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Communication

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Rh-Catalyzed Borylation of N-Adjacent C(sp^3)−H Bonds with a Silica-Supported Triarylphosphine Ligand

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Supporting Information

ABSTRACT: Direct C(sp^3)−H borylation of amides, ureas, and 2-aminopyridine derivatives at the position *α* to the N atom, which gives the corresponding *α*-aminoalkylboronates, has been achieved with a heterogeneous catalyst system consisting of $[Rh(OMe)(cod)]_2$ and a silica-supported triarylphosphine ligand (Silica-TRIP) that features an immobilized triptycene-type cage structure with a bridgehead P atom. The reaction occurs not only at terminal C−H bonds but also at internal secondary C−H bonds under mild reaction conditions (25−100 °C, 0.1−0.5 mol % Rh).

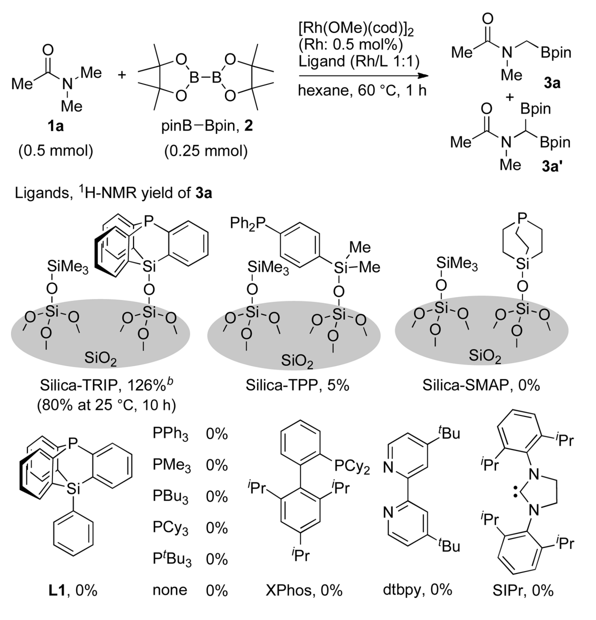
Alkylboronic acids and their derivatives find widespread utility not only as intermediates in organic synthesis but also as bioactive compounds in medicinal chemistry.[1] Conventionally, alkylboronic acid derivatives have been prepared through borylation of highly reactive organometallic reagents such as alkyllithium or Grignard reagents; however, these methods present problems in functional group compatibility.[2] Recently, transition-metal-based catalytic methods such as hydroboration of alkenes,[3] *β*-borylation of *α*,*β*-unsaturated carbonyl compounds,[4] addition of B to C−heteroatom double bonds,[5] and borylation of alkyl (pseudo)halides[6] have been developed.[7] These reactions proceed under neutral and mild reaction conditions, allowing access to functionalized alkylboronic acid derivatives. Even these catalytic methods, however, require prefunctionalization of the starting organic substrate at the C atom to which a B atom is to be introduced.

To achieve "atom efficiency," direct catalytic borylation of C(sp^3)−H bonds of functionalized organic compounds is a desirable strategy for obtaining alkylboronic acid derivatives.[8−10] This type of transformation remains highly challenging because of the chemical stability of C(sp^3)−H bonds, while direct borylations of C(sp^2)−H bonds have become relatively common methods.[8,11,12] Rh-, Ir-, Ru-, and Re-catalyzed direct borylations of alkanes are known, but they require relatively extreme conditions, such as high temperatures or light irradiation, and have a scope limited to the borylation of terminal C(sp^3)−H bonds of simple alkanes.[8,9]

This report describes a Rh-catalyzed C(sp^3)−H borylation of amides, ureas, and 2-aminopyridine derivatives at the position *α* to the N atom (N-adjacent position)[13] that yields the corresponding *α*-aminoalkylboronic acid derivatives.[1a,b,d,5a,d,14] The Rh catalysis occurs under mild conditions (25−100 °C, 0.1−0.5 mol % Rh) in the presence of the silica-supported triarylphosphine ligand Silica-TRIP,[12g,15] which contains an immobilized triptycene-type cage structure with a bridgehead P atom. This Rh catalysis even allows the preparation of secondary alkylboronates through selective borylation of internal C(sp^3)−H bonds. Direct secondary C(sp^3)−H borylations have been described only for the Pd/C-catalyzed nonregioselective borylation of ethylbenzene and the photochemical, stoichiometric, low-yield reaction of an isolated tungsten boryl complex with cyclohexane.[9c,10b] In both cases, the substrate was used as the solvent.

