Palladium catalyzed Br/D exchange of arenes: Selective deuterium incorporation with versatile functional group tolerance and high efficiency

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Supporting Information

General: Proton and carbon NMR spectra for all compounds were recorded in CDCl₃ on Varian VNMRS 500 MHz NMR spectrometer, operating at 499.717 MHz for proton. Chemical shifts were determined relative to residual CHCl₃ (7.26 ppm for ¹H-NMR and 77.2 ppm for ¹³C-NMR). All yields reported refer to isolated yields unless otherwise indicated. GC-MS experiments were carried out using an Agilent 6890 series GC and a 5973 Mass Selective Detector System. All the solvents were degassed by purging with dry nitrogen for 2 h before use. All the reagents were purchased from commercial sources and used as received.

General Procedure for Br/D exchange with Pd₂(dba)₃/t-Bu₃P as catalyst and DCOONa as deuterium source: In an argon glovebox, to an 8 mL vial containing Pd₂(dba)₃ (18.3 mg, 0.02 mmol), t-Bu₃P (12 mg, 0.06 mmol), DCOONa (138 mg, 2 mmol), and aryl bromide (1 mmol) was added DMSO (1 mL). Then the sealed vial was brought out of the glovebox and put into an oil bath with pre-set to the reaction temperature. The reaction was performed at 80 °C until the GC/MS showed the reaction was completed. The reaction was quenched with saturated NH₄Cl solution. The product was extracted with dichloromethane (3 x 15 mL). The combined organic layer was washed with brine and dried over Na₂SO₄. After removal of solvents under vacuum, the crude product was purified via column chromatography (silica gel) using the appropriate binary solvent system (vol/vol).

2a¹: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 95% colorless oil. ¹H NMR: δ 8.02 (d, J = 10.2 Hz, 2 H), 7.41 (d, J = 10.2 Hz, 2 H), 4.36 (d, J = 8.4 Hz, 2 H), 1.38 (t, J = 7.8 Hz, 3 H); ¹³C NMR: δ 166.6, 132.5 (t, J = 23.75 Hz), 130.5, 129.5, 128.2, 60.9, 14.3;

2b¹: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 91% colorless oil. ¹H NMR: δ 8.02 - 8.04 (m, 2 H), 7.53 (d, J = 9.0 Hz, 1 H), 7.41 (dd, J = 9.0 Hz, J = 9.6 Hz, 3 H), 4.36 (d, J = 8.4 Hz, 2 H), 1.38 (t, J = 7.8 Hz, 3 H); ¹³C NMR: δ 166.6, 132.7, 130.5, 129.5, 129.4, 128.3, 128.0 (t, J = 23.7 Hz), 60.9, 14.3;
2c: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 90% colorless oil. $^1$H NMR: δ 7.41 (t, $J = 8.4$ Hz, 1 H), 7.00 (m, 2 H), 6.94 (s, 1 H), 3.84 (s, 3 H); $^{13}$C NMR: δ 166.6, 132.8, 130.4, 129.5, 129.2 (t, $J = 23.7$ Hz), 128.3, 128.2, 60.9, 14.3

2d: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 90% colorless oil. $^1$H NMR: δ 7.78 - 7.80 (m, 4 H), 7.57 (t, $J = 9.0$ Hz, 1 H), 7.45 - 7.48 (m, 4 H); $^{13}$C NMR: δ 196.8, 137.7, 132.5, 132.2 (t, $J = 24.0$ Hz), 130.1, 128.4, 128.2;

2e: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 82% colorless oil. $^1$H NMR: δ 7.64 (d, $J = 9.6$ Hz, 2 H), 7.46 (d, $J = 9.6$ Hz, 2 H); $^{13}$C NMR: δ 132.5 (t, $J = 25.0$ Hz), 132.2, 129.0, 118.9, 112.4;

2f: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 94% colorless oil. $^1$H NMR: δ 8.21 (d, $J = 0.2$ Hz, 2 H), 7.53 (d, $J = 9.6$ Hz, 2 H); $^{13}$C NMR: δ 148.4, 134.5 (t, $J = 24.0$ Hz), 129.4, 123.6;

2g: Purified by column chromatography (hexane/dichloromethane = 2:1, Rf = 0.4), Yield: 80% colorless oil. $^1$H NMR: δ 7.30 (d, $J = 9.6$ Hz, 2 H), 6.81 (d, $J = 10.8$ Hz, 2 H), 3.00 (s, 6 H); $^{13}$C NMR: δ 150.8, 129.1, 116.6 (t, $J = 25.0$ Hz), 112.9, 40.8;

2h: Purified by column chromatography (hexane/dichloromethane = 10:1, Rf = 0.5), Yield: 93% white solid. $^1$H NMR: δ 7.28 (dd, $J = 10.2$ Hz, $J = 18.6$ Hz, 4 H), 4.13 (q, $J = 9.0$ Hz, 2 H), 3.59 (s, 2 H), 1.23 (t, $J = 8.4$ Hz, 3 H); $^{13}$C NMR: δ 171.6, 134.1, 129.2, 128.4, 126.7 (t, $J = 25.0$ Hz), 60.8, 41.4, 14.1; HRMS (ESI): calc. for C$_{10}$H$_{11}$DO$_2$ [M]$^+$ 165.0895; found 165.0894.

