A Practical Method for the Synthesis of Enantiomerically Pure 4-Borono-L-phenylalanine

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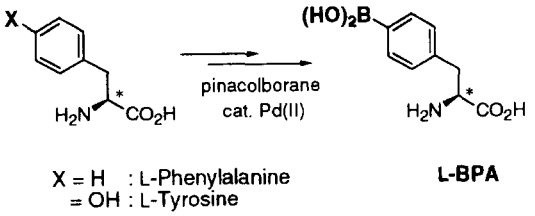
Enantiomerically pure L-BPA (4-borono-L-phenylalanine) was synthesized from L-tyrosine or 4-iodo-L-phenylalanine derivatives using the palladium-catalyzed cross-coupling reaction of pinacolborane (2,3-dimethyl-2,3-butanediolatoboron). Cbz–Tyr(Nf)–OBzl (**2b**) underwent the cross-coupling reaction with pinacolborane (**1**) in the presence of [$PdCl_2(PPh_3)_2$] catalyst to give *N*-benzyloxycarbonyl-4-(2,3-dimethyl-2,3-butanediolatoboryl)-L-phenylalanine benzyl ester (**3a**) in 58% yield. The reaction of the 4-iodo-L-phenylalanine derivatives, such as *N*-benzyloxycarbonyl-4-iodo-L-phenylalanine benzyl ester (**2c**), *N*,*N*-dibenzyl-4-iodo-L-phenylalanine benzyl ester (**2d**), (4*S*)-3-benzyloxycarbonyl-4-(4-iodobenzyl)-5-oxazolidinone (**2e**), and (4*S*)-3-*t*-butyloxycarbonyl-4-(4-iodobenzyl)-5-oxazolidinone (**2f**), with **1** proceeded very smoothly in the presence of [$PdCl_2$(dppf)] catalyst, giving *N*-benzyloxycarbonyl-4-(2,3-dimethyl-2,3-butanediolatoboryl)-L-phenylalanine benzyl ester (**3a**), *N*,*N*-dibenzyl-4-(2,3-dimethyl-2,3-butanediolatoboryl)-L-phenylalanine benzyl ester (**3b**), (4*S*)-3-benzyloxycarbonyl-4-[4-(2,3-dimethyl-2,3-butanediolatoboryl)benzyl]-5-oxazolidinone (**3c**), and (4*S*)-3-butyloxycarbonyl-4-[4-(2,3-dimethyl-2,3-butanediolatoboryl)benzyl]-5-oxazolidinone (**3d**), respectively, in high yields. Deprotection of **3a**—**d** gave enantiomerically pure L-BPA in high total yields.

Recently, many researchers have felt the need to develop a concise and enantioselective synthetic methodology of 4-borono-L-phenylalanine (L-BPA),[1] which is a clinically usable boron compound for the treatment of malignant melanoma and brain tumor on neutron capture therapy (NCT).[1—4] So far, four different methods for the synthesis of enantiomerically enriched L-BPA have been reported; (1) Enzymatic resolution via α-chymotrypsin hydrolysis[5] of the ethyl ester of racemic BPA synthesized by the traditional method;[1,6] (2) Asymmetric hydrogenation of *N*-benzoylamino-4-boronocinnamic acid, which gives L-BPA with enantiomeric excess of up to 88% (96%ee after recrystallization);[7] (3) Palladium-catalyzed coupling reaction of iodophenylboronate with a chiral organozinc derived from L-serine;[8] (4) Palladium-catalyzed carbon–boron bond formation reaction of alkoxydiboron with aryl triflates derived from L-tyrosine.[9—11] Although the last approach is more concise than the others, a drawback is that one of the two boron atoms of *alkoxydiboron* is wasted. This becomes an extra-serious problem if expensive ^{10}B-enriched alkoxydiboron is used. Herein we report a concise and practical method for the synthesis of enantiomerically pure 4-borono-L-phenylalanine from L-tyrosine or L-phenylalanine using the palladium-catalyzed coupling reaction with *pinacolborane* (Eq. 1).[11]



(1)

