



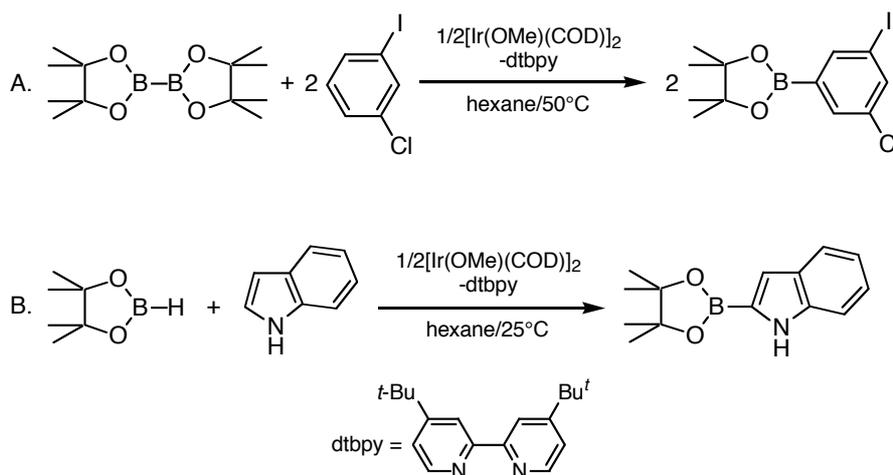
Title	Iridium-Catalyzed C-H Borylation of Arenes and Heteroarenes: 1-Chloro-3-iodo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene and 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)indole
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## IRIDIUM-CATALYZED C-H BORYLATION OF ARENES AND HETEROARENES:

### 1-CHLORO-3-iodo-5-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)BENZENE

### NZENE and 2-(4,4,5,5,-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)INDOLE



Submitted by Tatsuo Ishiyama, Jun Takagi, Yusuke Nobuta and Norio Miyaura.<sup>1</sup>

Checked by

## 1. Procedure

*Caution! The reactions produce hydrogen gas and should be conducted in a well-ventilated hood.*

A. 1-Chloro-3-iodo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene. A

50-mL, two-necked, round-bottomed flask is fitted with a magnetic stirring bar, a rubber septum, and a condenser to which a nitrogen inlet and an oil bubbler are attached, and flushed with nitrogen (Note 1). The septum is removed and the flask is charged with bis( $\eta^4$ -1,5-cyclooctadiene)-di- $\mu$ -methoxy-diiridium(I) ( $[\text{Ir}(\text{OMe})(\text{COD})]_2$ ) (33 mg, 0.050 mmol) (Note 2), 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) (27 mg, 0.10 mmol) (Note 3), and bis(pinacolato)diboron (2.67 g, 10.5 mmol) (Note 4). The septum is again placed on the flask, and the flask is purged with nitrogen for 1 min. Hexane (30 mL) (Note 5) is added, and the flask is immersed in an oil bath that is maintained at 50°C. The mixture is stirred for 10 min to give a dark red solution. The flask is charged with 1-chloro-3-iodobenzene (4.75 g, 19.9 mmol) (Note 6), and then the resulting dark red solution is stirred at 50°C for 6 hr (Note 7). The mixture is removed from the oil bath, allowed to cool to room temperature, and poured into a separatory funnel. The reaction flask is rinsed with hexane (2 x 10 mL). The rinses and water (30 mL) are added to the separatory funnel, the funnel is shaken, the layers are separated, and the organic extracts are dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and is washed with hexane (3 x 10 mL), and the filtrate is concentrated on a rotary evaporator to give a dark brown oil. The oil is distilled under reduced pressure (Note 8) to afford 6.34 g (87%) of

1-chloro-3-iodo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene as a white solid, bp 145-148°C (0.3 mm) (Note 9).

*B. 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)indole.* A 50-mL, two-necked, round-bottomed flask is fitted with a magnetic stirring bar, a rubber septum, and a condenser to which a nitrogen inlet and an oil bubbler are attached, and flushed with nitrogen (Note 1). The septum is removed and the flask is charged with bis( $\eta^4$ -1,5-cyclooctadiene)-di- $\mu$ -methoxy-diiridium(I) ( $[\text{Ir}(\text{OMe})(\text{COD})]_2$ ) (50 mg, 0.075 mmol) (Note 2) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) (40 mg, 0.15 mmol) (Note 3). The septum is again placed on the flask, and the flask is purged with nitrogen for 1 min. Hexane (30 mL) (Note 5) and pinacolborane (4.79 mL, 33.0 mmol) (Note 10) are added, and the flask is immersed in an oil bath that is maintained at 25°C. The mixture is stirred for 10 min to give a dark red solution. The flask is charged with indole (3.51 g, 30.0 mmol) (Note 11), and then the resulting dark red suspension is stirred at 25°C for 4 hr. The mixture is removed from the oil bath, allowed to cool to room temperature, and poured into a separatory funnel. The reaction flask is rinsed with ether (2 x 20 mL). The rinses and water (30 mL) are added to the separatory funnel, the funnel is shaken, the layers are separated, and the organic extracts are dried over anhydrous magnesium sulfate. The drying agent is removed by filtration

and is washed with ether (3 x 10 mL), and the filtrate is concentrated on a rotary evaporator to give a dark brown oil. The oil is distilled under reduced pressure (Note 12) to afford 5.70 g (78%) of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole as a colorless viscous oil, bp 149-153°C (0.15 mm) (Note 13).

## 2. Notes

1. All glassware is pre-dried in an oven at 120°C for 1 hr, assembled while hot, and allowed to cool under a stream of nitrogen.

2.  $[\text{Ir}(\text{OMe})(\text{COD})]_2$  is prepared from  $[\text{IrCl}(\text{COD})]_2$  by the reported procedure.<sup>2</sup> The complex can be handled in air, and stored in a tightly closed bottle and in a freezer.

3. dtbpy was purchased from Aldrich Chemical Company, Inc., and used without further purification.

4. Bis(pinacolato)diboron is prepared according to the literature procedure,<sup>3</sup> and dried under reduced pressure (0.1 mm) at room temperature for 16 hr prior to use. The reagent is air-stable and commercially available.

5. Hexane is distilled from lithium aluminum hydride under nitrogen before

use.

6. 1-Chloro-3-iodobenzene was purchased from Tokyo Kasei Kogyo Co., Ltd., and distilled from molecular sieves 4A under nitrogen before use.

7. The reaction by using 1.5 mol% of the catalyst is completed within 4 hr at room temperature, but the decrease of the amounts of the catalyst to 0.5 mol% sufficiently slows down the rate of the reaction and required heating to 50°C to complete the reaction in mean time.

8. 1-Chloro-3-iodobenzene (28 mg) that is unreacted or resulted by protodeboration of the desired product is also obtained, bp 60°C (0.05 mm).

9. Gas chromatographic analysis of the product (Hitachi G-3500, OV-101 on Uniport B, a glass column, 3 mm x 2 m) shows that the chemical purity is over 99%. The spectral data are as follows:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.33 (s, 12 H), 7.73 (d, 1 H,  $J = 2.0$ ), 7.78 (t, 1 H,  $J = 1.8$ ), 8.00 (t, 1 H,  $J = 0.8$ );  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 24.81, 84.46, 94.20, 133.72, 134.71, 139.42, 141.42;  $^{11}\text{B}$  NMR (128.3 MHz,  $\text{CDCl}_3$ )  $\delta$ : 29.58 ( $\text{BF}_3 \cdot \text{OEt}_2$  as external reference,  $\delta$  0.00); high resolution mass spectrum, calcd for  $\text{C}_{12}\text{H}_{15}\text{BClIO}_2$  [ $\text{M}^+$ ], 363.9899, found 363.9890.

10. Pinacolborane was purchased from Aldrich Chemical Company, Inc., and used without further purification.

11. Indole was purchased from Tokyo Kasei Kogyo Co., Ltd., and dried under reduced pressure (0.1 mm) at room temperature for 16 hr prior to use.

12. Indole (29 mg) that is unreacted or resulted by protodeboration of the desired product is also obtained, bp 120°C (0.7 mm).

13. Gas chromatographic analysis of the product (Hitachi G-3500, OV-101 on Uniport B, a glass column, 3 mm x 2m) shows that the chemical purity is 96%. The spectral data are as follows:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.37 (s, 12 H), 7.10 (dt, 1 H,  $J = 0.8, 8.7$ ), 7.12 (d, 1 H,  $J = 0.7$ ), 7.23 (dt, 1 H,  $J = 1.1, 7.6$ ), 7.39 (dd, 1 H,  $J = 1.0, 8.3$ ), 7.68 (dd, 1 H,  $J = 1.0, 8.1$ ), 8.56 (br s, 1 H);  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 24.81, 84.13, 111.24, 113.83, 119.77, 121.59, 123.62, 128.27, 138.19;  $^{11}\text{B}$  NMR (128.3 MHz,  $\text{CDCl}_3$ )  $\delta$ : 28.45 ( $\text{BF}_3 \cdot \text{OEt}_2$  as external reference,  $\delta$  0.00); high resolution mass spectrum, calcd for  $\text{C}_{14}\text{H}_{18}\text{BNO}_2$  [ $\text{M}^+$ ], 243.1431, found 243.1423.

### **Waste Disposal Information**

All toxic materials were disposed in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

### 3. Discussion

Aryl- and heteroarylboron derivatives are important class of compounds that have been applied to various fields of chemistry.<sup>4</sup> Traditional methods for their synthesis are based on the reactions of trialkylborates with aryl- and heteroarylmagnesium or -lithium reagents.<sup>5</sup> Pd-catalyzed cross-coupling of aryl and heteroaryl halides with tetra(alkxo)diborons<sup>6</sup> or di(alkoxo)boranes<sup>7</sup> is a milder variant where the preparation of magnesium and lithium reagents is avoided.

Alternatively, the catalytic C-H borylation of arenes and heteroarenes, which has been first reported by Smith,<sup>8</sup> is highly attractive as a halide-free process for the synthesis of aryl- and heteroarylboron compounds.<sup>9</sup> Among the catalyts developed to date, the combination of  $1/2[\text{Ir}(\text{OMe})(\text{COD})]_2$  and dtbpy described here exhibits high activity, which allows the formation of aryl- and heteroarylboronates in high yields at room temperature from an equimolar equivalent of bis(pinacolato)diboron ( $\text{pin}_2\text{B}_2$ , pin =  $\text{Me}_4\text{C}_2\text{O}_2$ ) or pinacolborane (pinBH) and arenes or heteroarenes (Table 1).<sup>9j-l</sup>

The regiochemistry of the borylation of arenes is primarily controlled by the steric effects of substituents. The reaction occurs at C-H bonds located meta or para to a substituent in preference to those located ortho. Thus, 1,2- and 1,4-disubstituted

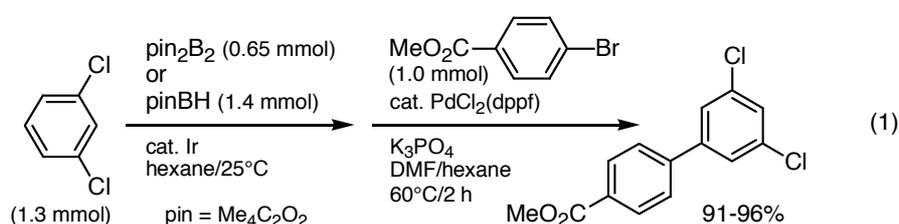
arenes bearing identical substituents yield arylboronates as single isomers. The borylation of 1,3-disubstituted arenes proceeds at the common meta position; therefore, regioisomerically pure products are obtained even for two distinct substituents on the arenes. In the case of five-membered heteroarenes, the electronegative heteroatom causes the C-H bonds at the  $\alpha$ -positions to be active so that the borylation occurs at the  $\alpha$ -positions. Thus, the regioselective monoborylation of 2-substituted or benzo-fused substrates can be possible. Although a mixture of 2-borylated and 2,5-diborylated products is formed from unsubstituted substrates, both products are selectively obtained by reactions with the appropriate ratio of substrate and reagent. On the other hand, six-membered heteroarenes such as pyridine shows significantly lower reactivity due to strong coordinating ability of the basic nitrogen for the catalyst. Exceptionally, 2,6-disubstituted pyridines undergo smooth borylation at the  $\gamma$ -position.

Functional group tolerance of the borylation is quite high. The reaction selectively occurs at the C-H bond for substrates possessing Cl, Br, I, CF<sub>3</sub>, OMe, CO<sub>2</sub>Me, and CN groups. The reaction occurs only at the aromatic C-H bonds even when the substrate has weaker benzylic C-H bonds.

Aryl- and heteroarylboronic acids and esters have been used for the synthesis

of biaryls via the palladium-catalyzed cross-coupling reaction with aryl electrophiles.<sup>10</sup>

The sequential reaction involving the aromatic C-H borylation and the cross-coupling with aryl electrophiles in the same flask provides an efficient and convenient route to unsymmetrical biaryls (eq. 1).

