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# The Improved *para*-Selective C(sp$^2$)-H Borylation of Anisole Derivatives Enabled by Bulky Lewis Acid

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**Abstract:** An improved *para*-selective C(sp$^2$)-H borylation of anisole derivatives is described. The selective borylation is probably dominated by the change in electron density on the aromatic ring when a Lewis acid is coordinated with an anisole substrate. In addition, a sterically hindered bipyridyl ligand used in the reaction also favors *para*-selectivity. With this strategy, it has been demonstrated that the ratio of *para*-borylated products could be dramatically improved. The reaction proceeds at a milder temperature, and most substrates display moderate to good site-selectivity.

**Keywords:** C-H borylation; regioselectivity; iridium-catalyst; Lewis acid-base interaction



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## 1. Introduction

In the past few decades, transition-metal-catalyzed C-H functionalization has emerged as a powerful tool in synthetic organic chemistry [1–10]. The C-H bond, as the most basic chemical bond in organic chemistry, can be directly converted into various functional groups to construct different chemical bonds such as the carbon-carbon bond or the carbon-heteroatom bond with transition metal catalysts (e.g., Fe [3], Co [4], Ni [5], Ru [6], Rh [7], Pd [8], Ir [9], and Pt [10]). Compared with traditional synthetic methods, this strategy does require the introduction of potentially reactive functional groups such as alkenyl, carbonyl, aryl, and so on, greatly improving the efficiency of organic synthesis. However, most transition-metal-catalyzed C-H transformations adopt the directing group strategy: functional groups with coordinating ability (e.g., pyridine, amide, imine, ether, and carboxylate) chelate with transition-metal catalysts to form five/six-membered cyclometallic intermediate to achieve C-H bond cleavage, and the following functionalization with other reagents proceeds through oxidative addition and reductive elimination [11–13]. As a result, the activated C-H bond will be restricted to the site capable of forming cyclometallic intermediate [14–16]. For example, in the C-H functionalization of 2-phenylpyridine, only C-H bonds at the two *ortho*-positions of the pyridine directing group can be functionalized, while the C-H bonds at the *meta*- or *para*-positions far away from the pyridyl are difficult to activate [17–19]. Moreover, the difficulty of distal site-selectivity is more obvious in iridium (I)-catalyzed C(sp$^2$)-H functionalization of aryl substrates, which is also a long-standing challenge in this area [20–22].

In recent years, some remote site-selective aromatic C-H functionalization has been accomplished with different methods mainly controlled by electronic effects, steric effects, and intermolecular non-covalent bond interactions. In 2003, Miyaura's group reported a *meta*-selective C(sp$^2$)-H borylation of 3-acylthiophene, in which the rich electronic effect of a five-membered aromatic heterocycle plays an important role in the remote regioselectivity [23,24]. As regards steric hindrance dominating distal regioselectivity, a *para*-selective aromatic C-H borylation of monosubstituted benzenes was disclosed by Itami's group,

which used a new iridium catalyst bearing a bulky diphosphine ligand. The *para*-selectivity increases with increasing bulkiness of the substituent on the arene, indicating that the regioselectivity of this reaction is primarily controlled by steric repulsion between substrate and catalyst [25–29]. In addition, Kanai's group developed an innovative approach for distal selective aromatic C-H borylation [30,31]. Hydrogen-bonding interactions, an intermolecular non-covalent bond interaction between bipyridyl ligand and substrate, lead to high *meta*-selectivity. Based on this novel strategy, Phipps [32–34] and Chattopadhyay [35–37] created another two kinds of *para*-selective C($sp^2$)-H borylation of aromatic substrates by using intermolecular electrostatic interaction and Lewis acid-base interaction. Previously, we also developed an *ortho*-selective C($sp^2$)-H borylation of thioanisole derivatives controlled by Lewis acid-base interaction between bipyridyl ligand and substrates [38,39].

## 2. Results and Discussion

Anisole borylated derivatives, as an important structural unit, are widely utilized in many areas of chemistry, including pharmaceuticals, perfumes, and dyestuffs [40]. However, the iridium-catalyzed C-H borylation of anisole, usually gives a mixture of *meta*- and *para*-borylated products, and the ratio is about 3:1. It is difficult to obtain a single isomer of a borylated product, especially for the *para*-isomer. Herein, we report an improved *para*-selective C-H borylation of anisole assisted by the combination of a Lewis acid and a bulky bipyridyl ligand. We proposed that the mechanism is that the methoxy group, as a strong electron-donating group, will increase electron density at the *ortho*- and *para*-positions of the anisole substrate, which makes the electron-deficient *meta*-position easily functionalized. Once the Lewis acid is coordinated with the methoxy group, it results in a decrease in electron density at the *para*-position, which will lead to an increase in *para*-selectivity (Figure 1 (4)).

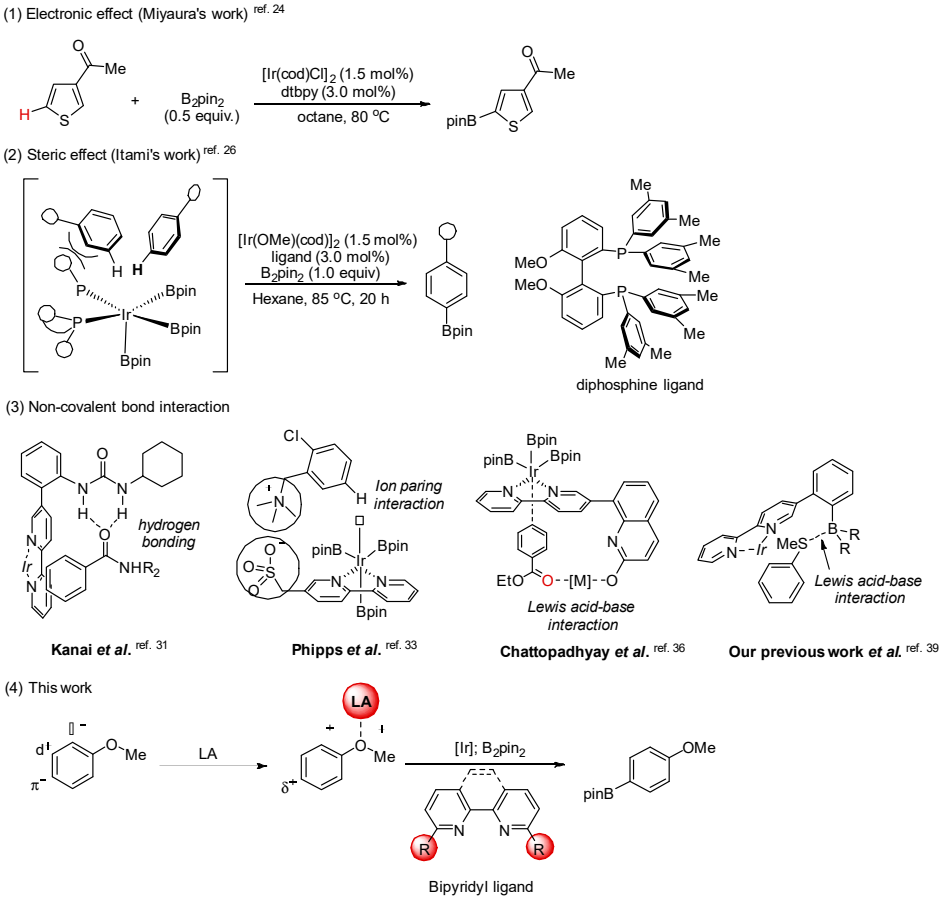
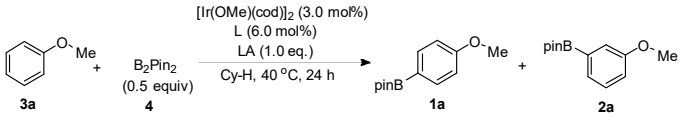


