

UC Berkeley

UC Berkeley Previously Published Works

Title

Iridium-Catalyzed, Hydrosilyl-Directed Borylation of Unactivated Alkyl C-H Bonds

Permalink

<https://escholarship.org/uc/item/7rw7n96h>

Journal

Journal of the American Chemical Society, 138(3)

ISSN

0002-7863

Authors

Larsen, Matthew A
Cho, Seung Hwan
Hartwig, John

Publication Date

2016-01-27

DOI

10.1021/jacs.5b12153

Peer reviewed



Published in final edited form as:

J Am Chem Soc. 2016 January 27; 138(3): 762–765. doi:10.1021/jacs.5b12153.

Iridium-Catalyzed, Hydrosilyl-Directed Borylation of Unactivated Alkyl C–H Bonds

Matthew A. Larsen, Seung Hwan Cho[†], and John Hartwig^{*}

Abstract

We report the iridium-catalyzed borylation of primary and secondary alkyl C–H bonds directed by a Si–H group to form alkylboronate esters site selectively. The reactions occur with high selectivity at primary C–H bonds γ to the hydrosilyl group to form primary alkyl bisboronate esters. In the absence of such primary C–H bonds, the borylation occurs selectively at a secondary C–H bond γ to the hydrosilyl group, and these reactions of secondary C–H bonds occur with high diastereoselectivity. The hydrosilyl-containing alkyl boronate esters formed by this method undergo transformations selectively at the carbon–boron or carbon–silicon bonds of these products under distinct conditions to give the products of amination, oxidation, and arylation.

The functionalization of alkyl C–H bonds with borane reagents¹ can provide a direct route to alkylboronate esters, which are versatile synthetic intermediates.² The undirected borylation of alkanes has been shown to occur with high selectivity at primary C–H bonds, but analogous reactions of more complex substrates and reactions at secondary C–H bonds are only beginning to be developed. Unlike the borylation of aryl^{1f,3} and benzyl⁴ C–H bonds, the borylation of unactivated alkyl C–H bonds currently requires high temperatures, high catalyst loadings, and neat substrate to form alkylboronate esters at synthetically useful rates.

One strategy to overcome the limitations of the borylation of alkyl C–H bonds is to conduct reactions with substrates containing a directing group.⁵ Sawamura et al. have reported the Rh- and Ir-catalyzed borylation of alkyl C–H bonds α to the nitrogen of amides or γ to a pyridyl nitrogen.⁶ Shi et al. have reported the Pd-catalyzed borylation of primary alkyl C–H bonds directed by an amide,⁷ and Yu recently reported a similar reaction that includes the borylation of secondary alkyl C–H bonds.⁸ Our group reported selective borylation of amines and ethers at the C–H bonds located β to nitrogen and oxygen, due to a set of weak attractive interactions.^{1e}

^{*}Corresponding Author. jhartwig@berkeley.edu.

[†]Present Address

Department of Chemistry and Division of Advanced Nuclear Engineering, Pohang University of Science and Technology (POSTECH), Pohang, 790-784, Republic of Korea.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12153.

Experimental procedures, spectra for all new compounds (PDF)

The authors declare no competing financial interest.

An alternative approach to the directed borylation of alkyl C–H bonds is to exploit the versatility of silanes. Our group reported the hydrosilyl-directed borylation of aryl and benzyl C–H bonds catalyzed by the combination of an Ir(I) precursor and a bipyridine or phenanthroline ligand⁹ (Scheme 1a and 1b, respectively). However, the silyl-directed borylation of alkyl C–H bonds has not been achieved. Here, we report a set of Ir-catalyzed, hydrosilyl-directed borylations of primary and secondary alkyl C–H bonds. These reactions occur with high site selectivity γ to silicon and with high diastereoselectivity in cases of reactions at secondary C–H bonds.

To develop a system for the borylation of alkyl C–H bonds, we considered that a hydrosilyl directing group could be installed by the hydrosilylation of an alkene to form a substrate more stable than the silyl ethers and silyl amines we studied previously (Scheme 1c). A silyl-directed borylation of the resulting alkylsilane could occur with high site selectivity and diastereoselectivity to form secondary alkyl boronate esters, and the products could undergo transformations at the C–B bond or the C–Si bond selectively. To evaluate this strategy, we investigated the hydrosilyl-directed borylation of the secondary C–H bonds of cyclohexylmethyl-diethylsilane (**1**) with various boron sources and various ligands on iridium (Table 1). At 100 °C with B₂pin₂ as the boron source and the combination of [Ir(COD)OMe]₂ (**3**) and dtbpy (**L1**) as catalyst, the borylation of **1** in octane formed **2a**, the product of borylation γ to the hydrosilyl directing group, as a single diastereomer in only 21% yield. The product of bisborylation (**2b**) and the product of Si–H borylation (**2c**) also formed in 3% and 21% yield, respectively.

