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Efficient Synthesis of Alkynylsilyl Ethers and Silaketals via Base-Induced Alkynylsilane Alcoholysis

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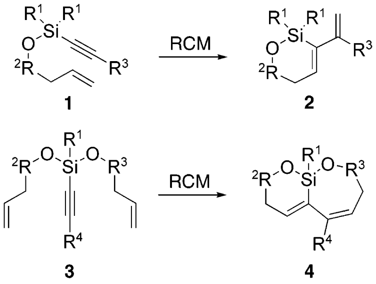
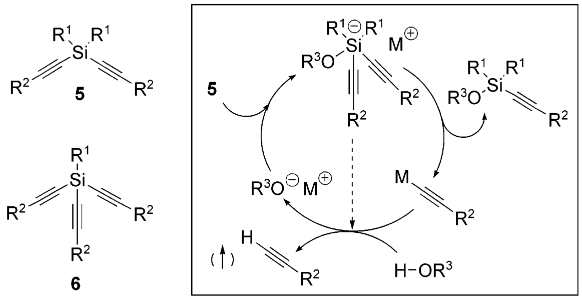
Abstract: The efficient silylation of alcohols with di- and trialkynylsilanes was achieved under base-catalyzed conditions to afford alkynyl silyl ethers and symmetrical alkynyl silaketals in good yield. A selective alcoholysis of dialkynyl silyl ethers to mixed silaketals was also demonstrated. These products served as substrates for enyne ring-closing metathesis and, consequently, as precursors to stereochemically defined 1,3-dienes.

The silyl ether is one of the most widely used protecting groups[1] and temporary tethers[2,3] in modern synthetic chemistry due to the ease of its formation and removal in the presence of other common protecting groups. Many silylating agents and reaction conditions have been developed, yet the use of reagents of the form R_3Si-X (X = Cl, OTf) and appropriate amine bases is most general.[1] In our study of silicon-tethered enyne metathesis of silyl ether **1** and silaketal **3** to the corresponding siloxanes **2** and **4** (Scheme 1), an efficient preparation of **1** and **3** was required. Although the typical silylation procedures serve well for the purpose of protecting hydroxyl groups with common silylating agents, the preparation of silyl ethers and silaketals possessing more elaborate substituents (as in **1** and **3**) requires a different silylation protocol.[4] Alternative silylation reactions such as transition-metal-catalyzed alcoholysis of hydrosilanes[5] and acid-catalyzed alcoholysis of allylsilanes[6] have been developed; however, their reaction scope has often been limited to simple, saturated alcohol substrates.

SCHEME 1. Silyl Ether- and Silaketal-Based Ring-Closing Enyne Metathesis



SCHEME 2. Catalytic Cycle of Alkynylsilane Alcoholysis



Conceptually, a new base-catalyzed silylation method can be developed with a silylating agent R_3Si-Y where Y is a reasonably good leaving group that retains a moderately high level of basicity. We deem alkynylsilanes **5** and **6** to possess these characteristics. As shown in the catalytic cycle (Scheme 2), the alkoxide generated by a base initiator would react with **5** (or **6**) to form the corresponding pentacoordinated silicate adduct, which would produce the silyl ether product by the dissociation of an alkynyl anion from the silicon center (or, alternatively, by a direct protonation of the C^{sp}–Si bond). A

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[1] (a) *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons: New York, 1999. (b) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817. (c) Muzart, J. *Synthesis* **1993**, 11.

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[3] For reviews of silicon tethers, see: (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813. (c) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2290. Examples of silicon tethers in other reactions: (d) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578. (e) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446. (f) Ishikawa, T.; Kudo, T.; Shigemori, K.; Saito, S. *J. Am. Chem. Soc.* **2000**, *122*, 7633. (g) Friestad, G. K.; Massari, S. E. *Org. Lett.* **2000**, *2*, 4237. (h) Mayasundari, A.; Young, D. G. J. *Tetrahedron Lett.* **2001**, *42*, 203. (i) Pearson, A. J.; Kim, J. B. *Org. Lett.* **2002**, *4*, 2837.

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[5] Recent examples: (a) Luo, X.-L.; Crabtree, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 2527. (b) Doyle, M. P.; High, K. G.; Bagheri, V.; Pieters, R. J.; Lewis, P. J.; Pearson, M. M. *J. Org. Chem.* **1990**, *55*, 6082. (c) Lorenz, C.; Schubert, U. *Chem. Ber.* **1995**, *128*, 1267. (d) Maifeld, S. V.; Miller, R. L.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 6363. (e) Field, L. D.; Messerle, B. A.; Rehr, M.; Soler, L. P.; Hambley, T. W. *Organometallics*, **2003**, *22*, 2387. (f) Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190. (g) Miller, R. L.; Maifeld, S. V.; Lee, D. *Org. Lett.* **2004**, *6*, 2773. Reviews: (h) Lukevics, E.; Dzintara, M. *J. Organomet. Chem.* **1985**, *295*, 265. (i) Corey, J. Y. *Adv. Silicon Chem.* **1991**, *1*, 327.

