

Enantioselective Synthesis of 4-Substituted Phenylalanines by Cross-Coupling Reactions

Fariborz Firooznia,* Candido Gude, Kenneth Chan, Nicholas Marcopulos, and Yoshitaka Satoh

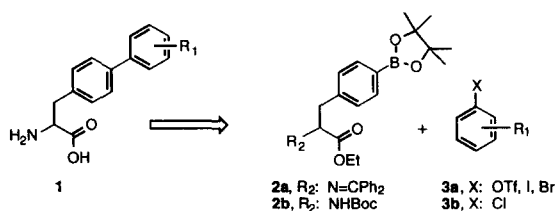
Metabolic and Cardiovascular Diseases Research, Novartis Pharmaceuticals Corporation

556 Morris Avenue, Summit, NJ 07901, U.S.A

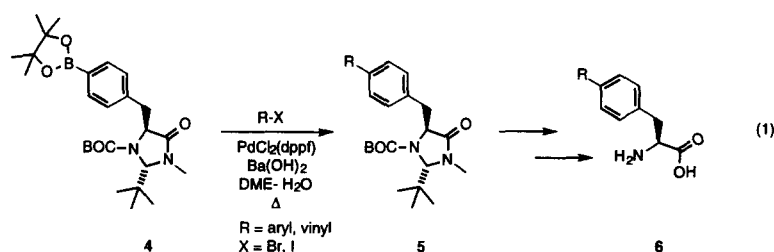
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Abstract: The enantiomerically enriched BOC-protected (4-pinacolylborono)phenylalanine methyl ester (**8**) is produced via enzymatic resolution of the racemic material, or direct synthesis from the corresponding iodide (or triflate), and undergoes Suzuki-Miyaura coupling reactions with aromatic halides and triflates in the presence of catalytic amounts of PdCl₂(dppf) to produce enantiomerically enriched 4-substituted phenylalanine derivatives. © 1998 Elsevier Science Ltd. All rights reserved.

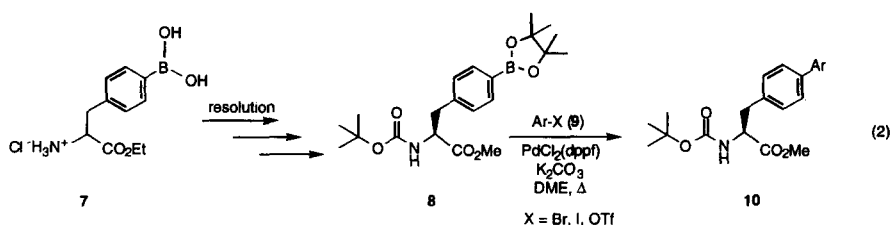
We recently reported a practical method for the synthesis of 4-substituted phenylalanine derivatives **1** via a Suzuki-Miyaura coupling¹ of a protected (4-pinacolylborono)phenylalanine (BPA) **2a** with aryl iodides, bromides, and triflates **3a**.^{2,3} The scope of this methodology was further expanded by the discovery of reaction conditions which allowed the utilization of aryl chlorides **3b**, through coupling with the BOC-protected derivative **2b**.⁴ With such conditions at hand, we were able to generate a *diverse* set of 4-aryl-phenylalanines due to the large number of aryl and heteroaryl halides commercially available. This Letter describes our latest efforts in extending this methodology to the *enantioselective* synthesis of 4-substituted phenylalanines.



Our initial efforts in the synthesis of enantiomerically enriched 4-substituted phenylalanines were summarized in a prior publication² in which we reported the coupling reactions of the homochiral BPA derivative **4**, derived from Seebach's imidazolinone (eq 1).⁵ In all examples tested, the formation of single diastereomers **5** were observed. This approach towards chiral biphenylalanines, though very promising, had one potential drawback: The removal of the Seebach imidazolinone often requires harsh acidic conditions, which may not be compatible with the desired functionality on the biphenylalanine moiety. In order to surmount this problem, we set out to find a synthetic route that did not require the removal of an external chiral auxiliary. Enantiomerically pure BPA thus seemed to be the logical reagent of choice to provide an efficient and practical entry into enantiopure 4-aryl-phenylalanines **6**.



