Partial Oxidation of Alkenylsilanes with Ozone: A Novel Stereoselective Approach to the Diol and Triol Derivatives

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Dedicated to Professor Paul A. Wender on the occasion of his 60th birthday

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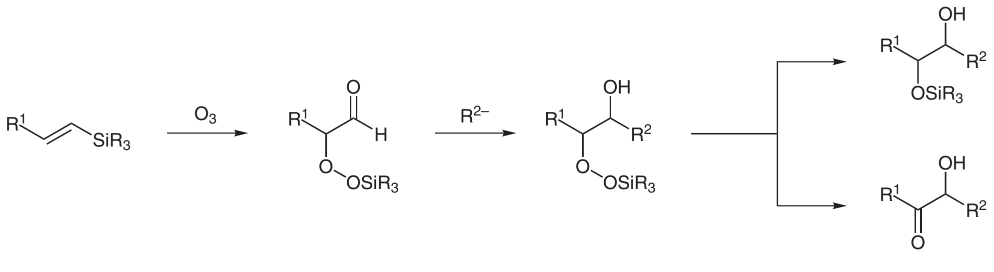
Abstract: The reaction of alkenylsilanes with ozone provides synthetically versatile β-hydroxy or α-formyl silyl peroxides in good yield without normal fission of the C=C bond. The obtained α-formyl silyl peroxides serve as good precursors for the stereochemically defined diol or triol derivatives via nucleophilic addition to the formyl group and reduction of the peroxide moiety.

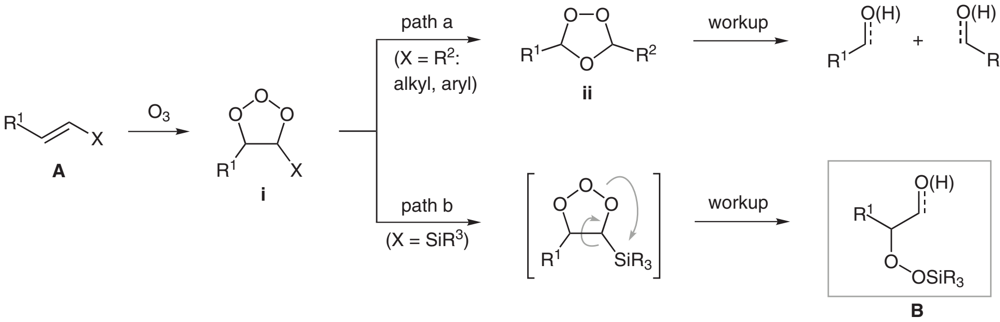
Key words: alkenes, oxidations, ozonolysis, peroxides, silicon



Scheme 1 Oxidation of alkenylsilanes and transformation of resulting α-formyl silyl peroxides

Introduction

Ozone is one of the most simple, economical, clean, and efficient oxidation agents, and is widely utilized in many facets of industry. Also in the field of organic synthesis, ozone is quite an important reagent, especially for the oxidative cleavage of the C=C bond (i.e. ozonolysis), which is well recognized as a 'textbook reaction'.[1] As illustrated in Scheme 2 (path a), this ozone-mediated oxidative cleavage reaction of the C=C bond consists of a [3+2] cycloaddition and subsequent rearrangement of the resultant primary ozonide **i**. Generally, the second rearrangement step proceeds much more rapidly than the first cycloaddition and therefore, there has long been inherent difficulty in stopping this process at the intermediate stage.[1,2] However, we recently found that a number of organosilyl groups directly bound to C=C bond successfully intercept the second rearrangement step by migrating from carbon to oxygen in the primary ozonide.[3,4] Furthermore, we have successfully isolated the resultant silyl peroxides in which



Scheme 2 Oxidation of alkenes using ozone

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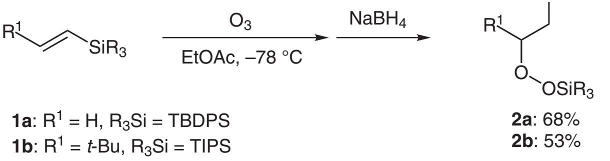
the original carbon skeletons in the starting alkenylsilanes are perfectly retained (path b). The synthetic potential of thus obtained silyl peroxides strongly suggested a new possibility for ozone as a unique agent in organic synthesis. This paper deals with an overview of our recent progress in this area (Scheme 1).

