

Supporting Information for:

# Water-Soluble Palladacycles as Precursors to Highly Recyclable Catalysts for the Suzuki Coupling of Aryl Bromides in Aqueous Solvents

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**General information.** Phosphine ligands *t*-Bu-Amphos,<sup>1</sup> *t*-Bu-Pip-phos,<sup>1</sup> Cy-Pip-phos,<sup>2</sup> and DCPES<sup>2</sup> were prepared by previously reported methods. Water (deionized), acetonitrile, and mixtures thereof were sparged with nitrogen for 15 minutes prior to use. All other reagents were used as received from commercial sources. Catalytic reactions were run in 1 dram vials with rubber/Teflon septa or in 1-neck round-bottom flasks sealed with rubber septa. All reaction temperatures for catalytic reactions refer to the temperature of pre-equilibrated oil baths. GC yields were determined by comparison to an internal standard using calibration data determined with authentic samples of the substrates and products. All <sup>31</sup>P NMR spectra were externally referenced to 85% phosphoric acid. <sup>13</sup>C NMR spectra obtained in D<sub>2</sub>O were spiked with methanol as an internal standard. All reported melting points are uncorrected.

**4-[(Dimethylamino)methyl]phenol (1).** Prepared by a modification of the synthesis reported by Bhattacharya.<sup>3</sup> Titanium (IV) isopropoxide (6.00 mL, 20.3 mmol) was added dropwise to a solution of dimethylamine in methanol (2 M, 20 mL, 40 mmol), followed by the addition of *p*-hydroxybenzaldehyde (1.22 g, 10.0 mmol). The reaction mixture was stirred at room temperature for 4-5 h. NaBH<sub>4</sub> (378 mg, 10.0 mmol) was added, and the mixture was further stirred for another 2 h. The reaction was quenched by the addition of water (2 mL). The resulting precipitate was filtered off and washed with diethyl ether (3 × 10 mL). Water (15 mL) was added to the residue. The aqueous layer was made slightly basic (pH 9-10) and extracted with diethyl ether (3 × 50 mL). The pH was adjusted after every extraction to remain at 9-10. The combined ether extracts were dried (K<sub>2</sub>CO<sub>3</sub>) and filtered. Removal of the solvent gave a pale yellow solid (1.04 g, 69 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 360 MHz): δ 7.09 (d, *J*=8.63 Hz, 2H), 6.63 (d, *J*=8.63 Hz, 2H), 3.40 (s, 2H), 2.27 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90.6 MHz): δ 156.6, 131.1, 128.0, 115.9, 63.5, 44.8. <sup>1</sup>H NMR data was consistent with previously reported values.<sup>4</sup>

***o*-Sulfonato-*N,N*-dimethylbenzylamine, sodium salt (2).** Dimethylamine in methanol (2.0 M, 10 mL, 20.0 mmol) was added to the solution of 2-formylbenzenesulfonic acid, sodium salt (purity: 75%, 1.39 g, 5.0 mmol) and NaBH<sub>3</sub>CN (470 mg, 7.5 mmol) in methanol (40 mL). The resulting solution was stirred at room temperature for 22 h. The organic solvent was removed under reduced pressure and water (15 mL) was added. The resulting solution was acidified (pH = 1) with 10% aqueous HCl. A saturated NaOH solution was added dropwise to reach a pH of 7. Water was removed under reduced pressure. Methanol (120 mL) was added to the residue and the resulting suspension was filtered. The remaining solid was washed with methanol (2 × 15 mL). The combined methanol filtrates were concentrated to approximate 25 mL and placed in a freezer overnight to give a white solid (0.5451 g, 46%). <sup>1</sup>H NMR (D<sub>2</sub>O, 360 MHz): δ 8.11-7.96

(m, 1H), 7.81-7.55 (m, 3H), 4.66 (s, 2H), 2.97 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 90.6 MHz):  $\delta$  143.9, 135.0, 133.0, 131.9, 128.7, 127.3, 60.5, 43.7.

