

Silylcarbonylation of Terminal and Internal Alkynes

Background

Current research is focused on investigating the utility and formation of oxasilacyclopentenes **3** from terminal and internal alkynes. High yields and regioselectivities of oxasilacyclopentenes can be achieved from the metal – catalyzed insertion of carbonyl compounds into silacyclopropenes **2**. The high regioselectivity of oxasilacyclopentene formation and the high diastereoselectivity of further transformations provide a useful synthetic strategy for further development in organic synthesis.

Silacyclopropenes **2** can be generated by transfer of “*t*-Bu₂Si:” to an alkyne; cyclohexene silacyclopropene **1** is a highly reactive source of “*t*-Bu₂Si:”. “*t*-Bu₂Si:” reacts similar to a carbene and adds to a π bond by a cycloaddition reaction.¹ Silver – catalyzed silylene transfer to both terminal and internal alkynes gave high yields of silacyclopropenes **2** (eq 1, Table 1).

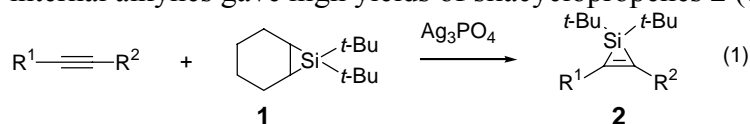


Table 1. Silacyclopropenation of alkynes (equation 1)

Entry	Alkyne	% NMR Yield
1	TMS—≡	82
2	Ph—≡—Me	91
3	Ph—≡	95
4	TIPSO—≡—Me	94

Various substituted silacyclopropenes **2** were investigated for their regioselectivity in carbonyl insertion (eq 2, Table 2). Due to the highly reactive nature of silacyclopropenes **2**, an in situ carbonyl insertion was developed. Ketones and aldehydes provided high yields and regioselectivities over the two-step sequence (Table 2, entries 1-3). Various internal alkynes were also shown to provide oxasilacyclopentenes in high yield and regioselectivity (Table 2, entries 5-6); Cu(OTf)₂, however, was required to provide the desired product.

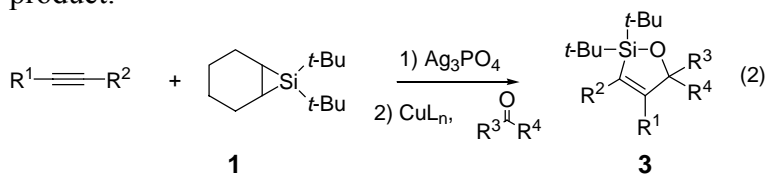


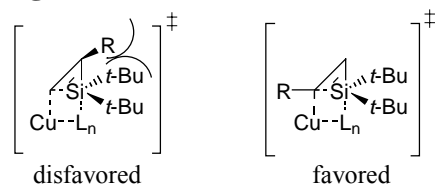
Table 2. Insertion of carbonyl compounds into silacyclopropenes (equation 2)

Entry	Alkynes	Oxasilacyclopentenes	% Yield	Regioselectivity	CuL _n
1	Ph—≡		83	≥97:3	CuBr ₂
2	Ph—≡		79	99:1	CuBr ₂
3	TMS—≡		88	≥99:1	CuI

4			94	97:3	Cu(OTf) ₂
5			90	95:5	Cu(OTf) ₂

The observed regioselectivity of oxasilacyclopentene formation results from insertion into the more sterically hindered C-Si bond. The favored transmetalation transition state displays that the copper catalyst preferentially breaks the more substituted C-Si bond of the silacyclopentene, avoiding steric interactions between the *t*-Bu groups and the substituent (Figure 1).²

