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LETTERS

Synthesis of 4-Substituted Phenylalanines by Cross-Coupling Reactions: Extension of the Methodology to Aryl Chlorides

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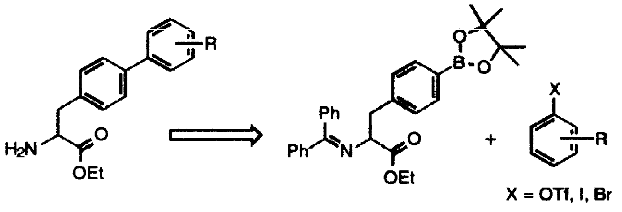
Abstract: The Boc-derivative of (4-pinacolylborono)phenylalanine ethyl ester (**6**) or the corresponding boronic acid **8** undergo Suzuki-Miyaura coupling reactions with aromatic chlorides in the presence of catalytic amounts of $PdCl_2(PCy_3)_2$ or $NiCl_2(dppf)$, respectively, to produce 4-substituted phenylalanine derivatives.

We recently reported a practical method for the synthesis of 4-substituted phenylalanine derivatives **1** via a Suzuki-Miyaura coupling[1] of a protected (4-pinacolylborono)phenylalanine **2** with aryl and vinyl iodides, bromides, and triflates **3**.[2,3] Even though this approach already affords access to a wide variety of 4-substituted phenylalanines, its scope would be considerably increased by the discovery of reaction conditions which allow the utilization of *aryl chlorides*. With such conditions at hand, the ability of our method to generate a *diverse* set of 4-aryl-phenylalanines is significantly enhanced, due to the large number of aryl and heteroaryl chlorides commercially available.



1 2 3

There have been a number of recent reports concerning the Suzuki-Miyaura coupling reactions of aromatic chlorides with arylboronic *acids*, utilizing highly active catalysts that undergo relatively facile oxidative addition. Most notable among these catalysts are $NiCl_2(dppf)$[4] and $PdCl_2(PCy_3)_2$.[5-7] To our knowledge, there have been no reports of such coupling reactions with *boronate esters* to date. Our initial efforts on finding the optimal reaction conditions for our system focused on investigating the coupling reaction of **2** and 2-chlorobenzonitrile using the latter catalyst (eq 1), since pinacolyl boronates do not undergo transmetallation with Ni.[8]

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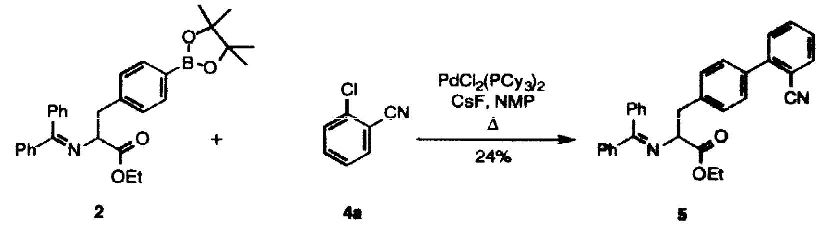
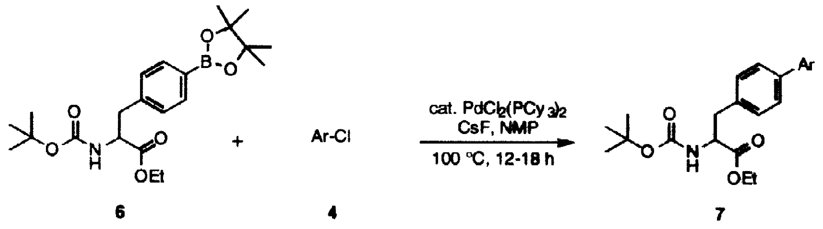


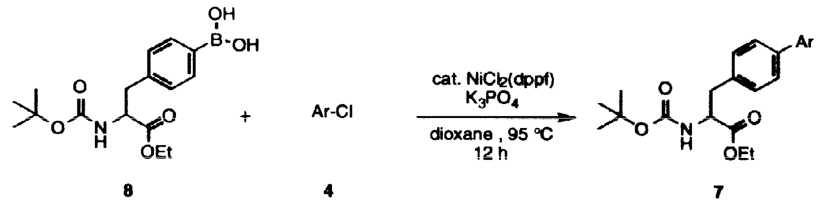
(1)

