Supplementary Material for:

The Copper Mediated Cross-Coupling of Phenylboronic Acids and *N*-Hydroxyphthalimide at Room Temperature: Synthesis of Aryloxyamines

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General Methods

Reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Pyridine, triethylamine and 1,2 dichloroethane were distilled from CaH_2. *N*-hydroxyphthalimide, copper (II) acetate, copper (I) chloride and several other copper salts were dried in a drying pistol at 110° C in the presence of phosphorous pentoxide overnight under high vacuum (< 1 mm Hg). Thin-layer chromatography on silica gel 60 F_{254} coated aluminum plates (EM Sciences) or analytical reverse phase high performance liquid chromatography (HPLC) were employed to monitor reaction progress. HPLC was performed using a Waters 600E multisolvent delivery system employing a Waters 486 tunable absorbance detector (λ_{det} = 225 nm) and a Waters 717 plus autosampler. A C18 Western Analytical column was utilized (model 033-715 150 Å, 3 –μ pore size) for all reverse phase HPLC analyses. An acetonitrile / water / trifluoroacetic acid solvent system was used; buffer A in the proportions of 4.8, 95, and 0.2 %, respectively, while buffer B was of 95, 4.8, and 0.2 % respectively (flow rate of 1.5 mL / min). Following 2 min of isocratic flow at 100% A, a linear gradient of 0

to 100 % B over 8 min was run. All flash chromatography was accomplished using 230-400 mesh silica gel 60 (EM Sciences). ^{1}H NMR spectra were recorded at 300, 400, 500 or 600 MHz on Bruker spectrometers. Chemical shifts are reported in parts per million downfield from the internal standard (Me_4Si, 0.0 ppm).

Representative Procedure for the copper mediated coupling of phenylboronic acids and *N*-hydroxyphthalimide. Synthesis of 3a.

A 20 mL scintillation vial equipped with a magnetic stirbar was charged with *N*-hydroxyphthalimide (163 mg, 1 mmol, 1 eq), copper (I) chloride (99 mg, 1 mmol, 1 eq), freshly activated 4 Å molecular sieves (~250 mg), and the phenylboronic acid (Aldrich, 244 mg, 2 mmol, 2 eq). The 1,2 dichloroethane (5 mL) solvent was added followed by pyridine (90 μL, 1.1 mmol, 1.1 eq) resulting in a light brown suspension. The cap was very loosely applied such that the reaction suspension was open to the atmosphere. The reaction was followed via analytical RP-HPLC (completed in 48 h). The color of the suspension turned from brown to emerald green as the reaction proceeded. The reaction mixture was absorbed onto ~ 6 g of silica gel by removing the solvent under reduced pressure in the presence of the SiO_2. Chromatography of the reaction mixture afforded **3a** as a white solid (216 mg, 90%); see below for characterization data.

During optimization of the simplest *N*-phenoxyphthalimide **3a,** determination of reaction yield was accomplished by RP-HPLC analysis of the reaction mixture. The reaction mixture was diluted with methylene chloride to a total volume of 25-mL (volumetric flask) and 10 μL of that solution was diluted into 990 μL of DMSO. The DMSO solution (10 μL injected) was then analyzed by analytical HPLC. The integrated area of the

product peak was compared to a calibration curve of purified *N*-phenoxyphthalimide **3a** to determine the yield.

***N*-Phenoxyphthalimide (3a)** Preparation of **3a** was described above as the representative procedure. Flash chromatographic purification (50g of SiO_2, 25% EtOAc in hexanes) afforded 216 mg (90%) of a white solid. mp 150.5-152 °C (Lit mp 144.5-146 °C), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11-7.20 (m, 3H), 7.31-7.37 (m, 2H), 7.78-7.83 (m, 2H), 7.89-7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.44, 123.95, 128.82, 129.72, 134.86, 158.87, 162.90; MALDIFTMS (DHB) 240.0656 m/z ($(M+H)^+$, $C_{14}H_{10}NO_3$, requires 240.0655).

***N*- (4-Trifluoromethyl)-phenoxyphthalimide (3b)** 4-Trifluoromethylphenyl boronic acid (Frontier, 380 mg, 2 mmol, 2 eq) was subjected to the representative coupling procedure with **1** outlined above. Flash chromatographic purification (50g of SiO_2, 30% EtOAc in hexanes) afforded 201 mg (66 %) of a white solid. mp 120-122 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 9.1 Hz, 2H), 7.60 (d, J = 9.1 Hz, 2H), 7.78-7.83 (m, 2H), 7.89-7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.00, 124.06, 127.20 (q, $J_{C\text{-}F}$ = 5.7 Hz), 128.56, 135.07, 160.94, 162.55; MALDIFTMS (DHB) 306.0383 m/z ($(M-H)^+$, $C_{15}H_7F_3NO_3$ requires 306.0373).

