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Author(s)	Ishiyama, Tatsuo; Miyaura, Norio
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Iridium-catalyzed borylation of arenes and heteroarenes via C–H activation*

Tatsuo Ishiyama and Norio Miyaura‡

Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

Abstract: Direct C–H borylation of aromatic compounds catalyzed by a transition-metal complex was studied as an economical protocol for the synthesis of aromatic boron derivatives. Iridium complexes generated from Ir(I) precursors and 2,2'-bipyridine ligands efficiently catalyzed the reactions of arenes and heteroarenes with bis(pinacolato)diboron or pinacolborane to produce a variety of aryl- and heteroarylboron compounds. The catalytic cycle involves the formation of a tris(boryl)iridium(III) species and its oxidative addition to an aromatic C–H bond.

Keywords: iridium catalyst; arylboron compounds; C–H activation; pinacolborane; bis(pinacolato)diboron.
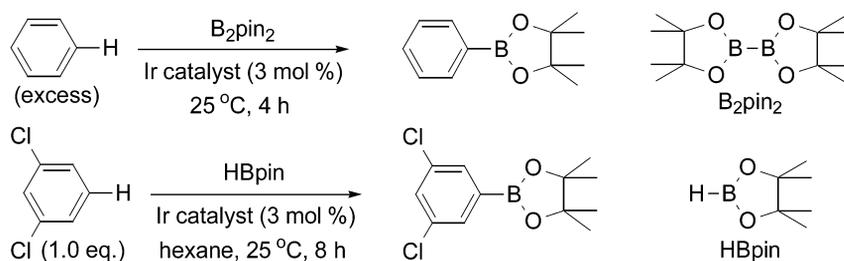
INTRODUCTION

Aromatic boron derivatives are an important class of compounds, the utility of which has been amply demonstrated in various fields of chemistry. Traditional methods for their synthesis are based on the reactions of trialkylborates with aromatic lithium or magnesium reagents derived from aromatic halides [1]. Pd-catalyzed cross-coupling of aromatic halides with tetra(alkoxo)diborons or di(alkoxo)boranes is a milder variant where the preparation of magnesium and lithium reagents is avoided [2,3]. Alternatively, transition-metal-catalyzed aromatic C–H borylation of aromatic compounds by pinacolborane (HBpin, pin = $O_2C_2Me_4$) or bis(pinacolato)diboron (B_2pin_2) is highly attractive as a convenient, economical, and environmentally benign process for the synthesis of aromatic boron compounds without any halogenated reactant, which has been studied extensively by Hartwig, Marder, and Smith [4–6]. Cp*Rh(η^4-C_6Me_6), which in situ generates a reactive unsaturated Cp*Rh(I) species by extruding hexamethylbenzene, is highly effective for aromatic C–H borylation, resulting in a 92 % yield with 5 mol % catalyst loading and an 82 % yield (328 TON) with 0.5 mol % loading at 150 °C in the reaction of B_2pin_2 with benzene [4b]. The reaction of pinBH in benzene at 140 °C in the presence of RhCl{P(*i*-Pr)$_3$}$_2$(N$_2$) (0.3 mol %) affords pinacol phenylboronate in 67 % yield [5]. Ir(I) complexes (0.02 mol %) ligated by a small and electron-donating PMe$_3$ or chelating 1,2-bis(dimethylphosphino)ethane (dmpe) also catalyzed the reaction of benzene with HBpin at 150 °C in a sealed ampule (4500 TON) [6d]. Here we describe more efficient aromatic C–H borylation of arenes and heteroarenes by B_2pin_2 or HBpin, which is catalyzed by Ir(I) complexes generated from Ir(I) precursors and 2,2'-bipyridine or its derivatives to produce the corresponding aryl- and heteroarylboron compounds in high yields with excellent regioselectivities.

