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Stereoselective C–H Borylations of Cyclopropanes and Cyclobutanes with Silica-Supported Monophosphane–Ir Catalysts

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Abstract: Heteroatom-directed C–H borylation of cyclopropanes and cyclobutanes was achieved with silica-supported monophosphane–Ir catalysts. Borylation occurred at the C–H bonds located γ to the directing N or O atoms with exceptional *cis* stereoselectivity relative to the directing groups. This protocol was applied to the borylation of a tertiary C–H bond of a ring-fused cyclopropane.

Cyclopropanes and cyclobutanes, categorized as small-ring carbocycles, are common units in natural products, biologically active compounds, and synthetic building blocks.[1,2] Recently, transition-metal-catalyzed C–H bond activation strategies were developed as direct methods for functionalizing small-ring frameworks, such as cyclopropanes and cyclobutanes.[3–6] Among these reactions, C–H borylation reactions are attractive because borylated small-ring compounds can act as "handles" for diverse molecular transformations.[7–11] Recently, Hartwig and co-workers reported the *trans*-selective borylation of substituted cyclopropanes by using Ir–phenanthroline catalyst systems.[4] However, introduction of a boron atom with *cis* stereochemistry relative to a substituent existing in small-ring systems is still difficult. Furthermore, C–H borylation of cyclobutane derivatives has not yet been achieved.

A previous report from our laboratory described the directed borylation of primary and secondary C(sp^3)–H bonds of N-alkylated amides, ureas, and aminopyridines[10b] and 2-alkylpyridines[10c] catalyzed by Ir- or Rh-catalyst systems based on immobilized monophosphane ligands, such as Silica-SMAP[12] and Silica-TRIP[12] (Figure 1). This strategy allowed the borylation of a cyclohexane ring substituted with a pyridine directing group with *trans* stereoselectivity, but its applicability for small-ring systems was not demonstrated.

The present report describes the heteroatom-directed C–H borylation reactions of cyclopropanes and cyclobutanes catalyzed by silica-supported monophosphane–Ir systems. The reactions proceeded under mild conditions with exceptional *cis* stereochemistry relative to the directing group, and thus complement Hartwig's *trans*-selective C–H borylation of cyclopropanes.[4,13] Applicability for borylation of a tertiary C–H bond and cyclobutane systems and the effectiveness of carbonyl-related directing groups are new features of this heterogeneous catalysis.

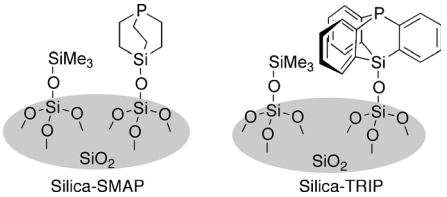
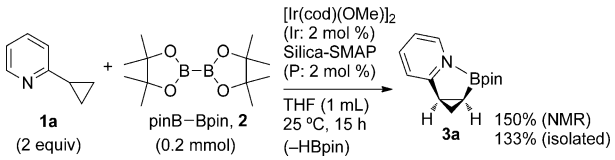


Figure 1. Silica-supported monophosphanes.

Initially, Ir and Rh catalyst systems based on various ligands ($[M(cod)(OMe)]_2$, M = Ir or Rh, 2 mol% M; cod = 1,5-cyclooctadiene) were evaluated for catalytic activity toward the borylation of 2-cyclopropylpyridine (**1a**, 0.4 mmol) with bis(pinacolato)diboron (**2**, 0.2 mmol) in THF.[14] As a result, the Ir complex coordinated with the commercially available silica-supported caged trialkylphosphane Silica-SMAP showed the greatest turnover efficiency (25 °C, 15 h), giving cyclopropylboronate **3a** (150% based on **2** by ^{1}H NMR spectroscopy, Scheme 1) along



Scheme 1. Silica-SMAP–Ir-catalyzed borylation of **1a**.

