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Stereoselective Oxy-Functionalization of γ-Silyl Allylic Alcohols with Ozone: A Facile Synthesis of Silyl Peroxide and Its Reactions

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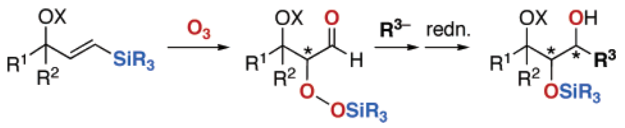
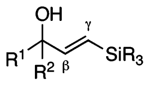
ABSTRACT



A reaction of γ-silyl allylic alcohol and its ether with ozone provides synthetically versatile α-formyl silyl peroxide in good yield without normal fission of carbon–carbon double bond. Thus, the provided silyl peroxide serves as a good precursor for the stereochemically defined triol derivative via alkylation and reduction of peroxide moiety.

The addition of hydroxy groups or their equivalents to the carbon−carbon double bond is a fundamental and valuable transformation in organic synthesis, and numerous methods to effect this transformation have been developed.[1] However, further development of this area is necessary to respond to the demand of modern fine organic synthesis. Herein, we report an efficient and unique oxyfunctionalization of the alkene moiety of γ-silyl allylic alcohol **i** using ozone, which provides synthetically versatile α-formyl silyl peroxyaldehyde **ii** without the normal fission of the carbon−carbon double bond. Thus, the provided **ii** serves as a good precursor for the stereochemically defined triol derivative **iii** via alkylation and reduction of peroxide moiety.



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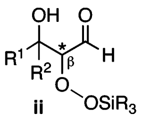

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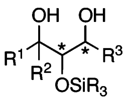
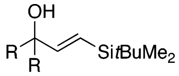
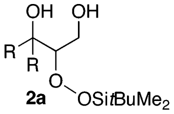


iii

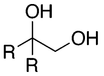
We found this oxidation during the course of our study on hydroalumination of γ-silyl propargylic alcohol providing γ-silyl allylic alcohol **i**.[2] To explore the synthetic utility of **i**, we planned to carry out the oxyfunctionalization of the vinyl silane moiety using other common oxidants such as OsO_4, *m*-CPBA, etc. Although most methods did not give any significant results, the reaction of **1a** (**i**: R^1, $R^2 = PhC_2H_4$, R_3Si = *t*-$BuMe_2Si$) with ozone in CH_2Cl_2 proceeded smoothly to give unexpected dihydroxy silyl peroxide **2a** (30%) in addition to the normal ozonolysis product **3a** (26%) after a reductive workup using $NaBH_4$.[3−8] In addition, the silyl peroxide **2a** was obtained exclusively in 75% yield by changing the solvent from CH_2Cl_2 to AcOEt.[9,10]



1a



2a



3a R=PhC_2H_4

To explore the scope and limitation of this unique ozonation, we examined a similar reaction using a variety of substrates as shown in Table 1.[11] Again, in a reaction of

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(1) For leading reviews on dihydroxylation of carbon−carbon double bonds, see: (a) Schröeder, M. *Chem. Rev.* **1980**, *80*, 187−213. (b) Haines, A. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 437−448. For leading reviews on epoxidation of carbon−carbon double bond, see: (c) Jörgensen, K. A. *Chem. Rev.* **1989**, *89*, 431−458. (d) Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 357−387.

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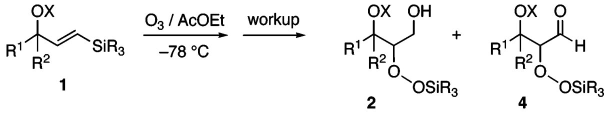
Table 1. Oxidation of γ-Silyl Allylic Alcohol and Its Ether **1**



