

Ruthenium-catalyzed C–H Silylation of Methylboronic Acid Using a Removable α -Directing Modifier on the Boron Atom

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Ruthenium-catalyzed C–H silylation of methylboronic acid was achieved by use of 2-(1*H*-pyrazol-3-yl)aniline as a removable α -directing modifier on the boron atom. Cross-coupling of the product, i.e., (phenyldimethylsilyl)methylpinacolborane, with aryl halides proceeded in the presence of a [PdCl₂(dppf)] catalyst and CsOH as a base.

Directed catalytic functionalization of the sp³-C–H bond is an attractive strategy for the synthesis of functionalized alkanes in organic synthesis.¹ Functional groups such as pyridyl, quinolinyl, oxazoliny, carboxyl, aminocarbonyl, and imino groups are attached to alkanes as directing groups for C–H functionalization through arylation,² amination,³ silylation,⁴ acetoxylation,⁵ halogenation,⁶ etc. Despite the remarkable acceleration of the catalytic reaction by the directing groups, the need for their installation in the substrates significantly limits the scope of the reaction. It is likely that the development of “traceless” or “convertible” directing groups will make directed C–H activation really useful and applicable to organic synthesis.⁷

We have developed removable α -directing groups, which are attached to the boron atoms of arylboronic acids, for Ru-catalyzed α -C–H silylation at their sp²-carbon atoms. 2-(1*H*-Pyrazol-3-yl)aniline and anthranilamide form six-membered diazaborine structures **1** and **2** containing N–B–N linkages upon condensation with arylboronic acids.^{8,9} The nitrogen atoms in the attached directing group coordinate to the transition-metal catalysts and enable the C–H functionalization at the *ortho*-positions. It would be highly attractive if the strategy could be extended to activation of alkylboronic acids. In particular, such a synthetic strategy is most attractive for the synthesis of α -functionalized methylboronic acids (Figure 1), because they are not accessible by hydroboration unlike the higher alkylboronic acids. It has been shown that even strong bases are not able to abstract α -hydrogen atoms of methylboronic acid

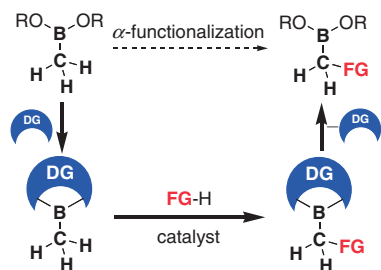
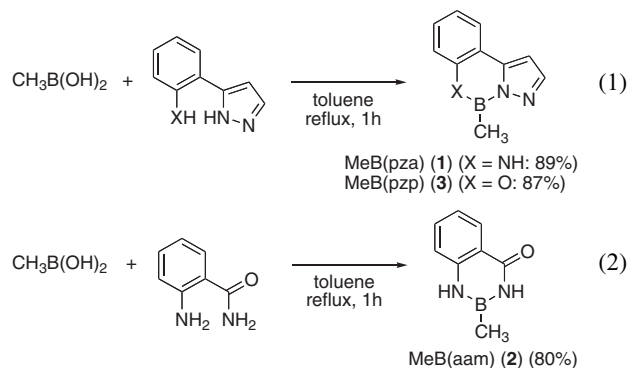


Figure 1. α -C–H functionalization of methylboronic acid via introduction of a directing group (DG) to the boron atom.

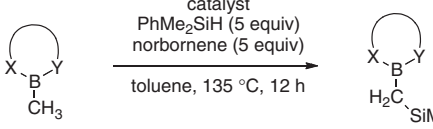
esters.¹⁰ It should be noted that, in spite of its potential usefulness, no catalytic C–H-functionalization at the α -hydrogen of alkylboronic acids has been reported. Herein, we describe α -C–H silylation of methylboronic acid using an α -directing modifier that is attached to the boron atom.

