

## A facile and convenient synthesis of functionalized *ortho*-nitrophenylboronic acids

Scott E. Collibee<sup>\*,†</sup> and Jiaxin Yu<sup>\*</sup>

Department of Medicinal Chemistry, Albany Molecular Research, Inc., PO Box 15098, Albany, NY 12212-5098, USA

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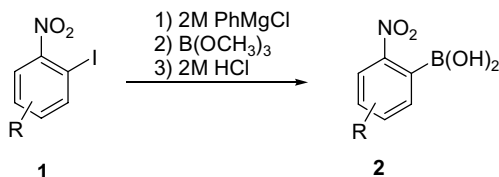
**Abstract**—A variety of *ortho*-nitrophenylboronic acids bearing functional groups such as cyano, nitro, halo,  $\alpha$ -bromomethyl, and ester were prepared in good yields via I–Mg exchange followed by quenching with trimethyl borate. All reagents employed in this procedure are commercially available and were used without further purification, and the procedure can be executed in about an hour. © 2005 Elsevier Ltd. All rights reserved.

Substituted *ortho*-nitrophenylboronic acids (or their esters) are useful building blocks toward the synthesis of heterocycles (carbazoles,<sup>1</sup> phenanthridines,<sup>2</sup> dibenzofurans,<sup>3</sup> benzo[*c*]cinnolines,<sup>4</sup> etc.) as well as for the construction of *ortho*-disubstituted biaryl moieties commonly found in various natural products such as vancomycin and (–)-rhazinilam.<sup>5–7</sup> Additional uses for *ortho*-nitro substituted biaryls include inhibition of chorismate mutase.<sup>8</sup> Arylboronic acids (or their esters) are typically prepared by (1) organoborates and Grignard or lithium reagents; (2) palladium-catalyzed cross-coupling between aryl halides or aryl triflates and tetraalkoxydiboron or dialkoxyhydroborane.<sup>9,10</sup> However, few synthetic methods exist for the synthesis of substituted *ortho*-nitrophenylboronic acids, and no direct route is known from the corresponding aryl halides.

As part of an ongoing research program, we needed to prepare a series of substituted *ortho*-nitrophenylboronic acids. Attempts to either directly nitrate the boronic acid derivatives or to prepare the corresponding boronate esters via palladium-catalyzed borylation of aryl halides were unsuccessful. It is preceded that Grignard or organolithium reagents can react with a nitro group by either nucleophilic attack or an electron-transfer reaction. However, Knochel and co-workers have recently

shown that *o*-nitrophenyl magnesium compounds can be prepared by I–Mg exchange at  $-40\text{ }^{\circ}\text{C}$  and then reacted with a variety of electrophiles.<sup>11</sup> The stability of the resulting Grignard reagent is thought to result from chelation of the nitro group to magnesium. This elegant approach was applied to the synthesis of *o*-nitrophenylboronic acids bearing functional groups such as cyano, nitro, halo,  $\alpha$ -bromomethyl, and ester in good yields via I–Mg exchange followed by quenching with trimethyl borate (Scheme 1).

The reaction conditions and subsequent quenching procedure were initially optimized using unfunctionalized *o*-iodonitrobenzene **1a** ( $R = \text{H}$ ). The stability of Grignard reagent **3** was probed by first treating **1a** with commercially available phenylmagnesium chloride (1.1 equiv) in THF at  $-75\text{ }^{\circ}\text{C}$ , and then gradually increasing reaction temperature while analyzing aliquots of reaction mixture quenched with methanol to yield **4** (Fig. 1). The reaction mixture was held constant at a given temperatures for 1 h. As shown in Figure 1, complete I–Mg exchange was observed at  $-75\text{ }^{\circ}\text{C}$  within 5 min and the resulting Grignard reagent **3** was stable at temperatures

