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Citation	Angewandte chemie-international edition, 54(52), 15859-15862 https://doi.org/10.1002/anie.201509218
Issue Date	2015-12-21
Doc URL	https://hdl.handle.net/2115/63832
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Type	journal article
File Information	morinaga_manuscript_revision_2.pdf

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

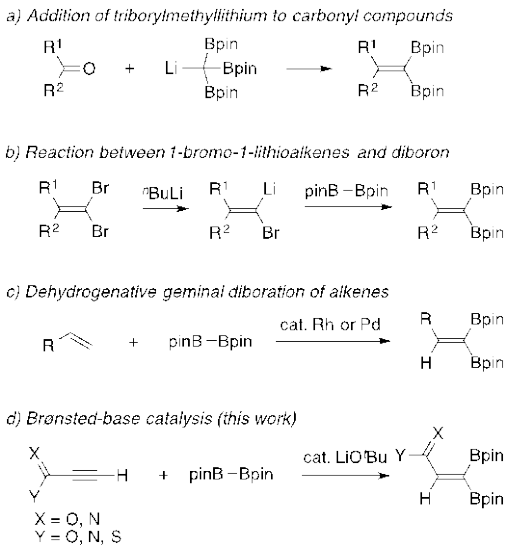
Akira Morinaga, Kazunori Nagao, Hirohisa Ohmiya,* and Masaya Sawamura*

Abstract: A 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.

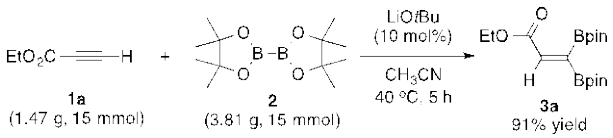
1,1-Diborylalkenes have gained increasing attention as versatile intermediates in organic synthesis due to their applicability toward various transformations. For example, the two geminal boron substituents can be differentiated and transformed in a stepwise manner, allowing the synthesis of a diverse 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).[1] 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 Li*O*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) 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 ^{11}B NMR spectroscopy.



Scheme 1. Synthesis of 1,1-diborylalkenes



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

Screening of base catalysts for the reaction between **1a** and **2** identified Li*O*t*Bu as the most effective (Table 1, entry 1). Na*O*t*Bu, K*O*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_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 *t*BuOH (54%).

Table 1. Catalyst effects in reaction between **1a** and **2**[a]

entry	catalyst	yield (%)[b]
1	Li*O*t*Bu	91
2	Na*O*t*Bu	79

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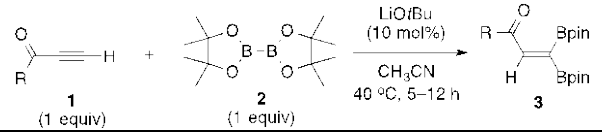
3	KO*t*Bu	78
4	LHMDS	74
5	LiOMe	3
6	DABCO	17
7	DMAP	15
8	PBu_3	33
9	none	0

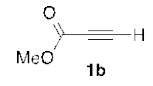
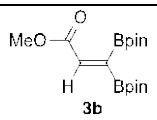
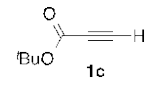
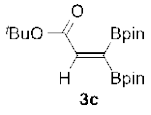
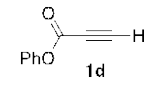
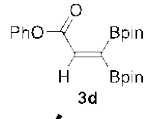
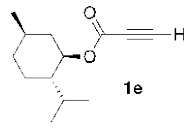
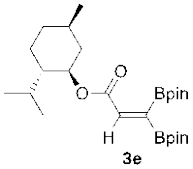
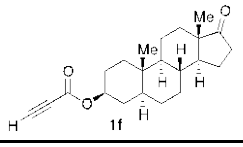
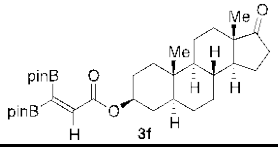
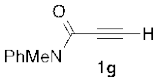
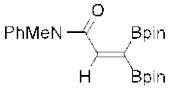
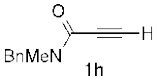
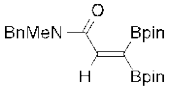
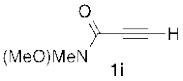
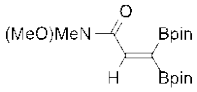
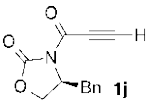
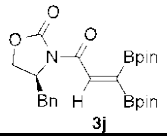
[a] Conditions: **1**, 0.2 mmol; **2a**, 0.2 mmol; catalyst, 10 mol%; CH_3CN, 40 °C, 5 h. [b] Yield of isolated product.

