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Iodocyclization of 2-Methylthiophenylacetylenes to 3-Iodobenzothiophenes and their coupling Reactions under More Sustainable Conditions

Raffaella Mancuso,*[a] Melania Lettieri,[a] Romina Strangis,[a] Patrizio Russo,[a] Antonio Palumbo Piccionello,[b] Sara De Angelis,[a, c] and Bartolo Gabriele*[a]

Abstract: We report the first example of iodocyclization of readily available 2-methylthiophenylacetylenes in a deep eutectic solvent (ChCl/urea 1/2, mol/mol) as recyclable and more sustainable solvent with respect to the classical VOCs employed so far. The process successfully afforded a variety of 3-iodobenzothiophenes in good to high yields starting from differently substituted substrates, with the possibility to recycle the DES several times without appreciable lowering of the product yield. The 3-iodothiophenes thus synthesized are known to be important precursors of biologically active molecules and functionalized heterocycles, and were successfully employed for performing representative Sonogashira and Suzuki cross-coupling reactions. The solvent-catalyst system could be conveniently recycled several times without any loss of activity in both coupling processes, thus further demonstrating the practical usefulness of our approach.

Introduction

3-Iodobenzothiophenes are very important benzothiophene derivatives. In fact, they are useful precursors for the formation of biologically relevant compounds[1] and as cross-coupling partners for the synthesis of functionalized benzothiophene derivatives and complex molecular architectures.[2] A simple and very convenient approach to the synthesis of 3-iodobenzothiophenes consists in the iodocyclization[3] of 2-alkylthiophenylacetylenes, as shown in Scheme 1 (R=Bn, Me). This process was first disclosed by Flynn (with R=Bn)[4] and Larock (with R=Me)[5] in 2001, and takes place through the formation of an iodonium intermediate that undergoes *anti* attack of sulfur atom of the thiomethyl group followed by sulfur demethylation by the ensuing iodide anion (Scheme 1).

Since then, this approach has been further developed and elaborated by the same research groups[6,7] and others[8] under various reaction conditions. However, to the best of our knowledge, all procedures reported so far have made use of VOCs (volatile organic compounds) as solvents (including methylene chloride, 1,2-dichloroethane and ethanol). On the other hand, the replacement of VOCs with non-volatile, non-flammable, less toxic, and more sustainable solvents is becoming a more and more stringent requirement in current organic synthesis.[9] Among the most promising unconventional solvents, which may comply with these characteristics, DES (deep eutectic solvents) are now playing a major role, due to their low toxicity, very low volatility, and non-flammability. Moreover, DES can be easily and inexpensively prepared from largely available natural sources and can also be conveniently recycled.[10]

In this work, we report on the use of particularly simple and inexpensive choline chloride (ChCl)-based DES[11,12] as more sustainable and recyclable solvents for the iodocyclization of 2-methylthiophenylacetilenes **1** to 3-iodobenzothiophenes **2** in good to excellent yields. ChCl-based DES have then been successfully employed for the conduction of paradigmatic examples of Sonogashira and Suzuki couplings of **2**, with the possibility to recycle both the solvent and the catalytic systems (Scheme 2).

Results and Discussion

2-Methyl-4-(2-(methylthio)phenyl)but-3-yn-2-ol **1a** was chosen as model substrate for optimization experiments. The reaction of **1a** with 2 equiv. of I_2, carried out in ChCl/urea (1/2, mol/mol) as the solvent (0.15 mmol of **1a** per mL of DES) at 80 °C for 18 h, mainly led to substrate decomposition, with formation of the desired 2-(3-iodobenzo[*b*]thiophen-2-yl)propan-2-ol **2a** in only 9% yield (Table 1, entry 1). This result could be significantly improved when adding 2 equiv. of KI, which probably favors sulfur demethylation, with formation of **2a** in 68% isolated yield

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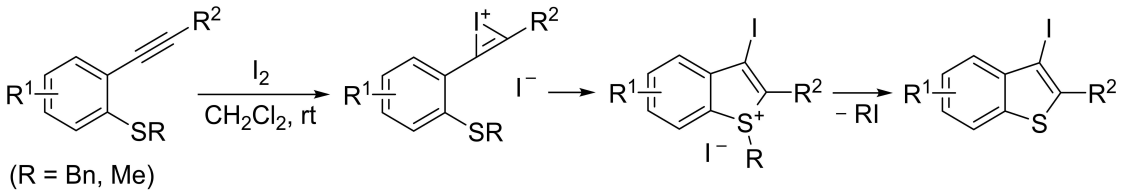
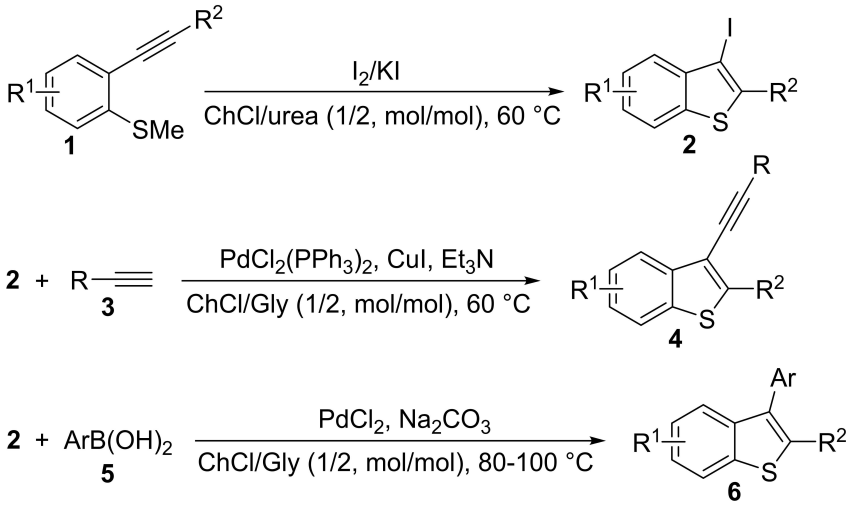
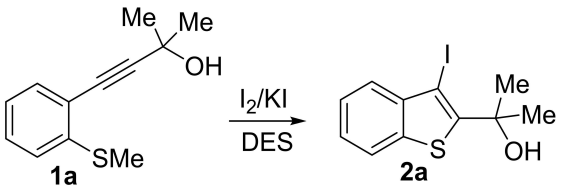


Scheme 1. Iodocyclization of 2-alkylthiophenylacetylenes to 3-iodobenzothiophenes.



Scheme 2. *This work:* Iodocyclization of 2-methylthiophenylacetylenes **1** to 3-iodobenzothiophenes **2** and subsequent Sonogashira and Suzuki couplings of **2** with terminal alkynes **3** and arylboronic acids **4**, respectively, to benzothiophenes **4** and **6**, in ChCl-based DES.

Table 1. Iodocyclization of 2-methyl-4-(2-(methylthio)phenyl)but-3-yn-2-ol **1a** in DES under different conditions.[a]



Entry	I_2 (equiv.)	KI (equiv.)	DES solvent [mol/mol]	T [°C]	Yield of **2a** [%][b]
1	2	0	ChCl/urea (1/2)	80	9
2	2	2	ChCl/urea (1/2)	80	68
3	2	5	ChCl/urea (1/2)	80	69
4	2	8	ChCl/urea (1/2)	80	67
5	2	10	ChCl/urea (1/2)	80	58
6[c]	2	10	ChCl/urea (1/2)	80	49
7	2	2	ChCl/glycerin (1/2)	80	40
8	2	2	ChCl/ethylene glycol (1/2)	80	53
9	1.5	2	ChCl/urea (1/2)	80	51
10[d]	2	2	ChCl/urea (1/2)	80	59
11	2	2	ChCl/urea (1/2)	60	81
12	1	2	ChCl/urea (1/2)	60	59

[a] Unless otherwise noted, all reactions were carried out for 18 h with a substrate concentration of 0.15 mmol per mL of DES. [b] Isolated yield based on starting **1a**. Unless otherwise noted, substrate conversion was quantitative. [c] The reaction was carried out for 15 h, and substrate conversion was 89%. [d] Substrate concentration was 0.10 mmol of **1a** per mL of DES.

under the same conditions (Table 1, entry 2). The use of a larger excess of KI did not cause a further yield increase (Table 1, entries 3–6), while the **2a** yield dropped by changing the solvent to ChCl/glycerol (1/2, mol/mol; Table 1, entry 7) or to ChCl/ethylene glycol (1/2, mol/mol; Table 1, entry 8). A lower **2a** yield was also observed when the amount of I_2 was lowered to 1.5 equiv. (Table 1, entry 9) or when conducting the process under more diluted conditions (Table 1, entry 10). On the other hand, a very good yield of **2a** (81%) was achieved under the same conditions of entry 2, when the reaction temperature was

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lowered to 60 °C (Table 1, entry 11). Also at 60 °C, the **2a** yield was lower when reducing the amount of I_2 (Table 1, entry 12).

The optimized conditions were then applied to other differently substituted substrates. As can be seen from the results reported in Table 2, the method was of general applicability. In fact, excellent results were observed with functionalized substrates bearing a 3-hydroxyalkynyl substituent (**1a–g**), as shown in Table 2, entries 1–7. Substrates with the triple bond substituted with a phenethyl (**1h**; Table 2, entry 8), a simple alkyl group (**1i**; Table 2, entry 9), a sterically demanding alkyl group (**1j**; Table 2, entry 10), trimethylsilyl (**1k**; Table 2, entry 11), 1-cyclohexenyl (**1l**; Table 2, entry 12), an aryl group (**1m–o**; Table 2, entries 13–15), or a heteroaryl group (such as 3-thienyl, **1p**; Table 2, entry 16) also reacted well, the corresponding iodocyclization products being formed in 71–89% yields. Substrates **1q** and **1r**, bearing an electron-donating (Me) or electron-withdrawing (F) on the aromatic ring, also reacted well, with formation of the corresponding 3-iodobenzothiophenes **2q** and **2r** in 68% and 77% yields, respectively (Table 2, entries 17 and 18). The possibility to recycle the DES solvent several times, without appreciable yield loss, was also assessed for representative substrates, as shown in Table 2, entries 2, 9, 13, and 15.

