# Tandem Intramolecular Silylformylation−Allylsilylation

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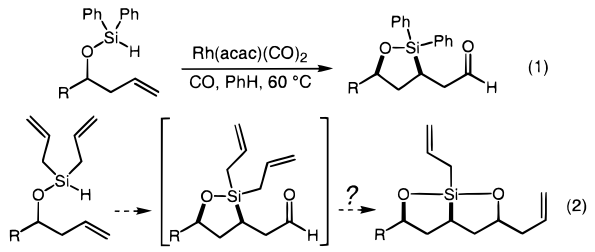
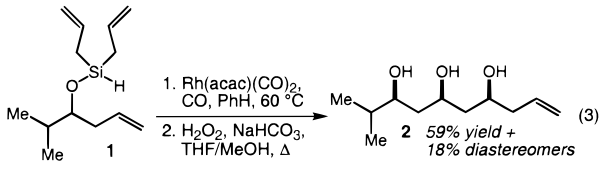
Due to the prevalence and clinical relevance of natural products with the skipped polyol structural motif,[1] we have been engaged in the development of efficient strategies for their synthesis.[2,3] Our efforts have focused on olefin carbonylation reactions and the general approach is summarized in Scheme 1. Special emphasis has been placed on the direct production of suitably protected polyhydroxy aldehydes, since the next step in the sequence is the addition of an allyl group. In this fashion a highly efficient three-step iterative sequence, with no protection steps or oxidation state adjustments, might be realized.

Another important advantage to the direct production of aldehydes is that, at least in principle, it is possible to envision the aldehyde allylation step being rendered in tandem with the carbonylation reaction. Given that the previously reported intramolecular alkene silylformylation reaction produces $\beta$-silylaldehydes directly (eq 1),[2b] and that allylsilanes are well-known



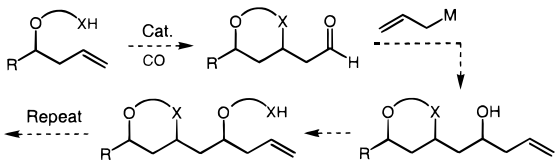

aldehyde allylation agents,[4] it seemed plausible that silylformylation of a diallylsilane might lead to spontaneous intramolecular aldehyde allylsilylation (eq 2). If successful, this tandem reaction would, upon Tamao oxidation of the product,[5] deliver 1,3,5-triols in a remarkably efficient manner.

Our studies commenced with diallylsilyl ether **1**, readily prepared from the corresponding homoallylic alcohol in a single step (eq 3).[6] Subjection of this silane to the action of 3 mol % of




$Rh(acac)(CO)_2$ in benzene under 1000 psi of CO at 60 °C in a stainless steel pressure reactor, followed by evaporation of solvent and subjection of the residue to the conditions of the Tamao oxidation ($H_2O_2$, $NaHCO_3$, THF/MeOH, reflux), led to a mixture

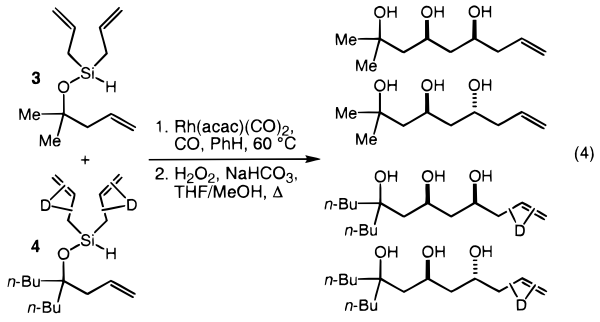
**Scheme 1**




of triols in 77% yield. The major product, easily separable from a mixture of minor diastereomers, was isolated in 59% yield and was identified as the *syn,syn* triol **2**.[7] $^1$H NMR analysis of the product of the carbonylation step revealed a complex spectrum with no peaks in the aldehyde region. Although the spectrum has resonances consistent with the dioxasilabicyclo[3.3.0]octane depicted in eq 2, the peaks are quite broad and featureless. Mass spectral analysis indicated high molecular weight material with a repeating fragment pattern suggestive of an oligomeric mixture. On the basis of these data it is proposed that the initially formed dioxasilabicyclo[3.3.0]octane undergoes a ring-opening oligomerization through O−Si bonds, a process driven by relief of ring strain. Regardless, it is clear that following the carbonylation an allyl group is transferred, forming a second C−C bond and a second new stereocenter in a single tandem reaction.

