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Iridium-catalyzed borylation of thiophenes: versatile, synthetic elaboration founded on selective C–H functionalization

Ghayoor A. Chotana, Venkata A. Kallepalli, Robert E. Maleczka, Jr., Milton R. Smith, III *

Department of Chemistry, Michigan State University, East Lansing, MI 48824-1322, USA

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ABSTRACT

Iridium-catalyzed borylation has been applied to various substituted thiophenes to synthesize polyfunctionalized thiophenes in good to excellent yields. Apart from common functionalities compatible with iridium-catalyzed borylations, additional functional group tolerance to acyl (COMe) and trimethylsilyl (TMS) groups was also observed. High regioselectivities were observed in borylation of 3- and 2,5-di-substituted thiophenes. Electrophilic aromatic C–H/C–Si bromination on thiophene boronate esters is shown to take place without breaking the C–B bond, and one-pot C–H borylation/Suzuki–Miyaura cross-coupling has been accomplished on 2- and 3-borylated thiophenes.

1. Introduction

Thiophenes comprise an important heterocyclic class with diverse applications ranging from the design of advanced materials[1–3] to the treatment of various diseases[4–7] (Fig. 1). Consequently, their synthesis has garnered keen interest.

There are two fundamentally different approaches for synthesizing substituted thiophenes. The first entails construction of the thiophene ring from appropriate precursors with the most common examples stemming from early syntheses of thiophene from C4 carbonyl compounds and P_2S_5.[8,9] The second general approach to substituted thiophenes involves derivatizing an existing thiophene core. Examples of the latter case include halogenations, alkylations, and metalations. The first metalation examples were mercurations reported by Volhard in 1892,[10] and Thomas described the generation and reactivity of 2-thiophenylmagnesium iodide by magnesium reduction of 2-iodothiophene in 1908.[11] Organolithiation reactions of thiophenes, pioneered by Gilman,[12] have proved to be particularly versatile because, like mercuration, the thiophene C–H bond can be functionalized directly. The thienyl lithium intermediates that result react readily with various electrophiles.[13] While biological systems can assemble, as well as functionalize, thiophenes,[14,15] their synthetic utility is limited when compared to non-biochemical methods.

Lithiation reactions are some of the oldest and most prevalent means for functionalizing C–H bonds in heterocycles. More recently, attention has turned to other methods for derivatizing C–H[16–18] and C–X[18–22] bonds in heterocycles with an emphasis on transition metal catalyzed processes that obviate the requirement for stoichiometric metal. While the emerging methodologies can

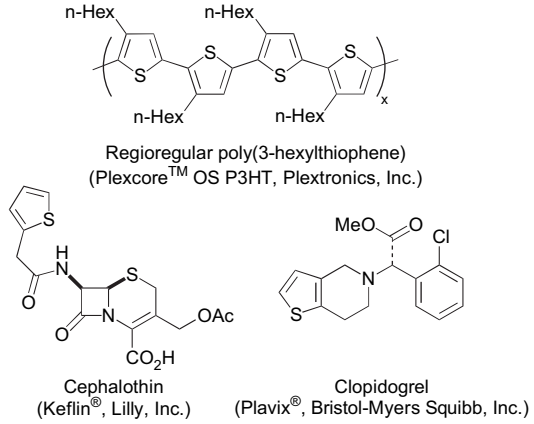

Figure 1. Selected thiophene-derived articles of commerce.

* Corresponding author. Tel.: +1 517 355 9715x166; fax: +1 517 353 1793.
E-mail address: smithmil@msu.edu (M.R. Smith III).

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sometimes bypass intermediates for certain syntheses, they can also offer selectivities that complement metalation reactions. In this contribution we examine the scope and limitations of Ir-catalyzed C–H borylation applied to the synthesis of thiophene boronate esters.

2. Results and discussion

Aryl boronate esters are versatile reagents that are widely used in the construction of carbon–carbon and carbon–heteroatom bonds. Prior to 1995, aryl boronate esters were typically prepared by reacting an organometallic intermediate, generated from an arene or aryl halide and stoichiometric quantities of a metalating agent, with a boron electrophile (Fig. 2). In 1995, Miyaura and co-workers reported the synthesis of arylboronates by the Pd-catalyzed cross-coupling of tetraalkoxydiboron reagents with haloarenes, including 3-iodobenzothiophene.[23] Subsequently, Masuda and co-workers devised related conversions using dialkoxyboranes,[24] including the synthesis of 2-thienyl boronate esters.[25] These transformations were important advances because (i) substoichiometric quantities of Pd catalysts served as the metalating agents, and (ii) the mild reaction conditions can accommodate functional groups that are incompatible with organomagnesium or organolithium reagents.

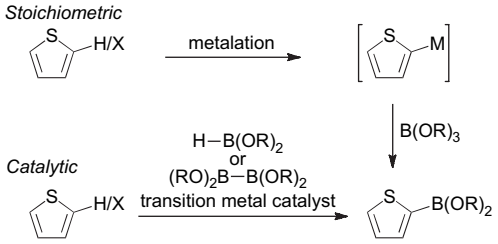


Figure 2. Routes to 2-thiophenyl boronate esters via stoichiometric or catalytic metalation protocols.

In 1999, we reported an Ir-catalyzed reaction that coupled benzene and pinacolborane (HBPin) to yield PhBPin generating hydrogen gas as the sole byproduct.[26] Recognizing that this transformation's simplicity could offer advantages over traditional routes to arylboron compounds, we explored the generality of this reaction with arenes, including the first extensions to heterocyclic substrates.[27–29] Despite improvements in catalyst generation,[28,30] application of this methodology to substituted thiophenes is limited to five substrates: 2-methylthiophene,[31–33] 2-cyanothiophene,[32] 2-bromothiophene,[32] 2-methoxythiophene,[33] and 2-trifluoromethylthiophene.[33] These reactions yield 5-borylated products exclusively in accord with the preference for borylation of C–H bonds adjacent to *formally* sp^3-hybridized heteroatoms in five-membered heterocycles. Clearly, the restriction of previous studies to 2-substituted substrates raises questions regarding the feasibility of this reaction when the substitution pattern is varied and the range of substituents is expanded.

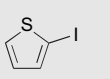
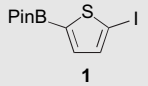
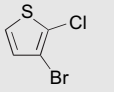
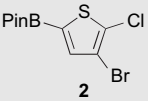
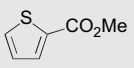
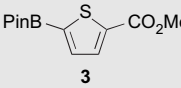
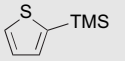
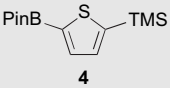
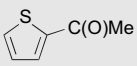
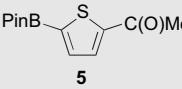
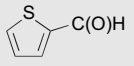
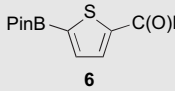
2.1. Borylation of 2-substituted thiophenes

As noted above, the reported borylations of 2-substituted thiophenes display excellent regioselectivity for 5-borylated products. Nevertheless, the range of substituents that have been surveyed is limited compared to aromatic substrates. Before detailing our findings, comments regarding the catalyst system are warranted. Most of the chemistry in this paper utilizes a dipyridyl-ligated catalyst that is generated in situ. However, this catalyst system was ineffective for electron-rich substrates. For these cases, phosphine supported catalysts gave better results. Comparisons between the ligand systems were not made when the dipyridyl system was effective.

For phosphine based catalysis, the phosphine (typically a bidentate ligand) and the Ir precatalyst, (η^5-Ind)Ir(cod) (Ind=indenyl, cod=1,4-cyclooctadiene), are simply combined with the borane, substrate, and solvent (if used) in a reaction vessel. The resulting mixture is then heated to effect borylation.[28] While the dtbpy system operates at room temperature, generation of the catalysts must be done as follows.[34,35] First, the HBPin and the Ir precatalyst, [Ir(μ_2-OMe)(η^4-cod)]$_2$ are combined. Then the dipyridyl ligand, in most cases 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbpy), is dissolved in a suitable solvent and the resulting solution is added to the HBPin/[Ir(μ_2-OMe)(η^4-cod)]$_2$ mixture, generating a deep orange solution. The order of operations is critical as addition of dtbpy to [Ir(μ_2-OMe)(η^4-cod)]$_2$ produces a pale green solution that exhibits diminished activity upon addition of HBPin followed by substrate. Although HBPin was used exclusively in this study, it should be noted that B_2Pin_2, a more active borylating agent, is less effective for catalyst generation. Should circumstances warrant use of B_2Pin_2, it is critical that the catalyst generation be carried out with HBPin. Lastly, we note that despite being touted for its air-stability, solid samples of [Ir(μ_2-OMe)(η^4-cod)]$_2$ gradually darken when stored on the bench top and catalytic activity of 'aged' precatalyst is diminished relative to pristine samples.

