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Synthesis of 2,3-Diarylbenzo[*b*]thiophenes *via* Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling and Palladium-Catalyzed Decarboxylative Arylation

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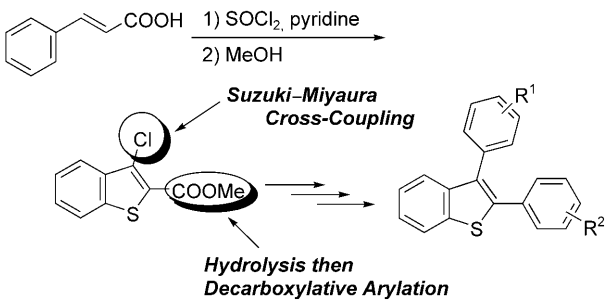
Abstract: We report a new approach to 2,3-diarylbenzo[*b*]thiophenes based on the nickel-catalyzed Suzuki–Miyaura cross-coupling/palladium-catalyzed decarboxylative arylation sequence of 3-chloro-2-methoxycarbonylbenzo[*b*]thiophenes, which are readily accessible from the corresponding cinnamic acids. In addition, this methodology can be applied to the concise synthesis of π-extended 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*′]dithiophenes. Their optical properties are also described.

Keywords: arylation; benzothiophenes; nickel; palladium

Introduction

The benzo[*b*]thiophene nucleus is ubiquitous in biologically active compounds and functional materials.[1] In particular, 2,3-diarylbenzo[*b*]thiophenes and their 3-carbonyl- or heteroatom-inserted analogues are known to work as selective estrogen receptor modulators,[2] tubulin-binding agents,[3] multidrug resistance-associated protein (MRP1) inhibitors,[4] angiogenesis inhibitors,[5] site-directed thrombin inhibitors,[6] anti-inflammatory agents,[7] and antifungal agents.[8] On the other hand, multiply arylated benzo[*b*]thiophenes[9] and further π-extended benzo[1,2-*b*;4,5-*b*′]dithiophenes as well as their condensed aromatics[10] have recently aroused considerable interest in the field of organic electronics including light-emitting diodes (LEDs) and field-effect transistors (FETs).[11] Therefore, the development of efficient and selective methods for the construction of these arylated benzothiophenes and benzodithiophenes is of considerable importance in organic synthesis.

Here we report an efficient, convergent protocol for the synthesis of various 2,3-diarylbenzo[*b*]thiophenes and 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*′]dithiophenes. As outlined in Scheme 1, our approach relies on the sequential Suzuki–Miyaura cross-coupling reaction and decarboxylative arylation of 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene. The benzothiophene scaffold is easily prepared from cinnamic acid and thionyl chloride.[12] The use of commercially available 1,4-phenylenediacrylic acid instead of cinnamic acid as the starting material also allows the concise synthesis of the benzodithiophene system. The decarboxylative arylation with aryl halides under palladium catalysis has very recently emerged as one of the potential cross-coupling methods.[13,14]

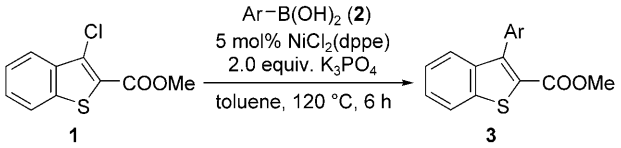


Scheme 1. Our synthetic approach.