We then verified the possibility to carry out paradigmatic examples of Sonogashira and Suzuki cross-couplings in a ChCl-based DES as the solvent, using the synthesized 3-iodobenzothiophenes **2** and different 1-alkynes **3** as coupling partners. We first tested the Sonogashira coupling of 2-(3-iodobenzo[*b*]thiophen-2-yl)propan-2-ol **2a** and 1-hexyne **3a** in the same DES solvent successfully employed for iodocyclizations [ChCl/urea (1/2, mol/mol)]. As shown in Table 3, entry, 1, the reaction led to the desired 2-(3-(hex-1-yn-1-yl)benzo[*b*]thiophen-2-yl)propan-2-ol **4aa** in 48% yield. On the other hand, by changing the solvent to ChCl/Gly (1/2, mol/mol; Gly = glycerin), the product yield improved significantly (77%, Table 3, entry 2). Accordingly, all the other experiments, leading to differently substituted 3-alkynylbenzothiophenes **4**, were carried out in this DES medium. As can be seen from the results reported in Table 3, entries 2–10, good yields of the coupling products were obtained in all the cases tested. Moreover, it has been possible to recycle the solvent-catalyst system (DES containing the palladium and copper catalysts still dissolved at the end of the process) several times without any decrease of the product yield, as exemplified in entries 6 and 9.

The results obtained in some representative Suzuki cross-couplings in ChCl/Gly (1/2, mol/mol) as the solvent are shown in Table 4. Also in this case, the process was of general applicability, and the solvent-catalyst system could be successfully recycled several times (Table 4, entries 1, 5, and 7).

Conclusion

In conclusion, we have shown that it is possible to perform the iodocyclization of 2-methylthiophenylacetylenes to 3-iodobenzothiophenes (particularly important precursors of biologically active molecules and functionalized heterocycles) in DES (ChCl/urea 1/2, mol/mol) as recyclable and more sustainable solvent with respect to the classical VOCs employed so far. Another simple DES (ChCl/Gly 1/2, mol/mol) has also been successfully used as solvent for performing representative Sonogashira and Suzuki cross-coupling reactions using the synthesized 3-iodothiophenes. The solvent-catalyst system has been easily recycled without any loss of activity in both coupling processes, thus further showing the practical usefulness of our approach.

Experimental Section

General Experimental Methods: Solvent and chemicals were reagent grade and were used without further purification. All reactions were analyzed by TLC on silica gel 60 F254 and by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70–230 mesh) or neutral alumina (90–170). Evaporation refers to the removal of solvent under reduced pressure. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a 300 or 500 Spectrometer in $CDCl_3$ and DMSO-d_6 with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage (normal resolution) and by electrospray ionization mass spectrometry (ESI-MS) (high resolution) with a UHD accurate-mass Q-TOF spectrometer equipped with a Dual AJS ESI source working in positive mode, and were recorded in the 150–1000 *m/z* range. The LC-MS experimental conditions were as follows: N_2 was employed as desolvation gas at 300 °C and a flow rate of 9 L/min. The nebulizer was set to 45 psig. The Sheat gas temperature was set at 350 °C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode. The fragmentor was set to 175 V.

Preparation of DESs and Substrates: DESs [ChCl–Gly (1:2 mol/mol); ChCl–Urea (1:2 mol/mol); ChCl–EG (1:1 mol/mol)] were prepared as we already reported.[13] Starting materials **1** were prepared as described in the Supporting Information.

Iodocyclization procedure leading to 3-iodothiophenes 2 in DES (Table 2): To a solution of **1** (0.30 mmol) (**1a**, 62.5 mg; **1b**, 67.0 mg; **1c**, 73.5 mg; **1d**, 70.2 mg; **1e**, 58.2 mg; **1f**, 76.0 mg; **1g**, 53.7 mg; **1h**, 76.0 mg; **1i**, 61.5 mg; **1j**, 61.7 mg; **1k**, 66.2 mg; **1l**, 68.2 mg; **1m**, 67.5 mg; **1n**, 71.6 mg; **1o**, 90.4 mg; **1p**, 69.2 mg; **1q**, 71.6 mg; **1r**, 72.8 mg) in ChCl/Urea (1:2, mol/mol; 2.0 mL) was added I_2 (152 mg, 0.60 mmol) and KI (99.5 mg, 0.60 mmol). The mixture was allowed to stir at 60 °C for 18 h and then extracted with Et_2O (6 × 3 mL) at 60 °C. After cooling, saturated aqueous $Na_2S_2O_3$ (15 mL) was added to the collected ethereal phases, and the mixture was allowed to stir for 10 min. Phases were separated, the aqueous phase was extracted with Et_2O (3 × 15 mL), while the DES phase was used for the next recycling experiments (see below). The collected organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, products **2a–r** were purified by column chromatography on silica gel using as eluent pure hexane to 9:1 hexane-AcOEt (**2a–d**, **2g**), pure hexane to 95:5 hexane-Et_2O (**2f**), pure hexane to 95:5 hexane-AcOEt (**2e**, **2m**), pure hexane to 99:1 hexane-AcOEt (**2h–l**, **2n–r**) (isolated yields are shown in Table 2).

Recycling procedure: To the DES residue obtained as described above was added a solution of **1** (0.30 mmol), I_2 (0.60 mmol) and KI (0.60 mmol) in Et_2O (1.5 mL). The Et_2O was removed under vacuum and then the same procedure described above was followed.

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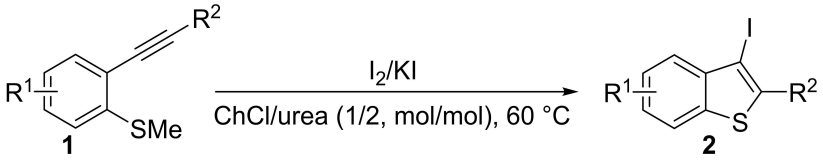
Table 2. Synthesis of 3-iodobenzothiophenes **2** by iodocyclization of 2-methylthiophenylacetylenes **1** in DES.[a]



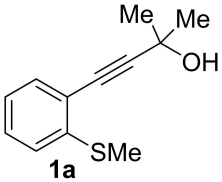
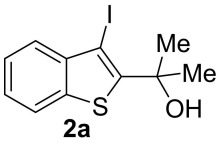
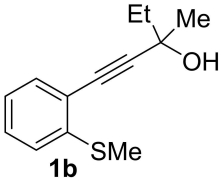
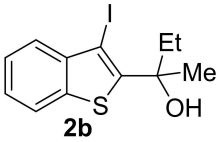
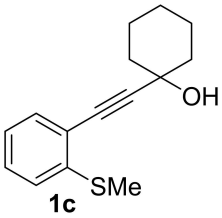
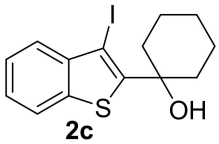
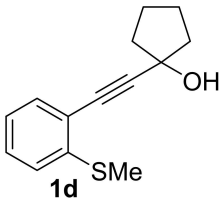
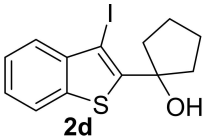
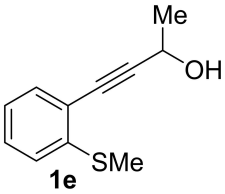
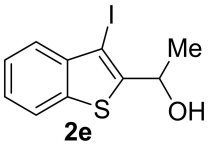
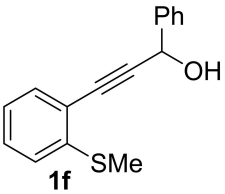
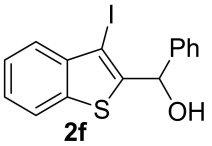
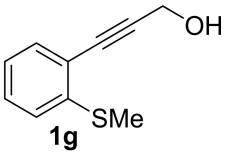
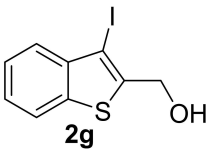
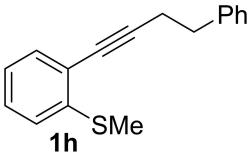
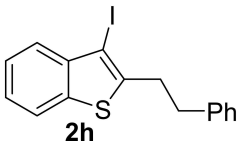
Entry	1	2	Yield of **2**[%][b]
1	 **1a**	 **2a**	81
2	 **1b**	 **2b**	81 (80, 78, 78, 77, 75)
3	 **1c**	 **2c**	86
4	 **1d**	 **2d**	80
5	 **1e**	 **2e**	75
6	 **1f**	 **2f**	80
7	 **1g**	 **2g**	78
8	 **1h**	 **2h**	83

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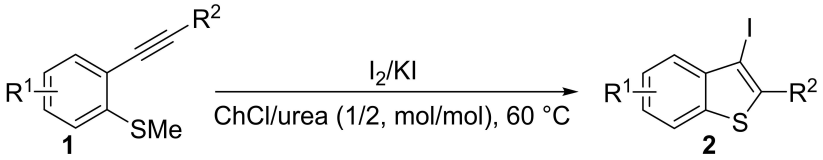
Table 2. continued



