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Supporting Information

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Supporting Information

Desulfitative Carbon–Carbon Cross-Coupling of Thioamide Fragments with Boronic Acids

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EXPERIMENTAL PROCEDURES

General Methods. TLC analysis was performed on Merck precoated 60 F₂₅₄ plates. Melting points were obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. ¹H and ¹³C NMR spectra were recorded on a Bruker AMX360 instrument in DMSO-d₆ operating at 360 and 90 MHz, respectively. Mass spectra were taken on a Hewlett-Packard LC/MSD 1100 series instrument in the atmospheric pressure chemical ionization positive APCI mode.

HPLC Analysis. For reaction monitoring and quality control of the synthesized compounds a Shimadzu LC-10 system, that included LC10-AT(VP) pumps, an autosampler (SIL-10AXL), and a dual wavelength UV detector set at 215 and 254 nm was used. The separation was carried out using a C 18 reversed phase analytical column, LiChrospher 100 (E. Merck, 100 x 3 mm, particle size 5 µm) at 25°C and mobile phase from (A) 0.1% TFA in 90:10 water/MeCN and (B) 0.1% TFA acid in MeCN (all solvents were HPLC grade, Acros; TFA was analytical reagent

grade, Aldrich). The following gradients were applied at a flow rate of 0.5 mL/min: linear increase from solution 30% B to 100% solution B in 8 min, hold at 100% solution B for 2 min.

Microwave Irradiation Experiments. Microwave irradiation experiments were carried out using the EmrysTM Synthesizer and Initiator eight from Biotage (Uppsala), including proprietary Workflow Manager software (version 2.1). Experiments were carried out in sealed microwave process vials utilizing the standard absorbance level (300 W maximum power). Reaction times under microwave conditions reflect total irradiation times rather than actual reaction times at a given temperature.

Preparation of Copper(I) thiophenecarboxylate (CuTC)¹

A 250 ml round-bottomed flask was charged with thiophene-2-carboxylic acid (60 g, 0.47 mmol), Cu₂O (16.7 g, 0.12 mol) and toluene (180 ml). The flask was then outfitted with a Dean-Stark trap and condenser and the mixture refluxed overnight with azeotropic removal of water. The brown/red suspension was cooled to 60 °C and the product was filtered with vacuum under argon atmosphere using inverted funnel. The filter cake was washed under Ar with dry methanol to remove excess of the acid, and then with dry ether until the eluent was colorless, and then with a small amount of hexane. The product was dried under a flow of Ar, then transferred to a flask and dried further under vacuum. The product was obtained as a dark brown/red, air stable powder in 80 % yield. CuTC is somewhat air-sensitive while wetted by solvent. Once the product is dry it can be stored and handled at room temperature without any special precautions.

General Procedure for the Pd⁰-catalyzed, Cu^I-mediated Carbon–Carbon Cross-Coupling of Thioamides with Phenylboronic acid (Table 1):

A dry microwave process vial was charged with a stir bar. To the vessel were added the corresponding thioamide (0.18 mmol), PhB(OH)₂ (26.3 mg, 0.22 mmol), Cu(I) thiophene-2-carboxylate (103 mg, 0.54 mmol) and [Pd(PPh₃)₄] (8.3 mg, 0.007 mmol, 4 mol%). The reaction vessel was flushed with Ar and sealed. Through the septum anhydrous and degassed THF (1.8 ml) was added. The mixture was subsequently heated in a microwave reactor at 100°C for 60 min. After this period an additional amount of Pd catalyst (8.3 mg, 0.007 mmol, 4 mol%) was added and the reaction mixture was again heated at 100 °C for 1 h. After cooling, the solvent was evaporated and CHCl₃ (120 mL) was added. The crude reaction mixture was subsequently

washed with 25% aqueous ammonia (3 x 40 ml). The aqueous ammonium layer was reextracted again with CHCl₃ (3 x 40 ml). The combined organic phase was dried with MgSO₄ and the residue after evaporation purified by flash chromatography. Products were identified by NMR and MS spectrometry in addition to comparison with literature data.

