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Synthesis of 4-Substituted Phenylalanine Derivatives by Cross-Coupling Reaction of *p*-Boronophenylalanines

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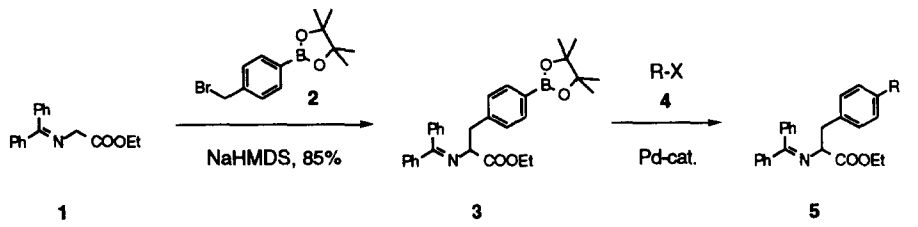
Abstract: The benzophenone imine of (4-pinacolylborono)phenylalanine ethyl ester (**3**) undergoes Suzuki-Miyaura coupling reactions with organic halides and triflates to give 4-substituted phenylalanine derivatives. A homochiral boronate ester (**7**), derived from Seebach's chiral imidazolidinone template, yields the corresponding coupling products under similar conditions with no or little loss of stereochemical integrity. © 1997 Elsevier Science Ltd.

The increasing importance of unnatural amino acids as building blocks in designing peptide-based biologically active molecules has led to rapid progress in the development of synthetic methodologies for the construction of such compounds.[1] In connection with our efforts toward identification of potent inhibitors of zinc metalloproteases such as neutral endopeptidase (NEP)[2] and endothelin converting enzyme (ECE),[3] we became interested in the modification of the distal phenyl group of *p*-biphenylalanine. Although a number of approaches for the synthesis of unnatural amino acids have been reported, only one method,[4] which utilizes a palladium-catalyzed cross-coupling reaction of organic boronic acids (Suzuki-Miyaura reaction)[5] with a tyrosine triflate derivative, appears to offer an entry to this class of compounds. However, the scarcity of readily available arylboronates does not allow rapid exploration of the structure-activity relationship (SAR) of biphenylalanine derivatives using this methodology. We postulated that appropriately protected *p*-boronophenylalanine[6] (BPA) derivatives would serve as ideal key intermediates for the preparation of modified phenylalanine derivatives in a highly flexible manner.

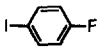
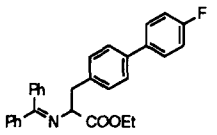
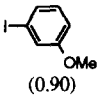
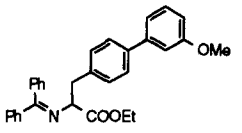
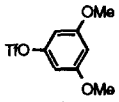
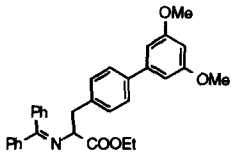
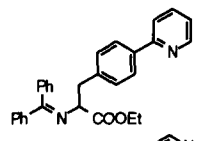
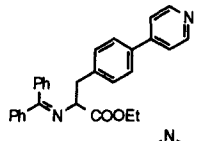
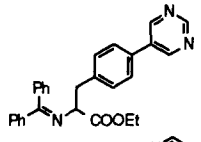
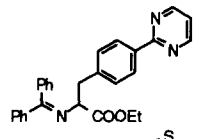
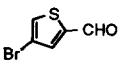
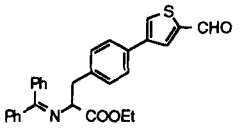
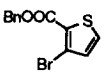
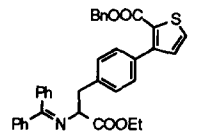


1 **3** **5**

The protected racemic BPA (**3**)[7] was readily prepared as a crystalline, air-stable solid by alkylation[8] of ethyl glycinate benzophenone imine (**1**) with the pinacol ester[9] of 4-bromomethylphenylboronic acid (**2**). Palladium-catalyzed coupling reactions of **3** were carried out in the presence of $PdCl_2$(dppf) using potassium phosphate as the base. The biarylalanines (**5**) were obtained in moderate to good yields (Table 1), except with a base-sensitive coupling partner (**4g**). Groups such as aldehyde (entry h) and ester (entry i) are well tolerated.

