Direct Synthesis of Arylboronic Pinacol Esters from Arylamines

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Direct Synthesis of Arylboronic Pinacol Esters from Arylamines

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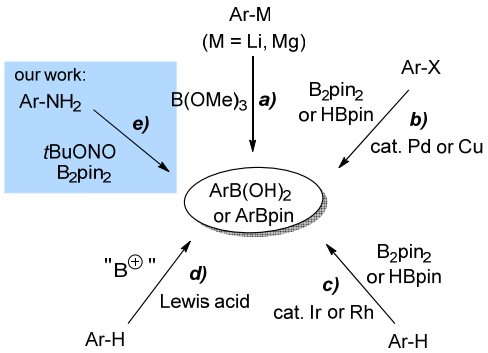
A metal-free synthetic method for arylboronic pinacol esters from easily available aromatic amines as starting materials has been described. This novel transformation affords borylation products in good yields under mild reaction conditions. This strategy can be easily carried out in gram-scale, demonstrating the practical usefulness of the method. Moreover, the Sandmeyer-type transformation can be followed by Suzuki-Miyaura cross-coupling reaction without the purification of the arylboronate products.

Introduction

Arylboronic compounds have shown wide applications in organic synthesis, pharmaceutical research and other fields.[1] In particular, functionalized arylboronic acids and arylboronates are valuable in constructing complex structures of target molecules by using Suzuki-Miyaura cross-coupling reaction.[2] Therefore, the synthesis of various functionalized arylboronic compounds has attracted great attention in recent years. Traditional method for preparing arylboronates involves the reaction between aryl Grignard reagents or aryllithium species with trialkyl boronates (Scheme 1, path *a*).[3] This general approach needs anhydrous conditions and has poor functional group tolerance. Transition-metal-catalyzed borylation from arylhalides with HBpin or B_2pin_2 has also been well established in recent decades (path *b*).[4] This method has favourable tolerance to a variety of functional groups. Besides, direct borylation *via* sp^2 C-H bond activation has been developed by Smith, Hartwig and other groups (path c).[5] However, expensive ligands and catalysts are necessary with these methods. The heavy metal contamination in the final products is also a serious problem. Recently, Lewis acid-promoted electrophilic borylation from electron-rich arenes has been explored (path *d*),[6] but these reactions have not proved to be practically useful.



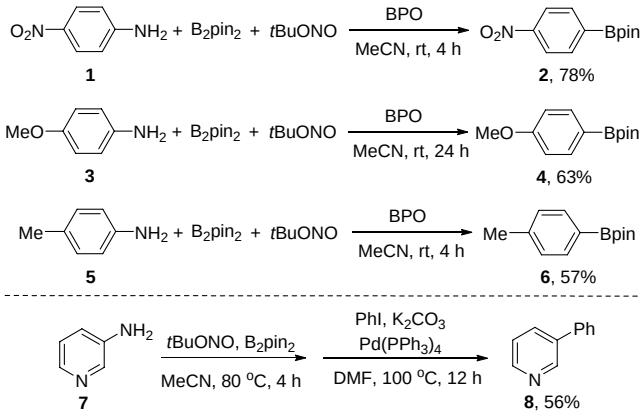
Scheme 1. Synthetic routes for arylboronic compounds.

Sandmeyer reactions and the related reactions have been well-established as valuable tools for synthetic organic chemists.[7] Based on Sandmeyer-type reaction, we have recently developed an entirely new approach toward pinacol arylboronate synthesis by direct conversion of the amino group of aniline derivatives to the boronate group (path *e*).[8] The reaction between arylamines and *tert*-butyl nitrite (*t*BuONO), an efficient diazotization reagent,[9] generates the aryl diazonium salts *in situ*, which further reacts with B_2pin_2 to afford pinacol arylboronates under open air. This borylation method has the following advantages: 1) the transformation is under metal-free conditions; 2) arylamines are inexpensive and ubiquitous starting materials; 3) the reaction has good tolerance to various functional groups, including electron-donating and electron-withdrawing groups, and also heterocyclic amines; 4) the reaction is under very mild reaction conditions and is easy to operate. As a result, this Sandmeyer-type borylation is expected to find wide application in organic synthesis.