2-Phenylpyridine (Entry 1).² Purification by flash chromatography on silicagel (ethyl acetate/CH₂Cl₂/hexanes 1:1:12) provided product (entry 1, yield 90 %) as a light yellow oil. ¹H NMR (DMSO-d₆): 8.67 (d, *J* = 4.5 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.90-7.86 (m, 1H), 7.51-7.41 (m, 3H), 7.31-7.36 (m, 1H); MS (pos. APCI): *m/z* 156.3.

2-Phenylpyrimidine (Entry 2).³ Purification by flash chromatography on silicagel (ethyl acetate/CH₂Cl₂/hexanes 1:1:12) provided product (entry 2, yield 83 %) as a light yellow solid. ¹H NMR (DMSO-d₆): 8.91 (d, *J* = 4.8 Hz, 2H), 8.41-8.38 (m, 2H), 7.54-7.52 (m, 3H), 7.45 (t, *J* = 4.8, 1H); MS (pos. APCI): *m/z* 157.2.

5-Bromo-2-phenylpyridine (Entry 3).⁴ Purification by flash chromatography on silicagel (THF/hexanes 1:10) provided product (entry 3, yield 87 %) as a light yellow solid, m.p.: 65-66 °C. ¹H NMR (DMSO-d₆): 8.78 (d, *J* = 2.3 Hz, 1H), 8.12 (dd, *J*₁ = 8.5 Hz, *J*₂ = 2.3 Hz, 1H), 8.08-8.06 (m, 2H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.52-7.43 (m, 3H); MS (pos. APCI): *m/z* 233.9.

4-(4-Methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (Entry 4). Purification by flash chromatography on silicagel (ethyl acetate/CH₂Cl₂/hexanes 1:3:6) provided product (entry 4, yield 97 %) as a light yellow solid, m.p.: 139-142 °C. ¹H NMR (DMSO-d₆, 360 MHz): 7.82-7.79 (m, 2H), 7.53-7.52 (m, 3H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 2.99 (t, *J* = 6.3 Hz, 2H), 2.50-2.46 (m, 2H), 1.88-1.81 (m, 2H), 1.71-1.65 (m, 2H); MS (pos. APCI): *m/z* 341.1.

2-Phenyl-1,4,5,6-tetrahydropyrimidine (Entry 5).⁵ Purification by flash chromatography on basic alumina (MeOH/CH₂Cl₂/Hexanes 1:3:6) provided product (entry 5, yield 96 %) as a light yellow solid. ¹H NMR (DMSO-d₆): 7.73-7.71 (m, 2H), 7.44-7.35 (m, 3H), 3.35 (t, *J* = 5.7 Hz, 4H), 1.71 (quin, *J* = 5.7 Hz, 2H); MS (pos. APCI): *m/z* 161.4.

2-Phenyl-4,5-dihydro-3H-pyrrole (Entry 6).⁶ Purification by flash chromatography on silicagel (ethyl acetate/CH₂Cl₂/hexanes 1:1:1) provided product (entry 6, yield 75 %) as a semi-solid. ¹H NMR (DMSO-d₆): 7.83-7.81 (m, 2H), 7.45-7.43 (m, 3H), 3.94 (t, *J* = 7.3 Hz, 2H), 2.91 (t, *J* = 8.2, 2H), 1.98-1.89 (m, 2H); MS (pos. APCI): *m/z* 146.2.

2,2,4-Trimethyl-5-phenyl-2H-imidazole (Entry 7). Purification by flash chromatography on neutral alumina (ethyl acetate/hexanes 1:10) provided product (entry 7, yield 52 %) as a semi-

solid. ¹H NMR (DMSO-d₆, 360 MHz): 7.83-7.81 (m, 2H), 7.52-7.50 (m, 3H), 2.40 (s, 3H), 1.38 (s, 6H); MS (pos. APCI): m/z 187.4.