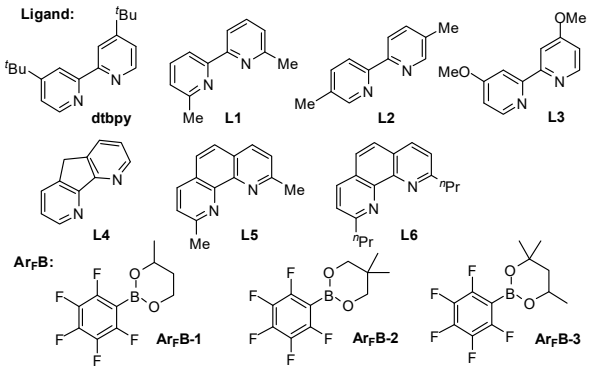

**Figure 1.** Some pioneering remote selective C($sp^2$)-H borylation reactions [30,32,35,38].

We initiated our investigation by treating anisole (**3a**) with bis(pinacolato)diboron (**4**) in the presence of an iridium catalyst [Ir(OMe)(cod)]$_2$ and dtbpy (4,4′-ditert-butyl-2,2′-dipyridyl) at 40 °C, which gave a mixture of *meta*- and *para*-borylated products **1a** and **2a** in 80% yield, and the [*para*/*meta*] ratio was only 27:73 (Scheme 1, entry 1). Firstly, several Lewis acids were investigated (Scheme 1, entries 2–10). The borylation did not occur when trimethylaluminum was used. However, in the case of triisobutylaluminum, the [*para*/*meta*] ratio was improved to 50:50 (entry 3), but with a low yield. Then, we focused on screening some boron Lewis acid. The [*para*/*meta*] ratio was decreased to 38:62 when B(OMe)$_3$ was used as Lewis acid. With increasing steric hindrance, the ratio was slightly increased to 58:42 (entry 5). We considered that the poor *para*-selectivity was probably due to the low Lewis acidity and steric hindrance [38]. Thus, we turned to tuning the electronic properties and steric hindrance of substituents on boron atoms. To our delight, B(Mes)$_3$ gave a good result, improving the [*para*/*meta*] ratio to 78:22 with a 50% yield (entry 6). Unexpectedly, B($C_6F_5$)$_3$ with stronger Lewis acidity did not improve the ratio (entry 7). In addition, changing its steric effect has no effect on the *para*-selectivity of this reaction (entries 8–10). In order to further increase the [*para*/*meta*] ratio, we also screened a series of bipyridyl ligands [25–30]. In the case of bipyridyl ligands with substituents at different positions (entries 11–13), ligand **1** with substituents at the 2,2′-position gave a good [*para*/*meta*] ratio reaching 81:19 (entry 11), while ligand **2** and ligand **3** gave poor results. We postulated that the steric hindrance at the 2,2′-position would be the determinant for the *para*-selectivity. Finally, we found that Ligand **6** with *n*-butyl at the 2,2′-position could further improve the [*para*/*meta*] ratio to 84:16 with a 54% yield.



