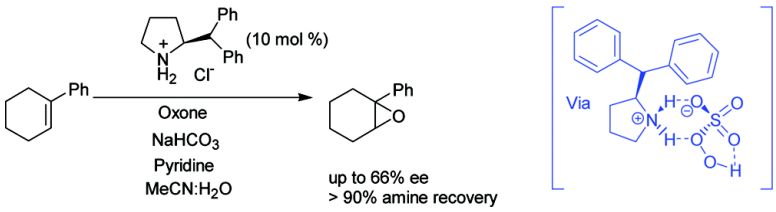
Article

New Insights in the Mechanism of Amine Catalyzed Epoxidation: Dual Role of Protonated Ammonium Salts as Both Phase Transfer Catalysts and Activators of Oxone

Varinder K. Aggarwal, Chrystel Lopin, and Franck Sandrinelli

J. Am. Chem. Soc., **2003**, 125 (25), 7596-7601• DOI: 10.1021/ja0289088 • Publication Date (Web): 28 May 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 8 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 05/28/2003

New Insights in the Mechanism of Amine Catalyzed Epoxidation: Dual Role of Protonated Ammonium Salts as Both Phase Transfer Catalysts and Activators of Oxone

Varinder K. Aggarwal,* Chrystel Lopin, and Franck Sandrinelli

Contribution from the School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK

Received January 11, 2002; E-mail: v.aggarwal@bristol.ac.uk

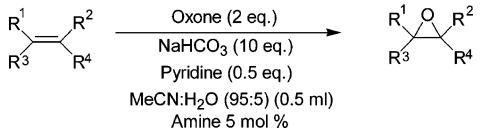
Abstract: Amines have previously been reported to catalyze the epoxidation of alkenes using Oxone ($2KHSO_5+KHSO_4+K_2SO_4$), and significant levels of asymmetric induction were observed. From screening a series of amines based on 2-substituted pyrrolidines, it has now been found that more consistent and reproducible results are achieved with the HCl salt of the amine compared to the amine itself. Up to 66% ee was achieved in epoxidation of 1-phenylcyclohexene. The chiral amine could be reisolated in >90% yield when reactions were conducted at −10 °C, indicating that the integrity of the amine was maintained during the oxidation process. At −10 °C, (*S*)-2-(diphenylmethyl)pyrrolidine **1** reacted with Oxone to give a mixture of ammonium salts containing the peroxymonosulfate salt **6b**. The enantioselectivity obtained with this salt was compared to the amine·HCl salt catalyzed process and identical results were observed, indicating that the true oxidant was the peroxymonosulfate salt **6b**. The relative rates of oxidation of *cis*- and *trans*-β-methylstyrenes together with the ρ value of a series of 1-arylcyclohexenes were determined. These studies indicated that the amine catalyzed process involved electrophilic oxidation. On the basis of these findings, a new mechanism is advanced in which the protonated amine not only acts as a PTC but also activates Oxone, through hydrogen bonding, toward electrophilic attack.

Introduction

We recently reported a novel process for epoxidation of alkenes, using Oxone ($2KHSO_5+KHSO_4+K_2SO_4$) as oxidant, which is catalyzed by simple amines.[1] This process is attractively simple and requires readily available cheap reagents in environmentally friendly solvents. This novel method, which does not require the use of transition metal catalyst,[2] utilizes Oxone buffered with $NaHCO_3$/pyridine in MeCN:H_2O and amines as catalyst (Scheme 1).

When a chiral amine was used significant asymmetric induction was observed which could only result from intimate association of the amine/amine derivative with either the alkene or the oxidant. In attempting to determine the mechanism of this novel process, we carried out competition experiments between structurally similar alkenes and compared our selectivities with both electrophilic epoxidation, using either *m*-CPBA or H_2O_2/MTO, and radical cation[3] mediated reactions using $Ar_3N^{+\bullet}$ $SbCl_6^-$. The very close similarity in selectivities of a range of alkenes between the aminium salt ($Ar_3N^{+\bullet}$ $SbCl_6^-$) catalyzed reaction of Bauld and Mirafzal[3] and our own results persuaded us that a similar radical cation mediated process was occurring in our amine catalyzed process. However, as we have recently discovered that these competition experiments are not reproducible, they make the radical cation mechanism both less credible and less compelling.[4] A further problem we encountered was the variable enantiomeric excess observed (32−38% ee[5]) in different runs of our standard test reaction (1-phenylcyclohexene was reacted with Oxone in the presence of 10% (*S*)-2-(diphenyl-methyl)pyrrolidine **1**[6]). We therefore set out to improve the reproducibility of the process, to improve the enantioselectivity, and most importantly, to establish the mechanism of the amine catalyzed epoxidation reaction. In this contribution we describe our success in achieving all of these goals.

