ChemComm



ChemComm

Iridium-Catalysed Borylation of Sterically Hindered C(sp3)– H bonds: Remarkable Rate Acceleration by the Catalytic Amount of Potassium tert-Butoxide

Journal:	ChemComm
Manuscript ID:	CC-COM-02-2014-001262.R1
Article Type:	Communication
Date Submitted by the Author:	06-Mar-2014
Complete List of Authors:	Ohmura, Toshimichi; Kyoto University, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering Torigoe, Takeru; Kyoto University, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering Suginome, Michinori; Kyoto University, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering

SCHOLARONE[™] Manuscripts CITE THIS: DOI: 10.1039/c0xx00000x

ARTICLE TYPE

Iridium-Catalysed Borylation of Sterically Hindered C(sp³)–H bonds: **Remarkable Rate Acceleration by the Catalytic Amount of Potassium** tert-Butoxide

13

 $Cs_2CO_3(2)$

Toshimichi Ohmura,*^a Takeru Torigoe^a and Michinori Suginome*^a

s Received (in XXX, XXX) Xth XXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX DOI: 10.1039/b000000x

The $C(sp^3)$ -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 10 acceleration by a catalytic amount of t-BuOK.

Alkylboron compounds are versatile intermediates in the synthesis of aliphatic compounds via carbon-carbon and carbonheteroatom bond-formation at the boron-bound carbon atoms.¹ In addition to their application in organic synthesis, the molecular 15 function of alkylboron compounds has been explored rapidly, as exemplified by the bioactivity of α -aminoalkylboronic acids.² The preparation of alkylboron compounds has mainly relied on the hydroboration of alkenes,^{1a,3} together with the reactions of alkylmagnesium and alkyllithium reagents with boron 20 electrophiles. 4, 5 Recently, the transition-metal-catalyzed conversion of C(sp³)-H bonds into C(sp³)-B bonds has been developed as an alternative and more efficient route to alkylboron

- compounds.^{6,7,8} This catalytic C(sp³)-H borylation has an advantage over the conventional methods in that it allows the 25 conversion of unfunctionalized inert alkane derivatives. However, this borylation is rather sensitive to steric hindrance. Indeed, the
- $C(sp^3)$ -H bonds that can be borylated with high efficiency have been limited to the sterically less-hindered methyl on alkyl termini of acyclic substrates^{6b,7a-f,7h-i} or methylene units in cyclic 30 substrates.^{6b,6d,7j-1} Hartwig and co-workers have reported the
- C(sp³)-H borylation of the sterically hindered methyl side chain of polypropylene,^{7g} which needs extremely high reaction temperatures (185-200 °C). Although C(sp3)-H borylation of methylene groups in 2-alkylpyridines^{6c,6e,6g,7m} and 2-
- ³⁵ (hydrosilyl)alkylbenzenes^{6f,6h} has been achieved under relatively mild conditions, the reaction requires directing groups such as 2pyridyl and hydrosilyl groups. For further utilization of catalytic $C(sp^3)$ -H borylation, the development of more powerful catalyst systems is highly desirable to broaden substrate scope 40 considerably.

We have recently reported the iridium-catalysed $C(sp^3)$ -H borylation of organosilicon compounds.9 The efficient borylation at the methyl group of alkyltrimethylsilanes^{9b} indicated the potential reactivity of C(sp³)-H bonds that are located at 45 sterically hindered positions. We focused our attention on substrates having isopropyl groups, which have never been

reported to participate in catalytic C(sp³)-H borylation

efficiently.¹⁰ Herein, we describe an efficient catalytic system for the $C(sp^3)$ -H borylation of aliphatic substrates that do not bear 50 strong directing groups. A remarkable rate acceleration of the borylation was achieved by a catalytic amount of basic additives such as t-BuOK.



Me₄phen 14 $CsOH \cdot H_2O(2)$ 58 Me₄phen 15 CsF (2) Me₄phen 56 ^a 1a (2.0 mmol), 2 (0.50 mmol), [Ir(OMe)(cod)]₂ (0.020 mmol), a ligand (0.040 mmol), and an additive (0-0.060 mmol) were stirred at 110 °C for 20 h. ^b GC yield based on 2. ^c 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)]2 (4 mol %, 8 mol % Ir) and 3,4,7,8-tetramethylphenanthroline (Me₄phen, 8 mol %) without an additional solvent (entry 1, Table 1). The borylated product 3a 65 was formed only in 11% yield after 20 h, indicating that the