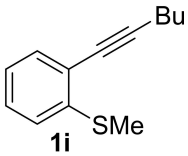
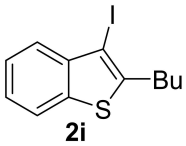
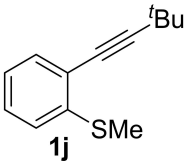
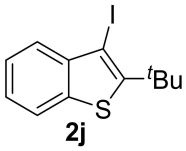
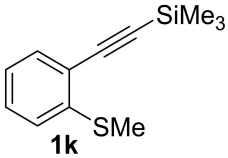
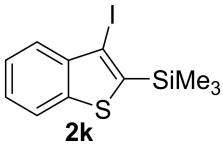
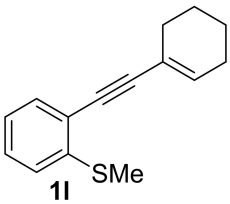
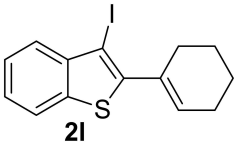
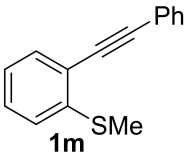
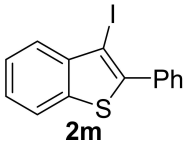
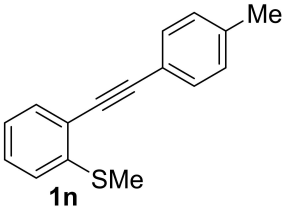
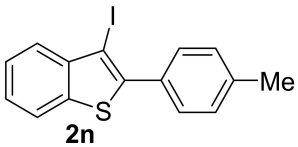
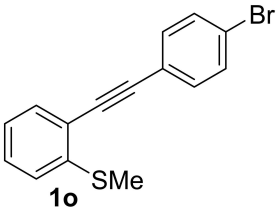
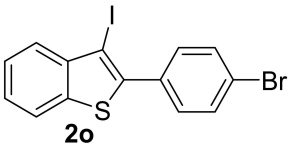
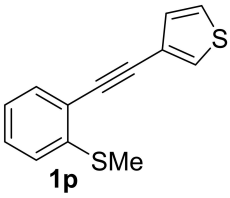
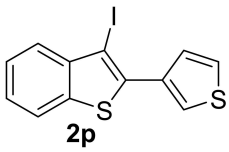
Entry	1	2	Yield of **2**[%][b]
9			89 (86, 86, 85, 83, 82)
10			79
11			80
12			79
13			84 (83, 82, 82, 80, 80)
14			88
15			88 (87, 85, 83, 80, 80)
16			71

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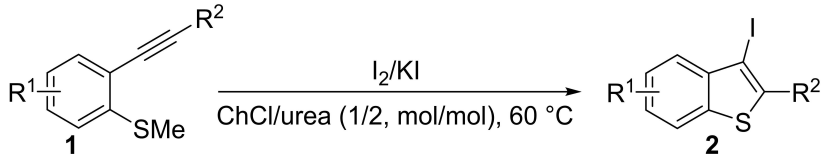
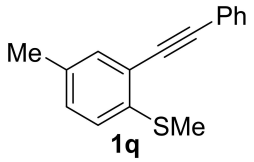
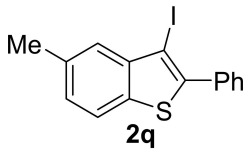
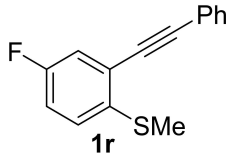
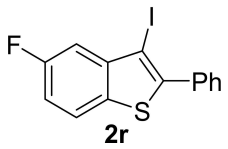
Table 2. continued



Entry	1	2	Yield of **2**[%][b]
17			68
18			77

[a] All reactions were carried out in ChCl/urea (1/2, mol/mol) (0.15 mmol of **1** per mL of solvent) at 60 °C for 18 h in the presence of 2 equiv of I_2 and 2 equiv of KI. [b] Isolated yield based on starting **1**. Data in parentheses refer to the yields obtained after solvent recycles.

Representative iodocyclization procedure in larger scale: To a solution of **1a** (250 mg, 1.21 mmol) in ChCl/Urea (1:2, mol/mol; 8.0 mL) was added I_2 (610 mg, 2.4 mmol) and KI (400 mg, 2.4 mmol). The mixture was allowed to stir at 60 °C for 18 h and then extracted with Et_2O (6×3 mL) at 60 °C. After cooling, saturated aqueous $Na_2S_2O_3$ (25 mL) was added to the collected ethereal phases, and the mixture was allowed to stir for 10 min. Phases were separated, and the aqueous phase was extracted with Et_2O (3× 20 mL). The collected organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, product **2a** was purified by column chromatography on silica gel using as eluent pure hexane to 9:1 hexane-AcOEt (yield: 309 mg, 80%).

2-(3-Iodobenzo[b]thiophen-2-yl)propan-2-ol (**2a**). Yield: 78.2 mg, starting from 62.5 mg of **1a** (81%) (Table 2, entry 1). Yellow solid, mp = 24–25 °C. IR (KBr): ν = 3410 (s, br), 1450 (m), 1435 (w), 1366 (m), 1242 (w), 1219 (m), 1165 (s), 1134 (s), 1018 (w), 949 (m), 895 (m), 756 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.77–7.71 (m, 2 H), 7.44–7.39 (m, 1 H), 7.36–7.30 (m, 1 H), 2.72 (s, 1 H), 1.83 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 151.9, 142.7, 136.8, 125.3, 125.13, 125.08, 122.0, 73.8, 73.1, 29.9; GC-MS (EI, 70 eV): *m/z* = 318 (M^+, 55), 303 (100), 300 (42), 171 (11), 147 (18), 129 (23), 115 (14), 89 (31); HRMS-ESI (*m/z*): $[(M–H_2O+H)^+]$ cald for $(C_{11}H_{10}IS)^+$: 300.9542; found: 300.9556.

2-(3-Iodobenzo[b]thiophen-2-yl)butan-2-ol (**2b**). Yield: 82.0 mg, starting from 67.0 mg of **1b** (81%) (Table 2, entry 2). Yellow oil. IR (film): ν = 3449 (s, br), 1451 (m), 1373 8 m), 1288 (w), 1242 (w), 1157 (s), 1034 (w), 995 (w), 918 (m), 756 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.77–7.72 (m, 2 H), 7.44–7.38 (m, 1 H), 7.36–7.31 (m, 1 H), 2.53 (s, 1 H), 2.45 (dq, *J* = 14.9, 7.4, 1 H), ;1.99 (dq, *J* = 14.6, 7.4, 1 H), 1.79 (s, 3 H), 0.90 (t, *J* = 7.4, 3 H) ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 151.5, 142.7, 137.1, 125.4, 125.0, 124.9, 122.0, 75.8, 73.4, 34.2, 28.3, 8.0; GC-MS (EI, 70 eV): *m/z* = 332 (M^+, 26), 303 (100), 161 (12), 147 (12), 89 (14); HRMS-ESI (*m/z*): $[(M–H_2O+H)^+]$ cald for $(C_{11}H_{12}IS)^+$: 314.9699; found: 314.9709.

1-(3-Iodobenzo[b]thiophen-2-yl)cyclohexan-1-ol (**2c**). Yield: 92.1 mg, starting from 73.5 mg of **1c** (86%) (Table 2, entry 3). Yellow oil. IR (film): ν = 3395 (m, br), 1443 (m), 1381 (w), 1319 (w), 1265 (w), 1242 (w), 1142 (m), 1065 (w), 1026 (m), 957 (s), 903 (m), 810 (m), 748 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.77 (d, *J* = 8.1, 1 H), 7.72 (d, *J* = 7.9, 1 H), 7.43–7.37 (m, 1 H), 7.31–7.29 (m, 1 H), 2.43 (s, 1 H), 2.40 (td, *J* = 13.4, 4.1, 2 H), 2.00–1.90 (m, 2 H), 1.84–1.63 (m, 5 H), 1.43–1.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 151.9, 142.6, 136.8, 125.3, 125.1, 125.0, 122.0, 74.1, 73.4, 36.3, 25.0, 21.7; GC-MS (EI, 70 eV): *m/z* = 358 (M^+, 36), 240 (67), 315 (21), 302 (15), 287 (17), 231 (39), 213 (44), 188 (75), 185 (73), 171 (26), 147 (100), 115 (34). The spectroscopic data agreed with those reported.[8e]

1-(3-Iodobenzo[b]thiophen-2-yl)cyclopentan-1-ol (**2d**). Yield: 83.6 mg, starting from 70.2 mg of **1d** (80%) (Table 2, entry 4). Brown oil. IR (film): ν = 3418 (s, br), 1435 (m), 1288 (w), 1242 (m), 1196 (m), 1003 (m), 756 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.75 (d, *J* = 8.3, 1 H), 7.73 (d, *J* = 8.1, 1 H), 7.43–7.38 (m, 1 H), 7.36–7.30 (m, 1 H), 2.53–2.41 (m, 3 H), 2.22–2.13 (m, 2 H), 2.06–1.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 149.3, 142.6, 136.8, 125.14, 125.11, 125.08, 122.0, 82.6, 74.9, 41.2, 24.0; GC-MS (EI, 70 eV): *m/z* = 344 (M^+, 70), 326 (100), 302 (29), 287 (38), 217 (66), 199 (34), 189 (42), 188 (48), 183 (45), 173 (28), 166 (26), 147 (72); HRMS-ESI (*m/z*): $[(M–H_2O+H)^+]$ cald for $(C_{13}H_{12}IS)^+$: 326.9699; found: 326.9708.

