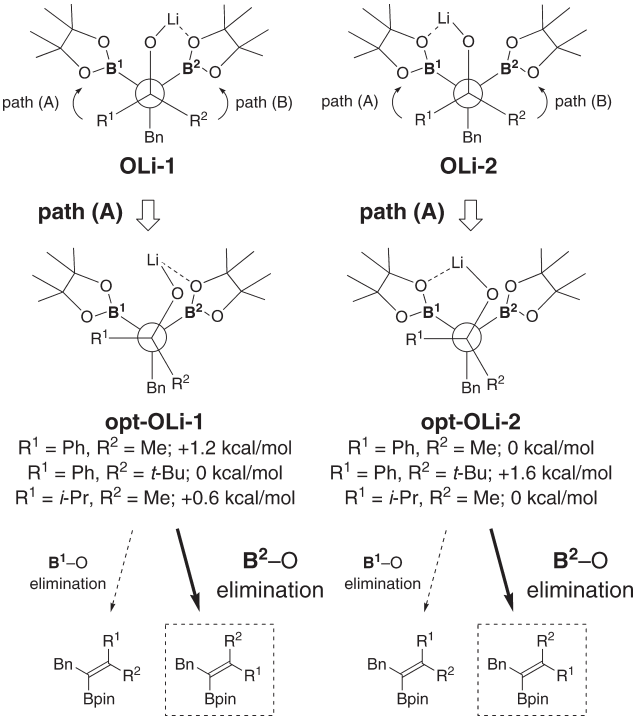


FIGURE 1. Plausible mechanism for stereoselectivity.

lithiated diboronates to ketones.[10,11] The intramolecular coordination of the oxygen atom in the pinacolboryl group on the lithium atom is feasible.[12] *syn*-Elimination through LiO−C−C−Bpin affords the corresponding product **3**. To identify their stereoselectivities, DFT computations of **OLi-1** and **OLi-2** at the B3LYP/6-31G* level of theory were performed for the geometry optimizations.[13] Surprisingly, the optimized geometries, **opt-OLi-1** and **opt-OLi-2**, show that path A could predominate via **OLi-1** or **OLi-2**. The difference in the relative energies, which include the zero-point vibrational energies (ZPEs), is not very large between **opt-OLi-1** and **opt-OLi-2**. Since the dihedral angle of LiO−C−C−B^2pin is less than 20° in **opt-OLi-1** and **opt-OLi-2**,

(9) Meegan, M. J.; Hughes, R. B.; Lloyd, D. G.; Williams, D. C.; Zisterer, D. M. *J. Med. Chem.* **2001**, *44*, 1072–1084.

(10) The *syn*-elimination after homologation of organoboronic acid pinacol ester using lithiated epoxides gave the tetrasubstituted olefin in excellent stereoselectivity: (a) Shimizu, M.; Fujimoto, T.; Minezaki, H.; Hata, T.; Hiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 6947–6948. (b) Shimizu, M.; Fujimoto, T.; Liu, X.; Minezaki, H.; Hata, T.; Hiyama, T. *Tetrahedron* **2003**, *59*, 9811–9823. The steric influence of mono-boron compounds and aldehydes or ketones realized the stereoselective synthesis of di- or tri-substituted olefins. The rationale of stereoselectivity was described in detail: (c) Pelter, A.; Buss, D.; Colclough, E.; Singaram, B. *Tetrahedron* **1993**, *49*, 7077–7103. (d) Pelter, A. *Pure Appl. Chem.* **1994**, *66*, 223–233. (e) Kawashima, T.; Yamashita, N.; Okazaki, R. *J. Am. Chem. Soc.* **1995**, *117*, 6142–6143. (f) Sakai, M.; Saito, S.; Kanai, G.; Suzuki, A.; Miyaura, N. *Tetrahedron* **1996**, *52*, 915–924.

(11) The in situ trapping of lithium alkoxide did not proceed at −78 and 0 °C before *syn*-elimination in our case. Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165–168.

(12) The intramolecular coordination of heteroatom to lithium center has been described in the nucleophilic addition of 1,1-disilylmethane to carbonyl compounds: Itami, K.; Nokami, T.; Yoshida, J.-i. *Org. Lett.* **2000**, *2*, 1299–1302.

(13) The DFT computational calculations were performed using the Spartan'08 suite for Mac (Wave function, Inc.). Zero-point vibrational energies (ZPEs) were calculated for all structures, and the geometry was verified as true minima using frequency analysis. The B3LYP/6-31G* and the B3LYP/6-31+G* level gave almost similar results; thus, the results using the B3LYP/6-31G* are shown. No coordination of the oxygen atom in the pinacolboryl group on the lithium atom gave the same optimized geometries at the expense of calculating time.

