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

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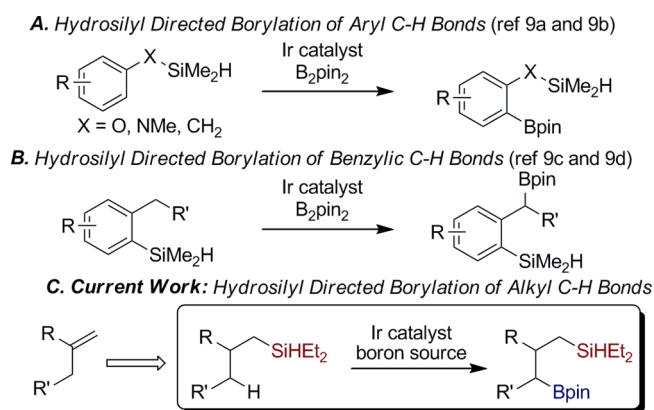
S *Supporting Information*

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.

Scheme 1. Hydrosilyl Directed Borylation of C−H Bonds

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*

The functionalization of alkyl C−H bonds with borane reagents[1] 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 benzyl[4] 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]

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 ligand[9] (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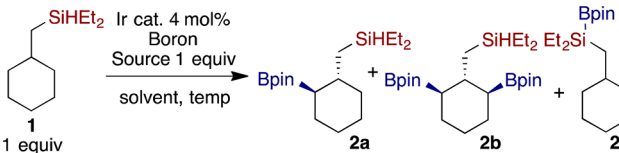. These reactions occur with high site selectivity γ to silicon and with high diastereoselectivity in cases of reactions at secondary C−H bonds.

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 B_2pin_2 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.
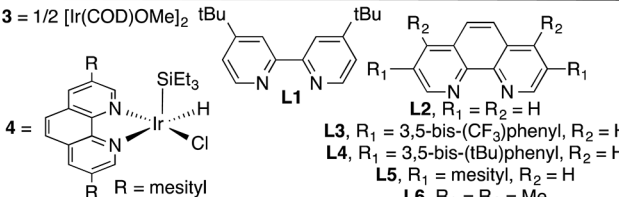
The yield of the borylation of **1** catalyzed by the combination of Ir and a phenanthroline (phen) depended strongly on the identity of the phen ligand. The reaction conducted with parent phen (**L2**), an electron-deficient diaryl phen (**L3**),[4] or an electron-rich diaryl phen (**L4**) as ligand 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

Table 1. Method Development for the Hydrosilyl Directed Borylation of 1[a]

Entry	Ir cat.	Boron Source	Solvent	temp. (°C)	% Yield (GC) 2a	2b	2c
1	3/L1	B_2pin_2	octane	100	21	3	21
2	3/L2	B_2pin_2	octane	100	5	<1	23
3	3/L3	B_2pin_2	octane	100	2	0	3
4	3/L4	B_2pin_2	octane	100	11	3	0
5[b]	3/L5	B_2pin_2	octane	100	43	12	0
6[b]	3/L6	B_2pin_2	octane	100	51	8	0
7	3/L6	B_2pin_2	isooctane	100	52	8	0
8	3/L6	B_2pin_2	isooctane	120	56	6	0
9	3/L6	B_2pin_2	isooctane	80	28	6	9
10	3/L6	$Et_3SiBpin$	isooctane	80	58	4	0
11	3/L5	$Et_3SiBpin$	isooctane	80	66	7	0
12	4	$Et_3SiBpin$	isooctane	80	65	8	0
13[c]	4	$Et_3SiBpin$	isooctane	80	77	21	0