The yield of the borylation of **1** catalyzed by the combination of Ir and a phenanthroline (phen) depended strongly on the identity of the phen ligand. The reaction conducted with parent phen (**L2**), an electron-deficient diaryl phen (**L3**),⁴ or an electron-rich diaryl phen (**L4**) as ligand formed the product **2a** in low yield, but the reaction with 3,8-dimesitylphen (dimesphen) (**L5**) or 3,4,7,8-tetramethylphen (tmphen) (**L6**) as ligand formed **2a** in 43% and 51% yield, respectively. The origin of the large difference in yield between reactions conducted with **L4** and **L5** is unclear, but we suggest it results from the distinct phen-Ar dihedral angle when Ar = mesityl. For reactions with **L5** and **L6** as ligand, *n*-octyl-Bpin (~10% yield) formed as a result of the borylation of the solvent. Borylation of the solvent was suppressed by conducting reactions in 2,2,4-trimethylpentane (isooctane).

The effect of the reaction temperature on the reaction yield was modest. The reaction at 120 °C occurred in 56% yield, while that at 80 °C occurred in 28% yield. However, the borylation of **1** conducted at 80 °C with Et₃SiBpin as the boron source formed **2a** in 58% yield.

With Et₃SiBpin as the boron source we repeated our survey of catalysts. The reaction of **1** occurred in a higher yield with the catalyst generated from **3** and **L5** (66% yield) than with that from **3** and **L6**. We have previously shown that precatalysts of the general formula L₂Ir(H)(Cl)(SiEt₃) react rapidly with Et₃SiBpin to form an active catalyst for borylation.⁴ Thus, we tested reactions initiated with complex **4** containing ligand **L5**. Indeed, the yields of hydrosilyl-directed borylation reactions were more reproducible when the reaction was

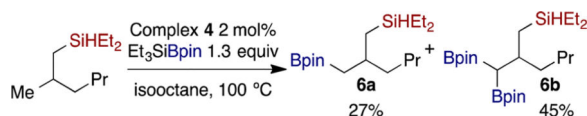
run with complex **4** instead of the combination of **3** and **L5**. The yield of **2a** was further increased from 65% to 77% by conducting the reaction with 1.3 equiv of Et₃SiBpin.

With the conditions in entry 12 of Table 1, we investigated the scope of the hydrosilyl-directed borylation of silanes synthesized by hydrosilylation of 1,1-disubstituted alkenes with diethylsilane¹⁰ (Chart 1). Hydrosilanes containing six-membered rings β to silicon reacted at a C–H bond γ to silicon to form the corresponding *trans* secondary alkyl boronate esters. This stereoselectivity mirrors that reported by Sawamura for pyridine-directed borylation.^{6b} These products were formed in moderate to good yield, with >20:1 diastereoselectivity. Ether, acetal, tertiary amine, and amide functional groups were tolerated. Like the borylation of **1**, the borylation of substrates lacking substituents at the 2- or 3-position of the six-membered ring formed significant amounts of the corresponding bisboryl product, leading to yields of the monoboryl product that were lower than those from the borylation of substrates bearing substituents at these positions (products **5a**, **5c**, and **5d**). The borylation of a hydrosilane containing a 3-tetrahydropyranyl substituent formed a 1:1 mixture of products, as determined by ¹H NMR spectroscopy of the reaction mixture. However, only one of the two products (**5i**) was stable to column chromatography, while the other decomposed.

The borylation of less conformationally biased substrates was slower (full conversion in >10 h) than the borylation of those containing six-membered rings (full conversion in <5 h) but formed the product in substantial yields. The borylation of (2-ethylbutyl)diethylsilane formed **5e** in 56% yield with >20:1 dr when conducted with 4 mol % of catalyst. The borylation of C–H bonds in 7- or 8-membered rings formed the corresponding alkyl boronate esters (**5j** and **5k**) in 66% and 70% yield with >20:1 dr, but the borylation of (cyclopentylmethyl) diethylsilane formed a mixture of products.

The reaction at vinyl C–H bonds is preferred over reactions at alkyl C–H bonds. As shown in Chart 1, the borylation of a silane containing both secondary C–H bonds and a vinyl C–H bond γ to silicon selectively formed vinyl boronate ester **5l** in 60% yield.

