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Iridium-catalyzed diborylation of benzylic C–H bonds directed by a hydrosilyl group: synthesis of 1,1-benzyldiboronate esters†

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We describe a regioselective diborylation of primary benzylic C–H bonds catalyzed by $[Ir(COD)OMe]_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy). The hydrosilyl group acts as a traceless directing group, providing access to a range of 1,1-benzyldiboronate esters in good yields. Transformations of the 1,1-benzyldiboronate ester products include chemoselective Suzuki–Miyaura cross-couplings and synthesis of tetrasubstituted alkenyl boronate esters.

Introduction

1,1-Organodimetallic reagents are valuable starting materials for the construction of multifunctionalized molecules.[1] Among them, 1,1-organodiboronate esters, which contain two boryl groups at the same carbon center, are particularly attractive due to their ease of handling, non-toxicity, stability, and propensity to undergo a variety of organic transformations.[2] Classical methods for the preparation of 1,1-organodiboronate esters involve the hydroboration of 1-alkynes with trimethylsilane and boron trichloride, followed by protection with 1,3-propandiol,[3] or the addition of bis(pinacolato)diboron (B_2pin_2) to lithiated substrates.[4] However, these methods require multistep synthetic sequences or harsh reaction conditions.

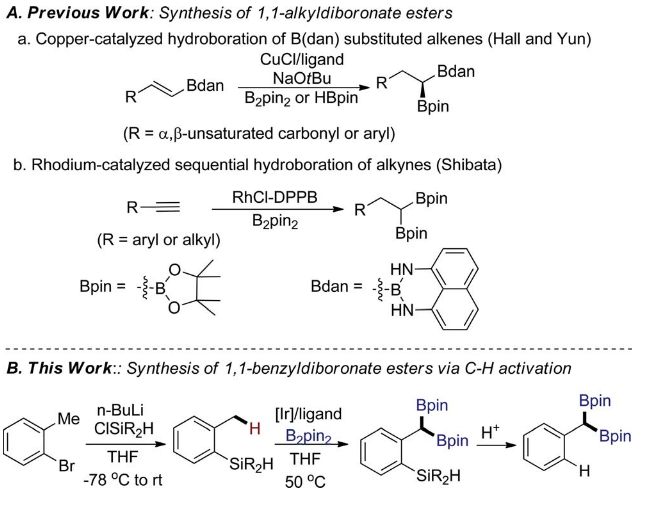
In recent years, transition-metal catalyzed methods have been developed for the preparation of 1,1-organodiboronate esters. Shibata and coworkers reported a rhodium(I)-catalyzed sequential hydroboration of alkynes with B_2pin_2 to afford 1,1-alkyldiboronate esters.[5] Hall[6a] and Yun[6b] independently reported copper(I)-catalyzed asymmetric addition of boron reagents to α,β-unsaturated carbonyl and styrene derivatives containing a 1,8-naphthalenediaminatoboryl (Bdan) substituent (Scheme 1).

However, methods to synthesize 1,1-benzyldiboron compounds, which are inaccessible by addition reactions, are rare. A platinum-catalyzed insertion reaction of a carbene derived from a diazoalkene into the B–B bond of B_2pin_2 has been reported; but, high reaction temperatures were required, and the scope was limited.[7,8]

Transition-metal catalyzed borylation of aliphatic C–H bonds[9–11] could provide a route to 1,1-diboryl compounds.[12,13] However, the borylation of a 1-alkylboronate ester previously led to the α,ω-diborylalkane. The diborylation of methylarenes could be valuable and might be envisioned to be more feasible than the 1,1-diborylation of an alkyl group, but one must overcome the typically faster borylation of arenes to accomplish this process.[14]

We recently showed that a hydrosilyl group directs borylation reactions catalyzed by $[Ir(COD)OMe]_2$ and Me_4phen to form products containing a new C–B bond *via* five-membered metalla silacyclopentane intermediates. This directing effect can be used for functionalization of aryl and heteroaryl C–H bonds or benzylic C–H bonds.[15] Thus, we sought to determine if this directing group could be used to form diborylbenzyl boronate esters from 2-methyl silylarenes.