Results and Discussion

In our previous study, a series of arylboronates have been synthesized by this transformation. To demonstrate the practical usefulness of this borylation strategy, this transformation has been carried out in gram-scale for representative arylamines at room temperature. To our delight, the anilines with either electron-rich or electron-deficient groups have provided the corresponding arylboronates in good yields in gram-scale experiments (Scheme 2).

Since heterocyclic boronates are not stable on silica gel in some cases, we have further developed a sequential borylation and Pd-catalyzed cross-coupling reaction, in particular for heterocyclic boronates. This sequential reaction can avoid the troublesome purification process and significantly strengthen the practical usefulness of this new borylation method. The sequential borylation and Suzuki-Miyaura cross-coupling reaction has also been scaled-up without the separation of heterocyclic boronate intermediate (Scheme 2).



Scheme 2. Gram-scale synthesis of arylboronates and the sequential cross-coupling reaction.

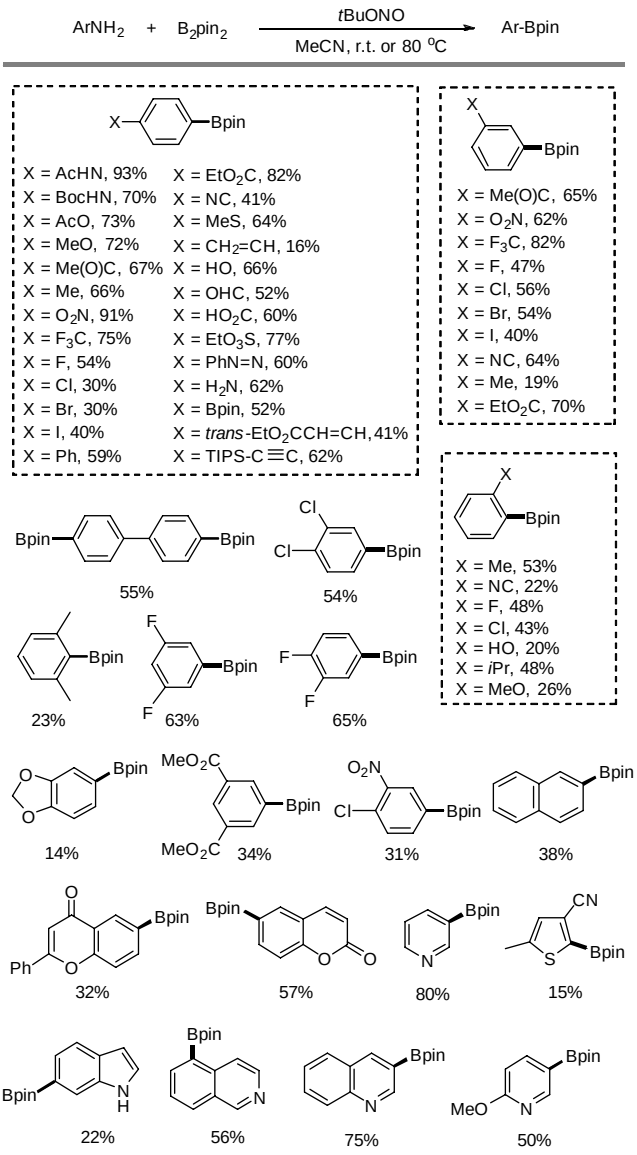
As summarized in Scheme 3, this strategy has been applied to synthesize a series of functionalized arylboronates. In most cases, moderate to good yields are obtained for the arylamines with either electron-donating or -withdrawing groups. However, several *ortho*-substituted substrates afford diminished yields because of the steric hindrance. Notably, the oxidation of diazonium intermediates and the deaminohydrogenation are the competing side reactions in this transformation. Preliminary mechanistic study suggests that this borylation follows a radical mechanism. Thus, in the case when the substrate bearing vinyl substituent is submitted to this reaction polymerization occurs, resulting in diminished yield of the desired boronate product.

Conclusions

We have developed a metal-free transformation for arylboronates from arylamines derivatives under mild reaction conditions. Functionalized arylboronates have been synthesized by this methods and the sequential Pd-catalyzed coupling reaction have been carried out in gram-scale, affording the desired products in moderate to good yields. The detailed experimental procedure for representative examples has been reported in this account.

