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Formation and Reactivity of Silacyclopropenes Derived from Siloxyalkynes: Stereoselective Formation of 1,2,4-Triols

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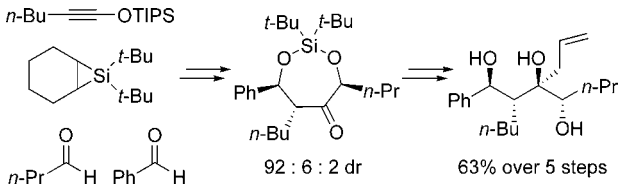
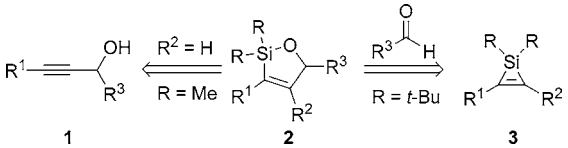
ABSTRACT



Silver phosphate-catalyzed silylene transfer to siloxyalkynes provided silacyclopropenes possessing a silyl enol ether functional group. Copper-catalyzed insertions of carbonyl compounds afforded the corresponding oxasilacyclopentenes. The embedded silyl enol ether functionality was treated with various aldehydes and a catalytic amount of $Sc(OTf)_3$ to provide dioxasilacycloheptanones, which resulted from an aldol addition/rearrangement. Stereoselective reduction or allylation of the cyclic ketone, followed by *n*-Bu_4NF deprotection, provided high yields of 1,2,4-triols possessing four contiguous stereocenters.

Oxasilacyclopentenes have proven to be versatile intermediates for the synthesis of a variety of valuable products, including highly substituted allylic alcohols, β-hydroxy ketones, 1,3-diols, and other polyoxygenated substrates.[1−4] The synthesis of oxasilacyclopentenes can be achieved with complementary regiochemistry either by intramolecular hydrosilylation of propargylic alcohols[1] (**1**, Scheme 1) or by the insertion of carbonyl compounds into silacyclopropenes (**3**).[3,5,6] We describe herein the construction of oxasilacyclopentene silyl enol ethers (**2**, $R^2 = OSiR_3$) from the ring expansion of 1-silyloxy silacyclopropenes. Subsequent treatment of the silyl enol ether with various aldehydes provided stereoselective formation of dioxasilacycloheptanones, precursors to 1,2,4-triols, through a $Sc(OTf)_3$-catalyzed Mukaiyama aldol reaction/1,3-Brook rearrangement sequence.

Scheme 1. Formation of Oxasilacyclopentenes



(1) (a) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028−10038. (b) Trost, B. M.; Ball, Z. T.; Jöge, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3415−3418.

(2) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450−8456.

(3) Clark, T. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9522−9523.

(4) For additional methods of oxasilacyclopentene formation, see: (a) Maifeld, S. V.; Lee, D. *Org. Lett.* **2005**, *7*, 4995−4998. (b) Miller, R. L.; Maifeld, S. V.; Lee, D. *Org. Lett.* **2004**, *6*, 2773−2776. (c) Clive, D. L. J.; Yang, W.; MacDonald, A. C.; Wang, Z.; Cantin, M. *J. Org. Chem.* **2001**, *66*, 1966−1983. (d) Gettwert, V.; Krebs, F.; Maas, G. *Eur. J. Org. Chem.* **1999**, 1213−1221.

(5) (a) Seyferth, D.; Vick, S. C.; Shannon, M. L. *Organometallics* **1984**, *3*, 1897−1905. (b) Seyferth, D.; Vick, S. C.; Shannon, M. L.; Lim, T. F. O.; Duncan, D. P. *J. Organomet. Chem.* **1977**, *135*, C37−C44. (c) Seyferth, D.; Duncan, D. P.; Vick, S. C. *J. Organomet. Chem.* **1977**, *125*, C5−C10.

(6) Weakly basic heteroatom substituents were intolerant of the carbonyl insertion conditions due to copper-catalyzed elimination: Clark, T. B.; Woerpel, K. A. *Organometallics* **2005**, *24*, 6212−6219.