Various Rh catalyst systems (0.5 mol % Rh loading) with different ligands were prepared in situ from $[Rh(OMe)(cod)]_2$ in hexane for evaluation of their activities toward the C(sp^3)−H borylation of *N*,*N*-dimethylacetamide (**1a**, 0.5 mmol) with bis(pinacolato)diboron (pinB−Bpin, **2**, 0.25 mmol) at 60 °C for 1 h. The results are summarized in Scheme 1. Specifically, an immobilized catalyst system using Silica-TRIP (0.5 mol %) and $[Rh(OMe)(cod)]_2$ (0.5 mol % Rh) (P/Rh 1:1) promoted

Scheme 1. Ligand Effects in Rh-Catalyzed N-Adjacent C(sp^3)−H Borylation of 1a with 2[a]



[a]Conditions: **1a** (0.50 mmol), **2** (0.25 mmol), $[Rh(OMe)(cod)]_2$ (0.00125 mmol of Rh), ligand (0.00125 mmol), hexane (1.0 mL), 60 °C, 1 h. Yields based on **2** were determined by ^{1}H NMR spectroscopy. [b]A 9% yield of **3a′** was detected in the crude product mixture.

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a smooth reaction resulting in complete consumption of **2** to afford the C(sp^3)−H monoborylation product **3a** and the geminal bisborylation product **3a′** in NMR yields of 126% and 9%, respectively, based on **2**.[16−18] Interestingly, the formation of *N,N*-bis(borylmethyl)acetamide did not occur, indicating that the first borylation is more effective in deactivating the second borylation at the unreacted *N*-methyl group than at the borylated methyl group. Furthermore, borylation at the most acidic C−H bond *α* to the carbonyl group did not occur. The yield in excess of 100% indicated that the byproduct pinB−H also functioned as a reagent, but its reactivity was much lower than that of **2**.[16] The C(sp^3)−H monoborylation proceeded even at 25 °C, giving **3a** with higher selectivity (80% yield, 10 h).

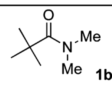
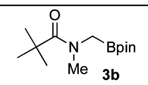
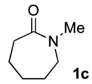
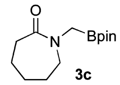
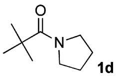
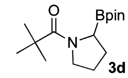
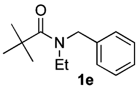
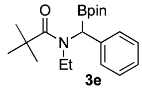
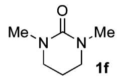
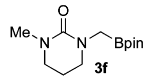
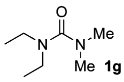
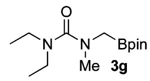
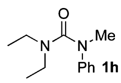
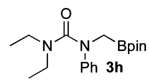
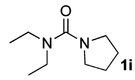
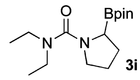
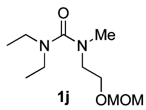
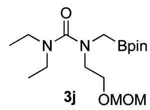
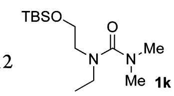
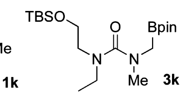
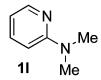
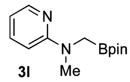
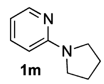
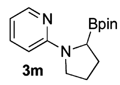
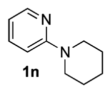
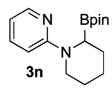
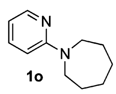
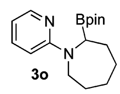
In contrast to the results using Silica-TRIP, the immobilized trialkylphosphine Silica-SMAP,[19,20] which has a similar cage-type structure with the same mode of immobilization, did not promote the reaction (see Scheme 1 for ligand effects). This is surprising because Silica-SMAP exhibited better performance in the Ir- or Rh-catalyzed ortho C(sp^2)−H borylation of functionalized arenes.[12b,g] The immobilized uncaged triphenylphosphine-type ligand Silica-TPP[12i] and the homogeneous triptycene-type ligand **L1**[15] induced little or no borylation activity. These results indicate that the triptycene-type structure and the immobilization are both critical factors. Other homogeneous ligands with different steric and electronic natures such as PPh_3, PMe_3, PBu_3, PCy_3, P^tBu_3, XPhos,[21] dtbpy,[8,11d−e] and the bulky NHC ligand SIPr[22] were ineffective. In addition, no reaction occurred with a ligand-free Rh system.

