Ortho-C-H borylation of benzoate esters with bis(pinacolato)diboron catalyzed by iridium-phosphine complexes†

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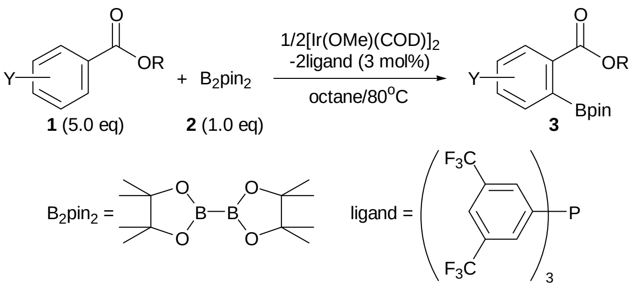
Iridium complexes generated from [Ir(OMe)(COD)]$_2$ and tris[3,5-bis(trifluoromethyl)phenyl]phosphine efficiently catalyzed the *ortho*-C-H borylation of benzoate esters with bis(pinacolato)diboron in octane at 80°C to produce the corresponding arylboronates in high yields with excellent regioselectivities.

Increasing attention has been focused on transition metal-catalyzed activation and the functionalization of unreactive C-H bonds of hydrocarbons.[1] An extension of this methodology to aromatic C-H borylation of arenes with bis(pinacolato)diboron (B_2pin_2, pin = $Me_4C_2O_2$) or pinacolborane (HBpin) is of significant value for the preparation of synthetically useful aromatic boron compounds[2] from the viewpoint of economy, efficiency, and environmental benignity.[3-6] The most efficient catalyst for this type of transformation is the combination of [IrCl(COD)]$_2$ or [Ir(OMe)(COD)]$_2$ with 2,2'-bipyridine or 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy).[6] The high level of catalytic activity of 1/2[Ir(OMe)(COD)]$_2$-dtbpy allows room temperature borylation of arenes with a stoichiometric amount of substrate to produce the corresponding arylboron compounds in high yields. The functional group tolerance of the borylation is quite high. The reaction occurs selectively at the aromatic C-H bond for arenes bearing MeO, Me, I, Br, Cl, F_3C, MeO_2C, and NC. The regioselectivity of this C-H borylation of arenes is primarily controlled by steric effects; the 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. One of the most reliable protocols would be a process involving use of chelation-assisted C-H bond cleavage.[1]

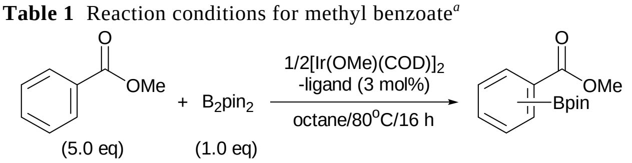


Scheme 1 *Ortho*-selective C-H borylation of benzoate esrers.

We disclose herein the *ortho*-C-H borylation of benzoate ester derivatives (**1**) with bis(pinacolato)diboron (B_2pin_2) (**2**) catalyzed by iridium complexes comprised of easily available [Ir(OMe)(COD)]$_2$ and commercial tris[3,5-bis(trifluoromethyl)phenyl]phosphine in octane at 80˚C to give the corresponding aromatic boron compounds (**3**) in high yields with excellent regioselectivities (Scheme 1).[7,8]

To achieve the *ortho*-C-H borylation of benzoate esters **1**, effects of ligands (0.03 or 0.06 mmol) were investigated for the reaction of methyl benzoate (5.0 mmol) with B_2pin_2 **2** (1.0 mmol) by using [Ir(OMe)(COD)]$_2$ (0.015 mmol) as a catalyst precursor in octane (6 ml) at 80˚C for 16 h (Table 1). Iridium complexes bearing dtbpy effectively catalyzed the aromatic C-H borylation, but they did not give any *ortho*-borylated products at all (Entry 1). Probably, the high coordinating ability of dtbpy retards the coordination of a carbonyl oxygen in the substrate to the iridium centre. The reaction afforded an *ortho*-borylated product in the absence of ligands; however, catalytic activity and regioselectivity were low (Entry 2). These results prompted us to examine monodentate ligands. Among iridium complexes having pyridine (Entry 3), triphenylphosphine (Entry 4), and triphenylarsine (Entry 5), the latter two complexes exhibited moderate *ortho*-selectivities but displayed low catalytic activities. Since a wide variety of triarylphosphines are commercially available, we decided to investigate them as ligands of iridium. Although catalysts having electron-rich phosphines such as

Table 1 Reaction conditions for methyl benzoate[a]



Entry	Ligand	Yield (%)[b]	*o*- : *m*- : *p*- (%)[c]
1	dtbpy	145	0 : 58 : 42
2	none	13	38 : 38 : 24
3	2 pyridine	7	14 : 58 : 28
4	2 P(C_6H_5)$_3$	11	64 : 18 : 18
5	2 As(C_6H_5)$_3$	9	67 : 22 : 11
6	2 P(4-MeO-C_6H_4)$_3$	3	34 : 33 : 33
7	2 P(4-F_3C-C_6H_4)$_3$	45	96 : 2 : 2
8	2 P(C_6F_5)$_3$	82	90 : 7 : 3
9	2 P(3,5-2F_3C-C_6H_3)$_3$	95	98 : 2 : 0

