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Metal-Free *Ortho* C–H Borylation of 2-Phenoxypyridines under Mild Conditions

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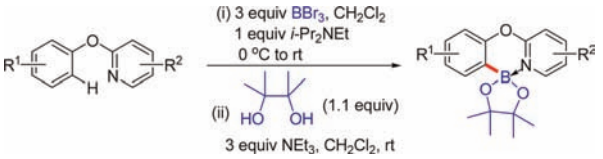
ABSTRACT



An efficient metal-free ortho C–H borylation has been developed via sequential borylation of substituted 2-phenoxypyridines with BBr_3 following esterification with pinacol. The corresponding aryl boronates were obtained in good yields. The synthesized aryl boronates can be easily transformed into various useful products. Therefore, the present method makes functionalizations of aryl C–H bonds easy.

Arylboronic acids and their derivatives are versatile reagents in modern organic synthesis because they are air stable and are readily transformed into other desired products.[1] On the other hand, intramolecular complexes of nitrogen-containing π-conjugated molecules with N–B coordination have gained increasing attention from the viewpoint of development of new π-electron materials.[2] Traditional methods for preparation of the boron compounds use the reactions of either organolithium or magnesium reagents with boron electrophiles, but they have a problem with functional-group compatibility. Later, various alternative approaches to aryl boronates were developed. Transition-metal-catalyzed, such as Pd-,[3] Ni-,[4] or Cu-catalyzed,[5] borylation of aryl halides is a popular strategy. Recently, the direct functionalization of unreactive C–H bonds has emerged as a very active field in organic synthesis.[6] The borylation of arene C–H bonds has also been developed under catalysis of transition-metal catalysts, especially iridium catalysts,[7,8] and the iridium-catalyzed regioselectivity is typically driven by steric

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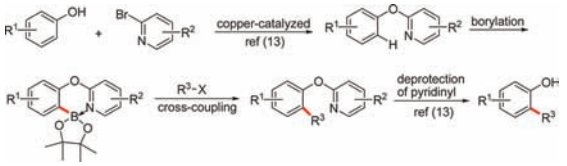
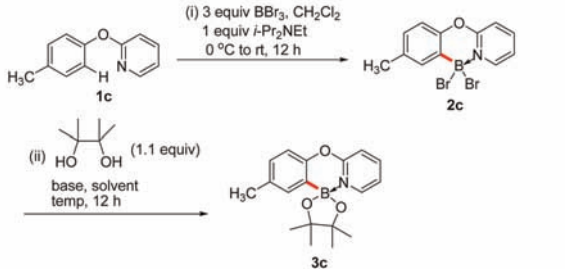


Figure 1. Our strategy for synthesis of various phenol derivatives through key C−H borylation.

factors.[9] The direct arene borylation by electrophilic substitution with Friedel−Crafts chemistry is rare,[10] although the strategy has been reported previously.[11] $AlCl_3$ as the Lewis acid is often required. Since phenol derivatives widely occur in natural products, biologically active molecules, and chemical products,[12] it is highly desired to develop a practical and efficient approach to diverse phenol derivatives.

In this paper, we report a novel strategy for synthesis of phenol derivatives as shown in Figure 1. 2-Phenoxypyridine derivatives are readily prepared via copper-catalyzed coupling of substituted phenols with pyridines.[13] Metal-free *ortho* C−H borylation of 2-phenoxypyridines under mild conditions leads to 2-phenoxypyridine boronates, and the aryl boronates are further transformed into various valuable compounds through cross-coupling and deprotection of pyridinyl. As shown in Table 1, borylation of 2-(*p*-tolyloxy)pyridine (**1c**) was chosen as the model reaction. The whole procedure undergoes sequential two-step couplings: metal-free pyridine-directing C−H borylation of **1c** gives a 2-(*p*-tolyloxy)pyridine−dibromoborane complex (**2c**), and esterification of **2c** with pinacol provides 2-(4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenoxy)pyridine (**3c**). In part A of Table 1, borylation conditions of 2-(*p*-tolyloxy)pyridine (**1c**) with BBr_3 was

