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Copper-Catalyzed Synthesis of Tetrasubstituted Alkenes via Regio- and *anti*-Selective Addition of Silylboronates to Internal Alkynes

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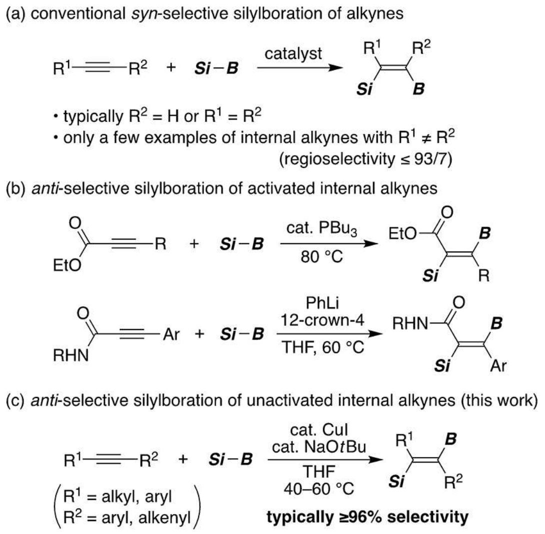
Abstract: As a new and complementary method for the synthesis of structurally defined tetrasubstituted alkenes, a copper-catalyzed regio- and *anti*-selective addition of silylboronates to unsymmetric internal alkynes has been developed. A variety of unactivated alkynes can be employed with high selectivity under simple and mild conditions, and the resulting products have been further functionalized by utilizing silyl and boryl groups on the alkene.

Alkenes constitute a fundamental structural component in various organic molecules and widely appear in biologically active compounds as well as functional organic materials. It is therefore highly important to develop efficient synthetic methods of alkenes with precise control of the regio- and stereochemistry. In particular, synthesis of tetrasubstituted alkenes can be quite challenging because of the steric congestion and the number of isomers that need to be distinguished when the substituents are different with one another.[1] Among the possible synthetic strategies to tetrasubstituted alkenes, 1,2-difunctionalization of internal alkynes is one of the most straightforward approaches, and addition of silylboronates would be highly attractive in view of the synthetic utility of silyl and boryl groups.[2] Indeed, silylboration of alkynes have been extensively investigated since pioneering work by Suginome, Nakamura, and Ito under palladium and platinum catalysis,[3a] and several effective catalyst systems have been developed to date.[3] However, most of the existing methods employ either terminal alkynes or symmetric internal alkynes as substrates, and silicon and boron are introduced *syn*-selectively across the C–C triple bond (Scheme 1a). With regard to the *anti*-selective addition of silylboronates to internal alkynes, only two approaches have been reported to date: a tributylphosphine-catalyzed addition to 3-substituted propiolates[4] and a PhLi/12-crown-4-mediated addition to 3-substituted propiolamides,[5] both of which require carbonyl substituted alkynes as substrates (Scheme 1b).[6] In this context, herein we describe a copper-catalyzed regio- and *anti*-selective addition of silylboronates to unactivated unsymmetric internal alkynes to give the corresponding tetrasubstituted alkenes under simple and mild conditions (Scheme 1c).



Scheme 1. Silylboration of alkynes for the synthesis of silicon- and boron-substituted alkenes.

Initially, we employed 1-phenyl-1-propyne (**1a**) as the substrate and conducted a reaction with silylboronate **2a** in the presence of CuI (10 mol%) and LiO*t*Bu (40 mol%) in THF at 40 °C (Table 1, entry 1). Under these conditions, silylboration product **3aa** was obtained in 81% yield with 96% selectivity *via* regio- and *anti*-selective addition.[7] We subsequently found that the use of NaO*t*Bu in place of LiO*t*Bu improved the selectivity to >99% in 79% yield (entry 2), but the use of KO*t*Bu led to a significant decrease of the yield while keeping the high selectivity (29% yield, >99% selectivity; entry 3). On the other hand, no reaction took place by using NaOMe (entry 4), and the reaction using NaO*t*Bu in the absence of CuI gave only 9% yield of the product with much lower selectivity (72% selectivity; entry 5). The present reaction also proceeded with similar efficiency and high regio- and *anti*-stereoselectivity by using several ligands for copper such as PPh_3, PCy_3, Xantphos, and IPr (entries 6–9), but no reaction occurred in the presence of Phen (entry 10).

Under the conditions in Table 1, entry 2, the scope of alkyl aryl alkynes **1** was found to be fairly broad in the addition of

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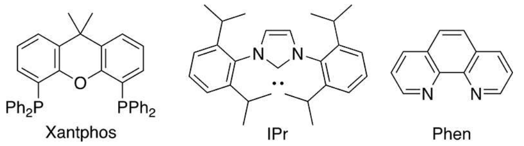
Table 1. Copper-catalyzed reaction of **1a** with **2a**: effect of base and ligand.