Methylboronic acid was condensed with 2-(1*H*-pyrazol-3-yl)aniline and anthranilamide, giving MeB(pza) (**1**) and MeB(aam) (**2**), respectively, in high yields (eqs 1 and 2). A phenol analog MeB(pzp) (**3**) of **1** was also prepared by the reaction with commercially available 2-(1*H*-pyrazol-3-yl)phenol in high yield (eq 1).



The modified methylboronic acids **1–3** were subjected to Ru-catalyzed reaction with triorganosilanes in the presence of norbornene as a hydrogen scavenger (Table 1).¹¹ With the [RhCl(cod)]₂ catalyst, a trace amount of the expected α -silylation product was detected by ¹H NMR (Entry 1). Ruthenium catalysts were found to be more effective for α -silylation. The [RuH₂(CO)(PPh₃)₃] catalyst, which served as the best catalyst in the α -C–H silylation of PZA- and AAM-modified arylboronic acids, afforded the α -silylation product in high yield after 12 h under reflux in toluene (Entry 3). Attempts at lowering the catalyst loading resulted in a decrease in the product yields (Entries 4 and 5). It should be remarked that the AAM-modified methylboronic acid **2** completely failed to give the α -silylation product (Entry 6). It is presumed that a four-membered metallacyclic intermediate or transition state, in which the AAM group assists the activation of the α -C–H bond, is not favorable, in contrast to the favorable formation of a five-membered metallacycle in the PZA-assisted reactions. It should also be noted that **3**, a phenol analog of **1**, was found to be totally unreactive in the α -silylation reaction despite our expectation of forming a favorable five-membered metallacycle, which is quite similar to that formed in the PZA-assisted reaction (Entry 7). The contrasting reactivity can be rationalized by the observed difference in the ¹¹B chemical shifts between **1** and **3**. The phenol analog **3** showed its ¹¹B signal at 4.2 ppm in

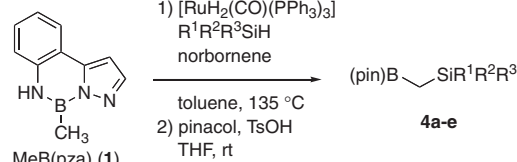
Table 1. Reaction of methylboronic acid derivatives **1–3** with dimethylphenylsilane in the presence of transition-metal catalysts^a



Entry	Substrate	Catalyst (mol % metal)	NMR yield/%
1	1	[RhCl(cod)] ₂ (6)	trace
2	1	[Ru ₃ (CO) ₁₂] (6)	37
3	1	[RuH ₂ (CO)(PPh ₃) ₃] (6)	97
4	1	[RuH ₂ (CO)(PPh ₃) ₃] (3)	58
5	1	[RuH ₂ (CO)(PPh ₃) ₃] (1)	52
6	2	[RuH ₂ (CO)(PPh ₃) ₃] (6)	0
7	3	[RuH ₂ (CO)(PPh ₃) ₃] (6)	0

^a**1–3** (0.25 mmol), a catalyst (15 μmol), norbornene (120 mg, 1.3 mmol), PhMe₂SiH (1.3 mmol), and anisole (13.6 μL, internal standard) in toluene (0.13 mL) were heated at 135 °C for 12 h.

Table 2. Ru-catalyzed α -silylation of MeB(pza) (**1**) with silyl hydrides^a



Entry	Silane	NMR yield/%	Isolated yield/%
1	PhMe ₂ SiH	97	85 (4a)
2	Et ₃ SiH	95	81 (4b)
3	BnMe ₂ SiH	94	86 (4c)
4	Ph ₂ MeSiH	73	67 (4d)
5	<i>t</i> -BuMe ₂ SiH	29	28 (4e)

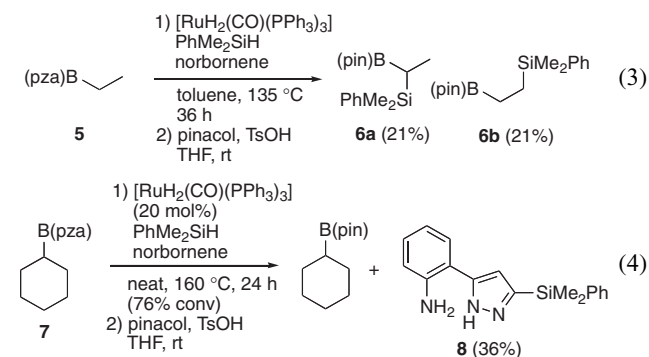
^a**1** (46 mg, 0.25 mmol), [RuH₂(CO)(PPh₃)₃] (14 mg, 15 μmol), norbornene (120 mg, 1.3 mmol), silane (1.3 mmol), and anisole (13.6 μL, internal standard) in toluene (0.13 mL) were heated at 135 °C for 12 h. The reaction mixture was treated with pinacol (59 mg, 0.5 mmol) and TsOH·H₂O (95 mg, 0.5 mmol) at rt for 1 h.

chloroform-*d*, which is unusually higher than typical three-coordinating organoboronic acid derivatives, including MeB(pza) (**1**, 32.7 ppm) and MeB(aam) (**2**, 32.3 ppm). The high-field shift of the ¹¹B signal can be ascribed to the formation of a four-coordinating species, in which the pyrazolyl nitrogen atoms coordinate to the boron atoms. Presumably, the lower donating ability of oxygen compared with nitrogen makes the boron atom of **3** more acidic than **1**, allowing the coordination of the pyrazolyl nitrogen to the boron atom.

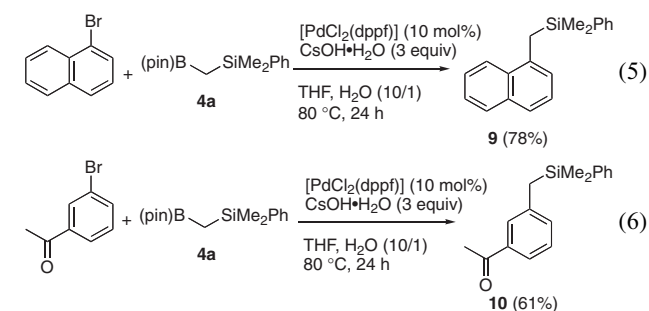
Under the optimized reaction conditions, α -C–H silylation with various hydrosilanes was carried out (Table 2). For these examinations, the primary silylation products were treated with pinacol in the presence of TsOH and isolated as pinacol esters. In the reactions with PhMe₂SiH, the one-pot procedure afforded the pinacol ester of (phenyldimethylsilyl)methylboronic acid in 85% isolated yield (Entry 1). Likewise, Et₃SiH afforded the

corresponding product in good yield (Entry 2). Silyl hydride having a benzyl group, which is easily convertible to a fluorine group for further transformation,¹² also provided the corresponding product in high yield (Entry 3). In the reaction of Ph₂MeSiH, a slight decrease in yield was encountered, presumably because of steric hindrance (Entry 4). With a more bulky silyl hydride such as *t*-BuMe₂SiH, the silylated product was obtained only in low yield (Entry 5). Neither (EtO)₃SiH nor (Me₃Si)Me₂SiH gave the silylated product at all under these reaction conditions.

We attempted the reaction of PZA-derivatives of ethylboronic acid and cyclohexylboronic acid under the same reaction conditions. In the reaction of EtB(pza) (**5**), two silylated products **6a** and **6b** via α - and β -silylation were obtained, although the consumption of EtB(pza) was sluggish and incomplete (eq 3). Reaction of CyB(pza) was found to be extremely slow under the standard reaction conditions. Use of 20 mol % catalyst without solvent resulted in C–H silylation at the pyrazolyl group (eq 4). After treatment with pinacol, silylated pyrazolylaniline **8** was isolated in 36% yield. No product formed via silylation at the cyclohexane ring was found in the reaction mixture.