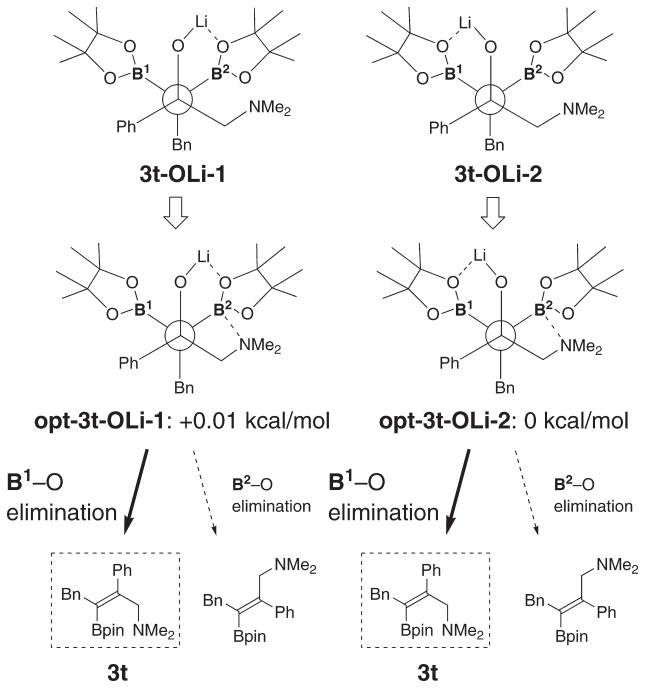


FIGURE 2. Intramolecular coordination on a boron atom.

syn-elimination could take place. The addition to aryl ketones induces the rotation in path A; the steric bulkiness of R^1 and R^2 did not change the stereolselectivity. Therefore, the steric influence of aryl ketones is unclear. The addition to aliphatic ketones **2k** induces the rotation in path A; the steric influence of aliphatic ketones seems essential. Although the exact driving force of stereoselectivity is unclear, the present DFT calculations support the experimental results.

The inversion of stereoselectivity using **2n** obviously indicates the coordination of the nitrogen atom on the boron atom in the pinacolboryl group (B^2pin). The coordination on the boron atom inhibits the *syn*-elimination through LiO−C−C−B^2pin. The DFT computations using the B3LYP/6-31G* level of theory could give the optimized geometries, **opt-3t-OLi-1** and **opt-3t-OLi-2**, including the coordination of the nitrogen atom on the boron atom in the pinacolboryl group (Figure 2). However, these optimized geometries did not show the predominant rotation from **3t-OLi-1** and **3t-OLi-2**. The inhibition of the coordination of the LiO moiety on the B^2pin suggests that *syn*-elimination through LiO−C−C−B^1pin would probably give **3t**.

In conclusion, we demonstrated the easy and practical approach to the stereocontrolled synthesis of the tetrasubstituted alkenylboronates in high to excellent yields. The almost complete stereoselectivity is a characteristic feature of the reactions presented in this paper. The stereoselectivity can be determined by NMR analyses, Pd-catalyzed cross-coupling reactions of alkenylboronates, X-ray diffraction analyses, and computational studies of the optimized geometries of intermediates. These results can serve as expedients for the synthesis of multisubstituted alkenylboronates, which are useful and powerful synthetic intermediates used in organic chemistry.

Experimental Section

To a solution of **1a** (84.6 mg, 0.3 mmol) in THF (0.5 mL) at 0 °C was added LTMP (0.3 mmol, 0.4 M in THF). After 5 min, ketone **2a** (24 mg, 0.2 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h and filtered through a pad of silica gel with ether (50 mL). Concentration and purification by silica gel column chlomatography (EtOAc/hexane = 1:30) gave the product **3a** in 48.5 mg, 94% yield: white solid; mp 63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.15 (m, 5H), 2.04 (d, J = 1.1 Hz, 3H), 1.84 (d, J = 1.1 Hz, 3H), 1.07 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.4, 146.3, 127.7, 127.6, 126.5, 82.9, 24.5, 20.2, 17.1; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 31.1; IR (KBr, cm^{-1}) 2979, 1620, 1373, 1300, 1124, 862, 771, 685; HRMS (FAB, positive) m/z calcd for $C_{16}H_{23}BO_2$ 258.1791, found 258.1805.

Acknowledgment. This work was financially supported by Grant-in-Aid for Young Scientists (B) (No. 21750108) from the Japan Society for the Promotion of Science and Waseda University Grant for Special Research Project. K.E. thanks the Society of Synthetic Organic Chemistry, Japan for a Teijin Pharma Award.

Supporting Information Available: General procedure, physical properties and NMR spectra of new compounds, and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.