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Mixed Diboration of Alkynes Catalyzed by LiOH: Regio- and Stereoselective Synthesis of *cis*-1,2-Diborylalkenes

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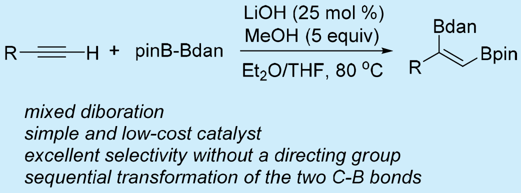
Supporting Information

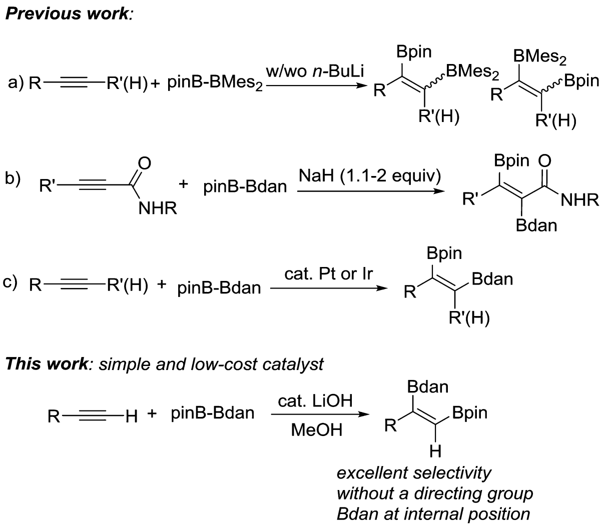


ABSTRACT: A diboration of terminal alkynes with an unsymmetrical diboron reagent pinBBdan has been achieved using LiOH as the catalyst in the presence of stoichiometric amounts of MeOH, affording 1,2-diborylalkenes with different boryl groups. The reaction proceeds in a highly regio- and stereoselective manner through *cis*-addition of pinBBdan to the C−C triple bond, with the Bdan moiety being incorporated at the internal position. By taking advantage of the different reactivities of the two boryl groups, the mixed diboration product can undergo the sequential, chemoselective cross-couplings with aryl bromides to form trisubstituted alkenes.

1,2-Diborylalkenes bearing two vicinal boron moieties for elaboration are valuable building blocks for the synthesis of multisubstituted alkenes, which are prevalent motifs present in bioactive compounds and π-conjugated materials.[1] Diboration of alkynes with a diboron reagent[2] provides a straightforward and eco-friendly route to diborylalkenes.[3] A range of transition-metal catalysts have proven to be efficient for this transformation to provide *cis*-1,2-diborylalkenes selectively.[4−9] Recently, transition-metal-free protocols have also been developed.[10] Notable examples include photocatalyzed diboration of terminal alkynes employing organosulfide[11] or organophosphine[12] catalysts under light irradiation, PBu$_3$-catalyzed *trans*-diboration of alkynoates,[13] and *trans*-diboration of propargylic alcohols with stoichiometric amounts of *n*-BuLi.[14] Although great advances have been achieved using symmetrical diboron reagents, such as B$_2$pin$_2$ [bis(pinacolato)-diborane], alkyne diboration with unsymmetrical diboron reagents is still in its infancy.

The addition of mixed diborons across the alkynes allows the synthesis of diborylalkenes with different protecting groups on the boron groups. Such diborylalkenes are synthetically valuable since the two nonequivalent C−B bonds exhibit different reactivity and could be easily discriminated during further transformation. However, a significant challenge exists in mixed diboration, with the difficulty of controlling regio- and stereoselectivity to deliver the two differentially masking borons to specific positions.[15] For example, in a direct and base-catalyzed diboration of alkynes with pinBBMes$_2$ (Mes = 2,4,6-Me$_3$C$_6$H$_2$) developed by Lin and Yamashita et al., a mixture of regio- or stereoisomers was obtained for some substrates (Scheme 1a).[16] The installation of a directing group in the alkyne substrate provides an efficient strategy to control selectivity. The Santos group developed a substrate-assisted *trans*-diboration of alkynamides with pinBBdan promoted by NaH, wherein an amide group in the alkynes acts as a directing group to assist *trans*-diboration with excellent selevtivity (Scheme 1b).[17] The only example of selective mixed diboration of alkynes without the aid of a directing group was reported by Suginome and co-workers, who have shown that the use of Ir and Pt catalysts was effective for *cis*-diboration of alkynes with pinBBdan (dan = naphthalene-1,8-diaminato) with Bdan being installed at the terminal carbon (Scheme 1c).[18] Therefore, it is of synthetic interest to develop a general catalytic system that promotes the mixed diboration of alkynes with high selectivity. In particular, a new catalytic method that provides selectivity complementary to that of the

Scheme 1. Diboration of Alkynes with Unsymmetrical Diborons



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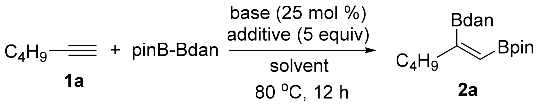
current methods without the use of a directing group is highly desired.

To accomplish synthetically useful alkyne diboration with unsymmetrical diboron reagents, it is essential to overcome the regio- and steroselectivity issues. The work of Carbó and Fernández et al. demonstrated that pinBBdan could be activated by an alkoxide, where the more Lewis-acidic Bpin moiety could interact with the Lewis-basic alkoxide preferentially over the Bdan unit.[15a,19] Inspired by these findings, we envisioned that this activation mode might be used to deliver Bpin and Bdan moieties across the C−C triple bond in a selective way. Given the low cost and ready accessibility, it is surprising that simple inorganic bases have rarely been used as catalysts in diboration of alkynes. We describe herein a LiOH-catalyzed *cis*-diboration of terminal alkynes with pinBBdan to afford *cis*-diborylalkenes with the Bdan group added to the internal carbon, featuring excellent regioselectivity complementary to that obtained in Suginome's transition-metal catalytic system.

We commenced our study by identifying a suitable base catalyst to effect mixed diboration of 1-hexyne (**1a**) with pinBBdan, and the results are summarized in Table 1.

Table 1. Catalyst Development for Diboration of 1-Hexyne[a]



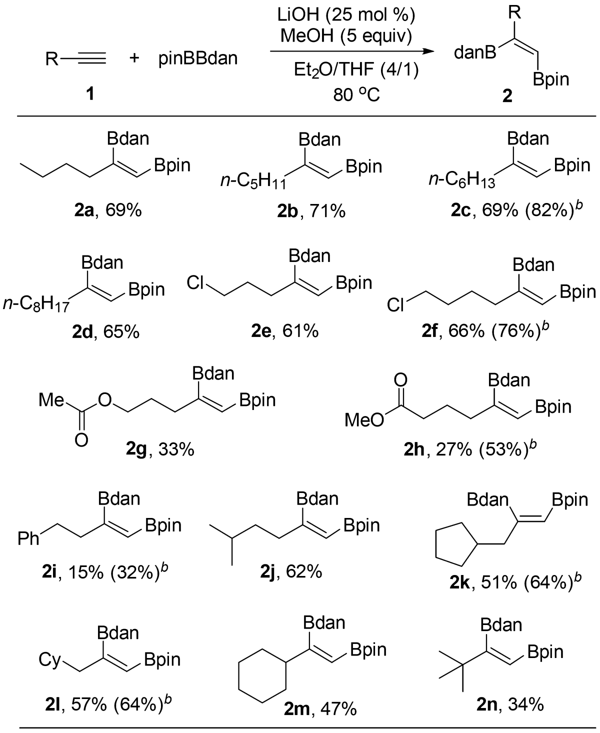
entry	base	additive	solvent	yield[b] (%)
1	LiOH	MeOH	THF	45
2	*t*-BuOLi	MeOH	THF	NR
3	NaOH	MeOH	THF	35
4	Cs_2CO_3	MeOH	THF	14
5	NaOMe	MeOH	THF	trace
6	CsF	MeOH	THF	trace
7	LiOH	EtOH	THF	37
8	LiOH	*i*-PrOH	THF	trace
9	LiOH	*t*-BuOH	THF	trace
10	LiOH	MeOH	Et_2O	36
11[c]	LiOH	MeOH	Et_2O/THF	65
12[c,d]	LiOH	MeOH	Et_2O/THF	76
13[c,d]	LiOH		Et_2O/THF	NR

[a] Reaction conditions: **1a** (0.2 mmol), pinBBdan (2 equiv), base (25 mol %), additive (5 equiv), and solvent (0.5 mL) at 80 °C for 12 h. [b] Yields are determined by GC with mesitylene as the internal standard. [c] Et_2O/THF = 4:1 (v/v). [d] 24 h.

Encouragingly, 1,2-diborylalkene **2a** was obtained in 45% GC yield when the reaction was performed in THF at 80 °C using LiOH (25 mol %) as the catalyst and MeOH (5 equiv) as the additive (entry 1). The structure of **2a** was unambiguously determined by NOE spectra,[20] which implied that diboration proceeds via *cis*-addition of pinB-Bdan to the C−C triple bond, with the Bdan moiety at the internal position. The choice of base and additive significantly influenced the reactivity. A screen of the bases revealed that LiOH was superior to other bases, such as LiO-*t*-Bu, NaOH, KOH, Cs_2CO_3, NaOMe, and CsF (entries 1−6). Replacing MeOH with EtOH led to a decline in yield (entry 7), and the use of *i*-PrOH or *t*-BuOH gave trace amounts of **2a** (entries 8 and 9). A survey of solvents established the mixed solvents of THF and ether as the optimal reaction medium, affording the diboration product in 65% yield (entry 11). Prolonging the reaction time to 24 h further improved the yield to 76% (entry 12). No reaction occurred in the absence of MeOH (entry 13). It is worth noting that, under the optimized conditions, GC analysis of the crude reaction mixture showed that **2a** was the only diboration product, which was accompanied by a structurally undefined triborylation product. These results indicate that this base catalysis enabled the mixed diboration with excellent regio- and stereoselectivity.

With the optimized catalytic conditions in hand, the scope and limitations of the base-catalyzed mixed diborylation were evaluated (Scheme 2). Specifically, linear aliphatic terminal alkynes underwent the reaction smoothly, affording the 1,2-diborylated products in 65−71% isolated yields (**2a**−**d**). The use of chloro-substituted alkynes led to moderate yields of the corresponding products, leaving the C(sp^3)−Cl bond intact (**2e** and **2f**). Ester-containing substrates derived from acid or alcohol could be diborylated, albeit with low yields (**2g** and **2h**). The reaction proceeded sluggishly for a substrate bearing a Ph group *β* to the alkyne group, giving the diborylated product (**2i**) in low yield. The mixed diboration could be extended to alkynes with a branched alkyl substituent, as demonstrated by the isolation of **2k**−**m** in useful yields. An alkyne with a bulky *t*-Bu substituent could be diborated to form the desired product **2n** in 34% isolated yield. The reaction using 1-hexyne in the presence of an equimolar amount of 3-hexyne or 4-methyl-1-pentene, only converted the terminal alkyne, which indicates the current protocol is chemoselective for terminal alkynes. It is also worth noting

Scheme 2. LiOH-Catalyzed Diboration of Alkyl Alkynes with BpinBdan[a]

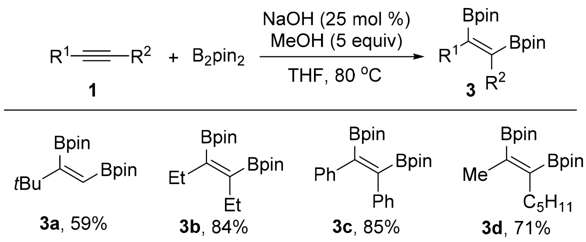


[a] Reaction conditions: alkynes (0.2 mmol), pinBBdan (2.0 equiv), LiOH (25.0 mol %), MeOH (5 equiv), in Et_2O (0.8 mL) and THF (0.2 mL) at 80 °C for 24−72 h. Isolated yields. [b] ^{1}H NMR yields are given in parentheses.

that many reactions gave moderate isolated yields of the desired products, partly because the alkenyl boronate products decompose relatively easily during the purification by chromatography. Although this simple base catalytic system is active toward alkyl acetylenes, aryl acetylenes do not react.

The application of this base catalyst in diboration of alkynes with B_2pin_2 as the diboron reagent was also investigated briefly, considering that such a transformation has rarely been effected by a simple base.[21] With NaOH as the catalyst, a range of alkynes, including a terminal alkyne (**3a**), alkyl or phenyl substituted symmetric internal alkynes (**3b** and **3c**) and an unsymmetric internal alkyne (**3d**) could be diborylated smoothly with B_2pin_2, affording 1,2-diborylalkenes in moderate to good yields (Scheme 3). In contrast, the unsymmetrical diboration of internal alkynes with pinBBdan was sluggish, which resulted in low conversion and only produced a low yield of the desired diboration product.[22]

Scheme 3. Base-Catalyzed Diborylation of Alkynes with B_2pin_2[a]



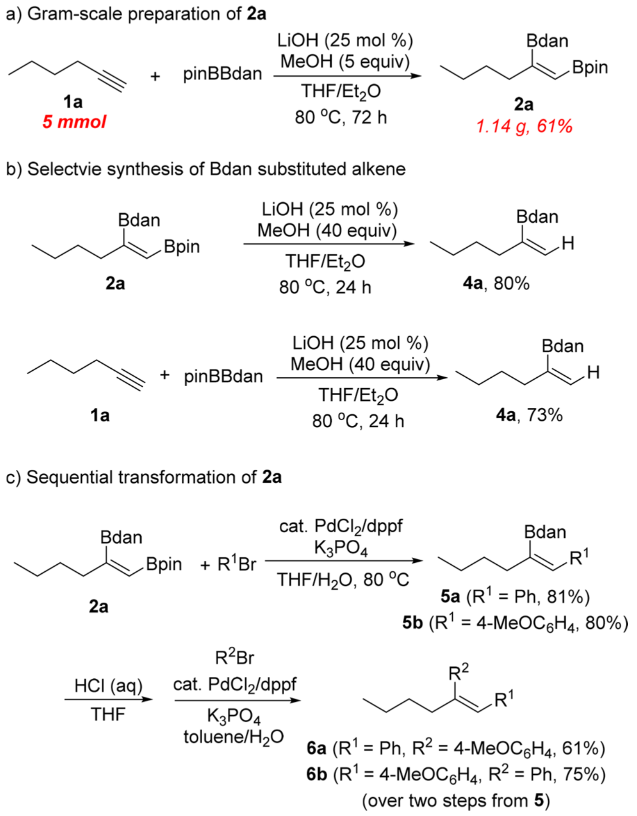
[a]Reaction conditions: alkynes (0.5 mmol), B_2pin_2 (2 equiv), base (25 mol %), MeOH (5 equiv), and THF (0.5 mL) at 80 °C.

To demonstrate the synthetic utility further, a gram-scale reaction and derivatization of the mixed diboration product were conducted. The reaction of **1a** with pinBBdan catalyzed by LiOH could be carried out on a 5 mmol scale to produce **2a** in 61% yield (Scheme 4a). Exposure of **2a** under basic conditions in the presence of a large excess of methanol (20 equiv) led to the selective protodeboration of the Bpin moiety, affording the Bdan-substituted alkene **4a** in 80% yield. Alternatively, **4a** could be synthesized directly from alkyne **1a** with BpinBdan using 25 mol % of LiOH and 40 equiv of MeOH (Scheme 4b).[23]

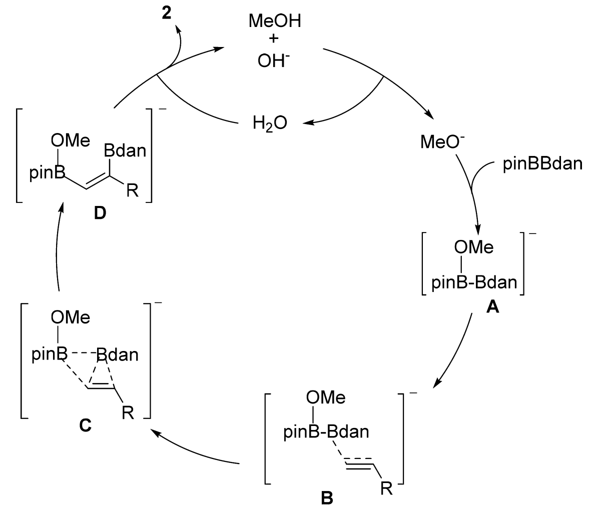
The orthogonal reactivity of two boron moieties in the mixed diboration product **2a** was further demonstrated in a sequential transformation. When the diboration product **2a** was submitted to the Suzuki−Miyaura coupling reaction with phenyl bromide (Scheme 4c), the coupling occurred at the Bpin part chemoselectively, leaving the Bdan moiety intact. Following the deprotection of the Bdan group in **5a** without the isolation of the boronic acid, the cross-coupling with another aryl bromide generated trisubstituted alkene **6a** stereoselectively with two newly incorporated aryl groups *cis* to each other. The regioisomer of **6a**, that is **6b**, could be synthesized by changing the order of the coupling partners.

A plausible catalytic cycle for the LiOH-catalyzed alkyne mixed diboration was proposed, mainly based on the precedents of alkene diborations under basic conditions (Scheme 5).[15a,19,24] A methoxide anion derived from the reaction of LiOH and MeOH is expected to attack the Bpin moiety selectively versus the less electrophilic Bdan unit.[25] The resulting [danB-Bpin(OMe)]$^-$ adduct **A** reacts with the alkyne via the addition of the nucleophilic Bdan moiety to the terminal carbon of the triple bond to form species **B**. This nucleophilic addition not only increases the negative charge of alkyne but also makes the Bpin(OMe) moiety electrophilic. Subsequently, the terminal carbon of the alkyne attacks the Bpin(OMe) moiety, accompanied by B−B bond cleavage and Bdan migration to the internal carbon, furnishing the methoxide adduct of the diborated product. Protonolysis of intermediate **D** produces the desired product and regenerates the base and MeOH.

Scheme 4. Gram-Scale Reaction and Derivatization of the Product



Scheme 5. Proposed Catalytic Cycle



In summary, we have developed a simple and efficient mixed diboration of terminal alkynes with pinBBdan catalyzed by low-cost and readily available LiOH. The most significant aspect of this method is the excellent regio- and stereoselectivity, affording the *cis*-diboration product with the Bpin moiety at the terminal position. Moreover, the method is scalable, and the two differentially masked boron parts could be sequentially transformed, which underscores its synthetic utility. Further work on the application of this protocol to other substrates is currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02830.

Experimental procedures and product characterization (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466. (b) Shimizu, M.; Nagao, I.; Tomioka, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 8096. (c) Yavari, K.; Moussa, S.; Hassine, B. B.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 6748. (d) Guo, X.; Nelson, A. K.; Slebodnick, C.; Santos, W. L. *ACS Catal.* **2015**, *5*, 2172. (e) Böhnke, J.; Braunschweig, H.; Deißenberger, A.; Dellermann, T.; Dewhurst, R. D.; Jiménez-Halla, J. O. C.; Kachel, S.; Kelch, H.; Prieschl, D. *Chem. Commun.* **2017**, *53*, 12132. (f) Ohmura, T.; Morimasa, Y.; Suginome, M. *Chem. Lett.* **2017**, *46*, 1793.

(2) For some reviews on diboration of alkynes, see: (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435. (b) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392. (c) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320. (d) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091. (e) Zhao, F.; Jia, X.; Li, P.; Zhao, J.; Zhou, Y.; Wang, J.; Liu, H. *Org. Chem. Front.* **2017**, *4*, 2235.

(3) (a) Weber, L.; Eickhoff, D.; Halama, J.; Werner, S.; Kahlert, J.; Stammler, H. G.; Neumann, B. *Eur. J. Inorg. Chem.* **2013**, *2013*, 2608. (b) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466. (c) Woerly, E. M.; Roy, J.; Burke, M. D. *Nat. Chem.* **2014**, *6*, 484. (d) Morinaga, A.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 15859−15862. (e) Krautwald, S.; Bezdek, M. J.; Chirik, P. J. *J. Am. Chem. Soc.* **2017**, *139*, 3868. (f) Mao, L.; Bertermann, R.; Emmert, K.; Szabo, K. J.; Marder, T. B. *Org. Lett.* **2017**, *19*, 6586.

(4) For some examples of Pt catalysis, see: (a) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018. (b) Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. *Organometallics* **1996**, *15*, 713. (c) Lillo, V.; Mata, J.; Ramírez, J.; Peris, E.; Fernandez, E. *Organometallics* **2006**, *25*, 5829. (d) Prokopcová, H.; Ramírez, J.; Fernández, E.; Kappe, C. O. *Tetrahedron Lett.* **2008**, *49*, 4831. (e) Hyodo, K.; Suetsugu, M.; Nishihara, Y. *Org. Lett.* **2014**, *16*, 440. (f) Miralles, N.; Cid, J.; Cuenca, A. B.; Carbó, J. J.; Fernández, E. *Chem. Commun.* **2015**, *51*, 1693.

(5) For Pd catalysis, see: (a) Braunschweig, H.; Kupfer, T.; Lutz, M.; Radacki, K.; Seeler, F.; Sigritz, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8048. For Rh catalyzed *trans*-diboration, see: (b) Curto, S. G.; Esteruelas, M. A.; Oliván, M.; Oñate, E.; Vélez, A. *Organometallics* **2018**, *37*, 1970.

(6) For Au-catalyzed diborations, see: (a) Chen, Q.; Zhao, J.; Ishikawa, Y.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2013**, *15*, 5766. (b) Kidonakis, M.; Stratakis, M. *Eur. J. Org. Chem.* **2017**, *2017*, 4265.

(7) For Cu-catalyzed diboration, see: (a) Yoshida, H.; Kawashima, S.; Takemoto, Y.; Okada, K.; Ohshita, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 235. (b) Zhao, T. S. N.; Yang, Y.; Lessing, T.; Szabó, K. J. *J. Am. Chem. Soc.* **2014**, *136*, 7563.

(8) For Fe-catalyzed diboration, see: Nakagawa, N.; Hatakeyama, T.; Nakamura, M. *Chem. - Eur. J.* **2015**, *21*, 4257.

(9) For Co catalysis, see: Adams, C. J.; Baber, R. A.; Batsanov, A. S.; Bramham, G.; Charmant, J. P. H.; Haddow, M. F.; Howard, J. A. K.; Lam, W. H.; Lin, Z.; Marder, T. B.; Norman, N. C.; Orpen, A. G. *Dalton Trans* **2006**, 1370.

(10) For a review, see: Cuenca, A. B.; Shishido, R.; Ito, H.; Fernández, E. *Chem. Soc. Rev.* **2017**, *46*, 415.

(11) Yoshimura, A.; Takamachi, Y.; Han, L. B.; Ogawa, A. *Chem. - Eur. J.* **2015**, *21*, 13930.

(12) Yoshimura, A.; Takamachi, Y.; Mihara, K.; Saeki, T.; Kawaguchi, S.-i.; Han, L.-B.; Nomoto, A.; Ogawa, A. *Tetrahedron* **2016**, *72*, 7832.

(13) Nagao, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2015**, *17*, 1304.

(14) Nagashima, Y.; Hirano, K.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2014**, *136*, 8532.

(15) (a) Miralles, N.; Cid, J.; Cuenca, A. B.; Carbó, J. J.; Fernández, E. *Chem. Commun.* **2015**, *51*, 1693. (b) Guo, X.; Nelson, A. K.; Slebodnick, C.; Santos, W. L. *ACS Catal.* **2015**, *5*, 2172.

(16) Kojima, C.; Lee, K.-H.; Lin, Z.; Yamashita, M. *J. Am. Chem. Soc.* **2016**, *138*, 6662.

(17) Verma, A.; Snead, R. F.; Dai, Y.; Slebodnick, C.; Yang, Y.; Yu, H.; Yao, F.; Santos, W. L. *Angew. Chem., Int. Ed.* **2017**, *56*, 5111.

(18) Iwadate, N.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 2548.

(19) Cid, J.; Carbó, J. J.; Fernández, E. *Chem. - Eur. J.* **2014**, *20*, 3616.

(20) Please see the NOSY spectra in the Supporting Information.

(21) During the preparation of this manuscript, a base-catalyzed diboration of alkynes with B_2pin_2 was reported by the Song group: Kuang, Z.; Gao, G.; Song, Q. *Sci. China: Chem.* **2018**, DOI: 10.1007/s11426-018-9344-4.

(22) The reactivity of pinBBdan toward internal alkynes is relatively low, probably because the Bdan moiety in the $[\text{danB-Bpin(OMe)}]^-$ adduct is not nucleophilic enough to react with internal alkynes. For diboron reagents that are activated with Lewis bases, the p/s ratio of the $B(sp^2)$ atom provides an indication of the intrinsic nucleophilicity. For the details, see: Cid, J.; Carbó, J. J.; Fernández, E. *Chem. - Eur. J.* **2012**, *18*, 12794. See also ref 19.

(23) Yang, K.; Song, Q. *Green Chem.* **2016**, *18*, 932.

(24) Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 7158.

(25) The formation of $[\text{Bdan-Bpin(OMe)}]^-$ adduct **A** is supported by ^{11}B NMR analysis. See the Supporting Information for details.