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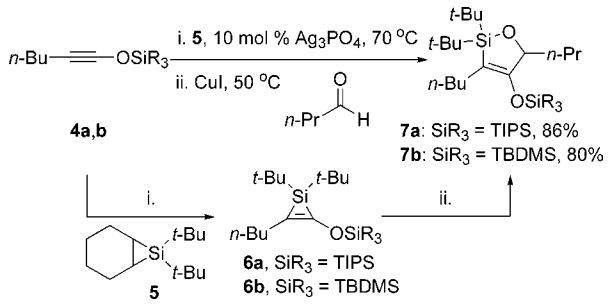
Oxasilacyclopentenes **7a**,**b** were constructed from alkynes **4a**,**b** by a two-step, one-flask procedure.[3,7] Silver phosphate-catalyzed silacyclopropenation of triisopropylsilyl- and *tert*-butyldimethylsilyl-protected ynols **4a**,**b** proceeded at 70 °C to provide high yields of silacyclopropenes **6a**,**b** with the desired silyl enol ether functionality (Scheme 2).[8,9] Although

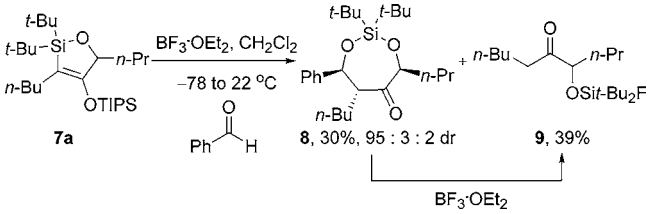
Scheme 2. Construction of Oxasilacyclopentenes **7a**,**b**



it was not clear that such highly functionalized silacyclopropenes would be stable, **6a**,**b** could be prepared and handled with little difficulty using silver-catalyzed di-*tert*-butylsilylene transfer conditions. Copper iodide-catalyzed insertion of butyraldehyde into silacyclopropenes **6a**,**b** provided oxasilacyclopentenes **7a**,**b**, with high regioselectivity (≥99:1). The selective functionalization of the C−Si bond in the presence of the silyl enol ether moiety demonstrates the high reactivity of the strained ring silane.[10]

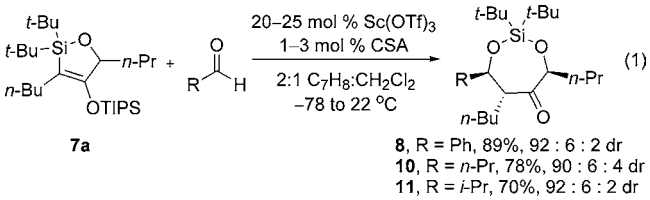
Although the silyl enol ether of silacyclopropene **6a** was less reactive than the C−Si bond, the enol ether moiety of oxasilacyclopentene **7a** participated in Lewis acid-catalyzed Mukaiyama aldol reactions[11] that incorporate a second aldehyde into the resulting product. Treatment of **7a** with benzaldehyde and a catalytic amount of $BF_3{\cdot}OEt_2$ provided aldol adduct **8** stereoselectively (Scheme 3).[12,13] Formation

Scheme 3. Boron Trifluoride-Catalyzed Mukaiyama Aldol of **7a**



of **8** may occur by addition of the enolate, resulting from desilylation of **7a**,[14] to benzaldehyde followed by a 1,3-Brook rearrangement.[15] In addition to the aldol addition/rearrangement product **8**, α-silyloxy ketone **9** was observed (Scheme 3). Treatment of isolated aldol adduct **8** with $BF_3{\cdot}OEt_2$ resulted in the formation of **9**, suggesting that a fluoride-mediated retro-aldol reaction had occurred.

