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# Iridium-Catalysed Borylation of Sterically Hindered C(sp<sup>3</sup>)-H bonds: Remarkable Rate Acceleration by the Catalytic Amount of Potassium *tert*-Butoxide

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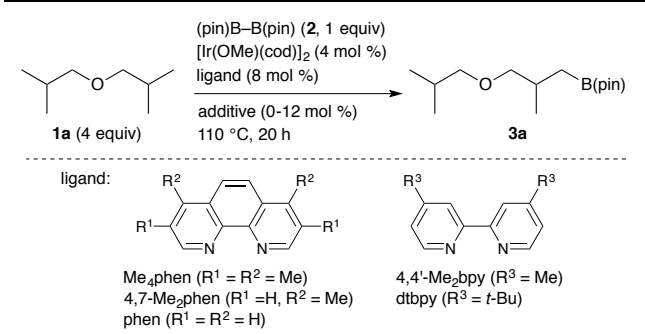
The C(sp<sup>3</sup>)-H bonds located at the methyl groups of the isopropyl group participate in iridium-catalysed C-H borylation with bis(pinacolato)diboron via a significant rate acceleration by a catalytic amount of *t*-BuOK.

Alkylboron compounds are versatile intermediates in the synthesis of aliphatic compounds via carbon-carbon and carbon-heteroatom bond-formation at the boron-bound carbon atoms.<sup>1</sup> In addition to their application in organic synthesis, the molecular function of alkylboron compounds has been explored rapidly, as exemplified by the bioactivity of  $\alpha$ -aminoalkylboronic acids.<sup>2</sup> The preparation of alkylboron compounds has mainly relied on the hydroboration of alkenes,<sup>1a,3</sup> together with the reactions of alkylmagnesium and alkyllithium reagents with boron electrophiles.<sup>4,5</sup> Recently, the transition-metal-catalyzed conversion of C(sp<sup>3</sup>)-H bonds into C(sp<sup>3</sup>)-B bonds has been developed as an alternative and more efficient route to alkylboron compounds.<sup>6,7,8</sup> This catalytic C(sp<sup>3</sup>)-H borylation has an advantage over the conventional methods in that it allows the conversion of unfunctionalized inert alkane derivatives. However, this borylation is rather sensitive to steric hindrance. Indeed, the C(sp<sup>3</sup>)-H bonds that can be borylated with high efficiency have been limited to the sterically less-hindered methyl on alkyl termini of acyclic substrates<sup>6b,7a-f,7h-i</sup> or methylene units in cyclic substrates.<sup>6b,6d,7j-1</sup> Hartwig and co-workers have reported the C(sp<sup>3</sup>)-H borylation of the sterically hindered methyl side chain of polypropylene,<sup>7g</sup> which needs extremely high reaction temperatures (185-200 °C). Although C(sp<sup>3</sup>)-H borylation of methylene groups in 2-alkylpyridines<sup>6c,6e,6g,7m</sup> and 2-(hydrosilyl)alkylbenzenes<sup>6f,6h</sup> has been achieved under relatively mild conditions, the reaction requires directing groups such as 2-pyridyl and hydrosilyl groups. For further utilization of catalytic C(sp<sup>3</sup>)-H borylation, the development of more powerful catalyst systems is highly desirable to broaden substrate scope considerably.

We have recently reported the iridium-catalysed C(sp<sup>3</sup>)-H borylation of organosilicon compounds.<sup>9</sup> The efficient borylation at the methyl group of alkyltrimethylsilanes<sup>9b</sup> indicated the potential reactivity of C(sp<sup>3</sup>)-H bonds that are located at sterically hindered positions. We focused our attention on substrates having isopropyl groups, which have never been reported to participate in catalytic C(sp<sup>3</sup>)-H borylation

efficiently.<sup>10</sup> Herein, we describe an efficient catalytic system for the C(sp<sup>3</sup>)-H borylation of aliphatic substrates that do not bear strong directing groups. A remarkable rate acceleration of the borylation was achieved by a catalytic amount of basic additives such as *t*-BuOK.

