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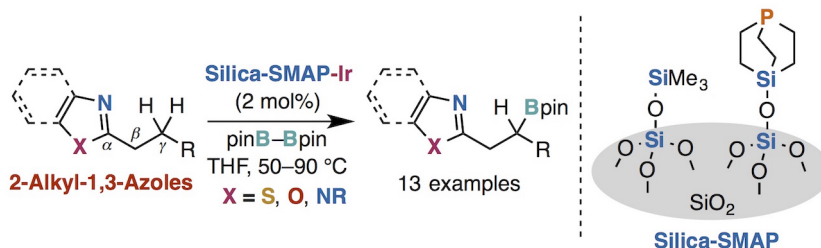
Title	Site-Selective and Stereoselective C(sp ³)-H Borylation of Alkyl Side Chains of 1,3-Azoles with a Silica-Supported Monophosphine-Iridium Catalyst
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Site-selective and Stereoselective C(sp³)-H Borylation of Alkyl Side Chains of 1,3-Azoles with a Silica-Supported Monophosphine-Ir Catalyst

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Abstract Site-selective and stereoselective C(sp³)-H borylation of alkyl side chains of 1,3-azoles with bis(pinacolato)diboron was effectively catalyzed by a silica-supported monophosphine-Ir catalyst. The borylation occurred under relatively mild conditions (2 mol% Ir, 50–90 °C), affording the corresponding primary and secondary alkylboronates. This system was applicable to a variety of 1,3-(benzo)azoles such as thiazoles, oxazoles, and imidazoles.

Key words 1,3-azole, C-H activation, borylation, Iridium, heterogeneous catalyst

1,3-Azoles are common structures in many biologically active natural compounds, pharmaceuticals and organic functional materials, and many of these molecules have an alkyl substituent at the 2-position (Figure 1).¹ Therefore, functionalization of the alkyl side chain of 1,3-azoles is of great importance for construction of complex molecules containing 1,3-azole scaffolds.² Among the methods for functionalization of alkyl groups, C(sp³)-H borylation is attractive because alkylboron compounds are versatile synthetic intermediates with broad functional group compatibility, and air- and moisture stability.^{3,4} Despite recent significant progress in this area, the site-selective borylation of unactivated C(sp³)-H bonds over potentially more reactive C-H bonds such as C(sp²)-H bonds remains challenging.^{5–10} Moreover, the stereoselective borylation of C(sp³)-H bonds is underdeveloped.^{5e,5g,5h,7,10a}

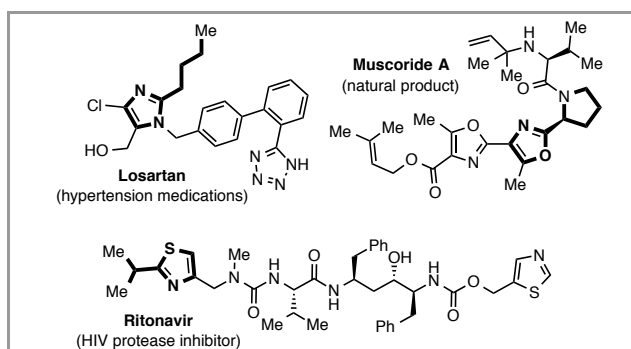


Figure 1. Representative Compounds Containing the 2-Alkyl-1,3-azole Scaffold.

Recently, we have reported the heteroatom-directed borylation of C(sp³)-H bonds bearing *N*-heteroarenes or carbonyl-based functional groups catalyzed by Rh- or Ir systems based on solid-supported monophosphines with mono-P-ligating features (Figure 2).¹⁰ This strategy allowed site-selective borylation of the *N*-adjacent^{10b} or unactivated^{7b,10a,c,d} C(sp³)-H bonds located γ to *N* or *O* atoms on the directing groups. The regioselectivity was due to the proximity effect by the heteroatom-to-metal coordination. In fact, cyclic and acyclic alkyl substituents at the 2-position of pyridines underwent the C(sp³)-H borylation with excellent site- and stereoselectivities.^{10a} Later, we found that 1,3-azoles also worked as suitable directing groups for the C(sp³)-H borylation of small-ring carbocycles such as cyclopropanes and cyclobutanes.^{7b} However, its applicability for linear alkyl groups and normal-sized (five-to-seven membered) carbocycles has not been explored.