The borylation of silanes containing primary C–H bonds γ to the hydrosilyl group occurred selectively at the primary over the secondary C–H bonds. However, a mixture of products from monoborylation and bisborylation of the methyl group formed.¹¹ For example, (2-methylhexyl)diethylsilane reacted with 1.3 equiv of Et₃SiBpin to form a mixture of monoboryl product **6a** and geminal bisboryl product **6b** in 27% and 45% yield, respectively (eq 1). However, the analogous reaction conducted with 2 equiv of Et₃SiBpin formed **6b** in 68% yield (Chart 2).



(1)

The scope of the bisborylation of primary alkyl C–H bonds with 2 equiv of Et₃SiBpin is summarized in Chart 2. The borylation of substrates containing a silyl ether or a trisubstituted olefin formed product **6c** or **6d** in good yield. Borylation of the silane derived from α -methyl-styrene formed product **6e** in 77% yield, with less than 10% product from borylation at the aryl and benzylic C–H bonds. This result demonstrates the high selectivity for the borylation of primary C–H bonds γ to silicon.

The hydrosilyl-directed borylation of secondary alkyl C–H bonds occurred with high diastereoselectivity. The origin of this diastereoselectivity is best rationalized for substrates containing conformationally rigid six-membered rings. For each of these substrates in Chart 1, the directing group would be expected to occupy an equatorial position. The reaction is likely to proceed by binding of the substrate to Ir to form an Ir–Si bond, followed by oxidative addition of the C–H bond.^{9a,c} The metallacycle containing Ir at an equatorial position should be more stable than that containing Ir at an axial position (Scheme 2a) due to 1,3-diaxial interactions. Assuming the relative rates correlate with the stability of the metallacycles, the *trans* product would be expected to form with high selectivity, as is observed experimentally.

To probe the selectivity of the borylation of a substrate in which the more favored conformation contains the directing group in the axial position, we conducted the borylation of silane **7** containing a 4-*tert*-butyl group (Scheme 2b). The conformation of the ring in which the *tert*-butyl group lies in the equatorial position is more stable than that with the *tert*-butyl in the axial position by ~ 3 kcal/mol.¹² The reaction formed the *cis* and *trans* products in 30% and 21% isolated yield, respectively. The diastereoselectivity in this case is different from those of the reactions in Chart 1 because the directing group is axial rather than equatorial in the ground state. Thus, the formation of **8a** involves a structure containing an axial silylmethyl group and the formation of the **8b** involves a structure with an axial *tert*-butyl group.

The synthetic utility of the products of the hydrosilyl directed borylation is illustrated by the transformations shown in Scheme 3 that occur selectively at the C–B and C–Si bonds of **5a**, which was prepared on a 2.4 mmol scale in 85% yield. The amination¹³ of **5a** formed Boc-protected amine **9a** in 55% yield. In a two-step, one-pot sequence involving conversion to the silyl ether^{9c} and oxidation, **9a** was converted to the β -amino alcohol **9b** in 70% yield. When **5a** was treated with H₂O₂ and KHCO₃, *trans*-diol **9c** formed in 86% yield. Compound **5a** also underwent an arylation reaction¹⁴ with benzofuran after the Si–H was converted to a silyl ether, forming **9d** in 40% yield. Oxidation¹⁵ of **9d** formed alcohol **9e** in 83% yield. The synthesis of **9b** and **9e** from **5a** demonstrates that the products of the silyl-directed borylation undergo site-selective transformations at the C–B and C–Si bonds.

In summary, we developed the first hydrosilyl-directed borylation of an unactivated alkyl C–H bond. Diastereoselective monoborylation of secondary C–H bonds, and diborylation of primary C–H bonds, occurs when directed by a hydrosilyl group located γ to the C–H bond. The products of the borylation were shown to undergo site-selective transformations at the C–B and C–Si bonds. We are currently investigating the mechanism of this borylation process

and the origin of both the high reactivity of the catalyst containing **L5** and the higher yields for reactions conducted with Et₃SiBpin than for those conducted with B₂pin₂.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the NSF (CHE-01213409) and NIH (GM-115812) for support. M.A.L. thanks Chevron and the ACS DOC for predoctoral fellowships. We thank Johnson Matthey for a generous donation of [Ir(COD)OMe]₂.