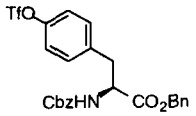
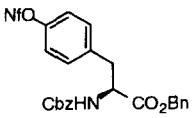
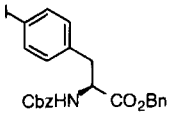
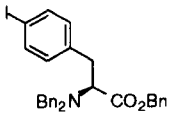
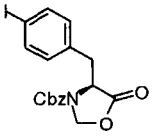
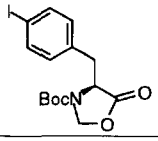
X = H : L-Phenylalanine
= OH : L-Tyrosine

L-BPA

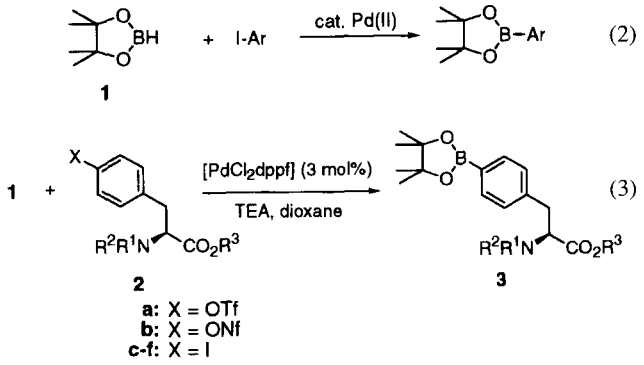
Results and Discussion

Quite recently, Masuda and co-workers reported the synthesis of arylboronic esters via the palladium-catalyzed cross-coupling reaction of pinacolborane with aryl iodides (Eq. 2).[12,13] We first applied this coupling reaction to aryl triflate **2a**.[14] The results are summarized in Table 1 and Eq. 3. The reaction of the triflate **2a** with pinacolborane **1**[15] in 1, 4-dioxane in a catalytic amount of [$PdCl_2$(dppf)] (dppf: 1, 1′-bis(diphenylphosphino)ferrocene) at 80 °C[16] gave **3a** in very poor yield (Entry 1). This result is in marked contrast to the previous observation[9] that the cross-coupling reaction of **2a** with bis(2,3-dimethyl-2,3-butanediolato)dinoron gives the corresponding arylboronic ester **3a** in high yield. It is known that the C–O bond of nonaflates (nonafluorobutanesulfonates)[17] is more reactive than that of triflates for the oxidative addition of palladium(0). In fact, the nonaflate **2b** underwent the cross-coupling reaction with **1** in the presence of [$PdCl_2(PPh_3)_2$] catalyst to give the corresponding arylboronic ester **3a** in 58% yield (Entry 2). The use of [$PdCl_2$(dppf)] as a catalyst gave **3a** in lower yield. Finally, we found that 4-iodo-phenylalanine derivatives are more suitable coupling partners than triflate **2a** and nonaflate **2b**. The reaction of the iodide **2c** proceeded very smoothly in the presence of [$PdCl_2$(dppf)] catalyst, giving the corresponding product **3a** in 82% yield (Entry 3). 4-Iodophenylalanine derivatives, whose amine moieties were protected by dibenzyl (**2d**) and oxazolidin-5-one (**2e**,**f**) groups,[18] also underwent the coupling reaction very smoothly to give the corresponding arylboronic esters (**3b**—**d**) in high yields (Entries 4, 5, and 6, respectively).