1-(3-Iodobenzo[b]thiophen-2-yl)ethan-1-ol (**2e**). Yield: 69.3 mg, starting from 58.2 mg of **1e**(75%) (Table 2, entry 5). Yellow oil. IR (film): ν = 3348 (s, br), 1435 (m), 1373 (w), 1319 (W), 1288 (w)m, 1250 (m), 1165 (m), 1096 (m), 1065 (s), 988 (w), 910 (w), 748 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.74 (d, *J* = 7.9, 1 H), 7.70 (d, *J* = 7.9, 1 H), 7.40 (t, *J* = 7.5, 1 H), 7.33 (t, *J* = 7.5, 1 H), 5.37–5.30 (m, 1 H), 2.69 (s, br, 1 H), 1.60 (d, *J* = 6.4, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.8, 140.8, 137.4, 125.3, 125.2, 125.0, 122.6, 76.8, 69.2, 24.0; GC-MS (EI, 70 eV): *m/z* = 304 (M^+, 30), 289 (29), 286 (32), 159 (20), 134 (98), 115 (100), 89 (21); HRMS-ESI (*m/z*): $[(M–H_2O+H)^+]$ cald for $(C_{10}H_{18}IS)^+$: 286.9386; found: 286.9398.

1-(3-Iodobenzo[b]thiophen-2-yl)(phenyl)methanol (**2f**). Yield: 87.8 mg, starting from 76.0 mg of **1f** (80%) (Table 2, entry 6). Yellow oil. IR (film): ν = 1643 (w), 1597 (w), 1489 (w), 1450 (m), 1273 (m), 1250 (m), 1188 (w), 1088 (s), 1026 (w), 972 (w), 910 (w), 756 (s), 702 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.74–7.70 (m, 2 H), 7.53–7.51 (m, 2 H), 7.42–7.37 (m, 1 H), 7.37–7.26 (m, 4 H), 6.30 (s, 1 H), 2.63 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.9, 141.4, 140.8, 138.0, 128.6, 128.3, 126.6, 125.5, 125.3, 125.2, 122.6, 79.3, 74.6; GC-MS (EI, 70 eV): *m/z* = 366 (M^+, 27), 237 (9), 221 (8), 161 (8), 134 (16), 105 (100). The spectroscopic data agreed with those reported.[8f]

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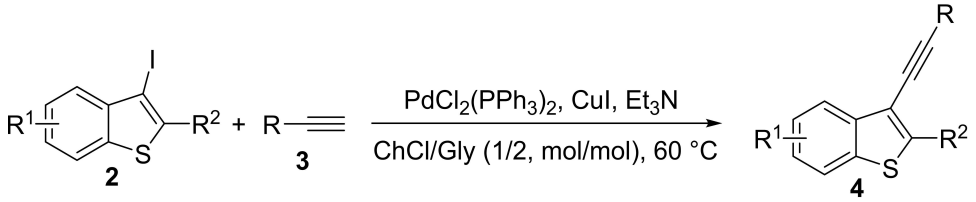
Table 3. Synthesis of 3-alkynylbenzothiophenes **4** by Sonogashira coupling of 3-iodobenzothiophenes **2** with 1-alkynes **3** in DES.[a]



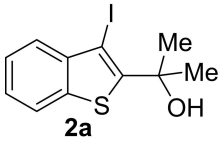
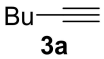
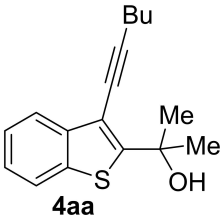
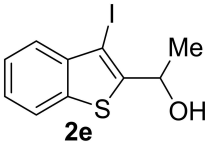
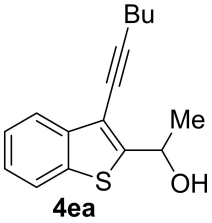
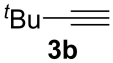
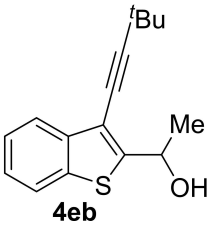
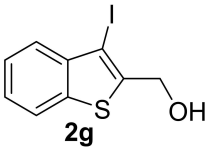
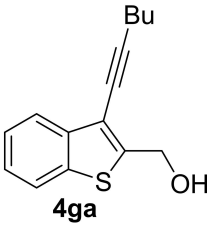
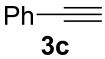
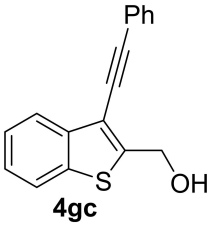
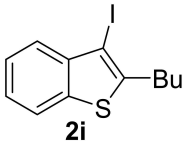
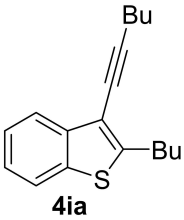
Entry	2	3	4	Yield of 4 [%][b]
1[c]				48
2	2a	3a	4aa	77
3		3a		75
4	2e			81
5		3a		76
6	2g			84 (83, 84, 83, 83, 83)
7		3a		80

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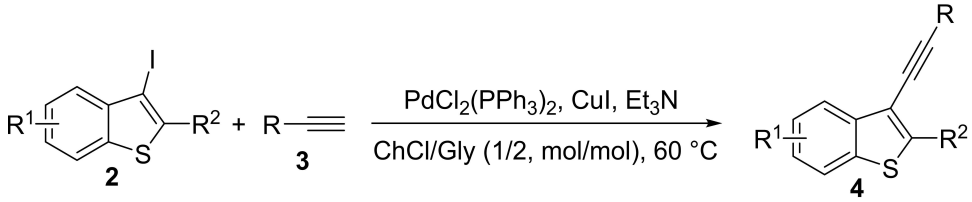
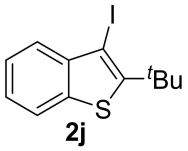
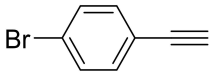
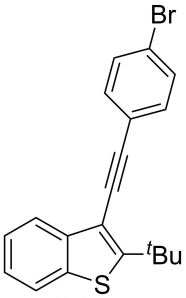
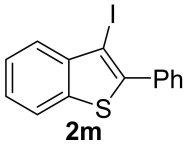
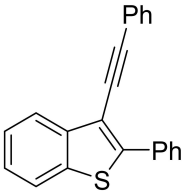
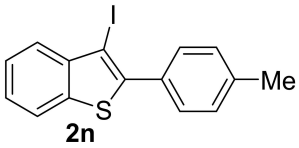
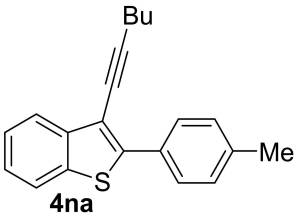
Table 3. continued



Entry	2	3	4	Yield of 4 [%][b]
8	 2j	 3d	 4jd	59
9	 2m	3c	 4mc	87 (86, 87, 85, 85, 86)
10	 2n	3a	 4na	74

[a] Unless otherwise noted, all reactions were carried out in ChCl/Gly (1/2, mol/mol) (0.17 mmol of **2** per mL of solvent) at 60 °C for 15 h, in the presence of 5 mol% of $PdCl_2(PPh_3)_2$, 20 mol% of CuI, 3 equiv. of Et_3N and 2.4 equiv. of 1-alkyne **3**. [b] Isolated yield based on starting **2**. Data in parentheses refer to the yields obtained after the recycling of the solvent-catalyst system [DES containing $PdCl_2(PPh_3)_2$ and CuI]. [c] The reaction was carried out using ChCl/urea (1/2, mol/mol) as the solvent.

(3-Iodobenzo[b]thiophen-2-yl)methanol (**2g**). Yield: 68.4 mg, starting from 53.7 mg of **1g** (78%) (Table 2, entry 7). Yellow oil. IR (film): ν = 3264 (m, br), 1481 (w), 1450 (w), 1427 (m), 1342 (m), 1242 (w), 1150 (m), 1034 (s), 903 (w), 748 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.75 (d, *J* = 7.9, 1 H), 7.70 (d, *J* = 8.2, 1 H), 7.44–7.39 (m, 1 H), 7.37–7.32 (m, 1 H), 4.93 (d, *J* = 5.2, 2 H), 2.46–2.41 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 143.0, 140.9, 138.3, 125.5, 125.3, 125.2, 122.6, 78.9, 62.9; GC-MS (EI, 70 eV): *m/z* = 290 (M^+, 72), 273 (7), 163 (28), 135 (100), 102 (12), 91 (66). The spectroscopic data agreed with those reported.[8n]

3-Iodo-2-phenethylbenzo[b]thiophene (**2h**). Yield: 91.2 mg, starting from 76.0 mg of **1h** (83%) (Table 2, entry 8). Colorless oil. IR (film): ν = 1605 (m), 1497 (m), 1450 (m), 1435 (s), 1250 (m), 1157 (w), 1111 (w), 1072 (w), 1018 (m), 903 (m), 748 (s), 703 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.71–7.66 (m, 2 H), 7.41–7.36 (m, 1 H), 7.32–7.26 (m, 3 H), 7.26–7,18 (m, 3 H), 3.27–3.21 (m, 2 H), 3.04–2.98 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 143.2, 141.1, 140.4, 138.1, 128.51, 128.47, 126.3, 125.1, 124.9, 122.2, 80.6, 36.6, 34.9; GC-MS (EI, 70 eV): *m/z* = 364 (M^+, 46), 273 (100), 237 (41), 146 (22); HRMS-ESI (*m/z*): $[(M+H)^+]$ cald for $(C_{16}H_{14}IS)^+$: 364.9855; found: 364.9870.