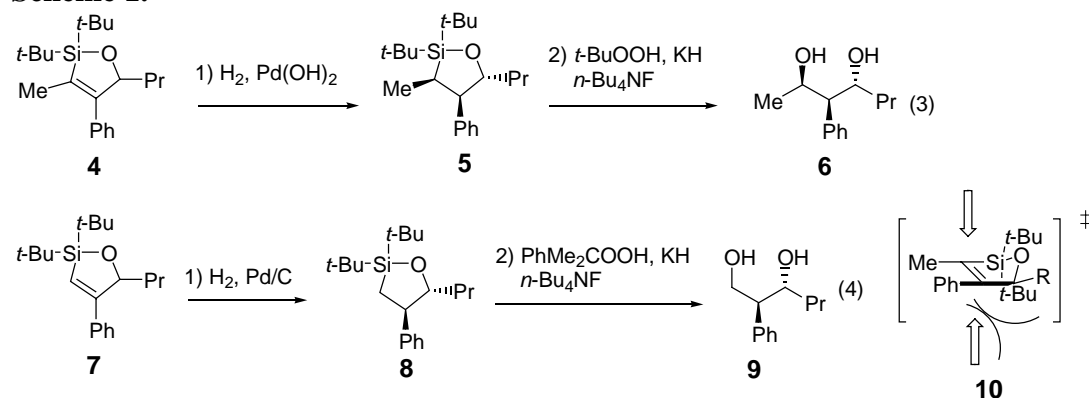
Figure 1. Transition state of the transmetalation process



The electronic components of the substituent also affect the rate of the transmetalation process. Since the transmetalation transition state is stabilized by polar bonds, an electron withdrawing group, such as phenyl would make the transmetalation process more facile.

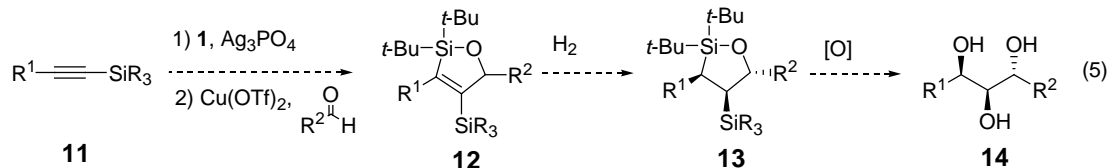
An example of the synthetic utility of oxasilacyclopentenes is realized in their diastereoselective hydrogenation and subsequent oxidation to provide 1,3 diols. The hydrogenation of oxasilacyclopentene was shown to be highly diastereoselective (Scheme 1). In the diastereoselective hydrogenation of oxasilacyclopentenes, the hydrogen atoms add syn to the allylic substituent of the carbonyl. Oxidation of oxasilacyclopentanes **5** and **8** result in the formation of 1,3-diols **6** and **9**.⁴ Diols occur in natural products so this could potentially be useful in the organic synthesis of pharmaceuticals, natural products and their analogs.³

Scheme 1.



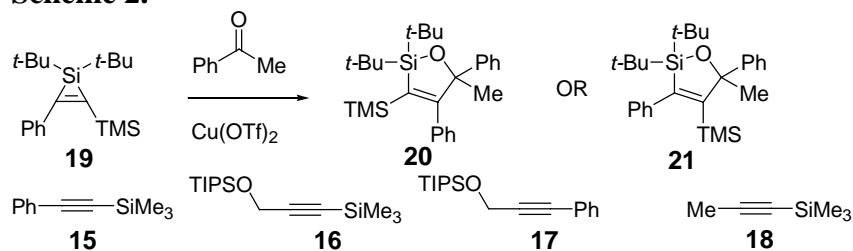
Objective

The goal of this project is to examine the effect of various alkyne substituents on the regioselectivity of carbonyl insertions and to utilize the observed trends to increase the synthetic utility of oxasilacyclopentenes. Use of internal alkynes such as **11** is expected to provide oxasilacyclopentenes **12**, which upon hydrogenation and global oxidation would result in 1,2,3-triol **14**. 1, 2, 3-triols are also very common functional group motifs in natural products and pharmaceuticals.