Table 1. Palladium-Catalyzed Cross-Coupling of Pinacolborane **1** with **2**

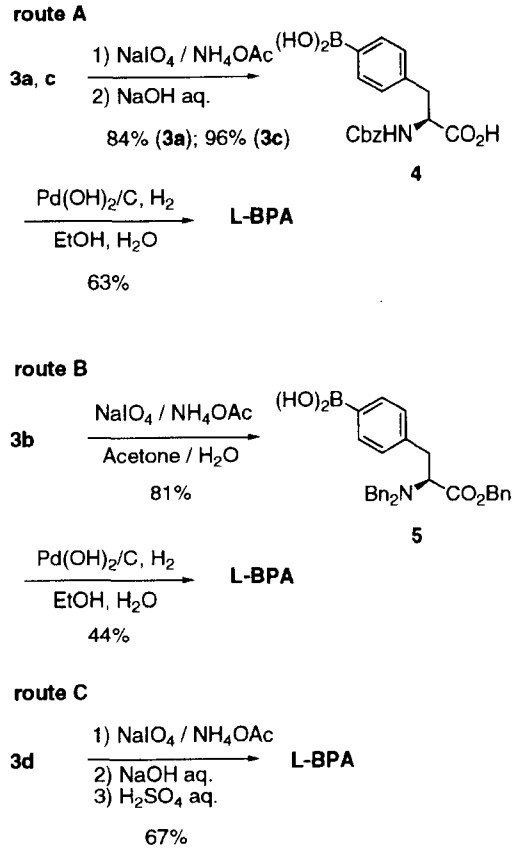
Entry	2		Product 3	Yield %[a]	Total chemical yields of L-BPA[b] Based on **1** (%),[c]	Based on **2** (%)[d]
1		**2a**	**3a**	> 5	—	—
2[e]		**2b**	**3a**	58	21	18
3		**2c**	**3a**	82	**29**	16
4		**2d**	**3b**	84	20	19
5		**2e**	**3c**	72	**29**	**35**
6		**2f**	**3d**	71	**32**	21

a) Isolated yield using silica-gel column chromatography. b) The coupling products (**3**) were converted into L-BPA via route A (Entries 2, 3, and 5), route B (Entry 4), and route C (Entry 6), as shown in Scheme 1. c) Pinacolborane **1** was readily prepared from 1 : 1 mixture of pinacol and $BH_3 \cdot SMe_2$ and used for the reaction without purification. Thus, the total yield of L-BPA based on **1** means the boron-based chemical yield from the commercially available boron source, $BH_3 \cdot SMe_2$. d) The total yield of L-BPA from L-tyrosine (Entry 2) 4-iodophenylalanine (Entries 3—6). e) $[PdCl_2(PPh_3)_2]$ was used as a catalyst.



Next, the deprotection of arylboronic esters **3** was examined (Scheme 1). The subsequent hydrolysis of pinacol ester **3a** with $NaIO_4$[19] followed by the treatment with NaOH gave the boronic acid **4** in 84% yield. The removal of the Cbz (benzyloxycarbonyl) protecting group of **4** was accomplished under $Pd(OH)_2$-carbon/H_2 condition and the desired L-BPA was obtained in 63% yield without racemization (route A). The hydrolysis of pinacol ester **3b** with $NaIO_4$ gave the boronic acid **5** in 81% yield. The dibenzyl protecting groups of **5** were removed under $Pd(OH)_2$-carbon/H_2 condition to give the desired L-BPA in 44% yield (route B). Further, the hydrolysis of pinacol ester **3c** with $NaIO_4$ and the removal of oxazolidinone protecting group by the treatment with NaOH also gave **4** in 96% yield (route A). The hydrolysis of pinacol ester **3d** with $NaIO_4$ followed by the removal of oxazolidinone and butyloxycarbonyl protective groups by the treatment with NaOH and H_2SO_4 gave the desired L-BPA in 67% yield by three steps (route C).

It is important to figure out not only the chemical yields of L-BPA based on **2**, but also those based on the boron source, pinacolborane **1**, since the cost of L-BPA strongly depends on that of B-10 enriched boron compounds. The chemical yield of α-chymotrypsin hydrolysis route,[5] which is now utilized for the bulk synthesis of L-BPA,[1] based on the substrate, 4-bromotoluene, is less than 5%. The chemical yield of the asymmetric hydrogenation route reported by Samsel et al.[7] and that of the palladium-catalyzed coupling route of iodophenylboronic acid with a chiral organozinc reported by Morin et al.[8] are around 20% from the corresponding 4-bromobenzaldehyde and L-serine, respectively. The chemical yield of our previous method using alkoxydiboron is 32% from L-tyrosine.[9] On the other hand, the chemical yield of α-



Scheme 1.