2-Butyl-3-iodobenzo[b]thiophene (**2i**). Yield: 85.0 mg, starting from 61.5 mg of **1i** (89%) (Table 2, entry 9). Colorless oil. IR (film): ν = 1458 (m), 1435 (m), 1381 (w), 1296 (w), 1250 (m), 1072 (w), 1018 (w), 903 (m), 748 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.68 (t, *J* = 8.6, 2 H), 7.37 (t, *J* = 7.3, 1 H), 7.28 (t, *J* = 7.3, 1 H), 2.94 (t, *J* = 7.5, 2 H), 1.71 (quintuplet, *J* = 7.5, 2 H), 1.43 (hexuplet, *J* = 7.5, 2 H), 0.96 (t, *J* = 7.5, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 144.7, 141.1, 138.0, 125.0, 124.7, 122.1, 80.1, 32.6, 29.7, 22.2, 13.9; GC-MS (EI, 70 eV): *m/z* = 316 (M^+, 55), 273 (93), 147 (100), 115 (17), 102 (21). The spectroscopic data agreed with those reported.[8f]

2-(tert-Butyl)-3-iodobenzo[b]thiophene (**2j**). Yield: 75.7 mg, starting from 61.7 mg of **1j** (79%) (Table 2, entry 10). Colorless oil. IR (film): ν = 1458 (m), 1427 (m), 1366 (w), 1234 (m), 1026 (w), 895 (w), 849 (w), 748 (s), 725 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.78 (d, *J* = 8.3, 1 H), 7.69 (d, *J* = 7.9, 1 H), 7.40–7.35 (m, 1 H), 7.31–7.26 (m, 1 H), 1.61 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 151.7, 142.8, 136.1, 125.2, 124.9, 124.7, 121.6, 74.7, 35.7, 30.2; GC-MS (EI, 70 eV): *m/z* = 316 (M^+, 82), 301 (100), 273 (30), 174 (85), 147 (55), 134 (40), 115 (91). The spectroscopic data agreed with those reported.[8f]

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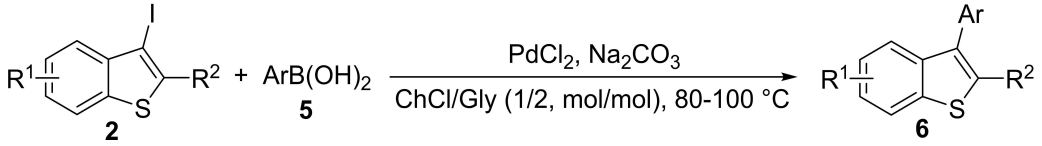
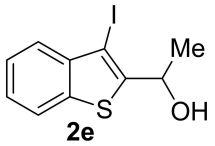
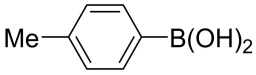
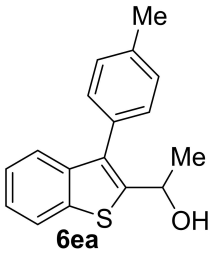
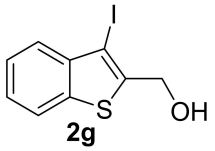
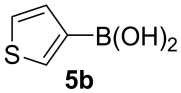
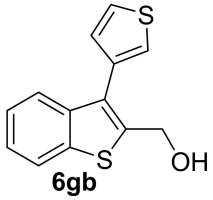
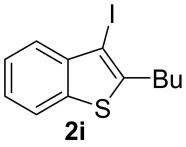
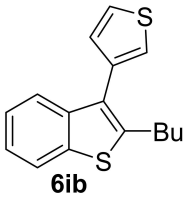
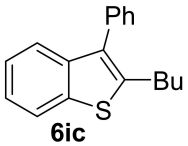
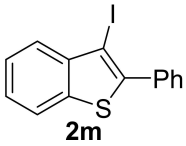
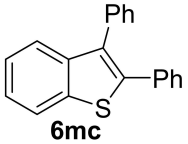
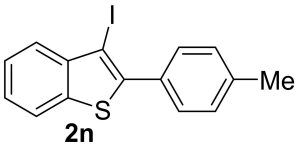
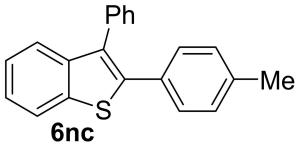
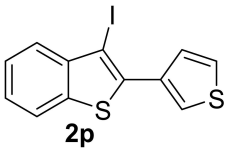
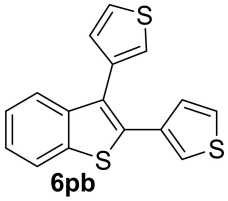
Table 4. Synthesis of arylbenzothiophenes **6** by Suzuki coupling of 3-iodobenzothiophenes **2** with arylboronic acids **5** in DES.[a]



Entry	2	5	T [°C]	t [h]	6	Yield of 6 [%][b]
1	 2e	 5a	80	15	 6ea	95 (94, 95, 94, 94, 93)
2	 2g	 5b	80	15	 6gb	92
3	 2i	5b	100	24	 6ib	70
4	2i	PhB(OH)2 5c	100	24	 6ic	68
5	 2m	5c	80	15	 6mc	73 (72, 73, 71, 71, 71)
6	 2n	5c	80	15	 6nc	69
7	 2p	5b	80	15	 6pb	80 (80, 79, 80, 80, 79)

[a] All reactions were carried out in ChCl/Gly (1/2, mol/mol) (0.17 mmol of **2** per mL of solvent), in the presence of 10 mol% of $PdCl_2$, 2 equiv. of Na_2CO_3 and 1.5 equiv. of arylboronic acid **5**. [b] Isolated yield based on starting **2**. Data in parentheses refer to the yields obtained after the recycling of the solvent-catalyst system (DES containing $PdCl_2$).

(3-Iodobenzo[b]thiophene-2-yl)trimethylsilane (**2k**). Yield: 80.1 mg, starting from 66.2 mg of **1k** (80%) (Table 2, entry 11). Colorless oil. IR (film): ν = 1466 (m), 1412 (w), 1250 (s), 1157 (w), 1072 (w), 1018 (w), 972 (s), 841 (s), 756 (s), 725 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.85–7.73 (m, 2 H), 7.45–7.37 (m, 1 H), 7.37–7.28 (m, 1 H), 0.50 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 143.1, 141.4, 140.8, 125.4, 125.2, 125.0, 121.9, 87.1, −0.61; GC-MS (EI, 70 eV): *m/z* = 332 (M^+, 95), 317 (100), 189 (43), 175 (26), 158 (9), 147 (18), 115 (50). The spectroscopic data agreed with those reported.[8f]

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2-(Cyclohex-1-en-1-yl)-3-iodobenzo[b]thiophene (**2l**). Yield: 80.3 mg, starting from 68.2 mg of **1l** (79%) (Table 2, entry 12). Colorless oil. IR (film): ν = 1435 (s), 1342 (w), 1242 (m), 1165 (w), 1134 (w), 1072 (w), 980 (w), 748 (s), 725 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.76–7.72 (m, 1 H), 7.72–7.68 (m, 1 H), 7.42–7.37 (m, 1 H), 7.33–7.28 (m, 1 H), 6.20–6.16 (m, 1 H), 2.48–2.42 (m, 2 H), 2.27–2.21 (m, 2 H), 1.83–1.76 (m, 2 H), 1.73–1.67 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 145.1, 141.5, 137.9, 132.5, 132.2, 125.7, 125.1, 125.0, 122.0, 77.4, 29.9, 25.6, 22.8, 21.7; GC-MS (EI, 70 eV): *m/z* = 340 (M^+, 100), 312 (5), 213 (22), 185 (49), 171 (14), 147 (31), 79 (26). The spectroscopic data agreed with those reported.[8f]

3-Iodo-2-phenylbenzo[b]thiophene (**2m**). Yield: 85.3 mg, starting from 67.5 mg of **1m** (84%) (Table 2, entry 13). Yellow solid, mp = 55–56 °C. IR (KBr): ν = 1481 (m), 1435 (s), 1242 (s), 1157 (w), 1072 (w), 1026 (w), 871 (w), 748 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.83 (d, *J* = 7.9, 1 H), 7.77 (d, *J* = 7.9, 1 H), 7.68 (d, *J* = 7.5, 2 H), 7.51–7.41 (m, 4 H), 7.38 (dist t, *J* = 7.5, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.2, 141.9, 138.9, 134.6, 130.0, 128.9, 128.5, 126.3, 125.48, 125.45, 122.1, 79.4; GC-MS (EI, 70 eV): *m/z* = 336 (M^+, 100), 208 (39), 165 (41), 104 (27). The spectroscopic data agreed with those reported.[14]

3-Iodo-2-(p-tolyl)benzo[b]thiophene (**2n**). Yield: 92.5 mg, starting from 71.6 mg of **1n** (88%) (Table 2, entry 14). Yellow oil. IR (film): ν = 1489 (m), 1435 (s), 1246 (m), 1111 (w), 1018 (w), 964 (w), 879 (w), 818 (m), 795 (m), 748 (s), 725 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.83–7.79 (m, 1 H), 7.75 (d, *J* = 8.0, 1 H), 7.59–7.55 (m, 2 H), 7.46–7.42 (m, 1 H), 7.38–7.33 (m, 1 H), 7.24 (d, *J* = 8.2, 2 H), 2.41 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.3, 141.9, 139.0, 138.9, 131.7, 129.9, 129.2, 126.2, 125.4, 125.38, 125.36, 122.1, 79.1, 21.4; GC-MS (EI, 70 eV): *m/z* = 350 (M^+, 100), 221 (21), 208 (34), 179 (21), 111 816).[8f]

2-(4-Bromophenyl)3-iodobenzo[b]thiophene (**2o**). Yield: 109.0 mg, starting from 90.4 mg of **1o** (88%) (Table 2, entry 15). Yellow oil. IR (film): ν = 1474 (m), 1427 (w), 1389 (w), 1242 (w), 1065 (m), 1011 (m), 964 (w), 826 (s), 772 (m), 748 (s), 718 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.81 (d, *J* = 8.0, 1 H), 7.77 (d, *J* = 7.9, 1 H), 7.64–7.57 (m, 2 H), 7.57–7.51 (m, 2 H), 7.46 (t, *J* = 7.5, 1 H), 7.39 (t, *J* = 7.5, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.8, 140.8, 138.9, 133.6, 131.8, 131.5, 126.4, 125.7, 125.6, 123.3, 122.1, 79.9; GC-MS (EI, 70 eV): *m/z* = 416 [$(M+2)^+$, 46], 414 (M^+, 53), 208 (100), 176 (3), 163 (37), 104 (45); HRMS-ESI (*m/z*): [$(M+H)^+$] cald for $(C_{14}H_9BrIS)^+$: 414.8648; found: 414.8675. The spectroscopic data agreed with those reported.[8a]

3-Iodo-2-(thiophen-3-yl)benzo[b]thiophene (**2p**). Yield: 73.2 mg, starting from 69.2 mg of **1p** (71%) (Table 2, entry 16). Yellow solid, mp = 40–41 °C. IR (KBr): ν = 1435 (m), 1358 (w), 1242 (m), 1165 (w), 1080 (w), 1018 (w), 910 (w), 849 (m), 779 (s), 748 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.90–7.67 (m, 3 H), 7.57–7.48 (m, 1 H), 7.48–7.27 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.1, 138.2, 137.3, 134.7, 128.4, 126.2, 125.8, 125.5, 125.4, 122.0, 78.6; GC-MS (EI, 70 eV): *m/z* = 342 (M^+, 100), 215 (20), 214 (19), 171 (78), 127 (12), 107 (25); HRMS-ESI (*m/z*): [$(M+H)^+$] cald for $(C_{12}H_8IS_2)^+$: 342.9107; found: 342.9144.

