ORGANIC LETTERS

2011
Vol. 13, No. 13
3368–3371

Chemoselective Suzuki Coupling of Diborylmethane for Facile Synthesis of Benzylboronates

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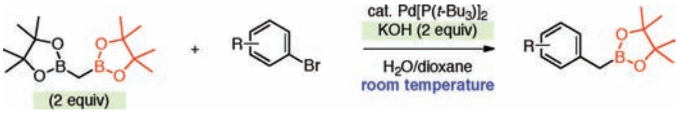
Received April 27, 2011

ABSTRACT



The chemoselective Pd-catalyzed Suzuki–Miyaura cross-coupling reaction using a diborylmethane is reported. The use of an equimolar amount of base with a diborylmethane realized chemoselective coupling for the synthesis of various benzylboronate derivatives. Sterically hindered aryl bromides can give products in moderate to excellent yields.

Suzuki–Miyaura cross-coupling (SMC) is a reliable method for C–C bond formation, typically between sp^2-carbons. There are numerous reports concerning improvements in catalysts, which realize the cross-coupling reaction of less-reactive substrates even under mild conditions.[1] However, the severe limitations of SMC at an sp^3-carbon require the further modification of catalysts and reaction conditions.[1b,2] We previously reported chemoselective and regiospecific SMC using 1,1-diborylalkanes at room temperature.[3] The key to success was the notable ability of a 1,1-diborylalkane to generate a monoborate intermediate with KOH as a base. The coupling reaction of a 1,1-diborylalkane facilitated SMC on a multisubstituted sp^3-carbon to give a monoboronate product; the subsequent cross-coupling to give a 1,1-diarylalkane is typically terminated due to the inefficient generation of a borate intermediate from a secondary alkylboron compound at room temperature. There have been several reports of SMC using secondary alkyl boronic acids or boronate esters under limited conditions. With a cyclopropylboronic acid, SMC proceeded in high to excellent yields.[4] Other cycloalkylboronic acids also participated in SMC with moderate to good yields.[5] The use of secondary alkylboron compounds, such as isopropyl and secondary butyl, gives the desired products, and some give a mixture of regioisomers.[6] Recently, the regiospecific and/or

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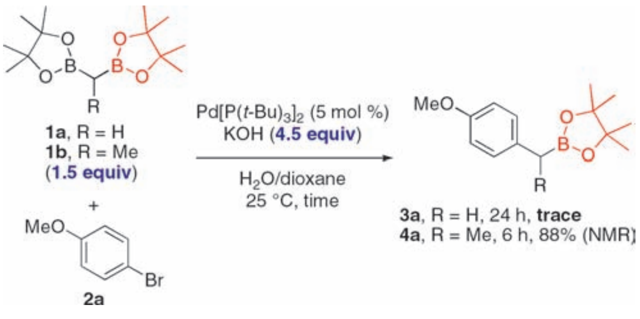
10.1021/ol201115k

stereospecific SMC of a secondary benzylboronate ester was reported.[7] Typically, the aforementioned SMC of secondary alkylboron compounds requires heating conditions. In this context, our previous strategy using 1,1-diborylalkanes is reasonable for obtaining unreactive secondary alkylboronate esters as products at room temperature for the chemoselective synthesis.

Scheme 1. SMC of Diborylalkanes



To further develop our strategy in the present paper, we focused on the reaction of bis(pinacolatoboryl)methane **1a**,[8] which gives a primary benzylboronate ester as a product. This reaction is challenging because SMC using primary alkylboron compounds including benzylboron compounds would take place under mild conditions in some cases.[9,10] Unexpectedly, our attempt to use diborylmethane **1a** with 4-bromoanisole (**2a**) failed in the presence of Pd[P(t-Bu)$_3$]$_2$ (5 mol %) and 3 equiv of KOH added to **1a** in H_2O and dioxane; **2a** was recovered almost quantitatively (Scheme 1). The typical reaction conditions for 1,1-diborylalkane **1b**[11] gave the corresponding product **4a** in high yield; accordingly, the same reaction conditions are not suitable for the use of diborylmethane **1a**.

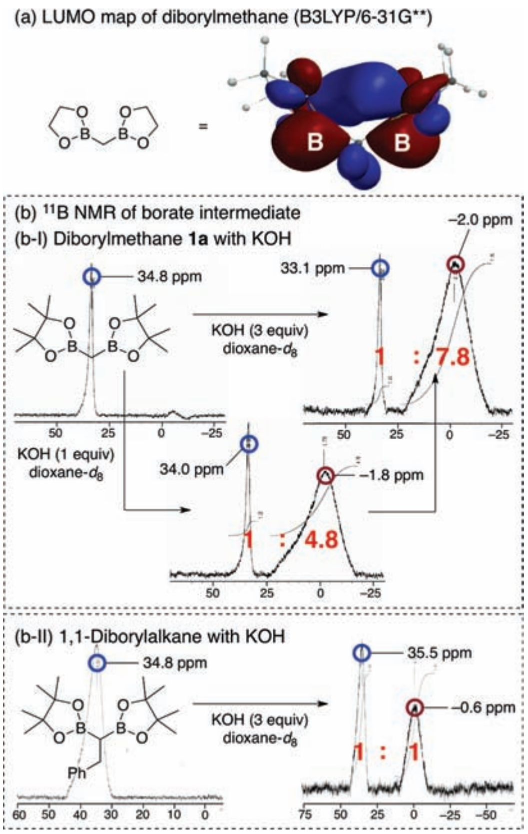


Figure 1. LUMO map and ^{11}B NMR spectra.

To clarify the difference between diborylmethane **1a** and 1,1-diborylalkane **1b**, the characteristic features of diborylmethane **1a** were considered (Figure 1). DFT calculation for a diborylmethane depicted a large distribution of LUMO around boron moieties, which is similar to that of a 1,1-diborylalkane.[3] NMR analyses of a borate generated in dioxane-d_8 showed an obvious difference; the strong intensity of a borate moiety was observed even in the presence of an equimolar amount of KOH (b-I). Two singlet peaks appeared at 34 and −2 ppm derived from diborylmethane **1a**, and their integration ratio was 1 to 4.8 when an equimolar amount of KOH was used. Notably, the borate detected at −2 ppm showed a very broad peak from −20 to 25 ppm. In contrast, the previous ^{11}B NMR analyses of a borate intermediate derived from a 1,1-diborylalkane showed that the integration ratio of a free boronate moiety and a borate moiety is almost 1 to 1 even in the presence of excess KOH; thus, a monoboronate intermediate could be generated exclusively (b-II). The spectrum of a ^{11}B NMR experiment using **1a** is unexpected since the presence of an equimolar amount of KOH should

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generate at most one borate moiety, and the integration ratio should be 1 to 1 if a borate is generated quantitatively. The addition of 3 equiv of KOH to **1a** increased the intensity of a borate peak, which might include a diborate intermediate.

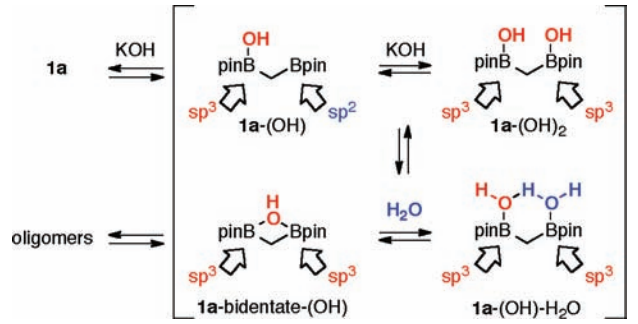
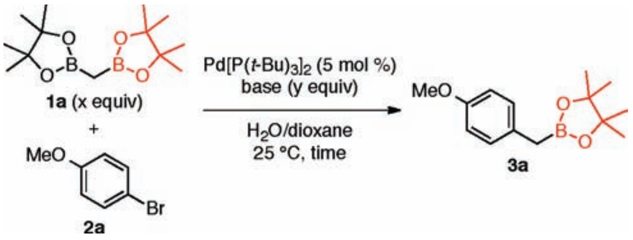


Figure 2. Possible borate intermediates.

The possible intermediates are shown in Figure 2. Since the mixture of **1a** and an equimolar amount of KOH showed a broad peak at −2 ppm, the generation of a monoborate intermediate **1a**-(OH), a monoborate intermediate **1a**-bidentate-(OH), the corresponding hydrated complex **1a**-(OH)-H_2O, and/or a diborate intermediate **1a**-$(OH)_2$ can be proposed.[12] The relatively strained cyclic structure of a **1a**-bidentate-(OH) intermediate would give a hydrated complex **1a**-(OH)-H_2O. The oligomeric borate intermediates might exist in equilibrium. The transmetalation of **1a**-(OH), **1a**-bidentate-(OH), and/or **1a**-(OH)-H_2O with ArPdX would lead to the product **3a**. Therefore, a borate-hydrated complex and/or oligomers could be predominant for the unexpected integration ratio in the presence of an equimolar amount of KOH as shown in (b-I).

We tested the reaction conditions of diborylmethane **1a** for SMC to investigate the influence of the amount of base (Table 1). The previous reaction conditions using excess KOH to diborylmethane **1a** gave a trace amount of the corresponding product **3a**. Under the previously reported conditions, SMC of 1,1-diborylalkane **1b** proceeded with an almost homogeneous mixture. In contrast, the same reaction conditions for diborylmethane **1a** gave a heterogeneous gel-like mixture (entry 1). As a result, the conversion of 4-bromoanisole (**2a**) was very low even after 24 h. A drastic change was observed when an equimolar amount of KOH added to diborylmethane **1a** was used (entry 2). The reaction took place under a homogeneous mixture to give the desired **3a** in high yield. In a typical SMC, excess base contributes to the generation of a more reactive borate intermediate, the hydrolysis of $Pd^{II}X$ occurs to the more reactive $Pd^{II}OH$ species, competitive complexation with $HOBR_2$ takes place, as well as other processes; therefore, typical SMC at an sp^3-carbon requires excess base to complete the reaction.[1b] In our previous report, 3 equiv of KOH to a 1,1-diborylalkane were required. In contrast, excess KOH prevented the present reaction using diborylmethane **1a**. We examined the effects of other bases, such as NaOH, LiOH, K_3PO_4, KF, Cs_2CO_3, and Ag_2O (entries 3−8). The reaction proceeded, but the yield was not improved. A slight increase in the amount of diborylmethane realized a quantitative yield of **3a** (entry 9).[13]

Table 1. Screening of Reaction Conditions



entry	base	*x*	*y*	time (h)	yield (%)[a]
1	KOH	1.5	4.5	24	trace
2	KOH	1.5	1.5	24	84
3	NaOH	1.5	1.5	24	82
4	LiOH	1.5	1.5	24	77
5	K_3PO_4	1.5	1.5	24	16
6	KF	1.5	1.5	24	6
7	Cs_2CO_3	1.5	1.5	24	14
8	Ag_2O	1.5	1.5	24	16
9[b]	**KOH**	**2**	**2**	**1**	**>98**

[a] NMR yields with internal standard were described. [b] The use of $Pd[P(t\text{-Bu})_3]_2$ (1 mol %) gave the product **3a** in 89% yield after 24 h.

A wide variety of coupling products were obtained under the optimum reaction conditions (Table 2).[14,15] The use of bromoanisole, -toluene, and -fluorobenzene gave the products in high to excellent yields (entries 1−8, and 11). Fluoro-compounds could be used without protodeboronation, as noted in our previous report.[3] Sterically hindered aryl bromides could also be used; 1-bromo-2-isopropylbenzene (**2i**) and 2-bromo-1,1′-biphenyl (**2j**) gave the desired products in high yields (entries 9 and 10). Furthermore, 2,6-disubstituted bromobenzene gave the products in high to

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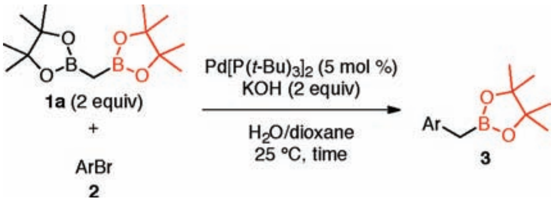
(12) See the Supporting Information for the DFT calculations of borate intermediates.

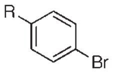
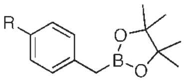
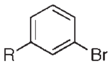
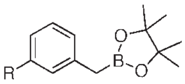
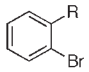
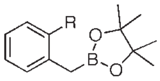
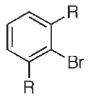
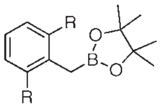
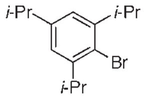
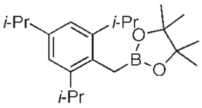
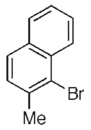
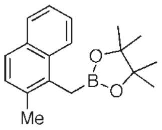
(13) The protodeboronation of primary alkylboron compounds in protic conditions proceeds much more rapidly than that of secondary and tertiary alkylboron compounds; see: (a) Brown, H. C.; Murray, K. J. *Tetrahedron* **1986**, *42*, 5497. The protodeboronation of benzylboron compounds proceeds more rapidly than other primary alkylboron compounds; see: (b) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1960**, *82*, 1504. (c) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1960**, *82*, 4708.

(14) Due to almost the same R_f values of diborylmethane **1a** and products **3a**−**p** as well as the instability of products to column chromatography purification, the isolated yields were generally lower than NMR yields.

(15) The reaction using *p*-chloroanisole did not proceed at all, although the typical Suzuki−Miyaura coupling between aryl chlorides and aryl boronic acids proceeds using $Pd[P(t\text{-Bu})_3]_2$ as a catalyst. See ref 5a.

Table 2. Scope of Aryl Bromides



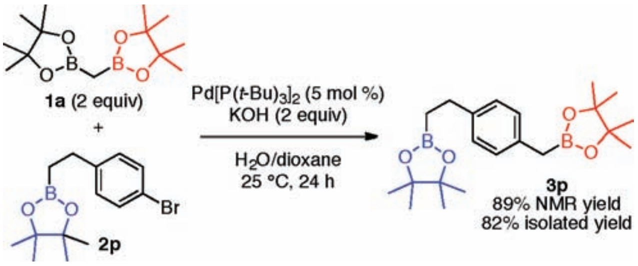
entry	ArBr	time (h)	product	yield (%)[a]
				
1	**2a**, R = OMe	1	**3a**	>98 (92)
2	**2b**, R = Me	5	**3b**	98 (92)
3	**2c**, R = F	2	**3c**	90 (83)
				
4	**2d**, R = OMe	3	**3d**	97 (88)
5	**2e**, R = Me	3	**3e**	91 (83)
6	**2f**, R = F	3	**3f**	82 (69)
				
7	**2g**, R = OMe	3	**3g**	98 (87)
8	**2h**, R = Me	3	**3h**	93 (88)
9	**2i**, R = *i*-Pr	3	**3i**	79 (64)
10	**2j**, R = Ph	24	**3j**	94 (86)
11	**2k**, R = F	3	**3k**	77 (62)
				
12	**2l**, R = OMe	24	**3l**	>98 (93)
13	**2m**, R = Me	2	**3m**	>98 (86)
14	 **2n**	24	 **3n**	60 (57)
15	 **2o**	24	 **3o**	88 (76)

[a] NMR yields with internal standard were described. Isolated yields were described in parentheses.

excellent yields (entries 12 and 13). Notably, the highly bulky aryl bromide 2-bromo-1,3,5-triisopropylbenzene (**2n**) could participate in the reaction to give the product **3n** in 57% isolated yield (entry 14). The reaction of the sterically hindered naphthalene derivative **2o** took place to give the product **3o** in a high yield (entry 15).

The compatibility of a primary alkylboronate moiety was demonstrated (Scheme 2). The reaction of diborylmethane **1a** and aryl bromide **2p** under the same conditions as described in Table 2 gave the desired product **3p** bearing benzylboronate and phenethylboronate moieties. The present result serves as an attractive chemoselective cross-coupling reaction exclusively with diborylmethane **1a**.

Scheme 2. Chemoselective SMC of Diborylmethane



In conclusion, we have demonstrated the chemoselective Pd-catalyzed Suzuki–Miyaura cross-coupling of diboryl methane for the synthesis of various benzylboronate derivatives. The key to success for efficient conversion is the predominant generation of a monoborate intermediate using an equimolar amount of KOH with diborylmethane **1a**. The generation of a diborate intermediate with excess KOH seems to be detrimental. The products, benzylboronate derivatives, are somewhat unstable under the reaction conditions for a long period of time; thus, the use of an equimolar amount of KOH is important to avoid side reactions. The further development of multiborylmethane derivatives are ongoing in our laboratory.

Acknowledgment. This work was supported by the JST PRESTO program, a Grant-in-Aid for Young Scientists (B) (No. 21750108 and 23750049) from the Japan Society for the Promotion of Science, and a Waseda University Grant for Special Research Projects. We appreciate valuable comments by the reviewers during the review process.

Supporting Information Available. The experimental procedure and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.