

Regioselective *Anti*-Silyllithiation of Propargylic Amines

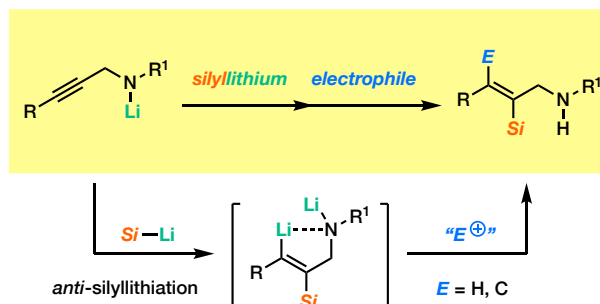
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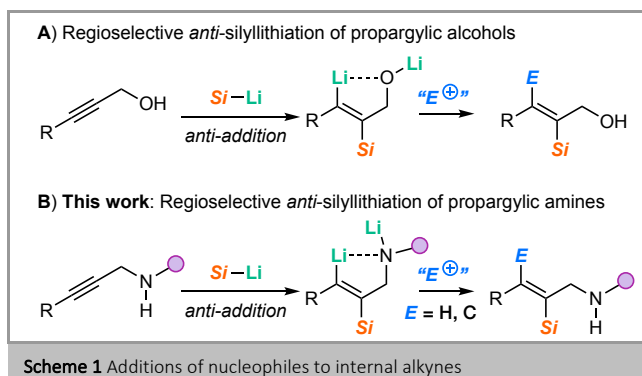
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Abstract The regioselective *anti*-silyllithiation of propargylic amines was developed to facilitate the efficient synthesis of alkenylsilanes. This reaction generates an alkenyllithium intermediate that is stabilized by the formation of a five-membered cyclic structure through intramolecular coordination of the nitrogen functional group. Upon subsequent treatment with an electrophile, the alkenyllithium intermediate can be further functionalized to afford tetrasubstituted allylic amines bearing a β -silicon substituent.

Key words silyllithium, alkenylsilane, allylamine, one-pot synthesis, remote stereocontrol

Alkenylsilanes are a fascinating class of compounds that are utilized as unique structural units for functional materials and as versatile reactive key intermediates for chemical transformations.¹ Considerable efforts have been devoted to the development of new methods for the preparation and transformation of alkenylsilanes.^{2–5} One of the most attractive strategies for the efficient synthesis of alkenylsilanes is silylmetalation of internal alkynes, particularly those bearing a coordinating group such as a propargylic hydroxy group.⁶ While regioselective *syn*-addition of silylmetals with either regioselectivity has been established in the presence of a transition metal catalyst,^{6–8} *anti*-additions of silylmetals have been rarely reported.^{9–12} In this context, we recently discovered the regioselective *anti*-addition of silyllithiums to propargylic alkoxides (Scheme 1A).¹³ The reaction affords an alkenyllithium bearing a silyl group in the proximal position to the hydroxy group. Upon subsequent treatment with a variety of electrophiles, the alkenyllithium intermediate can be further functionalized to provide tetrasubstituted allylic alcohols bearing a β -silicon substituent. The initial silyllithiation reaction would form an alkenyl metal intermediate that is stabilized by the formation of a five-membered cyclic structure through the intramolecular coordination of the alkoxide moiety. However, the utility of any type of nitrogen coordinating group for these reactions has not been extensively investigated, except for the seminal studies by Richey that confirmed a tertiary propargylic amine serves as a directing group for the regioselective carbolithiation or magnesiation of triple bonds.^{14,15} To

investigate the potential of a nitrogen functional group as a directing group for silyl metal species, we examined the use of variously functionalized propargylic amines as a substrate for regioselective *anti*-silyllithiation (Scheme 1B).