3-Iodo-5-methyl-2-phenylbenzo[b]thiophene (**2q**). Yield: 71.5 mg, starting from 71.6 mg of **1q** (68%) (Table 2, entry 17). Yellow solid, mp = 55–56 °C. IR (KBr): ν = 1605 (w), 1443 (s), 1381 (w), 1250 (w), 1157 (w), 1072 (w), 802 (m), 764 (m), 741 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.69–7.64 (m, 4 H), 7.48–7.39 (m, 3 H), 7.22–7.18 (m, 1 H), 2.52 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.3, 142.1, 136.1, 135.4, 134.8, 130.0, 128.8, 138.5, 127.2, 126.2, 121.8, 79.1, 21.5; GC-MS (EI, 70 eV): *m/z* = 350 (M^+, 100), 221 (20), 208 (34), 179 (18), 11); HRMS-ESI (*m/z*): [$(M+H)^+$] cald for $(C_{15}H_{12}IS)^+$: 350.9699; found: 350.9670.

5-Fluoro-3-Iodo-2-phenylbenzo[b]thiophene (**2r**). Yield: 81.8 mg, starting from 72.8 mg of **1r** (77%) (Table 2, entry 18). Yellow solid, mp = 55–56 °C. IR (KBr): ν = 1597 (m), 1566 (w), 1443 (s), 1273 (m), 1234 (w), 1165 (m), 1126 (w), 988 (w), 856 (m), 802 (m), 741 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.71 (dd, *J* = 8.7, 4.8, 1 H), 7.68–7.63 (m, 2 H), 7.52 (dd, *J* = 9.6, 2.3, 1 H), 7.50–7.42 (m, 3 H), 7.13 (td, *J* = 8.7, 2.3, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 161.7 (d, *J* = 242.5), 144.8, 143.5 (d, *J* = 8.9), 134.4 (d, *J* = 8.9), 129.9, 129.1, 128.6, 123.4 (d, *J* = 8.8), 114.3 (d, *J* = 25.1), 112.1 (d, *J* = 24.6), 74.5; GC-MS (EI, 70 eV): *m/z* = 354 (100), 226 (45), 183 (39), 113 (31); HRMS-ESI (*m/z*): [$(M+H)^+$] cald for $(C_{14}H_9FIS)^+$: 354.9448; found: 354.9429. The spectroscopic data agreed with those reported.[8a]

Sonogashira coupling leading to 3-alkynylbenzothiophenes 4 in DES (Table 3): To a solution of 3-iodobenzothiophenes **2** (0.25 mmol; **2a**, 80.0 mg; **2e**, 76.3 mg; **2g**, 72.8 mg; **2i**, 79.2 mg; **2j**, 80.0 mg; **2m**, 84.2 mg; **2n**, 87.8 mg) in ChCl/Gly (1:2, mol/mol; 1.5 mL) were added $PdCl_2(PPh_3)_2$ (8.8 mg, 1.25×10^{-2} mmol), CuI (9.5 mg, 0.05 mmol), the terminal alkyne (0.6 mmol; 1-hexyne **3a**, 50.0 mg; 3,3-dimethyl-1-butyne **3b**, 49.8 mg; phenylacetylene **3c**, 61.5 mg; 1-bromo-4-ethynylbenzene **3d**, 108.2 mg), and anhydrous Et_3N (105 μL, 76.2 mg, 0.75 mmol). The mixture was allowed to stir at 60 °C (oil bath) for 15 h. After cooling, the mixture was extracted with Et_2O (6×5 mL) at 60 °C, and the DES phase used again for the recycling experiments (see below). After evaporation of the solvent from the collected ethereal phases, products **4** were purified by column chromatography on silica gel using as eluent pure hexane to 95:5 hexane-AcOEt (**4aa**, **4ga**, **4gc**), pure hexane to 99:1 hexane-AcOEt (**4ea**, **4ia**, **4jd**, **4mc**, **4na**), hexane to 95:5 hexane-Et_2O (**4eb**) (isolated yields are shown in Table 3).

Recycling procedure: To the DES residue obtained as described above, still containing the catalysts $PdCl_2(PPh_3)_2$ and CuI, was added a solution of **2** (0.25 mmol) in Et_2O (1.5 mL). The Et_2O was removed under vacuum and the terminal alkyne **3** (0.6 mmol) followed by anhydrous Et_3N (105 μL, 0.75 mmol) were added. Then the same procedure described above was followed.

Representative Sonogashira coupling procedure in larger scale: To a solution of 2-(3-iodobenzo[*b*]thiophen-2-yl)propan-2-ol **2a** (1.0 mmol; 320.0 mg) in ChCl/Gly (1:2, mol/mol; 6 mL) were added $PdCl_2(PPh_3)_2$ (35.3 mg, 0.05 mmol), CuI (38.2 mg, 0.2 mmol), 1-hexyne (200.2 mg, 2.44 mmol), and anhydrous Et_3N (420 μL, 304.9 mg, 3.0 mmol). The mixture was allowed to stir at 60 °C (oil bath) for 15 h. After cooling, the mixture was extracted with Et_2O (6× 8 mL) at 60 °C. After evaporation of the solvent from the collected ethereal phases, product **4aa** was purified by column chromatography on silica gel using as eluent pure hexane to 95:5 hexane-AcOEt (yield: 220 mg, 81%).

2-(3-(Hex-1-yn-1-yl)benzo[b]thiophen-2-yl)propan-2-ol (**4aa**). Yield: 53.0 mg, starting from 80.0 mg of **2a** (77%) (Table 3, entry 2). Yellow oil. IR (film): ν = 2214 (vw), 1597 (w), 1489 (m), 1462 (m), 1435 (m), 1254 (w), 1069 (m), 752 (s), 667 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.84–7.78 (m, 1 H), 7.76–7.71 (m, 1 H), 7.41–7.35 (m, 1 H), 7.34–7.27 (m, 1 H), 3.04 (s, br, 1 H), 2.55 (t, *J* = 7.0, 2 H), 1.71–1.62 (m, 2 H), 1.57–1.48 (m, 1 H), 0.98 (t, *J* = 7.3, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.0, 141.4, 136.4, 131.6, 130.4, 124.5, 122.5, 122.1, 112.3, 98.1, 73.9, 72.9, 30.9, 30.4, 22.1, 19.4, 13.6; GC-MS (EI, 70 eV): *m/z* = 272 (M^+, 74), 257 (100), 254 (16), 238 (31), 225 (16), 211 (58), 197 (39), 185 (36), 184 (36), 171 (31), 165 (16), 152 (20), 147 (14), 139 (14), 147 (14), 139 (14), 127 (13), 115 (13); HRMS-ESI (*m/z*): [$(M-H_2O+H)^+$] cald for $(C_{17}H_{19}S)^+$: 255.1202; found: 255.1213.

1-(3-(Hex-1-yn-1-yl)benzo[b]thiophen-2-yl)ethan-1-ol (**4ea**). Yield: 48.7 mg, starting from 76.3 mg of **2e** (75%) (Table 3, entry 3). Yellow oil. IR (film): ν = 3356 (s, br), 1458 (m), 1435 (w), 1366 (w), 1319 (w), 1188 (m), 1096 (m), 1065 (s), 756 (s), 733 (m) cm^{-1}; ^1H

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NMR ($CDCl_3$, 500 MHz): δ = 7.82 (d, *J* = 7.6, 1 H), 7.75 (d, *J* = 7.6 1 H), 7.37 (t, *J* = 7.6, 1 H), 7.31 (t, *J* = 7.6, 1 H), 5.74 (q, *J* = 6.3, 1 H), 2.52 (t, *J* = 7.0, 2 H), 2.41 (s, br, 1H), 1.72–1.45 (m, 8 H), 0.98 (t, *J* = 7.3, 1 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.0, 140.3, 137.4, 124.8, 124.6, 122.8, 122.5, 114.7, 97.1, 73.1, 66.3, 31.1, 24.2, 22.1, 19.4, 13.6; GC-MS (EI, 70 eV): *m/z* = 258 (M^+, 31), 240 (53), 225 (16), 211 (34), 198 (48), 197 (100), 184 (31), 178 (22), 171 (27), 165 (34); HRMS-ESI (*m/z*): [(M–H_2O + H)$^+$] cald for ($C_{16}H_{17}S$)$^+$: 241.1045; found: 241.1056.