$3 = 1/2 [Ir(COD)OMe]_2$

L2, $R_1 = R_2 = H$
L3, $R_1 = $ 3,5-bis-(CF_3)phenyl, $R_2 = H$
L4, $R_1 = $ 3,5-bis-(tBu)phenyl, $R_2 = H$
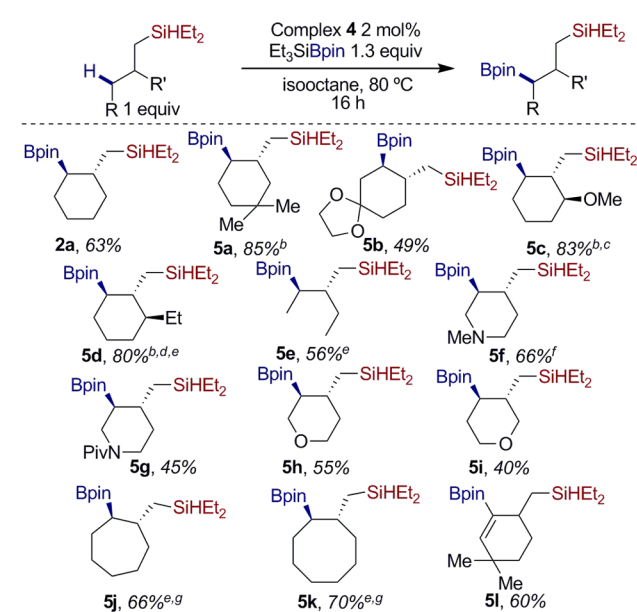L5, $R_1 = $ mesityl, $R_2 = H$
L6, $R_1 = R_2 = Me$

[a]Reactions conducted on a 0.10 mmol scale. Yields were determined by gas chromatography. [b]Formation of n-octyl-Bpin was observed in ca. 10% yield. [c]Reaction conducted with 1.3 equiv of $Et_3SiBpin$.

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 $Et_3SiBpin$ as the boron source formed 2a in 58% yield.

With $Et_3SiBpin$ 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 $L_2Ir(H)(Cl)(SiEt_3)$ react rapidly with $Et_3SiBpin$ 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 $Et_3SiBpin$.

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 diethylsilane[10] (Chart 1). Hydrosilanes containing six-mem-

Chart 1. Hydrosilyl Directed Borylation of Secondary Alkyl C−H Bonds[a]

2a, 63% 5a, 85%[b] 5b, 49% 5c, 83%[b,c]
5d, 80%[b,d,e] 5e, 56%[e] 5f, 66%[f]
5g, 45% 5h, 55% 5i, 40%
5j, 66%[e,g] 5k, 70%[e,g] 5l, 60%

[a]Reactions conducted on a 0.30 mmol scale. Yields are for isolated products. [b]Reaction conducted with 1.15 equiv of $Et_3SiBpin$. [c]The d.r. of the starting material was 11:1. [d]The d.r. of the starting material was 5:1. [e]Reaction conducted with 4 mol % of complex 4. [f]Yield determined by gas chromatography. [g]Reaction conducted at 100 °C.

bered 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 ^{1}H 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 (cyclopentyl-methyl)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 Et$_3$SiBpin 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 Et$_3$SiBpin formed **6b** in 68% yield (Chart 2).
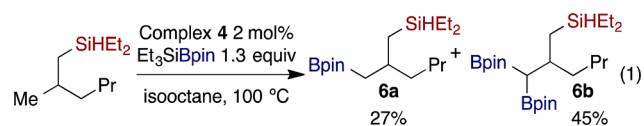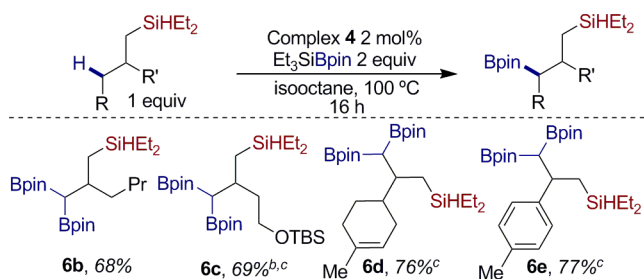

**Chart 2. Hydrosilyl Directed Bis-Borylation of Primary Alkyl C−H Bonds**[a]

[a]Reactions conducted on a 0.30 mmol scale. Reported yields are for isolated products. [b]Reaction conducted with 2.2 equiv of Et$_3$SiBpin. [c]Reaction conducted with 4 mol % of complex **4**.