Optimized conditions for the Lewis acid-catalyzed construction of aldol addition/rearrangement product **8** were established using oxasilacyclopentene **7a**. A Lewis acid that could catalyze the aldol reaction without decomposition of **8** was desired. Upon screening Lewis acids,[16] $Sc(OTf)_3$ provided aldol product **8** without formation of ketone **9**. The optimal reaction conditions utilized 20−25 mol % of $Sc(OTf)_3$, 1−3 mol % of camphorsulfonic acid (CSA), and 2/1 toluene/methylene chloride as solvent (eq 1). The reaction



(1)

selectivity and yield were sensitive to acid, but a catalytic amount of acid was required to initiate the process.[14] Both butyraldehyde and isobutyraldehyde participated in the aldol reaction with **7a** to provide dioxasilacycloheptanones **10** and **11** in high yield and selectivity (eq 1). Oxasilacyclopentene **7b** also provided aldol product **8**, but the observed yield and selectivity were diminished.

The scope of oxasilacyclopentenes that could be constructed and utilized in this transformation was extended by nucleophilic addition to oxasilacyclopentene acetals. Acetal **7c** was synthesized by the CuI-catalyzed insertion of ethyl formate into the C−Si bond of the in situ generated

(7) Ćiraković, J.; Driver, T. G.; Woerpel, K. A. *J. Org. Chem.* **2004**, *69*, 4007−4012.

(8) Silacyclopropene **6a** was isolated, purified, and characterized under inert conditions (88% yield). The yield of silacyclopropene **6b** (90%) was determined by ^{1}H NMR spectroscopic analysis of the product relative to an internal standard ($PhSiMe_3$).

(9) For recent applications of siloxyalkynes in organic synthesis, see: (a) Sun, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13512−13513. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806−11807. (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204−10205. (d) Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442−7443.

(10) The observed regioisomer lends further support to the proposed mechanism of carbonyl insertion (transmetalation of the C−Si bond by CuI) and discounts an alternative Lewis acid-catalyzed mechanism. See: Franz, A. K.; Woerpel, K. A. *Acc. Chem. Res.* **2000**, *33*, 813−820.

(11) For a review of the Mukaiyama aldol reaction, see: Carreira, E. M. In *Comprehensive Asymmetric Catalysis I*−*III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; pp 997−1065 and references therein.

(12) Proof of stereochemistry of the products is provided as Supporting Information.

(13) For a review on the diastereoselectivity of Mukaiyama aldol reactions, see: Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120.

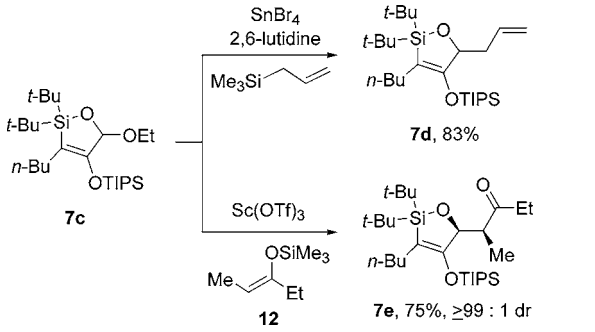
(14) (a) Lin, S.; Bondar, G. V.; Levy, C. J.; Collins, S. *J. Org. Chem.* **1998**, *63*, 1885−1892. (b) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570−4581. (c) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323−4326.

(15) For examples of 1,3-Brook rearrangements, see: (a) Naganuma, K.; Kawashima, T.; Okazaki, R. *Chem. Lett.* **1999**, *28*, 1139−1140. (b) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503−514. (c) Yamamoto, K.; Kimura, T.; Tomo, Y. *Tetrahedron Lett.* **1985**, *26*, 4505−4508. (d) Wilson, S. R.; Georgiadis, G. M. *J. Org. Chem.* **1983**, *48*, 4143−4144. (e) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809−6811.