***N,N*-Di(3-sulfonatopropyl)benzylamine, disodium salt (3).** Prepared by a modification of the procedure reported by Mizoguchi.<sup>5</sup> A mixture of benzylamine (0.44 mL, 4.0 mmol), 1,3-propanesultone (1.22 g, 10.0 mmol) and methanol (20 mL) was refluxed for 3 h, and then sodium carbonate (0.42 g, 4.0 mmol) was added. The resulting mixture was refluxed two days and then allowed to cool to room temperature. The solvent was removed under reduced pressure to give a white residue that was taken up in refluxing methanol (10 mL). Water (0.5 mL) was added to dissolve the solid. The solution was allowed to cool to room temperature and placed in a freezer overnight to give a white hygroscopic solid (0.349 g, 21%). The solid was stored in a drybox.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 360 MHz):  $\delta$  7.55-7.33 (m, 5H), 3.73 (s, 2H), 2.89 (t,  $J=7.72$  Hz, 4H), 2.65 (t,  $J=7.72$  Hz, 4H), 2.11-1.89 (m, 4H).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 90.6 MHz):  $\delta$  138.0, 131.0, 129.4, 128.5, 57.9, 52.3, 50.1, 21.6.

**4-(*N*-Benzyl-*N*-methylamino)benzoic acid, sodium salt (4).** A solution of 4-aminobenzoic acid (2.06 g, 15.0 mmol) and benzaldehyde (1.53 mL, 15.2 mmol) in methanol (100 mL) was refluxed for 18 h. The resulting mixture was cooled to room temperature. Portions of  $\text{NaBH}_3\text{CN}$  (1.13 g, 18.0 mmol) were added slowly and the reaction was stirred for 24 h at room temperature. Aqueous HCl (10%, 100 mL) was added and the resulting mixture was concentrated to approximate 120 mL. The mixture was then extracted with ethyl acetate (3  $\times$  120 mL). The combined ethyl acetate extracts were dried ( $\text{MgSO}_4$ ) and the solvent was removed under reduced pressure. The crude product was recrystallized from 50% methanol in water to obtain *N*-benzyl-*p*-aminobenzoic acid as a pale yellow solid (2.26 g, 66%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 360 MHz):  $\delta$  11.99 (s, 1H), 7.64 (d,  $J=8.60$  Hz, 2H), 7.38-7.29 (m, 4H), 7.28-7.20 (m, 1H), 7.02

(t,  $J=6.01$  Hz, 1H), 6.59 (d,  $J=8.59$  Hz, 2H), 4.33 (d,  $J=6.01$  Hz, 2H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 90.6 MHz):  $\delta$  167.4, 152.4, 139.4, 131.0, 128.3, 127.2, 126.8, 117.2, 111.1, 45.9.

*N*-Benzyl-*p*-aminobenzoic acid was reductively methylated by a literature procedure.<sup>6</sup> Trifluoroacetic acid (10 mL) was added dropwise over 60 minutes to a stirred mixture of *N*-benzyl-*p*-aminobenzoic acid (0.68 g, 3.00 mmol), paraformaldehyde (0.90 g, 30 mmol), and  $\text{NaBH}_4$  (0.568 g, 15.0 mmol) in dry THF (30 mL). After the addition was complete, the resulting mixture was stirred at room temperature for 24 h. Removal of THF under reduced pressure gave a white solid. Water (60 mL) was added to the residue, which was allowed to stand overnight. The mixture was filtered to give a white solid that was recrystallized twice from 95% ethanol to give 4-(*N*-benzyl-*N*-methylamino)benzoic acid (0.33 g, 46%).  $^1\text{H}$  NMR (DMSO- $d_6$ , 360 MHz):  $\delta$  12.07 (s, 1H), 7.73 (d,  $J=9.46$  Hz, 2H), 7.42-7.09 (m, 5H), 6.74 (d,  $J=8.60$  Hz, 2H), 4.67 (s, 2H), 3.10 (s, 3H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 90.6 MHz):  $\delta$  167.4, 152.2, 138.3, 131.0, 128.6, 126.8, 126.5, 117.1, 110.8, 54.8, 38.7. 4-(*N*-benzyl-*N*-methylamino)benzoic acid was treated with one equivalent of sodium hydroxide in methanol. Removal of methanol *in vacuo* gave **4**.  $^1\text{H}$  NMR (DMSO- $d_6$ , 360 MHz):  $\delta$  7.68 (d,  $J=8.59$  Hz, 2H), 7.39-7.11 (m, 5H), 6.59 (d,  $J=8.59$  Hz, 2H), 4.56 (s, 2H), 3.00 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 90.6 MHz):  $\delta$  176.4, 152.2, 139.3, 131.8, 129.5, 127.9, 127.8, 124.5, 112.3, 56.3, 39.0.