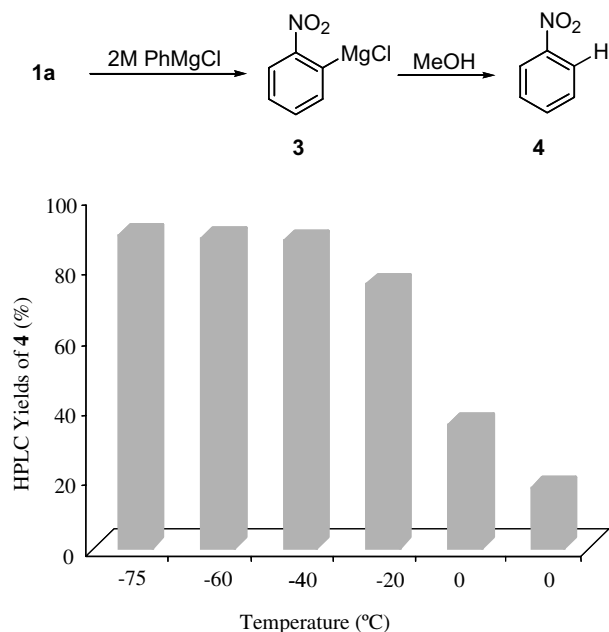


Scheme 1. Synthesis of functionalized *ortho*-nitrophenylboronic acids.

**Keywords:** Phenylboronic acids; Exchange reactions; Grignard reactions/reagents; Nitro compounds.

<sup>\*</sup> Corresponding authors. Tel.: +1 518 464 0279; fax: +1 518 464 0289; e-mail: jiaxin.yu@albomolecular.com

<sup>†</sup> Present address: Department of Medicinal Chemistry, Cytokinetics, Inc., 280 East Grand Avenue, South San Francisco, CA 94080, USA.



**Figure 1.** Temperature stability of *ortho*-nitrophenylmagnesium chloride.

below  $-40\text{ }^{\circ}\text{C}$  for at least 2 h. However, decomposition of the Grignard reagent (as inferred by the reduced HPLC yields of **4**) when the temperature increased above  $-40\text{ }^{\circ}\text{C}$  was observed. Compared with the initial measurement at  $-75\text{ }^{\circ}\text{C}$ , the available Grignard reagent **3** decreased by 60% at  $0\text{ }^{\circ}\text{C}$  after 1 h, and nearly complete decomposition was observed after stirring for an additional hour. The data in Figure 1 indicates that the reaction with Grignard reagent **3** should be performed at temperatures lower than  $-40\text{ }^{\circ}\text{C}$ .

Additional experimental parameters such as reaction concentration as well as the nature and addition sequence of borylation reagent were also examined. Increasing the concentration of the reaction from 0.10 to 0.95 M did not affect the isolated yield of boronic acid **2a** (Table 1, entries 1–3). Comparison of three borylation reagents (Table 1, entries 2, 4, and 5) indicated that the reaction was most rapid (complete within 30 min) and highest yielding when trimethyl borate was used. Contrary to a recent report describing improved yields when using an ‘in situ quench’ of an organolithium inter-

**Table 1.** Optimization of experimental parameters

Entry	Concentration of <b>1a</b> (M)	Borylating reagent	Quench sequence	<b>2a</b> (%) <sup>a</sup>
1	0.95	B(O- <i>i</i> Pr) <sub>3</sub>	Sequential	68 <sup>b</sup>
2	0.48	B(O- <i>i</i> Pr) <sub>3</sub>	Sequential	70 <sup>b</sup>
3	0.1	B(O- <i>i</i> Pr) <sub>3</sub>	Sequential	68 <sup>b</sup>
4	0.48	B[OSi(CH <sub>3</sub> ) <sub>3</sub> ] <sub>3</sub>	Sequential	46 <sup>c</sup>
5	0.48	B(OCH <sub>3</sub> ) <sub>3</sub>	Sequential	85 <sup>d</sup>
6	0.48	B(OCH <sub>3</sub> ) <sub>3</sub>	In situ	<10 <sup>e</sup>

<sup>a</sup> Isolated yields.

<sup>b</sup>  $-60\text{ }^{\circ}\text{C}$  (1 h) and  $-40\text{ }^{\circ}\text{C}$  (1 h).