In our hands, this coupling reaction (cat. $PdCl_2(PCy_3)_2$, CsF, NMP, 100 °C, 12 h) furnished the desired biphenylalanine derivative **5** in a disappointing 24% isolated yield. We postulated that the low yield was due to the possibility that the imine functionality in **2** was interfering with the catalytic cycle by acting as a ligand for Pd, thus further slowing (or completely shutting down) the already sluggish oxidative addition step.[9] In order to circumvent this problem, we chose to protect boronophenylalanine as its Boc-derivative **6**[10] instead of the corresponding benzophenone imine. This modification led to a significant improvement in the yield of the coupling reaction with 2-chlorobenzonitrile (Table 1, entry a). Encouraged by this result, we set out to investigate the scope and limitations of the coupling reaction of **6** with a variety of aryl chlorides (eq 2). Our findings are summarized in Table 1, entries a-f. Under these conditions[11] (equimolar amounts of **6** and aryl chloride, 5 mol% $PdCl_2(PCy_3)_2$, 2 equiv CsF, NMP, 100 °C, 12-18 h), 4-aryl-phenylalanines were generally produced in acceptable isolated yields. To our pleasant surprise, even aryl chlorides bearing *electron-donating* functional groups participate in the reaction (entry f), although the coupling products are produced in slightly lower yields than those containing electron-withdrawing groups.



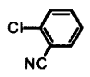
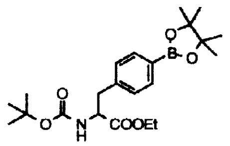
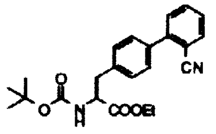
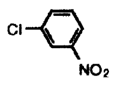
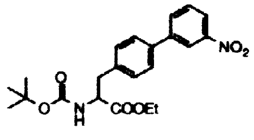
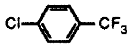
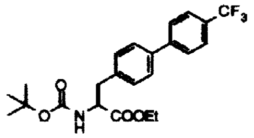
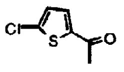
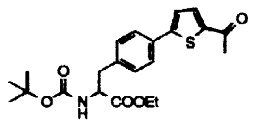
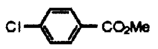
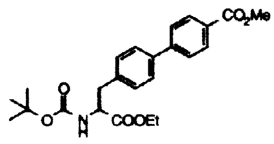
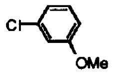
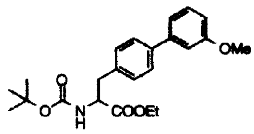
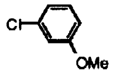
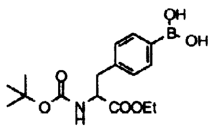
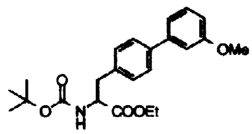
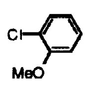
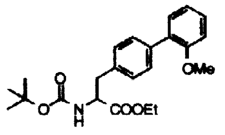
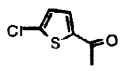
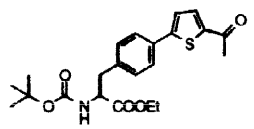
(2)

We then turned our attention to Ni-catalyzed coupling reactions (eq 3) of the free boronic acid **8**[12] and aryl chlorides (Table 1, entries g-i). Under these conditions (equimolar amounts of **8** and aryl chloride, 8 mol% $NiCl_2$(dppf), 5 equiv K_3PO_4, dioxane, 95 °C, 12 h), electron-rich aryl chlorides furnish the desired substituted phenylalanine derivatives with yields comparable to electron-deficient substrates (compare entry i with entries g and h), and with slightly better yields than the corresponding Pd-catalyzed reactions (compare entries f and g). In general, however, Ni-catalyzed reactions do not appear to offer a significant advantage over their Pd-catalyzed counterparts, especially since boronate **6** is more readily accessible, easier to purify, and more stable than boronic acid **8**,[13] which was prepared using **6** as an intermediate.



