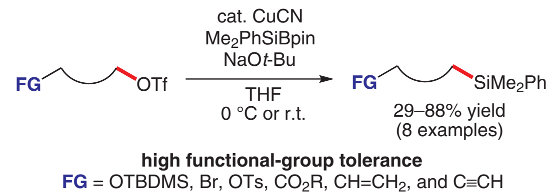
Copper-Catalyzed Si–B Bond Activation in the Nucleophilic Substitution of Primary Aliphatic Triflates

Jonas Scharfbier
Martin Oestreich*

Institut für Chemie, Technische Universität Berlin,
Straße des 17. Juni 115, 10623 Berlin, Germany
martin.oestreich@tu-berlin.de

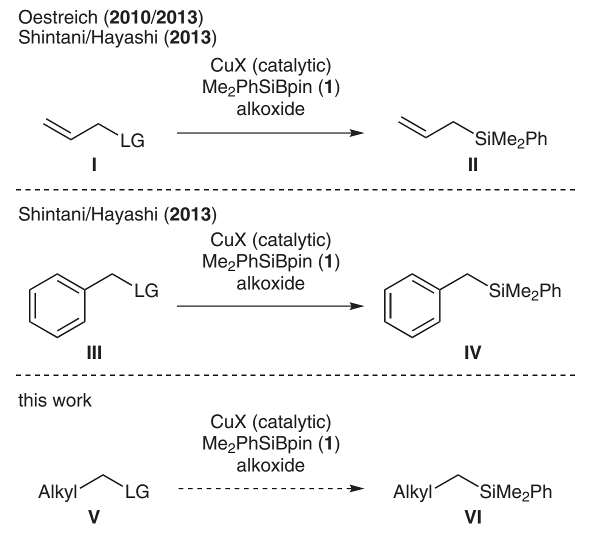


Received: 22.12.2015
Accepted after revision: 09.02.2016
Published online: 04.03.2016
DOI: 10.1055/s-0035-1561407; Art ID: st-2015-b0994-l

Abstract A method for the nucleophilic displacement of the triflate leaving group attached to terminally functionalized alkyl groups with nucleophilic silicon is reported. Copper catalysis is used to release the silicon nucleophile from Suginome's Si–B reagent. The functional group tolerance is excellent, and halide leaving groups do also work with the same protocol.

Key words chemoselectivity, copper, nucleophilic substitution, silicon, transmetalation

The transmetalation of the Si–B interelement bond for the catalytic formation of silicon nucleophiles has recently revolutionized synthetic silicon chemistry.[1] Methods based on copper have emerged as particularly broadly applicable.[2] The copper-based silicon nucleophile is usually generated by σ-bond metathesis of the Si–B bond and the Cu–O bond of an in situ generated copper(I) complex.[3] With Suginome's $Me_2PhSiBpin$ (**1**) as the typical silicon source,[4] several fundamental Si–C bond-forming reactions were realized in racemic and asymmetric fashion.[1,2] These include 1,4-[5–7] and 1,2-addition[8,9] as well as allylic substitution.[10–12] The displacement of a leaving group (LG) in the allylic position could be viewed as a nucleophilic substitution of an *activated* $C(sp^3)$–LG bond with nucleophilic silicon (**I** → **II**, Scheme 1, top).[11,12] A similar situation exists in benzylic positions, but there is just one example with a phosphate leaving group known to date (**III** → **IV**, Scheme 1, middle).[12] Conversely, the related nucleophilic substitution of aliphatic and as such *unactivated* $C(sp^3)$–LG bonds with silicon nucleophiles is unprecedented (**V** → **VI**, Scheme 1, bottom).

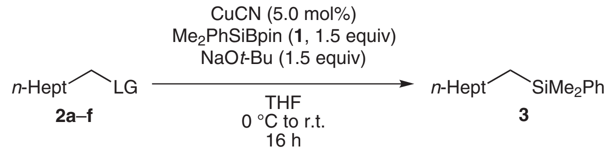


Scheme 1 Nucleophilic substitution of activated (allylic and benzylic) and unactivated (aliphatic) $C(sp^3)$–X bonds (X = CN or Cl)

While there are no examples for the case of silicon nucleophiles, the analogous copper-catalyzed transformation with boron nucleophiles[13] is now well established (LG = Cl, Br, I, and OTs).[14] Moreover, the corresponding reduction with Cu–H[15] was also disclosed (LG = I and OTf).[16] We herein report a new Si–C bond formation catalyzed by copper that converts primary alkyl triflates and halides into functionalized tetraorganosilanes.

We commenced our study with a survey of leaving groups, employing a straightforward catalytic setup (Table 1). Aliphatics **2a**–**f** were reacted with silyl boronic ester **1** in THF in the presence of catalytic amounts of CuCN and NaOt-Bu as stoichiometric base. The reactions were started at 0 °C, warmed to room temperature, and maintained at this temperature for 16 hours. All substrates **2a**–**c** with halide leaving groups showed conversions depending on their leaving group ability (entries 1–3). Yields of **3**, however, were significantly lower than conversions of **2**, indicating other competing pathways such as elimination. Tosylate **2d** did not react, but triflate **2e** afforded **3** in high yield at full conversion (entries 4 and 5). Phosphate **2f** was in turn inert under these reactions conditions (entry 6).

Table 1 Survey of Leaving Groups



Entry	Substrate	Leaving group	Conv. of **2** (%)[a]	Yield of **3** (%)[b]
1	**2a**	Cl	23	16
2	**2b**	Br	45	28
3	**2c**	I	>99	55
4	**2d**	OTs	n.r.[c]	–
5	**2e**	OTf	>99	92
6	**2f**	OP(O)(OEt)$_2$	n.r.[c]	–

[a] Determined by GLC analysis with tetracosane as internal standard.
[b] Determined by calibrated GLC analysis with tetracosane as internal standard.
[c] No reaction.

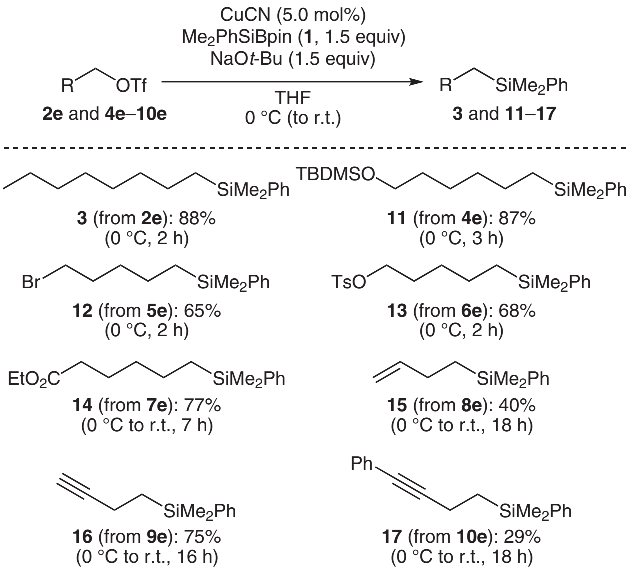
We continued with triflate **2e** for further optimization (Table 2). A closer look at the reaction time showed that full conversion is already reached at 0 °C within 1 hour, but the reaction rate decreased substantially at lower temperatures (entries 1–3). Other *tert*-butoxides, such as LiO*t*-Bu and KO*t*-Bu, were less effective, furnishing **3** in lower yields at full consumption of **2e** (entries 4 and 5); often-used NaOMe[1] led to decomposition (entry 6). A control experiment in the absence of CuCN demonstrated not only the chemical instability of triflate **2e** toward NaO*t*-Bu but also the ability of NaO*t*-Bu to promote this reaction alone (entry 7).[17] The catalyst loading had little or no effect, and results with 1.0 and 10 mol% of CuCN were in the same range as with 5.0 mol%.

Table 2 Screening of Temperature and Base in the Nucleophilic Substitution of *n*-Octyl Trifluoromethanesulfonate (**2e**)[a]

Entry	Base	Temp (°C)	Time (h)	Conversion of **2e** (%)[b]	Yield of **3** (%)[c]
1	NaO*t*-Bu	0	1	>99	92
2	NaO*t*-Bu	–25	1	56	52
3	NaO*t*-Bu	–50	1	32	26
4	LiO*t*-Bu	0	1	>99	83
5	KO*t*-Bu	0	1	>99	63
6	NaOMe	0	2	>99	14
7[d]	NaO*t*-Bu	0	3	>99	12

[a] Reactions were performed using CuCN (0.012 mmol), **1** (0.38 mmol, 1.5 equiv), and the indicated base (0.38 mmol, 1.5 equiv) in THF (1 mL) at the indicated temperature for 1 or 2 h.
[b] Determined by GLC analysis with tetracosane as internal standard.
[c] Determined by calibrated GLC analysis with tetracosane as internal standard.
[d] Without CuCN.

With a reliable procedure at hand,[18] we evaluated the scope of the method (Scheme 2). All triflates were freshly prepared by standard protocols (see the Supporting Information for characterization data) and immediately used. Our model compound afforded 88% isolated yield (**2e** → **3**), and the same yield was obtained for a substrate containing a TBDMS-protected hydroxy group (**4e** → **11**). Substrates with potential leaving groups at the other terminus of the alkyl chain reacted in decent yields of 65% and 68% (**5e** → **12** and **6e** → **13**). An ester group was also tolerated (**7e** → **14**), and the same applied to unsaturation in the form of C–C multiple bonds (**8e**–**10e** → **15**–**17**). The moderate yield of 40% for **15** is the result of its difficult purification, and the poor yield of 29% for **17** remains unexplained.



Scheme 2 Scope of the copper-catalyzed nucleophilic substitution of functionalized alkyl triflates

To summarize, we developed the displacement of *unactivated* C(sp^3)–LG bonds (LG = Cl, Br, I, and OTf) with the silicon nucleophile released from an Si–B reagent by copper catalysis. The reaction works best with the triflate leaving group, and various functionalized primary alkyl triflates were converted into the corresponding tetraorganosilanes in good to high isolated yields. Extension of this methodology to secondary alkyl electrophiles[19] and its mechanistic analysis (ionic or radical)[14,16] will be reported in due course.

Acknowledgment

M.O. is indebted to the Einstein Foundation (Berlin) for an endowed professorship.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561407.

References and Notes

(1) Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2013**, *113*, 402.

(2) (a) Sawamura, M.; Ito, H. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A.; Krause, N.; Woodward, S., Eds.; Wiley-VCH: Weinheim, **2014**. (b) Hensel A., Oestreich M.; *Top. Organomet. Chem.*; in press; doi: 10.1007/3418_2015_156.

(3) Hartmann, E.; Oestreich, M. *Chim. Oggi* **2011**, *29*, 34.

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

(5) Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2011**, *47*, 7917.

(6) (a) Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898. (b) Harb, H. Y.; Collins, K. D.; Garcia Altur, J. V.; Bowker, S.; Campbell, L.; Procter, D. J. *Org. Lett.* **2010**, *12*, 5446. (c) Pace, V.; Rae, J. P.; Harb, H. Y.; Procter, D. J. *Chem. Commun.* **2013**, *49*, 5150. (d) Pace, V.; Rae, J. P.; Procter, D. J. *Org. Lett.* **2014**, *16*, 476. (e) Plotzitzka, J.; Kleeberg, C. *Organometallics* **2014**, *33*, 6915.

(7) (a) Vercruysse, S.; Cornelissen, L.; Nahra, F.; Collard, L.; Riant, O. *Chem. Eur. J.* **2014**, *20*, 1834. (b) Calderone, J. A.; Santos, W. L. *Angew. Chem. Int. Ed.* **2014**, *53*, 4154. (c) Linstadt, R. T. H.; Peterson, C. A.; Lippincott, D. J.; Jette, C. I.; Lipshutz, B. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 4159. (d) Xu, Y.-H.; Wu, L.-H.; Wang, J.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 7195.

(8) (a) Vyas, D. J.; Fröhlich, R.; Oestreich, M. *Org. Lett.* **2011**, *13*, 2094. (b) Hensel, A.; Nagura, K.; Delvos, L. B.; Oestreich, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 4964. (c) Mita, T.; Sugawara, M.; Saito, K.; Sato, Y. *Org. Lett.* **2014**, *16*, 3028. (d) Zhao, C.; Jiang, C.; Wang, J.; Wu, C.; Zhang, Q.-W.; He, W. *Asian J. Org. Chem.* **2014**, *3*, 851.

(9) (a) Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. Eur. J.* **2011**, *17*, 13538. (b) Cirriez, V.; Rasson, C.; Hermant, T.; Petrignet, J.; Díaz Álvarez, J.; Robeyns, K.; Riant, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 1785.

(10) Delvos, L. B.; Oestreich, M. *Chim. Oggi* **2013**, *31*, 74.

(11) (a) Vyas, D. J.; Oestreich, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8513. (b) Delvos, L. B.; Vyas, D. J.; Oestreich, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4650. (c) Hazra, C. K.; Irran, E.; Oestreich, M. *Eur. J. Org. Chem.* **2013**, 4903. (d) Delvos, L. B.; Hensel, A.; Oestreich, M. *Synthesis* **2014**, *46*, 2957. (e) Delvos, L. B.; Oestreich, M. *Synthesis* **2015**, *47*, 924.

(12) Takeda, M.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2013**, *78*, 5007.

(13) Cid, J.; Gulyás, H.; Carbó, J. J.; Fernández, E. *Chem. Soc. Rev.* **2012**, *41*, 3558.

(14) (a) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528. (b) Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890. (c) Presset, M.; Fleury-Brégeot, N.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013**, *78*, 4615.

(15) (a) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916. (b) Rendler, S.; Oestreich, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 498.

(16) Dang, H.; Cox, N.; Lalic, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 752.

(17) (a) Kawachi, A.; Minamimoto, T.; Tamao, K. *Chem. Lett.* **2001**, *30*, 1216. (b) Ito, H.; Horita, Y.; Yamamoto, E. *Chem. Commun.* **2012**, *48*, 8006. (c) Kleeberg, C.; Borner, C. *Eur. J. Inorg. Chem.* **2013**, 2799.

(18) **Copper-Catalyzed Nucleophilic Substitution of Functionalized Alkyl Triflates; General Procedure**
A flame-dried Schlenk tube was charged with CuCN (1.1 mg, 5.0 mol%) and NaO*t*-Bu (36 mg, 1.5 equiv); when required, tetracosane was added as internal standard at this stage. THF was added (0.25 M), and the resulting solution was cooled to 0 °C. After 10 min, **1** (98 mg, 1.5 equiv) and the indicated triflate (0.25 mmol) were successively added. The purple solution was maintained at 0 °C or room temperature for the indicated time (monitoring by GLC analysis). The reaction was then diluted with MTBE (5 mL) and filtered through a short plug of silica gel, followed by rinsing with MTBE (2 × 5 mL). The solvents were evaporated under reduced pressure, and the crude material was purified by flash chromatography on silica gel with the indicated solvents as eluent (see the Supporting Information for details). The tetraorganosilanes were obtained as colorless oils.

(19) The current procedure was not applicable to secondary alkyl bromides, iodides, and triflates as a result of facile elimination. High and moderate conversion was obtained for bromides and iodides, respectively, but only traces of the desired tetraorganosilanes were detected by GLC analysis; triflates were generally too labile.