# Isopropoxide Protection of Boronates: Use in the Metal-Halogen Exchange of Arylboronates

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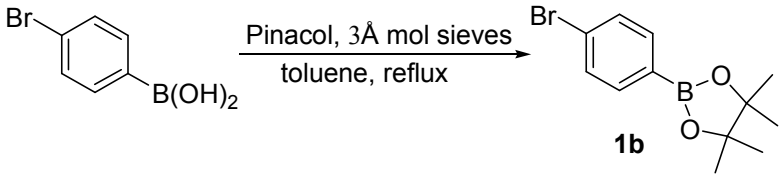
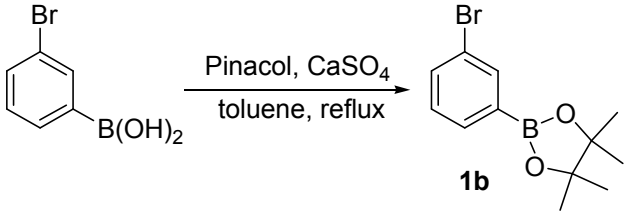
**General**: Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Spectra are given in ppm (δ) and coupling constants, *J*, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton and carbon spectra.

**Preparation of 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1a)[1].**



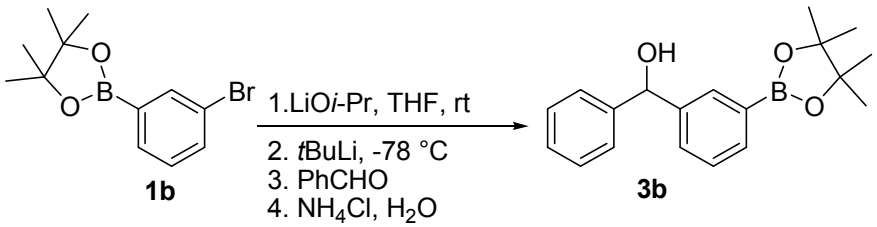

*p*-Bromophenylboronic acid (2.00 g, 10.0 mmol), pinacol (1.18 g, 10.0 mmol) and 3Å molecular sieves (5.0 g) were refluxed in toluene (30 mL) for 3 h. The mixture was then filtered hot, and the filtrate was evaporated. The resulting residue was purified by flash column chromatography (silica gel, gradient from 4% ethyl acetate in hexanes to 10% ethyl acetate in hexanes) to afford **1** (2.26 g, 80%) as a white solid: $^1$H NMR (300MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 1.34 (s, 12H).

**Preparation of 2-(3-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1b)[2].**




*m*-Bromophenylboronic acid (4.00 g, 20.0 mmol), pinacol (2.36 g, 20.0 mmol) and calcium sulfate (10.0 g) were refluxed in toluene (60 mL) for 3.5 h. The mixture was then filtered hot; the filter cake was washed with toluene (2 × 10 mL), and the filtrate was evaporated. The resulting **1b** obtained as a clear colorless oil (5.58 g; 99%) is sufficiently clean to be used in the following step without purification: $^1$H NMR (300MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.2 Hz, 1H), 7.71 (dt, *J* = 7.4, 0.9 Hz, 1H), 7.58 (dq, *J* = 8.0, 1.1 Hz), 7.24 (t, *J* = 7.0 Hz, 1H), 1.34 (s, 12H).

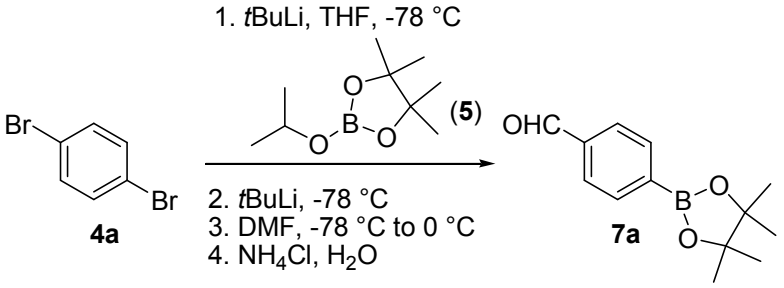
**Synthesis of phenyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3b)[3]. Procedure A.**




The procedure A for the preparation of **3a** has been followed, starting with **1b** (1.42 g, 5.02 mmol). Final purification by flash column chromatography (silica gel, 85:15

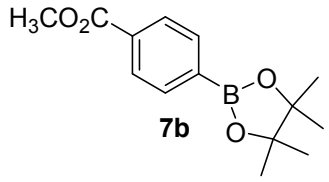
hexanes/ethyl acetate) afforded **3b** (1.09 g, 70%) as a colorless syrup: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.70 (s, 1H), 7.51 (d, $J$ = 7.3 Hz, 1H), 7.49 (d, $J$ = 6.5 Hz, 1H), 7.36 (d, $J$ = 7.2 Hz, 2H), 7.33–7.28 (m, 3H), 7.18 (dt, $J$ = 7.3, 1.2 Hz, 1H), 5.88 (d, $J$ = 4.0 Hz, 1H), 5.71 (d, $J$ = 4.0 Hz, 1H), 1.28 (s, 12H).