***N*- (4-Methoxy)-phenoxyphthalimide (3c)** 4-Methoxyphenyl boronic acid (Aldrich, 304 mg, 2 mmol, 2 eq) was subjected to the representative coupling procedure with **1** outlined above. Flash chromatographic purification (63 g of SiO_2, < 1 % hexanes in CH_2Cl_2) afforded 97 mg (36 %) of a white solid. mp 119-120 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H) 6.85 (d, J = 9.1 Hz, 2H), 7.23 (d, J = 9.1 Hz, 2H), 7.78-7.83 (m, 2H), 7.89-

7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.67, 114.59, 117.63, 123.84, 128.82, 134.74, 153.02, 156.91, 163.03; MALDIFTMS 270.0758 m/z $(M+H)^+$, $C_{15}H_{12}NO_4$ requires 270.0761).

***N*- (4-Iodo)-phenoxyphthalimide (3d)** 4-Iodophenyl boronic acid (Frontier, 496 mg, 2 mmol, 2 eq) was subjected to the representative coupling procedure with **1** outlined above. Flash chromatographic purification (63 g of SiO_2, 35% hexanes in CH_2Cl_2) afforded 211 mg (57 %) of a white solid. mp 158-160 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94-6.97 (m, 2H), 7.61-7.64 (m, 2H), 7.78-7.83 (m, 2H), 7.89-7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 87.58, 116.69, 123.99, 128.64, 134.95, 138.53, 158.82, 162.64; MALDIFTMS (DHB) 365.9627 m/z ($(M+H)^+$, $C_{14}H_9INO_3$ requires 365.9622).

***N*- (4-Bromo)-phenoxyphthalimide (3e)** 4-Bromophenyl boronic acid (Aldrich, 402 mg, 2 mmol, 2 eq) was subjected to the representative coupling procedure with **1** outlined above. Flash chromatographic purification (63 g of SiO_2, 40% hexanes in CH_2Cl_2) afforded 234 mg (73 %) of a white solid. mp 143-145 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-7.11 (m, 2H), 7.44-7.48 (m, 2H), 7.78-7.83 (m, 2H), 7.89-7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.39, 117.23, 124.08, 128.64, 132.63, 135.02, 157.95, 162.75; MALDIFTMS (DHB) 317.9759 m/z ($(M+H)^+$, $C_{14}H_9BrNO_3$ requires 317.9761).

***N*- (4-Methylcarboxylate)-phenoxyphthalimide (3f)** 4-Methylcarboxylatephenyl boronic acid (Combi-blocks, 360 mg, 2 mmol, 2 eq) was subjected to the representative coupling procedure with **1** outlined above. Flash chromatographic purification (75 g of SiO_2, 25% EtOAc in hexanes) afforded 191 mg (64 %) of a white solid. mp 191-193 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 9.1 Hz, 2H), 7.81-7.87 (m, 2H), 7.91-7.97 (m, 2H), 8.04 (d, J = 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.11, 113.41, 124.14,

126.35, 128.29, 131.72, 135.08, 162.05, 162.60, 166.08; MALDIFTMS 320.0531 m/z $(M+Na)^+$, $C_{16}H_{12}NO_5Na$ requires 320.0529).

***N*- (4-Vinyl)-phenoxyphthalimide (3g)** 4-Vinylphenyl boronic acid (Aldrich, 296 mg, 2 mmol, 2 eq) was subjected to the representative coupling procedure with **1** outlined above. Flash chromatographic purification (70 g of SiO_2, 20 % EtOAc in hexanes) afforded 239 mg (90 %) of a white solid. mp 117-119 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (d, J = 10.8 Hz, 1H), 5.66 (d, J = 17.6 Hz, 1H), 6.62-6.69 (dd, J = 6.7, 10.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.81-7.87 (m, 2H), 7.91-7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.11, 113.41, 124.14, 126.35, 128.29, 131.72, 135.08, 162.05, 162.60, 166.08; MALDIFTMS (DHB) *m/z* 266.0819 ($(M+H)^+$, $C_{16}H_{12}NO_3$ requires 266.0812).

***N*-(4-Formyl)-phenoxyphthalimide (3h)** 4-Formylphenyl boronic acid (Aldrich, 300 mg, 2 mmol, 2 eq) was subjected to the representative reaction procedure with **1** outlined above. Flash chromatographic purification (60 g of SiO_2, 30 % hexanes in CH_2Cl_2) afforded 142 mg (53 %) of a white solid. mp 172-174 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ, 7.16-7.19 (m, 2H), 7.74-7.78 (m, 2H), 7.79-7.82 (m, 2H), 7.83-7.87 (m, 2H), 9.85 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.05, 124.17, 128.65, 131.87, 132.96, 135.16, 162.47, 163.04, 190.37; MALDIFTMS (DHB) 268.0604 *m/z* ($(M+H)^+$, $C_{15}H_{10}NO_4$, requires 268.0604).

