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Synthesis of Silyl Monoperoxyketals by Regioselective Cobalt-Catalyzed Peroxidation of Silyl Enol Ethers: Application to the Synthesis of 1,2-Dioxolanes

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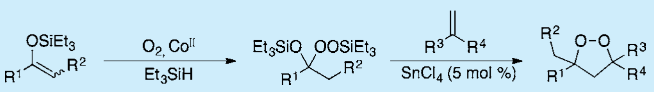
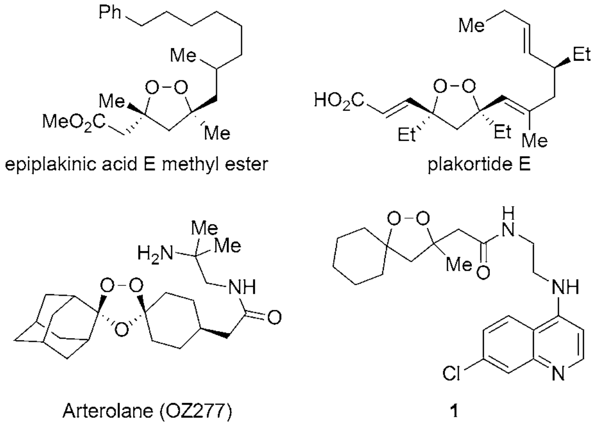
Ⓢ *Supporting Information*

ABSTRACT: The cobalt-catalyzed peroxidation of silyl enol ethers with molecular oxygen and triethylsilane provided silyl monoperoxyketals in 54%–96% yield. These compounds serve as precursors to peroxycarbenium ions, which undergo annulations to provide 1,2-dioxolanes.



The five-membered ring cyclic peroxide motif is found in biologically active natural and synthetic products such as epiplakinic acid E methyl ester, plakortide E, and Arterolane (OZ277).[1,2] These peroxides (Figure 1) possess a range of biological properties such as antimalarial,[3,4] antifungal,[5] and cytotoxic activity.[6] Although the development of new cyclic peroxides for applications as pharmaceutical agents would be valuable, the synthesis of these motifs remains challenging because of the weak oxygen–oxygen bond[7] and the dangers associated with peroxide formation.


epiplakinic acid E methyl ester

plakortide E

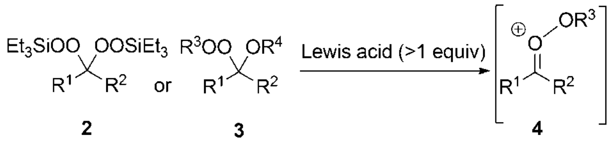
Arterolane (OZ277)

1

Figure 1. Biologically active five-membered ring peroxides.

Among the methods developed for the synthesis of exo- and endocyclic peroxides,[8−11] annulations of peroxycarbenium ions with alkenes have proven to be useful for the construction of peroxides such as 1,2-dioxolanes.[12−18] Peroxycarbenium ions are most commonly generated from either bisperoxyketals[3,14,19] such as **2** or alkoxyperoxyketals[20] such as **3** and an amount of Lewis acid (Scheme 1). The synthesis of monoperoxyketals as peroxycarbenium ion precursors[20,21] typically requires ozone[22] or excess hydrogen peroxide[23] as the source of oxygen atoms. Additional steps to protect the hydroperoxide functionality are often necessary to provide bench-stable compounds.[19,20]

Scheme 1. Formation of a Peroxycarbenium Ion[a]

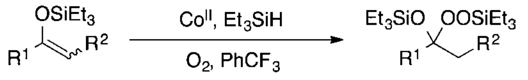


2 **3** **4**

[a]R^3 = H, TBS; R^4 = Me, Et, octyl, CH_2CH_2OMe; Lewis acid = $SnCl_4$, $TiCl_4$, Me_3SiOTf, or phosphomolybdic acid.

In this Letter, we report a method to prepare a new peroxycarbenium ion precursor using molecular oxygen as the source of oxygen atoms (Scheme 2). The cobalt-catalyzed peroxidation of silyl enol ethers also protects the peroxide functionality directly, minimizing the need to handle unstable hydroperoxy compounds. Compared to the use of bisperoxyketals (such as **2**), this method contains only the oxygen–oxygen bond required for synthesis of the peroxide functional group in the product. These substrates also have the advantage that only substoichiometric quantities of Lewis acid are needed to generate the peroxycarbenium ion intermediate required for annulation reactions leading to 1,2-dioxolanes.