chymotrypsin hydrolysis route[5] based on the boron source, tributyl borate, is less than 5%. The boron-based chemical yields of the asymmetric hydrogenation route[7] and chiral organozinc route[8] are 20% and 23% from the corresponding tributyl borate and iodophenylboronoic acid, respectively, and that of our previous method[9] is only 8% from boron tribromide. Our current method reported in this paper is more practical in comparison with the previous methods. The chemical yields based on **1** and **2** are shown in Table 1. L-BPA was synthesized from **1**, which was readily prepared from pinacol and $BH_3 \cdot SMe_2$, in higher yields (around 30% yields) in the case of the Entries 3, 5, and 6. Although the yields based on **2** were around 20% in most cases, the highest yield was obtained in the case of Entry 5 and L-BPA was synthesized from 4-iodophenylalanine in 35% yield. Judging from these observations, it is clear that the best procedure to synthesize L-BPA is route A via **2e** (Scheme 1).

We have accomplished the synthesis of L-BPA from L-phenylalanine with pinacolborane in high chemical yields. The key for the efficient synthesis is the use of palladium-catalyzed cross-coupling reaction between C–I and B–H bonding. We believe that the procedure reported here is practical to supply L-BPA for medical requirements.

Experimental

Cbz–Tyr(Nf)–OBzl (2b). To a solution of Cbz–Tyr–OBzl[9] (3.77 g, 9.3 mmol) and triethylamine (1.95 mL, 13.99 mmol) in CH_2Cl_2 (50 mL) was added nonafluorobutanesulfonyl (Nf) fluoride (4.21 g, 13.94 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 27 h at room temperature. The reaction was quenched with water and the organic portion was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 3 : 1) gave Cbz–Tyr(Nf)–OBzl **2b** (6.38 g, 99.8% yield) as a white solid: IR (KBr) 3371, 2847, 1744, 1697, 1242 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.40—7.20 (m, 10H), 7.20—7.10 (m, 4H), 5.28 (d, J = 7.7 Hz, 1H), 5.2—5.0 (m, 4H), 4.69 (m, 1H), 3.17 (dd, J = 13.9, 5.8 Hz, 1H), 3.05 (dd, J = 13.9, 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 155.5, 148.7, 136.2, 136.0, 134.8, 131.1, 128.8, 128.8, 128.7, 128.6, 128.3, 128.2, 121.3, 77.2, 67.5, 67.1, 54.6, 37.5. Found: C, 49.06; H, 3.33; N, 1.97%. Calcd for $C_{28}H_{22}F_9NO_7S$: C, 48.92; H, 3.23; N, 2.04%. $[\alpha]_D^{23}$ 1.9 (c = 0.65, $CHCl_3$).

***N*-Benzyloxycarbonyl-4-iodo-L-phenylalanine Benzyl Ester (2c).** To a solution of *N*-benzyloxycarbonyl-4-iodo-L-phenylalanine (748 mg, 1.76 mmol) in MeOH (10 mL) was added Cs_2CO_3 (287 mg, 0.88 mmol) at room temperature and the mixture was stirred until bubbling ceased. After DMF was added to the mixture, MeOH was evaporated under reduced pressure. Benzyl bromide (0.42 mL, 3.53 mmol) was added to the solution and the mixture was stirred for 2 h at room temperature. The reaction was quenched with water and the organic portion was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 4 : 1) gave **2c** (869 mg, 96% yield) as a white solid: IR (KBr) 3325, 1740, 1693, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.50 (d, J = 8.4 Hz, 2H), 7.37 (m, 10H), 6.71 (d, J = 8.4 Hz, 2H), 5.21 (m, 1H), 5.10 (m, 4H), 4.68 (m, 1H), 3.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.5, 155.5, 37.6, 136.1, 135.2, 131.3, 128.7, 128.9, 128.7, 128.5, 128.2, 128.1, 92.6, 67.3, 67.0, 54.6, 37.7. Found: C, 55.75; H, 4.31; N, 2.66%. Calcd for $C_{24}H_{22}INO_4$: C, 55.94; H, 4.03; N, 2.72. $[\alpha]_D^{24}$ 2.3 (c = 0.75, $CHCl_3$)