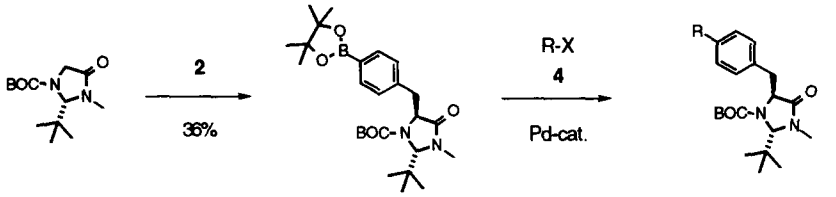
We then turned our attention to the asymmetric version of our method through a homochiral boronophenylalanine derivative. Though a few examples for the preparation of enantiomerically pure BPA have been reported, we decided to prepare **7**, derived from

Table 1. Synthesis of (±)-5

Entry	4, R-X (eq.)	$PdCl_2$(dppf), eq.	K_3PO_4, eq.	Time, h	5[a] (Yield, %)[b]
a	 (0.90)	0.05	4	12	 (72)[c]
b	 (0.90)	0.10	4	16	 (63)[c]
c	 (0.95)	0.10	4	15	 (61)[c]
d	 (1.5)	0.10	5	18	 (60)
e	 (1.8)	0.12	5	18	 (58)
f	 (1.3)	0.050	5	18	 (75)
g	 (2.0)	0.012	9	24	 (20)
h	 (1.5)	0.040	5	8	 (52)
i	 (1.0)	0.15	5	48	 (43)

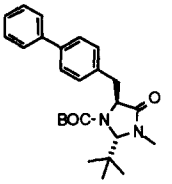
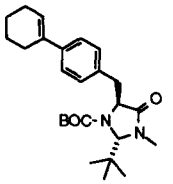
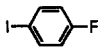
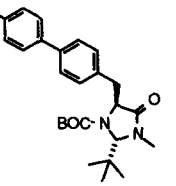
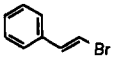
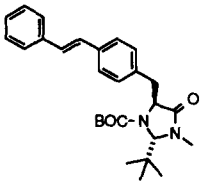
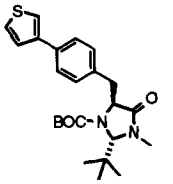
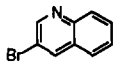
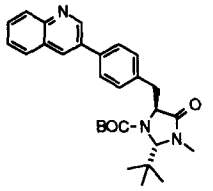
[a] The reactions were carried out in refluxing DME (b.p. 84 °C). [b] Isolated yields based on **3** unless otherwise noted.
[c] Yield based on **4**.

Seebach's imidazolidinone (**6**),[10] as the key intermediate since the preexisting chirality at C-2 makes the assessment of the diastereoselectivity of the coupling reaction exceedingly simple. Since it is known that, under certain conditions,[4] amino acid derivatives undergo partial racemization during palladium-catalyzed coupling reactions, drastic conditions were intentionally used in order to estimate the propensity of the imidazolidinone template toward epimerization during the coupling. Conversion of homochiral 5-substituted imidazolidinones to the corresponding free amino acids is known to proceed without racemization.[10]



6 **7** **8**

Table 2. Synthesis of 8

Entry	4, R-X (eq.)	8[a] (Yield, %)[b]		Entry	4, R-X (eq.)	8[a] (Yield, %)[b]	
a	 (1.2)		(87)	d	 (1.5)		(75)
b	 (1.5)		(90)	e	 (1.5)		(53)
c	 (1.5)		(56)	f	 (1.5)		(48)[c]

[a] The reaction was carried out using 3 mol% of $PdCl_2(dppf)$ and 2.5 equiv. of $Ba(OH)_2 \cdot 8H_2O$ in refluxing DME/water (1:1) for 16 h. [b] Isolated yield based on **7**. [c] Contaminated with ~5% C-5 epimer.