Results and Discussion

Initially, we carried out the first arylation of 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene (**1**) through nickel-catalyzed Suzuki–Miyaura cross-coupling reaction with arylboronic acids **2** (Table 1). The nickel-based method induced efficient activation of the C–

Table 1. Nickel-catalyzed Suzuki–Miyaura cross-coupling reaction of 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene (**1**) with arylboronic acids **2**.[a]



1 3

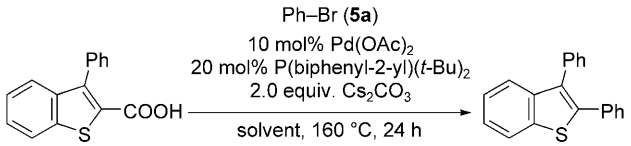
Entry	Ar in **2**	**3**,% yield[b]
1	Ph (**2a**)	**3a**, 91
2	4-MeC_6H_4 (**2b**)	**3b**, 83
3	4-$MeOC_6H_4$ (**2c**)	**3c**, 97
4	4-$CF_3C_6H_4$ (**2d**)	**3d**, 93
5	1-naphthyl (**2e**)	**3e**, 93

[a] A mixture of **1** (3.0 mmol), **2** (4.5 mmol), $NiCl_2$(dppe) (0.15 mmol), and K_3PO_4 (6.0 mmol) was stirred in boiling toluene (10 mL) for 6 h at 120 °C under N_2.
[b] Isolated yield.

Cl bond.[15] Thus, the benzothiophene **1** coupled with phenylboronic acid (**2a**) effectively in the presence of 5 mol% of $NiCl_2$(dppe) and 2.0 equivalents of K_3PO_4 in boiling toluene to furnish **3a** in 91% isolated yield (entry 1). Not only electron-rich and electron-deficient aryl groups but also the sterically demanding naphthalene motif could be introduced to the benzothiophene core without any difficulties (entries 2–5).

The monoarylated benzothiophenes **3** obtained above were readily hydrolyzed upon treatment with ethanolic KOH to afford the corresponding carboxylic acids **4a–e** quantitatively. Subsequently, we selected **4a** and bromobenzene (**5a**) as model substrates and performed the palladium-catalyzed second arylation accompanied by decarboxylation[13,14] (Table 2). Under our original reaction conditions,[14a] it was found that **4a** was transformed to **6aa** in 37% yield (entry 1). The addition of CuI had no positive effect on the yield (entry 2).[13a,c–f] On the other hand, the choice of solvent dramatically affected the reaction efficiency (entries 3–6). While the reaction proceeded sluggishly in DMSO, the use of amide solvents improved the yield of **6aa**, with DMAc proving to be optimal. Although we tested MS 4 Å and PCy_3 as a dehydrating reagent and ligand, respectively, based on our previous findings,[14b] the yield was decreased (en-

Table 2. Optimization for palladium-catalyzed decarboxylative arylation of 3-phenylbenzo[*b*]thiophene-2-carboxylic acid (**4a**) with bromobenzene (**5a**).[a]



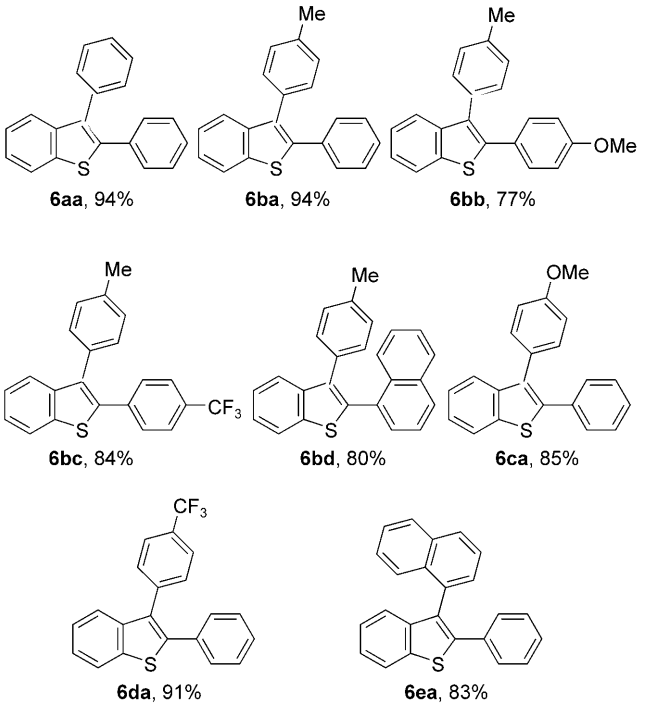
4a 6aa

Entry	**5a** (equiv.)	Solvent	**6aa**,% yield[b]
1	2.0	*o*-xylene	37
2[c]	2.0	*o*-xylene	10
3	2.0	DMAc	76
4	2.0	DMF	67
5	2.0	NMP	62
6	2.0	DMSO	10
7[d]	2.0	DMAc	49
8[e]	2.0	DMAc	24
9	3.0	DMAc	84
10[f]	3.0	DMAc	98 (94)

