Methanol-Promoted Borylation of Arylamines: A Simple and Green Synthetic Method to Arylboronic Acids and Arylboronates

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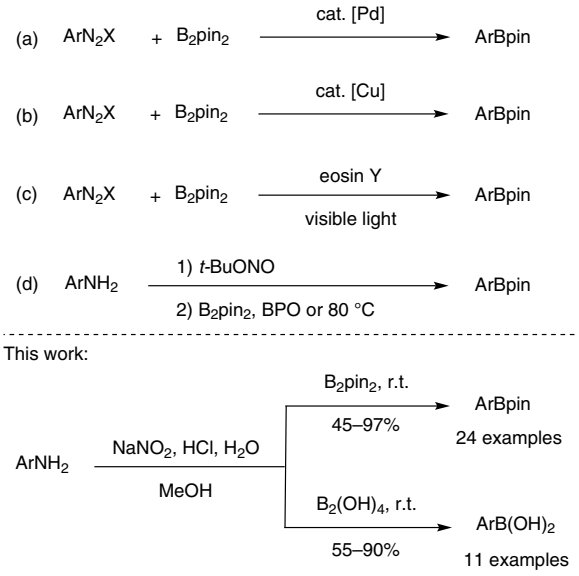
Abstract: A Sandmeyer borylation of arylamines via a SN_2Ar pathway promoted by methanol with sodium nitrite and hydrochloric acid as diazotization agent has been developed, which provide a simple and green synthetic method to arylboronic acids and arylboronates.

Key words: methanol, borylation, arylamines, arylboronic acids, arylboronates, diazotization

Arylboronic acids and boronates are useful building blocks in transition-metal-catalyzed cross-coupling reactions due to their low toxicity and high stability.[1,2] Generally, the reaction of Grignard or lithium reagents with trialkyl borates are the general synthetic routes.[3] Unfortunately, these methods have low functional-group compatibility because of the strong nucleophilicity of the reagents. The borylation of aryl halides[4] and arenes via C–H activation[5,6] catalyzed by transition metals have been developed as complementary synthetic methods, which show high functional-group tolerance. In addition, Lewis acid catalyzed electrophilic borylation of electron-rich arenes[7] and an alkoxy base promoted nucleophilic borylation of organic halides[8] provide useful transition-metal-free methods for the preparation of arylboronic acids and boronates, which avoid the high process cost and heavy-metal impurities in the final products.

Aryldiazonium salts are as commonly used as surrogates of aryl halides due to their rich reactivity and diverse transformations.[9,10] The borylation of arene diazonium salts catalyzed by transition metals[11] or by eosin Y under visible light promoted photoredox catalysis[12] provide an useful approach toward arylboronic ester synthesis (Scheme 1). Very recently, Wang reported a Sandmeyer-type borylation of arylamines by direct conversion of the amino group of aniline derivatives into the boronate group, which provide an entirely different approach toward arylboronate synthesis.[13] However, it is worth noting that arylboronic acids could not be synthesized with this method,[14] and radical initiators, high temperature, or diazotization agent *tert*-butyl nitrite (*t*-BuONO) are necessary for the synthesis of pinacol arylboronates. In continuing our recent work in aryldiazonium salts chemistry,[15] we would like to report a methanol-promoted Sandmeyer borylation of arylamines via a SN_2Ar pathway at room temperature with sodium nitrite and hydrochloric acid as diazotization agent, affording arylboronic acids and esters with high yields.



Scheme 1 The borylation of arene diazonium salts or arylamines

The most common method for the preparation of diazonium salts is the treatment of aromatic amines with nitrous acid. Usually, the nitrous acid is generated in situ from sodium nitrite and mineral acid.[16] Following this standard method, in our initial investigations, we focused on the direct borylation of 4-toluidine (**1a**) with sodium nitrite and hydrochloric acid as diazotization agent in the first step, and bis(pinacolato)diboron was utilized as boron source in the second step. The results shown in Table 1 reveal that solvent is vital to this transformation. For nonprotonic solvents, except for ethyl acetate, all gave no reaction within one hour at room temperature (Table 1, entries 1–9). To our delight, when protic solvents such as AcOH and MeOH were used, the yields increased to 50% and 74% under identical conditions, respectively (Table 1, entry 10). Other alcohols except for ethylene glycol and glycerin, ethanol, *tert*-butanol, 2-methoxyethanol, trifluoroethanol, and 2-PrOH, all afforded the borylation products,