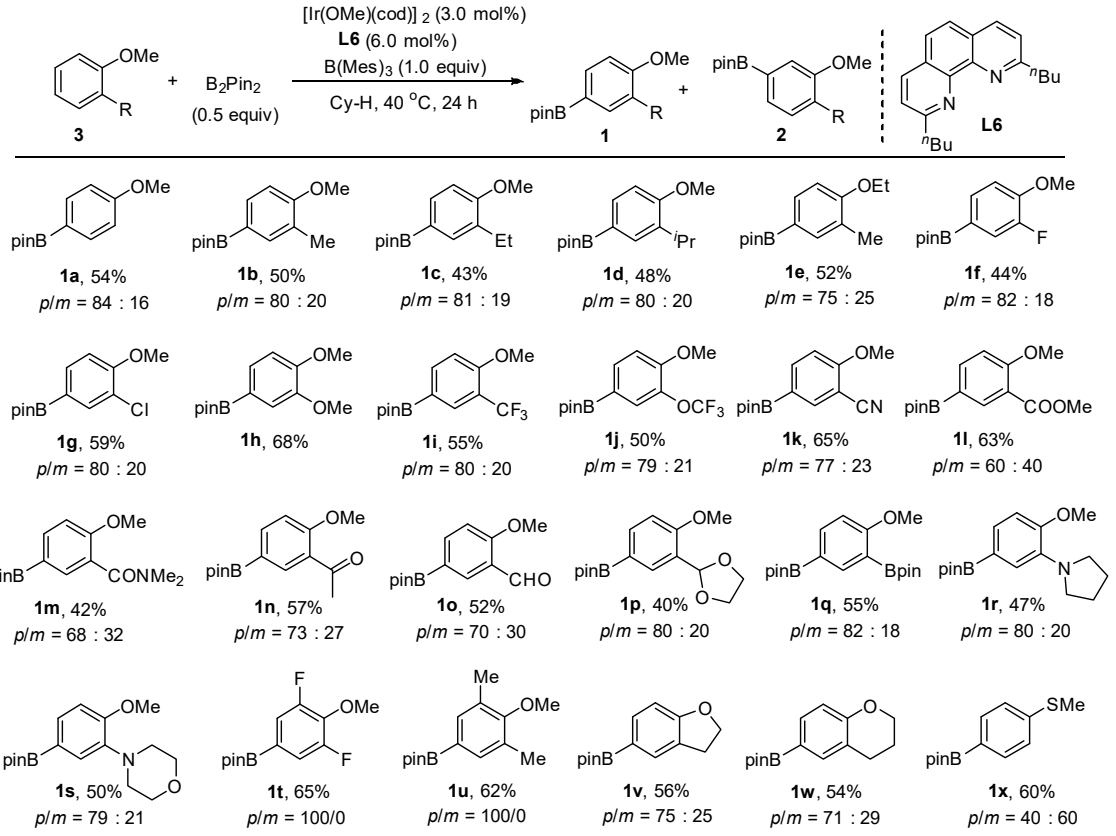

| Entry | LA | Ligand | Yield(%) 1a | Yield(%) 2a | Ratio (para : meta) |
|---|---|---|---|---|---|
| 1 | none | dtbpy | 22% | 58% | 27 : 73 |
| 2 | Al(Me)$_3$ | dtbpy | -- | -- | -- |
| 3 | Al($^i$Bu)$_3$ | dtbpy | 8% | 9% | 50 : 50 |
| 4 | B(OMe)$_3$ | dtbpy | 13% | 21% | 38 : 62 |
| 5 | B(O$^i$Pr)$_3$ | dtbpy | 16% | 11% | 58 : 42 |
| **6** | **B(Mes)$_3$** | **dtbpy** | **39%** | **11%** | **78 : 22** |
| 7 | B($C_6F_5$)$_3$ | dtbpy | 8% | 6% | 57 : 43 |
| 8 | Ar$_F$B-1 | dtbpy | 18% | 33% | 35 : 65 |
| 9 | Ar$_F$B-2 | dtbpy | 10% | 25% | 29 : 71 |
| 10 | Ar$_F$B-3 | dtbpy | -- | -- | -- |
| 11 | B(Mes)$_3$ | L1 | 44% | 10% | 81 : 19 |
| 12 | B(Mes)$_3$ | L2 | 35% | 13% | 72 : 28 |
| 13 | B(Mes)$_3$ | L3 | 34% | 11% | 75 : 25 |
| 14 | B(Mes)$_3$ | L4 | 27% | 12% | 69 : 31 |
| 15 | B(Mes)$_3$ | L5 | 48% | 10% | 82 : 18 |
| **16** | **B(Mes)$_3$** | **L6** | **46%** | **8%** | **84 : 16** |

[a] Yields and selectivities were calculated by crude $^1$H-NMR with 1,1,2,2-tetrachoroethane as internal standard




**Scheme 1.** Investigation of Lewis acid and bipyridyl ligands.

With the optimized reaction conditions in hand, we began to investigate the substrate scope of this *para*-selective borylation (Scheme 2). Substrates **3b**–**3d** bearing alkyl substituents at *ortho*-position gave good [*para*/*meta*] ratios with moderate yields ranging from 43% to 50%. In the case of **3e**, the [*para*/*meta*] ratio slightly decreased. On anisole substrates with halogen atoms at *ortho*-positions **3f**–**3g**, the desired *para*-selective C-H borylation occurred with a good [*para*/*meta*] ratio without inhibition by the functional groups. In addition, the electronic properties of *ortho*-substituents have obviously an impact on *para*-selectivity, which can be seen from the moderate [*para*/*meta*] ratio of substrates **3i**–**3o**, which indicated that *ortho*-substituents (such as trifluoromethyl, trifluoromethoxy, cyano, ester, amide, acetyl, and formyl groups) with electron-withdrawing effects would generate two electron-deficient centers (the *meta*- and *para*-position of the methoxy group), so that the worse *para*-selectivity was obtained. The *para*-selective borylation proceeded smoothly in the case of substrates **3p** to **3s** with heterocyclic substituents at the *ortho*-position. As regards **3t**–**3u**, the reaction is expected to proceed at the *para*-position of the methoxy group with good yields. Moreover, benzofuran **3v** and benzopyran **3w** could also give acceptable [*para*/*meta*] ratios, while with thioanisole as substrate, the reaction still predominantly gave a *meta*-borylated product.

