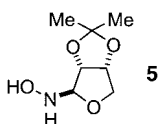


requiring a separate deprotonation or activation step. Given the fact that acetylenes are readily and conveniently converted into numerous other functional groups, the method provides access to a large range of *N*-hydroxylamines in optically active form for the first time. Such compounds are of increasing importance in medicinal chemistry, where the corresponding hydroxamic acids, for example, have been shown to possess potent broad-spectrum activities against matrix metalloproteases and tumor necrosis factor α (TNF- α) converting enzymes.^[12]

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A Stoichiometric Aromatic C–H Borylation Catalyzed by Iridium(I)/2,2'-Bipyridine Complexes at Room Temperature



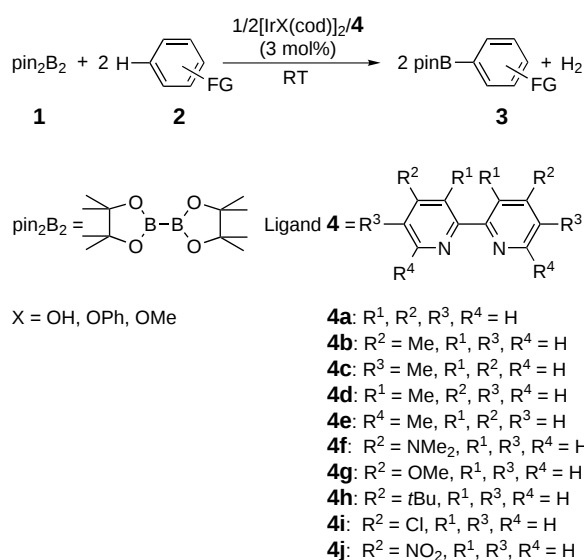
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Increasing attention has been devoted to the direct functionalization of unreactive hydrocarbons by metal-catalyzed reactions because of their wide availability and low cost.^[1] A recently developed protocol for hydrocarbon functionalization provides a convenient and direct method for the synthesis of arylboron compounds by the C–H borylation of arenes by bis(pinacolato)diboron (pin_2B_2 , $\text{pin} = \text{Me}_2\text{C}_2\text{O}_2$) or pinacolborane (pinBH) catalyzed by $[\text{Cp}^*\text{Ir}(\text{PMe}_3)(\text{H})(\text{Bpin})]$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$),^[2] $[\text{Cp}^*\text{Re}(\text{CO})_3]$,^[3] $[\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)]$,^[4] $[\text{RhCl}(\text{P}(\text{Pr})_3)_2(\text{N}_2)]$,^[5] $[(\text{Cp}^*\text{-RhCl}_2)_2]$,^[5] $[(\eta^5\text{-C}_9\text{H}_7)\text{Ir}(\text{cod})]/\text{dppe}$ or dmpe ($\text{cod} = 1,5\text{-cyclooctadiene}$; $\text{dppe} = 1,2\text{-bis}(\text{diphenylphosphanyl})\text{ethane}$; $\text{dmpe} = 1,2\text{-bis}(\text{dimethylphosphanyl})\text{ethane}$),^[6] and $1/2[\text{IrCl}(\text{cod})]_2/2,2'\text{-bipyridine}$.^[7] Among them, iridium(I) complexes generated from $[\{\text{IrCl}(\text{cod})\}_2]$ and 2,2'-bipyridine (bpy) exhibited exceptionally high catalyst activity and turnover numbers in neat arene substrate at 80 °C.^[7] Moreover, the combination of $[\text{IrCl}(\text{coe})_2]_2$ ($\text{coe} = \text{cyclooctene}$) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) catalyzed the same reaction at room temperature.^[7] We report here the development of catalysts that allow for the first time the direct borylation of arenes or heteroarenes at room temperature in an inert solvent with a stoichiometric ratio of pin_2B_2 ^[8] (**1**) to arene (**2**) to produce the corresponding arylboronates (**3**) in high yields (Scheme 1).

During subsequent studies of the aromatic C–H borylation, we found that the effect of varying the anionic ligands (X) on iridium(I) precursors could provide a greater effect on catalyst

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Scheme 1. Aromatic C–H borylation.

activity than varying the alkene ligands. To exploit this observation, we sought improved catalysts by studying the effect that variations on the (alkoxo)iridium(i) precursors (0.03 mmol of Ir) and substituents on the 2,2'-bipyridine ligands (**4**) (0.03 mmol) would have on the C–H borylation of neat benzene (60 mmol) by pin₂B₂ (**1**; 1.0 mmol) at room temperature (Table 1).

