Boration

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Synthesis of 1,1-Diborylalkenes through a Brønsted Base Catalyzed Reaction between Terminal Alkynes and Bis(pinacolato)diboron

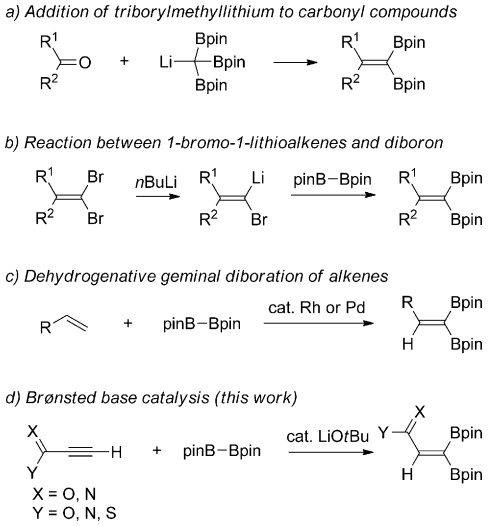
Akira Morinaga, Kazunori Nagao, Hirohisa Ohmiya, and Masaya Sawamura**

Abstract: *A method for the synthesis of 1,1-diborylalkenes through a Brønsted base catalyzed reaction between terminal alkynes and bis(pinacolato)diboron has been developed. The procedure allows direct synthesis of functionalized 1,1-diborylalkenes from various terminal alkynes including propiolates, propiolamides, and 2-ethynylazoles.*

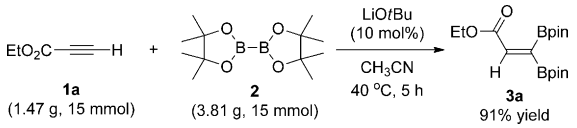
The use of 1,1-diborylalkenes as versatile intermediates in organic synthesis has gained considerable attention as a result of their applicability toward various transformations. For example, the two geminal boron substituents can be differentiated and transformed in a stepwise manner, allowing the synthesis of a diverse array of multisubstituted alkenes.[1] Several synthetic methods for accessing 1,1-diborylalkenes have been developed.[1–4] Specifically, 40 years ago Matteson reported the synthesis of 1,1-diborylalkenes through an addition reaction of triborylmethyllithium to carbonyl compounds (Scheme 1 a).[2] More recently, Shimizu, Hiyama, and co-workers reported a reaction between bis(pinacolato)diboron and 1-bromo-1-lithioalkenes, which were prepared from 1,1-dibromoalkenes by means of Br–Li exchange (Scheme 1 b).[1] Marder et al. and Iwasawa and co-workers reported the use of rhodium and palladium catalytic systems for dehydrogenative geminal diboration of terminal alkenes (Scheme 1 c).[3]

Herein, we report a new and efficient approach to the synthesis of 1,1-diborylalkenes through a Brønsted base catalyzed reaction between terminal alkynes and bis(pinacolato)diboron (Scheme 1 d).[5–7] The procedure allows the direct synthesis of functionalized 1,1-diborylalkenes from various terminal alkynes including propiolates, propiolamides, and 2-ethynylazoles. The mild and transition-metal-free reaction conditions are attractive features of this method.

Specifically, the reaction between ethyl propiolate (**1a**; 1.47 g, 15 mmol) and bis(pinacolato)diboron (**2**; 3.81 g, 15 mmol) in the presence of LiO*t*Bu (10 mol%) in CH_3CN (30 mL) at 40 °C over 5 h gave β,β-diborylacrylate **3a** (4.81 g, 13.7 mmol; Scheme 2). Compound **3a** was isolated in 91% yield (based on **1a**; 99% NMR yield; complete conversion of **1a**). The boron atoms of **3a** showed no interaction with the carbonyl oxygen, as indicated by ^{11}B NMR spectroscopy.



Scheme 1. Synthesis of 1,1-diborylalkenes. pin = pinacolato.



Scheme 2. Brønsted base catalyzed reaction between **1a** and **2**.

Screening of base catalysts for the reaction between **1a** and **2** identified LiO*t*Bu as the most effective (Table 1, entry 1). NaO*t*Bu, KO*t*Bu, and lithium hexamethyl disilazide (LHMDS) were also effective, but gave slightly lower product

Table 1: The effect of changing the catalyst on the reaction between **1a** and **2**.[a]

entry	catalyst	yield [%][b]
1	LiO*t*Bu	91
2	NaO*t*Bu	79
3	KO*t*Bu	78
4	LHMDS	74
5	LiOMe	3
6	DABCO	17
7	DMAP	15
8	PBu_3	33
9	none	0

[a] Conditions: **1** (0.2 mmol), **2a** (0.2 mmol), catalyst (10 mol%), CH_3CN, 40 °C, 5 h. [b] Yield of isolated product.

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yields (74–79% yields; entries 2–4), while weaker bases such as LiOMe, 1,4-diazobicyclo[2.2.2]octane (DABCO), 4-dimethylaminopyridine (DMAP), and PBu_3 were much less effective (3–33% yields; entries 5–8). No reaction occurred in the absence of base (entry 9). Aprotic solvents such as hexane, toluene, THF, and dichloromethane could also be used, but gave slightly lower yields (89%, 71%, 74%, and 78%). Significant reductions in yield were found for the reactions carried out in protic solvents such as *t*BuOH (54%).

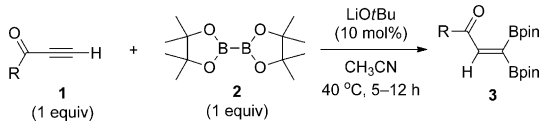
The optimal procedure was applied to various alkynoates (Table 2, entries 1–5). The ethoxy carbonyl group of **1a** could be replaced with a methoxy carbonyl group with only a slight reduction in the product yield (entry 1). More sterically demanding alkoxycarbonyl substituents such as *tert*-butoxy, phenoxy, or menthoxy groups were tolerated (entries 2–4). The steroidal alkynoate **1f**, which was prepared from *trans*-androsterone, was also found to be a suitable substrate (entry 5).

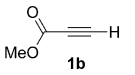
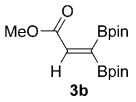
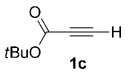
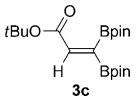
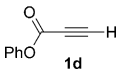
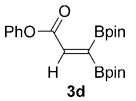
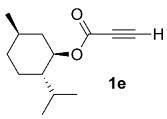
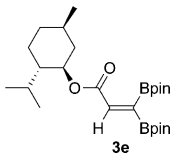
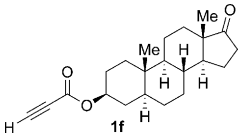
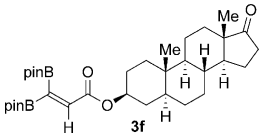
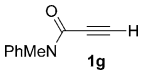
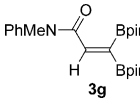
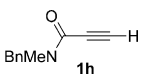
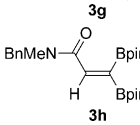
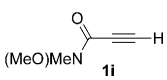
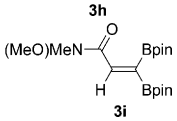
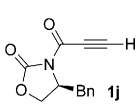
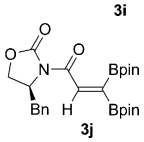
The reaction of propiolamides **1g–j** furnished the corresponding 1,1-diborylalkenes (Table 2, entries 6–9). For example, *N*-phenyl-*N*-methylamide, *N*-benzyl-*N*-methylamide, or Weinreb amide derivatives reacted with **2** efficiently (entries 6–8). The imide **1j**, prepared from chiral oxazolidinone, also participated in the reaction (entry 9). However, propiolaldehyde showed no reactivity under similar conditions.

2-Ethynylazoles were also suitable substrates (Table 3).[8] For example, the reaction of 2-ethynylbenzoxazole (**1k**), with an increased catalyst loading (20 mol% LiO*t*Bu), proceeded efficiently and cleanly, giving the corresponding 1,1-diborylalkene (entry 1). Benzothiazole and benzimidazole were also tolerated as azole groups (entries 2 and 3), but the use of phenylacetylene or 2-ethynylpyridine resulted in no reaction.

To gain insight into the mechanism of the LiO*t*Bu-catalyzed reaction between terminal alkynes and the diboron derivative, a deuterium labeling experiment was conducted (Scheme 3a). The reaction with C3-deuterated ethyl propiolate [D]-**1a** (90% D) instead of **1a** under optimum conditions afforded the C2-deuterated product [D]-**3a** with 86% incorporation of deuterium. This result indicated that the H atom

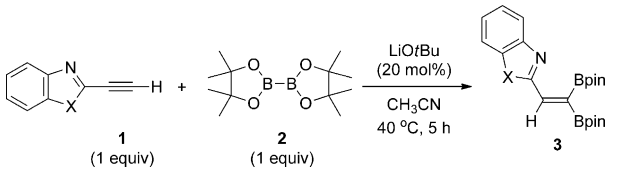
Table 2: Reaction scope: Terminal alkynes.[a]

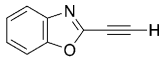
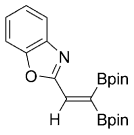
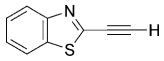
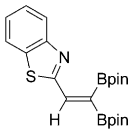
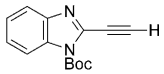
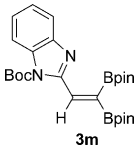


entry	alkyne	product	yield [%][b]
1	 **1b**	 **3b**	83
2	 **1c**	 **3c**	81
3	 **1d**	 **3d**	88
4	 **1e**	 **3e**	89
5	 **1f**	 **3f**	84
6	 **1g**	 **3g**	75[c]
7	 **1h**	 **3h**	63
8	 **1i**	 **3i**	63
9	 **1j**	 **3j**	55

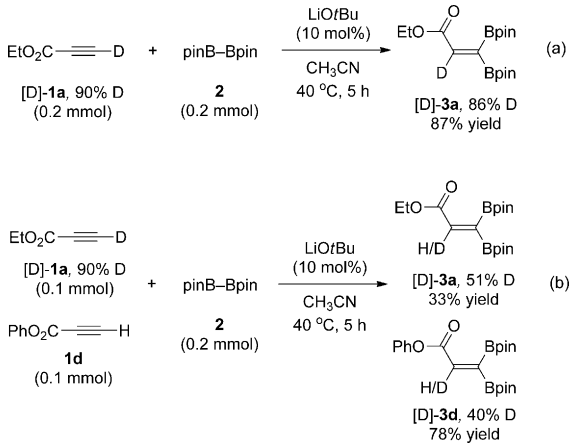
[a] Conditions: **2** (0.2 mmol), **1** (0.2 mmol), LiO*t*Bu (10 mol%), CH_3CN, 40 °C, 5 h (entries 1–4) or 12 h (entries 5–9). [b] Yield of isolated product. [c] The reaction was carried out on a 5.0 mmol scale. Bn = benzyl.

Table 3: Reaction scope: 2-Ethynylazoles.[a]



entry	alkyne	product	yield [%][b]
1	 **1k**	 **3k**	88
2	 **1l**	 **3l**	78
3	 **1m**	 **3m**	37 (80)[c]

[a] Conditions: **1** (0.2 mmol), **2** (0.2 mmol), LiO*t*Bu (20 mol%), CH_3CN, 40 °C, 5 h. [b] Yield of isolated product. Yield determined by ^{1}H NMR is in parentheses. [c] A loss of material occurred during purification because **3m** was unstable. As a result, the yield of isolated product was significantly reduced as compared with the yield determined by ^{1}H NMR spectroscopy.

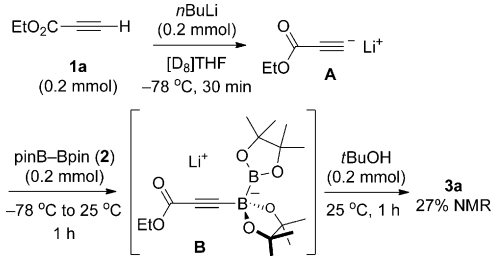


Scheme 3. Deuterium labeling experiments.

in **3** was derived from the terminal C(sp)–H bond of the alkyne substrate **1**.

A deuterium-labeled crossover experiment between [D]-**1a** (90% D) and **1d** resulted in nearly complete H/D scrambling in both products ([D]-**3a** and [D]-**3d**; Scheme 3b). Based on this result, intramolecular 1,2-H-migration should be ruled out.

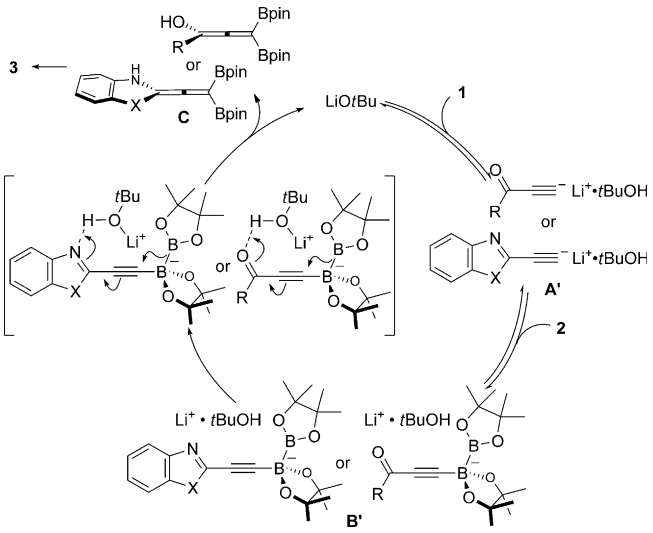
The screening of base catalysts discussed above found LHMDS to be effective regardless of its extreme steric demand (see Table 1, entry 4). Based on this result, a mechanism involving conjugate addition of the base catalyst to the terminal alkyne, as in the cases of phosphine-catalyzed 1,2-carboboration and 1,2-diboration of alkynoates,[6b,c] was ruled out. Instead, a Brønsted base mechanism involving acetylide formation is conceivable. To test this possibility, a stoichiometric reaction using *n*BuLi instead of the catalytic LiO*t*Bu base was conducted (Scheme 4). Thus, a lithium acetylide (**A**)



Scheme 4. Stoichiometric reaction using nBuLi in place of catalytic LiO*t*Bu.

was first prepared and was reacted with the diboron **2**. We assumed the formation of an alkynyl borate species (**B**), although signal assignment in the NMR spectra was unsuccessful because of the complexity of the spectra. Subsequent addition of one equivalent of *t*BuOH and leaving the mixture to stand at 25 °C for 1 h gave **3a** in 27% yield, as determined by NMR spectroscopy.[9]

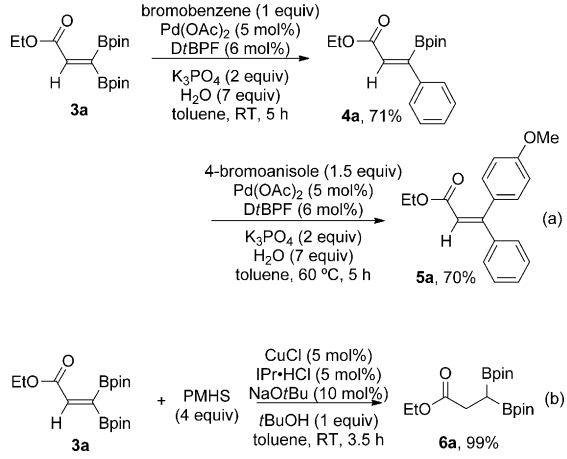
Taking into account the results of the deuterium labeling experiments and the stoichiometric reaction with *n*BuLi,



Scheme 5. Proposed catalytic cycle.

a mechanism for the reaction was proposed (Scheme 5). The catalytic cycle is initiated by deprotonation of the terminal alkyne of **1** with LiO*t*Bu to form a lithium acetylide (**A′**) coordinated with *t*BuOH in an equilibrium. Then, **A′** reacts with diboron **2** to form an alkynyl borate intermediate (**B′**). Migration of the terminal boryl group in **B′** to the sp-hybridized carbon atom of the alkyne moiety associated with protonation of the carbonyl oxygen atom or the azole nitrogen atom of **1** with the Li^+-coordinated *t*BuOH gave an allenol or allenamine intermediate **C**, which immediately isomerized to **3**. The boron migration–protonation of **B′** regenerates LiO*t*Bu.

It was found that the two geminal boron substituents of the 1,1-diborylalkenes could be differentiated and transformed in a stepwise manner (Scheme 6a). For example, Suzuki–Miyaura coupling between β,β-diborylacrylate **3a** and bromobenzene in the presence of a $Pd(OAc)_2$–D*t*BPF (D*t*BPF = 1,1′-bis(di-*tert*-butylphosphino)ferrocene) catalyst and K_3PO_4 as a base occurred selectively at the boron site *trans* to the ester group to give alkenylboronate **4a** (71%,



Scheme 6. Transformations of 1,1-diborylalkenes.

$E/Z > 99{:}1$) with the formation of a small amount of the diphenylated product (10%). This stereoselectivity is probably because of the steric effect of the ester group. (Note that no interaction exists between the B atoms and the ester O atom in **3a** (see above)). The second cross-coupling of **4a** with 4-bromoanisole produced isomerically pure trisubstituted alkene **5a** in good yield ($Z/E > 99{:}1$). Copper-catalyzed conjugate reduction of **3a** with poly(methylhydrosiloxane) (PMHS) afforded a functionalized geminal diborylalkane **6a** in quantitative yield with the two C–B bonds remaining untouched (Scheme 6b).[10]

In summary, we have developed a new method for the synthesis of 1,1-diborylalkenes through a Brønsted base catalyzed reaction between terminal alkynes and bis(pinacolato)diboron. The procedure allows direct synthesis of functionalized 1,1-diborylalkenes from various terminal alkynes including propiolates, propiolamides, and 2-ethynylazoles. The functionalized β,β-diborylacrylates and β,β-diborylacrylamides reported herein are difficult to obtain by other methods (Scheme 1a–c).[1–4] Importantly, the two geminally installed boron substituents of the 1,1-diborylalkenes could be differentiated and transformed in a stepwise manner, showing the potential of the new 1,1-diborylalkenes as versatile intermediates in organic synthesis.

Experimental Section

Gram-scale reaction (the reaction shown in Scheme 2 is representative): Bis(pinacolato)diboron (**2**; 3.81 g, 15 mmol) was placed in a Schlenk flask containing a magnetic stirring bar. The flask was evacuated and filled with argon. Acetonitrile (30 mL), ethyl propiolate (**1a**; 1.47 g, 15 mmol), and LiO*t*Bu (120 mg, 1.5 mmol) were sequentially added to the flask. After 5 h stirring at 40 °C, the mixture was filtered through a short plug of silica gel, which was then washed with diethyl ether. The solvent was removed under reduced pressure to give pure **3a** (4.81 g, 13.7 mmol, 91% yield).

Acknowledgements

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Keywords: boration · Brønsted bases · diborylalkenes · organocatalysis · synthetic methods

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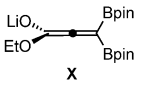

X

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