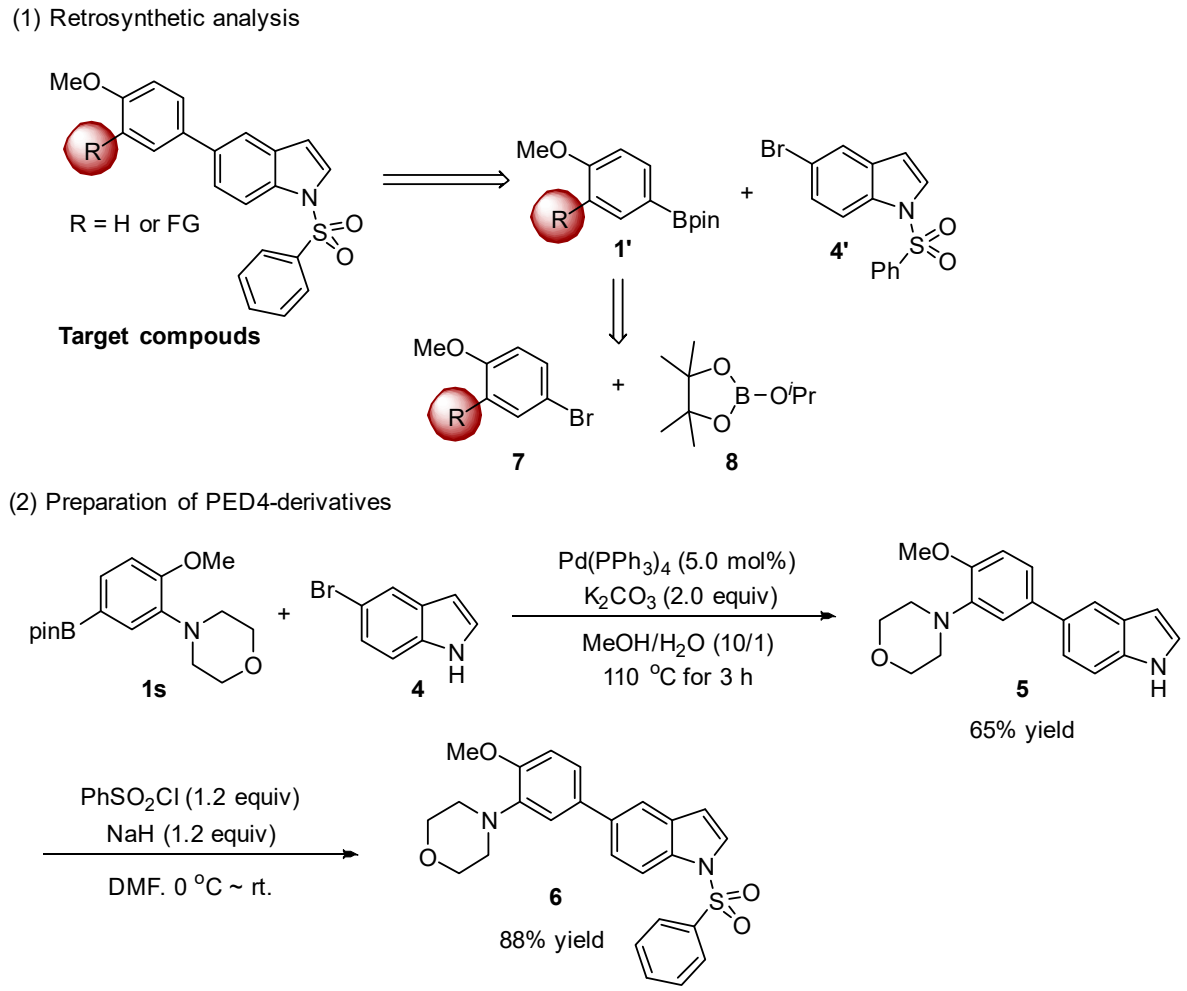



[a] The yield is a total yield of meta and para-products. [b] The [para/meta] ration is based on crude NMR.

**Scheme 2.** Substrates scope of anisole derivatives.

5-(4-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-indole (the target compound; R=H) as a PED4 inhibitor was usually synthesized through Suzuki–Miyaura cross-coupling between *para*-borylated anisole (**1′**) and phenylsulfonyl protected 5-bromoindole (**4′**) (Scheme 3 (1)). The introduction of functional groups on the moiety of *para*-borylated anisole is a useful way to enrich the diversity of PED4 inhibitor compounds. However, substituted *para*-borylated anisole generally needs to be prepared from the corresponding 4-bromoanisole (**7**) and borylate (**8**), which not only increases the synthesis cost but also does not comply

with the principle of atom economy [41]. On the contrary, the improved *para*-borylation of anisoles developed by us could easily synthesize a series of *para*-borylated anisoles with an *ortho*-substituent (**1′**). As a representative example, a derivative of PDE4 inhibitor (**6**) was synthesized from product **1s** with an *ortho*-morpholinyl group through two steps [42,43]. First, a palladium-catalyzed cross-coupling reaction between **1s** and 5-bromoindole (**4**) gave the coupling product (**5**) in a 65% yield without protecting the NH group. Then, the desired product (**6**) was obtained via acylation of **5** with phenylsulfonyl chloride in a yield of 88% (Scheme 3 (2)).




**Scheme 3.** Synthesis of a derivative of a PED4 inhibitor.

According to the initial hypothesis, the *para*-selective C-H borylation can be explained by a mechanism initiated by the formation of a bipyridyl-Ir-Bpin complex **A** with two *cis*-N ligands, three Bpin ligands, and a vacant coordination site (square). As anisole substrates and Lewis acid ($B(Mes)_3$) were added to the reaction system, the vacant coordination site of complex **A** would facilitate the cleavage of the C-H bonds at the *para*-position due to the lower electron density caused by the coordination of Lewis acid with anisole substrate and forming complex **B**. After eliminating a HBpin, the complex **C,** primarily activating the *para*-Ar-H bonds, was formed. Then, the *para*-borylates product was given after reductive elimination, and ligand exchange of complex **D** occurred with $B_2pin_2$ to regenerate complex **A** (Figure 2).

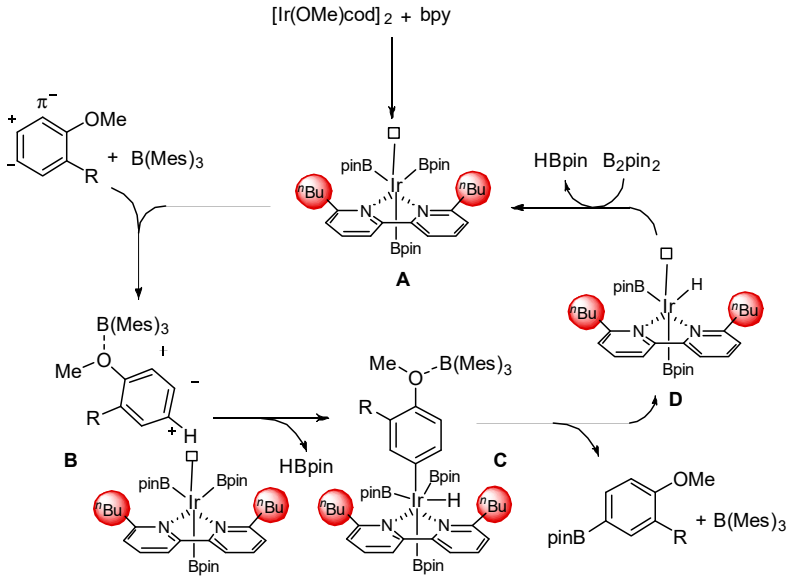



**Figure 2.** Proposed mechanism of the *para*-selective C-H borylation.

## 3. Material and Methods

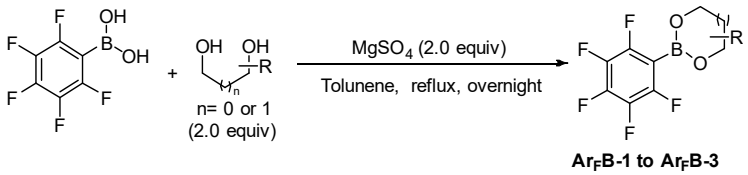
### *3.1. Materials*

All reactions were carried out in a dry and degassed solvent in a glove box. Compounds $B(Mes)_3$, $B_2Pin_2$, and $[Ir(OMe)(cod)]_2$, the most commonly used Ir(I) catalyst in the C-H borylation reaction, were purchased from Aldrich (St. Louis, MO, USA) and Bide Pharmatech (Shanghai, China) and used without further purification unless otherwise noted. Anhydrous solvents were distilled and degassed by refluxing over $CaH_2$ or a combination of sodium/benzophenone. Reactions were monitored by thin-layer chromatography (TLC) and visualized with UV light (254 nm). The *para*-borylated product was separated by preparative Gel Permeation Chromatography (GPC-JAI-LC9110NEXT) using chloroform (HPLC grade) as eluent. NMR spectra were recorded on 400 MHz (400 MHz for $^1$H NMR, 100 MHz for $^{13}$C NMR) and 800 MHz (800 MHz for $^1$H NMR, 201 MHz for $^{13}$C NMR) spectrometers. Proton and carbon chemical shifts are reported relative to the solvent used as an internal reference. The boron-bearing carbon atom was not observed due to quadrupolar relaxation. ESI-MS spectra were measured on a spectrometer for HRMS.

