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Palladium-Catalyzed Phosphine-Free Direct C–H Arylation of Benzothiophenes and Benzofurans Involving MIDA Boronates

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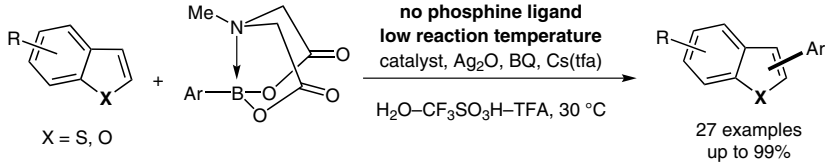

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Abstract With high regioselectivity, a series of benzoheterocyclic compounds were synthesized via palladiium-catalyzed phosphine-free C–H arylation of benzothiophenes/benzofurans with aryl MIDA boronates at 30–50 °C in moderate to excellent yields. MIDA boronates were used in C–H arylation of heterocycles for the first time. Under the optimal conditions, the benzothiophenes could be transformed into the β-arylbenzothiophenes, and the benzofurans gave only α-aryl-substituted products.

Key words C–H arylation, benzothiophene, benzofuran, MIDA boronate, bis(alkoxo)palladium(II) complex

Benzoheterocycles as an important class of fused heterocycles are ubiquitous in biologically active compounds, nature products, organic materials, and pharmaceuticals (anti-inflammatory, antipsoriasis, antiulcers, migraine drugs, and antiallergic).[1] Numerous effective routes to aryl benzoheterocycles exist, however, these generally require the appropriate functionalization of one or both coupling partners.[2] Due to the easy operations and high atom efficiency, direct C–H arylation of heterocycles represents a more efficient approach, and considerable progress has been made in this area using palladium catalysts.[3] For valuable benzothiophene and benzofuran motifs, palladium-catalyzed direct arylation has been well established with aryl halides.[4] Along this line, recent developments in direct arylation of benzothiophenes at the C3-position are built upon the pioneering works of the Itami group,[5] Bach group,[6] and Oi group.[7] Progress in the studies of Itami and Bach is that low-toxicity arylboronic acids are successfully used as one of the coupling partners to afford β-arylated heterocyles with high regioselectivity.[5,6] Nevertheless, there are only two examples for the arylation of benzothiophene in both studies. During the same period, Oi and co-workers[7] developed a direct arylation of benzothiophenes with expensive aryltrimethylsilanes, and limitations in the C3/C2 selectivity of this approach are also apparent. In addition, larger amounts of catalyst loading (5–10 mol%) or high reaction temperature were observed in all of these studies.

As an useful coupling partner, MIDA boronates have been successfully applied to synthesize biaryl compounds in Suzuki reaction[8] due to their versatility, low toxicity, and enhanced stability relative to hard organometallic carbon nucleophiles.[9] Up to now only one report employed aryl MIDA boronates to the oxidative arylation of *n*-butyl acrylate.[10] Accordingly, in the course of investigating catalytic activity of *N*,*O*-ligand palladacycle catalysts (Figure 1),[11] herein, we describe an operationally simple and highly regioselective protocol for the direct arylation of benzothiophenes/benzofurans with various MIDA boronates under mild reaction conditions.

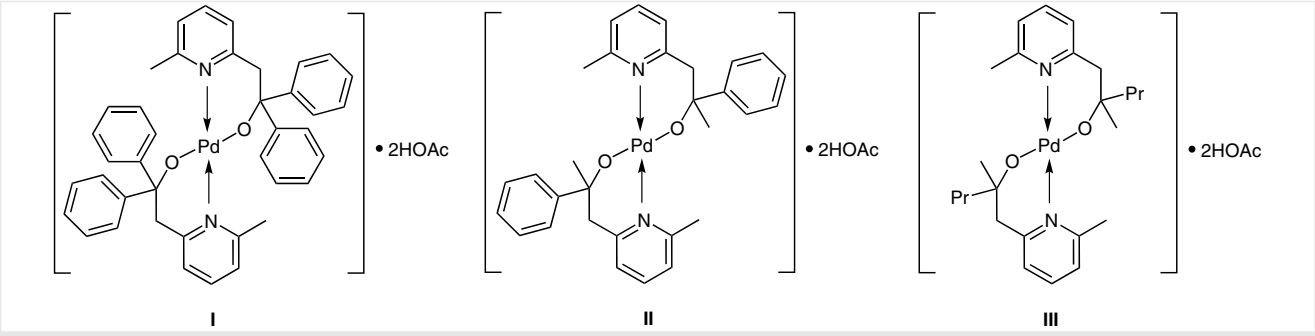
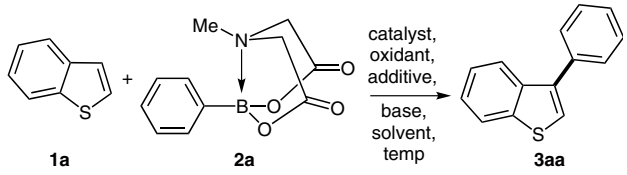


Figure 1 The structure of bis(alkoxo)palladium(II) complexes **I**–**III**

At the onset of our studies, the direct arylation of benzothiophene (**1a**) and phenyl MIDA boronate (**2a**) was chosen as a model reaction. Some of our results are shown in Table 1. The model reaction was carried out at 30 °C in TFA with 2 mol% **III** as catalyst, K_2CO_3 as base, and Ag_2O and BQ as oxidants to afford 3-phenylbenzothiophene in 23% (Table 1, entry 1). Several bases (e.g., K_2CO_3, Cs(tfa), and Na_2CO_3) were investigated, and the best choice was Cs(tfa) (Table 1, entries 1–4). It was found that large amounts of water could be permitted hydrolysis of MIDA boronates to increase the yield of **3aa**[12] [Figure 2, H_2O (%)[a]]. Pleasingly, when a small amount of CF_3SO_3H (2% of TFA) was introduced into the reaction mixture, the yield of product **3aa** could be increased to 89% [Figure 2, CF_3SO_3H (%)[b], and Table 1, entry 5].

Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3aa**

Entry	Base	Oxidant	Yield (%)[b]
1[c]	K_2CO_3	Ag_2O, BQ	23
2[c]	Na_2CO_3	Ag_2O, BQ	22
3[c]	Cs(tfa)	Ag_2O, BQ	32
4[c]	–	Ag_2O, BQ	18
5	Cs(tfa)	Ag_2O, BQ	89
6	Cs(tfa)	Ag_2CO_3, BQ	84
7	Cs(tfa)	AgOAc, BQ	65
8	Cs(tfa)	AgF, BQ	72
9	Cs(tfa)	$Cu(OA_c)_2$, BQ	24
10	Cs(tfa)	$K_2S_2O_4$, BQ	trace
11	Cs(tfa)	TBHP, BQ	trace
12[d]	Cs(tfa)	Ag_2O	22
13[e]	Cs(tfa)	BQ	12
14[f]	Cs(tfa)	Ag_2O, BQ	80
15[g]	Cs(tfa)	Ag_2O, BQ	75
16[h]	Cs(tfa)	Ag_2O, BQ	30

[a] Reaction conditions: benzothiophene (0.25 mmol), phenyl MIDA boronate (0.375 mmol), base (0.25 mmol), oxidant (0.5 mmol), BQ (0.125 mmol), catalyst (2 mol%), in the mixture solvent H_2O–CF_3SO_3H–TFA (15:2:83; 1 mL), under air, 20 h.
[b] Isolated yield.
[c] In TFA (1 mL).
[d] Ag_2O (0.625 mmol) without BQ.
[e] BQ (0.625 mmol) without Ag_2O.
[f] $Pd(OAc)_2$.
[g] Cat. **I**.
[h] Cat. **II**.

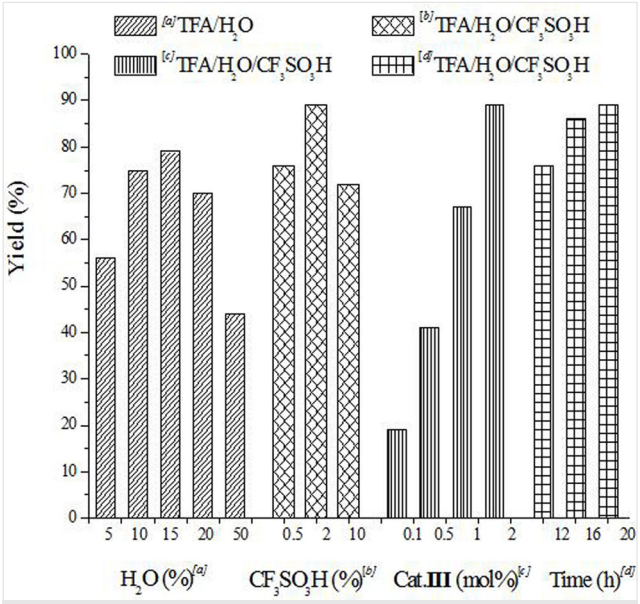
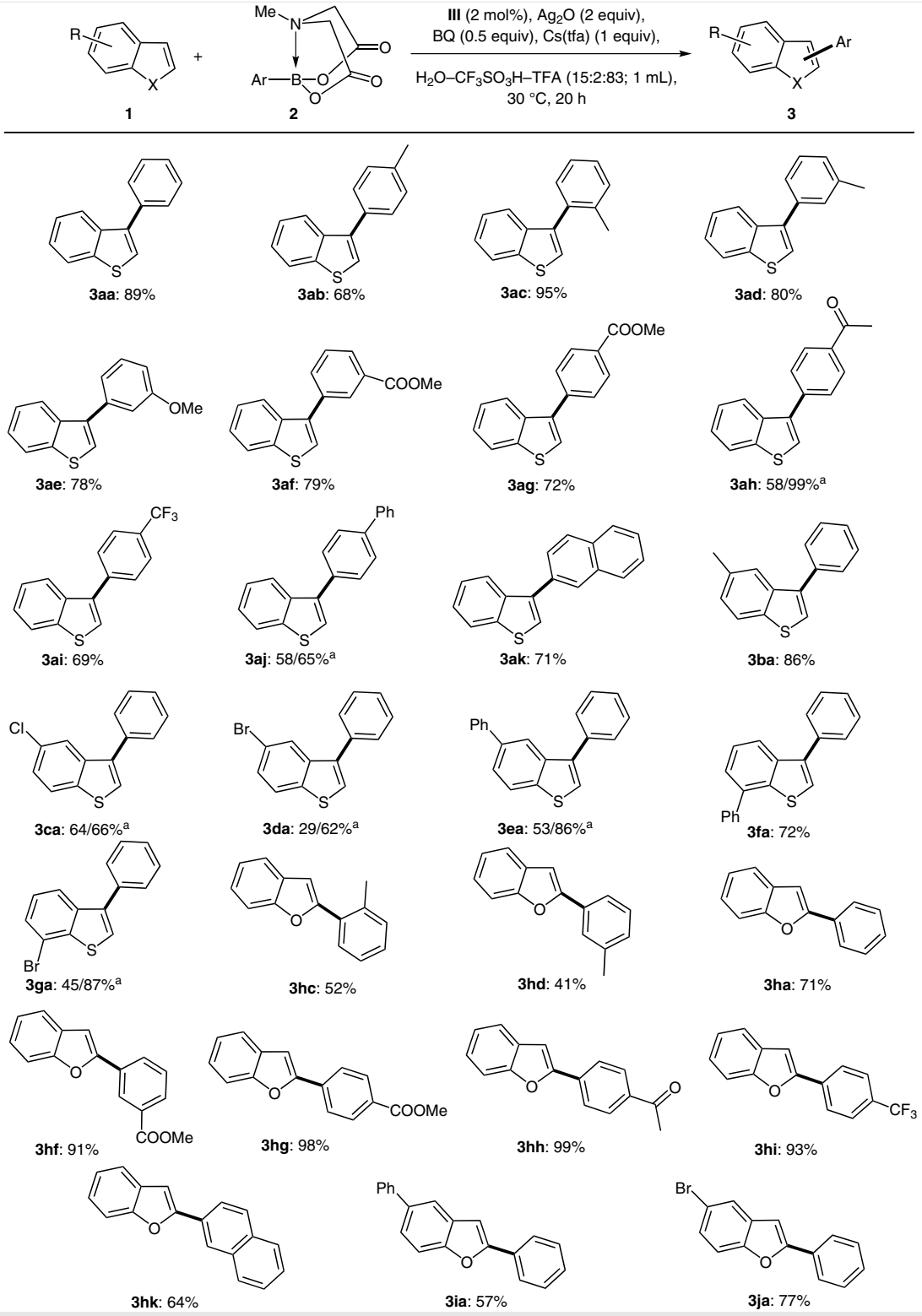


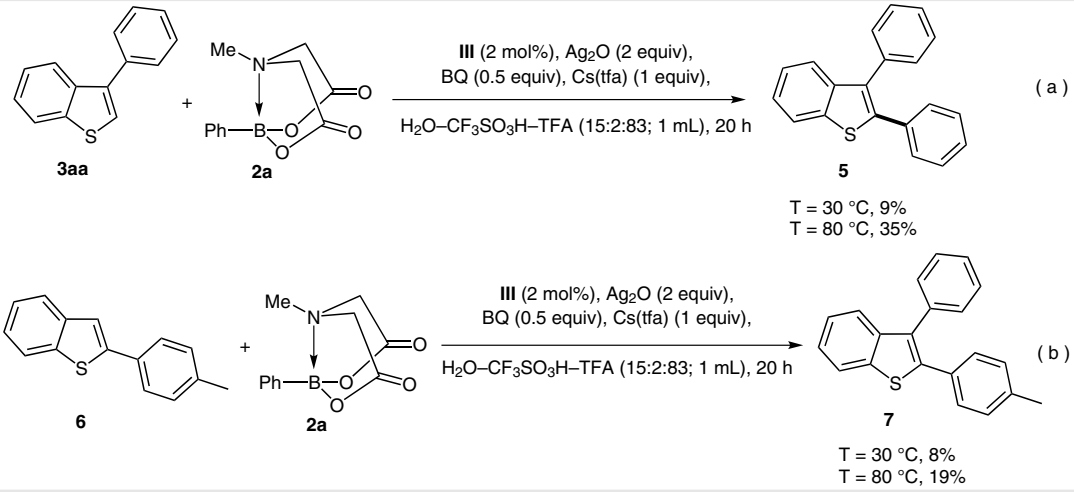
Figure 2 Optimization of reaction conditions. [a] The content of H_2O[V(H_2O)/V(H_2O+TFA)] was optimized with 2 mol% **III** in 20 h. [b] The content of CF_3SO_3H[V(CF_3SO_3H)/V(H_2O+TFA +CF_3SO_3H)] was optimized with 2 mol% **III** in 20 h. [c] The catalyst loading of **III** was optimized with H_2O–CF_3SO_3H–TFA (15:2:83; 1 mL) in 20 h. [d] Reaction time was optimized with H_2O–CF_3SO_3H–TFA (15:2:83; 1 mL) and 2 mol% **III**.

In an attempt to further increase the yield of this reaction, we proposed a number of oxidants. However, other tested oxidants did not provide a higher yield than Ag_2O and BQ (Table 1, entries 6–13). Subsequently, the catalytic activity was checked, and the bis(alkoxo)palldium complexes **I**, **II**, and $Pd(OAc)_2$ did not show better catalytic activity (Table 1, entries 14–16). A catalyst loading of 2 mol% was detemineted to be optimal [Figure 2, **III** (mol%)[c]]. In addition, the reaction time was not less than 20 hours [Figure 2, time (h)[d]].

Encouraged by the above results, diverse benzoheterocycles and aryl MIDA boronates were evaluated under the optimized conditions (Scheme 1).[13,14] The direct arylation of benzothiophene (**1a**) could proceed well with various aryl MIDA boronates to afford the β-arylbenzothiophenes in moderate to excellent yields at 30 °C (Scheme 1, **3aa**–**i**). Sterically hindered MIDA boronate **2c** was not found to have any influence on the product yield (95%; Scheme 1, **3ac**). In addition, this protocol was also compatible with biphenyl and naphthyl MIDA boronates (Scheme 1, **3aj**–**ak**). Surprisingly, the conversion yield of **3ah** could be promoted to 99% at 50 °C. Subsequently, the benzothiophene derivatives were tested using the standard conditions. All of the investigated benzothiophenes could smoothly react with phenyl MIDA boronates at 30 °C to give the corresponding products in moderate to good yields (Scheme 1, **3ba**–**ga**). The yields of **3da**, **3ea**, and **3ga** were obviously increased at 50 °C, higher than at 30 °C. Compared with the benzothiophenes the direct arylation of benzofurans with aryl MIDA



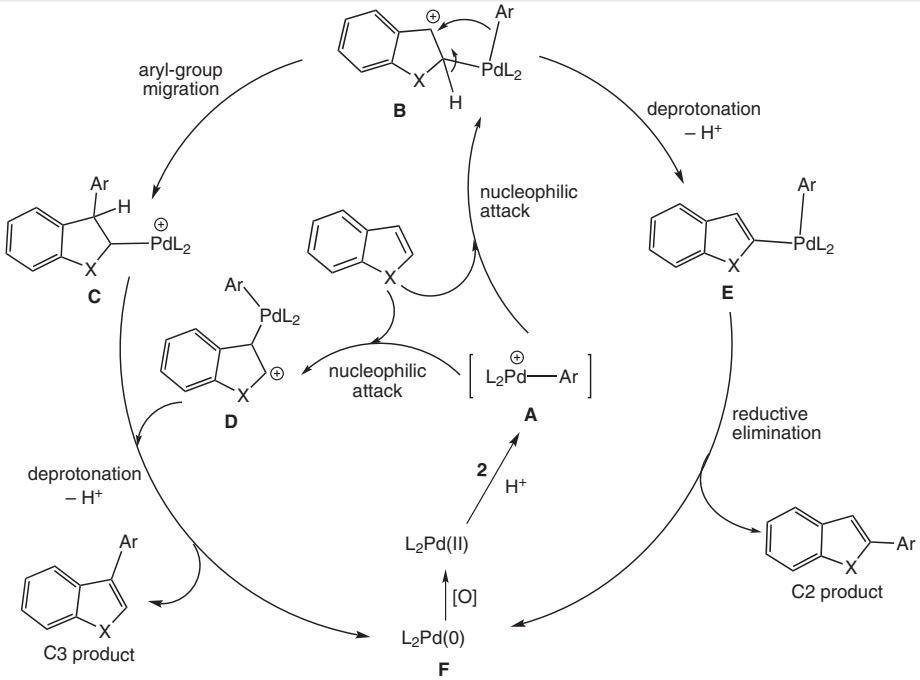
Scheme 1 Pd-catalyzed direct arylation of benzothiohenes and benzofurans with aryl MIDA boronates; isolated yields are given. *Reagents and conditions*: **III** (2 mol%), Ag_2O (0.5 mmol), benzoquinone (0.125 mmol), Cs(tfa) (0.25 mmol), benzothiophene or benzofuran (0.25 mmol), aryl MIDA boronates (0.375 mmol), H_2O–CF_3SO_3H–TFA (15:2:83; 1 mL), 30 °C, 20 h. [a] Reaction was carried out at 50 °C.



Scheme 2 Control experiments

boronates occured at the α-position to form α-arylbenzofurans at 30 °C (Scheme 1, **3ha**–**ja**). In contrast to benzothiophenes, the yields with the aryl MIDA boronates bearing electron-withdrawing groups were higher than that of electron-donating groups (Scheme 1, **3ha**–**hd** and **3hf**–**hi**). The structures of **3ia** and **3fa** were confirmed by X-ray diffraction analysis (see Supporting Information).

To gain insight into the mechanism of this transformation, a series of control experiments were carried out (Scheme 2). Under the optimized conditions, the 2,3-diphenylbenzothiophene (**5**)[15] was obtained from the reaction of the β-phenyl benzothiophene **3aa** with **2a** in 9% at 30 °C and in 35% at 80 °C (Scheme 2, a). These results showed that the primary reaction of the palladium(II) intermediate might occurs at C2, then the aryl group is delivered intra- or intermolecularly to the C3 carbon atom.[5] When the 2-tolylbenzothiophene (**6**)[16] was used, the 2,3-diarylbenzothiophene **7** was isolated in 8% at 30 °C, and 19% at 80 °C (Scheme 2, b). It proves that the ArPd(II) intermediate could also attack on the C3-positon of benzothiophenes, however, this is not a mainly route to get the β-aryl benzothiophenes.



Scheme 3 Possible mechanism

Based on the above results and previous works,[5] a plausible mechanism is depicted in Scheme 3. Firstly, transmetalation of **III** with aryl MIDA boronate in an acid environment might generate a cationic ArPd species **A**. Nucleophilic attack of benzothiophene/benzofuran to **A** (at the most nucleophilic C2-position) leads to cationic intermediate **B**. Aryl-group migration from palladium to the C3-position provides intermediate **C** (only for benzothiophenes). On the other hand, nucleophilic attack of benzothiophene/benzofuran to **A** could also occur at the C3-position to give cationic intermediate **D**. Subsequently, deprotonation of intermediates **C** and **D** eventually produces C3-arylated product **3** and the palladium(0) species **F**. Deprotonation of **B** produces intermediate **E**, which proceeds reductive elimination to give C2-arylated product and the palladium(0) species **F**. Finally, oxidation of **F** by oxidants regenerates palladium(II) to close the catalytic cycle.

In conclusion, we developed an efficient and regioselective palladium-catalyzed C–H arylation using aryl MIDA boronates as one of thecoupling partners to synthesize aryl-substituted benzothiophenes/benzofurans in moderate to excellent yields. MIDA boronates were applied in C–H arylation of heterocycles for the first time. The direct arylation of benzothiophenes could afford the β-arylbenzothiophenes, and the arylation of benzofurans gave only α-aryl-substituted products. The reaction mechanism was proposed by control experiments.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379606.

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(12) **Preparation of 3aa; Typical Procedure**

To a 10 mL round-bottom flask were added **III** (3.2 mg, 0.005 mmol, 2 mol%), Ag_2O (116 mg, 0.5 mmol, 2 equiv), benzoquinone (14 mg, 0.125 mmol, 0.5 equiv), Cs(tfa) (64 mg, 0.25 mmol, 1 equiv.), benzothiophene (**1a**; 34 mg, 0.25 mmol, 1 equiv), phenyl MIDA boronate (**2a**; 86 mg, 0.375 mmol, 1.5 equiv), and H_2O–CF_3SO_3H–TFA (15:2:83; 1 mL). The reaction mixture was stirred at 30–50 °C for 20 h. The suspension was cooled to r.t. and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 20% aq $NaHCO_3$ solution (40 mL). After evaporation of the solvent the crude product was purified by chromatography on silica gel to give 3-phenylbenzo[*b*]thiophene (**3aa**; 46.7 mg, 89% isolated yield) as a yellow oil. This product has been reported previously.[4f]

3-Phenylbenzo[*b*]thiophene (3aa)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.88 (m, 2 H), 7.61–7.56 (m, 2 H), 7.51–7.45 (m, 2 H), 7.43–7.35 (m, 4 H) ppm. ^{13}C NMR (100

MHz, $CDCl_3$): δ = 140.65, 138.06, 137.86, 135.98, 128.70, 128.69, 127.52, 124.38, 124.30, 123.39, 122.90 ppm. MS (EI): *m/z* calcd for $C_{15}H_{12}S$ $[M]^+$: 210.1; found: 210.0.

(13) CCDC-1008524 (**3fa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) CCDC-1008525 (**3ia**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) **Preparation of 5; Typical Procedure**

To a 10 mL round-bottom flask were added **III** (3.2 mg, 0.005 mmol, 2 mol%), Ag_2O (116 mg, 0.5 mmol, 2 equiv), benzoquinone (14 mg, 0.125 mmol, 0.5 equiv), Cs(tfa) (64 mg, 0.25 mmol, 1 equiv), **3aa** (52.5 mg, 0.25 mmol, 1 equiv), phenyl MIDA boronate (115 mg, 0.5 mmol, 2.0 equiv), and H_2O–CF_3SO_3H–TFA (15:2:83; 1 mL). The reaction mixture was stirred at 30 °C and 80 °C for 20 h. The suspension was cooled to r.t. and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 20% aq $NaHCO_3$ solution (40 mL). After evaporation of the solvent the crude product was purified by chromatography on silica gel to give 2,3-diphenylbenzo[*b*]thiophene (**5**; 6.4 mg, 9% at 30 °C/25.0 mg, 35% at 80 °C isolated yield) as a white solid; mp 111–113 °C. This product has been reported previously.[17]

2,3-Diphenylbenzo[*b*]thiophene (5)

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.84 (m, 1 H), 7.61–7.56 (m, 1 H), 7.42–7.28 (m, 9 H), 7.25–7.20 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.88, 139.54, 138.85, 135.52, 134.24, 133.24, 130.43, 129.61, 128.63, 128.33, 127.68, 127.36, 124.51, 124.42, 123.34, 122.05 ppm. MS (EI): *m/z* calcd for $C_{20}H_{14}S$ $[M]^+$: 286.1; found: 286.0.

(16) **Preparation of 6; Typical Procedure**

To a 10 mL round-bottom flask were added **III** (3.2 mg, 0.005 mmol, 2 mol%), Ag_2O (116 mg, 0.5 mmol, 2 equiv), benzoquinone (14 mg, 0.125 mmol, 0.5 equiv), Cs(tfa) (64 mg, 0.25 mmol, 1 equiv), **6** (56mg, 0.25 mmol, 1 equiv), phenyl MIDA boronates (115 mg, 0.5 mmol, 2.0 equiv), and H_2O–CF_3SO_3H–TFA (15:2:83; 1 mL). The reaction mixture was stirred at 30 °C and 80 °C for 20 h. The suspension was cooled to r.t. and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 20% aq $NaHCO_3$ solution (40 mL). After evaporation of the solvent the crude product was purified by chromatography on silica gel to give 3-phenyl-2-(*p*-tolyl)benzo[*b*]thiophene (6.0 mg, 8% at 30 °C/14.3 mg, 19% at 80 °C isolated yield) as a white solid; mp 149–151 °C. This product has been reported previously.[18]

3-Phenyl-2-(*p*-tolyl)benzo[*b*]thiophene (7)

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.85 (m, 1 H), 7.59 (d, *J* = 8.2 Hz, 1 H), 7.45–7.31 (m, 7 H), 7.27–7.21 (m, 2 H), 7.10–7.04 (m, 2 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.00, 139.73, 138.73, 137.61, 135.72, 132.80, 131.33, 130.46, 129.44, 129.08, 128.62, 127.30, 124.37, 123.22, 122.01, 21.17 ppm. MS (EI): *m/z* calcd for $C_{21}H_{16}S$ $[M]^+$: 300.1; found: 300.0.

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