2-Phenyl-4,5-dihydroimidazole (Entry 8).⁷ Purification by flash chromatography on basic alumina (acetone/CHCl₃ 1:5) provided product (entry 8, yield 93 %) as a light yellow solid. ¹H NMR (DMSO-d₆, 360 MHz): 7.82-7.80 (m, 2H), 7.47-7.39 (m, 3H), 3.37 (br s, 4H); MS (pos. APCI): m/z 147.0

2-Phenyl-1H-imidazole (Entry 9).⁸ Purification by flash chromatography on silicagel (ethyl acetate/hexanes 2:1, EA) provided product (entry 9, yield 8 %) as a semi-solid. ¹H NMR (DMSO-d₆, 360 MHz): 12.51 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.43 (dd, *J*₁ = 7.6 Hz, *J*₂ = 7.3 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.24 (br s, 1H), 7.02 (br s, 1H); MS (pos. APCI): m/z 144.9.

2-Phenylbenzimidazole (Entry 10).⁹ Purification by flash chromatography on silicagel (ethyl acetate/CH₂Cl₂/hexanes 1:1:2) provided product (entry 10, yield 67 %) as a white solid, m.p.: 291-292 °C. ¹H NMR (DMSO-d₆, 360 MHz): 12.91 (s, 1H), 8.18 (d, *J* = 7.5 Hz, 2H), 7.68-7.47 (m, 5H), 7.24-7.17 (m, 2H); MS (pos. APCI): m/z 195.1.

4-Phenylpyridine.¹⁰ Purification by flash chromatography on neutral alumina (ethyl acetate/CH₂Cl₂/hexanes 1:1:10) provided product (yield 15 %) as a white solid. ¹H NMR (DMSO-d₆, 360 MHz): 8.63 (d, *J* = 5.6 Hz, 2H), 7.81-7.79 (m, 2H), 7.71 (d, *J* = 5.6 Hz, 2H), 7.55-7.46 (m, 3H); MS (pos. APCI): m/z 155.9.

General Procedure for the Pd⁰-catalyzed, Cu^I-mediated Carbon–Carbon Cross-Coupling of 3-Cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-2(1H)-thione with Different Boronic acids:

A dry microwave process vial was charged with a stir bar. To the vessel were added 3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-2(1H)-thione (30 mg, 0.10 mmol), ArB(OH)₂ (0.12 mmol), Cu(I) thiophene-2-carboxylate (58 mg, 0.30 mmol) and [Pd(PPh₃)₄] (4.7 mg, 0.004 mmol, 4 mol%). The reaction vessel was flushed with Ar and sealed. Through the septum anhydrous and degassed THF (1 ml) was added. The mixture was subsequently heated in a microwave reactor at 100°C for 60 min. After this period an additional amount of Pd catalyst (4.7 mg, 0.004 mmol, 4 mol%) was added and the reaction mixture was again heated at 100 °C for 1 h. After cooling, the solvent was evaporated and CHCl₃ (90 mL) was added. The crude reaction mixture was subsequently washed with 25% aqueous ammonia (3 x 30 ml). The aqueous

ammonium layer was reextracted again with CHCl_3 (3 x 30 ml). The combined organic phase was dried with MgSO_4 and the residue after evaporation purified by flash chromatography.

2-(4-Cyanophenyl)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile.

Purification by flash chromatography on silicagel (ethyl acetate/ CH_2Cl_2 /hexanes 1:4:13) provided product (yield 76 %) as a yellow solid, m.p.: 198-201 °C. ^1H NMR (DMSO-d_6 , 360 MHz): 8.04-7.99 (m, 4H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.10 (d, $J = 8.6$ Hz, 2H), 3.83 (s, 3H), 3.01 (t, $J = 6.3$ Hz, 2H), 2.53-2.50 (m, 2H), 1.87-1.84 (m, 2H), 1.72-1.68 (m, 2H); ^{13}C NMR (DMSO-d_6 , 90 MHz): 161.9, 160.2, 156.2, 154.1, 142.5, 132.8, 131.2, 130.4, 130.3, 127.7, 118.6, 117.5, 114.6, 112.6, 106.1, 55.7, 33.5, 27.3, 22.3, 22.2; MS (pos. APCI): m/z 366.3

4-(4-Methoxyphenyl)-2-(3-tolyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile. Purification by flash chromatography on silicagel (CH_2Cl_2 /hexanes 3:1) provided product (yield 92 %) as a light yellow solid, m.p.: 134-136 °C. ^1H NMR (DMSO-d_6 , 360 MHz): 7.60-7.58 (m, 2H), 7.42 (dd, $J_1 = 8.3$ Hz, $J_2 = 7.7$ Hz, 1H), 7.36 (d, $J = 8.6$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.09 (d, $J = 8.6$ Hz, 2H), 3.83 (s, 3H), 2.99 (t, $J = 6.5$ Hz, 2H), 2.50-2.46 (m, 2H), 2.39 (s, 3H), 1.86-1.83 (m, 2H), 1.70-1.67 (m, 2H); MS (pos. APCI): m/z 355.3.

