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An Enantiomerically Pure Tetracoordinate Boron Compound: Stereochemistry of Substitution Reactions at the Chirogenic Boron Atom

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In contrast to extensive and exhaustive investigations on the substitution reactions at a chirogenic tetracoordinate carbon atom, less attention has been paid to the substitution reactions at an isoelectronic chirogenic boron atom.[1−4] Recently, the research group of Mioskowski has synthesized diastereomerically pure tetracoordinate boron compounds containing a chiral center at the boron atom, and they provided direct evidence of an S$_N$2 at the boron atom.[5] However, to our best knowledge, synthesis and substitution reactions of enantiomerically pure tetracoordinate boron compounds have not yet been reported. Here we report the first synthesis of a such compound and the stereochemical results of substitution reactions occurring at the boron atom.

As a model tetracoordinate boron compound bearing a leaving group, we chose a phosphine−borane derivative, because compounds of this kind are generally air- and moisture-stable and can be easily handled without special caution.[6] After various synthetic trials, we succeeded in the synthesis of an enantiomerically pure B-chirogenic phosphine−borane bearing a bromine atom at the boron atom, starting from tricyclohexylphosphine−monoiodoborane (**1**). The synthetic route is shown in Scheme 1.

Compound **1** was reduced by 2 molar equiv of lithium 4,4′-di-*tert*-butylbiphenylide (LDBB), followed by the reaction with dimethyl carbonate to give methoxycarbonyl derivative **2** in good yield. Subsequent reaction of **2** with bromine in methanol provided compound **3**. Hydrolysis of the methyl ester using aqueous HBr afforded carboxylic derivative **4**.[7] This compound was mixed with (*S*)-1-phenylethanol (97% ee, 2.5 molar equiv) and was heated at 120 °C for 10 min to give a mixture of diastereomers,[8] which were separated by fractional recrystallization to diastereomerically pure **(*S*$_B$,*S*)-5** (mp 135−136 °C dec, [α]$_D$ −29.2° (*c* 0.50, THF)) and **(*R*$_B$,*S*)-5** (mp 133−134 °C dec, [α]$_D$ −39.3° (*c* 0.50, THF)). The absolute configuration of the boron atom of **(*S*$_B$,*S*)-5** was determined to be *S* by single-crystal X-ray analysis. Therefore, another diastereomer **(*R*$_B$,*S*)-5** should possess *R* configuration of the boron atom. Compound **(*S*$_B$,*S*)-5** was converted to enantiomerically pure, tetracoordinate boron compound **(*S*)-3** in almost quantitative yield by dissolving it in MeOH−THF containing a catalytic amount of H$_2$SO$_4$. In a similar manner, another enantiomer **(*R*)-3** was obtained in enantiomerically pure form.

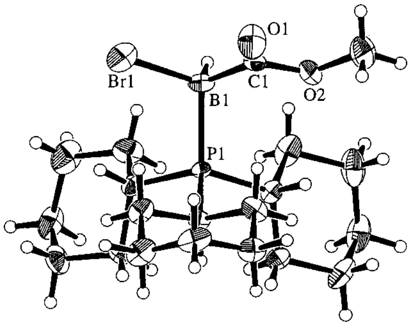
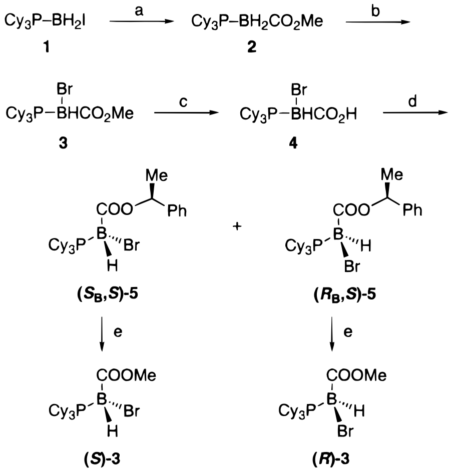


Figure 1. Molecular structure of **(*S*)-3** showing only selected atoms. Selected bond distances (Å) and angles (deg): B(1)−P(1) 1.957(7), B(1)−C(1) 1.637(10), B(1)−Br(1) 1.990(8), C(1)−O(1) 1.188(9); P(1)−B(1)−C(1) 112.7(4), P(1)−B(1)−Br(1) 110.3(4), Br(1)−B(1)−C(1) 108.4(4), B(1)−C(1)−O(1) 130.1(4), B(1)−C(1)−O(2) 109.6(6), O(1)−C(1)−O(2) 120.2(7).

Scheme 1[a]



[a] Conditions: (a) (i) LDBB (2.5 equiv)−TMEDA, THF, −78 °C. (ii) (MeO)$_2$CO, 66%. (b) Br$_2$, MeOH, 0 °C to room temperature, 88%. (c) aq 48% HBr, THF, room temperature, 12 h, 57% after recrystallization from AcOEt. (d) (*S*)-(−)-1-Phenylethanol, 120 °C, 10 min, fractional recrystallization from hexane, **(*S*$_B$,*S*)-5,** 24%; **(*R*$_B$,*S*)-5,** 24%. (e) H$_2$SO$_4$ (cat.), MeOH−THF, room temperature, 4 h, 96−98%.

