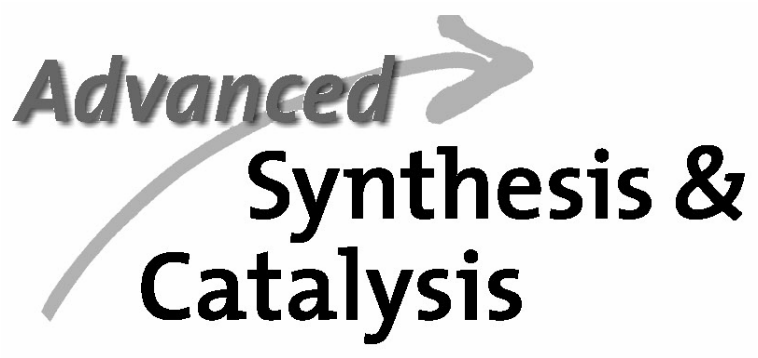


Supporting Information

2,3-Disubstituted Benzo[*b*]thiophenes from Diaryl Alkynes *via* Electrophilic Addition-Cyclization and Palladium Catalyzed Cross-Coupling

Giuseppe Lamanna[a] and Stefano Menichetti[a]*

[a]Dipartimento di Chimica Organica e Laboratorio di Progettazione Sintesi e Studio di Eterocicli Biologicamente Attivi (**H**etero**B**io**L**ab), Università di Firenze, Via della Lastruccia 13, I-50019 Sesto fiorentino (FI), Italy. Fax: (+39)-055-4573531; e-mail: stefano.menichetti@unifi.it

Experimental Section

Cross-coupling reactions were carried out on flame dried flasks under a positive pressure of dry Nitrogen. THF was distilled from sodium in the presence of the blue colour of benzophenone kethyl, toluene was distilled from sodium, and DCM was distilled from CaH_2. All reactions were monitored by TLC on commercially available precoated plates (silica gel 60 F254) and the products were visualized with acid vanillin solution. Silica gel 60, 230–400 mesh, was used for column chromatography. Petrol refers to light petroleum, bp 40–60 °C. Melting points were measured on a microscopic apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solutions. Residual $CHCl_3$ was used as reference at 7.26 and 77.00 ppm, respectively. FTIR spectra were recorded in KBr pellets or $CHCl_3$ solutions. Mass spectra were measured with a Shimadzu QP5050. Commercial available reagents, catalysts and ligands were used as obtained from freshly open container without further purifications. PEPPSI-IPr was purchase from Sigma-Aldrich. Phthalimidesulfenyl chloride was prepared from the corresponding commercial available disulfide (purchase from Chemper snc) as reported elsewhere.[14]

Solid-phase synthesis

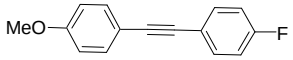
Carboxylic Merrifield resin was purchased from Novabiochem. It is an 1% cross-linked divinylbenzene-styrene copolymer of 100–200 mesh with a loading of 1.4 mmol/g. Solid-phase reactions were carried in sure sealed vials and the resin suspensions transferred by plastic-pipettes. Solid phase work-up was carried out by means of the plastic-syringe technique. Flat-bottom PE syringes were equipped with sintered Teflon filters, Teflon tubing and valves which allow suction to be applied to the syringe from below. The resins were washed with the solvent used for the reaction and sequentially with DCM, MeOH, diethyl ether and again DCM and the shrunken beads were dried in vacuum over KOH before further transformations and analyses. Functionalized resins were analysed with FTIR and/or MAS solid-phase NMR. MAS solid-phase NMR were acquired on a 400 MHz Varian MercuryPlus spectrometer using a PFGID-Varian Nanoprobe (Pulsed Field Gradient, Indirect Detection), at 25 °C using $CDCl_3$ as solvent with a CPMG modified sequence to minimise the resin signals.