The Rh-catalyzed C(sp^3)−H borylation was applicable to a range of N-containing compounds, including amides, ureas, and 2-aminopyridine derivatives (Table 1). The borylation of *N,N*-dimethylpivalamide (**1b**) proceeded regioselectively at a C(sp^3)−H bond of one of the *N*-methyl groups to give **3b** in 84% yield, despite the presence of the potentially reactive terminal C−H bonds in the pivaloyl group (entry 1). *N*-Methylcaprolactam (**1c**) was also suitable for selective C−H borylation at the *N*-methyl group (entry 2).

Remarkably, the Silica-TRIP−Rh system even allowed more challenging internal C(sp^3)−H borylation under mild conditions (Table 1, entries 3 and 4).[9c,10b] The borylation of *N*-pivaloylpyrrolidine (**1d**) proceeded smoothly at 80 °C to afford the secondary alkylboronate **3d**. Furthermore, benzylic secondary borylation with *N*-benzyl-*N*-ethylpivalamide (**1e**) occurred under even milder reaction conditions (50 °C) to give the corresponding pure *α*-aminobenzylboronate **3e** (entry 4). It should be noted that no aromatic C(sp^2)−H borylation occurred despite the intrinsic reactivity of the aromatic C(sp^2)−H bonds and the existence of a potential directing group on the aromatic ring.

Analogous to the reactivity of the amides, urea derivatives also underwent N-adjacent C(sp^3)−H borylation with Silica-TRIP−Rh (Table 1, entries 5−12). Borylation of the cyclic urea *N,N′*-dimethylpropyleneurea (DMPU, **1f**) proceeded smoothly at 25 °C to give the monoborylation product **3f** in 129% yield together with the geminal bisborylation product **3f′** in 7% yield (entry 5). Interestingly, the second borylation did not occur at the *N*-methyl group on the other side, which suggests that intramolecular coordination of the carbonyl oxygen to the B atom disturbs the binding of the Rh center to the carbonyl group and that, upon dissociation of the B−O bond, geminal bisborylation occurs selectively as a result of activation by the boryl substituent. The borylation of **1f** was also conducted on a

Table 1. Range of Silica-TRIP−Rh-Catalyzed N-Adjacent C(sp^3)−H Borylations with 2[a]

entry	substrate 1	product 3	temp. (°C)	time (h)	yield[b] (%)
1	 1b	 3b	80	12	84 (70)[c]
2	 1c	 3c	40	12	117 (86)
3	 1d	 3d	80	5	122 (107)
4	 1e	 3e	50	12	139 (139)
5	 1f	 3f	25	1	129 (97)[c]
6[d]			70	3	(146)[c]
7[e]			70	3	(85)[c]
8	 1g	 3g	70	5	92 (90)[c]
9	 1h	 3h	60	24	130 (120)[c]
10	 1i	 3i	60	3	184 (154)
11	 1j	 3j	70	22	101 (93)[c]
12	 1k	 3k	80	24	73 (66)[c]
13	 1l	 3l	80	12	197 (176)
14	 1m	 3m	80	5	152 (125)
15	 1n	 3n	80	12	153 (130)
16	 1o	 3o	100	12	112 (101)

[a]Conditions: **1** (1.0 mmol), **2** (0.5 mmol), $[Rh(OMe)(cod)]_2$ (0.0025 mmol of Rh), Silica-TRIP (0.0025 mmol of P), hexane (1.0 mL). [b]^{1}H NMR yields based on **2**. Isolated yields are given in parentheses. Yields in excess of 100% indicate that the byproduct pinB−H also functioned as a reagent, but its reactivity was much lower than that of **2**. [c]The geminal bisborylation product **3′** was also detected by ^{1}H NMR analysis of the crude product mixture (entry 1, 21%; entry 5, 7%; entry 6, 2%; entry 7, 6%; entry 8, 55%; entry 9, 12%; entry 11, 28%; entry 12, 11%). [d]**1** (10.0 mmol, 1.23 g), **2** (5.0 mmol, 1.27 g), $[Rh(OMe)(cod)]_2$ (0.005 mmol of Rh), and Silica-TRIP (0.005 mmol of P) were used. [e]**1** (5.0 mmol, 641 mg), **2** (5.0 mmol, 1.27 g), $[Rh(OMe)(cod)]_2$ (0.005 mmol of Rh), and Silica-TRIP (0.005 mmol of P) were used.