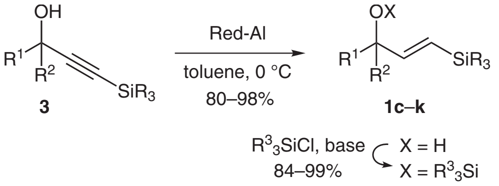
Scope and Limitations

The typical procedure for the ozone oxidation of alkenylsilanes is illustrated in the case of the simple *tert*-butyldiphenylsilylethene (**1a**) and *trans*-1-triisopropylsilyl-3,3-dimethylbut-1-ene (**1b**) (Scheme 3). At –78 °C, a stream of ozone/oxygen gas is bubbled through the solution of **1a** or **1b** in EtOAc, which is essential for the selective formation of the corresponding silyl peroxides, until the color of the solution turns from colorless to pale blue.[5] After removal of the excess ozone remaining in the solution with argon, powdered $NaBH_4$ is added portionwise into the solution at the same temperature. The standard extractive workup of the resulting mixture affords β-hydroxy silyl peroxides **2a** and **2b** in moderate to good yields. Although organic peroxides have been known as potentially hazardous compounds, we have never experienced any particular difficulties in handling new silyl peroxides including **2a** or **2b**.[6,7]



Scheme 3 Oxidation of alkenylsilanes **1a** and **1b**

The present ozone oxidation is applicable to the γ-silylallylic alcohol derivatives **1c**–**k**, which are readily available from the γ-silylpropargylic alcohols **3** by hydroalumination with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) as shown in Scheme 4.[8] As listed in Table 1, the ozone oxidation of **1c**–**k** gives silyl peroxides **2c**–**k** in good yields.

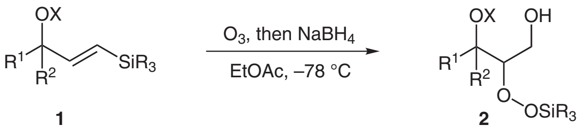


Scheme 4 Preparation of **1c**–**k** from γ-silylpropargylic alcohol **3**

Importantly, we have observed moderate to good diastereoselectivities in the ozone oxidation of **1g**–**k** bearing stereogenic center at their allylic positions. The *anti* selectivity becomes more pronounced as the R^1 group becomes more bulky, and the diastereoselectivity for **1j** (R^1 = *t*-Bu) reaches >99% to give the *anti*-**2j** exclusively (entry 8). It is worth noting that this oxidation was applicable to **1k** having an alkynyl substituent (entry 9). These results clearly show that the present oxidation provides an efficient approach to the multifunctionalized triol derivatives.

The intermediate α-formyl silyl peroxides can be successfully isolated by eliminating the reductive workup with $NaBH_4$ in the aforementioned protocol. As shown in Table 2, a variety of α-formyl silyl peroxides **4** were obtained in good yields by ozone oxidation of **1** followed by a concentration of the crude mixture under reduced pressure.

Table 1 Synthesis of β-Hydroxy Silyl Peroxides **2**



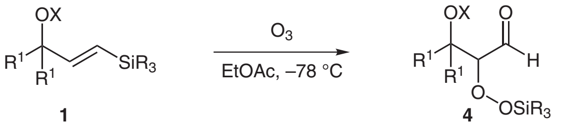
Entry	1	R^1	R^2	X	R_3Si	Yield (%)[a]	dr (*anti*/*syn*)[b]
1	**1c**	Me	Me	H	TBDMS	73	–
2	**1d**	$PhCH_2CH_2$	$PhCH_2CH_2$	H	TBDMS	75	–
3	**1e**	Me	Me	H	TBDMS	70	–
4	**1f**	H	H	TBDMS	TBDMS	90	–
5	**1g**	Me	H	TMS	TIPS	78	58:42
6	**1h**	Et	H	TMS	TIPS	84	67:33
7	**1i**	c-C_6H_{11}	H	TMS	TIPS	89	72:28
8	**1j**	*t*-Bu	H	TMS	TIPS	71	>99:<1
9	**1k**	C≡C-TIPS	Me	H	TIPS	90	74:26[c]

[a] Isolated yields after purification using silica gel column chromatography.