[6] (a) Morita, T.; Okamoto, Y.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 835. (b) Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* **1981**, 745. (c) Hosomi, A.; Sakurai, H. *Chem. Lett.* **1981**, 85. (d) Olah, G. A.; Husain, A.; Gupta, B. G. B.; Salem, G. F.; Narang, S. C. *J. Org. Chem.* **1981**, *46*, 5212. (e) Shimada, T.; Aoki, K.; Shinoda, Y.; Nakamura, T.; Tokunaga, N.; Inagaki, S.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 4688.

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TABLE 1. Base-Induced Silylation with Dialkynylsilane

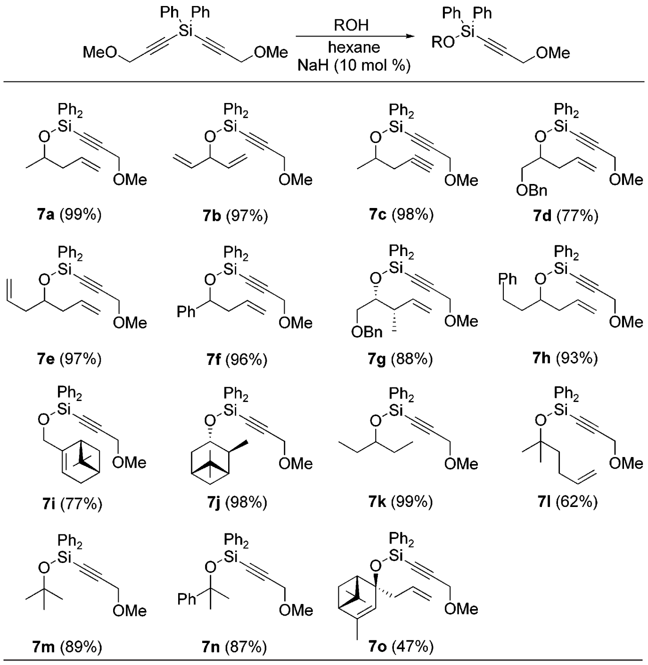


TABLE 2. Base-Induced Silylation with Trialkynylsilane

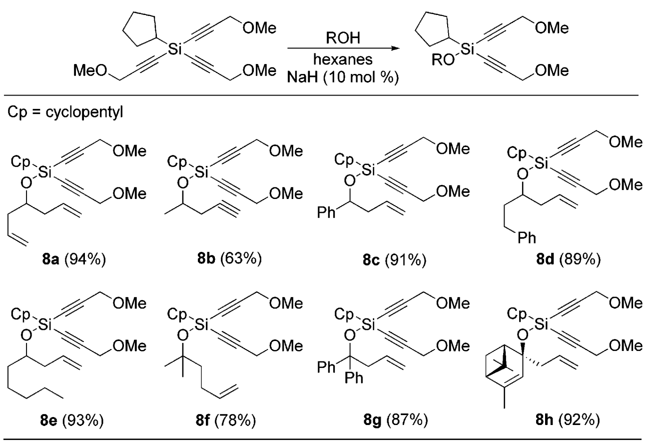
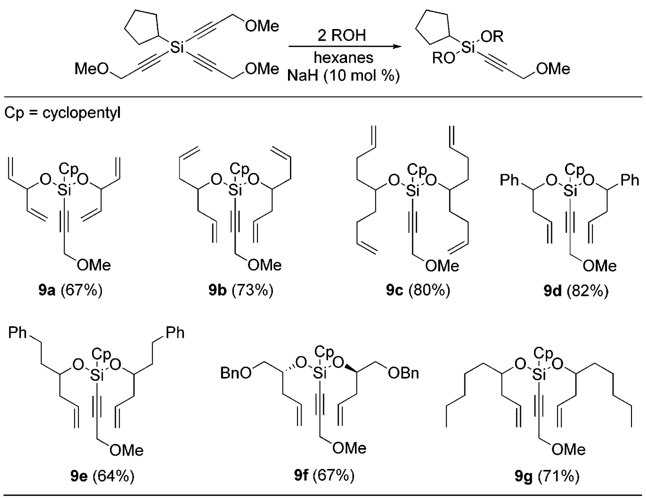


TABLE 3. Symmetrical Silaketals from Trialkynylsilane



subsequent proton abstraction by the alkynyl anion from another molecule of the substrate alcohol would regenerate the alkoxide, thereby establishing a smooth catalytic cycle and constituting an efficient method for the synthesis of mono- and dialkynyl silyl ethers. Although the base-induced alcoholysis of alkynylsilanes is a standard synthetic operation for the purpose of removing silyl groups from silylalkynes,[1a,7] this bond-making and bond-breaking process has never been exploited as an effective method of silyl ether synthesis. Herein we report the development of an efficient silylation protocol using di- and trialkynylsilanes as stable and reactive silylating agents and its successful implementation in the synthesis of alkynyl silyl ethers and silaketals.

