

Iridium-Catalyzed Borylation of Secondary Benzylic C–H Bonds Directed by a Hydrosilane

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S Supporting Information

ABSTRACT: Most functionalizations of C–H bonds by main-group reagents occur at aryl or methyl groups. We describe a highly regioselective borylation of secondary benzylic C–H bonds catalyzed by an iridium precursor and 3,4,7,8-tetramethyl-1,10-phenanthroline as the ligand. The reaction is directed to the benzylic position by a hydrosilyl substituent. This hydrosilyl directing group is readily deprotected or transformed to other functional groups after the borylation reaction, providing access to a diverse set of secondary benzyboronate esters by C–H borylation chemistry.

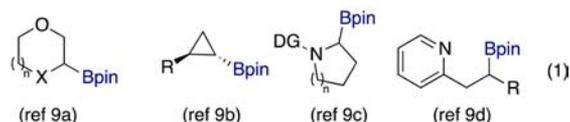
Alkylboron reagents are useful synthetic intermediates in a variety of organic transformations, and methods for their preparation have attracted much attention.¹ Such compounds are typically prepared by the reaction of organometallic nucleophiles (e.g., Grignard or organolithium reagents) with boron electrophiles² or by hydroboration of alkenes.^{1b,3} More recently, cross-coupling of boron reagents with alkyl electrophiles has been reported.⁴

Transition-metal-catalyzed functionalization of C–H bonds with bis(pinacolato)diboron (B_2pin_2) has become a practical method for the direct formation of boronate esters.⁵ Significant progress on the borylation of sp^2 C–H bonds has been made,^{6,7} but the borylation of sp^3 C–H bonds is less developed. Compared with the borylation of sp^2 C–H bonds, the borylation of sp^3 C–H bonds typically requires a higher catalyst loading and excess saturated substrate. The regioselectivity of the borylation of sp^3 C–H bonds strongly favors reaction at primary C–H bonds,⁸ making the functionalization of secondary C–H bonds challenging.

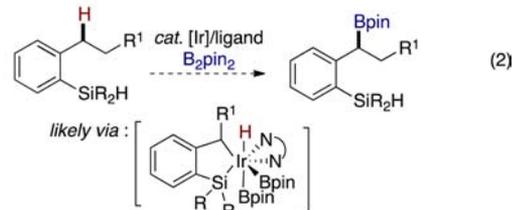
We recently disclosed a highly reactive catalytic system derived from the combination of $[Ir(COD)OMe]_2$ (COD = 1,5-cyclooctadiene) and 1,10-phenanthroline-derived ligands that functionalizes the secondary C–H bonds of cyclic ethers^{9a} and cyclopropanes.^{9b} Sawamura and co-workers also reported the borylation of secondary C–H bonds of cyclic amides^{9c} and alkyl pyridines^{9d} catalyzed by an immobilized-catalyst system (eq 1). Here we describe the development of an iridium-catalyzed borylation of secondary benzylic C–H bonds directed by a hydrosilyl ($-SiR_2H$) group. In contrast to a heteroaryl directing group, the hydrosilyl group can be traceless or converted to a series of functional groups.¹⁰

We previously showed that hydrosilyl groups can direct the sp^2 C–H borylation of arenes^{11a} and *N*-heteroarenes.^{11b} In these cases, the formation of a five-membered bisboryl

a. Previous secondary (sp^3) C–H borylation



b. This Work: Silyl-directed secondary (sp^3) C–H borylation

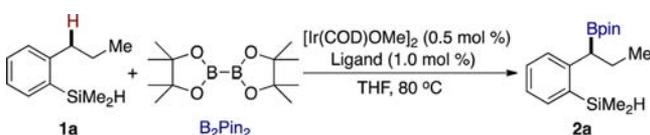


monosilyl complex was proposed to lead to the observed regioselectivity. If a ring of the same size could be generated from an alkylarylsilane, then the product would result from borylation at the benzylic position (eq 2). Because of the scarcity of borylations of benzylic C–H bonds,¹² it was unclear whether this sequence would lead to reaction at a secondary C–H bond over an aryl group. Thus, we conducted experiments to test the feasibility of this directed borylation process.