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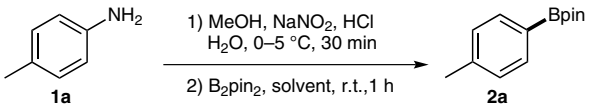
albeit with low yields (Table 1, entries 13–17). Further optimization was seen by changing the amount of B_2pin_2. The use of one and two equivalents of B_2pin_2 resulted in the borylation product **2a** with 38% and 60% yield at room temperature (Table 1, entry 18). However, the addition of four equivalents of B_2pin_2 to the reaction did not improve the isolated yield (Table 1, entry 20).

With the optimal conditions in hand, the substrate scope was subsequently investigated.[17] First, a wide range of aryl amines **1** with substitutes, such as alkyl, OMe, NO_2, COOEt, Br, CN, Cl, F, I, CN, NH_2, OCF_3, and OH in the phenyl, underwent coupling with B_2pin_2 (**2**) at ambient temperature, and the desired products were isolated in good yields. The results shown in Table 2 indicate that aryl amines with electron-withdrawing or electron-donating substituents all could give the desired products with good yields. The borylation showed good tolerance to various functional groups on the aryl amines such as OH, CO_2Et, CN, CX (X = F, Cl, Br, and I) under the reaction conditions, and excellent yields were achieved for the reactions (**2d**–**m**). Notably, the amine group could be transformed to the boronate group selectively simply by controlling the amount of hydrochloric acid and sodium nitrite. For the substrate *p*-phenylenediamine, the desired monoamine and monoproduct **2l** could be obtained with 53% yield without protection of the amino group. At the same time, for the substrate 4,4′-diaminobiphenyl, the desired diboronate product **2x** is obtained with 75% yield by doubling the amount of hydrochloric acid and sodium nitrite. Disubstituted aromatic amines were also tested, giving good yields (Table 2, 2u,v). The substrate scope could also be extended to amines with a naphthyl ring or biphenyl (Table 2, 2w–x). All these arylboronates have found widespread applications in organic synthesis, as represented by the Suzuki–Miyaura cross-coupling reaction. In addition, bis(neopentyl glycolato)diboron can play the same role that react with arylamine at the same reaction conditions. As shown in Scheme 2, the desired borylated product **4a** could be obtained with 65% isolated yield (Scheme 2), which suggested its potential application for the preparation of arylboronates.

In the next step, we apply our process toward the synthesis of arylboronic acids with tetrahydroxydiboron [$B_2(OH)_4$] as boron source.[14] A wide range of aryl amines **1** with substitutes, such as alkyl, OMe, F, Cl, Br, NO_2, and COOEt in the phenyl, underwent coupling with $B_2(OH)_4$ at ambient temperature, and the desired products were isolated in good yields. The results shown in Table 3[19] indicate that aryl amines with electron-withdrawing or electron-donating substituents all could give the desired products with good yields. Likewise, this borylation showed good tolerance to various functional groups on the aryl amines such as CO_2Et, NO_2, CX (X = F, Cl, Br) under the reaction con-

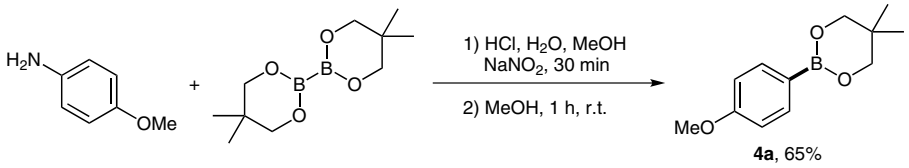
Table 1 Optimization of the Cross-Coupling of Amine with Bis(pinacolato)diboron[a]



