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Direct Conversion of Arylamines to Pinacol Boronates: A Metal-Free Borylation Process**

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Arylboronic acids or arylboronates have found widespread applications in transition-metal-catalyzed C−C bond forming reactions, as represented by the Suzuki–Miyaura cross-coupling reaction.[1] These applications have created an increasing demand for various boronic acids and esters.[2] The most commonly utilized method to prepare these boron compounds is the reaction of aryl Grignard reagents or aryllithium reagents with trialkyl borates followed by hydrolytic workup.[3] This traditional approach, although still widely used, suffers some obvious drawbacks such as rigorous anhydrous conditions and narrow functional group compatibility. In 1995, Miyaura and co-workers reported a Pd-catalyzed cross coupling of arylbromides or iodides with a diboron pinacol (pin).[4] The favorable tolerance of this method to a variety of functional groups means that it is now well-established as a complementary route to arylboronates.[5–8] In addition to these two important methods, it should be mentioned that great efforts have been made in transition-metal-catalyzed direct borylation of aromatic C−H bonds.[9,10]

Arylamines are cheap and abundant starting materials, which are easily available from arenes through nitration and subsequent reduction. The aromatic amino group can be converted into various functional groups by the Sandmeyer reaction.[11] The standard procedure for converting arylamines to arylboronic acids or boronates would need two steps, namely a Sandmeyer reaction to convert the amino group into a halogen group, followed by use of a Grignard reagent or a Pd-catalyzed borylation. Although the two-step procedure is highly reliable and widely used in organic synthesis, the combination of these reactions in the conversion of arylamines to arylboronates is usually not very efficient because of the generally low-yielding and tedious separation procedures required. Moreover, metals that might contaminate the final boron products and cause environmental problems in large-scale production are inevitably involved in these steps. In this context, the direct borylation of arylamines to arylboronates would be highly desirable. Herein, we describe a novel method for the synthesis of arylboronates by the reaction of the diboron pinacol ester B_2pin_2 with arylamines in the presence of *tert*-butyl nitrite. The reaction is metal-free and can be carried out under air at room temperature.

The Sandmeyer reaction is a classic reaction in which an aromatic amino group is replaced with a halogen,[12] as well as with other groups such as hydrogen,[13] hydroxy,[14] cyano,[15] and azido[16] groups. Diazonium ions are the common intermediates in these synthetically very useful transformations. In view of the diversity of transformations that occur via diazonium ions, we hypothesized that it might be possible to replace an aromatic amino group with a boron group under Sandmeyer reaction conditions. To the best of our knowledge, this type of transformation has not been reported to date. After some initial attempts, it was concluded that *tert*-butyl nitrite (*t*BuONO, **3**) was a suitable diazotization agent for this transformation.[17] Thus, a solution of aniline **1a**, B_2pin_2 **2**, and *t*BuONO **3** in acetonitrile was heated at 60°C for 1 h. To our delight, phenylboronate **4a** was formed in 40% yield as shown by GC–MS analysis (Table 1, entry 1). Encouraged by this initial result, we further proceeded to optimize the reaction conditions.

Initially, we explored the use of additives that could promote this transformation. Possible additives include KOAc (Table 1, entry 2), which may accelerate *trans*-borylation of B_2pin_2,[4] and metal salts (Table 1, entries 3–6), which may speed up the decomposition of the phenyldiazonium ion.[11b] However, the reaction was not significantly improved by these additives. Notably, Cu^I and Cu^{II} salts, which are commonly used in the classic Sandmeyer reaction, afforded **4a** in only 8% and 7% yields, respectively (Table 1, entries 3,4). In both cases, diphenylamine was the major product. It was noted that use of $Fe(OAc)_2$ significantly improved the yield (Table 1, entry 6). As it is suggested that the Sandmeyer reaction proceeds by a radical mechanism,[11b,18] the radical initiators 2,2'-azobisisobutyronitrile (AIBN) and benzoyl peroxide (BPO) were introduced into the reaction mixture in subsequent experiments. It was indeed observed that higher yields could be obtained in the presence of these radical initiators (Table 1, entries 7–13). Furthermore, when BPO was used as an additive, the reaction could be carried out at room temperature with improved yields, although the reaction time was extended from 1 to 3 hours

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Table 1: Reaction of aniline **1a**, B_2pin_2 **2**, and *t*BuONO **3**.[a]

$$\underset{\mathbf{1a}}{Ph{-}NH_2} + \underset{\mathbf{2}}{B_2pin_2} + \underset{\mathbf{3}}{tBuONO} \longrightarrow \underset{\mathbf{4a}}{Ph{-}Bpin}$$