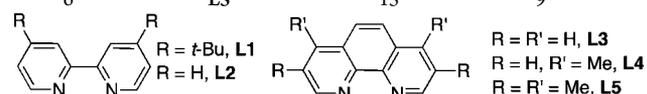
To evaluate potential catalysts for this transformation, we investigated the borylation of (2-propylphenyl)dimethylsilane (**1a**). We allowed **1a** to react with B_2pin_2 in tetrahydrofuran (THF) at 80 °C in the presence of the combination of $[Ir(COD)OMe]_2$ and each of a series of nitrogen ligands (Table 1). The reaction catalyzed by $[Ir(COD)OMe]_2$ and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy, **L1**), which is the ligand most frequently used for the borylation of aryl C–H bonds,⁵ proceeded to form benzyboronate ester **2a** with 90% conversion and 83% yield, as determined by NMR spectroscopy (entry 1). The reaction occurred selectively at the benzylic position; no borylation of the sp^2 bonds of the arene was observed. This result indicated that the hydrosilane could redirect the borylation reaction from the typically reactive aryl position to the benzylic position. Reactions conducted with ligands that should be less electron-donating than dtbpy occurred with moderate conversion and yield (entry 2).¹³ In contrast, reactions conducted with a series of ligands derived from 1,10-phenanthroline (entries 3–5) showed that the catalyst generated from 3,4,7,8-tetramethyl-1,10-phenanthroline

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Table 1. Effect of the Bipyridine Ligand on the Catalytic Borylation of Benzylic C–H bonds^a


entry	ligand	conv (%)	yield (%) ^b
1	L1	90	83
2	L2	80	61
3	L3	90	85
4	L4	94	89
5	L5	100	97 (93)
6 ^c	L5	15	9

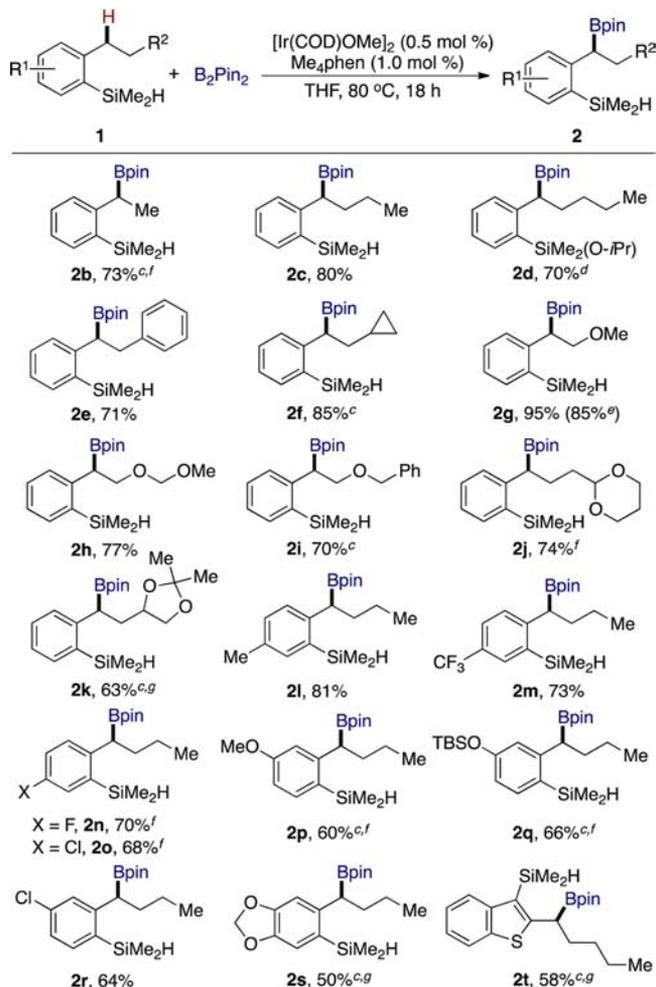


^aConditions: **1a** (0.3 mmol), B₂pin₂ (0.3 mmol), [Ir(COD)OMe]₂ (0.5 mol %), and ligand (1.0 mol %) in THF at 80 °C for 18 h. ^bDetermined by ¹H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. The value in parentheses is an isolated yield. ^cHBpin (0.6 mmol) was used in place of B₂pin₂ as the boron reagent.

(Me₄phen, L5) is highly active for the conversion of **1a** to **2a** in 93% isolated yield (entry 5).