**Table 1** Effect of additives and ligands in iridium-catalysed borylation of **1a**<sup>a</sup>



entry	additive (mol %)	ligand	% yield <sup>b</sup>
1	-	Me <sub>4</sub> phen	11
2	<i>t</i> -BuOK (12)	Me <sub>4</sub> phen	0
3	<i>t</i> -BuOK (8)	Me <sub>4</sub> phen	4
4	<i>t</i> -BuOK (6)	Me <sub>4</sub> phen	56
5	<i>t</i> -BuOK (4)	Me <sub>4</sub> phen	68
6	<i>t</i> -BuOK (2)	Me <sub>4</sub> phen	88 (77) <sup>c</sup>
7	<i>t</i> -BuOK (1)	Me <sub>4</sub> phen	80
8	<i>t</i> -BuOK (2)	4,7-Me <sub>2</sub> phen	1
9	<i>t</i> -BuOK (2)	phen	trace
10	<i>t</i> -BuOK (2)	4,4'-Me <sub>2</sub> bpy	trace
11	<i>t</i> -BuOK (2)	dtbpy	trace
12	NaOMe (2)	Me <sub>4</sub> phen	74
13	Cs <sub>2</sub> CO <sub>3</sub> (2)	Me <sub>4</sub> phen	59
14	CsOH·H <sub>2</sub> O (2)	Me <sub>4</sub> phen	58
15	CsF (2)	Me <sub>4</sub> phen	56

<sup>a</sup> **1a** (2.0 mmol), **2** (0.50 mmol), [Ir(OMe)(cod)]<sub>2</sub> (0.020 mmol), a ligand (0.040 mmol), and an additive (0-0.060 mmol) were stirred at 110 °C for 20 h. <sup>b</sup> GC yield based on **2**. <sup>c</sup> Isolated yield in 1.0 mmol scale reaction.

The reaction of diisobutyl ether (**1a**, 4 equiv) with bis(pinacolato)diboron (**2**, 1 equiv) was carried out at 110 °C in the presence of [Ir(OMe)(cod)]<sub>2</sub> (4 mol %, 8 mol % Ir) and 3,4,7,8-tetramethylphenanthroline (Me<sub>4</sub>phen, 8 mol %) without an additional solvent (entry 1, Table 1). The borylated product **3a** was formed only in 11% yield after 20 h, indicating that the

sterically demanding **1a** is an unreactive substrate, even with the Ir-Me<sub>4</sub>phen catalyst, which has been reported as an effective catalyst for C(sp<sup>3</sup>)-H borylation.<sup>6b,6d,6f,9</sup> To achieve the borylation of **1a**, we tested the reaction in the presence of *t*-BuOK, which has been reported by Eliseeva and Scott as an effective additive in the multiple borylation of C(sp<sup>2</sup>)-H bonds in aromatic compounds.<sup>11</sup> In that report, the role of *t*-BuOK was supposed to be the improvement of the iridium complex structure via the deprotonation of the ligand.<sup>11</sup> We found remarkable acceleration of the C(sp<sup>3</sup>)-H borylation of **1a** when the reaction was carried out in the presence of a catalytic amount of *t*-BuOK (2 mol %), which led to the formation of the alkylboronic ester **3a** in high yield (entry 6). It should be noted that the effect was highly sensitive to the amount of *t*-BuOK. This acceleration was not observed with 12 or 8 mol % catalyst loading (Ir:*t*-BuOK = 1:1.5-1, entries 2 and 3), whereas efficient borylation took place in the presence of less than 6 mol % catalyst loading (Ir:*t*-BuOK = 1:0.75-0.125) (entries 4-7). Me<sub>4</sub>phen is an essential ligand for the *t*-BuOK-accelerated C(sp<sup>3</sup>)-H borylation: other phenanthroline ligands, such as 4,7-dimethylphenanthroline (4,7-Me<sub>2</sub>phen, entry 8) and phenanthroline (phen, entry 9), showed no or much lower catalytic activities. It is also noted that 4,4'-dimethyl-2,2'-bipyridine (4,4'-Me<sub>2</sub>bpy), which has been reported as an effective ligand in C(sp<sup>2</sup>)-H borylation under the Ir/*t*-BuOK catalyst system,<sup>11</sup> was completely ineffective for the C(sp<sup>3</sup>)-H borylation (entry 10). No reaction took place with 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy, entry 11). In addition to *t*-BuOK, other bases, such as NaOMe, Cs<sub>2</sub>CO<sub>3</sub>, CsOH·H<sub>2</sub>O, and CsF, promoted the borylation efficiently (entries 12-15).<sup>12</sup> These results indicate the possibility of activation of **2** by the additives,<sup>13</sup> although Scott's proposal where the additives change the structure of the iridium complex can not be ruled out.<sup>11</sup> The reaction with pinacolborane [HB(pin)] instead of **2** under the conditions used for entry 6 resulted in the formation of **3a** in low yield (2%). This result indicates that HB(pin), which was formed as a by-product in the reaction of **1a** with **2**, hardly participated in the C(sp<sup>3</sup>)-H borylation of **1a**.

**Table 2** Iridium-catalysed C(sp<sup>3</sup>)-H borylation with or without *t*-BuOK<sup>a</sup>

Entry	Substrate	Product	Ir cat (mol %)	% yield <sup>b</sup> without <i>t</i> -BuOK	% yield <sup>c</sup> with <i>t</i> -BuOK
1 <sup>d</sup>			6	10	96 (71)
2			8	15	73 (63)
3			6	13	88 (75)

4 <sup>d</sup>			4	87	109 <sup>e</sup> (88)
5 <sup>d</sup>			6	35 <sup>f</sup>	87 (81) <sup>g</sup>
6			8	17	69 (64)
7			8	17	86 <sup>h</sup> (85)
8			10	26	71 (67)
9			10	10	45 (42)
10 <sup>d</sup>			10	8	42 (38)

<sup>a</sup> **1** (4.0 mmol), **2** (1.0 mmol), [Ir(OMe)(cod)]<sub>2</sub> (0.020-0.050 mmol), Me<sub>4</sub>phen (Ir:Me<sub>4</sub>phen = 1:1), and *t*-BuOK (Ir:*t*-BuOK = 1:0 or 1:0.25) were stirred at 110 °C for 20 h. <sup>b</sup> GC yield based on **2**. <sup>c</sup> GC yield based on **2** and isolated yield in parentheses. <sup>d</sup> **1** (6.0 mmol) was used. <sup>e</sup> HB(pin) formed as a byproduct also participated in the C-H borylation. <sup>f</sup> A mixture of **3f** and **3f'** (92:8). <sup>g</sup> A mixture of **3f** and **3f'** (92:8). <sup>h</sup> Diborylated product (5%, GC) was also formed (see ESI).

The aliphatic substrates **1b-1k** were subjected to the Ir/Me<sub>4</sub>phen-catalyzed C(sp<sup>3</sup>)-H borylation at 110 °C with or without a catalytic amount of *t*-BuOK (Ir:*t*-BuOK = 1:0.25) (Table 2).<sup>14</sup> Diisopropyl ether (**1b**) and diisopentyl ether (**1c**), which showed low reactivity in the absence of *t*-BuOK (10-15% yields), underwent C-H borylation at the isopropyl and isopentyl termini, giving the borylalkyl ethers **3b** and **3c** in high yields (entries 1 and 2). The Ir/*t*-BuOK catalyst system was also effective for the borylation of a sterically less-hindered di-*n*-butyl ether (**1d**) (entry 3). Although the rhenium- and rhodium-catalysed C(sp<sup>3</sup>)-H borylation of **1d** has been reported by Hartwig and co-workers,<sup>7a,7b</sup> the present iridium-catalysed method is more advantageous in avoiding irradiation or high temperature reaction conditions. Although C3 borylation of tetrahydrofuran (**1e**) took place efficiently without *t*-BuOK as expected by a precedent,<sup>6b</sup> appreciable acceleration was observed in the presence of *t*-BuOK (entry 4). Substantial improvement by *t*-BuOK was achieved in the borylation of tetrahydropyran (**1f**), which showed moderate reactivity under *t*-BuOK-free conditions (entry 5). The reaction gave a mixture of the 3-boryl- and 4-boryltetrahydropyrans **3f** and **3f'** in a ratio of 92:8. In addition to the ethers **1a-1c**, the borylation was applicable to sterically hindered triisobutylamine (**1g**) to afford **3g** in good yield (entry 6). The reaction with *t*-BuOK was also effective in the borylation of



