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Copper(I)-Catalyzed Regio- and Chemoselective Single and Double Addition of Nucleophilic Silicon to Propargylic Chlorides and Phosphates

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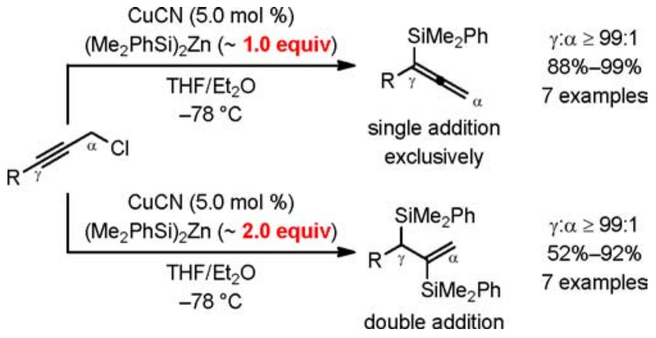
ABSTRACT



Copper(I)-catalyzed propargylic substitution of linear precursors with $(Me_2PhSi)_2Zn$ predominantly yields the γ isomer independent of the propargylic leaving group. The thus formed allenylic silane reacts regioselectively with another equivalent of $(Me_2PhSi)_2Zn$, yielding a bifunctional building block with allylic and vinylic silicon groups. The reaction rates of both steps are well-balanced for chloride (γ:α ≥ 99:1) where the propargylic displacement occurs quantitatively prior to the addition step. Substitutions of α-branched propargylic phosphates are also reported.

Silicon-based cuprates, e.g., $(Me_2PhSi)_2CuLi \cdot LiCN$ and $Me_2PhSiCu \cdot LiCN$, had been stoichiometric in copper[1] until the recent development of new methods to catalytically generate silicon–copper reagents with a silicon-to-copper 1:1 ratio. We introduced $(Me_2PhSi)_2Zn$ (**1**)[2] to copper(I) catalysis,[3] and we succeeded in applying the **1**–CuX (5.0 mol %) combination with X = I or CN in various carbon–silicon bond-forming reactions.[4] Another way of accessing the same silicon nucleophile (not accompanied by lithium and zinc salts) is a σ-bond metathesis of the Si–B bond in $Me_2PhSiBpin$ (**2**)[5] and a copper(I) alkoxide.[6] The copper(I)-catalyzed Si–B bond activation process is currently being actively investigated by several laboratories, and an impressive number of efficient

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(1) (a) Dieter, R. K. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 79–144. (b) Fleming, I. In *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford Academic Press: New York, 1994; pp 257–292.

(2) Morizawa, Y.; Oda, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1163–1166.

(3) Weickgenannt, A.; Oestreich, M. *Chem.—Eur. J.* **2010**, *16*, 402–412.

(4) (a) Oestreich, M.; Weiner, B. *Synlett* **2004**, 2139–2142 (conjugate addition). (b) Oestreich, M.; Auer, G. *Adv. Synth. Catal.* **2005**, *347*, 637–640 (allylic substitution). (c) Auer, G.; Oestreich, M. *Chem. Commun.* **2006**, 311–313 (addition across triple bonds). (d) Auer, G.; Weiner, B.; Oestreich, M. *Synthesis* **2006**, 2113–2116 (conjugate addition). (e) Schmidtmann, E. S.; Oestreich, M. *Chem. Commun.* **2006**, 3643–3645 (allylic substitution). (f) Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2010**, *46*, 568–570 (allylic substitution).

(5) For the preparation of **2**, see: (a) Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647–4649. For a recent summary of Si–B chemistry, see: (b) Ohmura, T.; Suginome, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29–49.

(6) Hartmann, E.; Oestreich, M. *Chim. Oggi* **2011**, *29*, 34–36.

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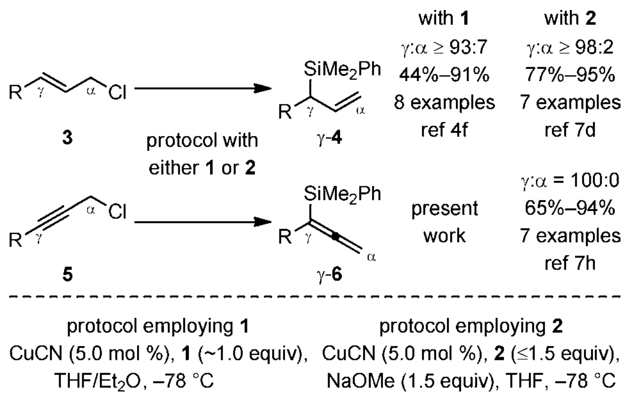
carbon−silicon bond formations have been reported in a short period of time.[7] We have also contributed to this chemistry, and our major focuses have been γ-selective allylic (**3**→γ-**4**, upper)[7d] and propargylic (**5**→γ-**6**, lower)[7h] substitutions of linear precursors with chloride (and phosphate) as leaving group(s) (Scheme 1).

