PROGRESS IN THE DEVELOPMENT OF NEW EPOXIDATION REAGENTS

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Dedicated to Professor Tetsuji Kametani

The work herein describes our experiences with new reagents for olefin epoxidation. In defining the scope of this work, we shall discuss neither the transition metal-catalyzed epoxidations[1a] nor the more specific systems involving epoxidation of olefinic alcohols[1b] as these subjects have been well treated elsewhere. At the outset, our goals were the rather ambitious ones that seem unique to newly-appointed assistant professors: asymmetric epoxidation and direct synthesis of arene oxides. As we shall see, the more modest goal of finding structural features necessary for oxygen transfer to olefins would have been more appropriate. Nonetheless, I cannot help but think that this review will be of interest to those who have thought deeply about such issues.

INTRODUCTION

Any discussion of olefin epoxidation must begin with the Prilaschajew reaction (eq. 1). Discovered in 1908, its reliability and simplicity have resulted in its popular use during the intervening 70 years. The reaction has been extensively investigated and several excellent reviews[2] are available; only a few general features will be discussed here.

$$(\text{eq. 1}) \quad R\text{-}CO_3H \; + \; \overset{R'}{\underset{}{\diagup}}\!\!=\!\! \longrightarrow \; R\text{-}CO_2H \; + \; \overset{R'}{\triangle O}$$
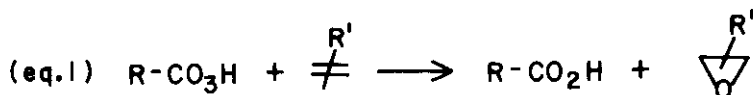
a) The peracid shows all of the earmarks of an electrophilic reagent. Electron-withdrawing groups in R increase the electrophilicity of the peracid and thereby the epoxidation rate, while electron-releasing groups in R' increase epoxidation rates and lead to the familiar sequence of olefin reactivity (Table).

Table[3]

Relative Reactivities of Olefins

Olefin	Br_2 Addition	H^+ Catalyzed Hydration	Peracid Epoxidation
═══	.016	--	.045
╱═	1.00	1.00	1.0
╲═╱	43	1.68	22
╱═╱	28	0.71	∿20
╲═	89	10^3-10^4	22
╲═╱	1500	10^3-10^4	230

Of particular interest is the lack of selectivity peracids show toward di-substituted olefins. Rate ratios with a number of olefin pairs[2b,4] show only a slight preference for the *cis*-isomer (1.2-2.2 times faster than the *trans*). In addition, the roughly twenty-fold increases in rate with increasing alkyl substitution indicate that the steric effects of alkyl groups on the double bond are not important in the transition state for epoxidation.

b) No intermediates have been detected. Studies involving secondary deuterium isotope effects have been interpreted[5] as evidence that the formation of one new C-O bond precedes the formation of the other C-O bond in the transition state, and this interpretation is supported by *ab initio* calculations.[6] However, the clean stereospecificity of the reaction suggests that intermediates, if any, must be very short-lived. Therefore, from the practical (synthetic) point of view, the reaction can be considered as concerted.

c) Asymmetric induction with optically active peracids is poor. The highest enantiomeric excess recorded for an unexceptional olefin is 9.2% (using highly purified and freshly prepared monopercamphoric acid[7]); more often 5% or less is observed.[8]

d) The epoxidation reaction appears to require an intact intramolecular hydrogen bond in the peracid. Reaction rates vary (decrease) with the basicity of the solvent (:S in eq. 2) rather than solvent polarity, and good correlations

(eq. 2)
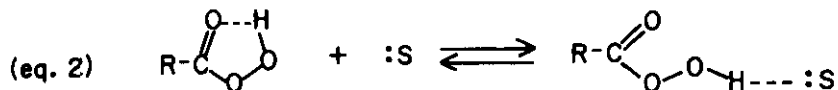
exist between epoxidation rates in a given solvent and the shift of the OH stretching frequency of the peracid's infrared spectrum in that solvent.[9]

These general observations can be combined to produce a reasonable picture for the geometry of the transition state.

A   B
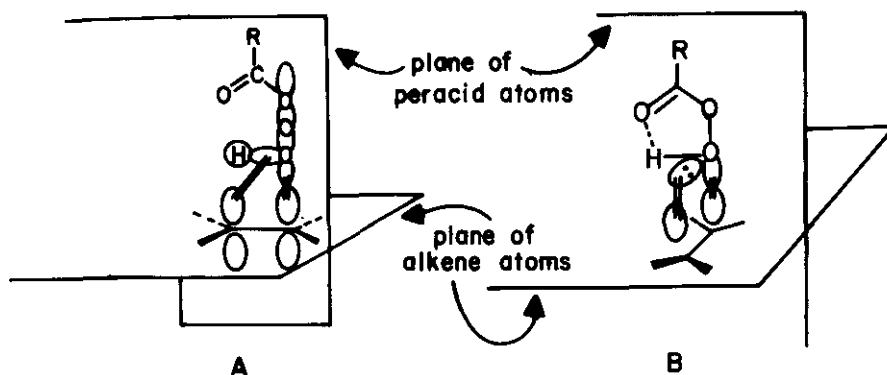
The important initial interactions are the π-bond (HOMO) and the σ* orbital of the electrophilic O-O bond (LUMO).[10] Electrons for the second new C-O bond could be supplied by the remnants of the O-H bond as the proton is transferred (A), or from a lone pair on the terminal oxygen (B). A concerted proton transfer is most economically accommodated by (A), whereas the MO calculations[6,10] favor the "spiro" mode (B).[11] Whichever the mode, the olefin approaches the system along a line defined by the O-O bond as though an S_N2 reaction were being performed on the terminal oxygen. In agreement with experiment *cis/trans* select-ivity should be minimal, as should asymmetric induction, since there is little opportunity for steric interactions between the R group of the peracid and groups attached to the π-bond. Indeed, the R group of the peracid could not be further away from the site of reaction.

This distance probably accounts for the difficulty of intramolecular epoxidation. For such epoxidation to occur with peracids, a large number of connecting atoms between the peroxy function and the olefin is required, and entropy renders an arrangement such as 1 unlikely if the connecting atoms are free to rotate. The first clear case of intramolecular epoxidation, peroxyarachidonic acid 2 recently reported by Corey[12] involves a 16½-membered transition state. Its remarkable success can be attributed, in part, to the restricted rotation provided by the 3 additional π-bonds.
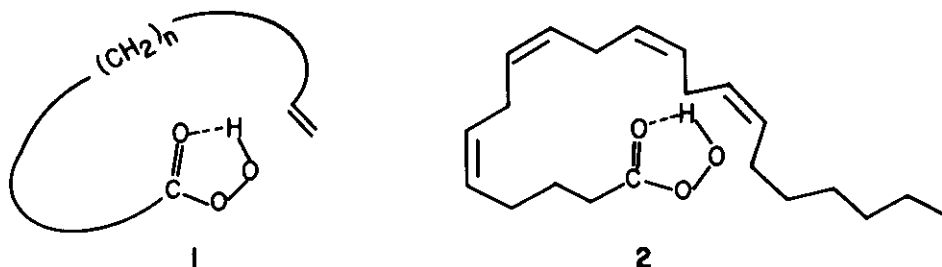

These considerations led us to believe that selectivity in epoxidation with peracids would require the construction of rigid structures in which bulky or chiral groups were forced to reside in the region near the terminal oxygen. Alternatively, new oxygen transfer agents might be developed in which epoxidation in a selective manner would not be subject to the unfavorable geometries seen for peracids. The former approach is well defined while the latter is more abstract in that it requires identification of structural and mechanistic features required for a useful epoxidant. Surprisingly, the more defined peracid problem has yielded largely negative results in our laboratories; accordingly, we will emphasize the new reagents in this review.

NEW REAGENTS

Reactions in which H_2O_2 is involved as an oxidant invariably lead to the formation of H_2O and it is useful to view oxygen atom transfers, such as epoxidation, as formal dehydrations of H_2O_2. Peracids are then seen to be stabilized intermediates which act as oxygen atom equivalents in this dehydration process (Scheme).

SCHEME
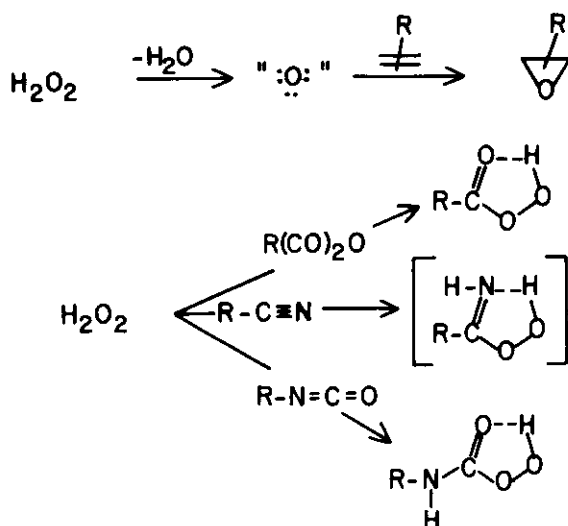
Apart from carboxylic acid anhydrides, nitriles[13], and isocyanates[14] are also viable dehydrating agents for epoxidation, and these systems share with peracids the availability of the intramolecular hydrogen bond. Percarbonic acids[15] **3** represent additional higher oxidation states of carbon, and perphosphoric[16] **4** and Caro's acid **5** represent hetero atoms in this view.
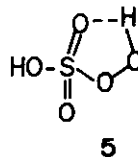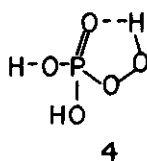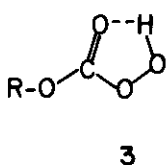
These systems are summarized in eq. 3, wherein the double bond between X and Y allows the charges created by oxygen transfer to be annihilated through resonance:
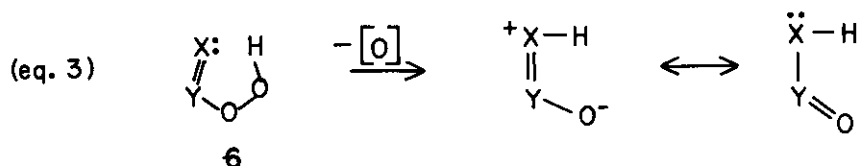
A number of dehydrating agents with H_2O_2 are capable of generating the structural features of 6 and we examined those which would lead to neutral side products.[17] Simple alkyl carbodiimides were tested first and we found only sluggish reactions and low yields of epoxides. However, a recent report[18] describes the successful use of this system in the direct epoxidation of arenes to arene oxides (eq. 4).

(eq. 4)

R = <u>iso</u>-propyl or
<u>cyclo</u>-hexyl
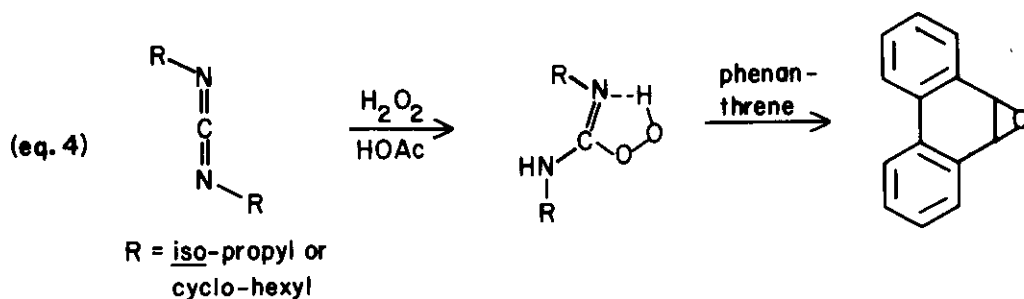
A more reactive system was found in the benzoyl derivative 7 prepared by Mitsunobu.[19] Epoxide yields with this reagent and H_2O_2 are given in Table 1.

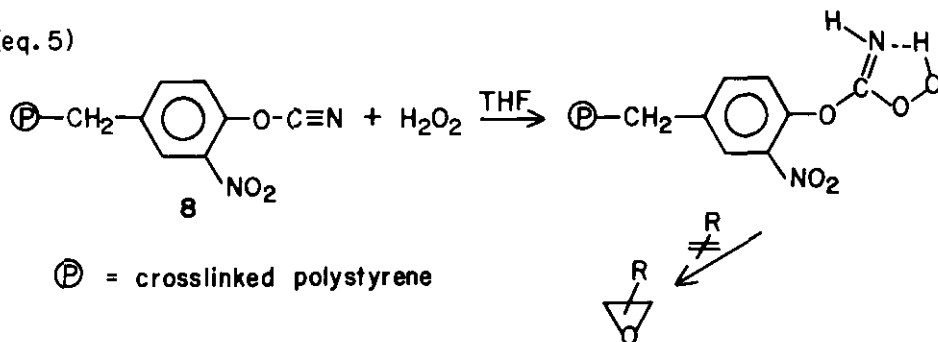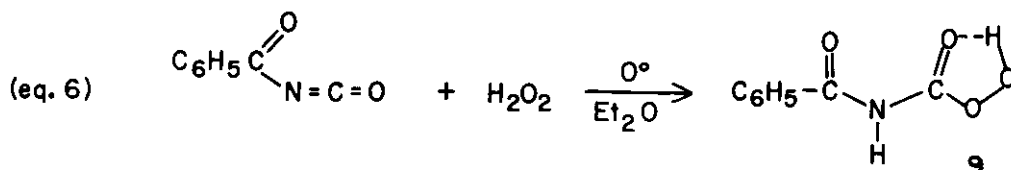Table 1[20] Epoxidation with 7 + H_2O_2
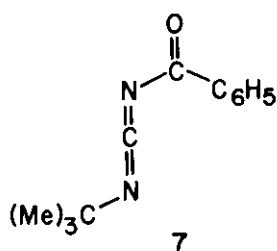
olefin	% epoxide	% olefin	material balance %
trans-5-decene	90	1	91
cis-4-methyl-2-pentene	88		
trans-4-methyl-2-pentene	86		
trans-ß-methylstyrene	1	16	17
cyclohexene	74	0	74
1-octene	51	24	75
2-octenes	76	10	86
1-heptene	53	35	88
trans-2-heptene	89	2	91
1-decene	69	37	100
1-methylcyclohexene	0	1	1
1-methylcyclopentene	0	0	0

As shown by the material balance, and further established by control experiments, several epoxides proved unstable to the reaction medium and we therefore searched for milder systems. Aryl cyanates were screened and the most successful of these proved to be the polystyrene-anchored 8 (eq. 5). Unfortunately, yields of epoxides were modest again due to their destruction by the reagent system.

(eq. 5)

$$\text{(P)}-CH_2-\underset{NO_2}{\underbrace{}}-O-C\equiv N + H_2O_2 \xrightarrow{\text{THF}} \text{(P)}-CH_2-\underset{NO_2}{\underbrace{}}-O-C\underset{O-O}{\overset{N-H}{\cdots}}$$

8

(P) = **crosslinked polystyrene**

A quite satisfactory reagent was found in the reaction of H_2O_2 with benzoyl isocyanate (eq. 6). The crystalline[21] **9** gave high yields of epoxides (Table 2) and the neutral products, benzamide and CO_2, insured the stability of even the most fragile epoxides. For example, this reagent gave good yields of the sensitive epoxide **10** when other methods resulted in rearranged products[22] (eq. 7).

(eq. 6)

$$C_6H_5\overset{O}{\underset{}{C}}N=C=O \quad + \quad H_2O_2 \quad \xrightarrow[Et_2O]{0^\circ} \quad C_6H_5-\overset{O}{C}-\underset{H}{N}-C\underset{O-O}{\overset{O-H}{\cdots}}$$

9

Table 2[20]

Epoxidation with **9** in THF

olefin	yield, %	olefin	yield, %
1-heptene	81[a]	*cis*-4-methyl-2-pentene	99
1-octene	68[a]	*trans*-4-methyl-2-pentene	79
1-decene	61[a]	1-methylcyclohexene	89
trans-5-decene	92	1-methylcyclopentene	92
trans-2-heptene	84	cyclohexene	99
2-octenes	92	allylbenzene	73[a]
cis-stilbene	54	α-methylstyrene	95
trans-stilbene	59	β-methylstyrene	92
indene	95		

[a] 1.5 equiv of **9**

(eq. 7)   **9** + ⟍⟍$_{N_3}$ ⟶ △$_{N_3}$ + CO_2 + $C_6H_5-CONH_2$

10
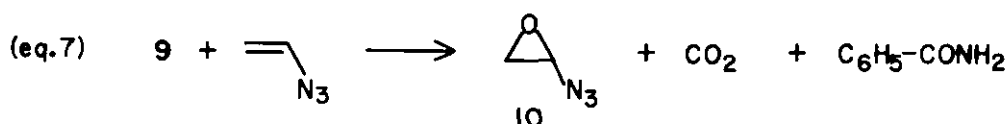
A second useful reagent was discovered in the reaction of H_2O_2 with carbonyl bitriazole 11 (eq. 8). *Nearly quantitative yields of epoxides were obtained when* 12 *is generated in situ in the presence of olefins.*[23] Here the side product, triazole, is water soluble and therefore easily removed. Evidence for the peculiar hydrogen bond, as shown in 12, rests on the observed *insensitivity* of the epoxidation rate to solvent basicity (Table 3).[20]
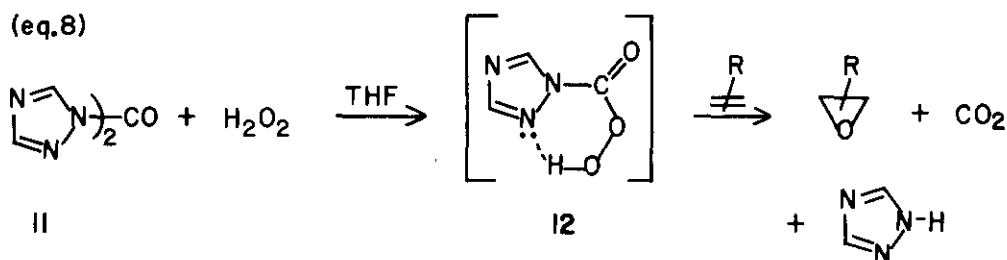
(eq.8)

Table 3
Epoxidation Rates of Cyclohexene[a]

	THF	CHCl$_3$	Et$_2$O	DMF
perbenzoic acid[24]	4.3	472	5.8	2.2
12 + H$_2$O$_2$	710	790	700	250

$^a M^{-1}s^{-1}$, X 10^4

While these systems helped reinforce our notion of dehydration of H_2O_2 using structural features described in 6, the high reactivity of these epoxidants was attended by lack of selectivity in two senses. Firstly, the reagents showed neither *cis/trans* selectivity nor asymmetric induction. For example, the chiral reagents[17] 13-16 gave only 2-8% enantiomeric excess of epoxide 18 when treated with H_2O_2 in the presence of the test olefin *trans*-β-methylstyrene 17 (eq. 9).
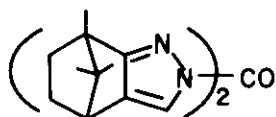
15

16
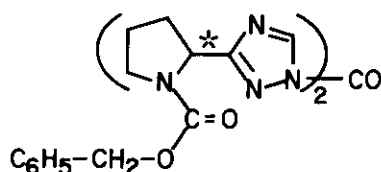
(eq. 9)   13-16 + H_2O_2 +

17

$\xrightarrow{\text{THF}}$

  (2-8% e.e.)
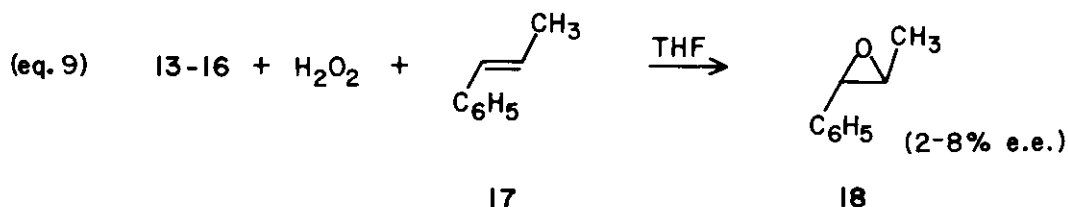
18
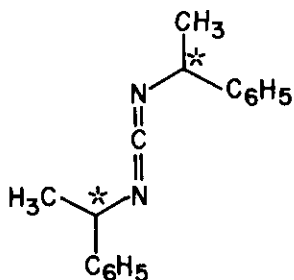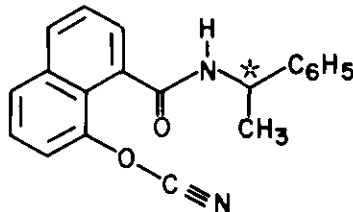
Secondly, the intermediates generated showed sufficient reactivity to oxidize H_2O_2 to oxygen. Such behavior has been observed during decomposition of peracids[25] or even H_2O_2[26] by bases, where the oxygen formed is initially in its singlet ($^1O_2$) state. Since oxygen is also evolved in H_2O_2/nitrile mixtures[27], we tested the possibility that the oxygen observed in our systems was $^1O_2$. Typically, $^1O_2$ is detected by its characteristic "ene" reactions with olefins[28] but this method can not be used when powerful epoxidants are also present. We selected the endoperoxide formation with 9,10-diphenyl anthracene as the trap for $^1O_2$ (eq. 10) and found that $^1O_2$ was formed in our systems. Indeed, in the absence of olefins, the action of dehydrating agents on H_2O_2 provides very high yields[29] of $^1O_2$ (Table 4).
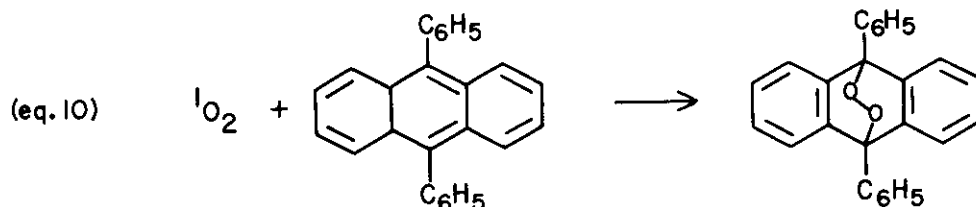
(eq. 10) $^1O_2$ +

$\longrightarrow$

Table 4[17]

Yields of Singlet Oxygen

H_2O_2 +	$^1O_2$(%)
C_6H_5CONCO	98
11	94
8	60
13	10

These efficient chemical sources of $^1O_2$, particularly the polymer-bound 8, have been an unexpected dividend from our research but $^1O_2$ formation is not desirable in epoxidation reagents. The process which forms $^1O_2$ competes with epoxidation, particularly with slowly reacting olefins, and thereby consumes reagent and reduces the epoxide yield. We therefore turned to inherently less reactive systems with the hope that greater selectivity could be attained in epoxidations.

The similarities in structure between our model 6 and α-hydroperoxy ethers 19 suggested that such reagents may also be capable of stereospecific oxygen transfer (eq. 11).

(eq. 11)

19
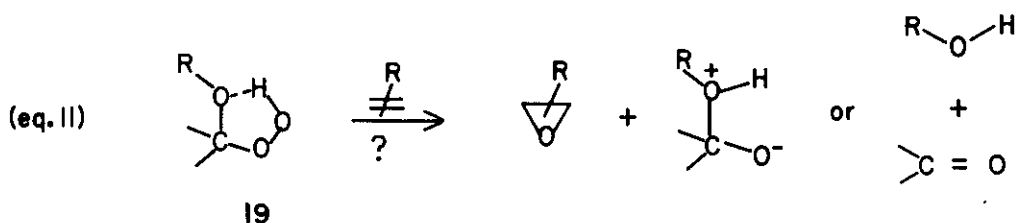
A few members of this notorious class of substances had already been characterized: Rieche[30] obtained the crystalline 20 from autoxidation of benzaldehyde ethylene acetal while Milas[31] distilled the mono THP ether of H_2O_2 21. In addition, Kim[32] had shown that the related alcohol 22 was capable of olefin epoxidation, so it was not surprising to find that 20 or 21 indeed epoxidized olefins, even if they did so only slowly.
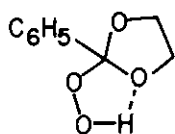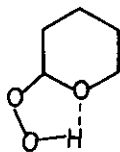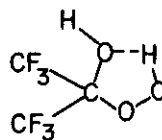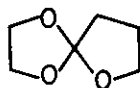
20   **21**   **22**

It seemed likely that such structures could be generated *in situ* from the
action of H_2O_2 on ortho esters and ketals so we screened a number of these
reagents with the test olefin 17. Yields of epoxide using only 1 equiv. of
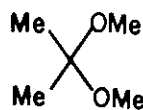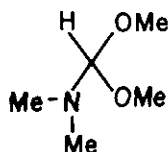23-29 in THF are given in Table 5.

R—C(OEt)₃

23   R = OEt
24   R = H
25   R = CH₃
26   R = C₆H₅

27   **28**
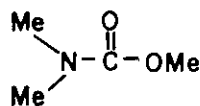
29   **30**

Table 5
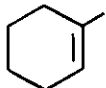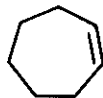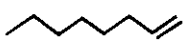
Epoxidation of *trans*-ß-methylstyrene with 31-37

Dehydrating agent	23	24	25	26	27	28	29
Yield of epoxide (%)	14	11	17	20	11	trace	0

The orthocarbonate 23 gave the fastest epoxidation rates, but its use in
preparative reactions was limited by the observed evolution of oxygen (this was
shown to be singlet oxygen by its trapping as previously described). In addition,
the side product, diethyl carbonate, proved difficult to separate from the
epoxide product. Epoxidations with the ketal 28 were very slow while 29 suffered
oxidation to the urethane 30 when treated with H_2O_2. Given these limitations we
selected the commercially available 25 as the most promising reagent. Its side
products are common volatile solvents, rates were satisfactory and no oxygen

formation was observed. In attempts to optimize yields it was found that EtOH
severely decreases the epoxidation rate. Highest yields were obtained when a $1\underline{M}$
solution of the olefin in 25 was treated with 90% H_2O_2.   After 4 hours
the system is diluted with CH_2Cl_2, washed free of EtOH with H_2O, dried, then
concentrated if the volatility of the olefin and epoxide products permit. Sub-
sequently another portion of 25 and H_2O_2 are added. Yields obtained by this
procedure are given in Table 6.

Table 6

Olefin epoxidations with 25 + H_2O_2

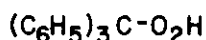| Olefin						
epoxide yield	99%	85%	68%	95%	81%	15%

Although α-hydroperoxy ethers are probably intermediates in this procedure,
we observed that epoxidations of olefins with 25 also proceed using $text$-butyl
hydroperoxide 31 (eq. 12). Since it seemed possible that 31 was acting merely as
a nascent source of H_2O_2 we examined the side products and found neither iso-
butylene nor its epoxide, but $Me_3C\text{-}OH$ as the only $text$-butyl containing product.
Therefore, other pathways seem to be involved. While these are not presently
known they are probably related to the epoxidation of olefins with borate esters[39]
and alkyl hydroperoxides (eq. 13) for which intermediates such as 32 have been
proposed.

(eq. 12) $Me_3C\text{-}O_2H$ + 25 +   olefin $\longrightarrow$ epoxide + EtOH

31

+ EtOAc + $Me_3C\text{-}OH$

(eq. 13)

$(R'\text{-}O\text{-}BO)_3$ + $R'O_2H$ $\longrightarrow$

R' = cyclohexyl R' = t-butyl
                      cumyl or
                      tetralyl

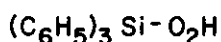$\xrightarrow{\text{olefins}}$ epoxides

32
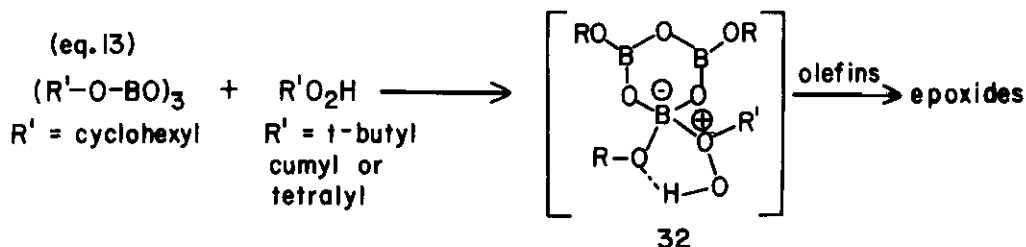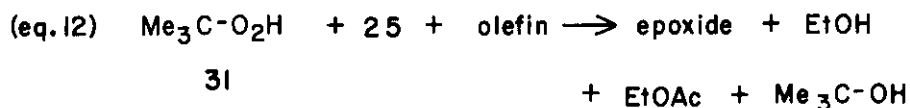
The olefin-induced decomposition of alkyl hydroperoxides is a well-known phenomenon and accounts for, *inter alia*, polymerization during autoxidation[35]. There is, however, a report[36] of epoxidation with *t*-Bu-O$_2$H in neat olefins 33a,b; many other products are formed and yields are low but the epoxide is produced in stereospecific manner (eq. 14).
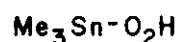
(eq.14)   33a   + Me$_3$COOH $\xrightarrow{90°, 19h}$ 5-10%

33b   + Me$_3$COOH $\longrightarrow$
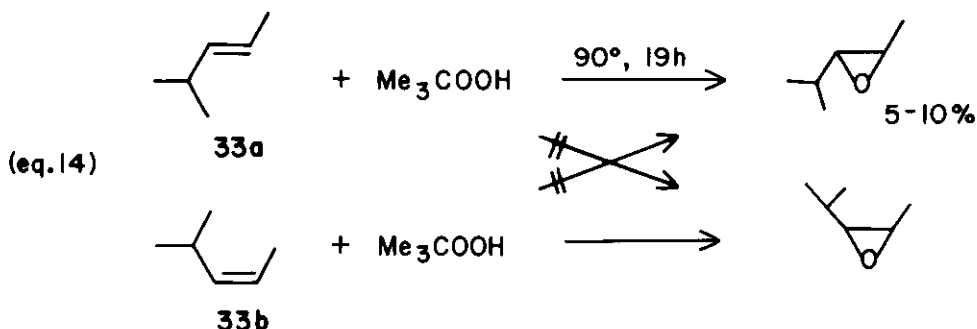
We explored modified conditions and found that in contact with alumina, either *t*-Bu-O$_2$H or H$_2$O$_2$ itself gave modest yields of epoxides, in stereospecific manner.[37] Since it seemed that only slight modification of alkyl hydroperoxides was required for stereospecific epoxidation we examined trityl hydroperoxide[38], 34 and triphenyl silyl hydroperoxide[39] 35. Both epoxidized olefins smoothly but the silyl derivative reacted faster and in a stereospecific manner (Table 7) while the trityl derivative required warming and gave *cis/trans* mixtures of epoxides from *cis* olefins.

$(C_6H_5)_3C-O_2H$ $(C_6H_5)_3Si-O_2H$ Me_3Sn-O_2H

34   35   36

Table 7[37]

35 (2 equiv.) + olefin $\xrightarrow[25°/1\ day]{CH_2Cl_2}$ epoxide

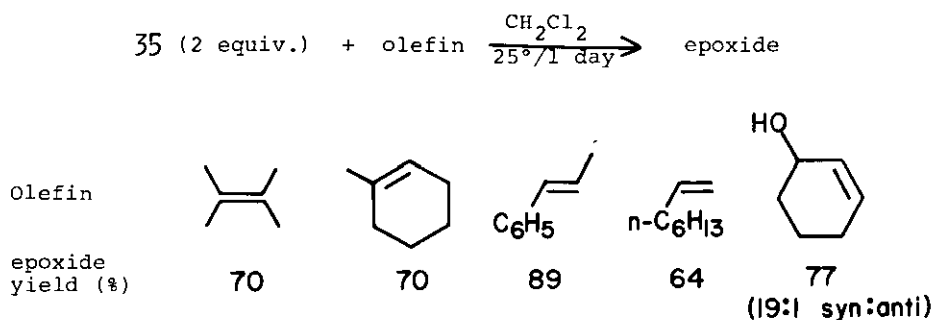| Olefin					
epoxide yield (%)	70	70	89 (C_6H_5)	64 (n-C_6H_{13})	77 (19:1 syn:anti)

In addition, the tin derivative[40] 36 was tested; epoxidation occurred but yields were low.[41] The contrasting behavior of 34 and 35 was a puzzlement, as was the different stereospecificity shown by 31 and 34. Some of the puzzle was resolved when epoxidation of *cis*-2-octene with 34 was conducted in the presence of a free radical inhibitor.[41b] The epoxide was now formed stereospecifically. Therefore two paths for olefin epoxidation exist with 34 only one of which involves free radicals and leads to *trans* epoxide from *cis* olefin. The epoxides formed under these conditions are unstable[35,36] and the preparative value of 34 or 31 is limited. However, the mechanistic questions raised by these reagents remain unresolved.

We undertook a survey of α-substituted hydroperoxides of carbon and examined first α-amino-hydroperoxides. Several of these, derived from the action of H_2O_2 on Schiff bases, had been characterized by Rieche[42] and we found that crystalline 37 (or 38 generated *in situ*) indeed epoxidized olefins (eq. 15).

37   38

(eq. 15)
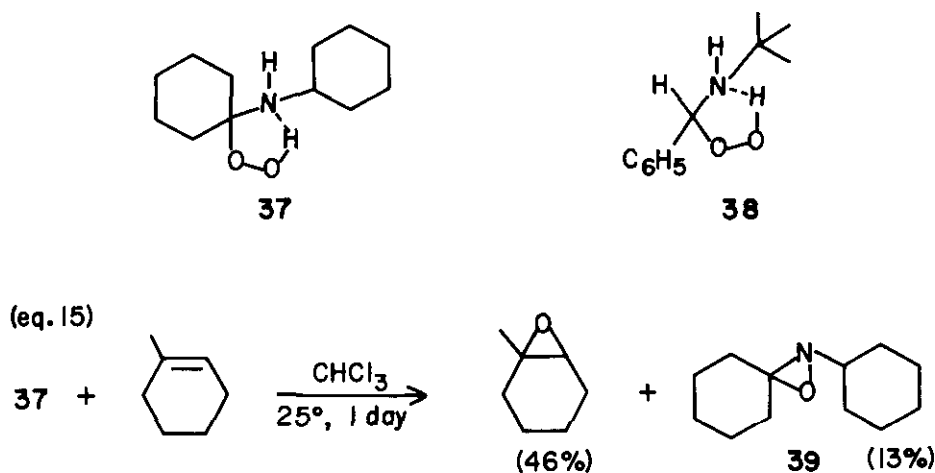
The competing formation of the oxaziridines (*e.g.* 39) led us to less oxidizable forms of nitrogen such as *o*-acylamino-hydroperoxides[43] 40. For example 41 was prepared from the ψ acid chloride of *o*-benzoyl benzoic acid and 2,6-dimethyl aniline followed by acidic H_2O_2. This substance indeed epoxidized olefins slowly but showed no unusual selectivity.
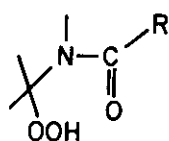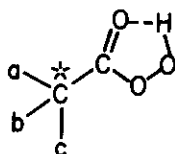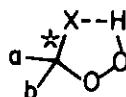
40

41
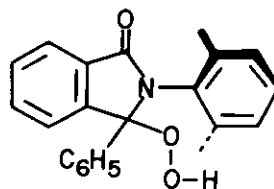
In all of these α-substituted hydroperoxides the intriguing possibility exists of generating chiral reagents in which an asymmetric center is one atom nearer the reaction site than is possible in conventional peracids (compare 42 with 43). A number of attempts to use this to advantage, however, proved cruelly disappointing.


42

43

For example the well-established *exo* attack on norbornyl derivatives[44] was used to generate the optically active agent 45 from 44[45] while the kinetic preference of *endo* attack on camphor derivatives was used to generate 46 from the corresponding ketal. Epoxidation of the test olefin (*trans*-β-methyl-styrene) was observed in either case but only ∿3% enantiomeric excess (e.e.) could be attained.
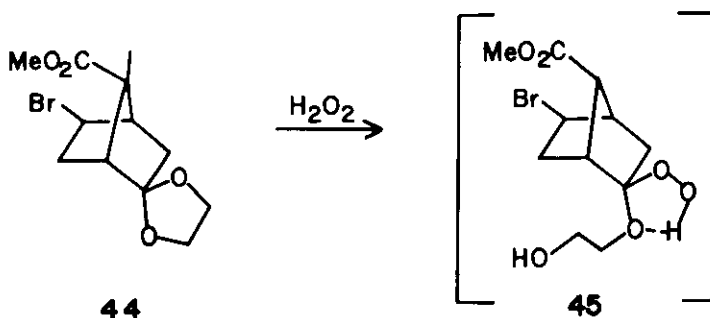
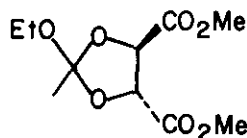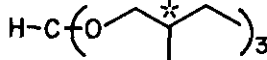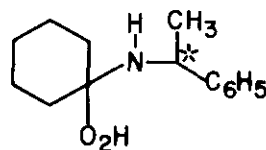**44** $\xrightarrow{H_2O_2}$ **45**
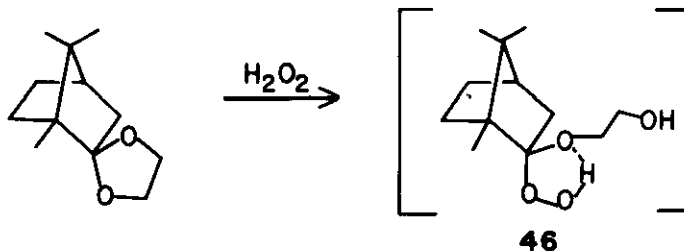
46

Two ortho esters were also used, 47^{46} and 48^{47} but neither gave more than 7% e.e. Evidently, the chirality in these systems is still not sufficiently near the oxygen transfer site. In the α-amino series 49 was generated *in situ* (from the Schiff base) with equally disappointing results.


| **47** | **48** | **49** |

In an effort to avoid resolution yet isolate a single, chiral hydroperoxide the diastereomers 50a,b were prepared.[48] These proved *readily separable on hplc* and quite stable to interconversion, as did the corresponding alcohols 51a,b. Exposure of either diastereomer 50 to the test olefin gave epoxide (5% e.e.) *and each gave* a single alcohol 51. Since control experiments established that no interconversions were occurring under the epoxidation conditions we conclude that oxygen transfer to the olefin occurs without opening of the 5-membered ring.[49]

$$R = (+)\text{-}\alpha\text{-phenyl-ethyl}$$
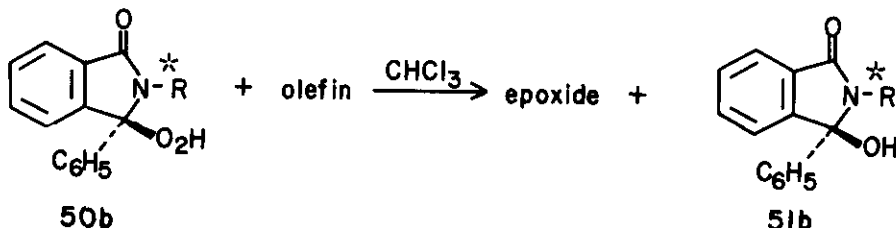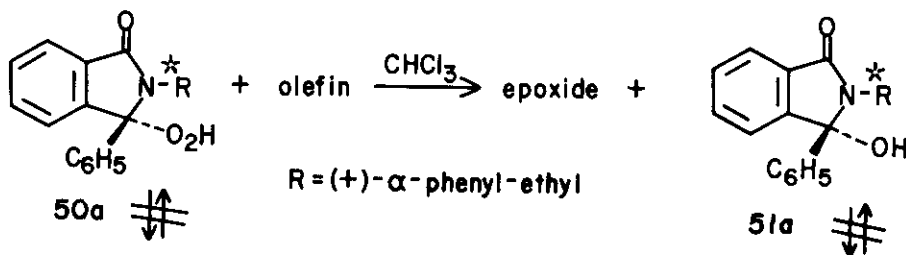
This observation is a curious piece of information since it relates to the fate of the original OH bond in the hydroperoxide. The epoxidation may be sufficiently exothermic to produce an N-protonated amide[50] (eq. 16). Transfer

of the proton, 52 → 53 perhaps mediated by the newly-formed epoxide, could then generate the cyclol without collapse of the zwitterionic intermediate 52.

(eq 16)

50   52   51
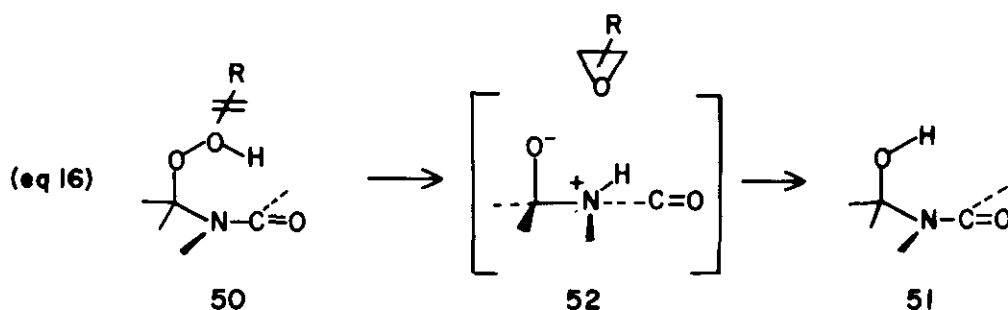
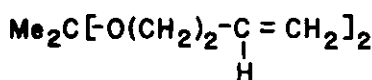The corresponding case with α-hydroperoxy ethers also deserves comment. The most economical mechanism for epoxidation with such reagents is the one-step path. Charged intermediates such as 53, (which are regarded as having short or even non-existent lifetimes[51]) are avoided. Prior dissociation to the carbonyl oxide 54 is inconsistent with the stereospecificity of the epoxidation, since carbonyl oxides are known to give mixtures of *cis* and *trans* epoxides from *cis* olefins.[52]
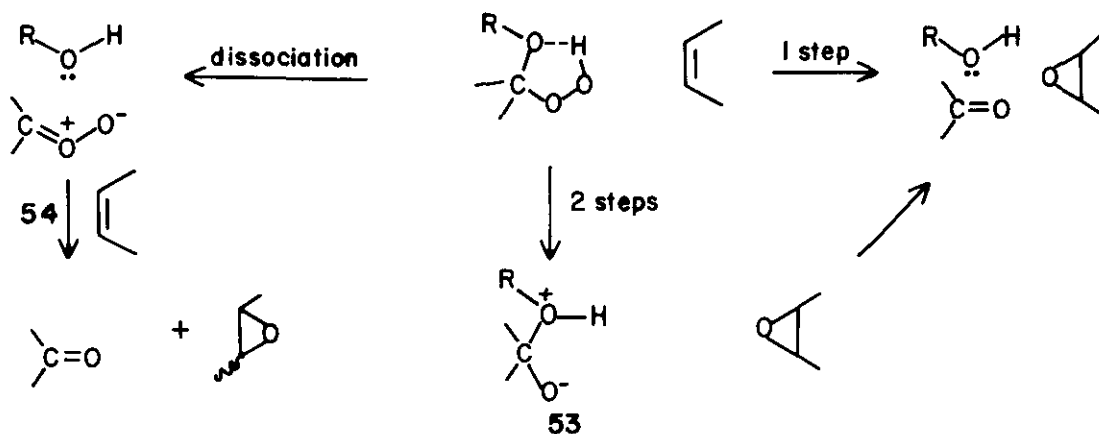
While the asymmetric epoxidations described here leave much to be desired from a synthetic standpoint, a successful study of intramolecular epoxidation was provided by the ortho ester/H_2O_2 system. As previously mentioned, intramolecular epoxidation with peracids is difficult because the first bond from the acyl carbon 55 is directed away from the site of oxygen transfer. The corresponding situation with α-hydroperoxy ethers is considerably more favorable. The direction of the first bond from the peroxy carbon 56 or the ether 57 permits the geometry required

for intramolecular epoxidation to be achieved with fewer connective atoms. Just how few could be tested as follows.

55   56   57

$$R-C[-O-(CH_2)_n-\underset{H}{C}=CH_2]_3 \qquad Me_2C[-O(CH_2)_2-\underset{H}{C}=CH_2]_2$$

58 n = 1, R = H
59 n = 2, R = CH$_3$
60 n = 3, R = H

61
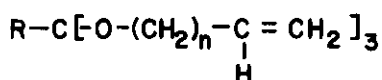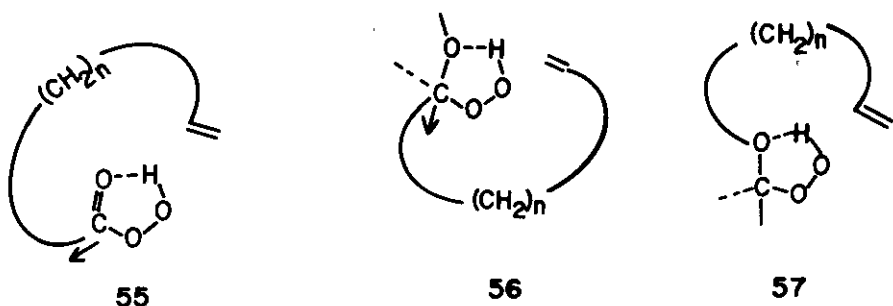
The ortho esters 58-60 derived from allyl, homoallyl and bishomoallyl alcohols were prepared by standard exchange reactions from the ethyl ortho esters while the ketal 61 was prepared similarly from 2,2-dimethoxy-propane. A competition experiment was designed as the test for intramolecular epoxidation using the more reactive (disubstituted $vs.$ monosubstituted) olefin β-methylstyrene 17. As shown in the generalized Scheme, the intermediate X, generated from the action of H$_2$O$_2$ on 58-60 in the presence of 17 has a number of olefin sites with which to react. Bimolecular reaction with 17 gives the styrene oxide 18; bimolecular reaction with 58-60 gives - after hydrolysis - alcohol 62 and formate 63; bimolecular reaction with 61 gives 62, and intramolecular reaction of X also yields 62. At low conversions, [61] is small and the principal sources of 62 involve k$_2$ and k$_{intra}$. If no intramolecular component exists, then the product ratio (62 + 63)/18 will remain constant with the dilution of the system, since these epoxides arise by bimolecular reactions. However, when a sizable intramolecular component exists then successive dilution of the system will increase the amount of 62 formed at the expense of 18. An entirely parallel argument holds for ketal 61.

SCHEME
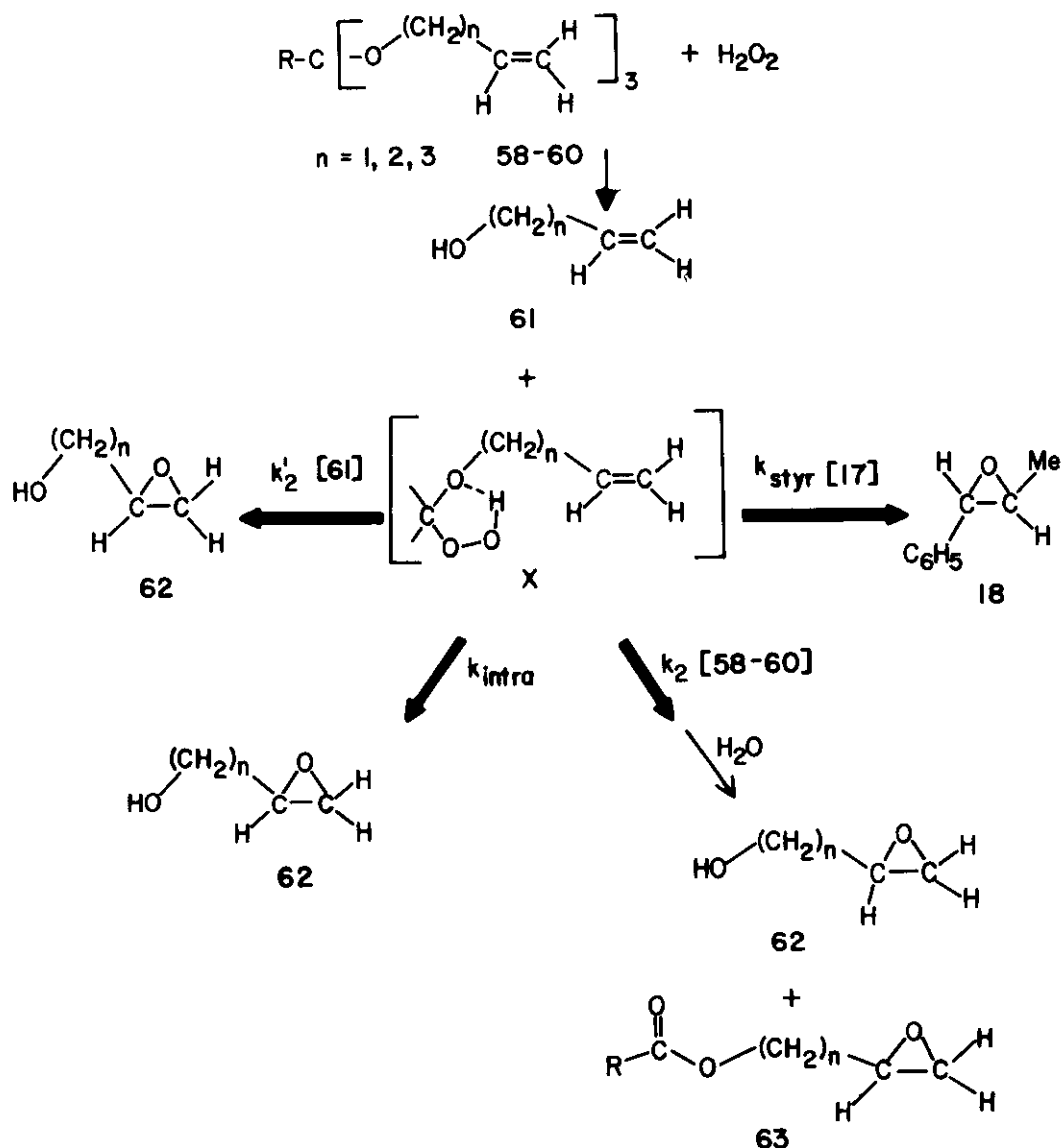
Each of the ortho esters 58-60 and the ketal 61 were placed in competition with 17 at four different dilutions in THF at ambient temperature. The initial molar ratios [58-61]/[17] were kept constant at 1/5 and low conversions (10%) were insured by monitoring the epoxide formed by glpc. Ortho esters remaining at the end of the reaction were decomposed by the addition of H_2O and the epoxide products were determined by glpc against internal standards. In practice, the

esters 63 represented only a small fraction of the epoxides obtained, yet all products were shown to be stable to the reaction and work-up conditions. The result of these competition experiments are summarized in Table 8.

Table 8[48]

$$58\text{-}61 + 17 \xrightarrow[\text{THF}]{H_2O_2} \xrightarrow{H_2O} 18 + 62 + 63$$

(1 mole)   (5 moles)
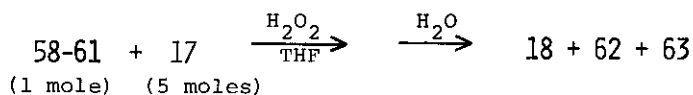
|	58-61	17	Epoxide Ratios (62 + 63)/18			
			from 58	from 59	from 60	from 61
Exp. 1	1M	5M	.39	1.5	8.8	2.5
2	0.5	2.5	.35	2.8	16.	3.8
3	0.33	1.67	.33	4.2	27.	6.9
4	0.25	1.25	.28	10	33.	9.9
			(allylic, n = 1)	(homo-allylic, n = 2)	(bis-allylic, n = 3	(homoallylic ketal, n = 2)
k_{intra}/k_{styr}			$\lesssim 1$	$\sim 7M$	$\sim 40M$	$\sim 11M$

The results show that for the allylic case (n = 1) no intramolecular component for epoxidation could be detected while the homo and bishomoallylic cases show clear evidence for the intramolecular epoxidation pathway. At all concentrations used these latter cases gave more epoxide derived from the intrinsically less reactive olefin; the approximately linear increase in the epoxide ratio with dilution is best accommodated by the rate ratios given in the lowest row of the Table. These were obtained from plots of (62 + 63)/18 against 1/[17].

Of particular interest is the case of the ketal 61. Its efficiency in intra-molecular epoxidation implies that structure 57 is sufficient to describe the nature of the intermediate involved in these reactions. A more refined picture of how the epoxidation occurs is postulated in structure 64. The π-bond can approach the backside of the terminal oxygen on a line defined by the O-O single bond of the peroxide.[53] With fewer connective atoms, i.e. the allylic case, this approach cannot be realized. Such geometries have been favored by calculations of peracid-olefin transition states[6,10,54]; in addition, this approach can place a lone pair of the terminal oxygen parallel with the approaching π-

bond as has recently been proposed for peracid epoxidations by Sharpless.[1]
However, this degree of refinement must await further experimental verification.

In order to test the feasibility of epoxidation *via* structure 56 we examined an ortho ester derived from an olefinic acid. Specifically, oleic acid was converted to the corresponding ortho ester 65. On treatment with H_2O_2 in CH_2Cl_2 for 24 hours, a 40% yield of the corresponding epoxide 66 was obtained.
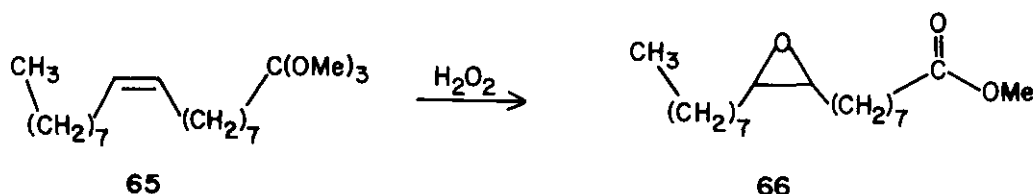
To establish that epoxidation was indeed intramolecular, a competition experiment was performed along the lines of those previously described.[55] Here the competing olefin was the amide 67. On successive dilutions of a THF solution containing equimolar amounts of 65 and 67 with H_2O_2, the yield of 66 increased at the expense of 68 (Table 9).
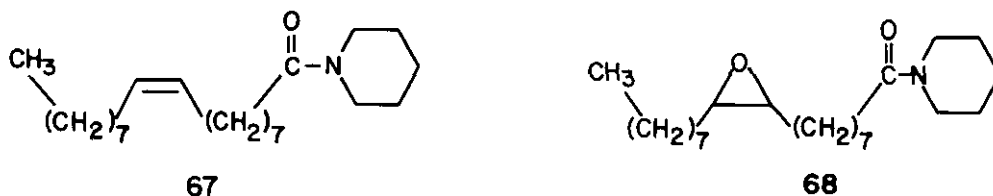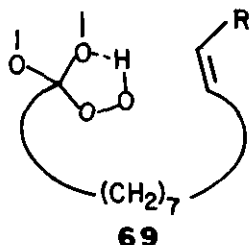

Table 9[55]

$$65 + 67 \xrightarrow[\text{THF}]{H_2O_2} 66 + 68$$

[65] = [67]	[66]/[68]
1M	7
1.5M	12
0.25M	27

Structures such as 69 are, consequently, likely candidates for this epoxidation. Systematic studies are underway to determine the fewest number of connective atoms necessary for intramolecular oxygen transfer in these cases.


69
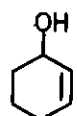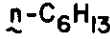
Returning now to the problem of selectivity, we made progress in an unexpected manner. Mild methods for the oxygenation of enolizable carbonyl compounds have made accessible α–hydroperoxy-acids[56], esters[57], ketones[58], amides[59], and nitriles[60]. While a number of studies have concerned themselves with the decomposition of these substances under acidic, basic and pyrolytic conditions[61], none had dwelt on their reaction with olefins. Instead, the curious instability of α-hydroperoxides of *olefinic* acids (compared with their saturated counterparts) had been noted.[56] This instability can be explained by our discovery[62] that α-hydroperoxy-carbonyl compounds are effective reagents for olefin epoxidation (eq. 17).

(eq. 17)

70   **71**   **72**   **73**
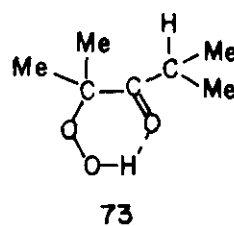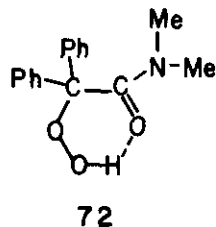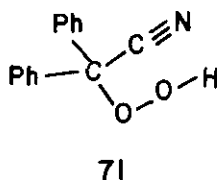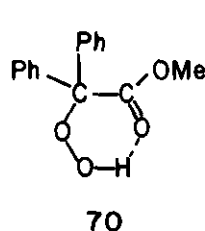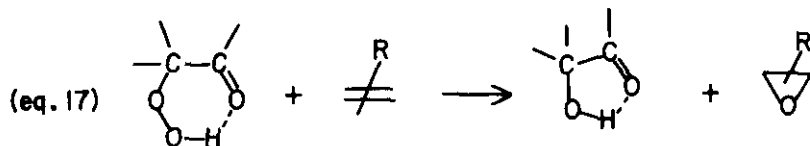
Specifically, hydroperoxides 70-73 were screened for their ability to epoxidize olefins. All proved active, but highest reactivity was observed with 70 and 71; results of epoxidations with these are given in Table 10. These yields were obtained by warming (60°) a 0.3M solution of 70 or 71 with the olefin for 24 hours followed by glpc analysis.

Table 10^{62}

Epoxide Yields, %,($CHCl_3$, 60°, 24 h)

| 70 | | 99 | 84 | 63 | 85 | 30^a | 3 |
| 71 | | 99 | 97 | 87 | 86 | 39^b | 12 |

^{a}syn:anti = 7:3; ^{b}syn:anti = 6:4

Kinetic studies established that the reaction is first order with respect to each olefin and hydroperoxide and the epoxidation is cleanly stereospecific. Like peroxyacids (of which 70 may be considered a homolog), intramolecular hydrogen bonding is observed, and epoxidation rates are slower in Et_2O than in CH_2Cl_2. Moreover, a preference for *syn* epoxidation of cyclohexenol is seen and Baeyer-Villiger reaction of cyclopentanone with 70 occurs. Unlike peroxyacids an unusual selectivity between *cis* and *trans* stilbenes was detected (Table 11). Typically peracids show a marginal preference for the *cis* isomer[2b,4], but 70 (and to a lesser extent 71) react more rapidly with *trans* stilbene.

Table 11^{62}

Selectivity (k_{cis}/k_{trans}) in Epoxidation, 60°, $CHCl_3$

Olefin Pairs

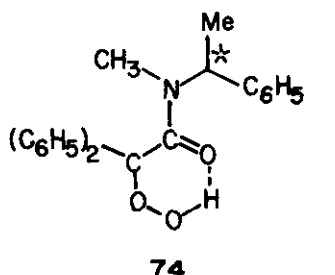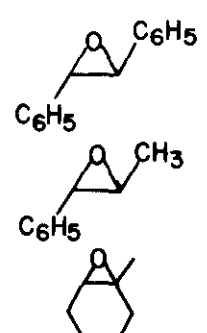| Reagent	(Me)(H)C≡ n-Hex	(Et)(H)C≡ t-Bu	(Me)(H)C≡ i-Pr	(Ph)(H)C≡ Ph	cyclo vs. hexene	Me Ph
MCPBA	1.6	1.1	1.4	1.5	2.8	
70	.92	1.0	$.58^a$	<.05 $0.54^{b,c}$	<.05 $.26^b$	
71	1.2	1.6	1.2	.46 0.55^b	0.75 0.95^b	

^{a}25°, CH_2Cl_2; ^{b}60°, C_6H_6; ^{c}some epoxide is converted to benzaldehyde

Competition studies with aliphatic olefin pairs showed little such general selectivity, but *trans*-β-methylstyrene was epoxidized much faster than cyclohexene. The selectivity is much diminished when benzene is used as a solvent. This implies that the unusual selectivity in CHCl$_3$ has its source in attractive forces between the aromatic rings of the reagent and substrate. This cannot be the entire reason since 73 also preferably reacted with *trans*-stilbenes (4 times faster than with *cis*).

At any rate, our belief that *cis*/*trans* selectivity and asymmetric epoxidation are intimately connected has encouraged us to follow up this lead. We have prepared the chiral derivative 74 and results are promising: epoxidation data are given in Table 12. These figures represent the highest asymmetric induction observed to date.[63] Again the phenyl substituted olefins showed much greater selectivity than alkylated olefins.

Table 12

Enantiomeric excess with
74 + olefins (CHCl$_3$, 25°; 3 days)

31 % e.e.

23

4

The intramolecular hydrogen bond of 74 apparently fixes the conformation shown (N-methyl between the two aryls) and reduces the rate of rotation about the amide (N-CO) bond. This may be used to advantage in forcing bulky or chiral groups even nearer the terminal oxygen. Structures such as 75 and 76 are presently being investigated to this end.
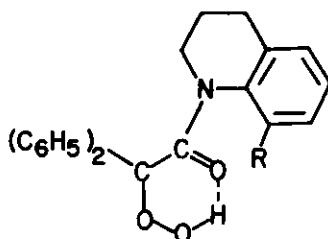
75 R = C6H5

76 R = chiral group

PERACIDS

In order to obtain empirically the spatial requirements for the approach of olefins to peracids we have prepared a number of U-shaped peracids and used their relative reactivities to *cis* vs. *trans* stilbenes as a probe. The o-substituted derivatives of perbenzoic acid **77** failed to show selectivity which differed from the parent compound. Surprisingly, even the *peri* substituted pernaphthoic acids **78** were unexceptional.[64]
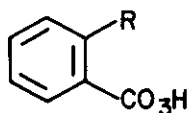
77

R = H
R = CH3
R = CH(CH3)C6H5
R = CH(C6H5)2

78
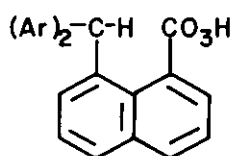
Ar = C6H6
Ar = 1-naphthyl

An even more rigid system was envisioned in **79**, but it, too, failed to show selectivity between *cis* and *trans* disubstituted olefin pairs.[65] Apparently this is due to the "splay" (exaggerated in **80**) between the peri substituents, resulting from the molecular deformations detected by x-ray analysis of such systems.[66]
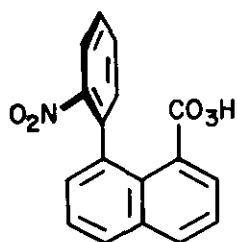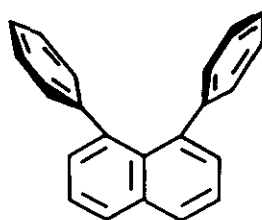
79　　　　　　**80**

Given these disappointments, the reader may wonder why we are pursuing even less accessible systems, such as the C-shaped $\underline{81}$. This may be our folly, but a synthetic reagent which epoxidizes, say, *cis* olefins exclusively in the presence of *trans* would, in large part, reverse the normal trend of reactivity.

81　　　　　　**82**

decreasing rates
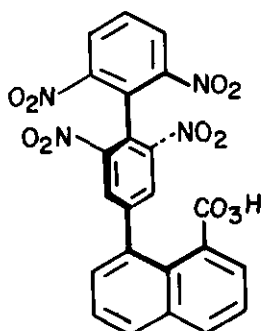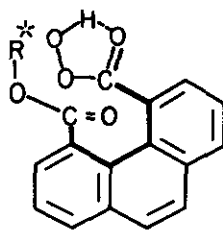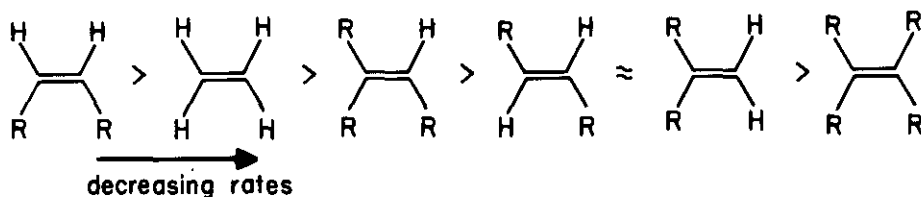
This reversal is the counterpart of reactivity "umpolung"[67], the impact of which on modern synthesis has been enormous. Moreover, given the unsatisfactory methods for epoxide resolution, any general reagents which provide access to chiral epoxides would be welcomed.

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