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One-Pot Primary Aminomethylation of Aryl and Heteroaryl Halides with Sodium Phthalimidomethyltrifluoroborate

Norio Murai,[†,‡] Masayuki Miyano,[‡] Masahiro Yonaga,[*,†,‡] and Keigo Tanaka[*,‡]

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and Discovery Research Laboratories, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba, Ibaraki 300-2635, Japan

k6-tanaka@hhc.eisai.co.jp; m-yonaga@hhc.eisai.co.jp

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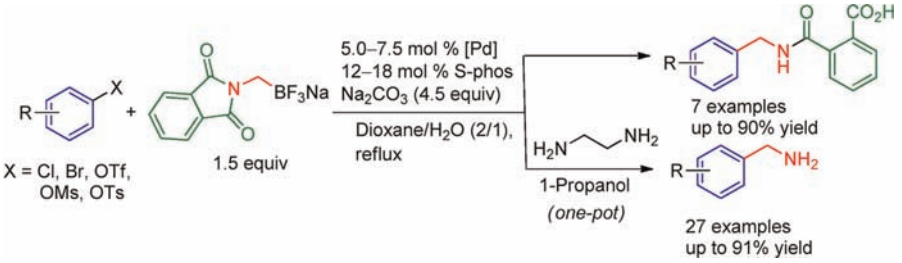
ABSTRACT



A one-pot primary aminomethylation of aryl halides, triflates, mesylates, and tosylates via Suzuki−Miyaura cross-coupling reactions with sodium phthalimidomethyltrifluoroborate followed by deamidation with ethylenediamine is reported.

Aromatic rings bearing a primary aminomethyl group are widely used in bioactive molecules and their synthetic precursors (Figure 1).[1] Common starting materials for the synthesis of primary aminomethyl aromatic compounds include aryl aldehydes,[2] cyanides,[3] amides,[4] oximes,[5] methyl halides,[6] and methyl azides.[5a,7] However, the utility of these starting materials is limited by the number of functional groups that are stable under reductive conditions and by the number of commercially available chemically diverse compounds. There have been several reports on the use of palladium-catalyzed aminomethylation reactions of aryl halides with *N*-protected primary

[†] University of Tokyo.
[‡] Eisai Co., Ltd.

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(6) For recent examples, see: (a) Lehmann, F.; Koolmeister, T.; Odell, L. R.; Scobie, M. *Org. Lett*. **2009**, *11*, 5078. (b) Majumdar, K. C.; Mondal, S.; De, N. *Synthesis* **2009**, *18*, 3127.

(7) For recent examples, see: (a) Norcliffe, J. L.; Conway, L. P.; Hodgson, D. R. W. *Tetrahedron Lett*. **2011**, *52*, 2730. (b) Percec, V.; Peterca, M.; Tadjiev, T.; Zeng, X.; Ungar, G.; Leowanawat, P.; Aqad, E.; Imam, M. R.; Rosen, B. M.; Akbey, U.; Graf, R.; Sekharan, S.; Sebastiani, D.; Spiess, H. W.; Heiney, P. A.; Hudson, S. D. *J. Am. Chem. Soc*. **2011**, *133*, 12197. (c) Chang, M.; Park, S.-R.; Kim, J.; Jang, M.; Park, J. H.; Park, J. E.; Park, H.-G.; Suh, Y.-G.; Jeong, Y. S.; Park, Y.-H.; Kim, H.-D. *Bioorg. Med. Chem*. **2010**, *18*, 111.