Experimental Section

*4,4,5,5-Tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane (**2**)*. A 250 mL, round-bottomed flask equipped with a 2.5 cm rod-shaped, Teflon coated magnetic stir bar is charged with 4-nitroaniline **1** (5.520 g, 40.0 mmol, 1 equiv), diboron pinacol ester (B_2pin_2, 10.668 g, 42.0 mmol, 1.05 equiv), and benzoyl peroxide (BPO, 194 mg, 0.8 mmol, 0.02 equiv) in ambient atmosphere. The mixture is then dissolved in MeCN (60 mL) in the same flask, and the resulting solution is kept stirred (700 rpm) at room temperature while *tert*-butyl nitrite (*t*BuONO, 6.180 g, 60.0 mmol, 1.5 equiv) diluted by MeCN (40 mL) is added with a glass dropper. A silicone oil seal is used, and the reaction solution is allowed to stir at room temperature maintained by a water bath for 4 hours. The resulting solution is concentrated on a rotary evaporator to remove MeCN (40 °C, 5 kPa). The crude residue is filtered over a flash silica gel plug (60 g) eluting with petroleum ether/ethyl acetate, 20/1 (1000 mL) until TLC analysis shows that



Scheme 3. Arylboronates prepared by Sandmeyer-type transformation.[8]

no arylboronate **2** remains. The filtrate is then concentrated on a rotary evaporator (25 °C, 5 kPa), and the residue is purified by silica gel column chromatography (eluted with petroleum ether until product emerge as indicated by TLC, and then eluted with petroleum ether/ethyl acetate, 100/1). The combined elutes are concentrated on a rotary evaporator (25 °C, 5 kPa) and dried over oil vacuum pump for 10 minutes at room temperature to get the product **2** (7.787 g, 78%) as a pale yellow solid, mp = 109-110 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 1.37 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 135.6, 122.3, 84.6, 24.8; IR (film): 2975, 1788, 1518, 1363, 1349, 1147, 860, 851, 697 cm^{-1}; EI-MS (*m/z*, relative intensity): 249 (M^+, 18), 234 (100), 163 (85), 150 (43), 149 (22), 104 (22), 85 (23), 58 (46), 43 (46), 42 (59).

*2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4**)*. A 250 mL, round-bottomed flask equipped with a 2.5 cm rod-shaped, Teflon coated magnetic stir bar is charged with 4-

methoxyaniline **3** (4.920 g, 40.0 mmol, 1 equiv), B_2pin_2 (10.668 g, 42.0 mmol, 1.05 equiv), and benzoyl peroxide (BPO 194 mg, 0.8 mmol, 0.02 equiv) in ambient atmosphere. The mixture is then dissolved in MeCN (100 mL) in the same flask, and the resulting solution is kept stirred (700 rpm) in room temperature when *tert*-butyl nitrite (*t*BuONO, 6.180 g, 60.0 mmol, 1.5 equiv) is directly added. A silicone oil seal is used, and the reaction solution is allowed to stir at room temperature maintained by a water bath for 24 hours. The resulting solution is concentrated on a rotary evaporator to remove MeCN (40 °C, 5 kPa). The residue is filtered over a flash silica gel plug (60 g) eluting with petroleum ether/ethyl acetate, 20/1 (1000 mL) until TLC analysis shows that no arylboronate **4** remains. The filtrate is then concentrated on a rotary evaporator (25 °C, 5 kPa), and the residue is purified by silica gel column chromatography (eluted with petroleum ether). The combined elutes are concentrated on a rotary evaporator (25 °C, 5 kPa) and evaporated over oil vacuum pump for 10 minutes at room temperature to get the product **4** (5.930 g, 63%) as a pale yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 1.33 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 136.4, 113.2, 83.5, 55.0, 24.8; IR (film): 2978, 1604, 1396, 1360, 1318, 1277, 1247, 1175, 1143, 1091, 1030, 962, 860, 831, 736 cm^{-1}; EI-MS (*m/z*, relative intensity): 234 (M^+, 62), 219 (27), 148 (39), 135 (86), 134 (100), 133 (22), 43 (30), 41 (33).