***N*,*N*-Dibenzyl-4-iodo-L-phenylalanine Benzyl Ester (2d).** To a solution of 4-iodo-L-phenylalanine (3.065 g, 10.53 mmol) in H_2O (100 mL) was added Na_2CO_3 (5.022 g, 47.38 mmol) and the mixture was stirred at 50 °C until the solution became clear. Benzyl bromide (4.0 mL, 33.7 mmol) was added to the reaction mixture and the mixture was stirred at 130 °C for 24 h. The reaction was quenched with water and the organic portion was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 20 : 1) gave **2d** (3.342 mg, 57% yield) as yellow liquid: IR (KBr) 3061, 1728, 1211, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.51 (d, J = 8.3 Hz, 2H), 7.38 (m, 5H), 7.21 (m, 5H), 7.12 (m, 5H), 6.71 (d, J = 8.3 Hz, 2H), 5.22 (d, J = 12.2 Hz, 1H), 5.13 (d, J = 12.2 Hz, 1H), 3.89 (d, J = 13.9 Hz, 2H), 3.63 (d, J = 7.8 Hz, 1H), 3.51 (d, J = 13.9 Hz, 2H), 3.04 (dd, J = 13.9, 7.2 Hz, 1H), 2.91 (dd, J = 13.9, 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.6, 138.8, 137.6, 137.0, 131.4, 131.3, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 126.9, 91.4, 66.0, 62.0, 52.5, 35.0. HRMS (EI) Calcd for $C_{30}H_{28}INO_2$: M, 561.1165. Found: m/z 561.1165. $[\alpha]_D^{20}$ −37.5 (c = 0.98, $CHCl_3$).

(4*S*)- 3- *t*- Benzyloxycarbonyl- 4- (4- iodobenzyl)- 5- oxazolidinone (2e). *N*-Benzyloxycarbonyl-4-iodo-L-phenylalanine (6.628 g, 15.59 mmol) was suspended in toluene (300 mL), and paraformaldehyde (3.12 g) and *p*-TsOH·H_2O (326 mg, 1.71 mmol) were added. The water generated in the reaction was separated by benzene azeotropic distillation for 3 h. The reaction mixture was washed with $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel

(hexane/ethyl acetate = 3 : 1) gave **2e** (6.583 g, 97% yield) as colorless oil: IR (KBr) 3342, 1744, 1693, 1221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.51 (d, J = 8.3 Hz, 2H), 7.38 (s, 5H), 6.77 (br, 2H), 5.22 (br, 3H), 4.50 (br, 1H), 4.38 (d, J = 3.4 Hz, 1H), 3.4—3.0 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.1, 151.6, 137.3, 135.1, 133.9, 131.2, 128.3, 128.0, 92.9, 77.4, 67.4, 55.6, 35.4, 34.2; HRMS (EI) Calcd for $C_{18}H_{16}BINO_4$: M, 437.0125. Found: m/z 437.0129. $[\alpha]_D^{23}$ 162.0 (c = 2.60, $CHCl_3$).

(4*S*)-3-*t*-Butyloxycarbonyl-4-(4-iodobenzyl-5-oxazolidinone (2f). *N*-*t*-Butyloxycarbonyl-4-iodo-L-phenylalanine (6.02 g, 15.4 mmol) was suspended in toluene (250 mL), and paraformaldehyde (3.08 g) and *p*-TsOH·H_2O (293 mg, 1.54 mmol) were added to the solution. The water generated in the reaction was separated by benzene azeotropic distillation for 3 h. The reaction mixture was washed with $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 5 : 1) gave **2f** (3.36 g, 54% yield) as a white solid: IR (KBr) 2976, 1790, 1690, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.62 (d, J = 8.1 Hz, 2H), 6.91 (d, J = 8.1 Hz, 2H), 5.4—5.1 (br, 1H), 4.53—4.3 (br, 2H), 3.4—3.0 (br, 2H), 1.5 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.9, 137.7, 134.5, 131.5, 130.3, 93.0, 82.0, 77.9, 55.8, 28.2. HRMS (EI) Calcd for $C_{15}H_{18}BINO_4$: M, 403.0281. Found: m/z 403.0274. $[\alpha]_D^{22}$ 140.8 (c = 1.10, $CHCl_3$).

