

# Synthesis

## Bromide as the directing group for $\beta$ -arylation of thiophenes

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### Abstract:

Direct  $\beta$ -arylation of thiophene derivatives with bromide as the directing group is disclosed. The reaction is conducted with PdCl<sub>2</sub>(p-tolyl)<sub>3</sub>P as catalyst, silver salt as additive and aryl iodide as coupling partner, affording brominated biaryl compounds as product. Control experiments indicated that presence of bromide group enhances the reactivity of C-H bond, enabling  $\beta$ -arylation. Furthermore, the C-Br bond can be facilely converted to many useful functional groups via versatile cutting-edge methodologies. The mechanistic study suggests that silver salt plays a key role in C-H bond activation step.

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# Bromide as the directing group for $\beta$ -arylation of thiophenes

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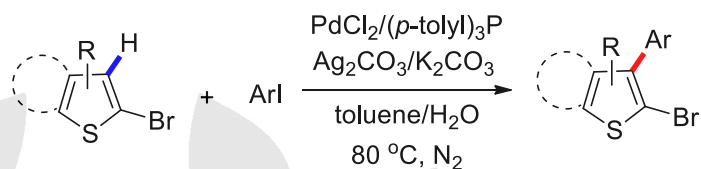
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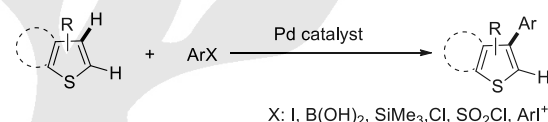
**Abstract** Direct  $\beta$ -arylation of thiophene derivatives with bromide as directing group is disclosed. The reaction is conducted with  $\text{PdCl}_2/(\text{p-tolyl})_3\text{P}$  as catalyst, silver carbonate as additive and aryl iodide as coupling partner, affording brominated biaryl compounds as product. Control experiments indicated the presence of bromide group enhances the reactivity of C-H bond, enabling  $\beta$ -arylation. Furthermore, the C-Br bond can be facilely converted to many useful functional groups via a wide range of methodologies. The mechanistic study suggests that silver salt plays a key role in C-H bond activation step.

**Key words**  $\beta$ -arylation, bromide, thiophene, silver

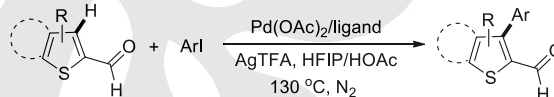
Functionalized thiophenes are important heterocycles and are common motifs in a good range of biological molecules, and are components in many organic functional materials.<sup>2</sup> Over the past decade, direct  $\alpha$ -arylation of thiophene has been widely investigated due to high reactivity of C-H bond at  $\alpha$  position.<sup>3</sup> On the other hand, explorations of direct  $\beta$ -arylation are less reported due to low reactivity of the corresponding C-H bond. The primary strategy for direct  $\beta$ -arylation is via Heck type mechanism with palladium complex as catalyst. For instant, Itami and co-workers reported a  $\text{PdCl}_2/\text{P}[\text{OCH}(\text{CF}_3)_2]_3$  catalyzed  $\beta$ -selective-arylation of thiophenes with iodoarenes as coupling partners.<sup>4</sup> The following reports focusing on exploring other coupling partners including aryl boronic acids,<sup>5</sup> aryltrimethyl silanes,<sup>6</sup> aryl chlorides,<sup>7</sup> benzenesulfonyl chlorides<sup>8</sup> and diaryliodonium salts<sup>9</sup> were subsequently reported in order to expand substrate scope and lower reaction temperature. Despite great progress has been made, moderate  $\beta$ -selectivity were still obtained in some cases. Therefore, it limited further application of these methods in precise synthesis of thiophene-containing functional materials and drug precursors since it required much effort to remove  $\alpha$ -arylated isomers for high quality samples.



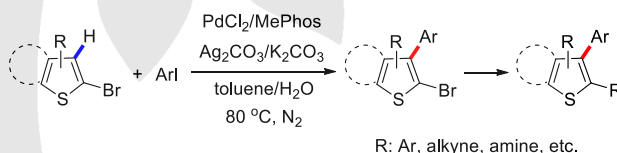
## Heck type mechanism



## Aldehyde as transient directing group



## This work

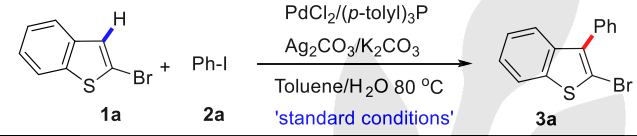


**Scheme 1.** Methods for direct  $\beta$ -arylation of thiophenes

Directing groups involved C-H bond activation showed both great efficiency and precise regioselectivity.<sup>10</sup> However, the removal of directing groups is one major issue to hinder its further application. In this context, the use of directing groups, which can be easily converted into other useful functional groups, is one convenient strategy to solve this problem.<sup>11</sup> For instant, Ge and co-workers reported an aldehyde directed  $\beta$ -arylation reaction, which then gave mechanochromic materials via post-modification of aldehyde groups.<sup>12</sup> However, high temperature (130°C) was required to achieve reasonable yields, due to the reluctant reactivity of C-H bond at  $\beta$  position of thiophene. To enhance C-H bond activity, bromide group was considered to be installed at  $\alpha$  position of thiophene as directing group. After  $\beta$ -arylation, C-Br bond can be easily converted to other useful functional groups via versatile transformations. However, due to the fragile nature of C-Br bond in the presence of transition metals, the use of bromide as directing group for C-

H bond activation was rarely reported. Recently, Hartwig, Larrosa, and Sanford separately discovered the unique role of silver salt in C-H bond activation and subsequently it has been applied in direct functionalization of several arenes.<sup>13</sup> We then realized the silver salt catalyzed H/D exchange reaction of many aromatic compounds, which further proved the unique effect of silver salt in C-H bond activation.<sup>14</sup> Herein, we report our finding on silver salt-mediated direct  $\beta$ -arylation of brominated thiophene derivatives.