[b] Determined by ^1H NMR analysis.

[c] Stereochemisrty of the major product has not been determined yet.

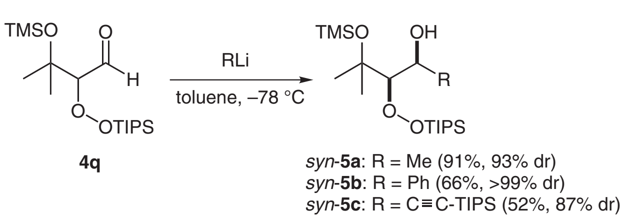
Table 2 Synthesis of α-Formyl Silyl Peroxides **4**



Entry	1	R^1	X	R_3Si	Yield (%)[a]
1	**1l**	H	TBDMS	TBDMS	82
2	**1f**	H	TBDMS	TBDMS	89
3	**1m**	H	TBDMS	TIPS	80
4	**1c**	Me	H	TBDMS	73
5	**1n**	Me	H	TIPS	80
6	**1o**	Me	TBDMS	TBDMS	82
7	**1p**	Me	TMS	TBDMS	67
8	**1q**	Me	TMS	TIPS	75

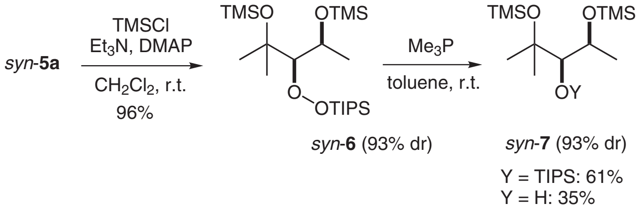
[a] Isolated yields after purification using silica gel column chromatography.

The α-formyl silyl peroxides **4** thus obtained are valuable building blocks for polyol derivatives. Thus, the reaction of **4q** with alkyllithiums in toluene gave *syn*-**5** with preservation of peroxide moiety in good to excellent diastereoselectivity (Scheme 5). This stereochemical outcome is explainable on the basis of chelation-controlled mechanism, in which the lithium cation coordinates to carbonyl oxygen and peroxide oxygen.



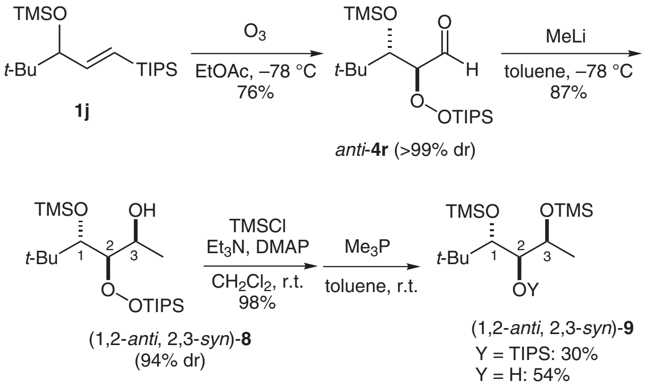
Scheme 5 Nucleophilic addition reaction of RLi to **4q**

The obtained chiral racemic silyl peroxides **5** are stereospecifically deoxygenated by Me_3P to give the silyl ethers **7**. For example, the reduction of *syn*-**6** using Me_3P at room temperature yielded *syn*-**7** without loss of diastereopurity (Scheme 6). This result indicates that the α-silyl oxygen of the peroxide moiety is selectively removed in this process.[9]



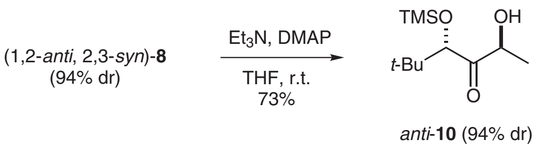
Scheme 6 Transformation of silyl peroxide *syn*-**5a** to *syn*-**7**

A combination of these transformations and the ozone oxidation of chiral γ-silylallylic alcohol enable the stereoselective construction of three continuous chiral centers in triol derivatives. As shown in Scheme 7, the aforementioned diastereoselective ozone oxidation of **1j** followed by nucleophilic addition of MeLi provides (1,2-*anti*, 2,3-*syn*)-**8** with 94% dr. Again, reduction of TMS-ether of **8** using Me_3P proceeds in a stereospecific manner to obtain silyl ether of triol (1,2-*anti*, 2,3-*syn*)-**9**.



