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Ester-Directed Regioselective Borylation of Heteroarenes Catalyzed by a Silica-Supported Iridium Complex

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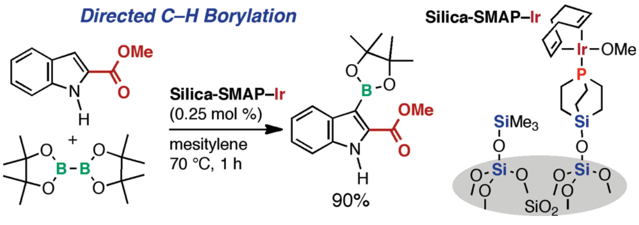

The ester-directed regioselective borylation of arenes catalyzed by a silica-supported monophosphine−Ir complex displayed a significantly broad substrate scope toward heteroaromatic compounds, including thiophene, pyrrole, furan, benzothiophene, benzofuran, indole, and carbazole derivatives. The regioselectivity is complementary to the selectivities observed in the heteroarene C−H borylation with the dtbpy-Ir catalyst system.

Transition metal-catalyzed direct functionalization of aromatic C−H bonds has recently emerged as an area of active research in organic synthesis. Catalytic C−H borylation of arenes has allowed efficient synthesis of various borylated arenes, which are versatile synthetic intermediates.[1−5] We reported recently that an immobilized monophosphine−Ir system [Silica-SMAP−Ir (**1**)], which was prepared in situ from a silica-supported, compact monophosphine (Silica-SMAP) and [Ir(OMe)(cod)]$_2$, showed high activity and selectivity for the directed ortho borylation of functionalized arenes with bis(pinacolato)diboron (pinB−Bpin, **2**).[5−7] Extension of this method to the regioselective borylation of heteroarenes would be of particular interest due to the importance of heteroarene structures in pharmaceuticals, bioactive natural compounds, and functional organic materials. We were, however, faced with at least two challenges. First, the heteroatom in the heteroarene cores might prevent the coordination of the directing group to the metal center. Second, the electronic effect of the heteroatom, which potentially induces the borylation at the 2-position as observed by Miyaura−Ishiyama's[8] and Smith's[9] groups with the dtbpy−Ir system (dtbpy: 4,4′-di-*tert*-butylbipyridine), might compete with the coordination-based directing effect.

Herein we report that the borylation of ester-functionalized heteroarenes with the Silica-SMAP−Ir (**1**) catalyst system results in coordination-based regioselectivity that complements the selectivities observed in sterically and/or electronically controlled heteroarene borylations with the dtbpy−Ir catalyst system. The use of the immobilized ligand (Silica-SMAP) was crucial for the ester-directed regioselectivity in the borylation of various types of heteroarenes including thiophene, pyrrole, benzothiophene, furan, benzofuran, indole, and carbazole derivatives.[8−10]

The reaction of 5-methyl-2-methoxycarbonylthiophene (**3a**, 1 mmol) with an equimolar amount of **2** (1 mmol) in hexane in the presence of 0.25 mol % of Silica-SMAP−Ir-(OMe)(cod) (**1**) proceeded at 70 °C and was complete within 10 h to give borylation product **4a** in 99% isolated yield (based on **3**, 100% NMR yield) (Scheme 1).[11] The reaction

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(1) For a review, see: Mkhalid, I. A.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931.

(2) (a) Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **1999**, *121*, 7696–7697. (b) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305–308. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (d) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056–3058. (e) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278. (f) Chotana, G. A.; Rak, M. A.; Smith, M. R., III *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544.

(3) For the directed ortho borylation of benzoate derivatives catalyzed by the Ir−P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ system, see: Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159–161.

(4) For ortho borylation of arenes directed by a Me$_2$HSi group, see: Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535.

(5) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058–5059.

