Iridium-Catalyzed Direct Borylation of Five-Membered Heteroarenes by Bis(pinacolato)diboron: Regioselective, Stoichiometric, and Room Temperature Reactions

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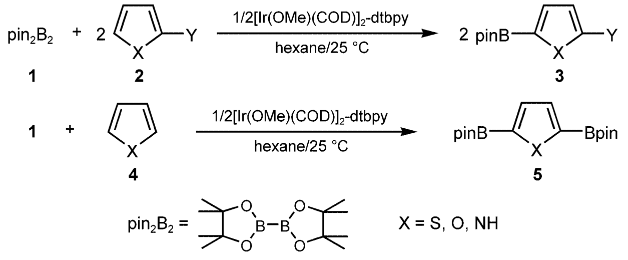
Abstract: An iridium(I) complex generated from 1/2[Ir(OMe)(COD)]$_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine catalyzed the direct borylation of 2-substituted thiophenes, furans and pyrroles in stoichiometric amounts relative to bis(pinacolato)diboron in hexane at room temperature. The heteroarylboronates from regioselective C–H activation at the 5-position were formed in high yields. Similar borylations of unsubstituted heteroarenes with an equimolar amount of the diboron regioselectively provided 2,5-bis(boryl)heteroarenes.

Keywords: boron; C–H activation; heterocycles; homogeneous catalysis; iridium

Heteroarylboronic acids and esters are useful intermediates for the synthesis of natural products, medicinal compounds and functional materials.[1] Traditional methods for their synthesis are based on the reaction of trialkyl borates with heteroarylmagnesium or -lithium reagents.[2] Pd-catalyzed cross-coupling of heteroaryl halides or triflates with tetra(alkoxo)diborons[3] or di(alkoxo)boranes[4] provides a milder alternative to prepare heteroarylboronic acid derivatives. However, both methods require a heteroaryl halide reactant, which generates the magnesium or lithium reagents or the reactive palladium intermediates. Moreover, these processes generate halogen by-products and display limited functional group compatibility.

C–H bond functionalization catalyzed by transition metal complexes has attracted considerable attention recently.[5] Direct conversion of heteroarene substrates to heteroarylboronates by C–H bond functionalization with bis(pinacolato)diboron (pin$_2$B$_2$, pin = Me$_4$C$_2$O$_2$) or pinacolborane (pinBH) as reagent would eliminate several of the limitations mentioned above. Although a number of transition metal complexes, such as Cp*Ir(PMe$_3$)(H)(Bpin),[6] Cp*Re(CO)$_3$,[7] Cp*Rh(η^4-C$_6$Me$_6$),[8] RhCl{P(*i*-Pr)$_3$}$_2$(N$_2$)[9] and [Cp*RhCl$_2$]$_2$,[9] or those generated *in situ* from Ir(η^5-C$_9$H$_7$)(COD) and either dppe or dmpe[10] or that generated *in situ* from 1/2[IrCl(COD)]$_2$ and 2,2′-bipyridine (bpy),[11] catalyze the direct borylation of arenes, an extension of this protocol to heteroarenes is less developed. Recently, the direct borylation of heteroarenes by pin$_2$B$_2$ catalyzed by the combination of 1/2[IrCl(COD)]$_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) at 80 °C in octane solutions containing excess of heteroarene has been reported.[12] Now, we report a more efficient borylation of five-membered heteroarenes (**2** or **4**) by pin$_2$B$_2$ (**1**) catalyzed by the combination of 1/2[Ir(OMe)(COD)]$_2$ with dtbpy. The increased efficiency of this catalyst generated from the methoxide complex allows the formation of 5-boryl- (**3**) or 2,5-bis(boryl)heteroarenes (**5**) in high yields at room temperature from equimolar equivalents of diboron reagent and heteroarene substrate (Scheme 1).

Previous studies on the direct borylation of five-membered heteroarenes reported by Smith's group[8c] and by us[12] are summarized briefly in Scheme 2. The electronegative heteroatom causes the C–H bonds at the α-positions to be active toward oxidative addition and reactions to occur regioselectively at the α-positions.[13] Regioselectivities are also controlled by steric effects of substituents on heteroarenes. The reaction of 1-triisopropylsilylpyrrole with pinBH or pin$_2$B$_2$ produces only a 3-borylated product.[8c,12] Although a mixture of 2-borylated and 2,5-diborylated products is formed



Scheme 1. Stoichiometric direct borylation of five-membered heteroarenes at room temperature.

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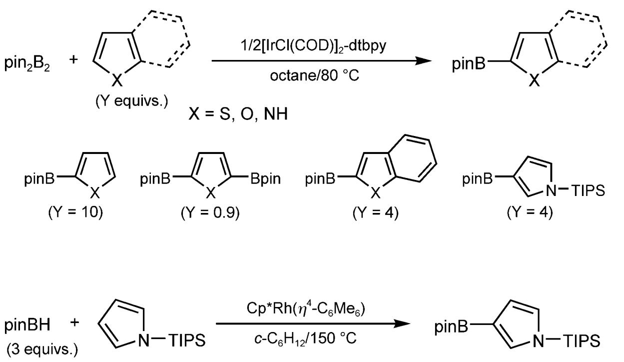


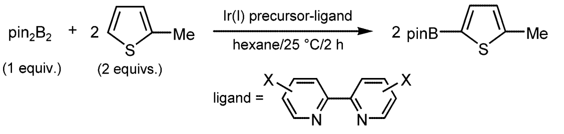
Scheme 2. Overview of direct borylation of five-membered heteroarenes.

from unsubstituted heteroarenes, both 2-borylated and 2,5-diborylated products are selectively obtained by reactions with the appropriate ratio of substrate and pin_2B_2. The borylation of 2.5 equivs. of thiophene results in a mixture of 2-boryl- and 2,5-bis(boryl)thiophene in a ratio of 56 : 44; however, the ratio is improved to 83 : 17 and 1 : 99 when using 10 equivs. and 0.9 equivs. of thiophene, respectively.[12] The selective monoborylation of benzo-fused substrates occurs at the 2-position because one of the α-positions is blocked, and the C–H bond at the α-position of the heteroaromatic ring is more reactive than the aromatic C–H bonds.[12] These high regioselectivities under mild reaction conditions would create a highly efficient method for the preparation of heteroarylboronates if a stoichiometric ratio of heteroarene to boron reagent could be used instead of the excess amounts of heteroarene used to date.

To achieve the borylation of heteroarenes **2** or **4** at room temperature with equimolar equivalents of diboron reagent and heteroarene, several combinations of an Ir(I) precursor (0.03 mmol/Ir) and a ligand (0.03 mmol) were investigated as catalyst for the reaction of 2-methylthiophene (2.0 mmol) with pin_2B_2 **1** (1.0 mmol) in hexane (6 mL) (Table 1). Among the catalysts examined, the combination of $1/2[Ir(OMe)(COD)]_2$ and dtbpy, which exhibited high activity toward the direct borylation of arenes by **1** at room temperature,[14] catalyzed the borylation of 2-methylthiophene at room temperature. Isomerically pure 5-boryl-2-methylthiophene was formed in 95% yield based on boron atom in **1** (Entry 1). In contrast, catalytic amounts of the analogous Ir(I) chloride complex or the similar cationic Ir(I) complex in combination with dtbpy formed no borylated product (Entries 2 and 3). The high catalyst efficiency of the methoxide complex can be attributed to the more facile formation of a tris(boryl)Ir(III) intermediate,[10,11,15] which is reactive toward C–H activation and functionalization of aromatic C–H bonds at room temperature.[14]

2,2′-Bipyridine (bpy) and derivatives of this structure were particularly effective as ligand for Ir (Entry 4). The catalysts bearing dtbpy, bpy, 3,3′-di-Me-bpy, 4,4′-di-Me-bpy and 5,5′-di-Me-bpy displayed similar reactivity (Entries 1, 5–8), but the catalyst bearing 6,6′-di-Me-bpy led to no reaction (Entry 9). This result indicated the importance of steric effects at the Ir center. Reactions catalyzed by complexes containing electron-rich derivatives of bpy generated more active catalysts than those containing electron-poor derivatives (Entries 10–13).

Table 1. Reaction conditions for 2-methylthiophene.[a]



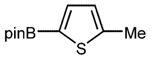
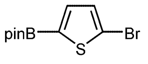
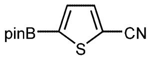
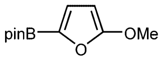
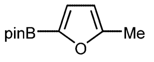
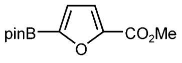
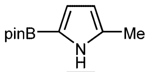
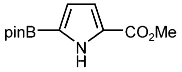
Entry	Ir(I) Precursor	Ligand	Yield [%][b]
1	$1/2[Ir(OMe)(COD)]_2$	dtbpy	95
2	$1/2[IrCl(COD)]_2$	dtbpy	0
3	$[Ir(COD)_2]BF_4$	dtbpy	0
4	$1/2[Ir(OMe)(COD)]_2$	none	0
5	$1/2[Ir(OMe)(COD)]_2$	bpy	85
6	$1/2[Ir(OMe)(COD)]_2$	3,3'-di-Me-bpy	61
7	$1/2[Ir(OMe)(COD)]_2$	4,4'-di-Me-bpy	87
8	$1/2[Ir(OMe)(COD)]_2$	5,5'-di-Me-bpy	86
9	$1/2[Ir(OMe)(COD)]_2$	6,6'-di-Me-bpy	0
10	$1/2[Ir(OMe)(COD)]_2$	4,4'-di-NMe_2-bpy	91
11	$1/2[Ir(OMe)(COD)]_2$	4,4'-di-OMe-bpy	90
12	$1/2[Ir(OMe)(COD)]_2$	4,4'-di-Cl-bpy	35
13	$1/2[Ir(OMe)(COD)]_2$	4,4'-di-NO_2-bpy	0

[a] All reactions were carried out at 25 °C for 2 h by using pin_2B_2 (1.0 mmol), 2-methylthiophene (2.0 mmol), Ir(I) precursor (0.03 mmol/Ir), ligand (0.03 mmol), and hexane (6 mL).

[b] GC yields based on boron atom in pin_2B_2.

Representative results of stoichiometric C–H borylation of 2-substituted, five-membered heteroarenes **2** by pin_2B_2 **1** catalyzed by the combination of $1/2[Ir(OMe)(COD)]_2$ and dtbpy at room temperature in hexane are summarized in Table 2. In addition to thiophene derivatives (Entries 1–3), furan (Entries 4–6) and pyrrole (Entries 7 and 8) derivatives smoothly underwent borylation to form the corresponding borylfurans and -pyrroles **3** in high yields. In all cases, the borylation occurred exclusively at the 5-position.[13] The reaction was suitable for **2** possessing a variety of functional groups, such as MeO, Br, CO_2Me and CN, as well as for substrates with potentially more reactive benzylic C–H bonds.[9,16] Although some transition metal complexes exhibit high reactivity toward oxidative addition of Ar–Br bonds,[17] 2-bromothiophene underwent borylation at the C–H bond in the 5-position (Entry 2). The borylation of 2-thiophenecarbonitrile required longer times than borylation of other substrates, and the borylation product was formed in a moderate yield (Entry 3). Perhaps, coordination of the cyano group to the Ir center retards formation of an unsaturated Ir species that undergoes oxidative addition of **1** or **2**.

Table 2. Stoichiometric direct borylation of 2-substituted five-membered heteroarenes at room temperature.[a]

Entry	Product **3**[b]	Time [h]	Yield [%][c]
1		2	95
2		2	91
3		24	60
4		2	90
5		2	85
6		2	80
7		1	96
8		1	99

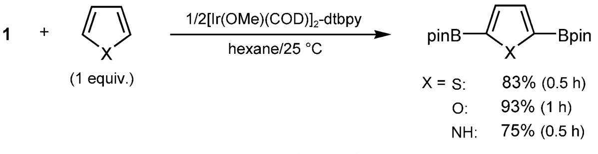
[a] All reactions were carried out at 25 °C by using pin_2B_2 (1.0 mmol), heteroarene (2.0 mmol), $[Ir(OMe)(COD)]_2$ (0.015 mmol), dtbpy (0.03 mmol), and hexane (6 mL).

[b] Isomeric purity over 98% was determined by ^1H NMR and GC.

[c] GC yields based on boron atom in pin_2B_2.

The regioselective synthesis of bis(boryl)heteroarenes is shown in Scheme 3. Thiophene, furan and pyrrole **4** were all converted to the 2,5-diborylated products **5** at room temperature in high yields with excellent regioselectivity when using an equimolar amount of **4** and pin_2B_2 **1**. The Pd-catalyzed cross-coupling of **5** with dihaloarenes has been used for the synthesis of functional polymers, including conducting materials and components of electroluminescence devices.[18]

The mechanism of the catalytic borylation of arenes and heteroarenes by these Ir(I)-bpy catalysts remains under investigation. Yet, we suggest that the present reaction may proceed through an Ir(III)-Ir(V) cycle that involves generation of a $(pinB)_3Ir(III)$ intermediate (**6**) by the reaction of an Ir(I) precursor with pin_2B_2 **1**. Oxidative addition of a C–H bond at the α-position of a heteroarene **2** or **4** to **6** would give bpy-ligated $(Ar)(H)(pinB)_3Ir(V)$ (**7**), and reductive elimination of the borylated heteroarene **3** or **5** from **7** would give $(H)(pinB)_2Ir(III)$ as the first intermediate after the C–H borylation.[10,11] The assumption may be supported by the exclusive formation of 5-boryl-2-bromothiophene from 2-bromothiophene which may be active toward oxidative addition of the C–Br bond to an Ir(I) species,[17] while a possibility of an Ir(I)-Ir(III) cycle cannot be completely avoided.



Scheme 3. Synthesis of 2,5-bis(boryl)heteroarenes.

In summary, C–H borylation of 2-substituted thiophene, furan and pyrrole derivatives by pin_2B_2 without excess of heteroarene afforded 5-borylated heteroarenes at room temperature in hexane in the presence of an Ir(I) catalyst generated from $1/2[Ir(OMe)(COD)]_2$ and dtbpy. Unsubstituted thiophene, furan and pyrrole underwent selective borylation at the 2- and 5-positions when equimolar amounts of heteroarene and pin_2B_2 were used. This process provides a convenient and efficient route to regiodefined 5-boryl- and 2,5-bis(boryl)heteroarenes without generation of magnesium or lithium reagents and halogenated intermediates. Further investigations to survey the scope and limitation of this catalyst systems for C–H borylation of other types of C–H bonds, including those in alkenes and alkanes, as well as the application of this catalyst to other types of C–H functionalizations are in progress.

Experimental Section

Typical Procedure for the Reaction of pin_2B_2 with 2-Methylthiophene

A 25-mL flask assembled a magnetic stirring bar, a septum inlet, and a condenser was charged with $[Ir(OMe)(COD)]_2$[19] (0.015 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.03 mmol), and bis(pinacolato)diboron (1.0 mmol) and then flushed with nitrogen. Dry hexane (6 mL) and 2-methylthiophene (2.0 mmol) were added, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was analyzed by GC and GC-mass spectroscopy. The product was extracted with benzene, washed with brine, and dried over $MgSO_4$. Kugelrohr distillation (90 °C/0.5 mm Hg) gave analytically pure 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene.
^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.33$ (s, 12H), 2.54 (s, 3H), 6.84 (d, 1H, $J = 3.4$ Hz), 7.45 (d, 1H, $J = 3.4$ Hz) [the irradiation of the aromatic proton at 6.84 ppm resulted in an 2.3% enhancement of the methyl signal at 2.54 ppm and an 3.9% enhancement of the aromatic signal at 7.45 ppm, respectively]; ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 15.35$, 24.71, 83.83, 126.96, 137.60, 147.50; MS: *m/e* = 125 (87), 138 (100), 209 (33), 224 (M^+, 60); exact mass calcd. for $C_{11}H_{17}BO_2S$: 224.1042; found: 224.1059.

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