Scheme 2. Silyl Monoperoxyketal Synthesis



5 **6**

The method reported here extends the utility of the cobalt-catalyzed peroxidation of alkenes,[24] a powerful method for the synthesis of peroxides. The addition of molecular oxygen and triethylsilane to alkenes forms silylated peroxides with unfunctionalized alkenes[25−28] and 1,2-dioxanes and 1,2-dioxolanes with dienes.[29] Application of this reaction to alkenes

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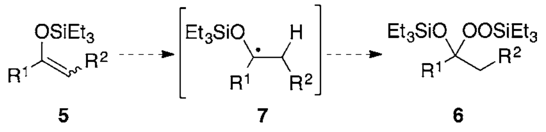
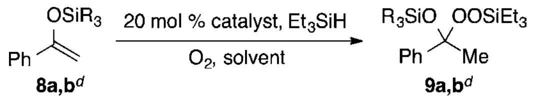
with heteroatom substituents, however, has not been explored. On the basis of previous mechanistic investigations,[30] we hypothesized that peroxidation of silyl enol ethers would proceed via a stabilized alkoxy-substituted radical intermediate[31] **7**, which would allow for the synthesis of silyl monoperoxyketal intermediates such as **6** (Scheme 3).

Scheme 3. Formation of a Stabilized Radical



The cobalt-catalyzed peroxidation reaction with oxygen and triethylsilane was an effective method for the synthesis of silyl monoperoxyketals. Treatment of trimethylsilyl enol ether **8a** under standard conditions[24] (20 mol % Co(acac)$_2$, 1 atm of O_2, and 2 equiv of Et_3SiH) gave the desired silyl monoperoxyketal **9a** in 38% yield after 12 h (Table 1, entry 1). The remainder of the starting material decomposed to acetophenone. Reaction of the more stable triethylsilyl[32] enol ether **8b** led to fewer decomposition products in the unpurified reaction mixture, leading to easier purification and a higher yield of the desired product (54%, entry 2).

Table 1. Optimization of Reaction Conditions



entry	R	catalyst	solvent	yield (%)[a,b]
1	Me	Co(acac)$_2$	$ClCH_2CH_2Cl$	38
2	Et	Co(acac)$_2$	$ClCH_2CH_2Cl$	54
3	Et	Co(acac)$_2$	MeCN	57
4	Et	Co(acac)$_2$	$PhCF_3$	25
5	Et	Co(modp)$_2$	MeCN	48
6	Et	Co(modp)$_2$	$PhCF_3$	22
7	Et	Co(thd)$_2$	MeCN	68
8	Et	Co(thd)$_2$[e]	$PhCF_3$	80[c]

[a] The main byproduct was acetophenone. [b] The reaction was complete in 12 h. [c] The reaction was complete in 1 h. [d] **8,9a**, R = Me; **8,9b**, R = Et. [e] 10 mol % Co(thd)$_2$.

The peroxidation of silyl enol ethers was optimized by changing the catalyst and solvent. A limited selection of solvents that have the propensity to dissolve oxygen were chosen for screening.[33] Slightly higher yields could be obtained using acetonitrile as the solvent in place of 1,2-dichloroethane. Use of the catalysts Co(modp)$_2$[24] (bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedione)cobalt(II)) and Co(thd)$_2$[34] (bis(2,2,6,6-tetramethylheptane-3,5-dione)cobalt(II)) (Figure 2) was effective in delivering the desired product (entries 5 and 7). Changing the solvent from acetonitrile to trifluorotoluene with Co(thd)$_2$ afforded the desired product **9b** in 80% yield in a shorter time (1 h, entry 8). Analysis of the unpurified reaction mixture obtained under these conditions showed that the product was clean enough to use in the subsequent reactions without purification.

A range of aromatic and aliphatic silyl enol ethers were prepared from commercially available ketones to test the generality of the peroxidation reaction (Table 2). In most cases, these enol ethers were prepared in one step by enolization of the ketone with a lithium amide base followed by the addition of triethylsilyl chloride. Some substrates required no further purification, but if purification was necessary, column chromatography over silica gel or distillation provided analytically pure products.

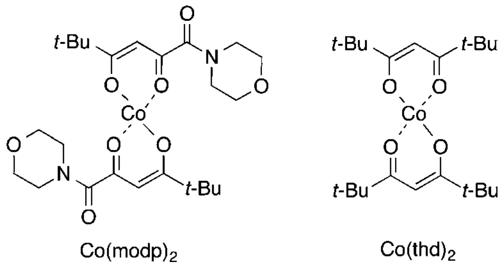
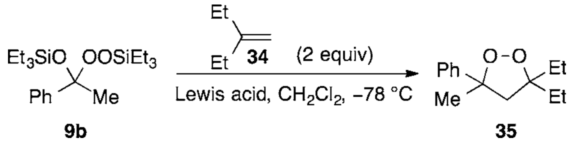


Figure 2. Structures of Co^{II} catalysts.

The peroxidation of silyl enol ethers is general for a range of substrates (Table 2). Aromatic silyl enol ethers with electron-withdrawing groups reacted to form products in the highest yields (entries 2 and 3), while reactions of silyl enol ethers with electron-donating groups resulted in lower yields (entry 1) or more decomposition (entry 5). Electron-withdrawing groups likely stabilize the radical intermediate **7**, giving a greater yield of the peroxide and presumably stabilizing the silyl monoperoxyketal products by disfavoring their decomposition by mild acids such as silica gel. Cyclic compounds **30** and **32** gave the corresponding peroxides in similar yields in a 1:1 diastereomeric ratio (entries 11 and 12). It was not important that the enolization step be regio- or stereoselective, because each component of the mixture of silyl enol ethers led to the same product (entries 6, 9, and 10).

To probe the effectiveness of the silyl monoperoxyketal functional group as a peroxycarbenium ion precursor, a [3 + 2] annulation reaction with silyl monoperoxyketal **9b** and 1,1-disubstituted alkene **34** was attempted (Scheme 4). A variety of Lewis acids were screened in stoichiometric and substoichiometric amounts, including $BF_3{\cdot}OEt_2$, $AlCl_3$, $TiCl_4$, $HfCl_4$, $SnBr_4$, Et_3SiCl, and Bu_3SnCl. All Lewis acids were found to give unreacted starting material or acetophenone as the final product. The use of 5 mol % $SnCl_4$, however, provided the 1,2-dioxolane **35** in 51% yield. The use of larger quantities of $SnCl_4$ provided no increase in yield.

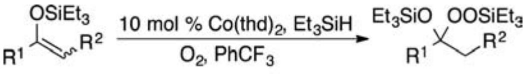
Scheme 4. [3 + 2] Annulation of Silyl Monoperoxyketal



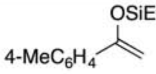
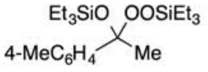
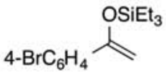
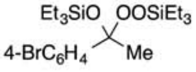
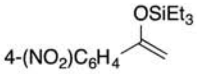
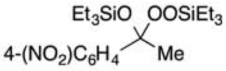
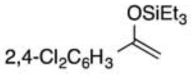
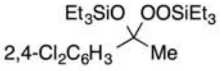
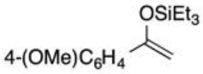
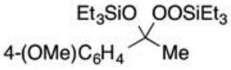
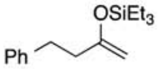
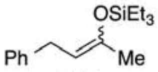
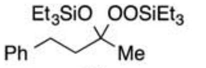
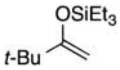
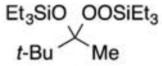
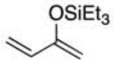
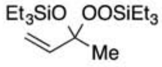
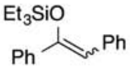
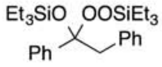
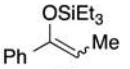
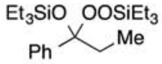
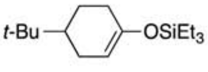
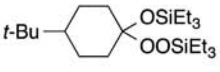
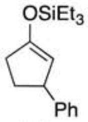
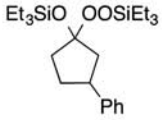
The selective ionization of the silyloxy group by a strong Lewis acid is consistent with previous studies on the ionization of mixed acetals.[35] Complexation of a strong Lewis acid to the more basic silyloxy group is favored, leading to ionization of that group (complex **36**, Figure 3). Association of a Lewis acid to form complex **37** is disfavored due to the electron-withdrawing silyloxy group, which causes the complexing oxygen atom to become less basic.[36]

The purity of $SnCl_4$ has a significant influence on the effectiveness of the silyl monoperoxyketal **9b** as a peroxycarbenium ion precursor. The reaction of silyl monoperoxyketal **9b**

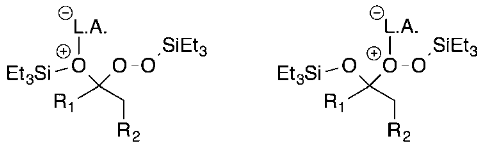
Table 2. Silyl Monoperoxyketal Synthesis



5 6

entry	substrate	product	yield (%)[a]
1	 10	 11	67
2	 12	 13	92
3	 14	 15	96
4	 16	 17	54
5	 18	 19	0[b]
6	 20a  20b,c	 21	79
7	 22	 23	76
8	 24	 25	55
9	 26	 27	63
10	 28	 29	69
11	 30	 31	65[c]
12	 32	 33	69[c]

[a] Isolated yield. [b] The silyl monoperoxyketal **19** was observed by ^{1}H NMR spectroscopy, but it was unstable to chromatography on silica gel. [c] Isolated as a 1:1 mixture of diastereomers.



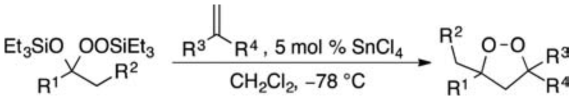
36 37

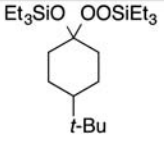
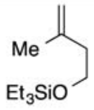
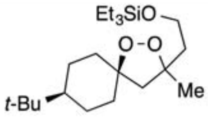
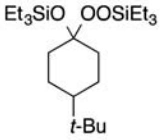
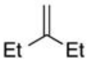
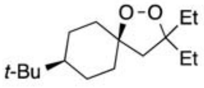
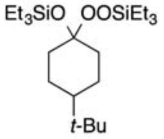
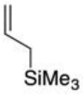
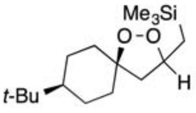
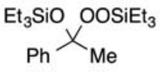
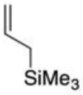
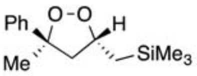
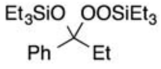
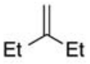
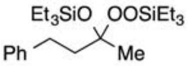
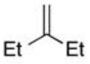
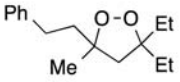
Figure 3. Possible ionization pathways of silyl monoperoxyketals.

and alkene **34** with stoichiometric or trace ethereal HCl gave only acetophenone with no formation of annulation product **35**. This result indicates that even small quantities of HCl in solutions of Lewis acid are detrimental to the reaction.[37]

To demonstrate the utility of the [3 + 2] annulation, a range of 1,2-dioxolanes were synthesized from silyl monoperoxyketals and nucleophilic alkenes (Table 3). The reaction of silyl monoperoxyketal **31** with alkene **38** gave the cyclic peroxide **39**, which resembles the core of synthetic 1,2-dioxolane **1**

Table 3. 1,2-Dioxolane Synthesis



peroxyketal	alkene	product	yield (%)[a]
 31	 38	 39	44[b,c]
 31	 34	 40	72[b]
 31	 41	 42	81[b]
 9b	 41	 43	53[d]
 29	 34	 44	55
 21	 34	 45	76

[a] Isolated yield. [b] The product was formed as a single diastereomer. [c] In situ deprotection with n-Bu$_4$NF gave the alcohol in 53% yield. [d] Isolated as an 87:13 mixture of diastereomers.

(Figure 1). The protected hydroxyl group of **39** allows for further functionalization to either the carboxylic acid or ester moiety present in many natural products.[16,19] The annulation of ethyl-substituted silyl monoperoxyketal **29** using diethyl-substituted alkene **34** afforded cyclic peroxide **44**, which resembles the ethyl-substituted core of plakortide E (Figure 1). Installation of long alkyl chains present in many 1,2-dioxolane natural products can be achieved, as shown by the synthesis of cyclic peroxide **45**. The diastereoselectivity observed in annulation product **43** can be ascribed to a synclinal transition state, analogous to the annulation of allylic silanes with aldehydes.[38] The synthesis of 1,2-dioxolane **42** demonstrates the advantage of silyl monoperoxyketals as peroxycarbenium ion precursors, because previous syntheses have required up to 10 equiv of Lewis acid to effect the transformation.[19,39]

In conclusion, the cobalt-catalyzed peroxidation of silyl enol ethers using molecular oxygen and triethylsilane provides an efficient method for the synthesis of silyl monoperoxyketals. The reaction is general for aryl- and alkyl-substituted silyl enol ethers, and the enol ether can be embedded in a five- or six-membered ring. These silyl monoperoxyketals also serve as effective peroxycarbenium ion precursors, requiring only substoichiometric amounts of Lewis acid for their formation. This development allows for the rapid synthesis of the 1,2-dioxolane core found in many natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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