

Chemoselective and Regiospecific Suzuki Coupling on a Multisubstituted sp^3 -Carbon in 1,1-Diborylalkanes at Room TemperatureKohei Endo,^{*,†} Takahiro Ohkubo,[‡] Munenao Hirokami,[‡] and Takanori Shibata^{*,‡}

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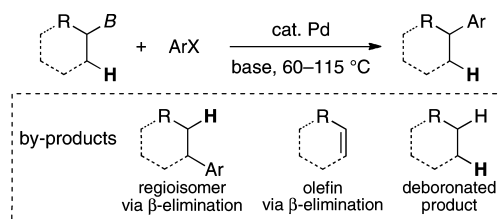
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Abstract: The palladium-catalyzed Suzuki–Miyaura cross-coupling on a multisubstituted sp^3 -carbon in 1,1-diborylalkanes was achieved at room temperature. The generation of a monoborate intermediate by virtue of the adjacent B atom could result in the chemoselective coupling reaction under ambient conditions.

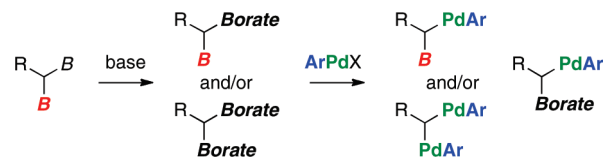
Suzuki–Miyaura cross-coupling (SMC) has been identified as a reliable method for C–C bond formation, especially for the synthesis of complex molecules.^{1,2} However, cross-coupling on an sp^3 -carbon has recently been shown to have severe drawbacks. β -Hydride elimination, regioisomerization, and protodeboronation are challenging processes that generate side-products. There have been only a few reports^{2a,3} of successful SMC on a multisubstituted sp^3 -carbon in organoboron compounds except for cyclopropylborane derivatives.⁴ Fu and Hartwig independently reported the use of secondary alkylboronic acids.³ Dreher and Molander as well as van den Hoogenband independently reported the use of secondary alkyl potassium trifluoroborate salts, which are a relatively tolerable coupling partner against protodeboronation.⁵ Recently, Sugimoto reported the use of α -(acylamino)benzylboronates without β -C–H bonds and Crudden reported the use of benzylboronate derivatives for the coupling reaction.⁶ These studies revealed some challenging, and still unsolved, problems: (1) the structure of multisubstituted alkylboron compounds is limited, such as to cycloalkyl, isopropyl, and benzyl boron compounds; (2) a high reaction temperature and long reaction time are required; and (3) isomerized byproducts are generated in many cases (Scheme 1). In this paper, we describe a new approach to the chemoselective and regiospecific SMC of 1,1-diborylalkanes⁷ on a multisubstituted sp^3 -carbon atom bearing β -C–H bonds at room temperature.

The cross-coupling reaction of alkylboron compounds generally suffers from a slow transmetalation step,^{2d,8} subsequent β -hydride elimination and/or protodeboronation, which requires a high reaction temperature and/or an excess amount of alkylboron compounds to achieve a high yield. We assumed that the use of 1,1-diborylalkanes could overcome these unsolved problems through rapid transmetalation and/or stabilization of the corresponding σ -alkylpalladium intermediate due to the boronate moiety attached at the carbon atom α to the Pd atom.⁹ The subsequent cross-coupling reaction gives *mono*-boronate compounds, which would resist transmetalation under mild conditions. However, the chemoselectivity for *mono*-borate and/or *di*-borate intermediates, which generate α -Pd,B, α -Pd,Pd, and/or α -Pd,Borate intermediates, would be problematic (Scheme 2). We examined the reaction of 1,1-diborylalkane **1a** (1.5 equiv) and 4-iodoanisole (**2a-I**) in the presence of 5 mol % Pd-

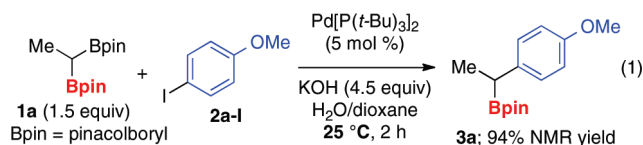
Scheme 1. Typical Byproducts in SMC Using Alkylborans



Scheme 2. Possible Scheme of SMC Using 1,1-Diborylalkanes



[P(*t*-Bu)₃]₂^{3a} in dioxane. To our surprise, the reaction proceeded efficiently at room temperature to give the desired product **3a** in 94% yield (eq 1). Side products, which are typical for the SMC of alkylboronates, were not observed. The boronate moiety attached to the product **3a** was intact and did not participate in further coupling, even in the presence of excess amounts of **2a-I**.



Screening of the reaction conditions clarified that the reaction at elevated temperature promotes protodeboronation; accordingly, the reaction at room temperature prevented side reactions. The Ni catalyst system reported by Fu for the cross-coupling reaction using primary alkylboron compounds with secondary alkyl halides^{8b,c} was not suitable and gave only the protodeboronated compound derived from **1a**. Therefore, the use of a Pd catalyst is required to achieve the present reaction. The choice of base was important; the use of strong bases, such as LiOH, NaOH, and KOH, was effective, and other bases, such as K₃PO₄, Cs₂CO₃, Na₂CO₃, and Ag₂O, did not give the product **3a** at room temperature.

The scope of haloarenes and 1,1-diborylalkanes is shown in Table 1. Every reaction proceeded at room temperature.¹⁰ A wide variety of aryl bromides were available and gave the corresponding products in good to excellent yields. The use of 1-mol % Pd-[P(*t*-Bu)₃]₂ gave the corresponding product in high yield (entry 4). The electron-rich aryl bromides **2e**, **2h**, **2l**, and **2p** afforded the corresponding boronates **3**, respectively (entries 4, 7, 11, and 15). Bromofluorobenzenes could take part in the reaction (entries 5, 8, and 12). The sterically hindered aryl bromides **2k**, **2o**, and **2q** gave

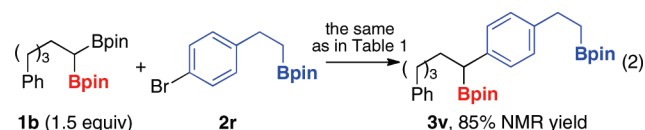
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Table 1. Wide Scope of 1,1-Diborylalkanes **1** and Aryl Bromides **2**

$\text{R}-\text{Bpin} + \text{ArBr} \xrightarrow[\text{H}_2\text{O/dioxane, 25}^\circ\text{C, 6-24 h}]{\text{Pd[P}(t\text{-Bu)}_3\text{]}_2 \text{ (5 mol \%), KOH (4.5 equiv)}} \text{R}-\text{Ar}$				
entry	R	Ar	Y	3 yield (%) ^a
1			2b , H	3b , 80 (74)
2	1b , Ph(CH ₂) ₄		2c , Me	3c , 98 (72)
3			2d , <i>tert</i> -Bu	3d , 94 (71)
4			2e , OMe	3e , 98 (75) ^b
5			2f , F	3f , 88 (73)
6			2g , Me	3g , 98 (95)
7			2h , OMe	3h , 83 (67)
8			2i , F	3i , ^c (65) ^d
9			2j , Me	3j , 98 (74)
10			2k , <i>i</i> -Pr	3k , 73 (61)
11			2l , OMe	3l , 97 (91)
12			2m , F	3m , ^c (73) ^d
13			2n , 3,5-(Me) ₂	3n , 98 (83)
14			2o , 2,6-(Me) ₂	3o , 98 (84)
15			2p , 3,5-(OMe) ₂	3p , 88 (70)
16			2q , 2,4,6-(Me) ₃	3q , ^c (69)
17	1a , Me			3a , 88 (68)
18	1c , Et			3r , 93 (79)
19	1d , <i>n</i> -C ₅ H ₁₁			3s , 91 (53)
20	1e , Bn			3t , 73 (65) ^e
21	1f , BnO(CH ₂) ₂			3u , 55 (42) ^e

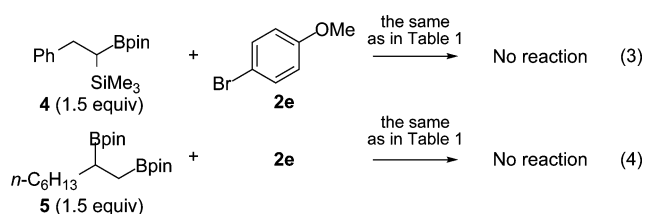
^a NMR yields. Isolated yields were described in parentheses. ^b The reaction in the presence of Pd[P(*t*-Bu)₃]₂ (1 mol %) gave the product **3e** in 92% NMR yield. ^c NMR yields could not be determined due to the complicated spectra. ^d The yield of corresponding deboronated product of **3** was described. ^e The yield of corresponding alcohol after oxidation was described.



the corresponding products in good yields (entries 10, 14, and 16). The reactions of various 1,1-diborylalkanes gave the corresponding products **3a**, **3r–u** in good yields (entries 17–21). The characteristic feature of the present reaction is shown in the chemoselective cross-coupling on an sp³-carbon derived from 1,1-diborylalkane **1b** with aryl bromide **2r** bearing a primary alkyl-(Bpin) moiety; the reaction gave the product **3v** selectively (eq 2; see Supporting Information for details). We next carried out the reactions of congeners of 1,1-diborylalkanes, such as 1,1-borylsilylalkane **4**^{11a} and 1,2-diborylalkane **5**,^{11b} to ascertain the influence of the bis(pinacolboryl) group (eqs 3 and 4). The reactions of **4** and **5** did not give the coupling product under the same reaction conditions as those in Table 1. These results suggest that the bis(pinacolboryl) group plays a pivotal role in promoting the coupling reaction on a multisubstituted sp³-carbon under mild conditions. This influence of the bis(pinacolboryl) group can be explained as follows. Primary alkyl-(9-BBN) and primary alkylboronic acids readily give the corresponding borate intermediate at room temperature with a relatively strong base, such as KOH, TIOH, or KO*t*-Bu.^{1,2,8a} Nevertheless, alkyl-(Bpin) scarcely gives the corresponding borate intermediate at room temperature. SMC of primary alkyl-(Bpin) using PdCl₂(dppf) and TIOH or some other bases gave the coupling product in low yield; accordingly, a relatively stronger Lewis acidic boron moiety should be required for alkylboron compounds to achieve SMC.

Table 2. Generation of Borate Intermediate at Room Temperature

$\text{R}-\text{X}-\text{Y}-\text{Bpin} + \text{KOH (3 equiv)} \xrightarrow{\text{in dioxane-}d_8}$		
entry	R, X, Y (¹¹ B, δ ppm)	+ KOH (¹¹ B, δ ppm, ratio)
1	1e ; Ph, H, Bpin (34.8)	35.5, −0.6 (1/1)
2	4 ; Ph, H, SiMe ₃ (34.8)	34.6 (no borate)
3	5 ; <i>n</i> -C ₆ H ₁₃ , Bpin, H (33.4)	34.0, 10.5 (15/1)
4	6 ; Ph, H, H (34.4)	34.4 (no borate)



To investigate the selective formation of a monoborate intermediate, we performed the NMR analyses of a mixture of **1e** and KOH (3 equiv) in dioxane-*d*₈ (see Supporting Information for details). As a result, two singlet peaks appeared at 35.5 and −0.6 ppm, and their integration ratio was almost 1 to 1; the high field shift suggests the formation of a borate moiety (Table 2, entry 1).^{1b} Therefore, the treatment of **1** could give a monoborate intermediate even in the presence of an excess amount of KOH; the further addition of KOH did not change the integration ratio. The subsequent addition of a stoichiometric amount of Pd[P(*t*-Bu)₃]₂ and 4-bromoanisole (**2e**) to the mixture of borate in dioxane-*d*₈ from **1e** and KOH gave the product **3t**. In stark contrast, the treatment of 1,1-borylsilylalkane **4**, and primary alkyl-(Bpin) **6** with KOH (3 equiv) in dioxane-*d*₈ did not change the chemical shift (entries 2 and 4). The Si atom of **4** does not induce the generation of a borate intermediate at room temperature; the impressive virtue of the adjacent B atom of 1,1-diborylalkanes is seen as being for borate generation. Although 1,2-diborylalkane **5** gave a small borate peak, the coupling reaction did not proceed at room temperature (entry 3, eq 4). Thus, the adjacent B atom in 1,1-diborylalkanes could promote the transmetalation between a borate intermediate and ArPdX. The influence of the adjacent B atom on a borate moiety as a β-anion equivalent seems to be a characteristic feature in the present study, since a Si atom generally stabilizes an α-carbanion. In addition, there are no side products via β-hydride elimination from 1,1-diborylalkanes; the adjacent B atom could stabilize σ-alkylpalladium intermediates as an α-carbanion congener. DFT calculations were performed using the B3LYP/6-31G** level of theory. The LUMO maps of 1,1-diborylalkane and 1,1-borylsilylalkane are shown in Figure 1. A large LUMO distribution is observed around the B–B moiety in **1,1-BB**, and a delocalized LUMO distribution is observed around each B atom and Si atom in **1,1-BSi**. The LUMO map indicates that the assistance of an adjacent B atom in 1,1-diborylalkanes could result in the generation of a monoborate intermediate at room temperature.

There are two possible pathways in SMC: the stepwise transmetalation of ArPdX with a borate intermediate and the direct transmetalation of ArPdOH with boron compounds.^{1b} The former mechanism is more likely in the present study (Figure 2). Transmetalation between ArPdX and potassium borate provides a σ-alkyl-PdAr intermediate, which undergoes reductive elimination to give the product **3**. Since the vacant orbital of boron can stabilize a C–metal bond, the relatively stabilized α-B,Pd intermediate would prevent the β-hydride elimination to generate alkenes and regio-

somers as side products (see Supporting Information for details).⁹ The present study clearly indicates that SMC on a multisubstituted sp^3 -carbon could proceed at room temperature when the corresponding borate intermediate is generated with a suitable base and a σ -alkyl-PdAr intermediate bearing β -C–H bonds is sufficiently stable before reductive elimination.

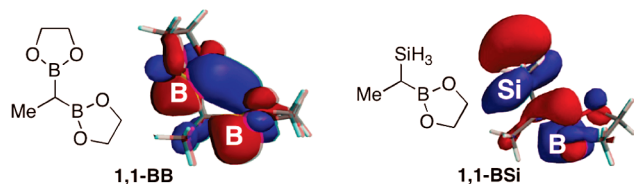


Figure 1. LUMO maps of 1,1-BB and 1,1-BSi.

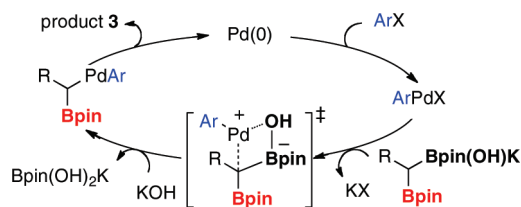


Figure 2. Plausible reaction mechanism.

In conclusion, we have demonstrated the usefulness of 1,1-diborylalkanes for chemoselective and regiospecific SMC at room temperature. The key to success is the generation of a monoborate intermediate by virtue of the adjacent B atom in 1,1-diborylalkanes. The present results constitute a new example of protection-free chemoselective cross-coupling on a multisubstituted sp^3 -carbon.¹² Therefore, the use of 1,1-diborylalkanes may be a convenient and practical approach for the coupling of functionalized molecules at room temperature.^{1b} Other types of reactions, including cross-coupling reactions using multimetallic compounds and an asymmetric version, and mechanistic studies are underway in our laboratory.

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Supporting Information Available: The experimental procedure, NMR experiments, DFT calculations, and physical properties of new

compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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