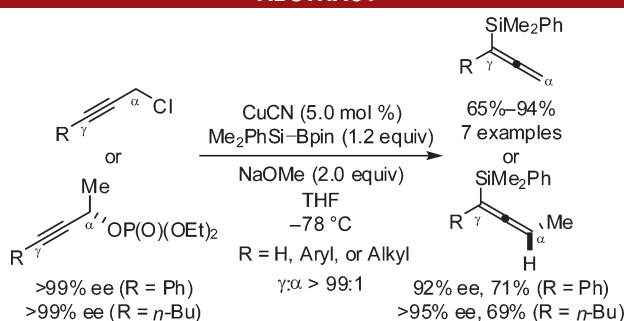


Copper(I)-Catalyzed Regioselective
Propargylic Substitution Involving Si–B
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ABSTRACT



The silicon nucleophile generated by copper(I)-catalyzed Si–B bond activation allows several γ -selective propargylic substitutions. The regioselectivity (γ : α ratio) is strongly dependent on the propargylic leaving group. Chloride is superior to oxygen leaving groups in linear substrates (γ : α > 99:1), and it is only the phosphate group that also shows promising regiocontrol (γ : α = 90:10). That leaving group produces superb γ -selectivity (γ : α > 99:1) in α -branched propargylic systems, and enantioenriched substrates react with excellent central-to-axial chirality transfer.

The ability of Rh–O and Cu–O complexes to activate interelement linkages through σ -bond metathesis is a facile entry into the chemistry of main group element nucleophiles.¹ The synthetic potential of both rhodium(I)-² and copper(I)-catalyzed³ transmetalations of the Si–B bond⁴

and subsequent C–Si bond-forming reactions are currently being actively explored. The copper(I) catalysis is particularly useful as an alternative method for the formation of silicon-based cuprates.⁵ We recently developed a γ -selective synthesis of branched allylic silanes from linear allylic chlorides using that copper(I)-catalyzed Si–B bond activation (γ : α $\geq$ 98:2).⁶ The excellent regiocontrol led us to consider the related propargylic substitution (**I** $\rightarrow$ γ -**II** but not α -**II**, Scheme 1). The Fleming group had accomplished the copper(I)-mediated (enantioselective) preparation of allenyl silanes from propargylic substrates with different leaving groups.⁷ The corresponding catalysis is not known,⁵ but there are reports of transition-metal-catalyzed

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(2) (a) Walter, C.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2006**, 45, 5675–5677. (b) Walter, C.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, 47, 3818–3820. (c) Walter, C.; Fröhlich, R.; Oestreich, M. *Tetrahedron* **2009**, 65, 5513–5520. (d) Hartmann, E.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, 49, 6195–6198.

(3) (a) Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, 132, 2898–2900. (b) Welle, A.; Petignat, J.; Tinant, B.; Wouters, J.; Riant, O. *Chem.–Eur. J.* **2010**, 16, 10980–10983. (c) Ibrahim, I.; Santoro, S.; Himo, F.; Córdova, A. *Adv. Synth. Catal.* **2011**, 353, 245–252. (d) Tobisu, M.; Fujihara, H.; Koh, K.; Chatani, N. *J. Org. Chem.* **2010**, 75, 4841–4847. (e) Wang, P.; Yeo, X.-L.; Loh, T. P. *J. Am. Chem. Soc.* **2011**, 133, 1254–1256. (f) Vyas, D. J.; Fröhlich, R.; Oestreich, M. *Org. Lett.* **2011**, 13, 2094–2097.

(4) For a recent summary of Si–B chemistry, see: Ohmura, T.; Sugimoto, M. *Bull. Chem. Soc. Jpn.* **2009**, 82, 29–49.

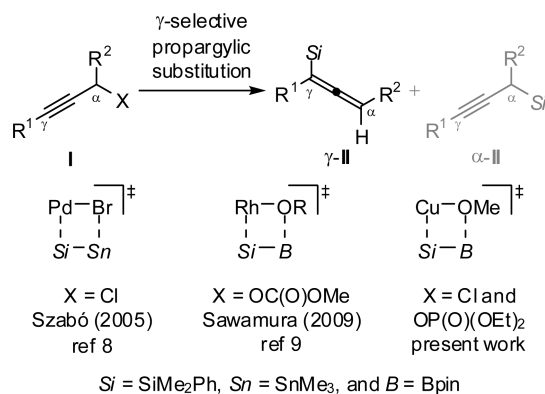
(5) For a review of silicon-based cuprates catalytic in copper, see: Weickgenannt, A.; Oestreich, M. *Chem.–Eur. J.* **2010**, 16, 402–412.

