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Highly Regio- and Stereoselective Synthesis of Boron-Substituted Enynes via Copper-Catalyzed Borylation of Conjugated Diynes

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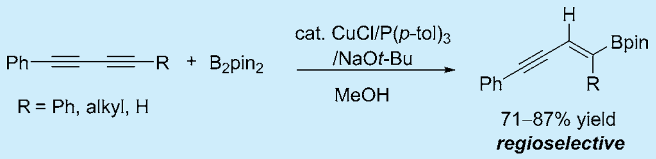
Ⓢ *Supporting Information*

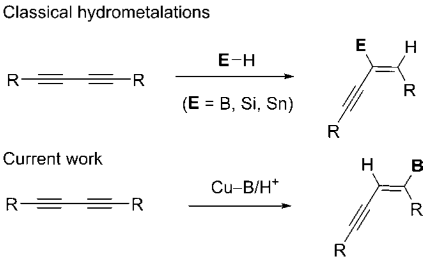
ABSTRACT: A mild copper-catalyzed regio- and stereoselective monoborylation of conjugated diynes with bis(pinacolato)diboron that affords enynylboronates is reported. The reaction is efficient for different types of conjugated diynes including unsymmetrical diynes and produces enynylboron compounds with high and complementary regioselectivity compared with classical hydrometalation reactions. In particular, the reactions of internal conjugated diynes with a silyl substitution produced highly functionalized enynes with high regio- and stereoselectivity, which can be used in further transformations.



Organoboron compounds are versatile reagents, and vinylboronates represent especially useful reagents in synthetic organic chemistry, as evidenced by their use in transition-metal catalyzed cross-coupling reactions.[1] Hydroboration of alkynes is one of the most convenient and straightforward methods of producing a variety of vinylboronates.[2,3] However, control of regio- and stereochemistry is a frequent obstacle faced in hydroboration.

Organic molecules with extended π-conjugation have garnered much attention due to their wide application as important building blocks for designing nanostructures, polymer synthesis, and organic synthesis.[4] In this context, the development of efficient methods for the synthesis of enynylboronates with high regio- and stereoselectivity is of considerable importance. While the hydroboration of monoynes has been widely studied, reports on the hydroboration of conjugated diynes are scarce.[5] Indeed, there has been only one study by Polston et al. on the selective hydroboration of conjugated diynes with dialkylboranes as a hydroborating reagent.[5a] In the report, the monohydroboration of symmetrically alkyl-substituted diynes with disiamylborane afforded enynes with boron in the internal positions of the diyne system which are less sterically hindered positions (Scheme 1). Other related hydrometalation processes such as hydrosilylation[6] and hydrostannation[7] offered similar regioselectivities with the metallic moiety (**E**) in internal positions. Therefore, development of synthetic methods displaying complementary regioselectivity to existing methods is valuable.

Scheme 1. Regioselectivity in Hydrometalations



We have previously shown that catalytic borylcupration (Cu–B) to C–C multiple bonds and protonolysis by methanol can produce hydroborylated products.[8] In contrast to copper-catalyzed borylation of monoynes,[9] the selective reaction of diynes has not yet been reported.[10] Indeed, selective monoborylation of diynes is quite challenging because the borylenyne products still possess reactive π-conjugated C–C multiple bonds in the presence of the nucleophilic Cu–B catalyst, in contrast to other π-conjugated starting substrates.[10] Herein, we present our results on the monoborylation of conjugated diynes to produce enynylboron compounds with the boron at the end position of various diynes.

We initially investigated the reaction of 1,4-diphenylbutadiyne (**1a**) as a model substrate under various reaction conditions (Table 1). The reaction was optimized by the combination of a catalytic copper chloride, NaO*t*-Bu, and P(*p*-tol)$_3$ in THF at 11 °C. The reaction yielded a high conversion in 3 h and afforded the monoborylated product **2a** as the major product (entry 1).[11] The structure of **2a** was confirmed by derivatizing it to the known structure,[12] and the regioselectivity was found to be complementary to the conventional hydroboration reaction,[5] with the boron in external positions of the diyne system. Reactions using the weaker electron-donating P(OEt)$_3$ or PPh$_3$ ligands resulted in a decreased yield or longer reaction time (entries 2 and 3). Use of a bidentate ligand or other bases was not beneficial to the reaction (entries 4 and 5). Controlling the amount or concentration of the diboron reagent or the temperature was not effective in increasing the efficiency of the reaction (entries 6–8).

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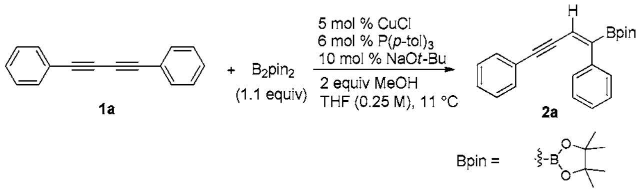
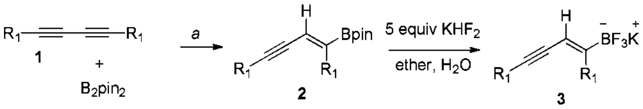
Table 1. Screening under Various Conditions

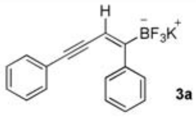
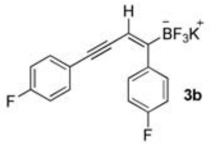
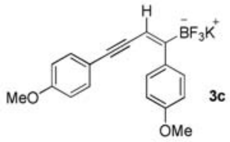
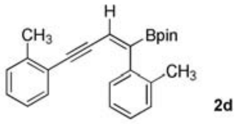
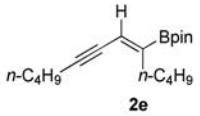
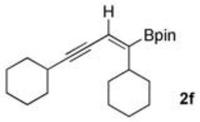
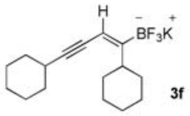
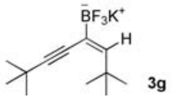


entry	condition change	time (h)	conv (%)[a]	NMR yield (%)[b]
1	no change	3	95	83 (70)[c]
2	$P(OEt)_3$	3.5	93	61
3	PPh_3	9	92	84
4	Xantphos[d]	24	–	64
5	LiO*t*-Bu	24	–	35
6	1.0 equiv of B_2pin_2	3	86	68
7	0.125 M THF	8	95	78
8	0 °C	6	93	70

[a] Determined by GC analysis with an internal standard based on consumption of **1a**. [b] NMR yield was determined using DMF as an internal standard. [c] Isolated yield was obtained by column chromatography at low temperature (0 °C). [d] Xantphos = 9,9′-dimethyl-4,5-bis(diphenylphosphino)xanthene.

Table 2. Regioselective Monoborylation of Symmetrical Conjugated Diynes[a]



entry	substrate (**1**)	product (**2** or **3**)	yield (%)[b]
1	**1a**; R_1 = Ph		76
2[c]	**1b**; R_1 = 4-FC_6H_4		74
3[d]	**1c**; R_1 = 4-$MeOC_6H_4$		70
4	**1d**; R_1 = 2-$CH_3C_6H_4$		72
5[e]	**1e**; R_1 = *n*-C_4H_9		83
6[d]	**1f**; R_1 = Cyclohexyl		70
7	**1f**		75
8[d]	**1g**; R_1 = *t*-Bu		68

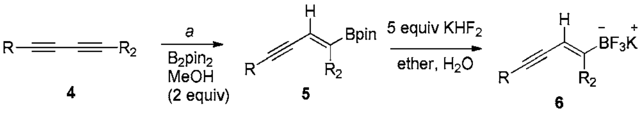
[a] The reaction was conducted with the combination of 5 mol % CuCl, 6 mol % $P(p\text{-tol})_3$, 10 mol % NaO*t*-Bu, and 2 equiv of MeOH in THF at 11 °C for 2–4 h. [b] Isolated yield of **2** or **3**. See Supporting Information for details [c] PPh_3 was used. [d] $P(OEt)_3$ ligand was used at room temperature. [e] Reaction was performed at room temperature.

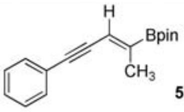
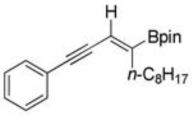
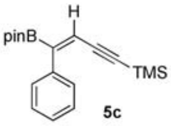
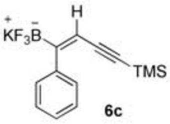
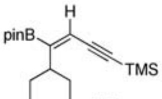
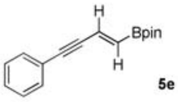
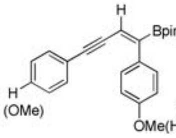
We next investigated the reaction of symmetrical diynes[13] with various aryl or alkyl substituents (Table 2). Gratifyingly, the reaction with the diynes afforded the desired monoborylated enyne products without the other regioisomer.[14] The B-substituted enyne products were isolated in good yields as the Bpin derivatives (**2**) or the corresponding and more stable trifluoroborate salts (**3**). Diyne substrates with electron-withdrawing or -donating aryl substituents were suitable substrates for the reaction (entries 2 and 3). The more sterically hindered *o*-tolyl-substituted diyne (**1d**) also afforded the product in good yield (entry 4). The reaction of electron-rich diynes with alkyl or electron-donating aryl substituents proceeded well with $P(OEt)_3$ as the ligand at room temperature. Primary (**1e**) and secondary (**1f**) alkyl-substituted diynes reacted smoothly to give the desired products with the boron in the external position, but the tertiary alkyl-substituted diyne (**1g**) afforded the product **3g** with the opposite regioselectivity (entries 5–8).[15] The results indicated that severe steric bulkiness of the *tert*-butyl group of diynes could alter the regioselectivity of the current catalytic reaction.

We further investigated the monoborylation of unsymmetrically substituted conjugated diynes, the results of which are shown in Table 3. Surprisingly, the reaction of 1-phenyl-1,3-pentadiyne (**4a**) afforded **5a** with excellent regioselectivity with the boron at the external position close to the methyl group (Table 3, entry 1). The reaction of primary alkyl-substituted diyne **4b** gave product **5b** with the same type of regioselectivity as that of **4a** (entry 2). In contrast to the aryl-substituted conjugated diynes (**4a** and **4b**), silyl-substituted diynes (**4c** and **4d**) showed an alternative regioselectivity in which the boron was attached at the external carbon positioned away from the silyl group via regioselective borylcupration to the more electrophilic triple bond (entries 3–5).[16] These results indicate that the silyl group acted as a strong directing group. In all of these examples, the boron addition occurred at the external positions with excellent regioselectivity with no observation of the other regioisomers. Finally, other diyne substrates such as terminal or electronically different aryl-substituted diynes were investigated. The terminal diyne **4e** gave the monoborylation product in good yield without significant formation of the diborylated compound (entry 6). However, diyne **4f** with different aryl substituents resulted in poor regioselectivity and produced both regioisomeric products in a 1:1 ratio[17] (entry 7), which indicated no strong directing bias between the two aryl groups.

Synthetic applications of boron-substituted enynes were carried out to illustrate their usefulness in organic synthesis (Scheme 2). Palladium-catalyzed cross-coupling of borylenynes (**2a** and **5a**) with iodobenzene gave the corresponding enynes[12,18] in good yields. Protonolysis of **3a** gave an 86% yield of the corresponding *cis*-enyne **9**. Selective desilylation of **6c** was possible to yield **10** with a terminal alkynyl group, which

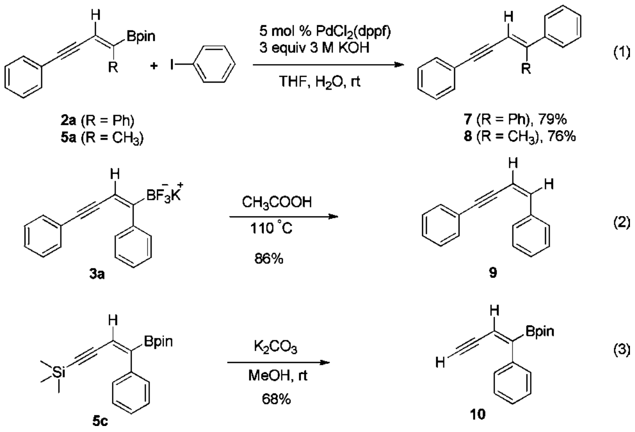
Table 3. Monoborylation of Unsymmetrical Conjugated Diynes[a]



entry	substrate (4)	product (5 or 6)	yield (%)[b]
1	**4a**; R = Ph, R_2 = CH_3	 **5a**	87
2	**4b**; R = Ph, $R_2 = n\text{-}C_8H_{17}$	 **5b**	71
3	**4c**; R = Ph, $R_2 = Si(CH_3)_3$	 **5c**	75
4	**4c**	 **6c**	82
5	**4d**; R = Cy, $R_2 = Si(CH_3)_3$	 **5d**	84
6	**4e**; R = Ph, R_2 = H	 **5e**	85
7	**4f**; R = Ph, R_2 = 4-$MeOC_6H_4$	 **5f** + **5f'** = 1:1	72[c]

[a] The reaction was conducted with the combination of 5 mol % CuCl, 6 mol % $P(OEt)_3$, and 10 mol % NaO*t*-Bu in THF at 11 °C or room temperature for 2−6 h. [b] Isolated yield of **5** or **6**. [c] Isolated yield of a mixture of **6f** and **6f'**.

Scheme 2. Derivatization of Boron-Substituted Enynes



showed a complementary regioselectivity to that of **5e**, obtained from the monoborylation of the terminal diyne (Table 3, entry 6).

In summary, we have developed a copper-catalyzed regio- and stereoselective monoborylation of conjugated diyne compounds that affords boron-containing enynes. The reaction is efficient for different types of conjugated diynes including unsymmetrical diynes. The regioselectivity obtained was complementary to that of classical hydrometalation reactions, with the boron moiety at the external carbons of conjugated diynes. In particular, the reactions of silyl-substituted conjugated diynes produced highly functionalized enynes with high regio- and stereoselectivity, which can be used in further transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization of products and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) A crude reaction mixture was analyzed by NMR spectroscopy for detection of regioisomers.

(15) The structures of **2e** and **2f** were confirmed by NMR coupling constants of the vinylic protons demonstrating allylic coupling as opposed to vicinal coupling. The structure of **3g** was confirmed by comparing its vinylic proton with that of the corresponding trifluoroborate salt obtained by hydroboration as in ref 5 and KHF_2 treatment.

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(17) The ratio (1:1) was determined by ^1H NMR analysis of a crude reaction mixture of **5f** and **5f′**. The crude mixture was treated with KHF_2, and isolation of **6f** and **6f′** afforded a regioisomeric mixture of 67:33 in 72% yield.

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