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Mechanism of Oxygen Transfer in the Epoxidation of an Olefin by Molecular Oxygen in the Presence of an Aldehyde

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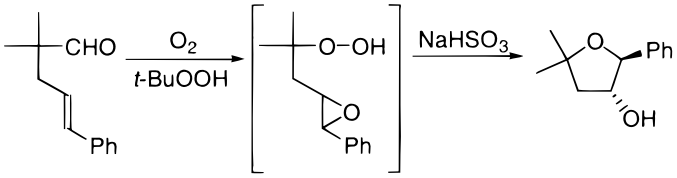
ABSTRACT



4 **8** **6**
80 %

The reaction pathway for peroxide-initiated aldehyde-mediated oxidation of olefins to epoxides by molecular oxygen has been studied. The pathways of reaction via a peroxy acid or an acyl peroxy radical have been differentiated by investigation of the reaction of 4 with oxygen to provide 6 via 8.

Development of oxidation processes using molecular oxygen as a safe, inexpensive, and readily available oxidant is of considerable interest. While a number of metal catalysts have been used to achieve this end, Kaneda and co-workers recently reported an uncatalyzed, stereospecific epoxidation of olefins by pretreatment of an aldehyde with molecular oxygen.[1,2] Valentine and Mizuno each report a similar, but in situ, epoxidation protocol that provides epoxides nonstereospecifically.[3] The present work identifies the active oxygen transfer agents, as well as the mechanism, of the epoxidation reactions.

Reaction of pivaldehyde with oxygen for 30 min, followed by addition of *trans*-stilbene, provided the *trans*-epoxide in good yields. However, when the aldehyde, olefin, and oxygen were all initially present, the yields were highly variable. We found the yields to be reproducible if 10−15 mol % of *tert*-butyl hydroperoxide was added to the aldehyde and olefin immediately following the addition of oxygen. Control experiments established that epoxidation did not proceed in the absence of aldehyde with or without the peroxide present. Our studies have been carried out with 10 mol % of the peroxide.[4]

The requirement of the aldehyde and an initiator suggests that the reaction proceeds via formation of acyl radical **1** which reacts with oxygen to afford acyl peroxy radical **2**. This species could then lead to the corresponding peroxy acid **3**. Kaneda favors **3**, while Valentine and Mizuno favor **2**, as the active oxidizing agent (Scheme 1).

We have used the reaction of substrate **4** to differentiate between the two possible oxidants for an in situ reaction. If the reaction proceeds via the peracid as the oxidant, the expected product would be the epoxide **5**, formed by an

(1) (a) *Catalytic Activation of Dioxygen by Metal Complexes*; Simandi, L. I., Ed.; Kluwer Academic Publishers: Dordrect, The Netherlands, 1992; pp 318−331. (b) Yamada, T.; Takai, T.; Rhode, O.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2109. (c) Haber, J.; Mlodnicka, T.; Poltowicz, J. *J. Mol. Catal.* **1989**, *54*, 451.

(2) Kaneda, K.; Haruna, S.; Imanaka, T.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1992**, *33*, 6827.

(3) (a) Nam, W.; Kim, H. J.; Kim, S. H.; Ho, R. Y. N.; Valentine, J. S. *Inorg. Chem.* **1996**, *35*, 1045. (b) Mizuno, N.; Weiner, H.; Finke, R. G. *J. Mol. Catal. A* **1996**, *114*, 15.

(4) We believe that the reactions without added initiator are being initiated by adventitious initiators and propagated by a radical chain mechanism (vide infra).