**4-[*N*-(Benzylidene)amino]benzenesulfonic acid, sodium salt (5)**. Prepared by a literature procedure.<sup>7</sup> Sodium hydroxide (0.693 g, 17.32 mmol) and sulfanilic acid (3.000 g, 17.32 mmol) were added to water (8 mL). The mixture was stirred until all the solids dissolved. Benzaldehyde (1.94 mL, 19.1 mmol) was added to the resulting solution. The resulting mixture was stirred at room temperature for 5 minutes at which point a white precipitate had formed. The reaction mixture was cooled in 0 °C in an ice-water bath for 10 minutes, filtered, and the

solid washed with cold water. The product was recovered as a pale yellow solid (2.45 g, 50%). <sup>1</sup>H NMR (D<sub>2</sub>O, 360 MHz): δ 9.90 (s, 1H), 7.93 (d, *J*=7.40 Hz, 2H), 7.79-7.68 (m, 1H), 7.67-7.50 (m, 4H), 6.84 (d, *J*=8.63 Hz, 2H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 90.6 MHz): δ 160.9, 151.4, 145.9, 136.0, 131.5, 128.8, 128.7, 126.6, 120.2.

**4-[(1-Phenylethylidene)amino]benzoic acid, sodium salt (6).** Prepared by a method reported by Sonola<sup>8</sup> and Shukla.<sup>9</sup> Acetophenone (2.40 mL, 20.3 mmol) and 4-aminobenzoic acid (2.74 g, 20.0 mmol) were taken up in glacial acetic acid (17 mL). The resulting mixture was cooled in an ice bath while portions of potassium cyanide (1.30 g, 20.0 mmol) were added. Stirring was continued overnight. The mixture was then cooled to 0 °C and filtered. The solid residue was recrystallized from methanol to give *N*-(1-cyano-1-phenylethyl)-*p*-aminobenzoic acid as a white solid (3.72 g, 70%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 360 MHz): δ 12.24 (s, 1H), 7.65 (d, *J*=8.85 Hz, 2H), 7.57 (s, 1H), 7.53-7.31 (m, 5 H), 6.53 (d, *J*=8.85 Hz, 2H), 1.91 (s, 3H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 90.6 MHz): δ 167.1, 148.4, 139.9, 130.5, 129.3, 128.4, 124.5, 120.6, 119.9, 113.8, 56.0, 32.2.

Sodium hydroxide (541 mg, 13.5 mmol) and *N*-(1-cyano-1-phenylethyl)-*p*-aminobenzoic acid (1.20 g, 4.51 mmol) were taken up in methanol (70 mL). After the solution was refluxed for 2 h, the reaction was allowed to cool to room temperature. The methanol was removed under reduced pressure. The residue was recrystallized from water-acetone to give **6** as a pale yellow solid (1.051 g, 89%). <sup>1</sup>H NMR (D<sub>2</sub>O, 360 MHz): δ 7.91 (d, *J*=8.59 Hz, 2H), 7.82 (d, *J*=7.74 Hz, 2 H), 7.62-7.42 (m, 3H), 6.88 (d, *J*=7.73, 2H), 2.17 (s, 3H). <sup>13</sup>C NMR (D<sub>2</sub>O, 90.6 MHz): δ 175.8, 171.3, 153.8, 140.0, 133.4, 132.0, 131.3, 129.6, 128.1, 120.5, 18.8.

**Synthesis of palladacycle 7.** The palladacycles were prepared by a modification of the procedure reported by Cope.<sup>10</sup> PdCl<sub>2</sub> (177 mg, 1.00 mmol) was added to the solution of **1** (150 mg, 1.00 mmol) and sodium acetate (82 mg, 1.0 mmol) in methanol (5 mL). The resulting

heterogeneous mixture was stirred at room temperature overnight. All of the palladium chloride was dissolved and replaced with a yellow precipitate. The precipitate was filtered off, washed with methanol ( $2 \times 10$  mL) and dried *in vacuo* to give **7** as a yellow solid (246 mg, 84%). Recrystallization from methanol gave an analytically pure sample of **7**.  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ , 360 MHz):  $\delta$  6.99-6.31 (m, 8H), 3.85 (brs, 4H), 2.76 (brs, 12H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 90.6 MHz):  $\delta$  154.0, 150.7, 138.3, 122.3, 119.7, 111.7, 72.1, 51.0. Calculated for  $\text{C}_{18}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_2\text{Pd}_2$ : C, 37.01; H, 4.14; N, 4.80. Found: C, 36.56; H, 3.99; N, 4.53.