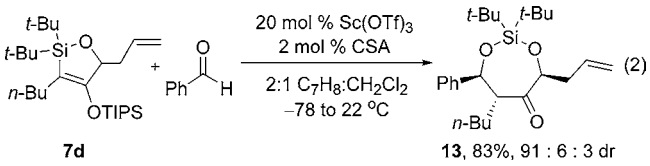
(16) With nonfluoride-containing Lewis acids, a dual activation of the carbonyl and silicon groups is postulated. A subset of the Lewis acids that were examined for this transformation are as follows: SnX_4, SnX_2, TiX_4, ZnX_2, R_3SiOTf, and $Ln(OTf)_3$ (where X = Br, Cl, F, OTf).

silacyclopropene **6a** in 83% yield and >99:1 regioselectivity. Lewis acid-mediated nucleophilic substitution reactions of acetal **7c** provided oxasilacyclopentenes **7d** and **7e** (Scheme 4).[17] Addition of allyltrimethylsilane proceeded in high yield

Scheme 4. Nucleophilic Addition to Acetal **7c**

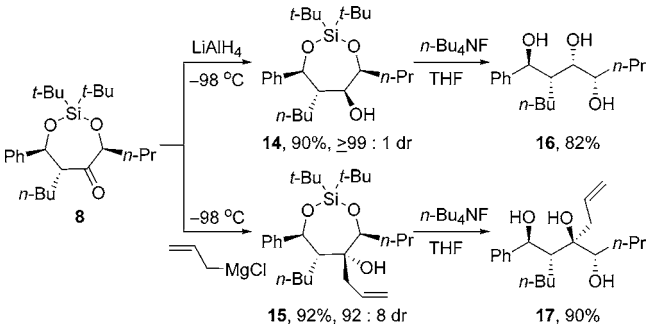


with $SnBr_4$ and 2,6-lutidine. Nucleophilic addition of silyl enol ether **12** was catalyzed by $Sc(OTf)_3$ to provide **7e** as a single diastereomer. Oxasilacyclopentene **7d** also participated in the aldol addition/rearrangement reaction to provide the desired adduct **13** in high yield and selectivity (eq 2).



The cyclic ketone **8** provided access to 1,2,4-triols with four contiguous stereocenters in high selectivity. Reduction of aldol product **8** with $LiAlH_4$ at −98 °C provided alcohol **14** in ≥99:1 diastereoselectivity (Scheme 5). Addition of

Scheme 5. Formation of 1,2,4-Triols **16** and **17**



allylmagnesium chloride to **8** at −98 °C afforded tertiary alcohol **15** in 92:8 diastereoselectivity. Deprotection of **14** and **15** with *n*-Bu_4NF[18] provided 1,2,4-triols[19] **16** and **17** possessing four contiguous stereocenters.

Functionalizations of ketone **8** with the two different nucleophiles (Scheme 5) involve addition to opposite faces, which was not anticipated. The selectivity of the addition of $LiAlH_4$ is consistent with the solid-state structure of the starting material. Analysis of the X-ray crystal structure of **8** reveals the steric congestion that blocks hydride addition syn to the propyl substituent (Figure 1). The butyl (at C2)

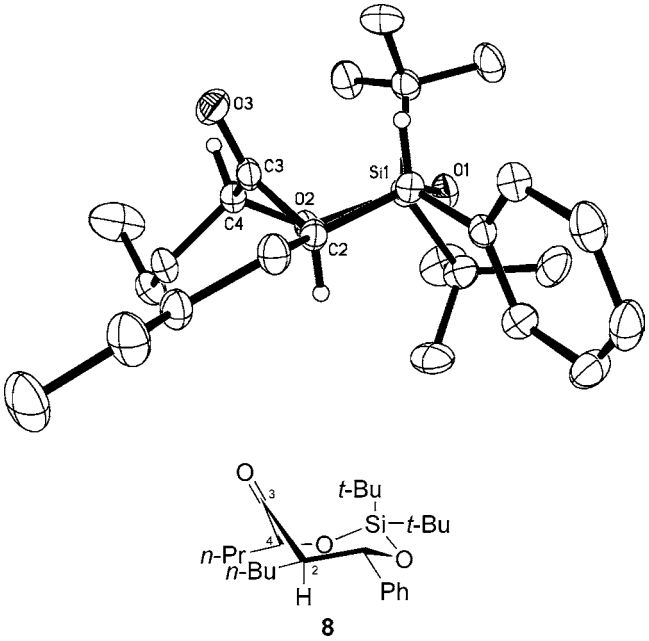


Figure 1. X-ray crystal structure of **8**.