In choosing specific alkynylsilanes for the development of this methodology, moderate reactivity and stability of the silanes—as well as high volatility of the alkyne byproduct—were considered important attributes. Diphenyl dialkynylsilane **5** (R = Ph, R′ = CH_2OMe) and cyclopentyl trialkynylsilane **6** (R = cyclopentyl, R′ = CH_2OMe) were found to possess these characteristics. A series of silylation reactions were then performed with silane **5** and a variety of alcohols to generate silyl ethers **7a**−**o** (Table 1). The optimal conditions involved the use of a catalytic amount of NaH (10 mol %) in hexanes.[8] For the primary and secondary alcohols, the reaction was generally complete in a few minutes at room temperature, affording **7a**−**k** in good to excellent yields after chromatography (without an aqueous workup). The low steric hindrance of these alcohol substrates necessitated the use of an excess amount of **5** (1.5−2.0 equivalents) to minimize the formation of symmetrical silaketals. In the case of the tertiary alcohols, the silylation could be performed with equimolar amounts of silane and alcohol but often required an elevated reaction temperature (50 °C) for 2−3 h. One particularly hindered alcohol underwent only partial conversion (47%) to the desired silyl ether **7o**.

In a similar fashion, trialkynylsilane **6** was treated with substrate alcohols in the presence of a catalytic amount of base (10 mol % NaH) to accrue silyl ethers **8a**−**h** in moderate to good yields (Table 2). Once again, the efficient formation of silyl ethers **8a**−**e** from secondary alcohols demanded the use of excess silane (2.0−2.5 equiv). The slightly lower efficiency of **6** in this reaction (relative to that of **5**) was due to increased formation of silaketals and trialkoxy adducts resulting from the apparently higher reactivity of the trialkynylsilane. More sterically hindered alcohols (such as the tertiary alcohol precursors to **8f**−**h**) required only a single equivalent of silane and proceeded in high yield at 50 °C without the formation of the aforementioned byproducts.

We then examined the feasibility of generating symmetrical alkynyl silaketals of the form **3** ($R^2 = R^3$) from trialkynylsilane **6** through a double displacement of alkynyl groups. Pleasingly, the same reaction conditions optimized for silyl ether formation gave **9a**−**g** in moderate to good yields by using 2 equiv of the alcohol substrates (Table 3). Although the trialkoxysilane was a

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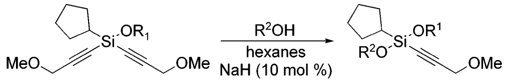
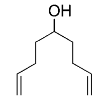
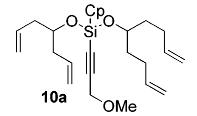
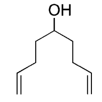
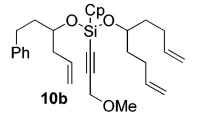
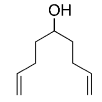
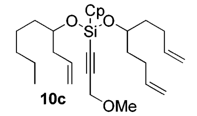
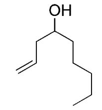
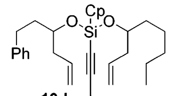
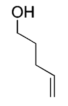
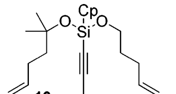
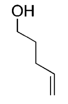
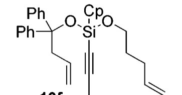
[7] (a) Ben-Efraim, D. A. In *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1978; Vol. 2, Chapter 18. (b) Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1965**, *4*, 217.

[8] Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890.