Entry	Ratio (**1a**/**2**/**3**)	Solvent	Additive [mol %]	*T* [°C]	Yield [%][b]
1	1:1:1	MeCN	none	60	40
2	1:1:1	MeCN	KOAc (100)	60	30
3	1:1:1	MeCN	$CuPF_6(MeCN)_4$ (100)	60	8
4	1:1:1.5	MeCN	$Cu(OAc)_2$ (100)	60	7
5	1:1.2:1.5	MeCN	$SnCl_2$ (100)	60	29
6	1:1.2:1.5	MeCN	$Fe(OAc)_2$ (100)	60	62
7	1:1:1	MeCN	BPO (10)	60	49
8	1:1:1	MeCN	AIBN (10)	60	47
9	1:1.2:1.5	MeCN	BPO (10)	60	57
10	1:1.2:1.5	MeCN	BPO (10)	RT	66
11	1:0.5:1.5	MeCN	BPO (10)	RT	11
12	1:1.1:1.5	MeCN	BPO (5)	RT	70
13[c]	**1:1.1:1.5**	**MeCN**	**BPO (2)**	**RT**	**77**
14	1:1.1:1.5	CH_2Cl_2	BPO (2)	RT	49
15	1:1.1:1.5	dichloroethane	BPO (2)	RT	65
16	1:1.1:1.5	toluene	BPO (2)	RT	65
17	1:1.1:1.5	EtOAc	BPO (2)	RT	66

[a] Reaction conditions: aniline **1a** (1 mmol), solvent (3 mL). Reaction time: 1 h for 60°C; 3 h for RT. [b] GC–MS yield with mesitylene (1 mmol) as internal standard. [c] The entry in bold represents the optimized reaction conditions.

(Table 1, entries 9, 10). The optimized reaction conditions use only 2 % of BPO to afford a yield of 77 % (Table 1, entry 13). Finally, it was observed that the reaction was marginally affected by solvents (Table 1, entries 14–17).

A series of arylamines were then subjected to the optimized reaction conditions (Table 2). All of the reactions were complete within 2 hours, and afforded the corresponding arylboronates in moderate to good yields. The reaction occurred smoothly with *para*- and *meta*-substituted arylamines, while the reactions with *ortho*-substituted arylamines gave lower yields or only trace amounts of product in the case of *o*-nitroaniline (Table 2, entries 8, 11, 22). This result might be attributed to steric hindrance of the *ortho* substituent. In general, substrates with electron-withdrawing groups at the *meta* and *para* positions exhibit good reactivity (Table 2, entries 1, 3, 5, 6, 9, 10, 13, 14, 20). Substrates with an electron-donating group at the *para* position gave trace amounts or even no products. These results indicate that this reaction is significantly affected by steric and electronic effects of the substituents. Finally, it was worth noting that substrates bearing halo substituents could also be employed in this reaction, although the yields were slightly reduced (Table 2, entries 15–19).

The chromatographic separation of arylboronate products is usually tedious and in some cases the boron products are not stable. Therefore, it is desirable to develop procedures that can combine both borylation and the subsequent Suzuki–Miyaura coupling into a one-pot reaction.[9b,10u,v] We subse-

Table 2: Reaction of arylamines **1b–w**, B_2pin_2 **2**, and *t*BuONO **3**.

$$\underset{\mathbf{1b{-}w}}{ArNH_2} + \underset{\mathbf{2}}{B_2pin_2} + \underset{\mathbf{3}}{tBuONO} \xrightarrow[\text{MeCN, RT}]{\text{BPO (2 mol\%)}} \underset{\mathbf{4b{-}w}}{Ar{-}Bpin}$$

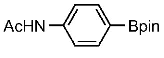
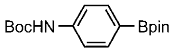
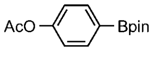
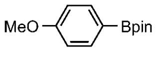
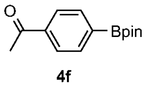
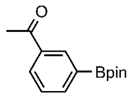
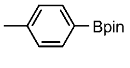
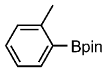
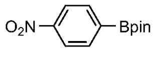
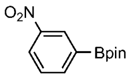
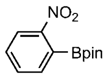
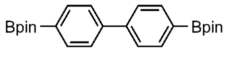
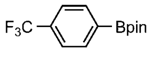
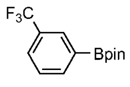
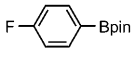
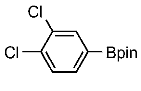
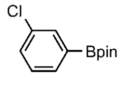
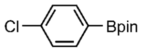
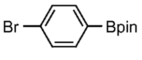
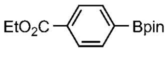
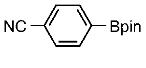
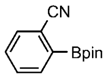
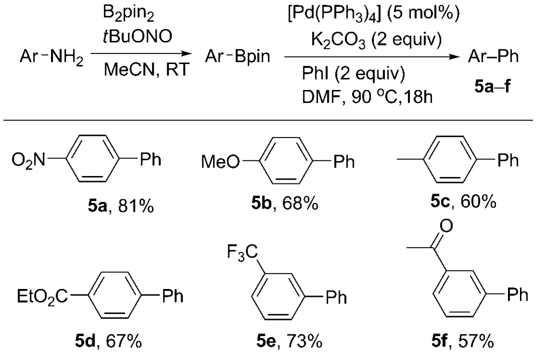
Entry	*t* [h]	Product **4b–w**		Yield [%][a]
1	2	 **4b**	**4b**	93
2	2	 **4c**	**4c**	70
3	2	 **4d**	**4d**	73
4	2	 **4e**	**4e**	72
5	1	 **4f**	**4f**	67
6	2	 **4g**	**4g**	65
7	1	 **4h**	**4h**	66
8	2	 **4i**	**4i**	53
9	1	 **4j**	**4j**	91
10	1	 **4k**	**4k**	62
11	1	 **4l**	**4l**	trace[b]
12[c]	2	 **4m**	**4m**	55
13	2	 **4n**	**4n**	75
14	2	 **4o**	**4o**	82
15	2	 **4p**	**4p**	54
16	2	 **4q**	**4q**	54