(3)

Table 1. Coupling Reactions of 6 and 8 with Aryl Chlorides

Entry	Aryl Chloride 4	Boron Reagent	Catalyst	Product 7 (Yield, %)[a]	
a		 **6**	$PdCl_2(PCy_3)_2$		(59)
b		//	//		(50)
c		//	//		(62)
d		//	//		(57)
e		//	//		(47)
f		//	//		(41)
g		 **8**	$NiCl_2(dppf)$		(50)
h		//	//		(56)
i		//	//		(51)

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[a] Isolated yields (not optimized) after chromatography on silica gel.

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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 and 4-vinylphenylalanines by *Stille cross-coupling* reactions of *N-Boc-4-trimethylstannylphenylalanine methyl ester*: Morera, E.; Ortar, G. *Synlett* **1997**, 1403. (b) For a review of other approaches for the synthesis of unnatural amino acids, see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.

(4) (a) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513. (b) Saito, S.; Oh-Tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024.

(5) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575.

(6) For a report on the coupling of π-deficient heteroaryl chlorides and arylboronic acids using $PdCl_2$(dppb) as the catalyst, see: Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273.

(7) For palladium-catalyzed coupling reactions of aryl chlorides and *tetraphenylborate sodium*, see: Bumagin, N. A.; Bykov, V. *Tetrahedron* **1997**, *53*, 14437, and references cited therein.

(8) (a) Firooznia, F.; Gude, C. unpublished results. (b) N. Miyaura, private communication.

(9) This problem was not encountered in our previous work (ref. 2), which used the bidentate $PdCl_2$(dppf) as the catalyst for the coupling reactions, since the ligands on Pd were not labile phosphine groups that could be easily replaced with the imine functionality.

(10) **6**: White solid, mp 89-91 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, 2 H), 7.14 (d, 2 H), 4.96 (br d, 1 H), 4.55 (app q, 1 H), 4.15 (q, 2 H), 3.05-3.18 (m, 2 H), 1.42 (s, 9 H), 1.34 (s, 12 H), 1.23 (t, 3 H); IR (CH_2Cl_2, cm^{-1}) 3425, 1737, 1712, 1500, 1392, 1361, 1166, 1143, 1089, 1022, 858. MS (ESI, 1:1 CH_3CN:H_2O, 0.2% NH_4OH) for $C_{22}H_{34}NO_6B$ 420 (M+1).

(11) A representative experimental procedure is as follows: A 5-mL, round-bottomed flask fitted with a reflux condenser was charged with **6** (150 mg, 0.357 mmol), 2-chlorobenzonitrile (49 mg, 0.357 mmol), $PdCl_2(PCy_3)_2$ (13 mg, 0.018 mmol), CsF (108 mg, 0.714 mmol), and 2 mL of NMP. The reaction mixture was heated at 100 °C for 16 h, then cooled to room temperature, and partitioned between Et_2O and water. The aqueous phase was extracted twice with Et_2O, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated to produce a pale yellow oil. Chromatography on silica gel (20% EtOAc/hexane) furnished 83 mg (59%) of **7a**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, 1 H), 7.64 (dt, 1 H), 7.48-7.52 (m, 3 H), 7.43 (dt, 1 H), 7.28 (d, 2 H), 5.05 (br d, 1 H), 4.60 (dd, 1 H), 4.18 (q, 2 H), 3.00-3.20 (m, 2 H), 1.43 (s, 9 H), 1.24 (t, 3 H); IR ($CDCl_3$, cm^{-1}) 2256, 1736, 1711, 1597, 1500, 1444, 1393, 1369, 1348, 1265, 1165, 1061, 1028. MS (DCI/NH_3) for $C_{23}H_{26}N_2O_4$ 395 (M+1).

(12) **8**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 2 H), 7.29 (d, 2 H), 5.04 (d, 1 H), 4.62 (br dd, 1 H), 4.19 (q, 2 H), 3.10-3.28 (m, 2 H), 1.44 (s, 9 H), 1.26 (t, 3 H); IR (KBr, cm^{-1}) 3425 (broad), 3350, 1733, 1685, 1612, 1525, 1369, 1357, 1338, 1191, 1166, 1022. MS (ESI, 1:1 CH_3CN:H_2O, 0.2% NH_4OH) for $C_{16}H_{24}NO_6B$ 338 (M+1), 336 (M-1).

(13) The boronate ester **6** is more readily purified by chromatography on silica gel than the more polar **8**. Moreover, **8** is often contaminated with its trimer, a problem common to boronic acids.