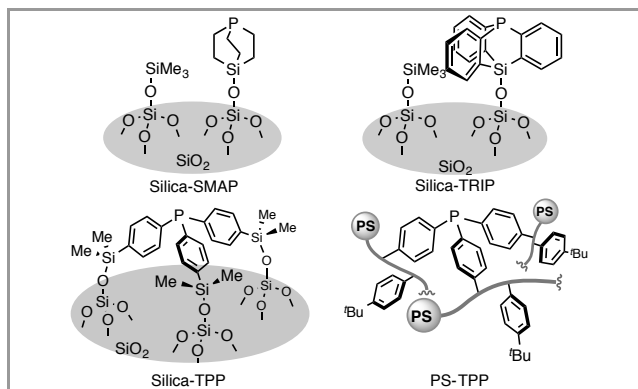


Figure 2. Solid-Supported Monophosphines.

Herein, we report a heteroatom-directed $C(sp^3)$ -H borylation of alkyl side chains of 1,3-azoles with a silica-supported monophosphine-Ir catalyst. Owing to the proximity effect by N-to-Ir coordination, the borylation occurred under relatively mild reaction conditions with high site- and stereoselectivities. This catalytic system was applicable for the reaction of primary and secondary $C(sp^3)$ -H bonds of linear and cyclic alkyl substituents in 1,3-azoles, including thiazoles, oxazoles, and imidazoles.

Initially, we examined the borylation of 2-ethylbenzothiazole (**1a**, 0.6 mmol) with bis(pinacolato)diboron (B_2pin_2) (**2**, 0.2 mmol) in THF at 60 °C for 15 h in the presence of various Ir catalysts (2 mol% Ir), which were prepared *in situ* from $[Ir(OMe)(cod)]_2$ and different ligands. The results are summarized in Table 1.

In contrast to the $C(sp^3)$ -H borylation of 2-alkylpyridines reported previously,^{10a} for which all solid-supported monophosphines shown in Figure 1 were effective ligands (Silica-SMAP,^{10a} Silica-TRIP,^{10b} Silica-TPP^{10c} and PS-TPP^{10d}), the borylation of **1a** was specifically promoted by commercially available Silica-SMAP, affording the terminal $C(sp^3)$ -H borylation product **3a** and the geminal bisborylation product **4a** in 82% and 32% NMR yields, respectively (Table 1, entry 1).^{11,12} The reactivity of the alkyl side chain in **1a** seems to be lower than that in the pyridine analogue. Indeed, 2-ethylpyridine underwent efficient $C(sp^3)$ -H borylation with the Silica-SMAP-Ir system at 25 °C,^{10a} while **1a** was intact under identical conditions (data not shown). The ligand specificity of Silica-SMAP in the present borylation reaction may suggest a requirement for the high electron density of the metal and/or sparse nature of the catalytic environment provided by the compact ligand. The total borylation yields over 100% based on B_2pin_2 (**2**) indicated that pinacolborane (HBpin), which was a byproduct of the reaction with B_2pin_2 , also served as a borylating reagent, although it was less reactive than **2**. The $C(sp^2)$ -H bonds of the benzothiazole ring and the $C(sp^3)$ -H bonds at the position α to the azole group were intact. A larger-scale reaction (5 mmol for **2**) at 0.5 mol% Ir loading proceeded efficiently at 90 °C to give **3a** in 54% isolated yield (entry 2). The geminal diborylation product **4a** could be obtained as a major product in 89% isolated yield by the reaction with 2 equiv of **2** (2 mol% Ir, 60 °C) (entry 3).

Table 1 also shows the inefficiency of homogeneous catalytic systems. The use of monophosphines such as Ph-SMAP¹³ and PPh_3 did not promote the $C(sp^3)$ -H borylation (entries 7 and 8). Bipyridine-based ligands such as Dtbpy and Me_4Phen resulted in only aromatic C-H borylation with lower efficiencies (<4% yields of arylboronates, entries 9 and 10).¹⁴ No reaction occurred without an exogenous ligand (entry 11).

Table 1. Ligand Effects in Ir-catalyzed Borylation of 2-Ethylbenzothiazole (**1a**) with Bis(pinacolato)diboron (**2**)^a

Entry	Ligand	Yield of 3a [%] ^b	Yield of 4a [%] ^b
1	Silica-SMAP	82 ^c (75) ^d	32
2 ^e	Silica-SMAP	71 (54)	12
3 ^f	Silica-SMAP	2	97 (89) ^g
4	Silica-TRIP	0	0
5	Silica-TPP	0	0
6	PS-TPP	0	0
7	Ph-SMAP	0	0
8	PPh_3	0	0
9 ^h	Dtbpy	0	0
10 ^h	Me_4Phen	0	0
11	none	0	0

^a Conditions: **1a** (0.6 mmol), **2** (0.2 mmol), $[Ir(OMe)(cod)]_2$ (2 mol% Ir), ligand (2 mol%), THF (1 mL), 60 °C, 15 h.

