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Synthesis of Stereodefined 1,1-Diborylalkenes via Copper-Catalyzed Diboration of Terminal Alkynes

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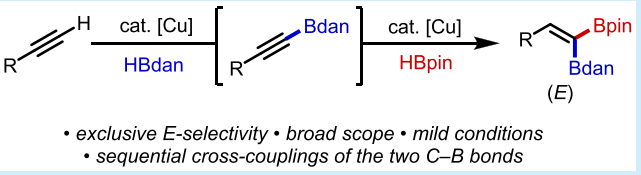
ABSTRACT: A copper-catalyzed method for the *E*-selective 1,1-diboration of terminal alkynes is described. The tandem process involves sequential dehydrogenative borylation of the alkyne substrate with HBdan (1,8-diaminonaphthalatoborane), followed by hydroboration with HBpin (pinacolborane). This method proceeds efficiently under mild conditions, furnishing 1,1-diborylalkenes with excellent stereoselectivity and broad functional group tolerance. Taking advantage of the different reactivities of the two boryl moieties, the products can then be employed in stepwise cross-couplings with aryl halides for the stereocontrolled construction of trisubstituted alkenes.



Alkenyl boronic acids and their derivatives are nontoxic, shelf-stable organometallic compounds that react with high fidelity in a range of C−C and C−heteroatom couplings, making them useful reagents in organic synthesis.[1] 1,1-Diborylalkenes make up an emerging subclass that offers exciting potential for accessing multisubstituted olefins in a stereocontrolled manner through sequential reaction at each of the two C−B bonds.[2] To this end, many approaches to synthesize 1,1-diboryl alkenes bearing two −Bpin (pinacolatoboryl) groups have been developed from alkene[2c,3] and alkyne starting materials.[4] When such compounds are then employed in cross-coupling, the inherently similar reactivity of the two C−Bpin bonds makes it challenging to achieve high selectivity for a monofunctionalized product. Indeed, successful monoselectivity at the less hindered position has been demonstrated only when the 1,1-diborylalkene contains an aryl group at the C2 position and when an aryl iodide is employed as the electrophile (Scheme 1A).[2c,4b]

We reasoned that the scope of substrates and coupling partners could be expanded if the two boron centers were differentially protected with one −(pin) (pin = pinacolate) group and one −(dan) (dan = naphthalene-1,8-diaminato) group (Scheme 1A). The Bdan group is well-known to possess diminished Lewis acidity and to be generally inactive toward transmetalation, a key step of cross-coupling.[5] This so-called protected boron moiety can be reactivated by either deprotection under acidic conditions[5] or interaction with KO*t*Bu or $Ba(OH)_2$.[6] The sequential masking/unmasking strategy enabled by the Bdan group has been successfully applied to iterative cross-coupling, providing efficient and concise approaches to functional organic molecules including complex oligoarenes[5a,c,6c] and optoelectronic materials.[5d] Moreover, these isomerically pure 1,1-diborylalkenes represent a promising class of prochiral substrates to generate enantioenriched 1,1-diborylalkanes,[7] which are valuable and versatile

Scheme 1. (A) Synthesis and Reactivity of 1,1-Diborylalkenes, (B and C) Prior Steps to Access *Z*-Configured 1,1-Diborylalkenes, and (D) This Work

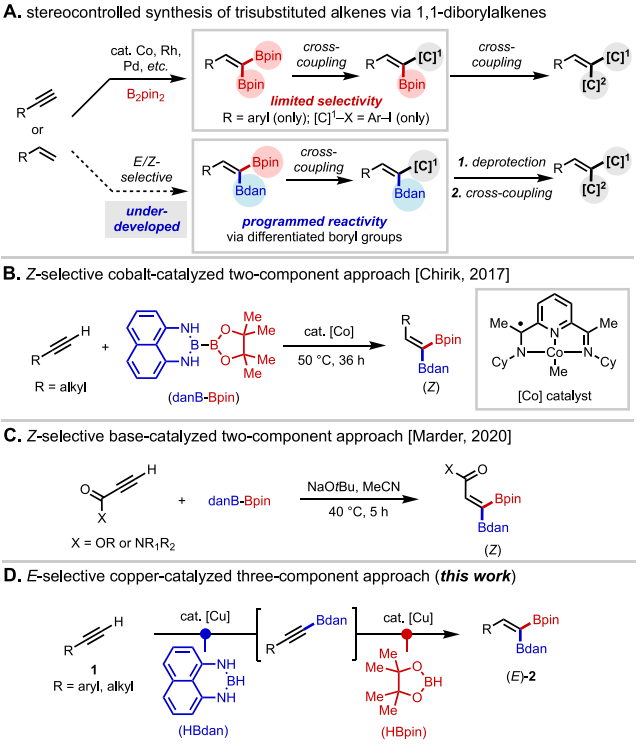


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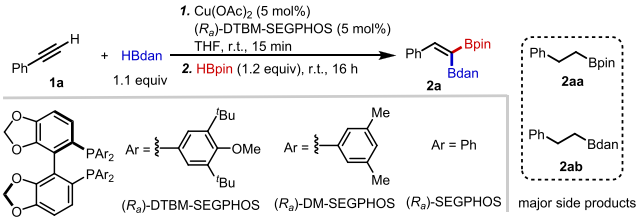
Table 1. Optimization of Reaction Conditions for Cu-Catalyzed 1,1-Diboration of Phenylacetylene



entry[a]	variation from standard conditions	yield[b] (%) 2a	yield[b] (%) 2aa + 2ab
1	none	69	17
2	HBpin added after 8 min	52	23
3	HBpin added together with **1a**	31	20[c]
4	CuOAc in place of $Cu(OAc)_2$	55	20
5	CuBr in place of $Cu(OAc)_2$[d]	0	0
6	CuCl in place of $Cu(OAc)_2$[d]	0	0
7	PPh_3 as the ligand	23	5
8	PCy_3 as the ligand	0	0
9	dppp as the ligand	4	0
10	dppf as the ligand	9	4
11	(R_a)-SEGPHOS as the ligand	23	5[e]
12	(R_a)-DM-SEGPHOS as the ligand	64	10[e]
13	no ligand	0	0
14	toluene as the solvent	48	46

[a]Standard reaction conditions: **1a** (0.10 mmol), HBdan (0.11 mmol), HBpin (0.12 mmol), $Cu(OAc)_2$ (5 mol %), and (R_a)-DTBM-SEGPHOS (5 mol %) in THF (0.25 mL). [b]^1H NMR yield using CH_2Br_2 as the internal standard. [c]Also observed was 10% PhCHCH(Bpin). [d]Together with NaO*t*Bu (10%). [e]Also observed was 9% $PhCHC(Bpin)_2$.

building blocks for accessing enantioenriched functionalized alkanes.[8]

In view of the unique synthetic value of differentially protected 1,1-diborylalkenes, practical synthetic methods for accessing such compounds in a stereodefined manner are desirable. However, few methods are currently available. In 2017, Chirik and colleagues described a Co-catalyzed 1,1-diboration of aliphatic alkynes to synthesize (*Z*)-1,1-diborylakenes with use of the mixed diboron reagent pinB−Bdan (Scheme 1B).[4b] Later, Marder reported a base-catalyzed stereoselective diboration of alkynyl esters and amides with pinB−Bdan (Scheme 1C).[9] Both methods, though highly enabling in their own right, have limited substrate scope and provide access to only the *Z*-configured products.

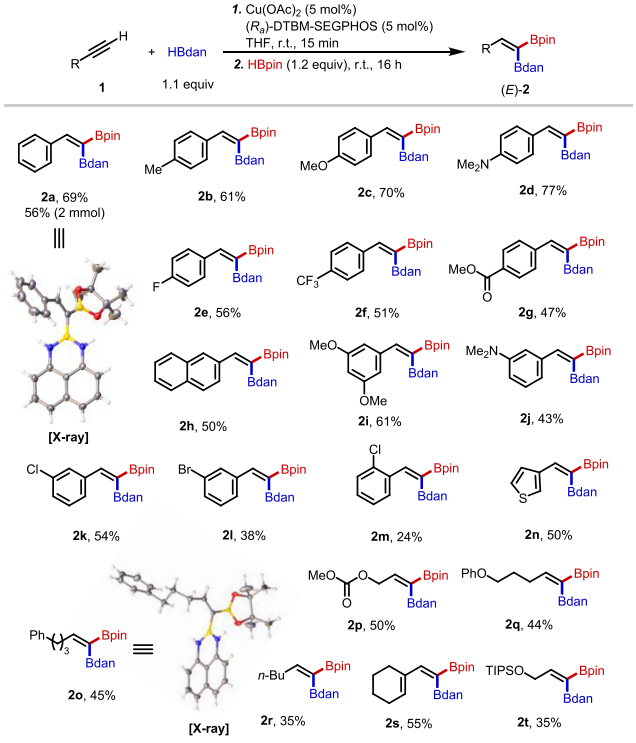
Driven by our interest in developing new metal-catalyzed alkyne functionalization methods,[10] we recently reported a CuH-catalyzed cascade process to access enantioenriched α-aminoboron compounds via sequential hydroboration and hydroamination of terminal alkynes.[11,12] Here we report an exclusively *E*-selective Cu-catalyzed three-component reaction to produce 1,1-diborylalkenes through a tandem sequence comprised of dehydrogenative C(sp)−H borylation with HBdan and hydroboration of the resulting alkynylBdan intermediate with HBpin (Scheme 1D).[13]

Our investigation commenced by examining reaction conditions using phenylacetylene (**1a**) as a pilot substrate, with HBdan and HBpin as coupling partners. After extensive optimization, we identified an effective protocol in which HBdan is first mixed with **1a** in the presence of 5 mol % $Cu(OAc)_2$ and 5 mol % (R_a)-DTBM-SEGPHOS in THF for 15 min. After this period, HBpin is added, and the reaction mixture is allowed to stir for an additional 16 h at room temperature, at which point the desired product **2a** is isolated in 69% yield (Table 1, entry 1). The timing of HBpin addition was found to be important. The yield of **2a** decreased when HBpin was added earlier, with a larger amount of side products observed (Table 1, entries 2 and 3).

Another key finding from these studies was that the acetate counteranion and the (R_a)-DTBM-SEGPHOS ligand were both required (Table 1, entries 4−12). CuOAc was slightly less effective than $Cu(OAc)_2$ (Table 1, entry 4), while other copper sources such as CuBr and CuCl, together with NaO*t*Bu, showed no catalytic activity. In terms of other ligands tested, (R_a)-DM-SEGPHOS gave a yield of **2a** that was slightly lower than that of (R_a)-DTBM-SEGPHOS (Table 1, entry 12). Unfortunately, other phosphine ligands led to either a low yield or no reaction. There was no reaction in the absence of a ligand (Table 1, entry 13). The structure and (*E*)-stereochemical configuration of **2a** were unambiguously assigned by X-ray crystallography (Table 1, top left).

Next, we evaluated the scope and functional group compatibility of this stereoselective process (Scheme 2). The

Scheme 2. Copper-Catalyzed Stereoselective 1,1-Diboration of Terminal Alkynes[a]



[a]Conditions: 0.10 mmol scale, THF (0.25 mL). Percentages correspond to isolated yields.

reactions with aryl-substituted alkynes were found to be sensitive to both electronic and steric effects. Aryl acetylenes with electron-donating groups normally performed better than those with electron-withdrawing groups. For example, *p*-MeO-substituted phenylacetylene gave product **2c** in70% yield, while *p*-CF_3-substituted phenylacetylene gave product **2f** in 47% yield. Diboration of *para*-substituted phenylacetylenes generally occurred smoothly, while *meta*- and *ortho*-substituted phenyl-

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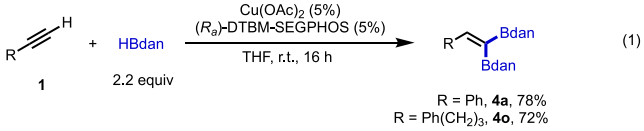
acetylenes gave relatively low yields. A range of functional groups, such as halides (**2e** and **2k**−**2m**), an ester (**2g**), ethers (**2c** and **2i**), and amines (**2d** and **2j**), were well tolerated. 2-Ethynyl-naphthalene and 3-ethynylthiophene underwent diboration as well to give corresponding 1,1-diborylalkenes (**2h** and **2n**).

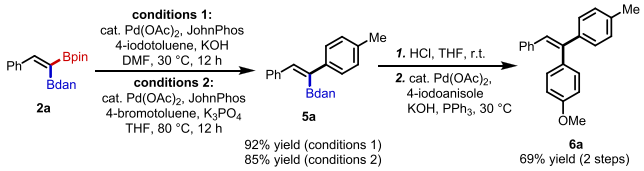
1,1-Diboration was similarly effective with aliphatic alkynes, furnishing the corresponding *E*-configured products. The structure of 1,1-diborylalkene **2o** was confirmed by X-ray crystallography (Table 1, bottom left). Remarkably, 1-ethynylcyclohexene underwent 1,1-diboration to furnish product **2s** with the C═C bond intact. Functional groups like carbonate (**2p**), ether (**2q**), and silyl ether (**2t**) were tolerated, with products isolated in useful yields.

Interestingly, when terminal alkynes **1** were reacted with 2.2 equiv of HBdan in the absence of HBpin, 1,1-homodiboration proceeded smoothly, furnishing 1,1-diborylalkenes **4** bearing two −Bdan groups in excellent yields (eq 1).



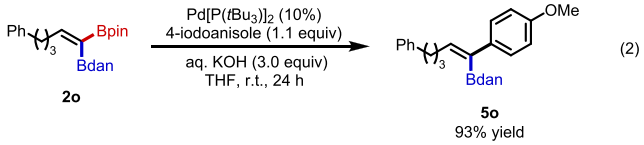
To illustrate the practical utility of this procedure, we performed stepwise Suzuki−Miyaura cross-couplings of the 1,1-diborylalkenes (Scheme 3). The selective monoarylation of

Scheme 3. Stepwise Suzuki−Miyaura Coupling Reactions of 2a

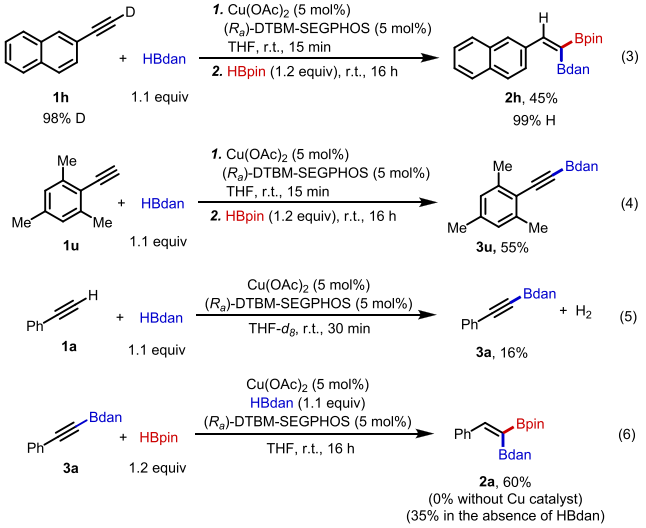


2a worked well using 4-iodotoluene as a coupling partner under standard cross-coupling conditions, giving 92% **5a** after 12 h at 30 °C. Notably, the reaction with 4-bromotoluene also proceeded, albeit at a higher temperature of 80 °C, giving product **5a** in 85% yield with no diarylation product detected. Next, the Bdan group of **5a** was deprotected, and the resulting boronic acid was carried forward without purification in a second cross-coupling reaction with 4-iodoanisole to produce triarylated alkene **6a** as a single stereoisomer.

Selective Suzuki−Miyaura cross-coupling of the Bpin group of **2o** also proceeded smoothly, furnishing **5o** in 94% yield (eq 2). The olefin geometry in **5o** was confirmed by NOESY (see the Supporting Information).[4b,9]

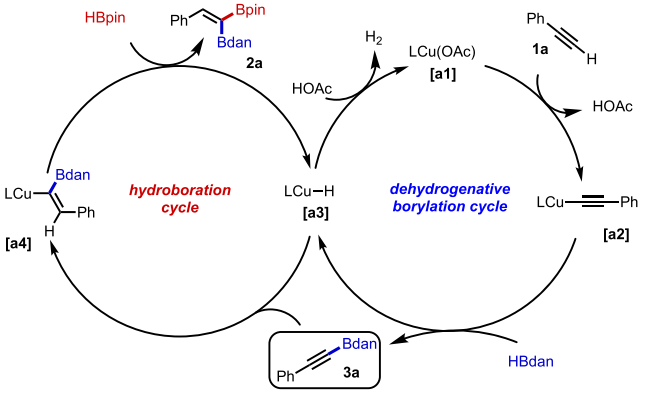


Having established the scope and utility of the (*E*)-selective alkyne 1,1-diboration method, we shifted our attention to investigating the reaction mechanism. First, we performed copper-catalyzed 1,1-diboration of 2-(ethynyl-*d*)naphthalene (98% isotopic purity) under the standard reaction conditions, which furnished 1,1-diborylalkene **2h** with no deuterium label at the internal alkenyl carbon atom, as judged by ^{1}H NMR spectroscopy (eq 3). This result is consistent with an initial dehydrogenative borylation event. Next, subjecting sterically bulky mesitylacetylene to the standard reaction conditions did not lead to formation of the typical 1,1-diborylated product; instead, alkynylBdan **3u** was isolated in 55% yield (eq 4). This result suggests that alkynylBdan is the product from the first step of the tandem process and that the second hydroboration step is sensitive to steric hindrance. Consistent with this notion, the reaction between **1a** and HBdan before addition of HBpin was monitored by ^{1}H NMR spectroscopy (eq 5), and alkynylBdan **3a** (16%) and H_2 were both observed after 30 min (Figure S2).[14] To further support our hypothesis, the proposed intermediate **3a** was independently synthesized and submitted to the reaction with HBpin under the standard conditions. Hydroboration of **3a** proceeded smoothly to furnish **2a** in 60% yield (eq 6). Control experiments revealed that hydroboration of **3a** with HBpin requires copper as a catalyst[15] and that the presence of HBdan improves the hydroboration efficiency of **3a** (60% compared to 35% yield). An explanation for this latter result is that HBdan could be involved in regeneration of the active [LCuH] catalyst.[11] On the basis of our experimental observations and



previous reports,[11−13,16,17] a Cu-catalyzed tandem process comprised of dehydrogenative borylation of the terminal alkyne and subsequent hydroboration is proposed (Scheme 4). [LCuOAc] **a1**, generated by reduction of $Cu(OAc)_2$ in the

Scheme 4. Proposed Mechanism



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presence of phosphine and HBdan,[18−20] reacts with the terminal alkyne to give the alkynylcopper intermediate **a2** and HOAc.[18b] Following σ-bond metathesis between **a2** and HBdan, alkynylBdan **3** and [LCuH] **a3** are formed.[16,21] Next, *syn*-insertion of intermediate **3** into the Cu−H bond of **a3** generates alkenyl copper species **a4**,[15,17,18,22] which then undergoes σ-bond metathesis with HBpin to furnish the (*E*)-1,1-diborylalkene with concomitant regeneration of [LCuH] **a3**.

Under the optimal conditions, prior to the addition of HBpin, the dehydrogenative borylation cycle (right, Scheme 4) alone proceeds through several turnovers to build up **3a**, and upon addition of HBpin, the hydroboration cycle (left, Scheme 4) turns on.[23] This strategy limits the formation of side products caused by the high reactivity of HBpin. In the 1,1-homodiboration system with HBdan only, both cycles presumably proceed in parallel.[24]

In conclusion, we have reported the first (*E*)-selective synthesis of 1,1-diborylalkenes bearing one −Bpin group and one −Bdan group from terminal alkynes via a Cu-catalyzed tandem process.[25] A wide range of aryl- and alkyl-substituted alkynes participate in this transformation, giving the corresponding 1,1-diborylalkenes with broad functional group tolerance. We have also demonstrated that differentially protected 1,1-diborylalkenes are useful synthetic intermediates for the construction of multisubstituted alkenes with stereocontrol. Further applications of 1,1-diborylalkenes for the synthesis of more complex compounds are being pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01901.

Detailed experimental procedures, compound characterization data, and ^{1}H NNR and ^{13}C NMR spectra for new compounds (PDF)

Processed NMR data for all new compounds in MNova format (ZIP)

FAIR data file, including the primary NMR FID files, for compounds **2a−2t**, **3u**, **4a**, **4o**, **5a**, **5o**, and **6a** (ZIP)

Accession Codes

CCDC 1996915−1996916 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(23) The origin of the high selectivity for product **2a** is likely the preferential reaction of [LCuH] with the more polarized alkyne of **3a**, as compared to that of **1a**.

(24) In the 1,1-homodiboration reaction of phenylacetylene with HBdan, the dehydrogenative borylation cycle was found to be much faster than the hydroboration cycle. After 2 h, 50% of **3a** and <5% of **4a** were observed by ^{1}H NMR spectroscopy.

(25) A previous version of this paper was deposited on a preprint server: Gao, Y.; Wu, Z.-Q.; Engle, K. M. Synthesis of Stereodefined 1,1-Diborylalkenes via Copper-Catalyzed Diboration of Terminal Alkynes. *ChemRxiv* **2020**, DOI: 10.26434/chemrxiv.12133404.v1.

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