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aminomethyltrifluoroborate derivatives.[8] This method is attractive because the reaction conditions are mild, and aryl halides are generally inexpensive and are commercially available with various substitution patterns. However, several problems with this method remain to be solved: (i) *N*-Boc-protected aminomethylation reactions of aryl mesylates and tosylates do not proceed; (ii) the chemical yields of aminomethylation reactions of *N*-phthalimide-protected compounds are only moderate in many cases; and (iii) *N*-deprotection of *N*-acyl- and *N*-sulfonyl-protected aminomethyl compounds commonly requires strongly basic or acidic conditions.[9] Furthermore, although we previously reported one-pot primary aminomethylation reactions involving phthalimidomethyltrifluoroborate and hydrazine, the chemical yields were only low to moderate.[8a]

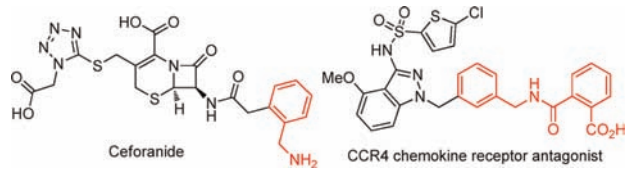


Figure 1. Bioactive compounds containing a primary aminomethyl-substituted aromatic ring and an *N*-(arylmethyl)phthalamic acid.

Therefore, we have been working on developing a more general, higher yielding method for the introduction of a primary aminomethyl group into aromatic rings.

In addition, we hoped to use the developed method for the synthesis of compounds with an *N*-(arylmethyl)-phthalamic acid moiety, which is also found in various bioactive compounds (Figure 1).[10] *N*-(Arylmethyl)phthalamic acids are commonly synthesized by reactions of arylmethyl amines with either phthalic anhydride[11] or phthalic acid.[12] To the best of our knowledge, there have been no reports of the synthesis of *N*-(arylmethyl)phthalamic acids directly from aryl halides, which are ideal substrates from the viewpoint of cost and commercial availability, as mentioned above.

Scheme 1. Preparation of Sodium Phthalimidoylmethyltrifluoroborate **1**

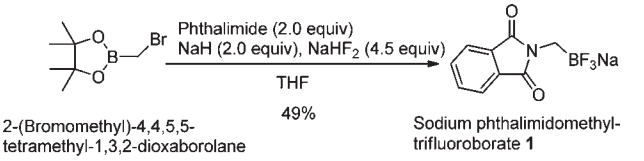
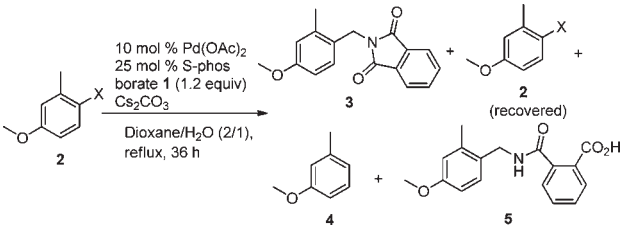


Table 1. Optimization of the Suzuki–Miyaura Cross-Coupling Reaction Conditions



			NMR yield (%)[a]			
entry	X	Cs_2CO_3 (equiv)	**3**	**2**	**4**	**5**
1	Br	0.6	16	61	12	
2	Br	1.2	58	<1	15	6
3	Br	1.8	57	<1	9	16
4	Br	2.4	29	<1	6	60
5	Br	3.0	2	<1	5	72
6	Br	4.0	2	<1	5	73
7[b]	Br	3.0	1	<1	3	95
8[b]	Cl	3.0	<1	42	<1	18
9	Cl	3.0	<1	<1	<1	86
10[b,c]	Br	3.0	<1	<1	<1	92
11[d]	Cl	3.0	<1	<1	<1	82
12[b,e]	Br	3.0	<1	<1	<1	95

[a] Determined by ^{1}HNMR. [b] $Pd(dba)_2$ was used instead of $Pd(OAc)_2$. [c] 5.0 mol % of $Pd(dba)_2$ and 12 mol % of S-phos. [d] 5.0 mol % of $Pd(OAc)_2$ and 12 mol % of S-phos. [e] 3.0 equiv of Na_2CO_3 was used instead of Cs_2CO_3.

Herein, we report a versatile method for one-pot primary aminomethylation of aryl and heteroaryl halides, triflates, mesylates, and tosylates using sodium phthalimidomethyltrifluoroborate (**1**). Furthermore, we report the first example of direct synthesis of *N*-(arylmethyl)-phthalamic acid derivatives from aryl and heteroaryl halides with **1**.