Entry	Ligand	MOR	Yield [%][a]	**3aa**/other isomers[a]
1	None	LiO*t*Bu	81	96/4
2	None	NaO*t*Bu	79	>99/1
3	None	KO*t*Bu	29	>99/1
4	None	NaOMe	0	–
5[b]	None	NaO*t*Bu	9	72/28
6	PPh_3	NaO*t*Bu	71	96/4
7	PCy_3	NaO*t*Bu	78	99/1
8	Xantphos[c]	NaO*t*Bu	75	>99/1
9	IPr[c,d]	NaO*t*Bu	75	99/1
10	Phen[c]	NaO*t*Bu	0	–

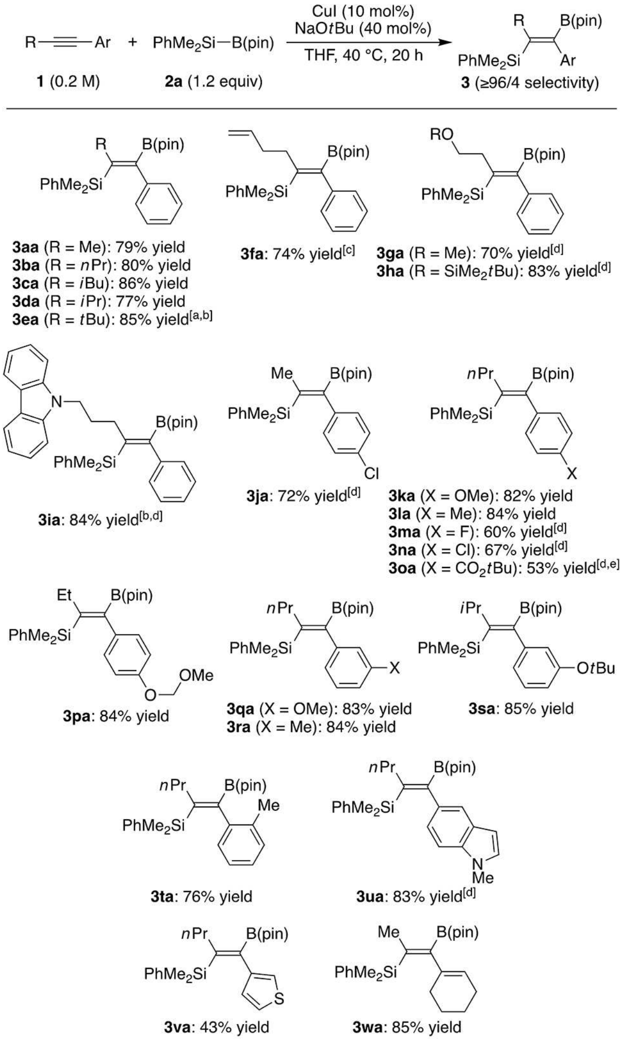


[a] Determined by ^{1}H NMR against internal standard (dimethyl terephthalate). [b] No CuI was used. [c] 10 mol% of ligand was used. [d] (IPr)CuCl was used instead of CuI/ligand.

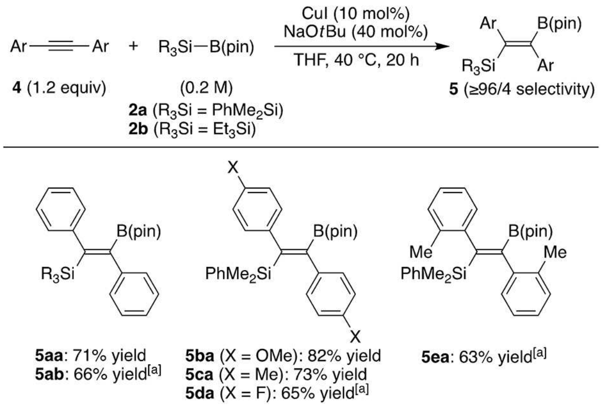
2a, giving products **3** with high regio- and *anti*-selectivity as summarized in Scheme 2 (typically ≥96% selectivity). For example, in addition to compound **3aa** having a methyl group, primary, secondary, and even tertiary alkyl group-substituted compounds **3ba**–**ea** could be synthesized in 77–86% yield with ≥94% selectivity. Several functional groups such as alkene, ether, silyl ether, and carbazole on the alkyl chain were tolerated as shown for the synthesis of compounds **3fa**–**ia**. Regarding the substituents on the aromatic rings, various groups including ether (**3ka**, **3qa**, **3sa**), halide (**3ja**,[8] **3ma**, **3na**), ester (**3oa**), and acetal (**3pa**) could be introduced at either *para*-, *meta*-, or *ortho*-position without affecting the regio- and *anti*-stereoselectivity. Heteroaryl groups as well as an alkenyl group could also be used in place of an aryl group to give the corresponding products **3ua**–**wa**[8] with similarly high selectivity.

The present *anti*-selective silylboration reaction is also applicable to symmetric diarylalkynes **4** as briefly examined in Scheme 3. In addition to (dimethylphenylsilyl)boronate **2a**, (triethylsilyl)boronate **2b** could be used for the reaction of diphenylacetylene (**4a**) to give the corresponding products **5aa**–**ab** with high selectivity.[9] Several substituted diphenylacetylenes including a sterically congested one underwent silylboration with **2a** to give compounds **5ba**–**ea** as well.[10]

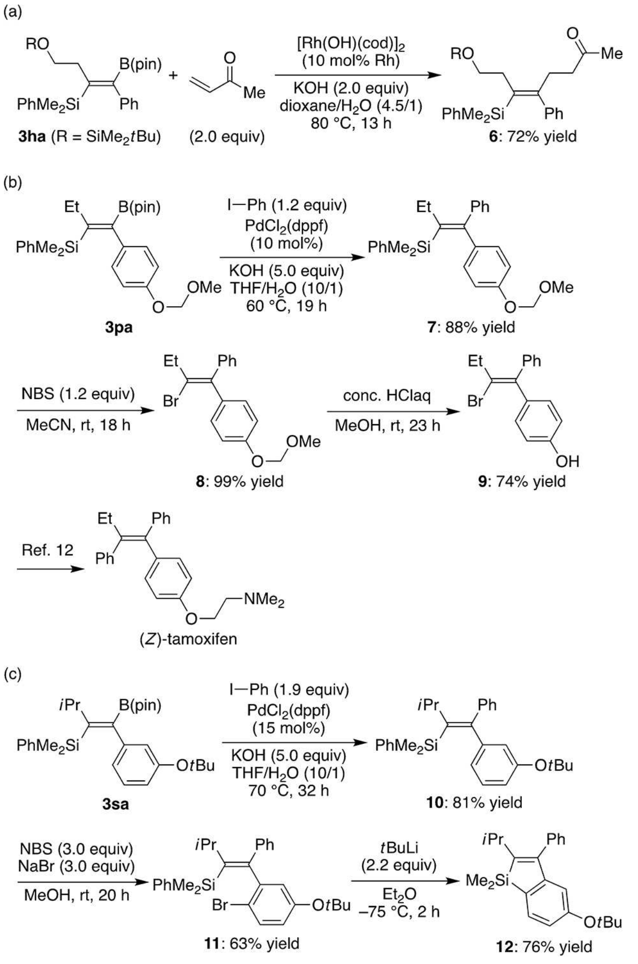
The tetrasubstituted alkenes obtained in the present catalysis can be further transformed into various other compounds by utilizing the silyl and/or boryl groups installed into the molecules. For example, alkylation of the alkenylboronate of **3ha** could be achieved by a rhodium-catalyzed 1,4-addition to a vinyl ketone to give stereochemically defined γ,δ-unsaturated ketone **6** in 72% yield (Scheme 4a).[11] In addition, Suzuki coupling of **3pa** with iodobenzene efficiently proceeded



Scheme 2. Scope of copper-catalyzed silylboration of unsymmetric internal alkynes. [a] The reaction was conducted using **2a** (2.0 equiv), CuI (20 mol%), and NaO*t*Bu (80 mol%) at 10 °C for 70 h. [b] Selectivity = 94/6. [c] Selectivity = 93/7. [d] The reaction was conducted at 60 °C. [e] The reaction was conducted using **1o** (1.2 equiv) and **2a** (1.0 equiv).



Scheme 3. Scope of copper-catalyzed silylboration of symmetric diarylalkynes. [a] The reaction was conducted at 60 °C.



Scheme 4. Functionalization of silylborated tetrasubstituted alkenes **3**.

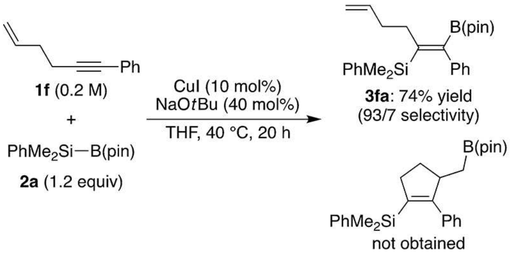
Table 2. Effect of the amount of base in the copper-catalyzed reaction of **1 a** with **2 a**.