[a] A mixture of **4a** (0.50 mmol), **5a**, $Pd(OAc)_2$ (0.050 mmol), P(biphenyl-2-yl)(*t*-Bu)$_2$ (0.10 mmol), and Cs_2CO_3 (2.0 mmol) was stirred in solvent (2.5 mL) for 24 h at 160 °C under N_2.
[b] GC yield. Isolated yield is in parentheses.
[c] With CuI (0.50 mmol).
[d] With MS 4 Å (400 mg).
[e] With PCy_3 instead of P(biphenyl-2-yl)(*t*-Bu)$_2$.
[f] 48 h.

Table 3. Palladium-catalyzed decarboxylative arylation of **4a–e** with various aryl bromides **5**.[a]

Products and Yield [%][b]

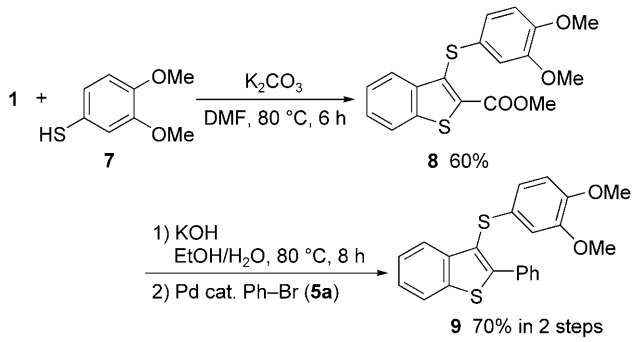


[a] A mixture of **4** (0.50 mmol), **5** (1.5 mmol), $Pd(OAc)_2$ (0.050 mmol), P(biphenyl-2-yl)(*t*-Bu)$_2$ (0.10 mmol), and Cs_2CO_3 (2.0 mmol) was stirred in DMAc (2.5 mL) for 48 h at 160 °C under N_2. Ar–Br **5**: Ar = Ph; **5a**, Ar = 4-$MeOC_6H_4$; **5b**, Ar = 4-$CF_3C_6H_4$; **5c**, and Ar = 1-naphthyl; **5d**.
[b] Isolated yield.

tries 7 and 8). Finally, with 3.0 equivalents of **5a** and a prolonged reaction period (48 h), the desired product **6aa** was obtained in 94% isolated yield (entry 10).[16]

By employing the optimized conditions, we examined the decarboxylative arylation of **4a–e** with various aryl bromides **5**. The results are illustrated in Table 3. As observed in the first arylation, electron-donating and electron-withdrawing groups as well as the bulky naphthyl core were tolerant toward the reaction.

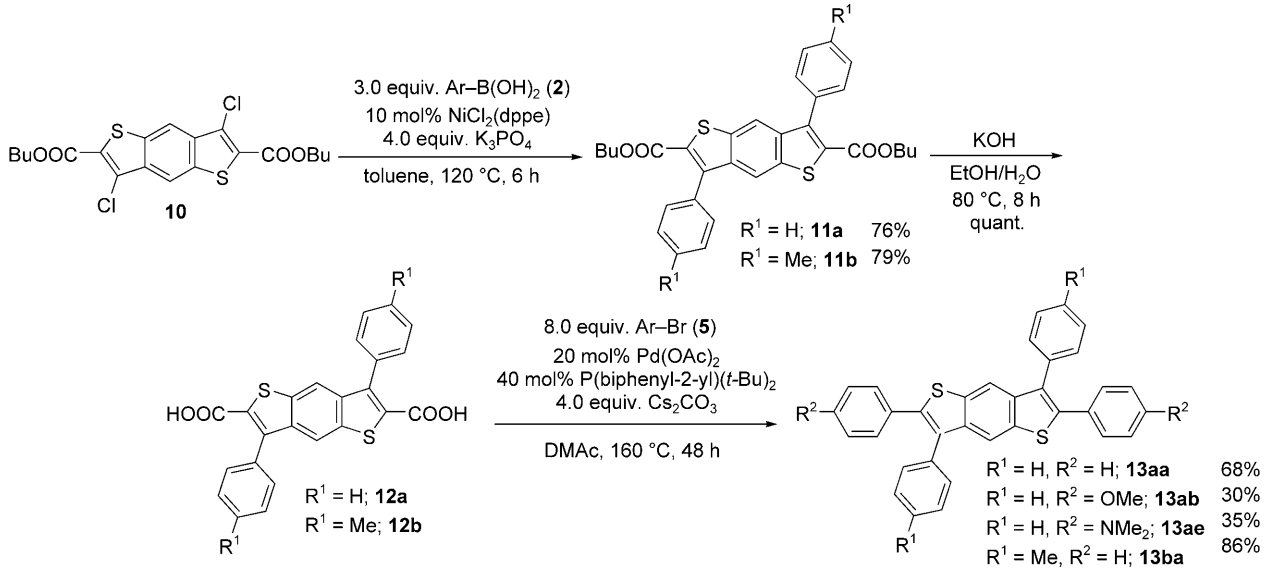
3-Chloro-2-methoxycarbonylbenzo[*b*]thiophene (**1**) may also be useful building block for the synthesis of 3-heteroatom-substituted 2-arylbenzothiophenes of high pharmaceutical value (Scheme 2).[17] The carbon-chlorine bond in **1** is activated toward the nucleophilic substitution reaction with the aid of the electron-withdrawing nature of the proximal methoxycarbonyl group so that the coupling with thiols is possible through an S_NAr reaction even in the absence of transition metal catalysts. Thus, the reaction of **1** with 3,4-dimethoxybenzenethiol (**7**) gave the expected product **8** and subsequent hydrolysis followed by palladium-catalyzed arylation under the same conditions as in Table 3 produced compound **9** in good yield.



Scheme 2. Synthesis of 2-phenyl-3-sulfanylbenzo[*b*]thiophene **9**.

Next, we applied the strategy to the construction of 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*′]dithiophenes. The readily accessible 2,6-bis(butoxycarbonyl)-3,7-dichlorobenzo[*b*]thiophene (**10**) from 1,4-phenylenediacrylic acid[12c] was employed as a platform, and the Suzuki–Miyaura coupling/ester hydrolysis/decarboxylative arylation sequence led to the facile preparation of tetraarylbenzodithiophenes **13** (Scheme 3). It is noted that the corresponding dimethyl ester as the starting material was sparingly soluble in common organic solvents so that we employed the dibutyl ester **10**.

With the above benzodithiophenes **13**, the investigation into their optical properties in $CHCl_3$ solution was conducted. The results are summarized in Table 4, and the spectra are shown in Figure 1 and Figure 2. The absorption and emission spectra of tetraphenyl derivative **13aa** exhibited the major bands with maximum absorption λ_{abs} and emission λ_{em} at 344 and 412 nm, respectively (entry 1). By the installation of the strongly electron-donating dimethylamino group to the benzene ring at the 2- and 6-positions, these peaks were red-shifted by about 35 nm to 378 and 447 nm, respectively (entry 3). The methoxy substituent caused similar shifts, although the effects were relatively small (entry 2). In accordance with the trend, the optical band gap E_{00} decreased in the order **13aa** > **13ab** > **13ae**. On the other hand, the modification at the 3- and 7-positions with *p*-tolyl functions that may enhance the solubility gave only a minor change in the optical properties of the parent structure **13aa** (entry 4).



Scheme 3. Synthesis of 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*′]dithiophenes **13**.

Table 4. Optical properties of 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*′]dithiophenes **13**.

Entry	13	λ_{abs} [nm][a]	log ε	λ_{em} [nm][b]	Φ_f[c]	E_{00} [eV][d]
1	**13aa**	344	4.31	412	0.30	3.29
2	**13ab**	349	4.41	421	0.51	3.21
3	**13ae**	378	4.60	447	0.35	2.94
4	**13ba**	345	4.35	412	0.31	3.26

[a] Absorption maximum in $CHCl_3$ (5.0×10^{-5} M).
[b] Emission maximum in $CHCl_3$ (5.0×10^{-5} M).
[c] Determined by comparison with $CHCl_3$ solution (5.0×10^{-6} M) of quinine sulfate ($\Phi_f=0.55$) exited at 366 nm.
[d] Optical band gap.

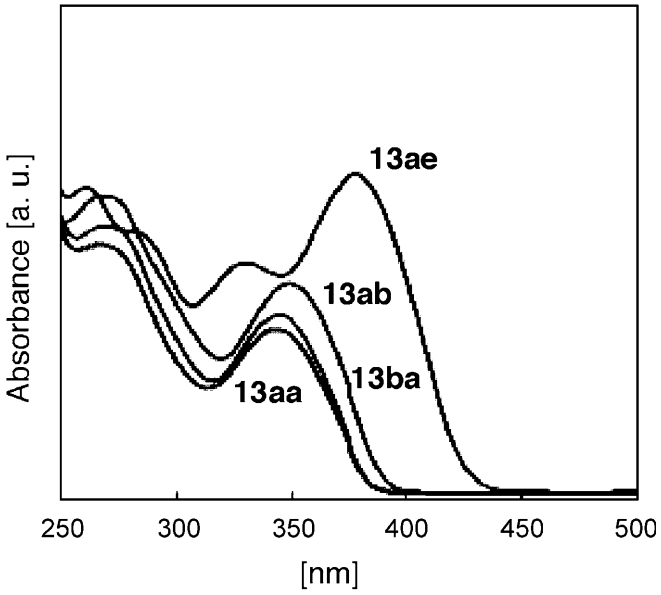


Figure 1. Absorption spectra of the $CHCl_3$ solution of **13**.

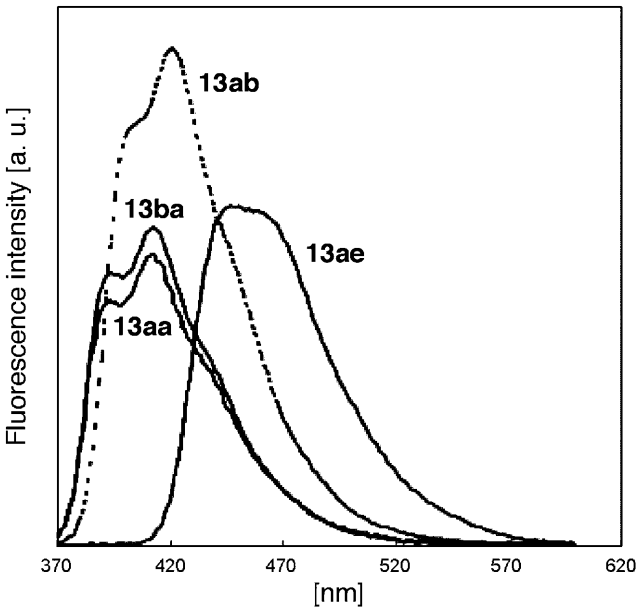


Figure 2. Photoluminescence spectra of the $CHCl_3$ solution of **13**.

Conclusions

In summary, we have developed an effective method for the concise and convergent synthesis of 2,3-diarylbenzo[*b*]thiophenes from 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene *via* nickel-catalyzed Suzuki–Miyaura cross-coupling and palladium-catalyzed decarboxylative arylation as the key transformations. Its application to the construction of 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*′]dithiophene π systems appears to demonstrate the high synthetic utility of this methodology.

Experimental Section

General Remarks

^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, for $CDCl_3$ solutions. MS data were obtained by the EI method. GC analysis was carried out using a silicon OV-17 column (i.d. 2.6 mm × 1.5 m) or a CBP-1 capillary column (i.d. 0.5 mm × 25 m). Photoluminescence spectra were measured as described previously.[18]

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene and *N,N*-dimethylacetamide (DMAc) were freshly distilled from CaH_2 prior to use. $NiCl_2$(dppe) was synthesized from $NiCl_2$ and dppe.[19] Methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate (**1**)[12a] and 3,7-dichlorobenzo[1,2-*b*;4,5-*b*′]dithiophene-2,6-dicarbonyl dichloride[12c] were prepared by the methods reported previously. Other starting materials were commercially available. All reactions were carried out under nitrogen atmospheres.

Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction of 3-Chloro-2-methoxycarbonylbenzo[*b*]thiophene (1) with Phenylboronic Acid (2a) (Table 1, entry 1)

In a 20-mL two-necked flask were added methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate (**1**) (3.0 mmol, 680 mg), phenylboronic acid (**2a**) (4.5 mmol, 549 mg), $NiCl_2$(dppe) (0.15 mmol, 79 mg), K_3PO_4 (6.0 mmol, 1.3 g), and toluene (10 mL). The resulting mixture was stirred under N_2 (balloon) at 120 °C (bath temperature) for 10 h. The product **3a** (yield: 732 mg, 2.7 mmol, 91%) was isolated by filtration of the mixture through a filter paper with diethyl ether as an eluent, evaporation of the solvents, and column chromatography on silica gel using hexane-ethyl acetate (98:2, v/v); mp 154–155 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3H), 7.32–7.55 (m, 8H), 7.88 (d, J = 8.1 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ = 52.2, 122.5, 124.8, 125.3, 127.2, 127.8, 128.0, 128.1, 129.6, 134.5, 140.1, 140.4, 144.2, 162.9; HR-MS: m/z = 268.0557 (M^+), calcd. for $C_{16}H_{12}O_2S$: 268.0558.

Hydrolysis of Methyl 3-Phenylbenzo[*b*]thiophene-2-carboxylate (3a)

In a 100-mL flask were added methyl 3-phenylbenzo[*b*]thiophene-2-carboxylate (**3a**) (2.0 mmol, 536 mg), potassium hydroxide (12 mmol, 673 mg), water (4.0 mL), and ethanol (8.0 mL). The mixture was heated at 80 °C (bath temperature) for 8 h under N_2. After cooling and acidification with aqueous HCl (2.0 M), a white precipitate was collected, washed with water, and dried under vacuum to afford carboxylic acid **4a**;[20] yield: quantitative; mp 188–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.38–7.56 (m, 8H), 8.08 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 122.9, 124.6, 125.2, 127.3, 127.9, 128.0, 129.69, 129.72, 134.3, 139.4, 139.8, 142.3, 163.3; HR-MS: m/z = 254.0399 (M^+), calcd. for $C_{15}H_{10}O_2S$: 254.0402.

Palladium-Catalyzed Decarboxylative Arylation of 3-Phenylbenzo[*b*]thiophene-2-carboxylic Acid (4a) with Bromobenzene (5a) (Table 2, entry 10)