							yield (%)^b		
entry	**1**	R^1	R^2	X	R_3Si	workup procedure^a	**2**	dr (anti/syn)^c	**4**
1	**1b**	Me	Me	H	t-BuMe$_2$Si	A	73		nd
2	**1b**	Me	Me	H	t-BuMe$_2$Si	B	nd		73
3	**1c**	Me	Me	H	i-Pr$_3$Si	B	nd		80
4	**1d**	Me	Me	H	t-BuPh$_2$Si	A	70		nd
5	**1e**	Me	Me	TMS	i-Pr$_3$Si	B	nd		75
6	**1f**	Me	Me	TMS	t-BuMe$_2$Si	B	nd		67
7	**1g**	H	H	TBS	t-BuPh$_2$Si	A	90		nd
8	**1h**	Me	H	TMS	i-Pr$_3$Si	A	78	58:42	nd
9	**1i**	Et	H	TMS	i-Pr$_3$Si	A	84	67:33	nd
10	**1j**	c-Hex	H	TMS	i-Pr$_3$Si	A	89	72:28	nd
11	**1k**	t-Bu	H	TMS	i-Pr$_3$Si	A	71	>99:<1	nd
12	**1l**	i-Pr$_3$ Si−≡	Me	H	i-Pr$_3$Si	A	90	74:26^d	nd

[a] A: Reductive workup using $NaBH_4$. B: Reaction was worked up without any reducing agent. [b] Isolated yields. nd = not detected by ^{1}H NMR and TLC analyses. [c] Determined by ^{1}H NMR analysis. [d] Stereochemistry of the major product was not determined yet.

1b, AcOEt was the solvent of choice to obtain **2b** in good yield (entry 1). Furthermore, α-formyl silyl peroxide **4b** was isolated in good yield by concentration of the crude mixture under reduced pressure (entry 2).[12] Equally good yields of silyl peroxides were obtained from γ-i-Pr$_3$Si or γ-t-BuPh$_2$Si allylic alcohols **1c** and **d** (entries 3 and 4). Moreover, silyl peroxides were also obtained upon ozonation of the corresponding trimethylsilyl ethers **1e** and **f**, indicating that a free hydroxyl group is not essential for the reaction (entries 5 and 6). Primary ether **1g** also gave silyl peroxide **2g** in excellent yield (entry 7). We have observed diastereoselective addition of ozone onto substrates **1h**−**k** which bear an α-stereogenic center. The *anti*-selectivity is more pronounced as the R^1 group becomes more bulky. In particular, a reaction of **1k** (R^1 = t-Bu) gave *anti*-**2k** exclusively (>99% dr) (entry 11).[13,14] It is worth noting that this oxidation was applicable to the γ-silyl allylic alcohol **1l** having an alkynyl substituent (entry 12). These results clearly show that the present oxidation provides an efficient approach to the well-functionalized silyl peroxides, in which otherwise difficult triorganosilicon-sp^2 carbon bond cleavage may be involved.[15]

Since organic peroxides are potentially hazardous compounds, they must be handled with due care.[16] However, no particular difficulties were experienced in handling any of the new silyl peroxides synthesized in this work. Also, we have observed thermal stability of **2b** and **4e** by thermogravimetry analysis (TGA) under nitrogen. It shows that the slow thermal degradation occurred at >80 °C (Figure 1).

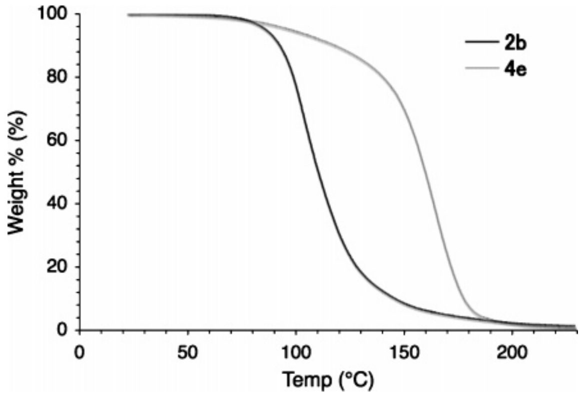


Figure 1. TGA of **2b** and **4e**.

To gain information on the mechanism of this oxidation, the reaction of **1b** with ozone at −78 °C in hexane was monitored by IR spectroscopy (Figure 2).[17,18] When ozone was passed through a substrate solution with a constant flow,

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(2) Igawa, K.; Tomooka, K. *Angew. Chem., Int. Ed*. **2006**, *45*, 232−234.

(3) For example, both reactions of **1a** with OsO_4 or m-CPBA at rt did not proceed, only the starting material being recovered.