**Palladacycle 8.** To the solution of **2** (237 mg, 1.00 mmol) and sodium acetate (82 mg, 1.0 mmol) in methanol (20 mL) was added palladium chloride (177 mg, 1.00 mmol). The resulting mixture was stirred overnight at room temperature until the palladium chloride dissolved to give a wine colored solution. The solvent was removed under reduced pressure. The residue was taken up in a hot methanol and water mixture (10 mL methanol and 2 mL water). Acetone (5 mL) was added and the flask was placed in a freezer overnight. The mixture was filtered and the precipitate was dried *in vacuo* to give a yellow powder (186 mg, 53%).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 360 MHz):  $\delta$  7.55 (d,  $J=8.09$  Hz, 2H), 7.46 (d,  $J=7.35$  Hz, 2H), 7.08 (dd,  $J=8.09$  Hz, 2H), 4.35 (s, 4H), 2.82 (s, 12H).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 90.6 MHz):  $\delta$  145.3, 143.8, 138.2, 126.1, 123.9, 72.3, 52.9. One of the aromatic peaks was not observed. Calculated for  $\text{C}_{18}\text{H}_{22}\text{Cl}_2\text{N}_2\text{Na}_2\text{O}_6\text{Pd}_2\text{S}_2$ : C, 28.59; H, 2.93; N, 3.70. Found: C, 28.74; H, 2.82; N, 3.93.

**Palladacycle 9.**  $\text{PdCl}_2$  (124 mg, 0.70 mmol) was added to a solution of **3** (280 mg, 0.70 mmol) and sodium acetate (57.4 mg, 0.70 mmol) in methanol (12 mL). The mixture was stirred at room temperature overnight. The resulting mixture was then filtered and washed with methanol ( $2 \times 10$  mL). The product was dried *in vacuo* to give a yellow powder (281 mg, 75%).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 360 MHz):  $\delta$  7.20-6.85 (m, 8H), 4.15 (s, 4H), 3.13-2.96 (m, 12H), 2.92-2.75 (m, 4H),

2.75-2.76 (m, 8H).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 90.6 MHz):  $\delta$  150.1, 141.3, 134.0, 126.8, 126.4, 123.2, 67.8, 61.1, 49.2, 23.9. Calculated for  $\text{C}_{26}\text{H}_{36}\text{Cl}_2\text{N}_2\text{Na}_4\text{O}_{12}\text{Pd}_2\text{S}_4 \cdot 2\text{H}_2\text{O}$ : C, 28.17; H, 3.64; N, 2.53. Found: C, 28.23; H, 3.54; N, 2.46.

**Palladacycle 10.**  $\text{PdCl}_2$  (0.1773 g, 1.0 mmol) was added to the solution of Schiff base **5** (0.2831 g, 1.0 mmol) and sodium acetate (0.0820 g, 1.0 mmol) in methanol (25 mL). The resulting heterogeneous mixture was stirred at room temperature for 24 h. The reaction was filtered to give a black solid that was taken up in DMSO (5 mL) and filtered through Celite to remove precipitated Pd(0). Diethyl ether (60 mL) was added slowly to the filtrate to form two layers. After standing for 24 h, the mixture was filtered. The product was recovered as a yellow solid (0.2205 g, 52%).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 360 MHz):  $\delta$  9.06 (d,  $J=7.40$  Hz, 4H), 8.36 (s, 2 H), 8.05 (d,  $J=8.01$  Hz, 4H), 7.89-7.70 (m, 5 H), 7.69-7.50 (m, 3H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 90.6 MHz):  $\delta$  172.8, 150.6, 147.9, 133.9, 132.1, 131.6, 128.6, 126.6, 126.3, 123.4, 112.2. Calculated for  $\text{C}_{26}\text{H}_{18}\text{Cl}_2\text{N}_2\text{Na}_2\text{O}_6\text{Pd}_2\text{S}_2$ : C, 36.81; H, 2.14; N, 3.30. Found: C, 37.44; H, 2.64; N, 3.51.