Synthesis of alkynes 2a and 2b by Sonogashira cross-coupling: A mixture of aryl iodide (1.0 mmol), Bu_4NOAc (1.5 mmol), $Pd(OAc)_2$ (3 mol%) and DMF (3 mL) was added to an oven-dried Schlenk flask under a nitrogen atmosphere. After 5 min of stirring an alkyne (1.2 mmol) was added. Stirring was continued at rt under nitrogen for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (3x10 mL). The combined ether layers were dried over Na_2SO_4, filtered, concentrated, and purified by silica gel flash chromatography to afford the desired coupling product.

4-[(4-Methoxyphenyl)ethynyl]phenyl acetate (2a)

The product was isolated, after column chromatography (eluent: petroleum ether/CH_2Cl_2 1:1), as a yellow solid (92% yield), mp 122-124 °C; IR (KBr): *?* = 2929, 2212 (C=C), 1748 (C=O), 1602, 1513, 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *d* = 2.30 (s, 3H), 3.83 (s, 3H), 6.84-6.91 (m, 2H), 7.05-7.10 (m, 2H), 7.42-7.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): *d* = 21.19, 55.27, 87.20, 89.37, 113.87, 115.06, 121.13, 121.48, 132.36, 132.86, 149.99, 159.43, 168.85; MS: *m/z* (%) = 266 ($M^{\bullet+}$, 23), 224 (100), 209 (47); Anal. calcd. for $C_{17}H_{14}O_3$: C 76.68, H 5.30; found: C 76.88, H 5.32.

1-Fluoro-4-((4-methoxyphenyl)ethynyl)benzene (2b)

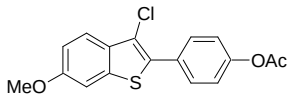


The product was isolated, after column chromatography (eluent: petroleum ether/CH_2Cl_2 4:1), as a white solid (91% yield), mp 96-98 °C; IR (KBr): *?* = 2974, 2212 (C=C), 1602, 1507, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *d* = 3.83 (s, 3H), 6.85-6.91 (m, 2H), 6.99-7.08 (m, 2H), 7.43-7.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): *d* = 55.28, 86.91, 88.97, 113.89, 115.04, 115.21, 115.65, 119.52, 119.58, 132.83, 133.01, 133.18, 159.43, 159.58, 164.53; MS: *m/z* (%) = 226 ($M^{\bullet+}$, 100), 211 (63), 183 (52); Anal. calcd. for $C_{15}H_{11}FO$: C 79.63, H 4.90; found: C 79.96, H 4.97.

Addition of PhtNSCl to alkynes 2a and 2b: To a solution of alkyne (1.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise, at 0 °C, a solution of phthalimidesulfenyl chloride (1.1 mmol) in dry CH_2Cl_2 (8 mL) under a nitrogen atmosphere. The mixture was stirred at rt for 3 h then diluted with CH_2Cl_2 (10 mL), and washed with saturated $NaHCO_3$ solution (2x30 mL) and water (2x30 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give **3a** and **3b** as mixtures of *E*/*Z* diastereoisomers in 1:1 (d OMe = 3.68 and 3.84 ppm) or 5:2 ratio (d OMe_{major} = 3.68 ppm, OMe_{minor} = 3.83 ppm) respectively.

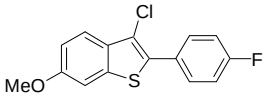
Aluminium trichloride cyclization to benzo[*b*]thiophenes 4a and 4b: To a solution of thiophthalimide **3**, as mixture of *E*/*Z* diastereoisomers, (1.0 mmol) in dry CH_2Cl_2 (15 mL), $AlCl_3$ (4.0 mmol) was added under a nitrogen atmosphere. After stirring at rt for 2-4 h the reaction mixture was diluted with CH_2Cl_2 (10 mL), and washed with saturated $NaHCO_3$ solution (2x30 mL) and water (2x30 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the crude product was purified by flash chromatography to provide the desired benzo[*b*]thiophene.