(6) SMAP: **s**ilicon-constrained **m**onodentate tri**a**lkyl**p**hosphine. See: (a) Ochida, A.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2003**, *5*, 2671–2674. (b) Ochida, A.; Ito, S.; Miyahara, T.; Ito, H.; Sawamura, M. *Chem. Lett.* **2006**, *35*, 294–295. (c) Ochida, A.; Hamasaka, G.; Yamauchi, Y.; Kawamorita, S.; Oshima, N.; Hara, K.; Ohmiya, H.; Sawamura, M. *Organometallics* **2008**, *27*, 5494–5503.

(7) For the synthesis and applications of Silica-SMAP, see: (a) Hamasaka, G.; Ochida, A.; Hara, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5381–5383. (b) Hamasaka, G.; Kawamorita, S.; Ochida, A.; Akiyama, R.; Hara, K.; Fukuoka, A.; Asakura, K.; Chun, W. J.; Ohmiya, H.; Sawamura, M. *Organometallics* **2008**, *27*, 6495–6506. (c) Kawamorita, S.; Hamasaka, G.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *Org. Lett.* **2008**, *10*, 4697–4700.

(8) (a) Takagi, J.; Sao, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649–5651. (b) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103–1106.

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(10) (a) Chen, J.; Aratani, N.; Shinokubo, H.; Osuka, A. *Chem. Asian J.* **2009**, *4*, 1126–1133. (b) Chen, J.; Mizumura, M.; Shinokubo, H.; Osuka, A. *Chem.—Eur. J.* **2009**, *15*, 5942–5949. (c) Klecka, M.; Pohl, R.; Klepetarova, B.; Hocek, M. *Org. Biomol. Chem.* **2009**, *7*, 866–868. (d) Mertins, K.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2004**, 21–25. (e) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068–4069.

(11) The isolated products were contaminated with traces of unidentified compounds that stem from pinacolborane (H−Bpin) alone (ca. 0.1−3%) based on the ratio of the integral of the methyl protons of the pinacol moiety (12H).

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SCHEME 1

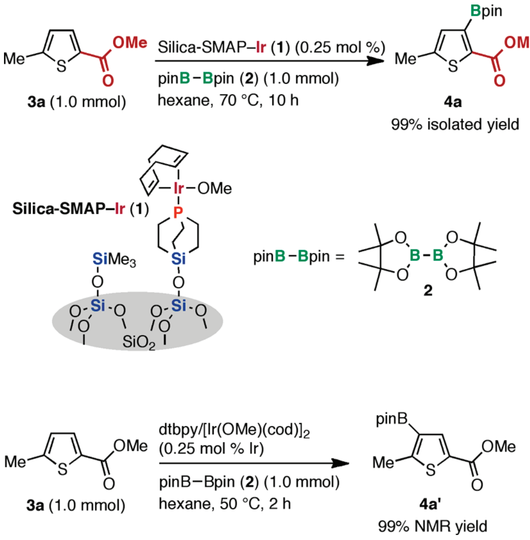
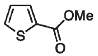
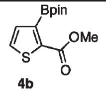
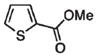
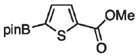
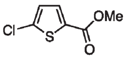
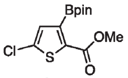
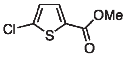
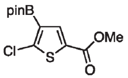
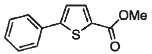
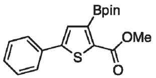
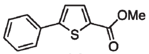
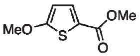
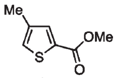
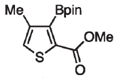
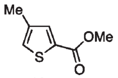
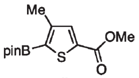
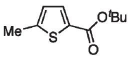
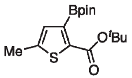


TABLE 1. Ir-Catalyzed Borylation of 2-Thiophenecarboxylic Acid Esters[a,b]

entry	thiophene	catalyst	temp (°C)	time (h)	product	yield (%)[c]
1[d]	 **3b**	**1**	70	4	 **4b**	74[e] (88)
2	 **3b**	dtbpy–Ir	50	2	 **4b'**	(99)
3	 **3c**	**1**	70	10	 **4c**	99
4	 **3c**	dtbpy–Ir	100	40	 **4c'**	(71)
5[f]	 **3d**	**1**	70	20	 **4d**	97 (99)
6[f]	 **3d**	dtbpy–Ir	70	20	complex mixture	–
7	 **3e**	dbpy–Ir	70	24	no reaction	
8	 **3f**	**1**	70	5	 **4f**	92[g] (92)
9	 **3f**	dtbpy–Ir	70	5	 **4f'**	(99)
10	 **3g**	**1**	100	1	 **4g**	93