**Stability of palladacycle (10).** Palladacycle **10** (5.8 mg) and sodium carbonate (21 mg) were added to a NMR tube in a drybox. The NMR tube was sealed and moved from the drybox. After  $\text{D}_2\text{O}$  was added (0.5 mL), the NMR tube was placed in an 80 °C oil bath.  $^1\text{H}$  NMR data were obtained at a regular intervals. The  $^1\text{H}$  NMR spectrum showed that palladacycle **10** decomposed to **6** in two hours under basic conditions.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 360 MHz):  $\delta$  9.97(s, 1H), 7.99(d,  $J=8.02$  Hz, 2H), 7.79-7.68 (m, 1H), 7.67-7.50 (m, 4H), 6.88 (d,  $J=8.62$  Hz, 2H).

**Reaction of palladacycles with *t*-Bu-Amphos.** Palladacycle dimer (0.01 mmol, 0.02 mmol in Pd), *t*-Bu-Amphos (5.4 mg, 0.02 mmol) and were taken up in an NMR tube in a drybox. The NMR tube was then sealed and charged with deoxygenated water (0.5 mL). In the case of palladacycle **7**, the mixture was heated at 80 °C for several minutes to give a clear yellow

solution. The formation of palladacycle phosphine adducts was monitored by  $^{31}\text{P}$  NMR spectroscopy: **11**, 53.0 and 50.7 ppm (1:2.5); **12**, 52.7 ppm; **13**, 52.9 ppm; **14**, 41.6 and 39.9 ppm (4:1).

**Palladacycle phosphine adduct (11).** Palladacycle **7** (29.2 mg, 0.05 mmol) and *t*-Bu-Amphos (26.7 mg, 0.10 mmol) were taken up in deoxygenated methanol (3 mL). The mixture was refluxed 20 minutes. Methanol was evaporated *in vacuo*. The residue was dissolved in minimum amount of methanol and precipitated with ether (10 mL) to give a pale yellow solid (20 mg, 36%).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 360 MHz):  $\delta$  7.10 (d,  $J=8.32$  Hz, 1H), 6.90 (s, 1H), 6.62 (d,  $J=7.77$  Hz, 1H), 4.01 (s, 2H), 3.26-3.06 (m, 2H), 2.86 (s, 9H), 2.53 (s, 6H), 2.48-2.36 (m, 2H), 1.52 (d,  $J_{\text{P-H}}=13.87$ , 18H).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 90.6 MHz):  $\delta$  155.8, 141.4, 140.1, 125.5, 124.3 (brs), 112.2, 73.8 (brs), 65.2 (brs), 53.4 (brs), 38.1 (d,  $J_{\text{C-P}}=16.79$  Hz), 31.04 (d,  $J_{\text{C-P}}=4.58$  Hz), 30.96 (d,  $J_{\text{C-P}}=4.58$  Hz).  $^{31}\text{P}$  NMR ( $\text{D}_2\text{O}$ , 202.5 MHz):  $\delta$  53.6 (s).

**General procedure for ligand screening trials.** Under nitrogen, a vial was charged with appropriate amount of palladacycle, ligand, sodium carbonate (42.4 mg, 0.4 mmol), and phenylboronic acid (36.6 mg, 0.3 mmol). To this was added deoxygenated 1:1  $\text{H}_2\text{O}:\text{CH}_3\text{CN}$  (1.5 mL). 4-Bromoanisole (25  $\mu\text{L}$ , 0.2 mmol) and an internal standard, mesitylene (22  $\mu\text{L}$ ), were added via syringe. The reactions were run at the desired temperature. Aliquots were removed at a regular interval from organic layer and analyzed by GC. In the case of water (1.5 mL) as the solvent, the reaction was run at desired time and was then allowed to cool to room temperature. Ethyl acetate (1 mL) and mesitylene were added to the reaction mixture. Yields were calculated using response factors determined with authentic samples of 4-bromoanisole and 4-methoxybiphenyl.

**General procedure for low catalyst loading trials.** Stock solutions were prepared by dissolving appropriate amount of palladacycle **7** in deoxygenated acetonitrile to give solutions that were  $3.5 \times 10^{-2}$  to  $3.5 \times 10^{-4}$  M in Pd. Appropriate amount of *t*-Bu-Amphos was dissolved in deoxygenated water to give solutions that were  $7.5 \times 10^{-2}$  to  $7.5 \times 10^{-4}$  M in P. Under nitrogen, a vial was charged with sodium carbonate (42.4 mg, 0.4 mmol), and phenylboronic acid (36.6 mg, 0.3 mmol). To this were added deoxygenated water (1.5 mL) and 4-bromoanisole (25  $\mu$ L, 0.2 mmol). The catalyst and ligand solutions were added via syringe. The reaction was allowed for 4 h at 80 °C. The reaction then was allowed to cool to room temperature and ethyl acetate (1 mL) was added. Aliquots were removed from organic layer and analyzed by GC. Yields were calculated using response factors determined with authentic samples of 4-bromoanisole and 4-methoxybiphenyl.