Table 1 displays borylation results for an expanded slate of 2-substituted thiophenes. Entries 1–3 show that the tolerance for heavier halogens and esters exhibited for arenes extends to thiophenes. Entry 4 is noteworthy in that the TMS group can be transformed while leaving the BPin intact (vide infra). It seemed likely that substituents that compromise arene borylations might be compatible for thiophenes since heterocyclic substrates are usually more susceptible to borylation than arenes. This indeed proved to be the case for entry 5 where the acyl product **5** was obtained. This appears to be a limit for compatibility as the analogous product **6**, though generated in small quantities, was not isolated from the

Table 1
Ir-catalyzed borylations of 2-substituted thiophenes[a]

Entry	Substrate	Reaction time	Product	Yield[b] %
1		1 h	 **1**	92
2		10 min	 **2**	78
3		30 min	 **3**	94
4		30 min	 **4**	93
5		30 min	 **5**	85
6		—	 **6**	—[c]

[a] Reactions were carried out with 3 mol % Ir catalyst in *n*-hexane at room temperature with 1.5–2.0 equiv HBPin. For details see Section 4.
[b] Yields are for isolated products.
[c] GC/MS data show that **6** (or an isomer) accounts for ~10% of the reaction mixture. GC/MS and NMR data indicate that significant reduction of the formyl group occurs.

borylation of 2-formylthiophene owing to reduction of the formyl group by HBPin. In the absence of Ir catalyst, HBPin does not reduce 2-formylthiophene at room temperature. It is noteworthy that Christophersen and co-workers have successfully performed a Pd-catalyzed Masuda coupling of HBPin with 2-bromo-3-formylthiophene without complications arising from reduction.[36]

2.2. Borylation of 3-substituted thiophenes

In contrast to 2-substituted thiophenes, both C–H bonds flanking S in 3-substituted thiophenes are potentially accessible for borylation. In the absence of electronic effects, borylation at the 5-position should be generally favored. However, selectivities will likely be lower than those for arenes since the distance between neighboring substituents increases as the number of ring atoms decreases.[37]

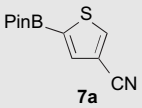
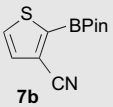
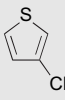
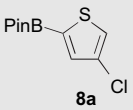
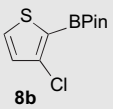
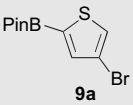
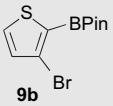
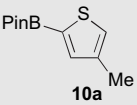
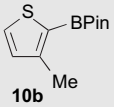
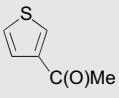
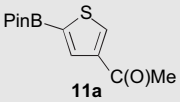
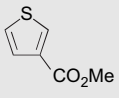
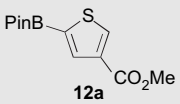
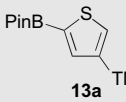
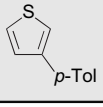
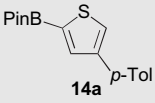
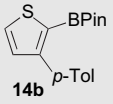
Indeed, some of these expectations are born by the data in Table 2. In cases where isomer mixtures resulted (Table 2 entries 1–4 and 8), 2.0 equiv of thiophene was used to minimize losses arising from diborylation. Regiochemical assignment is straightforward from the magnitudes of $|^4J_{HH}|$ (~2 Hz) and $|^3J_{HH}|$ (~5 Hz) for the respective **a** and **b** isomers. 3-Cyanothiophene gave the poorest regioselectivity with 2-borylated product **7b** being the major isomer. While CN is one of the smallest substituents, previous work shows that borylation *ortho* to H is preferred relative to CN for arenes,[37] and the results for entry 1 are the first where borylation *ortho* to CN appears to be favored. Contrary to a literature report noting its instability,[36] **7b** was sufficiently stable to be persistent in the isolated isomer mixture.

Isomer mixtures were also observed for Cl, Br, Me, and *p*-tolyl (*p*-Tol) substituents (entries 2–4 and 8). For these substrates, the 5-borylated isomers are the major products and the relative isomer ratios (**a**/**b**) for Cl, Br, and Me follow the trend seen in arenes.[37] For the *p*-Tol substituted substrate (entry 8) the selectivity is sufficiently high for **14a** to be synthetically useful. As compared to Rh and Pd catalysts that favor borylation of benzylic C–H bonds,[38–40] Ir catalysts are highly selective for aromatic over benzylic C–H bond functionalization,[27,28] even for substrates with hindered arene C–H bonds like *p*-xylene.[41] Thus, it is noteworthy that borylation of the thiophene C–H bonds is favored. In particular, formation of **14b** indicates that functionalization of relatively hindered thiophene C–H bonds is possible when arene C–H bonds are present. This might not prove to be general, particularly for compounds where electron-deficient *o*- or *m*-substituted aryl groups are present.

The selectivity for acyl, ester, and trimethylsilyl substituents was excellent and 2-borylated products were not detected. For the methyl ester substrate (entry 6), the selectivity is consistent with that observed in borylations of 4-benzonitriles, and the steric profiles of acyl and TMS groups are likely similar or greater.

Certainly, the closest comparison to our work is the related Ir-catalyzed silylations described by Ishiyama and Miyaura.[42] Even though these reactions require much higher temperatures, which

Table 2
Borylations of 3-substituted thiophenes[a]

Entry	Substrate	Conditions	5-Borylated product	3-Borylated product	**a**/**b**[b]	Yield[c] %
1		0.5 equiv HBPin, 1 h	 **7a**	 **7b**	1:1.13	54[d]
2		0.5 equiv HBPin, 1 h	 **8a**	 **8b**	3.5:1	66[d]
3		0.5 equiv HBPin, 1 h	 **9a**	 **9b**	8.9:1	72[d]
4		0.5 equiv HBPin, 1 h	 **10a**	 **10b**	8.9:1	67[d]
5		1.2 equiv HBPin, 15 min	 **11a**	—	>99:1	82
6		1.2 equiv HBPin, 1 h	 **12a**	—	>99:1	95
7		1.2 equiv HBPin, 30 min	 **13a**	—	>99:1	79
8		0.9 equiv HBPin, 1 h	 **14a**	 **14b**	>32:1	74[d]

[a] Reactions were carried out with 3 mol % or pregenerated Ir catalyst in *n*-hexane at room temperature with 1.5–2.0 equiv HBPin. For details see Section 4.
[b] Isomer ratios were determined by GC analysis of the crude reaction mixture.
[c] Yields are reported for isolated products and are based on starting thiophene unless otherwise noted. Isomers were not separated.
[d] Yield based on HBPin.

we frankly consider to be a very minor drawback, their selectivities for silylation at the 5-position relative to the 2-position of 3-methyl- and 3-chlorothiophene (99:1 and 49:1, respectively) are better than those for borylation, while regioselectivity for silylation of methyl 3-thiophenecarboxylate (49:1) was marginally worse than that for borylation (Table 2, entry 6) It must be emphasized that 2-*tert*-butyl-1,10-phenanthroline was the ligand that engendered these selectivities. The silylation selectivity for dtbpy-ligated catalysts is more appropriate for directly comparing silylation and borylation. Though limited to a single example, the silylation regioselectivity for 3-methylthiophene (5-isomer/2-isomer=2.5:1) is considerably worse than the 8.9:1 selectivity for borylation using the same precatalyst and ligand (Table 2, entry 4). Borylations using 2-*tert*-butyl-1,10-phenanthroline were not attempted because the ligand is not commercially available. Nevertheless, regioselectivities for thiophene borylations can be improved by altering the catalyst's coordination sphere.

In spite of the regioselectivity that silylation offers, two factors limit its synthetic utility. First, the silylating agent (*tert*-$Bu_2F_2Si_2$) is not commercially available. Second, the synthetic elaborations of aryl and heteroaryl silanes are less well developed compared to the analogous boron chemistry. Certainly, future developments in arylsilane chemistry could change this situation.[43,44]

There are other existing methods for selectively functionalizing 3-substituted thiophenes at the 5-position. The two most common approaches are (i) electrophilic substitutions that are selective for 5-substitution when the 3-substituent is electron withdrawing and/or the electrophile is sterically hindered,[45,46] and (ii) directed *ortho* metalations (DoMs) where the 3-substituent is a poor directed metalation group (DMG).[47–49]

When compared to DoMs, the selectivities for entries 2, 3, 5, and 6, are atypical. Even with relatively poor DMGs like Cl or Br at C-3, DoM at C-2 for thiophenes is often favored. Consequently, protection/deprotection at C-2 can be required for selective synthesis of 3,5-substituted compounds via DoM.[50] Since Ir-catalyzed borylation favors functionalization at the 5-position, it complements DoM nicely.

2.3. Borylation of 2,5-disubstituted thiophenes

Borylation of 2,5-disubstituted thiophenes are more challenging for two reasons. First, the 3- and 4-C–H bonds are less reactive towards borylation even in the absence of steric constraints, as evidenced by the results in Table 1. Second, the 2- and 5-substituents will further impede borylation.

The results for borylations of 2,5-disubstituted thiophenes are shown in Table 3. For the symmetrically substituted substrates in entries 1–3, regioselectivity is not an issue, making them the logical starting points for discussion. The first obvious difference from the data in Tables 1 and 2 is that borylation requires prolonged reactions times with Cl>Br≫Me. *ortho*-Substituents impede borylations of C–H bonds of substituted arenes, with steric effects almost certainly being responsible.

The relative ordering of the rates for thiophenes may not be a simple matter of steric effects. For example, borylation of 2,5-dichlorothiophene slowed markedly after an initial conversion surge. This rate diminution was accompanied by precipitation of brown particles, suggesting that catalyst may be decomposing. Nevertheless the conversion was complete in 20 h and product **15** was isolated in good yield (Table 3, entry 1). The borylation of 2,5-dibromothiophene was more problematic, and only 89% conversion of the substrate was observed after 48 h at room temperature with 9 mol % Ir catalyst loadings. Consequently, compound **16** was isolated in modest yield (Table 3, entry 2). Given the highly reactive nature of C–X bonds in α-halogenated thiophenes, it would not be surprising if C–X scission led to catalyst deactivation for these substrates.