We report the diborylation of 2-methyl hydrosilylarenes to form diborylbenzylic compounds. The silyl directing group can be removed and the diborylbenzyl products converted to useful intermediates. We also report conditions for selective



Scheme 1 Transition-metal catalyzed diborylation reactions.

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monoarylation of the diborylbenzyl compounds to form diarylmethylboronate ester products poised for further transformations and the conversion of the diborylbenzyl compounds to vinylboronate esters.

Results and discussion

To assess the ability to direct C–H borylation to the methyl group of methylarenes, we studied the effect of a series of reaction parameters on the yield of monoborylbenzyl compound **2a** and diborylbenzyl compound **3a** (Table 1). These studies showed that diborylated product **3a** was obtained in high yield when **1a** was allowed to react with 2.0 equivalents of B_2pin_2 in the presence of $[Ir(COD)OMe]_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) at 50 °C in THF (entry 1). With pinacolborane (HBpin) as the boron reagent, we observed lower yield than we did with B_2pin_2 (entry 2). Substituents on the silyl group had a negligible impact on this diborylation reaction; good to excellent yields of the corresponding diborylated products were obtained with methyl or phenyl groups on silicon (entries 3 and 4). Reducing the ratio of diboron reagent to arene **1** did not provide monoboryl compound **2a**. When an excess of silyltoluene **1a** (4.0 equiv. based on B_2pin_2) was subjected to the reaction conditions, large amounts of the diborylated product were still detected (entries 5–7).

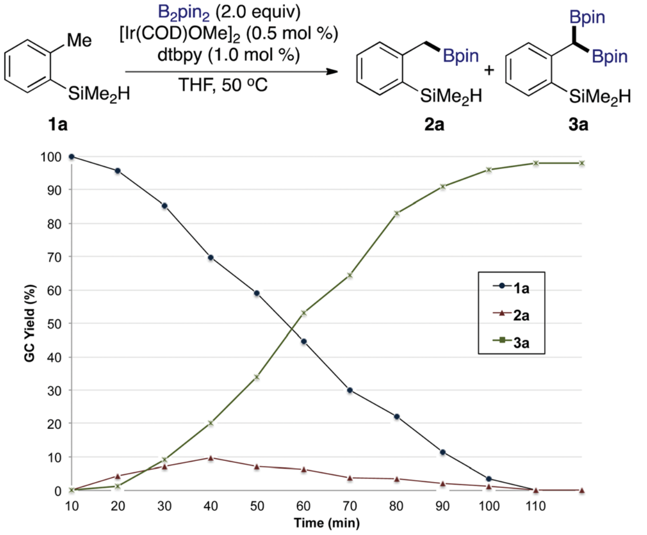
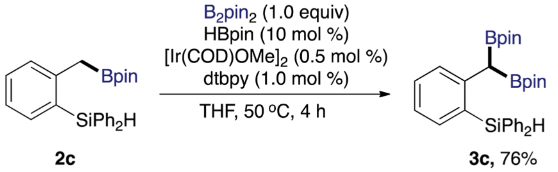


Fig. 1 Profile of the decay of (*o*-tolyl)dimethylsilane (**1a**) and appearance of monoborylation product (**2a**) and diborylation product (**3a**) from the reaction of **1a** with B_2pin_2 at 50 °C in THF catalyzed by 0.5 mol% $[Ir(COD)OMe]_2$ and 1.0 mol% dtbpy.

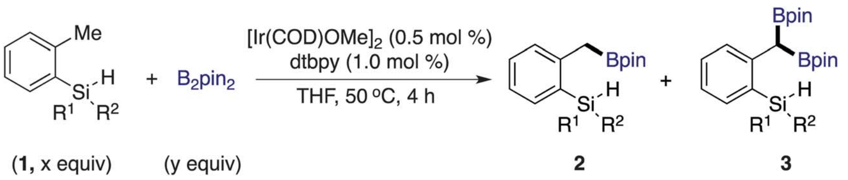
To probe the relative reactivity of the benzylic C–H bond and benzylboronate C–H bond toward the borylation process, we monitored the reaction of iridium-catalyzed diborylation of **1a** by GC. As shown in Fig. 1, the yield of monoborylation product **2a** formed in a maximum yield of 10% within 40 min. These results indicate that the monoborylated species **2** is more reactive than the methylarene **1a** under the reaction conditions, presumably because of increased acidity of the benzylic hydrogens adjacent to boron functionality.[2d] Indeed, the isolated monoborylated product **2c** underwent the second borylation reaction with nearly equal yield to the diborylation of **1c** under the standard conditions in the presence of a catalytic amount of HBpin (eqn (1)).