<sup>c</sup>  $-40\text{ }^{\circ}\text{C}$  for 8 h.

<sup>d</sup>  $-60\text{ }^{\circ}\text{C}$  for 30 min.

<sup>e</sup>  $-60\text{ }^{\circ}\text{C}$  (30 min) and  $-40\text{ }^{\circ}\text{C}$  (6 h).

mediate to prepare a series of monosubstituted boronic acids,<sup>12</sup> sequential quenching of Grignard reagent **2** with trimethyl borate gave better results (Table 1, entries 5 and 6) for our I-Mg exchange methodology.

The examples summarized in Table 2 demonstrate the versatility of our method.<sup>13</sup> A broad range of function-

**Table 2.** *o*-Nitrophenylboronic acid synthesis

Entry	Aryl iodide	Product <sup>a</sup>	Isolated yield (%)
1	<b>1a</b>	<b>2a</b>	85
2	<b>1b</b>	<b>2b</b>	75
3	<b>1c</b>	<b>2c</b>	79
4	<b>1d</b>	<b>2d</b>	85
5	<b>1e</b>	<b>2e</b>	78
6	<b>1f</b>	<b>2f</b>	75
7	<b>1g</b>	<b>2g</b>	79
8	<b>1h</b>	<b>2h</b>	72
9	<b>1i</b>	<b>2i</b>	74
10	<b>1j</b>	<b>2j</b>	76
11	<b>1k</b>	<b>2k</b>	50 (76) <sup>b</sup>
12	<b>1l</b>	<b>2l</b>	73

<sup>a</sup> All products are >95% pure as determined by <sup>1</sup>H NMR and HPLC and gave satisfactory <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra.<sup>8</sup> <sup>1</sup>H NMR data and HPLC retention times of **2a**, **2b**, and **2h** are consistent with commercial samples.

<sup>b</sup> Mesitylmagnesium bromide was used as the metalation reagent.

ality (including many that are reactive toward Grignard reagents) such as cyano, nitro, bromo, iodo,  $\alpha$ -bromo-methyl, methoxy, fluoro, and ester was tolerated, allowing for further manipulation after cross-coupling reactions. Interestingly, 2,4-dinitro and 2-nitro-4-iodo-phenylboronic acids were prepared in 75% and 79% yields, respectively, again demonstrating the aforementioned chelation effect (Table 2, entries 6 and 7).

In conclusion, we have developed a facile and convenient method for the preparation of functionalized *ortho*-nitrophenylboronic acids, complementing existing synthesis of aryl boronic acids. All reagents used in this procedure are commercial available and were used without further purification. The combined reaction and purification time of about an hour allows for rapid access to these analogs. The *ortho*-nitrophenylboronic acids prepared by our methods are potentially useful building blocks in organic synthesis.