The potential for C–X activation also raises questions regarding the regiochemistry of the monoborylated products. Even though halogen tolerance is a hallmark of Ir-catalyzed C–H borylations, the observation of a single regioisomer from the borylation does not prove that the halogen regiochemistry is maintained. Assumptions of this type have led to mischaracterization of products arising from directed metalations of 2,5-dihalothiophenes,[51] where rearrangement of the metalated intermediates via 'halogen dance' mechanisms can lead to 2,4-dihalogenated products.[52]

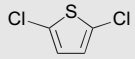
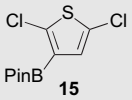
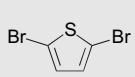
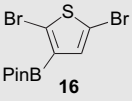
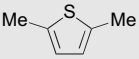
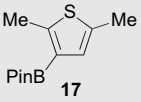
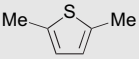
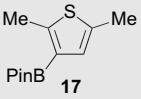
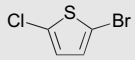
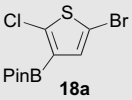
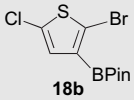
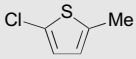
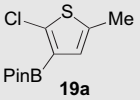
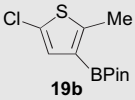
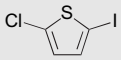
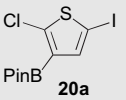
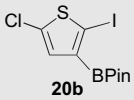
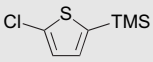
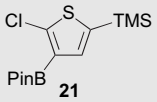
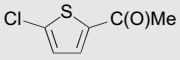
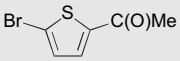
^{13}C NMR data offer the first line of evidence against a similar rearrangement occurring in C–H borylations. By comparing the ^{13}C chemical shifts of monosubstituted thiophene **I** to thiophene and **17** (vide infra) to 2,5-dimethylthiophene (Fig. 3), increments of the ^{13}C chemical shifts (I_B^{C-2} and I_B^{C-3}) for the BPin group can be estimated (Table 4). While we are not aware of previous reports of I_B^{C-3} values, the magnitudes and trends for the BPin I_B^{C-2} values are in line with those in the literature.[53]

Using I_B^{C-2} and I_B^{C-3} for the BPin group and the ^{13}C increment values for Br substitution on a thiophene nucleus,[52] the δ (^{13}C) values for **16** and isomers **A**–**D**, which are generated by permuting H, Br, and BPin positions, have been calculated and the data are listed in Table 5. The C_{ipso} resonances attached to BPin are not observed and assignment of the quaternary carbons is not certain. However, the methine carbon can be unambiguously assigned and the calculated methine shifts are indicated by boldface type. Isomer **16** gives the best fit to the data with the largest deviation observed for the C-2. This error is considerably smaller than the magnitude of the corresponding I_B^{C-2} value. The two remaining calculated shifts for **16**, which include the methine resonance, fit the data very well. The fit to calculated shifts for isomer **A**, the analogue to the regioisomer that arises when lithiated 2,5-dibromothiophene rearranges, is poor with a large error in the shift for C-3, which is adjacent to BPin substituted carbon. Of the remaining isomers **B**–**D**, isomer **C** is the only candidate whose calculated values approach the fit found for **16**. We discount this possibility because (i) there is no precedent for 'halogen dance' rearrangement to this regioisomer, and (ii) the error in the methine shift, which is assigned unambiguously, is large. The final piece of confirming evidence comes from a chemical reaction of **16**. We have observed that borylated products in crude reaction mixtures are susceptible to protodeborylation when heated with a source of acidic protons.[54] Protodeborylation of **16** regenerates 2,5-dibromothiophene, which is consistent with the assigned regiochemistry (Fig. 4).

For 2,5-dimethylthiophene, electronic effects likely impact the borylation rates since the steric energies of methyl and bromine substituents are similar. The overall rate reduction in this case is consistent with results from arene borylations, where electron-rich substrates are significantly less reactive than electron poor ones. Thus, borylation at room temperature with the dtbpy-ligated catalyst is impractical (Table 3, entry 3). Although this catalyst system has been reported to operate effectively at elevated temperatures, only 12% conversion was achieved after 16 h when the borylation was carried out with the Ir/dtbpy catalyst at 80 °C. We find that phosphine ligated catalysts are well-suited for substrates of this type, even though elevated temperatures are required for borylation. Indeed, the combination of the Ir precatalyst (Ind)Ir(cod) and 1,2-bis(dimethylphosphino)ethane (dmpe) promoted smooth borylation at 150 °C, and compound **17** was isolated in excellent yield (Table 3, entry 4).

For unsymmetrical chlorothiophene substrates, borylations typically gave isomer mixtures (Table 3, entries 5–7). The borylation regiochemistries were assigned either from the relative chemical shifts of the methine protons (**18a**,**b** and **20a**,**b**) or by $|J_{HH}|$ values (**19a** and **b**). Compound **18a** was also prepared independently (vide

Table 3
Borylations of 2,5-disubstituted thiophenes

Entry	Substrate	Conditions	3-Borylated product	4-Borylated product	**a**/**b**[a]	Yield[b] %
1		3 mol % Ir/dtbpy, 1.5 equiv HBPin, rt, 20 h	 **15**	—	—	86
2		9 mol % Ir/dtbpy, 2.5 equiv HBPin, rt, 48 h[c]	 **16**	—	—	56
3		3 mol % Ir/dtbpy, 1.5 equiv HBPin, rt, 20 h	 **17**	—	—	—
4		2 mol % Ir/dmpe, 1.5 equiv HBPin, 150 °C, 16 h	 **17**	—	—	97
5		6 mol % Ir/dtbpy, 2.0 equiv HBPin, rt, 28 h[d]	 **18a**	 **18b**	2.0:1[e,f]	87
6		3 mol % Ir/dtbpy, 1.5 equiv HBPin, rt, 18 h	 **19a**	 **19b**	2.3:1[g]	86
7		3 mol % Ir/dtbpy, 1.5 equiv HBPin, rt, 20 h	 **20a**	 **20b**	5.7:1[h]	89
8		3 mol % Ir/dtbpy, 1.5 equiv HBPin, rt, 6 h	 **21**	—	>99:1	93
9		—	—	—	—	—
10		—	—	—	—	—

[a] Isomer ratios were determined by GC analysis of the crude reaction mixtures.
[b] Yields are reported for isolated products and are based on starting thiophene unless otherwise noted. Isomers were not separated.
[c] Initially, 6 mol % Ir/dtbpy catalyst loading and 1.5 equiv HBPin was used. After 36 h, conversion had ceased and the reaction flask was charged with an additional 3 mol % Ir/dtbpy and 1.0 equiv HBPin.
[d] Initially, 3 mol % Ir/dtbpy catalyst loading and 1.5 equiv HBPin was used. After 8 h, the reaction flask was charged with an additional 3 mol % Ir/dtbpy and 0.5 equiv HBPin.
[e] Assignment of isomers based on the ^{1}H chemical shifts of the methine protons: **18a**, 7.10 ppm, **18b**, 6.94 ppm.
[f] Compound **18a** was prepared independently. See Scheme 2.
[g] Compound **19a** was identified by $|^4J_{HH}|$=1.2 Hz for the coupling between the methine and methyl protons. $|^5J_{HH}|$ was not resolved for **19b**.
[h] Assignment of isomers based on the ^{1}H chemical shifts of the methine protons: **20a**, 7.31 ppm, **18b**, 6.87 ppm.

infra). The variations in isomer ratios reflect relative differences in steric energies for the substituents. When the relative steric are sufficiently great, single isomers can be attained as indicated by compound **21** (Table 3, entry 8). The acyl compatibility seen in Tables 1 and 3 did not extend to the 2-acyl-5-halothiophenes in entries 9 and 10.

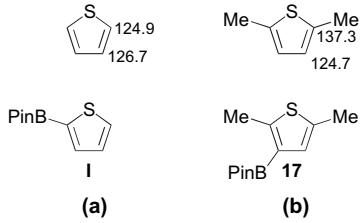


Figure 3. Compounds and ^{13}C NMR chemical shift data used to estimate (a) I_B^{C-2} and (b) I_B^{C-3} values.

The synthetic utility for the unsymmetrically 2,5-disubstituted thiophenes is more limited than for the other substrates that have been discussed to this point; however, it should be noted that certain substrates for which we would expect good selectivities (e.g., 2-fluoro compounds) were not surveyed because of their limited commercial availability.

Table 4
Carbon-13 chemical shifts δ (^{13}C) (ppm) and BPin increments I_B^{C-2} for **I** and I_B^{C-3} for **17**

Position	**I**		**17**	
	δ	I_B^{C-2}	δ	I_B^{C-3}
C-2	—[a]	—	150.8	13.5
C-3	137.1	10.4	—[a]	—
C-4	128.2	1.5	130.7	6.0
C-5	132.3	7.4	136.1	−1.2

[a] C_{ipso} resonance was not observed.

Table 5
Calculated carbon-13 chemical shifts δ (^{13}C) (ppm) for **16** and isomers **A–D** (methine resonances indicated in bold)

Position	**16**	**A**	**B**	**C**	**D**
C-2	125.0 (3.1)[b]	—[a]	118.5 (−3.4)	109.9 (−1.0)	—[a]
C-3	—[a]	119.9 (9.0)	115.4 (4.5)	119.9 (−2.0)	124.4 (2.5)
C-4	**136.2** (**0.4**)	**133.3** (**−2.5**)	**140.4** (**4.6**)	—[a]	115.5 (4.6)
C-5	110.3 (−0.6)	120.3 (−1.6)	—[a]	**140.3** (**4.5**)	**131.2** (**−4.6**)

[a] No data was calculated for C_{ipso} resonances.
[b] Deviations from fit to experimental data are shown in parentheses.

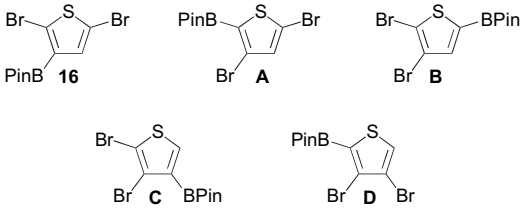


Figure 4. Compound **16** and its regioisomers **A–D**.

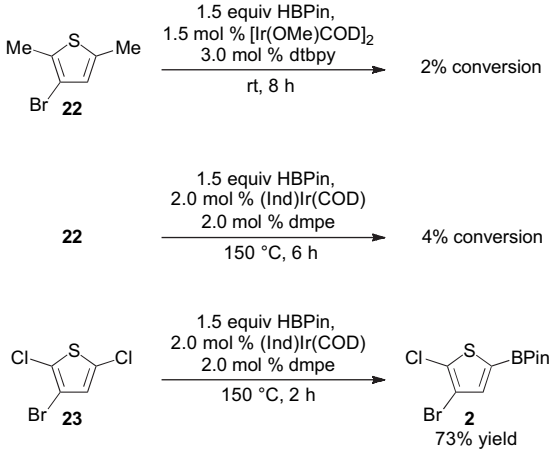


Figure 5. Attempted borylations of 2,3,5-trisubstituted thiophenes.