(6) Vyas, D. J.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, 49, 8513–8515.

(7) Regioselective propargylic substitution by copper-mediated C–Si bond formation: (a) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, 264, 99–118. (b) Fleming, I.; Takaki, K.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2269–2273. (c) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, 65, 630–633.

propargylic displacements with silicon nucleophiles involving the transmetalation of interelement linkages. A seminal paper by Szabó et al. showed that palladium(II) pincer complexes indeed catalyze the heterolytic cleavage of a Si–Sn bond (left, Scheme 1), and the thus-formed reactive Pd–Si intermediate participates in the γ -selective substitution of propargylic chlorides.⁸ Later, Sawamura et al. adopted our rhodium(I)-catalyzed Si–B transmetalation (yet without added water) and elaborated a practical functional-group-tolerant allenyllic silane synthesis with a carbonate leaving group (middle, Scheme 1).⁹ In this Letter, we demonstrate that our straightforward reaction setup for copper(I)-catalyzed Si–B bond activation⁶ is applicable to the γ -selective substitution of propargylic chlorides as well as phosphates (right, Scheme 1).^{10–13}

Scheme 1. Transition-Metal-Catalyzed Interelement Activation in Propargylic Substitution with Nucleophilic Silicon



As we continued using the protocol for the allylic substitution,⁶ we immediately began with a survey of leaving groups (Table 1). Again, CuCN (5.0 mol %) and NaOMe (2.0 equiv) in THF at -78°C were routinely used, but this time, only a slight excess of Sugimoto's $\text{Me}_2\text{PhSi-Bpin}$ reagent¹⁴ (1.2 equiv as opposed to 1.5 equiv) was necessary. We were delighted to find that the γ : α ratios in the propargylic substitution largely parallel those obtained in the allylic transposition. The chloride leaving group secured perfect regiocontrol (γ : α = 100:0), and γ -selectivity

was also high for phosphate (γ : α = 90:10). The propargylic bromide reacted, however, with poor selectivity (γ : α = 67:33) (Table 1, entries 1–3). The remaining common oxygen leaving groups all favor α substitution, and γ : α ratios are in fact good for carbamate and benzoate (Table 1, entries 4 and 6). It is noteworthy that, compared to Sawamura's investigations,^{9,12a,13} the carbonate leaving group yielded a poor γ : α ratio (Table 1, entry 5). Chemical yields were generally lower for oxygen leaving groups than those for chloride and bromide (quantitative yield).

Table 1. Copper-Catalyzed Propargylic Substitution: Survey of Leaving Groups

entry	propargylic precursor	leaving group X	γ : α ratio ^a	yield (%) ^b
1	1a	Cl	100:0 ^c	94
2	2a	Br	67:33	98
3	3a	OP(O)(OEt) ₂	90:10	66
4	4a	OC(O)NHPH	6:94	42
5	5a	OC(O)OMe	24:76	49
6	6a	OC(O)Ph	5:95	47

^a Ratio of regioisomers determined by GLC analysis prior to purification. ^b Combined isolated yield after flash chromatography on silica gel. ^c No linear regioisomer detected by GLC analysis.

The leaving group-dependent propargylic substitution provides an access to both allenyllic (γ -selectivity) and propargylic (α -selectivity) silanes in synthetically useful γ : α ratios. With our focus on S_{N}' -type substitution, we extended the substrate scope for propargylic chlorides (**1a–1h**, Table 2). All aryl- and alkyl-substituted precursors were cleanly converted into allenes (Table 2, entries 1–6). The parent compound, propargylic chloride, also yielded the allene exclusively (Table 2, entry 7). In agreement with our previous findings,⁶ the γ : α ratio was completely eroded by a terminal Me_3Si group (Table 2, entry 8).

While the chloride leaving group emerged as superior, it would not be useful in enantioselective displacements as enantioenriched α -chiral propargylic chlorides are not available. Instead, α -chiral phosphates are easy to make, and the γ : α ratio was also promising (Table 1, entry 3).