### *3.2. Methods*

#### 3.2.1. Preparation of Lewis Acid (Pentafluorophenyl Borate $Ar_F$B-1 to $Ar_F$B-3) [44]

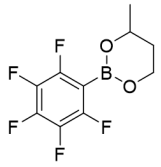
Pentafluorophenyl boronic acid (1.00 g, 4.72 mmol), substituted diol (2.0 equiv.), and $MgSO_4$ (1.14 g, 9.44 mmol) were dissolved in toluene (40 mL) in a 100 mL round-bottom flask equipped with a magnetic stir bar, and the mixture was refluxed for 12 h. After removal of the solvent, the crude product was purified by column chromatography on silica gel (petroleum/ethyl acetate = 10:1).




4-Methyl-2-(pentafluorophenyl)-1,3,2-dioxaborinane ($Ar_F$B-1)

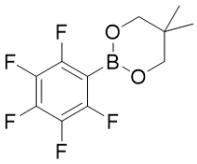
Yield: 0.98 g, 78%; $^1$H NMR (800 MHz, $CDCl_3$) 4.37–4.34 (m, $^1$H), 4.24–4.19 (m, 1H), 4.18–4.14 (m, 1H), 2.10–2.08 (m, 1H), 1.90–1.84 (m, 1H), 1.36 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 149.1 (d, $J$ = 247 Hz), 142.7 (d, $J$ = 249 Hz), 137.8 (d, $J$ = 255 Hz), 68.9,

62.0, 34.0, 22.5; IR (KBr, ν/cm$^{-1}$) 1507, 1404, 1320, 1283, 1068, 954, 763, 667; HRMS (ESI$^+$) Calcd for $C_{10}H_9BF_5O2^+$ ([M + H]$^+$) 267.0610, found 267.0598.



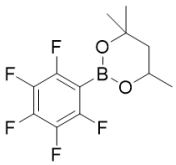
5,5-Dimethyl-2-(pentafluorophenyl)-1,3,2-dioxaborinane ($Ar_F$B-2)

Yield: 0.91 g, 70%; $^1$H NMR (800 MHz, $CDCl_3$) δ 3.81 (s, 4H), 1.07 (s, 6H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 149.1 (d, *J* = 243 Hz), 142.8 (d, *J* = 253 Hz), 137.8 (d, *J* = 251 Hz), 72.8, 31.9, 21.6; IR (KBr, ν/cm$^{-1}$) 1651, 1508, 1429, 1321, 1259, 1045, 988, 969, 809, 691; HRMS (ESI$^+$) Calcd for $C_{11}H_{11}BF_5O_2^+$ ([M + H]$^+$) 281.0767, found 281.0762.



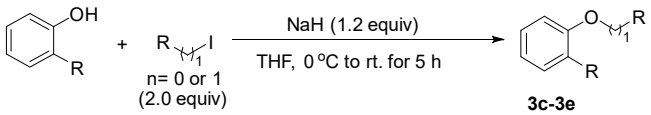
4,4,6-Trimethyl-2-(pentafluorophenyl)-1,3,2-dioxaborinane ($Ar_F$B-3)

Yield: 0.80 g, 62%; $^1$H NMR (800 MHz, $CDCl_3$) δ 4.43–4.39 (m, 1H), 1.93 (dd, *J* = 14.1, 3.0 Hz, 1H), 1.71–1.66 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 148.9 (d, *J* = 245 Hz), 142.5 (d, *J* = 255 Hz), 137.8 (d, *J* = 251 Hz), 73.0, 66.4, 45.9, 30.8, 28.0, 22.8; IR (KBr, ν/cm$^{-1}$) 1520, 1482, 1408, 1315, 1238, 1160, 975, 926, 891, 767, 720; HRMS (ESI$^+$) Calcd for $C_{12}H_{13}BF_5NO_2^+$ ([M + H]$^+$) 295.0923, found 295.0918.



3.2.2. Preparation of 2-alkyl Anisole Derivatives (**3c** to **3e**) [45]

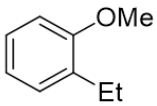
To a solution of 2-alkyl phenol (5.0 mmol) in anhydrous THF (20 mL), sodium hydride (1.2 equiv.) was slowly added at 0 °C. After stirring for 1.5 h at the same temperature, 1-iodoalkane (2.0 equiv.) was added dropwise. The mixture was slowly warmed to room temperature for 5 h. After that, the reaction was quenched by adding a saturated $NH_4Cl$ aqueous solution (20 mL). The organic layer was separated and dried with $Na_2SO_4$. The mixture was filtered, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel (petroleum/ethyl acetate = 15:1).




1-Ethyl-2-methoxylbenzene (**3c**)

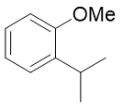
Yield: 0.58 g, 85%; $^1$H NMR (800 MHz, $CDCl_3$) δ 7.25–7.22 (m, 2H), 7.00–6.95 (m, 1H), 6.93– 6.89 (m, 1H), 3.89 (s, 3H), 2.76–2.71 (m, 2H), 1.30–1.27 (m, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 157.3, 132.5, 128.9, 126.7, 120.4, 110.1, 55.1, 23.2, 14.1; IR (KBr, ν/cm$^{-1}$) 1683, 1514,

1457, 1376, 1204, 838, 796, 724; HRMS (ESI$^+$) Calcd for $C_9H_{13}O^+$ ([M + H]$^+$) 137.0961, found 137.0946.



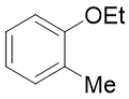

1-Isopropyl-2-methoxylbenzene (**3d**)

Yield: 0.55 g, 73%; $^1$H NMR (800 MHz, $CDCl_3$) δ 7.29–7.26 (m, 1H), 7.25–7.21 (m, 1H), 7.00–6.97 (m, 1H), 6.92–6.88 (m, 1H), 3.87 (s, 3H), 3.43–3.35 (m, 1H), 1.28 (d, *J* = 6.2, 6H); $^{13}$C NMR (201 MHz, $CDCl_3$) 156.7, 136.9, 126.5, 125.9, 120.5, 110.3, 55.3, 26.6, 22.7; IR (KBr, ν/cm$^{-1}$) 1704, 1651, 1379, 1190, 815, 788, 755; HRMS (ESI$^+$) Calcd for $C_{10}H_{15}O^+$ ([M + H]$^+$) 151.1117, found 151.1121.