2.4. Attempted borylation of 2,3,5-trisubstituted thiophenes

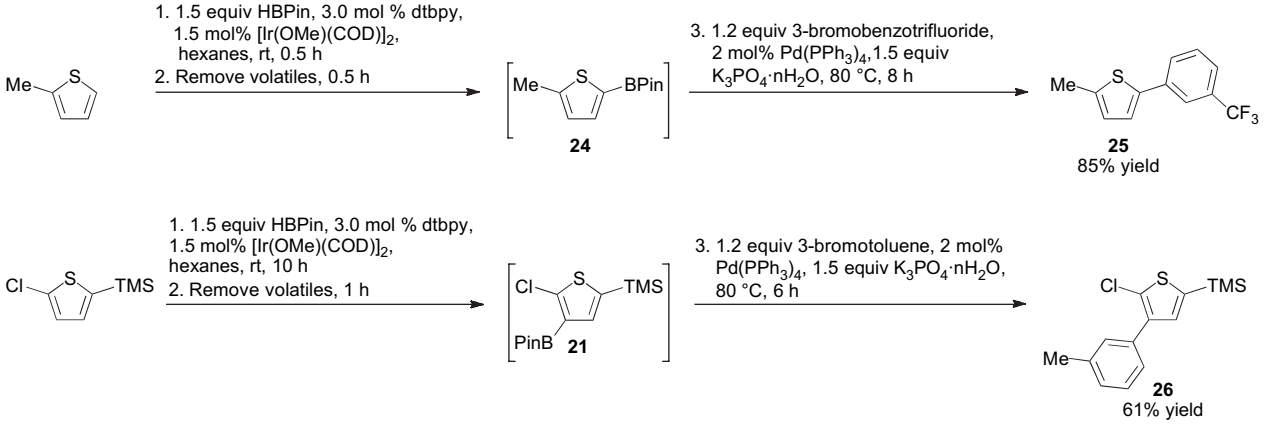
For 2,3,5-trisubstituted thiophenes, the 4-position is flanked by two *ortho* substituents. Since the H–C–C bond angles in five-membered heterocycles are larger than those in six-membered rings, the 4-position in 2,3,5-trisubstituted thiophenes should be more accessible for borylation. However, only about 2% borylation was observed for 3-bromo-2,5-di-methylthiophene (**22**) for attempted room temperature borylation with the [Ir(μ_2-OMe)-(COD)]$_2$/dtbpy catalyst (Fig. 5). The outcome was similar for the (Ind)Ir(COD)/dmpe system at 150 °C. Apart from steric hindrance for borylation, the electron-rich nature of 3-bromo-2,5-di-methylthiophene could also be responsible for this low reactivity. Thus, borylation of an electron-deficient substrate, 3-bromo-2,5-dichlorothiophene (**23**), was attempted using the [Ir(μ_2-OMe)(COD)]$_2$/dtbpy system at room temperature and the borylation reaction stalled after ~5% conversion. The borylation of this substrate was also tested using (Ind)Ir(COD) and dmpe at 150 °C. This reaction gave a 73% isolated yield of a single product, which surprisingly proved to be compound **2**.

The conversion of **23** to **2** is noteworthy in that the least hindered chloride is selectively cleaved. Although there is no direct supporting evidence, a plausible mechanism for the formation of **2** involves selective reduction of the 5-chloro substituent in **23** by HBPin to afford 3-bromo-2-chlorothiophene, which is then borylated to give **2**. Alternatively, the transformation could proceed via C–Cl oxidative addition of **23** to Ir, C–B reductive elimination, and Ir–Cl reduction by HBPin to regenerate the active catalyst. Either scenario requires 2 equiv of HBPin for each equivalent of compound **2** that is produced. Hence, the 73% yield for 1.5 equiv of HBPin indicates that the transformation is nearly quantitative.

2.5. Synthetic elaborations of borylated thiophenes

The synthetic utility of the thiophene boronate esters in Tables 1–3 hinges on their ability to participate in subsequent transformations. One attractive feature of Ir-catalyzed borylations is their amenability to one-pot reactions where subsequent transformations of the crude boronate esters can be accomplished without removing the spent Ir catalysts.

Preliminary studies show that one-pot C–H borylation/Suzuki–Miyaura cross-couplings can be accomplished on 2- and 3-borylated intermediates **21** and **24** (Scheme 1). The Suzuki–Miyaura couplings utilized aryl bromides to avoid the potential homocoupling of intermediates **21** and **24**, and Pd(PPh$_3$)$_4$ was used as the

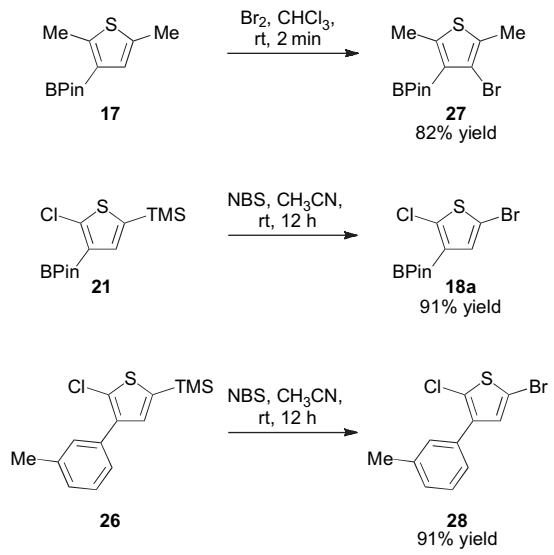


Scheme 1. One-pot C–H borylation/Suzuki–Miyaura cross-couplings of substituted thiophenes.

catalyst. The yields for the two-step sequences in Scheme 1 are respectable and may improve with use of more efficient Pd catalysts.

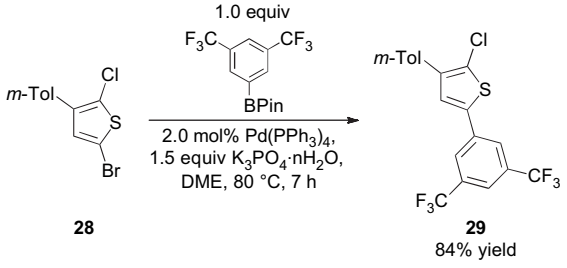
Although aromatic C–H bromination of aryl boronic esters (to synthesize brominated aryl boronic esters) is unknown, there are examples where aryl/heteroaryl boronic acids have been brominated.[55–57] Thus, we reasoned that the products of the inefficient borylations of 2,3,5-trisubstituted thiophenes could conceivably be obtained by brominating borylation products **15** and **17**.

Attempted bromination of **15** with Br_2 in $CHCl_3$ was ineffective even after 24 h at 100 °C, and the reaction between **15** and NBS in acetonitrile[58] yielded a mixture of products. In addition to the desired C–H brominated product, GC/MS analysis indicated that products were resulting from C–BPin scission. In contrast, compound **17** reacted rapidly with Br_2 in $CHCl_3$ to give tetrasubstituted **27** in 82% yield (Scheme 2). Excess bromine led to bromination of the thiophene methyl groups and should hence be avoided. The enhanced reactivity of **17** relative to **15** arises from replacing chlorides with more electron donating methyl groups.



Scheme 2. Bromination reactions of thiophenyl boronate esters.

Although we have evaluated the scope of C–H brominations of other substrates, related brominations of trimethylsilyl groups offer synthetic utility as indicated in Scheme 2. The TMS group in **21** is selectively cleaved by *N*-bromosuccinimide (NBS) yielding boronate ester **18a** as a single isomer. This route is clearly preferable to borylation of 5-bromo-2-chlorothiophene, which yielded appreciable quantities of isomer **18b** (Table 3, entry 5). We also found that compound **26** reacts with NBS in similar fashion to afford thiophene **28** in excellent yield, indicating that α-TMS cleavage is selective over benzylic and aromatic bromination. This is significant because the C(sp^2)–Si bonds in TMS substituted arenes and heterocycles do not readily undergo cross-coupling reactions. Thus,



Scheme 3. A Suzuki–Miyaura cross-coupling reaction of thiophene **29**.

the bromination of **26** confers synthetic utility for the selective coupling of BPin over TMS in compound **21**. Compound **28** can be further derivatized as indicated by the Suzuki–Miyaura cross-coupling that yields **29** in Scheme 3. 2-Halo-3,5-diarylthiophenes are quite rare.[59–61] Nevertheless, related compounds substituted at the 2-position exhibit interesting physical[62] and biological[63,64] properties.

3. Conclusions

From this study, Ir-catalyzed borylations offer significant versatility for derivatizing thiophene scaffolds. In general, regioselectivities complement those established for D*o*M, making the combination of these two methodologies particularly attractive. In addition, the results concerning the elaboration of these boronate esters are encouraging, even though subsequent transformations are not extensively surveyed in this contribution. It should be emphasized that even though the procedures reported herein were carried out using a glovebox, this chemistry is amenable to more standard laboratory settings. We plan on publishing these details separately. We are actively exploring the chemistry of these compounds, as well as applying these synthetic approaches to other heterocyclic systems.

4. Experimental

4.1. General considerations

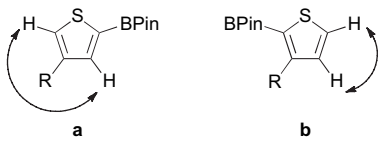
4.1.1. Materials

[Ir(μ$_2$-OMe)(COD)]$_2$ and (Ind)Ir(COD) were prepared as per the literature procedures.[65,66] Pinacolborane (HBPin) was generously supplied by BASF and was distilled before use. 2-Trimethylsilylthiophene,[67] 3-trimethylsilylthiophene,[68] and 3-*p*-tolylthiophene[69] were prepared per the literature procedures. 2-Chloro-5-trimethylsilylthiophene was prepared following the literature procedure for the synthesis of 2-bromo-5-trimethylsilylthiophene.[70] All other commercially available chemicals were purified before use. Solid substrates were sublimed under vacuum. Liquid substrates were distilled before use. *n*-Hexane was refluxed over sodium, distilled, and degassed. Dimethoxy ethane (DME), ether, and tetrahydrofuran were obtained from dry stills packed with activated alumina and degassed before use. Silica gel (230–400 Mesh) was purchased from EMD™.