(4) To confirm the structure of silyl peroxide **2a**, we compared it with an authentic sample of TBS ether which had been prepared from dibenzylideneacetone in five steps ((i) H_2, Pd/C, (ii) $CH_2{=}CHMgBr$, (iii) OsO_4, N-methylmorphorin N-oxide, (iv) t-BuMe$_2$SiCl, imidazole, (v) H_3O^+). On ^{13}C NMR analyses, the β-carbon of **2a** appears in much lower field (88.9 ppm) than that of TBS ether (75.7 ppm); see the Supporting Information.

(5) For leading reviews on ozonolysis, see: (a) Bailey, P. S. *Ozonation in Organic Chemistry, Vol. 1: Olefinic Compounds*; Academic Press: London, 1978. (b) Bailey, P. S. *Ozonation in Organic Chemistry, Vol. 2: Nonolefinic Compounds*; Academic Press: London, 1982.

(6) Büchi and Wüest reported the ozonation of trimethylsilyl-substituted alkenes in the 1970s, in which they proposed a similar silyl peroxide as an intermediate; see: Büchi, G.; Wüest, H. *J. Am. Chem. Soc*. **1978**, *100*, 294−295. Although their trimethylsilyl peroxide is too reactive to be handled with ease, our t-BuMe$_2$Si peroxide **2a** is tolerant not only to the reductive workup process using $NaBH_4$ but also to purification on silica gel, most probably due to the bulky silyl group on the peroxide moiety.

(7) Synthetic application of ozonation of vinylsilane is rather limited, so far. For references on synthesis of artemisinin, see: (a) Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974−979. For a reference on the synthesis of α-hydroxyketone, see: (b) Renaud, P.; Gerster, M.; Ribezzo, M. *Chimia* **1994**, *48*, 366−369.

(8) 1,2-Diol synthesis via the ozonation of alkenylstannane has been reported; see: Gómez, A. M.; Company, M. D.; Valverde, S.; López, J. C. *Org. Lett.* **2002**, *4*, 383−386.

(9) The reaction in MeOH instead of AcOEt only afforded decomposed materials resulting from a concomitant retro-aldol reaction.

(10) For representative references on silyl peroxide, see: (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573−576. (b) Dussault, P. H.; Lee, I. Q.; Lee, H.-J.; Lee, R. J.; Niu, Q. J.; Schultz, J. A.; Zope, U. R. *J. Org. Chem.* **2000**, *65*, 8407−8414. (c) O'Neill, P. M.; Pugh, M.; Davies, J.; Ward, S. A.; Park, B. K. *Tetrahedron Lett.* **2001**, *42*, 4569−4571. (d) Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595−3598 and references therein.

(11) All of the substrates **1** were readily available by the hydroalumination of the corresponding propargylic alcohol using Red-Al in toluene.

(12) α-Formyl silyl peroxide was utilized as a precursor of peroxide hemiketal; see: Clark, G. R.; Nikaido, M. M.; Fair, C. K.; Lin, J. *J. Org. Chem.* **1985**, *50*, 1994−1996.

(13) The stereochemistry of **2h**−**k** was determined by the ^{1}H NMR analysis of their cyclic acetal derivatives; see the Supporting Information.

(14) **Typical Procedures of Ozonation (Procedure B).** A stream of ozone (1.2 v/v % in oxygen, 150 mL/min) was bubbled through a solution of allylic alcohol **1e** (747 mg, 2.38 mmol) in AcOEt (30 mL) at −78 °C. After 1 h, the solution turned pale blue, indicating the complete oxidation. Dissolved ozone was removed by bubbling the solution with argon for 15 min followed by allowing the temperature to rise to rt. After the solvent was removed by evaporation, the residue was purified by silica gel chromatography (hexane: Et_2O = 100:1) to afford silyl peroxide **4e** (644 mg, 1.78 mmol, 75%) as a colorless oil.

(15) For review on the oxidation of the silicon−carbon bond, see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.