Table 1. Borylation of 2-(*p*-Tolyloxy)pyridine (**1c**) with BBr_3 and Pinacol to 2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine (**3c**)[a]



A. Borylation of 2-(*p*-Tolyloxy)pyridine (**1c**) with BBr_3

entry	BBr_3 (equiv)	base	solvent	yield[b] (%)
1	BBr_3 (3)	Et_3N	CH_2Cl_2	75
2	BBr_3 (3)	K_2CO_3	CH_2Cl_2	45
3	BBr_3 (3)	pyridine	CH_2Cl_2	trace
4	**BBr_3 (3)**	**iPr_2NEt**	**CH_2Cl_2**	**90**
5	BBr_3 (3)	iPr_2NEt	dioxane	55
6	BBr_3 (3)	iPr_2NEt	DMF	10
7	BBr_3 (2)	iPr_2NEt	CH_2Cl_2	45
8	BBr_3 (1)	iPr_2NEt	CH_2Cl_2	11

B. Borylation of 2-(*p*-Tolyloxy)pyridine (**1c**) with BBr_3 and Pinacol Leading to 2-(4-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine (**3c**)

entry	base	solvent	temp (°C)	yield[c] (%)
9	K_2CO_3	CH_2Cl_2	25	trace
10	K_3PO_4	CH_2Cl_2	25	15
11	pyridine	CH_2Cl_2	25	38
12	2,6-lutidine	CH_2Cl_2	25	40
13	**Et_3N**	**CH_2Cl_2**	**25**	**70**
14	iPr_2NEt	CH_2Cl_2	25	60
15	Et_3N	EtOAc	25	10
16	Et_3N	THF	25	15
17	Et_3N	$CHCl_3$	25	55
18	Et_3N	CH_3CN	25	18
19	Et_3N	CH_2Cl_2	0	35
20	Et_3N	CH_2Cl_2	50	20

[a] Reaction conditions: 2-(*p*-tolyloxy)pyridine (**1c**) (1 mmol), BBr_3 (3 mmol), base (3 mmol), solvent (4 mL) under nitrogen atmosphere. Reaction time (12 h). [b] Isolated yield from **1c** to **2c**. [c] Isolated yield (total yield from **1c** to **3c**).

first investigated. We attempted various bases using 3 equiv of BBr_3 as the borylating agent in CH_2Cl_2 under nitrogen atmosphere (entries 1−4), and i-Pr_2NEt provided the highest yield (entry 4) (see the Supporting Information for the workup procedure). Pure 2-(*p*-tolyloxy)pyridine−dibromoborane complex (**2c**) was obtained by crystallization in CH_2Cl_2/hexane, and its structure was confirmed by ^1H and ^{13}C NMR and EI-MS. Other solvents were also used (entries 5 and 6), and CH_2Cl_2 proved to be a suitable solvent (compare entries 4−6). The amount of BBr_3 was changed (entries 7 and 8), and 3 equiv of BBr_3 gave the best result (entry 4). In order to reduce the loss of **2c** during crystallization, we used crude product **2c** to optimize conditions of esterification including bases, solvents, and temperature as

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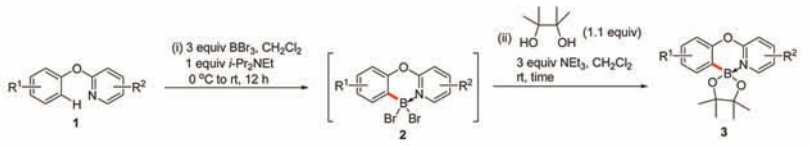
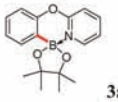
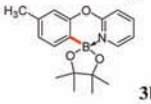
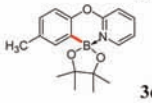
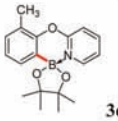
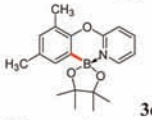
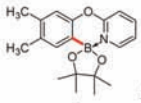
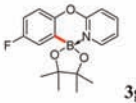
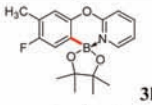
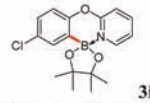
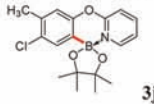
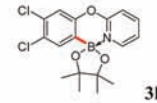
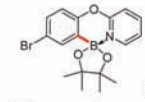
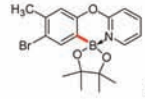
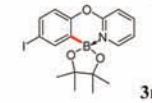
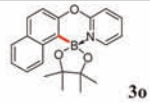
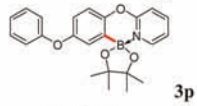
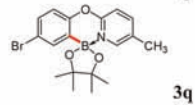
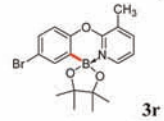
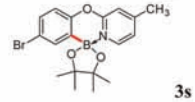
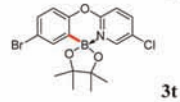
Table 2. Borylation of Substituted 2-Phenoxypyridines[a]