and propyl (at C4) substituents lie nearly perpendicular to the carbonyl group (C3), blocking access to this face of the carbonyl through the Bürgi−Dunitz angle.[20] Approach to the other face is impeded by the *tert*-butyl substituents. Only small nucleophiles, such as a hydride,[21] are able to approach over the *t*-Bu substituent. Because neither trajectory is favorable, nucleophiles with increased steric bulk (as compared to a hydride) are too hindered to add to either face of the carbonyl.[22]

The reversal in selectivity of the Grignard reagent results from the different mechanism of its nucleophilic addition. The addition of allylmagnesium chloride to **8** does not proceed through standard nucleophilic attack on the carbonyl. Unlike other Grignard reagents,[22] allylmagnesium chloride

(17) Attempts to prove the relative stereochemistry of **7e** by chemical derivatization and crystallization were unsuccessful, so the stereochemistry was assigned by close analogy. See: Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056−2064.

(18) Direct deprotection of **8** with *n*-Bu_4NF was unsuccessful due to a competitive retro-aldol reaction.

(19) For additional examples of 1,2,4-triol formation utilizing silicon-masked precursors, see: (a) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487−6498. (b) Murakami, M.; Oike, H.; Sugawara, M.; Suginome, M.; Ito, Y. *Tetrahedron* **1993**, *49*, 3933−3946.

(20) Bürgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460−473.

(21) Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377−1386.

(22) Substrate **8** was unreactive with other Grignard reagents.

can react with carbonyl compounds via single-electron transfer (SET)[23,24] or through a six-membered ring transition state.[25] In the case of ketone **8**, the six-membered transition state is unlikely due to the steric congestion of **8**. A mechanism involving SET would result in an oxygen-stabilized radical with two possible conformers **A** and **B** (Figure 2).[26] Addition of the allyl radical to conformer **A**

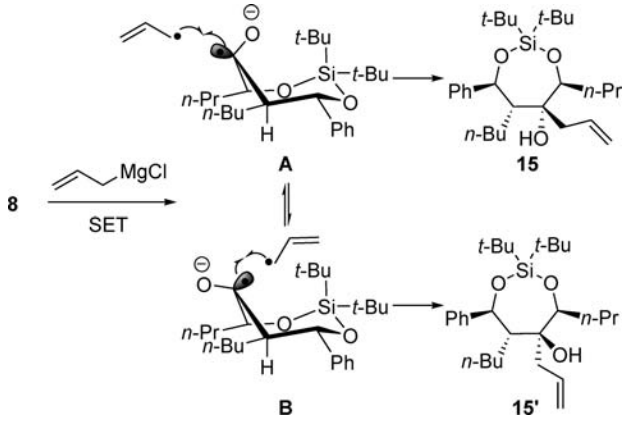


Figure 2. Formation of alcohol **15** by radical **A**.

was preferred due to decreased steric congestion of the required trajectory. The conformational change induced by SET allows addition by pseudoaxial attack to anomeric radical **A** by requiring an alternative trajectory (compared to ketone **8**) by which the allyl radical adds to the anomeric radical.

In summary, siloxyalkynes could be converted to 1,2,4-triols stereoselectively via silacyclopropenes and oxasilacyclopentenes through an aldol addition/rearrangement reaction. Oxasilacyclopentene acetal **7c** allowed access to substrates with various substitution patterns. Upon stereoselective allylation or reduction of the ketone, 1,2,4-triols **16** and **17** were obtained in five steps and 56−63% overall yield from siloxyalkyne **4a**.

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Supporting Information Available: Experimental procedures and spectroscopic, analytical, and X-ray data for the products (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225−230.
(25) Gajewski, J. J.; Bocian, W.; Brichford, N. L.; Henderson, J. L. *J. Org. Chem.* **2002**, *67*, 4236−4240.
(26) Rychnovsky, S. D.; Powers, J. P.; Lepage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−8384.