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Acid-Catalyzed Cyclization of Epoxyallylsilanes. An Unusual Rearrangement Cyclization Process

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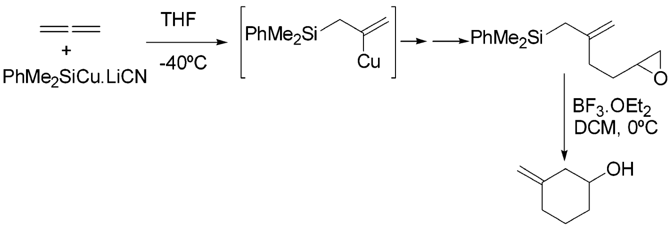
ABSTRACT



A new route for the synthesis of epoxyallylsilanes bearing the phenyldimethylsilyl group is reported that involves silylcupration of allene, conjugate addition to enones, and sulfur-ylide-mediated epoxidation. The Lewis acid-catalyzed cyclization of these substrates is presented. The expected normal products derived from 5-*exo* and/or 6-*endo* attack are not observed; instead, methylenecyclohexanols resulting from a tandem rearrangement–cyclization process are formed.

The use of organosilicon compounds as useful reagents in the construction of natural products has become a powerful tool in organic synthesis.[1] In particular, allylsilanes have proved to be one of the most versatile silicon-containing synthons in allylation reactions.[2] It is well-known that Lewis Acids promote the reaction of allylsilanes with carbonyl compounds (Sakurai−Hosomi reaction),[2a,3] enones,[2a,4] α,β-unsaturated esters,[5] and iminium ions.[2a,6] The corresponding intramolecular process, often called allylsilane-terminated cyclization, is an easy entry to ring formation.

Despite its synthetic potential, the cyclization of epoxyallylsilanes has not been widely explored. It has been reported that the stabilization of the incipient charge in the Lewis acid-mediated intramolecular process overrides entropic and stereoelectronic factors. Under Lewis acid conditions, nucleophilic substitution usually takes place at the most substituted carbon center of the epoxide[7] unless the presence of electron-withdrawing groups next to the epoxide destabilizes the developing carbocation.[8]

Epoxyallylsilanes have been previously prepared by Wittig reaction of an aldehyde with $Ph_3P{=}CHCH_2SiMe_3$ followed

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[2] (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (b) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167. (c) Organ, M. G.; Winkle, D. D.; Huffmann, J. *J. Org. Chem.* **1997**, *62*, 5254. (d) Suginome, M.; Iwanami, T.; Yamamoto, A.; Ito, Y. *Synlett* **2001**, 1042.

[3] (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354. (c) Schlosser, M.; Franzini, L.; Bauer, C.; Leroux, F. *Chem. Eur. J.* **2001**, *7*, 1909. (d) Yadav, J. S.; Chand, P. K.; Anjaneyulu, S. *Tetrahedron Lett.* **2002**, *43*, 3783.

[4] For selected examples, see: (a) Jeroncic, L. O.; Cabal, M.-P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387. (b) Kraus, G. A.; Bougie, D. *Tetrahedron* **1994**, *50*, 2681. (c) Knölker, H.-J.; Wanzel, G. *Synlett* **1995**, 378. (d) Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3230. (e) Wu, M.-J.; Yeh, J.-Y. *Tetrahedron* **1994**, *50*, 1073. (f) Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Satheesh, G. *Tetrahedron Lett.* **2002**, *43*, 9695.

[5] (a) Knölker, H.-J.; Baum, G.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1612. (b) Organ, M. G.; Dragan, V.; Miller, M.; Froese, R. D. J.; Goddart, J. D. *J. Org. Chem.* **2000**, *65*, 3666.

[6] (a) Katagiri, N.; Okada, M.; Kaneko, C.; Furuya, T. *Tetrahedron Lett.* **1996**, *37*, 1801. (b) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223. (c) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255. (d) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858. (e) Stahl, A.; Steckham, E.; Nieger, M. *Tetrahedron Lett.* **1994**, *35*, 7371. (f) Kaptein, B.; Schoemaker, H. E. *Tetrahedron Lett.* **1994**, *35*, 1087.