[a] Conditions: **3** (1.0 mmol), **2** (1.0 mmol), Silica-SMAP–Ir(OMe)(cod) (**1**, 0.25 mol %), hexane or octane (2.0 mL). [b] Conditions: **3** (1.0 mmol), **2** (1.0 mmol), [Ir(OMe)(cod)]$_2$ (0.125 mol %), dtbpy (0.25 mol %), hexane or octane (2.0 mL). [c] Isolated yield of **4** based on **3**. ^{1}H NMR yield is in parentheses. [d] 3,5-Bis-borylation product was detected in the crude mixture (12%). [e] The product was obtained as a mixture of **4b** and **4b'** (**4b**/**4b'** 91:9). [f] *p*-Xylene was used as a solvent. [g] The product was obtained as a mixture of **4f** and **4f'** (**4f**/**4f'** 97:3).

was completely regioselective, delivering the boryl group to the 3-position. Notably, the reaction was also selective for monoborylation; no diborylation was observed, even with use of stoichiometric quantities of the reactants. The corresponding homogeneous catalysts that were prepared in situ from [Ir(OMe)(cod)]$_2$ and Ph-SMAP[6] (0.25 mol % Ir, Ir/P 1:1 or 1:2) afforded no borylation products under otherwise similar reaction conditions, indicating that phosphine immobilization is crucial, as was the case in the directed ortho borylation of carbocyclic arenes.[3]

The regioselectivity observed with the Silica-SMAP–Ir system is in sharp contrast to that seen with the dtbpy–Ir(OMe)(cod) system.[8,9] In our hands, the application of the dtbpy–Ir system to the reaction between **3a** and **2** resulted in the exclusive formation of isomer **4a'** (Scheme 1). The regioselectivity of the reaction catalyzed by the dtbpy–Ir system seems to be controlled by steric factors.

The ester-directed borylation was applicable to various thiophene derivatives (**3b**–**g**).[11] The results are summarized in Table 1 along with those obtained with the dtbpy–Ir system.[2,8,9] The borylation of 2-methoxycarbonylthiophene **3b** occurred at the 3-position to form **4b** selectively but also formed the minor isomer **4b'** with the boryl group at the 5-position, which is α to the sulfur atom (C3/C5 91:9; **4b**/diborylation product 87:13) (entry 1).[12] In contrast, the dtbpy–Ir-catalyzed borylation took place exclusively at the 5-position (entry 2).

The substitution at the 5-position of 2-methoxycarbonylthiophene with Cl (**3c**) or Ph (**3d**) groups resulted in the recovery of complete ester-directed regioselectivity (entries 3 and 5). When dtbpy was used as a ligand, the reaction of **3c** was sluggish even at 100 °C, and showed C-4 regioselectivity (entry 4). Notably, the reaction of the phenyl-substituted thiophene **3d** with the dtbpy ligand resulted in a complex mixture, which included isomers derived from borylation not only at the thiophene ring but also the phenyl group (entry 6). The comparison between entries 5 and 6 demonstrates the utility of the ester-directed methodology in the preparation of multiaromatic organoboron compounds. Unfortunately, the 5-methoxy-2-carbomethoxythiophene (**3e**) did not react at all. This result seems to be due to an electronic rather than a steric effect (entry 7).

The borylation of 4-methyl-2-methoxycarbonylthiophene (**3f**) proceeded with excellent selectivity at 70 °C regardless of the considerable steric congestion at the 3-position (C3/C5 97:3) (entry 8). With dtbpy–Ir, however, the borylation occurred exclusively at the 5 position (entry 9). In addition to the methyl ester substituent, the *tert*-butyl ester

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[12] The lithiation of **3b** with LDA and subsequent trapping with B(O^{i}Pr)$_3$ followed by treatment with pinacol provided compound **4b'** with the boryl group at the 5-position, which is α to the sulfur atom (74%). On the other hand, the lithiation–borylation of **3a** resulted in a complex mixture. See: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (b) Mackin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519–2522.