Borate **1** was prepared by reaction of 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane with phthalimide, NaH, and $NaHF_2$ in 49% yield (Scheme 1).

(8) (a) Tanaka, K. WO2008007670, priority application July 2006. (b) Molander, G. A.; Hiebel, M.-A. *Org. Lett.* **2010**, *12*, 4876. (c) Molander, G. A.; Fleury-Brégeot, N.; Hiebel, M.-A. *Org. Lett.* **2011**, *13*, 1694. (d) Molander, G. A.; Shin, I. *Org. Lett.* **2011**, *13*, 3956. (e) Devulapally, R.; Fleury-Brégeot, N.; Molander, G. A.; Seapy, D. G. *Tetrahedron Lett.* **2012**, *53*, 1051.

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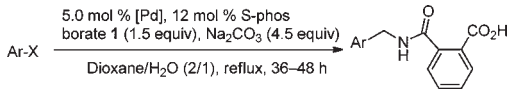
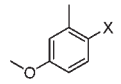
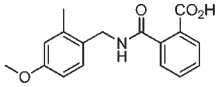
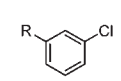
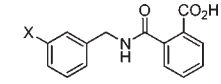
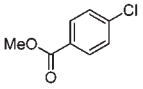
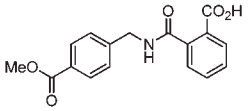
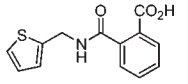
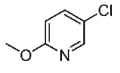
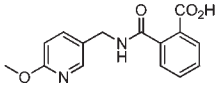
Table 2. Synthesis of *N*-(Arylmethyl)phthalamic Acid Using Suzuki–Miyaura Cross-Coupling Reaction[a]



entry	substrate	product		method[b]		isolated yield (%)
1			X = Cl	A	**6a**	85
			Br	B		90
2			R = CN	A	**6b**	84
			CHO	A	**6c**	86
3				A	**6d**	87
4				B	**6e**	62
5				A	**6f**	42

[a] Reaction conditions: 1.0 equiv of substrate, 5 mol % of [Pd], 12 mol % of S-phos, 1.5 equiv of borate **1**, 4.5 equiv of Na_2CO_3, 1,4-dioxane/H_2O (2/1), reflux. [b] Method A: [Pd] = $Pd(OAc)_2$. Method B: [Pd] = $Pd(dba)_2$.

With **1** in hand, we optimized the conditions for the Suzuki–Miyaura cross-coupling reaction.[13] We initially selected S-phos/$Pd(OAc)_2$[14] as the catalyst, Cs_2CO_3 as the base, and dioxane/H_2O as the solvent. Preliminary results indicated that the optimal dioxane/H_2O ratio was 2/1; at this ratio, all the reaction materials, including the reaction intermediates, were dissolved; and the chemical yields and reproducibility were the highest. In addition, a higher than usual S-phos/$Pd(OAc)_2$ ratio (2.4–3.0/1.0 compared to 2.0/1.0) gave high reproducibility with commercially available solvents that had not been distilled prior to use, as is the case for palladium-catalyzed hydroxymethylation reactions of aryl halides and triflates.[15] We then used these initial reaction conditions to optimize the base and the palladium source (Table 1). When the Cs_2CO_3/borate **1** ratio was 1.2–1.8/1.2, the major product was phthalimide **3**, accompanied by phthalamic acid **5** (Table 1, entries 2 and 3). In contrast, **5** was efficiently obtained when the Cs_2CO_3/borate **1** ratio was 3.0–4.0/1.2 (Table 1, entries 5 and 6).

Interestingly, we found that the optimal palladium sources differed for the aryl bromide and the aryl chloride (Table 1, entries 7–9): $Pd(OAc)_2$ was optimal for the aryl chloride, whereas $Pd(dba)_2$ was optimal for the aryl bromide. Further investigation revealed that the optimal palladium sources were $Pd(dba)_2$ for the aryl triflate, and $Pd(OAc)_2$ for the tosylate and the mesylate. The catalyst loading could be reduced to 5 mol % (Table 1, entries 10 and 11). As the base, Cs_2CO_3 and Na_2CO_3 gave similar yields of **5** (Table 1, entry 12). For subsequent reactions, we selected Na_2CO_3 because it gave a better yield in the one-pot deamidation reaction.

