Dioxiranes Are the Active Agents in Ketone-Catalyzed Epoxidations with Oxone

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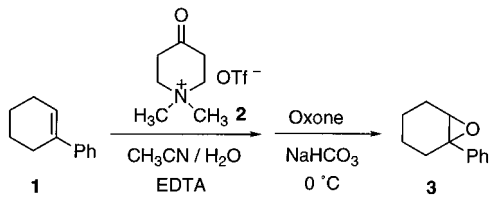
The scope and utility of dioxirane-based oxidations have earned them high regard in the practice of organic synthesis.[1] Both isolated solutions of dioxiranes[2] (principally dimethyldioxirane) and in situ generated[3] congeners have found increasing acceptance as routine reagents for mild epoxidation of alkenes. The structural characterization of dimethyldioxirane ensures that this is the actual reagent in isolated solutions. Moreover, the ketone-catalyzed decomposition of Oxone was demonstrated to proceed via dioxiranes by classic isotope labeling studies.[3b] However, the intermediacy of dioxiranes in the in situ epoxidatation[3] of alkenes was still not verified. In view of the increasing importance of in situ methods, in particular for catalytic asymmetric epoxidations,[4] we carried out O-18 labeling studies with our recently reported catalyst[5] and indeed found that dioxiranes were involved. While we viewed this outcome as unexceptional, two recent and conflicting reports have prompted us to disclose these experiments and to also clarify the likely origin of the discrepancies and pitfalls in the previous studies.[6]

In designing the appropriate experimental protocol for this study, we considered the following criteria: (1) the catalytic epoxidation should be rapid and high yielding, (2) there should be no background or uncatalyzed pathway, (3) there should be no opportunity for scrambling or dilution of label, and (4) a sensitive analytical method for accurate measurement and isotope enrichment is required. The system we designed, Scheme 1, employed 1-phenylcyclohexene (**1**) as substrate and 1,1-dimethyl-4-oxopiperidinium triflate[7] (**2**) as the promoter in 1.5/1 CH_3CN/H_2O at 0 °C with $NaHCO_3$ as the buffer. In a reaction with 1.0 equiv of **2**, the substrate was completely

Scheme 1



consumed in 3 h and the epoxide **3** was isolated in 90% yield. Control experiments established that only 0.7−0.8% conversion of **1** to **3** took place under identical conditions in the absence of **2** or if **2** was substituted with 1,1-dimethylpiperidinium triflate. Thus, it is demonstrated that epoxidation requires the carbonyl function in **2**.

For the labeling experiment, the O-18 must be efficiently incorporated into the ketone. This was accomplished by allowing **2** to exchange with H_2O (90% O-18) at 0 °C.[8] The rate of incorporation was monitored by FI mass spectrometric analysis and was found to be rapid, but still required 60 min to nearly come to equilibrium with the bulk water (time, O-18 incorporation: 10 min, 63%; 30 min, 74%; 60 min, 86%). Thus, to carry out the labeling experiment, a solution of 1 equiv of **2** in 1.5/1 CH_3CN/H_2O (90% O-18) was stirred at rt for 1 h/0 °C and the substrate **1** was added neat. The solution was then treated with a solid mixture of 1.0 equiv of Oxone[9] and 2.6 equiv of $NaHCO_3$ (total) in four portions over 2 h. After an additional 1 h at 0 °C, the reaction mixture was partitioned with CH_2Cl_2. The product epoxide **3** was isolated in 90% yield after purification and the water was recovered by distillation. Mass spectrometric analysis revealed that **3** contained 34 ± 1% O-18[10] and the recovered water contained 86 ± 1% O-18.[11]

Under the two limiting mechanistic scenarios, we expected the epoxide to contain 50% of the original O-18 label if a dioxirane were involved and 0% if some other ketone derived species, i.e., tetrahedral Criegee intermediate, were involved, Scheme 2. The disparity between the expected (43%) and observed (34%) enrichments could be due either to competitive mechanisms operating simultaneously, or to some other source of label loss.[12] The slow rate of exchange of **2** in labeled H_2O provided an intriguing explanation. If the rate of dioxirane formation and oxygen atom transfer (to either **1** or Oxone itself[3b,13]) is faster than O-18 exchange from water,[14] then the O-18 content of the ketone will be depleted over the course of the reaction and the extent

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(3) (a) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. (b) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. Photobiol.* **1979**, *30*, 63. (c) Gallopo, A. R.; Edwards, J. O. *J. Org. Chem.* **1981**, *46*, 1684. (d) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670.

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(5) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; Depue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391.

(6) (a) Armstrong, A.; Clarke, P. A.; Wood, A. *Chem. Commun.* **1996**, 849. (b) Schulz, M.; Liebsch, S.; Kluge, R.; Adam, W. *J. Org. Chem.* **1997**, *62*, 188.

(7) The corresponding nitrate salt has been shown to display dramatic acceleration of Oxone decomposition. Montgomery, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 7820.

(8) The isotopic enrichement in the H_2O was determined by the CSA catalyzed conversion of DCC to DCU followed by FI mass spectral analysis. Norris, W. P.; Osmundsen, J. *J. Org. Chem.* **1965**, *30*, 2407.

(9) This constitutes two oxidizing equivalents since Oxone is best represented by the formula $2KHSO_5 \cdot K_2SO_4 \cdot KHSO_4$.

(10) A control experiment showed O-18 exchange between H_2O and the product epoxide **3** did not take place under the reaction conditions.

(11) The loss in isotopic enrichment in the water may be due to a small amount of exchange of O-18 with $NaHCO_3$, K_2SO_4 or $KHSO_4$ in the epoxidation mixture.

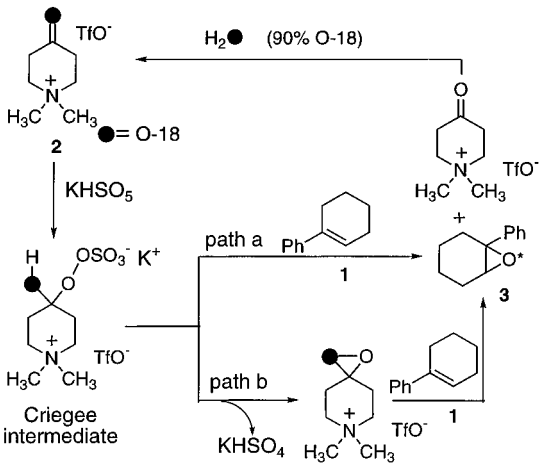
(12) The $k_{O\text{-}16}/k_{O\text{-}18}$ isotope effect has a theoretical maximum of 1.19: Bigeleisen, J.; Wolfsberg, M. *Adv. Chem Phys.* **1958**, *1*, 15. Measured values of 1.041 and 1.035 were observed for the hydrazinolysis of methyl benzoate (O'Leary, M. H.; Marlier, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3300) and the decomposition of acetyl peroxide (Goldstein, M. J.; Jutson, H. A.; Yoshida, M. *J. Am. Chem. Soc.* **1970**, *92*, 4122). This could account for 2−3% of the O-18 shortage.

(13) We have also demonstrated that **2** is a very effective catalyst for the decomposition of Oxone to oxygen; see ref 5.

(14) The rate of addition of H_2O_2 to trifluoroacetophenone is greater than the rate of hydration: Ritchie, C. D. *J. Am. Chem. Soc.* **1984**, *106*, 7187.

S0022-3263(97)01500-4 CCC: $14.00

Scheme 2



of label in the product would not represent the maximum available from the medium. This could be resolved by the use of increased loadings of labeled **2** to reduce the probability that any one ketone would have to enter the oxidation cycle more than once. Indeed, with increased loadings of **2** the O-18 incorporation in **3** increased: 2 equiv, 37 ± 1%; 5 equiv, 39 ± 1%. Thus, we concluded that, within experimental error, dioxiranes are the active intermediates in ketone promoted in situ epoxidations with Oxone.

How then can one explain the observation from Armstrong et al. that no O-18 was incorporated when labeled 4-*tert*-butylcyclohexanone is employed under biphasic conditions with cyclohexene as the substrate.[6a,15] We believe that there are two important clues to the discrepancy. First, the meager conversion observed (15% epoxidation) implies that 4-*tert*-butylcyclohexanone is at best a poor promoter under biphasic conditions, and independent studies in our laboratories have verified this (vide infra). Furthermore, the O-18 label is not lost from the ketone in the presence of unlabeled water. These two facts cast considerable doubt on the involvement of any tetrahedral intermediate derived from 4-*tert*-butylcyclohexanone and thus rule out the possibility that the label could have been transferred in the oxidation process. The incremental production of cyclohexene oxide in the presence of the ketone may result from an improved miscibility of the phases or emulsification. Water solubility of the promoter is critical in the biphasic epoxidation process. Under the conditions employed by Armstrong (except with strict pH control (7.8)[5]), we found that (*E*)-6-(benzyloxy)-2-hexene underwent only 2% epoxidation[16] with 4-*tert*-butylcyclohexanone (log P 3.10)[17] and 34% epoxidation with cyclohexanone (log P 0.96). If, however, the reaction mixture became emulsified, as much as 25% of the epoxide could be produced without the promoter. Therefore, the problem in this system is that there is no mechanistically significant, ketone-catalyzed pathway due to the insolubility of the ketone in the aqueous phase.

In the second report, Schulz et al. describe similar experiments with O-18 labeled acetone under monophasic conditions to define the involvement of dimethyldioxirane from in situ generated organo sulfonic peroxyacids.[6b] These authors conclude that dioxiranes are involved as they find that approximately 50% of the O-18 label from the *recovered* acetone was incorporated into the epoxide product. However, this number is considerably lower than the amount of the label introduced and no explanation is provided for the loss of label in the ketone (which occurs only in the presence of olefin). Furthermore, this oxidation system is plagued by a significant competitive background reaction that cannot deliver the label. Thus, it is not at all clear how the authors have ruled out alternative or competing mechanisms.[18] We suggest that the loss in O-18 label in the acetone is exactly analogous to our observation that exchange with the medium is slower (most certainly slower for acetone than **2**) than formation and consumption of dimethyldioxirane. Further, we suggest that the significant discrepancy in the extent of label in the product compared to the original level in the acetone arises from both background epoxidation and the loss of label from slow exchange. Indeed, the use of 10 equiv of acetone increases the O-18 incorporation level in the epoxide. Therefore, the problems in this system are that there is a significant noncatalyzed pathway and a significant erosion of the label from the ketone due to slow exchange.

In summary, neither of the two previous studies allows an unambiguous conclusion to be drawn concerning the nature of the intermediates in ketone-promoted epoxidation of olefins. The O-18 labeling studies reported herein do provide the most compelling evidence that, within experimental error, dioxiranes are the reactive oxidants in monophasic epoxidations with Oxone. Current efforts are directed at the experimental elucidation of the reaction geometry and the development of new concepts for chiral catalysts.

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Supporting Information Available: Methods for the isotope analyses and epoxidation procedures are provided (7 pages).

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(15) We have also carried out the labeling study under biphasic conditions with (*E*)-1-(benzyloxy)-4-hexene[5] and have again concluded that dioxiranes are intermediates. These experimets are complicated by O-18 exchange with the buffer and less reproducible mass spectrometry.

(16) This is the same as the background epoxidation level in the absence of ketone.

(17) Pomper, M. G.; VanBrocklin, H.; Thieme, A. M.; Thomas, R. D.; Kiesewetter, D. O.; Carlson, K. E.; Mathias, C. J.; Welch, M. J.; Katzenellenbogen, J. A. *J. Med. Chem.* **1990**, *33*, 3143.

(18) The authors have assumed that the ketone-catalyzed pathway involves dioxiranes and that the low level of label incorporation must therefore be due to the background reaction. This may well be true, but the data cannot be used to rule out the existence of a ketone-catalyzed pathway that does not involve dioxiranes of the kind that Armstrong et al.[6a] have suggested.