1-(3-(3,3-Dimethylbut-1-yn-1-yl)benzo[b]thiophen-2-yl)ethan-1-ol (**4eb**). Yield: 52.5 mg, starting from 76.0 mg of **2e** (81%) (Table 3, entry 4). Yellow oil. IR (film): ν = 3356 (s, br), 1450 (m), 1366 (m), 1319 (w), 1250 (m), 1188 (m), 1096 (s), 756 (m), 733 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.82–7.77 (m, 1H), 7.78–7.71 (m, 1 H), 7.41–7.35 (m, 1H), 7.34 (m, 1H), 5.46 (q, *J* = 6.4, 1 H), 2.67 (s, br, 1H), 1.63 (d, *J* = 6.5, 3H), 1.38 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 152.8, 140.0, 137.3, 124.8, 124.5, 122.7, 122.5, 114.3, 105.5, 71.5, 66.2, 34.0, 28.4, 24.1; GC-MS (EI, 70 eV): *m/z* = 258 (M^+, 100), 243 (43), 240 (34), 227 (32), 215 (46), 227 (28), 201 (98), 184 (48), 161 (28); HRMS-ESI (*m/z*): [(M–H_2O + H)$^+$] cald for ($C_{16}H_{17}S$)$^+$: 241.1045; found: 241.1055.

(3-(Hex-1-yn-1-yl)benzo[b]thiophen-2-yl)methanol (**4ga**). Yield: 46.8 mg, starting from 72.8 mg of **2g** (76%) (Table 3, entry 5). Yellow oil. IR (film): ν = 2222 (vw), 1458 (m), 1435 (m), 1188 (m), 1126 (w), 1026 (s), 756 (m), 733 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88–7.81 (m, 1H), 7.80–7.72 (m, 1H), 7.43–7.36 (m, 1H), 7.36–7.30 (m, 1H), 2.51 (t, *J* = 7.0, 2 H), 2.39 (s, br, 1H), 1.70–1.61 (m, 2H), 1.59–1.48 (m, 2H), 0.97 (t, *J* = 7.3, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.8, 139.9, 138.1, 125.0, 124.6, 123.0, 122.4, 116.2, 96.7, 72.8, 59.7, 30.9, 22.0, 19.3, 13.6; GC-MS (EI, 70 eV): *m/z* = 244 (M^+, 100), 225 (18), 211 (21), 201 (27), 187 (32), 171 (29), 147 (30), 129 (23), 115 (14); HRMS-ESI (*m/z*): [(M–H_2O + H)$^+$] cald for ($C_{15}H_{15}S$)$^+$: 227.0889; found: 227.0897.

(3-(Phenylethynyl)benzo[b]thiophen-2-yl)methanol (**4gc**). Yield: 56.0 mg, starting from 73.0 mg of **2g** (84%) (Table 3, entry 6). Yellow solid, mp = 138–140 °C. IR (KBr): ν = 2206 (vw), 1597 (w), 1435 (m), 1381 (m), 1219 (w), 1157 (w), 1026 (m), 772 (s) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.01 (d, *J* = 7.9, 1H), 7.93 (d, *J* = 7.9, 1H), 7.67–7.63 (m, 2H), 7.53–7.38 (m, 5H), 5.94 (t, *J* = 5.6, 1H), 5.00 (d, *J* = 5.6, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 152.6, 139.0, 137.2, 131.4, 128.80, 128.75, 125.03, 124.97, 122.9, 122.3, 122.1, 112.2, 95.0, 81.7, 58.2; GC-MS (EI, 70 eV): *m/z* = 264 (M^+, 100), 235 (64), 234 (52), 202 (23), 186 (17); HRMS-ESI (*m/z*): [(M–H_2O + H)$^+$] cald for ($C_{17}H_{11}S$)$^+$: 247.0576; found: 247.0587.

2-Butyl-3-(hex-1-yn-1-yl)benzo[b]thiophene (**4ia**). Yield: 54.5 mg, starting from 79.2 mg of **2i** (80%) (Table 3, entry 7). Yellow oil. IR (film): ν = 2183 (vw), 1458 (m), 1435 (m), 1373 (m), 1319 (w), 1180 (w), 1065 (w), 756 (m), 733 (m), cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.82–7.77 (m, 1H), 7.73–7.68 (m, 1H), 7.39–7.33 (m, 1H), 7.30–7.24 (m, 1H), 3.02 (t, *J* = 7.6, 2H), 2.53 (m, 2H), 1.77–1.69 (m, 2H), 1.69–1.61 (m, 2H), 1.59–1.50 (m, 2H), 1.47–1.38 (m, 2H), 0.98 (t, *J* = 7.3, 3H), 0.96 (t, *J* = 7.4, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 149.3, 140.3, 137.4, 124.4, 124.1, 122.4, 122.0, 115.7, 95.3, 73.8, 33.1, 31.1, 29.5, 22.2, 22.0, 19.4, 13.8, 13.6; GC-MS (EI, 70 eV): *m/z* = 270 (M^+, 96), 227 (100), 199 (18), 185 (61), 171 (21), 147 (34); HRMS-ESI (*m/z*): [(M + H)$^+$] cald for ($C_{18}H_{23}S$)$^+$: 271.1515; found: 271.1512.

3-((4-Bromophenyl)ethynyl)-2(tert-butyl)benzo[b]thiophene (**4jd**). Yield: 55.2 mg, starting from 80.0 mg of **2j** (59%) (Table 3, entry 8). Yellow solid, mp = 68–70 °C. IR (KBr): ν = 2207 (w), 1474 (m), 1358 (w), 1234 (w), 1204 (w), 1065 (m), 1011 (m), 818 (s), 756 (s), 725 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.90 (d, *J* = 7.9, 1H), 7.75 (d, *J* = 7.9, 1H), 7.53–7.47 (m, 2H), 7.46–7.42 (m, 2H), 7.42–7.38 (m, 1H), 7.33 (t, *J* = 7.5, 1H), 1.63 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 160.6, 141.3, 135.9, 133.8, 132.6, 131.7, 127.7, 124.6, 124.4, 122.2, 121.9, 112.3, 95.0, 85.3, 35.9, 30.7; GC-MS (EI, 70 eV): *m/z* = 370 [(M + 2)$^+$, 39], 368 (36, M^+), 355 (28), 353 (27), 274 (100), 258 (30), 129 (22); HRMS-ESI (*m/z*): [(M + H)$^+$] cald for ($C_{20}H_{18}BrS$)$^+$: 369.0307; found: 369.0316.

2-Phenyl-3-(phenylethynyl)benzo[b]thiophene (**4mc**). Yield: 67.8 mg, starting from 84.2 mg of **2m** (87%) (Table 3, entry 9). Yellow solid, mp = 70–71 °C. IR (KBr):ν = 2199 (vw), 1597 (w), 1481 (m), 1435 (m), 1219 (m), 1072 (w), 1018 (w), 949 (w), 756 (s), 687 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.07–8.03 (m, 2H), 8.02 (d, *J* = 8.0, 1H), 7.78 (d, *J* = 8.0, 1H), 7.58–7.54 (m, 2H), 7.47–7.40 (m, 3H), 7.40–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.2, 141.0, 137.6, 133.9, 131.6, 128.8, 128.7, 128.43, 128.35, 125.25, 124.9, 123.4, 123.3, 122.1, 113.6, 94.7, 84.1; GC-MS (EI, 70 eV): *m/z* = 310 (M^+, 100), 309 (67), 308 (74), 276 (9), 154 (22); HRMS-ESI (*m/z*): [(M + H)$^+$] cald for ($C_{22}H_{15}S$)$^+$: 311.0889; found: 311.0892.

3-(Hex-1-yn-1-yl)-2(p-tolyl)benzo[b]thiophene (**4na**). Yield: 56.6 mg, starting from 87.8 mg of **2n** (74%) (Table 3, entry 10). Yellow oil. IR (film): ν = 2214 (vw), 1597 (w), 1489 (m), 1462 (m), 1435 (m), 1254 (w), 1069 (m), 752 (s), 667 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94–7.87 (m, 3H), 7.75 (d, *J* = 7.9), 7.40 (t, *J* = 7.5, 1 H), 7.32 (t, *J* = 7.4, 1H), 7.24 (d, *J* = 7.9, 2H), 2.54 (t, *J* = 7.0, 2H), 2.39 (s, 3H), 1.71–1.60 (m, 2H), 1.59–1.49 (m, 2H), 0.98 (t, *J* = 7.3, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 145.0, 141.6, 138.5, 137.4, 131.3, 129.3, 128.2, 124.9, 124.7, 123.2, 121.9, 113.9, 96.0, 75.1, 30.9, 22.1, 21.3, 19.5, 13.7; GC-MS (EI, 70 eV): *m/z* = 304 (M^+, 67), 289 (7), 261 (100), 247 (30), 245 (28), 202 (7); HRMS-ESI (*m/z*): [(M + H)$^+$] cald for ($C_{21}H_{21}S$)$^+$: 305.1358; found: 305.1364.

Suzuki coupling leading to 3-arylbenzothiophenes 6in DES (Table 4): To a solution of 3-iodobenzothiophenes **2** (0.25 mmol; **2e**, 76.3 mg; **2g**, 72.8 mg; **2i**, 79.3 mg; **2m**, 84.2 mg; **2n**, 87.9 mg; **2p**, 85.8 mg) in ChCl/Gly (1 : 2, mol/mol; 1.5 mL) were added $PdCl_2$ (4.5 mg, 2.5×10^{-2} mmol), Na_2CO_3 (53.0 mg, 0.5 mmol), and the boronic acid (0.375 mmol; *p*-tolylboronic acid **5a**, 51.0 mg; thiophen-3-ylboronic acid **5b**, 48.0 mg; phenylboronic acid **5c**, 45.8 mg). The reaction mixture was allowed to stir at 80 °C (oil bath) for 15 h (for **6ea**, **6gb**, **6mc**, **6nc**, and **6pb**), or 100 °C (oil bath) for 24 h (for **6ib** and **6ic**). After cooling, the mixture was extracted with Et_2O (6 × 2 mL) at 60 °C, and the DES phase used again for the recycling experiments (see below). After evaporation of the solvent from the collected ethereal phases, products **6** were purified by column chromatography on silica gel using hexane to 99 : 1 hexane-AcOEt as the eluent (isolated yields are shown in Table 4).