***N*-(4-Cyano)-phenoxyphthalimide (3i)** 4-Cyanophenyl boronic acid (Frontier, 300 mg, 2 mmol, 2 eq) was subjected to the representative coupling procedure with **1** outlined above. Flash chromatographic purification (60 g of SiO_2, 30 % hexanes in CH_2Cl_2) afforded 175 mg (66 %) of a white solid. mp 214-215 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ,

7.21-7.25 (m, 2H), 7.65-7.68 (m, 2H), 7.79-7.82 (m, 2H), 7.83-7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.23, 114.63, 118.12, 124.25, 128.62, 134.20, 135.26, 161.66, 162, 44; MALDIFTMS (DHB) 287.0425 *m/z* ($(M+Na)^+$, $C_{15}H_8N_2O_3Na$, requires 287.0427).

***N*- (3-Trifluoromethyl)-phenoxyphthalimide (3j)** 3-Trifluoromethylphenyl boronic acid (Lancaster, 380 mg, 2 mmol, 2 eq) was subjected to the represenative coupling procedure with **1** outlined above. Flash chromatographic purification (50 g of SiO_2, 40 % EtOAc in hexanes) afforded 270 mg (88 %) of a white solid. mp 104-106 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ, 7.34-7.38 (m, 1H), 7.40-7.45 (m, 2H), 7.47 (t, J = 8.4 Hz, 2H), 7.82-7.87 (m, 2H), 7.92-7.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.61, 117.76, 118.11, 121.40, 122.30, 124.19, 128.75, 130.45, 132.19, 135.12, 158.96, 162.75; LC-MS 309 *m/z* $(M+H)^+$, $C_{15}H_{19}F_3NO_3$ requires 309).

***N*- (3-Methyoxy)-phenoxyphthalimide (3k)** 3-Methoxyphenyl boronic acid (Aldrich, 304 mg, 2 mmol, 2 eq) was subjected to the represenative coupling procedure with **1** outlined above. Flash chromatographic purification (50 g of SiO_2, 50 % CH_2Cl_2 in toluene) afforded 157 mg (57 %) of a white solid. mp 120-122 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ, 3.73 (s, 3H), 6.62-6.66 (m, 1H), 6.67-6.73 (m, 2H), 7.16-7.22 (m, 1H), 7.82-7.87 (m, 2H), 7.92-7.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.23, 100.43, 105.81, 109.82, 123.69, 128.46, 130.04, 134.72, 159.74, 160.64, 162.61; LC-MS 270 m/z $(M+H)^+$, $C_{15}H_{12}NO_4$ requires 270).

***N*- (3-Fluoro)-phenoxyphthalimide (3l)** 3-Fluorophenyl boronic acid (Lancaster, 280 mg, 2 mmol, 2 eq) was subjected to the represenative coupling procedure with **1** outlined above. Flash chromatographic purification (60 g of SiO_2, 30 % EtOAc in hexanes)

afforded 167 mg (65 %) of a white solid. mp 134-135 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83-6.92 (m, 2H), 6.94-6.98 (m, 1H), 7.26-7.34 (m, 1H), 7.82-7.87 (m, 2H), 7.92-7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.50, 109.77, 111.33, 124.06, 128.61, 130.75, 135.02, 159.71, 161.97, 164.43; MALDIFTMS (DHB) 257.0451 *m/z* $(M)^+$, $C_{14}H_{18}FNO_3$ requires 257.0488).

***N*- (3-Isopropyl)-phenoxyphthalimide (3m)** 3-Isopropylphenyl boronic acid (Lancaster, 328 mg, 2 mmol, 2 eq) was subjected to the represenative coupling procedure with **1** outlined above. Flash chromatographic purification (60 g of SiO_2, 50 % CH_2Cl_2 in hexanes) afforded 207 mg (74 %) of a white solid. mp 102-104 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, J = 7.0 Hz, 6H), 2.88 (sept, J = 7.0 Hz, 1H), 6.92-6.96 (m, 1H), 7.01 (d, J = 7.7 Hz, 1H), 7.06-7.08 (m, 1H), 7.23 (t, J = 7.7 Hz, 1H), 7.82-7.87 (m, 2H), 7.92-7.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.62, 33.87, 111.10, 112.61, 122.52, 123.72, 128.60, 129.34, 134.71, 150.98, 158.81, 162.80; MALDIFTMS (DHB) 282.1128 *m/z* $(M+H)^+$, $C_{17}H_{16}NO_3$ requires 282.1125).