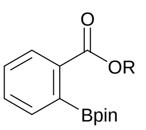
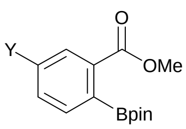
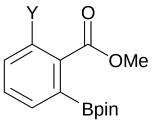
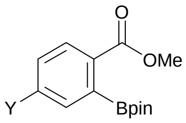
[a] Reactions were carried out at 80˚C for 16 h by using methyl benzoate (5.0 mmol), **2** (1.0 mmol), [Ir(OMe)(COD)]$_2$ (0.015 mmol), ligand (0.03 or 0.06 mmol), and octane (6 ml). [b] GC yields based on **2**. [c] Isomer ratios were determined by ^{1}H NMR.

tris(4-methoxyphenyl)phosphine exhibited low activity and regioselectivity (Entry 6), those having electron-poor phosphines such as tris(4-trifluoromethylphenyl)phosphine displayed high *ortho*-selectivity and moderate catalytic activity (Entry 7). Complexes bearing more electron-poor tris(pentafluorophenyl)phosphine improved the catalytic activity while maintaining high regioselectivity (Entry 8). Finally, high yield (95%) and highest *ortho*-selectivity (98%) were achieved when tris[3,5-bis(trifluoromethyl)phenyl]phosphine ($P(3,5\text{-}2F_3C\text{-}C_6H_3)_3$) was used as a ligand of iridium (Entry 9).

The choice of iridium precursor was crucial for the borylation. Although the combination of $[IrCl(COD)]_2$ and $P(3,5\text{-}2F_3C\text{-}C_6H_3)_3$ gave borylated products in good yield (62%), *ortho*-selectivity was low (55%). No borylated product was obtained when the combination of $[Ir(COD)_2]BF_4$ and the phosphine was used. The choice of inert solvent was also important for efficient borylation. The reactions using $1/2[Ir(OMe)(COD)]_2$-$2P(3,5\text{-}2F_3C\text{-}C_6H_3)_3$ were faster in non-polar solvents such as octane than in more polar and coordinating solvents. The order of reactivity in different solvents was octane (95%) > mesitylene (3%) > diglyme (0%) = DMF (0%).

Representative results of *ortho*-C-H borylation of benzoate esters **1** with B_2pin_2 **2** catalyzed by the combination of $1/2[Ir(OMe)(COD)]_2$ and $2P(3,5\text{-}2F_3C\text{-}C_6H_3)_3$ in octane at 80˚C for 16 h are shown in Table 2. Not only methyl but also ethyl, isopropyl and *tert*-butyl benzoates were all viable substrates for producing the corresponding *ortho*-borylated products in high yields with excellent regioselectivities, whilst their reactivity slightly decreased in the above order (Entries 1-4). The reactions were suitable for substrates possessing various functional groups, such as Me_2N, Br, and F_3C as well as for substrates with potentially more reactive benzylic C-H bonds (Entries 5-16).[9] Although some transition metal complexes exhibit high reactivity toward oxidative addition of Ar-Br bonds,[10] methyl 2-, 3-, and 4-bromobenzoates underwent borylation at the C-H bond (Entries 7, 11, and 15). Reactions of substrates having a substituent at the 3-position only occurred at the 6-position, presumably due to steric reasons (Entries 9-12).

Table 2 *Ortho*-selective aromatic C-H borylation of **1** with **2**[a]

Entry	Product[b]	Yield (%)[c]	Entry	Product[b]	Yield (%)[c]
1		R = Me 95	9		Y = Me_2N 99
2		R = Et 92	10		Y = Me 98
3		R = *i*-Pr 89	11		Y = Br 64
4		R = *t*-Bu 83	12		Y = F_3C 94
5		Y = Me_2N 97	13		Y = Me_2N 93
6		Y = Me 92	14		Y = Me 99
7		Y = Br 60	15		Y = Br 57[d]
8		Y = F_3C 98	16		Y = F_3C 98

[a] All reactions were carried out at 80˚C for 16 h by using **1** (5.0 mmol), **2** (1.0 mmol), $[Ir(OMe)(COD)]_2$ (0.015 mmol), tris[3,5-bis(trifluoromethyl)phenyl]phosphine (0.06 mmol), and octane (6 ml). [b] Isomeric purities over 98% were determined by ^1H NMR. [c] GC yields based on **2**. [d] The reaction was conducted in a mixture of octane and mesitylene (1:1).

In summary, *ortho*-borylated products were obtained with excellent regioselectivities by the reaction of benzoate esters with bis(pinacolato)diboron in the presence of a catalytic amount of iridium complexes generated from $[Ir(OMe)(COD)]_2$ and commercial tris[3,5-bis(trifluoromethyl)phenyl]phosphine in octane at 80˚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 ketones and amides, as well as to elucidate the reaction mechanisms are in progress.

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† Electronic Supplementary Information (ESI) available: experimental procedures and spectral analyses. See DOI: 10.1039/b000000x/

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