The scope of the bisborylation of primary alkyl C−H bonds with 2 equiv of Et$_3$SiBpin 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 metallacyle 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

Scheme 2. Effect of Six-Membered Ring Conformation on Diastereoselectivity
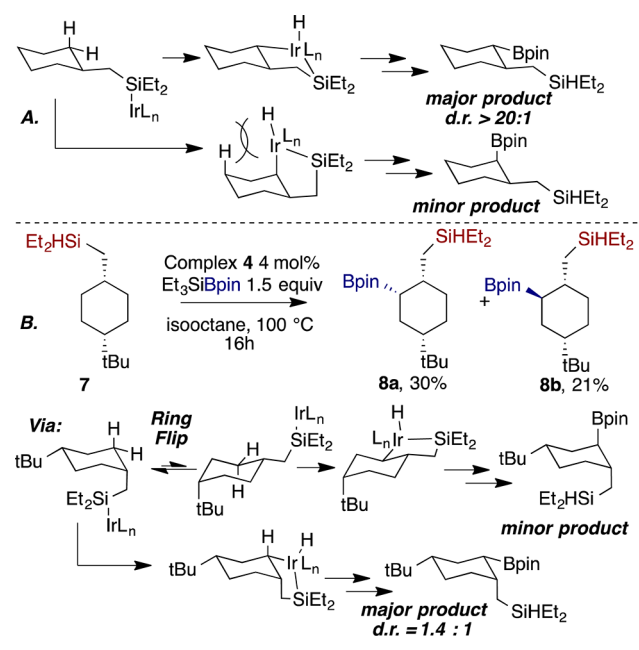
formed the *cis* and *trans* products in 30% and 21% isolated yield, respectively. The diastereoselectivity in this case is different from those of the reactions in Chart 1 because the directing group is axial rather than equatorial in the ground state. Thus, the formation of **8a** involves a structure 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 amination[13] of **5a** formed Boc-protected amine **9a** in 55%

Scheme 3. Functionalization of the Borylation Products[a]
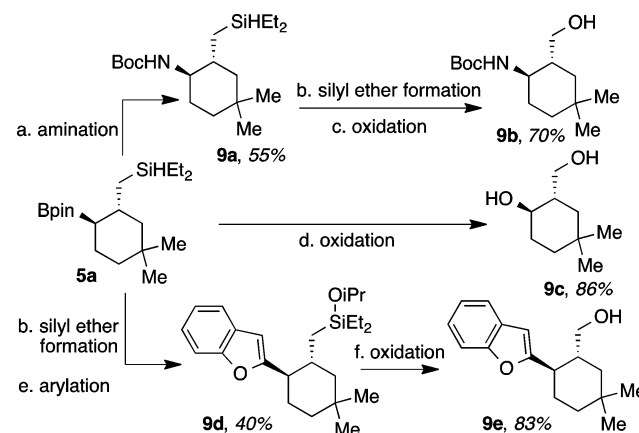
[a]Conditions: (a) NH$_2$OMe (3 equiv), *n*-BuLi (3 equiv), Boc$_2$O (3.3 equiv), THF, −78 to 65 °C, 14 h. (b) iPrOH (3 equiv), [Ir(COD)Cl]$_2$ (2 mol %), MeCN, rt, 24 h. (c) H$_2$O$_2$ (60 equiv, 3 portions), KHCO$_3$ (10 equiv), KF (10 equiv), THF, MeOH, 65 °C, 3 h. (d) H$_2$O$_2$ (10 equiv), KHCO$_3$ (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) tBuOOH (14 equiv), CsOH (12 equiv), TBAF (5 equiv), THF, 50 °C, 2 h.

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 H_2O_2 and $KHCO_3$, *trans*-diol **9c** formed in 86% yield. Compound **5a** also underwent an arylation reaction[14] with benzofuran after the Si–H was converted to a silyl ether, forming **9d** in 40% yield. Oxidation[15] 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 $Et_3SiBpin$ than for those conducted with B_2pin_2.

■ 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)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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