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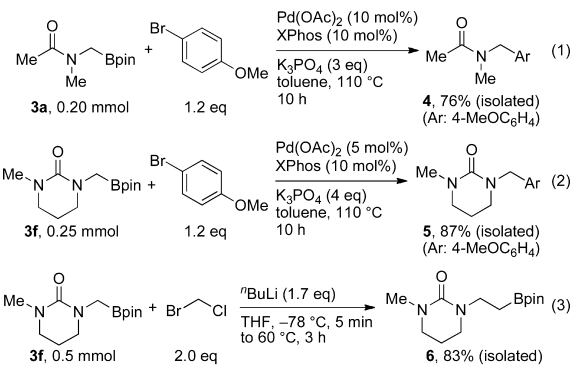
gram scale with a reduction of the catalyst loading to 0.1 mol % Rh at 70 °C, which afforded **3f** in 146% isolated yield with 2 equiv of **1f** and in 85% yield with 1 equiv of **1f** (entries 6 and 7). The unsymmetrical, acyclic urea derivatives **1g** and **1h** underwent selective borylation at their methyl groups (entries 8 and 9); no isomer was detected in either case, but the reaction of **1g** produced the geminal bisborylation product **3g′** in a significant amount. Remarkably, the reaction of **1i**, an unsymmetrical urea having an acyclic diethylamino group and a cyclic pyrrolidino group, was also site-selective, showing exclusive selectivity for ring borylation to afford α-borylpyrrolidine derivative **3i** as the sole product (entry 10). As shown in Table 1, entries 11 and 12, an alkoxy group or a siloxy group at the β-position of the *N*-alkyl group had little effect on the borylation activity; compounds **1j** and **1k** were selectively borylated at an *N*-methyl group.[23]

The N-adjacent C(sp^3)−H borylation using Silica-TRIP−Rh was not limited to reactions with the N−C═O-type catalyst-directing groups but could also be applied to 2-aminopyridine derivatives (entries 13−16). The simplest substrate, 2-(*N,N*-dimethylamino)pyridine (**1l**), reacted cleanly at 80 °C with exclusive site selectivity at one of the *N*-methyl groups (entry 13). No borylation at the pyridine ring was observed, and interestingly, no geminal bisborylation occurred in this case. With pyridine as an N-heterocyclic catalyst-directing group, various saturated cyclic amino groups with different ring sizes, such as pyrrolidino (**1m**), piperidino (**1n**), and azepanyl (**1o**) groups, were successfully borylated at the N-adjacent position to give the corresponding cyclic α-aminoalkylboronic acid derivatives (Table 1, entries 14−16).

Despite the potential importance of α-aminoalkylboronic acids as building blocks for organic synthesis, their utility has not been fully explored, mainly because of the lack of methods for accessing this class of compounds. The lithiation of an N-adjacent C(sp^3)−H bond using stoichiometric organolithium reagents is not generally applicable to amides, ureas, and pyridine derivatives because these functional groups are susceptible to nucleophilic addition of the organolithium reagent under C(sp^3)−H lithiation conditions.[24] Accordingly, the α-aminoalkylboronic acid pinacol esters obtained by the Rh-catalyzed N-adjacent C(sp^3)−H borylation were used to demonstrate their synthetic utility (eqs 1−3). For instance,



amide- or urea-based aminomethylboronates **3a** and **3f** underwent Suzuki−Miyaura coupling with 4-bromoanisole with the $Pd(OAc)_2$−XPhos catalyst system,[23] affording the corresponding sp^3−sp^2 coupling products **4** and **5**, respectively (eqs 1 and 2).[25] Another C−C bond formation involving **3f** was conducted using one-carbon homologation with the bromochloromethane/BuLi reagent, furnishing the corresponding β-aminoalkylboronic acid derivative **6** (eq 3).[26]