REFERENCES

- (a) Waltz KM, Hartwig JF. *Science*. 1997; 277:211.(b) Chen H, Schlecht S, Semple TC, Hartwig JF. *Science*. 2000; 287:1995. [PubMed: 10720320] (c) Murphy JM, Lawrence JD, Kawamura K, Incarvito C, Hartwig JF. *J. Am. Chem. Soc.* 2006; 128:13684. [PubMed: 17044685] (d) Liskey CW, Hartwig JF. *J. Am. Chem. Soc.* 2012; 134:12422. [PubMed: 22804581] (e) Li Q, Liskey CW, Hartwig JF. *J. Am. Chem. Soc.* 2014; 136:8755. [PubMed: 24836159] (f) Mkhaliid IAI, Barnard JH, Marder TB, Murphy JM, Hartwig JF. *Chem. Rev.* 2010; 110:890. [PubMed: 20028025]
- (a) Pelter, A.; Smith, K.; Brown, HC. *Borane reagents*. Academic Press; 1988. (b) Burgess K, Ohlmeyer MJ. *Chem. Rev.* 1991; 91:1179.(c) Crudden, Cathleen M, Edwards D. *Eur. J. Org. Chem.* 2003; 2003:4695.
- (a) Ishiyama T, Takagi J, Ishida K, Miyaura N, Anastasi NR, Hartwig JF. *J. Am. Chem. Soc.* 2002; 124:390. [PubMed: 11792205] (b) Cho JY, Tse MK, Holmes D, Maleczka RE, Smith MR. *Science*. 2002; 295:305. [PubMed: 11719693]
- Larsen MA, Wilson CV, Hartwig JF. *J. Am. Chem. Soc.* 2015; 137:8633. [PubMed: 26076367]
- Ros A, Fernandez R, Lassaletta JM. *Chem. Soc. Rev.* 2014; 43:3229. [PubMed: 24553599]
- (a) Kawamorita S, Miyazaki T, Iwai T, Ohmiya H, Sawamura MJ. *Am. Chem. Soc.* 2012; 134:12924.(b) Kawamorita S, Murakami R, Iwai T, Sawamura M. *J. Am. Chem. Soc.* 2013; 135:2947. [PubMed: 23398347] (c) Iwai T, Harada T, Hara K, Sawamura M. *Angew. Chem., Int. Ed.* 2013; 52:12322.(d) Iwai T, Murakami R, Harada T, Kawamorita S, Sawamura M. *Adv. Synth. Catal.* 2014; 356:1563.
- Zhang L-S, Chen G, Wang X, Guo Q-Y, Zhang X-S, Pan F, Chen K, Shi Z-J. *Angew. Chem., Int. Ed.* 2014; 53:3899.
- He J, Jiang H, Takise R, Zhu R-Y, Chen G, Dai H-X, Dhar TGM, Shi J, Zhang H, Cheng PTW, Yu J-Q. *Angew. Chem., Int. Ed.* 2016; 55:785.
- (a) Boebel TA, Hartwig JF. *J. Am. Chem. Soc.* 2008; 130:7534. [PubMed: 18494474] (b) Robbins DW, Boebel TA, Hartwig JF. *J. Am. Chem. Soc.* 2010; 132:4068. [PubMed: 20199022] (c) Cho SH, Hartwig JF. *J. Am. Chem. Soc.* 2013; 135:8157. [PubMed: 23682736] (d) Cho SH, Hartwig JF. *Chem. Sci.* 2014; 5:694.
- (a) Tondreau AM, Atienza CCH, Weller KJ, Nye SA, Lewis KM, Delis JGP, Chirik PJ. *Science*. 2012; 335:567. [PubMed: 22301315] (b) Rubin M, Schwier T, Grevorgyan V. *J. Org. Chem.* 2002; 67:1936. [PubMed: 11895414]
- See ref 6b for an example of geminal bisborylation of alkyl C–H bonds
- We assumed the A value of the silyl group is approximately equal to that of a neopentyl group: Anslyn EV, Dougherty DA. *Modern Physical Organic Chemistry*. 2006University Science
- Mlynarski SN, Karns AS, Morken JP. *J. Am. Chem. Soc.* 2012; 134:16449. [PubMed: 23002712]
- Bonet A, Odachowski M, Leonori D, Essafi S, Aggarwal VK. *Nat. Chem.* 2014; 6:584. [PubMed: 24950327]