**General procedure for catalyst recycling trials.** Under nitrogen, a vial was charged with catalyst **7** or **10** (1 mmol%), *t*-Bu-Amphos (5.4 mg, 2 mmol%), sodium carbonate (42.4 mg, 0.4 mmol), and phenylboronic acid (27 mg, 0.22 mmol). To this mixture was added deoxygenated water (1.5 mL). 4-Bromotoluene was added via syringe (25  $\mu$ L, 0.2 mmol). The reactions were run at 80 °C for 1 h. After the reaction mixture was cooled to room temperature, deoxygenated ethyl acetate (1 mL) was added and stirred for one minute. The upper layer was separated *via* cannula and mesitylene (15  $\mu$ L) as internal standard was added to this layer. Aliquots were removed from organic layer and analyzed by GC. The aqueous layer was transferred *via* cannula to a vial that was charged with phenylboronic acid (27 mg, 0.22 mmol) and sodium carbonate (21 mg, 0.2 mmol). 4-Bromotoluene (25  $\mu$ L, 0.2 mmol) was added via syringe for the subsequent cycle.

**General procedure for the preparatory scale Suzuki coupling reaction of water insoluble aryl halides and arylboronic acids.** In a drybox, a round bottom flask was charged with palladacycle dimer (0.01 mmol), *t*-Bu-Amphos (5.4 mg, 0.02 mmol), sodium carbonate (212 mg, 2.00 mmol), and arylboronic acid (1.5 mmol). The flask was sealed and removed from the drybox. Deoxygenated water (5 mL) and aryl halide (1.0 mmol) were added via syringe and the reaction was stirred at 80 °C for 4 h unless noted. After the reaction was allowed to cool to room temperature, saturated sodium bicarbonate (20 mL) was added to the reaction mixture. The resulting mixture was extracted with ether (3 × 30 mL). The combined ether extracts were dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. The crude material was flash chromatographed on a short silica gel column.

**General procedure for the coupling of water-soluble aryl halides and arylboronic acids.** Reactions were assembled as described for water-insoluble aryl bromides. After the reaction was allowed to cool to room temperature, 10 % aqueous HCl (20 mL) was added to the reaction mixture. The resulting suspension was extracted with ether (3 × 30 mL). The combined ether extracts were dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. The crude material was flash chromatographed on a short silica gel column.

**4-Methoxybiphenyl** (Table 3, entry 1). 4-Bromoanisole (125  $\mu$ L, 1.00 mmol) and phenylboronic acid (183 mg, 1.5 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with 5 % ethyl acetate in hexanes to give the product as white, crystalline solid (174.8 mg, 95 %). <sup>1</sup>H NMR and <sup>13</sup>C NMR (CDCl<sub>3</sub>) data were identical to the commercially available material (Aldrich Catalog). mp: 84-85 °C.

Literature mp: 90 °C.<sup>11</sup>

**4-Hydroxybiphenyl** (Table 3, entry 2). 4-Bromophenol (173 mg, 1.00 mmol), phenylboronic acid (183 mg, 1.50 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with 15 % ethyl acetate in hexanes. The product was recovered as a white, crystalline solid (153.8 mg, 90 %). <sup>1</sup>H NMR and <sup>13</sup>C NMR (CDCl<sub>3</sub>) spectra were identical to the commercially available material (Aldrich). mp: 160-161 °C. Literature mp: 164-165 °C.<sup>12</sup>

**4-Methylbiphenyl** (Table 3, entry 3). 4-Bromotoluene (125 μL, 1.01 mmol) and phenylboronic acid (183 mg, 1.5 mmol) were coupled by the above procedure. The crude product was purified by flash chromatography eluting with hexanes to give the product as a white, low melting point solid (151.8 mg, 90 %). <sup>1</sup>H and <sup>13</sup>C NMR (CDCl<sub>3</sub>) data were identical to the commercially available material (Aldrich Catalog).