Scheme 7 Construction of three continuous chiral centers by diastereoselective ozone oxidation/nucleophilic addition

Furthermore, at the expense of the loss of stereogenic center at the middle carbon, silyl peroxide **8** was also convertible to the α,α′-dihydroxyketone derivative *anti*-**10** upon base treatment (Scheme 8). These results clearly show that the silyl peroxide functionality acts as not only a synthetic equivalent of silyl ether, but also as masked carbonyl.[10]



Scheme 8 Transformation of silyl peroxide **8** to ketone **10**

In summary, we have described an oxidation of alkenylsilanes using ozone, which provides an access to synthetically versatile silyl peroxides with retention of σ-bond of alkene moiety. Furthermore, concise and stereoselective synthesis of triol derivatives from γ-silylpropargylic alcohols has been accomplished by the combination of hydroalumination, ozone oxidation, and nucleophilic alkylation.

Procedures

Herein we describe typical procedures for the preparation of alkenylsilanes **1** (depicted in Scheme 4), its ozone oxidation (depicted in Tables 1 and 2), and the reaction of α-formyl silyl peroxides with alkyllithium (depicted in Scheme 5).

All reactions were carried out in dried glassware under argon unless otherwise noted. ^1H NMR spectra were recorded on a Varian Mercury (300 MHz) spectrometer using $CDCl_3$ as solvent; $CHCl_3$ (^1H,

$\delta = 7.26$) was used as an internal reference. ^{13}C NMR spectra were recorded on a Varian Mercury (75 MHz) spectrometer using $CDCl_3$ as solvent; $CDCl_3$ (^{13}C, $\delta = 77.1$) was used as an internal reference. Infrared spectra were recorded on a Perkin Elmer SpectrumOne as neat liquid samples on NaCl plates. MS spectra were recorded on a JEOL JMS-T100CS.

Procedure 1

(*E*)-4-(*tert*-Butyldimethylsilyl)-2-methylbut-3-en-2-ol (1c); Typical Procedure for Hydroalumination

To a solution of 4-*tert*-butyldimethylsilyl-2-methylbut-3-yn-2-ol (**3c**; 497 mg, 2.50 mmol) in toluene (10 mL) at r.t. was added Red-Al (2.32 mL of 1.62 M solution in toluene, 3.75 mmol) and the mixture was stirred at that temperature for 1.5 h. Then, the reaction was quenched with powdered $Na_2SO_4 \cdot 10H_2O$ (1.0 g), diluted with hexane (20 mL), and Na_2SO_4 (10.0 g) was added for absorption of aluminum hydroxide. After the organic layer had changed to a clear solution, the mixture was filtered through a pad of Celite and the solvent was removed in vacuo. The crude product was purified by silica gel chromatography (hexane–EtOAc, 8:1) to afford 451 mg of **1c** (90%) as a colorless oil.

IR (neat): 3365, 2953, 2857, 1616, 1471, 1361, 1248, 1147, 991, 831 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.16$ (d, $J = 18.9$ Hz, 1 H), 5.80 (d, $J = 18.9$ Hz, 1 H), 1.50 (s, 1 H), 1.31 (s, 6 H), 0.87 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.65$, 121.54, 72.22, 29.61, 26.57, 16.71, –5.91.

Procedure 2

2-(*tert*-Butyldimethylsilylperoxy)-3-methylbutane-1,3-diol (2c); Typical Procedure for the Ozone Oxidation of Alkenylsilanes with $NaBH_4$ Workup

A stream of O_3 (ca. 1.2 v/v% in O_2, ca. 150 mL/min) was bubbled through a solution of allylic alcohol **1c** (127 mg, 0.636 mmol) in EtOAc (7 mL) at –78 °C. After 30 min, the solution turned pale blue, indicating the completion of oxidation. Dissolved O_3 was removed by bubbling argon through the solution for 10 min. To the solution was added $NaBH_4$ (100 mg, 2.64 mmol) and stirred at that temperature for 1.5 h. After quenching the reaction with sat. aq NH_4Cl (5 mL), the aqueous layer was extracted with EtOAc (3×5 mL), dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The crude product was purified by silica gel chromatography (hexane–EtOAc, 3:1) to afford the silyl peroxide **2c** (116 mg, 73%) as a colorless oil.

IR (neat): 3391, 2931, 2859, 1472, 1410, 1363, 1252, 1182, 1038, 838 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.98$–3.92 (m, 2 H), 3.88 (dd, $J = 4.5, 4.5$ Hz, 1 H), 2.96 (br s, 1 H), 2.56 (br s, 1 H), 1.26 (s, 6 H), 0.95 (s, 9 H), 0.22 (s, 3 H), 0.20 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 91.18$, 73.05, 61.68, 27.27, 26.76, 26.49, 18.51, –5.38, –5.30.

MS (ESI, +): $m/z = 273$ $[M + Na]^+$.

Procedure 3

2-Triisopropylsilylperoxy-3-trimethylsilyloxy-3-methylbutyraldehyde (4q); Typical Procedure for the Ozone Oxidation of Alkenylsilanes without Reductive Workup

A stream of O_3 (ca. 1.2 v/v% in O_2, 150 mL/min) was bubbled through a solution of the ether **1q** (747 mg, 2.38 mmol) in EtOAc (30 mL) at –78 °C. After 1 h, the solution turned pale blue, indicating the completion of oxidation. Dissolved O_3 was removed by bubbling argon through the solution for 10 min, followed by allowing the temperature to rise to r.t. After removal of the solvent by evaporation, the residue was purified by silica gel chromatography (hexane–Et_2O, 100:1) to afford the silyl peroxide **4q** (644 mg, 75%) as a colorless oil.

IR (neat): 2947, 2869, 1740, 1465, 1367, 1252, 1172, 1044, 842 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.70$ (d, $J = 3.9$ Hz, 1 H), 3.88 (d, $J = 3.9$ Hz, 1 H), 1.30 (s, 3 H), 1.29 (s, 3 H), 1.21 (qq, $J = 6.6, 6.6$ Hz, 3 H), 1.15–1.05 (m, 18 H), 0.10 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 203.34$, 94.10, 75.36, 28.31, 26.83, 18.06, 11.67, 2.49.

MS (ESI, +): $m/z = 385$ $[M + Na]^+$.

Procedure 4

syn-3-Triisopropylsilylperoxy-4-methyl-4-trimethylsilyloxypentan-2-ol (*syn*-5a)

To a solution of **4q** (153 mg, 0.423 mmol) in toluene (12 mL) was slowly added MeLi (0.619 mL of 1.03 M solution in Et_2O, 0.634 mmol) at –78 °C. After 20 min, the reaction was quenched by phosphate buffer (pH 7, 5 mL), the aqueous layer was extracted with hexane (3×10 mL), dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The crude product was purified by silica gel chromatography (hexane–EtOAc, 20:1) to afford **5a** (147 mg, 91%, 93% dr) as a colorless oil.

Major Isomer

IR (neat): 3582, 2947, 2868, 1465, 1384, 1367, 1251, 1170, 1040, 869, 841 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.21$ (ddq, $J = 6.6, 2.4, 2.4$ Hz, 1 H), 3.61 (d, $J = 2.4$ Hz, 1 H), 3.38 (d, $J = 6.6$ Hz, 1 H), 1.39 (d, $J = 2.4$ Hz, 3 H), 1.35 (s, 3 H), 1.29 (s, 3 H), 1.22 (qq, $J = 6.3, 6.3$ Hz, 3 H), 1.12–1.08 (m, 18 H), 0.14 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 92.91$, 76.39, 66.86, 29.69, 26.00, 23.33, 18.06, 11.55, 2.54.

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(7) Although Büchi's trimethylsilyl peroxide is too reactive to be handled with ease (see ref. 4), our silyl peroxides are 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. Furthermore, slow thermal degradation was observed at >80 °C in thermogravimetric analysis (TGA) of **2c** and **4q**; see ref. 3.

(8) (a) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595. (b) Igawa, K.; Tomooka, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 232.

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