N-BOC-(4-pinacolylborono)-L-phenylalanine methyl ester (**8**)⁶ was thus prepared (93-97% ee, >99% ee after a single recrystallization) via the enzymatic resolution of the DL-ethyl ester hydrochloride **7** with α -chymotrypsin according to published procedures (eq 2).^{7,2} Coupling reactions (eq 2) of **8** with aryl halides and triflates **9** (Table 1) were then carried out in the presence of catalytic amounts of $PdCl_2(dppf)$.^{8,9} Among the limited number of solvents¹⁰ and bases¹¹ investigated, DME and K_2CO_3 consistently provided **10** in the best yields and highest enantiomeric purity, except when aryl chlorides were used.⁴ The coupling reaction of **8** with 4-chlorobenzotrifluoride in *NMP* in the presence of $PdCl_2(PCy_3)_2$ ⁴ resulted in *almost completely racemized product* (ca. 60% yield).¹² In general, however, 4-substituted phenylalanines were produced in good to excellent yields, and with very high enantiomeric purity.



We then turned our attention to developing alternative syntheses for **8**, by Pd-catalyzed reactions (eq 3) of the tyrosine triflate derivative **11a**, or the corresponding iodide **11b**, with either the Miyaura reagent **12a**,¹³ or pinacolborane (**12b**),¹⁴ with the ultimate goal of developing a *one-pot procedure* for the synthesis of 4-aryl-phenylalanines from tyrosine derivatives. The results of these coupling reactions are summarized in Table 2. As indicated, the coupling reactions with the Miyaura reagent **12a** were successful only in *NMP* and *DMSO*, and *not in DME*. However, both the triflate **11a** and the iodide **11b** provided **8** in good yields using the Miyaura reagent.¹⁵ Pinacolborane (**12b**), however, failed to produce **8** from the triflate **11a**, and only provided synthetically useful yields of **8** from **11b** when *dioxane* was used as the solvent.¹⁶

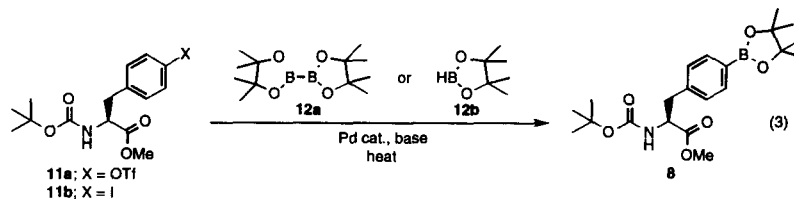


Table 1. Coupling Reactions of **8** with Ar-X (carried out according to the general procedure described in reference 8)

Entry	9, Ar-X	10, Product	%Yield, % ee ^a	Entry	9, Ar-X	10, Product	%Yield, % ee
a			82, >99	f			75, >99
b			90, >99	g			74, 99
c			87, 92	h			88, 86
d			60, 91	i			81, 85
e			65, 84	j			50, >99

^a Determined via the analysis of the ¹H and ¹⁹F NMR spectra of the Mosher amide derivativesTable 2. Preparation of Chiral Boronophenylalanine **8**

substrate	boron reagent	Pd cat.	solvent	temp (°C)	time (h)	yield	%ee
11b	12a	PdCl ₂ (dppf)	NMP	100	24	47%	88
11b	12a	PdCl ₂ (PCy ₃) ₂	NMP	100	18	54%	88
11b	12a	PdCl ₂ (dppf)	DMSO	80	18	72%	90
11b	12a	PdCl ₂ (dppf)	DME	80	18	<20%	ND
11a	12a	PdCl ₂ (PCy ₃) ₂	NMP	100	18	48%	88
11a	12a	PdCl ₂ (dppf)	NMP	100	18	58%	70
11b	12b	PdCl ₂ (dppf)	dioxane	100	18	72%	94
11b	12b	PdCl ₂ (dppf)	CH ₃ CN	100	18	37%	ND
11b	12b	PdCl ₂ (dppf)	DME	80	18	<20%	ND
11a	12b	PdCl ₂ (dppf)	dioxane	100	18	<5%	ND

In summary, we have developed a new method for the *enantioselective synthesis of 4-substituted phenylalanines*, via Pd-catalyzed cross-coupling reactions of a protected boronophenylalanine (BPA) with aromatic halides and triflates. These reactions proceed in good to excellent yields, and furnish the desired products in high enantiomeric purity. A variety of methods for the synthesis of the BPA reagent were also investigated, resulting in conditions that may be adapted for a *one-pot* synthetic procedure upon further investigation.