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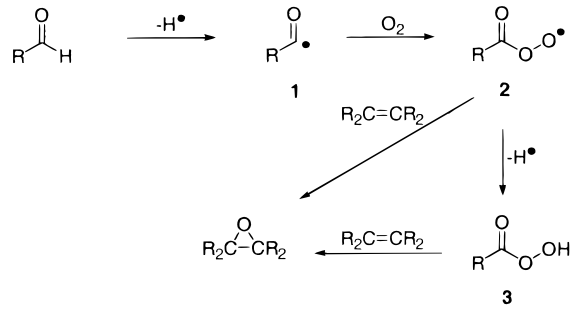
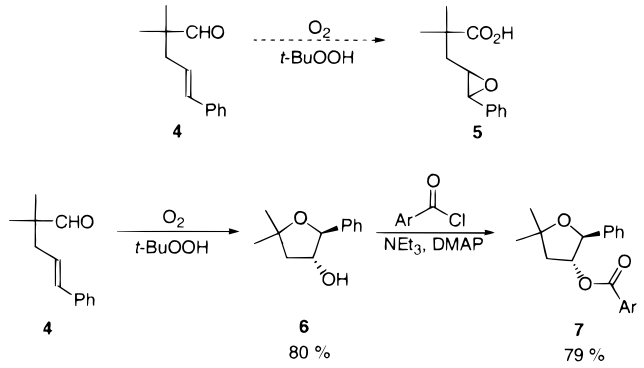
Scheme 1



intermolecular reaction.[5] If the oxidant is the acyl peroxy radical, the epoxy acid **5** is a possible product, and it could arise by either an intramolecular or intermolecular pathway.

The enal **4** was synthesized by reaction of the potassium enolate of isobutyraldehyde with *trans*-cinnamyl bromide.[6] We find reaction of **4** with molecular oxygen in the presence of 10 mol % of *tert*-butyl hydroperoxide to provide 3-hydroxy-5,5-dimethyl-2-phenyltetrahydrofuran **6** in 80% yield as a single diastereomer, after extractive workup with aqueous sodium bisulfite (Scheme 2).[7]

Scheme 2



The structure of **6** was confirmed by conversion to *p*-bromobenzoyl ester **7**, which was unambiguously identified by X-ray crystallographic analysis of crystals grown by slow evaporation of Et_2O. The X-ray crystal structure reveals that **7** has a *trans* relationship between the phenyl and hydroxyl groups.

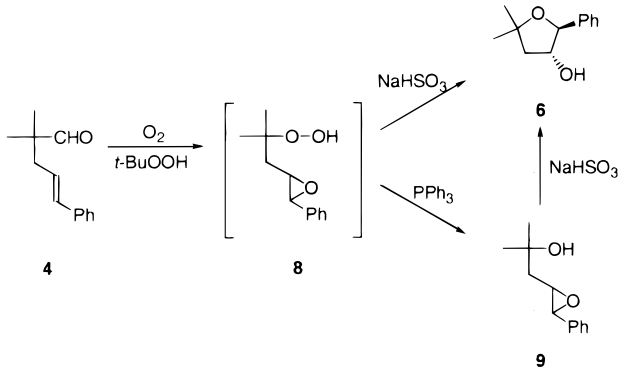
Examination of the reaction by TLC prior to extractive workup reveals a single product, different from the cyclic ether **6**, along with starting material. This product affords **6** upon exposure to aqueous $NaHSO_3$ (Scheme 3). The ^1H

(5) For evidence establishing an intramolecular peracid epoxidation cannot occur within a small endocyclic ring, see: Woods, K. W.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 6281. For a review of the endocyclic restriction test, see: Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215.

(6) Groenewegen, P.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* **1978**, *5*, 491.

(7) Control experiments were performed in the absence of either the aldehyde functionality or the oxygen atmosphere to test for direct oxidation by the initiator. No oxidation was detected.

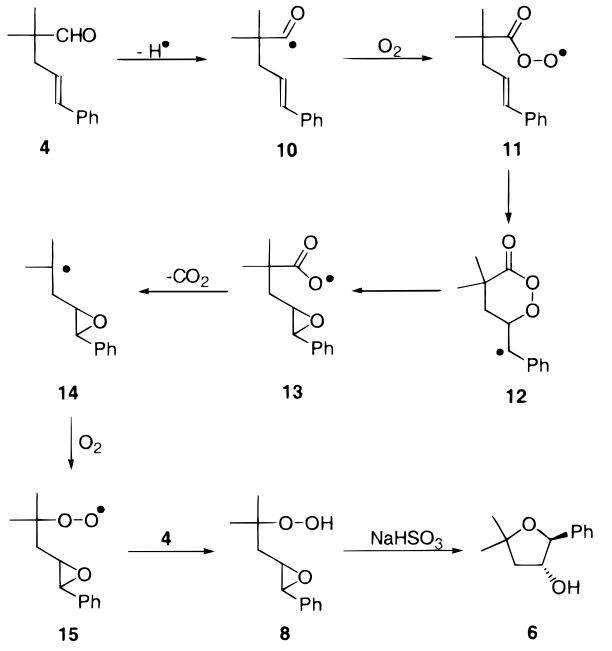
Scheme 3



NMR spectrum of this compound is consistent with the structure assigned as **8**.[8] Treatment of **8** with triphenylphosphine provides epoxy alcohol **9**. This alcohol cyclizes quantitatively to **6** upon exposure to an aqueous bisulfite wash.

We propose the mechanism in Scheme 4 to account for the formation of **6** via **8** from **4**. This mechanism begins with an aldehyde autoxidation, which is followed by intramolecular olefin epoxidation of the acyl peroxy radical **11**.[3,9,10] The oxygen transfer occurs via **12** to provide **13**, which undergoes decarboxylation to **14**. Reaction of **14** with molecular oxygen affords the radical chain propagating species **15** and subsequently the peroxide **8**.[11,12] Reaction of **8** with $NaHSO_3$ to **9** followed by a 6-*endo-tet* ring opening of the epoxide then provides **6**.[13] A number of experiments were performed to evaluate this reaction pathway.

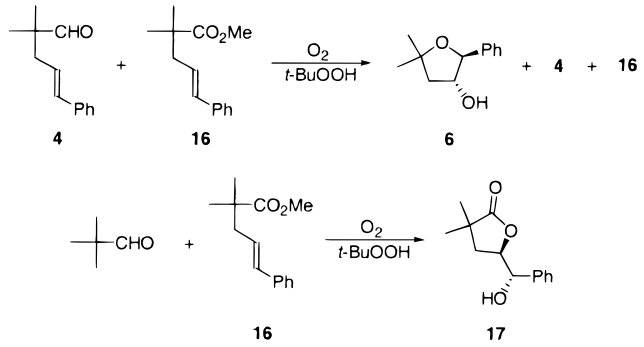
Scheme 4. Proposed Reaction Mechanism



To determine the molecularity of the epoxidation, a mixture of **4** and the methyl ester **16** was employed in an

application of the endocyclic restriction test.[5] The potential crossover experiment was performed with a 1.00:1.05 molar ratio of **4** to **16**, at a total olefin concentration of 60 mM, as shown in Scheme 5. Normal reaction conditions provided a

Scheme 5. Endocyclic Restriction Test

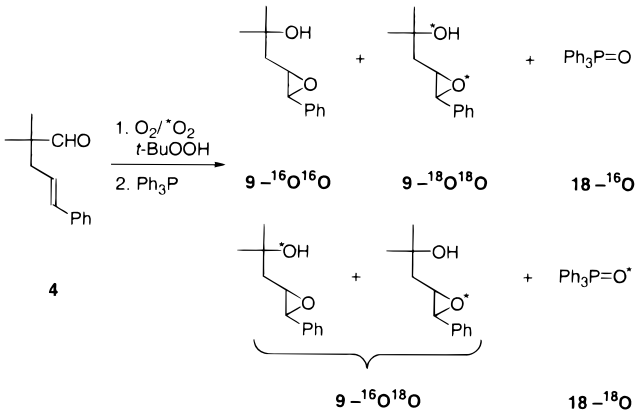


mixture of **4**, **6**, and **16**, as determined by both GC and ^{1}H NMR examination of the reaction mixture. A 40% conversion of **4** to **6** was observed, while no oxidation product of **16** was detected. This result is consistent with the intramolecular transfer of oxygen within **11**, as shown in Scheme 4. If the olefin of **16** is assumed to be as reactive as the olefin of **4**, an intermolecular oxygen transfer would have afforded oxidation of both substrates. In a control experiment **16** was shown to be oxidized to **17** by intermolecular oxygen transfer with pivaldehyde, oxygen, and *tert*-butyl hydroperoxide.[14]

This evidence of intramolecular reaction establishes that the oxygen transfer from the acyl peroxy radical may proceed through a six-membered ring. A transition state geometry for oxygen transfer of less than 180° is required for this reaction, thus excluding the peroxy acid as the active oxidant in this case.[5]

To establish the stoichiometry of the reaction with respect to oxygen, and to further evaluate the identity of **8**, the oxygen transfer reaction was performed using a 50/50 mixture of $^{18}O-^{18}O$ and $^{16}O-^{16}O$ (Scheme 6). After a

Scheme 6



reaction time of 40 h, triphenylphosphine was added as the reductant. Both the epoxy alcohol **9** and triphenylphosphine oxide **18** were analyzed by FI/MS and FD/MS, respectively, for isotopic oxygen incorporation. The isotopic enrichments of **9** and **18** are given in Table 1.

Table 1. Isotopic Distribution of Oxygen Transfer Reaction

	exptl[a]	calcd (1 equiv)[b]	calcd (2 equiv)[b]
9-^{16}O^{16}O	27 (±5%)	50	25
9-^{16}O^{16}O	50 (±5)		50
9-^{18}O^{18}O	23 (±5%)	50	25

	exptl[c]	calcd[d]	calcd[e]
18-^{16}O	64 (±5%)	50	70
18-^{18}O	35 (±5%)	50	30

[a] Determined by FI/MS, assuming a 5% error in the analysis. [b] Calculated assuming a statistical insertion of $^{16}O-^{16}O$ and $^{18}O-^{18}O$ and an intramolecular transfer (vide supra). Number of equivalents refers to the number of separate O_2 molecules incorporated into the product. [c] Determined by FD/MS, assuming a 5% error in the analysis. [d] Calculation assumes a statistical insertion of ^{16}O and ^{18}O. [e] Calculation takes into account the excess **18** formed relative to the recovered mass of **9**.

From the data in Table 1, it is clear that two molecules of oxygen are incorporated upon the intramolecular reaction of **4** to **9**, consistent with the mechanism shown in Scheme 4. The first equivalent donates the epoxide oxygen atom, while the other oxygen atom is lost in the decarboxylation of **13**. Following the trapping of the second equivalent of oxygen by radical **14**, both atoms are incorporated within the hydroperoxide functionality of **8**. Upon reduction, **9** then contains two atoms of oxygen, each from separate molecules. The statistical distribution of non-, mono-, and di-labeled epoxy alcohol **9** shows that these two atoms are incorporated by the consumption of two separate oxygen molecules. This result also rules out a pathway in which the initial step is decarbonylation of the acyl radical **10**, followed by formation of a peroxy radical and intramolecular transfer to afford **9**.

Triphenylphosphine oxide **18** is also produced in this reaction. On the basis of the isotope ratio of the starting

(8) Out of concern for the potential hazards of peroxides, this compound was isolated only once in a small quantity.

(9) (a) Maslov, S. A.; Blyumberg, E. A. *Russ. Chem. Rev.* **1976**, *45* (2), 155. (b) McNesby, J. R.; Heller, C. A. *Chem. Rev.* **1954**, *54*, 325.

(10) Filippova, T. V.; Blyumberg, E. A. *Rus. Chem. Rev.* **1982**, *51* (2), 582.

(11) Martin, J. C.; Dombchik, S. A. *Adv. Chem. Ser.* **1968**, *75*, 269.

(12) The formation and decarboxylation of an acyl radical, followed by oxygen trapping and hydroperoxide reduction, has been reported as a synthetic method of converting a carboxylic acid to an alcohol, less a single carbon unit. Barton, D. H. R.; Géro, S. D.; Holliday, P.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 6751.

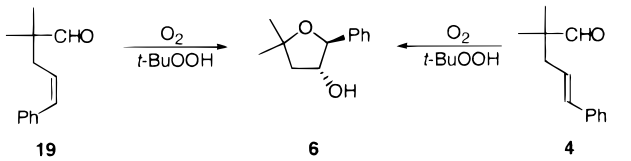
(13) This cyclization is, according to Baldwin's rules for ring closures, a formally disfavored process. However, Hevko and co-workers have reported a similar epoxide-opening reaction under basic conditions, where the product of the 6-*endo*-cyclization is preferred over that from a 4-*exo*-process. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Hevko, J. M.; Dua, S.; Talyor, M. S.; Bowie, J. H. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1629.

(14) Product **17** is presumed to be formed by olefin epoxidation, followed by ester carbonyl oxygen-assisted ring-opening of the epoxide and hydrolysis. This compound was provided in 94% conversion (^{1}H NMR), while a single recrystallization provided 12% of **17** suitable for X-ray crystallographic analysis.

oxygen atmosphere, it is be predicted that 50% of **18** isolated would contain the ^{18}O label. From the data in Table 1, it is shown that there is considerable isotopic incorporation into **18**, but it is in a 65:35 ratio. However, the recovered quantities of **9** and **18** (0.23 and 0.39 mmol, respectively) suggest that the oxidation of triphenylphosphine may be occurring not only by **8** but by a secondary oxidant as well. If the excess phosphine oxide is assumed to have been formed during workup by an oxygen source with a natural abundance of ^{18}O, the calculated ratio of **18** to **18-^{18}O** is ~70:30, in closer accordance with the experimental results.[15]

A stereochemical test has been used to probe the nature of **12**. *cis*-Olefin **19** was prepared using *cis*-cinnamyl bromide.[16] Reaction of **19** with initiator under an O_2 atmosphere gave **6** as the major product (Scheme 7).[17] This

Scheme 7



observed change in geometry of the olefin with respect to the epoxide upon reaction with oxygen is consistent with the pathway in Scheme 4. Intermediate **12** must have a sufficient lifetime for rotational equilibration and must undergo preferential ring closure to **13**, with the *trans* arrangement of substituents.

The present experimental results provide support for the formation of **6** from **4** by the path depicted in Scheme 4. The intramolecular transfer of oxygen excludes the peroxy acid as the active oxidant. Additionally, the loss of a carbon, presumably as carbon dioxide, is consistent with the formation of the carboxyl radical **13** resulting from oxygen transfer within **11**. The formation of **6** from both **4** and **19** is further support for radical **12** as an intermediate.

These results are consistent with the acyl peroxy radical as the oxidizing agent under the in situ conditions of Valentine and Mizuno. The epoxidation of olefins by molecular oxygen in the presence of aldehydes may be considered to proceed by formation of an acyl peroxy radical followed by an addition−elimination mechanism of epoxidation of the olefin. However, under the sequential conditions of Kaneda, the acyl peroxy radical may give the peroxy acid, thereby affording a different oxidizing agent.

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Supporting Information Available: Experimental procedures for the preparation of all compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org. The crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC-137494 and CCDC-137495. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax (+44)1223-336-033; email deposit@ccdc.cam.ac.uk).

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(15) A control experiment exposing triphenylphosphine to workup conditions afforded only about 3% the phosphine oxide. This control, however, does not include the possible oxidation by residual *tert*-butyl hydroperoxide, nor does it exclude the formation of a phoshine complex in the presence of the reaction mixture that is more easily oxidized during workup. Thus, at this time, we are unable to provide a definitive source of the excess phosphine oxide.

(16) To test for an initiator-influenced preisomerization path to the *E*-olefin prior to epoxidation, *tert*-butyl hydroperoxide was stirred with **19** in the absence of O_2. This control experiment resulted in no detectable isomerization, indicating that the formation of **6** from **19** presumably proceeds via **12**.

(17) By ^1H NMR, **6** is the major product (>70% by integration) of the reaction of **19**. Although the *cis*-diastereomer was not identified, we believe that, if present, it would have constituted <10% of the total reaction mixture.