Entry	x	Yield [%][a]	**3 aa**/other isomers[a]
1	0–30	0	–
2	40	79	>99/1
3	50	74	99/1
4	100	66	99/1
5	200	50	>99/1

[a] Determined by ^{1}H NMR against internal standard (dimethyl terephthalate).

to give alkenylsilane **7** and this could be readily transformed into the corresponding bromoalkene **8** by reacting it with *N*-bromosuccinimide (NBS) (Scheme 4b). Subsequent deprotection of the MOM group of **8** led to compound **9**, a known precursor for the synthesis of (*Z*)-tamoxifen.[12] On the other hand, similarly cross-coupled compound **10** obtained from **3 sa** having 3-*tert*-butoxyphenyl group preferentially underwent bromination on the aromatic ring, rather than desilylative bromination on the alkene, by the reaction with NBS/NaBr to give compound **11**,[13] and this could be converted to benzosilole **12** by treating it with *t*BuLi (Scheme 4c).

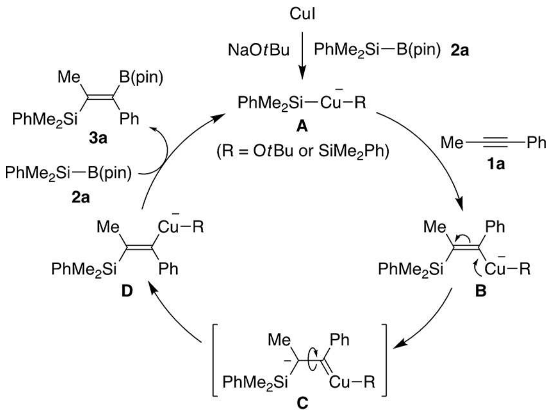
With regard to the mechanism of the present catalysis, although we do not have full understanding at this stage, the following observations have been made so far. The reaction of **1 f** having 3-buten-1-yl group on the alkyne with silylboronate **2 a** under the standard conditions gave the corresponding silylboration product **3 fa** with no formation of a cyclized product through a 5-*exo-trig* process, indicating that the present reaction does not involve a radical mechanism [Eq. (1)]. In addition, the amount of NaO*t*Bu used in the present catalysis showed a significant impact on the reaction outcome (Table 2). Thus, in the presence of 10 mol% of CuI, no reaction took place when the amount of NaO*t*Bu was 0–30 mol% (entry 1). In contrast, high yields of **3 aa** were realized with 40–50 mol% (entries 2 and 3), and the yield became gradually lower by further increasing the amount to 100–200 mol% (entries 4 and 5). Because alkoxides are known to displace halogens on copper(I) and can form cuprate complexes when an excess amount is used with respect to copper,[14] alkoxycuprates could be the key catalytically active species, considering that the amount of NaO*t*Bu needs to be sufficiently high ($\geq$40 mol%) to promote the present reaction. In addition, alkoxides are also known to coordinate to the boron of silylboronates[15] and the resulting species become less electrophilic at boron, which could lead to lower efficiency of the borylation process. This is probably why the yields become lower when a stoichiometric amount of NaO*t*Bu is used in the present reaction.



(1)

On the basis of the above information as well as the related literature reports on the *anti*-selective addition to alkynes under transition metal catalysis,[16] a possible catalytic cycle for the reaction of 1-phenyl-1-propyne (**1 a**) with silylboronate **2 a** is illustrated in Scheme 5.[2] Thus, the reaction of CuI, NaO*t*Bu, and **2 a** generates catalytically active silylcuprate species **A**. This then undergoes regioselective *syn*-insertion of alkyne **1 a** to give alkenylcuprate **B**, which presumably isomerizes to **D** *via* **C**. Subsequent transmetalation with **2 a** gives *anti*-addition product **3 aa** along with regeneration of **A**.[17] The isomerization from **B** to **D** would be facilitated by electron-rich cuprates and by α-carbanion stabilization effect of the silyl group.[18] Once **D** is formed, this could be more reactive toward borylation with **2 a** due to the electron-donating nature of the silyl group at the β-*anti*-position.[19]

In summary, we developed a copper-catalyzed regio- and *anti*-selective addition of silylboronates to unsymmetric internal alkynes to give the corresponding tetrasubstituted alkenes



Scheme 5. Possible catalytic cycle for the reaction of **1 a** with **2 a** to give **3 a**.

under simple and mild conditions. A variety of alkynes could be employed with high selectivity and the resulting products were further functionalized by utilizing silyl and boryl groups on the alkene, demonstrating the complementary nature of the present catalysis to the existing methods. Future studies will be directed toward further mechanistic understanding of the present catalysis including theoretical investigations as well as further development of new and efficient synthetic methods based on the present discovery.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: *anti*-addition · copper · regio-control · silylboration · tetrasubstituted alkenes

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