59

This journal is © The Royal Society of Chemistry [year]

sterically demanding **1a** is an unreactive substrate, even with the Ir-Me₄phen catalyst, which has been reported as an effective catalyst for $C(sp^3)$ –H borylation.^{6b,6d,6f,9} To achieve the borylation of **1a**, we tested the reaction in the presence of *t*-BuOK, which

- ^s has been reported by Eliseeva and Scott as an effective additive in the multiple borylation of C(sp²)–H bonds in aromatic compounds.¹¹ 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.¹¹ We found remarkable acceleration
- ¹⁰ of the $C(sp^3)$ -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
- ¹⁵ 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). Me₄phen is an essential ligand for the *t*-BuOK-accelerated $C(sp^3)$ -H borylation: other phenanthroline
- ²⁰ ligands, such as 4,7-dimethylphenanthroline (4,7-Me₂phen, 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'-Me₂bpy), which has been reported as an effective ligand in C(sp²)–H borylation under the Ir/t-BuOK catalyst
- ²⁵ system,¹¹ was completely ineffective for the C(sp³)–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, Cs₂CO₃, CsOH•H₂O, and CsF, promoted the borylation efficiently (entries 12-15).¹² These results indicate the ³⁰ possibility of activation of **2** by the additives,¹³ although Scott's
- ³⁰ possibility of activation of **2** by the additives, ⁴ although Scott's proposal where the additives change the structure of the iridium complex can not be ruled out.¹¹ 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
- ³⁵ indicates that HB(pin), which was formed as a by-product in the reaction of **1a** with **2**, hardly participated in the $C(sp^3)$ -H borylation of **1a**.

Table 2 Iridium-catalysed	$C(sp^3)$ -H borylation with or without	ut t-BuOK ^a
---------------------------	---	------------------------

			J (1) J			
			(pin)B–B(pin) (2 , 1 equiv) [Ir(OMe)(cod)] ₂ (2-5 mol %) Me₄phen (Ir:Me₄phen = 1:1) t-BuOK (Ir:t-BuOK = 1:0 or 1:0.25) 110 °C, 20 h		R—B(pin) 3	
40		н—н 1 (4 equiv)				
	Entry	Substrate	Product	Ir cat (mol %	% yield ^b without t-BuOK	% yield with <i>t</i> -BuOK
	1 ^{<i>d</i>}			ⁿ⁾ 6	10	96 (71)
	2		$\Big)_{2} \qquad \begin{array}{c} RO \\ BO $) 8	15	73 (63)
	3	0 () ₂ On-Bu B(pin) 3d	6	13	88 (75)



^a 1 (4.0 mmol), 2 (1.0 mmol), [Ir(OMe)(cod)]₂ (0.020-0.050 mmol), Me₄phen (Ir:Me₄phen = 1:1), and *t*-BuOK (Ir:*t*-BuOK = 1:0 or 1:0.25) were stirred at 110 °C for 20 h. ^b GC yield based on 2. ^c GC yield based on 2 and isolated yield in parentheses. ^d 1 (6.0 mmol) was used. ^e HB(pin)
⁴⁵ formed as a byproduct also participated in the C–H borylation. ^f A mixture of 3f and 3f' (92:8). ^g A mixture of 3f and 3f' (92:8). ^h Diborylated product (5%, GC) was also formed (see ESI).

The aliphatic substrates 1b-1k were subjected to the 50 Ir/Me4phen-catalyzed C(sp3)-H borylation at 110 °C with or without a catalytic amount of t-BuOK (Ir:t-BuOK = 1:0.25) (Table 2).¹⁴ 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 55 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 rhodiumcatalysed $C(sp^3)$ -H borylation of 1d has been reported by 60 Hartwig and co-workers, 7a,7b 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,^{6b} appreciable acceleration was observed 65 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 4boryltetrahydropyranes 3f and 3f' in a ratio of 92:8. In addition to 70 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

2 | Journal Name, [year], [vol], 00-00

This journal is © The Royal Society of Chemistry [year]

the unfunctionalized hydrocarbons **1h-1k** (entries 7-10). In the borylation of 1,3,5-triisopropylbenzene (**1h**), the $C(sp^3)$ -H on the isopropyl group reacted selectively over the $C(sp^2)$ -H on the aromatic ring, giving **3h** in high yield (entry 7). 2,4-Dimethylpentane (**1i**) gave a branched alkylboronate **3i** more

- s Dimethylpentane (11) gave a branched alkylboronate 31 more efficiently under the *t*-BuOK-modified conditions (entry 8). The borylation of isooctane (1j) took place selectively at the lessbranched terminus to afford 3j in moderate yield probably because of the high steric demand of the *tert*-butyl group (entry
- ¹⁰ 9). The Ir/*t*-BuOK catalyst system was effective even for the borylation of cyclohexane (**1k**), which has been achieved only by the (η^6 -mesitylene)Ir[B(pin)]₃/Me₄phen catalyst at 140 °C.^{6b}

The Ir/t-BuOK catalyst system could be applied to the gramscale synthesis of 3a (eq 1). The borylation of 1a took place 15 efficiently in a larger scale to give 1.9 g of 3a (74%).

