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Chemoselective and Regiospecific Suzuki Coupling on a Multisubstituted sp^3-Carbon in 1,1-Diborylalkanes at Room Temperature

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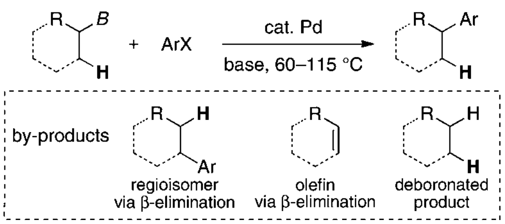
Abstract: The palladium-catalyzed Suzuki−Miyaura cross-coupling on a multisubstituted sp^3-carbon in 1,1-diborylalkanes was achieved at room temperature. The generation of a monoborate intermediate by virtue of the adjacent B atom could result in the chemoselective coupling reaction under ambient conditions.

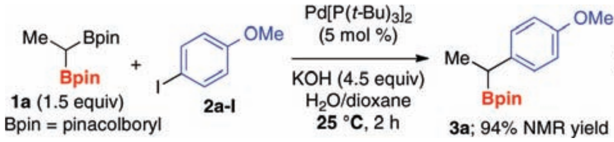
Suzuki−Miyaura cross-coupling (SMC) has been identified as a reliable method for C−C bond formation, especially for the synthesis of complex molecules.[1,2] However, cross-coupling on an sp^3-carbon has recently been shown to have severe drawbacks. β-Hydride elimination, regioisomerization, and protodeboronation 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, Suginome 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-diborylalkanes[7] 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-$[P(t\text{-}Bu)_3]_2$[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**.

Scheme 1. Typical Byproducts in SMC Using Alkylborans



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

 (1)

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 K_3PO_4, Cs_2CO_3, Na_2CO_3, and Ag_2O, 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-$[P(t\text{-}Bu)_3]_2$ 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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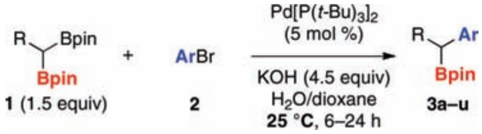
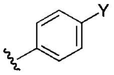
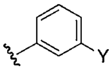
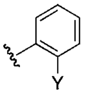
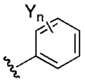
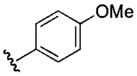
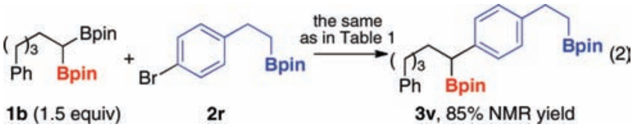
Table 1. Wide Scope of 1,1-Diborylalkanes **1** and Aryl Bromides **2**



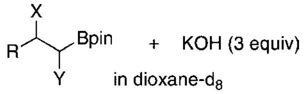
entry	R	Ar	Y	**3** yield (%)[a]
1	**1b**, Ph(CH$_2$)$_4$		**2b**, H	**3b**, 80 (74)
2			**2c**, Me	**3c**, 98 (72)
3			**2d**, *tert*-Bu	**3d**, 94 (71)
4			**2e**, OMe	**3e**, 98 (75)[b]
5			**2f**, F	**3f**, 88 (73)
6			**2g**, Me	**3g**, 98 (95)
7			**2h**, OMe	**3h**, 83 (67)
8			**2i**, F	**3i**, –[c] (65)[d]
9			**2j**, Me	**3j**, 98 (74)
10			**2k**, *i*-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		**2e**	**3a**, 88 (68)
18	**1c**, Et			**3r**, 93 (79)
19	**1d**, *n*-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.

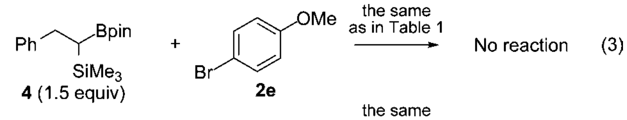


the corresponding products in good yields (entries 10, 14, and 16). The reactions of various 1,1-diborylalkanes gave the corresponding products **3a**, **3r**−**u** in good yields (entries 17−21). The characteristic feature of the present reaction is shown in the chemoselective cross-coupling on an sp^3-carbon 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 sp^3-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, TlOH, 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 PdCl$_2$(dppf) and TlOH 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.

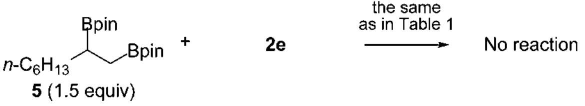
Table 2. Generation of Borate Intermediate at Room Temperature



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**; *n*-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**)



(3)



(4)

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 regioisomers 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.

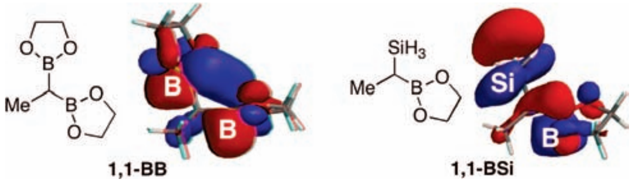


Figure 1. LUMO maps of **1,1-BB** and **1,1-BSi**.

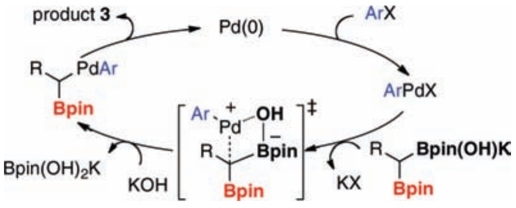


Figure 2. Plausible reaction mechanism.

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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(10) Due to the almost same R_f value of 1,1-diborylalkanes **1** and products **3** as well as the instability of **3** to column chromatography purification, the isolated yields are generally lower than NMR yields. Therefore, we reconfirmed the yield of products as alcohols after the oxidation of the crude mixture (see Supporting Information).

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