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B(III)-Catalyzed C2-selective C–H Borylation of Heteroarenes

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Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday

Abstract: A BF₃•Et₂O catalyzed C2-selective C–H borylation of indoles with bis(pinacolato)diboron was developed to afford indole-2-boronic acid pinacol esters. A variety of functional groups were tolerated, and other heteroarenes like pyrrole and benzo[*b*]thiophene were also suitable substrates. An electrophilic substitution mechanism was proposed based on the preliminary mechanistic studies. This novel transformation utilizes simple and cheap BF₃•Et₂O as catalyst and exhibits unusual C2 regioselectivity, providing an significant implement to non-transition-metal catalyzed C–H borylation and an efficient method towards the synthesis of C2 functionalized heteroarenes.

Due to the synthetic versatility of organoboron compounds in organic synthesis,^[1] C–H borylation has become one of the most important C–H functionalization transformations and attracted considerable attentions in the past decade.^[2] Noble transition-metal-catalysis dominated C–H borylation, in which Iridium proved to be the most effective.^[3] Recently, several non-noble transition-metal catalysts have been reported to catalyze C–H borylation.^[4] Although these transition-metal-catalyzed processes exhibit high efficiency, non-transition-metal catalyzed C–H borylation is attractive for good reasons.



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Electrophilic C-H borylation has emerged to be a promising strategy in non-transition-metal-catalyzed C-H borylation.^[5] Early reports utilized BX₃ and BX₂H as boron electrophiles under harsh reaction conditions.^[6] Significant advance made by Vedejs,^[7] Ingleson,^[8] and others^[9] enabled the use of stoichiometric cationic boron electrophiles in C-H borvlation. Later on, catalytic C–H borylation employing catalytic initiators to generate boron electrophile was developed.^[10] Recently, Fontaine,^[11] Repo,^[12] Oestreich,^[13] Erker,^[14] Uchivama^[15] and Zhang^[16] achieved the electrophilic C3–H borylation of indoles with either HBpin or HBcat with the aid of catalytic FLPs and Lewis acid activators. On the other hand, Ingleson reported an I2-catalyzed electrophilic C2-H borylation of indole with Nheterocyclic carbene boranes (NHC•BH₃).^[17] The key to accessing C2-regioisomer products arises to the presence of a competent Brønsted acid. Although these reports well demonstrated the non-transition-metal-catalyzed electrophilic C-H borylation of indoles, an efficient and practical protocol for C2-H borylation is highly desirable. Herein, we communicate the simple and cheap BF3•Et2O catalyzed C2-selective C-H borylation of indoles and other heteroarenes with stable bis(pinacolato)diboron. Remarkably, the mechanism of this novel C-H borylation was briefly investigated indicating a S_EAr process.

N Me 1a	■H + B ₂ pin ₂ BF ₃ ·Et ₂ O(20 mol%) ⁿ octane/THF 140 °C, 16 h	N Me 2a
Entry	Variation from "standard conditions" ^[a]	Yield [%] ^[b]
1	none	88(81) ^[c]
2	no BF ₃ •Et ₂ O	0
3 ^[d]	BCl ₃ instead of BF ₃ •Et ₂ O	68
4	BPh ₃ instead of BF ₃ •Et ₂ O	68
5	$B(C_6F_5)_3$ instead of $BF_3 \bullet Et_2O$	4
6	no THF	45
7	HBpin instead of $B_2 pin_2$	10
8	1,4-dioxane instead of "octane	0
9	toluene instead of "octane	trace
10	120 °C instead of 140 °C	0

Table 1. BF3•Et2O catalyzed C2-H borylation of 1a with B2pin2: effects of

reaction parameters.

[a] Standard reaction conditions: **1a** (0.2 mmol), B_2pin_2 (0.4 mmol), $BF_3 \cdot Et_2O$ (0.04 mmol), ^{*n*} octane (1.5 mL), THF (0.1 mL), 140 °C, 16 h. [b] The yield was determined by GC, and calibrated using naphthalene as internal standard. [c] Isolated yield in parenthesis. [d] BCl₃ in ^{*n*} hexane (1.0 M).

We began by investigating the C–H borylation of 1-methyl indole **1a** with B_2pin_2 in the presence of various Lewis acid catalyst to prepare C2-borylated indole **2a**. After extensive

screening, the best result was obtained when the reaction was conducted under the conditions consisting of BF3•Et2O (20 mol%) in ⁿoctane/THF at 140 °C for 16 h affording the product 2a in 88% GC yield and 81% isolated yield (Table 1).

The effect of alteration to the "standard conditions" is listed in Table 1. In the absence of BF3•Et2O, essentially no reaction occurred. The use of boron catalysts like BCl3 and BPh3 both afforded 2a in 68% yield, while B(C₆F₅)₃ as catalyst afforded 2a in 4% yield. The use of THF as co-solvent is essential as lower yield of 2a was obtained with low reaction reproducibility in the absence of THF. Unlike other electrophilic C-H borylations, only 10% of 2a was obtained utilizing HBpin as boron source. 1,4-Dioxane and toluene proved to be non-suitable solvents for this C-H borylation. Lowering the reaction temperature to 120 °C gave no product.



Scheme 2. BF₃•Et₂O-catalyzed C2-H borylation of heteroarenes.^{[a][b]} [a] Reaction conditions: 1 (0.2 mmol), B₂pin₂ (0.4 mmol), BF₃•Et₂O (0.04 mmol), ⁿoctane (1.5 mL), THF (0.1 mL), 140 °C, 16 h. [b] Isolated yield. [c] BF₃•Et₂O (0.08 mmol). [d] 160 °C. [f] BPh3 (0.02 mmol).

With the optimized reaction conditions in hand, the C-H borylation of a variety of indoles 1 with B₂pin₂ was tested and the

results are compiled in Scheme 2. Similar to 1-methyl indole, the C-H borylation of 1-ⁿbutyl indole and 1-benzyl indole occurred smoothly affording the desired product in good yields. The reaction of C3 substituted indole produced the boronic ester 2d in 72% yield. To our delight, C4, C5, C6 and C7 substituted indoles worked well in the optimized system, and the corresponding reactions afforded moderate to good yields of C2 borylated products. Generally, both electron-donating and electron-withdrawing substituents on indole ring were well tolerated in this C-H borylation conditions. The reaction of indoles containing phenyl, methoxy and triisopropylsilyl groups produced the corresponding products in good yields. Halo substituents, such as F, Cl and Br, were all well tolerated, which provided the possibility for further functionalization. The borylation product was achieved in low yield when electrondeficient 7-azaindole was borylated. Remarkably, N-H indole was also suitable substrate, albeit in low yield. To our delight, Nbenzyl pyrrole also reacted to give the desired C2-borylated product in 23% yield. The borylation of benzo[b]thiophene also occurred at C2 position afforded 2s using BPh₃ as catalyst. Other heteroarenes such as 3-bromothiophene and N-methyl carbazole gave only trace products under the present reaction conditions.





The synthetic versatility of 2-boryl indoles obtained by the present BF₃•Et₂O-catalyzed C2–H borylation was demonstrated (Scheme 3). A copper-mediated cyanation of 2a with TMSCN 3 was conducted to give bioactive 2-cyanoindole 4 whose structure exists in many natural compounds and pharmaceutical agents.^[18] 1,2-Bis(indol-2-yl)benzene 6 was also obtained in 95% yield via Suzuki coupling between 2-borylindole 2g and 1,2diiodobenzene 5, which serves as an effective skeleton in materials chemistry.[19]

Furthermore, the mechanism of this C-H borylation was briefly investigated by performing various control experiments. To test the possibility of radical mechanism, [20] indole bearing cyclopropyl group at C3 position 7 was synthesized and subjected to the borylation reaction conditions (Scheme 4A). The C2-borylated product 8 was obtained in 25% yield without the detection of ring-opening product. On the other hand, the C-H borylation of **1a** with the addition of one equivalent of radical scavenger 9 was conducted affording the product 2a in 76% vield (Scheme 4A). These results ruled out the possibility of radical process. Notably, this protocol afforded C2-borylated indoles instead of C3 regioisomers normally obtained by SEAr C-H borylation. To figure out the reason for the unusual C2 regioselectivity, several experiments were conducted to probe

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the reversibility of the borylation reaction (Scheme 4B). Treatment of **2a**' under standard conditions resulted in complete protodeborylation to **1a** while most **2a** reserved with partial protodeborylation to **1a**.^[21] The treatment of **2a** and **2a**' in same pot resulted in the formation of stoichiometric amount of **2a** and **1a**. These results ruled out the possibility of mutual reversibility between **2a**' and **2a**, and indicated that C2 isomers are more thermodynamically stable than C3 isomers under the present reaction conditions. Therefore, the dominant C2 regioselectivity was observed. The intermolecular competition experiment of **[CD₃]-1a** and **[D]-1a** in the same pot was also performed (Scheme 4C). A reverse kinetic isotope effect was observed, indicating that C–H bond cleavage is not the rate-determining step.

(A) Radical Clock and Trapping Experiments





Scheme 5. Proposed mechanism.

On the basis of the above results and previous reports,^[22] we proposed a mechanism for the C2–H borylation of **1a** (for the proposed mechanism for the C2–H borylation of **1r** see Supporting Information file) (Scheme 5). An initial attack of BF₃ to C3 position of **1a** affords intermediate **I**, which reacts with B₂pin₂ to generate intermediate **II**. Then intermediate **II** forms intermediate **III** and **IV**. The subsequent deprotonation of **III** by **IV** yields product **2a** and HBpin,^[23] and regenerates BF₃.

In summary, a novel BF₃·Et₂O-catalyzed C2-selective C–H borylation of indoles as well as other heteroarenes with bis(pinacolato)diboron was disclosed. A variety of functional groups were tolerated, and various indole-2-boronic acid pinacol esters were obtained in moderate to good yields. Preliminary mechanistic studies indicated a possible electrophilic substitution borylation mechanism. Additional exploration of the substrate scope and mechanistic studies are currently underway and will be reported in the due course.

Experimental Section

An oven-dried 25-mL Schlenk tube equipped with a magnetic stirring bar was charged with B₂pin₂ (0.4 mol, 101.6 mg) and flushed with nitrogen gas. Heteroarene (0.2 mmol), BF₃•Et₂O (0.04 mmol, 5.0 µL), THF (0.1 mL) and ⁿoctane (1.5 mL) were added to the tube under nitrogen atmosphere. The sealed tube was heated at 140 °C for 16 h in a heating module or oil bath with stirring. After cooling the reaction mixture to room temperature, the mixture was concentrated and directly purified by flash column chromatography over silica gel eluting with petroleum/ethyl acetate to afford the product.

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Keywords: C–H borylation • heteroarenes • BF₃•Et₂O • C2 selectivity • bis(pinacolato)diboron

a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483; b) D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933-2936; c) D. Hall in *Boronic Acids: Preparation and Applications*, Wiley, Weinheim, **2011**.

 a) T. Ishiyama, N. Miyaura, J. Organomet. Chem. 2003, 680, 3-11; b) I.
 A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, Chem. Rev. 2010, 110, 890-931; c) J. F. Hartwig, Chem. Soc. Rev. 2011, 40, 1992-2002; d) J. F. Hartwig, Acc. Chem. Res. 2012, 45, 864-873; e) A. Ros, R.
 Fernandez, J. M. Lassaletta, Chem. Soc. Rev. 2014, 43, 3229-3243.

[3] a) H. Chen, S. Schlecht, T. C. Semple, J. F. Hartwig, *Science* 2000, 287, 1995-1997; b) J.-Y. Cho, C. N. Iverson, M. R. Smith, III, *J. Am. Chem. Soc.* 2000, *122*, 12868-12869; c) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith, III, *Science* 2002, *295*, 305-308; d) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* 2002, *124*, 390-391; e) T. Furukawa, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* 2015, *137*, 12211-12214; f) J. Takaya, S. Ito, H. Nomoto, N. Saito, N. Kirai, N. Iwasawa, *Chem. Commun.* 2015, *51*, 17662-17665.