With the feasibility of the tandem reaction established, a brief survey of the substrate scope was undertaken (Table 1). As with our previous silylformylation study,[2b] best results were obtained in benzene under 1000 psi of CO at 60 °C; below ∼800 psi of CO or ∼45 °C, the rate of the silylformylation reaction becomes impracticably slow. Entries 1, 2, and 3 establish the tolerance for both silyloxy and alkenyl groups, and reveal the trend of increasing diastereoselectivity with increasing size of the homoallylic substituent. The increased diastereoselectivity of entry 4 relative to entry 1 due to the presence of an *anti* allylic methyl group mirrors a similar increase observed in the diphenylsilane silylformylation reaction.[2b] This suggests that the modest diastereoselectivity observed for entries 1−3 is due mainly to the modest diastereoselectivity of the silylformylation reaction, and that the diastereoselectivity of the allylation reaction is quite high. Entry 5 corroborates this interpretation and provides a useful benchmark diastereoselectivity (93:7) for the allylation. Finally, we note that in every case we have thus far studied, the major *syn,syn* triol is easily separable from a mixture of the other diastereomers.

To gain mechanistic insight into this unusual allylation reaction, we began by establishing the intramolecular nature of the process with the crossover experiment shown in eq 4. Thus, a 1:1 mixture




of diallylsilane **3** and deuterium-labeled diallylsilane **4** was subjected to the standard conditions and produced the four indicated products, each of which could be cleanly isolated. No evidence

(1) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2012−2040.
(2) (a) Leighton, J. L.; O'Neil, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 11118−11119. (b) Leighton, J. L.; Chapman, E. *J. Am. Chem. Soc.* **1997**, *119*, 12416−12417. (c) Sarraf, S. T.; Leighton, J. L. *Tetrahedron Lett.* **1998**, *39*, 6423−6426. (d) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403−405.
(3) For reviews of other approaches, see ref 1 and the following: (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635−645. (b) Schneider, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1375−1378.
(4) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293.
(5) For a review on the Tamao and Fleming oxidations, see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.
(6) The alcohol is treated with $HSiCl_3$, followed by 2 equiv of allyl-MgBr. This reaction provides the desired diallylsilyl ethers in 50−90% yields, with more sterically hindered alcohols giving better results. See the Supporting Information for details.
(7) Stereochemical determinations were made using the method of Rychnovsky: Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515. See the Supporting Information for details.

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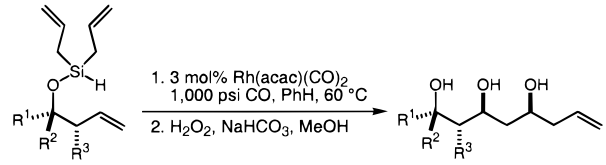
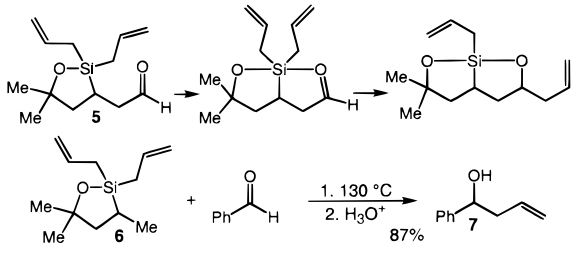
**Table 1.**[a]




| entry | $R^1$ | $R^2$ | $R^3$ | d.s.[b] | *y* (%)[c] |
|---|---|---|---|---|---|
| 1 | H | *i*-Pr | H | 77:23 | 59 |
| 2 | H | $TBSOCH_2CH_2$ | H | 71:29 | 45 |
| 3 | H | $CH_2{=}CHCH_2$ | H | 69:31 | 50 |
| 4 | H | *i*-Pr | Me | 92:8 | 59 |
| 5 | Me | Me | H | 93:7 | 65 |

[a] All reactions were conducted in a stainless steel pressure reactor equipped with a pressure gauge and a glass liner. [b] *Syn,syn* triol: sum of all other diastereomers. [c] Isolated yield of purified major product.

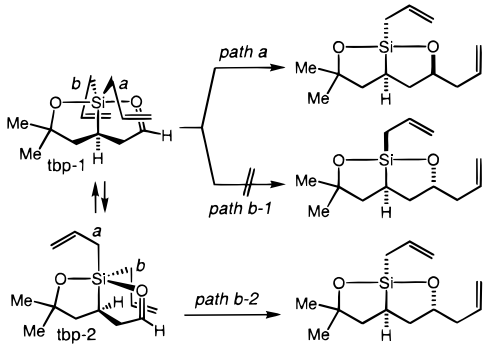
**Scheme 2**




for the incorporation of any deuterium in the products derived from **3** could be detected by $^1$H, $^2$H, and $^{13}$C NMR spectroscopy.