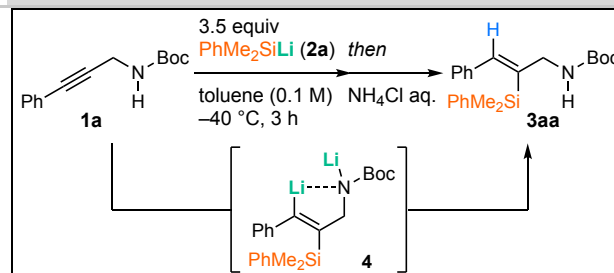


We employed *N*-Boc propargylic amine **1a** and PhMe₂SiLi **2a** as substrates for the *anti*-silyllithiation of the triple bond. Through optimization, we established standard conditions as follows: *tert*-butyl (3-phenylprop-2-yn-1-yl)carbamate (**1a**, 0.1 M in toluene), 3.5 equiv PhMe₂SiLi (**2a**, 1.5 M in THF), –40 °C, 3 h. We employed the mixed solvent system previously optimized for the silyllithiation reaction again for this transformation.¹³ Table 1 illustrates the yields of **3aa** associated with variations in the deviations listed. Under the standard conditions (Entry 1), initial deprotonation of **1a** and *anti*-addition of PhMe₂SiLi **2a** proceeded to afford the silyllithiated intermediate **4**. Subsequent protonation with NH₄Cl aq. provided the *anti*-hydrosilylated (*Z*)-allylic carbamate **3aa** in 83% NMR yield and in 81% isolated yield. The impact of the reaction temperature was significant and the reaction at 0 °C resulted in a low yield of **3aa** due to the decomposition of the carbamate starting material. The use of either 2.5 equiv or 4.5 equiv of PhMe₂SiLi **2a** resulted in lower yields (Entry 3, 4). By changing the concentration of **1a** to 0.07 M or 0.2 M, slightly reduced yields were observed (Entry 5, 6). Initial deprotonation using 1.0 equiv of *n*BuLi followed by 1.5 equiv of PhMe₂SiLi **2a** led to lower conversion (Entry 7), while 2.5 equiv of **2a** resulted in complete conversion of **1a** to