4-(3-Chloro-6-methoxybenzo[*b*]thiophen-2-yl)phenyl acetate (4a)



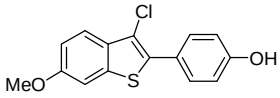
The product was isolated, after column chromatography (eluent: CH_2Cl_2/petroleum ether 4:1), as a pale-brown solid (72% yield), mp 121-123 °C; IR (KBr): *?* = 2941, 1759 (C=O), 1608, 1474, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 2.33 (s, 3H), 3.89 (s, 3H), 7.08 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.17-7.21 (m, 2H), 7.25 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.75-7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): *d* = 21.14, 55.68, 104.80, 115.12, 116.39, 121.84, 123.02, 130.18, 131.78, 132.46, 138.08, 150.56, 158.41, 169.28; MS: *m/z* (%) = 332 ($M^{\bullet+}$, 44), 290 (100), 275 (72); Anal. calcd. for $C_{17}H_{13}ClO_3S$: C 61.35, H 3.94; found: C 61.25, H 3.81.

3-Chloro-2-(4-fluorophenyl)-6-methoxybenzo[*b*]thiophene (4b)



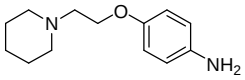
The product was isolated, after column chromatography (eluent: petroleum ether/CH_2Cl_2 4:1), the as a white solid (68% yield), mp 86-87 °C; IR (KBr): *?* = 2929, 1608, 1496, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 3.89 (s, 3H), 7.08 (dd, *J* = 2.2, 9.0 Hz, 1H), 7.13-7.18 (m, 2H), 7.25 (s, 1H), 7.70-7.75 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *d* = 55.68, 104.82, 115.13, 115.60, 115.82, 116.29, 123.01, 128.57, 130.86, 130.93, 131.73, 132.30, 137.99, 158.40, 161.40, 163.88; MS: *m/z* (%) = 292 ($M^{\bullet+}$, 100), 277 (90), 249 (40); Anal. calcd. for $C_{15}H_{10}ClFOS$: C 61.54, H 3.44; found: C 61.84, H 3.45.

Solid-phase synthesis of 4-(3-chloro-6-methoxybenzo[*b*]thiophen-2-yl)phenol (4c):



Commercial Merrifield resin (1.0 mmol) was swelled in dry toluene (2 mL) under mechanical stirring for 30 min, then $SOCl_2$ (5.0 mmol) was added and the mixture was heated at 60 °C for 2 h. The same procedure was repeated to ensure the complete halogenation: IR (KBr): *?* = 1770 and 1731 (C=O), 870 (C–Cl) cm^{-1}. The solid supported acyl chloride (1.0 mmol) was swelled in dry CH_2Cl_2 (4 mL) under mechanical stirring. After 30 min, DMAP (0.1 mmol), 4-iodophenol (2.0 mmol) and DIPEA (2.0 mmol) were added in sequence and stirring was continued for 24 h at rt to afford the ester-supported resin: IR (KBr): *?* = 1737 (C=O) cm^{-1}. An oven-dried Schlenk flask was charged with the ester-resin (1.0 mmol), Bu_4NOAc (3.0 mmol), $Pd(OAc)_2$ (6 mol %) and DMF (5 mL) under a nitrogen atmosphere. After 10 min of stirring 4-ethynylanisole (2.0 mmol) was added and stirring was continued at rt under nitrogen for 24h to give the alkyne-resin: IR (KBr): *?* = 2207 (C=C), 1734 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 3.73 (s, OMe). Alkyne pending resin (1.0 mmol) was swelled in dry CH_2Cl_2 (3 mL) under mechanical stirring for 30 min. To the suspension a solution of phthalimidesulfenyl chloride (1.5 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise at 0 °C under a nitrogen atmosphere, and stirring was continued for 16 h at rt to obtain a 2:1 mixture of *E/Z* supported *N*-thiophthalimides: IR (KBr): *?* = 1787, 1742 and 1714 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 3.63 (s, OMe_{minor}), 3.81 (s, OMe_{major}), 7.50-7.80 (m, H_{arom}Pht). The *N*-thiophthalimide modified resin (1.0 mmol) was swelled in dry CH_2Cl_2 (5 mL) under mechanical stirring. After 30 min, $AlCl_3$ (4.0 mmol) was added and stirring was continued for 4 h at rt to afford the benzo[*b*]thiophene resin pre-**4c**: IR (KBr): *?* = 1734 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 3.70 (s, OMe). Supported benzothiophene pre-**4c** (1.0 mmol) was swelled in dry THF (3.5 mL) under mechanical stirring for 30 min, then a solution of sodium methoxide 1.35 M (5.0 mmol) in MeOH was added and the mixture was stirred for 3 h at rt. The resin was filtered and washed with several portions of CH_2Cl_2 and MeOH. The organic phase was washed with saturated NH_4Cl solution and water, and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided derivative **4c** as a pure compound: White solid (50% yield), mp 157-159 °C; IR (KBr): *?* = 3422 (O–H), 3008, 1608, 1479, 1216 cm^{-1}; ^1H NMR [$(CD_3)_2CO$, 400 MHz]: *d* = 3.88 (s, 3H), 6.97-7.01 (m, 2H), 7.10 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.61-7.65 (m, 2H), 7.67 (d, *J* = 8.8 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz): *d* = 56.04, 105.92, 115.11, 116.00, 116.57, 123.17, 124.36, 131.16, 132.44, 134.70, 138.57, 158.83, 159.36; MS: *m/z* (%) = 290 ($M^{\bullet+}$, 100), 275 (91), 247 (27); Anal. calcd. for $C_{15}H_{11}ClO_2S$: C 61.96, H 3.81; found: C 61.91, H 3.82.