^b ¹H NMR yield based on **2**. Isolated yields shown in parentheses.

^c The C=N reduction product of **1a** (4%) was formed.

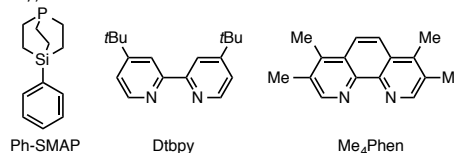
^d The isolated product **3a** was contaminated with **4a** (<1%) and traces of impurities.

^e **1a** (15 mmol), **2** (5 mmol), $[Ir(OMe)(cod)]_2$ (0.5 mol% Ir), Silica-SMAP (0.5 mol%), THF (5 mL), 90 °C, 24 h.

^f **1a** (0.2 mmol), **2** (0.4 mmol), $[Ir(OMe)(cod)]_2$ (2 mol% Ir), Silica-SMAP (2 mol%), THF (1 mL), 60 °C, 24 h. Yields of **3a** and **4a** were based on **1a**.

^g The isolated product **4a** was contaminated with **3a** (2%).

^h Arylboronates were formed in entries 9 and 10 (4% and 3%, respectively).



The Silica-SMAP-Ir system was applicable to various 1,3-(benzo)azoles **1**, including thiazoles, oxazoles, and imidazoles. Some of the borylation products **3** obtained in this manner were converted into the corresponding alcohols **5** through subsequent oxidation for facile product isolation.¹⁵ The results are summarized in Table 2.

The reaction with 2-ethylbenzoxazole (**1b**) proceeded smoothly at 60 °C to give the monoborylation product **3b** and the geminal diborylation product **4b** in 78% and 26% yields, respectively, with the formation of small amounts of $C(sp^2)$ -H borylation products (5%) (Table 2, entry 1). 2-

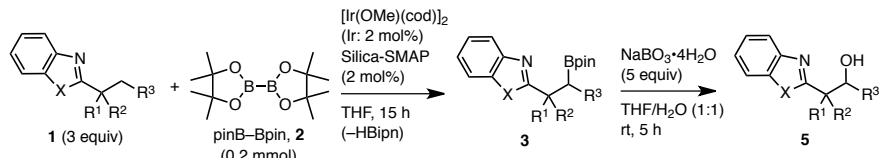
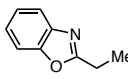
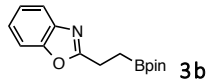
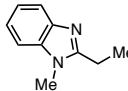
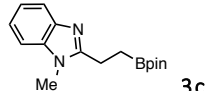
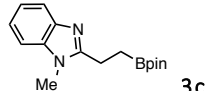
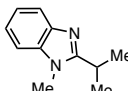
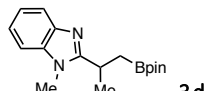
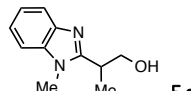
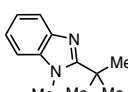
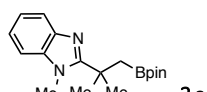
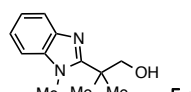
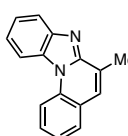
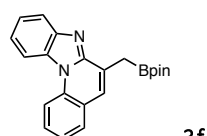
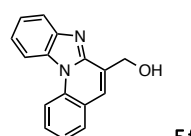
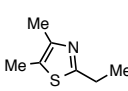
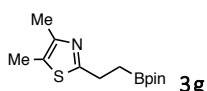
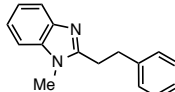
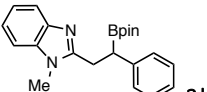
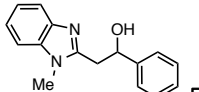
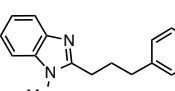
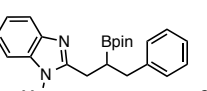
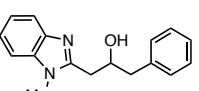
Ethylbenzimidazole (**1c**) was borylated at 50 °C, affording the monoborylation product **3c** and the diborylation product **4c** in 38% and 19% yields, respectively (entry 2). However, the formation of a significant amount of a C=N reduction product of **3c** (structure not determined, ca. 20%) was observed in the ¹H NMR spectrum of the crude reaction mixture. The use of cyclooctene as an additive effectively suppressed the C=N reduction of **3c**, resulting in an increase in yields of **3c** and **4c** to 60% and 31%, respectively (entry 3).¹⁶ Benzimidazoles bearing bulky alkyl groups, such as isopropyl (**1d**) and *tert*-butyl (**1e**) groups, at their 2-positions were successfully borylated at the terminal C(sp³)-H bonds (entries 4 and 5). The methyl C(sp³)-H borylation of polycyclic compound **1f** gave primary alkylboronate **3f** as a sole product (entry 6). Monocyclic 1,3-thiazole **1g** was also a suitable substrate for the terminal C(sp³)-H borylation (entry 7).¹⁷