4.1.2. General methods

All reactions were monitored by GC-FID (Varian CP-3800; column type: WCOT fused silica 30 m×0.25 mm ID coating CP-SIL 8 CB), GC-FID method: 70 °C, 2 min; 20 °C/min, 9 min; 250 °C, 20 min. All reported yields are for isolated materials. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-300 (300.11 and 75.47 MHz, respectively), Varian VXR-500 or Varian Unity-500-Plus spectrometer (499.74 and 125.67 MHz, respectively) and referenced to residual solvent signals (7.24 and 77.0 ppm for $CDCl_3$, respectively). ^{11}B NMR spectra were recorded on a Varian VXR-300 operating at 96.29 MHz and were referenced to neat $BF_3{\cdot}Et_2O$ as the external standard. All coupling constants are apparent *J* values measured at the indicated field strengths. Elemental analyses were performed at Michigan State University using a Perkin–Elmer Series II 2400 CHNS/O Analyzer. GC/MS data were obtained using a Varian Saturn 2200 GC/MS (column type: WCOT fused silica 30 m×0.25 mm ID coating CP-SIL 8 CB). High-resolution mass spectra were obtained at the Mass Spectrometry Core of the Research Technology Support Facility (RTSF) at Michigan State University. Melting points were measured on a MEL-TEMP® capillary melting apparatus and are uncorrected.

4.1.3. Regioisomer assignment of borylation products of 3-substituted thiophenes by ^{1}H NMR spectroscopy



From the ^{1}H NMR coupling constants *J*, the two regioisomers obtained by the borylation of 3-substituted thiophenes can be distinguished unambiguously. In case of the 2,4-borylated product, the value of the four-bond (*meta*) coupling constant $^4J_{H-H}$ is usually around 0.7–1.2 Hz. While in case of the 2,3-borylated product, the value of the three-bond (*ortho*) coupling constant $^3J_{H-H}$ is usually around 4.5–5.0 Hz. Since these two ranges of coupling constants are quite far apart, the two regioisomers can easily be distinguished by the value of ^{1}H NMR coupling constant.

4.2. Catalytic borylation of substituted thiophenes

4.2.1. General procedure A (borylation with heteroaromatic substrate as the limiting reactant)

The [Ir] catalyst was generated by a modified literature protocol,[34] where in a glove box, two separate test tubes were charged with [Ir(μ$_2$-OMe)(COD)]$_2$ (10 mg, 0.015 mmol, 3 mol % Ir) and dtbpy (8 mg, 0.03 mmol, 3 mol %). Excess HBPin (1.5–2 equiv) was added to the [Ir(μ$_2$-OMe)(COD)]$_2$ test tube. *n*-Hexane (1 mL) was added to the dtbpy containing test tube in order to dissolve the dtbpy. The dtbpy solution was then mixed with the [Ir(μ$_2$-OMe)(COD)]$_2$ and HBPin mixture. After mixing for 1 min, the resulting solution was transferred to the 20 mL scintillation vial equipped with a magnetic stirring bar. Additional *n*-hexane (2×1 mL) was used to wash the test tubes and the washings were transferred to the scintillation vial. Substituted thiophene (1 mmol, 1 equiv) was added to the scintillation vial. The reaction was stirred at room temperature and was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was dissolved in CH_2Cl_2 and passed through a short plug of silica to afford the corresponding borylated product.

4.2.2. General procedure B (borylation with HBPin as the limiting reactant)

In a glove box, two separate test tubes were charged with [Ir(μ$_2$-OMe)(COD)]$_2$ (10 mg, 0.015 mmol, 3 mol % Ir) and dtbpy (8 mg, 0.03 mmol, 3 mol %). HBPin (1 mmol, 1 equiv) was added to the [Ir(μ$_2$-OMe)(COD)]$_2$ test tube. *n*-Hexane (1 mL) was added to the dtbpy containing test tube in order to dissolve the dtbpy. The dtbpy solution was then mixed with the [Ir(μ$_2$-OMe)(COD)]$_2$ and HBPin mixture. After mixing for one minute, the resulting solution was transferred to the 20 mL scintillation vial equipped with a magnetic stirring bar. Additional *n*-hexane (2×1 mL) was used to wash the test tubes and the washings were transferred to the scintillation vial. Excess 3-substituted thiophene (2–4 equiv) was added to the scintillation vial. The reaction was stirred at room temperature and was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was dissolved in CH_2Cl_2 and passed through a short plug of silica to afford the corresponding borylated product/products.

4.2.3. General procedure C

In a glove box, (Ind)Ir(COD) (8.3 mg, 0.02 mmol, 2.00 mol % Ir) and dmpe (3 mg, 0.02 mmol, 2.00 mol %) were weighed in two separate test tubes. HBPin (218 μL, 190 mg, 1.50 mmol, 1.50 equiv) was added to the dmpe test tube and the resulting solution was then mixed with (Ind)Ir(COD). This catalyst solution was added to a Schlenk flask equipped with a magnetic stirring bar. Substituted thiophene (1 mmol, 1 equiv) was added to the Schlenk flask. The Schlenk flask was closed, brought out of the glove box, and was heated at 150 °C in an oil bath. The reaction was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was dissolved in CH_2Cl_2 and passed through a short plug of silica to afford the corresponding borylated product.

*4.2.3.1. 2-(5-Iodothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**).* The general borylation procedure A was applied to 2-iodothiophene (111 μL, 210 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 1 h. The product was isolated as a white solid (310 mg, 92% yield, mp 48–49 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, *J*=3.5 Hz, 1H), 7.25 (d, *J*=3.5 Hz, 1H), 1.31 (br s, 12H, 4CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 138.5 (CH), 138.3 (CH), 84.3 (2C), 81.5 (C), 24.7 (4CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.7; FTIR (neat) $\tilde{\nu}_{max}$: 2978, 2932, 1522, 1418, 1314, 1267, 1142, 1064, 1018, 853, 663 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M$^+$ 336 (100), 321 (13), 250 (6), 236 (14), 209 (12), 167 (43). Anal. Calcd for $C_{10}H_{14}BIO_2S$: C, 35.75; H, 4.20. Found: C, 36.04; H, 4.24.

*4.2.3.2. 2-(4-Bromo-5-chlorothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2**).* The general borylation procedure A was applied to 2-chloro-3-bromothiophene (110 μL, 197 mg, 1 mmol, 1 equiv) and HBPin (192 μL, 218 mg, 1.50 mmol, 1.50 equiv) for 10 min. The product was isolated as a white solid (253 mg, 78% yield, mp 60–61 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (s, 1H), 1.30 (br s, 12H, 4CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 138.9 (CH), 133.2 (C), 112.0 (C), 84.6 (2C), 24.7 (4CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 2932, 1523, 1425, 1340, 1267, 1142, 1041, 852, 661 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M$^+$ 324 (100), 322 (73), 309 (45), 281 (26), 264 (29), 243 (38). Anal. Calcd for $C_{10}H_{13}BBrClO_2S$: C, 37.13; H, 4.05. Found: C, 37.20; H, 4.16.

Note. Attempted borylation of 2,5-dichloro-3-bromothiophene with borylation procedure C also gave the same product where C–Cl bond was borylated and the single monoborylated product was isolated in 73% yield (see attempted borylation of tri-substituted thiophene). Only one of the two C–Cl bonds is activated with chemoselectivity greater than 99%. The NMR data matched with the borylated product of 2-chloro-3-bromothiophene as described above.

*4.2.3.3. Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (**3**).* The general borylation procedure A was applied to methyl-2-thiophenecarboxylate (116 μL, 142 mg, 1 mmol, 1 equiv) and HBPin (192 μL, 218 mg, 1.50 mmol, 1.50 equiv) for 0.5 h. The product was isolated as a white solid (252 mg, 94% yield, mp 114–117 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, *J*=3.7 Hz, 1H), 7.53 (d, *J*=3.7 Hz, 1H), 3.87 (s, 3H, CO_2CH_3), 1.33 (br s, 12H, 4CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 162.6 (C=O), 139.4 (C), 136.9 (CH), 133.9 (CH), 84.6 (2C), 52.2 (CO_2CH_3), 24.7 (4CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FTIR (neat) $\tilde{\nu}_{max}$: 2970, 1719, 1527, 1354, 1248, 1145, 1097, 852, 832, 752, 665 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M$^+$ 268 (71), 253 (91), 237 (56), 182 (100). Anal. Calcd for $C_{12}H_{17}BO_4S$: C, 53.75; H, 6.39. Found: C, 53.44; H, 6.44.

*4.2.3.4. Trimethyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)silane (**4**).* The general borylation procedure A was applied to 2-trimethylsilylthiophene (312 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equiv) for 30 min. The product was isolated as a white solid (523 mg, 93% yield, mp

61–62 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, J=3.3 Hz, 1H), 7.31 (d, J=3.3 Hz, 1H), 1.32 (br s, 12H, $4CH_3$ of BPin), 0.30 (s, 9H, $3CH_3$ of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 148.4 (C), 137.8 (CH), 135.0 (CH), 84.0 (2C), 24.8 ($4CH_3$ of BPin), −0.1 ($3CH_3$ of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.6; FTIR (neat) $\tilde{\nu}_{max}$: 3054, 2980, 2957, 1514, 1435, 1346, 1331, 1259, 1250, 1142, 1072, 981, 841, 821, 758, 699 cm^{-1}; GC/MS (EI) m/z (% relative intensity): M^+ 282 (14), 267 (100), 239 (31), 167 (8). Anal. Calcd for $C_{13}H_{23}BO_2SSi$: C, 55.31; H, 8.21. Found: C, 54.85; H, 8.74; HRMS (EI): m/z 282.1285 [(M^+); calcd for $C_{13}H_{23}BO_2SSi$: 282.1281].

*4.2.3.5. 1-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)ethanone (**5**).* The general borylation procedure A was applied to 2-acetylthiophene (108 μL, 126 mg, 1 mmol, 1 equiv) and HBPin (175 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 0.5 h. The product was isolated as a white solid (213 mg, 85% yield, mp 64–66 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (d, J=3.8 Hz, 1H), 7.54 (d, J=3.8 Hz, 1H), 2.53 (s, 3H, $COCH_3$), 1.31 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 190.6 (C=O), 149.4 (C), 137.2 (CH), 132.6 (CH), 84.6 (2C), 27.4 ($COCH_3$), 24.7 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.2; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 2934, 1669, 1520, 1348, 1288, 1267, 1142, 1020, 852, 667 cm^{-1}; GC/MS (EI) m/z (% relative intensity): M^+ 252 (77), 237 (100), 209 (15), 195 (8), 179 (5), 166 (33), 153 (14), 137 (12), 109 (6). Anal. Calcd for $C_{12}H_{17}BO_3S$: C, 57.16; H, 6.80. Found: C, 56.88; H, 7.06.