give **3aa** in competitive 76% yield (Entry 8). When the reaction was quenched with D₂O, **3aa-D** with the deuterated vinylic position was obtained in 82% yield. The deuterated content of **3aa-D** was 65%, indicating the partial protonation of the alkenyllithium moiety of silylated intermediate **4** before quenching (Entry 9).

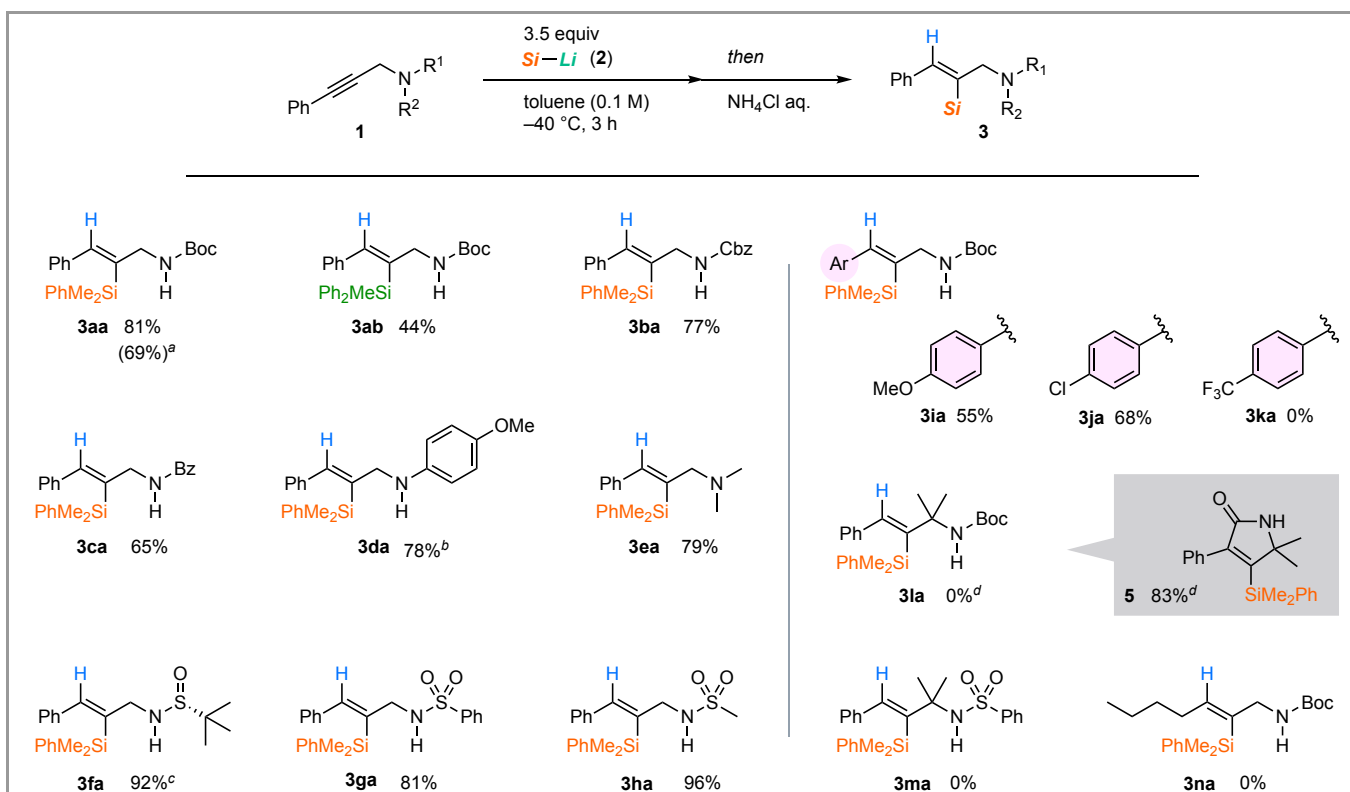
The effect of substituents on the nitrogen atom was next investigated under the standard conditions (Scheme 2A). *N*-Boc-propargylic amine **1a** gave **3aa** under the optimized conditions with PhMe₂SiLi **2a** in 81% isolated yield.¹⁶ This reaction can be scaled up to 5 mmol and afforded **3aa** in 69% yield. In the case of Ph₂MeSiLi **2b**, the yield of **3ab** was moderate, though **1a** was completely consumed. *N*-Cbz-propargylic amine **1b** also furnished the desired product **3ba** in good yield, while the yield of **3ca** derived from *N*-benzoyl-protected amine **1c** was moderate due to partial decomposition during the transformation. With a 4-methoxyphenyl group as a substituent on the nitrogen atom, **1d** underwent the reaction to afford **3da** in 78% yield at –20 °C. The reaction also proceeded with *N,N*-dimethyl propargylic amine **1e** to provide **3ea** in 79% yield. This result indicates that a tertiary amine without an acidic proton, without forming an anionic nitrogen functional group can also direct the reaction with the same regio- and stereoselectivity. Chiral *N*-sulfinyl-protected **1f** gave **3fa** in 49% yield while recovering 29% of **1f**. However, the use of 4.5 equiv of PhMe₂SiLi **2a** increased the yield of **3fa** to 92%. Benzenesulfonamide **1g** smoothly furnished **3ga** in 81% yield. In the case of methanesulfonamide **1h**, **3ha** was obtained in 96% yield.

Table 1 Optimization of Reaction Conditions

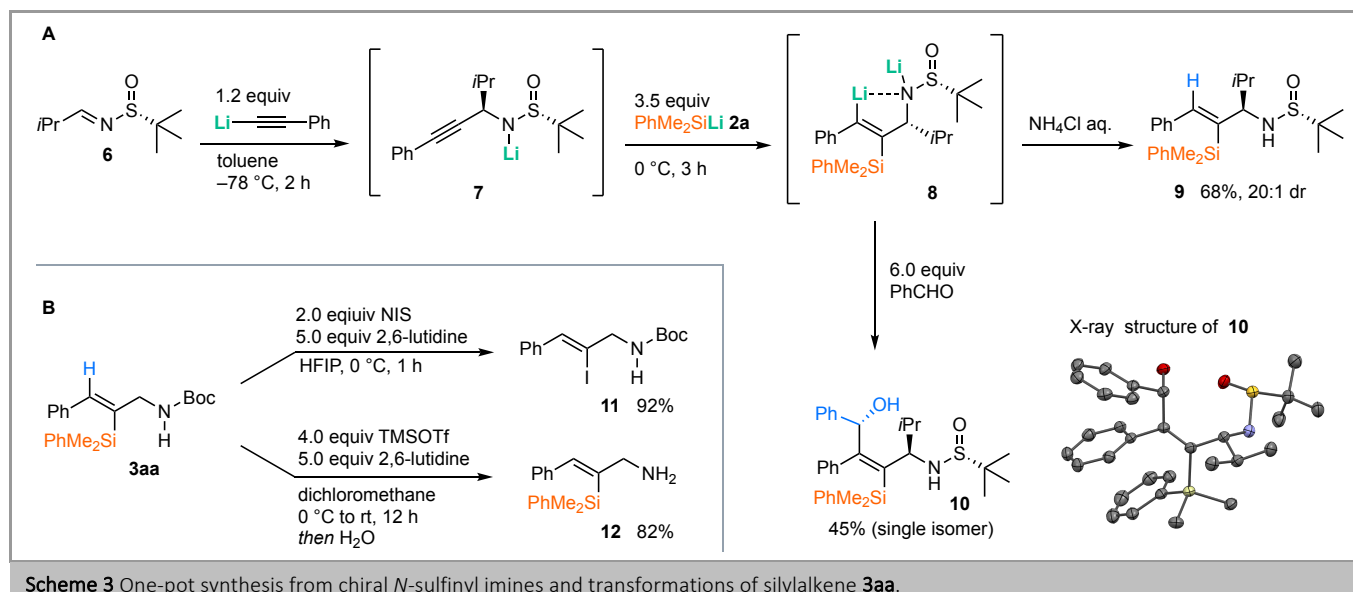


Entry ^a	Deviations from the standard conditions	NMR yield ^b [%]
1	none	83
2	0 °C	40
3	2.5 equiv Me ₂ PhSiLi	65
4	4.5 equiv Me ₂ PhSiLi	79
5	0.07 M	73
6	0.2 M	82
7	1.0 equiv <i>n</i> BuLi, then 1.5 equiv PhMe ₂ SiLi	55 (70% conv.)
8	1.0 equiv <i>n</i> BuLi, then 2.5 equiv PhMe ₂ SiLi	76
9	10 equiv D ₂ O instead of NH ₄ Cl aq.	82 (65%D) ^c

^a PhMe₂SiLi was prepared as a 1.5 M solution in THF. ^b All yields were determined by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. ^c Deuterium content of the alkenyl proton.



Scheme 2 Effect of *N*-substituents. ^a 5 mmol scale; ^b –20 °C; ^c 4.5 equiv PhMe₂SiLi; ^d 0 °C.



We next surveyed the scope of the reaction with respect to the substituents on propargylic amines. The reactions of propargylic carbamates bearing 4-methoxyphenyl (**1i**) and 4-chlorophenyl (**1j**) furnished the desired products in 55% and 68% yield respectively. However, 4-trifluoromethylphenyl propargylic carbamate **1k** gave a complex mixture, likely due to the facile deprotonation at the propargylic position. Introduction of two methyl groups at the propargylic position of **1l** did not give the expected product **3la**, but instead yielded the cyclized product **5** in 83% yield, probably through the formation of an isocyanate intermediate and cyclization from the alkenyllithium intermediate. Interestingly, similar disubstituted *N*-benzenesulfonyl amide **1m** was unreactive and no silylated **3ma** was formed. **1n** also proved to be inactive for the transformation, suggesting that terminal aryl groups are required to lower the activation energy for this silyllithiation reaction.

Inspired by the result of utilizing chiral *N*-sulfinyl-substituted **1f**, we sought to achieve a formation of silylated allylic amines through a one-pot transformation from chiral *N*-sulfinyl imines (Scheme 3A).^{17,18} *tert*-Butanesulfinimine **6** was treated with (phenylethynyl)lithium at -78°C for 3 h to give lithium sulfinamide **7** *in situ*. Subsequently, the intermediate **7** was subjected to reaction with PhMe_2SiLi **2a** at 0°C for an additional 3 h, resulting in the formation of silyllithiated intermediate **8**. This intermediate was then quenched with NH_4Cl aq. to give **9** in 68% yield with high diastereoselectivity (20:1 dr). Notably, alkenyllithium intermediate **8** gave rise to the corresponding alcohol **10** upon reaction with benzaldehyde. Allylic alcohol **10** was isolated as a single isomer whose stereochemistry was confirmed through X-ray crystallographic analysis.¹⁹ The stereochemistry of the propargylic position of **9**, which was initially formed in **7**, is dictated by the established chemistry of *tert*-butanesulfinimines. It is likely that the cyclic structure of alkenyllithium **8** plays a crucial role in controlling the high stereoselectivity observed during the formation of the secondary hydroxy group in **10**.

The products resulting from this reaction can serve as precursors to other stereodefined alkenes (Scheme 3B). The silyl group present in product **3aa** can easily be converted to iodo in

11 upon treatment with NIS.²⁰ Furthermore, the Boc group of **3aa** can be removed without loss of the silyl group to furnish allylic amine **12** in 82% yield by using trimethylsilyl triflate and 2,6-lutidine.²¹

In conclusion, we have developed regioselective *anti*-addition of silyllithiums to variously protected propargylic amines, which selectively provide (*Z*)-2-silylated allylic amines after the protonation or the reaction with an electrophile. In the case of a chiral propargylic sulfinamide as a substrate, the silyllithiated intermediate can further react with an aldehyde to stereoselectively furnish the secondary allylic alcohol. This high selectivity of 1,4-stereochemical control of the hydroxy group reinforces the formation of a cyclic lithium amide intermediate.

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Supporting Information

Supporting information for this article is available online.

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes

- Hiyama, T.; Oestreich, M. *Organosilicon Chemistry: Novel Approaches and Reactions*; John Wiley & Sons, **2020**.
- Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320.
- Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221.
- Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, *2005*, 853.
- Lim, D. S. W.; Anderson, E. A. *Synthesis* **2012**, *44*, 983.
- Wilkinson, J. R.; Nuyen, C. E.; Carpenter, T. S.; Harruff, S. R.; Van Hoveln, R. *ACS Catal.* **2019**, *9*, 8961.

- (7) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491.
- (8) Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1997**, *53*, 5061.
- (9) Trost, B. M.; Ball, Z. T.; Jöge, T. *Angew. Chem. Int. Ed.* **2003**, *42*, 3415.
- (10) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644.
- (11) Rummelt, S. M.; Radkowski, K.; Roşca, D.-A.; Fürstner, A. *J. Am. Chem. Soc.* **2015**, *137*, 5506.
- (12) Roşca, D.-A.; Radkowski, K.; Wolf, L. M.; Wagh, M.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2017**, *139*, 2443.
- (13) Karad, S. N.; Saito, H.; Shimokawa, J.; Yorimitsu, H. *J. Org. Chem.* **2022**, 10.1021/acs.joc.2c01795.
- (14) Richey, H. G., Jr; Moses, L. M.; Domalski, M. S.; Erickson, W. F.; Heyn, A. S. *J. Org. Chem.* **1981**, *46*, 3773.
- (15) Richey, H. G., Jr; Heyn, A. S.; Erickson, W. F. *J. Org. Chem.* **1983**, *48*, 3821.
- (16) **General procedure for Regioselective *anti*-Silyllithiation of Propargylic Amines 1:**
The synthesis of **3aa** is representative. A 20-mL Schlenk tube was charged with *tert*-butyl (3-phenylprop-2-yn-1-yl)carbamate (**1a**, 115.5 mg, 0.499 mmol) and toluene (5.0 mL) under nitrogen atmosphere, and the resulting solution was cooled to $-40\text{ }^{\circ}\text{C}$. To the mixture was added PhMe_2SiLi (**2a**, 1.5 M in THF, 1.2 mL, 1.75 mmol, 3.5 equiv) dropwise. After the mixture was stirred for 3 h at $-40\text{ }^{\circ}\text{C}$, saturated aqueous NH_4Cl (1.0 mL) was added at $0\text{ }^{\circ}\text{C}$. The resulting biphasic solution was extracted with EtOAc (10 mL $\times$ 3). The combined organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ CH_2Cl_2 = 1/2) to provide **3aa** (148.6 mg, 0.404 mmol, 81%) as a pale yellow solid.
3aa: ^1H NMR (600 MHz, CDCl_3): δ 7.53–7.50 (m, 2H), 7.40 (brs, 1H), 7.38–7.34 (m, 3H), 7.24–7.20 (m, 3H), 7.15–7.12 (m, 2H), 4.66 (br, 1H), 3.99 (d, J = 6.1 Hz, 2H), 1.49 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (151 MHz, CDCl_3): δ 155.6, 143.6, 139.4, 139.1, 138.6, 133.8, 129.0, 128.6, 127.9, 127.8, 127.2, 79.3, 47.7, 28.5, -1.5 ; HRMS (APCI-MS, positive): m/z $[\text{M}-t\text{Bu}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_2\text{Si}$: 310.1258; found: 310.1269.
- (17) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
- (18) Patterson, A. W.; Ellman, J. A. *J. Org. Chem.* **2006**, *71*, 7110.
- (19) CCDC 1982977 contains the supplementary crystallographic data for compound **10**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures
- (20) Feng, Q.; Wu, H.; Li, X.; Song, L.; Chung, L. W.; Wu, Y.-D.; Sun, J. *J. Am. Chem. Soc.* **2020**, *142*, 13867.
- (21) Urbanaitė, A.; Jonušis, M.; Bukšnaitienė, R.; Balkaitis, S.; Čikotienė, I. *Eur. J. Org. Chem.* **2015**, 7091.