2810 *J. Org. Chem.* **1998,** *63,* 2810−2811

# 6-Oxo-1,1,4,4-tetramethyl-1,4-diazepinium Salts. A New Class of Catalysts for Efficient Epoxidation of Olefins with Oxone[†]

Scott E. Denmark* and Zhicai Wu

*Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801*

*Received February 26, 1998*

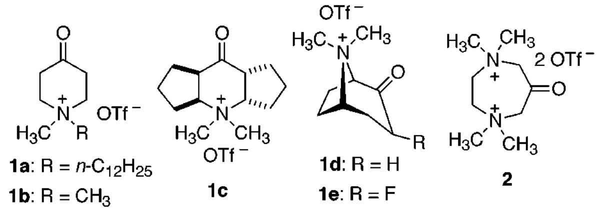
Dioxiranes are now among the most useful oxidants for epoxidation of alkenes under mild conditions.[1] These reagents are generated from potassium peroxomonosulfate (Oxone) and the parent ketones and are used either in situ or in distilled solution as isolated species.[2] In recent years, as less volatile ketones have been employed, the convenient in situ methods have become the protocol of choice, in which the epoxidation can be performed either in a biphasic solvent system[2a−d,3] or in a homogeneous aqueous organic solution.[4]

It is now well-recognized that oxygen atom transfer from the dioxirane to the substrate can in principle be catalytic and that, with suitably designed chiral ketones, asymmetric epoxidation of olefins is possible. Indeed, high enantioselectivities have been reported in recent years for the epoxidation of unfunctionalized olefins with various ketonic promoters.[5] Nevertheless, a truly general and efficient catalyst remains an elusive target. Toward that end, there is considerable interest in understanding those structural features that will lead to powerful catalysts and provide new templates for the design of asymmetric reagents.[3,6,7] Recently, we developed two efficient families of catalysts for epoxidation; 4-oxopiperidinium salts[3] and simple fluoro ketones.[6a] In continuation of our effort to develop novel frameworks for general catalysts, we describe a new class of agents, α,α′-bis(ammonium) ketones, for catalytic epoxidation with Oxone under monophasic conditions.

Our previous studies revealed that 4-oxopiperidinium salts could be customized to function as excellent catalysts under either biphasic conditions (methyl, dodcecyl (**1a**))[3] or in homogeneous medium (dimethyl (**1b**))[8] by simply altering the lipophilicity of the ammonium group, Chart 1. By modification of this framework, we designed the asymmetric oxoammonium salts **1c**[3b] and **1d**[6a] but found that they were ineffective as promoters of epoxidation. Only with the added activation provided by an α-fluorine substituent (**1e**) was suitable catalytic efficiency for epoxidation found.[6] The low reactivities of these potential dioxirane precursors most likely result from the unavoidable steric congestion caused by the substitution required to create an asymmetric environment adjacent to the ketone moiety. Clearly, greater activation of the carbonyl carbon is needed to increase its electrophilicity for the generation of an efficient asymmetric epoxidation catalyst.

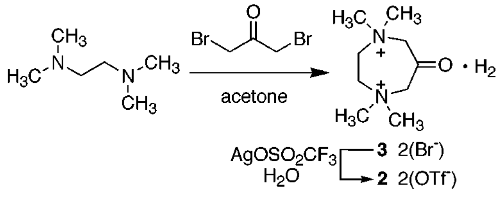
To enhance the electrophilicity of the carbonyl group, maintain water solubility, and provide a foundation for asymmetric modification, we envisaged the use of α,α′-bis(ammonium) ketones and formulated as point of entry the oxodiazepinium salt **2**, Chart 1. Compared to the monoammonium ketones **1a** and **1b**, the carbonyl carbon in **2** should be much more electrophilically activated by the proximity of two ammonium groups. Thus, we expected that the rate of formation and subsequent reaction of the corresponding dioxirane would be greatly increased. Moreover, the symmetrical disposition of the carbonyl group between two cationic units ensures that **2** will be highly resistant to degradation by Baeyer−Villiger oxidation, unlike the simple 3-oxopiperidinium salts examined previously.[3] On the basis of the greatly enhanced reactivity, stability, and water solubility, ketone **2** was expected to be a promising catalyst for epoxidation with Oxone.

**Chart 1**



The synthesis of **2** follows logically by a simple albeit remarkable two-step route outlined in Scheme 1. Double alkylative cyclization of tetramethyl ethylenediamine (TMEDA) with 1,3-dibromoacetone in acetone at room temperature afforded the dibromide **3**, which was directly converted to the ditriflate **2** by ion exchange with silver triflate. The bis(ammonium) salt **2** is a stable (mp 204−205 °C), highly crystalline solid that exists as a molecular hydrate.

**Scheme 1**



The potential for any ketone to serve as a promoter for Oxone-based epoxidation involves two critical features, the efficiency of dioxirane formation and the ability to transfer an oxygen atom to the substrate. To evaluate the ability of **2** to be converted to a dioxirane, we measured the rate of Oxone consumption of in the presence of a catalytic amount of **2** and compared that to the rate with other ketones. Dioxiranes are known to be the intermediates responsible

---

[†] Catalytic Epoxidation of Alkenes with Oxone. 3.

[1] For reviews of dioxirane chemistry see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: Greenwich, 1990; Vol. 2, Chapter 1. (d) Adam, W.; Hadjiarapoglou, L.; Curci, R.; Mello, R. In *Organic Peroxide*; Ando, W., Ed.; J. Wiley & Sons: New York, 1992; Chapter 4. (e) Adam, W.; Hadjiarapoglou, L. P. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1993; Vol. 164, p 45. (f) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811.

[2] (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. (e) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

[3] (a) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; Depue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. (b) Forbes, D. C. Ph.D. Thesis, University of Illinois at Urbana-Champaign, 1996.

[4] Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887.

[5] (a) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (b) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (c) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (d) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.

[6] (a) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (b) See also: Armstrong, A.; Hayter, B. R. *J. Chem. Soc., Chem. Commun.* **1998**, 621.

[7] (a) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S.-G.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. (b) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. (c) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622.

[8] Denmark, S. E.; Wu, Z. Unpblished results.

S0022-3263(98)00342-9 CCC: $15.00

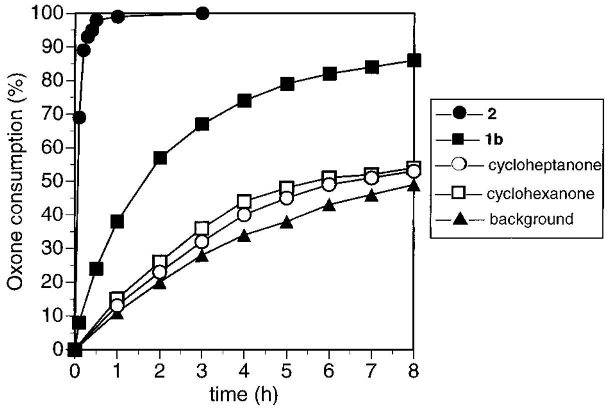
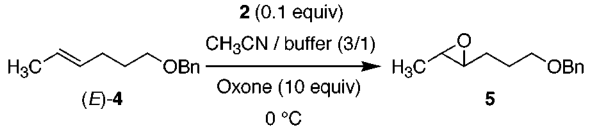


**Figure 1.** Rate of Oxone consumption by ketones.

**Scheme 2**



for the ketone-catalyzed decomposition of Oxone.[2b] Therefore, the ability of a ketone to catalyze the consumption of Oxone would reflect its ability to form a dioxirane. The rate of consumption of 15 mmol of Oxone at pH 7.0 and 0 °C in the presence of 0.1 mmol of each of four ketones (**1b**, **2** cyclohexanone and cycloheptanone) is graphically presented in Figure 1.[9] Whereas Oxone is unstable at pH 7.0, we first measured a background rate (s). Under these conditions, 45% of the active oxidant was consumed in ca. 8 h. The dramatic acceleration of this decomposition by the 4-oxopiperidinium salt **1b** (first noted by Montgomery[10]) is apparent. However, the rate of consumption of Oxone catalyzed by the bis(ammonium) salt **2** dwarfs that of **1b** reaching completion in less than 30 min. To illustrate the effect of the ammonium moieties within the cyclic ketones, the data for cyclohexanone and cycloheptanone are provided. Clearly, these ketones do not efficiently form dioxiranes under these conditions. The rapid consumption of Oxone in the presence of **2** indicated its facility toward dioxirane formation and presaged its potential as an epoxidation catalyst.

The second stage in the catalytic process was examined by optimizing the ability of **2** to epoxidize a test olefin (*E*)-**4**[6] in monophasic solution (acetonitrile/water) at 0 °C, Scheme 2. Since Oxone decomposition by the dioxirane from **2** was extremely fast, it was necessary to keep the concentration of Oxone in the reaction mixture as low as possible so that oxygen atom transfer to the substrate could be maximized. Accordingly, for efficient use of oxidant, 10 equiv of aqueous Oxone solution (0.56 M) was added over 10 h by a syringe pump. Because the volume of water increased during the reaction, the initial acetonitrile/phosphate buffer (pH 7.0) ratio was set at 3/1 to avoid oiling out of the olefin substrate. The optimum pH for the epoxidation was found to be 7.0 (maintained throughout by a pH stat) whereby 100% conversion of (*E*)-**4** to **5** was obtained after 11 h with a catalytic amount (10 mol %) of **2**. Interestingly, epoxidation at pH 6.0 proceeded almost as well as at pH 7.0. Presumably, the increased electrophilicity of the carbonyl center allows the reaction to proceed under slightly acidic conditions.

**Table 1. Catalytic Epoxidation of Selected Olefins**[a]

| entry | alkene | time, h | conversion,[b] % | yield,[c] % |
|---|---|---|---|---|
| 1 | (*E*)-2-methylstyrene | 8 | 100 | 83 |
| 2 | (*Z*)-2-methylstyrene[d] | 6 | 100[e] | 78 |
| 3 | indene | 6 | 100 | 85 |
| 4 | 1-phenylcyclohexene | 4 | 100 | 93 |
| 5 | (*E*)-cinnamyl alcohol | 11 | 100 | 94 |
| 6 | geraniol | 6 | 100[f] | 90 |
| 7 | geraniol | 2.4 | 96[g] | 89 |
| 8 | 1-octene | 11 | 98 | 74 |
| 9 | (*E*)-5 | 11 | 96 | 89 |
| 10[h] | (*E*)-5 | 22 | 97 | 91 |
| 11 | stilbene | 22 | 39 | 33 |

[a] Reactions done in $CH_3CN/H_2O$ (pH 7.0) with 0.1 equiv of **2** and 10 equiv of Oxone (10 h addition) at 0 °C. [b] GC analysis. [c] Chromatographically homogeneous material. [d] (*Z*)-olefin/(*E*)-olefin, 93/7. [e] *cis*-epoxide/*trans*-epoxide, 93/7. [f] Diepoxide. [g] 6,7-Monoepoxide/diepoxide, 77/19. [h] Reaction done with 0.05 equiv of **2** and 20 equiv of Oxone (20 h addition).

To illustrate the generality of the epoxidation procedure, various olefin types were examined. The results collected in Table 1 are 1 mmol scale oxidations with 10 mol % of **2** at pH 7.0 under otherwise the same conditions as above. All of the alkenes were efficiently oxidized (96–100% conversion) to afford the epoxides in very good yield (74–94%). Stilbene is the only exception (entry 11, 39% conversion, 33% yield) because of its poor solubility. The important reactivity trends for this epoxidation mirror those for **1b**. As expected, the epoxidation was stereospecific (entries 1 and 2). The rate of oxidation increased with increasing olefin substitution. An allylic hydroxyl group decreased the epoxidation rate (entries 1 and 5), while highly electron-deficient olefins (methyl cinnamate) failed to react at an appreciable rate. Thus, excellent regioselectivity can be achieved for the epoxidation of geraniol (entry 7, no 2,3-monoepoxide detected during the reaction). Moreover, the extreme reactivity and oxidative stability of **2** allows for the catalyst loading to be further reduced. With 5 mol % of **2**, even the unreactive olefin (*E*)-**5** was epoxidized to 97% conversion afforded a 91% yield of **5** in 22 h (entry 10).

In summary, we have demonstrated that the readily available bis(ammonium) ketone **2** is a general and efficient catalyst for epoxidation of a wide variety of olefins with Oxone under mild conditions. In addition, the availability of many chiral nonracemic diamines of significant structural diversity bodes well for the development of asymmetric catalysts with enhanced catalytic activity and enantioselectivity.

**Acknowledgment.** We are grateful to the Pharmacia and Upjohn Co. for generous financial support. Z.W. thanks the University of Illinois for a Graduate Fellowship.

**Supporting Information Available:** The preparation and characterization of **2** along with epoxidation procedures are provided (5 pages).

JO980342B

---

(9) Experimentally, the rate was determined by monitoring the volume of aqueous potassium hydroxide solution added to neutralize the acid generated to maintain pH 7.0. See the Supporting Information for details.

(10) Montgomery, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 7820. Montgomery estimated that **1b** was more efficient than acetone in this process by a factor of 1300.