1a **2a**

Entry	Solvent	Yield (%)[b]
1	CH_2Cl_2	trace
2	EtOAC	22
3	MeCN	trace
4	acetone	trace
5	THF	trace
6	toulene	trace
7	DMF	trace
8	DMSO	trace
9	AcOH	50
10	MeOH	74
11	ethylene glycol	trace
12	glycerin	trace
13	EtOH	51
14	Me_3COH	47
15	2-methoxyethanol	25
16	Me_2CHOH	61
17	trifluorethanol	63
18[c]	MeOH	38
19[d]	MeOH	60
20[e]	MeOH	73

[a] Reaction conditions: in the first step: amine (0.5 mmol), MeOH (1.0 mL), HCl (3 M, 0.5 mL), H_2O (0.5 mL), $NaNO_2$ (0.035 g), 0–5 °C, 30 min; in the second step: B_2pin_2 (1.5 mmol), solvent (1.0 mL), r.t., 1 h.
[b] Isolated yield;
[c] Conditions: 1 equiv bis(pinacolato)diboron was used.
[d] Conditions: 2 equiv bis(pinacolato)diboron were used.
[e] Conditions: 4 equiv bis(pinacolato)diboron were used.

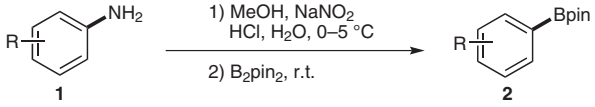


Scheme 2 The coupling of *p*-anisidine with bis(neopentyl glycolato)diboron

ditions, and excellent yields were achieved for the reactions (**3d**–**f**,**h**,**i**), which are available for further functionalization.

To test the viability of the method with more complex substrates, we applied the borylation to the preparation of heterocyclic boronate **2z**, which is usually not easy to synthesize and use as the key intermediate for the synthesis of **3z**,[18] a potent inhibitor for the treatment of osteoporosis (Scheme 3).

Table 2 The Synthesis of Arylboronates from Arylamines with Bis(pinacolato)borane as Boron Source



1 2

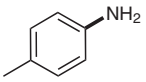
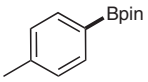
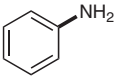
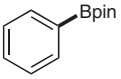
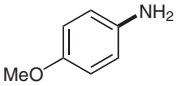
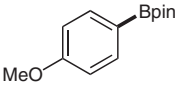
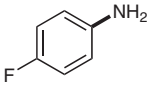
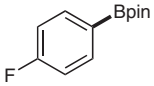
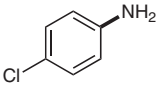
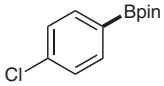
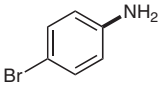
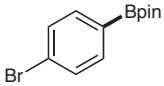
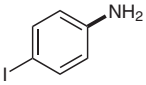
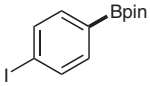
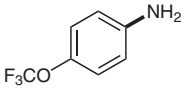
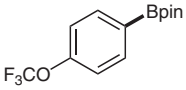
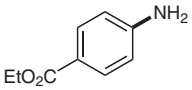
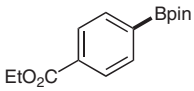
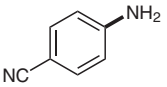
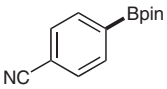
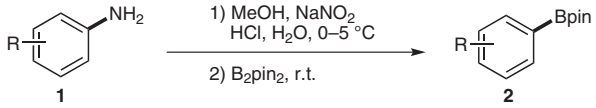
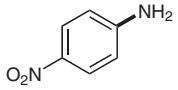
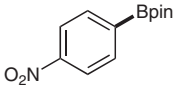
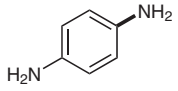
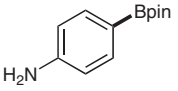
Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **2a**	74
2	 **1b**	 **2b**	57
3	 **1c**	 **2c**	86
4	 **1d**	 **2d**	54
5	 **1e**	 **2e**	62
6	 **1f**	 **2f**	73
7	 **1g**	 **2g**	77
8	 **1h**	 **2h**	55
9	 **1i**	 **2i**	75
10	 **1j**	 **2j**	57

Table 2 The Synthesis of Arylboronates from Arylamines with Bis(pinacolato)borane as Boron Source (continued)