**4-Acetylbiphenyl** (Table 3, entry 4). 4-Acetylbromobenzene (199.1 mg, 1.0 mmol) and phenylboronic acid (183 mg, 1.5 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with 75:25:5 hexane:CH<sub>2</sub>Cl<sub>2</sub>:ethyl acetate. The product was recovered as a white crystalline solid (168.5 mg, 86 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 360 MHz): δ 8.02 (d, *J* = 7.40 Hz, 2H), 7.67 (d, *J* = 8.02 Hz, 2H), 7.62 (d, *J* = 8.02 Hz, 2H), 7.55-7.30 (m, 3H), 2.62 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90.6 MHz): δ 197.9, 146.0, 140.0, 136.1, 129.15, 129.10, 128.4, 127.46, 127.42, 26.8. Spectral data were identical to previously reported data.<sup>13</sup> mp: 119-120 °C. Literature mp: 119-120 °C.<sup>14</sup>

**4-Carboxybiphenyl** (Table 3, entry 5). 4-Bromobenzoic acid (201 mg, 1.00 mmol) and phenylboronic acid (183 mg, 1.50 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with 5 % methanol in CH<sub>2</sub>Cl<sub>2</sub> to give the product as white solid (191.2 mg, 96 %). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 360 MHz): δ 12.96 (brs, 1H),

8.03 (d,  $J = 7.32$  Hz, 2H), 7.78 (d,  $J = 7.73$  Hz, 2H), 7.63 (d,  $J = 8.59$  Hz, 2H), 7.47 (t,  $J = 7.31$  Hz, 2H), 7.43 (t,  $J = 7.31$  Hz, 1H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 360 MHz):  $\delta$  167.1, 144.3, 139.0, 129.9, 129.6, 129.1, 128.3, 126.9, 126.7. Spectral data were identical to previously reported data.<sup>15</sup> mp: 221-222 °C. Literature mp 225-226 °C (Aldrich Catalog)

**2-Methylbiphenyl** (Table 3, entry 6). 2-Bromotoluene (120  $\mu\text{L}$ , 1.0 mmol) and phenylboronic acid (183 mg, 1.5 mmol) were coupled by the above procedure. The crude product was purified by flash chromatography eluting with hexanes to give the product as a colorless oil (115.0 mg, 68 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 360 MHz):  $\delta$  7.43-7.35 (m, 2H), 7.34-7.27 (m, 3H), 7.26-7.18 (m, 4H), 2.26 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90.6 MHz):  $\delta$  142.18, 142.15, 135.5, 130.5, 130.0, 129.4, 128.3, 127.4, 127.0, 126.0, 20.7. The spectral data was identical to that previously reported.<sup>16</sup>

**2,6-Dimethylbiphenyl** (Table 3, entry 7). 2-Bromo-*m*-xylene (135  $\mu\text{L}$ , 1.0 mmol) and phenylboronic acid (183 mg, 1.5 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with hexanes to recover the product as a colorless oil (118.4 mg, 64 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 360 MHz):  $\delta$  7.46-7.36 (m, 2H), 7.35-7.26 (m, 1H), 7.20-7.05 (m, 5H), 2.02 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90.6 MHz):  $\delta$  142.1, 141.3, 136.2, 129.2, 128.6, 127.5, 127.2, 126.8, 21.0. The  $^1\text{H}$  NMR spectrum is consistent with that previously reported.<sup>17</sup>

**4-Cyanobiphenyl** (Table 3, entry 8). 4-Chlorobenzonitrile (137.8 mg, 1.00 mmol) and phenylboronic acid (183 mg, 1.50 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with 75:25:5 hexane: $\text{CH}_2\text{Cl}_2$ :ethyl acetate to give the product as a pale yellow solid (121.7 mg, 68 %).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) spectra were identical to the commercially available material (Aldrich Catalog).