Table 2: (Continued)

Entry	*t* [h]	Product **4b–w**		Yield [%][a]
17[d]	2	 **4r**	**4r**	56
18[d]	2	 **4s**	**4s**	30
19[d]	1	 **4t**	**4t**	30
20	2	 **4u**	**4u**	82
21	1	 **4v**	**4v**	41
22	1	 **4w**	**4w**	22

[a] Yields after isolation by column chromatography. [b] The reaction gave a complex mixture with a trace amount of **4l**. [c] Benzidine was used as the substrate with B_2pin_2 (2.2 equiv) and *t*BuONO (3 equiv). [d] Reaction was carried out at 60°C with 10% BPO and 1.2 equiv of B_2pin_2.

quently investigated the compatibility of our borylation conditions with the conventional Suzuki–Miyaura coupling conditions. As demonstrated by the examples summarized in Scheme 1, the borylation and Pd-catalyzed coupling can be carried out without chromatographic separation of the arylboronate intermediates. In a typical experiment, the arylamine was first converted into the corresponding arylboronate under the standard conditions described above. The reaction mixture was then decolorized by addition of activated charcoal and filtered though celite. The crude product was then subjected to the standard Suzuki–Miyaura cross-coupling with iodobenzene. This two-step reaction afforded satisfactory yields.



Scheme 1. Sequential borylation and Pd-catalyzed reactions.

The mechanism of this novel metal-free borylation process is not yet clear, but some preliminary observations are included here.[19] When the borylation was carried out in the presence of 1.5 equivalents of the radical scavenger 2,2,6,6-tetramethyl-1-piperidin-1-oxyl (TEMPO), the reaction became sluggish and phenylboronate was formed in only 8% yield after 4 h, thus indicating a possible radical process, as a control experiment demonstrated that TEMPO does not react directly with B_2pin_2 under these conditions. To further substantiate the possible radical process, a 1:1 mixture of BPO and B_2pin_2 was heated in MeCN at 100 8C for 1 hour. The phenylboronate was isolated in 37% yield [Eq. (1)]. Since BPO decomposes to give the phenyl radical at temperatures higher than 100 8C, this experiment provides supportive evidence for radical mechanism.

$$\underset{\text{1 equiv}}{(PhCOO)_2} + \underset{\text{1 equiv}}{B_2pin_2} \xrightarrow[\text{100 °C, 4h}]{\text{MeCN}} \underset{37\%}{\text{PhBpin}} \qquad (1)$$

However, when the phenyl radical was generated in an alternative process (PhI, Bu_3SnH, and AIBN),[20] and was allowed to react with B_2pin_2, the PhBpin product was formed only in 7% yield. Moreover, mechanisms involving direct homolytic substitution (an S_H2 process) of the boron compounds by aryl radicals do not seem likely.[21–23] Detailed mechanistic investigations are in progress and will be reported in due course.

In conclusion, we have developed an entirely new approach to the synthesis of arylboronates. The advantages of this method can be summarized as follows: 1) the starting arylamines are inexpensive and readily available; 2) the reaction is metal-free reaction, thus avoiding possible metal contamination of the boron product; 3) the conditions are mild and the reaction can be carried out under air at room temperature; 4) the boronate product can be used in subsequent Pd-catalyzed Suzuki–Miyaura couplings without purification. Consequently, this method serves as an important supplement to the existing methods of arylboronate synthesis.

Experimental Section

Typical procedure for the reaction of aryl amines **1a–w**, B_2pin_2 **2**, and *t*BuONO **3**: B_2pin_2 (1 mmol, 254 mg) and BPO (0.02 mmol, 5 mg) were weighed in a 25 mL round-bottom flask. MeCN (3 mL), arylamines (1 mmol), and *t*BuONO (1.5 mmol, 154 mg) were then added in succession. The resulting reaction mixture was allowed to stir for 1–2 h at room temperature. The solution was then concentrated under reduced pressure and the residue was purified by flash column chromatography.

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