*4.2.3.6. Borylation of 3-cyanothiophene (**7a** and **7b**).* The general borylation procedure B was applied to 3-cyanothiophene (182 μL, 218 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two borylated products at the end of reaction was 1:1.13 by GC-FID. The borylated product mixture was isolated as a white solid (126 mg, 54% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**7a**) 8.13 (d, J=1.2 Hz, 1H), 7.75 (d, J=1.2 Hz, 1H), 1.33 (br s, 12H, $4CH_3$ of BPin), (**7b**) 7.62 (d, J=4.9 Hz, 1H), 7.38 (d, J=4.9 Hz, 1H), 1.36 (br s, 12H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**7a**) 140.8 (CH), 138.1 (CH), 114.7 (C), 111.9 (C), 85.1 (2C), 24.7 ($4CH_3$ of BPin), (**7b**) 132.7 (CH), 131.3 (CH), 118.2 (C), 115.1 (C), 84.8 (2C), 24.7 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.6; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 2231, 1429, 1319, 1142, 1039, 850, 628 cm^{-1}; GC/MS (EI) m/z (% relative intensity): (**7a**) M^+ 235 (7), 220 (100), 192 (9), 149 (37), 136 (15), (**7b**) M^{+1} 236 (100), 220 (78), 194 (51), 178 (33), 149 (36), 136 (31). Anal. Calcd for $C_{11}H_{14}BNO_2S$: C, 56.19; H, 6.00; N, 5.96. Found: C, 55.74; H, 5.99; N, 6.00.

*4.2.3.7. Borylation of 3-chlorothiophene (**8a** and **8b**).* The general borylation procedure B was applied to 3-chlorothiophene (186 μL, 237 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two borylated products at the end of reaction was 3.5:1 by GC-FID. The borylated product mixture was isolated as a white solid (160 mg, 66% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**8a**) 7.43 (d, J=1.0 Hz, 1H), 7.35 (d, J=1.0 Hz, 1H), 1.32 (br s, 12H, $4CH_3$ of BPin), (**8b**) 7.51 (d, J=5.0 Hz, 1H), 7.01 (d, J=5.0 Hz, 1H), 1.34 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**8a**) 136.9 (CH), 131.8 (C), 126.7 (CH), 84.4 (2C), 24.7 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.0; FTIR (neat) $\tilde{\nu}_{max}$: 3107, 2980, 2932, 1522, 1421, 1356, 1336, 1142, 1026, 854, 665 cm^{-1}; GC/MS (EI) m/z (% relative intensity): M^+ 244 (100), 246 (38), 231 (15), 229 (38), 209 (24), 158 (27). Anal. Calcd for $C_{10}H_{14}BClO_2S$: C, 49.11; H, 5.77. Found: C, 49.33; H, 5.81.

*4.2.3.8. Borylation of 3-bromothiophene (**9a** and **9b**).* The general borylation procedure B was applied to 3-bromothiophene (190 μL, 326 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two borylated products at the end of reaction was 8.9:1 by GC-FID. The borylated product mixture was isolated as a white solid (209 mg, 72% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**9a**) 7.49 (d, J=1.2 Hz, 1H), 7.46 (d, J=1.2 Hz, 1H), 1.32 (br s, 12H, $4CH_3$ of BPin), (**9b**) 7.48 (d, J=5.0 Hz, 1H), 7.08 (d, J=5.0 Hz, 1H), 1.34 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**9a**) 139.3 (CH), 129.5 (CH), 111.2 (C), 84.4 (2C), 24.7 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.0; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 1518, 1415, 1350, 1143, 1026, 852, 665 cm^{-1}; GC/MS (EI) m/z (% relative intensity): (**9a**) M^+ 289 (51), 290 (98), 288 (100), 275 (61), 273 (55), 247 (18), 245 (21), 230 (19), 204 (41), (**9b**) M^+ 289 (13), 290 (25), 288 (27), 275 (10), 273 (9), 209 (100), 189 (11), 167 (67). Anal. Calcd for $C_{10}H_{14}BBrO_2S$: C, 41.56; H, 4.88. Found: C, 41.74; H, 4.88.

*4.2.3.9. Borylation of 3-methylthiophene (**10a** and **10b**).* The general borylation procedure B was applied to 3-methylthiophene (194 μL, 196 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two borylated products at the end of reaction was 8.9:1 by GC-FID. The borylated product mixture was isolated as colorless oil (150 mg, 67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**10a**) 7.42 (d, J=0.7 Hz, 1H), 7.17 (t, J=1.1 Hz, 1H), 2.27 (d, J=0.5 Hz, 1H), 1.32 (br s, 12H, $4CH_3$ of BPin), (**10b**) 7.46 (d, J=4.6 Hz, 1H), 6.95 (d, J=4.6 Hz, 1H), 2.47 (s, 1H), 1.30 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**10a**) 139.4 (CH), 138.9 (C), 128.0 (CH), 83.9 (2C), 24.7 ($4CH_3$ of BPin), 14.9 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FTIR (neat) $\tilde{\nu}_{max}$: 2978, 2930, 1550, 1441, 1371, 1327, 1302, 1271, 1143, 1028, 962, 854, 665 cm^{-1}; GC/MS (EI) m/z (% relative intensity): (**10a**) M^+ 224 (100), 209 (27), 181 (18), 138 (44), (**10b**) M^+ 224 (100), 209 (68), 167 (64), 138 (54), 124 (61). Anal. Calcd for $C_{11}H_{17}BO_2S$: C, 58.95; H, 7.65. Found: C, 58.65; H, 8.09.

*4.2.3.10. 1-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)ethanone (**11a**).* The general borylation procedure A was applied to 3-acetylthiophene (126 mg, 1 mmol, 1 equiv) and HBPin (174 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 15 min. The product was isolated as colorless oil (206 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.26 (d, J=1.1 Hz, 1H), 8.00 (d, J=1.1 Hz, 1H), 2.50 (s, 3H, $COCH_3$), 1.32 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 192.0 (C=O), 143.8 (C), 138.1 (CH), 137.0 (CH), 84.5 (2C), 27.8 ($COCH_3$), 24.8 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.2; FTIR (neat) $\tilde{\nu}_{max}$: 3098, 2980, 2934, 1680, 1530, 1448, 1381, 1373, 1340, 1305, 1215, 1143, 1024, 850, 667 cm^{-1}; GC/MS (EI) m/z (% relative intensity): M^+ 252 (21), 237 (55), 209 (100), 195 (9), 153 (22), 137 (19). Anal. Calcd for $C_{12}H_{17}BO_3S$: C, 57.16; H, 6.80. Found: C, 56.77; H, 7.19.

*4.2.3.11. Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-3-carboxylate (**12a**).* The general borylation procedure A was applied to methyl 3-thiophenecarboxylate (121 μL, 142 mg, 1 mmol, 1 equiv) and HBPin (174 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 1 h. The product was isolated as a white solid (256 mg, 95% yield, mp 84–85 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.31 (d, J=1.0 Hz, 1H), 8.01 (d, J=1.0 Hz, 1H), 3.84 (s, 3H, CO_2CH_3), 1.33 (br s, 12H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 163.1 (C=O), 138.8 (CH), 137.9 (CH), 134.9 (C), 84.4 (2C), 51.6 (CO_2CH_3), 24.7 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.4; FTIR (neat) $\tilde{\nu}_{max}$: 3107, 2980, 2951, 1722, 1537, 1458, 1431, 1388, 1373, 1336, 1307, 1224, 1143, 1024, 987, 852, 752, 667 cm^{-1}; GC/MS (EI) m/z (% relative intensity): M^+ 268 (65), 253 (100), 237 (22), 225 (39), 211 (29), 193 (12), 182 (45), 169 (41), 137 (27). Anal. Calcd for $C_{12}H_{17}BO_4S$: C, 53.75; H, 6.39. Found: C, 53.54; H, 6.66.

*4.2.3.12. Trimethyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)silane (**13a**).* The general borylation procedure A was applied to 3-trimethylsilylthiophene (156 mg, 1 mmol, 1 equiv) and HBPin (174 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 30 min. The product was isolated as a white solid (222 mg, 79% yield, mp 87–89 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, J=1.0 Hz, 1H), 7.69 (d, J=1.0 Hz, 1H), 1.33 (br s, 12H, $4CH_3$ of BPin), 0.24 (s, 9H, $3CH_3$ of

TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 142.4 (C), 141.9 (CH), 138.4 (CH), 83.8 (2C), 24.6 ($4CH_3$ of BPin), −0.6 ($3CH_3$ of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 2955, 1510, 1410, 1325, 1263, 1250, 1143, 1105, 1028, 902, 852, 839, 754, 667 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M^+ 282 (7), 267 (100), 239 (2), 167 (7). Anal. Calcd for $C_{13}H_{23}BO_2SSi$: C, 55.31; H, 8.21. Found: C, 54.68; H, 8.47; HRMS (EI): *m*/*z* 282.1283 [(M^+); calcd for $C_{13}H_{23}BO_2SSi$: 282.1281].

*4.2.3.13. Borylation of 3-p-tolylthiophene (**14a** and **14b**).* The general borylation procedure B was applied to 3-*p*-tolylthiophene (192 mg, 1.1 mmol, 1.1 equiv) and HBPin (145 μL, 128 mg, 1.00 mmol, 1.00 equiv) for 1 h. The ratio of two borylated isomers at the end of reaction was 32:1 by GC-FID. The product was isolated as colorless oil (223 mg, 74% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**14a**) 7.91 (d, *J*=1.2 Hz, 1H), 7.68 (d, *J*=1.2 Hz, 1H), 7.48–7.52 (m, 2H), 7.17–7.20 (m, 2H), 2.35 (s, 3H, CH_3), 1.36 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**14a**) 143.8 (C), 136.8 (C), 136.2 (CH), 132.9 (C), 129.5 (CH), 126.9 (CH), 126.4 (CH), 84.2 (2C), 24.8 ($4CH_3$ of BPin), 21.1 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.4; FTIR (neat) $\tilde{\nu}_{max}$: 3090, 2978, 2928, 1547, 1441, 1379, 1371, 1329, 1311, 1269, 1143, 1026, 850, 819, 771, 667 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M^+ 300 (100), 285 (12), 214 (12). Anal. Calcd for $C_{17}H_{21}BO_2S$: C, 68.01; H, 7.05. Found: C, 68.54; H, 6.97; HRMS (EI): *m*/*z* 300.1360 [(M^+); calcd for $C_{17}H_{21}BO_2S$: 300.1355].