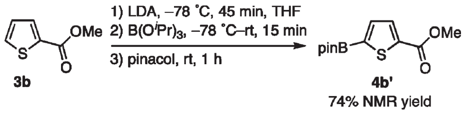
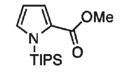
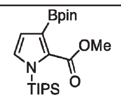
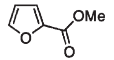
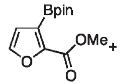
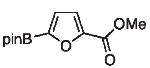
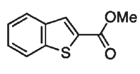
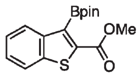
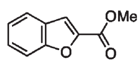
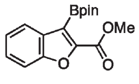
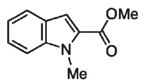
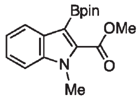
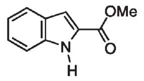
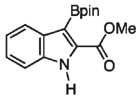
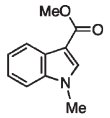
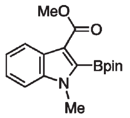
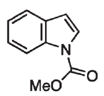
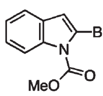
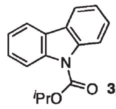
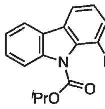


TABLE 2. Borylation of Hetereoarenes Catalyzed by the Silica-SMAP−Ir System[a]

entry	heteroarene	product	temp (°C)	time (h)	yield (%)[b]
1[c]	 **3h**	 **4h**	70	7	96
2[c]	 **3i**	 **4i** +  **4i'**	50	3	56[f]
3	 **3j**	 **4j**	100	20	85
4	 **3k**	 **4k**	50	1	92
5	 **3l**	 **4l**	100	2	84
6[d]	 **3m**	 **4m**	70	1	90
7	 **3n**	 **4n**	100	4	99
8[c]	 **3o**	 **4o**	50	12	83
9[e]	 **3p**	 **4p**	100	6	79

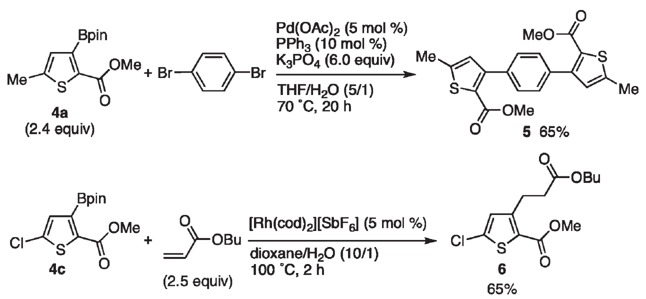
[a] Conditions: **3** (1.0 mmol), **2** (1.0 mmol), Silica-SMAP−Ir(OMe)(cod) (**1**, 0.25 mol %), solvent (2.0 mL, entries 1 and 8, hexane; entries 2, 3, 5−7, and 9, mesitylene; entry 4, *p*-xylene). [b] Isolated yield of **4** based on **3**. [c] Bis-borylation products were detected in the crude mixture (entry 1, 3,5-isomer, 3%; entry 2, 3,5-isomer, 21%; entry 8, 2,7-isomer, 5%). [d] 2.0 mmol of **2** was used. [e] 0.5 mol % of Silica-SMAP−Ir(OMe)(cod) was used. [f] The product was obtained as a mixture of **4i** and **4i′** (**4i**/**4i′** 79:21).

moiety also served as a directing group to deliver the boryl functionality to the adjacent position with complete selectivity (entry 10).

Heteroarenes other than thiophenes also participated in the ester-directed regioselective borylation (Table 2).[11] For instance, 3-borylation of *N*-TIPS-protected 2-pyrrole carboxylic acid ester (**3h**) was successfully carried out under essentially the same conditions (entry 1). The borylation of 2-methoxycarbonylfuran (**3i**) also occurred but with lower selectivity than that observed for **3b** (entry 2).

