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Regioselective synthesis of highly functionalized alkenylboronates by Cu-catalyzed borylation of propargylic silylalkynes

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High regioselectivity was achieved in the Cu(I)-catalyzed borylation of internal propargylic alkynes with a silyl substituent to afford mutifunctionalized alkenylboron compounds. While both the silyl and propargylic substituents are known to act as a directing group, a *N*-heterocyclic carbene (NHC)–Cu complex furnished β-vinylboronate products (relative to Si) with high selectivity.

The development of catalytically selective methods efficiently producing multifunctional compounds is of great importance in organic synthesis. Alkenylboronate compounds containing C–B bonds are especially useful intermediates in the synthesis because of their diverse applications in catalytic cross coupling reactions.[1] While controlling the regioselectivity is a challenge for selective functionalization of alkynes via hydrometallation,[2] the regioselective borylation of alkynes by catalytic Cu–B species[3] has recently attracted significant attention since its first development with bis(pinacolato)diboron (B_2pin_2) and methanol.[4] The ligand-controlled, copper-catalyzed borylation of alkynes has greatly advanced, demonstrating its applicability to diverse alkyne substrates including terminal and internal alkynes.[5,6]

In general, the control of the regioselectivity of internal alkynes in the copper-catalyzed borylation has been directed by electronic control rather than steric control by the functional substituents of the substrate,[6] except for the cases of severe steric interactions between catalyst and substrates (Scheme 1). For example, the borylation of internal propargyl alkynes with alkyl substituents was reported to show high β-regioselectivity relative to the propargyl moiety with either copper-PCy_3 complex[7] or a NHC–Cu catalyst (SIMes–Cu).[8] With the use of even bulkier 6-NHC–Cu catalyst, however, McQuade and coworkers reported the site-selectivity reversal from β to α in the borylation of internal propargylic alkynes.[8] Recently, silyl groups were also reported to act as a directing group of boron to the β-carbon (from the Si group) of internal silylalkynes, driven by electronic effect.[9]

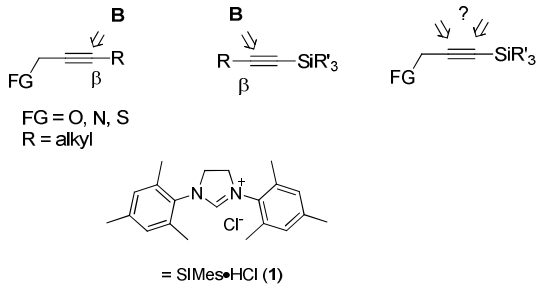


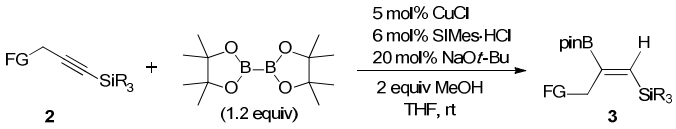
Figure 1 Regioselective positions for functionalized alkynes.

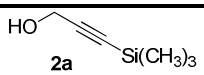
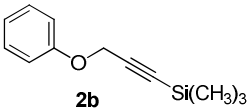
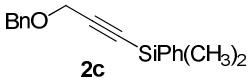
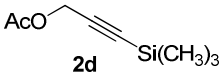
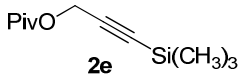
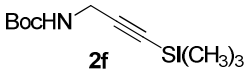
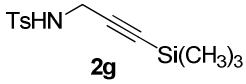
The highly regioselective copper-catalyzed borylations have been investigated dominantly with the substrates having one directing group so far,[5] because of the possible complex formation of regioisomeric mixtures. Therefore, we became interested in developing highly regiocontrolled borylation reaction for substrates with competing directing substituents, which would enable the efficient synthesis of highly functionalized alkenylboron compounds. Functionalized silylalkynes have not been investigated in the copper-catalyzed borylation,[10] while directing effect of a silyl group has been reported in the copper-catalyzed reaction of silyl-substituted allylic carbonates with a diboron reagent.[11] Herein, we report a highly regio- and stereoselective synthesis of trisubstituted and mutifunctionalized alkenylboronates via the copper-catalyzed borylation of internal propargylic silylalkynes.

We began our investigation with linear propargyl alcohol derivatives with a silyl substituent at the other end using a catalytic combination of CuCl, SIMes•HCl (**1**) and NaO*t*-Bu in the presence of B_2pin_2 (1.2 equiv) and MeOH (2 equiv) (Table 1). We were delighted to find that the regio- and stereoselective boron addition to the propargyl alcohol **2a** took place, furnishing the product **3a** in good yield with selectivity of β from the Si group and α from the propargyl functionality. The other regioisomer was not detected by ^{1}H NMR analysis of the crude reaction mixture

(entry 1). Propargyl ethers (**2b** and **2c**) and esters (**2d** and **2e**) afforded the β-addition products in good yields and with excellent regioselectivities (entries 2–5). The protected propargyl amines **2f** and **2g** were also found to be suitable substrates, regioselectively affording the β-addition products (entries 6 and 7). These results indicate that the directing effect of silyl group[9] on the regioselectivity is greater than the propargylic substituents, and that the group could be utilized as versatile directing and transforming functionality in the borylation. However, the unprotected propargyl amine and sulfide-substituted silylalkynes were found to be inefficient substrates, affording very low conversions.[12] Regarding the Si group, trimethylsilyl or dimethylphenylsilyl group were tolerated and high conversions were observed.

Table 1 Borylation of primary propargylic silylalkynes.

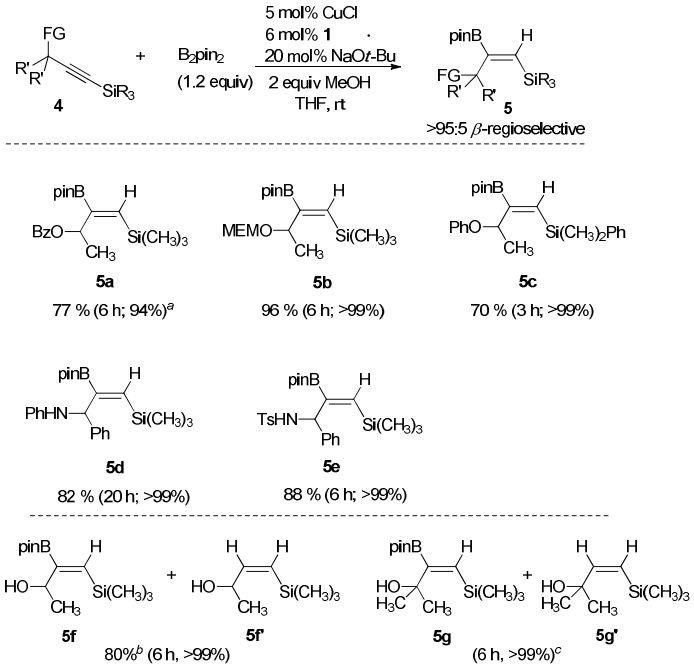


Entry	Substrate (**2**)	Time (h)	Product (**3**)	Yield (%)[a]
1[b]	 **2a**	3	**3a**	79
2	 **2b**	3	**3b**	61
3	 **2c**	6	**3c**	72
4	 **2d**	6	**3d**	85
5[c]	 **2e**	6	**3e**	82
6	 **2f**	12	**3f**	71
7	 **2g**	6	**3g**	60

[a] Isolated yield. [b] 1.5 mol% CuCl was used. [c] 95% conversion was obtained by GC analysis.

We then investigated the size effect of the propargylic moiety of silylalkynes on the reactivity and regioselectivity under the optimized catalytic conditions (Scheme 2). Fortunately, the steric bulk of the propargylic moiety did not significantly affect the reactivity and regioselectivity, broadening the substrate scope of the reaction catalyzed by **1**. Branched propargyl ester **4a** and propargyl ethers (**4b** and **4c**) afforded the addition products with high β-regioselectivity and in good yields. The reaction of propargyl amine **4d** required a longer reaction time for completion, but the desired product **5d** was obtained in high yield. Tosyl-protected amine **4e** also afforded the product in good yield.

The reaction of **4f** bearing a secondary alcohol moiety proceeded well, but the desired product **5f** was obtained along with deboronated product **5f'**. Other unprotected alcohol substrates with different substituent patterns produced deboronated products similar to **4f**.[13] Next, we increased the steric bulk of the propargylic moiety to tertiary alcohol **4g**. Again, the reaction proceeded smoothly, but the corresponding deboronated product **5g'** was obtained as the major isomer. Deboronation from the resulting alkenylboronates obtained by the borylation of silylalkynes with secondary or tertiary free OH group was facile and could not be completely controlled under our reaction conditions.[14]



[a] Reaction times and conversions are shown in the parentheses. [b] Isolated yield of a mixture (80:20) of **5f** and deboronated product **5f'**. [c] **5g**:**5g'** = 30:70 by ^{1}H NMR.

Scheme 2 β-Regioselective borylation of branched propargylic silylalkynes.

In summary, we developed a highly regio- and stereoselective synthesis of mutifunctionalized alkenylboronates by the copper-catalyzed borylation of internal propargylic silylalkynes. The β-addition products (relative to Si) were obtained with high regioselectivity using a NHC-Cu catalyst at room temperature. This reaction protocol uses inexpensive copper to afford a convenient and selective approach to multifunctionalized trisubstituted alkenes. Currently, synthetic applications of the multifunctionalized alkenylboron compounds and methods for the construction of tetrasubstituted alkenes are being investigated in our laboratory.

General procedure for the borylation of propargylic silylalkynes: to a Schlenk tube equipped with a stir bar were added CuCl (2.5 mg, 0.025 mmol), NaO*t*-Bu (9.6 mg, 0.10 mmol), 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (10.2 mg, 0.03 mmol) and THF (0.50 mL) under nitrogen. After the

mixture was stirred at room temperature for 15 min, bis(pinacolato)diboron (153 mg, 0.60 mmol) in THF (0.50 mL) was added. The reaction mixture was stirred for 10 min. Then, alkyne (**2** or **4**) (0.50 mmol) was added, followed by MeOH (0.04 mL, 1 mmol). The reaction was washed with THF (0.50 mL), sealed, and stirred until no starting material was detected by TLC and GC. The reaction mixture was filtered through a pad of Celite and concentrated. The product was purified by silica gel chromatography.

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† Electronic Supplementary Information (ESI) available: Experimental details and full characterization of compounds. See DOI: 10.1039/c000000x/

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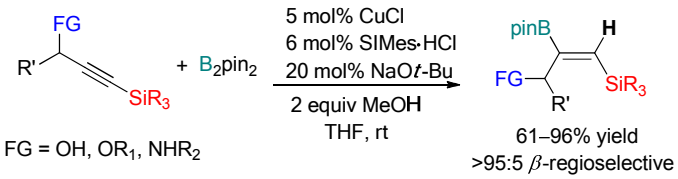

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