4-(2-(Piperidin-1-yl)ethoxy)aniline (8)

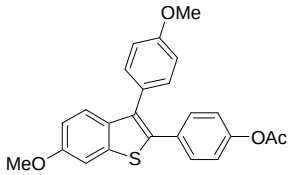


a) Mitsunobu reaction: 4-acetamidophenol (1.0 mmol) and PPh_3 (1.5 mmol) was stirred, under nitrogen, in dry THF (8 mL) for 5 min. 1-(2-Hydroxyethyl)piperidine (1.1 mmol) and DEAD (1.5 mmol) were subsequently added. After refluxing for 48 h, the solvent was removed under vacuum, and the crude product was purified by flash chromatography on silica gel (eluent: CH_3OH/EtOAc 1:1) to give the required acetamide as a brown solid (70% yield), mp 94-96 °C; IR (KBr): *?* = 3277 (N–H), 2929, 1664 (C=O), 1608, 1507, 1239 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *d* = 1.30-1.61 (m, 6H), 2.03 (s, 3H), 2.36-2.50 (m, 4H), 2.65-2.74 (m, 2H), 3.95-4.07 (m, 2H), 6.70-6.78 (m, 2H), 7.25-7.39 (m, 2H), 8.32-8.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): *d* = 24.13, 24.18, 25.81, 54.94, 57.83, 65.91, 114.54, 121.78, 131.05, 155.21, 168.35; MS: *m/z* (%) = 262 ($M^{\bullet+}$, 10), 112 (34), 98 (100); Anal. calcd. for $C_{15}H_{22}N_2O_2$: C 68.67, H 8.45, N 10.68; found: C 68.63, H 8.56, N 10.46.

b) Deacetylation reaction: The amide (1.0 mmol) was dissolved in 3 N HCl solution (15 mL) and the resulting mixture was heated to reflux for 2 h. The reaction was quenched by the careful addition of solid NaOH until basic pH and then extracted with EtOAc (3x20 mL). The organic layers was combined and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided the ammine as a brown oil (90% yield) that was used in the next step without purification; IR ($CHCl_3$): *?* = 3435 and 3366 (N–H), 2935, 1610, 1511, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 1.40-1.46 (m, 2H), 1.54-1.63 (m, 4H), 2.45-2.55 (m, 4H), 2.70-2.74 (m, 2H), 3.31-3.42 (m, 2H), 4.00-4.04 (m, 2H), 6.59-6.63 (m, 2H), 6.70-6.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): *d* = 23.96, 25.63, 54.66, 57.74, 66.15, 115.26, 115.83, 139.75, 151.28; MS: *m/z* (%) = 220 ($M^{\bullet+}$, 9), 112 (85), 98 (100); Anal. calcd. for $C_{13}H_{20}N_2O$: C 70.87, H 9.15, N 12.72; found: C 70.91, H 9.09, N 12.65.

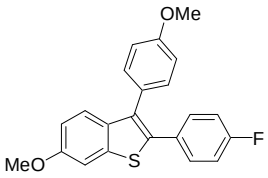
General procedure for the PEPPSI-IPr catalyzed Suzuki-Miyuara cross-coupling reactions: An oven-dried Schlenk flask was charged with 3-chlorobenzo[*b*]thiophene (1.0 mmol), boronic acid (1.5 mmol), K_2CO_3 (3.0 mmol), PEPPSI-IPr catalyst (2 mol%) and dry toluene (8 mL), under a nitrogen atmosphere. The mixture was stirred at 100 °C under nitrogen until complete consumption of the starting material as judged by TLC (3-7h). Upon cooling, the reaction mixture was diluted with diethyl ether (20 mL), washed with brine (3x30 mL), and dried over Na_2SO_4. Concentration in vacuum afforded the desired coupling product that was chromatographed on silica gel.

4-(6-Methoxy-3-(4-methoxyphenyl)benzo[*b*]thiophen-2-yl)phenyl acetate (5a)



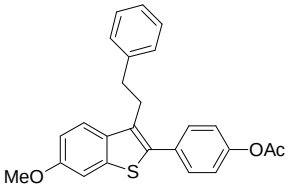
The product was isolated, after column chromatography (eluent: CH_2Cl_2), as a white solid (85% yield), mp 160-162 °C; IR (KBr): *?* = 2929, 1753 (C=O), 1602, 1468, 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 2.29 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.93-7.01 (m, 5H), 7.23-7.27 (m, 2H), 7.29-7.35 (m, 3H), 7.46 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): *d* = 21.10, 55.20, 55.62, 104.57, 114.19, 114.37, 121.42, 124.09, 127.60, 130.33, 131.39, 132.22, 132.69, 135.17, 135.26, 140.02, 149.79, 157.64, 158.92, 169.25; MS: *m/z* (%) = 404 ($M^{\bullet+}$, 76), 362 (100), 347 (64); Anal. calcd. for $C_{24}H_{20}O_4S$: C 71.27, H 4.98; found: C 71.44, H 5.07.

2-(4-Fluorophenyl)-6-methoxy-3-(4-methoxyphenyl)benzo[*b*]thiophene (5b)



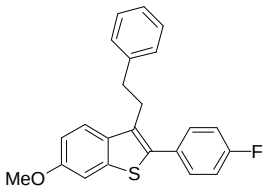
The product was isolated, after column chromatography (eluent: petroleum ether/CH_2Cl_2 2:1), as a white solid (89% yield), mp 159-161 °C; IR (KBr): *?* = 2924, 1600, 1510, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 3.86 (s, 3H), 3.90 (s, 3H), 6.92-6.99 (m, 5H), 7.21-7.29 (m, 4H), 7.34 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): *d* = 55.21, 55.64, 104.62, 114.15, 114.18, 114.39, 115.23, 115.45, 124.08, 127.57, 127.70, 130.63, 130.66, 131.01, 131.09, 131.38, 135.10, 139.95, 158.93, 160.81, 163.27; MS: *m/z* (%) = 364 ($M^{\bullet+}$, 100), 349 (46), 277 (13); Anal. calcd. for $C_{22}H_{17}FO_2S$: C 72.51, H 4.70; found: C 72.84, H 4.99.

4-(6-Methoxy-3-phenethylbenzo[b]thiophen-2-yl)phenyl acetate (6a)



The product was isolated, after column chromatography (eluent: petroleum ether/CH_2Cl_2 4:1), as a white solid (90% yield), mp 119-121 °C; IR (KBr): *?* = 2929, 1753 (C=O), 1597, 1474, 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 2.34 (s, 3H), 2.96-3.00 (m, 2H), 3.12-3.17 (m, 2H), 3.91 (s, 3H), 7.05-7.14 (m, 5H), 7.19-7.28 (m, 3H), 7.32-7.35 (m, 3H), 7.70 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): *d* = 21.12, 28.91, 36.17, 55.61, 104.89, 114.15, 121.56, 122.03, 122.79, 126.05, 127.17, 128.37, 130.56, 131.14, 132.25, 134.14, 140.59, 141.30, 150.16, 157.39, 169.33; MS: *m/z* (%) = 402 ($M^{\bullet+}$, 28), 269 (100), 238 (23); Anal. calcd. for $C_{25}H_{22}O_3S$: C 74.60, H 5.51; found: C 74.50, H 5.25.

2-(4-Fluorophenyl)-6-methoxy-3-phenethylbenzo[*b*]thiophene (6b)

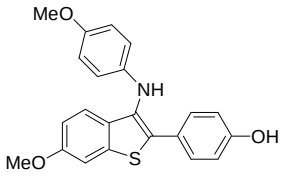


The product was isolated, after column chromatography (eluent: petroleum ether/CH_2Cl_2 3:1), as a white solid (92% yield), mp 74-76 °C; IR (KBr): *?* = 2958, 1600, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 2.94-2.99 (m, 2H), 3.09-3.14 (m, 2H), 3.92 (s, 3H), 7.05-7.10 (m, 5H), 7.19-7.29 (m, 5H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): *d* = 28.91, 36.15, 55.63, 104.92, 114.18, 115.27, 115.48, 122.78, 126.08, 128.36, 128.39, 130.58, 130.61, 131.09, 131.21, 131.28, 134.07, 135.23, 140.52, 141.31, 157.42, 161.15, 163.61; MS: *m/z* (%) = 362 ($M^{\bullet+}$, 42), 271 (100), 240 (45); Anal. calcd. for $C_{23}H_{19}FOS$: C 76.21, H 5.28; found: C 76.53, H 5.07.

General procedure for the PEPPSI-IPr catalyzed the Buchwald-Hartwig cross-coupling reactions: Under nitrogen, 3-chlorobenzo[*b*]thiophene (1.0 mmol), aniline (1.3 mmol), NaO*t*-Bu (3.0 mmol), PEPPSI-IPr catalyst (4 mol%) and dry toluene (6 mL) were added to an oven-dried Schlenk flask. The resulting mixture was stirred at 100 °C for the desired time until complete consumption of the starting material as judged by TLC, (4-24h). Upon cooling, the

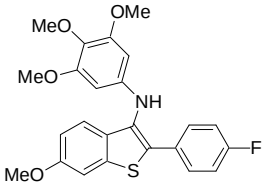
reaction mixture was diluted with diethyl ether (20 mL), washed with brine (3x30 mL), and dried over Na_2SO_4. The crude amine was purified by flash chromatography to provide the desired coupling product.

4-(6-Methoxy-3-(4-methoxyphenylamino)benzo[*b*]thiophen-2-yl)phenol (7a)



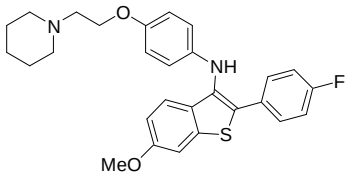
The product was isolated, after column chromatography (eluent: CH_2Cl_2), as a brown solid (78% yield), mp 175-177 °C; IR (KBr): *?* = 3299 (O–H), 2929, 1602, 1507, 1239 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 400 MHz): *d* = 3.68 (s, 3H), 3.86 (s, 3H), 6.65-6.69 (m, 3H), 6.71-6.75 (m, 2H), 6.82-6.86 (m, 2H), 6.93 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.50-7.54 (m, 2H), 8.53 (s, 1H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz): *d* = 55.70, 55.93, 106.12, 114.75, 115.44, 116.19, 116.37, 116.46, 123.69, 126.00, 130.20, 131.69, 132.77, 138.68, 141.70, 153.71, 158.08, 158.76; MS: *m/z* (%) = 377 ($M^{\bullet+}$, 100), 362 (45), 136 (23); Anal. calcd. for $C_{22}H_{19}NO_3S$: C 70.00, H 5.07, N 3.71; found: C 69.90, H 5.18, N 3.72.

2-(4-Fluorophenyl)-6-methoxy-N-(3,4,5-trimethoxyphenyl)benzo[*b*]thiophen-3-amine (7b)



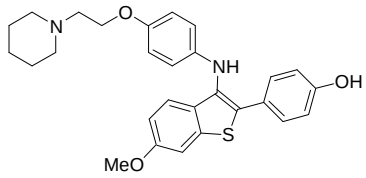
The product was isolated, after column chromatography (eluent: CH_2Cl_2), as a brown solid (80% yield), mp 120-122 °C; IR (KBr): *?* = 3411 (N–H), 2959, 1602, 1503, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 3.68 (s, 6H), 3.79 (bs, 3H), 3.89 (s, 3H), 5.41 (bs, 1H), 5.93 (bs, 2H), 6.95 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.05-7.11 (m, 2H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.52-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): *d* = 55.62, 55.72, 55.97, 104.95, 114.01, 114.07, 115.48, 115.91, 123.04, 128.84, 129.25, 129.32, 129.70, 129.84, 130.70, 130.90, 137.93, 142.12, 153.66, 157.59, 159.51, 164.44; MS: *m/z* (%) = 439 ($M^{\bullet+}$, 73), 424 (100), 204 (16); Anal. calcd. for $C_{24}H_{22}FNO_4S$: C 65.59, H 5.05, N 3.19; found: C 65.42, H 5.20, N 3.39.

2-(4-Fluorophenyl)-6-methoxy-N-(4-(2-(piperidin-1-yl)ethoxy)phenyl)benzo[*b*]thiophen-3-amine (7c)



The product was isolated, after column chromatography (eluent: EtOAc) as a yellow solid (86% yield), mp 116-118 °C; IR (KBr): *?* = 3378 (N–H), 3154, 2929, 1597, 1507, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 1.42-1.47 (m, 2H), 1.58-1.64 (m, 4H), 2.51-2.58 (m, 4H), 2.71-2.76 (m, 2H), 3.87 (s, 3H), 4.02-4.06 (m, 2H), 5.33 (s, 1H), 6.63-6.68 (m, 2H), 6.75-6.79 (m, 2H), 6.90 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.02-7.07 (m, 2H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.51-7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): *d* = 24.14, 25.85, 54.99, 55.58, 58.04, 66.35, 105.18, 114.16, 115.63, 115.76, 115.97, 116.29, 123.26, 128.57, 129.55, 129.58, 129.95, 130.03, 130.85, 138.28, 139.79, 152.64, 157.82, 161.01, 163.47; MS: *m/z* (%) = 476 ($M^{\bullet+}$, 6), 112 (100), 98 (85); Anal. calcd. for $C_{28}H_{29}FN_2O_2S$: C 70.56, H 6.13, N 5.88; found: C 70.30, H 6.10, N 5.80.

4-(6-Methoxy-3-(4-(2-(piperidin-1-yl)ethoxy)phenylamino)benzo[*b*]thiophen-2-yl)phenol (7d)



The product was isolated by flash chromatography (eluent: CH_3OH/EtOAc 1:1) as a brown solid (75% yield), mp 174-176 °C; IR ($CHCl_3$): *?* = 3583 (O–H), 3393 (N–H), 2941, 1606, 1507 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *d* = 1.42-1.50 (m, 2H), 1.60-1.67 (m, 4H), 2.51-2.53 (m, 4H), 2.76-2.80 (m, 2H), 3.84 (s, 3H), 4.00-4.04 (m, 2H), 5.32 (s, 1H), 6.57-6.66 (m, 4H), 6.76-6.80 (m, 2H), 6.86 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.37-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): *d* = 23.93, 25.21, 54.71, 55.56, 57.80, 65.33, 105.12, 113.66, 115.30, 116.01, 116.26, 122.84, 124.38, 128.58, 129.47, 130.22, 130.95, 137.73, 140.16, 151.78, 156.79, 157.14; MS: *m/z* (%) = 474 ($M^{\bullet+}$, 26), 112 (100), 98 (89); Anal. calcd. for $C_{28}H_{30}N_2O_3S$: C 70.86, H 6.37, N 5.90; found: C 70.64, H 6.70, N 5.70.