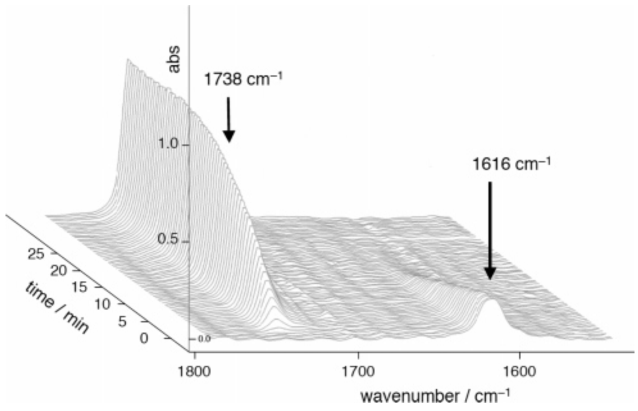
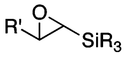


Figure 2. In situ IR of the reaction of **1b** with ozone.

we observed a time-dependent diminution in the intensity of the C=C absorption of **1b** (1616 cm^{-1}) with the emergence of C=O absorption of silyl peroxide **4b** (1738 cm^{-1}). This clear correlation between decreasing of **1b** and the increasing of **4b** and the absence of significant absorption for any species other than **1b** or **4b** in this functional group region suggests that the reaction proceeds rapidly via a short-lived intermediate.[19]

Although the present reaction could proceed via intermediacy of epoxide **5**[20] or silylenol ether **6**,[21] a control experiment showed that separately prepared epoxide **5a** (R_3Si = *i*-Pr_3Si, R′ = C(OH)MeC≡CH) or enol ether **6a** (R_3Si = *t*-BuMe$_2$Si, R′ = C(OTBS)Me$_2$) did not give the corresponding silyl peroxides.[22]



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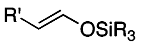

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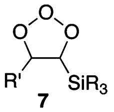

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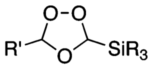

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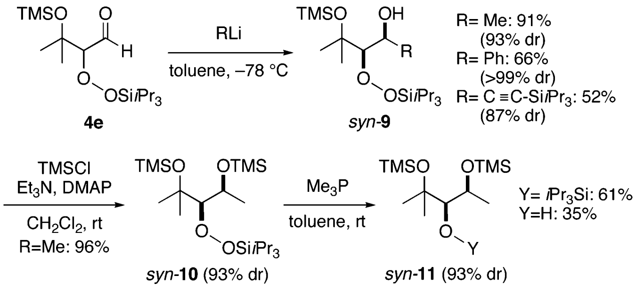
On the basis of the above-mentioned results, we believe that the primary ozonide pathway (**7** → **4**) is the most suitable, in which the R$_3$Si group migrates from carbon to oxygen more rapidly than a normal ozonide rearrangement (**7** → **8**).[23,24]

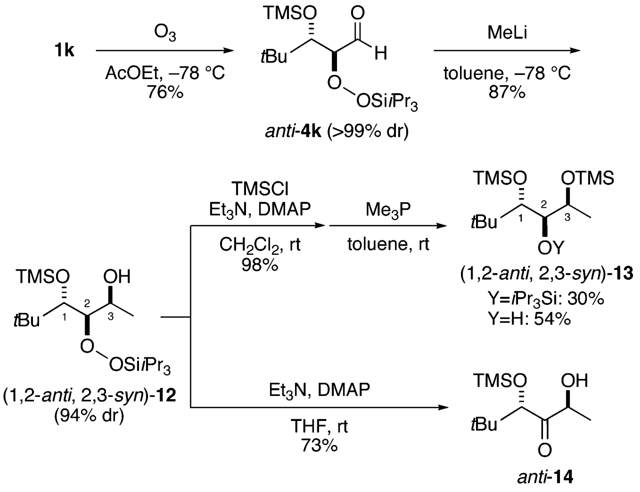
Our attention was next directed toward further transformation of silyl peroxides. The reaction of **4e** with alkyllithiums in toluene gave *syn*-**9** (racemic) with the preservation of peroxide moiety with good to excellent diastereoselectivity (Scheme 1).[25,26] We also found that the chiral silyl peroxides are convertible to the corresponding mono-deoxygenated products in a stereospecific manner. For example, a reduction of *syn*-**10** using Me$_3$P at rt yielded *syn*-**11** without loss of diastereopurity.[27]