**Synthesis of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (7a)[4].**



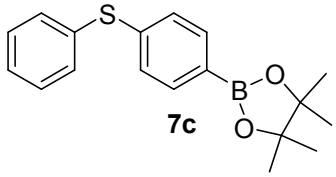

To a stirred solution of **4a** (1.17 g, 5.00 mmol) and **5** (0.948 g, 5.10 mmol) in anhydrous THF (20 mL) *tert*-butyllithium (5.90 mL, 1.7M in pentane, 10.0 mmol) was added dropwise over 3 min at -78 °C under nitrogen. After 30 min, to the reaction mixture more *tert*-butyllithium (5.90 mL, 1.7M in pentane, 10.0 mmol) was added dropwise over 3 min and the reaction stirred for an additional 20 min. After this time DMF (0.42 mL, 5.54 mmol) was added, the reaction mixture was slowly warmed to room temperature over 1 h and quenched with saturated aqueous ammonium chloride (20 mL). The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined extracts were dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes/ethyl acetate) to provide **7a** (0.810 g, 74%) as a white solid: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.06 (s, 1H), 7.92 (d, $J$ = 8.0 Hz, 2H), 7.88 (d, $J$ = 8.0 Hz, 2H), 1.32 (s, 12H).

**Synthesis of methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (7b)[5].**



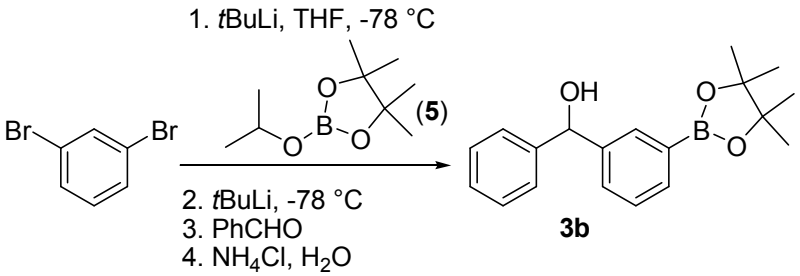

The procedure for the preparation of **7a** has been followed, starting with **4a** (1.17 g, 5.00 mmol), **5** (0.948 g, 5.10 mmol) and methyl cyanoformate (0.44 mL, 5.54 mmol). Final purification by flash column chromatography (silica gel, 95:5 hexanes/ethyl acetate) afforded **7b** (1.00 g, 76%) as a yellow solid: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.97 (d, $J$ = 8.2 Hz, 2H), 7.81 (d, $J$ = 8.2 Hz, 2H), 3.87 (s, 3H), 1.31 (s, 12H).

**Synthesis of 4,4,5,5-tetramethyl-2-(4-(phenylthio)phenyl)-1,3,2-dioxaborolane (7c).**



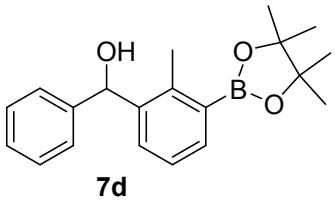
The procedure for the preparation of **7a** has been followed, starting with **4a** (1.17 g, 5.00 mmol), **5** (0.948 g, 5.10 mmol) and phenyl disulfide (1.21 g, 5.54 mmol). Final purification by flash column chromatography (silica gel, 95:5 hexanes/ethyl acetate) afforded **7c** (0.984 g, 63%) as a white solid: mp 64–67 °C; $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 7.69 (s, 1H), 7.61 (t, $J$ = 7.8 Hz, 2H), 7.42–7.38 (m, 4H), 7.24 (d, $J$ = 8.2 Hz, 2H), 1.29 (s, 12H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 135.2, 133.6, 132.0, 129.7, 128.3, 128.1, 83.7, 24.5; HRMS Calcd for $C_{18}H_{21}BO_2S$+H: 313.1433. Found: 313.1446.

**Synthesis of phenyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3b)[3]. Procedure B.**



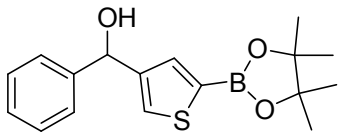

To a stirred solution of 1,3-dibromobenzene (1.17 g, 5.00 mmol) and **5** (0.948 g, 5.10 mmol) in anhydrous THF (20 mL) *tert*-butyllithium (5.90 mL, 1.7M in pentane, 10.0 mmol) was added dropwise over 3 min at -78 °C under nitrogen. After 30 min, to the reaction mixture more *tert*-butyllithium (5.90 mL, 1.7M in pentane, 10.0 mmol) was added dropwise over 3 min and the reaction stirred for an additional 20 min. After this time benzaldehyde (0.588 g, 5.54 mmol) was added, the reaction stirred for 10 min and quenched with saturated aqueous ammonium chloride (20 mL). The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined extracts were dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash column chromatography (silica gel, 85:15 hexanes/ethyl acetate) to provide **3b** (1.02 g, 66%) as a colorless syrup.