2i: Purified by column chromatography (hexane/dichloromethane = 10:1, Rf = 0.5), Yield: 87% colorless oil. $^1$H NMR: δ 9.96 (s, 1 H), 7.82 (d, $J = 9.6$ Hz, 2 H), 7.47 (d, $J = 9.0$ Hz, 2 H); $^{13}$C NMR: δ 192.3, 136.4, 134.1 (t, $J = 25.0$ Hz), 129.7, 128.8;
2j: Purified by column chromatography (hexane/ethyl acetate = 10:1, Rf = 0.4), Yield: 82% colorless oil. $^1$H NMR: $\delta$ 9.02 (d, $J = 6.6$ Hz, 1 H), 7.81 (d, $J = 9.0$ Hz, 1 H), 7.73 (d, $J = 9.6$ Hz, 1 H), 7.43 ~ 7.46 (m, 2 H); $^{13}$C NMR: $\delta$ 155.4, 129.6, 120.6 (t, $J = 25.0$ Hz), 115.3;

2k: Purified by column chromatography (hexane/ethyl acetate = 10:1, Rf = 0.4), Yield: 94% colorless oil. $^1$H NMR: $\delta$ 7.35 (s, 4 H), 4.67 (s, 2 H); $^{13}$C NMR: $\delta$ 140.9, 128.6, 127.5 (t, $J = 25.0$ Hz), 127.1, 65.5;

2l: Purified by column chromatography (hexane/dichloromethane = 40:1, Rf = 0.7), Yield: 89% colorless oil. $^1$H NMR: $\delta$ 7.50 (d, $J = 9.6$ Hz, 4 H), 7.33 - 7.36 (m, 4 H), 7.20 ~ 7.26 (m, 1 H), 7.10 (s, 2 H); $^{13}$C NMR: $\delta$ 137.4, 128.7, 128.6, 127.7, 127.4 (t, $J = 25.0$ Hz), 126.6; HRMS (ESI): calc. for C$_{14}$H$_{11}$D [M]$^+$ 181.1002; found 181.0998.

2m: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 97% white solid. $^1$H NMR: $\delta$ 8.59 (s, 1 H), 8.04 (d, $J = 12.0$ Hz, 1 H), 7.91 (d, $J = 12.0$ Hz, 1 H), 7.53 (d, $J = 9.6$ Hz, 2 H), 7.83 - 7.85 (m, 2 H), 7.50 (d, $J = 9.0$ Hz, 1 H); $^{13}$C NMR: $\delta$ 167.4, 135.6, 132.6, 131.2, 129.5, 128.3, 128.0 (t, $J = 25.0$ Hz), 127.1, 127.5, 125.6, 125.3, 125.3, 52.3; HRMS (ESI): calc. for C$_{12}$H$_9$DO$_2$ [M]$^+$ 187.0744; found 187.0961.

2n: Purified by column chromatography (hexane/dichloromethane = 2:1, Rf = 0.5), Yield: 95% white solid. $^1$H NMR: $\delta$ 7.98 (d, $J = 9.6$ Hz, 1 H), 7.82 (d, $J = 9.6$ Hz, 1 H), 7.51 (dd, $J = 6.0$ Hz, $J = 9.0$ Hz, 1 H); $^{13}$C NMR: $\delta$ 138.5, 135.0, 134.0, 130.8, 129.4, 126.9, 126.4, 124.8, 123.6, 121.6, 113.7, 109.2 (t, $J = 25.0$ Hz); HRMS (ESI): calc. for C$_{14}$H$_{11}$DNO$_2$S [M+H]$^+$ 259.0646; found 259.0640.