Scheme 1. Transformation of **4e**



Moreover, these stereoselective transformations along with a diastereoselective formation of silyl peroxide (vida supra) enable the stereoselective construction of three continuous chiral centers in (1,2-*anti*, 2,3-*syn*)-**13** as shown in Scheme 2. The intermediary silyl peroxide **12** was also convertible to the α,α′-dihydroxyketone derivative *anti*-**14** upon base

Scheme 2. Constraction of Three Continuous Chiral Centers



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(16) (a) Castrantas, H. M.; Banerjee, D. K.; Noller, D. C. *Fire and Explosion Hazards of Peroxy Compounds, ASTM STP 394*; American Society for Testing and Materials: Philadelphia, PA, 1965. (b) Castrantas, H. M.; Banerjee, D. K. *Laboratory Handling and Storage of Peroxy Compounds, ASTM STP 471*; American Society for Testing and Materials: Philadelphia, PA, 1970.

(17) In situ IR spectra were recorded on MCT detector fitted with the mid-IR fiber-optic probe (Remspec). The spectra were acquired using 10 scans per spectrum at a resolution of 4 cm^{-1} using Time Base software (Perkin Elmer).

(18) AcOEt was not employed as a solvent in this experiment due to its large background absorption in IR spectroscopy.

(19) Oxidation in hexane provides not only a silyl peroxide, but also a small amount of normal ozonolysis product.

(20) It has been reported that an epoxide can be formed in ozonation of alkene; see: (a) Gillies, C. W. *J. Am. Chem. Soc.* **1975**, *97*, 1276−1278. (b) Bailey, P. S.; Hwang, H. H.; Chiang, C. Y. *J. Org. Chem.* **1985**, *50*, 231−234 and references therein.

(21) It has been reported that an α-silyloxy ketone was provided in ozonation of silyl enol ether; see: Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396−1403.

(22) The reaction of epoxide **5a** and O$_3$/O$_2$ gas did not give any oxidized products. Under the same conditions, silyl enol ether **6a** gave a complex mixture including no silyl peroxide.

(23) A similar silyl migration mechanism was speculated by Bailey to explain Büchi's result; see ref 5b. As a part of a mechanistic study for ozonolysis of alkene, Pola and colleagues investigated an oxidation of trimethylvinylsilane in a cryogenic system. They proposed that the silyl peroxide was formed from primary ozonide via homolytic cleavage of the oxygen−oxygen bond; see: Fajgar, R.; Roithová, J.; Pola, J. *J. Org. Chem.* **2001**, *66*, 6977−6981.

treatment. These results clearly show that the silyl peroxide functionality acts as a synthetic equivalent of silyl ether or masked carbonyl.[28]

In summary, we have described an oxidation of γ-silyl allylic alcohol using ozone, which provides an access to synthetically versatile silyl peroxides. Further studies using chiral-nonracemic allylic alcohols prepared by recently developed enantioselective hydroalumination protocol in our laboratory are now underway.[29]

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

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(24) A related silyl migration in furan-derived peroxide has been reported; see: (a) Adam, W.; Rodriguez, A. *Tetrahedron Lett*. **1981**, *22*, 3505−3508. (b) Katsumura, S.; Hori, K.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett*. **1985**, *26*, 4625−4628.

(25) The stereochemistry of **9**−**14** was determined through the ^{1}H NMR analysis of their cyclic acetal derivatives; see the Supporting Information.

(26) This stereochemical outcome is explicable on the basis of chelation-controlled mechanism, in which the lithium cation coordinates to carbonyl oxygen and α-silyl oxygen.

(27) This result means that the α-silyl oxygen of peroxide was selectively removed in the reduction. A related reduction of silyl peroxide in a norcamphor derivative has been reported; see: Jefford, C. W.; Rimbault, C. G. *J. Am. Chem. Soc*. **1978**, *100*, 6437−6445.

(28) Cyclic peroxide has been utilized as a synthetic equivalent of ketone; see: Singh, C.; Malik, H. *Org. Lett*. **2005**, *7*, 5673−5676.

(29) These results will be reported in due course.