TABLE 4. Unsymmetrical Silaketals from Trialkynylsilane



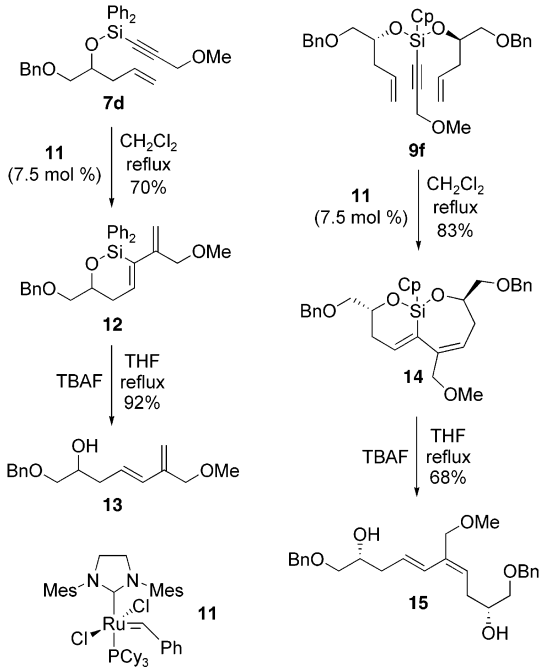
Entry	Silyl ether	Alcohol	Silaketal	Yield (%)
1	**8a**		 **10a**	77
2	**8d**		 **10b**	66
3	**8e**		 **10c**	66
4	**8d**		 **10d**	64
5	**8f**		 **10e**	60
6	**8g**		 **10f**	65

Cp = cyclopentyl

minor product in most of these reactions, sterically unhindered alcohols provided significant amounts of this byproduct (**9a** and **9f**), which could be minimized through the use of less alcohol (1.5 equiv). The employment of racemic secondary alcohols to form **9d**, **9e**, and **9g** led to the generation of each product as the expected mixture of three diastereomers. The ^{1}H and ^{13}C NMR of **9d** show three sets of complex signals, with evident differences in chemical shifts among the three diastereomers (the two meso compounds *RS* and *SR* and the enantiomeric pair *RR*/*SS*). Interestingly, the spectra of **9e** and **9g** were much simpler, with substantially less (if any) distinction between the diastereomeric resonances. Only a single set of signals was seen in the NMR spectra of **9f**, as it was derived from a homochiral sample of the secondary alcohol.

Encouraged by the efficient formation of alkynylsilyl ethers and symmetrical silaketals, we also pursued the synthesis of unsymmetrical silaketals of type **3** ($R^2 \neq R^3$) by the second alcoholysis of dialkynyl silyl ethers among **8a**–**i**. Although these silyl ethers possess two alkynyl leaving groups on silicon, the alkoxide moiety could also serve as a potential leaving group. Such an alkoxide-exchange process would greatly complicate the reaction by generating a mixture of the symmetrical and unsymmetrical silaketals. Hence, it was with some trepidation that the second alkynyl displacement reaction was attempted with silyl ether **8a** and 1,8-nonadien-5-ol (Table 4, entry 1) under the same conditions optimized for symmetrical silaketals. The desired unsymmetrical silaketal **10a** was obtained in 77% yield with only trace

SCHEME 3. Enyne Metathesis of Siloxane Products



amounts of the symmetrical silaketals. A number of secondary and tertiary silyl ethers were similarly reacted with secondary and primary alcohols, respectively, to generate silaketals **10b**–**f** in moderate yield (Table 4, entries 2–6). In all cases, the reactions were performed with equimolar amounts of silyl ether and alcohol, providing the silaketals in less than 60 min at room temperature. Small amounts of the symmetrical silaketals were seen in a few of these examples (**10b** and **10d**), but the desired product was easily separated from these minor components by chromatography. Silaketals **10b**–**d** possessed the added complexity of existing as diastereomeric mixtures. For each of these compounds, however, the corresponding NMR signals of the various diastereomers were often not distinguishable.

To demonstrate the utility of these silyl ethers and silaketals in synthetic transformations such as enyne ring-closing metathesis,[9] **7d** and **9f** were treated with a catalytic amount of second-generation Grubbs catalyst **11** in CH_2Cl_2,[10] providing enyne RCM product **12** (70%) and tandem enyne–diene RCM[11] product **14** (83%), respectively (Scheme 3). Removal of the temporary silicon

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(9) Recent reviews on enyne metathesis: (a) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (b) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 176–204. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.

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tether from these siloxanes with TBAF[12] proceeded smoothly with retention of double-bond configuration to afford the corresponding homoallylic alcohol **13** and homoallylic diol **15** as single stereoisomers.

In summary, we have developed an efficient silylation protocol by taking advantage of the basicity and leaving group ability of alkynyl anions. Under these base-induced silylation conditions, a variety of mono- and dialkynyl silyl ethers as well as symmetrical and unsymmetrical alkynyl silaketals have been prepared. The utility of these compounds has also been demonstrated via ring-closing metathesis and subsequent protodesilylation to form stereochemically defined 1,3-dienes. Further exploration of the ring-closing metathesis of alkynylsilyl ethers and alkynyl silaketals to form more complex siloxacycles is in progress.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915.