The optimal protocol was applicable 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 *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, propiolaldehyde showed no reactivity under similar conditions.

Table 2. Reaction scope: Terminal alkynes[a]

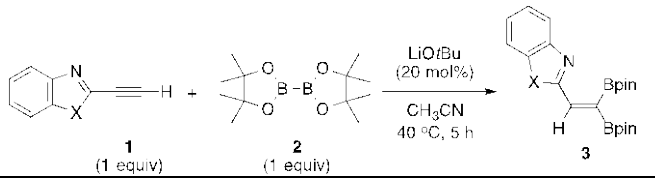


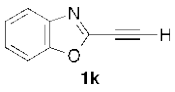
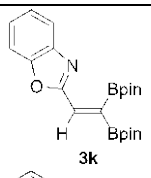
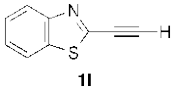
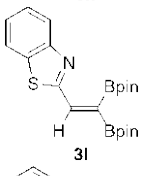
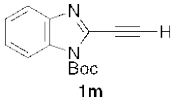
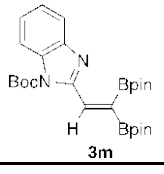
entry	alkyne	product	yield (%)[b]
1	 **1b**	 **3b**	83
2	 **1c**	 **3c**	81
3	 **1d**	 **3d**	88
4	 **1e**	 **3e**	89
5	 **1f**	 **3f**	84
6	 **1g**	 **3g**	75[c]
7	 **1h**	 **3h**	63
8	 **1i**	 **3i**	63
9	 **1j**	 **3j**	55

[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. ^{1}H NMR yield is in parentheses. [c] The reaction was carried out on a 5.0 mmol scale.

2-Ethynylazoles were also suitable substrates (Table 3).[8] For example, the reaction of 2-ethynylbenzoxazole derivatives, with an increased catalyst loading (20 mol% LiO^{t}Bu), 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-ethynylpyridine resulted in no reaction.

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

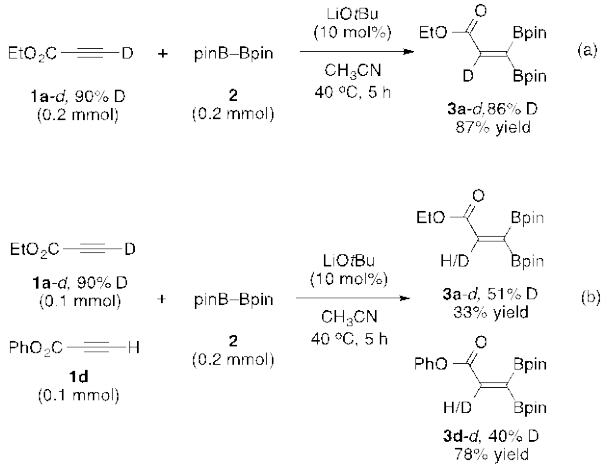


entry	alkyne	product	yield (%)[b]
1	 **1k**	 **3k**	88
2	 **1l**	 **3l**	78
3	 **1m**	 **3m**	37 (80)[c]

[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. ^{1}H NMR yield is in parentheses. [c] A loss of material occurred during purification because **3m** was unstable. As a result, the isolated yield was significantly reduced as compared with the ^{1}H NMR yield.

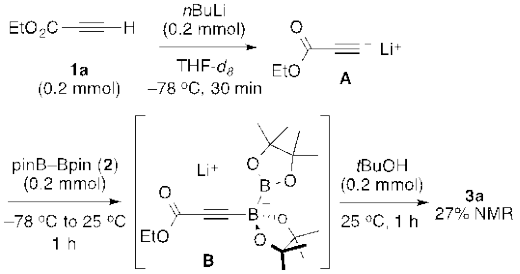
To gain insight into the mechanism of the LiO*t*Bu-catalyzed reaction between terminal alkynes and the diboron, a deuterium labeling experiment was conducted (Scheme 3a). The reaction with C3-deuterated ethyl propiolate **1a**-*d* (90% D) instead of **1a** under optimum conditions afforded the C2-deuterated 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.