a) J. V. Obligacion, S. P. Semproni, P. J. Chirik, J. Am. Chem. Soc. [4] 2014, 136, 4133-4136; b) W. N. Palmer, J. V. Obligacion, I. Pappas, P. J. Chirik, J. Am. Chem. Soc. 2016, 138, 766-769; c) J. V. Obligacion, S. P. Semproni, I. Pappas, P. J. Chirik, J. Am. Chem. Soc. 2016, 138, 10645-10653; d) N. G. Leonard, M. J. Bezdek, P. J. Chirik, Organometallics 2017, 36, 142-150; e) K. M. Waltz, X. He, C. Muhoro, J. F. Hartwig, J. Am. Chem. Soc. 1995, 117, 11357-11358; f) G. Yan, Y. Jiang, C. Kuang, S. Wang, H. Liu, Y. Zhang, J. Wang, Chem. Commun. 2010, 46, 3170-3172; g) T. Hatanaka, Y. Ohki, K. Tatsumi, Chem. - Asian J. 2010, 5, 1657-1666; h) T. J. Mazzacano, N. P. Mankad, J. Am. Chem. Soc. 2013, 135, 17258-17261; i) T. Dombray, C. G. Werncke, S. Jiang, M. Grellier, L. Vendier, S. Bontemps, J.-B. Sortais, S. Sabo-Etienne, C. Darcel, J. Am. Chem. Soc. 2015, 137, 4062-4065; j) T. J. Mazzacano, N. P. Mankad, Chem. Commun. 2015, 51, 5379-5382; k) H. Zhang, S. Hagihara, K. Itami, Chem. Lett. 2015, 44, 779-781; I) T. Furukawa, M. Tobisu, N. Chatani, Chem. Commun. 2015, 51, 6508-6511; m) S. K. Bose, A. Deissenberger, A. Eichhorn, P. G. Steel, Z. Lin, T. B. Marder, Angew. Chem., Int. Ed. 2015, 54, 11843-11847.

[5] M. J. Ingleson, Synlett 2012, 23, 1411-1415.

a) D. T. Hurd, J. Am. Chem. Soc. 1948, 70, 2053-2055; b) S. M.
 McElvain, P. L. Weyna, J. Am. Chem. Soc. 1959, 81, 2579-2588; c) E. L.
 Muetterties, J. Am. Chem. Soc. 1960, 82, 4163-4166; d) E. L. Muetterties, F. N.
 Tebbe, Inorg. Chem. 1968, 7, 2663-2664.

[7] a) T. S. De Vries, A. Prokofjevs, J. N. Harvey, E. Vedejs, *J. Am. Chem.* Soc. 2009, 131, 14679-14687; b) A. Prokofjevs, J. W. Kampf, E. Vedejs,
 Angew. Chem., Int. Ed. 2011, 50, 2098-2101; c) T. S. De Vries, A. Prokofjevs,
 E. Vedejs, *Chem. Rev.* 2012, *112*, 4246-4282.

[8] a) A. Del Grosso, P. J. Singleton, C. A. Muryn, M. J. Ingleson, Angew. Chem., Int. Ed. 2011, 50, 2102-2106; b) A. Del Grosso, M. D. Helm, S. A. Solomon, D. Caras-Quintero, M. J. Ingleson, Chem. Commun. 2011, 47, 12459-12461; c) S. A. Solomon, A. Del Grosso, E. R. Clark, V. Bagutski, J. J. W. McDouall, M. J. Ingleson, Organometallics 2012, 31, 1908-1916; d) V. Bagutski, A. Del Grosso, J. A. Carrillo, I. A. Cade, M. D. Helm, J. R. Lawson, P. J. Singleton, S. A. Solomon, T. Marcelli, M. J. Ingleson, J. Am. Chem. Soc. 2013, 135, 474-487; e) A. Del Grosso, J. Ayuso Carrillo, M. J. Ingleson, Chem. Commun. 2015, 51, 2878-2881; f) M. J. Ingleson, Top. Organomet. Chem. 2015, 49, 39-71.

[9] a) R. Köster, Angew. Chem. Int. Ed. Engl. 1964, 3, 174-185; b) P.
Koelle, H. Noeth, Chem. Rev. 1985, 85, 399-418; c) H. Laaziri, L. O. Bromm, F.
Lhermitte, R. M. Gschwind, P. Knochel, J. Am. Chem. Soc. 1999, 121, 6940-6941; d) B. Goldfuss, P. Knochel, L. O. Bromm, K. Knapp, Angew. Chem., Int. Ed. 2000, 39, 4136-4139; e) A. M. Genaev, G. E. Salnikov, V. G. Shubin, S. M.
Nagy, Chem. Commun. 2000, 1587-1588; f) J. A. Varela, D. Pena, B. Goldfuss, D. Denisenko, J. Kulhanek, K. Polborn, P. Knochel, Chem. - Eur. J. 2004, 10, 4252-4264; g) W. E. Piers, S. C. Bourke, K. D. Conroy, Angew. Chem., Int. Ed. 2005, 44, 5016-5036; h) B. Goldfuss, Chem. - Eur. J. 2009, 15, 12856-12861; i) N. Ishida, T. Moriya, T. Goya, M. Murakami, J. Org. Chem. 2010, 75, 8709-8712; j) T. Hatakeyama, S. Hashimoto, S. Seki, M. Nakamura, J. Am. Chem. Soc. 2011, 133, 18614-18617.