In summary, Rh catalysis with the silica-supported triarylphosphine ligand Silica-TRIP, which features a triptycene-type cage structure, enabled the site-selective borylation of N-adjacent C(sp^3)−H bonds of amides, ureas, and 2-aminopyridines under mild conditions with reasonable catalyst loadings (25−100 °C, 0.1−0.5 mol % Rh) to produce derivatives of α-aminoalkylboronic acids, which are boron analogues of α-amino acids.[1a,b,d] *N*-Methyl groups are the preferred borylation sites, but this Rh catalysis is also effective for the reaction of N-adjacent internal C(sp^3)−H bonds of cyclic amino groups to produce N-heterocyclic secondary alkylboronates. The α-aminoalkylboronic acid derivatives underwent C−C bond formation reactions, such as Suzuki−Miyaura coupling with an aryl bromide and one-carbon homologation to a β-aminoalkylboronate. This novel transition-metal catalysis with an immobilized phosphine ligand offers a new method for the development of useful molecular transformations through heterogeneous approaches.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Borissenko, L.; Groll, M. *Chem. Rev.* **2007**, *107*, 687. (b) Snow, R. J.; Bachovchin, W. W.; Barton, R. W.; Campbell, S. J.; Coutts, S. J.; Freeman, D. M.; Gutheil, W. G.; Kelly, T. A.; Kennedy, C. A.; Krolikowski, D. A.; Leonard, S. F.; Pargellis, C. A.; Tong, L.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 10860. (c) Suzuki, N.; Suzuki, T.; Ota, Y.; Nakano, T.; Kurihara, M.; Okuda, H.; Yamori, T.; Tsumoto, H.; Nakagawa, H.; Miyata, N. *J. Med. Chem.* **2009**, *52*, 2909. (d) Milo, L. J., Jr.; Lai, J. H.; Wu, W.; Liu, Y.; Maw, H.; Li, Y.; Jin, Z.; Shu, Y.; Poplawski, S. E.; Wu, Y.; Sanford, D. G.; Sudmeier, J. L.; Bachovchin, W. W. *J. Med. Chem.* **2011**, *54*, 4365. (e) Ilies, M.; Costanzo, L. D.; Dowling, D. P.; Thorn, K. J.; Christianson, D. W. *J. Med. Chem.* **2011**, *54*, 5432.

(2) Brown, H. C. In *Organic Synthesis via Organoboranes*; Wiley Interscience: New York, 1975.

(3) (a) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. (b) Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734. (c) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160. (d) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226.

(4) (a) Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145. (b) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664. (c) O'Brien, J. M.; Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630.

(5) (a) Mann, G.; John, K. D.; Baker, R. T. *Org. Lett.* **2000**, *2*, 2105. (b) Carter, C. A. G.; Vogels, C. M.; Harrison, D. J.; Gagnon, M. K. J.; Norman, D. W.; Langler, R. F.; Baker, R. T.; Westcott, S. A. *Organometallics* **2001**, *20*, 2130. (c) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036. (d) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910.

(6) (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (b) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588. (c) Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890. (d) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528. (e) Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 10693.

(7) Li, H.; Wang, L.; Zhan, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2943.

(8) Mkhalid, I. A.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(9) Transition-metal-catalyzed C(sp^3)−H borylation reactions: (a) Chen, H.; Hartwig., J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391. (b) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (c) Waltz, K. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 11358. (d) Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 15334. (e) Hartwig, J. F.; Cook, K. S.; Hapke, M.; Incarvito, C. D.; Fan, Y.; Webster, C. E.; Hall, M. B. *J. Am. Chem. Soc.* **2005**, *127*, 2538. (f) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 13684. (g) Wei, C. S.; Jiménez-Hoyos, C. A.; Videa, M. F.; Hartwig, J. F.; Hall, M. B. *J. Am. Chem. Soc.* **2010**, *132*, 3078.

(10) Transition-metal-catalyzed benzylic C(sp^3)−H borylation reactions: (a) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168. (b) Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. *Chem. Lett.* **2001**, *30*, 1082. (c) Boebel, T. A.; Hartwig, J. F. *Organometallics* **2008**, *27*, 6013.

(11) Ir- or Rh-catalyzed C(sp^2)−H borylations: (a) Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696. (b) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000**, *122*, 12868. (c) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305. (d) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (e) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056.

(12) Transition-metal-catalyzed regioselective C(sp^2)−H borylations with directing groups: (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (b) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058. (c) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159. (d) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068. (e) Itoh, H.; Kikuchi, T.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2011**, *40*, 1007. (f) Ros, A.; Estepa, B.; López-Rodríguez, R.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11724. (g) Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310. (h) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134. (i) Ros, A.; López-Rodríguez, R.; Estepa, B.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 4573.