Scheme 3. Deuterium labeling experiments

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.[6b,c] Instead, a Brønsted-base mechanism involving acetylide formation is conceivable. To test this possibility, the stoichiometric reaction using *n*BuLi instead of the catalytic LiO*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 *t*BuOH and standing the mixture at 25 ˚C for 1 h gave **3a** in 27% NMR yield.[9]



Scheme 4. Stoichiometric Reaction

Taking into account the results of the deuterium labeling experiments and the stoichiometric reaction with *n*BuLi, a mechanism described in Figure 1 is proposed. A 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 azole nitrogen atom of **1** with the Li^+-coordinated *t*BuOH gave an allenol or allenamine intermediate (**C**), which immediately isomerized to **3**. This B-migration-protonation reaction regenerates LiO*t*Bu.

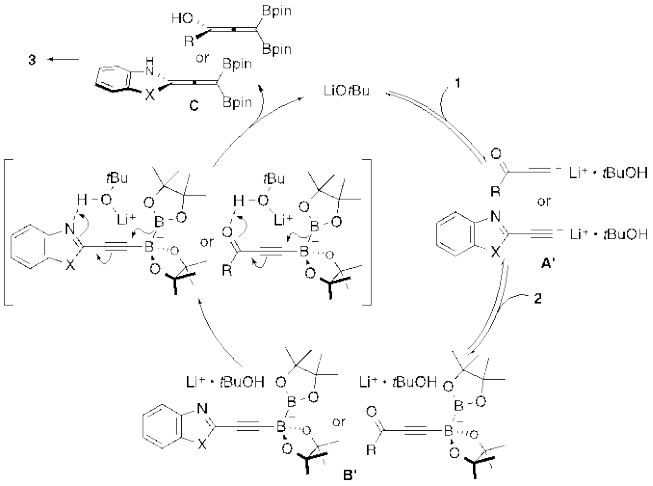
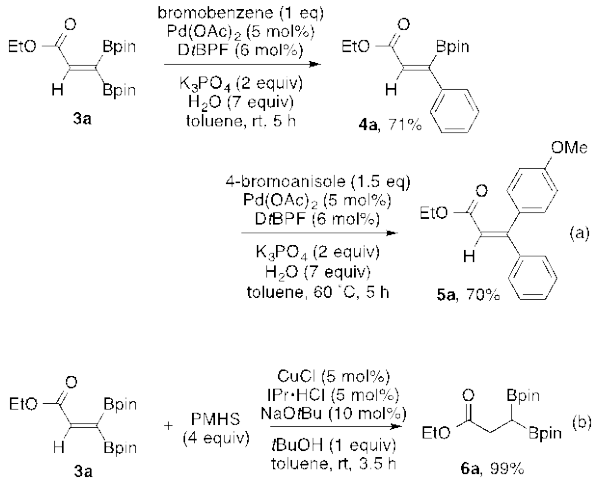


Figure 1. Possible catalytic cycle.

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 β,β-diborylacrylate **3a** and bromobenzene under the influence of a $Pd(OAc)_2$–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%, *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(methylhydrosiloxane) (PMHS) afforded a functionalized geminal diborylalkane (**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 alkynes including propiolates, propiolamides and 2-ethynylazoles. 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 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

This work was supported by Grants-in-Aid for Scientific Research (B) (No. 15H03803), JSPS, to H.O., and by CREST, JST, to M.S. Additionally, K.N. thanks JSPS for scholarship support.

Keywords: organocatalysis • 1,1-diborylalkene • diboration

[1] a) T. Hata, H. Kitagawa, H. Masai, T. Kurahashi, M. Shimizu, T. Hiyama, *Angew. Chem* **2001**, *113*, 812; *Angew. Chem. Int. Ed.* **2001**, *40*, 790; b) T. Kurahashi, T. Hata, H. Masai, H. Kitagawa, M. Shimizu, T. Hiyama, *Tetrahedron* **2002**, *58*, 6381; c) M. Shimizu, C. Nakamaki, K. Shimono, M. Schelper, T. Kurahashi, T. Hiyama, *J. Am. Chem. Soc.* **2005**, *127*, 12506; d) M. Shimizu, K. Shimono, M. Schelper, T. Hiyama, *Synlett* **2007**, 1969; e) M. Shimizu, T. Hiyama, *Proc. Jpn. Acad., Ser. B* **2008**, *84*, 75.

[2] D. S. Matteson, *Synthesis* **1975**, 147.

[3] a) R. B. Coapes, F. E. S. Souza, R. L. Thomas, J. J. Hall, T. B. Marder, *Chem. Commun*. **2003**, 614; b) I. A. I. Mkhalid, R. B. Coapes, S. N. Edes, D. N. Coventry, F. E. S. Souza, R. L. Thomas, J. J. Hall, S.-W. Bi, Z. Lin, T. B. Marder, *Dalton Trans.* **2008**, 1055; c) J. Takaya, N. Kirai, N. Iwasawa, *J. Am. Chem. Soc*. **2011**, *133*, 12980.

[4] Diboration or hydroboration of alkynylborons allowed the preparation of 1,1-diborylalkenes: a) K. Hyodo, M. Suetsugu, Y. Nishihara, *Org. Lett.* **2014**, *16*, 440; b) H. E. Ho, N. Asao, Y. Yamamoto, T. Jin, *Org. Lett.* **2014**, *16*, 4670; c) L. Weber, D. Eickhoff, J. Halama, S. Werner, J. Kahlert, H.-G. Stammler, B. Neumann, *Eur. J. Inorg. Chem.* **2013**, 2608; d) C.-I. Lee, W.-C. Shih, J. Zhou, J. H. Reibenspies, O. V. Ozerov, *Angew. Chem* **2015**, *127*, DOI: 10.1002/ange.201507372; *Angew. Chem. Int. Ed.* **2015**, *54*, DOI: 10.1002/anie.201507372.

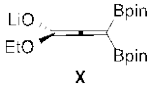
[5] For reviews on diboration of unsaturated compounds, see: a) T. B. Marder, N. C. Norman, *Top. Catal.* **1998**, *5*, 63; b) G. J. Irvine, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice, E. G. Robins, W. R. Roper, G. R. Whittell, L. J Wright, *Chem. Rev.* **1998**, *98*, 2685; c) J. Takaya, N. Iwasawa, *ACS Catal.* **2012**, *2*, 1993.

[6] For vicinal diborations of alkynes under transition-metal-free conditions, see: a) Y. Nagashima, K. Hirano, R. Takita, M. Uchiyama, *J. Am. Chem. Soc.* **2014**, *136*, 8532; b) K. Nagao, H. Ohmiya, M. Sawamura, *Org. Lett.* **2015**, *17*, 1304; See also: c) K. Nagao, H. Ohmiya, M. Sawamura, *J. Am. Chem. Soc.* **2014**, *136*, 10605.

[7] For base-catalyzed reactions of diboron reagents, see: a) A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández, *Angew. Chem.* **2011**, *123*, 7296; *Angew. Chem., Int. Ed.* **2011**, *50*, 7158; b) C. Pubill-Ulldemolins, A. Bonet, C. Bo, H. Gulyás, E. Fernández, *Chem.–Eur. J.* **2012**, *18*, 1121. c) K.-S. Lee, A. R. Zhugralin, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 7253; d) H. Wu, S. Radomkit, J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 8277; e) A. Bonet, H. Gulyás, E. Fernández, *Angew. Chem.* **2010**, *122*, 5256; *Angew. Chem., Int. Ed.* **2010**, *49*, 5130; f) C. Pubill-Ulldemolins, A. Bonet, H. Gulyás, C. Bo, E. Fernández, *Org. Biomol. Chem.* **2012**, *10*, 9677. See also ref 6b.

[8] S. R. Roscales, A. G. Csákÿ, *Org. Lett.* **2015**, *17*, 1605.

[9] The addition of Me_3SiCl 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**.

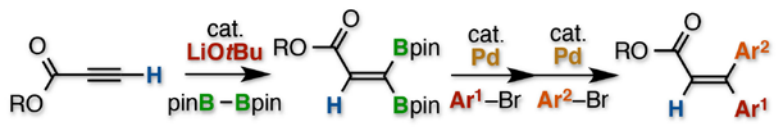


X

[10] a) J. C. H. Lee, R. McDonald, D. G. Hall, *Nat. Chem.* **2011**, *3*, 894; b) J. Ding, D. G. Hall, *Tetrahedron* **2012**, *68*, 3428; c) J. Ding, J. C. H. Lee, D. G. Hall, *Org. Lett.* **2012**, *14*, 4462.

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Page No. – Page No.

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