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‡Corresponding author

AROMATIC C–H BORYLATION CATALYZED BY Ir(I)-2,2'-BIPYRIDINES

A class of Ir(I) complex (**1**) possessing 2,2'-bipyridine (bpy) or 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) ligands exhibits excellent activity and selectivity for aromatic C–H borylation with B_2pin_2 [7] or HBpin [8]. An Ir catalyst prepared from $1/2[IrCl(COE)_2]_2$ (COE = cyclooctene) and dtbpy achieves a maximum turnover number (8000 TON) with 0.02 mol % catalyst loading at 100 °C. The reaction was first demonstrated at 80–100 °C using an Ir–Cl complex, but it was found to proceed smoothly even at room temperature when the catalyst is prepared from $1/2[Ir(OMe)(COD)]_2$ (COD = 1,5-cyclooctadiene) and dtbpy (Scheme 1) [7c,d,8]. Thus, there is a large effect from the anionic ligands (X in **1**) on catalyst activity [7c,d,8]. Halide and cationic complexes (X = Cl or BF_4) do not catalyze the reaction at room temperature (entry 1), but Ir(I) complexes possessing an OH, OPh, or OMe ligand lead to completion within 4 h (entries 3–5). The reaction of pinacolborane in hexane also takes place at room temperature under analogous conditions using an Ir(OMe) precursor. The high catalyst efficiency of (hydroxo)- or (alkoxo)iridium complexes can be attributed to their more facile conversion into (boryl)iridium complexes compared to the (halo)iridium complexes, as is discussed in the mechanistic section. Among bipyridine derivatives employed, 3,3'-dimethylbipyridine (R^1 = Me), which features a twist between the two pyridyl units, is less active (entry 6), and a 6,6'-dimethyl derivative (R^4 = Me) does not promote the reaction due to increased steric hindrance around the iridium metal center (entry 7) [7c,d,8]. An investigation of the electronic effect of 4,4'-disubstituted derivatives shows the superiority of electron-rich bipyridines containing NMe_2, OMe, or *t*-Bu substituents compared to the Cl or NO_2 derivatives for both coupling reactions of diboron and pinacolborane (entries 8–13). Among the catalysts examined, the dtbpy complex (R^4 = *t*-Bu) shows a high efficiency for most arenes including heteroaromatic compounds (entry 10).


| entry	IrX	**1**				B_2pin_2 yield/%	HBpin yield/%
		R^1	R^2	R^3	R^4		
1	IrCl(COD)	H	H	H	H	0	-
2	Ir(OAc)(COD)	H	H	H	H	1	-
3	Ir(OPh)(COD)	H	H	H	H	84	-
4	Ir(OH)(COD)	H	H	H	H	88	-
5	Ir(OMe)(COD)	H	H	H	H	90	49
6	Ir(OMe)(COD)	Me	H	H	H	48	8
7	Ir(OMe)(COD)	H	H	H	Me	0	1
8	Ir(OMe)(COD)	H	NMe_2	H	H	88	88
9	Ir(OMe)(COD)	H	OMe	H	H	90	27
10	Ir(OMe)(COD)	H	*t*-Bu	H	H	83	86
11	Ir(OMe)(COD)	H	Me	H	H	89	75
12	Ir(OMe)(COD)	H	Cl	H	H	0	7
13	Ir(OMe)(COD)	H	NO_2	H	H	0	0
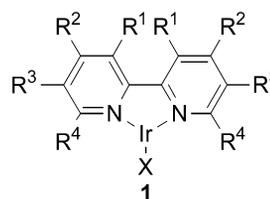
Scheme 1