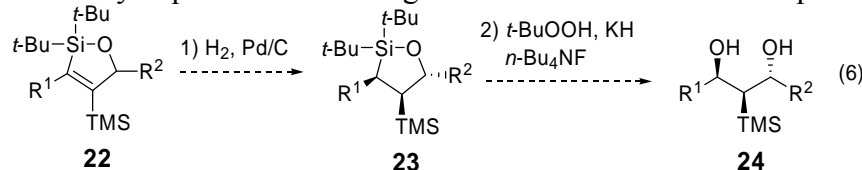


The alkynes used in previous experiments had sterically large or electron withdrawing substituents which led to the regioselective formation of oxasilacyclopentenes. Our group would like to investigate the regioselectivity of silacyclopropanation and carbonyl insertion of alkynes having substituents with competing regioselective groups. Compounds **15-18** contain substituents that were previously shown to give high regioselectivity in terminal and some internal alkynes (Table 2). Initial experimentation will utilize alkynes **15-18** to examine the effect of substituents such as $\text{Me}_3\text{Si-}$, Ph- , and $\text{TIPSOCH}_2\text{-}$ on the regioselectivity of carbonyl insertion. For example, we predict that silacyclopropene **21** will be formed and the regioselectivity of carbonyl insertion will be determined (Scheme 2). Both Ph- and TMS- substituents provide regioselectivity in the carbonyl insertion of silacyclopropenes derived from terminal alkynes (Table 2, entries 1, 4). These alkynes are commercially available or can be made in one step from commercially available compounds. Experiments will determine the dominant substituent for regioselective insertions. If the carbonyl insertion is not regioselective, various metal salts and carbonyls will be examined to establish a regioselective reaction.

Scheme 2.

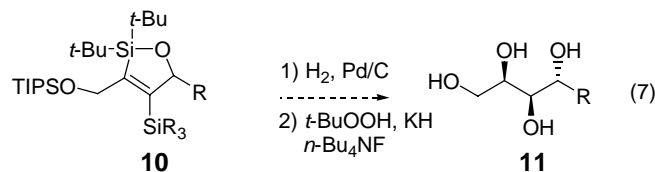


Upon establishing the regioselectivity of carbonyl insertion into silacyclopropenes derived from alkynes **15-18**, the hydrogenation and oxidation of the resultant oxasilacyclopentenes will be examined. Hydrogenation of these substrates are expected to be diastereoselective (vide supra) and oxidation of oxasilacyclopentanes with the general substitution of **23** is expected to give 1,3-diol **24**.



After establishing the formation and reactivity of trimethylsilyl substituted oxasilacyclopentenes, we will investigate the effect of oxidizable silyl substituents. The C-Si bond of trimethylsilyl groups cannot be directly oxidized into alcohols. Oxidation of the C-Si bond typically requires an aryl or alkoxy substituent on the silicon to afford oxidation products.⁴ Alkynes containing a SiMe_2Ph group will then be explored under the reaction conditions of $\text{Me}_3\text{Si-}$ substituted alkynes. Formation of the aforementioned alkynes will be achieved by deprotonation of the terminal alkyne with a base and subsequent substitution reactions to generate the desired alkynes. The SiMe_2Ph substituent is expected to react similarly to the TMS group, however, upon oxidation of the resultant oxasilacyclopentane, 1,2,3-triols will be achieved (eq 5).

In addition to 1,2,3-triols, this methodology would expand the application of oxasilacyclopentene to various polyoxygenated natural products. For example, hydrogenation and oxidation of protected alcohol **10** could potentially generate tetraol **11**.



References

- (1) Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 10659-10663.
- (2) Franz, A. K.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 949-957.
- (3) For a review on some 1,3-diols found in natural products, see: Rychnovsky, S. D.; *Chem. Rev.* **1995**, *95*, 2021-2040.
- (4) For a review of C-Si bond oxidation, see: Tamao, K. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI: Greenwich, CT, 1996; Vol. 3, pp 1-62. b) Fleming, I. *Chemtracts-Org. Chem.* **1996**, *9*, 1-64. c) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599-7662.

SURP – Timeline for Summer

June:

- synthesize and characterize silacycloprenes (including synthesis of desired alkynes)
- determine the regioselectivity of carbonyl insertion

July:

- optimize the regioselectivity and yield of carbonyl insertion
- hydrogenate oxasilacyclopentenes and determine the diastereoselectivity of the reaction
- oxidize oxasilacyclopentanes and prove the major diastereomers that were formed

August:

- synthesize and characterize alkynes with oxidizable silicon to form triols and tetraols
- determine the regioselectivity of carbonyl insertion
- synthesize and characterize silacycloprenes with oxidizable silicon
- hydrogenate and oxidize oxasilacyclopentenes