***N*-*t*-Benzyloxycarbonyl-4-(2,3-dimethyl-2,3-butanediolatoboryl)-L-phenylalanine Benzyl Ester (3a).** The representative procedure for the synthesis of **3a** is as follows. To a solution of **2c** (437 mg, 0.85 mmol) and [$PdCl_2$(dppf)] (19 mg, 0.026 mmol) in 1,4-dioxane (6 mL) was added Et_3N (0.35 mL, 2.5 mmol) and the mixture was stirred at room temperature under argon atmosphere for 20 min. After pinacolborane **1** (162 mg, 1.3 mmol) in 1,4-dioxane solution (2 mL) was added, the reaction mixture was heated to 100 °C and stirred overnight. The reaction was quenched with water and the organic portion was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 3 : 1) gave **3a** (361 mg, 82% yield) as a white solid: IR (KBr) 3425, 1750—1680, 1359, 1146 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.68 (d, J = 7.9 Hz, 2H), 7.32 (m, 10H), 7.03 (d, J = 7.9 Hz, 2H), 5.28 (m, 1H), 5.08—5.12 (m, 4H), 4.75 (m, 1H), 3.10 (m, 2H), 1.34 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.1, 155.5, 138.7, 135.0, 134.9, 128.7, 128.6, 128.6, 128.4, 128.4, 128.0, 127.9, 83.7, 67.2, 66.9, 54.7, 38.3, 24.9. HRMS (EI) Calcd for $C_{30}H_{34}BNO_6$: M, 515.2480. Found: m/z 515.2495. Found: C, 69.52; H, 6.56; N, 2.70%. Calcd for $C_{30}H_{34}BNO_6$: C, 69.91; H, 6.65; N, 2.72%. $[\alpha]_D^{22}$ 6.5 (c = 1.03, $CHCl_3$).

***N*,*N*-Dibenzyl-4-(2,3-dimethyl-2,3-butanediolatoboryl)-L-phenylalanine Benzyl Ester (3b).** To a solution of **2d** (7.15 g, 12.7 mmol) and [$PdCl_2$(dppf)] (279 mg, 0.38 mmol) in 1,4-dioxane (40 mL) was added Et_3N (5.3 mL, 38.2 mmol) and the mixture was stirred at room temperature under argon atmosphere for 20 min. After pinacolborane **1** (2.44 g, 19.1 mmol) in 1,4-dioxane solution (40 mL) was added to the reaction mixture at room temperature, the mixture was stirred at 80 °C for 36 h. The reaction was quenched with water and the organic portion was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 7 : 1) gave **3b** (6.0 g, 84% yield) as a yellow solid: IR (KBr) 3030, 1732, 1612, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.67 (d, J = 6.8 Hz, 2H), 7.4—7.1 (m, 15H), 7.03 (d, J = 6.8 Hz, 2H), 5.22 (d, J = 12.3 Hz, 1H), 5.10 (d, J = 12.3 Hz, 1H), 3.91 (d, J = 13.9 Hz, 2H), 3.71 (t, J = 7.6 Hz, 1H), 3.53 (d, J = 13.9 Hz, 2H), 3.14 (dd, J = 13.9, 7.4 Hz, 1H), 3.01 (dd, J = 13.9, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.0, 141.5, 139.1, 135.9, 134.7, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 126.9, 83.7, 66.1, 62.3, 35.9, 24.9. HRMS (EI) Calcd for $C_{36}H_{40}BNO_4$: M, 561.3051. Found: m/z 561.3058. Found: C, 77.19; H, 7.18; N, 2.48%. Calcd for $C_{36}H_{40}BNO_4$: C, 77.00; H, 7.18; N, 2.49%. $[\alpha]_D^{21}$ 247.4 (c = 1.35, $CHCl_3$).