We then tried to optimize the Suzuki–Miyaura coupling of the pinacol ester of α -silylmethylboronic acid with aryl halides.¹³ We found that the coupling of **4a** with 1-naphthyl bromide proceeded in good yield in the presence of [PdCl₂(dppf)] as a catalyst and CsOH as a base (eq 5). Use of Cs₂CO₃ as a base or [PdCl₂(PPh₃)₂] as a catalyst lowered the yields significantly. These reaction conditions could be applied to the coupling of 3-bromoacetophenone with **4a**, which afforded the products in 61% yield (eq 6). Although use of an excess amount of Ag(I) salt¹⁴ or use of the corresponding trifluoroborates¹⁵ has been recommended for cross-coupling of alkylboronic acid derivatives because of their low reactivity, we found that the coupling of silylmethylboronic ester **4a** proceeded without applying such modified reaction conditions.^{16,17}



In summary, we have established that use of 2-(1*H*-pyrazol-3-yl)aniline as a modifier on the boron atom of methylboronic acid allows α -silylation with silyl hydrides in the presence of a ruthenium catalyst. The corresponding reaction of EtB(pza) afforded a mixture of α - and β -silylated products. In the silylation of PZA-modified cyclohexylboronic acid, silylation takes place at the PZA group rather than at the methyl group. Cross-coupling of the α -silylated products with aryl halides has been achieved with a [PdCl₂(dppf)] catalyst and CsOH as a base. Exploration of more efficient and selective C–H functionalization of alkylboronic acids is now being undertaken in this laboratory.

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References and Notes

- # A temporary graduate student from Sumitomo Chemical Co., Ltd.
- For recent review on C–H functionalization at sp³ carbon atoms, see: R. Jazsar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem.—Eur. J.* **2010**, *16*, 2654.
 - a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154. b) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510. c) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886.
 - H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048.
 - F. Kakiuchi, K. Tsuchiya, M. Matsumoto, E. Mizushima, N. Chatani, *J. Am. Chem. Soc.* **2004**, *126*, 12792.
 - a) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300. b) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542. c) B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391.
 - a) R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. b) R. Giri, X. Chen, X.-S. Hao, J.-J. Li, J. Liang, Z.-P. Fan, J.-Q. Yu, *Tetrahedron: Asymmetry* **2005**, *16*, 3502. c) K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134.
 - For removable directing groups for C–H and C–C activation, see: a) S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220. b) T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 7534. c) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222. d) M. Tobisu, R. Nakamura, Y. Kita, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 3174. e) D. W. Robbins, T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 4068.
 - H. Ihara, M. Sugimoto, *J. Am. Chem. Soc.* **2009**, *131*, 7502.
 - H. Ihara, M. Koyanagi, M. Sugimoto, submitted.
 - D. S. Matteson, R. J. Moody, *Organometallics* **1982**, *1*, 20.
 - a) F. Kakiuchi, K. Igi, M. Matsumoto, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 422. b) F. Kakiuchi, K. Igi, M. Matsumoto, T. Hayamizu, N. Chatani, S. Murai, *Chem. Lett.* **2002**, 396.
 - a) K. Miura, T. Hondo, T. Takahashi, A. Hosomi, *Tetrahedron Lett.* **2000**, *41*, 2129. b) K. Miura, S. Okajima, T. Hondo, T. Nakagawa, T. Takahashi, A. Hosomi, *J. Am. Chem. Soc.* **2000**, *122*, 11348.
 - a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437. b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
 - G. Zou, Y. K. Reddy, J. R. Falck, *Tetrahedron Lett.* **2001**, *42*, 7213.
 - a) G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393. b) G. A. Molander, C.-S. Yun, M. Ribagorda, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 5534.
 - Successful use of [PdCl₂(dppf)] with carbonates such as Cs₂CO₃ and K₂CO₃ in cross-coupling of alkylboronic acids with aryl triflates and halides was reported. G. A. Molander, C.-S. Yun, *Tetrahedron* **2002**, *58*, 1465.
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