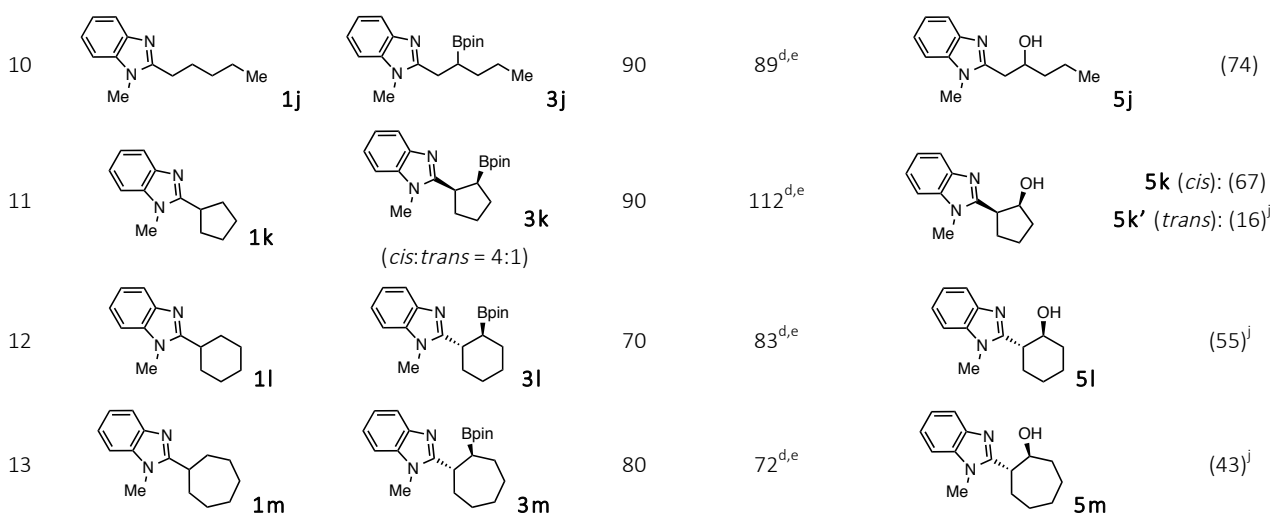
Internal C(sp³)-H bonds in 2-alkyl-1,3-azoles successfully participated in the borylation with the Silica-SMAP-Ir

system under relatively mild conditions (2 mol% Ir, 70–90 °C), affording the corresponding secondary alkylboronates (Table 2, entries 8–13). For example, the reactions of **1h** or **1i** containing a phenyl substituent proceeded with excellent site-selectivity at the C(sp³)-H bonds located γ to the directing sp²-hybridized N atoms (entries 8 and 9). The site-selective borylation occurred efficiently with 2-pentylbenzimidazole (**1j**) to provide alkylboronate **3j** (entry 10).

As was the case for the small-sized carbocycles,^{7b} normal-sized ring compounds were also borylated site- and stereoselectively. Specifically, the reaction of 2-cyclopentyl-*N*-methylbenzimidazole (**1k**) at 90 °C afforded the borylation product **3k** as a mixture of *cis* and *trans* isomers in a 4:1 ratio (Table 2, entry 11). The cyclohexyl and cycloheptyl groups in **1l** and **1m**, respectively, reacted at 70–80 °C with exceptional *trans* selectivity (entries 12 and 13).