2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile.

Purification by flash chromatography on silicagel (ethyl acetate/ CH_2Cl_2 /Hexanes 1:3:13) provided product (yield 77 %) as a offwhite solid, m.p.: 197-199 °C. ^1H NMR (DMSO-d_6 , 360 MHz): 7.84 (d, $J = 8.6$ Hz, 2H), 7.60 (d, $J = 8.6$ Hz, 2H), 7.36 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 2H), 3.83 (s, 3H), 2.99 (t, $J = 6.4$ Hz, 2H), 2.54-2.47 (m, 2H), 1.86-1.81 (m, 2H), 1.70-1.67 (m, 2H); MS (pos. APCI): m/z 375.2.

4-(4-Methoxyphenyl)-2-(2-tolyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile. Purification by flash chromatography on silicagel (ethyl acetate/ CH_2Cl_2 /hexanes 1:3:10) provided product (yield 25 %) as a light yellow solid. ^1H NMR (DMSO-d_6 , 360 MHz): 7.38-7.32 (m, 6H), 7.09 (d, $J = 8.7$ Hz, 2H), 3.82 (s, 3H), 2.95 (t, $J = 6.4$ Hz, 2H), 2.52 (t, $J = 6.4$ Hz, 2H), 2.21 (s, 3H), 1.87-1.84 (m, 2H), 1.71-1.68 (m, 2H); MS (pos. APCI): m/z 355.1.

2-(3-Methoxyphenyl)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile.

Purification by flash chromatography on silicagel (ethyl acetate/ CH_2Cl_2 /hexanes 1:3:10) provided product (yield 93 %) as a light yellow solid, m.p.: 143-145 °C. ^1H NMR (CDCl_3 , 360 MHz): 7.46-7.38 (m, 3H), 7.27-7.23 (m, 2H), 7.06-7.00 (m, 3H) 3.89 (s, 6H), 3.11 (t, $J = 6.4$ Hz, 2H), 2.56 (t, $J = 6.4$ Hz, 2H), 1.97- 1.90 (m, 2H), 1.80-1.75 (m, 2H); MS (pos. APCI): m/z 371.3.

Procedure for Carbon–Sulfur Cross-Coupling of 5-Bromopyridine-(1*H*)-thione **1 with Phenylboronic acid (Scheme 1).**

A microwave process vial was charged with a stir bar. To the vessel were added 5-bromopyridine-(1*H*)-thione **1** (30 mg, 0.16 mmol), PhB(OH)₂ (77 mg, 0.63 mmol), Cu(OAc)₂ (28.7 mg, 0.16 mmol), 1,10-phenanthroline (56.9 mg, 0.32 mmol) and 1,2-dichloroethane (1.5 ml). The reaction mixture was stirred under air. After 15 minutes the reaction vessel was sealed and irradiated at 110 °C for 2 h. After cooling, the mixture was transferred to a round bottom flask, and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (CH₂Cl₂/hexanes 1:1) to provide 5-bromo-2(phenylthio)pyridine **3**¹¹ (yield 71 %) as a semi-solid. ¹H NMR (DMSO-d₆, 360 MHz): 8.53 (d, *J* = 2.5 Hz, 1H), 7.88 (dd, *J*₁ = 8.6 Hz, *J*₂ = 2.5 Hz, 1H), 7.60-7.57 (m, 2H), 7.51-7.49 (m, 3H), 6.91 (d, *J* = 8.6 Hz, 1H); MS (pos. APCI): *m/z* 267.9.

