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# Epoxidation of Alkenes by Amine Catalyst Precursors: Implication of Aminium Ion and Radical Cation Intermediates

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We report herein the discovery of a novel process for epoxidation of alkenes, using Oxone, which, remarkably, is catalyzed by simple amines. This process, which does not rely on transition metal catalysts, utilizes Oxone/$NaHCO_3$ as the oxidant and simple, cheap, and readily available amines (see Table 1) as catalyst precursors for alkene epoxidation. The standard reaction procedure is illustrated in Scheme 1.

Normally, Oxone buffered with $NaHCO_3$ in MeCN:$H_2O$ epoxidizes unfunctionalized alkenes only when oxygen-transfer reagents such as ketones,[1] imines,[2] or iminium salts,[3] are present. Aqueous solutions of Oxone at approximately neutral pH are also known to oxidize alkenes to give epoxides but in variable yield.[4,5] At lower pH, mixtures of epoxides and diols are obtained.[4]

During our studies on iminium salt-catalyzed epoxidations of alkenes[3b] we discovered that simple amines were also capable of epoxidizing our test substrate, 1-phenylcyclohexene and so we tested a broad range of amines (Table 1). In a control experiment, alkene and oxidant were combined in the absence of amine, and essentially no epoxide was obtained (entry 1). Primary amines were not effective (entry 2), but in the presence of secondary and tertiary amines (entries 3, 4, 6−9) rapid epoxidation ensued. Secondary amines gave the highest yields, and within this class, pyrrolidine (entry 6) was optimum. 1,2-Diamines (entry 10) and amides (entry 11) were not effective catalysts. We therefore tested pyrrolidine at loadings of 10 and 5 mol % and discovered that good levels of turnover could be achieved (entries 12−15). Unfortunately, with lower amine loadings (entries 12,14) a significant amount of hydrolysis of the epoxide occurred despite the fact that an excess of $NaHCO_3$ was present. Although less hydrolysis could be achieved by increasing the ratio of water present, this also resulted in reduced conversion.[6] Attempts to increase the pH of the media with other inorganic bases were unsuccessful but the use of 0.5 equiv of pyridine did largely suppress epoxide hydrolysis[7] (entries 13 and 15). A control experiment showed that pyridine itself was not able to catalyze the epoxidation process (entry 16). Pyrrolidine and a chiral derivative [(*S*)-2-(diphenylmethyl)pyrrolidine-**1**[8]] were tested as catalysts at just 5 mol % loading[9] with a range of alkenes (Table 2) and it was found that good yields of epoxides could be obtained in most cases although the reaction was sensitive to both the structure of the alkene and the amine. The substituted pyrrolidine **1** was a more effective catalyst for a broader range of alkenes than pyrrolidine itself (compare entries 5−7, and 9) and gave up to 57% enantioselectivity with 1-phenylcyclohexene (entry 5). Amine **1** was an effective catalyst for most alkenes; only stilbenes, aliphatic disubstituted and terminal alkenes gave low yields.

**Scheme 1.** Epoxidation of 1-Phenylcyclohexene by Oxone/$NaHCO_3$

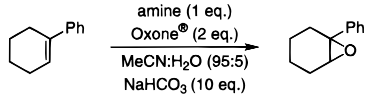

**Table 1.** Epoxidation of 1-Phenylcyclohexene[a]

| entry | amine | conversion[b,c] (%) | epoxide[c] yield (%) | diol[c] yield (%) |
|---|---|---|---|---|
| 1 | none | 2 | 0 | 2 |
| 2 | $EtNH_2$ | 0 | 0 | 0 |
| 3 | $Et_2NH$ | 40 | 36 | 4 |
| 4 | $Et_3N$ | 16 | 13 | 2 |
| 5 | $NEt_4OAc$ | 2 | 0 | 2 |
| 6 | pyrrolidine | 100 | 90 | 10 |
| 7 | piperidine | 90 | 87 | 3 |
| 8 | morpholine | 60 | 58 | 2 |
| 9 | *N*-methylpyrrolidine | 65 | 62 | 3 |
| 10 | EDTA | 0 | 0 | 0 |
| 11 | pyrrolidinone | 2 | 2 | 0 |
| 12[d] | pyrrolidine 10% | 100 | 60 | 40 |
| 13[d] | pyrrolidine 10% + Py (0.5eq) | 100 | 95 | 4 |
| 14[d] | pyrrolidine 5% | 65 | 35 | 30 |
| 15[d] | pyrrolidine 5% + Py (0.5 equiv) | 59 | 56 | 3 |
| 16[d] | pyridine | 1 | 1 | 0 |

[a] Unless otherwise stated all reactions conducted with 1-phenylcyclohexene (0.125 mmol), 1 equiv amine, 2 equiv Oxone, 10 equiv $NaHCO_3$, 0.5 mL *d*-MeCN:$D_2O$ (95:5), 2 h. [b] Remainder is alkene. [c] Yields determined by $^1H$ NMR relative to an internal standard (nitrobenzene). [d] Concentration of 1-phenylcyclohexene increased to 0.85 mol/L.

We have carried out competition experiments with structurally similar alkenes, and found that the amine-catalyzed epoxidation reactions showed much greater selectivity compared to MTO-catalyzed epoxidations[10] (Table 3).

The mechanism of the reaction is intriguing. We found that in the presence of Oxone (1 equiv) pyrrolidine was oxidized[11] to the corresponding hydroxylamine (10%), nitrone (60%), and *N*-hydroxylactam (2−3%), but none of these oxidation products either transferred their oxygen or acted as catalysts for epoxidation. Tertiary amine *N*-oxides were similarly inactive catalysts. However, the fact that asymmetric induction is observed means that the amine is intimately involved in the oxygen transfer process, but not simply as phase-transfer catalyst as quaternary ammonium salts were also inactive (Table 1, entry 5). We have considered the possibility that a single electron-transfer process may be involved (Scheme 2). It is possible that the amine is oxidized to its radical cation[12,13] which in turn oxidizes the alkene

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[1] (a) Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224−11235. (b) For a review, see: Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847−849.

[2] Davis, F. A.; Reddy, R. T.; Han, W.; Reddy, R. E. *Pure Appl. Chem.* **1993**, *65*, 633−640.

[3] (a) Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727-13738. (b) Aggarwal, V. K.; Wang, M. *J. Chem. Soc., Chem. Commun.* **1996**, 191−192. (c) Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774−2777. (d) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron,* **1999**, *55*, 2341−2352.

[4] Zhu, W. M.; Ford, W. T. *J. Org. Chem.* **1991**, *56*, 7022−7026.

[5] Zheng, T. C.; Richardson, D. E. *Tetrahedron Lett.* **1995**, *36*, 833−836.

[6] For details see Supporting Information. It should be noted that small variation in results have been experienced with different batches of Oxone, as noted by others.[1a]

[7] Pyridine has also been used to suppress hydrolysis in MTO-catalysed epoxidation.[10]

[8] Bailey, D. J.; O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1997**, *8*, 149−153.

[9] We have not been able to reisolate the amine; it is ultimately oxidised by the excess Oxone. Tertiary amines are oxidized more rapidly than secondary amines which may account for their poor catalytic activity.

[10] (a) Ruldolph, J.; Reddy, L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189−6190 and references therein.

[11] Details are presented in the Supporting Information. Oxone is known to oxidise amines in the presence of acetone (Neset, S. M.; Benneche, T.; Undheim, K. *Acta. Chem. Scan.* **1993**, *47*, 1141−1143). However, we are not aware of any report on the direct oxidation of amines with Oxone.

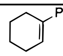
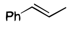
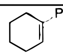
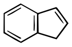
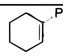
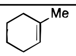
10.1021/ja0004433 CCC: $19.00

**Table 2.** Alkene Epoxidation Using 5 Mol % of Either Pyrrolidine or Amine **1**[a]

| | | pyrrolidine catalyst | | | (*S*)−2-diphenylmethylpyrrolidine-**1** catalyst | | |
|---|---|---|---|---|---|---|---|
| entry | alkene | conv.[c] % | epoxide[d] | diol[d] | conv.[c] % | epoxide[d] (ee[e]%) | diol[d] |
| 1 | methylenecyclohexene | 33 | 29 | 4 | 33 | 29 | 4 |
| 2 | 1-methylcyclohexene[b] | 100[f] | 90 | 10 | 100[f] | 90 (15 *R,S*) | 10 |
| 3 | octahydronaphthalene | 100[f] | 92 | 8 | 100[f] | 93 | 7 |
| 4 | indene[b] | 29 | 19 | 10 | 31 | 20 (25) | 11 |
| 5 | 1-phenylcyclohexene | 59[f] | 56 | 3 | 100[f] | 96 (57 *S,S*) | 4 |
| 6 | α-methylstyrene[b] | 77[f] | 38 | 38 | 88[f] | 65 (15 *S*) | 23 |
| 7 | *β*-methylstyrene | 15 | 15 | 0 | 21 | 21 (13 *S,S*) | 0 |
| 8 | norbornylene | 77 | 74 | 2 | 80 | 74 | 6 |
| 9 | styrene | 30 | 27 | 2 | 100 | 93 (9 *S*) | 6 |
| 10 | octa-4-ene | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 | *trans*-stilbene | 2 | 2 | 0 | 6 | 6 | 0 |
| 12 | *cis*-stilbene[g] | 6 | 6 | 0 | 9 | 9[h] | 0 |
| 13 | dec-1-ene | 0 | 0 | 0 | 0 | 0 | 0 |

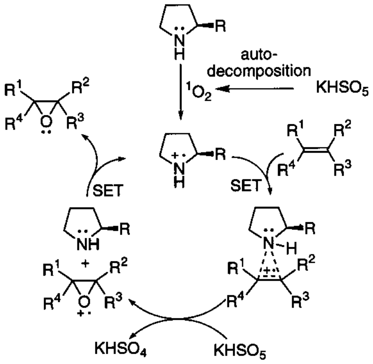
[a] Alkene (0.424 mmol), 5 mol % amine, 2 equiv Oxone, 10 equiv $NaHCO_3$, 0.5 mL *d*-MeCN:$D_2O$ (95:5), 0.5 equiv pyridine, 4 h, rt. [b] 1 equiv pyridine. [c] Remainder is alkene. [d] Yields determined by $^1$H NMR relative to an internal standard (nitrobenzene). See Supporting Information for isolated yields. [e] Enantioselectivities determined by chiral HPLC using a Chiracel OD column and correlated with literature data.[1a] [f] Conversion after 2 h. [g] The same results are obtained in the absence of amine. [h] 6:1 ratio of *cis:trans* epoxides.

**Table 3.** Competition Experiments with Structurally Similar Alkenes and Comparison of Different Oxidation Procedures[a]

| Entry | Alkenes | | Amine[b] | | $Ar_3N^{+\bullet}SbCl_6^-$ [c] | MTO [d] |
|---|---|---|---|---|---|---|
| | **A** | **B** | Pyrrolidine | **1** | | |
| 1 |  |  | 100:0 | 100:0 | 100:0 | 70:50 |
| 2 |  |  | 100:0 | 100:0 | 100:0 | 70:50 |
| 3 |  |  | 4:100 | 7:100 | 5:100 | 65:75 |

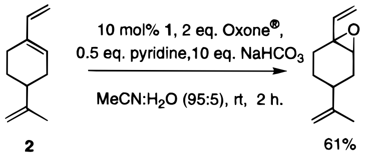
[a] 1 equiv of each alkene is used in all experiments. $^1$H NMR conversion of the two alkenes A:B are given relative to an internal standard (nitrobenzene). [b] Alkene (each 0.424 mmol); amine (0.04 mmol), Oxone (0.85 mmol), $NaHCO_3$ (4.24 mmol) 0.5 mL of *d*-MeCN:$D_2O$ (95:5), pyridine (0.424 mmol), 4 h, rt. [c] 20 mol % $Ar_3N^{+\bullet}SbCl_6^-$, 3 equiv $SeO_2$, *d*-$CH_2Cl_2$, rt, 5 min. [d] 0.5 mol % MTO (methyltrioxorhenium), 12 mol % pyridine, 1.5 equiv $H_2O_2$, *d*-$CH_2Cl_2$, 6 h.

**Scheme 2.** Proposed Catalytic Cycle for Alkene Epoxidation



to the radical cation.[14] In the presence of suitable oxidants alkene radical cations are converted to epoxides,[15−17] in what is often a diffusion-controlled process. In our case the amine must still be associated (complexed) with the alkene radical cation at the time of the epoxidation process for asymmetric induction to be observed.

**Scheme 3.** Epoxidation of Triene **2**



**2**

We have circumstantial evidence for the intermediacy of radical cations. (i) In competition experiments similar selectivity is observed to Bauld's aminium-catalyzed reactions[16] which have been shown to occur via radical cations (Table 3). (ii) Triene **2** gave a single mono epoxide, uncontaminated by other regioisomers (Scheme 3). The same selectivity has been observed in aminium ion-catalyzed epoxidation[17] and cyclopropanation of the same substrate.[18] (iii) In competition experiments *trans*-stilbene reacted ∼2.5 times faster than *cis*-stilbene[19] (similar observations for radical cations[20]), whereas in electrophilic oxidations the *cis* isomer is more reactive. (iv) Most substrates that are inert to Bauld's radical cation-mediated oxidations[17] are also inert in our system (Table 2, entries 10, 13).[21]

In summary, we have discovered a novel process for oxidation of alkenes which is catalyzed by simple amines. It is believed that the reactions are mediated by chiral amine radical cations, and this is the first report of such a species. The plethora of readily available chiral amines makes the likelihood of finding highly enantioselective catalysts a real possibility. Efforts in this area are in progress.

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**Supporting Information Available:** General procedures for alkene epoxidation, the effect of water, pyridine, and base on yields of epoxide and diol; tables of isolated yields of epoxides and results obtained using 1 mol % of amine **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) $^1O_2$ oxidises amines to the corresponding radical cation (Ferroud, C.; Rool, P.; Santamaria, J. *Tetrahedron Lett.* **1998**, *39*, 9423−9426 and references therein).

(13) $^1O_2$ is produced during auto-decomposition of Oxone (Evans, D. F.; Upton, M. W. *J. Chem. Soc., Dalton Trans.* **1985**, *6*, 1151−1153). We believe that only a small amount of $^1O_2$ is generated from auto-decomposition of Oxone which leads to a small amount of the amine radical cation. Ample Oxone remains for alkene epoxidation.

(14) Aminium radical cations readily react with alkenes to give alkene radical cations (Mirafzal, G. A.; Liu, J.; Bauld, N. L. *J. Am. Chem. Soc.* **1993**, *115*, 6072−6077 and references therein).

(15) Bosch, E.; Kochi, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 1319−1329.

(16) Bauld, N.; Mirafzal, G. A. *J. Am. Chem. Soc.* **1991**, *113*, 3613−3614.

(17) Kim, T.; Mirafzal, G. A.; Liu, J.; Bauld, N. L. *J. Am. Chem. Soc.* **1993**, *115*, 7653−7664.

(18) Mirafzal, G. A.; Lozeva, A. M.; Oslon, J. A. *Tetrahedron Lett.* **1998**, *39*, 9323−9326.

(19) These experiments were done at 10 mol % loading of amine **1** with limited amount of oxidant (0.5 equiv) and ratios determined by $^1$H NMR after 1 h at 0.21 M in each alkene (12% conversion for *trans*-stilbene). It is important to ensure that both alkenes are completely dissolved at the start.

(20) Bauld, N. L.; Yeuh, W. *J. Am. Chem. Soc.* **1994**, *116*, 8845−8846.

(21) A few substrates do not show the same reactivity as Bauld's: stilbene was expected to be a good substrate but is rather poor, and norbornene was expected to be a poor substrate but is in fact good. We do not have a good explanation for this at present.