*4.2.3.14. 2-(2,5-Dichlorothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**15**).* The general borylation procedure A was applied to 2,5-di-chlorothiophene (107 μL, 153 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 20 h. The product was isolated as a white solid (240 mg, 86% yield, mp 35–36 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94 (s, 1H), 1.30 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 137.1 (C), 131.1 (CH), 126.2 (C), 84.0 (2C), 24.8 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 1535, 1437, 1371, 1313, 1263, 1142, 1032, 966, 889, 848, 692 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M^+ 278 (100), 280 (68), 263 (32), 265 (22), 243 M−35 (79), 245 (30), 201 (51). Anal. Calcd for $C_{10}H_{13}BCl_2O_2S$: C, 43.05; H, 4.70. Found: C, 43.26; H, 4.74.

*4.2.3.15. 2-(2,5-Dibromothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**16**).* The general borylation procedure A was applied to 2,5-di-bromothiophene (113 μL, 142 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) with 6 mol % [Ir] catalyst loading for 36 h. Additional 3 mol % [Ir] catalyst and 1 equiv of HBPin was added at this stage and the reaction was run for 12 more hours at room temperature. The ratio of the starting material to product after 48 h was 11:89. The product was isolated as a white solid (206 mg, 56% yield, mp 72–73 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09 (s, 1H), 1.31 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 135.8 (CH), 121.9 (C), 110.9 (C), 84.0 (2C), 24.8 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FTIR (neat) $\tilde{\nu}_{max}$: 2978, 1525, 1365, 1307, 1248, 1143, 991, 962, 883, 848, 690 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M^+ 368 (100), 370 (51), 366 (52), 353 (18), 287 (56), 289 (59), 268 (28), 208 (77), 166 (69). Anal. Calcd for $C_{10}H_{13}BBr_2O_2S$: C, 32.65; H, 3.56. Found: C, 32.92; H, 3.57.

*4.2.3.16. 2-(2,5-Dimethylthiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**17**).* The general borylation procedure C was applied to 2,5-di-methylthiophene (228 μL, 224 mg, 2 mmol, 1 equiv) and neat HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equiv) for 16 h at 150 °C. The product was isolated as a colorless semi solid (460 mg, 97% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.81 (d, *J*=1.2 Hz, 1H), 2.59 (s, 3H, CH_3), 2.38 (d, *J*=0.4 Hz, 3H, CH_3), 1.30 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 150.8 (C), 136.1 (C), 130.7 (CH), 83.0 (2C), 24.8 ($4CH_3$ of BPin), 15.6 (CH_3), 14.7 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.3; FTIR (neat) $\tilde{\nu}_{max}$: 2978, 2924, 1493, 1394, 1304, 1265, 1145, 868, 700 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M^+ 238 (100), 223 (8), 181 (37). Anal. Calcd for $C_{12}H_{19}BO_2S$: C, 60.52; H, 8.04. Found: C, 60.62; H, 8.18.

*4.2.3.17. Borylation of 2-chloro-5-bromothiophene (**18a** and **18b**).* The general borylation procedure A was applied to 2-chloro-5-bromothiophene (110 μL, 197 mg, 1 mmol, 1 equiv) and HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) with 3 mol % [Ir] catalyst loading for 8 h. Additionally 3 mol % [Ir] and 0.5 equiv of HBPin were added and the reaction was run for 20 more hours at room temperature. The ratio of the two borylated products at the end of reaction was 2:1 by GC-FID. The borylated product mixture was isolated as a white solid (281 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**18a**) 7.10 (s, 1H), 1.30 (br s, 12H, $4CH_3$ of BPin), (**18b**) 6.94 (s, 1H), 1.30 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**18a**) 139.6 (C), 134.9 (CH), 108.3 (C), 84.0 (2C), 24.8 ($4CH_3$ of BPin), (**18b**) 132.0 (CH), 128.9 (C), 119.5 (C), 84.1 (2C), 24.8 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 1527, 1427, 1371, 1253, 1140, 1028, 962, 848, 693 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): (**18a**) M^+ 324 (100), 322 (78), 289 (67), 287 (64), 208 (40), 166 (34), (**18b**) M^+ 324 (89), 322 (69), 309 (23), 245 (41), 243 (99), 203 (43), 201 (100), 166 (50). Anal. Calcd for $C_{10}H_{13}BBrClO_2S$: C, 37.13; H, 4.05. Found: C, 37.25; H, 4.05.

Note. The data for the pure **18a** is described in Section 4.2.6.

*4.2.3.18. Borylation of 2-chloro-5-methylthiophene (**19a** and **19b**).* The general borylation procedure A was applied to 2-chloro-5-methylthiophene (133 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 18 h. The ratio of two borylated products at the end of reaction was 2.3:1 by GC-FID. The borylated product mixture was isolated as a colorless semi solid (221 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**19a**) 6.77 (q, *J*=1.2 Hz, 1H), 2.35 (d, *J*=1.2 Hz, 3H, CH_3), 1.31 (br s, 12H, $4CH_3$ of BPin), (**19b**) 6.95 (s, 1H), 2.60 (s, 3H, CH_3), 1.28 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**19a**) 137.4 (C), 137.0 (C), 130.1 (CH), 83.6 (2C), 24.8 ($4CH_3$ of BPin), 14.9 (CH_3), (**19b**) 151.1 (C), 131.6 (CH), 125.4 (C), 83.4 (2C), 24.8 ($4CH_3$ of BPin), 15.7 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 2926, 1556, 1475, 1390, 1371, 1309, 1257, 1143, 1026, 966, 898, 850, 696 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): (**19a**) 258 M^+ (100), 243 (17), 223 (51), 181 (36), 153 (37), (**19b**) 258 M^+ (100), 243 (18), 223 (7), 201 (93), 172 (23). Anal. Calcd for $C_{11}H_{16}BClO_2S$: C, 51.10; H, 6.24. Found: C, 51.66; H, 6.58; HRMS (EI): *m*/*z* 258.0653 [(M^+); calcd for $C_{11}H_{16}BClO_2S$: 258.06526].

*4.2.3.19. Borylation of 2-chloro-5-iodothiophene (**20a** and **20b**).* The general borylation procedure A was applied to 2-chloro-5-iodothiophene (122 mg, 0.5 mmol, 1 equiv) and HBPin (109 μL, 96 mg, 0.75 mmol, 1.50 equiv) for 20 h. The ratio of two borylated products at the end of reaction was 5.7:1 by GC-FID. The borylated product mixture was isolated as a white solid (165 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**20a**) 7.31 (s, 1H), 1.30 (br s, 12H, $4CH_3$ of BPin), (**20b**) 6.87 (s, 1H), 1.31 (br s, 12H, $4CH_3$ of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**20a**) 143.4 (C), 142.3 (CH), 84.0 (2C), 69.3 (C), 24.8 ($4CH_3$ of BPin), (**20b**) 132.8 (CH), 84.2 (2C), 81.1 (C), 24.8 ($4CH_3$ of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.3; FTIR (neat) $\tilde{\nu}_{max}$: 2978, 1523, 1414, 1371, 1248, 1140, 1024, 966, 881, 848, 690 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): (**20a**) M^+ 370 (100), 355 (13), 335 (29), 270 (25), 208 (15), 166 (11), (**20b**) M^+ 370 (100), 355 (10), 270 (24), 243 (13), 201 (32), 166 (21). Anal. Calcd for $C_{10}H_{13}BIClO_2S$: C, 32.42; H, 3.54. Found: C, 32.58; H, 3.38.

*4.2.3.20. (5-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)trimethylsilane (**21**).* The general borylation procedure A was applied to 2-chloro-5-trimethylsilylthiophene (382 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equiv) for 6 h. The single borylated product was isolated as a solid (589 mg, 93%

yield, mp 68–69 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (s, 1H), 1.32 (br s, 12H, 4CH_3 of BPin), 0.26 (s, 9H, 3CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 144.7 (C), 139.42 (CH), 139.37 (C), 83.7 (2C), 24.8 (4CH_3 of BPin), −0.24 (3CH_3 of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FTIR (neat) $\tilde{\nu}_{max}$: 2980, 1525, 1415, 1363, 1307, 1253, 1238, 1143, 993, 841, 758, 696 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity) M$^+$ 316 (33), 301 (100), 281 (6), 201 (15). Anal. Calcd for $C_{13}H_{22}BClO_2SSi$: C, 49.30; H, 7.00. Found: C, 49.16; H, 7.16.

4.2.4. Attempted borylation of trisubstituted thiophene

*4.2.4.1. 2-(4-Bromo-5-chlorothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2**).* The general borylation procedure C was applied to 2,5-di-chloro-3-bromothiophene (232 mg, 1 mmol, 1 equiv) and neat HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 2 h at 150 °C. The product was isolated as a colorless solid (233 mg, 73% yield). The spectroscopic data of this product matched with the data of borylated product obtained from 2-chloro-3-bromo-thiophene as described earlier.