[7] (a) Wang, D.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1984**, 1273. (b) Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 584. (c) Tan, T. S.; Mather, A. N.; Procter, G.; Davidson, A. H. *J. Chem. Soc., Chem. Commun.* **1984**, 585. (d) Overman, L. E.; Renhowe, P. A. *J. Org. Chem.* **1994**, *59*, 4138.

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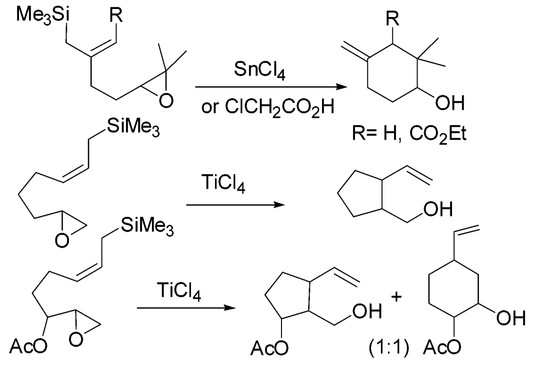
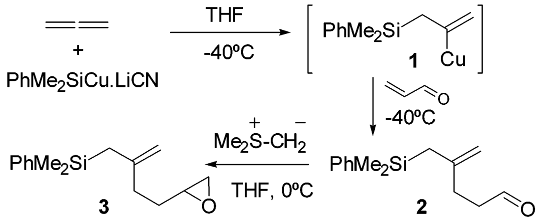
by epoxidation[9] and by cross metathesis of alkenyl epoxides and allylsilanes.[10] We now report a new route for the synthesis of epoxyallylsilanes by silylcupration of allene, followed by capture of the intermediate cuprate with enones and final formation of the epoxide.

Scheme 1



For the past decade, we have been involved in the study of the metallocupration reactions of allenes and acetylenes and their synthetic applications.[11,12] These reactions involve the addition of copper to one end of a multiple bond and a metal (Si or Sn) to the other, allowing the formation of intermediates of type **1** (Scheme 2).

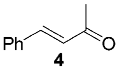
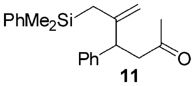
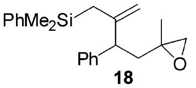
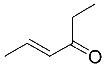
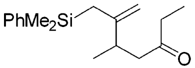
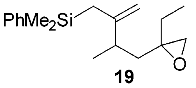
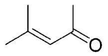
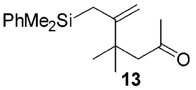
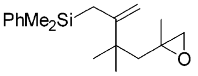
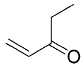
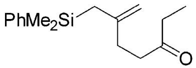
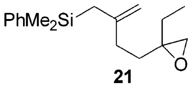
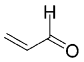
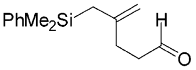
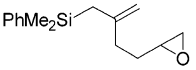
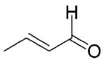
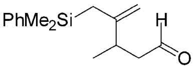
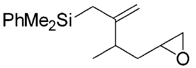
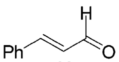
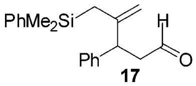
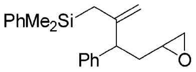
Scheme 2



The intermediate cuprate **1** can be captured by a great variety of electrophiles.[11,12] In particular, the use of α,β-unsaturated oxocompounds affords oxoallylsilanes of type **2** (Scheme 2), which are useful building blocks for cyclopentane annelations.[13]

In this paper, we describe the synthesis and cyclization of epoxyallylsilanes of type **3**, carrying the phenyldimethylsilyl group. As it is shown below, Lewis acid-catalyzed intramolecular cyclization occurs with concomitant rearrangement of the epoxy group (Table 2), thus showing that the behavior of phenyldimethylsilyl derivatives is perceptibly different from that observed for the trimethylsilyl analogues (Scheme 1).

Table 1. Synthesis of Oxo- and Epoxyallylsilanes

entry	enone	oxoallylsilane[a]	yield(%)	epoxyallylsilane[a]	yield(%)
1	 **4**	 **11**	89[b]	 **18**	72
2	 **5**	 **12**	85[b]	 **19**	65
3	 **6**	 **13**	90[b]	 **20**	78
4	 **7**	 **14**	75[c]	 **21**	76
5	 **8**	 **15**	89[c]	 **22**	75
6	 **9**	 **16**	72[c]	 **23**	67
7	 **10**	 **17**	90[b]	 **24**	60

[a] THF was used as a solvent. [b] $BF_3{\cdot}Et_2O$ was used as a catalyst. [c] TMSCl was used as a catalyst.

Phenyldimethylsilylcopper[13] reacted readily with allene at −40 °C to give a vinyl copper intermediate **1**, which was smoothly added to the α,β-unsaturated ketones **4**−**7** and the enals **8**−**10** to afford compounds **11**−**17** in good yield. All the reactions were carried out in the presence of $BF_3{\cdot}OEt_2$ or TMSCl, which considerably increased the yield (Table 1). The oxoallylsilanes thus obtained were treated with dimethylsulfonium methylide to give in good yield the

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(8) (a) Proctor, G.; Russell, A. T.; Murphy, P. J.; Tan, T. S.; Mather, A. N. *Tetrahedron* **1988**, *44*, 3953. (b) Molander, G. A.; Andrews, S. W. *J. Org. Chem*. **1989**, *54*, 3114.

(9) Seyferth, D.; Wursthorn, K. R.; Mammarella, R. E. *J. Org. Chem*. **1977**, *42*, 3104.

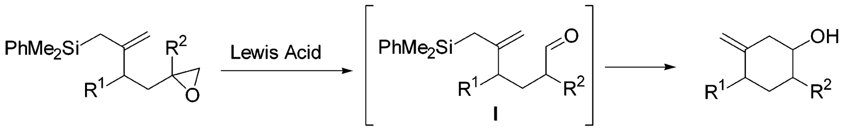
(10) Langer, P.; Holtz, E. *Synlett* **2002**, 110.

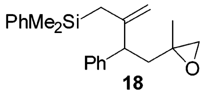
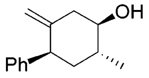
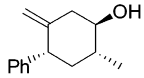
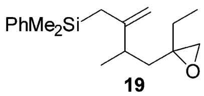
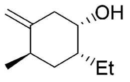
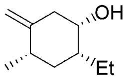
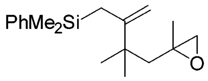
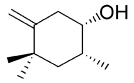
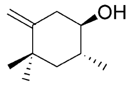
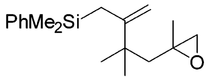
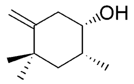
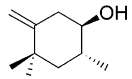
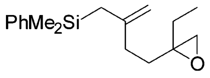
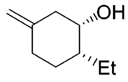
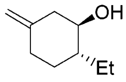
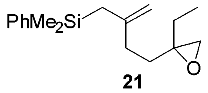
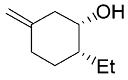
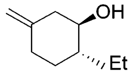
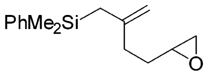
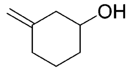
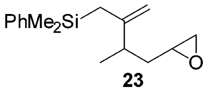
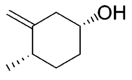
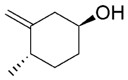
(11) SiCu of allenes and acetylenes: (a) Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *Tetrahedron Lett.* **1988**, *29*, 1825. (b) Fleming, I.; Rowley, M.; Cuadrado, P.; González, A. M.; Pulido, F. J. *Tetrahedron* **1989**, *45*, 413. (c) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I.; Sánchez, A. *J. Chem. Soc., Perkin Trans. I* **1995**, 1525. (d) Blanco, F. J.; Cuadrado, P.; González, A. M.; Pulido, F. J. *Synthesis* **1996**, 42. (e) Barbero, A.; Blanco, Y.; García, C.; Pulido, F. J. *Synthesis* **2000**, 1223. (f) Barbero, A.; García, C.; Pulido, F. J. *Synlett* **2001**, 824.

(12) SnCu of allenes and acetylenes: (a) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1990**, 1030. (b) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1992**, 327. (c) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Res.* **1990**, 291. (d) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Soc., Chem. Commun*. **1992**, 351. (e) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Rubio, R.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1657. (f) Barbero, A.; Cuadrado, P.; García, C.; Rincón, J. A.; Pulido, F. J. *J. Org. Chem*. **1998**, *63*, 7531. (g) Barbero, A.; Pulido, F. J.; Rincón, J. A.; Cuadrado, P.; Galisteo, D.; Martínez-García, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 2101.

(13) (a) Blanco, F. J.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *Tetrahedron Lett*. **1994**, *35*, 8881. (b) Barbero, A.; García, C.; Pulido, F. J. *Tetrahedron Lett*. **1999**, *40*, 6652. (c) Barbero, A.; García, C.; Pulido, F. J. *Tetrahedron* **2000**, *56*, 2739. (d) Barbero, A.; Castreño, P.; García, C.; Pulido, F. J. *J. Org. Chem*. **2001**, *66*, 7723.

Table 2. Cyclization of Epoxyallylsilanes



entry	epoxyallylsilane	lewis acid solvent	T (°C) reaction time (min)	methylenecyclohexanols ratio	yield (%)
1	 **18**	BF$_3$.OEt$_2$ DCM	0 30	 +  **25** 80:20 **26**	75
2	 **19**	BF$_3$.OEt$_2$ DCM	0 30	 +  **27** 75:25 **28**	68
3	 **20**	BF$_3$.OEt$_2$ DCM	0 30	 +  **29** 67:33 **30**	78
4	 **20**	TiCl$_4$ DCM	-78 15	 +  **29** 9:91 **30**	80
5	 **21**	BF$_3$.OEt$_2$ DCM	0 30	 +  **31** 72:28 **32**	82
6	 **21**	TiCl$_4$ DCM	-78 15	 +  **31** 17:83 **32**	79
7	 **22**	BF$_3$.OEt$_2$ DCM	0 30	 **33**	80
8	 **23**	BF$_3$.OEt$_2$ DCM	0 30	 +  **34** 60:40 **35**	70

corresponding epoxides **18**−**24** as mixtures of diastereoisomers (Table 1).

For compound **18**, both diastereomers (**18a** and **18b**) could be separated by chromatography, and their stereochemistry was assigned by X-ray analysis of one of them (Figure 1). In the other cases, they were used as a mixture of diastereomeric epoxides in the subsequent cyclization, which apparently does not represent a limitation since it was verified that both diastereomers **18a** and **18b** lead separately to the same result.

The most noteworthy feature of the epoxyallylsilane cyclization is the absence of products derived from 5-*exo* or 6-*endo* attack. Instead, we selectively obtained methylenecyclohexanols **25**−**35** from a rearrangement−cyclization process (Table 2). The rearrangement of epoxides to carbonyl compounds is a well-known reaction.[14] However, this is the first time that this sequential type of process has been observed[15] in the acid-catalyzed cyclization of epoxyallylsilanes. The nature of the silyl group clearly is playing an important role in these reactions since structurally similar epoxiallylsilanes bearing a trimethylsilyl group, instead of the phenyldimethylsilyl group, give the normal product of 5-*exo* or 6-*endo* attack[16] (Scheme 1).

The former observation seems to indicate that in the case of epoxyallylsilanes with a phenyldimethylsilyl group, rearrangement of the epoxide occurs much faster than nucleophilic substitution on the epoxy group. In this sense, the fact that cyclization of **18a** and **18b** gives the same result when

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[14] (a) Rickborn, B. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 3, pp 733−771. (b) Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, *66*, 8779. (c) Marson, C. M.; Campbell, J.; Hursthouse, M. B.; Abdul Malik, K. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1122.

[15] Products of epoxide rearrangement have been obtained in a similar cyclization reaction: Xiao, X.-Y.; Park, S.-K.; Prestwich, G. D. *J. Org. Chem.* **1988**, *53*, 4869.

[16] (a) Corey, E. J.; Staas, D.D. *J. Am. Chem. Soc.* **1998**, *120*, 3526. (b) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, *109*, 576.

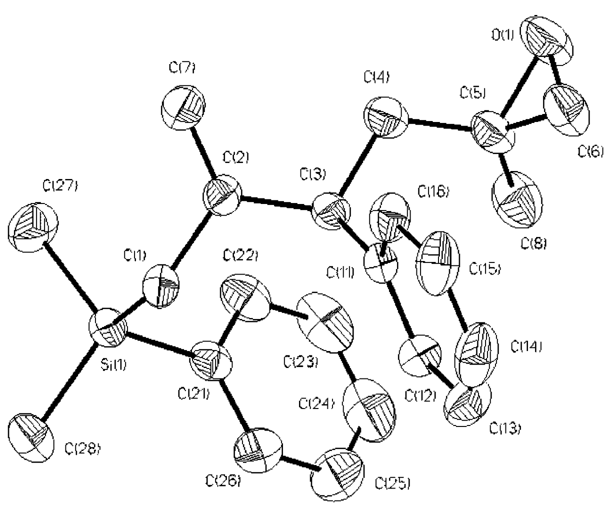
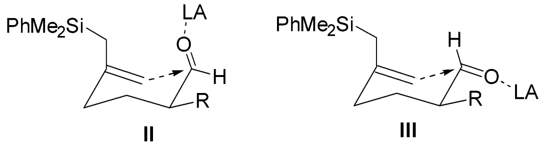


Figure 1. X-ray crystal structure of **18a** (2*R**,4*R**).

treated with Lewis acids points out that the reaction proceeds through common intermediates, and it could be considered evidence that rearrangement takes place prior to cyclization. A two-step pathway involving rearrangement to intermediate **I** and cyclization seems to be the most feasible mechanism for the general reaction we have reported. The degree of concertedness between the two steps is still uncertain.[17] The cyclization reaction was examined with several Lewis acids under a variety of solvents and temperature conditions (Table 2). The diastereomeric pairs collected in Table 2 could be adequately separated by chromatography.

The diastereoselectivity and product outcome of the process depends on the Lewis acid used. Aluminum-based Lewis acids give low yields of the cyclized products. By way of contrast, boron trifluoride etherate gives good yields of methylenecyclohexanols. The results obtained with boron trifluoride show that, except for entry 1, the ratio of diastereomers formed is in favor of the 1,2-cis isomer (Table 2, entries 2, 3, 5). The preference for the cis isomer could be due to the countercurrent flow of electrons in the Csp^2–C(Si) and C=O bonds, which would be parallel as it is shown in the transition state **II**. This point has been recently rationalized by Schlosser et al.[3c] A comparative inspection of transition states **II** and **III** (Scheme 3) shows that **II** fits better with that geometry, whereas in **III**, the above-mentioned bonds occupy a skew position.[18] The use of a bulkier Lewis acid such as titanium tetrachloride (Table 2, entries 4 and 6), leads to the 1,2-trans isomer as the major one, suggesting the intervention of transition state **III** with both the R and the carbonyl-LA groups equatorial for minimal steric repulsions (Scheme 3).

Scheme 3



In summary, a new route for the synthesis of epoxyallylsilanes having the PhMe$_2$Si group is described and their acid-catalyzed cyclization has been studied. The so-called normal products derived from 5-*exo* or 6-*endo* attack were never obtained. On the contrary, an interesting rearrangement–cyclization was observed, which led to methylenecyclohexanols selectively.

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Supporting Information Available: Typical experimental procedures for the synthesis of oxoallylsilanes and epoxyallylsilanes, experimental procedure for the cyclization of epoxyallylsilanes, and characterization data for compounds **11**, **13**, **16**, **18**, **20**, **23**, **25**, **26**, **29**, **30**, **34**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] We were not able to isolate or detect aldehydes resulting from isomerization of the starting epoxiallylsilane.

[18] A better picture can be obtained using molecular models.