2o: Purified by column chromatography (hexane/dichloromethane = 1:1, Rf = 0.4), Yield: 80% white solid. $^1$H NMR: $\delta$ 8.70 - 8.72 (m, 1 H), 7.82 (d, $J = 9.6$ Hz, 1 H), 7.51 (dd, $J = 6.0$ Hz, $J = 9.0$ Hz, 1 H); $^{13}$C NMR: $\delta$ 151.4, 137.1, 134.2, 128.4 (t, $J = 25.0$ Hz), 127.1, 117.3;

**General Procedure for synthesis of deuterium-labeled aryl chloride with DCOONa as**
**deuterium source:** In an argon glovebox, to an 8 mL vial containing Pd$_2$(dba)$_3$ (18.3 mg, 0.02 mmol), t-Bu$_3$P (12 mg, 0.06 mmol), DCOONa (138 mg, 2 mmol), and aryl bromide (1 mmol) was added DMSO (1 mL). Then the sealed vial was brought out of the glovebox and put into an oil bath with pre-setting temperature. The reaction was performed at 80 °C until the GC/MS showed the reaction was completed. The reaction was quenched with saturated NH$_4$Cl solution. The product was extracted with dichloromethane (3 x 15 mL). The combined organic layer was washed with brine and dried over Na$_2$SO$_4$. After removal of solvents under vacuum, the crude product was purified via column chromatography (silica gel).

3a: Purified by column chromatography (hexane/dichloromethane = 20:1, Rf = 0.5), Yield: 73% colorless oil. $^1$H NMR: δ 7.68 (s, 1 H), 7.45 ~ 7.50 (m, 2 H); $^{13}$C NMR: δ 132.9, 132.5, 131.6, 128.6 (q, $J = 30.4$ Hz), 127.6 (q, $J = 4.8$ Hz), 126.6 (t, $J = 25.0$ Hz), 124.1, 121.9;

3b: Purified by column chromatography (hexane/dichloromethane = 40:1, Rf = 0.7), Yield: 81% colorless oil. $^1$H NMR: δ 7.42 ~ 7.43 (m, 2 H), 7.18 (d, $J = 9.6$ Hz, 1 H); $^{13}$C NMR: δ 132.5, 130.5, 130.4, 127.6, 127.4 (t, $J = 25.0$ Hz);

3c: Purified by column chromatography (hexane/dichloromethane = 1:1, Rf = 0.5), Yield: 92% white solid. $^1$H NMR: δ 7.25 (d, $J = 9.0$ Hz, 2 H), 6.84 (d, $J = 10.2$ Hz, 2 H), 4.91 (s, 1H); $^{13}$C NMR: δ 151.1, 144.5, 136.4 (t, $J = 25.0$ Hz), 133.5, 129.8, 129.6, 127.0, 126.7, 121.9; HRMS (ESI): calc. for C$_9$H$_6$DClN [M+H]$^+$ 165.0324; found 165.0323.
General Procedure for synthesis of deuterium-labeled aryl boronic acid ester with NaBD₄ as deuterium source: In an argon glovebox, to 8 mL vial containing Pd₂dba₃ (18.3 mg, 0.02 mmol), t-Bu₃P (12 mg, 0.06 mmol), NaBD₄ (80 mg, 2 mmol), and aryl bromide (1 mmol) was added DMSO (2 mL). The reaction was performed at 80 °C until the GC-MS showed the reaction was completed. The reaction was quenched with saturated NH₄Cl solution. The product was extracted with dichloromethane (3 x 15 mL). The combined organic layer was washed with brine and dried over Na₂SO₄. After removal of solvents under vacuum, the crude product was purified via column chromatography (silica gel).

3d: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 74% colorless oil. ¹H NMR: δ 7.79 (d, J = 7.8 Hz, 2 H), 7.34 (d, J = 9.0 Hz, 2 H), 1.33 (s, 12 H); ¹³C NMR: δ 134.8, 131.2 (t, J = 25.0 Hz), 127.7, 83.9, 25.0; HRMS (ESI): calc. for C₁₂H₆DBO₂ [M]⁺ 205.1379; found 205.1382.

3e: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 88% colorless oil. ¹H NMR: δ 7.79 ~ 7.80 (m, 2 H), 7.44 (d, J = 9.0 Hz, 1 H), 7.35 (t, J = 9.0 Hz, 1 H), 1.33 (s, 12 H); ¹³C NMR: δ 134.8, 134.7, 131.2, 127.8, 127.5 (t, J = 25.0 Hz), 83.9, 25.0; HRMS (ESI): calc. for C₁₂H₆DBO₂ [M]⁺ 205.1379; found 205.1380.

3f: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 76% colorless oil. ¹H NMR: δ 7.79 (d, J = 7.8 Hz, 1 H), 7.44 (t, J = 9.0 Hz, 1 H), 7.35 (t, J = 7.8 Hz, 2 H), 1.33 (s, 12 H); ¹³C NMR: δ 134.8, 134.6 (t, J = 25.0 Hz), 131.4, 127.8, 127.7, 83.9, 25.0; HRMS (ESI): calc. for C₁₂H₆DBO₂ [M]⁺ 205.1379; found 205.1374.