**Table 1. Variation from standard conditions for  $\beta$ -arylation<sup>a</sup>**



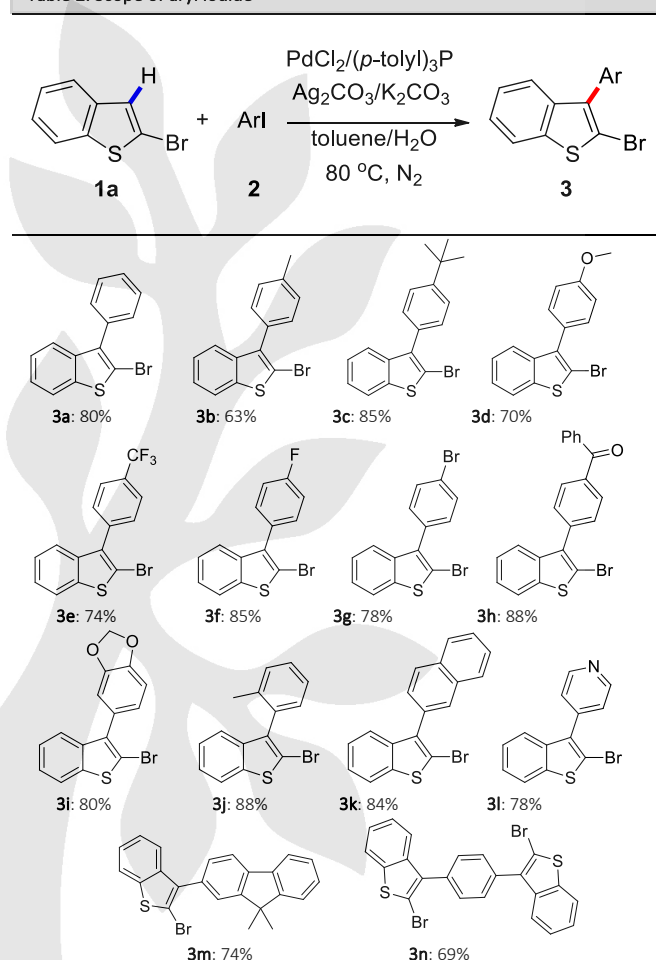
Entry	Variation from 'standard conditions'	Conversion (%) <sup>b</sup>
1	none	80
2	no PdCl <sub>2</sub>	0
3	Pd(OAc) <sub>2</sub> instead of PdCl <sub>2</sub>	40
4	Pd <sub>2</sub> (dba) <sub>3</sub> instead of PdCl <sub>2</sub>	45
5	no ( <i>p</i> -tolyl) <sub>3</sub> P	0
6	( <i>o</i> -tolyl) <sub>3</sub> P instead of ( <i>p</i> -tolyl) <sub>3</sub> P	30
7	Cy <sub>3</sub> P instead of ( <i>p</i> -tolyl) <sub>3</sub> P	10
8	dppe instead of ( <i>p</i> -tolyl) <sub>3</sub> P	40
9	SPhos instead of ( <i>p</i> -tolyl) <sub>3</sub> P	5
10	DavePhos instead of ( <i>p</i> -tolyl) <sub>3</sub> P	5
11	No Ag <sub>2</sub> CO <sub>3</sub>	0
12	AgOAc instead of Ag <sub>2</sub> CO <sub>3</sub>	20
13	AgCl instead of Ag <sub>2</sub> CO <sub>3</sub>	5
14	Ag <sub>2</sub> O instead of Ag <sub>2</sub> CO <sub>3</sub>	73
15	no toluene	53
16	no H <sub>2</sub> O	59
17	60 °C instead of 80 °C	52

[a] The reaction was conducted on 2 mmol of **1a**, 1 mmol of **2a**, 0.1 mmol of PdCl<sub>2</sub>, 0.2 mmol of (*p*-tolyl)<sub>3</sub>P, 2 mmol of Ag<sub>2</sub>CO<sub>3</sub>, 1 mmol of K<sub>2</sub>CO<sub>3</sub> in the mixture of H<sub>2</sub>O and toluene (0.3 mL/0.3 mL) at 80 °C. [b] Determined by GC-MS

We began our study on exploring direct  $\beta$ -arylation of 2-bromobenzo[*b*]thiophene, with iodobenzene as coupling partner. We screened a number of catalysts, ligands, solvents and additives in order to obtain good yields. The control experiments indicated that the palladium catalyst, phosphine ligands and silver salts were all essential for the reaction (entries 2, 5, 11, table 1). The reaction was totally stopped without any of them. Other palladium source such as Pd<sub>2</sub>(dba)<sub>3</sub> and Pd(OAc)<sub>2</sub> were proved to be less effective than PdCl<sub>2</sub>, resulting in lower yields (entries 3, 4, table 1). The use of other phosphine ligands instead of (*p*-tolyl)<sub>3</sub>P was also carried out (entries 6-10, table 1). We found several ligands have positive effect on  $\beta$ -arylation, providing coupling products in moderate yields. On the other hand, Buchwald's ligands showed nearly no reactivity. For the test of silver salts, the reaction with Ag<sub>2</sub>O can give a reasonable yield, since it may in situ generate Ag<sub>2</sub>CO<sub>3</sub> in the presence of K<sub>2</sub>CO<sub>3</sub>. However, the use of AgOAc or AgCl led to much lower yields (entries 12-14 table 1). These results indicated the choice of silver salts is very important for this  $\beta$ -arylation reaction. The following mechanistic study suggested that silver-thiophene complex generated from C-H bond activation and subsequently reacted with aryl palladium complex to form a key intermediate bi-aryl palladium(II) complex. What interested is that the reaction can be performed in pure water despite giving a lower yield of 53% (entry 15, table 1). On the other hand, the yield will decrease to 59% without

adding water (entry 16, table 1). Although the exact function of water is still unknown, the solubility of water is considered to play a role in this reaction.<sup>15</sup> We also performed the reaction at lower temperature, however, dramatic decrease of yield was observed at 60°C (entry 17, table 1). Therefore, the optimal condition was established with PdCl<sub>2</sub>/*(p*-tolyl)<sub>3</sub>P as catalyst, Ag<sub>2</sub>CO<sub>3</sub> as additive and the combination of water and toluene as solvent at 80°C.

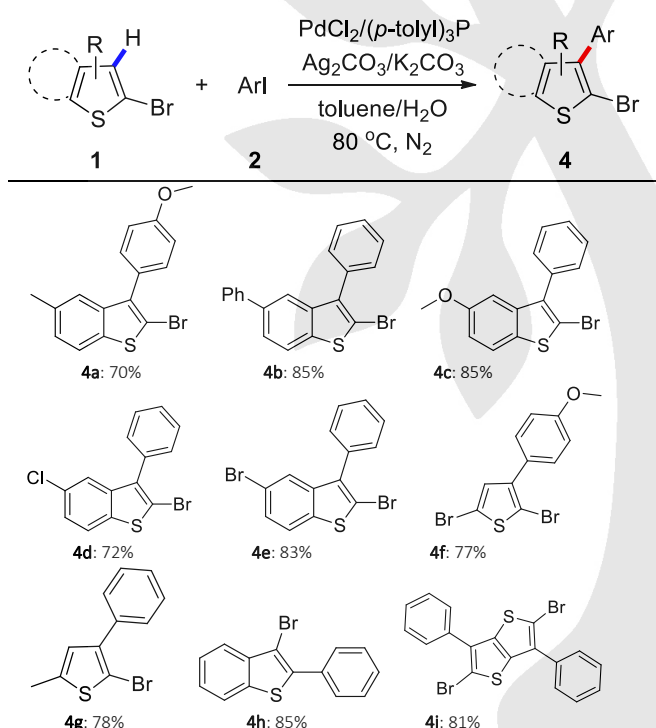
**Table 2. Scope of aryl iodide<sup>a</sup>**



[a] The reaction was conducted on 2 mmol of **1a**, 1 mmol of **2**, 0.1 mmol of PdCl<sub>2</sub>, 0.2 mmol of (*p*-tolyl)<sub>3</sub>P, 2 mmol of Ag<sub>2</sub>CO<sub>3</sub>, 1 mmol of K<sub>2</sub>CO<sub>3</sub> in the mixture of H<sub>2</sub>O and toluene (0.3 mL/0.3 mL) at 80 °C, isolated yield.