4,4,5,5-Tetramethyl-2-p-tolyl-1,3,2-dioxaborolane ***(6)***. A 500 mL, round-bottomed flask equipped with a 2.5 cm rod-shaped, Teflon coated magnetic stir bar is charged with *p*-toluidine **5** (5.350 g, 50.0 mmol, 1 equiv), B_2pin_2 (13.335 g, 52.5 mmol, 1.05 equiv), and benzoyl peroxide (BPO 242 mg, 1.0 mmol, 0.02 equiv) in ambient atmosphere. The mixture is then dissolved in MeCN (120 mL) in the same flask, and the resulting solution is kept stirred (700 rpm) in room temperature when *tert*-butyl nitrite (*t*BuONO, 7.730 g, 75.0 mmol, 1.5 equiv) is directly added. A silicone oil seal is used, and the reaction solution is allowed to stir at room temperature maintained by a water bath for 4 hours. The resulting solution is concentrated on a rotary evaporator to remove MeCN (40 °C, 5 kPa). The residue is filtered over a flash silica gel plug (60 g) eluting with petroleum ether/ethyl acetate, 20/1 (1000 mL) until TLC analysis shows that no arylboronate **6** remains. The filtrate is then concentrated on a rotary evaporator (25 °C, 5 kPa), and the residue is purified by silica gel column chromatography (eluted with petroleum ether until product emerge which is verified by TLC and then eluted with petroleum ether/ethyl acetate, 100/1). The combined eluates are concentrated on a rotary evaporator (25 °C, 5 kPa) and evaporated over oil vacuum pump for 10 minutes at room temperature to get the product **6** (6.162 g, 57%) as a pale yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 2.36 (s, 3H), 1.33 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 134.7, 128.4, 83.5, 24.8, 21.7; IR (film): 2978, 1613, 1398, 1359, 1144, 1089, 859, 656 cm^{-1}; EI-MS (*m/z*, relative intensity): 218 (M^+, 34), 203 (38), 132 (60), 119 (100), 118 (55), 41 (15).

3-Phenylpyridine ***(8)***. B_2pin_2 (5.334 g, 21 mmol, 1.05 equiv) and 3-aminopyridine **7** (1.880 g, 20 mmol, 1 equiv) were weighed in a 250 mL round-bottom flask. MeCN (60 mL) and *tert*-butyl nitrite (*t*BuONO, 3.090 g, 30.0 mmol, 1.5 equiv) were then added in succession. The resulting reaction solution was stirred for 4 h at 80 °C (N_2 evolution completed within 5 min to 15 min). The resulting solution is concentrated on a rotary evaporator to remove MeCN (40 °C, 5 kPa). The system was degassed 3 times and was set under nitrogen atmosphere. Then $Pd(PPh_3)_4$ (1.154 g, 1 mmol, 0.05 equiv), K_2CO_3 (5.440 g, 40 mmol, 2 equiv). DMF (60 mL) and PhI (4.896 g, 24 mmol, 1.2 equiv) were added and the solution was stirred at 100 °C for 12 h. The solution was then concentrated by rotovap under reduced pressure to leave a crude reside which was purified by silica gel column chromatography (petroleum ether:EtOAc = 50:1, then 5:1). The combined elutes are then concentrated on a rotary evaporator (40 °C, 5 kPa) and then dried over oil vacuum pump for 10 minutes at room temperature to give 3-phenylpyridine **8** (1.739 g, 56%) as pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.59 (d, *J* = 4.1 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.42-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 148.3, 137.7, 136.5, 134.2, 129.0, 128.0, 127.0, 123.4; IR (film): 3031, 1582, 1473, 1407, 1024, 1006, 754, 697 cm^{-1}. EI-MS (*m/z*, relative intensity): 155 (M^+, 100), 154 (50), 127 (14), 102 (10), 63 (8), 51 (13).

Notes

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*†Electronic Supplementary Information (ESI) available: ^{1}H, ^{13}C NMR spectra of compounds **2**, **4**, **6**, and **8**. See DOI: 10.1039/b000000x/*

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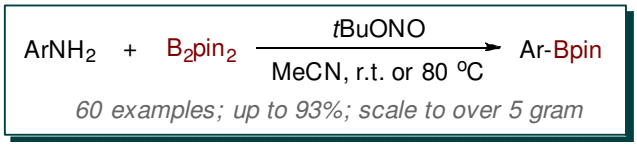

- Aromatic amine as starting material
- Transition-metal-free and mild conditions
- Excellent funtional group tolerance
- Operational simple and easily scalable

A Sandmeyer-type transformation of converting aromatic amines into the corresponding arylboronic pinacol esters has been developed.