3g: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 90% white solid. ¹H NMR (CDCl₃, ppm): δ 8.43 (d, J = 9.6 Hz, 2 H), 7.97 (d, J = 9.0 Hz, 2 H), 7.41 ~ 7.48 (m, 4 H), 1.57 (s, 12 H); ¹³C NMR (CDCl₃, ppm): δ 136.0, 131.1, 129.2 (t, J = 25.0 Hz), 128.8, 128.4, 125.9, 124.9, 84.4, 25.2; HRMS (ESI): cald. For C₂₀H₂₁DBO₂ [M+H]⁺ 306.1770; found 306.1778.
3h: Purified by column chromatography (hexane/dichloromethane = 4:1, Rf = 0.4), Yield: 95% white solid. $^1$H NMR: $\delta$ 8.00 (d, $J_1$ = 9.6 Hz, 1 H), 7.74 (s, 1 H), 7.00 (dd, $J_2 = 10.2$ Hz, $J_3 = 12.6$ Hz, 2 H), 7.32 (s, 1 H), 7.30 (d, $J_4 = 9.6$ Hz, 1 H), 1.94 ~ 1.99 (m, 4 H), 1.38 (s, 12 H), 0.98 ~ 1.10 (m, 12 H), 0.74 (t, $J_5 = 9.0$ Hz, 6 H), 0.55 ~ 0.59 (m, 4 H); $^{13}$C NMR: $\delta$ 151.4, 150.0, 144.2, 141.0, 133.8, 128.9, 127.4 (t, $J = 25.0$ Hz), 126.7, 122.9, 120.2, 119.1, 55.2, 40.3, 31.6, 30.4, 29.8, 25.0, 23.8, 22.7, 14.1; HRMS (ESI): calc. for C$_{31}$H$_{45}$DBO$_2$ [M+H]$^+$ 462.3648; found 462.3653.
General Procedure for synthesis of perdeuterium-labeled aryl compounds: In an argon glovebox, to 8 mL vial containing Pd$_2$(dba)$_3$ (18.3 mg, 0.02 mmol), t-Bu$_3$P (12 mg, 0.06 mmol), DCOONa or NaBD$_4$ (2 equivalent to bromide), and aryl bromide (1 mmol) was added DMSO (1 mL). The reaction was performed at 80 °C until the GC-MS showed the reaction was completed. The reaction was quenched with saturated NH$_4$Cl solution. The product was extracted with dichloromethane (3 x 15 mL). The combined organic layer was washed with brine and dried over Na$_2$SO$_4$. After removal of solvents under vacuum, the crude product was purified via column chromatography (silica gel).

4a: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.5), Yield: 95% colorless oil. $^1$H NMR: δ 7.79 (d, $J = 10.2$ Hz, 4 H), 7.46 (d, $J = 9.6$ Hz, 4 H); $^{13}$C NMR: δ 197.0, 137.8, 132.3 (t, $J = 25.0$ Hz), 128.4; HRMS (ESI): calc. for C$_{13}$H$_8$D$_2$O [M]$^+$ 184.0852; found 184.0859.

4b: Purified by column chromatography (hexane/dichloromethane = 6:1, Rf = 0.4), Yield: 95% white solid. $^1$H NMR: δ 6.80 (s, 2 H), 3.87 (t, $J = 7.8$ Hz, 4 H), 1.70 ~ 1.76 (m, 4 H), 1.39 ~ 1.43 (m, 4 H), 1.25 ~ 1.33 (m, 24 H), 0.86 (t, $J = 9.0$ Hz, 6 H); $^{13}$C NMR: δ 153.3, 115.5, 115.3 (t, $J = 25.0$ Hz), 68.8, 32.1, 29.8, 29.7, 29.6, 29.5, 26.2, 22.9, 14.3; HRMS (ESI): calc. for C$_{26}$H$_{25}$D$_2$O$_2$ [M+H]$^+$ 393.3696; found 393.3704.

4c: Purified by column chromatography (hexane/dichloromethane = 5:1, Rf = 0.5), Yield: 74% colorless oil. $^1$H NMR: δ 7.79 (s, 2 H), 7.43 (s, 1 H), 1.32 (s, 12 H); $^{13}$C NMR: δ 134.6, 131.0, 127.4 (t, $J = 25.0$ Hz), 83.7, 24.8; HRMS (ESI): calc. for C$_{12}$H$_5$D$_2$BO [M]$^+$ 206.1442; found 206.1437.

4d: Purified by column chromatography (hexane/dichloromethane = 10:1, Rf = 0.6), Yield: 65% colorless oil. $^1$H NMR: δ 7.29 (s, 2 H), 3.80 (s, 3 H); $^{13}$C NMR: δ 159.4, 129.2, 120.3 (t, $J = 25.0$ Hz), 113.6 (t, $J = 25.0$ Hz), 55.1;
References cited:

$^1$H and $^{13}$C NMR Spectra: