Pergamon

Tetrahedron Letters 43 (2002) 5649–5651

TETRAHEDRON
LETTERS

Iridium-catalyzed C–H coupling reaction of heteroaromatic compounds with bis(pinacolato)diboron: regioselective synthesis of heteroarylboronates

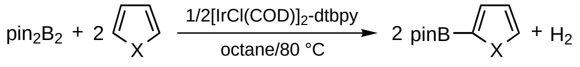
Jun Takagi,[a] Kazuaki Sato,[a] John F. Hartwig,[b] Tatsuo Ishiyama[a,]* and Norio Miyaura[a,]*

[a]*Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan*
[b]*Department of Chemistry, Yale University, PO Box 208107, New Haven, CT 06520-8107, USA*

Received 9 May 2002; revised 5 June 2002; accepted 7 June 2002

Abstract—The C–H coupling of aromatic heterocycles with bis(pinacolato)diboron was carried out in octane at 80–100°C in the presence of a 1/2[IrCl(COD)]$_2$-(4,4′-di-*tert*-butyl-2,2′-bipyridine) catalyst (3 mol%). The reactions of five-membered substrates such as thiophene, furan, pyrrole, and their benzo-fused derivatives exclusively produced 2-borylated products, whereas those of six-membered heterocycles including pyridine and quinoline selectively occurred at the 3-position. Regioselective synthesis of bis(boryl)heteroaromatics was also achieved by using an almost equimolar amount of substrates and the diboron. © 2002 Elsevier Science Ltd. All rights reserved.

The transition metal-catalyzed cross-coupling reaction of aromatic substrates with (alkoxo)diborons has attracted considerable attention as a powerful tool for the synthesis of arylboron compounds. Aryl electrophiles such as halide and triflate derivatives have been efficiently employed as substrates for this protocol.[1] Although the utility of the reaction has been amply demonstrated by elegant synthesis of natural products,[2] biologically active compounds,[3] and functional materials,[4] an extension of the methodology toward the direct borylation of aromatic hydrocarbons would provide a more efficient and convenient route to arylboron compounds because of the wide availability and low cost of hydrocarbons. Hartwig has reported the C–H coupling of benzene with bis(pinacolato)diboron (pin_2B_2, pin = $Me_4C_2O_2$) catalyzed by $Cp^*Re(CO)_3$[5] or $Cp^*Rh(\eta^4\text{-}C_6Me_6)$[6] under photoirradiation or at temperatures above 150°C. Similar reactions with pinacolborane in the presence of a $(\eta^5\text{-}C_9H_7)Ir(COD)$-dppe (-dmpe)[7] or a $(Cp^*RhCl_2)_2$[8] catalyst also have been presented by Smith and Marder, respectively. On the other hand, we recently found that iridium(I) complexes generated from an air-stable, commercially available [IrCl(COD)]$_2$ precursor and a simple 2,2′-bipyridine (bpy) ligand exhibited high catalytic activity toward the C–H coupling of various arenes with pin_2B_2 at 80°C.[9] We wish to disclose here the C–H coupling between pin_2B_2[10] (**1**) and heteroaromatic substrates (**2**) catalyzed by 1/2[IrCl(COD)]$_2$-(4,4′-di-*tert*-butyl-2,2′-bipyridine) (dtbpy) in octane at 80–100°C to give the corresponding heteroarylboronates (**3**) in high yields with high regioselectivity (Eq. (1)).



1 **2** X = S, O, NH **3** (1)

dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine

The borylation of thiophene (60 mmol) with pin_2B_2 **1** (1.0 mmol) in the presence of a catalyst generated from [IrCl(COD)]$_2$ (0.015 mmol) and bpy (0.03 mmol) resulted in no conversion of **1** even after 16 h at 80°C,[9] presumably due to the high coordinating ability of thiophene which strongly retards the formation of a coordinatively unsaturated iridium species active for C–H activation. The result prompted us to use an appropriate solvent inactive toward the C–H coupling. Indeed, the desired monoborylation product **3** was obtained in 64% yield when 10 mmol of thiophene was diluted in 6 ml of octane. The dtbpy complex exhibited higher catalytic activity (83%) than that of bpy due to its higher solubility in octane. The selectivity of monoborylation versus diborylation depended on the relative stoichiometry of thiophene and **1**. For instance,

---

Keywords: boron and compounds; arenes; iridium and compounds; coupling reactions.

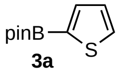
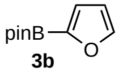
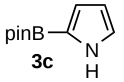
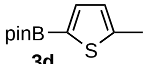
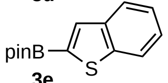
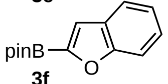
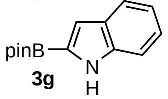
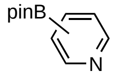
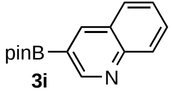
* Corresponding authors. Tel.: +81-11-706-6562; fax: +81-11-706-6562; e-mail: ishiyama@org-mc.eng.hokudai.ac.jp

0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)01135-8

the use of 10 mmol of thiophene produced mono- and bis(boryl)thiophene in a ratio of 83:17. The ratio was decreased to 56:44 in the presence of 2.5 mmol of thiophene and improved to 93:7 when using 20 mmol of thiophene. However, the increase in concentration of thiophene retarded the reaction and gave only 69% yield. The borylation regioselectively occurred at the 2-position of thiophene in all cases.