entry	time (h)	3	yield (%)[b]
1	12	 **3a**	70
2	8	 **3b**	75
3	5	 **3c**	89
4	9	 **3d**	70
5	11	 **3e**	60
6	10	 **3f**	65
7	8	 **3g**	72
8	9	 **3h**	70
9	6	 **3i**	78
10	7	 **3j**	73
11	8	 **3k**	79
12	6	 **3l**	80
13	8	 **3m**	76
14	5	 **3n**	86
15	9	 **3o**	72
16	6	 **3p**	85
17	8	 **3q**	75
18	9	 **3r**	77
19	9	 **3s**	81
20	10	 **3t**	73

[a] Reaction conditions: substituted 2-phenyloxypyridine (**1**) (1 mmol), BBr_3 (3 mmol), *i*-Pr_2NEt (1 mmol), NEt_3 (3 mmol), CH_2Cl_2 (4 mL for two steps) under nitrogen atmosphere. Reaction time (12 h for borylation; 5−12 h for esterification). [b] Isolated yield (total yield from **1** to **3**).

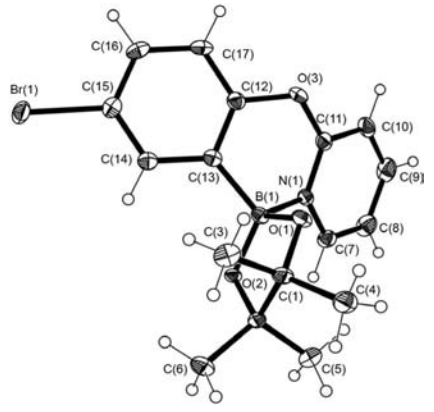


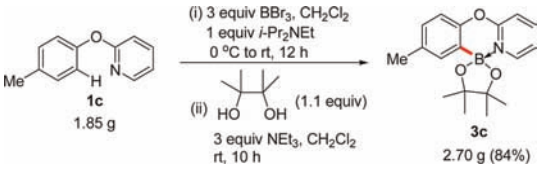
Figure 2. Crystal structure of compound **3l**.

shown in part B of Table 1 (see the Supporting Information for details). Various bases were screened in CH_2Cl_2 under nitrogen atmosphere (entries 9−14), and NEt_3 provided the highest yield (entry 13). The effect of solvents was investigated (compare entries 13 and 15−18), and CH_2Cl_2 gave the best result (entry 13). Different reaction temperatures were attempted (compare entries 13, 19, and 20), and 25 °C was a suitable temperature.

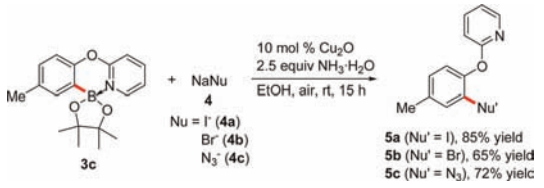
With these optimized conditions in hand, we investigated the substrate scope of this borylation reaction. As shown in Table 2, the examined substrates provided good yields for the sequential two-step process: borylation and esterification. Arenes with mono- or dimethyl gave yields between 60 and 89% yield (entries 2−6, 8, 10, 13, and 17−19). Borylation of halogenated (F, Cl, Br, and I) arenes performed well to give the corresponding products in yields of 70−86% yield (entries 7−14, 17−20), and the arenes containing both boronate and halogens provided further opportunity for synthesis of diverse molecules. A good yield (72%) was afforded with a naphthalene substrate (entry 15). The borylation reaction showed high monoselectivity, and no diborylated products were observed.