Examples of intramolecular silicon-tethered allylsilane additions to aldehydes,[8] acetoxyazetidinones,[9] and acetals[10] have been reported, but require the use of external Lewis acids. There has been one report of uncatalyzed additions, both inter- and intramolecular, of tetracoordinate allylsilanes to aldehydes and ketones based on the use of strained allylsilacyclobutanes.[11] This report followed the disclosures of Myers[12] and Denmark[13] that enoxysilacyclobutanes engage in uncatalyzed aldol addition reactions. These uncatalyzed reactions proceed through the agency of what Denmark has termed "strain release Lewis acidity".[14] In this model the ~80° C−Si−C bond angle imposed by the silacyclobutane favors complexation of an aldehyde with concomitant Si rehybridization to a trigonal-bipyramid with the silacyclobutane spanning apical and equatorial positions (90° ideally). Although we cannot rule out a role for the rhodium in the present allylation reaction, we believe that the reaction (of **3**, e.g.) proceeds, after silylformylation to produce aldehyde **5**, by way of a trigonal-bipyramidal Si−O(aldehyde) complex (Scheme 2). The O−Si−C bond angle in an oxasilacyclopentane is ~95°,[15] which would be expected to favor a trigonal-bipyramidal geometry at Si in analogy to the silacyclobutane chemistry.[16] Support for this mechanism was then secured when it was shown that

**Scheme 3**




pyrolysis of oxasilacyclopentane **6** (obtained by rhodium-catalyzed hydrosilylation[17] of **3**) with benzaldehyde (6.0 equiv) in a sealed tube at 130 °C produced homoallylic alcohol **7** in 87% yield.[18]

Analysis of the four possible[19] trigonal-bipyramidal (tbp) conformations for the Si−O(aldehyde) complex of the aldehyde **5** reveals two wherein both the oxasilacyclopentane ring and the five-membered ring formed by Si−O(aldehyde) complexation span apical and equatorial positions (Scheme 3). Transfer of allyl group a in tbp-1 (path a) is expected to be favored, since it is closer to the aldehyde than allyl group b, and leads to the observed major *syn* product. Transfer of allyl group b (path b-1) could be the source of the minor *anti* product, but this pathway should be highly disfavored since the initial product would be a highly strained *trans*-fused dioxasilabicyclo[3.3.0]octane. Instead, it is proposed that the minor diastereomer is formed by way of a pseudorotation to tbp-2,[20,21] followed by transfer of allyl group b (path b-2), leading to production of the illustrated *cis*-fused dioxasilabicyclo[3.3.0]octane.

The reported tandem silylformylation−allylsilylation reaction forms the basis of a highly efficient approach to polyol synthesis and comprises the first demonstration of the utility of oxasilacyclopentanes in an uncatalyzed C−C bond forming process. Homoallylic alcohols are converted into new two-polyol unit extended homoallylic alcohols in three simple steps, and the complete roster of required stoichiometric reagents is $HSiCl_3$, allyl-MgBr, CO, $H_2O_2$, and $NaHCO_3$. The utility of the oxasilacyclopentanes as synthons in and of themselves, their ease of generation, and the resultant opportunity for tandem reactions distinguish this chemistry and suggest multiple possibilities for further development.

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**Supporting Information Available:** Representative experimental procedures and spectral data for the starting materials and products in Table 1 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889−3898.
(9) Uyeo, S.; Itani, H. *Tetrahedron Lett.* **1991**, *32*, 2143-2146.
(10) Linderman, R. J.; Chen, K. *J. Org. Chem.* **1996**, *61*, 2441−2453.
(11) Matsumoto, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 7152−7155.
(12) (a) Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922−7923. For another example of an uncatalyzed silicon-mediated aldol reaction, see: (b) Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672−9674. (c) Myers, A. G.; Widdowson, K. L.; Kukkola, P. *J. Am. Chem. Soc.* **1992**, *114*, 2765−2767.
(13) (a) Denmark, S. E.; Griedel, B, D.; Coe, D. M. *J. Org. Chem.* **1993**, *58*, 988−990. (b) Denmark, S. E.; Griedel, B, D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026−7043.
(14) Denmark, S. E.; Jacobs, R. T.; Dai-Ho, G.; Wilson, S. *Organometallics* **1990**, *9*, 3015−3019.
(15) Several relevant X-ray structures have been reported. See, for example: Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 6706−6707.
(16) Hoveyda has reported relevant observations regarding the Lewis acidity of oxasilacyclopentanes of this type. See: Young, D. G. J.; Hale, M. R.; Hoveyda, A. H. *Tetrahedron Lett.* **1996**, *37*, 827−830.
(17) (a) Tamao, K.; Tanaka, T.; Nakajima, T.; Sumiya, R.; Arai, H.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 3377−3380. (b) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090−6093.
(18) These are the conditions employed by Utimoto. See ref 11.
(19) We exclude a fifth possible tbp isomer, wherein the oxasilacyclopentane and the aldehyde O span only eqatorial positions, since it is expected to be highly strained.
(20) Myers has elegantly established a mechanism involving pseudorotation for the uncatalyzed aldol reactions of *O*-silyl ketene *N*,*O*-acetals. See ref 12c.
(21) For an excellent discussion of pseudorotation of pentacoordinate silicon and lead references, see: (a) Stevenson, W. H., III; Wilson, S.; Martin, J. C.; Farnham, W. B. *J. Am. Chem. Soc.* **1985**, *107*, 6340−6352. (b) Stevenson, W. H., III; Martin, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 6352−6358.