(4*S*)-3-Benzyloxycarbonyl-4-[4-(2,3-dimethyl-2,3-butanediolatoboryl)benzyl]-5-oxazolidinone (3c). To a solution of **2e** (3.40 g, 7.78 mmol) and [$PdCl_2$(dppf)] (171 mg, 0.23 mmol) in 1,4-dioxane (20 mL) was added Et_3N (3.25 mL, 23.3 mmol) and the mixture was stirred at room temperature under argon atmosphere for 20 min. After pinacolborane **1** (1.49 g, 11.7 mmol) in 1,4-dioxane solution (30 mL) was added to the reaction mixture at room temperature, the mixture was stirred at 80 °C for 27 h. The reaction was quenched with water and the organic portion was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 4 : 1) gave **3c** (2.46 g, 72% yield) as a white solid: IR (KBr) 3036, 1796, 1684, 1433, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.68 (d, J = 7.9 Hz, 2H), 7.0 (m, 7H), 5.20 (br, 3H), 4.57 (br, 1H), 4.25 (d, J = 4.0 Hz, 1H), 3.5—3.2 (br, 2H), 1.35 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.7, 152.0, 137.5, 135.4, 135.1, 129.5, 129.0, 128.7, 128.2, 83.9, 77.9, 67.7, 56.2, 36.3, 35.2, 24.8. HRMS (EI) Calcd for $C_{24}H_{28}BNO_6$: M, 437.2010. Found: m/z 437.2010. $[\alpha]_D^{22}$ 168.2 (c = 0.75, $CHCl_3$).

(4*S*)-3-*t*-Butyloxycarbonyl-4-[4-(2,3-dimethyl-2,3-butanediolatoboryl)benzyl]-5-oxazolidinone (3d). To a solution of **2f** (2.62 g, 6.50 mmol) and [$PdCl_2$(dppf)] (143 mg, 0.20 mmol) in 1,4-dioxane (15 mL) was added Et_3N (2.7 mL, 19.4 mmol) and the mixture was stirred at room temperature under argon atmosphere for 20 min. After pinacolborane **1** (1.25 g, 9.77 mmol) in 1,4-dioxane solution (30 mL) was added to the reaction mixture at room temperature, the mixture was stirred at 80 °C for 27 h. The reaction was quenched with water and the organic portion was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 5 : 1) gave **3d** (1.86 g, 71% yield) as a white solid: IR (KBr) 2984, 1796, 1692, 1414, 1364 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.73 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.4—5.2 (br, 1H), 4.6—4.1 (br, 2H), 3.5—3.1 (br, 2H), 1.51 (s, 9H), 1.34 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.4, 138.0, 135.0, 129.0, 83.8, 81.9, 78.0, 56.3, 48.5, 28.2, 24.7. HRMS (EI) Calcd for $C_{21}H_{30}BNO_6$: M, 403.2167. Found: m/z 403.2182. Found: C, 62.66; H, 7.45; N, 3.58%. Calcd for $C_{21}H_{30}BNO_6$: C, 62.55; H, 7.50; N, 3.47%. $[\alpha]_D^{23}$ 158.4 (c = 1.45, $CHCl_3$).

***N*-Benzyloxycarbonyl-4-borono-L-phenylalanine (4): (a) Derived from 3a.** To a solution of **3a** (368 mg, 0.71 mmol) in acetone (30 mL) were added $NaIO_4$ (458 mg, 2.14 mmol), NH_4OAc (165 mg, 2.14 mmol), and water (15 mL) at room temperature, and the mixture was stirred for 48 h. The acetone was evaporated and NaOH solution (2 M, 30 mL, 1 M = 1 mol dm^{-3}) was added to the residue. The mixture was stirred for 1 h, washed with CH_2Cl_2, and then acidified with HCl (12 M) to pH 3. White precipitate was filtrated and purified by column chromatography on silica gel ($AcOH/CHCl_3/EtOH$ = 1 : 90 : 10), which gave **4** (207 mg, 84% yield) as a white solid.

(b) Derived from 3c. To a solution of **3c** (1.73 g, 3.94 mmol) in acetone (40 mL) were added $NaIO_4$ (2.53 g, 11.8 mmol), NH_4OAc (670 mg, 8.69 mmol), and water (40 mL) at room temperature, and the mixture was stirred for 48 h. The acetone was evaporated and NaOH solution (2 M, 100 mL) was added to the

residue. The mixture was stirred for 1 h, washed with CH_2Cl_2, and then acidified with HCl (12 M) to pH 3. The white precipitate was filtrated and purified by column chromatography on silica gel (AcOH/$CHCl_3$/EtOH = 1 : 90 : 10), which gave **4** in 96% yield (1.30 g): IR (KBr) 3323, 1699, 1541, 1373, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.62 (d, J = 7.5 Hz, 2H), 7.26 (m, 5H), 7.19 (d, J = 7.5 Hz, 2H), 5.01 (s, 2H), 4.44 (dd, J = 9.3, 4.8 Hz, 1H), 3.19 (dd, J = 13.8, 4.8 Hz, 1H), 2.92 (dd, J = 13.8, 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.2, 158.3, 140.5, 138.1, 134.9, 129.5, 129.3, 128.8, 128.5, 67.4, 56.6, 38.6; $[\alpha]_D^{21}$ −2.6 (c = 0.46, CH_3OH).