Next, we used the optimized reaction conditions for the direct synthesis of phthalamic acid derivatives from aryl and heteroaryl halides using an amount (1.5 equiv) of

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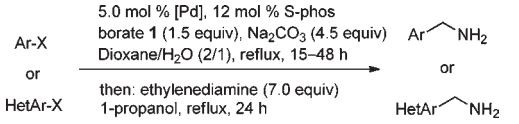
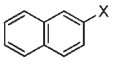
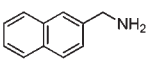
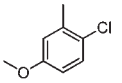
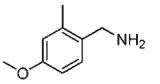
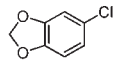
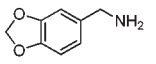
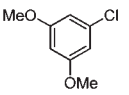
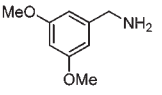
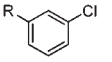
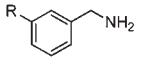
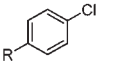
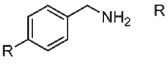
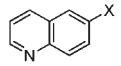
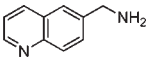
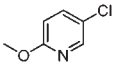
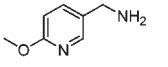
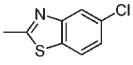
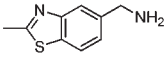
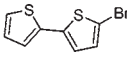
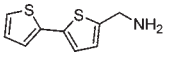
Table 3. One-Pot Primary Aminomethylation of Aryl and Heteroaryl Halides and Triflates[a]

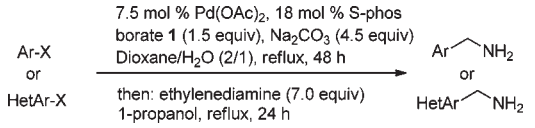


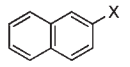
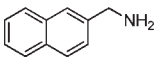
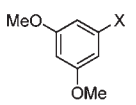
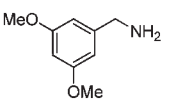
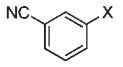
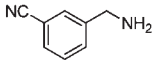
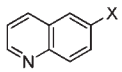
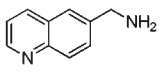
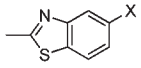
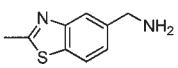
entry	substrate	product		method[b]		isolated yield (%)
1			X = Cl	A		85
			Br	B		79
			I	B	**7a**	53
			OTf	B		74
2				A	**7b**	85
3				A	**7c**	89
4				A	**7d**	91
5			R = CN	A	**7e**	81
			NO_2	A	**7f**	83
6			R = COMe	A	**7g**	67
			CO_2Me	A	**7h**	<1 (70[c])
7			X = Cl	A		81
			Br	B	**7i**	78
			OTf	B		76
8				A	**7j**	61[d]
9				A	**7k**	83
10				B	**7l**	57

[a] Reaction conditions: 1.0 equiv of substrate, 5 mol % of [Pd], 12 mol % of S-phos, 1.5 equiv of borate **1**, 4.5 equiv of Na_2CO_3, dioxane/H_2O (2/1), reflux; then 7.0 equiv of ethylenediamine and 1-propanol were added, and the mixture was stirred at reflux for 24 h. [b] Method A: [Pd] = $Pd(OAc)_2$. Method B: [Pd] = $Pd(dba)_2$. [c] 7.0 equiv of ethylenediamine and *t*-BuOH was added after isolation of phthalamic acid **6d**; then the reaction mixture was stirred at reflux for 24 h. [d] 10 mol % of $Pd(OAc)_2$ and 24 mol % of S-phos.

borate **1** that was sufficient to give high reproducibility (Table 2). Aldehyde, ester, and cyano groups were compatible with the reaction conditions (Table 2, entries 2 and 3). Moreover, heteroaryl halides containing thiophene and pyridine rings were converted to the corresponding phthalamic acids in 62% and 42% yields, respectively (Table 2, entries 4 and 5).