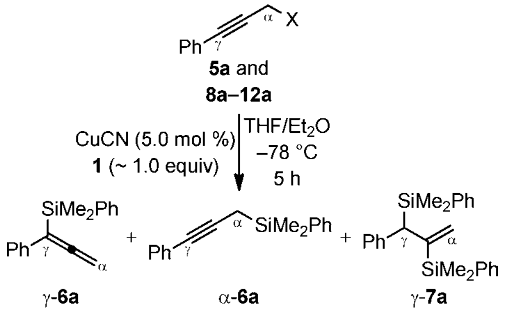
Scheme 1. Copper(I)-Catalyzed γ-Selective Allylic and Propargylic Substitution with either (Me$_2$PhSi)$_2$Zn (**1**) or Me$_2$PhSiBpin (**2**)



The protocol employing interelement compound **2**[7d,8] as the source of nucleophilic silicon is somewhat superior to that with zinc reagent **1**[4f] in the allylic displacement (γ:α ≥ 98:2 versus γ:α ≥ 93:7 in **3**→γ-**4**, Scheme 1, upper). The related substitution of propargylic chlorides involving activation of the Si−B bond also proceeds with excellent levels of regiocontrol (γ:α = 100:0 in **5**→γ-**6**, Scheme 1, lower),[7h,9,10] and those findings appeared to make an investigation of the zinc chemistry seem unnecessary. We found, however, for the propargylic displacement, unlike similar trends for both protocols in the allylic substitution, the copper(I) catalysis with **1** to be significantly different from that with **2**. In this Letter, we disclose a copper(I)-catalyzed $S_N{}'$ substitution of propargylic chlorides with the silicon nucleophile released from easy-to-prepare (Me$_2$PhSi)$_2$-Zn (**1**).[11] The **1**−CuCN (5.0 mol %) combination also allows for double addition with complete regiocontrol in both steps, affording bifunctional building blocks with allylic and vinylic silicon groups.

Our investigation began with the usual survey of leaving groups using approximately equimolar amounts of the propargylic precursor and **1** (Table 1). As expected, the chloride leaving group was regioselectively displaced (γ:α ≥ 99:1) in high yield (Table 1, entry 1). The outcome agreed with that using the reported protocol with **2** (cf. Scheme 1, lower),[7h] and the same was found with the bromide (γ:α = 59:41) and phosphate (γ:α ≥ 99:1) as X groups (Table 1, entries 2 and 3). With the latter, we found a new compound with allylic and vinylic silicon groups, resulting from the regioselective addition of **1** to the central carbon atom of the intermediate allene (γ-**6a**→γ-**7a**). To our surprise, the double addition of the silicon nucleophile even became the major reaction with the other oxygen leaving groups (Table 1, entries 4−6). Also, these substitutions either were not going to completion (phosphate, carbonate, and benzoate) or were accompanied by substantial decomposition of the propargylic precursor (carbamate). For that reason, an excess of **1** is available for the subsequent addition. As detailed later, deliberate addition of a two-fold excess of **1** resulted in full consumption of the γ (except for the propargylic phosphate) but not the α isomer (for the propargylic bromide).

Table 1. Copper-Catalyzed Propargylic Substitution Competing with Subsequent Addition to the γ Adduct: Survey of Leaving Groups



entry	propargylic precursor	leaving group X	γ:α:double ratio[a]	yield (%)[b]
1	**5a**	Cl	>99:<1:0	93 (γ-**6a**)
2	**8a**	Br	58:41:1	77 (γ/α-**6a**)
3	**9a**	OP(O)(OEt)$_2$	82:0:18	87 (γ-**6a**)[c]
4	**10a**	OC(O)NHPh	4:17:79	30 (γ-**7a**)[d]
5	**11a**	OC(O)OMe	3:11:86	48 (γ-**7a**)[c]
6	**12a**	OC(O)Ph	2:4:94	47 (γ-**7a**)[c]

[a] Ratio of regioisomers (γ and α) and double addition determined by GLC analysis without internal standard prior to purification. [b] γ-**6a** and α-**6a** separated from γ-**7a** by flash chromatography on silica gel. [c] Considerable amounts of unreacted starting material remained. [d] Partial decomposition of the propargylic precursor.

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(7) (a) Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900 (conjugate addition). (b) Welle, A.; Petrignet, J.; Tinant, B.; Wouters, J.; Riant, O. *Chem.—Eur. J.* **2010**, *16*, 10980–10983 (conjugate addition). (c) Tobisu, M.; Fujihara, H.; Koh, K.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4841–4847 (nitrile insertion). (d) Vyas, D. J.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8513–8515 (allylic substitution). (e) Ibrahem, I.; Santoro, S.; Himo, F.; Córdova, A. *Adv. Synth. Catal.* **2011**, *353*, 245–252 (conjugate addition). (f) Wang, P.; Yeo, X.-L.; Loh, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 1254–1256 (addition across triple bonds). (g) Vyas, D. J.; Fröhlich, R.; Oestreich, M. *Org. Lett.* **2011**, *13*, 2094–2097 (1,2-addition to imines). (h) Vyas, D. J.; Hazra, C. K.; Oestreich, M. *Org. Lett.* **2011**, *13*, 4462–4465 (propargylic substitution). (i) Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem.—Eur. J.* **2011**, *17*, 13538–13543 (1,2-addition to aldehydes). (j) Kleeberg, C.; Cheung, M. S.; Lin, Z.; Marder, T. B. *J. Am. Chem. Soc.* **2011**, *133*, 19060–19063 (1,2-addition to carbon dioxide).

(8) For an allylic substitution involving copper(I)-catalyzed Si−Si bond activation, see: Ito, H.; Horita, Y.; Sawamura, M. *Adv. Synth. Catal.* **2012**, *354*, 813–817.

(9) For a related propargylic substitution involving palladium(II)-catalyzed Si−Sn bond activation, see: Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 1787–1796.

(10) With carbonate as a leaving group: (a) Ohmiya, H.; Ito, H.; Sawamura, M. *Org. Lett.* **2009**, *11*, 5618–5620 (rhodium(I)-catalyzed Si−B bond activation). For a related transformation, see: (b) Shimizu, M.; Kurahashi, T.; Kitagawa, H.; Hiyama, T. *Org. Lett.* **2003**, *5*, 225–227 (uncatalyzed Si−B bond cleavage by reaction with terminally metalated propargyl substrates).

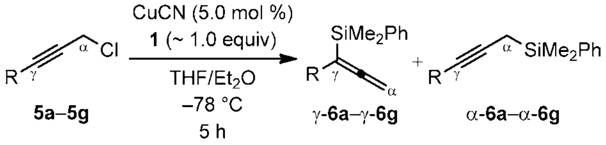
These findings are noteworthy in three respects: (1) For three oxygen leaving groups (Table 1, entries 4–6), a reverse γ:α ratio is seen with **1** (favoring γ) compared to that obtained with interelement compound **2** (favoring α).[7h] (2) The degree of double addition is a reflection of the dependence of the reaction rate of the propargylic substitution on the leaving group. For $X = Cl$ and Br as well as phosphate, that rate is significantly higher than that of the addition step (Table 1, entries 1–3). For the other leaving groups, the substitution step is slow enough for the intermediate allene to also react with the remaining excess of the silicon nucleophile (Table 1, entries 4–6). (3) The addition step is highly chemoselective because it is the γ but not the α isomer that is reactive toward **1** in the presence of CuCN.

Addition of $(Me_2PhSi)_2CuLi\cdot LiCN$[12] and (to a lesser extent) less reactive $Me_2PhSiCu\cdot LiCN$[13] to allenes in fact is a well-investigated transformation.[14] Its regioselectivity is subtly influenced by many parameters, and even the reversibility of the addition has been discussed.[15] There is also an example of the addition of $(Me_2PhSi)_2CuLi\cdot LiCN$ to the central carbon atom of an Me_2PhSi-substituted allene.[11b] A related experiment with stoichiometrically added $Me_2PhSiCu\cdot LiCN$, the nucleophile catalytically generated from **1**–CuCN,[3,4] has not been reported yet.

The high-yielding, selective substitution seen with the propargylic chloride prompted us to test the generality of the single (with ~1.0 equiv of **1**, Table 2) and the double additions (with ~2.0 equiv of **1**, Table 3). The scope of both transformations indeed is excellent. With equimolar amounts of **1**, the propargylic substitution occurred in almost quantitative yields, and double addition is not even detected in traces (**5a**–**5g**→γ-**6a**–γ-**6g**, Table 2). Double the amount of **1** afforded the bifunctional building blocks in good yields (**5a**–**5g**→γ-**7a**–γ-**7g**, Table 3).

Unlike Me_2PhSi-derived cuprates, use of the bulkier t-$BuPh_2Si$ group is far less common. The propargylic substitution was expected to work with $(t\text{-}BuPh_2Si)_2Zn$ (**13**),[4c] but double addition might be prevented by its steric demand. As shown for three representative precursors, the corresponding allenes were formed in high yields (Scheme 2). No further addition to the allene, at neither the central nor the terminal carbon atom, was observed when using double the amount of **13**.[16]

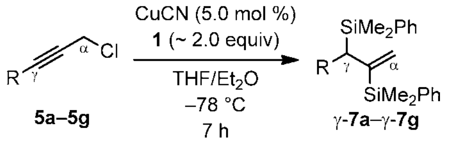
Table 2. Copper-Catalyzed γ-Selective Propargylic Substitution of Linear Propargylic Chlorides



entry	propargylic precursor	R	γ:α ratio[a]	yield (%)[b]
1	**5a**	Ph	>99:<1	93
2	**5b**	$4\text{-}MeC_6H_4$	>99:<1	94
3	**5c**	$4\text{-}FC_6H_4$	>99:<1	94
4	**5d**	n-Bu	>99:<1	88
5	**5e**	n-Pen	>99:<1	97
6	**5f**	c-Pr	>99:<1	99
7[c]	**5g**	H	>99:<1	89

[a] Ratio of regioisomers determined by GLC analysis prior to purification. [b] Isolated yield after flash chromatography on silica gel. [c] 3 h reaction time.

Table 3. Copper-Catalyzed Regioselective Double Addition of Silicon Nucleophiles to Linear Propargylic Chlorides



entry	propargylic precursor	R	double:others ratio[a]	yield (%)[b]
1	**5a**	Ph	>99:<1	92
2	**5b**	$4\text{-}MeC_6H_4$	>99:<1	74
3	**5c**	$4\text{-}FC_6H_4$	>99:<1	77
4	**5d**	n-Bu	>99:<1	64
5	**5e**	n-Pen	>99:<1	61
6	**5f**	c-Pr	>99:<1	52
7[c]	**5g**	H	>99:<1	76

[a] Ratio of double addition (γ-selective propargylic displacement and addition to the central allene carbon atom) and other possible regioisomers determined by GLC analysis prior to purification. [b] Isolated yield after flash chromatography on silica gel. [c] 5 h reaction time.

As with the copper(I)-catalyzed propargylic substitution with the silicon nucleophile released from the interelement compound **2**,[7h] chloride was again superior to all other common leaving groups. For enantioselective displacements though, we had used α-chiral phosphates (S)-**9h** and (S)-**9i** as model compounds before.[7h] Applying the standard protocol with **1** (~1.0 equiv) to these produced (aR)-γ-**6h** and (aR)-γ-**6i** in high yield and with excellent regiocontrol (γ:α > 99:1) and enantiomeric excesses

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(11) For propargylic substitution with the stoichiometric silicon-based cuprate $Me_2PhSiCu\cdot LiCN$, see: (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.

(12) (a) Fleming, I.; Pulido, F. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1010–1011. (b) Fleming, I.; Rowley, M.; Cuadrado, P.; Gonzáles-Nogal, A. M.; Pulido, F. J. *Tetrahedron* **1989**, *45*, 413–424. (c) Fleming, I.; Landais, Y.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 715–719.

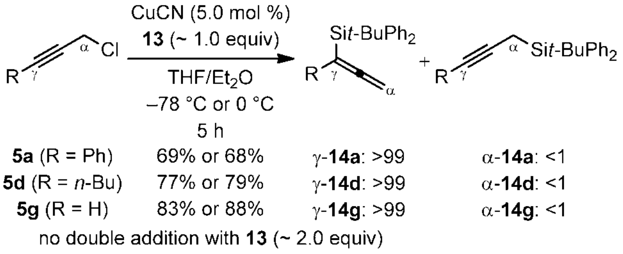
(13) Blanco, F. J.; Cuadrado, P.; Gonzáles, A. M.; Pulido, F. J.; Fleming, I. *Tetrahedron Lett.* **1994**, *35*, 8881–8882.

(14) Barbero, A.; Pulido, F. J. *Acc. Chem. Res.* **2004**, *37*, 817–825.

(15) (a) Cuadrado, P.; Gonzáles, A. M.; Pulido, F. J.; Fleming, I. *Tetrahedron Lett.* **1988**, *29*, 1825–1826. (b) de Dios, M. A. C.; Fleming, I.; Friedhoff, W.; Woode, P. D. W. *J. Organomet. Chem.* **2001**, *624*, 69–72.

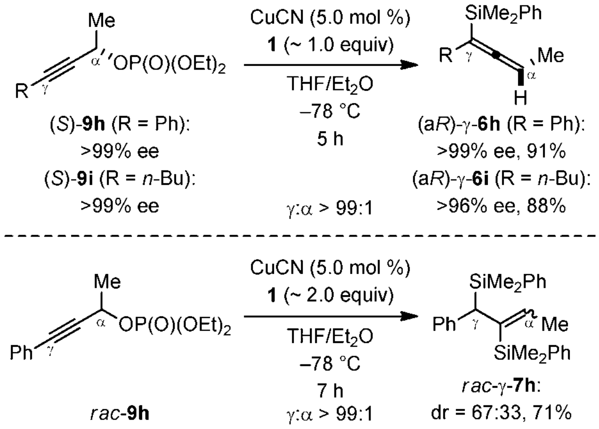
(16) Both $(t\text{-}BuPh_2Si)_2CuLi\cdot LiCN$ and $t\text{-}BuPh_2SiCu\cdot LiCN$ were shown to react with allenes: (a) Barbero, A.; Cuadrado, P.; Gonzáles, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2811–2816. (b) Barbero, A.; Blanco, Y.; Héctor, F.; Pulido, F. J. *Synlett* **2004**, 2833–2835.

Scheme 2. Copper-Catalyzed γ-Selective Propargylic Substitution with Bulky Silicon Nucleophile



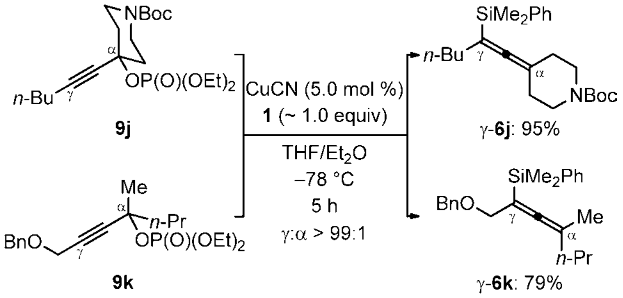
of >99% ee and >96% ee, respectively (Scheme 3, upper). The central-to-axial chirality transfer is comparable to previous cases reported by us[7h] and also by Sawamura[10a] (with carbonates). Double addition was also possible in one example (R = Ph but not *n*-Bu), and the trisubstituted alkene was isolated as a mixture of double bond isomers (*rac*-**9h**→*rac*-γ-**7h**, Scheme 3, lower).

Scheme 3. Central-to-Axial Chirality Transfer in the Copper-Catalyzed Propargylic Substitution of α-Chiral Phosphates and a Double Addition



Tertiary propargylic phosphates are transformed into fully substituted allenylic silanes in high yields (Scheme 4). Again, yields compare nicely with the copper(I)- and rhodium(I)-catalyzed propargylic substitutions of phosphates[7h] and carbonates[10a] involving Si−B bond activation. Double addition was not possible.

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



In summary, we have developed a straightforward protocol for γ-selective propargylic substitution to access allenylic silanes. We have made use of readily available $(Me_2PhSi)_2Zn$ (**1**) and $(t\text{-}BuPh_2Si)_2Zn$ (**13**) as silicon sources in this copper(I) catalysis. The new method shows several features that are distinct from the reported procedure employing $Me_2PhSiBpin$ (**2**).[7h] The regioselectivity is not dependent on the leaving group, with the γ isomer always forming predominantly. Moreover, a second equivalent of **1** adds to the central carbon atom of the allenylic silane, yielding bifunctional building blocks with both an allylic and a vinylic silicon group.[17] Except for chloride (and bromide), the subsequent addition competes with the initial substitution. With X = Cl, the reaction rates of both steps are well-balanced, with the single (with ~1.0 equiv of **1**) and double additions (with ~2.0 equiv of **1**) both being fully regio- and chemoselective.

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Supporting Information Available. General procedure, characterization data, and ^1H, ^{13}C, ^{29}Si, and ^{31}P NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] Trace amounts of double addition were also seen with **2** (2.0 equiv): Vyas, D. J. Ph.D. Thesis, Westfälische Wilhelms-Universität Münster, Germany, 2011.

The authors declare no competing financial interest.