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INTER- AND INTRAMOLECULAR EPOXIDATION UTILIZING SILYL-PROTECTED PEROXY ESTERS AND COPPER SALT

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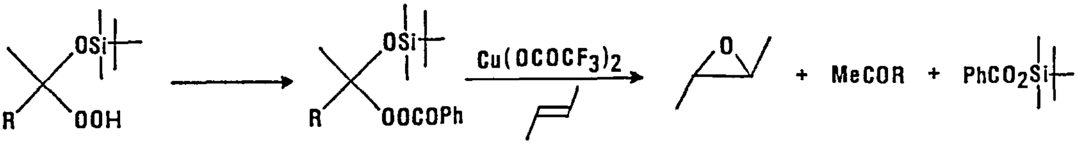
Summary: A new epoxidation method utilizing α-siloxyalkyl peroxybenzoate and $Cu(OCOCF_3)_2$ is described. Regioselective epoxidation of all trans farnesol is accomplished by the intramolecular version of this method.

Several approaches to the goal of selective epoxidation of a polyene at a particular double bond have been reported.[1,2] Breslow demonstrated the template-directed remote epoxidation of polyenes,[1,3] whereas Corey reported the first clear case of synthetically useful intramolecular epoxidation using peroxyarachidonic acid.[4] We report herein a new method for olefin epoxidation using α-siloxyalkyl peroxy esters and copper salt that can be directly applicable to intramolecular epoxidation of polyenes with a high degree of regiochemical control. We previously demonstrated that α-siloxyalkyl peroxybenzoate (**2**) obtained from easily available α-siloxyalkyl hydroperoxide **1**[5] is capable of epoxidizing olefins in the presence of Pd(II) catalyst.[6] While this method is effective for epoxidation of a range of olefins including weakly nucleophilic olefins under mild conditions, terminal or simple internal olefins which are prone to form π-allylpalladium complexes were only sluggishly oxidized to give low yields of epoxides.[6] We found a remarkably efficient method for olefin epoxidation by using $Cu(OCOCF_3)_2$ as a catalyst. A characteristic feature of our method using α-siloxyalkyl hydroperoxide **1** lies in its easy applicability to intramolecular epoxidation by connecting with substrates through perester linkage.



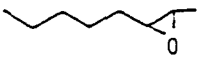
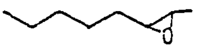
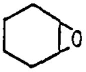
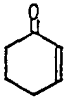
1

2 ; R = cyclopropyl

3 ; R = Me

In a typical experiment, a solution of **2** and olefin in dry dichloromethane was mixed with $Cu(OCOCF_3)_2$(10 mol%), and the solution was stirred under nitrogen at room temperature. As shown in Table I, various olefins including terminal olefins were epoxidized in high yields under mild conditions.[7] When trans olefins were oxidized, only trans epoxides were formed, whereas cis olefins gave a mixture of cis and trans epoxides with cis products predominating. Notably, the formation of benzaldehyde from stilbene was negligible, in contrast to the oxidation with Cu(II) salts-PhIO system[8] where benzaldehyde formation is inevitable.

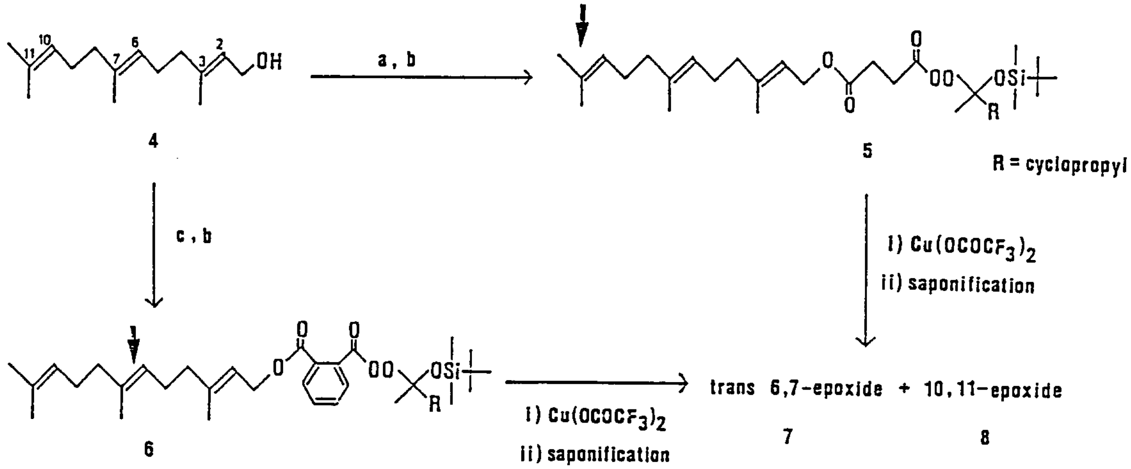
Table I. Oxidation of olefins by α-siloxyalkyl peroxybenzoate 2 catalyzed by $Cu(OCOCF_3)_2$[a]

entry	substrate	reaction time (h)	product (yield %)[b]
1	trans-stilbene	16	trans-stilbene oxide (66)[c]
2	cis-stilbene	16	cis-stilbene oxide (56)[c] trans-stilbene oxide (9)[c]
3		16	 (83)[d]
4		16	 (5)[d]
			 (72)[d]
5		40	 (43)[d]
6	cyclohexene	16	 (40)[d]  (3)[d]

[a]Reaction was conducted in dry CH_2Cl_2 containing 2 (250 mM), $Cu(OCOCF_3)_2$ (10 mol%) and substrate (500 mM) under stirring at room temperature. [b]Yields were based on 2 initially used. [c]Determined by ^1H NMR. [d]Determined by GLC.

Intramolecular version of this epoxidation was examined by choosing all trans farnesol as a typical polyene substrate. Farnesol (4) was converted to peroxy ester 5 or 6 by treatment with succinic anhydride or phthalic anhydride followed by condensation with α-siloxyalkyl hydroperoxide 1. Separation with flash column chromatography on silica gel provided almost pure 5 (76%) and 6 (85%). To a solution of 5 (4 mM) in dry dichloromethane was added $Cu(OCOCF_3)_2$ (15 mol%), and the solution was stirred under nitrogen at room temperature for 12 h. Saponification (LiOH/aq THF) of the crude mixture followed by silica gel column chromatography gave a mixture of 7 and 8 in a ratio of 2:9 in 82% yield.[9]
In a control reaction intermolecular epoxidation of farnesyl benzoate with 2 under similar conditions proceeded nonselectively to give a 1:1 mixture of 7 and 8 after saponification.
In contrast, a similar treatment of 6 (4 mM) with $Cu(OCOCF_3)_2$ (15 mol%) gave trans 6,7-epoxide 7 predominantly together with 8 in a ratio of 8:2 in 91% yield. These results apparently

indicate that no significant intermolecular oxidation is contributing in the reaction of 5 or 6 at a concentration of 4 mM. 2,3-Epoxide has never been found in the inter- and intramolecular oxidations.



a; succinic anhydride/DMAP/CH_2Cl_2
b; 1/DCC/DMAP/CH_2Cl_2
c; phthalic anhydride/DMAP/CH_2Cl_2

5 ; 2 : 9
6 ; 8 : 2

Selective epoxidation at the 6,7-double bond of farnesol cannot be readily accomplished by conventional methods or even by the template-directed epoxidation using $Mo(CO)_6$-t-BuOOH system.[3] Usually, there is a preference for the attack at the end 10,11-double bond of the flexible chain as actually observed in the reaction of 5. By sharp contrast, the remarkably selective 6,7-epoxidation observed with 6 may be attributable to the preference of the geometry in which the peroxy ester group more easily reaches the 6,7-double bond through the folded phthaloyl linker as anticipated form the molecular model.

The present result demonstrated that a combination of silyl-protected peroxy esters and $Cu(OCOCF_3)_2$ serves as a convenient oxygen-atom-transfer reagent for inter- and intramolecular epoxidation. By choosing an appropriate linker, regioselective epoxidation of a polyene at a particular double bond can be accomplished by the intramolecular reaction.

Studies on the nature of the reactive species and the synthetic utility of this reaction are in progress.

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2. J. Rebeck, Jr. and R. McCready, *J. Am. Chem. Soc.*, **102**, 5602 (1980).
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7. Oxidation with other α-siloxyalkyl peroxybenzoates such as **3** gave similar results.[6] However, longer reaction time is required and the product formation is not so clean.
8. (a) G. C. Franklin, R. B. VanAtta, A. F. Tai and J. S. Valentine, *J. Am. Chem. Soc.*, **106**, 814 (1984); (b) R. B. VanAtta, C. C. Franklin and J. S. Valentine, *Inorg. Chem.*, **23**, 4121 (1984).
9. The ratio was determined by 400 MHz ^{1}H NMR by comparison with authentic samples independently separated by medium-pressure liquid chromatography using pre-packed silica gel column.

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