References and Notes:

- (1) For a recent review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
- (2) Satoh, Y.; Gude, C.; Chan, K.; Firooznia, F. *Tetrahedron Lett.* **1997**, *38*, 7645.
- (3) (a) Subsequent to our report (ref. 2), a recent publication described a synthesis of 4-aryl-phenylalanines by *Stille cross-coupling* reactions of *N*-Boc-4-trimethylstannylphenylalanine methyl ester: Morera, E.; Ortar, G. *Synlett* **1997**, 1403.
- (4) Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985.
- (5) Fitz, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.
- (6) **8**: Light tan solid; ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, 2 H), 7.12 (d, 2 H), 4.95 (br d, 1 H), 4.58 (app q, 1 H), 3.70 (s, 3 H), 3.00-3.20 (m, 2 H), 1.42 (s, 9 H), 1.34 (s, 12 H); [α]_D +44.31 (5.1 mg/mL in CH₂Cl₂).
- (7) (a) Roberts, D. C.; Suda, K.; Samanen, J.; Kemp, D. S. *Tetrahedron Lett.* **1980**, *21*, 3435, and references cited therein. (b) For an alternative approach to the synthesis of 4-borono-*L*-phenylalanine see: Malan, C.; Morin, C. *Synlett* **1996**, 167.
- (8) A representative experimental procedure is as follows: A 25 mL, round-bottomed flask fitted with a reflux condenser was charged with **8** (250 mg, 0.617 mmol), triflate **9j** (210 mg, 0.740 mmol), PdCl₂(dppf) (35 mg, 0.043 mmol), K₂CO₃ (426 mg, 3.08 mmol), and 8 mL of DME. The reaction mixture was heated at 80 °C for 18 h, then cooled to room temperature, and partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over MgSO₄, filtered, and concentrated. Chromatography on silica gel (15% EtOAc/hexane) furnished 155 mg (50%) of **10j**. ¹H NMR (250 MHz, CDCl₃) δ 7.45 (d, 2 H), 7.12 (d, 2 H), 6.68 (d, 2 H), 6.43 (dd, 1 H), 4.98 (br d, 1 H), 4.60 (app q, 1 H), 3.82 (s, 6 H), 3.73 (s, 3 H), 3.00-3.20 (m, 2 H), 1.43 (s, 9 H); Anal. Calcd for C₂₃H₂₉NO₆: C, 66.49; H, 7.04; N, 3.37. Found: C, 64.35; H, 6.81; N, 3.22.
- (9) For a discussion on using boronic acids in place of boronate esters in our coupling reactions, see reference 4.
- (10) Coupling reactions in toluene and acetonitrile provided unacceptably low yields of **10**. In dioxane, **10** was produced in lower yields than in DME, but with high enantiomeric purity. Varying degrees of loss of enantiomeric purity were observed when NMP was used as the solvent for the coupling reactions. Use of DMSO also led to *almost completely racemized 10*, presumably due to adventitious water, and the higher pK_a of bases in DMSO than in DME.
- (11) Reactions with KOAc or KHPO₄ as base failed to produce significant amounts of **10**. The use of CsF did not significantly improve reaction time, yield, or % ee compared with K₂CO₃. Couplings performed in the presence of K₃PO₄ as base led to significant loss of enantiomeric purity.
- (12) When the coupling of this chloride was performed with the boronic acid of **8** and NiCl₂(dppf) as the catalyst (see reference 4), the coupling product was produced in ca. 30% yield and 42% ee. The best results for this coupling were achieved when Pd₂(dba)₃ and *t*-Bu₃P were used as the catalyst, in dioxane (Fu, G. C.; Littke, A. F. *Angew. Chem., Int. Ed. Engl.* **1998**, in press) to produce the coupling product in 30-36% yield, *but with 99% ee*.
- (13) (a) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. (b) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
- (14) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458.
- (15) Remarkably, and in contrast to the coupling reactions of **8**, very little loss of enantiomeric purity was observed during the Pd-catalyzed coupling reactions of **11a** and **11b** in NMP and DMSO, probably due to the lower basicity of KOAc.
- (16) This approach provides the best possibility for a *one-pot procedure*, since the coupling reactions of **8** in dioxane were not accompanied by significant loss of enantiomeric purity (see reference 9). Unfortunately, our preliminary attempts at a one-pot reaction in dioxane have so far failed to produce the desired biarylalanine products in synthetically useful yields. Efforts are currently on their way to develop and optimize the conditions for such one-pot procedures.