**Synthesis of (2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(phenyl)methanol (7d).**




The procedure B for the preparation of **3b** has been followed, starting with 2,6-dibromotoluene (1.25 g, 5.00 mmol), **5** (0.948 g, 5.10 mmol) and benzaldehyde (0.588 g, 5.54 mmol). Final purification by flash column chromatography (silica gel, 90:10 hexanes/ethyl acetate) afforded **7d** (1.26 g, 78%) as white solid: mp 105–108 °C; $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 7.58 (dd, $J$ = 7.7, 1.3 Hz, 1H), 7.51 (dd, $J$ = 7.4, 1.4 Hz, 1H), 7.30–7.25 (m, 4H), 7.21–7.18 (m, 2H), 5.88 (s, 1H), 5.74 (d, $J$ = 3.9 Hz, 1H), 2.37 (s, 3H), 1.28 (s, 12H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 144.4, 143.1, 140.6, 134.0, 129.2, 128.0, 127.0, 126.7, 124.8, 83.3, 71.2, 24.59, 24.56, 17.8; ESI MS *m/z* 307 [M + H – $H_2O$]$^{+}$; HRMS Calcd for $C_{20}H_{25}BO_3$+H–$H_2O$: 307.1869. Found: 307.1873.

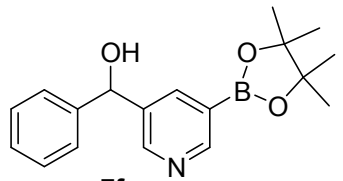
**Synthesis of phenyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)methanol (7e).**




**7e**

The procedure B for the preparation of **3b** has been followed, starting with 2,4-dibromothiophene (1.21 g, 5.00 mmol), **5** (0.948 g, 5.10 mmol) and benzaldehyde (0.588 g, 5.54 mmol). Final purification by flash column chromatography (silica gel, 85:15 hexanes/ethyl acetate) afforded **7e** (0.965 g, 61%) as light yellow syrup: $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 7.67 (s, 1H), 7.38 (d, $J$ = 7.3 Hz, 2H), 7.34–7.30 (m, 3H), 7.22 (dt, $J$ = 7.3, 1.2 Hz, 1H), 5.87 (d, $J$ = 4.4 Hz, 1H), 5.76 (d, $J$ = 4.4 Hz, 1H), 1.25 (s, 12H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 148.9, 145.2, 136.6, 128.2, 128.1, 126.8, 126.1, 83.9, 70.7, 24.5; ESI MS *m/z* 299 $[M + H - H_2O]^+$; HRMS Calcd for $C_{17}H_{21}BO_3S$+H–$H_2O$: 299.1277. Found: 299.1274.

**Synthesis of phenyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanol (7f).**




**7f**

The procedure B for the preparation of **3b** has been followed, starting with 3,5-dibromopyridine (1.18 g, 5.00 mmol), **5** (0.948 g, 5.10 mmol) and benzaldehyde (0.588 g, 5.54 mmol). Final purification by trituration with a mixture of diethyl ether (10 mL) and hexanes (10 mL) afforded **7f** (0.671 g, 47%) as a white solid: mp 88–92 °C; $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 8.69 (s, 1H), 8.62 (s, 1H), 7.93 (s, 1H), 7.39 (d, $J$ = 7.5 Hz, 2H), 7.33 (t, $J$ = 7.3 Hz, 2H), 7.23 (t, $J$ = 7.0 Hz, 1H), 6.08 (d, $J$ = 3.5 Hz, 1H), 5.81 (d, $J$ = 3.5 Hz, 1H), 1.30 (s, 12H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 153.0, 150.3, 144.7, 140.2, 139.3, 128.2, 127.0, 126.1, 84.0, 71.9, 24.5; ESI MS *m/z* 312 $[M + H]^+$; HRMS Calcd for $C_{18}H_{22}BNO_3$+H: 312.1771. Found: 312.1762.

## References


[1] Ma, Y.; Song, C.; Jiang, W.; Xue, G.; Cannon, J. F.; Wang, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 4635.

[2] Shimada, S.; Yamazaki, O.; Tanaka, T.; Rao, M. L. N.; Suzuki, Y.; Tanaka, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1845.

[3] Baron, O.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 3133.

[4] Vogels, C. M.; Nikolcheva, L. G.; Norman, D. W.; Spinney, H. A.; Decken, A.; Baerlocher, M. O.; Baerlocher, F. J.; Westcott, S. A. *Can. J. Chem.* **2001**, *79*, 1115.

[5] Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447.