The structure of **(*S*)-3** was confirmed by X-ray crystallography. The ORTEP drawing shown in Figure 1 apparently indicates a tetrahedral, chirogenic boranate structure.[9] The absolute configuration of the boron atom determined by the Flack parameter method is *S*, the same as the configuration of compound **(*S*$_B$,*S*)-5**.

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(4) Hawthorne et al. studied the substitution reactions at the tetracoordinate boron atom using achiral amine−borane complexes and presented good kinetic evidence for the S$_N$2 and S$_N$1 nucleophilic displacement mechanism at tetrahedral boron. (a) Hawthorne, M. F.; Budde, W. L. *J. Am. Chem. Soc*. **1964**, *86*, 5337. (b) Hawthorne, M. F.; Budde, W. L.; Walmsley, D. *J. Am. Chem. Soc*. **1964**, *86*, 5337−5338.

(5) Vedrenne, P.; Le Guen, V.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Am. Chem. Soc*. **1999**, *121*, 1090−1091.

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(7) Formation of tricyclohexylphosphine−chloro(carboxyl)borane occurred when concentrated HCl was used instead of HBr.

(8) It is noted that this esterification occurred smoothly even in the absence of catalysts such as sulfuric acid or condensation reagents.

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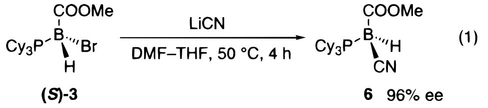
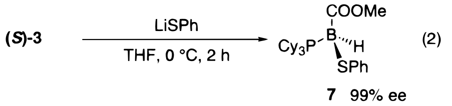
To reveal the stereochemical aspect of the nucleophilic substitution reactions at the chirogenic boron atom, compound **(*S*)-3** was allowed to react with lithium cyanide or lithium phenylthiolate. The reaction with LiCN proceeded smoothly in DMF−THF (2:3) at 50 °C for 4 h to give a substitution product **6** in 87% yield (eq 1). The enantiomeric excess of the product was determined to be 96% ee by HPLC analysis using a chiral column. The absolute configuration of this compound was determined to be *R* by the Flack parameter method. These results clearly demonstrate that the nucleophilic substitution reaction took place with inversion of configuration at the boron atom in 96% stereospecificity. The reaction of **(*S*)-3** with lithium phenylthiolate also afforded in 83% yield the corresponding substitution product **7**, whose ee was determined to be 99% ee (eq 2). Unfortunately, the product was unstable and did not give rise to good crystals for X-ray crystallography. Although the absolute configuration was not determined, we envisage that this substitution reaction also takes place via an S_N2 manner with inversion of configuration in exceedingly high stereospecificity.

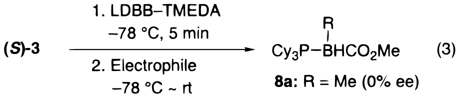


(*S*)-3 **6** 96% ee



(*S*)-3 **7** 99% ee

We considered that compound **(*S*)-3** would be a most suitable substrate for the stereochemical study on electrophilic substitution reactions at a boron atom,[10] and it was reacted with LDBB, followed by reaction with iodomethane, 1-bromo-2-methylpropane, or diphenyl disulfide at −78 °C through to room temperature. From the reaction mixtures, *B*-substitution products, **8a**, **8b**, and **8c** were isolated in 62, 55, and 54% yields, respectively (eq 3). HPLC analyses of these products using chiral columns demonstrated that they all were racemates.



$Cy_3P{-}B(R)HCO_2Me$

8a: R = Me (0% ee)
8b: R = *i*-Bu (0% ee)
8c: R = SPh (0% ee)

These reactions are considered to involve a boranyl radical and a boron dianion species which is in isoelectronic relationship with tricoordinate carbanions. The formation of completely racemized products is due to the rapid racemization of the intermediate boranyl radical or the boron dianionic species.

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Supporting Information Available: Experimental details and full characterization data for all new compounds; X-ray structural information on compounds **(S_B,*S*)-5**, **(*S*)-3**, and **6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Crystal data for **(*S*)-3**: $C_{20}H_{37}BBrO_2P$; space group $P2_1$ (No. 4); $a = 7.666(2)$ Å, $b = 17.200(2)$ Å, $c = 8.955(2)$ Å, $\beta = 109.84(2)°$, $V = 1110.8(4)$ Å, $Z = 2$, $D_{calcd} = 1.289$ g/cm^3, μ(Cu Kα) = 32.71 cm^{-1}, λ (Cu Kα) = 1.54178 Å; temperature of data collection 296 K.; 4517 reflections measured, 4217 observed ($I > 1.50\sigma(I)$); 227 variables; $R = 0.096$, $R_w = 0.129$, GOF = 1.87, flack parameter = 0.01(4).

[10] Imamoto, T.; Hikosaka, T. *J. Org. Chem.* **1994**, *59*, 6753−6759.