In order to identify structures of the newly synthesized 2-phenoxypyridine boronates (**3**), we prepared a single crystal of **3l**, and its structure was unambiguously confirmed by X-ray diffraction (Figure 2) (see the Supporting Information for details). The results show a clear N−B coordination (distance N(1)−B(1) = 1.663(3) Å).

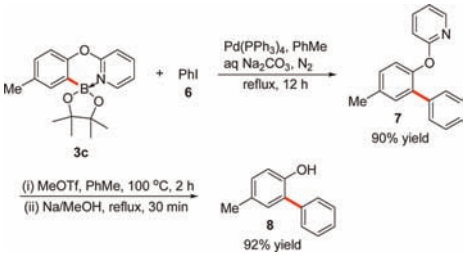
Scheme 1. Borylation of **1c** Leading to **3c** on Gram Scale



Scheme 2. Copper-Catalyzed Functionization of **3c** under Mild Conditions



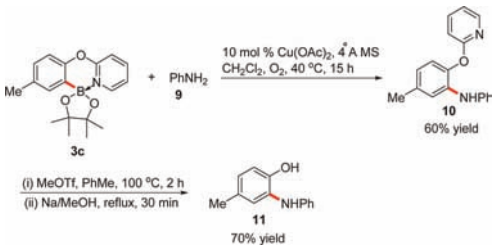
Scheme 3. Suzuki Coupling of **3c** with 1-Iodobenzene and Deprotection of Pyridyl Group



Further, we explored the utility of this borylation method. As shown in Scheme 1, this borylation reaction of **1c** on gram scale worked well under the standard conditions, and the reaction afforded **3c** in 84% yield (Scheme 1). Subsequently, copper-catalyzed iodination, bromination, and azidonation of **3c** were performed at room temperature according to the previous methods,[14] and the corresponding products containing iodo, bromo, azido groups were obtained in good yields (Scheme 2). The results showed that the direct C−H bond borylation of arenes was particularly valuable.

The 2-arylphenol unit is a key structural motif[15] found in important natural products, medicinal targets,[16] and privileged ligands.[17] We used 2-(4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine (**3c**) as the starting material, palladium-catalyzed Suzuki coupling

Scheme 4. Amination of **3c** and Deprotection of Pyridyl Group



of **3c** with 1-iodobenzene yielded **7**,[18] and easy deprotection of **7** provided 2-phenylphenol derivative (**8**) in high yield according to the reported procedure (Scheme 3).[13]

We also attempted copper-catalyzed coupling of **3c** with phenylamine via the Chan−Lam−Evans amination strategy,[8,19] and the amination provided **10** in 60% yield. Deprotection of the pyridyl group in **10** gave 4-methyl-2-(phenylamino)phenol (**11**) using the similar procedure.[13] The *o*-aminophenol derivatives are important intermediates of biologically active molecules,[20] so the present method is an efficient strategy for the synthesis of *o*-aminophenol derivatives (Scheme 4).

In summary, we have developed a simple and efficient metal-free *ortho* C−H borylation of 2-phenoxypyridines. The borylation protocol uses readily available 2-phenoxypyridines as the starting materials, inexpensive BBr_3 as the borylating reagent, and cheap pinacol as the esterifying agent. The corresponding aryl boronates were obtained in good yields. The synthesized aryl boronates are versatile intermediates in modern organic synthesis, and they can be readily transformed into various useful products. Therefore, the present method makes functionalizations of phenol-directing C−H bonds easy. The convenient and efficient approach will attract much attention in academic and industrial fields.

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Supporting Information Available. Synthetic procedures, characterization data, X-ray diffraction data for crystal of compound **3l**, and ^1H and ^{13}C NMR spectra for these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

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The authors declare no competing financial interest.