The highly regioselective nature of the ester-directed borylation enabled the use of benzofused heteroaromatic compounds as substrates, regardless of the presence of multiple aromatic C−H bonds (Table 2, entries 3−9).[13] The reactions of benzothiophene (**3j**) and benzofuran (**3k**) derivatives with a 2-methoxycarbonyl substituent occurred exclusively at the position adjacent to the ester group (entries 3 and 4). The reaction was also effective for the functionalization of indoles (entries 5−8). The ester groups at the 2-position or the 3-position in 1-methylindole directed the borylation to the adjacent positions with complete selectivity (entries 5 and 7). Even the NH-free indole **3m** underwent the regioselective borylation, although the occurrence of *N*-borylation required the use of an excess amount of **2** (entry 6). In addition, the methoxycarbonyl group on the nitrogen atom of the *N*-protected indole **3o** delivered the boryl group to the 2-position of the nitrogen-containing five-membered-ring moiety (entry 8). Likewise, *N*-isopropoxycarbonylcarbazole **3p** underwent selective monoborylation at the 1-position (entry 9).

SCHEME 2. Transformations with Borylated Thiophenes



Transformations of selected borylated thiophenes were conducted to demonstrate their reactivity (Scheme 2). Suzuki−Miyaura coupling between **4a** and 1,4-dibromobenzene afforded bisthiophenylbenzene **5**. The Rh-catalyzed conjugate addition of **4c** to butyl acrylate furnished the thiophene derivative with a functionalized alkyl group at the 3-position in good yield.

In summary, the ester or carbamate-directed borylation of arenes catalyzed by a silica-supported monophosphine−Ir complex displayed a broad substrate scope toward heteroaromatic compounds, including thiophene, pyrrole, furan, benzothiophene, benzofuran, indole, and carbazole derivatives. The regioselectivities observed with the Silica-SMAP−Ir system are complementary to those obtained in the sterically and/or electronically controlled heteroarene C−H borylation reactions carried out with the dtbpy−Ir catalyst system.

Experimental Section

Typical Procedure for the Borylation of Heteroarenes Catalyzed by the Ir−Silica-SMAP System (Scheme 1, the upper side). In a glovebox, Silica-SMAP (0.064 mmol P g^{-1}, 39 mg, 0.0025 mmol), bis(pinacolato)diboron (**2**, 253.9 mg, 1.0 mmol), and anhydrous, degassed hexane (1.6 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar, then the mixture was stirred for 1 min at 25 °C. A solution of [Ir(OMe)(cod)]$_2$ (0.8 mg, 0.00125 mmol) in hexane (0.4 mL) and thiophene-2-carboxylic acid methyl ester (**3a**, 156.2 mg, 1.0 mmol) were added to the tube, which was then sealed with a screw cap. The tube was removed from the glovebox and the solution was stirred at 70 °C for 10 h. The mixture was then filtered through a glass pipet equipped with a cotton filter. Solvent was removed

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[13] For the regioselective borylation of benzothiophene, benzofuran, and indole at the 2-position, see refs 2d and 8a.

under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the reaction mixture and the product yield was determined by ^{1}H NMR. The crude material was then purified by Kugelrohr distillation to give the borylation product **4a** (283.1 mg, 0.99 mmol) in 99% isolated yield (contaminated with 3% impurity). **4a**: white solid. ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 12H), 2.49 (d, J = 1.2 Hz, 3H), 3.85 (s, 3H), 6.85 (d, J = 1.2 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ 15.12, 24.66, 51.89, 84.24, 130.77, 135.42, 147.42, 163.14. A signal for the carbon directly attached to the boron atom was not observed. HRMS-EI (m/z) $[M]^+$ calcd for $C_{12}H_{19}BO_4S$ 282.10998, found 282.10971. Mp 94.2 °C.

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Supporting Information Available: Experimental procedures and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.