With an active catalyst in hand, we investigated the scope of the hydrosilyl-directed benzylic borylation (Table 2). Simple alkylarenes (**2b–d**) underwent the borylation reaction in high yield. Analytically pure **2d** was isolated after conversion of the hydrosilane to the silyl ether with 2-propanol in the presence of 0.5 mol % [Ru(*p*-cymene)Cl]₂.¹⁴ Substrates containing alkyl chains substituted with phenyl and cyclopropyl substituents, which were previously shown to undergo borylation at the C–H bonds of these groups by the Ir/Me₄phen catalytic system, gave the corresponding benzylboronate esters (**2e** and **2f**) in good yields.^{6,9a} This selectivity for the benzylic C–H bonds over the aryl and cyclopropyl C–H bonds underscores the impact of the hydrosilyl directing group. The directed borylation reaction of ether-containing substrates also proceeded in high yield at the benzylic position to form products **2g–i**. Moreover, this process led to the benzylic borylation of alkyl chains containing a masked aldehyde (**2j**) or diol (**2k**). The present reaction occurred equally well on a 5 mmol scale as on the smaller 0.3 mmol scale (**2g**). Variation of the electronic properties of the arene had little influence on the yield (**2l**, **2m**, and **2p**). Substrates bearing a fluoro (**2n**), chloro (**2o** and **2r**), or silyl ether (**2q**) group and a protected catechol (**2s**) were compatible with this catalytic system. Finally, a heteroaromatic benzothiazole derivative formed product **2t** in 58% yield.

The hydrosilyl group can be removed or used for diversification of the arene. Such transformations of the hydrosilyl directing group are shown in Scheme 1. The reactions of **2c** and **2g** with the combination of in situ-generated trimethylsilyl iodide (TMSI) and water resulted in cleavage of the hydrosilyl group, affording the corresponding desilylated benzylboronate esters (**3a** and **3b**) or deuterated analogues (**3a–d**) in almost quantitative yields at room temperature.¹⁵ Alternatively, the hydrosilane was cleaved by reaction with AgF and H₂O [see the Supporting Information (SI)]. This cleavage of the C–Si bond occurred while the benzylic carbon–Bpin linkage remained intact.

Table 2. Substrate Scope^{a,b}


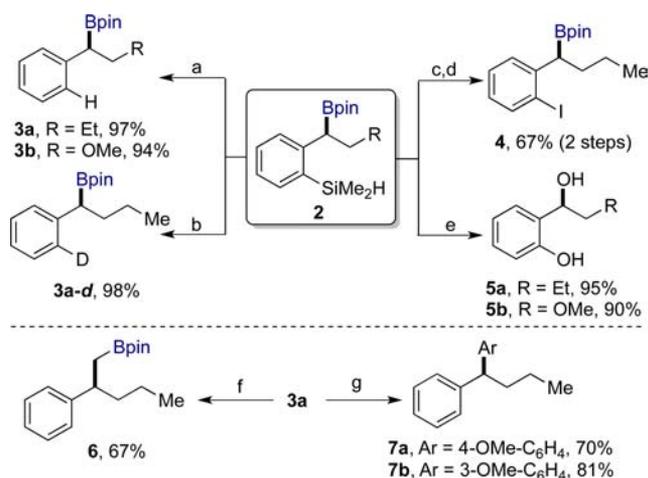
^aConditions: **1** (0.3 mmol), B₂pin₂ (0.3 mmol), [Ir(COD)OMe]₂ (0.5 mol %), and L5 (1.0 mol %) in THF at 80 °C for 18 h. ^bIsolated yields are shown. ^c1.5 equiv of **1** with respect to B₂pin₂ (0.3 mmol) was used; the yield based on B₂pin₂ was determined. ^dIsolated yield after conversion of the hydrosilane to the silyl ether with 2-propanol (see the SI). ^eConducted on a 5 mmol scale. ^fRun for 24 h. ^gRun for 36 h.

In addition, the aryl–hydrosilyl unit was transformed into an aryl iodide without affecting the benzyl–Bpin linkage after Ru-catalyzed conversion of the hydrosilane to a hydrosilyl ether with 2-propanol. Treatment of the resulting silyl ether with AgF and *N*-iodosuccinimide (NIS) formed the aryl iodide. This sequence converted **2c** into **4** in 67% yield over two steps.¹⁰

Both the hydrosilane and Bpin functionalities could be converted to the corresponding hydroxyl groups. For example, the reactions of **2c** and **2g** in the presence of excess NaOH(aq) and H₂O₂ in THF gave the corresponding 2-(α -hydroxylalkyl)-phenols **5a** and **5b** in excellent yield.