**4-Methoxy-4'-Methyl biphenyl** (Table 4 entry 1). 4-Bromotoluene (122  $\mu\text{L}$ , 1.00 mmol) and 4-methoxyphenylboronic acid (228 mg, 1.5 mmol) were coupled by the above procedure. The crude product was purified by flash chromatography eluting with 5 % ethyl acetate in hexanes to give the product as a white, crystalline solid (145.7 mg, 80 %).  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ , 360 MHz):  $\delta$  7.50 (d,  $J = 8.63$  Hz, 2H), 7.44 (d,  $J = 8.01$  Hz, 2H), 7.22 (d,  $J = 8.01$  Hz, 2H), 6.96 (d,  $J = 8.63$  Hz, 2H), 3.84 (s, 3H), 2.38 (s, 3 H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90.6 MHz):  $\delta$  159.1, 138.2, 136.5, 129.6, 128.1, 127.7, 126.7, 114.3, 55.5, 21.2. mp: 106-107  $^\circ\text{C}$ . Literature mp: 107-108  $^\circ\text{C}$ .<sup>18</sup>

**4-Methyl-4'-fluorobiphenyl** (Table 4, entry 2). 4-Bromotoluene (125  $\mu\text{L}$ , 1.02 mmol), 4-fluorophenylboronic acid (209.9 mg, 1.50 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with 5 % ethyl acetate in hexanes. The product was recovered as white, crystalline solid (174.4 mg, 92 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 360 MHz):  $\delta$  7.51 (dd,  $J = 8.63$  Hz,  $J = 5.50$  Hz, 2H), 7.42 (d,  $J = 8.02$  Hz, 2H), 7.23 (d,  $J = 8.02$  Hz, 2H), 7.09 (dd,  $J = 8.63$  Hz, 2H), 2.38 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90.6 MHz):  $\delta$  162.5 (d,  $^1J_{\text{C-F}} = 245.52$  Hz), 137.6, 137.4, 137.2, 129.7, 128.6 (d,  $^3J_{\text{C-F}} = 8.32$  Hz), 127.0, 115.7 (d,  $^2J_{\text{C-F}} = 20.81$  Hz), 21.2. The spectral data were identical to previously reported data.<sup>19</sup> mp: 77-78  $^\circ\text{C}$ . Literature mp: 77-78  $^\circ\text{C}$ .<sup>20</sup>

**4-Carboxy-4'-methylbiphenyl** (Table 4, entry 3). 4-Bromotoluene (125  $\mu\text{L}$ , 1.02 mmol) and 4-carboxyphenylboronic acid (199 mg, 1.20 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with 5 % methanol in  $\text{CH}_2\text{Cl}_2$ . The product was recovered as a white solid (172.4 mg, 80 %).  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 360 MHz):  $\delta$  12.92 (brs, 1H), 8.00 (d,  $J = 8.60$  Hz, 2H), 7.77 (d,  $J = 8.60$  Hz, 2H), 7.63 (d,  $J = 8.60$  Hz, 2H), 7.31 (d,  $J = 7.74$  Hz, 2H), 2.36 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ , 90.6 MHz):  $\delta$  167.1, 144.2, 137.8,

136.1, 130.0, 129.6, 129.3, 126.8, 126.4, 20.7. The spectra data were identical to previously reported data.<sup>21</sup> mp: 248-250 °C. Literature mp: 244-246 °C.<sup>21</sup>

**4-Cyano-4'-methylbiphenyl** (Table 4, entry 4). 4-Bromotoluene (125  $\mu$ L, 1.02 mmol) and 4-cyanophenylboronic (220 mg, 1.50 mmol) acid were coupled by the above procedure. The crude product was purified by flash chromatography eluting with 10 % ethyl acetate in hexanes to give the product as pale yellow solid (164.1 mg, 85%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 360 MHz):  $\delta$  7.75-7.61 (m, 4H), 7.48 (d,  $J$  = 8.63 Hz, 2H), 7.28 (d,  $J$  = 7.40 Hz, 2 H), 2.41 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90.6 MHz):  $\delta$  145.7, 138.9, 136.4, 132.7, 130.0, 127.6, 127.2, 119.1, 110.7, 21.3. The spectral data were identical to previously reported data.<sup>22</sup> mp: 104-106 °C.

**2,4'-Dimethylbiphenyl** (Table 4, entry 5). 4-Bromotoluene (125  $\mu$ L, 1.02 mmol), *o*-tolylphenylboronic acid (203.9 mg, 1.50 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography eluting with hexanes. The product was recovered as colorless oil (159.4 mg, 86 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 360 MHz):  $\delta$  7.29-7.12 (m, 8H), 2.38 (s, 3H), 2.26 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90.6 MHz):  $\delta$  142.0, 139.2, 136.5, 135.5, 130.4, 130.0, 129.2, 128.9, 127.2, 125.9, 21.3, 20.6. The spectral data were identical to previously reported values.<sup>13</sup>

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