Table 4. One-Pot Primary Aminomethylation of Aryl and Heteroaryl Mesylates and Tosylates[a]



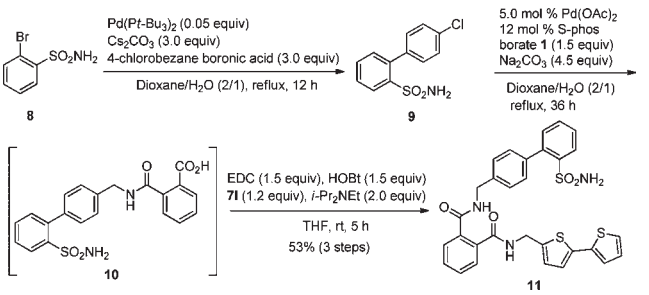
entry	substrate	product		isolated yield (%)	
1			X = OTs	**7a**	85
			OMs		80
2			X = OTs	**7d**	80
			OMs		70
3			X = OTs	**7e**	45
			OMs		35
4			X = OTs	**7i**	73
			OMs		71
5			X = OTs	**7k**	75
			OMs		70

[a] Reaction conditions: 1.0 equiv of substrate, 7.5 mol % of $Pd(OAc)_2$, 18 mol % of S-phos, 1.5 equiv of borate **1**, 4.5 equiv of Na_2CO_3, dioxane/H_2O (2/1), reflux, 48 h; then 7.0 equiv of ethylenediamine and 1-propanol were added, and the mixture was stirred at reflux for 24 h.

Next, we optimized the conditions for the primary aminomethylation of aryl halides via the one-pot deamidation of *N*-(arylmethyl)phthalamic acid. We found that the addition of an alcohol as a cosolvent was necessary for the one-pot deamidation reaction. 1-Propanol was optimal because the reflux temperature of the reaction mixture was higher than that with methanol or 2-methyl-2-propanol, and the higher temperature promoted the deamidation reaction. Ethylenediamine was selected as the amine because it is more reactive and safer than hydrazine, which we used previously.[8a]

We used the optimized primary aminomethylation conditions for reactions of various aryl and heteroaryl halides and triflates (Table 3). 2-Naphthyl chloride, bromide, and triflate were converted to **7a** in yields ranging from 71% to 85%, whereas the yield from the iodide was slightly lower (53%; Table 2, entry 1). The electron density of the benzene ring had little effect on the yield (Table 3, entries 2–6). The reaction conditions were compatible with cyano, nitro, and ketone functional groups. To our surprise, an ester group remained intact as long as the reaction was conducted by a stepwise process involving the isolation of phthalamic acid **6d** followed by deamidation with ethylenediamine in 2-methyl-2-propanol (Table 3, entry 6). The primary aminomethylation of heteroaryl halides and triflates proceeded smoothly to afford the desired primary aminomethyl compounds in moderate to good yields (Table 3, entries 7–10).

Scheme 2. Concise Synthesis of Sodium Channel Blocker **11**



To explore the scope of the reaction, we examined the primary aminomethylation of aryl and heteroaryl mesylates and tosylates (Table 4). As we expected, we obtained primary aminomethyl compounds in yields ranging from 35% to 85% (Table 4, entries 1–5).

To demonstrate the utility of these methods for medicinal chemistry, we used them to synthesize sodium channel blocker **11**[10c] (Scheme 2). We synthesized **11** in fewer than the eight or nine reaction steps required for the previously reported synthesis.

In summary, we developed two versatile synthetic methods involving sodium phthalimidomethyltrifluoroborate (**1**): (i) a one-pot primary aminomethylation of aryl and heteroaryl halides, triflates, mesylates, and tosylates and (ii) a direct synthesis of *N*-(arylmethyl)phthalamic acids from aryl and heteroaryl halides. Moreover, we used the methods for a concise synthesis of a bioactive compound **11**.

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Supporting Information Available. Experimental procedures and spectral data for relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.