***N*- (2-Methyl)-phenoxyphthalimide (3n)** 2-Tolyl boronic acid (Frontier, 268 mg, 2 mmol, 2 eq) was subjected to the represenative coupling procedure with **1** outlined above. Flash chromatographic purification (70 g of SiO_2, 50 % CH_2Cl_2 in hexanes) afforded 156 mg (61%) of a white solid. mp 155-156 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (s, 3H), 6.93-6.96 (m, 1H), 7.03 (td, J = 7.7, 1.1 Hz, 1H), 7.09-7.14 (m, 1H), 7.22 (dd, J = 7.7, 0.7 Hz, 1H), 7.82-7.87 (m, 2H), 7.92-7.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.69, 112.63, 123.79, 124.24, 125.91, 126.94, 128.79, 131.41, 134.75, 156.94, 162.94; MALDIFTMS (DHB) 254.0817 *m/z* $(M+H)^+$, $C_{15}H_{12}NO_3$ requires 254.0812).

***N*- (3,5- Difluorophenyl)-phenoxyphthalimide (3o)** 3,5-Difluorophenyl boronic acid (Aldrich, 316 mg, 2 mmol, 2 eq) was subjected to the represenative coupling procedure with **1** outlined above. Flash chromatographic purification (70 g of SiO_2, 10 % CH_2Cl_2 in toluene) afforded 197 mg (72 %) of a white solid. mp 172-174 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58-6.63 (m, 1H), 6.68-6.73 (m, 2H), 7.82-7.87 (m, 2H), 7.92-7.97 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 98.23 (m), 100.07 (t, J_{C-F} = 25.3 Hz), 124.20, 128.55, 135.18, 160.36 (t, J_{C-F} = 13.8 Hz), 162.44; MALDIFTMS (DHB) 276.0456 *m/z* $(M+H)^+$, $C_{14}H_8F_2NO_3$ requires 276.0467).

Representative Procedure for the hydrazinolysis of the *N*-aryloxyphthalimides to the corresponding aryloxyamine. Synthesis of 4.

A 50 mL round bottom flask, equipped with a magnetic stirbar, was charged the *N*-aryloxyphthalimide **3a** (652 mg, 2.73 mmol, 1 eq), 10 % MeOH in $CHCl_3$ (25 mL), and hydrazine monohydrate (0.401 mL, 8.2 mmol, 3 eq) resulting in a colorless solution. The reaction was allowed to stir at room temperature. Upon completion (TLC monitoring, 12 h) a white precipitate appeared (the phthalizine) in a colorless reaction solution. The reaction mixture was adsorbed to 6 g of silica gel and passed through a plug of silica gel (50 g) washing with 30% EtOAc in Hexane (300 mL). Removal of the Hexane/EtOAc produced a slightly pale yellow oil which upon Kugelrohr distillation from K_2CO_3 (< 10 mg) provided pure aryloxyamine **4** as a clear colorless oil (238 mg, 80%); See below for characterization data. Alternatively the after removal of the Hexane/EtOAc the yellow oil was taken up in Et_2O and cooled to 0°C. After 10 min of being at 0°C 4 N HCl in Dioxane was added dropwise until pH 3 was reached (pH paper). The resulting white

solid was filtered and washed with Et_2O (2 x 10 mL) to afford the pure HCl salt of **4** (306 mg, 77%).

Phenoxyamine (**4**) *N*-aryloxyphthalimide **3a** (652 mg, 2.7 mmol) was subjected to the representative hydrazinolysis reaction outlined above. Distillation (85 °C, 10 mm Hg) provided 238 mg (80%) of pure phenoxyamine as a clear colorless liquid or the HCl salt prepared as described above gave 306 mg (77%) of a white solid mp 132 °C dec (lit mp 132 °C dec). ^{1}H NMR (400 MHz, MeOD) δ 6.84-6.89 (m, 1H), 7.03-7.09 (m, 2H), 7.19-7.25 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 114.05, 121.64, 130.28, 163.06; LC-MS 110 m/z $(M+H)^+$, C_6H_8NO requires 110.

3-Trifluoromethylaryloxyamine (**5**) was used as the specific example above in the representative procedure. Distillation (85 °C, 6 mm Hg) provided 582 mg (90%) of pure 3-trifluoromethyl aryloxyamine as a clear colorless liquid. ^{1}H NMR (500 MHz, CDCl3) δ 6.00 (s, 2H), 7.19-7.21 (m, 1H), 7.30 (dd, J = 8.4, 2.6 Hz, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.45-7.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.37, 117.19, 117.93, 130.94, 162.06; LC-MS 178 m/z $(M+H)^+$, $C_7H_7F_3NO$ requires 178.