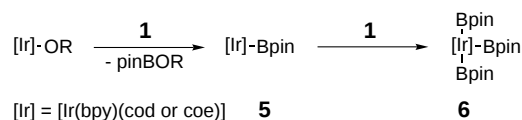
Although halide and cationic complexes containing a bpy ligand (**4a**) did not catalyze the reaction (Table 1, entries 1 and 2), air-stable iridium complexes possessing OH, OPh, or OMe ligands catalyzed the borylation within 4 h (Table 1, entries 3–5, respectively). Reactions conducted by preparing [[Ir(OMe)(cod)]₂] from [[IrCl(cod)]₂] and NaOMe in situ gave a comparable result (Table 1, entry 6). The less-basic

Table 1. Effect of ligands on the borylation of benzene by pin₂B₂ **1** at room temperature.^[a]

Entry	Ir ^I precursor	Ligand	Time [h]	Conversion ^[b] [%]	Yield ^[c] [%]
1	[[IrCl(cod)] ₂]	4a	24	0	0
2	[[Ir(cod) ₂]BF ₄]	4a	24	3	0
3	[[Ir(OH)(cod)] ₂]	4a	4	100	88
4	[[Ir(OPh)(cod)] ₂]	4a	4	100	84
5	[[Ir(OMe)(cod)] ₂]	4a	4	100	90
6	[[IrCl(cod)] ₂]/4NaOMe	4a	4	100	73
7	[[Ir(OAc)(cod)] ₂]	4a	24	19	1
8	[[Ir(OMe)(cod)] ₂]	4b	4	100	89
9	[[Ir(OMe)(cod)] ₂]	4c	2	100	82
10	[[Ir(OMe)(cod)] ₂]	4d	8	100	60
11	[[Ir(OMe)(cod)] ₂]	4e	24	27	0
12	[[Ir(OMe)(cod)] ₂]	4f	2	100	89
13	[[Ir(OMe)(cod)] ₂]	4g	4	100	90
14	[[Ir(OMe)(cod)] ₂]	4h	4	100	83
15	[[Ir(OMe)(cod)] ₂]	4i	24	16	0
16	[[Ir(OMe)(cod)] ₂]	4j	24	46	0

[a] A mixture of pin₂B₂ (**1**; 1.0 mmol), benzene (60 mmol), an Ir^I precursor (0.03 mmol of Ir), and a ligand **4** (0.03 mmol) was stirred at 25 °C for the time given. [b] Conversions of pin₂B₂ (**1**). [c] GC yields based on boron atom in **1**.

OAc complex did not catalyze the reaction (Table 1, entry 7). The high catalyst efficiency of the (hydroxo)- or (alkoxo)iridium complexes can be attributed to the more facile formation of (boryl)iridium complexes. Tris(boryl)iridium(III) complexes (**6**) have been independently isolated by Marder et al.,^[9] Smith et al.,^[6] and Hartwig et al.^[7] as possible intermediates in the borylation of arenes. Presumably, mono-(boryl)iridium(I) complexes (**5**), which would be generated by oxidative addition of **1** to (alkoxo)iridium(I) complexes and **1**, undergo oxidative addition of **1** to yield **6** (Scheme 2).



Scheme 2. Tris(boryl)iridium intermediate.

The steric and electronic effects of substituents in 2,2'-bipyridine ligand **4** are shown in (Table 1, entries 8–16).^[10] No large difference between the efficiency of catalysts bearing 4,4'- and 5,5'-dimethyl-2,2'-bipyridine (**4b** and **4c**) was observed at room temperature (Table 1, entries 8 and 9). In contrast, the catalyst bearing the 3,3'-dimethyl derivative (**4d**) was less active and gave a moderate yield (Table 1, entry 10). This result revealed the importance of a parallel arrangement of two pyridine rings. Complexes of the 6,6'-dimethyl derivative (**4e**) did not promote the reaction at all due to steric congestion around the iridium center (Table 1, entry 11). Further investigation of the electronic effect of 4,4'-disubstituted 2,2'-bipyridines revealed the superiority of electron-rich derivatives containing NMe₂, OMe, or *t*Bu groups (**4f**, **4g**, or **4h**) (Table 1, entries 12–14). Complexes of the electron-poor ligands with Cl or NO₂ groups (**4i** or **4j**) showed no catalyst activity at room temperature (Table 1, entries 15 and 16). Complexes of the NMe₂, OMe, and *t*Bu derivatives and of bpy itself exhibited catalyst activities at room temperature that were comparable to each other.

Although the borylation has been carried out in the presence of a large excess of substrate to pin₂B₂ (**1**) to avoid multiple borylation of arenes **2**, reaction of a stoichiometric amount of substrate in an inert solvent would be desirable for solid or expensive substrates. Among the solvents and catalysts screened, a combination of hexane and 1/2[[Ir(OMe)(cod)]₂]/dtbpy (**4h**) was found to be most effective for reactions of such stoichiometric ratios of **1** and **2** at room temperature that form arylboronates **3** (Table 2). The reactions were fast in nonpolar solvents, such as hexane, but the reactions were slow in more coordinating solvents and showed an order of reactivity of hexane > DME > DMF.^[11] The superiority of the dtbpy complex can be ascribed to its greater solubility in hexane. This protocol is suitable for the C–H borylation of disubstituted arenes that have one site for borylation and that can not undergo polyborylation. It is also suitable for the C–H borylation of benzo-fused

Table 2. Synthesis of arylboronates **3** (Scheme 1).^[a]

Entry	3	Time [h]	Yield ^[b] [%]	Entry	3	Time [h]	Yield ^[b] [%]
1		8	82	7		2	84
2		24	53	8		2	83
3		2	84	9		8	80
4		4	91	10		2	81
5		8	81	11		4	83
6		4	82	12		0.5	88

[a] A mixture of pin₂B₂ (**1**; 1.0 mmol), an arene **2** (2.0 mmol), [[Ir(OMe)(cod)]₂] (0.015 mmol), and dtbpy (0.03 mmol) was stirred in hexane (6 mL) at 25 °C for the period shown in the Table. [b] GC yields based on boron atom in pin₂B₂ (**1**).

heteroarenes that have one site that is much more reactive than others.

Previous studies demonstrated that the borylation occurs at C–H bonds located *para* or *meta* to a substituent and does not occur at sterically hindered C–H bonds *ortho* to a substituent. In addition, there is a weak electronic effect that directs reaction at the more electron-poor carbon.^[7] Thus, the reaction occurs regiospecifically with disubstituted arenes **2**. 1,2-, 1,4-, and 1,3-Dichlorobenzenes all gave a single product **3** (Table 2, entries 1–3). The reaction at the *o*-carbon atom of the 1,4 isomer was slow due to steric hindrance of the substituent. The borylation of 1,3-disubstituted **2** selectively occurred only at the common *meta* position; therefore, isomerically pure **3** were obtained in excellent yields even with two distinct substituents on **2** (Table 2, entries 4–9). The reaction was suitable for **2** possessing a wide variety of functional groups, such as Cl, Br, I, CF₃, OMe, CO₂Me, and CN. The borylation of benzo[*b*]thiophene, benzo[*b*]furan, or indole in hexane occurred selectively at the 2-position because the C–H bond at the 2-position in these substrates is activated by the heteroatom (Table 2, entries 10–12).^[12]

In summary, iridium complexes comprised of [[Ir(OMe)(cod)]₂] and 4,4'-di-*tert*-butyl-2,2'-bipyridine are highly active catalysts for the aromatic C–H borylation by bis(pinacolato)-diboron. This high activity allowed for the first room temperature borylation of arenes with a stoichiometric amount of arene to produce the corresponding arylboronates in high yields. With this advance, the aromatic C–H borylation provides a practical tool for preparing arylboronates. The catalytic C–H borylation of other hydrocarbons is being actively investigated.

Experimental Section

A representative procedure for **3**: A flask containing [[Ir(OMe)(cod)]₂] (0.015 mmol), dtbpy (0.03 mmol), and pin₂B₂ (**1**; 1.0 mmol) was flushed with nitrogen, and then charged with hexane (6 mL) and 1,2-dichlorobenzene (2.0 mmol). The mixture was then stirred at 25 °C for 8 h. The product was isolated by Kugelrohr distillation to give an analytically pure sample: ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 1.34 (s, 12H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.60 (dd, *J* = 1.3 and 7.9 Hz, 1H), 7.87 ppm (d, *J* = 1.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25 °C, TMS): δ = 24.82, 84.32, 129.99, 132.24, 133.73, 135.48, 136.54 ppm; ¹¹B NMR (128 MHz, CDCl₃, 25 °C, BF₃·OEt₂): δ = 30.61 ppm; HRMS calcd for C₁₂H₁₅BCl₂O₂: 272.0542; found: 272.0515.

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