In a 20-mL two-necked flask were added 3-phenylbenzo[*b*]-thiophene-2-carboxylic acid (**4a**) (0.50 mmol, 127 mg), bromobenzene (**5a**) (1.5 mmol, 235 mg), $Pd(OAc)_2$ (0.050 mmol, 11 mg), P(biphenyl-2-yl)(*t*-Bu)$_2$ (0.10 mmol, 30 mg), Cs_2CO_3 (1.0 mmol, 325 mg), 1-methylnaphthalene (*ca.* 50 mg) as internal standard, and DMAc (2.5 mL). The resulting mixture was stirred under N_2 (balloon) at 160 °C (bath temperature) for 48 h. Analysis of the mixture by GC confirmed the formation of compound **6aa** (yield: 140 mg, 98%). After cooling, the reaction mixture was poured into diluted aqueous HCl, extracted with diethyl ether, and dried over Na_2SO_4. The product **6aa**[21] (yield: 135 mg, 0.47 mmol, 94%) was isolated by column chromatography on silica gel using hexane as eluent; mp 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.27 (m, 3H), 7.30–7.42 (m, 9H), 7.58–7.61 (m, 1H), 7.85–7.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.1, 123.4, 124.4, 124.5, 127.4, 127.7, 128.3, 128.6, 129.6, 130.4, 133.2, 134.2, 135.5, 138.8, 139.5, 140.9; HR-MS: m/z = 286.0811 (M^+), calcd. for $C_{20}H_{14}S$: 286.0816.

Reaction of 3-Chlorobenzo[*b*]thiophene-2-carboxylate (1a) with 3,4-Dimethoxybenzenethiol (7)

In a 100-mL two-necked flask were added 3-chlorobenzo[*b*]-thiophene-2-carboxylate (**1a**) (3.0 mmol, 680 mg), 3,4-dimethoxybenzenethiol (**7**) (3.6 mmol, 612 mg), K_2CO_3 (6.0 mmol, 829 mg), and DMF (20 mL). The resulting mixture was stirred under N_2 (balloon) at 80 °C (bath temperature) for 6 h. After cooling, the reaction mixture was poured into diluted aqueous HCl, extracted with diethyl ether, and dried over Na_2SO_4. The product **8** (yield: 623 mg, 1.8 mmol, 60%) was isolated by column chromatography on silica gel using hexane-ethyl acetate as eluent (90:10, v/v); mp 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3H), 3.82 (s, 3H), 3.95 (s, 3H), 6.72 (d, J = 8.4 Hz, 1H), 6.83–6.90 (m, 2H), 7.29–7.33 (m, 1H), 7.42–7.46 (m, 1H), 7.78–7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.5, 55.87, 55.92, 111.6, 113.3, 122.6, 122.7, 125.0, 125.5, 126.6, 127.4, 132.7, 132.9, 139.8, 139.9, 148.3, 149.2, 162.4; HR-MS: m/z = 360.0488 (M^+), calcd. for $C_{18}H_{16}O_4S_2$: 360.0490.

Preparation of 2,6-Bis(butoxycarbonyl)-3,7-dichlorobenzo[1,2-*b*;4,5-*b*′]dithiophene (10)

In a 100-mL two-necked flask were added 3,7-dichlorobenzo[1,2-*b*;4,5-*b*′]dithiophene-2,6-dicarbonyl dichloride[12c] (5.0 mmol, 1.9 g), *n*-butanol (20 mmol, 1.8 mL), pyridine (20 mmol, 1.6 mL), and chlorobenzene (10 mL). The resulting mixture was stirred under N_2 (balloon) at 100 °C (bath temperature) for 6 h. After cooling, the reaction mixture was filtered through a filter paper with diethyl ether as an eluent followed by evaporation of the solvent. The resulting solid was washed with water, and dried under vacuum. The diester **10** (yield: 1.9 g, 4.2 mmol, 83%) was isolated by recrystallization from toluene/hexane; mp 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.3 Hz, 6H), 1.48–1.57 (m, 4H), 1.76–1.84 (m, 4H), 4.40 (t, J = 6.6 Hz, 4H), 7.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 19.5, 30.8, 66.1, 121.4, 126.5, 128.4, 133.1, 137.3, 161.0; HR-MS: m/z = 458.0172 (M^+), calcd. for $C_{20}H_{20}Cl_2O_4S_2$: 458.0180.

Acknowledgements

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