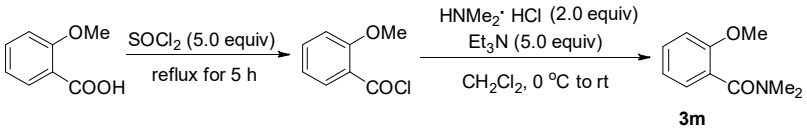

1-Methyl-2-ethoxylbenzene (**3e**)

Yield: 0.44 g, 64%; $^1$H NMR (800 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 6.96–6.92 (m, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 4.17–4.08 (m, 2H), 2.36 (s, 3H), 1.55–1.51 (m, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 157.1, 130.5, 126.7, 126.7, 120.1, 110.9, 63.3, 16.2, 14.9; IR (KBr, ν/cm$^{-1}$) 1778, 1490, 1389, 1138, 854, 760, 697, 598; HRMS (ESI$^+$) Calcd for $C_9H_{13}O^+$ ([M + H]$^+$) 137.0961, found 137.0958.




3.2.3. Preparation of 2-Methoxy-N,N-Dimethylbenzamide (**3m**) [46]

2-Methoxybenzoic acid (5.00 g, 32.9 mmol) was added in a 100 mL round-bottom flask equipped with a reflux condenser. Thionyl chloride (11.9 mL, 165 mmol) and five drops of DMF were added, and the mixture was refluxed for 4 h. The reaction was allowed to cool to room temperature, and the excess of $SOCl_2$ was carefully removed under vacuum. The crude acid chloride was dissolved in $CH_2Cl_2$ (80 mL), and $Et_3N$ (23.0 mL, 165 mmol) was added. The mixture was cooled to 0 °C in an ice-water bath, and dimethylamine hydrochloride (5.40 g, 65.8 mmol) was added. The reaction was stirred for 19 h at room temperature, concentrated, and purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 3:1).



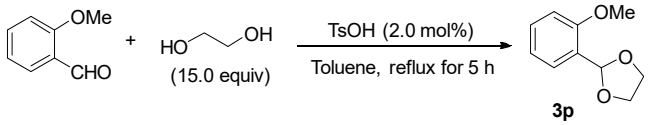

**3m**

Yield: 3.24 g, 55%; H NMR (800 MHz, $CDCl_3$) δ 7.33–7.30 (m, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.09 (s, 3H), 2.82 (s, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 169.3, 155.2, 130.2, 127.8, 126.2, 120.8, 110.8, 55.5, 38.1, 34.6; IR (KBr, ν/cm$^{-1}$) 1622, 1471, 1395, 1246, 1075, 1021, 853, 755, 596; HRMS (ESI$^+$) Calcd for $C_{10}H_{14}NO_2^+$ ([M + H]$^+$) 180.1019, found 180.1017.

3.2.4. Preparation of 2-(2-Methoxylphenyl)-1,3-dioxolane (**3p**) [47]

In a 100 mL round-bottom flask equipped with a reflux condenser, *o*-Methoxy-benzaldehyde (3.00 g, 22.0 mmol) and ethane-1,2-diol (18.2 mL, 330 mmol) were dissolved in toluene

(20 mL). TsOH (69.6 mg, 0.441 mmol) was added at room temperature and allowed the reaction mixture to stir at 115 °C for 5 h. After cooling to room temperature, the solvent was removed under vacuum, and the mixture was extracted with ethyl acetate (20 mL × 2). The organic layer was separated and dried over $Na_2SO_4$, filtered, and the solvent removed in vacuo. The crude product was purified by column chromatography on silica gel (petroleum/ethyl acetate = 5:1).

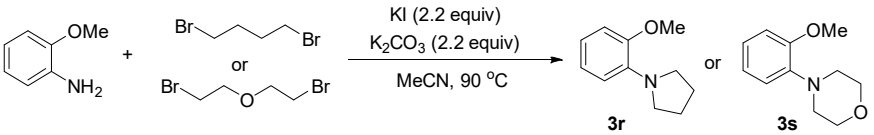



**3p**

Yield: 1.94 g, 49%; $^1$H NMR (800 MHz, $CDCl_3$) 7.55 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.18 (s, 1H), 4.16–4.12 (m, 2H), 4.06–4.02 (m, 2H), 3.87 (s, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 157.6, 130.2, 126.6, 125.7, 120.3, 110.6, 99.2, 65.2, 55.5; IR (KBr, ν/cm$^{-1}$) 1685, 1598, 1484, 1466, 1394, 1285, 1244, 1161, 1021, 834, 756, 647; HRMS (ESI$^+$) Calcd for $C_{10}H_{13}O_3^+$ ([M + H]$^+$) 181.0859, found 181.0865.

3.2.5. Preparation of 2-heterocycle Substituted Anisole (**3r** and **3s**) [48]

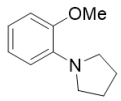
In a 100 mL round-bottom flask equipped with a reflux condenser, a mixture of *o*-anisidine (5.00 g, 40.6 mmol), 1,4-dibromobutane (10.5 g, 48.7 mmol), bis(2-bromoethyl)-ether (11.3 g, 48.7 mmol), potassium iodide (14.8 g, 89.3 mmol), and potassium carbonate (14.8g, 89.3 mmol) in acetonitrile (100 mL) was heated at 90 °C for 12 h. Then the reaction mixture was cooled to room temperature and filtered. The filtrate was extracted with dichloromethane (2 × 20.0 mL). The organic layer was separated and dried, and $Na_2SO_4$ was concentrated in vacuo. The crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to afford an oily product.




**3r** **3s**

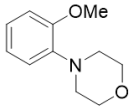
1-(2-methoxyphenyl)pyrrolidine (**3r**)

Yield: 3.0 g, 42%; $^1$H NMR (800 MHz, $CDCl_3$) 6.93 (t, *J* = 7.3 Hz, 1H), 6.90–6.86 (m, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.87 (s, 3H), 3.36–3.30 (m, 4H), 1.99–1.96 (m, 4H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 150.4, 139.8, 121.0, 119.5, 115.3, 111.5, 55.4, 50.3, 24.6; IR (KBr, ν/cm$^{-1}$) 1595, 1488, 1454, 1330, 1229, 1147, 1027, 956, 735; HRMS (ESI$^+$) Calcd for $C_{11}H_{16}NO^+$ ([M + H]$^+$) 178.1226, found 178.1213.



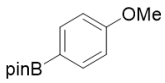

4-(2-methoxyphenyl)morpholine (**3s**)

Yield: 2.80 g, 35%; $^1$H NMR (800 MHz, $CDCl_3$) δ 7.04–7.01 (m, 1H), 6.94 (d, *J* = 4.6 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 3.90 (t, *J* = 4.4 Hz, 4H), 3.87 (s, 3H), 3.07 (t, *J* = 4.6 Hz, 4H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 152.2, 141.0, 123.1, 121.0, 117.9, 111.2, 67.2, 55.3, 51.1; IR (KBr, ν/cm$^{-1}$) 1607, 1506, 1443, 1225, 1168, 1047, 967, 874, 794, 746; HRMS (ESI$^+$) Calcd for $C_{11}H_{16}NO_2^+$ ([M + H]$^+$) 194.1176, found 194.1170.