The synthesis of mono(boryl)heteroaromatics **3** by the C–H coupling between pin_2B_2 **1** and representative heteroaromatic substrates **2** in the presence of a catalytic amount of $1/2[IrCl(COD)]_2$-dtbpy complex at 80–100°C in octane is shown in Table 1.[11] As for five-membered **2**, not only thiophene (entry 1) but also furan and pyrrole regioselectively provided 2-borylated products **3** in high yields accompanied by diborylated products (ca. 15%) (entries 2 and 3). On the other hand, 2-methylthiophene selectively yielded a monoborylation product (entry 4). The selective monoborylation of benzothiophene, benzofuran, and indole was easily achieved because the second borylation of the aromatic ring was significantly slower than the first borylation at the 2-position (entries 5–7). Although the reactions of pyridine and quinoline were slow at 80°C, the borylation smoothly proceeded at 100°C (entries 8 and 9). Pyridine afforded a mixture of 3- and 4-borylated products (**3h** and **3h′**) in a ratio of 67:33, while quinoline exclusively yielded a 3-borylated product.

Table 1. Synthesis of mono(boryl)heteroaromatics **3** (Eq. (1))[a]

entry	boronate **3**	**2**/equiv	temp/°C	yield/%[b]	I.P./%[c]
1	 **3a**	10	80	83[d]	> 99
2	 **3b**	10	80	83[d]	92[e]
3	 **3c**	10	80	67[d]	99
4	 **3d**	10	80	91	> 99
5	 **3e**	4	80	89	> 99
6	 **3f**	4	80	91	97[e]
7	 **3g**	4	80	92	> 99
8	 **3h + 3h'**	2	100	42[d]	67:33[f]
9	 **3i**	10	100	84	> 99

[a] A mixture of diboron **1** (1.0 mmol), heteroaromatic compound **2** (2-10 mmol), $[IrCl(COD)]_2$ (0.015 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.03 mmol), and octane (6 ml) was stirred at 80-100 °C for 16 h.

[b] GC yields based on boron atom in **1**.

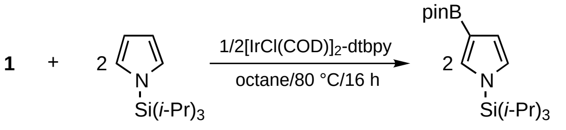
[c] Isomeric purities (I.P.) were determined by ^1H NMR and GC.

[d] Diborylated products were also produced (12-17%).

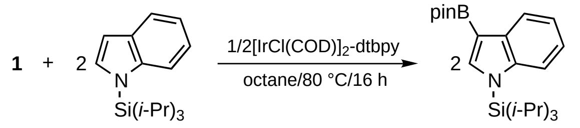
[e] Reactions were accompanied by 3-borylated products.

[f] Ratio of 3- and 4-borylpyridine.

As reported for arene C–H borylation, coupling at C–H bonds located *ortho* to substituents was very slow due to steric hindrance.[9] This effect allows a regioselective synthesis of 3-borylpyrrole and -indole by using *N*-substituted substrates. Although 1-methylpyrrole and -indole still showed preferential reactivity at the 2-position (76:24 and 89:11), sterically more hindered triisopropylsilyl derivatives reacted to provide 3-boryl isomers selectively (Eqs. (2) and (3)).[12] The triisopropylsilyl group can be deprotected by treatment with TBAF or CF_3CO_2H to provide isomerically pure 3-borylpyrrole or -indole.[13]

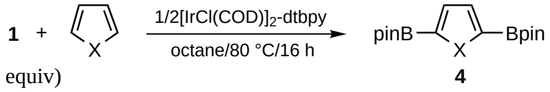


(4 equiv) 79% (I.P. > 99%) (2)



(4 equiv) 83% (I.P. > 99%) (3)

The synthesis of bis(boryl)heteroaromatics (**4**) is shown in Eq. (4). Thiophene, furan, and pyrrole were all converted to the corresponding 2,5-diborylated products **4** in high yields with excellent regioselectivity in the presence of 1.1 equiv. of pin_2B_2 **1**. The formation of the 2,5-diborylated product from furan (62%) was accompanied by a small amount of alternative 2,4-diborylated product (9%). The palladium-catalyzed cross-coupling reaction of bis(boryl)arenes with dihaloarenes has been used for the synthesis of functional polymers such as conducting materials.[14]



