Organic LETTERS

Silicon-Tethered Strategy for Copper(I)-Catalyzed Stereo- and Regioselective Alkylboration of Alkynes

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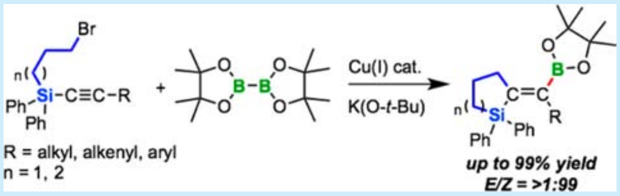
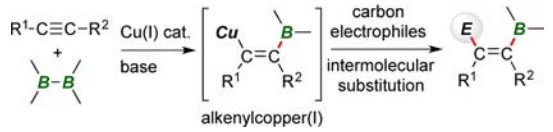
Ⓢ *Supporting Information*

ABSTRACT: Stereoselective silicon-tethered alkylboration of alkynes in the presence of a copper(I) catalyst and a diboron reagent provided the corresponding cyclic alkenylboronates in high yields (up to 99% yield) with excellent regio- and *syn*-selectivities (E/Z = <1:99). The products, which can be considered as the formal alkyne intermolecular alkylboration products, undergo subsequent selective derivatization, including ring opening, to give functionalized *trans*-stilbene derivatives.



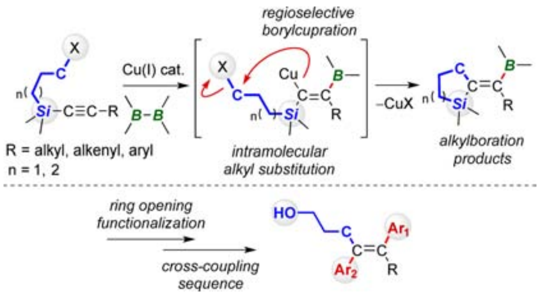
Alkenylboronates are useful and versatile intermediates for the synthesis of multisubstituted alkenes because they undergo stereospecific C−C bond forming reactions.[1−3] In recent years, much effort has been devoted to the development of efficient methods for boryl addition across alkynes.[4−9] Copper(I)-catalyzed carboboration of alkynes is a particularly useful method for the preparation of multisubstituted alkenylboron compounds.[10−13] In this procedure, the alkenylcopper(I) intermediate generated by addition of a borylcopper(I) species to an alkyne subsequently reacts with a carbon electrophile (Scheme 1). However, this method has some limitations: reactions using unactivated alkyl electrophiles required long reaction times (up to 51 h), and the yields were moderate (36−60%).[10b] This is probably because of the low reactivity of such electrophiles in substitutions by an alkenylcopper(I) nucleophile. Furthermore, the regioselectivity of borylcupration to C−C triple bonds was poor in reactions with unsymmetrical diaryl and aliphatic alkynes, so this process is not widely applicable.[10]

Scheme 1. Copper(I)-Catalyzed 1,2-Carboboration of Alkynes



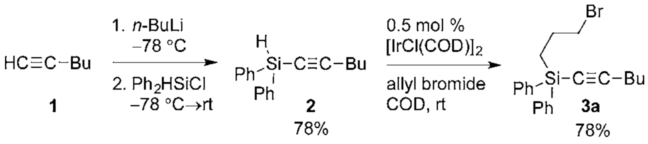
To achieve highly reactive and regioselective alkylboration of alkynes, we designed a silicon-tethered carboboration reaction (Scheme 2).[14] This novel strategy has the following advantages. The low reactivity of unactivated alkyl electrophile substitution by alkenylcopper(I) can be improved by changing from an intermolecular to an intramolecular reaction mode.[15,16] Moreover, the regioselectivity of the addition of the borylcopper(I) intermediate to the alkyne moiety can be controlled by the electronic effect of a silyl group.[9g] The products in this strategy can be considered as formal alkyne intermolecular alkylboration products, which undergo subsequent selective derivatization, including ring opening via tethered Si−C bond cleavage, to give functionalized multisubstituted alkenes.

Scheme 2. Copper(I)-Catalyzed Formal Alkyne Intermolecular Alkylboration Using Silicon-Tethered Strategy



We initially focused on the efficient preparation of silicon-tethered alkyne derivatives. The desired silicon-tethered alkynes **3a** can be easily synthesized in three steps through iridium-catalyzed regioselective hydrosilylation of an allyl bromide with an alkynylhydrosilane **2**, derived from terminal alkyne **1**, as recently reported by Rahaim and co-workers (Scheme 3).[17]

Scheme 3. Preparation of Silicon-Tethered Alkyne 3a



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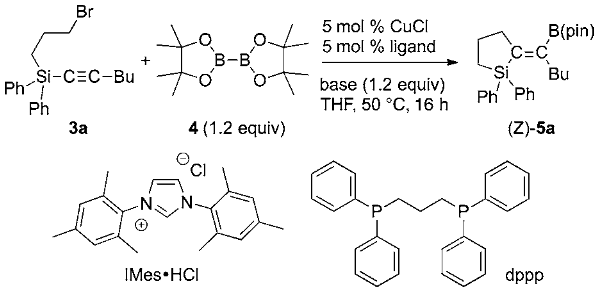
With an efficient route for the synthesis of silylalkyne **3a** in hand, we then investigated the intramolecular alkylboration in the presence of a CuCl/phosphine ligand complex catalyst (5 mol %), bis(pinacolato)diboron **4** (1.2 equiv), and a stoichiometric amount of K(O-*t*-Bu) base (1.2 equiv) in THF at 50 °C (Table 1). Phosphine ligand screening (entries 1–6, Table 1) showed that the reaction using dppp as the ligand afforded the desired cyclic alkenylboronate (*Z*)-**5a** in high yield with perfect regioselectivity and excellent *syn* selectivity (93%, *E*/*Z* = <1:99, entry 4, Table 1). We found that the reaction using electron-donating *N*-heterocyclic carbene ligands also provided the desired product (*Z*)-**5a** (entries 7–10, Table 1). The IMes (IMes·HCl: 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride) ligand gave the best result (99%, *E*/*Z* = <1:99, entry 7, Table 1). We then investigated the base effects, using a CuCl/IMes complex catalyst system (entries 11–13, Table 1). The use of other alkoxide bases such as Na(O-*t*-Bu) and NaOMe instead of K(O-*t*-Bu) did not affect the product yield or stereoselectivity, and gave good results (98% and 95%, *E*/*Z* = <1:99, entries 11 and 12, Table 1, respectively). The weaker base KOAc gave a lower yield (entry 13). The reaction using toluene as the solvent also gave good results (95%, *E*/*Z* = <1:99, entry 14, Table 1).

Table 1. Copper(I)-Catalyzed Alkylboration of Silicon-Tethered Alkynes under Various Conditions[a]

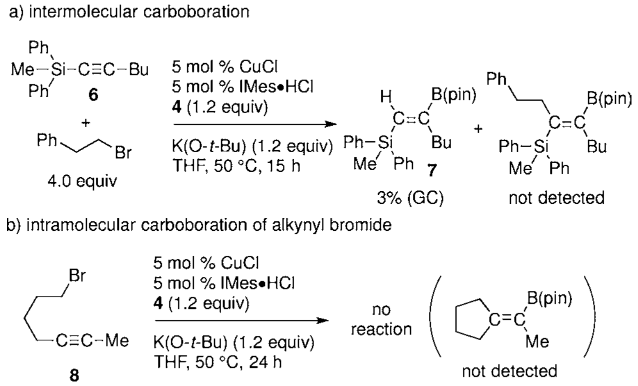


entry	ligand	base	E/Z^{b}	yield (%)[c]
1	PPh_3	K(O-*t*-Bu)	<1:99	61
2	dppe	K(O-*t*-Bu)	<1:99	18
3	dppp	K(O-*t*-Bu)	<1:99	93
4	dppb	K(O-*t*-Bu)	<1:99	27
5	dppf	K(O-*t*-Bu)	<1:99	14
6	Xantphos	K(O-*t*-Bu)	<1:99	72
7[d]	IMes·HCl	K(O-*t*-Bu)	<1:99	99
8[e]	SIMes·HCl	K(O-*t*-Bu)	<1:99	94
9[f]	ICy·HCl	K(O-*t*-Bu)	<1:99	97
10[g]	IPr·HCl	K(O-*t*-Bu)	<1:99	34
11	IMes	Na(O-*t*-Bu)	<1:99	98
12	IMes	NaOMe	<1:99	95
13	IMes	KOAc	<1:99	54
14[h]	IMes	K(O-*t*-Bu)	<1:99	95

[a] Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **3a** (0.5 mmol), bis(pinacolato)diboron **4** (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL). [b] Determined by GC and NMR analysis. [c] Determined by GC analysis of the crude reaction mixture with an internal standard. [d] IMes·HCl: 1,3-bis(2,4,6-trimethylphenyl)-imidazolium chloride. [e] SIMes·HCl: 1,3-bis(2,4,6-trimethylphenyl)-imidazolinium chloride. [f] ICy·HCl: 1,3-dicylohexylimidazolium chloride. [g] IPr·HCl: 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride. [h] Toluene was used as a solvent instead of THF.

To confirm the effectiveness of the silicon-tethered strategy, inter- and intramolecular 1,2-carboboration reactions of non-silicon-tethered alkynes, using unactivated alkyl electrophiles, were investigated under the optimized conditions (Scheme 4).

Scheme 4. Attempted 1,2-Carboboration of Non-Silicon-Tethered Alkyne Substrates Using Unactivated Alkyl Bromides



The intermolecular carboboration of nontethered alkynylsilane **6**, using 2-phenylethyl bromide as an alkyl electrophile, did not provide a carboboration product, while the hydroboration product **7** was detected (3% GC yield) (Scheme 4a). This result indicates that the intermolecular halide substitution of alkenylcopper(I) derived from the insertion of borylcopper(I) to the alkyne is very slow (see Supporting Information, p S21). The intramolecular carboboration of alkynyl bromide **8** also failed to provide any alkylboration products (Scheme 4b). These results clearly show that the present silicon-tethered borylation strategy has a significant effect on the reactivity in the carboboration of alkynes using unactivated alkyl electrophiles.

Next, various silicon-tethered alkynes were subjected to the intramolecular alkylboration reaction in the presence of the CuCl/IMes complex catalyst system (Table 2). The reactions proceeded with complete *syn*-selectivities. Alkenylboronates bearing alkyl substituents [R = *n*-Bu (**5a**), CH_2CH_2Ph (**5b**), and CH_2Cy (**5c**)] were successfully obtained in good yields (92–98%) from the corresponding silicon-tethered alkynes (entries 1–3, Table 2). The reaction exhibited high functional group tolerance and afforded the corresponding alkylboration products containing silyl ether (**5d**), alkyl chloride (**5e**), acetal (**5f**), and ether (**5g**) moieties in high yields (entries 4–7, Table 2). The alkylborations of aromatic alkynes also proceeded to provide the products **5h** and **5i** with high regioselectivities in the presence of a CuCl/dppp catalyst (entries 8 and 9, Table 2). Furthermore, we found that this catalytic system was also effective for the synthesis of the six-membered ring product (*Z*)-**10** from the corresponding silicon-tethered alkyne **9** (entry 10, Table 2).

π-Conjugated systems are challenging substrates for borylation reactions, because of multiborylation, and regio- and stereoselectivity problems.[18] We found that the reaction of **3j** under the optimized conditions produced the desired 2-boryl-1,3-butadiene (*Z*)-**5j** in good yield, with perfect regioselectivity, and without any side products such as diborylated compounds (Scheme 5). The Diels–Alder reaction of (*Z*)-**5j** with maleimide gave the desired cycloaddition product **11** as a single isomer in good yield (79%). The structure of **11** was confirmed by single-crystal X-ray crystallography and NOE experiments.[19]

The obtained cyclic alkenylboronates can be considered as the formal alkyne intermolecular alkylboration products, because they undergo ring opening of the cyclic silicon functional group

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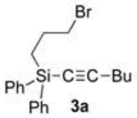
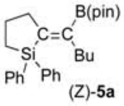
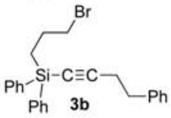
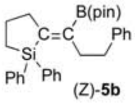
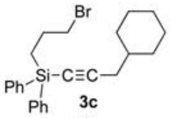
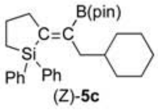
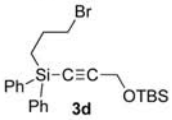
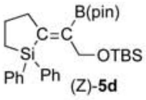
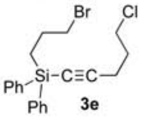
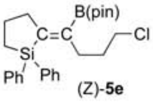
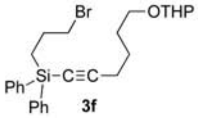
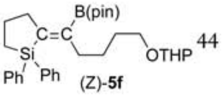
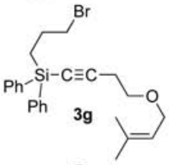
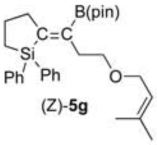
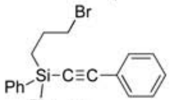
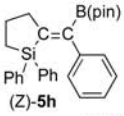
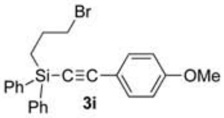
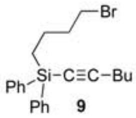
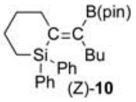
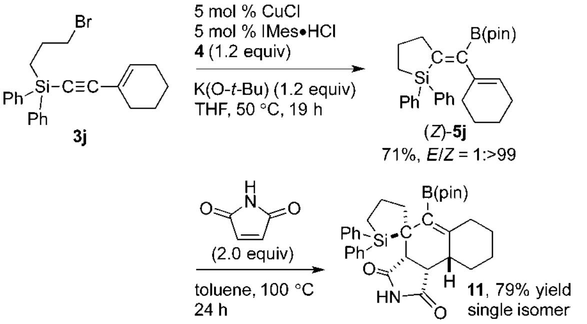
Table 2. Substrate Scope for Intramolecular Alkylboration of Silicon-Tethered Alkynes[a]

entry	substrate	product	time (h)	yield (%)[b]
1	 3a	 (Z)-5a	16	92
2	 3b	 (Z)-5b	19	93
3	 3c	 (Z)-5c	18	98
4	 3d	 (Z)-5d	17	86
5	 3e	 (Z)-5e	15	80
6[c]	 3f	 (Z)-5f	44	79
7	 3g	 (Z)-5g	23	89
8[d]	 3h	 (Z)-5h	12	67
9[d]	 3i	 (Z)-5i	29	75
10	 9	 (Z)-10	44	42

[a] Conditions: CuCl (0.025 mmol), IMes/HCl (0.025 mmol), **3** (0.5 mmol), **4** (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL). [b] Isolated yield. [c] THP: 2-Tetrahydropyranyl group. [d] dppp was used instead of IMes ligand and reaction temperature was 40 °C.

Scheme 5. Alkylboration of Conjugated Enyne 3j and Subsequent Diels–Alder Reaction

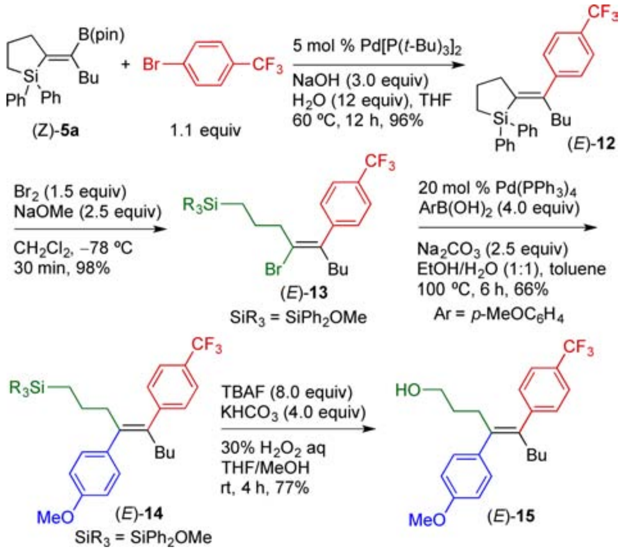


3j

(*Z*)-**5j**
71%, *E*/*Z* = 1:>99

11, 79% yield
single isomer

Scheme 6. Selective Transformation of Silicon-Tethered Alkylboration Product



(*Z*)-**5a**

(*E*)-**12**

(*E*)-**13**

(*E*)-**14**

(*E*)-**15**

(Scheme 6). The Suzuki–Miyaura cross-coupling reaction of alkylboration product (*Z*)-**5a** with 1-bromo-4-trifluoromethylbenzene proceeded in the presence of the Pd[P(*t*-Bu)$_3$]$_2$ catalyst to give the arylation product (*E*)-**12** in high yield (96%). Treatment with bromine and NaOMe cleaved the Si–C bond to produce the alkenyl bromide (*E*)-**13**, with retention of the stereochemistry.[20] Subsequent Suzuki–Miyaura cross-coupling of (*E*)-**13** afforded the *trans*-stilbene (*E*)-**14** with complete stereospecificity. Furthermore, the resulting silyl ether (*E*)-**14** was converted to the corresponding alcohol (*E*)-**15** via Tamao oxidation using H_2O_2 and tetra-*n*-butylammonium fluoride (TBAF).

A proposed reaction mechanism for the intramolecular alkylboration is shown in Figure 1. First, Cu(O-*t*-Bu) **A**, generated via the reaction between CuCl and K(O-*t*-Bu) base, reacts with a diboron compound to form the borylcopper(I) active species **B**. Subsequent regioselective insertion of **B** into silylalkyne **3** affords the alkenylcopper(I) intermediate **C**, which would be stabilized by the electronic effect of the silyl group,[9g]

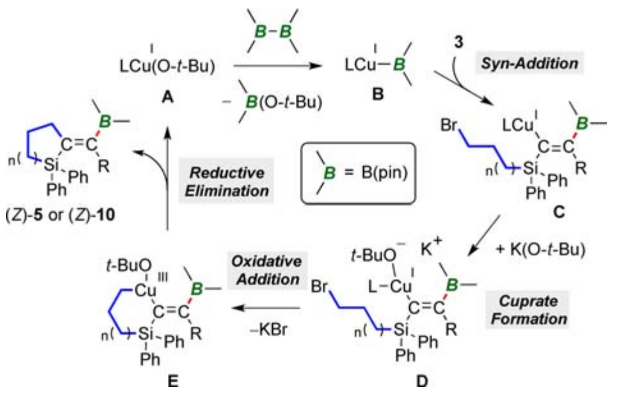


Figure 1. Proposed reaction mechanism.

followed by formation of an ate complex **D** through coordination of the alkoxide to the copper center. Oxidative addition and elimination of the bromide moiety then produce the cyclic copper(III) intermediate **E**, in a manner similar to the nucleophilic substitution of alkyl electrophiles by cuprates. Finally, reductive elimination generates the intramolecular alkylboration products (*Z*)-**5** ($n = 1$) or (*Z*)-**10** ($n = 2$) and Cu(O-*t*-Bu) **A**.

In summary, we have developed a novel strategy for the copper(I)-catalyzed carboboration of alkynes using unactivated alkyl electrophiles, based on a silicon-tethered reaction. The alkylboration of silicon-tethered alkynes gave excellent yields (up to 99%) with high regioselectivities and complete *syn* selectivities ($E/Z = <1{:}99$), even in the presence of various functional groups. The low reactivity of unactivated alkyl electrophile substitution by an alkenylcopper(I) intermediate was improved by changing from an intermolecular to an intramolecular reaction mode through silicon tethering. The products can be considered as formal alkyne intermolecular alkylboration products, which undergo subsequent selective derivatization, including ring opening via tethered Si−C bond cleavage, to give the functionalized *trans*-stilbene derivatives. The synthesis of products with various ring sizes and functional groups will be investigated; we believe that this will increase the use of silicon-tethered alkylboration reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. 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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