15. Li B, Driess M, Hartwig JF. *J. Am. Chem. Soc.* 2014; 136:6586. [PubMed: 24734777]

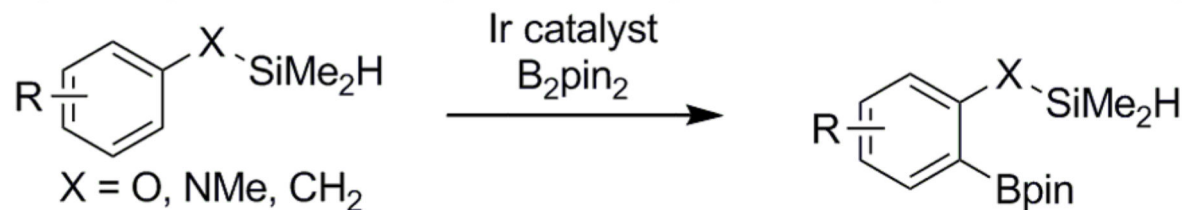
Author Manuscript

Author Manuscript

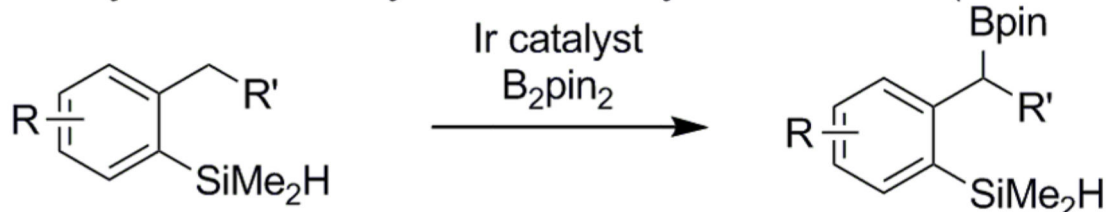
Author Manuscript

Author Manuscript

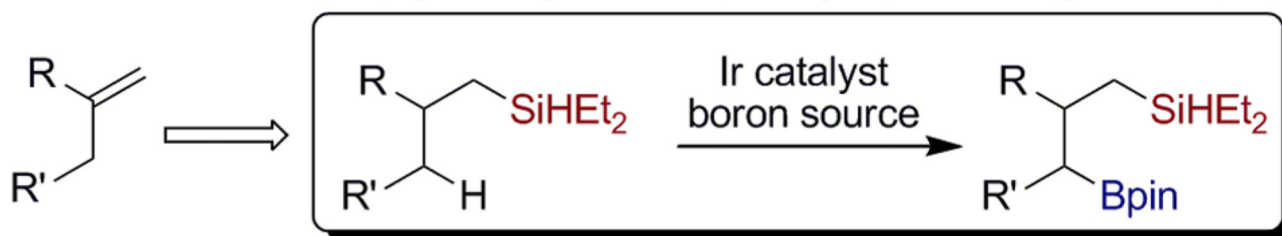
A. Hydrosilyl Directed Borylation of Aryl C-H Bonds (ref 9a and 9b)



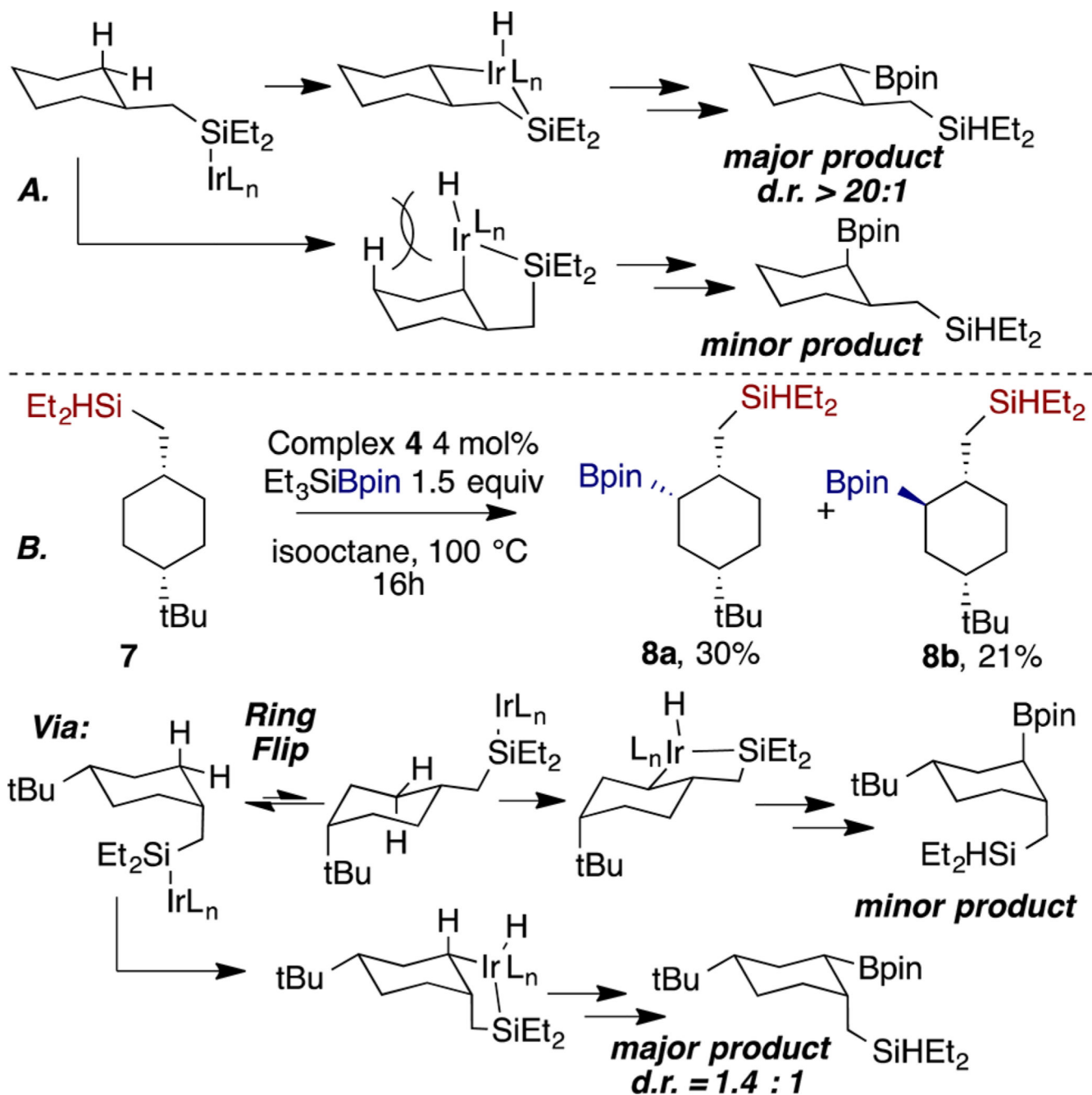
B. Hydrosilyl Directed Borylation of Benzylic C-H Bonds (ref 9c and 9d)