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- General procedure for the synthesis of *ortho*-nitrophenylboronic acids: A dry nitrogen-flushed 25 mL round-bottomed flask equipped with a magnetic stirrer, and a septum was charged with aryl iodide (4 mmol). Dry THF (6 mL) was added, and the resulting solution was cooled to  $-60^{\circ}\text{C}$  using a dry ice/acetone bath, to which was added  $\text{PhMgCl}$  (2 M in THF, 2.2 mL, 4.4 mmol, Aldrich) dropwise. The I–Mg exchange was complete within 5 min (monitored by TLC or HPLC of reaction aliquots). Trimethyl borate (4.8 mmol, 536  $\mu\text{L}$ ) was added dropwise into the reaction solution. The reaction mixture was stirred for 30 min at  $-60^{\circ}\text{C}$  and then quenched with 2 M aq HCl (4 mL) at  $-20^{\circ}\text{C}$ . The reaction was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL), and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The crude residue was recrystallized from acetonitrile or ethyl acetate. Spectral data for new boronic acids. Compound **2c**: white solid, mp  $158$ – $160^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 3.92 (s, 3H), 6.98 (d,  $J = 2.6$  Hz, 1H), 7.08 (dd,  $J = 2.6$ , 9.2 Hz, 1H), 8.21 (d,  $J = 9.2$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 57.0, 116.1, 117.6, 127.0, 145.0, 166.7; HR-EIMS:  $m/z$  calcd for  $\text{C}_7\text{H}_8\text{BNO}_5$ , 197.0496. Found, 197.0492. Compound **2d**: off-white solid, mp  $165$ – $167^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 7.58 (dd,  $J = 1.3$ , 7.3 Hz, 2H), 7.99 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 111.9, 123.3, 135.3, 153.2, 162.9, 166.2; HR-EIMS:  $m/z$  calcd for  $\text{C}_6\text{H}_5\text{BFNO}_4$ , 185.0296. Found, 185.0292. Compound **2e**: white solid, mp  $256$ – $258^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  (ppm) 2.41 (s, 3H), 7.36 (m, 2H), 8.03 (d,  $J = 8.3$  Hz, 1H), 8.13 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 124.3, 131.8, 133.6, 147.8, 150.0; HR-EIMS:  $m/z$  calcd for  $\text{C}_7\text{H}_8\text{BNO}_4$ , 181.0546. Found, 181.0543. Compound **2f**: white solid, mp  $282$ – $284^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 7.84 (d,  $J = 8.1$  Hz, 1H), 8.60 (d,  $J = 8.1$  Hz, 1H), 8.98 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 119.6, 130.1, 135.1, 150.5, 152.5; HR-EIMS:  $m/z$  calcd for  $\text{C}_6\text{H}_5\text{BN}_2\text{O}_6$ , 212.0241. Found, 212.0240. Compound **2g**: white solid, mp  $169$ – $171^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 7.31 (d,  $J = 7.9$  Hz, 1H), 8.13 (d,  $J = 7.9$  Hz, 1H), 8.57 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 95.0, 133.2, 134.7, 144.9, 152.4; HR-EIMS:  $m/z$  calcd for  $\text{C}_6\text{H}_5\text{BINO}_4$ , 292.9356. Found, 292.9361. Compound **2i**: pale yellow solid, mp  $130$ – $132^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 3.90 (s, 3H), 7.35 (dd,  $J = 2.3$ , 8.1 Hz, 1H), 7.43 (d,  $J = 8.1$  Hz, 1H), 7.74 (d,  $J = 2.3$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 109.1, 122.6, 134.3, 153.3, 162.6; HR-EIMS:  $m/z$  calcd for  $\text{C}_7\text{H}_8\text{BNO}_5$ , 197.0496. Found, 197.0501. Compound **2j**: off-white solid, mp  $274$ – $276^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 7.51 (d,  $J = 7.9$  Hz, 1H), 7.96 (dd,  $J = 1.9$ , 7.9 Hz, 1H), 8.30 (d,  $J = 1.9$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 124.4, 127.4, 134.9, 139.0, 152.8; HR-EIMS:  $m/z$  calcd for  $\text{C}_6\text{H}_5\text{BBrNO}_4$ , 244.9495. Found, 244.9490. **2k**: white solid, mp  $328$ – $330^{\circ}\text{C}$  (dec);  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 7.76 (d,  $J = 7.9$  Hz, 1H), 8.11 (d,  $J = 7.9$  Hz, 1H), 8.62 (s,  $J = 1\text{H}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 115.4, 118.3, 128.2, 134.8, 138.8, 152.1; HR-EIMS:  $m/z$  calcd for  $\text{C}_7\text{H}_5\text{BN}_2\text{O}_4$ , 192.0372. Found, 192.0344. Compound **2l**: off-white solid, mp  $125$ – $127^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 4.68 (s, 2H), 7.54 (d,  $J = 7.5$  Hz, 1H), 7.83 (dd,  $J = 1.3$ , 7.5 Hz, 1H), 8.30 (d,  $J = 1.3$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) 32.2, 124.7, 133.8, 136.5, 142.6, 152.3; HR-EIMS:  $m/z$  calcd for  $\text{C}_7\text{H}_7\text{BBrNO}_4$ , 258.9651. Found, 258.9647.