(1)

With these results in hand, we examined the scope of the diborylation reaction (Table 2). We found that various

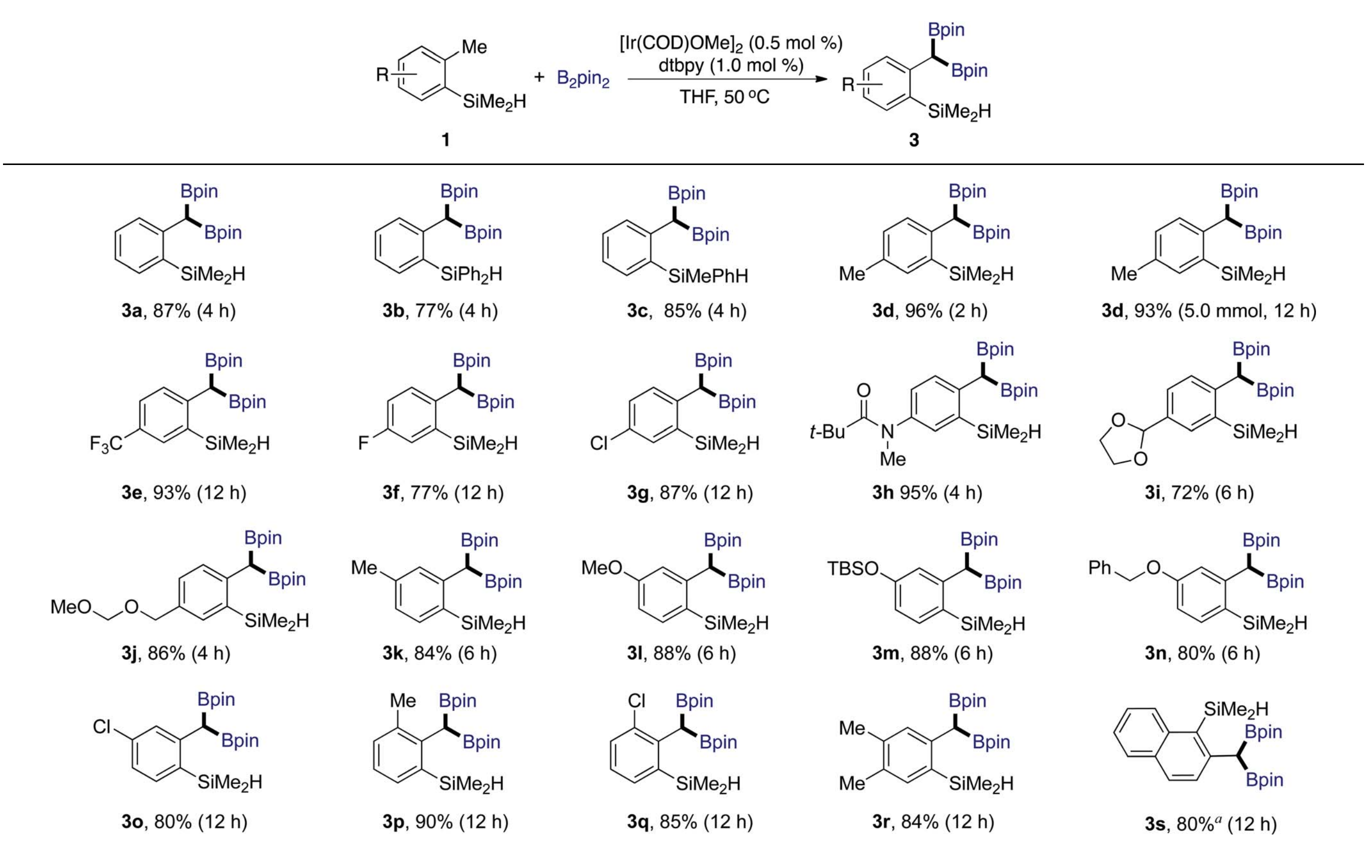
Table 1 Stoichiometry control of borylation of benzylic C–H bonds[a]