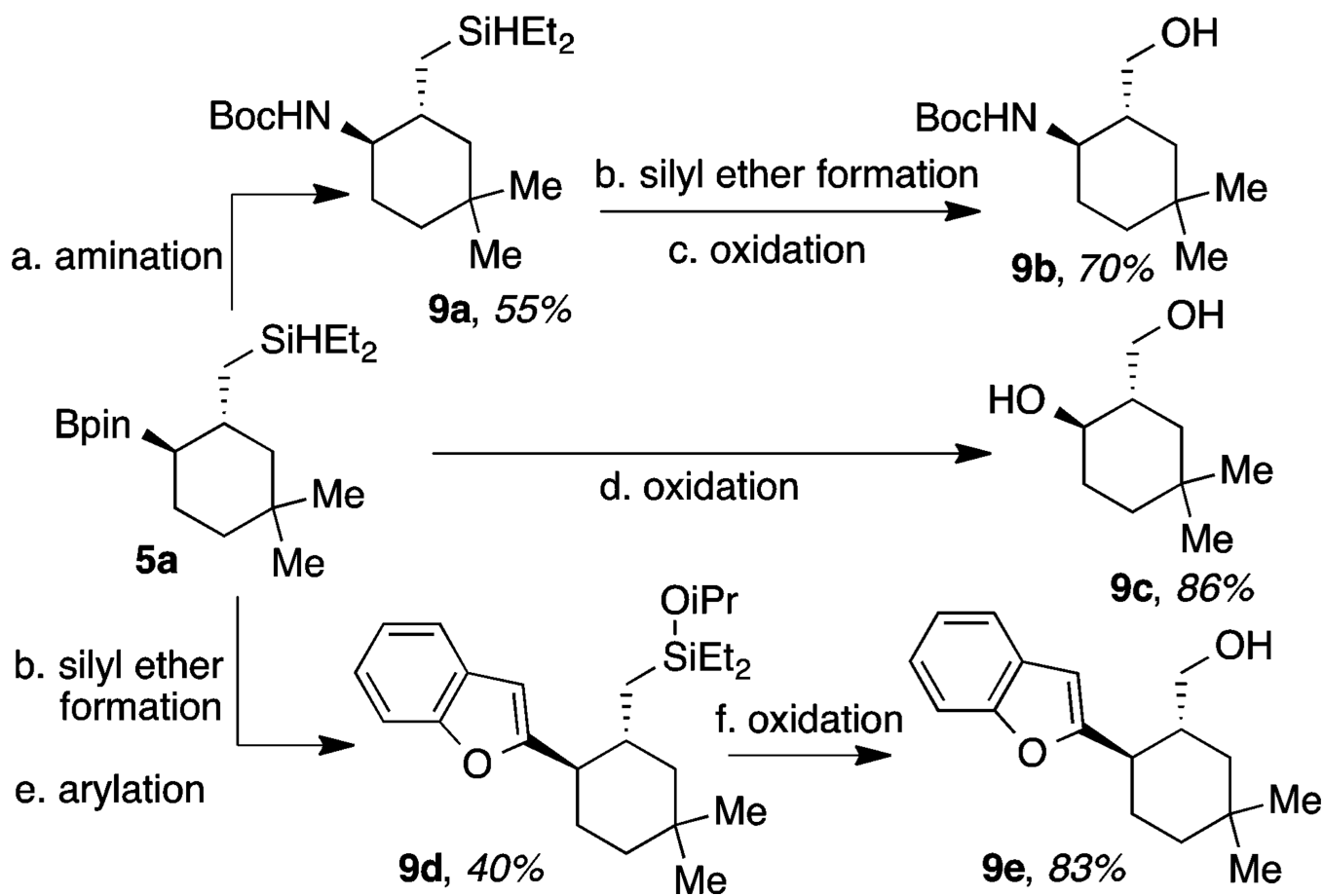
C. Current Work: Hydrosilyl Directed Borylation of Alkyl C-H Bonds