We therefore prepared the α -chiral propargylic phosphates (*S*)-**3i** ($\text{R} = \text{Ph}$) and (*S*)-**3j** ($\text{R} = n\text{-Bu}$) from the known corresponding enantiopure alcohols, obtained by enzymatic kinetic resolution. Subjecting those to our standard protocols afforded the chiral allenes with superb γ : α ratios [(*S*)-**3i**]/[(*S*)-**3j**] $\rightarrow$ [(*aR*)-**7i**]/[(*aR*)-**7j**], Scheme 2].¹⁵ Gratifyingly, the central-to-axial chirality transfer was also

(8) Kjellgren, J.; Sundén, H.; Szabó, K. *J. Am. Chem. Soc.* **2005**, *127*, 1787–1796.

(9) Ohmiya, H.; Ito, H.; Sawamura, M. *Org. Lett.* **2009**, *11*, 5618–5620.

(10) For an uncatalyzed reaction of terminally metalated propargyl substrates with $\text{Me}_2\text{PhSi-Bpin}$, see: Shimizu, M.; Kurahashi, T.; Kitagawa, H.; Hiyama, T. *Org. Lett.* **2003**, *5*, 225–227.

(11) We think that the current investigation is closely connected to the recent progress in Cu–O-mediated transmetalation of Si–H and B–B bonds. The resultant Cu–H and Cu–B nucleophiles undergo γ -selective propargylic reduction¹² (with carbonate^{12a} or acetate^{12b} leaving groups) and borylation¹³ (with carbonate leaving group).

(12) (a) Zhong, C.; Sasaki, Y.; Ito, H.; Sawamura, M. *Chem. Commun.* **2009**, 5850–5852. (b) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Org. Lett.* **2009**, *11*, 5010–5012.

(13) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774–15775.

(14) Sugimoto, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647–4649.

(15) It is important to note that we had also tested the cognate ($\text{R} = \text{Ph}$) carbonate **5i** and benzoate **6i** but both showed no conversion.

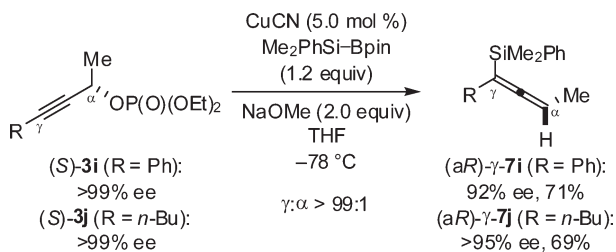
Table 2. Copper-Catalyzed Propargylic Substitution of Linear Propargylic Chlorides

$\text{R}-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}(\text{Cl})-\text{R}' \xrightarrow[\text{THF, } -78^\circ\text{C}]{\text{CuCN (5.0 mol \%), Me}_2\text{PhSi-Bpin (1.2 equiv), NaOMe (2.0 equiv)}} \text{R}-\text{C}\equiv\text{C}-\text{CH}(\text{SiMe}_2\text{Ph})-\text{CH}(\text{R}')-\text{R}'' + \text{R}-\text{C}\equiv\text{C}-\text{CH}(\text{SiMe}_2\text{Ph})-\text{CH}_2-\text{R}''$				
1a–1h γ-7a–γ-7h α-7a–α-7h				
entry	propargylic precursor	R	γ : α ratio ^a	yield (%) ^b
1	1a	Ph	100:0 ^c	94
2	1b	4-MeC ₆ H ₄	100:0 ^c	78
3	1c	4-FC ₆ H ₄	100:0 ^c	88
4	1d	<i>n</i> -Bu	100:0 ^c	71
5	1e	<i>n</i> -Pen	100:0 ^c	80
6	1f	<i>c</i> -Pr	100:0 ^c	77
7	1g	H	100:0 ^c	65 ^d
8	1h	SiMe ₃	56:44	88

^a Ratio of regioisomers determined by GLC analysis prior to purification. ^b Combined isolated yield after flash chromatography on silica gel. ^c No linear regioisomer detected by GLC analysis. ^d Volatile compound.

good, and regioisomerically pure (*aR*)- γ -**7i** and (*aR*)- γ -**7j** were isolated with 92% ee and > 95% ee, respectively. The absolute configurations of the allenylic silane were assigned by comparison with the reported optical rotation of (*aR*)- γ -**7j**.⁹

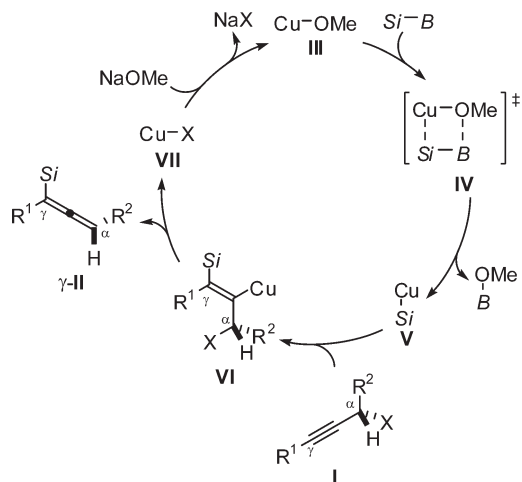
Scheme 2. Central-to-Axial Chirality Transfer in the Copper-Catalyzed Propargylic Substitution of α -Chiral Phosphates



The stereochemical course, that is *S*→*aR*, is identical to that determined by the Sawamura group in related rhodium(I)-⁹ and copper(I)-catalyzed^{12a,13} propargylic substitutions involving interelement bond activation. That was rationalized by *syn*-selective 1,2-addition of the transition metal nucleophile across the C–C triple bond followed by *anti*-selective β -elimination. Based on that reasonable mechanism, we propose the catalytic cycle depicted in Scheme 3. The Cu–Si reagent **V** is generated from the Cu–OMe complex **III** through σ -bond metathesis (**III**→**IV**→**V**). The chemoselectivity in that step is likely to be determined by the electronegativity and/or Lewis acidity of boron over silicon in Si–B. Intermediate **V** then reacts with **I** according to the above-mentioned two-step sequence to yield γ -**II** (**I**→**VI**→ γ -**II**). Salt metathesis of Cu–X complex **VII** and

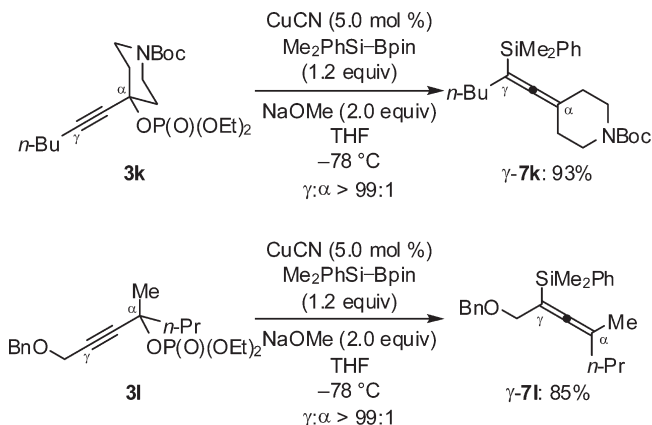
NaOMe regenerates **III** thereby closing the catalytic cycle (**VII**→**III**).

Scheme 3. Proposed Catalytic Cycle



Our protocol is also applicable to tertiary propargylic phosphates. Representative functionalized **3k** and **3l** yielded fully substituted allenes γ -**7k** and γ -**7l** as single regioisomers (Scheme 4). These results compare nicely with the rhodium(I)-catalyzed propargylic substitutions of the corresponding tertiary carbonates.⁹

Scheme 4. Copper-Catalyzed Propargylic Substitution of Tertiary Propargylic Phosphates



In summary, we elaborated a general and practical propargylic substitution with the silicon nucleophile generated

(16) For a summary, see: Pornet, J. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, 2002; Vol. 4, pp 669–683.

(17) Regioselective propargylic substitution by copper-mediated C–C bond formation: (a) Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390–392. (b) Guinchin, B. K.; Bienz, S. *Organometallics* **2004**, 23, 4944–4951 (enantioselective). By Johnson orthoester Claisen rearrangement: (c) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2007**, 9, 2689–2692 (enantioselective).

from a Si–B precursor. The reaction setup is simple, and only CuCN and NaOMe are needed. The new protocol is a useful addition to the existing repertoire of regioselective and enantioselective allenyllic silane syntheses.^{16–19}

(18) For selected transition-metal-catalyzed syntheses of allenyllic silanes through C–Si bond formation, see: (a) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392–6393. (b) Suginome, M.; Matsumoto, A.; Ito, Y. *J. Org. Chem.* **1996**, *61*, 4884–4885. (c) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915–12916.

(19) For a recent summary of the use of chiral allenyllic metal reagents, see: Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153–8166.

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Supporting Information Available. General procedure, characterization data as well as ¹H and ¹³C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.