Entry	R^1	R^2	*x*	*y*	Yield (%)[b] 2	Yield (%)[b] 3
1	Me	Me	1.0	2.0	<1	87 (**3a**)[c]
2[d]	Me	Me	1.0	2.0	<1	13 (**3a**)
3	Me	Ph	1.0	2.0	<1	85 (**3b**)[c]
4	Ph	Ph	1.0	2.0	<1	77 (**3c**)[c]
5[e]	Me	Me	4.0	1.0	8 (**2a**)	47 (**3a**)
6[e]	Me	Ph	4.0	1.0	39 (**2b**)	31 (**3b**)
7[e]	Ph	Ph	4.0	1.0	40 (**2c**)	30 (**3c**)

[a] *Reaction Conditions*: **1** (*x* equiv.), B_2pin_2 (*y* equiv.), $[Ir(COD)OMe]_2$ (0.5 mol%), and dtbpy (1.0 mol%) in THF at 50 °C for 4 h. [b] Determined by ^1H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] 4 equiv. of HBpin was used in place of B_2pin_2. [e] The yield was determined based on the amount of B_2pin_2. COD = 1,5-cyclooctadiene.

Table 2 Scope of diborylation of benzylic C–H bonds[a]

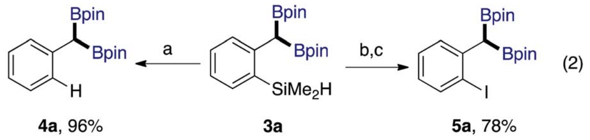


3a, 87% (4 h)
3b, 77% (4 h)
3c, 85% (4 h)
3d, 96% (2 h)
3d, 93% (5.0 mmol, 12 h)
3e, 93% (12 h)
3f, 77% (12 h)
3g, 87% (12 h)
3h 95% (4 h)
3i, 72% (6 h)
3j, 86% (4 h)
3k, 84% (6 h)
3l, 88% (6 h)
3m, 88% (6 h)
3n, 80% (6 h)
3o, 80% (12 h)
3p, 90% (12 h)
3q, 85% (12 h)
3r, 84% (12 h)
3s, 80%[a] (12 h)

[a] *Reaction Conditions*: **1** (0.5 mmol), B_2pin_2 (2.0 equiv.), $[Ir(COD)OMe]_2$ (0.5 mol%), and dtbpy (1.0 mol%) in THF at 50 °C for an indicated time. In each case, the yield of isolated product is given. [b] Run at 80 °C. TBS = *tert*-butyldimethyl silyl.

substituted arenes underwent selective diborylation reactions exclusively at the benzylic position, irrespective of the electronic nature of the substituent. Arenes possessing electron-neutral (**3a–3c**), electron-donating (**3d**, **3k**, **3l**, **3p**, and **3r**), or electron-withdrawing (**3e**) substituents on the phenyl ring all reacted to form the diboryl product in good yields. A variety of functional groups, including halides (**3f**, **3g**, **3o**, and **3q**), amide (**3h**), masked aldehyde (**3i**), protected alcohol (**3j** and **3n**), and silyl ethers (**3m**) all were found to be compatible with the reaction conditions. The diborylation also occurred at the benzylic position of a naphthyl moiety (**3s**), albeit at a higher temperature (80 °C). The present reaction occurred equally well on a 5.0 mmol scale as on a 0.5 mmol scale (**3d**) under the standard conditions, but with a longer reaction time. The obtained 1,1-benzyldiboronate esters are stable and isolable by silica-gel chromatography.

To demonstrate the synthetic utility of the 1,1-benzyldiboronate ester products obtained from the new reaction, we first sought to identify conditions for a selective cleavage of the hydrosilyl–aryl bond without affecting the benzyl-(bis)Bpin linkage. Indeed, the aryl–silicon bond was cleaved in high yield upon treatment of **3a** with the combination of TMSI (TMS = trimethylsilyl) and H_2O in CH_3CN at room temperature (eqn (2)).[16] In addition, the hydrosilyl group was transformed into an aryl iodide after Ru-catalyzed conversion of the hydrosilane to a hydrosilyl ether with 2-propanol. Addition of iodine monochloride to the silyl ether formed **5a** from **3a** in 78% yield over two steps.

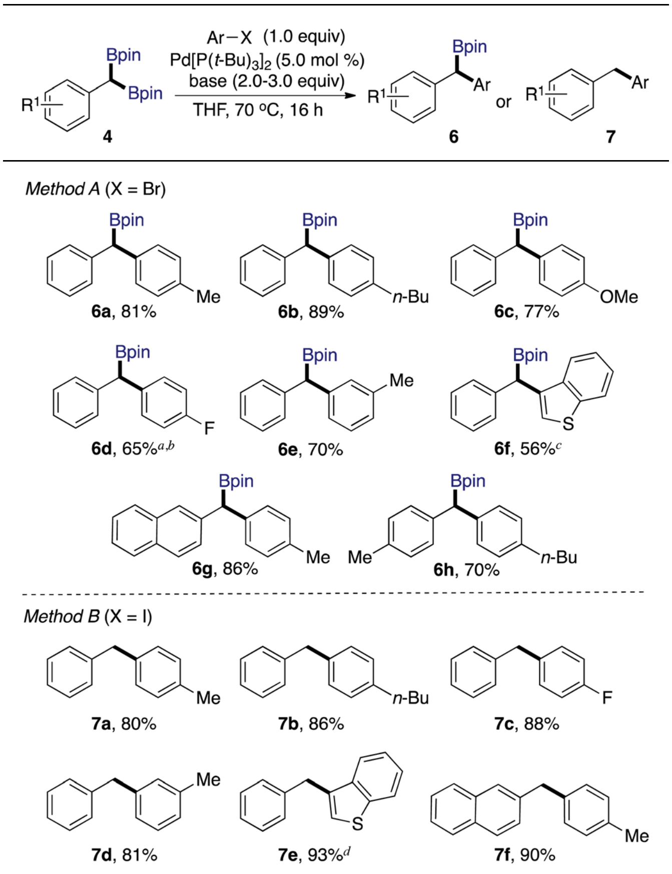


4a, 96%
3a
5a, 78%

Reaction Conditions:[a]TMSCl (1.2 equiv), KI (1.2 equiv), H_2O (1.2 equiv) in CH_3CN at 25 °C.[b]$[Ru(p\text{-cymene})Cl_2]_2$ (0.5 mol%), 2-propanol (0.1 mL), 25 °C.[c]ICl (1.1 equiv) in CH_2Cl_2 at 25 °C.

Having developed a method to prepare diborylarenes, we also developed a chemoselective Suzuki–Miyaura cross-coupling.[17] After evaluating a series of reaction conditions, we found that the combination of $Pd[P(t\text{-}Bu)_3]_2$ (5.0 mol%) and CsF (2.0 equiv.), in THF at 70 °C mediated the coupling of substrates **4a**, **4d**, and **4s** with various aryl bromides to form the monosubstitution product (**6**) in good to moderate yields (Table 3, Method A). The CsF base was most effective for inducing reaction of one, but not both, of the Bpin groups (see the ESI† for details). This desilylation and chemoselective Suzuki–Miyaura coupling sequence can be conducted in one-pot; the two steps run in this fashion provided **6a** in 76% isolated yield.

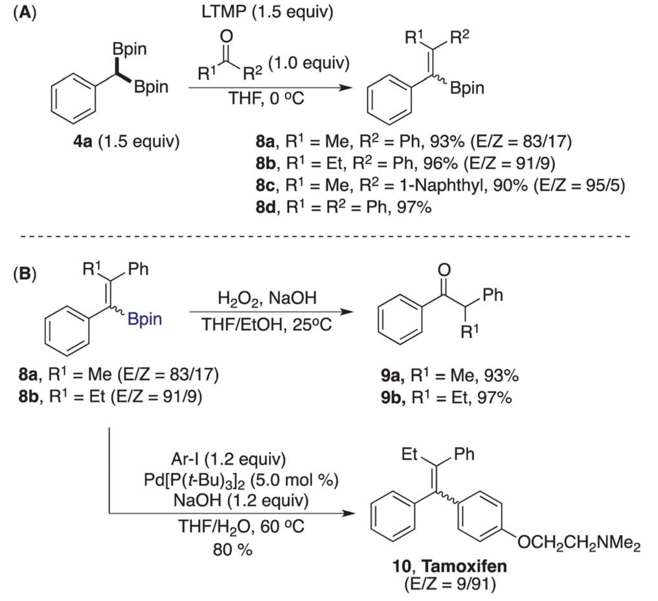
Table 3 Chemoselective Suzuki–Miyaura cross-couplings[a]



[a] *Method A*: aryl bromide (0.2 mmol), **4** (1.5 equiv.), Pd[P(*t*-Bu)$_3$]$_2$ (5.0 mol%), CsF (2.0 equiv.), THF, 70 °C, 16 h. *Method B*: aryl iodide (0.2 mmol), **4** (1.5 equiv.), Pd[P(*t*-Bu)$_3$]$_2$ (5.0 mol%), NaOH (3.0 equiv.), THF/H_2O, 70 °C, 16 h. In each case, the yield of isolated product based on aryl halide is given. [b] 1,4-Dioxane was used in place of THF as a solvent. [c] Run for 24 h. [d] Aryl bromide was used in place of aryl iodide.

While surveying the effect of base on the chemoselective cross-coupling, we also discovered that the reaction conducted with aryl iodides and NaOH base gave diarylmethanes (**7**) selectively under the reaction conditions (Table 3, Method B). This coupling and cleavage sequence provides a method to form the products from monoarylation of a benzylic methyl group by a sequence of diborylation and the combination of cross coupling and protodeborylation. This process is the equivalent of monoborylation and cross coupling of a monoborylmethylarene.

In addition to the chemoselective cross-coupling with aryl halides, we found that the desilylated diboronate ester **4a** could be used to afford the tetrasubstituted alkenylboronate esters **8**, which are valuable synthetic building blocks in organic synthesis.[18] Based on a literature procedure,[2d,19] the desired tetrasubstituted alkene **8** could be formed in the presence of 2,2,6,6-tetramethylpiperidide (LTMP) and the corresponding ketone. The alkene was formed with high diastereoselectivity favoring the *E* product when the reaction was conducted at 0 °C in THF (Scheme 2A).



Scheme 2 Synthesis of tetrasubstituted alkenylboronate esters, α-substituted ketones, and (*Z*)-tamoxifen. *E*/*Z* ratios were determined by NMR spectroscopy. In each case, the yield of isolated product is given.

The resulting tetrasubstituted boronate esters **8a** and **8b** react with an excess amount of NaOH and H_2O_2 to form α-substituted ketones **9a** and **9b** in excellent yield. Finally, (*Z*)-tamoxifen **10**, an antagonist of the estrogen receptor in breast tissue, was prepared in good yield from the tetrasubstituted alkenylboronate ester **8b** by Suzuki–Miyaura cross-coupling with the corresponding aryl iodide. This reaction occurred with retention of the ratio of *E* to *Z* configuration of the double bond (Scheme 2B).[4c,20]

Conclusions

In summary, we have developed a new synthetic method for the preparation of 1,1-benzyldiboronate esters by iridium-catalyzed C–H activation with a hydrosilane as a traceless directing group. This transformation operates under mild conditions and occurs with a wide range of aryl substituents and high functional group compatibility. The utility of the 1,1-benzyldiboronate esters has been demonstrated by chemoselective Suzuki–Miyaura cross-coupling at one of the two benzylboronate linkages. The desilylated 1,1-benzyldiboronate ester is also suitable for the synthesis of tetrasubstituted alkenylboronate esters with high (*E*)-selectivity. Further studies to develop an asymmetric monoarylation of the benzylic diboronate by Suzuki–Miyaura cross-coupling is ongoing.

Acknowledgements

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