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

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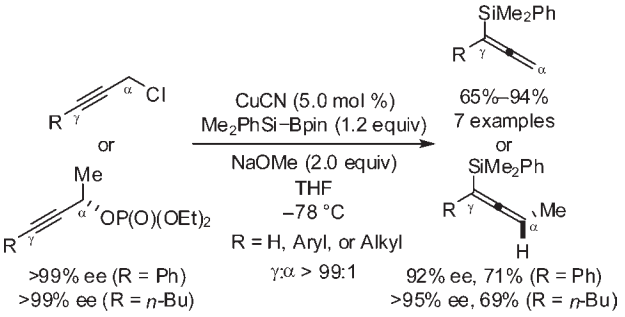
ABSTRACT



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)-catalyzed[3] transmetalations of the Si–B bond[4] 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:$\alpha \geq$ 98:2).[6] The excellent regiocontrol led us to consider the related propargylic substitution (**I**→γ-**II** but not α-**II**, Scheme 1). The Fleming group had accomplished the copper(I)-mediated (enantioselective) preparation of allenylic 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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(1) (a) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717–4725. (b) Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2011**, *47*, 7917–7932. (c) Hartmann, E.; Oestreich, M. *Chimica Oggi – Chemistry Today* **2011**, *29*, in press.

(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.; Petrignet, J.; Tinant, B.; Wouters, J.; Riant, O. *Chem.–Eur. J.* **2010**, *16*, 10980–10983. (c) Ibrahem, 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.; Suginome, 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.

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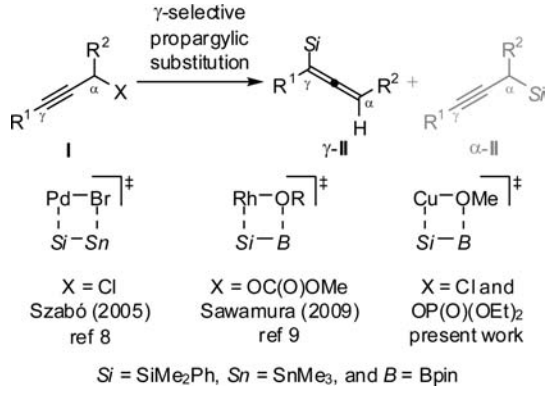
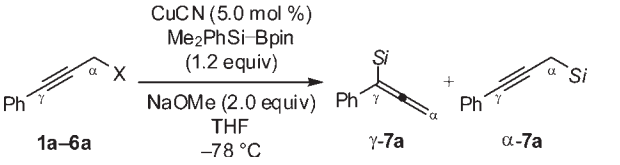
propargylic displacements with silicon nucleophiles involving the transmetalation of interelement linkages. A seminal paper by Szabó et al. showed that palladium(II) pincer complexes indeed catalyze the heterolytic cleavage of a Si−Sn bond (left, Scheme 1), and the thus-formed reactive Pd−Si intermediate 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 allenylic 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 activation[6] 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 Suginome's Me_2PhSi−Bpin reagent[14] (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 allenylic (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** (R = Ph) and (*S*)-**3j** (R = *n*-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**→(a*R*)-γ-**7i**/(a*R*)-γ-**7j**, Scheme 2].[15] Gratifyingly, the central-to-axial chirality transfer was also

(8) Kjellgren, J.; Sundén, H.; Szabó, K. J. *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 Me_2PhSi−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 reduction[12] (with carbonate[12a] or acetate[12b] leaving groups) and borylation[13] (with carbonate leaving group).

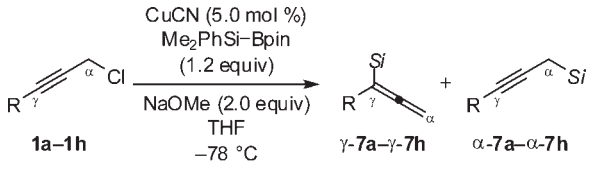
(12) (a) Zhong, C.; Sasaki, Y.; Ito, H.; Sawamura, M. *Chem. Commun.* **2009**, 5850–5852. (b) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Org. Lett.* **2009**, *11*, 5010–5012.

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

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

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

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

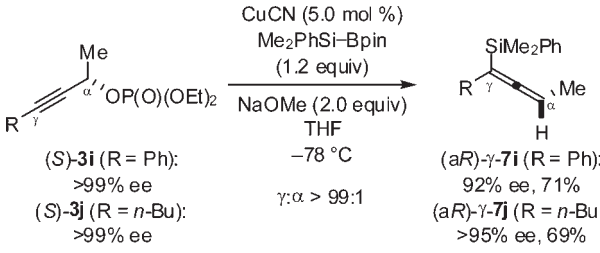


entry	propargylic precursor	R	γ:α ratio[a]	yield (%)[b]
1	**1a**	Ph	100:0[c]	94
2	**1b**	4-MeC_6H_4	100:0[c]	78
3	**1c**	4-FC_6H_4	100:0[c]	88
4	**1d**	*n*-Bu	100:0[c]	71
5	**1e**	*n*-Pen	100:0[c]	80
6	**1f**	*c*-Pr	100:0[c]	77
7	**1g**	H	100:0[c]	65[d]
8	**1h**	$SiMe_3$	56:44	88

[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.

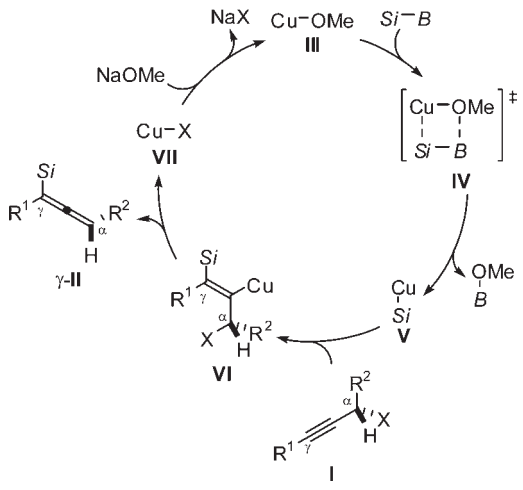
good, and regioisomerically pure (a*R*)-γ-**7i** and (a*R*)-γ-**7j** were isolated with 92% ee and >95% ee, respectively. The absolute configurations of the allenylic silane were assigned by comparison with the reported optical rotation of (a*R*)-γ-**7j**.[9]

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



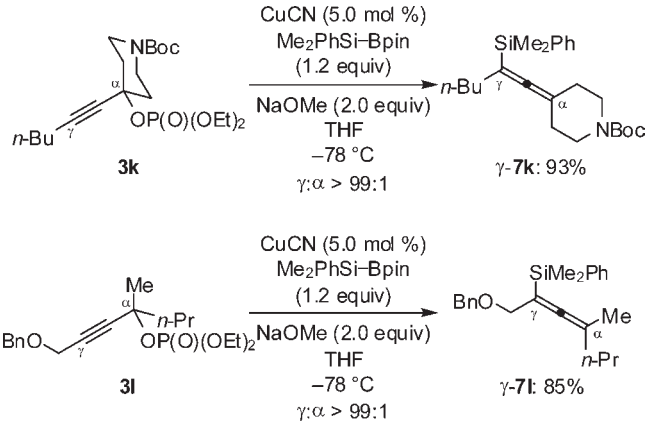
The stereochemical course, that is *S*→a*R*, is identical to that determined by the Sawamura group in related rhodium(I)-[9] and copper(I)-catalyzed[12a,13] propargylic substitutions involving interelement bond activation. That was rationalized by *syn*-selective 1,2-addition of the transition metal 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) Guintchin, 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 allenylic silane syntheses.[16−19]

(18) For selected transition-metal-catalyzed syntheses of allenylic 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 allenylic 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 ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.