Entry	Substrate	Product	Yield (%)[b]
11			97
	1k	**2k**	
12			53
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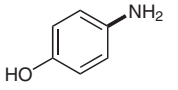
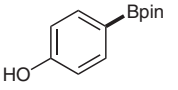
13			93
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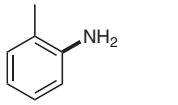
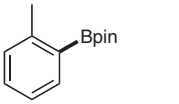
14			45
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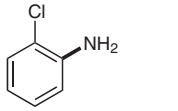
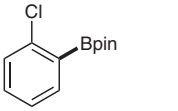
15			48
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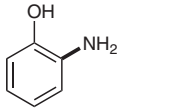
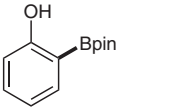
16			60
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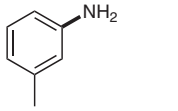
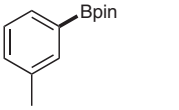
17			62
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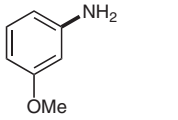
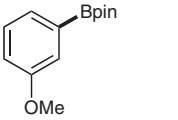
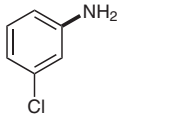
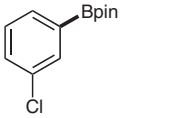
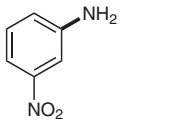
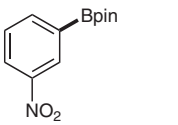
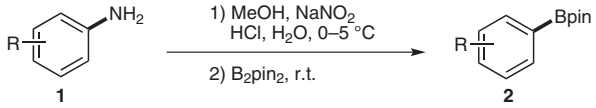
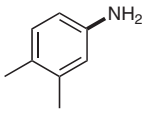
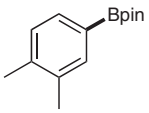
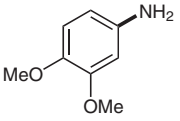
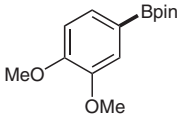
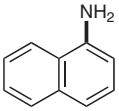
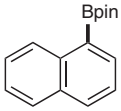
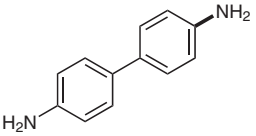
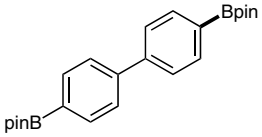
18			52
	1r	**2r**	
19			55
	1s	**2s**	
20			96
	1t	**2t**	

Table 2 The Synthesis of Arylboronates from Arylamines with Bis(pinacolato)borane as Boron Source (continued)



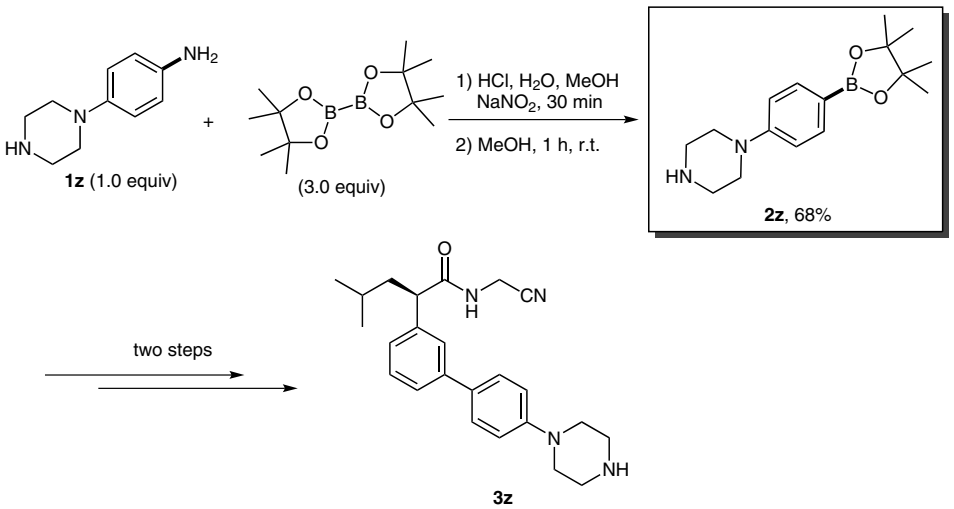
1 2

Entry	Substrate	Product	Yield (%)[b]
21	 **1u**	 **2u**	72
22	 **1v**	 **v**	96
23	 **1w**	 **2w**	85
24	 **1x**	 **2x**	75