Recycling procedure: To the DES residue obtained as described above, still containing $PdCl_2$, was added a solution of **2** (0.25 mmol) in Et_2O (1.5 mL). The Et_2O was removed under vacuum, then Na_2CO_3 (0.5 mmol) and the boronic acid **5** (0.375 mmol) were added. Then the same procedure described above was followed.

Representative Suzuki coupling procedure in larger scale: To a solution of (3-iodobenzo[*b*]thiophen-2-yl)methanol **2e** (305.0 mg, 1.00 mmol) in ChCl/Gly (1 : 2, mol/mol; 6 mL) were added $PdCl_2$ (18.0 mg, 0.1 mmol), Na_2CO_3 (212.0 mg, 2.0 mmol), and *p*-tolylboronic acid **5a** (204.0 mg, 1.5 mmol). The reaction mixture was allowed to stir at 80 °C (oil bath) for 15 h. After cooling, the mixture was extracted with Et_2O (6 × 5 mL) at 60 °C. After evaporation of the solvent from the collected ethereal phases, product **6ea** was purified by column chromatography on silica gel using as eluent pure hexane to 99 : 1 hexane-AcOEt (yield: 245 mg, 91%).

1-(3-(p-Tolyl)benzo[b]thiophen-2-yl)ethan-1-ol (**6ea**). Yield: 64.0 mg, starting from 76.3 mg of **2e** (95%) (Table 4, entry 1). White solid, mp = 110–112 °C. IR (KBr): ν = 2214 (vw), 1597 (w), 1489 (m), 1462 (m), 1435 (m), 1254 (w), 1069 (m), 752 (s), 667 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.86 (d, *J* = 7.4, 1H), 7.49 (d, *J* = 7.4), 7.35–7.25 (m, 6H), 5.24–5.18 (m 1H), 2.44 (s, 3 H), 2.00 (s, br, 1H), 1.59 (d, *J* = 6.4, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.0, 140.2, 138.3, 137.5,

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133.5, 131.8, 129.8, 129.4, 124.5, 124.2, 123.2, 122.5, 65.0, 25.4, 21.3; GC-MS (EI, 70 eV): *m/z* = 250 [(M–H_2O)$^+$, 59], 235 (100), 234 (69), 202 (12), 117 (16); HRMS-ESI (*m/z*): [(M–H_2O + H)$^+$] cald for ($C_{17}H_{15}S$)$^+$: 251.0889; found: 251.0898.

(3-(Thiophen-3-yl)benzo[b]thiophen-2-yl)methanol (**6gb**). Yield: 56.9 mg, starting from 72.8 mg of **2g** (92%) (Table 4, entry 2). White solid, mp = 75–78 °C. IR (KBr): ν = 1450 (m), 1366 (m), 1327 (w), 1219 (m), 1156 (s), 1134 (m), 949 (m), 895 (m), 849 (w), 756 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.87–7.82 (m, 1H), 7.71–7.65 (m, 1H), 7.47 (dd, *J* = 4.9, 3.0, 1H), 7.41–7.37 (m, 1H), 7.37–7.32 (m, 2H), 7.25 (dd, *J* = 4.9, 1.3, 1H), 4.88 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 140.2, 139.8, 138.8, 134.4, 129.9, 128.8, 125.9, 124.8, 124.5, 124.3, 123.3, 122.6, 59.0; GC-MS (EI, 70 eV): *m/z* = 248 [(M + 2)$^+$, 11], 246 (M$^+$, 100), 229 (25), 228 (23), 227 (23), 217 (44), 213 (28), 184 (40), 171 (16), 139 (10); HRMS-ESI (*m/z*): [(M–H_2O + H)$^+$] cald for ($C_{13}H_9S_2$)$^+$: 229.0140; found: 229.0149.

2-Butyl-3-(thiophen-3-yl)benzo[b]thiophene (**6ib**). Yield: 47.9 mg, starting from 79.3 mg of **2i** (70%) (Table 4, entry 3). Yellow solid, mp = 26–28 °C. IR (KBr): ν = 1458 (m), 1435 (m), 1381 (w), 1211 (w), 1173 (w), 1072 (m), 849 (m), 787 (m), 764 (s), 733 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.56–7.52 (m, 1H), 7.45 (dd, *J* = 4.9, 3.0, 1H), 7.31–7.23 (m, 3H), 7.17 (dd, *J* = 4.9, 1.0, 1H), 2.88 (t, *J* = 7.7, 2H), 1.71–1.63 (m, 2H), 1.41–1.31 (m, 2H), 0.87 (t, *J* = 7.4), 3H; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 143.1, 140.4, 138.1, 135.4, 129.1, 128.3, 125.4, 124.1, 123.8, 123.7, 122.5, 122.1, 33.9, 28.8, 22.3, 13.8; GC–MS (EI, 70 eV): *m/z* = 274 [(M + 2)$^+$, 8], 272 (M$^+$, 70), 229 (100), 185 (31), 184 (28), 115 (7); HRMS-ESI (*m/z*): [(M + H)$^+$] cald for ($C_{17}H_{17}S_2$)$^+$: 273.0766; found: 273.0771.

2-Butyl-3-phenylbenzo[b]thiophene (**6ic**). Yield: 45.6 mg, starting from 79.2 mg of **2i** (68%) (Table 4, entry 4). Yellow oil. IR (film): ν = 1605 (m), 1489 (m), 1435 (s), 1265 (m), 1196 (m), 1150 (m), 1072 (m), 1018 (m), 764 (s), 733 (m), 702 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.84–7.76 (m, 1H), 7.53–7.41 (m, 3H), 7.41–7.33 (m, 3H), 7.31–7.23 (m, 2H), 2.84 (t, *J* = 7.5, 2H), 1.66 (quintuplet, *J* = 7.5, 2H), 1.33 (hexuplet, *J* = 7.5, 2H), 0.86 (t, *J* = 7.5, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.6, 140.5, 138.3, 135.7, 133.5, 131.1, 128.5, 127.3, 124.1, 123.7, 122.6, 122.1, 33.9, 28.6, 22.3, 13.8; GC-MS (EI, 70 eV): *m/z* = 266 (M$^+$, 53), 223 (100), 221 (33), 178 (13); The spectroscopic data agreed with those reported.[15]

2,3-Diphenylbenzo[b]thiophene (**6mc**). Yield: 52.5 mg, starting from 84.2 mg of **2m** (73%) (Table 4, entry 5). White solid, mp = 112–114 °C. IR (KBr): ν = 1597 (m), 1489 (w), 1435 (m), 1227 (w), 1072 (w), 1026 (w), 756 (s), 694 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.85 (d, *J* = 7.8, 1H), 7.58 (d, *J* = 7.3, 1H), 7.41–7.28 (m, 9H), 7.25–1.17 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 140.9, 139.6, 138.9, 135.5, 134.3, 133.3, 130.5, 129.6, 128.7, 128.4, 124.5, 124.4, 123.4, 122.1; GC-MS (EI, 70 eV): *m/z* = 286 (M$^+$, 100), 271 (16), 252 (15), 142 (8). The spectroscopic data agreed with those reported.[8c]

3-Phenyl-2-(p-tolyl)benzo[b]thiophene (**6nc**). Yield: 52.1 mg, starting 87.9 mg of **2n** (69%) (Table 4, entry 6). White solid, mp = 167–168 °C. IR (KBr): ν = 1597 (w), 1481 (w), 1435 (m), 1242 (m), 1157 (m), 1026 (w), 872 (w), 748 (s), 694 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.83 (d, *J* = 6.9, 1H), 7.56 (d, *J* = 8.0, 1H), 7.42–7.25 (m, 7H), 7.22–7.17 (m, 2H), 7.05–7.00 (m, 2H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 141.0, 139.8, 138.8, 137.6, 135.7, 132.8, 131.4, 130.5, 129.5, 129.1, 128.6, 127.3, 129.4, 123.2, 122.0, 21.2; GC-MS (EI, 70 eV): *m/z* = 300 (M$^+$, 100), 285 (37), 284 (41), 252 (11), 142 (14). The spectroscopic data agreed with those reported.[8q]

2,3-Di(thiophen-3-yl)benzo[b]thiophene (**6pb**). Yield: 60.0 mg, starting from 85.8 mg of **2p** (80%) (Table 4, entry 7). White solid, mp = 123–127 °C. IR (KBr): ν = 1597 (m), 1489 (w), 1435 (m), 1227 (w), 1072 (w), 1026 (w), 756 (s), 694 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.86–7.77 (m, 1H), 7.61–7.52 (m, 1H), 7.46–7.39 (m, 1H), 7.37–7.26 (m, 3H), 7.25–7.15 (m, 2H), 7.06 (d, *J* = 4.7, 1H), 6.97–6.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 141.0, 138.1, 135.5, 134.84, 134.81, 129.2, 127.8, 127.7, 125.8, 125.5, 124.62, 124.55, 124.4, 123.5, 123.2, 122.0; GC-MS (EI, 70 eV): *m/z* = 300 [(M + 2)$^+$, 19], 298 (M$^+$, 100), 297 (65), 264 (41), 253 (43), 221 (16), 149 (9), 132 (18); HRMS-ESI (*m/z*): [(M + H)$^+$] cald for ($C_{16}H_{11}S_2$)$^+$: 299.0017; found: 299.0045.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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