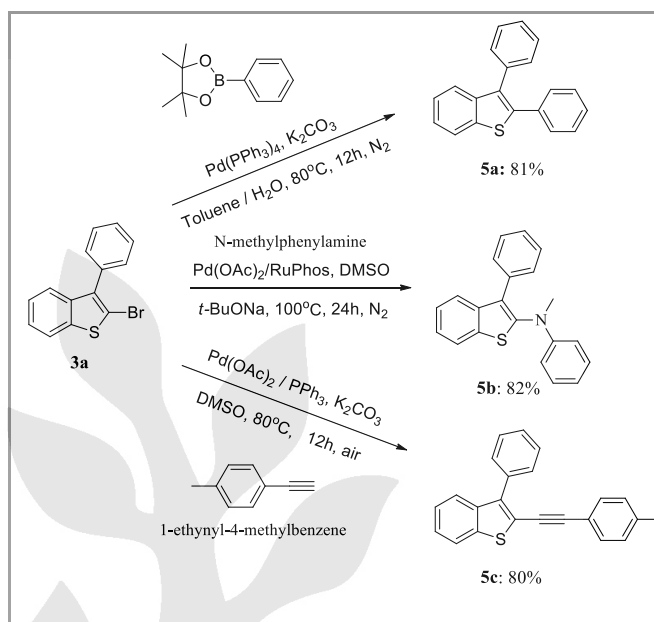
With the optimized condition in hand, the substrate scope for  $\beta$ -arylation was next explored as shown in table 2. We first examined the scope of aryl iodide. The reaction presented great tolerance to a variety of functional groups. Aryl iodides with either electron-withdrawing groups or electron-donating groups at *para*-position were proved to be good substrates, providing coupling products in good to excellent yields (63% - 88%) (**3a-3i**). Aryl iodide with *ortho*-substitute was also tested, giving the product without any decrease of yield (**3j**). It suggested that steric effect of aryl iodide may have little influence on arylation. In addition, 4-iodopyridine is also a good coupling partner, affording coupling product with 78% yield (**3l**). The reaction with 1,4-diiodobenzene as coupling partner was also conducted, affording diarylation product in 69% yield (**3n**). Debromination or self-coupling of 2-bromobenzo[*b*]thiophene was not observed in any case.

After testing the scope of aryl iodide, we turned our attention to expand the scope of bromothiophene derivatives. As shown in table 3, substituted 2-bromobenzothiophenes are good substrates under the optimal condition, providing the coupling products in 70% to 85% yields (**4a-4e**). The bromide group at phenyl ring will not disturb the regioselectivity of the reaction, observing the  $\beta$ -arylation compound as the only product (**4e**). Furthermore, 2,5-dibromothiophene and 2-bromo-5-methylthiophene are also tested, affording single  $\beta$ -arylated thiophenes exclusively (**4f** and **4g**). The regioselectivity of product **4g** was controlled by bromide substitute (see competitive experiment for details). When 3-bromobenzothiophene was employed, the  $\alpha$ -arylation product was also formed in high yield (**4h**). Since thieno(3,2-*b*)thiophene (TT) is a common structure in functional materials as electron donor, we then tested the possibility of direct  $\beta$ -arylation of 2,5-dibromothieno(3,2-*b*)thiophene. When the reaction was carried out with 0.2 equivalent of PdCl<sub>2</sub>, the bis- $\beta$ -arylation product can be isolated in 81% yield (**4i**). Herein, our finding may provide a facial way to synthesize this kind of thiophene skeletons from commercial-available starting materials in one step, which may increase the synthetic efficiency of thiophene-based functional materials.

Table 3. Scope of brominated thiophenes<sup>a</sup>

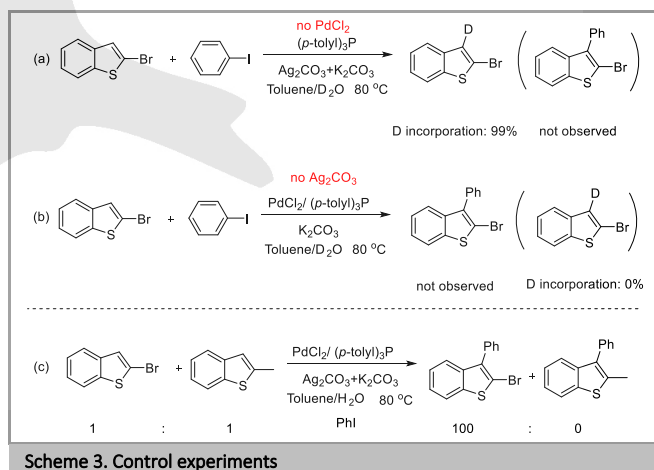
[a] The reaction was conducted on 2 mmol of **1**, 1 mmol of **2**, 0.1 mmol of PdCl<sub>2</sub>, 0.2 mmol of (*p*-tolyl)<sub>3</sub>P, 2 mmol of Ag<sub>2</sub>CO<sub>3</sub>, 1 mmol of K<sub>2</sub>CO<sub>3</sub> in the mixture of H<sub>2</sub>O and toluene (0.3 mL/0.3 mL) at 80 °C, isolated yield.

Further transformation of C-Br bond to other useful functional groups via versatile cross-coupling reactions is a great advantage of this direct  $\beta$ -arylation reaction. Therefore, we conducted the cross-coupling reaction between **3a** and phenyl boronic acid, N-methylphenylamine as well as 1-ethynyl-4-methylbenzene, affording different kinds of benzothiophene derivatives (Scheme 2).



Scheme 2. Transformations of C-Br bond

As shown in scheme 3, we then designed a series of experiments to investigate the nature of C-H bond activation. When the reaction was conducted without PdCl<sub>2</sub> as catalyst in D<sub>2</sub>O, deuterated 2-bromo-benzothiophene was obtained with 99% deuterium incorporation. In addition, the reaction catalyzed by PdCl<sub>2</sub> without Ag<sub>2</sub>CO<sub>3</sub> afforded only starting material. These results suggested that Ag<sub>2</sub>CO<sub>3</sub> should be responsible for C-H bond activation step. The one-pot competitive reaction between 2-bromobenzothiophene and 2-methylbenzothiophene showed a significant reactive difference, demonstrating the importance of bromide group for  $\beta$ -arylation. On the basis of these results and previous reports, we proposed the mechanistic pathway as follow. First, an aryl Pd(II) complex is formed by oxidative addition of Pd(0) to aryl iodide. Then, the palladium complex will react with a silver complex, which generates from C-H bond activation of brominated thiophene derivatives, to form a diaryl-palladium species. Finally, reductive elimination affords the coupling product and regenerates a Pd(0) catalyst.



Scheme 3. Control experiments







**Reaction in D<sub>2</sub>O without Ag<sub>2</sub>CO<sub>3</sub>:** A 10 mL oven-dried Schlenk-tube was charged with 2-bromobenzothiophene (424 mg, 2 mmol), iodobenzene (204 mg, 1 mmol), palladium chloride (18 mg, 0.1 mmol), tri-*p*-tolylphosphine (60 mg, 0.20 mmol) and potassium carbonate (138 mg, 1 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). D<sub>2</sub>O (0.3 mL) and toluene (0.3 mL) were added by syringe under a counter flow of argon at room temperature. The tube was then sealed and the mixture was allowed to stir at the appointed temperature (80 °C) for 12 hours. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate. The solution was directly analyzed by GC-MS, which showed no cross coupling product and no deuterated 2-bromobenzothiophene formed.

**Reaction with both of 2-bromobenzothiophene and 2-methylbenzothiophene :** A 10 mL oven-dried Schlenk-tube was charged with 2-bromobenzothiophene (212 mg, 1 mmol), 2-methylbenzothiophene (148 mg, 1 mmol), iodobenzene (204 mg, 1 mmol), palladium chloride (18 mg, 0.1 mmol), tri-*p*-tolylphosphine (60 mg, 0.20 mmol), Silver carbonate (552 mg, 2 mmol) and potassium carbonate (138 mg, 1 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). D<sub>2</sub>O (0.3 mL) and toluene (0.3 mL) were added by syringe under a counter flow of argon at room temperature. The tube was then sealed and the mixture was allowed to stir at the appointed temperature (80 °C) for 12 hours. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate. The solution was directly analyzed by GC-MS, which showed cross coupling product **3a** was formed but no **3o** observed.