 1a
 +
 2
 [[r(OMe)(cod)]_2 (4 mol %)]

 (40 mmol)
 (10 mmol)
 Me₄phen (8.4 mol %)
 3a
 (1)

 110 °C, 20 h
 110 °C, 20 h
 (1.9 g, 74%)
 3a
 (1)

We also found that $[IrCl(cod)]_2$, which is more stable and less expensive than $[Ir(OMe)(cod)]_2$, serves as a catalyst precursor for the $C(sp^3)$ -H borylation in the presence of *t*-BuOK. Use of the ²⁰ chloride with *t*-BuOK with the ratio of 1:1.25 resulted in comparable catalyst efficiency in the C-H borylation of **1e** (see ESI).

The present new C(sp³)–H borylation allows the use of inert, unfunctionalized organic feedstocks as new starting materials for 25 organic synthesis. The borylation products were successfully used

in Suzuki-Miyaura coupling^{1d} and one-carbon homologation reactions^{1c} (eqs 2 and 3).



30 Conclusions

In conclusion, we have established an efficient iridium catalyst system for the borylation of $C(sp^3)$ -H bonds. Significant improvement of catalyst efficiency was achieved via the use of a catalytic amount of *t*-BuOK with a Ir/Me₄phen catalyst. Using the ³⁵ iridium catalyst system, sterically hindered $C(sp^3)$ -H bonds in the

isopropyl group could be converted to C(sp³)–B bonds efficiently. This work is supported by Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed Toward Straightforward Synthesis (No. 23105520)" from MEXT and ⁴⁰ ACT-C FS from JST.

Notes and references

This journal is © The Royal Society of Chemistry [year]

^a Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan. Fax: +81-75-383-2722; Tel: +81-75-383-2723; E-