The borylation of arenes with B_2pin_2 [7c,d] or HBpin [8] proceeds at room temperature in the presence of an $[Ir(OMe)(COD)]_2$-2dtbpy catalyst (3 mol % for Ir), and various functional groups are tolerated (Scheme 2). The reaction is suitable for arenes possessing OMe, I, Br, Cl, CO_2Me, CN, and CF_3 substituents or benzylic C–H bonds. It is interesting that the reaction selectively takes place at the much stronger C–H bond in preference to a C–I bond (entry 3). Both 1,2- and 1,4-disubstituted arenes bearing identical substituents yield the corresponding borylarenes as single isomers (entries 1 and 2). The borylation of 1,3-disubstituted arenes occurs at the common meta position; therefore, isomerically pure products are obtained even with arenes containing two distinct substituents (entries 3–6). Under conditions analogous to those used for typical arenes, heteroarenes are also borylated with B_2pin_2 or HBpin (entries 7–13) [7c,d,8]. Five-membered heteroarenes such as thiophene, pyrrole, furan, and their derivatives are selectively borylated at the α-carbon of a heteroatom. Reactions of pyrrole, thiophene, and furan, which have two active C–H bonds, result in a mixture of mono- and di-borylation products. Mono-coupling products are predominant when 10 equiv of a substrate is used toward B_2pin_2. On the other hand, 2,5-diboryl compounds are formed selectively when equimolar amounts of heteroarenes and B_2pin_2 are reacted (entries 7 and 8), while mono-borylation selectively occurs for 2-substituted five-membered hetreoarenes (entries 9–11) and benzo-fused heteroarenes (entries 12 and 13). Most reactions of five-membered heteroarenes are completed within 1–2 h at room temperature, which is much faster than the borylation of typical aromatic compounds.
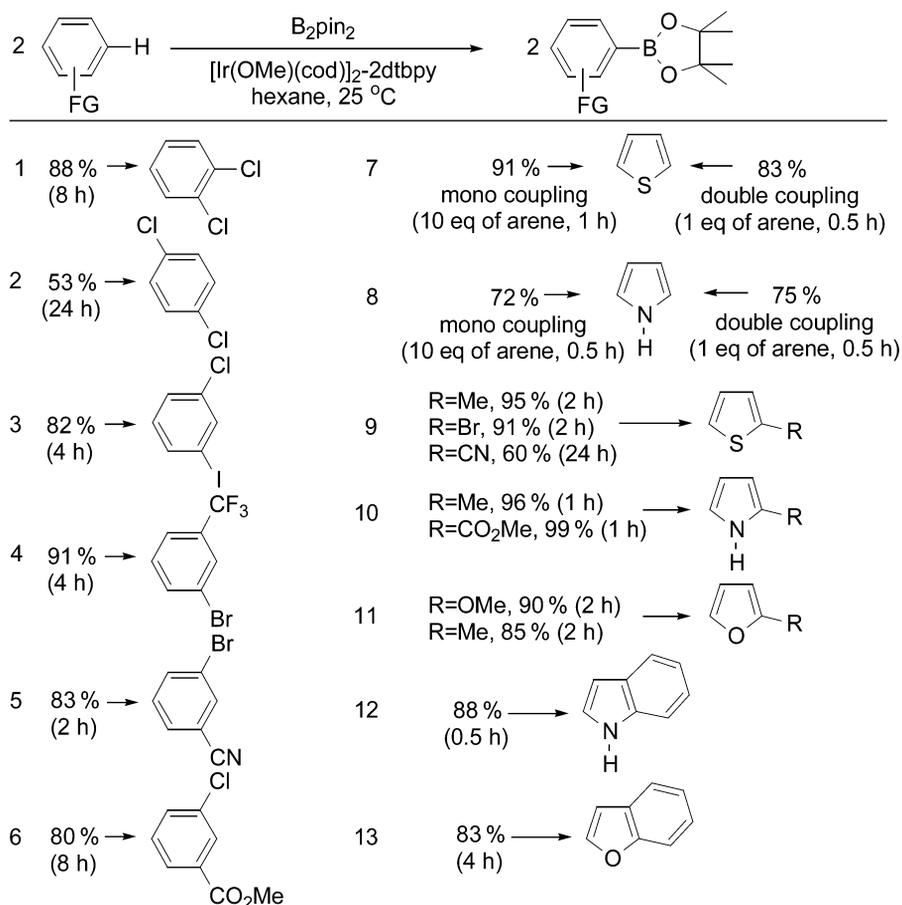
Scheme 2