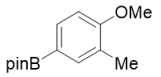

3.2.6. Preparation of Para-Selective C-H Borylation of Anisole Derivatives (**1a** to **1x**)

In a glove box, an oven-dried 10 mL sealed tube with a magnetic stir bar was charged with $[Ir(OMe)(cod)]_2$ (3.0 mol%), **L6** (6.0 mol%), $B_2Pin_2$ (0.5 equiv.), and cyclohexane (1.0 mL). The seal tube was moved to a preheated metal heating block (50 °C) for 30 min, after which the color of the mixture turned deep green. Upon cooling to room temperature, anisole substrate **3** (0.5 mmol), $B(Mes)_3$ (1.0 equiv), and cyclohexane (1.0 mL) were added sequentially. The reaction vessel was removed from the glovebox and stirred at 40 °C. After 24 h, the reaction mixture was cooled to room temperature, volatiles were removed under reduced pressure, and the yield and the regio-isomer ratio were checked by $^1$H NMR using 1,1,2,2-tetrachloroethane as an internal standard. The *para*-borylated product was separated by GPC.



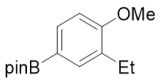

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**)

The mixture of product (63 mg, 54% yield, *para/meta* = 84:16); *para*-borylated product **1a** was obtained by further purification of the crude mixture by GPC (53 mg); $^1$H NMR (800 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 162.1, 136.5, 113.3, 83.5, 55.0, 24.8; IR (KBr, ν/cm$^{-1}$) 1419, 1354, 1313, 1143, 1072, 963, 875, 705; HRMS (ESI$^+$) Calcd for $C_{13}H_{20}BO_3^+$ ([M + H]$^+$) 235.1500, found 235.1490.



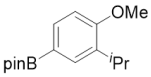

2-(4-methoxy-3-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1b**)

The mixture of product (62 mg, 50% yield, *para*/*meta* = 80:20); *para*-borylated product **1b** was obtained by further purification of the crude mixture by GPC (49 mg); $^1$H NMR (800 MHz, $CDCl_3$) δ 7.67 (d, *J* = 9.9 Hz, 1H), 7.62 (s, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 2.24 (s, 3H), 1.35 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 160.4, 137.1, 134.2, 125.8, 109.4, 83.4, 55.1, 24.8, 15.9; IR (KBr, ν/cm$^{-1}$) 1605, 1406, 1353, 1248, 1134, 1031, 964, 854, 669; HRMS (ESI$^+$) Calcd for $C_{14}H_{22}BO_3^+$ ([M + H]$^+$) 249.1657, found 249.1653.



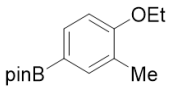

2-(4-methoxy-3-ethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1c**)

The mixture of product (57 mg, 43% yield, *para*/*meta* = 81:19); *para*-borylated product **1c** was obtained by further purification of the crude mixture by GPC (46 mg); $^1$H NMR (800 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.4 Hz, 1H), 7.60 (s, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 3.85 (s, 3H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.34 (s, 12H), 1.19 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 160.05, 135.61, 134.28, 131.89, 109.47, 83.45, 55.14, 24.83, 23.30, 14.28; IR (KBr, ν/cm$^{-1}$) 1591, 1352, 963, 863, 791, 702, 667; HRMS (ESI$^+$) Calcd for $C_{15}H_{24}BO_3^+$ ([M + H]$^+$) 263.1813, found 263.1804.



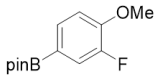

2-(4-methoxy-3-isopropylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1d**)

The mixture of product (66 mg, 48% yield, *para*/*meta* = 80:20); *para*-borylated product **1d** was obtained by further purification of the crude mixture by GPC (53 mg); $^{1}$H NMR (800 MHz, $CDCl_3$) δ 7.66–7.64 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.30 (p, *J* = 6.9 Hz, 1H), 1.34 (s, 12H), 1.23 (d, *J* = 6.9 Hz, 6H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 159.5, 136.1, 134.1, 132.6, 109.6, 83.4, 55.2, 26.9, 24.8, 22.6; IR (KBr, ν/$cm^{-1}$) 1676, 1501, 1438, 1256, 1071, 947, 805, 720, 658; HRMS ($ESI^+$) Calcd for $C_{16}H_{26}BO_3^+$ ($[M + H]^+$) 277.1970, found 277.1980.



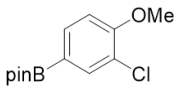

2-(4-ethoxy-3-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1e**)

The mixture of product (68 mg, 52% yield, *para*/*meta* = 75:25); *para*-borylated product **1e** was obtained by further purification of the crude mixture by GPC (51 mg); $^{1}$H NMR (800 MHz, $CDCl_3$) δ 7.64 (d, *J* = 9.9 Hz, 1H), 7.61 (s, 1H), 6.81 (d, *J* = 5.7 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 2.23 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H), 1.34 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 159.8, 137.1, 134.1, 126.0, 110.1, 83.4, 77.2, 76.8, 63.2, 24.8, 16.0, 14.8; IR (KBr, ν/$cm^{-1}$) 1605, 1353, 1285, 1247, 1133, 1046, 982, 854, 669; HRMS ($ESI^+$) Calcd for $C_{15}H_{24}BO_3^+$ ($[M + H]^+$) 263.1813, found 263.1809.



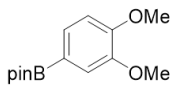

2-(3-fluoro-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1f**)

The mixture of product (55 mg, 44% yield, *para*/*meta* = 82:18); *para*-borylated product **1f** was obtained by further purification of the crude mixture by GPC (45 mg); $^{1}$H NMR (800 MHz, $CDCl_3$) δ 7.53 (d, *J* = 9.1 Hz, 1H), 7.49 (d, *J* = 11.8 Hz, 1H), 6.94 (t, *J* = 8.1 Hz, 1H), 3.90 (s, 3H), 1.33 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 152.6, 151.4, 150.2, 150.2, 131.5, 131.4, 121.7, 121.6, 112.5, 83.8, 56.0, 24.8; IR (KBr, ν/$cm^{-1}$) 1615, 1422, 1354, 1292, 1265, 1130, 967, 853, 758, 692; HRMS ($ESI^+$) Calcd for $C_{13}H_{19}BFO_3^+$ ($[M + H]^+$) 253.1406, found 253.1395.