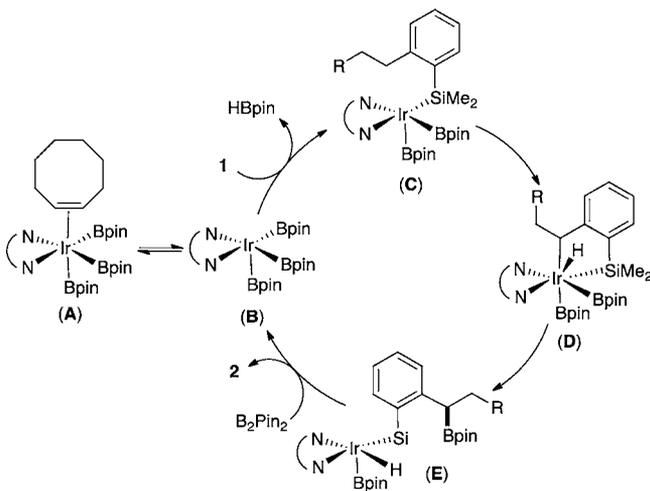
The benzylboronate unit could also be used for C–C bond formation. The desilylated secondary benzylboronate ester **3a** underwent one-carbon homologation with bromochloromethane and *n*-BuLi to produce the corresponding homo-benzylic boronate ester **6** in 67% yield. In addition, Suzuki–Miyaura cross-coupling of **3a** with two representative aryl iodides in the presence of a catalytic amount of Pd₂(dba)₃ and PPh₃ and the combination of Ag₂O and K₂CO₃ as a base at 70 °C in THF formed the arylated products **7a** and **7b** in good yields (70% and 81%, respectively).¹⁶

Scheme 1. Functionalization of the Hydrosilane and Boronate Ester



Conditions: (a) TMSCl (1.2 equiv), KI (1.2 equiv), H₂O (1.2 equiv), CH₃CN, 25 °C. (b) TMSCl (1.2 equiv), KI (1.2 equiv), D₂O (1.2 equiv), CH₃CN, 25 °C. (c) [Ru(*p*-cymene)Cl]₂ (0.5 mol %), 2-propanol (2.0 equiv), 0 °C. (d) AgF (4.0 equiv), NIS (4.0 equiv), THF, 25 °C. (e) NaOH/H₂O₂ (excess), THF, 0 to 25 °C. (f) BrCH₂Cl (2.0 equiv), *n*-BuLi (2.0 equiv), THF, -78 to 25 °C. (g) Pd₂(dba)₃ (5 mol %), PPh₃ (40 mol %), Ag₂O (1.5 equiv), K₂CO₃ (1.5 equiv), ArI (2.0 equiv), THF, 80 °C.

Scheme 2. Proposed Mechanism



A proposed mechanism for the silyl-directed benzylic borylation is presented in Scheme 2. The borylation of aryl C–H bonds has been shown to occur through a trisboryl complex, such as complex A,¹³ containing a chelating nitrogen ligand. We suggest that A reacts with 1 to afford silylbis(boryl) iridium complex C via unsaturated complex B. Addition of the benzylic C–H bond would then form five-membered metallacycle D, and coupling of the benzyl group with a Bpin ligand would give silyliridium hydride complex E. Reductive elimination of silane and oxidative addition of B₂pin₂ would produce the borylated product and regenerate the tris(boryl)-iridium intermediate B.

In summary, we have developed an iridium-catalyzed borylation of secondary benzylic C–H bonds directed by a hydrosilane to give benzylboronate esters. This reaction constitutes a rare example of secondary C–H borylation and

an example of directed borylation of secondary C–H bonds with a directing group that can be removed or used for further transformations. The formation of a bisboryl monosilyl complex is proposed to trigger the benzylic C–H activation through a five-membered metallacycle. Further studies to expand the scope of the borylation of saturated C–H bonds and develop an asymmetric version of this transformation are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra for all new compounds. 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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