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### Supporting Information

YES (this text will be updated with links prior to publication)

### Primary Data

NO.

### Conflict of Interest

The authors declare no conflict of interest.

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# Bromide as the directing group for $\beta$ -arylation of thiophenes

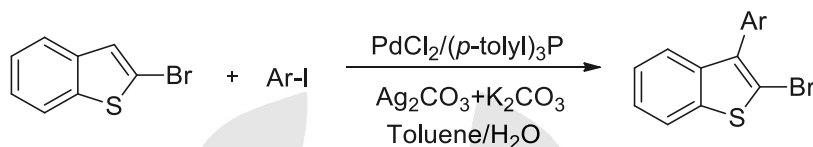
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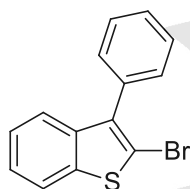
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## Supporting Information

**General:** NMR spectra were recorded at 23 °C on a Varian VNMRS 400 MHz NMR spectrometer in CDCl<sub>3</sub> unless otherwise noted. Chemical shifts were determined relative to residual CHCl<sub>3</sub> (7.26 ppm) for proton, and to the CDCl<sub>3</sub> “triplet” at 77.23 ppm for carbon. GC-MS experiments were carried out using an Agilent GC/MS instrument consisting of a 6890N series GC and a 5973 Mass Selective Detector System. All yields reported refer to isolated yields unless otherwise indicated. All the reagents and solvents were purchased from commercial sources and used as received. The HRMS data was obtained from ThermoFisher LCQTM Deca XP plus ion trap LC/MS.



**General Procedure for PdCl<sub>2</sub> Catalyzed Coupling reaction with 2-bromothiophene and iodobenzene as example:** 2-bromothiophene (424 mg, 2 mmol) and iodobenzene (204 mg, 1 mmol) were added to a vigorously stirred solution of silver carbonate (540 mg, 2 mmol), palladium chloride (17.7 mg, 0.1 mmol), tri(*p*-tolyl)phosphine (60 mg, 0.2 mmol), potassium carbonate (138 mg, 1 mmol) in H<sub>2</sub>O (0.3 mL) and toluene (0.3 mL) under N<sub>2</sub>. The reaction mixture was stirred at 80 °C in oil bath for 12 hours. Then the reaction was quenched with saturated NH<sub>4</sub>Cl solution. The product was extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of solvents under vacuum, the crude product was purified via column chromatography.



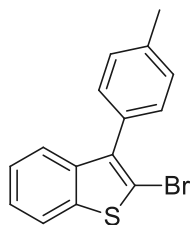
**3a:** Isolated yield: 232 mg (80%); yellow oil.

Purified via column chromatography (petroleum ether 100%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.98 (d, *J* = 8.4 Hz, 1 H), 7.55 – 7.51 (m, 2 H), 7.4 – 7.42 (m, 4 H), 7.39 – 7.32 (m, 2 H).

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 139.5, 138.5, 137.2, 133.6, 130.2, 129.4, 129.3, 129.3, 128.9, 125.9, 125.7, 122.9, 122.9, 113.4.

HRMS (EI) *m/z*: calcd for C<sub>14</sub>H<sub>9</sub>BrS<sup>+</sup> ([M]<sup>+</sup>) 287.9608; Found 287.9597.



**3b:** Isolated yield: 190 mg (63%); yellow oil.

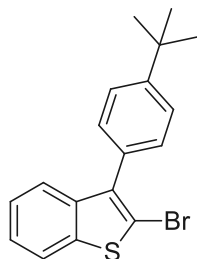
Purified via column chromatography (petroleum ether 100%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.78 (d, *J* = 7.6 Hz, 1 H), 7.60 (d, *J* = 7.2 Hz, 1 H), 7.43 – 7.31 (m, 6 H), 2.48 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 139.9, 138.9, 138.0, 137.2, 131.0, 129.9, 129.4, 124.8, 123.0, 121.7,

113.1, 21.5.

HRMS (EI)  $m/z$ : calcd for  $C_{15}H_{11}BrS^+$  ( $[M]^+$ ) 301.9765; Found 301.9751.



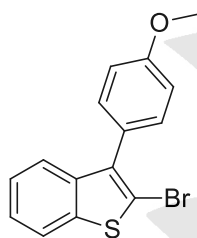
**3c**: Isolated yield: 294 mg (85%); yellow oil.

Purified via column chromatography (petroleum ether 100%).

$^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  7.96 (d,  $J = 8.0$  Hz, 1 H), 7.54 (d,  $J = 8.8$  Hz, 2 H), 7.44 (d,  $J = 7.2$  Hz, 1 H), 7.40 – 7.31 (m, 4 H), 1.31 (s, 9 H).

$^{13}C$  NMR (100 MHz,  $DMSO-d_6$ ):  $\delta$  151.2, 139.5, 138.6, 137.0, 130.7, 129.9, 126.1, 125.8, 125.7, 123.0, 122.8, 113.2, 35.0, 31.6.

HRMS (EI)  $m/z$ : calcd for  $C_{18}H_{17}BrS^+$  ( $[M]^+$ ) 344.0234; Found 344.0219.



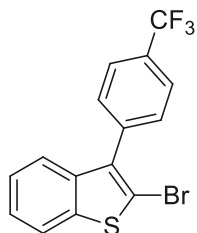
**3d**: Isolated yield: 222 mg (70%); yellow solid, m.p. 101 °C – 103 °C

Purified via column chromatography (petroleum ether/dichloromethane = 8:1).

$^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  7.96 (d,  $J = 8.0$  Hz, 1 H), 7.50 – 7.34 (m, 7 H).

$^{13}C$  NMR (100 MHz,  $DMSO-d_6$ ):  $\delta$  159.6, 139.4, 138.7, 137.0, 131.5, 125.8, 125.6, 125.6, 123.0, 122.9, 114.7, 113.0, 55.7.

HRMS (EI)  $m/z$ : calcd for  $C_{15}H_{11}BrOS^+$  ( $[M]^+$ ) 317.9714; Found 317.9704.



**3e**: Isolated yield: 263 mg (74%); yellow oil.

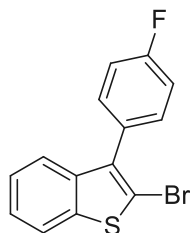
Purified via column chromatography (petroleum ether/dichloromethane = 8:1).

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.78 (d,  $J = 8.0$  Hz, 2 H), 7.73 – 7.67 (m, 1 H), 7.62 – 7.49 (m, 2 H), 7.39 – 7.30 (m, 3 H).

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.9 (s, 3 F).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  139.6, 138.1, 137.9 (q,  $J_F = 1.4$  Hz), 135.8, 131.2, 129.4 (q,  $J_F = 31.8$  Hz), 126.2 (q,  $J_F = 3.8$  Hz) 126.1, 125.9, 124.7 (q,  $J_F = 270.9$  Hz), 123.0, 122.7, 114.6.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{15}\text{H}_8\text{BrF}_3\text{S}^+$  ( $[\text{M}]^+$ ) 355.9482; Found 355.9472.



**3f**: Isolated yield: 260 mg (85%); colorless oil.

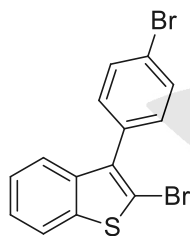
Purified via column chromatography (petroleum ether 100%).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  7.52 (d,  $J = 8.4$  Hz, 1 H), 7.44 (d,  $J = 2.4$  Hz, 1 H), 7.42 – 7.40 (m, 2 H), 7.35 – 7.31 (m, 3 H).

$^{19}\text{F}$  NMR (376 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  -114.2 (s, 1 F).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  162.5 (d,  $J_F = 244.4$  Hz), 139.5, 138.4, 136.2, 132.4 (d,  $J_F = 8.5$  Hz), 129.9 (d,  $J_F = 3.3$  Hz), 125.9, 125.8, 122.9, 122.8, 116.4 (d,  $J_F = 21.5$  Hz), 113.8 (d,  $J_F = 1.4$  Hz).

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{14}\text{H}_8\text{BrFS}^+$  ( $[\text{M}]^+$ ) 305.9514; Found 305.9504.



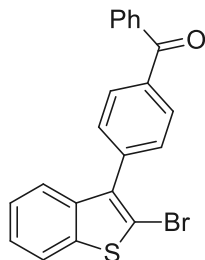
**3g**: Isolated yield: 286 mg (78%); white solid, m.p. 125 °C – 127 °C

Purified via column chromatography (petroleum ether 100%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78 – 7.76 (m, 1 H), 7.67 – 7.64 (m, 2 H), 7.52 – 7.50 (m, 1 H), 7.38 – 7.30 (m, 4 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  139.9, 138.4, 135.9, 132.8, 131.9, 131.7, 125.0, 125.0, 122.7, 122.4, 121.8, 113.7.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{14}\text{H}_8\text{Br}_2\text{S}^+$  ( $[\text{M}]^+$ ) 367.8693; Found 367.8678.



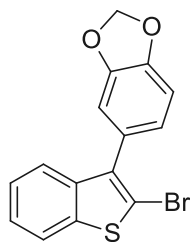
**3h:** Isolated yield: 345 mg (88%); white solid, m.p. 136 °C – 138 °C

Purified via column chromatography (petroleum ether/dichloromethane = 8:1).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.98 (d,  $J$  = 8.4 Hz, 2 H), 7.91 – 7.89 (m, 2 H), 7.80 – 7.78 (m, 1 H), 7.64 – 7.52 (m, 6 H), 7.40 – 7.33 (m, 2 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  196.3, 139.9, 138.4, 138.2, 137.5, 137.1, 136.1, 132.6, 130.4, 130.2, 130.0, 128.4, 125.1, 122.7, 121.9, 114.1.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{21}\text{H}_{13}\text{BrOS}^+$  ( $[\text{M}]^+$ ) 391.9870; Found 391.9860.



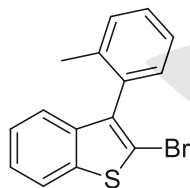
**3i:** Isolated yield: 266 mg (80%); yellow oil.

Purified via column chromatography (petroleum ether/dichloromethane = 8:1).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.95 (d,  $J$  = 8.4 Hz, 1 H), 7.46 (d,  $J$  = 8.0 Hz, 1 H), 7.40 – 7.33 (m, 2 H), 7.06 (d,  $J$  = 8.0 Hz, 1 H), 6.99 (t,  $J$  = 1.6 Hz, 1 H), 6.88 (dd,  $J$  = 1.6 Hz,  $J$  = 8.0 Hz, 1 H), 6.09 (s, 2 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  148.0, 147.8, 139.4, 138.6, 136.9, 127.1, 125.8, 125.7, 124.0, 123.0, 122.8, 113.4, 110.5, 109.2, 101.9.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{15}\text{H}_9\text{BrO}_2\text{S}^+$  ( $[\text{M}]^+$ ) 331.9507; Found 331.9497.



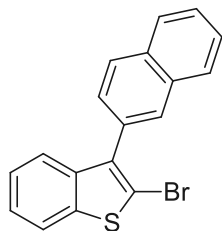
**3j:** Isolated yield: 268 mg (88%); yellow oil.

Purified via column chromatography (petroleum ether 100%).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.97 (d,  $J$  = 8.4 Hz, 1 H), 7.44 – 7.34 (m, 4 H), 7.32 – 7.20 (m, 3 H), 7.36 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  139.5, 138.6, 138.6, 137.3, 133.6, 130.6, 129.5, 129.2, 127.3, 125.8, 125.7, 123.0, 122.8, 21.5.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{15}\text{H}_{11}\text{BrS}^+$  ( $[\text{M}]^+$ ) 301.9765; Found 301.9751.



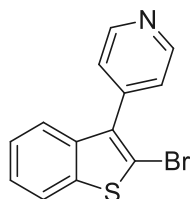
**3k:** Isolated yield: 284 mg (84%); white solid, m.p. 105 °C – 107 °C

Purified via column chromatography (petroleum ether 100%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.06 – 7.79 (m, 5 H), 7.57 – 7.35 (m, 6 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 139.6, 138.7, 137.2, 133.4, 133.0, 131.2, 129.5, 128.8, 128.6, 128.2, 127.8, 127.2, 125.9, 125.8, 123.0, 122.9, 113.9.

HRMS (EI) *m/z*: calcd for C<sub>18</sub>H<sub>11</sub>BrS<sup>+</sup> ([M]<sup>+</sup>) 337.9765; Found 337.9752.



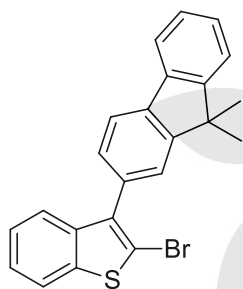
**3l:** Isolated yield: 226 mg (78%); green solid, m.p. 85 °C – 87 °C

Purified via column chromatography (petroleum ether/dichloromethane = 4:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.78 (d, *J* = 8.4 Hz, 2 H), 7.80 – 7.78 (m, 1 H), 7.55 – 7.53 (m, 1 H), 7.45 (d, *J* = 6.0 Hz, 2 H), 7.41 – 7.32 (m, 2 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 150.3, 142.1, 140.0, 137.9, 134.6, 125.3, 125.3, 124.8, 122.3, 121.9, 114.7.

HRMS (EI) *m/z*: calcd for C<sub>13</sub>H<sub>8</sub>BrNS<sup>+</sup> ([M]<sup>+</sup>) 288.9561; Found 288.9550.



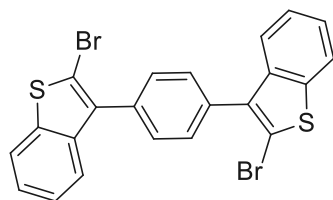
**3m:** Isolated yield: 296 mg (74%); white solid, m.p. 142 °C – 144 °C

Purified via column chromatography (petroleum ether 100%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.66 (d, *J* = 8.0, 1 H), 7.53 – 7.47 (m, 2 H), 7.05 (s, 1 H), 6.98 (s, 2 H), 2.34 – 2.28 (s, 6 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 153.9, 153.9, 139.9, 139.2, 138.9, 138.8, 137.6, 128.8, 127.1, 124.9, 124.9, 124.4, 122.7, 121.8, 120.3, 113.2, 47.1, 27.2.

HRMS (EI) *m/z*: calcd for C<sub>23</sub>H<sub>17</sub>BrS<sup>+</sup> ([M]<sup>+</sup>) 404.0234; Found 404.0220.



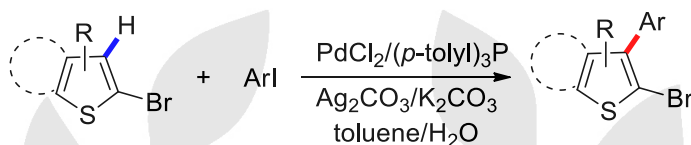
**3n**: Isolated yield: 345 mg (69%), white solid, m.p. 138 °C – 140 °C

Purified via column chromatography (petroleum ether / dichloromethane = 8:1).

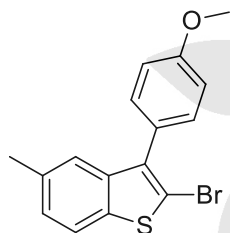
<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.04 (d, *J* = 6.8 Hz, 2 H), 7.69 (s, 4 H), 7.61 (d, *J* = 8.0 Hz, 2 H), 7.48 – 7.41 (m, 2 H).

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 139.8, 138.6, 136.9, 133.7, 130.6, 125.9, 125.8, 123.0, 122.8.

HRMS (EI) *m/z*: calcd for C<sub>22</sub>H<sub>12</sub>Br<sub>2</sub>S<sub>2</sub><sup>+</sup> ([M]<sup>+</sup>) 499.8727; Found 499.8713.



**General Procedure for PdCl<sub>2</sub> Catalyzed Coupling reaction with 4-iodoanisole and 2-bromo-5-methylbenzo[*b*]thiophene as example:** 2-bromo-5-methylbenzo[*b*]thiophene (450 mg, 2 mmol) and 4-iodoanisole (234 mg, 1 mmol) were added to a vigorously stirred solution of silver carbonate (540 mg, 2 mmol), palladium chloride (17.7 mg, 0.1 mmol), tri(*p*-tolyl)phosphine (60 mg, 0.2 mmol), potassium carbonate (138 mg, 1 mmol) in H<sub>2</sub>O (0.3 mL) and toluene (0.3 mL) under N<sub>2</sub>. The reaction mixture was stirred at 80 °C in oil bath for 12 hours. The reaction was then quenched with saturated NH<sub>4</sub>Cl solution. The product was extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of solvents under vacuum, the crude product was purified via column chromatography.



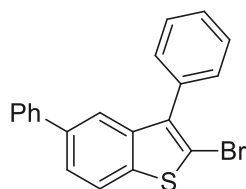
**4a**: Isolated yield: 231 mg (70%); white solid, m.p. 115 °C – 117 °C

Purified via column chromatography (petroleum ether / dichloromethane = 8:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.71 – 7.63 (m, 4 H), 7.20 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 3.86 (s, 3 H), 2.51 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 150.0, 139.4, 138.3, 135.2, 134.6, 130.9, 130.9, 127.0, 125.6, 123.4, 121.8, 114.0, 103.9, 55.4, 21.6.

HRMS (EI) *m/z*: calcd for C<sub>16</sub>H<sub>13</sub>BrOS<sup>+</sup> ([M]<sup>+</sup>) 331.9870; Found 331.9858.



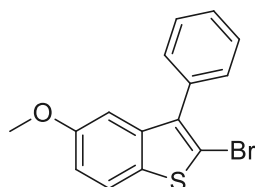
**4b:** Isolated yield: 309 mg (85%); white solid, m.p. 114 °C – 116 °C

Purified via column chromatography (petroleum ether 100%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.07 (d, *J* = 1.2 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 7.79 – 7.76 (m, 2 H), 7.72 – 7.69 (m, 2 H), 7.66 – 7.63 (m, 1 H), 7.52 – 7.37 (m, 6 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 141.0, 139.7, 139.0, 138.9, 136.8, 133.1, 129.7, 129.0, 128.9, 128.7, 127.5, 127.5, 125.1, 122.6, 122.1, 105.2.

HRMS (EI) *m/z*: calcd for C<sub>20</sub>H<sub>13</sub>BrS<sup>+</sup> ([M]<sup>+</sup>) 363.9921; Found 363.9907.



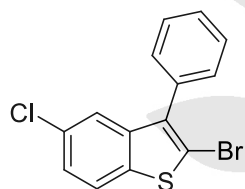
**4c:** Isolated yield: 270 mg (85%); white solid, m.p. 118 °C – 120 °C

Purified via column chromatography (petroleum ether / dichloromethane = 8:1).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.92 (d, *J* = 8.8 Hz, 1 H), 7.77 (d, *J* = 7.2 Hz, 2 H), 7.70 (s, 1 H), 7.45 (t, *J* = 7.2 Hz, 2 H), 7.39 (d, *J* = 7.2 Hz, 1 H), 7.20 (d, *J* = 8.8 Hz, 1 H), 3.88 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 146.6, 141.6, 133.5, 131.7, 129.8, 129.6, 126.7, 123.1, 119.6, 111.9, 104.5, 57.0.

HRMS (EI) *m/z*: calcd for C<sub>15</sub>H<sub>11</sub>BrOS<sup>+</sup> ([M]<sup>+</sup>) 317.9714; Found 317.9704.



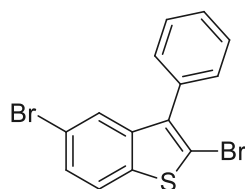
**4d:** Isolated yield: 267 mg (72%); white solid, m.p. 104 °C – 106 °C

Purified via column chromatography (petroleum ether 100%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.09 (d, *J* = 8.4 Hz, 1 H), 7.75 (d, *J* = 2.0 Hz, 1 H), 7.71 – 7.69 (m, 2 H), 7.55 – 7.46 (m, 4 H).

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 140.9, 140.2, 136.1, 132.4, 131.5, 130.0, 129.7, 129.5, 125.6, 125.3, 122.7.

HRMS (EI) *m/z*: calcd for C<sub>14</sub>H<sub>8</sub>BrClS<sup>+</sup> ([M]<sup>+</sup>) 321.9219; Found 321.9206.



**4e:** Isolated yield: 305 mg (83%); white solid, m.p. 126 °C – 128 °C

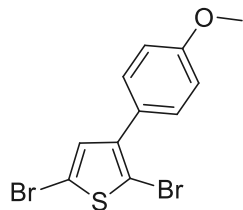
Purified via column chromatography (petroleum ether 100%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.01 (d, *J* = 1.6 Hz, 1 H), 7.75 – 7.72 (m, 2 H), 7.66 (d, *J* = 8.4 Hz, 1 H),

7.50 – 7.41 (m, 4 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.8, 140.2, 136.4, 132.6, 129.6, 129.2, 128.7, 128.6, 125.4, 123.6, 119.4.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{14}\text{H}_8\text{Br}_2\text{S}^+$  ( $[\text{M}]^+$ ) 367.8693; Found 367.8677.



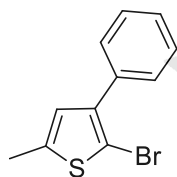
**4f**: Isolated yield: 268 mg (77%); yellow oil.

Purified via column chromatography (petroleum ether / dichloromethane = 8:1).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.47 (d,  $J = 8.0$  Hz, 2 H), 7.33 (s, 1 H), 7.00 (d,  $J = 7.2$  Hz, 2 H), 3.77 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  159.6, 142.1, 132.8, 130.0, 126.1, 114.5, 111.3, 106.8, 55.6.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{11}\text{H}_8\text{Br}_2\text{OS}^+$  ( $[\text{M}]^+$ ) 347.8642; Found 347.8632.



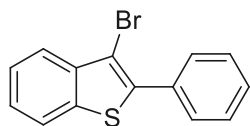
**4g**: Isolated yield: 196 mg (78%); yellow oil.

Purified via column chromatography (petroleum ether 100%).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.53 – 7.50 (m, 2 H), 7.46 – 7.42 (m, 2 H), 7.38 – 7.34 (m, 1 H), 6.89 (d,  $J = 1.2$  Hz, 1 H), 2.41 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  140.9, 140.7, 135.0, 128.7, 128.4, 127.7, 127.4, 104.5, 15.4.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{11}\text{H}_9\text{BrS}^+$  ( $[\text{M}]^+$ ) 251.9608; Found 251.9597.



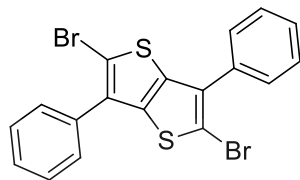
**4h**: Isolated yield: 245 mg (85%); white solid, m.p. 62 °C – 63 °C

Purified via column chromatography (petroleum ether 100%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.89 – 7.87 (m, 1 H), 7.83 – 7.80 (m, 1 H), 7.78 – 7.75 (m, 2 H), 7.51 – 7.39 (m, 5 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  139.2, 138.3, 137.8, 133.1, 129.7, 128.9, 128.7, 125.5, 125.3, 123.7, 122.2, 105.0.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{14}\text{H}_9\text{BrS}^+$  ( $[\text{M}]^+$ ) 287.9608; Found 287.9596.



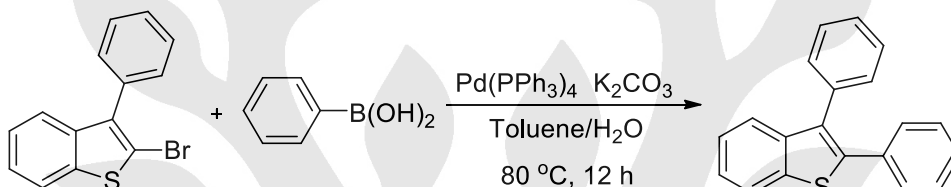
**4i:** Isolated yield: 364 mg (81%); colorless oil.

Purified via column chromatography (petroleum ether / dichloromethane = 8:1).

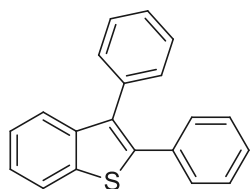
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.68 – 7.66 (m, 4 H), 7.51 (t,  $J = 7.2$  Hz, 4 H), 7.46 – 7.43 (m, 4 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  136.9, 133.9, 133.2, 128.9, 128.7, 128.5, 109.9.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{18}\text{H}_{10}\text{Br}_2\text{S}_2^+$  ( $[\text{M}]^+$ ) 449.8570; Found 449.8553.



**Procedure for Palladium Catalyzed Suzuki coupling reaction:** A 25 mL oven-dried Schlenk-tube was charged with  $\text{Pd}(\text{PPh}_3)_4$  (116 mg, 10 mol%), phenylboronic acid (182 mg, 1.5 mmol), 2-bromo-3-phenylbenzo[b]thiophene (289 mg, 1 mmol) and potassium carbonate (552 mg, 4 mmol) in the mixture of toluene (2 mL) and  $\text{H}_2\text{O}$  (1 mL). The tube was evacuated and backfilled with argon (this procedure was repeated three times). The tube was then sealed and the mixture was allowed to stir at the 80 °C for 12 hours. The reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature and the product was extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . After removal of solvents under vacuum, the crude product was purified via column chromatography. A white solid was isolated in 81% yield (232 mg).



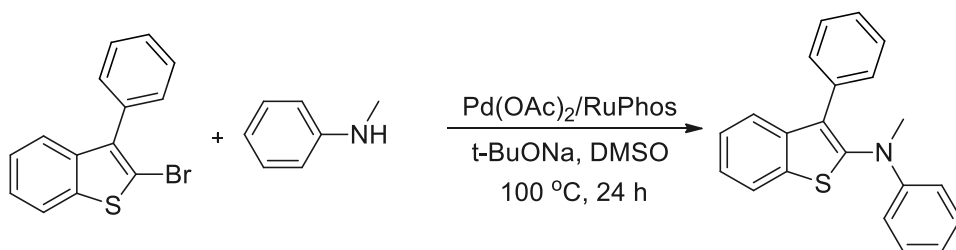
**5a:** Isolated yield: 232 mg (81%); white solid, m.p. 113 °C – 115 °C

Purified via column chromatography (petroleum ether 100%).

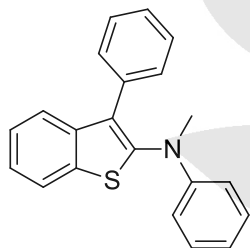
$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.03 (d,  $J = 7.6$  Hz, 1 H), 7.47 – 7.36 (m, 6 H), 7.30 – 7.28 (m, 7 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  140.9, 139.6, 138.9, 135.6, 134.3, 133.3, 130.5, 129.7, 128.7, 128.4, 127.8, 127.5, 124.6, 124.5, 123.4, 122.1.

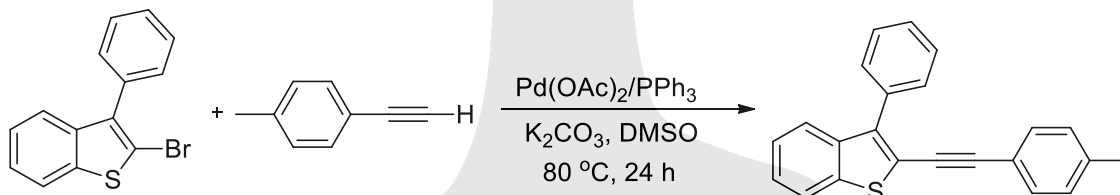
HRMS (EI)  $m/z$ : calcd for  $\text{C}_{20}\text{H}_{14}\text{S}^+$  ( $[\text{M}]^+$ ) 286.0816; Found 286.0820.



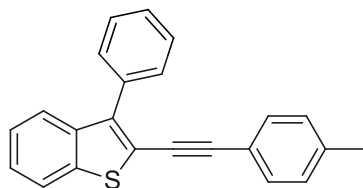
**Procedure for Palladium Catalyzed Buchwald-Hartwig Amination:** A screw-cap vial equipped with a magnetic stir bar was charged with the 2-bromo-3-phenylbenzo[b]thiophene (289 mg, 1 mmol), *N*-Methyl aniline (129 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (3 mg, 0.01 mmol), RuPhos (9 mg, 0.02 mmol), and powdered Na<sup>t</sup>Bu (115 mg, 1.2 mmol) in DMSO (2 mL). The vial was transferred to a preheated oil bath (100 °C). After 12 h, the reaction mixture was cooled and dissolved in CH<sub>2</sub>Cl<sub>2</sub> /H<sub>2</sub>O mixture (1:1). The organic phase was separated and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography on a silica gel column. A white solid was obtained in 82% yield (258 mg).



**5b:** Isolated yield: 258 mg (82%); white solid, m.p. 118 °C – 120 °C  
Purified via column chromatography (petroleum ether / ethyl acetate = 4:1).  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.79 – 7.69 (m, 2 H), 7.45 – 7.32 (m, 7 H), 7.25 – 7.21 (m, 2 H), 6.91 – 6.89 (m, 2 H), 6.84 (t, *J* = 8.8 Hz, 1 H), 3.08 (s, 3 H).  
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 148.8, 147.5, 138.3, 137.1, 134.1, 131.7, 129.2, 128.9, 128.7, 127.6, 124.8, 124.4, 123.0, 122.9, 119.0, 114.5, 40.0.  
HRMS (EI) *m/z*: calcd for C<sub>21</sub>H<sub>17</sub>NS<sup>+</sup> ([M]<sup>+</sup>) 315.1082; Found 315.1092.



