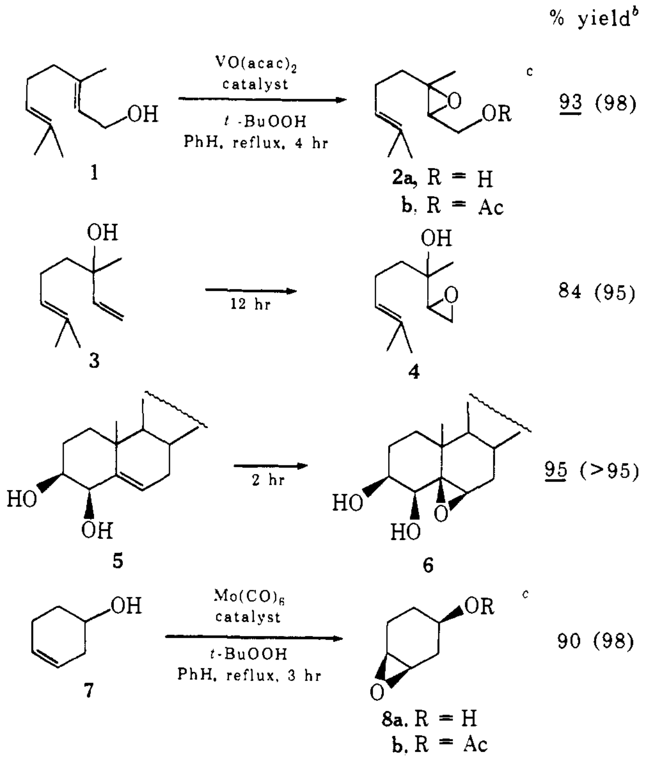
High Stereo- and Regioselectivities in the Transition Metal Catalyzed Epoxidations of Olefinic Alcohols by *tert*-Butyl Hydroperoxide

Sir:

Although the use of vanadium and molybdenum catalysts for the epoxidation of simple olefins by alkyl hydroperoxides is well known in the patent literature,[1] no use of these systems has yet been reported in the area of complex molecule synthesis. We have now found that these transition metal–hydroperoxide reagents exhibit remarkable reactivity toward olefinic alcohols.[2] As revealed in Chart I, these systems effect selective epoxidations not obtainable with any other reagent.

Chart I[a]



[a] These reactions were run on a medium scale using the stoichiometry described below in detail for the oxidation of geraniol (**1**). [b] Isolated yields are underlined, all others are by glc relative to internal standard. The figure in parentheses is the isomeric purity. [c] Epoxy alcohols **2a** and **8a** decomposed thermally upon attempted distillation or glc analysis and therefore were acetylated *in situ* (pyridine–acetic anhydride) to give epoxy acetates **2b** and **8b**.

Thus geraniol (**1**) and linalool (**3**) were selectively oxidized to the previously unknown monoepoxides **2a** and **4**. 4β-Hydroxycholesterol (**5**) gave only the 5,6-β-oxide, whereas epoxidation of **5** with *m*-chloroperbenzoic acid in methylene chloride produced an ~2/1 mixture of the β-oxide[3a] and the corresponding α-oxide.[3b] In contrast to its reaction with peracids,[4] the homoallylic alcohol **7** afforded only the *syn*-epoxy alcohol **8a** with the molybdenum system.

The following procedure for the oxidation of geraniol (**1**) to its 2,3-epoxide **2a** illustrates how readily these epoxidations are effected on a preparative scale.

To a solution of pure (*E*)-geraniol (Fritsche, 20 g, 0.129 mol) and of vanadyl acetyl acetonate (J. T. Baker, 0.5 g, 0.0018 mol) in 150 ml of refluxing benzene was added, dropwise over a period of 20 min, 17.6 g (0.142 mol) of 72.5%[5] *tert*-butyl hydroperoxide (MCB). The initially colorless solution of geraniol in benzene turned bright green upon addition of the $VO(acac)_2$. The color faded as the reflux temperature was approached and then turned deep red as the *t*-BuOOH was added. The reaction was monitored by tlc and judged complete after 4 hr at reflux. During this time the deep red color turns to yellow and then to light green.[6]

The reaction mixture was cooled to 25° and a solution of 50 ml of acetic anhydride in 70 ml of pyridine was added. After stirring for 6 hr the resulting solution was poured onto ice and then washed sequentially with water, 1 *N* hydrochloric acid, sodium bisulfite solution, sodium bicarbonate solution, and saturated sodium chloride, dried over $MgSO_4$, and concentrated to give 33.7 g of crude epoxy acetate. Analysis by glc (3% OV-17) revealed only one component and no geranyl acetate (from starting material). Distillation afforded 25.2 g (93%) of 2,3-epoxygeranyl acetate, bp 104–106° (0.025 mm), which by glc was shown to contain only 2% of its isomer, 6,7-epoxygeranyl acetate. All spectral and analytical data were consonant with the assigned structure.

It is interesting to compare the selectivity of these molybdenum and vanadium reagents with that of the peracids, which have been the reagents of choice for epoxidation of olefins. The syn-directive effect of the hydroxyl group of allylic alcohols is well known. Henbest[4b] was the first to establish that peracid epoxidation of allylic alcohols (**10**) occurs principally cis to the hydroxyl and that the rate of epoxidation of the alcohol is about ten times that of the corresponding allylic acetate (**11**) and about one-half that of the parent hydrocarbon (**9**, Table I, part A). However, the directing effect is rather weak and is subject to steric interference, as noted by Henbest[4b] for several steroidal allylic alcohols and in the present work for allylic alcohol **5**. We have determined (Table I, part A) the relative rates and stereospecificities for the molybdenum and vanadium reagents and compared them to Henbest's results[7] with perbenzoic acid. In contrast to the

---

(1) For a recent review see R. Hiatt in "Oxidation," Vol. 2, R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1971, Chapter 3.

(2) (a) F. List and L. Kuhnen, *Erdol. Kohle*, **20**, 192 (1967); (b) M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970). These two groups had noted that allylic alcohols were especially good substrates for these metal–hydroperoxide reagents. However, neither group determined the rates relative to parent olefin or the stereochemistry in the three interesting cyclic examples that were reported.

(3) (a) O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 377 (1937); (b) L. F. Tiesen, T. Goto, and B. K. Bhatlacharyya, *J. Amer. Chem. Soc.*, **82**, 1700 (1960).

(4) (a) D. Swern in "Organic Peroxides," Vol. 2, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1971, pp 466–470, and references cited therein; (b) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(5) Although 72% *tert*-butyl hydroperoxide was sufficient for most cases we generally used 94% *tert*-butyl hydroperoxide which is readily available from the Lucidol Division of the Pennwalt Corporation. The higher strength reagent is preferred for use with the vanadium catalyst, which is more sensitive to inhibition[4b] by *tert*-butyl alcohol and water than the molybdenum catalyst.

(6) If the organic phase is washed at this point with aqueous bisulfite and concentrated the desired epoxy alcohol **2a** is obtained in 98% yield. However, since this epoxy alcohol decomposed upon attempted distillation, it was acetylated *in situ* to facilitate isolation of a pure product.

(7) Although the relative rates are those reported by Henbest, we redetermined the stereospecificities of the peracid epoxidation using glc; this technique had not been available when the original work was done. It should be noted that even in the best case (**10**) 8% of the *anti*-epoxy alcohol is formed.

Table I

Olefin	Relative Rates Peracid	 $Mo(CO)_6{}^b$ t-BuOOH	 $VO(acac)_2{}^b$ t-BuOOH
	Part A[c]		
Cyclohexene (**9**)	1^a	1	1
2-Cyclohexen-1-ol (**10**)	0.55^a $(92/8)^7$	4.5 (98/2)	>200 (98/2)
1-Acetoxy-2-cyclohexene (**11**)	0.046^a $(37/63)^7$	0.07 (40/60)	
3-Cyclohexen-1-ol (**7**)	0.42^a $(60/40)^7$	11.0 (98/2)	10.0 (98/2)
	Part B		
trans-5-Decene (**12**)		1	1
1-Hydroxy-(*E*)-4-nonene (**13**)		0.98	13.4
	Part C[d]		
Geraniol (**1**)	0.5	45	~100
Geranyl acetate (**14**)	0.04		
Linalool (**3**)	0.11	0.62	10.3

[a] With the exception of the peracid relative rates (ref 4b) in part A all the data in this table are from the present work. [b] All the competition studies were carried to about 5% completion based on "total olefin" (*i.e.*, based on number of moles of double bonds present, thus 1 mol of geraniol = 2 mol of cyclohexene) by limiting the amount of t-BuOOH added. The ratios of the epoxide products were determined by glc. All reactions were run at reflux in benzene with a "total olefin" concentration of 0.35 *M*. [c] In part A the figures in parentheses refer to (% *syn*-epoxide/*anti*-epoxide). It is important to note that the relative rates in part A apply only in vertical columns (*i.e.*, no correlation of rates has been made for the different reagents). [d] Unlike parts A and B, in part C the double bonds in competition are in the same molecule and each entry corresponds to the ratio of epoxidation at the double bond proximate to the oxygen function *vs.* the double bond further removed from it.

results with peracids, one notes that the vanadium and molybdenum catalyzed epoxidations of the allylic alcohol **10** and even the homoallylic alcohol **7** are essentially stereospecific. Furthermore, alcohols **10** and **7** were oxidized considerably faster than cyclohexene in both of the transition metal systems. It is interesting that the molybdenum system reacted faster with the homoallylic alcohol **7** than with the allylic alcohol **10**, whereas with the vanadium catalyst the opposite was true.

Even the bishomoallylic alcohol **13**[8] is epoxidized by the vanadium system over ten times faster than the purely hydrocarbon olefin **12** (Table I, part B). These olefins (**12** and **13**) exhibit identical reactivity toward the molybdenum system. The above result suggests that the vanadium catalyst may be capable of selective epoxidation of the 6,7 double bond in natural polyene alcohols such as squalene-2,3-glycol.

Both geraniol (**1**) and geranyl acetate (**14**) are epoxidized by peracids preferentially at the olefinic site ($\Delta^{6,7}$) furthest removed from the hydroxyl group (Table I, part C). Indirect epoxidation *via* bromohydrin formation would also favor the more electron-rich 6,7 double bond. As expected from the results in part A, the molybdenum- and vanadium-hydroperoxide systems showed high regioselectivity for the 2,3 double bond or geraniol. Even the vinyl group of linalool was selectively epoxidized by the vanadium reagent which is exceptionally reactive toward allylic alcohols. Although we have not measured any absolute rates, we have made the qualitative observation that the molybdenum catalyst is faster with most olefins than the vanadium catalyst. The exceptions occur with allylic alcohols, where the rate accelerations are so great with the vanadium catalyst that the absolute rates actually exceed those with the molybdenum catalyst.

We are continuing our studies on the mechanism[9] and synthetic utility of these transition metal catalyzed epoxidations. The rate accelerations and high stereoselectivities observed in the present work clearly support mechanisms[2b] where the alcohol is coordinated to the metal in the rate determining step. It would not be surprising if olefinic acids and amides showed similar synthetically useful effects with these reagents.

Acknowledgment. We are grateful to Professor Robert Ireland of the California Institute of Technology for kindly providing a sample of 4β-hydroxycholesterol. We thank the National Science Foundation (GP-30485X), Hoffmann-La Roche Inc., and the Mobil Foundation for support of this research.

---

(8) Alcohol **13** was produced by reaction of butyllithium with dihydropyran as described by F. L. M. Pattison and R. E. A. Dear, *Can. J. Chem.*, **41**, 2602 (1963).

(9) K. B. Sharpless, J. M. Townsend, and D. R. Williams, *J. Amer. Chem. Soc.*, **94**, 295 (1972).

K. B. Sharpless,* R. C. Michaelson
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

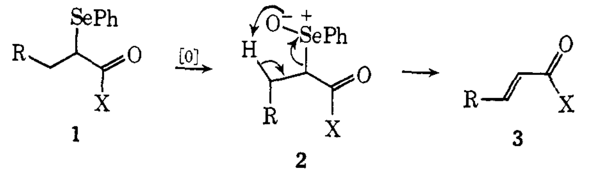
Received June 23, 1973

Electrophilic and Nucleophilic Organoselenium Reagents. New Routes to α,β-Unsaturated Carbonyl Compounds

Sir:

We recently established that alkylphenyl selenoxides undergo facile syn elimination to form olefins[1] and that this process can be useful for introducing unsaturation into organic structures under mild conditions.[1,2] We now report the application of organoselenium reagents to syntheses of α,β-unsaturated carbonyl compounds. In each case the penultimate step involves oxidation of an α-phenylselenocarbonyl compound (**1**) to the corresponding selenoxide **2** which eliminates at room temperature to the desired olefin **3**. We have found that X (**1**, Scheme I) can be hydrogen, alkyl, or alkoxy; thus α,β-unsaturated aldehydes, ketones, and esters can be prepared by this method. The α-phenylselenocarbonyl compounds (**1**) are readily formed in a variety of ways from the previously employed[1,2] nucleophilic selenium reagent $PhSe^-Na^+$ (**4**) and from the electrophilic selenium reagents[3] PhSeCl (**5**) and PhSeBr (**6**).

Scheme I



---

(1) K. B. Sharpless, M. W. Young, and R. F. Lauer, *Tetrahedron Lett.*, 1979 (1973).

(2) K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **95**, 2697 (1973).

(3) PhSeCl (**5**) and PhSeBr (**6**) are obtained in quantitative yield when PhSeSePh (ref 2) is cleaved with sulfuryl chloride or bromine, respectively. Although both of the benzene selenyl halides are stable solids, it is often more convenient to prepare them *in situ* from the diselenide.