The orientation of aromatic C–H borylation is shown in Scheme 3. The proportion of coupling products at the ortho carbon is negligible because of the high sensitivity of the catalyst to steric hindrance, and the reaction rather results in a mixture of meta and para products in statistical ratios (ca.2:1) for mono-substituted arenes (entries 1–3) [7a]. The reaction behaves as a nucleophilic substitution of aromatic C–H bonds. Thus, trifluoromethylbenzene reacts 6 times faster than does anisole, but such electronic properties of the substituents do not have significant influences on regioselectivities of the substitution. The orientation can be controlled by varying the steric hindrance of substituents. For example, orientation changes from a selective borylation at the 2-position of pyrrole to a mixture of 2- and 3-boryl derivatives for *N*-methyl pyrrole (entry 4), and to a selective 3-borylation of *N*-triisopropyl-silylpyrrole (entry 5). The orientation of pyridine derivatives shows a different regioselectivity than those of five-membered compounds [7b]. Since unsubstituted pyridine has an exceptionally strong coordination ability for Lewis acids, including transition metals, the reaction does not proceed at room temperature. The reaction results in a mixture of 3- and 4-borylpyridine in 42 % yield when carried out at 100 °C (entry 6). In contrast, mono-substitution at an α-carbon effectively blocks the coordination of pyridines to allow the smooth reaction at room temperature. For example, 2-chloropyrine yields a mixture of 4- and 5-borylpyridine (entry 7), and 2,6-disubstituted derivatives give 4-borylpyridines at room temperature (entries 8 and 9). A pyridine ring has a higher reactivity than that of a benzene ring since quinoline selectively yields 3-borylquinoline (entry 10). Thus, the borylation of pyridines gives β- or γ-coupling products depending upon steric or electronic effect of substituents, but it does not provide α-coupling products.
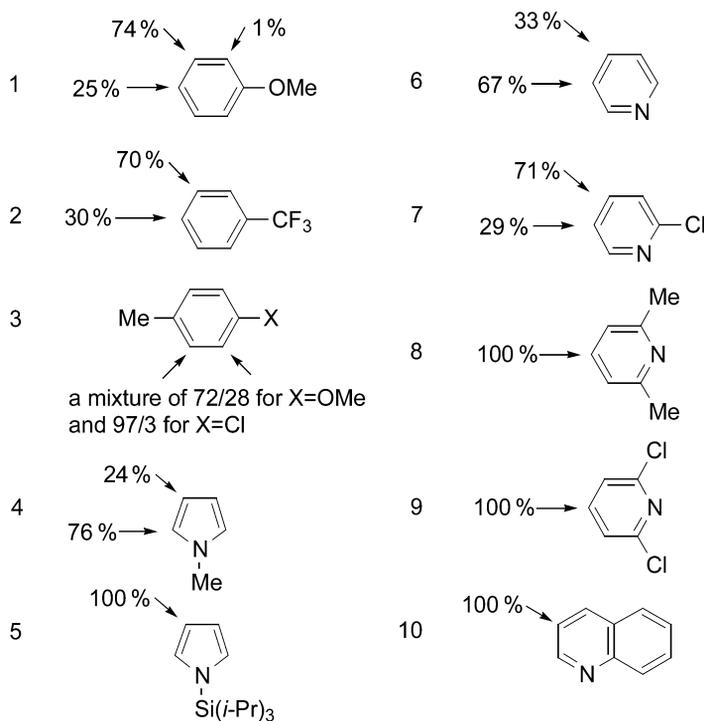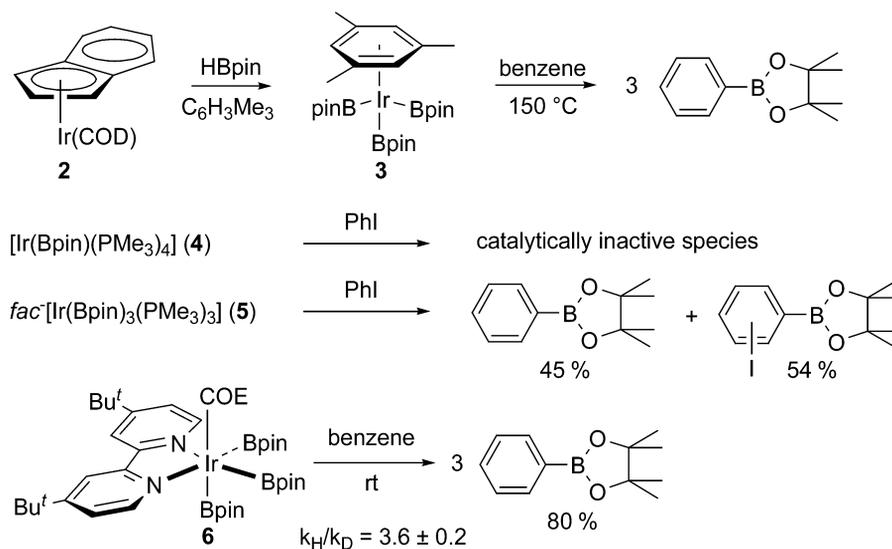

Scheme 3

The reaction has been used successfully for borylation of aromatic C–H bonds of azulene [9]; ferrocene and Cp-metal complexes [10]; polycyclic aromatic hydrocarbons such as naphthalene, pyrene, and perylene [11]; porphyrins [12]; and nitrogen-containing heterocycles [13].

CATALYTIC CYCLE

Interaction between Ir(η^5-C$_9$H$_7$)(COD) (**2**) and an excess of pinacolborane [6d] or catecholborane [14] yields an arene-tris(boryl)iridium complex (**3**), which reacts with benzene to produce 3 equiv of PhBpin at 150 °C (Scheme 4).
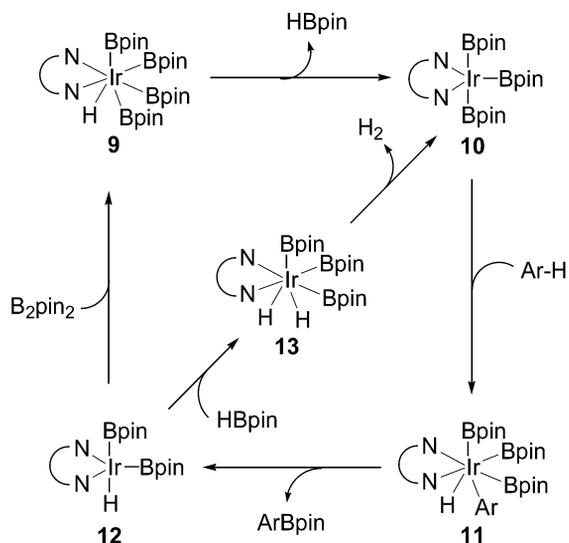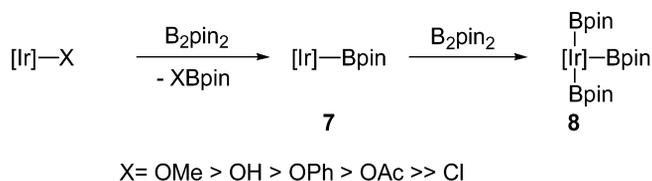

Scheme 4

Although **3** itself is not effective for a catalytic reaction, addition of PMe$_3$ to **3** provides a species (**4** or **5**) effective for borylation of arenes with HBpin [6d]. The rhodium analogs of **4** and **5** had been structurally characterized previously [15]. and the fac-Ir(PEt$_3$)$_3$(Bcat)$_3$ analog of **5** had also been reported [14]. Trimethylphosphine complexes (**4** and **5**) react cleanly with benzene to produce PhBpin and [Ir(H)(PMe$_3$)$_4$] or *fac*-[Ir(Bpin)$_2$(H)(PMe$_3$)$_3$] at room temperature, thus indicating that both Ir(I)- and Ir(III)-boryl species are viable for aromatic C–H borylation [6d]. However, there is a large difference in reactivity for iodobenzene between Ir(I) and Ir(III) complex. The Ir(I)-boryl complex (**4**) does not yield coupling product whereas Ir(III)-tris(boryl) complex (**5**) affords two coupling products which are the same as that of catalytic borylation of iodobenzene. Mechanistic studies by Hartwig's group have also shown that an Ir(III)-tris(boryl) complex is an active component involved in the catalytic cycle [7a]. ^{1}H NMR spectroscopy for the reaction of B$_2$pin$_2$ in benzene at a high catalyst loading of 1/2[IrCl(COD)]$_2$/dtbpy shows the formation of a dtbpy-ligated tris(boryl)Ir(III) complex (**6**) that is finally isolated and characterized by X-ray analysis. When **6** is dissolved in benzene at room temperature, 3 equiv of pinacol phenylboronate (80 %) are produced instantaneously. Thus, Ir(III)-tris(boryl) complexes (**5** and **6**) have both been shown to be chemically and kinetically competent to be an intermediate involved in the catalytic process.

The reaction proceeds through a catalytic cycle analogous to that proposed for the Rh(I)-catalyzed borylation of alkanes [4b] (Scheme 5). Thus, oxidative addition of an arene to a tris(boryl)Ir(III) intermediate (**10**) yields an Ir(V) species (**11**) that reductively eliminates ArBpin to give an Ir(III) hydride complex (**12**). Oxidative addition of B$_2$pin$_2$ to **12** can be followed by reductive elimination of HBpin to regenerate **10**. The resulting HBpin participates in the catalytic cycle via a sequence of oxidative addition to **12** and hydrogen reductive elimination from an 18-electron Ir(V) intermediate (**13**). Borylation of arenes with HBpin may occur after consumption of B$_2$pin$_2$, since the catalytic reaction shows a two-step process: fast borylation by B$_2$pin$_2$ followed by slow borylation by HBpin [7a]. Although catalytic

cycles involving Ir(III)-Ir(V) intermediates are rare, the ease of elimination of HBpin or H_2 from an 18-electron Ir(V) intermediate (**9** and **13**) without irradiation of light or a hydrogen-trapping reagent (e.g., alkenes) should greatly contribute to such smooth borylation under mild conditions. A small steric hindrance from the planar bipyridine ligand as well as its electron donation to the metal center allows oxidative addition of an arene C–H bond, giving intermediate **11**. The small steric influence of the planar dioxaboryl rings (Bpin) and an arene substrate (Ar) can also be critical for the formation of such sterically hindered hepta-coordinated Ir(V) intermediates. These processes have been supported by recent theoretical studies by Sakaki [16].

Scheme 5

A tris(boryl)Ir(III) intermediate (**8**) can be produced by oxidative addition of B_2pin_2 to a mono(boryl)Ir(I) complex (**7**). Thus, smooth formation of **7** from an Ir(I) source is critical for in situ generation of a reactive species via σ-bond metathesis between [Ir]-OMe and B_2pin_2, or by an oxidative addition/reductive elimination sequence. The (methoxo)iridium(I) complex [Ir(OMe)(COD)]$_2$ is a better precursor than [IrCl(COD)]$_2$, since it smoothly yields the mono(boryl) complex **7** at room temperature due to the higher bond energy of the resulting B–O bond than that of the B–Cl bond. Thus, the catalyst activity parallels the order of basic strength of the anionic ligand; X = MeO > HO > PhO > AcO >> Cl. Analogous effect of anionic ligands has been reported for transmetalation involved in palladium-catalyzed cross-coupling reactions of B_2pin_2 with aryl electrophiles [2].

ACKNOWLEDGMENTS

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