[10] a) A. Del Grosso, R. G. Pritchard, C. A. Muryn, M. J. Ingleson, Organometallics 2010, 29, 241-249; b) A. Prokofjevs, E. Vedejs, J. Am. Chem. Soc. 2011, 133, 20056-20059; c) T. Stahl, K. Muether, Y. Ohki, K. Tatsumi, M. Oestreich, J. Am. Chem. Soc. 2013, 135, 10978-10981; d) A. Prokofjevs, J. Jermaks, A. Borovika, J. W. Kampf, E. Vedejs, Organometallics 2013, 32, 6701-6711.

[11] a) M.-A. Legare, M.-A. Courtemanche, E. Rochette, F.-G. Fontaine, *Science* 2015, 349, 513-516; b) M.-A. Legare, E. Rochette, J. Legare Lavergne, N. Bouchard, F.-G. Fontaine, *Chem. Commun.* 2016, 52, 5387-5390.

[12] K. Chernichenko, M. Lindqvist, B. Kotai, M. Nieger, K. Sorochkina, I. Papai, T. Repo, *J. Am. Chem. Soc.* **2016**, *138*, 4860-4868.

[13] Q. Yin, H. F. T. Klare, M. Oestreich, Angew. Chem., Int. Ed. 2017, 56, 3712-3717.

[14] Y.-L. Liu, G. Kehr, C. G. Daniliuc, G. Erker, *Chem. - Eur. J.* 2017, 23, 12141-12144.

[15] F. Kitani, R. Takita, T. Imahori, M. Uchiyama, *Heterocycles* **2017**, *95*, 158-166.

 S. Zhang, Y. Han, J. He, Y. Zhang, J. Org. Chem. 2018, 83, 1377-1386.
 J. S. McGough, J. Cid, M. J. Ingleson, Chem. - Eur. J. 2017, 23, 8180-8184.

[18] a) I. Borza, S. Kolok, K. Galgoczy, A. Gere, C. Horvath, S. Farkas, I. Greiner, G. Domany, *Bioorg. Med. Chem. Lett.* 2007, *17*, 406-409; b) Y. Ye, Y. Wang, P. Liu, F. Han, *Chin. J. Chem.* 2013, *31*, 27-30; c) L. Almagro, F. Fernandez-Perez, M. A. Pedreno, *Molecules* 2015, *20*, 2973-3000; d) N. Zeidan, S. Bognar, S. Lee, M. Lautens, *Org. Lett.* 2017, *19*, 5058-5061.

a) T. Tanaka, A. Osuka, *Chem. Commun.* 2015, *51*, 8123-8125; b) Y.
 Ren, M. Sezen, F. Guo, F. Jakle, Y.-L. Loo, *Chem. Sci.* 2016, *7*, 4211-4219.

[20] Radical mechanism is proposed in C–H silylation and C–X/C–H borylation processes. a) W.-B. Liu, D. P. Schuman, Y.-F. Yang, A. A. Toutov, Y. Liang, H. F. T. Klare, N. Nesnas, M. Oestreich, D. G. Blackmond, S. C. Virgil, S. Banerjee, R. N. Zare, R. H. Grubbs, K. N. Houk, B. M. Stoltz, *J. Am. Chem. Soc.* 2017, *139*, 6867-6879; b) G. Yan, D. Huang, X. Wu, *Adv. Synth. Catal.* 2018, *360*, 1040-1053, and references therein.

[21] Preliminary studies indicated the proton source of protodeborylation might be the water within the quenching solvents.

[22] a) F. Focante, I. Camurati, D. Nanni, R. Leardini, L. Resconi, Organometallics 2004, 23, 5135-5141; b) L. Wang, T. Zhang, W. Sun, Z. He, C. Xia, Y. Lan, C. Liu, J. Am. Chem. Soc. 2017, 139, 5257-5264.

[23] 11% to 12% GC yield of HBpin was detected in the C-H borylation reaction of indoles (1a, 1b, 1f).

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