with 2,3-bisborylation product **3a′** (6%, vide infra for details on this compound) in total yields of over 100%, which indicated that the HBpin formed during catalytic turnover also worked as a borylating reagent (theoretical maximum yield based on B atom is 200%).[15] The C–H borylation occurred with exclusive regio- and stereoselectivity at the three-membered ring C–H bond located γ to the pyridine N atom in favor of the *cis* configuration, which indicates N-to-Ir coordination leading to a five-membered iridacyclic reaction pathway. The existence of an intramolecular N–B interaction in the product (**3a**) was indicated by ^{11}B NMR spectroscopy in $CDCl_3$.[16] Aromatic C–H borylation on the pyridine ring, benzylic C–H borylation, and ring-opening of the cyclopropane were not observed. No reaction occurred with the corresponding Rh catalyst under identical reaction conditions.

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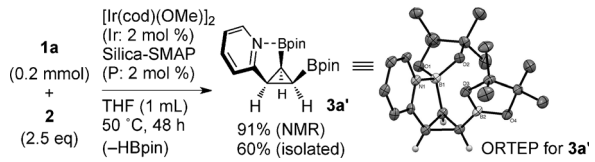


Scheme 2. Silica-SMAP–Ir-catalyzed bisborylation of **1a**.

When the Silica-SMAP-Ir-catalyzed reaction of **1a** was conducted with 2.5 equivalents of **2**, a novel 1,2,3-trisubstituted cyclopropane derivative (**3a**′) with all-*cis* configuration was obtained selectively (Scheme 2).[17] Single-crystal X-ray diffraction confirmed the stereochemistry and intramolecular N–B coordination.[18]

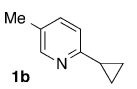
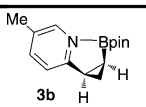
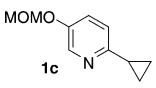
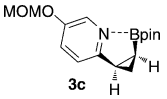
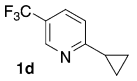
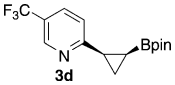
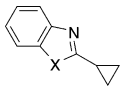
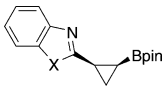
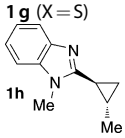
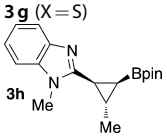
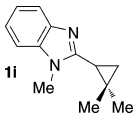
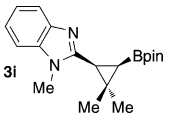
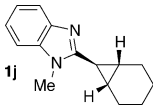
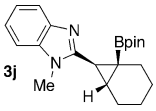
Homogeneous Ir catalyst systems with Ph-SMAP,[19] PPh_3, PMe_3, PCy_3, or P*t*Bu_3 as well as $[Ir(cod)(OMe)]_2$ without exogenous ligands induced much lower borylation activity (0–54% yields of **3a**, 2 mol% of Ir at 25 or 50 °C for 15 h),[14] which indicated the importance of immobilization. The phenanthroline-based ligand (2,9-Me_2phen), which was the optimal ligand in the Hartwig's study for the *trans*-selective cyclopropane borylation,[4] caused borylation of the pyridine ring (C4- and C5-positions, 78 and 59%, respectively, at 50 °C),[14] but not at the cyclopropane ring.

Various heteroarenes functioned as a directing group (Table 1, entries 1–7). Electron-donating (**1b**,**c**) or -withdrawing (**1d**) substituents at the 5-position of 2-cyclopropylpyridine had little effect on the effectiveness of the cyclopropane C–H borylation (entries 1–3).