Scheme 1.
Hydrosilyl Directed Borylation of C-H Bonds



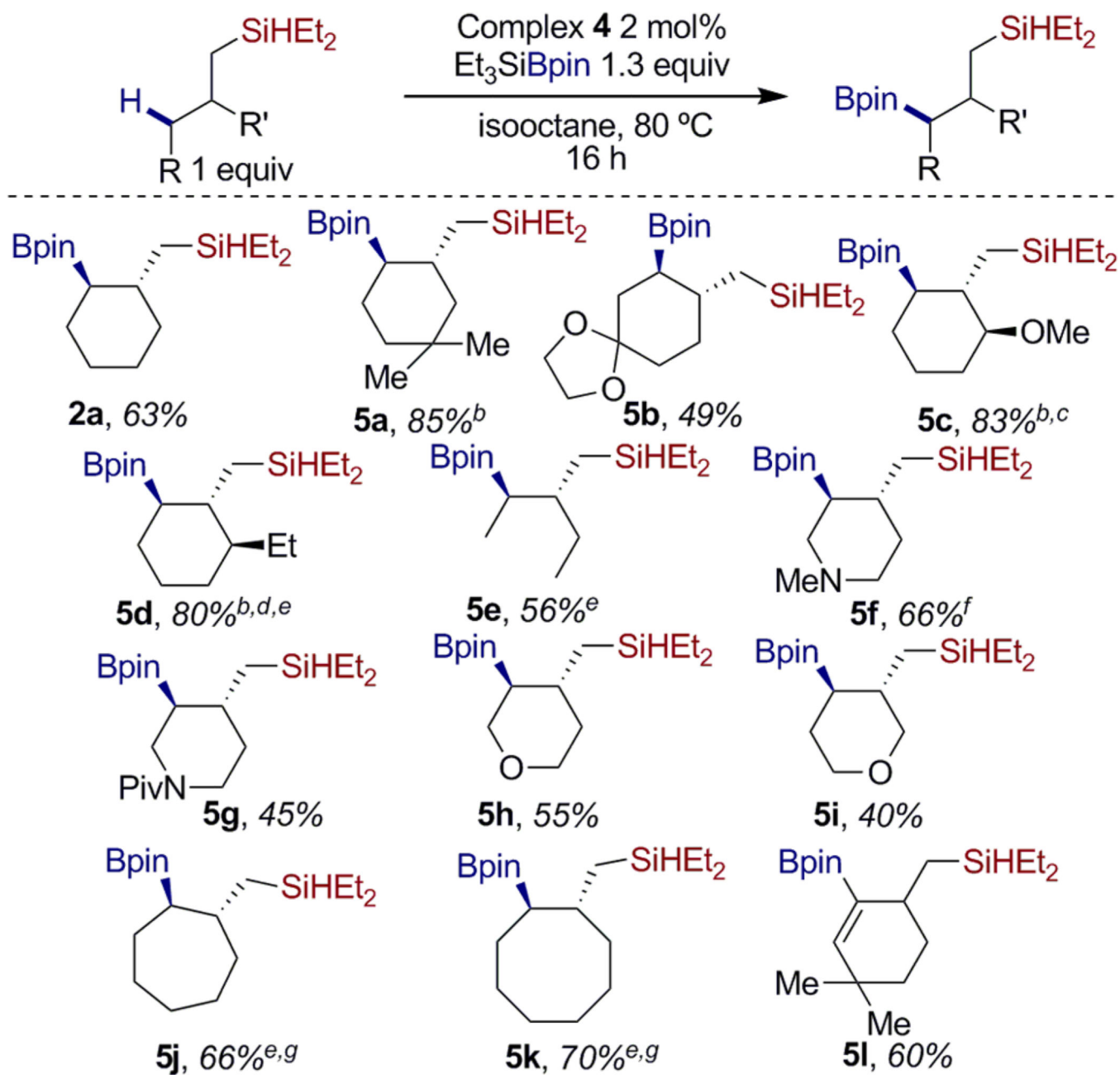
Scheme 2.
Effect of Six-Membered Ring Conformation on Diastereoselectivity