- 11 M. N. Eliseeva and L. T. Scott, *J. Am. Chem. Soc.* 2012, **134**, 15169.
- 12 Effectiveness of these additives has been reported also in the C(sp<sup>2</sup>)-H borylation of aromatic rings. See ref. 11.
- 13 For catalytic activation of the B-B bond of **2** by Lewis basic compounds, see: (a) K. Lee, A. R. Zhugralin and A. H. Hoveyda, *J. Am. Chem. Soc.* 2009, **131**, 7253; (b) A. Bonet, H. Gulyás and E. Fernández, *Angew. Chem. Int. Ed.* 2010, **49**, 5130; (c) A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás and E. Fernández, *Angew. Chem. Int. Ed.* 2011, **50**, 7158; (d) C. Kleeberg, A. G. Crawford, A. S. Batsanov, P. Hodgkinson, D. C. Apperley, M. S. Cheung, Z. Lin and T. B. Marder, *J. Org. Chem.* 2012, **77**, 785. For stoichiometric activation of **2** by *t*-BuOK, see: (e) C. Kleeberg, L. Dang, Z. Lin, T. B. Marder, *Angew. Chem. Int. Ed.* 2009, **48**, 5350. For activation of the B-B bond by forming sp<sup>3</sup> boron center, see: (f) M. Gao, S. B. Thorpe, C. Kleeberg, C. Slebodnick, T. B. Marder, W. L. Santos, *J. Org. Chem.* 2011, **76**, 3997. For a review, see: (g) J. Cid, H. Gulyás, J. J. Carbó and E. Fernández, *Chem. Soc. Rev.* 2012, **41**, 3558.
- 14 *General procedure for the C(sp<sup>3</sup>)-H borylation of 1 with t-BuOK:* In a glove box, a glass tube (outside diameter: 20 mm) having PTFE stopcock (J. Young), equipped with a magnetic stirring bar, was charged with [Ir(OMe)(cod)]<sub>2</sub> (0.020-0.050 mmol), Me<sub>4</sub>phen (0.040-0.10 mmol, Ir:Me<sub>4</sub>phen = 1:1), *t*-BuOK (0.01-0.025 mmol, Ir:*t*-BuOK = 1:0.25), **2** (254 mg, 1.0 mmol), and **1** (4.0 or 6.0 mmol). The tube was sealed by the stopcock and was taken out from the glove box. The mixture was stirred at 110 °C by a heating magnetic stirrer with an aluminum heating block (hole size: 21 mm diameter x 33 mm depth). After 20 h, the mixture was cooled to room temperature and undecane (39 mg, 0.25 mmol, internal standard) was added. The resulting mixture was analyzed by GC to determine the yield of the borylated products. After removal of the volatiles including HB(pin) under reduced pressure, the crude product was purified by column chromatography on silica gel and/or bulb-to-bulb distillation. *Caution: HB(pin) is readily decomposed by protic compounds such as water and generates hydrogen gas. The collected volatile materials during the concentration process should be treated carefully with MeOH to convert HB(pin) into MeOB(pin) before throw them away.*