Table 2. Silica-SMAP-Ir Catalyzed C(sp³)-H Borylation of 2-Alkyl-1,3-azoles **1** with Diboron **2** Followed by Oxidation^a

						
Entry	Substrate 1	Borylation Product 3	Temp (°C)	Yield of 3 (%) ^b	Oxidation Product 5 ^c	Yield of 5 (%) ^b
1	 1b	 3b	60	78 ^{c,d,e} (48) ^f	—	—
2	 1c	 3c	50	38 ^{c,d,g}	—	—
3 ^h		 3c	50	60 ^{c,d} (54) ⁱ		
4	 1d	 3d	80	83 ^d	 5d	(59)
5	 1e	 3e	80	87	 5e	(68)
6	 1f	 3f	70	86	 5f	(71)
7	 1g	 3g	60	80 ^c (63)	—	—
8	 1h	 3h	80	81 ^{d,e}	 5h	(69)
9	 1i	 3i	80	89 ^{d,e}	 5i	(70)



^a Conditions for C–H borylation: **1** (0.6 mmol), **2** (0.2 mmol), [Ir(OMe)(cod)]₂ (2 mol% Ir), Silica-SMAP (2 mol% P), THF (1 mL), 15 h. Conditions for oxidation: the crude products of the C(sp³)–H borylation (**3**), NaBO₃·4H₂O (1 mmol), THF (1 mL), H₂O (1 mL), rt, 5 h.

^b ¹H NMR yield based on **2**. Isolated yields shown in parentheses.

^c Geminal diborylation products **4** were formed in entries 1, 2, 3 and 7 (26%, 19%, 31%, and 34%, respectively).

^d The C=N reduction products of **1** were formed in entries 1, 2, 3, 4, 8, 9, 10, 11, 12 and 13 (30%, 64%, 42%, 85%, 40%, 59%, 84%, 35%, 83%, and 41%, respectively).

^e Arylboronates were formed in entries 1, 8, 9, 10, 11, 12 and 13 (5%, 7%, 6%, 11%, 4%, 8%, and 2%, respectively).

^f Isolated product was contaminated with arylboronates (9%) and the diborylation product (1%).

^g The C=N reduction product of **3c** (structure not determined, ca. 20%) was formed.

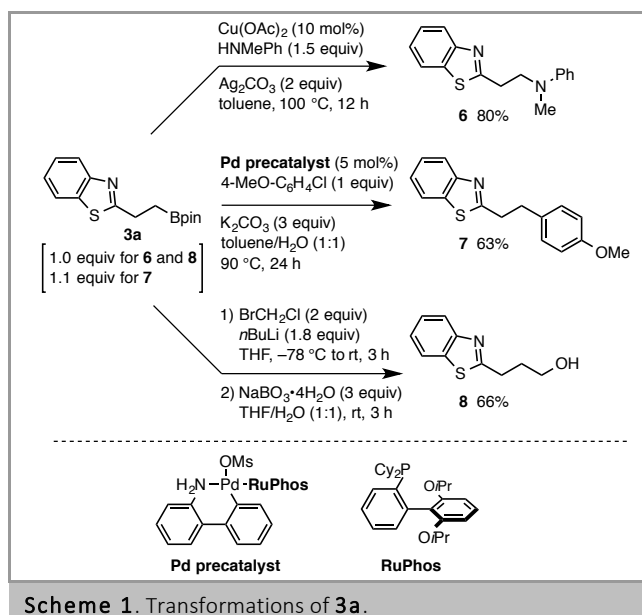
^h Cyclooctene (0.2 mmol) was used as an additive.

ⁱ Isolated product was contaminated with the diborylation product (<1%).

^j Isolated products in entries 11, 12, and 13 were contaminated with phenol derivatives (1%, 5%, and 2%, respectively), which were derived from the corresponding arylboronates.

To demonstrate the synthetic utility of the present borylation reaction, transformations of alkylboronate **3a** were performed as shown in Scheme 1. The boronate **3a** was converted into tertiary amine **6** through a Cu-catalyzed reaction with *N*-methylaniline in the presence of Ag₂CO₃ as an oxidant.¹⁸ The Suzuki–Miyaura cross-coupling of 4-chloroanisole with a RuPhos-ligated palladacycle precatalyst provided the sp³–sp² coupling product **7**.^{19–21} The one-carbon-homologation-oxidation sequence afforded the corresponding primary alcohol **8**.²²

In summary, a heterogeneous Ir catalyst system with silica-supported cage-type trialkylphosphine Silica-SMAP enabled C(sp³)–H borylation of alkyl side chains of 1,3-azoles, including thiazoles, oxazoles, and imidazoles, under relatively mild conditions with high site- and stereoselectivities. The borylation occurred not only at terminal C(sp³)–H bonds but also at internal secondary C(sp³)–H bonds in linear alkyl groups or carbocyclic rings. The obtained alkylboronates serve as precursors for C–N and C–C bond formation reactions. Thus, this heterogeneous Ir catalysis offers a useful method for rapid access to functionalized molecules with 1,3-azole scaffolds.