(13) Selected examples of transformations of N-adjacent C(sp^3)−H bonds via direct C(sp^3)−H activation by transition metals: (a) Jun, C.-J.; Hwang, D.-C.; Na, S.-J. *Chem. Commun.* **1998**, 1405. (b) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, Y.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882. (c) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2534. (d) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (e) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (f) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (g) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 6690. (h) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821. (i) Bexrud, J. A.; Eisenberger, P.; Leitch, D. C.; Rayne, P. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 2116. (j) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692.

(14) Selected examples of syntheses of α-aminoalkylboronic acid derivatives: (a) Ingold, K. U.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99*, 6435. (b) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1981**, *103*, 5241. (c) Kelly, T. A.; Fuchs, V. U.; Perry, C. W.; Snow, R. J. *Tetrahedron* **1993**, *49*, 1009. (d) Zheng, B.; Deloux, L.; Pereira, S.; Skrzypczak-Jankun, E.; Cheesman, B. V.; Sabat, M.; Srebnik, M. *Appl. Organomet. Chem.* **1996**, *10*, 267. (e) Batsanov, A. S.; Grosjean, C.; Schütz, T.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 6276. (f) He, Z.; Zajdlik, A.; Denis, J. D. S.; Aseem, N.; Yudin, A. K. *J. Am. Chem. Soc.* **2012**, *134*, 9926.

(15) Tsuji, H.; Inoue, T.; Kaneta, Y.; Sase, S.; Kawachi, A.; Tamao, K. *Organometallics* **2006**, *25*, 6142.

(16) After the reaction, pinB−H was detected in the crude product mixture by ^{1}H NMR spectroscopy. Borylation of **1a** using pinB−H instead of **2** under otherwise identical conditions afforded **3a** in 50% yield and the bisborylation product in 16% yield.

(17) With 1 equiv of **1a**, the reaction gave **3a** and **3a′** in 53% and 7% yield, respectively, under otherwise identical conditions. The addition of 1 equiv of tetraethylurea improved the yield of **3a** to 73% (**3a′**, 9%) with the tetraethylurea remaining intact. The reason for these effects of added tetraethylurea and excess **3a** is not clear at present.

(18) The Silica-TRIP−Rh catalyst was easily removed from the products by Celite filtration but could not be reused.

(19) (a) Ochida, A.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2003**, *5*, 2671. (b) Ochida, A.; Hamasaka, G.; Yamauchi, Y.; Kawamorita, S.; Oshima, N.; Hara, K.; Ohmiya, H.; Sawamura, M. *Organometallics* **2008**, *27*, 5494.

(20) (a) Hamasaka, G.; Ochida, A.; Hara, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5381. (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. (c) Kawamorita, S.; Hamasaka, G.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *Org. Lett.* **2008**, *10*, 4697. (d) Kawamorita, S.; Ohmiya, H.; Iwai, T.; Sawamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8363.

(21) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358.

(22) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768.

(23) Substrates having an ester (OAc) group or a sterically demanding siloxy (OTIPS) group instead of the OMOM group in **1j** were unreactive even at 120 °C (octane). Borylation of **1a** (2 equiv relative to **2**, hexane, 60 °C, 1 h) in the presence of ethyl decanoate or dicyclohexyl ketone (1 equiv relative to **2**) gave **3a** in 119% and 112% NMR yield, respectively: 67% of the dicyclohexyl ketone underwent hydroboration with H-Bpin. Addition of 5-decene, 4-decyne, cyclohexyl chloride or bromide, 2-methylpropanonitrile, or nitroethane (1 equiv relative to **2a**) inhibited the reaction completely.

(24) Lithiations at N-adjacent benzylic positions are exceptional. Furthermore, steric protection of N-functional groups made N-adjacent lithiation successful: Clayden, J. In *Organolithiums: Selectivity for Synthesis*; Elsevier: Dordrecht, The Netherlands, 2002; Chapter 2. See ref 14e for lithiation/borylation of *N*-Boc-pyrrolidine.

(25) Suzuki−Miyaura couplings with secondary alkylboron compounds have been reported, but we have not yet successfully found appropriate conditions for the coupling of **3e** or **3i**. For stereospecific Suzuki−Miyaura coupling of secondary alkylboron compounds, see: (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (b) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (c) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-Y.; Drenher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108. (d) Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738. (e) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894.

(26) (a) Brown, H. C.; Singh, S. M.; Rangaishevi, M. V. *J. Org. Chem.* **1986**, *51*, 3150. (b) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535.