- 45 mail: ohmura@sbchem.kyoto-u.ac.jp; suginome@sbchem.kyoto-u.ac.jp † Electronic Supplementary Information (ESI) available: Experimental details and characterization data of the products. See DOI: 10.1039/b
 - (a) A. Pelter, K. Smith and H. C. Brown, *Boron Reagents*, Academic Press, London, 1988; (b) N. Miyaura and A. Suzuki, *Chem. Rev.* 1995, **95**, 2457; (c) D. S. Matteson, In *Boronic Acids*, D. Hall Ed.; Wiley-VCH, 2005, p. 305; (d) D. L. Sandrock In *Science of Synthesis: Cross Coupling and Heck-Type Reactions*, G. A. Molander, Ed.; Thieme, 2013; Vol 1, p 323.
 - (a) W. Yang, X. Gao and B. Wang, *Med. Res. Rev.* 2003, 23, 346; (b)
 L. R. Dick and P. E. Fleming, *Drug Discovery Today* 2010, 15, 243.
 - 3 (a) K. Burgess and M. J. Ohlmeyer, *Chem. Rev.* 1991, **91**, 1179; (b) I. Beletskaya and A. Pelter, *Tetrahedron* 1997, **53**, 4957; (c) C. M. Crudden and D. R. Edwards, *Eur. J. Org. Chem.* 2003, 4695.
 - 4 (a) H. R. Snyder, J. A. Kuck and J. R. Johnson, J. Am. Chem. Soc. 1938, 60, 105; (b) H. C. Brown and T. E. Cole, Organometallics 1983, 2, 1316.
 - 5 Examples of recent catalytic routes to unfunctionalized alkylboronic esters, see: (a) C.-T. Yang, Z.-Q. Zhang, H. Tajuddin, C.-C. Wu, J. Ling, J.-H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder and L. Liu, Angew. Chem. Int. Ed. 2012, 51, 528; (b) H. Ito and K. Kubota, Org. Lett. 2012, 14, 890; (c) A. S. Dudnik and G. C. Fu, J. Am. Chem. Soc. 2012, 134, 10693; (d) J. Yi, J.-H. Liu, J. Liang, J.-J. Dai, C.-T. Yang, Y. Fu and L. Liu, Adv. Synth. Catal. 2012, 354, 1685; (e) K. Kabuto, E. Yamamoto and H. Ito, J. Am. Chem. Soc. 2013, 135, 2635; (f) S. K. Bose, K. Fucke, L. Liu, P. G. Steel and T. B. Marder, Angew. Chem. Int. Ed. 2014, 53, 1799.
 - For Ir-catalysed C(sp³)–H borylation, see: (a) T. A. Boebel and J. F. Hartwig, *Organometallics* 2008, 27, 6013; (b) C. W. Liskey and J. F. Hartwig, *J. Am. Chem. Soc.* 2012, 134, 12422; (c) S. Kawamorita, R. Murakami, T. Iwai and M. Sawamura, *J. Am. Chem. Soc.* 2013, 135, 2947; (d) C. W. Liskey and J. F. Hartwig, *J. Am. Chem. Soc.* 2013, 135, 3375. (e) T. Mita, Y. Ikeda, K. Michigami and Y. Sato, *Chem. Commun.* 2013, 49, 5601; (f) S. H. Cho and J. F. Hartwig, *J. Am. Chem. Soc.* 2013, 135, 8157; (g) T. Iwai, T. Harada, K. Hara and M. Sawamura, *Angew. Chem. Int. Ed.* 2013, 52, 12322; (h) S. H. Cho and J. F. Hartwig, *Chem. Sci.* 2014, 5, 694.
 - 7 For Re-, Rh-, Pd-, and Ru-catalysed C(sp³)-H borylation, see: (a) H. Chen and J. F. Hartwig, Angew. Chem. Int. Ed. 1999, 38, 3391; (b) H. Chen, S. Schlecht, T. C. Semple and J. F. Hartwig, Science 2000, 287, 1995; (c) S. Shimada, A. S. Batsanov, J. A. K. Howard and T. B. Marder, Angew. Chem. Int. Ed. 2001, 40, 2168; (d) T. Ishiyama, K. Ishida, J. Takagi and N. Miyaura, Chem. Lett. 2001, 1082; (e) Y. Kondo, D. García-Cuadrado, J. F. Hartwig, N. K. Boaen, N. L. Wagner and M. A. Hillmyer, J. Am. Chem. Soc. 2002, 124, 1164; (f) J. D. Lawrence, M. Takahashi, C. Bae and J. F. Hartwig, J. Am. Chem. Soc. 2004, 126, 15334; (g) C. Bae, J. F. Hartwig, N. K. B. Harris, R. O. Long, K. S. Anderson and M. A. Hillmyer, J. Am. Chem. Soc. 2005, 127, 767; (h) C. Bae, J. F. Hartwig, H. Chung, N. K. Harris, K. A. Switek and M. A. Hillmyer, Angew. Chem. Int. Ed. 2005, 44, 6410; (i) J. M. Murphy, J. D. Lawrence, K. Kawamura, C. Incarvito and J. F. Hartwig, J. Am. Chem. Soc. 2006, 128, 13684; (j) V. J. Olsson and K. J. Szabó, Angew. Chem. Int. Ed. 2007, 46, 6891; (k) A. Caballero and S. Sabo-Etienne, Organometallics 2007, 26, 1191; (1) V. J. Olsson and K. J. Szabó, J. Org. Chem. 2009, 74, 7715; (m) S. Kawamorita, T. Miyazaki, T. Iwai, H. Ohmiya and M. Sawamura, J. Am. Chem. Soc. 2012, 134, 12924.
 - 8 For reviews, see: (a) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.* 2010, **110**, 890; (b) T. Ishiyama and N. Miyaura, In *Boronic Acids Second Edition*, D. Hall, Ed.; Wiley-VCH, 2011; Vol 1, p 135.
 - 9 (a) T. Ohmura, T. Torigoe and M. Suginome, *J. Am. Chem. Soc.* 2012, 134, 17416; (b) T. Ohmura, T. Torigoe and M. Suginome, *Organometallics* 2013, 32, 6170.
 - 10 It has been reported that the branched termini of 2-methylbutane and 2-methylheptane undergo the C–H borylation, although the borylation at the non-branched termini proceeds much faster. See ref. 7a and 7b.

- 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(sp²)– 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 sp³ 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 $C(sp^3)$ -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)]₂ (0.020-0.050 mmol), Me₄phen (0.040-0.10 mmol, Ir:Me₄phen = 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.

4 | Journal Name, [year], [vol], 00–00