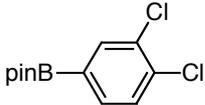
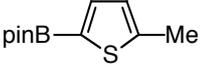
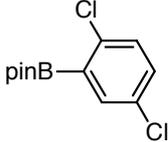
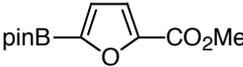
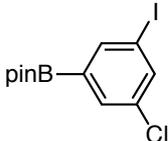
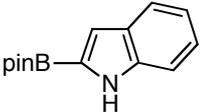
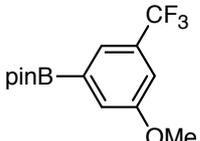
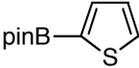
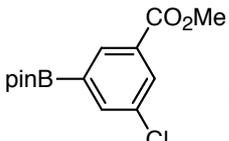
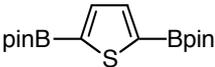
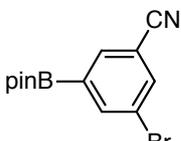
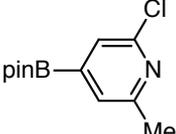


1. Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan.
2. Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126.
3. (a) Nöth, H. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1984**, *39B*, 1463; (b) Ishiyama, T.; Murata, M.; Ahiko, T.-a.; Miyaura, N. *Org. Synth.* **2000**, *77*, 176.
4. Reviews see: (a) Vaultier, M.; Carboni, B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 11, p 191; (b) Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem.* **1999**, 527; (c) Shinkai, S.; Ikeda, M.; Sugasaki, A.; Takeuchi, M. *Acc. Chem. Res.* **2001**, *34*, 494; (d) Entwistle, C. D.; Marder, T. B. *Angew. Chem., Int. Ed.*

- 2002**, *41*, 2927; (e) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515; (f) Yang, W.; Gao, X.; Wang, B. *Med. Res. Rev.* **2003**, *23*, 346.
5. Nesmeyanov, A. N.; Sokolik, R. A. *Methods of Elemento-Organic Chemistry*; North-Holland: Amsterdam, 1967; Vol. 1.
6. (a) A review see: Ishiyama, T.; Miyaura, N. *J. Synth. Org. Chem., Jpn.* **1999**, *57*, 503; (b) A review see: Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392; (c) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508; (d) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N.; *Tetrahedron Lett.* **1997**, *38*, 3447; (e) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813.
7. Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164.
8. Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696.
9. (a) A review see: Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *680*, 3; (b) Chen, H.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391; (c) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995; (d) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000**, *122*, 12868; (e) Tse, M. K.; Cho, J. Y.; Smith, M. R., III. *Org. Lett.* **2001**, *3*, 2831; (f) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*,

- 305; (g) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168; (h) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390; (i) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649; (j) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056; (k) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* in press; (l) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* in press.
- 10.** (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11; (c) Suzuki, A.; Brown, H. C. *Organic Syntheses Via Boranes*; Aldrich Chemical Company, Inc.: Milwaukee, 2003; Vol. 3.

TABLE 1. SYNTHESIS OF ARYL- AND HETEROARYLBORONATES<sup>a</sup>

Product	Yield (%) <sup>b</sup>		Product	Yield (%) <sup>b</sup>	
	A <sup>c</sup>	B <sup>d</sup>		A <sup>c</sup>	B <sup>d</sup>
	82 (8 h)	73 (8 h)		95 (2 h)	91 (2 h)
	53 (24 h)	22 (24 h)		80 (2 h)	95 (0.5 h)
	82 (4 h)	67 (8 h)		88 (0.5 h)	99 (0.5 h)
	81 (8 h)	73 (24 h)		91 <sup>e</sup> (1 h)	75 <sup>f</sup> (0.5 h)
	80 (8 h)	70 (24 h)		83 <sup>g</sup> (0.5 h)	86 <sup>h</sup> (2 h)
	83 (2 h)	74 (2 h)		84 (4 h)	75 (2 h)

<sup>a</sup> Reactions were carried out at 25°C in hexane (6 mL) by using substrate (1.0 mmol) and 1/2[Ir(OMe)(COD)]<sub>2</sub>-dtbpy catalyst. <sup>b</sup> GC yields based on substrates. <sup>c</sup> Method A: pin<sub>2</sub>B<sub>2</sub> (0.50 mmol)/Ir cat. (0.015 mmol). <sup>d</sup> Method B: pinBH (1.1 mmol)/Ir cat. (0.03 mmol). <sup>e</sup> 5.0 mmol of thiophene was used. The yield is based on pin<sub>2</sub>B<sub>2</sub>. <sup>f</sup> 5.0 mmol of thiophene and 1.0 mmol of pinBH was used. The yield is based on pinBH. <sup>g</sup> 1.0 mmol of pin<sub>2</sub>B<sub>2</sub> was used. <sup>h</sup> 2.2 mmol of pinBH was used.