Alkylation of the BOC derivative (**6**) with **2** gave yet another crystalline boronate (**7**)[11] in 36% yield and >99% stereoselectivity according to ^1H NMR. The trans stereochemistry of **7**, as expected, was established by NOE experiments.[12] Coupling was effected under the catalysis of $PdCl_2(dppf)$ in the presence of barium hydroxide[13] at 100 °C for 16 h (Table 2).

Reactions with aromatic iodides are generally more effective than the corresponding bromides. Alkenyl halides also proved to be good substrates for the cross-coupling reaction (entries d,e). The NOE studies[12] on **8a** showed the stereochemistry to be trans. This indicates that, despite rather basic and forcing conditions used in the coupling, the relative stereochemistry of the imidazolidinone was preserved throughout the course of the reaction. Although compounds of high diastereomeric purity were obtained in most cases, we observed partial (~ 5%) epimerization in the reaction with 3-bromoquinoline. Peptide residues with certain polar side chains are known to be more prone toward partial racemization (side-chain induced racemization[14]).

In conclusion, a highly versatile and facile synthesis of the precursors for racemic and homochiral 4-substituted phenylalanines was developed using protected forms of p-boronophenylalanine. Application of this methodology in drug discovery efforts is subject of future publications.

Acknowledgment: We thank Mr. K. Gunderson for the N.O.E. experiments on **7** and **8a**, and Professor D. Seebach, Drs. S. De Lombaert, G. Ksander, and J. Stanton for helpful discussion and encouragement.

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(7) **3**: mp 123-4 °C. ^{1}H NMR (500 MHz, δ, $CDCl_3$) 1.27 (t, *J* = 7 Hz, 3 H), 1.34 (s, 12 H), 3.17-34 (m, 2 H), 4.20 (m, 3 H), 6.64 (br d, *J* = 6.4 Hz, 2 H), 7.07 (d, *J* = 7.7 Hz, 2 H), 7.25 (m, 6 H), 7.58 (d, *J* = 7 Hz, 2 H), 7.64 (d, *J* = 7.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, δ, $CDCl_3$) 171.71, 170.91, 141.47, 139.40, 136.13, 144.70, 130.28, 129.27, 83.69, 67.12, 61.07, 39.90, 24.95, 24.82, 14.23 ppm. IR (KBr) 1733, 1628, 1612, 1359, 1214, 1140, 1091 cm^{-1}. MS (DCI/CH_4) 484 (M+1). Anal. Calcd for $C_{30}H_{34}BNO_4$: C, 74.54; H, 7.09; N, 2.90. Found: C, 74.20; H, 7.09; N, 2.58.

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(11) **7**: mp. 158-9 °C. $[\alpha]_D$ +35.97 (c 1.06, $CHCl_3$). ^{1}H NMR (500 MHz, δ, DMSO-d_6, 80 °C) 0.89 (s, 9 H), 1.30 (s, 12 H), 1.42 (s, 9 H), 2.76 (s, 3 H), 3.11 (dd, *J* = 2.4 and 14.3 Hz, 1 H), 3.64 (dd, *J* = 5.3 and 14.3 Hz, 1 H), 4.25 (m, 1 H), 4.66 (d, *J* = 1.4 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 8.0 Hz, 2 H) ppm. IR (KBr) 1694, 1517, 1323, 1142, 861 cm^{-1}. MS (DCI/CH_4) 473 (M+1). Anal. Calcd for $C_{26}H_{41}BN_2O_5$: C, 66.10; H, 8.75; N, 5.93. Found: C, 66.00; H, 8.86; N, 5.62. In this reaction, the starting material **6** was recovered in a 45% yield.

(12) Saturation of either C-2 or C-5 proton of **7** and **8b** showed no appreciable enhancement of protons at C-5 or C-2. On the other hand, irradiation of the C-2 tert-butyl group resulted in a strong enhancement of both C-2 and C-5 protons, but not the methylene protons attached to C-5.

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