2-(3-chloro-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1g**)

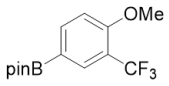
The mixture of product (79 mg, 59% yield, *para*/*meta* = 80:20); *para*-borylated product (**1g**) was obtained by further purification of the crude mixture by GPC (63 mg); $^{1}$H NMR (800 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 3.92 (s, 3H), 1.33 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 157.3, 136.5, 134.7, 122.1, 111.3, 83.9, 56.0, 24.8; IR (KBr, ν/$cm^{-1}$) 1599, 1406, 1351, 1261, 1138, 1063, 963, 872, 818, 701, 669; HRMS ($ESI^+$) Calcd for $C_{13}H_{19}BClO^+$ ($[M + H]^+$) 253.1406, found 253.1400.




2-(3,4-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1h**)

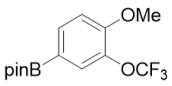
The mixture of products (89 mg, 68% yield, *para*/*meta* = 100/0); $^{1}$H NMR (800 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 3.92 (s, 3H), 3.90 (s,

3H), 1.33 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 151.58, 148.29, 128.51, 116.50, 110.43, 83.60, 55.80, 55.69, 24.81; IR (KBr, ν/cm$^{-1}$) 1408, 1352, 1296, 1220, 1027, 968, 855, 755, 682; HRMS (ESI$^+$) Calcd for $C_{14}H_{22}BO_4^+$ ([M + H]$^+$) 265.1606, found 265.1613.



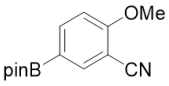

2-(4-methoxy-3-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1i**)

The mixture of product (83 mg, 55% yield, *para*/*meta* = 80:20) and *para*-borylated product (**1i**) was obtained by further purification of the crude mixture by GPC (67 mg); $^1$H NMR (800 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 1H), 7.64 (s, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 3.90 (s, 3H), 1.33 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 154.5, 134.9, 128.9, 121.9 (q, *J* = 257 Hz), 112.1, 83.9, 55.9, 24.8; IR (KBr, ν/cm$^{-1}$) 1615, 1361, 1307, 1258, 1169, 1053, 824, 685; HRMS (ESI$^+$) Calcd for $C_{14}H_{19}BF_3O_3^+$ ([M + H]$^+$) 303.1374, found 303.1369.




2-(4-methoxy-3-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1j**)

The mixture of product (79 mg, 50% yield, *para*/*meta* = 79:21); *para*-borylated product **1j** was obtained by further purification of the crude mixture by GPC (62 mg); $^1$H NMR (800 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 1H), 7.64 (s, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 1.33 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 154.5, 137.7, 134.9, 121.3 (q, *J* = 257 Hz), 112.07, 83.9, 55.9, 24.8; IR (KBr, ν/cm$^{-1}$) 1609, 1418, 1328, 1245, 1132, 1028, 969, 851, 818, 699; HRMS (ESI$^+$) Calcd for $C_{14}H_{19}BF_3O_4^+$ ([M + H]$^+$) 319.1323, found 319.1320.




2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (**1k**)

The mixture of product (84 mg, 65% yield, *para*/*meta* = 77:23); *para*-borylated product **1k** was obtained by further purification of the crude mixture by GPC (65 mg); $^1$H NMR (800 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 3H), 1.33 (s, 12H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ 163.2, 140.9, 140.6, 116.4, 110.5, 101.6, 84.2, 56.0, 24.8; IR (KBr, ν/cm$^{-1}$) 1602, 1507, 1402, 1381, 1261, 1127, 956, 850, 739, 675; HRMS (ESI$^+$) Calcd for $C_{14}H_{19}BNO_3^+$ ([M + H]$^+$) 260.1453, found 260.1448.

The NMR data of *para*-borylated products **1l** to **1x** are shown in the Supplementary Materials.

### 3.2.7. Preparation of PED4 Inhibitor [41]

In a 50 mL two-necked flask equipped with a reflux condenser, **1s** (500 mg, 1.56 mmol), 5-bromoindole (**4**, 456 mg, 2.34 mmol), $Pd(PPh_3)_4$ (90.1 mg, 0.078 mmol, 5.0 mol%), $K_2CO_3$ (431 mg, 3.12 mmol, 2.0 equiv.), MeOH (30 mL), and $H_2O$ (3.0 mL) were added. Then, the mixture was heated at 100 °C for 3 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (2 × 20.0 mL). The organic layer was separated and dried over $Na_2SO_4$. After filtration, the solvent was removed under vacuum, and the residue was directly used in the next step without purification. Compound **5** (200 mg, 0.649 mmol) was dissolved in 20 mL of anhydrous THF and cooled to 0 °C. NaH (29.5 mg, 0.779 mmol) was slowly added to the solution, and the reaction mixture was stirred at the same temperature for 1 h. Then, $PhSO_2Cl$ (172 mg, 0.974 mmol, 1.5 equiv.) was dropped in the mixture and stirred at room temperature for 8 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (PE/EtOAc = 5:1). Yield: 256 mg, 88%,

$^1$H NMR (800 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.67 (s, 1H), 7.58 (s, 1H), 7.56–7.49 (m, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.21–7.23 (m, 1H), 7.13 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 3.96–3.89 (m, 7H), 3.20–3.10 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.6, 141.3, 138.2, 136.8, 134.2, 133.9, 133.8, 131.3, 129.3, 126.8, 126.7, 124.1, 121.8, 119.4, 117.2, 113.6, 111.5, 109.4, 67.2, 55.5, 51.2; IR (KBr, ν/cm$^{-1}$) 2926, 2765, 1880, 1653, 1580, 1421, 1345, 1021, 967, 855, 791; HRMS (ESI$^+$) Calcd for $C_{25}H_{25}N_2O_4S^+$ $([M + H])^+$ 449.1503, found 449.1512.

## 4. Conclusions

In summary, we developed an improved *para*-selective C-H borylation of anisole derivatives. The regioselectivity was probably controlled by the change in electron density on the aromatic ring when a Lewis acid was coordinated with anisole. Most substrates could give an acceptable [*para*/*meta*] ratio. In addition, a bioactive molecule was synthesized from the *para*-borylated product. Investigations into the diversified regioselectivity of aromatic compounds are ongoing in our laboratory.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal13081193/s1, screening tables, $^1$H and $^{13}$C NMR spectra (**1l** to **1x**), more detailed materials, and methods. Table S1: Reaction optimization for the amount of $B(Mes)_3$. Table S2: Reaction optimization for different solvents.

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**Data Availability Statement:** The data presented in this study are available on request from the corresponding author.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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