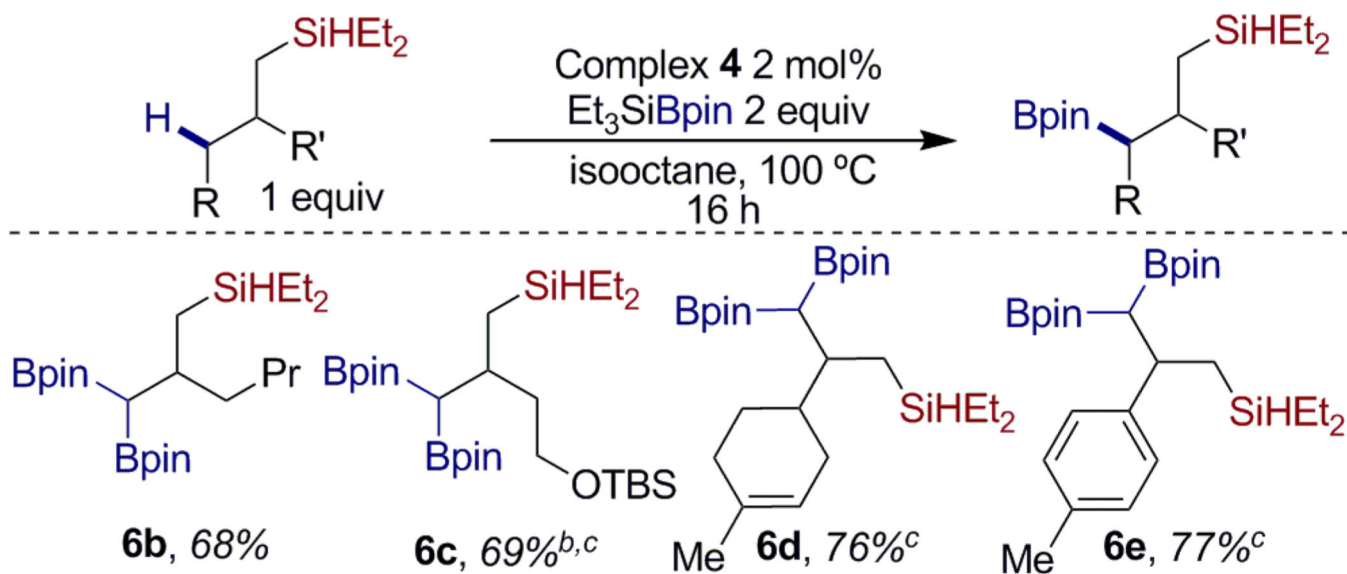
Scheme 3.

Functionalization of the Borylation Products^a

^aConditions: (a) NH₂OMe (3 equiv), *n*-BuLi (3 equiv), Boc₂O (3.3 equiv), THF, -78 to 65 °C, 14 h. (b) *i*PrOH (3 equiv), [Ir(COD)Cl]₂ (2 mol %), MeCN, rt, 24 h. (c) H₂O₂ (60 equiv, 3 portions), KHCO₃ (10 equiv), KF (10 equiv), THF, MeOH, 65 °C, 3 h. (d) H₂O₂ (10 equiv), KHCO₃ (5 equiv), THF, MeOH, 50 °C, 40 h. (e) benzofuran (1.4 equiv), *n*-BuLi (1.5 equiv), NBS (1.55 equiv), -78 to -40 °C. (f) *t*BuOOH (14 equiv), CsOH (12 equiv), TBAF (5 equiv), THF, 50 °C, 2 h.

**Chart 1.**Hydrosilyl Directed Borylation of Secondary Alkyl C-H Bonds^a

^aReactions conducted on a 0.30 mmol scale. Yields are for isolated products. ^bReaction conducted with 1.15 equiv of Et₃SiBpin. ^cThe d.r. of the starting material was 11:1. ^dThe d.r. of the starting material was 5:1. ^eReaction conducted with 4 mol % of complex 4. ^fYield determined by gas chromatography. ^gReaction conducted at 100 °C.

**Chart 2.**Hydrosilyl Directed Bis-Borylation of Primary Alkyl C–H Bonds^a^aReactions conducted on a 0.30 mmol scale. Reported yields are for isolated products.^bReaction conducted with 2.2 equiv of Et_3SiBpin . ^cReaction conducted with 4 mol % of complex **4**.

^b Formation of *n*-octyl-Bpin was observed in ca. 10% yield.

^c Reaction conducted with 1.3 equiv of Et₃SiBpin.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript