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 new 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 protocol allows direct synthesis of functionalized 1,1-diborylalkenes from various terminal alkynes including propiolates, propiolamides and 2-ethynylazoles.

1,1-Diborylalkenes have gained increasing attention as versatile intermediates in organic synthesis due to 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, more than 40 years ago, Matteson reported the synthesis of 1,1-diborylalkenes through an addition reaction of triborylmethyllithium to carbonyl compounds (Scheme 1a).[2] 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 via Br–Li exchange (Scheme 1b).[3] Marder and Iwasawa reported the use of rhodium and palladium catalyst systems for dehydrogenative geminal diboration of terminal alkenes (Scheme 1c).[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 1d).[5–7] The protocol allows 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\textsubscript{t}Bu (10 mol%) in CH\textsubscript{3}CN (30 mL) at 40 °C over 5 h gave β,β-diborylacrylate 3a (4.81 g, 13.7 mmol) in 91% yield (based on 1a; 99% NMR yield; complete conversion of 1a) (Scheme 2). The boron atoms of 3a showed no interaction with the carbonyl oxygen, as indicated by \textsuperscript{11}B NMR spectroscopy.

Table 1. Catalyst effects in reaction between 1a and 2

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<th>entry</th>
<th>catalyst</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>LiO\textsubscript{t}Bu</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>NaO\textsubscript{t}Bu</td>
<td>79</td>
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Screening of base catalysts for the reaction between 1a and 2 identified LiO\textsubscript{t}Bu as the most effective (Table 1, entry 1). NaO\textsubscript{t}Bu, KO\textsubscript{t}Bu and LHMDS were also effective, but gave slightly lower product yields (74–79% yields, entries 2–4), while weaker bases such as LiOMe, DABCO, DMAP and PBu\textsubscript{3} were much less effective (15–33% 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 observed for the reactions with protic solvents such tBuOH (54%).
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The optimal protocol was applicable to various alkynoates (Table 2, entries 1–5). The ethoxycarbonyl 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 alkoxy carbonyl substituents such as t-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-methyl- 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, propionaldehyde showed no reactivity under similar conditions.

Table 2. Reaction scope: Terminal alkynes[a]

| entry | alkyne | product | yield (%) |[b]
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<tbody>
<tr>
<td>1</td>
<td>HO</td>
<td>1b</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>NO</td>
<td>2b</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>CO</td>
<td>3d</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>SO</td>
<td>4e</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>CO</td>
<td>5f</td>
<td>84</td>
</tr>
</tbody>
</table>

[a] Conditions: 1, 0.2 mmol; 2a, 0.2 mmol; catalyst, 10 mol%; CH3CN, 40 °C, 5 h. [b] Yield of isolated product.

2-Ethynylazoles were also suitable substrates (Table 3).[8] For example, the reaction of 2-ethylbenzoxazole derivatives, with an increased catalyst loading (20 mol% LiOttBu), proceeded efficiently and cleanly, giving the corresponding 1,1-diborylalkenes (entry 1). Benzothiazole and benzimidazole were also tolerated as azole groups (entries 2 and 3), but the use of phenylacetylene or 2-ethylpyridine resulted in no reaction.

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

| entry | alkyne | product | yield (%) |[b]
<table>
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<tr>
<td>1</td>
<td>NO</td>
<td>1k</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>NO</td>
<td>2l</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>NO</td>
<td>3m</td>
<td>37 (80)</td>
</tr>
</tbody>
</table>

[a] Conditions: 2, 0.2 mmol; LiOttBu, 10 mol%; CH3CN, 40 °C, 5 h (entries 1–4) or 12 h (entries 5–9). [b] Yield of isolated product. 1H NMR yield is in parentheses. [c] The reaction was carried out on a 5.0 mmol scale.
To gain insight into the mechanism of the LiO\textsubscript{t}Bu-catalyzed reaction between terminal alkynes and the diboron, a deuterium labeling experiment was conducted (Scheme 3a). The reaction with C3-deuterated ethyl propiolate 1a-d (90% D) instead of 1a under optimum conditions afforded the C2-deuterated product 3a-d with 86% deuterium incorporation. This result indicated that the H atom in 3 stemmed from the terminal C(sp)–H bond of the alkyne substrate 1.

A deuterium-labeled crossover experiment between 1a-d (90% D) and 1d resulted in nearly complete H/D scrambling in both products (3a-d and 3d-d) (Scheme 3b). Based on this observation, 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 observation, 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, was ruled out.\textsuperscript{6b,c} Instead, a Brønsted-base mechanism involving acetylide formation is conceivable. To test this possibility, the stoichiometric reaction using \( n \text{BuLi} \) instead of the catalytic LiO\textsubscript{t}Bu base was conducted (Scheme 4). Thus, a lithium acetylide (A) was first prepared and was reacted with the diboron 2. We assumed the formation of an alkynyl borate species (B), while signal assignment in the NMR spectroscopy was unsuccessful due to the complexity of spectra. Subsequent addition of one equiv of tBuOH and standing the mixture at 25 \(^\circ\)C for 1 h gave 3a in 27% NMR yield.\textsuperscript{9}

Taking into account the results of the deuterium labeling experiments and the stoichiometric reaction with \( n \text{BuLi} \), a mechanism described in Figure 1 is proposed. A catalytic cycle is initiated by deprotonation of the terminal alkyne of 1 with LiO\textsubscript{t}Bu to form a lithium acetylide (A') coordinated with tBuOH 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\textsuperscript{2}-hybridized carbon atom of the alkyne moiety associated with protonation of the carbonyl oxygen atom or azole nitrogen atom of 1 with the Li\textsuperscript{+}-coordinated tBuOH gave an allenol or allenamine intermediate (C), which immediately isomerized to 3. This B-migration-protonation reaction regenerates LiO\textsubscript{t}Bu.

It was found that the two geminally-installed boron substituents of the 1,1-diborylalkenes could be differentiated and transformed in a stepwise manner (Scheme 5a). For example, Suzuki–Miyaura coupling between \( \beta,\beta \)-diborylacrylate 3a and bromobenzene under the influence of a Pd(OAc)\textsubscript{2}–D\textsubscript{2}BPF (1,1'-bis(di-tert-butylphosphino)ferrocene) catalyst and K\textsubscript{3}PO\textsubscript{4} as a base occurred selectively at the boron site trans to the ester group to give alkenylboronate 4a (71%, \( E/Z > 99:1 \)) with the formation of a small amount of diphenylated product (10%). This stereoselectivity is probably due to the steric effect of the ester group (Note that no interaction exists between the B atoms and...
the ester O atom in 3a; vide supra). 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(methylhydroxiloxane) (PMHS) afforded a functionalized geminal diborylalkene (6a) in quantitative yield with the two C–B bonds remaining untouched (Scheme 5b).[10]

Scheme 5. Transformations of 1,1-diborylalkenes

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 protocol allows direct synthesis of functionalized 1,1-diborylalkenes from various terminal alkyne including propiolates, propiolamides and 2-ethylazoles. The functionalized [β,β]-diborylacrylates and [β,β]-diborylacrylamides reported here are difficult to obtain by other methods (Schemes 1a–c).[1–4] Importantly, the two geminally installed boron substituents of the 1,1-diborylalkenes were 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 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 LiOBU (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).

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Keywords: organocatalysis • 1,1-diborylalkene • diboration


[9] The addition of Me3SiCl or aldehydes to a solution containing B did not give the corresponding coupling products but gave 3a after work-up. These results are incompatible to the formation of a lithium allenolate intermediate (X) as a precursor to 3a.

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