***N,N*-Dibenzyl-4-borono-L-phenylalaninen Benzyl Ester (5).** To a solution of **3b** (1.106 g, 1.97 mmol) in acetone (50 mL) were added NH_4OAc (319 mg, 4.14 mmol) and water (50 mL) at room temperature, and the mixture was stirred for 48 h. The acetone was evaporated, and the residue was dissolved in ethyl acetate, washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (AcOH/$CHCl_3$/EtOH = 6 : 90 : 4) gave **5** (768 mg, 81% yield) as yellow liquid: IR (KBr) 3510, 1730, 1323 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.65 (d, J = 7.6 Hz, 2H), 7.22—7.02 (m, 15H), 6.89 (d, J = 7.6 Hz, 2H), 5.09 (d, J = 12.3 Hz, 1H), 4.95 (d, J = 12.3 Hz, 1H), 3.76 (d, J = 13.9 Hz, 2H), 3.62 (t, J = 7.8 Hz, 1H), 3.42 (d, J = 13.9 Hz, 2H), 2.98 (dd, J = 13.8, 7.6 Hz, 1H), 2.86 (dd, J = 13.8, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.8, 143.0, 139.0, 135.8, 135.5, 129.1, 128.9, 128.8, 128.6, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 126.9, 126.8, 66.0, 62.1, 54.3, 35.8; $[\alpha]_D^{22}$ −54.7 (c = 2.28, CH_3OH).

4-Borono-L-phenylalanine (L-BPA): route A. To a mixture of **4** (377 g, 1.10 mmol) and $Pd(OH)_2/C$ (20%, 340 mg) in EtOH solution (7.5 mL) was added HCl (6 M, 0.36 mL) under hydrogen atmosphere and the reaction mixture was stirred at room temperature for 19 h. Palladium catalyst was removed by filtration through Celite® and the reaction mixture was neutralized with NaOH solution (25%) to pH 7.0 and stirred for 30 min. The white solid generated was filtrated and washed with water to afford pure L-BPA (144 mg, 63% yield);

(b) route B. Enantiomerically pure L-BPA (112 mg, 44% yield) was also obtained from **5** (588 mg, 1.28 mmol) by the same procedure described above;

(c) route C. To a solution of **3d** (3.24 g, 8.03 mmol) in acetone (80 mL) were added $NaIO_4$ (5.16 g, 24.1 mmol), NH_4OAc (1.36 g, 1.36 mmol), and water (80 mL) at room temperature, and the mixture was stirred for 48 h. The acetone was evaporated and NaOH solution (2 M, 100 mL) was added to the residue. The mixture was stirred for 1 h, washed with CH_2Cl_2, and then acidified with HCl (12 M) to pH 3. White precipitates were filtrated and dissolved in 1, 4-dioxane (30 mL). H_2SO_4 (2 M, 30 mL) was added to the solution and the mixture was stirred for 1 h at room temperature. Removal of the solvent followed by neutralization with 2 M of aqueous NaOH solution gave L-BPA in 67% yield (431 mg). ^1H NMR (300 MHz, DCl+D_2O) δ = 7.61 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.7 Hz, 2H), 4.11 (bt, J = 6.8 Hz, 1H), 3.21 (dd, J = 14.5, 5.5 Hz, 1H), 3.06 (dd, J = 14.5, 7.7 Hz, 1H); $[\alpha]_D^{22}$ −7.80——8.12 (c = 0.8, 1 M HCl), >95%ee; Lit,[5] $[\alpha]_D^{23}$ −8.2 (c = 0.7, 1 M HCl).

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