(1.1 equiv) **4**

X = S: 80% (I.P. > 99%) (4)
O: 71% (I.P. = 87%)
NH: 80% (I.P. > 99%)

The borylation of these heteroaromatic substrates **2** most likely proceeds through tris(boryl)iridium(III) intermediates that were isolated by Marder,[15] Smith,[7] and Hartwig[9] and shown to give arylboronates upon thermolysis with arenes. A number of transition metal complexes are known to activate a C–H bond at the 2-position of **2**.[16] Therefore, C–H activation at the 2-position of **2** by tris(boryl)iridium(III) intermediates, followed by C–B bond formation, is a reasonable mechanism for borylation of **2**. However, the regioselectivity of the borylation of pyridine and quinoline to give 3-borylated products is perplexing. One possibility is that an iridium complex or a boron compound binds reversibly to the basic nitrogen and both activates the substrate for reaction and blocks borylation at the 2-position.

References

1. (a) For a review: Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392; (b) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508; (c) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447; (d) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 8683; (e) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813; (f) Fürstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541.
2. (a) Zembower, D. E.; Zhang, H. *J. Org. Chem.* **1998**, *63*, 9300; (b) Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1999**, *64*, 2976; (c) Elder, A. M.; Rich, D. H. *Org. Lett.* **1999**, *1*, 1443; (d) Lin, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1967; (e) Lin, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 512.
3. (a) Nakamura, H.; Fujiwara, M.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7529; (b) Malan, C.; Morin, C. *J. Org. Chem.* **1998**, *63*, 8019; (c) Firooznia, F.; Gude, C.; Chan, K.; Marcopulos, N.; Satoh, Y. *Tetrahedron Lett.* **1999**, *40*, 213; (d) Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477; (e) McKenna, J. M.; Moliterni, J.; Qiao, Y. *Tetrahedron Lett.* **2001**, *42*, 5797.
4. (a) Deng, Y.; Chang, C. K.; Nocera, D. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1066; (b) Wang, S.; Oldham, W. J., Jr.; Hudack, R. A., Jr.; Bazan, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 5695; (c) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500; (d) Iovine, P. M.; Kellett, M. A.; Redmore, N. P.; Therien, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 8717; (e) Sakai, N.; Gerard, D.; Matile, S. *J. Am. Chem. Soc.* **2001**, *123*, 2517.
5. Chen, H.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391.
6. Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995.
7. Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305.
8. Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168.
9. Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.
10. (a) Nöth, H. *Z. Naturforsch.* **1984**, *39b*, 1463; (b) Ishiyama, T.; Murata, M.; Ahiko, T.-a.; Miyaura, N. *Org. Synth.* **2000**, *77*, 176.
11. A representative procedure for **3**: A flask placed with $[IrCl(COD)]_2$ (0.015 mmol), dtbpy (0.03 mmol), and pin_2B_2 **1** (1.0 mmol) was flushed with nitrogen, and then charged with octane (6 ml) and thiophene (10 mmol). The mixture was then stirred at 80°C for 16 h. The product was isolated by Kugelrohr distillation to give an analytically pure sample: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.35 (s, 12H), 7.20 (dd, 1H, $J=3.7$ and 4.6 Hz), 7.64 (d, 1H, $J=4.6$ Hz), 7.66 (d, 1H, $J=3.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 24.75, 84.07, 128.21, 132.35, 137.14; exact mass calcd for $C_{10}H_{15}BO_2S$ 210.0886, found 210.0881.
12. Tse, M. K.; Cho, J.-Y.; Smith, M. R., III *Org. Lett.* **2001**, *3*, 2831.
13. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p. 389.
14. (a) Zotti, G.; Gallazzi, M. C.; Zerbi, G.; Meille, S. V. *Synth. Met.* **1995**, *73*, 217; (b) Parakka, J. P.; Jeevarajan, J. A.; Jeevarajan, A. S.; Kispert, L. D.; Cava, M. P. *Adv. Mater.* **1996**, *8*, 54; (c) Remonen, T.; Hellberg, J.; Slätt, J. *Synth. Met.* **1999**, *101*, 107; (d) Jayakannan, M.; van Dongen, J. L. J.; Janssen, R. A. J. *Macromolecules* **2001**, *34*, 5386.
15. Nguyen, P.; Blom, H. P.; Westcott, S. A.; Taylor, N. J.; Marder, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 9329.
16. (a) Dong, L.; Duckett, S. B.; Ohman, K. F.; Jones, W. D. *J. Am. Chem. Soc.* **1992**, *114*, 151; (b) Morikita, T.; Hirano, M.; Sasaki, A.; Komiya, S. *Inorg. Chim. Acta* **1999**, *291*, 341; (c) Ringelberg, S. N.; Meetsma, A.; Hessen, B.; Teuben, J. H. *J. Am. Chem. Soc.* **1999**, *121*, 6082; (d) Arndt, S.; Spaniol, T. P.; Okuda, J. *Eur. J. Inorg. Chem.* **2001**, 73.