Scheme 1. Transformations of **3a**.

Acknowledgments

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Supporting Information

Experimental details and characterization data for new compounds is available online at [...].

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- (11) **Typical Procedure for the C(sp³)–H Borylation of Alkyl Side Chains on 1,3-Azoles with a Silica-SMAP-Ir Catalyst System (Table 1, Entry 1)**: In a glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.0040 mmol, 2 mol%), bis(pinacolato)diboron (**2**) (50.8 mg, 0.20 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]₂ (1.3 mg, 0.0020 mmol, 1 mol%) in THF (0.7 mL) and 2-ethylbenzo[d]thiazole (**1a**) (97.9 mg, 0.60 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 60 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. The solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yields of the products **3a** and **4a** were determined by ¹H NMR spectroscopy (82% and 32% yields, respectively). The crude material was then purified by Kugelrohr distillation (1 mmHg, 145 °C), to give the corresponding product **3a** (43.1 mg, 0.15 mmol, 75% yield) contaminated with the diborylation product **4a** (<1%) and traces of impurities, as estimated by ¹H NMR spectroscopy. Total yield over 100% based on **2** indicates that HBpin formed during catalytic turnover also served as a borylating reagent (theoretical maximum yield is 200%). ¹H NMR (CDCl₃): δ 1.24 (s, 12H), 1.38 (t, J = 7.6 Hz, 2H), 3.24 (t, J = 7.6 Hz, 2H), 7.32 (td, J = 8.4, 1.2 Hz, 1H), 7.42 (td, J = 7.6, 0.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H). ¹³C NMR (CDCl₃): δ 11.10 (br), 24.75 (4C), 28.85, 83.36 (2C), 121.42, 122.41, 124.42, 125.67, 135.19, 153.19, 173.81. ¹¹B NMR (CDCl₃): δ 32.6. IR (ATR): 2976, 2931, 1519, 1436, 1370, 1313, 1142, 1082, 967, 845, 758 cm⁻¹. HRMS–ESI (m/z): [M+H]⁺ Calcd for C₁₅H₂₁O₂N¹⁰BS, 289.14169; found, 289.14170.
- (12) The Silica-SMAP-Ir catalyst was easily separated from the reaction mixture by filtration. However, attempts to reuse the catalyst were unsuccessful.
- (13) Ochida, A.; Hamasaka, G.; Yamauchi, Y.; Kawamorita, S.; Oshima, N.; Hara, K.; Ohmiya, H.; Sawamura, M. *Organometallics* **2008**, *27*, 5494–5503.
- (14) The C(sp²)–H borylation of heteroarenes including 1,3-benzazoles catalyzed by the Ir–Me₃Phen system: Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287–4299.
- (15) In some cases, the formation of C=N reduction products of starting materials (**1**) was indicative by ¹H NMR analyses of the crude products. Similar C=N reduction was observed in the C(sp³)–H borylation of small-ring carbocycles bearing 1,3-azoles with the Silica-SMAP-Ir catalyst system (ref. 7b). The desired products **3** or **5** could be isolated by bulb-to-bulb distillation or silica gel column chromatography.
- (16) Cyclooctene would act as a scavenger of H₂ or HBpin. The use of alkene derivatives as a H₂ or HBpin scavenger in an Ir-catalyzed aromatic C–H borylation of aldimines was also reported: (a) Sasaki, I.; Amou, T.; Ito, H.; Ishiyama, T. *Org. Biomol. Chem.* **2014**, *12*, 2041–2044. (b) Sasaki, I.; Ikeda, T.; Amou, T.; Taguchi, J.; Ito, H.; Ishiyama, T. *Synlett*, **2016**, in press (DOI: 10.1055/s-0035-1561578).
- (17) Methyl groups on the thiazole ring in **1g** were necessary for the C(sp³)–H borylation. In fact, the reaction of 2-ethylthiazole with **2** in the presence of the Silica-SMAP-Ir catalyst (2 mol%, 60 °C, 15 h) gave the corresponding arylboronates exclusively via the C(sp²)–H borylation.
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- (21) Isolated product **7** was contaminated with 4,4'-dimethoxy-1,1'-biphenyl (2%), probably generated through homocoupling of 4-chloroanisole.
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