Suzuki Coupling of 5-Bromo-2-phenylpyridine **2 with Phenylboronic acid (Scheme 1).**

A microwave process vial was charged with a stir bar. To the vessel were added 5-bromo-2-phenylpyridine **2** (15 mg, 0.06 mmol), PhB(OH)₂ (11.7 mg, 0.10 mmol), Pd(PPh₃)₄ (7.4 mg, 0.006 mmol, 10 mol%) and dissolved in dimethoxyethane (0.75 ml). To the reaction mixture was added a solution of Na₂CO₃ (10.2 mg, 0.10 mmol) in H₂O (0.25 ml). The reaction vessel was sealed and irradiated at 150 °C for 30 min. After cooling, the mixture was transferred to a round bottom flask, and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (ethyl acetate/CH₂Cl₂/hexanes 1:3:20) to provide 2,5-diphenylpyridine **4**¹² (yield 90 %) as a white solid. ¹H NMR (DMSO-d₆, 360 MHz): 8.99 (d, *J* = 2.4 Hz, 1H), 8.17 (dd, *J*₁ = 8.3 Hz, *J*₂ = 2.4 Hz, 1H), 8.16-8.13 (m, 2H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 2H), 7.54-7.41 (m, 6H); MS (pos. APCI): *m/z* 232.4.

Suzuki Coupling of 5-Bromo-2(phenylthio)pyridine **3 with Phenylboronic acid (Scheme 1).**

A microwave process vial was charged with a stir bar. To the vessel were added 5-bromo-2(phenylthio)pyridine **3** (32 mg, 0.12 mmol), PhB(OH)₂ (22.1 mg, 0.18 mmol), Pd(PPh₃)₄ (7 mg, 0.006 mmol, 5 mol%) and dissolved in dimethoxyethane (1.2 ml). To the reaction mixture was added solution of Na₂CO₃ (19.2 mg, 0.18 mmol) in H₂O (0.4 ml). The reaction vessel was sealed and irradiated at 150 °C for 30 min. After cooling, the mixture was transferred to a round bottom flask, and was adsorbed on silica gel. The residue was purified by flash chromatography on silica

gel (CH₂Cl₂/Hexanes 1:1) to provide 5-phenyl-2(phenylthio)pyridine **5** (yield 81 %) as a semi-solid. ¹H NMR (DMSO-d₆, 360 MHz): 8.73 (d, *J* = 2.5 Hz, 1H), 7.95 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.5 Hz, 1H), 7.69-7.67 (m, 2H), 7.64-7.61 (m, 2H), 7.53-7.38 (m, 6H), 7.03 (d, *J* = 8.4 Hz, 1H); MS (pos. APCI): m/z 264.2.

Preparation of Bis-(5-bromo-[2]pyridyl)-disulfide.

To a solution of the 5-bromopyridine-2(1*H*)-thione (100 mg, 0.53 mmol) in CH₂Cl₂ (2 ml) was added dropwise at 0 °C a solution of SO₂Cl₂ (23 μl, 0.29 mmol) in CH₂Cl₂ (1 ml).¹³ The reaction mixture was stirred for 30 min at 0 °C and evaporated to dryness to provide a product (91 %) as a yellow solid, m.p.: 114-115 °C. ¹H NMR (DMSO-d₆, 360 MHz): 8.63 (d, *J* = 2.2 Hz, 2H), 8.03 (dd, *J*₁ = 8.6 Hz, *J*₂ = 2.2 Hz, 2H), 8.59 (d, *J* = 8.6 Hz, 2H); MS (pos. APCI): m/z 378.9.

Procedure for Cu^I-mediated Coupling of Bis-(5-bromo-[2]pyridyl)-disulfide with Phenylboronic Acid.

A microwave process vial was charged with a stir bar. To the vessel were added bis-(5-bromo-[2]pyridyl)-disulfide (20 mg, 0.05 mmol), PhB(OH)₂ (26 mg, 0.21 mmol), Cu(I) thiophene-2-carboxylate (10 mg, 0.05 mmol), 1,10-phenanthroline (19.2 mg, 0.12 mmol) and 1,2-dichloroethane (1 ml). The reaction mixture was stirred under air. After 15 minutes the reaction vessel was sealed and irradiated at 110 °C for 1 h. After cooling, the mixture was transferred to a round bottom flask, and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (CH₂Cl₂/hexanes 2:1) to provide product **3** (yield 66%) as a semi-solid.

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