4.2.5. One-pot borylation/Suzuki coupling of substituted thiophenes

*4.2.5.1. 2-Methyl-5-(3-(trifluoromethyl)phenyl)thiophene (**25**).* The general borylation procedure A was applied to 2-methylthiophene (484 μL, 491 mg, 5 mmol, 1 equiv) and HBPin (870 μL, 768 mg, 6.00 mmol, 1.20 equiv) in a Schlenk flask for 0.5 h. The reaction mixture was pumped down under high vacuum for 0.5 h to remove the volatile materials. Pd(PPh_3)$_4$ (116 mg, 0.10 mmol, 2 mol %), 3-bromo-benzotrifluoride (837 μL, 1350 mg, 6.00 mmol, 1.2 equiv), and DME (6 mL) were added to the Schlenk flask inside the glove box. The Schlenk flask was then brought out of the glove box and attached to a Schlenk line. $K_3PO_4 \cdot nH_2O$ (1592 mg, 1.50 equiv) was added under N_2 counter flow to the Schlenk flask. The flask was stoppered and the mixture was heated at 80 °C for 8 h. The flask was cooled down to room temperature and 20 mL of water were added to the reaction mixture. The reaction mixture was extracted with ether (3×20 mL). The combined ether extractions were washed with brine (20 mL), followed by water (10 mL), dried over $MgSO_4$ before being concentrated under reduced pressure on a rotary evaporator. Column chromatography (hexanes, R_f 0.5) furnished the product as white semi solid (1026 mg, 85% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (t, *J*=0.8 Hz, 1H), 7.68 (d, *J*=7.6 Hz, 1H), 7.42–7.48 (m, 2H), 7.15 (d, *J*=3.5 Hz, 1H), 6.73–6.75 (m, 1H), 2.51 (s, 3H, CH_3); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 140.7 (C), 140.1 (C), 135.5 (C), 131.2 (q, $^2J_{C-F}$=32.6 Hz, C), 129.3 (CH), 128.5 (CH), 126.4 (CH), 124.1 (q, $^1J_{C-F}$=273 Hz, CF_3), 124.0 (CH), 123.4 (q, $^3J_{C-F}$=3.6 Hz, CH), 122.0 (q, $^3J_{C-F}$=3.6 Hz, CH), 15.4 (CH_3); FTIR (neat) $\tilde{\nu}_{max}$: 3073, 2922, 2865, 1497, 1340, 1325, 1165, 1126, 1074, 790, 694 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M$^+$ 242 (100), 223 (4), 173 (6). Anal. Calcd for $C_{12}H_9F_3S$: C, 59.49; H, 3.74. Found: C, 59.38; H, 3.56.

*4.2.5.2. (5-Chloro-4-m-tolylthiophen-2-yl)trimethylsilane (**26**).* The general borylation procedure A was applied to 2-chloro-5-trimethylsilylthiophene (382 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equiv) in a Schlenk flask for 10 h. The reaction mixture was pumped down under high vacuum for 1 h to remove the volatile materials. Pd(PPh_3)$_4$ (46 mg, 2 mol %), 3-bromo-toluene (291 μL, 410 mg, 2.40 mmol, 1.2 equiv), and DME (3 mL) were added to the Schlenk flask inside the glove box. The Schlenk flask was then brought out of the glove box and attached to a Schlenk line. $K_3PO_4 \cdot nH_2O$ (637 mg, 1.50 equiv) was added under N_2 counter flow to the Schlenk flask. The flask was stoppered and the mixture was heated at 80 °C for 6 h. The flask was cooled down to room temperature and 10 mL of water were added to the reaction mixture. The reaction mixture was extracted with ether (3×10 mL). The combined ether extractions were washed with brine (10 mL), followed by water (10 mL), dried over $MgSO_4$ before being concentrated under reduced pressure on a rotary evaporator. Column chromatography (hexanes, R_f 0.5) furnished the product as a colorless liquid (369 mg, 66% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27–7.37 (m, 3H), 7.13–7.16 (m, 1H), 7.12 (s, 1H), 2.39 (s, 3H, CH_3), 0.31 (s, 9H, 3CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 139.6 (C), 138.2 (C), 138.0 (C), 135.3 (CH), 134.3 (C), 129.3 (C), 129.1 (CH), 128.29 (CH), 128.27 (CH), 125.6 (CH), 21.5 (CH_3), −0.3 (3CH_3 of TMS); FTIR (neat) $\tilde{\nu}_{max}$: 3040, 2957, 2922, 1606, 1408, 1252, 993, 839, 781, 756, 700, 630 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M$^+$ 280 (49), 282 (19), 266 (100), 267 (48). Anal. Calcd for $C_{14}H_{17}ClSSi$: C, 59.86; H, 6.10. Found: C, 59.56; H, 6.21.

4.2.6. Bromination

*4.2.6.1. 2-(4-Bromo-2,5-dimethylthiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**27**).* 2-(2,5-Dimethylthiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**17**) (238 mg, 1 mmol, 1 equiv) was dissolved in 2 mL of $CHCl_3$ in a 20 mL scintillation vial equipped with a magnetic stirring bar. Bromine (160 mg, 1 mmol, 1 equiv, dissolved in 2 mL of $CHCl_3$) was added dropwise during two minutes. The reaction was then quenched with water. The product was extracted with CH_2Cl_2 (3×20 mL) and dried over $MgSO_4$. Column chromatography (hexane/CH_2Cl_2 1:1, R_f 0.7) furnished the desired product as a white solid (260 mg, 82%, mp 55–56 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.54 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 1.32 (br s, 12H, 4CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 147.9 (C), 131.2 (C), 113.1 (C), 83.5 (2C), 24.8 (4CH_3 of BPin), 16.2 (CH_3), 14.5 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FTIR (neat) $\tilde{\nu}_{max}$: 2978, 2922, 1537, 1377, 1315, 1234, 1143, 852 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M$^+$ 317 (46), 318 (84), 316 (81), 303 (11), 301 (10), 261 (100), 259 (99), 237 (27), 195 (38), 180 (41). Anal. Calcd for $C_{12}H_{18}BBrO_2S$: C, 45.46; H, 5.72. Found: C, 45.54; H, 5.91.

4.2.7. General procedure D (substitution of TMS with Br)

TMS group were replaced with bromine by employing the literature conditions used for aromatic C–H bromination.[58] Substrate (1 mmol, 1 equiv) was added to a 20 mL scintillation vial equipped with a magnetic stirring bar. *N*-Bromosuccinamide (1 mmol, 1 equiv) was added in to the vial. Acetonitrile (3–5 mL) was also added to the vial. The reaction mixture was stirred at room temperature and was monitored by GC-FID/MS. After the completion of the reaction, the volatile materials were removed on a rotary evaporator and the crude product was passed through a short silica plug to afford the brominated product.

*4.2.7.1. 2-(5-Bromo-2-chlorothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**18a**).* The general bromination procedure D was applied to (5-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)trimethylsilane (**21**) (317 mg, 1 mmol) for 12 h. The product was isolated as a white solid (295 mg, 91%, mp 51–53 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10 (s, 1H), 1.30 (br s, 12H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 139.6 (C), 134.9 (CH), 108.3 (C), 84.1 (2C), 24.8 (4CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FTIR (neat) $\tilde{\nu}_{max}$: 2978, 1530, 1427, 1373, 1311, 1253, 1142, 1028, 962, 848, 883, 848, 692 cm^{-1}; GC/MS (EI) *m*/*z* (% relative intensity): M$^+$ 323 (48), 324 (100), 322 (81), 309 (21), 307 (14), 289 (38), 287 (36), 208 (23), 166 (22). Anal. Calcd for $C_{10}H_{13}BBrClO_2S$: C, 37.13; H, 4.05. Found: C, 37.25; H, 4.19.

*4.2.7.2. 5-Bromo-2-chloro-3-m-tolylthiophene (**28**).* The general bromination procedure D was applied to (5-chloro-4-*m*-tolylthiophen-2-yl)trimethylsilane (**26**) (280 mg, 1 mmol) for 12 h. The product was isolated as a colorless liquid (261 mg, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.31 (m, 3H), 7.15–7.18 (m, 1H), 7.02 (s, 1H), 2.38 (s, 3H, CH_3); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 139.3 (C),

138.2 (C), 133.1 (C), 131.2 (CH), 129.1 (CH), 128.8 (CH), 128.4 (CH), 125.5 (CH), 124.0 (C), 108.3 (C), 21.4 (CH_3); FTIR (neat) $\tilde{\nu}_{max}$: 3042, 2920, 2858, 1604, 1487, 1028, 972, 831, 789, 779, 700 cm^{-1}; GC/MS (EI) *m/z* (% relative intensity): M^+ 287 (63), 288 (100), 290 (29), 287 (63), 251 (5), 171 (19). Anal. Calcd for $C_{11}H_9BrClS$: C, 45.94; H, 2.80. Found: C, 45.96; H, 2.79.

*4.2.7.3. 5-(3,5-Bis(trifluoromethyl)phenyl)-2-chloro-3-m-tolylthiophene (**29**).* In a glove box, a Schlenk flask, equipped with a magnetic stirring bar, was charged with 2-(3,5-bis(trifluoromethyl)-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (82 mg, 0.24 mmol, 1.0 equiv). Two separate test tubes were charged with $Pd(PPh_3)_4$ (5.5 mg, 0.0048 mmol, 2 mol %) and 5-bromo-2-chloro-3-*m*-tolylthiophene (**28**) (69 mg, 0.24 mmol, 1.0 equiv). DME (2 mL) was used to transfer the contents of the test tubes into the Schlenk flask. The Schlenk flask was then brought out of the glove box and attached to a Schlenk line. $K_3PO_4 \cdot nH_2O$ (319 mg, 1.50 equiv) was added under N_2 counter flow to the Schlenk flask. The flask was stoppered and the mixture was heated at 80 °C for 7 h. At this point the reaction mixture was allowed to cool to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluting with CH_2Cl_2) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel (hexanes, R_f 0.5) to provide the Suzuki product as a white solid (85 mg, 84% yield, mp 77–79 °C). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.94 (s, 2H), 7.80 (s, 1H), 7.41–7.40 (m, 2H), 7.38 (s, 1H), 7.37–7.33 (t, J=7.8 Hz, 1H), 7.22–7.20 (d, J=7.3 Hz, 1H), 2.43 (s, 3H, CH_3); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 140.1 (C), 138.3 (C), 137.1 (C), 135.6 (C), 133.4 (C), 132.6 (q, $^2J_{C-F}$=33.6 Hz, 2C), 129.1 (CH), 128.9 (CH), 128.5 (CH), 126.4 (CH), 126.2 (C), 125.5 (CH), 125.2 (q, $^3J_{C-F}$=3.8 Hz, 2 CH), 123.1 (q, $^1J_{C-F}$=272.8 Hz, CF_3), 121.1 (septet, $^3J_{C-F}$=3.9 Hz, CH), 21.4 (CH_3); FTIR (neat) $\tilde{\nu}_{max}$: 3048, 2926, 1618, 1474, 1433, 1369, 1330, 1279, 1227, 1181, 1136, 1109, 1011, 891, 845, 789, 698, 684 cm^{-1}; HRMS (FAB^+): *m/z* 420.0174 [M^+; calcd for $C_{19}H_{11}ClF_6S$: 420.0177].

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