Benzoannulated N-heteroaryls, such as benzoimidazole, benzooxazole, and benzothiazole, were suitable directing groups, showing exclusive diastereoselectivity (Table 1, entries 4–7). For instance, reaction of 2-cyclopropyl-*N*-methylbenzoimidazole (**1e**) proceeded smoothly at 25 °C to afford borylation product **3e** in 133% isolated yield based on **2** (entry 4).[20] Gram-scale borylation of **1e** was possible by decreasing catalyst loading to 0.1 mol% Ir at 80 °C (entry 5). Benzooxazole (in **1f**) also functioned as a directing group, but C(sp^2)–H borylations were minor reaction paths (entry 6). 2-Cyclopropylbenzothiazole (**1g**) reacted cleanly at 70 °C to provide cyclopropylboronate **3g** as a sole product (entry 7). The ^{11}B NMR spectra of **3e**–**g** indicated that their azole groups were not coordinated to the boron atom.[16]

Effects of alkyl substituents on the cyclopropane ring are shown in Table 1 (entries 8–10). Methyl-group substitution with *trans* geometry in **1h** and geminal dimethyl substitution in **1i** had little effect on either reaction effectiveness or diastereoselectivity. Interestingly, a tertiary C–H bond on the cyclopropane ring of 2-(7-bicyclo[4.1.0]heptyl)-1-methyl-1*H*-benzoimidazole (**1j**) successfully participated in borylation under mild conditions (50 °C, entry 10). The structure of **3j** was confirmed by single-crystal X-ray diffraction analysis (Figure 2).[18] This is the first catalytic borylation of a tertiary C–H bond. These experimental results demonstrating good tolerance toward substituted cyclopropanes likely reflect the increased acidity of the small-ring C–H bonds with relatively high s-character, and are consistent with the report of Hartwig's group describing successful nondirected cyclopropane borylation.[4]

Table 1. Silica-SMAP–Ir-catalyzed C–H borylation of cyclopropane derivatives (**1**) with diboron (**2**).[a]

Entry	Substrate **1**	Product **3**	*T* [°C]	Yield[b] [%]
1[c]			25	168[d] (150)
2[c]			25	108[e,f] (82)
3[c]			25	164[d] (158)
				
4	**1e** (X = NMe)	**3e** (X = NMe)	25	148[g] (133)
5[h]	**1e** (X = NMe)	**3e** (X = NMe)	80	82[g] (78)
6	**1f** (X = O)	**3f** (X = O)	40	98 (87)[i]
7	**1g** (X = S)	**3g** (X = S)	70	156 (130)
8			30	137[g] (123)[j]
9			40	86[g] (61)
10			50	91[g] (80)

[a] Conditions: **1** (0.4 mmol), **2** (0.2 mmol), $[Ir(cod)(OMe)]_2$ (0.004 mmol Ir), Silica-SMAP (0.004 mmol P), THF (2 mL), 15 h. [b] Yields based on **2** were determined by ^{1}H NMR spectroscopy. Isolated yields are in parentheses. Yield in excess of 100% indicates that HBpin formed during catalytic turnover also worked as a borylating reagent (theoretical maximum yield is 200%). [c] THF (1 mL). [d] Bisborylation products **3**′ were observed in the crude mixture (entry 1, 6%; entry 3, 11%). [e] Diboron **2** remained in the crude mixture. [f] A partial N–B interaction was indicated by ^{11}B NMR spectroscopy. [g] The C=N reduction product of **1** was observed in the crude mixture (entry 4, 39%; entry 5, 68%; entry 8, 48%; entry 9, 17%; entry 10, 26%). [h] **1e** (10 mmol), **2** (5 mmol), $[Ir(cod)(OMe)]_2$ (0.005 mmol Ir), Silica-SMAP (0.005 mmol P), THF (5 mL), 80 °C, 15 h. [i] Isolated product was contaminated with arylboronates (10%). [j] Isolated product was contaminated with regioisomers (8%).

Carbonyl-related functional groups also acted as directing groups for cyclopropane C–H borylation as shown in Table 2. *N*-Methoxyimine derived from dicyclopropyl ketone (**1k**) reacted at 25 °C to give monoborylation product **3k** selectively (Table 2, entries 1 and 2). For *N*-methoxyimine (**1l**) derived from an unsymmetrical ketone, only the *E* isomer was converted to the corresponding cyclopropylboronate (**3l**) while the *Z* isomers remained intact (entries 3 and 4, respectively). *N*-Mesitylimine **1m** was more efficiently borylated by using Silica-TRIP than using Silica-SMAP (entries 5 and 6, respectively). Again, only the *E* isomers participated in the transformation. *N*,*N*-Diisopropylamide **1n** reacted at 80 °C using Silica-SMAP with ex-

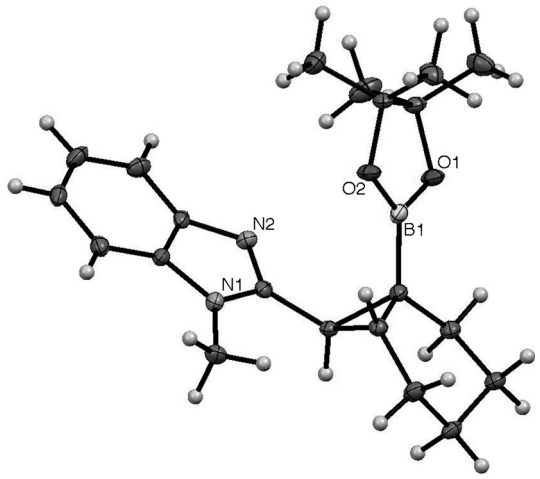


Figure 2. Molecular structure of the tertiary alkylboronate **3j**.

Table 2. Ir-catalyzed C–H borylation of cyclopropanes (**1**) with carbonyl-related functional groups.[a]

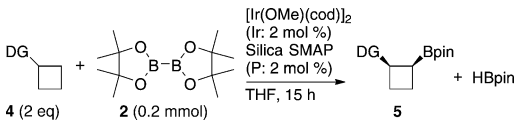
Entry	Substrate **1**	Product **3**	Ligand	*T* [°C]	Yield[b] [%]
1	MeO, N, **1k**	MeO, N, Bpin, **3k**	Silica-SMAP	25	107 (66)
2			Silica-TRIP	25	88
3	MeO, N, Bu, (*E*/*Z* 2.3:1), **1l**	MeO, N, Bu, Bpin, **3l**	Silica-SMAP	25	115[c] (64)
4			Silica-TRIP	25	104[c]
5[d]	Mes, N, Me, (*E*/*Z* 2.7:1), **1m**	Mes, N, Me, Bpin, **3m**	Silica-SMAP	100	85[c,e]
6[d]			Silica-TRIP	100	113[c,e] (98)
7[f]	O, N, ^{i}Pr, ^{i}Pr, **1n**	^{i}Pr, N, ^{i}Pr, O, Bpin, H, H, **3n**	Silica-SMAP	80	77 (75)
8[f]			Silica-TRIP	80	0

[a] Conditions: **1** (0.4 mmol), **2** (0.2 mmol), $[Ir(cod)(OMe)]_2$ (0.004 mmol Ir), ligand (0.004 mmol P), THF (1 mL), 24 h. [b] Yields based on **2** were determined by ^{1}H NMR spectroscopy. Isolated yield is in parentheses. Yields in excess of 100% indicate that HBpin also worked as a borylating reagent (theoretical maximum yield is 200%). [c] The *Z* isomers of substrates remained intact in the crude mixture. [d] In THF (2 mL), for 15 h. [e] The C=N reduction product of **3** was observed in the crude mixture (entry 5, 9%; entry 6, 4%). [f] In hexane (1 mL).

ceptional *cis* selectivity to afford cyclopropylboronate **3n** (entries 7 and 8). Coordination of the carbonyl oxygen atom to the Ir atom is thought to be responsible for the regio- and stereoselectivities.

Next, the Silica-SMAP–Ir system was applied to the C–H borylation of cyclobutanes, which had not been reported previously. Results are summarized in Table 3. Reaction of 2-cyclobutylpyridine (**4a**) occurred at 25 °C to give cyclobutylboronate **5a** as the sole product (Table 3, entry 1). The borylation showed exceptional *cis* selectivity, and no ring opening was detected. *N*-Methylbenzoimidazole and benzooxazole were also suitable directing groups (entries 2–4).[18] Gram-scale borylation of **4b** with a reduced catalyst loading (0.1 mol% Ir, at 80 °C) proceeded efficiently to give **5b** in 94% isolated yield (entry 3).

Table 3. Silica-SMAP–Ir-catalyzed C–H borylation of cyclobutane derivatives (**4**) with diboron (**2**).[a]

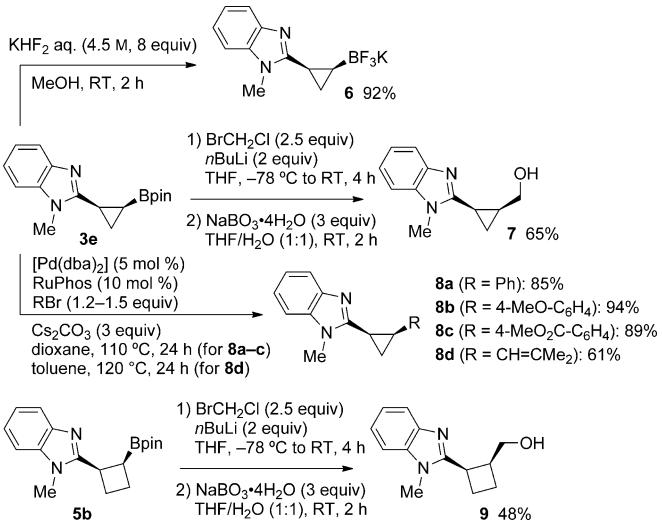


4 (2 eq) **2** (0.2 mmol) **5**

Entry	Substrate **4**	Product **5**	*T* [°C]	Yield[b] [%]
1[c]	N, **4a**	N, Bpin, **5a**	25	105 (85)[d]
2	N, N, Me, **4b**	N, N, Bpin, Me, **5b**	40	109[e] (99)[f]
3[g]			80	96[e] (94)[f]
4	N, O, **4c**	N, O, Bpin, **5c**	50	99 (94)[f]

[a] Conditions: **4** (0.4 mmol), **2** (0.2 mmol), $[Ir(cod)(OMe)]_2$ (0.004 mmol Ir), ligand (0.004 mmol P), THF (2 mL), 15 h. [b] Yields based on **2** were determined by ^{1}H NMR spectroscopy. Isolated yield is in parentheses. Yield in excess of 100% indicates that HBpin also worked as a borylating reagent (theoretical maximum yield is 200%). [c] In THF (1 mL). [d] Isolated **5a** was contaminated with traces of impurities. [e] The C=N reduction products of **4** were observed in the crude mixture (entry 2, 39%; entry 3, 21%). [f] Isolated products were contaminated with arylboronates (entry 2, 6%; entry 3, 6%; entry 4, 20%). [g] **4b** (10 mmol), **2** (5 mmol), $[Ir(OMe)(cod)]_2$ (0.005 mmol Ir), Silica-SMAP (0.005 mmol P), THF (5 mL), 80 °C, 15 h.

The cyclopropyl and cyclobutyl boronates (**3e** and **5b**, respectively) obtained through C–H borylation were used for transformations as shown in Scheme 3. Cyclopropylboronate **3e** underwent transformation to a trifluoroborate salt,[11a] one-carbon-homologation/oxidation sequence,[21] and Pd-catalyzed Suzuki–Miyaura coupling with aryl or alkenyl bromides.[11a,22] The alkenylated cyclopropane **8d** is structurally related to chrysanthemic acid derivatives, which is a class of pyrethroids insecticides.[23] Cyclobutylboronate **5b** was converted to pri-



Scheme 3. Transformations of borylation products.

mary alcohol **9** through the one-carbon-homologation/oxidation sequence. These transformations occurred with retention of configuration to give the corresponding 1,2-*cis*-disubstituted small-ring compounds.[18]

In summary, silica-supported monophosphane–Ir catalyst systems enabled N- or O-atom-directed C–H borylation of cyclopropanes and cyclobutanes. Borylation occurred with exceptional regio- and stereoselectivities with the assistance of various directing groups, including *N*-heteroarenes, an oxime, imine, and amide, resulting in formation of *cis*-substituted cyclopropyl- and cyclobutylboronates. The successful borylation of sterically congested C–H bonds of substituted cyclopropanes, including a tertiary C–H bond, demonstrates the potential of this heterogeneous borylation strategy toward functionalization of small-ring systems.

Experimental Section

Procedure for the borylation of 2-cyclopropylpyridine (1 a) with Silica-SMAP–Ir catalyst (Scheme 1)

In a nitrogen-filled glove box, Silica-SMAP (0.07 mmol g^{-1}, 57.1 mg, 0.004 mmol, 2 mol%), bis(pinacolato)diboron (**2**) (50.8 mg, 0.2 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. A solution of $[Ir(cod)(OMe)]_2$ (1.3 mg, 0.002 mmol, 1 mol%) in THF (0.7 mL) and 2-cyclopropylpyridine (**1 a**) (47.7 mg, 0.4 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 25 °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 **3 a** and **3 a′** were determined by ^{1}H NMR spectroscopy (150 and 6% based on **2**, respectively). The crude material was then purified by Kugelrohr distillation (1 mmHg, 75 °C), to give the corresponding product **3 a** (65.4 mg, 0.27 mmol, 133% yield). Yields in excess of 100% indicate that HBpin formed during catalytic turnover also worked as a borylating reagent (theoretical maximum yield is 200%).

Acknowledgements

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Keywords: borylation · C–H activation · cyclobutanes · cyclopropanes · iridium catalysts

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[15] The reaction using HBpin instead of **2** under otherwise identical reaction conditions gave **3 a** in 77% yield.

[16] The presence or absence of an N–B interaction of the borylation products in solution was determined by ^{11}B NMR spectroscopic analysis (see the Supporting Information). See also: a) A. Ros, B. Estepa, R. López-Rodríguez, E. Álvarez, R. Fernández, J. M. Lassaletta, *Angew. Chem.* **2011**, *123*, 11928; *Angew. Chem. Int. Ed.* **2011**, *50*, 11724; b) L. Zhu, S. H. Shabbir, M. Gray, V. M. Lynch, S. Sorey, E. V. Anslyn, *J. Am. Chem. Soc.* **2006**, *128*, 1222.

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[20] The crude reaction mixture contained a significant amount of a byproduct (2-cyclopropyl-1-methyl-2,3-dihydro-1*H*-benzoimidazole, 39%) resulting from C=N reduction of the starting material (**1e**); however, the borylation product **3e** did not undergo C=N reduction. Therefore, **3e** could be isolated easily by bulb-to-bulb distillation.

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Organic Synthesis

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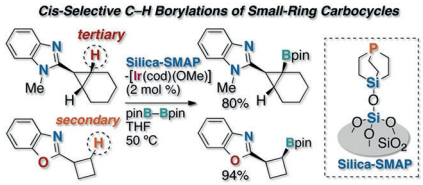
Stereoselective C–H Borylations of Cyclopropanes and Cyclobutanes with Silica-Supported Monophosphane–Ir Catalysts



Heteroatom-directed C–H borylations of small-ring carbocycles, such as cyclopropanes and cyclobutanes, were achieved with silica-supported monophosphane–Ir catalysts (see scheme). Borylation occurred at the C–H bonds located γ to the directing N or O atoms with exceptional *cis* stereoselectivity relative to the directing groups.