[a] Reaction conditions: in the first step: amine (0.5 mmol), MeOH (1.0 mL), HCl (3 M, 0.5 mL), H_2O (0.5 mL), $NaNO_2$ (0.035 g), 0–5 °C, 30 min; in the second step: B_2pin_2 (1.5 mmol), MeOH (1.0 mL), r.t., 1 h.
[b] Isolated yield.
[c] Conditions: HCl (1.0 mL), H_2O (1.0 mL).

In addition, the borylation of *p*-anisidine at a 2 g scale was carried out under the conditions of Scheme 4, giving the desired 4-methoxyphenylboronic ester in 83% isolated yield, which demonstrate the practical applicability of the method (Scheme 4).

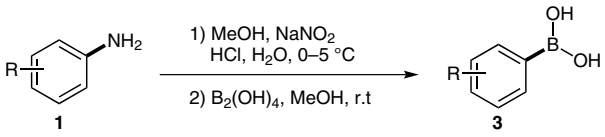
To gain understanding of the reaction mechanism, the following borylation reaction of 4-toluidine with bis(pinacolato)diboron as boron source in methanol was carried out. In the presence of radical trap, 2,2,6,6-tetramethylpiperidinoxyl (TEMPO), the desired compound was obtained



Scheme 3 The coupling of 1-(4-aminophenyl)piperazine with bis(pinacolato)diboron

with 74% isolated yield (Scheme 5, eq. 1). However, unlike the results reported by Wang,[13] the addition of TEMPO to the borylation reaction of 4-toluidine with bis(pinacolato)diboron did not suppressed the borylation process significantly, the same borylated product was isolated with 68% yield (Scheme 5, eq. 2), which lends support that the radical species were not involved in our borylation reaction and a direct nucleophilic borylation via a SN_2Ar pathway maybe preferred.

Table 3 The Synthesis of Arylboronic Acids from Arylamines with Tetrahydroxydiboron $B_2(OH)_4$ as Boron Source[a]



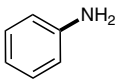
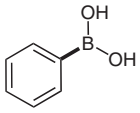
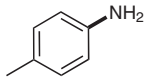
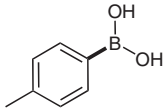
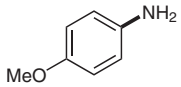
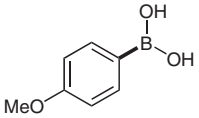
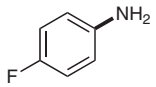
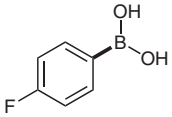
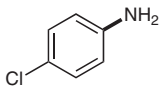
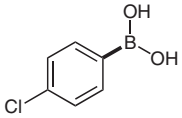
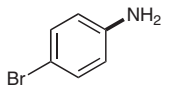
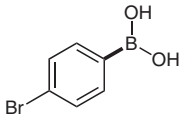
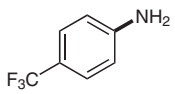
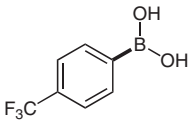
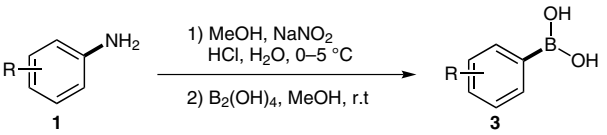
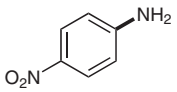
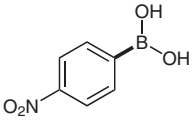
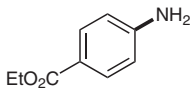
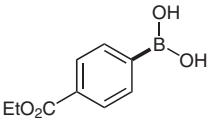
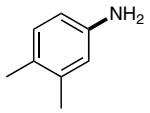
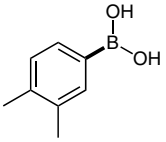
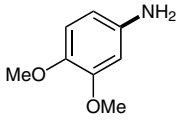
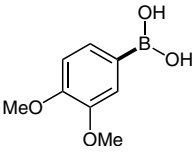
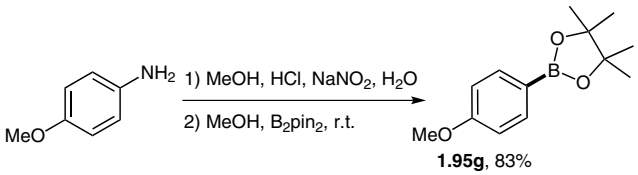
Entry	Substrate	Product	Yield (%)[b]
1	 **1b**	 **3b**	72
2	 **1a**	 **3a**	90
3	 **1c**	 **3c**	86
4	 **1d**	 **3d**	67
5	 **1e**	 **3e**	73
6	 **1f**	 **3f**	74
7	 **1y**	 **3g**	62

Table 3 The Synthesis of Arylboronic Acids from Arylamines with Tetrahydroxydiboron $B_2(OH)_4$ as Boron Source[a] (continued)



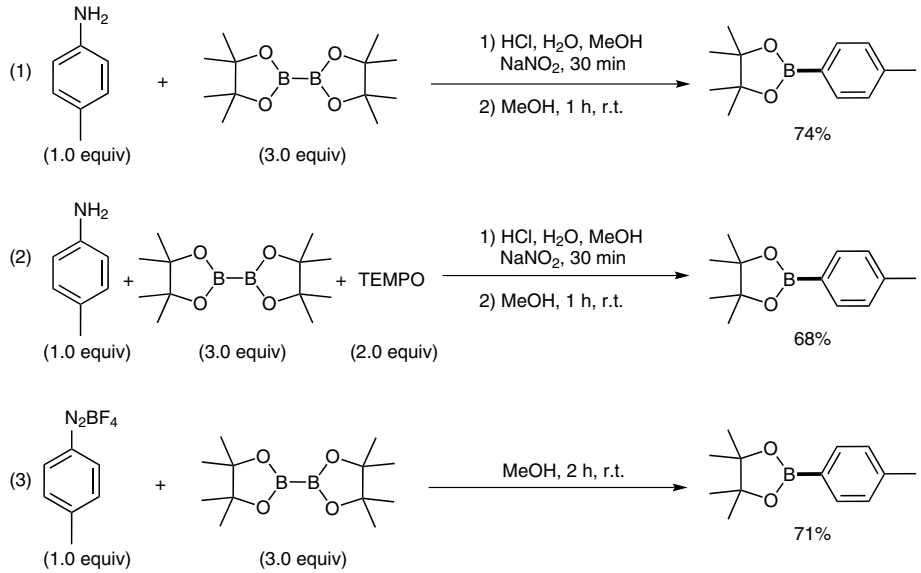
Entry	Substrate	Product	Yield (%)[b]
8	 **1k**	 **3h**	55
9	 **1i**	 **3i**	65
10	 **1u**	 **3j**	73
11	 **1v**	 **3k**	65

[a] Reaction conditions: in the first step: amine (0.5 mmol), MeOH (1.0 mL), HCl (3 M, 0.5 mL), H_2O (0.5 mL), $NaNO_2$ (0.035 g), 0–5 °C, 30 min; in the second step: $B_2(OH)_4$ (1.5 mmol), MeOH (1.0 mL), r.t., 1 h.
[b] Isolated yield.

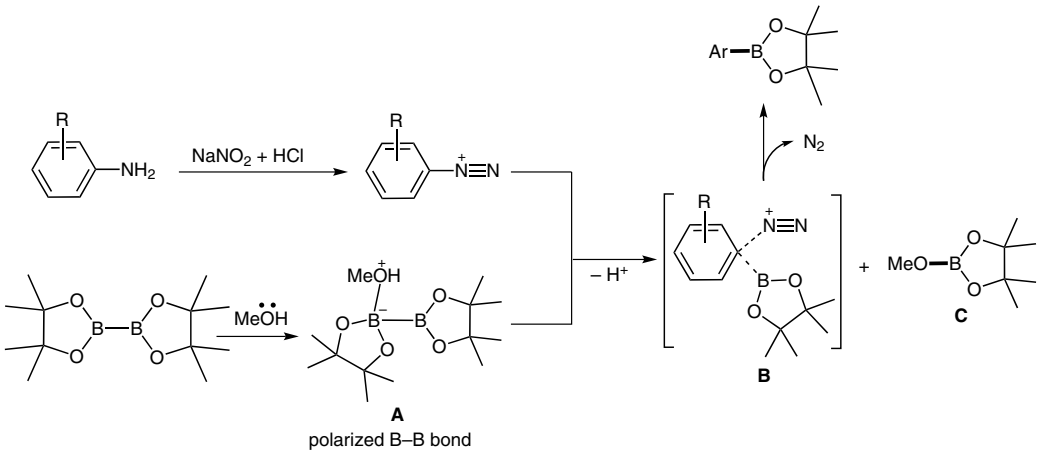


Scheme 4 A large-scale coupling of *p*-anisidine with bis(pinacolato)-diboron

A plausible mechanism is shown in Scheme 6 on the basis of the above experiments. First, a nucleophilic boryl moiety was formed by activation of the diboron reagent under the effect of methanol, this preactivation increases the reactivity of the diboron compounds. The aryldiazonium cation generated from aryl amine is the electrophile (Scheme 5, eq. 3) and the activated diboron reagent is a nucleophile. Then, the activated boron intermediate **A** attacks the aryl diazonium salt to form transient intermediate **B** via a SN_2Ar pathway, which is subsequently



Scheme 5 Mechanistic investigations



Scheme 6 Possible reaction pathway

transformed into the borylation product through N_2 elimination and 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **C** formation. The latter compound is confirmed by ^{11}B NMR spectroscopic study.

In conclusion, an effective methanol-promoted coupling of arylamine with diboron compounds at room temperature has been developed under metal-free conditions. This protocol could be applied to the synthesis of arylboronic acids utilizing arylamine and tetrahydroxydiboron $B_2(OH)_4$, bis(pinacolato)diboron and bis(neopentyl glycolato)diboron as boron source. This borylation process has the following features: (1) arylamines are inexpensive and easily available starting materials; (2) the borylation showed good tolerance to various functional groups on the aryl amines; (3) sodium nitrite is used as diazotization agent; (4) the reaction is carried out at room temperature without the use of catalyst, which provide a simple and green synthetic method to arylboronic acids and arylboronates.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(17) **General Procedure for the Synthesis of Aryboronate Esters**

To a solution of arylamine (0.5 mmol, 1.0 equiv) in MeOH (1.0 mL) was added HCl (0.5 mL, 1.5 mmol, 3.0 equiv) followed by H_2O (0.5 ml). This mixture was stirred 2 min, and the $NaNO_2$ solution (0.25 mL) was then added. The $NaNO_2$ solution was prepared by dissolving 35 mg of $NaNO_2$ in H_2O (0.25 mL). This mixture was stirred 30 min at 0–5 °C followed by B_2pin_2 (**2**, 381 mg, 1.5 mmol, 3.0 equiv) in MeOH (1.0 mL). This mixture was stirred 60 min. H_2O (10 mL) was added to the reaction mixture, then extracted with CH_2Cl_2 (50 mL, 3×). The combined organic layers were washed with sat. $NaHCO_3$, dried over Na_2SO_4, followed by evaporation, and the crude residue was purified by flash chromatography.

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To a solution of arylamine (0.5 mmol, 1.0 equiv) in MeOH (1.0 mL) was added HCl (0.5 mL, 1.5 mmol, 3.0 equiv), followed by H_2O (0.5 ml). This mixture was stirred 2 min, and the $NaNO_2$ solution (0.25 mL) was then added. The $NaNO_2$ solution was prepared by dissolving 35 mg of $NaNO_2$ in H_2O (0.25 mL). This mixture was stirred 30 min at 0–5 °C, followed by HCl (135 mg, 1.5 mmol, 3.0 equivalents) in MeOH (1.0 mL). This mixture was stirred 60 min. H_2O (10 mL) was added to reaction mixture, then extracted with CH_2Cl_2 (50 mL, 3×). The combined organic layer was dried over Na_2SO_4, followed by evaporation to give the products.