**Procedure for Palladium Catalyzed Sonogashira Reaction:** In a 25 mL flask, a mixture of 4-ethynyltoluene (174 mg, 1.5 mmol), 2-Bromo-3-phenyl-1-benzothiophene (289 mg, 1 mmol), PPh<sub>3</sub> (53 mg, 0.2 mmol), Pd(OAc)<sub>2</sub> (12 mg, 2 mmol %), and K<sub>2</sub>CO<sub>3</sub> (207 mg, 1.5 mmol) in DMSO (5 mL) was heated at 80 °C. After 24 hours, the resulting mixture was poured into H<sub>2</sub>O and extracted with EtOAc three times. Combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude product was purified by flash chromatography on a silica gel column. A white solid was isolated in 80% yield (259 mg).



**5c:** Isolated yield: 259 mg (80%); White solid, m.p. 122 °C – 123 °C

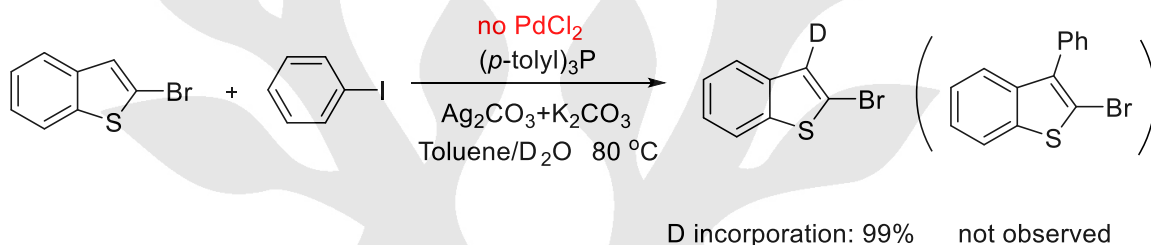
Purified via column chromatography (petroleum ether / ethyl acetate = 8:1).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 (d,  $J = 7.2$  Hz, 1 H), 7.69 – 7.64 (m, 3 H), 7.55 (t,  $J = 7.2$  Hz, 2 H), 7.47 – 7.39 (m, 3 H), 7.28 (d,  $J = 8.4$  Hz, 2 H), 7.16 (d,  $J = 7.6$  Hz, 2 H), 2.23 (s, 3 H).

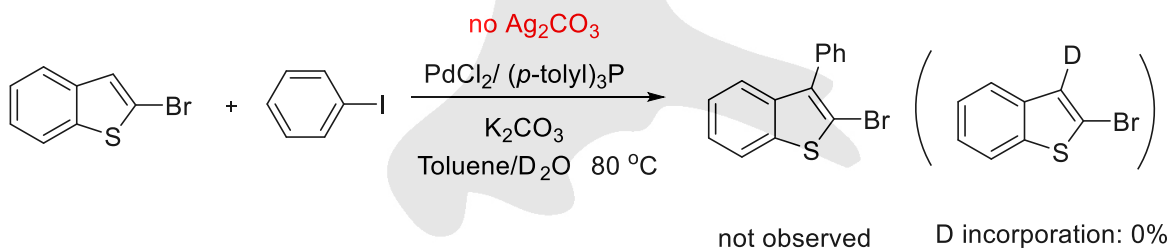
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  141.0, 139.8, 139.3, 137.8, 134.0, 131.6, 130.0, 129.9, 129.2, 128.8, 126.7, 125.0, 123.7, 123.3, 119.0, 119.0, 96.8, 82.9, 21.7.

HRMS (EI)  $m/z$ : calcd for  $\text{C}_{23}\text{H}_{16}\text{S}^+$  ( $[\text{M}]^+$ ) 324.0973; Found 324.0976.

### Experiments for mechanistic study

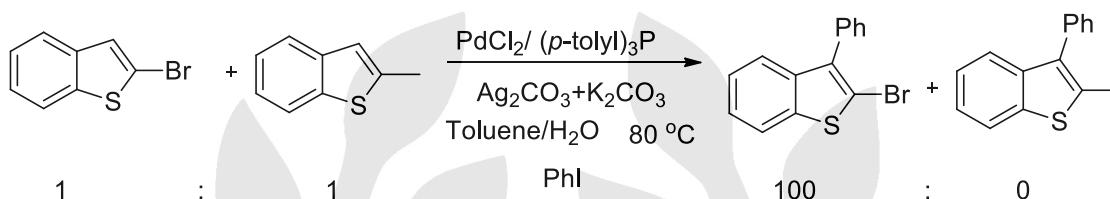


**Reaction in  $\text{D}_2\text{O}$  without  $\text{PdCl}_2$  as catalyst:** A 10 mL oven-dried Schlenk-tube was charged with 2-bromobenzothiophene (424 mg, 2 mmol), iodobenzene (204 mg, 1 mmol), Silver carbonate (552 mg, 2 mmol), tri-*p*-tolylphosphine (60 mg, 0.20 mmol) and potassium carbonate (138 mg, 1 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times).  $\text{D}_2\text{O}$  (0.3 mL) and toluene (0.3 mL) were added by syringe under a counter flow of argon at room temperature. The tube was then sealed and the mixture was allowed to stir at the appointed temperature (80 °C) for 12 hours. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate. The solution was directly analyzed by GC-MS, which showed no cross coupling product formed. On the contrary, the starting material, 1,4-dibromobenzene, is obviously deuterated, providing deuterated 2-bromobenzothiophene with deuterium incorporation of 99%.



**Reaction in  $\text{D}_2\text{O}$  without  $\text{Ag}_2\text{CO}_3$ :** A 10 mL oven-dried Schlenk-tube was charged with 2-bromobenzothiophene (424 mg, 2 mmol), iodobenzene (204 mg, 1 mmol), palladium chloride (18 mg, 0.1

mmol), tri-*p*-tolylphosphine (60 mg, 0.20 mmol) and potassium carbonate (138 mg, 1 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). D<sub>2</sub>O (0.3 mL) and toluene (0.3 mL) were added by syringe under a counter flow of argon at room temperature. The tube was then sealed and the mixture was allowed to stir at the appointed temperature (80 °C) for 12 hours. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate. The solution was directly analyzed by GC-MS, which showed no cross coupling product and no deuterated 2-bromobenzothiophene formed.



**Reaction with both of 2-bromobenzothiophene and 2-methylbenzothiophene :** A 10 mL oven-dried Schlenk-tube was charged with 2-bromobenzothiophene (212 mg, 1 mmol), 2-methylbenzothiophene (148 mg, 1 mmol), iodobenzene (204 mg, 1 mmol), palladium chloride (18 mg, 0.1 mmol), tri-*p*-tolylphosphine (60 mg, 0.20 mmol), Silver carbonate (552 mg, 2 mmol) and potassium carbonate (138 mg, 1 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). D<sub>2</sub>O (0.3 mL) and toluene (0.3 mL) were added by syringe under a counter flow of argon at room temperature. The tube was then sealed and the mixture was allowed to stir at the appointed temperature (80 °C) for 12 hours. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate. The solution was directly analyzed by GC-MS, which showed cross coupling product **3a** was formed but no **3o** observed.

# Proton and Carbon NMR Spectra:

