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Author(s)	Itoh, Hiroshi; Kikuchi, Takao; Ishiyama, Tatsuo et al.
Citation	Chemistry Letters, 40(9), 1007-1008 https://doi.org/10.1246/cl.2011.1007
Issue Date	2011
Doc URL	https://hdl.handle.net/2115/56367
Type	journal article
File Information	(52) B-B + H-ArylKetone (Com).pdf

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Iridium-catalyzed *ortho*-C-H Borylation of Aryl Ketones with Bis(pinacolato)diboron

Hiroshi Itoh, Takao Kikuchi, Tatsuo Ishiyama,* and Norio Miyaura*

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

ortho-Selective C-H borylation of aryl ketones with bis(pinacolato)diboron proceeded at 120 °C in octane in the presence of a catalytic amount of iridium(I) complexes comprising 1/2[Ir(OMe)(cod)]$_2$ and $AsPh_3$.

Arylboronic acids and esters are an important class of intermediates for the synthesis of natural products, medicinal compounds, and functional materials.[1] Traditional methods for their synthesis are reactions of trialkylborates with aryllithium or -magnesium compounds.[2] Pd-Catalyzed cross-coupling of aryl halides with bis(pinacolato)diboron (B_2pin_2) or pinacolborane (HBpin) is a milder variant for most functional groups.[3,4] Rhodium- or iridium-catalyzed C-H borylation of arenes with HBpin or B_2pin_2, studied extensively by Hartwig,[5] Marder,[6] and Smith,[7] is highly attractive as a direct, economical, and environmentally benign process to synthesize organoboronic esters without using any halogenated starting materials. We have reported unusually high efficiency of a 1/2[Ir(OMe)(cod)]-2dtbpy catalyst, which allowed stoichiometric borylation of arenes and heteroarenes at room temperature.[8] The regioselectivity of this C-H borylation of arenes is primarily controlled by steric effects; functionalization occurs at the least hindered aromatic C-H bond. Thus, 1,2-disubstituted arenes having identical substituents and 1,3-disubstituted arenes even having distinct substituents produce borylated products as single isomers. A drawback of this method is therefore difficulty in achieving *ortho*-C-H borylation.[9,10] One of the most reliable protocols would be a process involving use of chelation-assisted C-H bond cleavage. Recently, we developed a new catalyst system (1/2[Ir(OMe)(cod)]$_2$-2P(3,5-$(CF_3)2C_6H_3)_3$) for *ortho*-C-H borylation of benzoate esters with B_2pin_2.[11] We report here analogous reaction of aryl ketones **1** with B_2pin_2 (**2**) for

synthesis of *ortho*-borylated products **3** (Scheme 1). The reaction selectively took place at the *ortho*-carbon when iridium(I) complexes comprising $[Ir(OMe)(cod)]_2$ and $AsPh_3$[12] was used as a catalyst at 120 °C in octane.

(Scheme 1)

To achieve the *ortho*-C-H borylation of aryl ketones **1**, effects of iridium(I) precursors (0.03mmol/Ir), ligands (0.06 mmol), and solvents (6 mL) were investigated for the reaction of acetophenone (5.0mmol) with B_2pin_2 (**2**) (1.0mmol) at 120 °C for 16 h (Table 1). Among the conditions screened, a combination of $[Ir(OMe)(cod)]_2$ or $[IrCl(cod)]_2$, $AsPh_3$, and octane gave the best yields (124-134%) and excellent *ortho*-selectivities (98%) (Entries 1 and 2). A cationic iridium(I) precursor, $[Ir(cod)_2]BF_4$, also worked well (Entry 3). The choice of ligand was crucial for the borylation. In the absence of ligands, the reaction afforded the borylated product in low yield with moderate selectivity (Entry 4). Iridium complexes bearing other monodentate ligands such as pyridine (Entry 5), PPh_3 (Entry 6) and $SbPh_3$ (Entry 7) also displayed low catalytic activities. The catalyst having $P(3,5\text{-}(CF_3)_2C_6H_3)_3$, which has been efficiently utilized in the *ortho*-C-H borylation of benzoate esters with **2**, displayed the best selectivities (100%), but catalytic activity was moderate (56%) (Entry 8). The choice of inert solvent was also important for efficient borylation. The reactions using $1/2[Ir(OMe)(cod)]_2\text{-}2AsPh_3$ were faster in nonpolar solvents such as octane than in more polar and coordinating solvents. The order of reactivity in different solvents was octane (124%) (Entry 1) = mesitylene (126%) (Entry 9) > diglyme (12%) (Entry 10) > DMF (0%) (Entry 11).

(Table 1)

Yields over 100% observed in the above borylation indicate that both boryl groups in diboron **2** participated in the reaction. Because the catalytic reaction shows a two-step process, fast borylation by **2** followed by slow borylation by HBpin, the borylation of acetophenone with HBpin may occur after consumption of **2**. Indeed, reaction of acetophenone with HBpin under the conditions used for the borylation with **2** gave the borylated product in 30% yield (Scheme 2). To improve the yield, the

reaction with **2** was carried out in the presence of various alkenes that have frequently been used as hydrogen acceptors in C-H silylation with hydrosilanes;[13] however, addition of such reagents retarded the present borylation.

(Scheme 2)

Representative results of *ortho*-CH borylation of aryl ketones **1** with B_2pin_2 (**2**) catalyzed by the combination of $1/2[Ir(OMe)(cod)]_2$, $2AsPh_3$, and octane at 120 °C for 16 h are shown in Table 2. Not only methyl but also ethyl, isopropyl, and *tert*-butyl ketones were all viable substrates for producing the corresponding *ortho*-borylated products **3** in high yields with excellent regioselectivities (Entries 14). The reactions were suitable for substrates possessing various functional groups, such as MeO, Cl, and F_3C, as well as for substrates with potentially more reactive benzylic C-H bonds (Entries 5-8, 10, and 11).[14] Although some transition-metal complexes exhibit reactivity toward oxidative addition of Ar-Cl bonds,[15] 4-chloroacetophenone underwent borylation at the C-H bond (Entry 7). The low reactivities in the borylation of acetophenone having an F_3C or a O_2N group may be attributable to the low coordinating ability of carbonyl oxygen (Entries 8 and 9). Reaction of a substrate bearing a substituent at the 3-position only occurred at the 6-position, presumably due to steric reasons (Entry 10).

(Table 2)

In summary, *ortho*-borylated products were obtained with excellent regioselectivities by the reaction of aryl ketones with bis(pinacolato)diboron in the presence of a catalytic amount of iridium complexes generated from $[Ir(OMe)(cod)]_2$ and $AsPh_3$ in octane at 120 °C. Further investigations to survey the scope and limitations of this C-H borylation, including C-H borylation of other aromatic carbonyl compounds such as amides, as well as to elucidate the reaction mechanisms are in progress.

This work was supported by Grant-in-Aid for Scientific Research (B) (No. 21350049) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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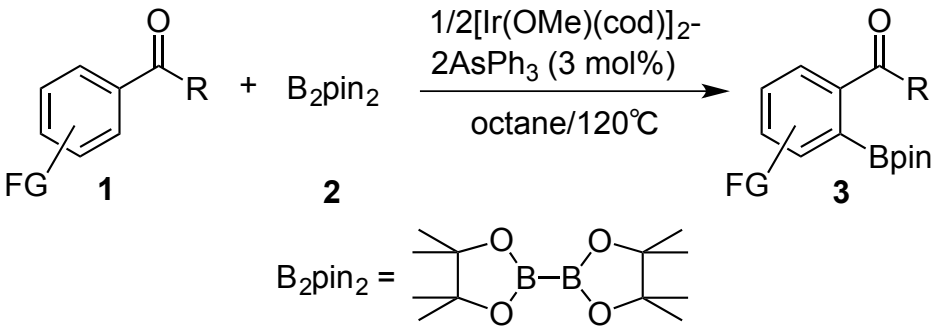
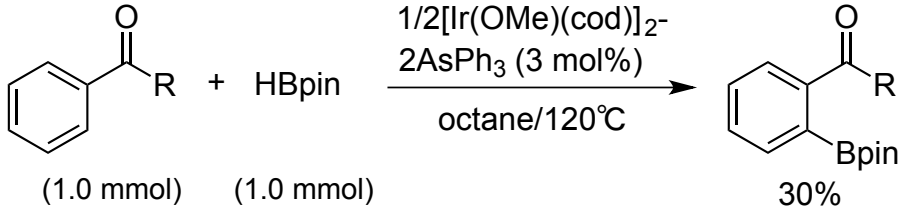
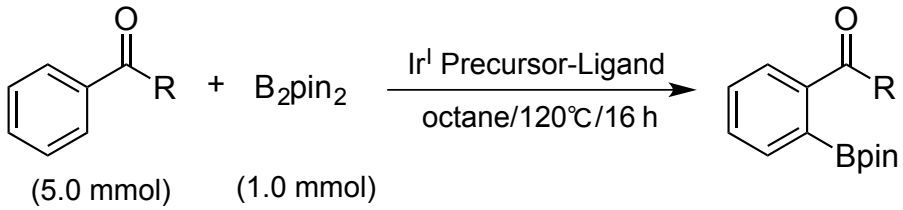


Scheme 1.



Scheme 2.

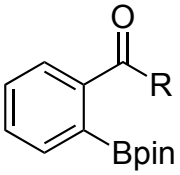
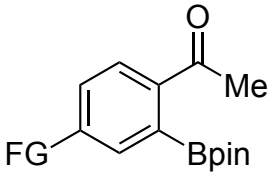
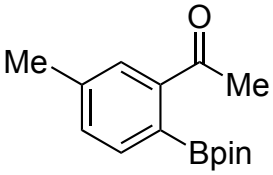
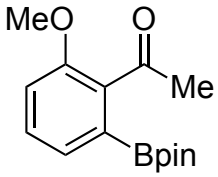
Table 1. Reaction conditions for acetophenone[a]



Entry	Ir(I) Precursor	Ligand	Solvent	Yield /%[b]	Sel %[c]
1	1/2[Ir(OMe)(cod)]$_2$	2AsPh$_3$	octane	124	98
2	1/2[IrCl(cod)]$_2$	2AsPh$_3$	octane	134	98
3	[Ir(cod)$_2$]BF$_4$	dtbpy	octane	96	98
4	1/2[Ir(OMe)(cod)]$_2$	none	octane	32	75
5	1/2[Ir(OMe)(cod)]$_2$	2Pr	octane	38	79
6	1/2[Ir(OMe)(cod)]$_2$	2PPh$_3$	octane	16	92
7	1/2[Ir(OMe)(cod)]$_2$	2SbPh$_3$	octane	4	13
8	1/2[Ir(OMe)(cod)]$_2$	2P((CF$_3$)$_2$C$_6$H$_3$)$_3$	octane	56	100
9	1/2[Ir(OMe)(cod)]$_2$	2AsPh$_3$	Me$_3$C$_6$H$_3$	126	98
10	1/2[Ir(OMe)(cod)]$_2$	2AsPh$_3$	diglyme	12	100
11	1/2[Ir(OMe)(cod)]$_2$	2AsPh$_3$	DMF	0	—

[a]A mixture of acetophenone (5.0 mmol), B_2pin_2 (1.0 mmol), Ir(I) precursor (0.03 mmol/Ir), ligand (0.06 mmol), and solvent (6 mL) were stirred at 120°C for 16h. [b]GC yields based on the number of equinalents of B_2pin_2. [c]*ortho*-Selectivities.

Table 2. *ortho*-C-H borylation of aryl ketones[a]

Entry	Product		Yield/%[b]
1		R = Me	124
2		R = Et	126
3		R = *i*-Pr	132 (83)
4		R = *t*-Bu	130 (73)
5		FG = MeO	114 (50)
6		FG = Me	122
7		FG = Cl	154
8		FG = F_3C	48
9		FG = O_2N	NR
10			80
11			108

[a]All reactions were carried out at 120 °C for 16 h by using an aryl ketone (5.0mmol), B_2pin_2 (1.0mmol), $[Ir(OMe)(cod)]_2$ (0.015mmol), $AsPh_3$ (0.06mmol), and octane (6 mL). [b]GC yields based on the number of equivalents of B_2pin_2 and isolated yields are in paretheses.