Scheme 1. Epoxidation of Alkenes by Oxone/$NaHCO_3$ Catalyzed by Amines



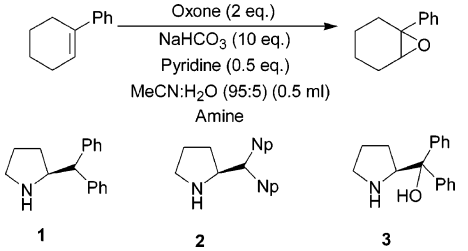
Results and Discussion

Improvements in Reproducibility and Enantioselectivities. In our amine catalyzed epoxidations, the difficulty in obtaining

(1) Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317−8318.
(2) Jacobsen, E. N.; Wu, M. H. *Comprehensive Asymmetric Catalytsis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; pp 649−677.
(3) (a) Bauld, N. L. T*etrahedron* **1989**, *45*, 5307−5363. (b) Bauld, N. L.; Mirafzal, G. A. *J. Am. Chem. Soc.* **1991**, *113*, 3613−3614.
(4) The corrected data for the competition experiments have now been reported. See: Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 11223−11223. We have also been unable to reproduce Bauld and Mirafzal radical cation mediated epoxidations described in ref 3.
(5) In the original work this was erroneously reported as 57% ee.
(6) Bailey, D. J.; O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1997**, *8*, 149−153.

10.1021/ja0289088 CCC: $25.00

Table 1. Asymmetric Epoxidation of 1-Phenylcyclohexene Using Chiral Amines as Catalyst



entry	catalyst[a]	time	yield (%)[b]	ee (%)[e,f]
1	10% amine **1**	30 min	87−99	32−38
2	10% **1**·HCl	20 min	93 (5[c])	46
3	5% **1**·HCl	40 min	91 (8[c])	46
4	10% **1**·HCl (−10 °C)	2 h	68[d]	52
6	10% **2**·HCl	60 min	89 (7[c])	59
7	10% **2**·HCl (−10 °C)	2 h	49[d]	66
8	10% **3**·HCl	2 h	79 (11[c])	54
9	10% **3**·HCl (−10 °C)	2 h	7[d]	49

[a] Standard conditions: 1-phenylcyclohexene (0.424 mmol), Oxone (0.848 mmol), $NaHCO_3$ (4.24 mmol), pyridine (0.212 mmol), MeCN:H_2O (95:5) (0.5 mL), amine or amine·HCl (0.042 or 0.021 mmol). [b] Yields determined by ^1H NMR relative to an internal standard (*p*-dimethoxybenzene). [c] Yield of diol. [d] Remainder is alkene. [e] Enantioselectivities determined by chiral GC using a α-CD column. [f] The epoxide has the (*S*,*S*) configuration. The absolute configuration was determined by comparison of the optical rotation with literature data (see Supporting Information).

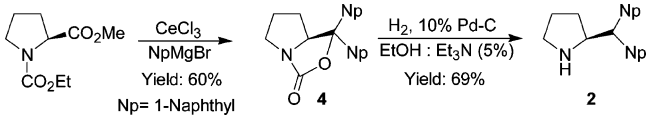
consistent and reproducible results was solved by employing the hydrochloride salt of amine **1**. Not only did this modification give completely reproducible results, it also provided higher enantiomeric excesses and shorter reaction times (Table 1, entry 2).

Even though a large excess of bicarbonate is employed, it is almost entirely present in the solid phase with very little entering the solution phase. Thus, under these conditions it seems reasonable to assume that the protonated amine remains as the HCl salt in the heterogeneous reaction mixture. Pyridine is present to reduce the amount of epoxide hydrolysis, and it is believed that it buffers the system by acting as a proton carrier between the inorganic hydrogen sulfate and inorganic $NaHCO_3$. In the absence of pyridine, substantial amounts of diol were formed.

The use of the protonated ammonium salt also resulted in greater reproducibility with a broader range of amine catalysts. This is exemplified in the case of the pyrrolidine derivatives **2** and **3**,[7] both of which gave higher enantioselectivity than **1** (Table 1). These amines were chosen as they provide substantially greater steric hindrance and an additional polar group with potential binding capabilities, respectively.

Pyrrolidine **2** was prepared in an analogous way to that for **1**[6] (Scheme 2) although some modifications were required. The reaction of the α-naphthyl Grignard with the ester derived from proline was carried out using the cerium-complexed ester[8] which was superior to the procedure using the organocerium reagent (7% yield).[9] Hydrogenolysis of carbamate **4** was carried out in the presence of triethylamine, which resulted in an acceleration of the reduction.[10]

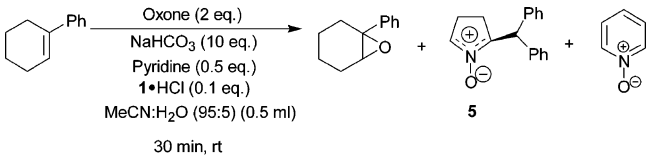
Scheme 2. Synthesis of (*S*)-2-(Di-α-naphthylmethyl)pyrrolidine **2**



The epoxidation was equally effective at 5% loading of **1**·HCl (Table 1, entry 3) or using fewer equivalents of Oxone (1 equiv)[11] and $NaHCO_3$ (5 equiv) (see Supporting Information). Further reduction in the amounts of bicarbonate was less effective.

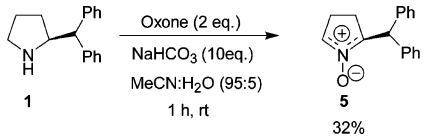
Fate of Amine and Pyridine. At the end of the reaction (for example, from Table 1, entry 2), neither amine **1** nor pyridine were present, only their oxidation products (nitrone **5** and pyridine-*N*-oxide) were observed (Scheme 3).

Scheme 3. Fate of Amine and Pyridine after Reaction



As an excess of oxidant was used and the amines were employed in substoichiometric amount, it is reasonable to expect oxidation of the amine to occur. Indeed, Oxone in aqueous acetic acid[12] is known to oxidize amines but no reaction had been conducted under our conditions of higher pH. We therefore subjected amine **1** to our standard conditions for alkene oxidation and obtained nitrone **5** in 32% yield. No starting material remained (Scheme 4).

Scheme 4. Oxidation of the Amine **1**

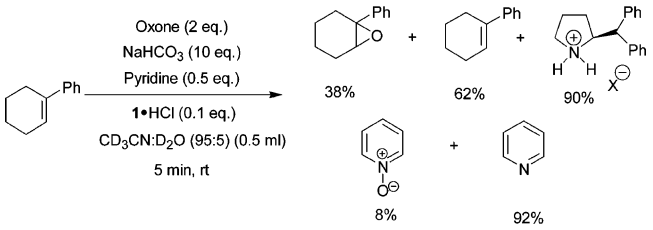


If amine **1** and pyridine are both oxidized, what then are their roles in the epoxidation process? We knew from earlier experiments that in the absence of amine **1**, no epoxidation occurred and that none of the possible oxidation products (hydroxylamine, nitrone, or *N*-hydroxylactam) were able to promote epoxidation either. To answer this question, we repeated the reaction shown in Scheme 3 but quenched the reaction after 5 min (Scheme 5).

In this case, even though substantial epoxidation had occurred, the amine remained intact, and only a small amount of pyridine-*N*-oxide was observed. Thus, it is clear that the alkene is oxidized at a much faster rate than pyridine so that pyridine is able to fulfill its role in acting as a proton shuttle during the oxidation process, thus limiting epoxide hydrolysis. Amine **1**

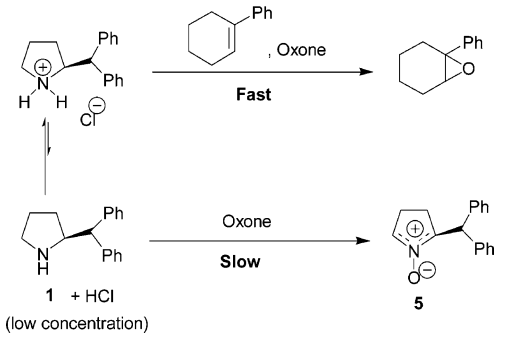
(7) (*S*)-diphenylprolinol **3** was purchased from Aldrich.
(8) (a) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787−6790. (b) Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, *35*, 6713−6716. (c) Aggarwal, V. K.; Sandrinelli, F.; Charmant, J. P. H. *Tetrahedron: Asymmetry* **2002**, *13*, 87−93.
(9) (a) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763−4766. (b) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233−4236.
(10) (a) Effenberger, F.; Jäger, J. *Chem. Eur. J.* **1997**, *3*, 1370−1374. (b) Zymalkowski, F.; Schuster, T.; Scherer, H. *Arch. Pharm. (Weinhiem, Ger.)* **1969**, *302*, 272−284.
(11) One equivalent of Oxone provides two equivalents of $KHSO_5$. An excess of $KHSO_5$ is needed as Oxone is known to decompose to produce $^1O_2$. The rate of decomposition is maximum at pH 9: Evans, D. F.; Upton, M. W. *J. Chem. Soc., Dalton Trans.* **1985**, *6*, 1151−1153.
(12) For examples of oxidation of amines with Oxone see: Kennedy, R. J.; Stock, A. M. *J. Org. Chem.* **1960**, *25*, 1901−1906.

Scheme 5. Quench of the Epoxidation Reaction after 5 Min



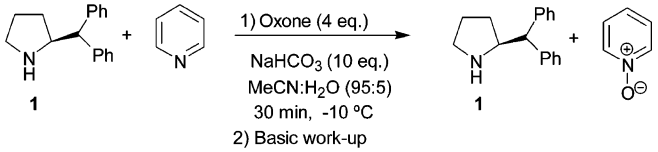
is protected from oxidation by protonation. However, once all of the alkene is consumed, the very small amount of free base present in equilibrium with the protonated salt is slowly oxidized by the excess oxidant to give the nitrone (Scheme 6). These experiments implicate an ammonium salt as being the active species responsible for promoting epoxidation.

Scheme 6



Conducting Reaction at Low Temperature (Reisolation of Amine). The epoxidation reaction could also be conducted at −10 °C which resulted in an additional increase in enantioselectivity (Table 1, entries 4, 7, 9). Furthermore, *at the lower temperature, the amine could be reisolated in >90% yield, indicating that amine oxidation was essentially inhibited at −10 °C*. This was remarkable as we had shown that at room temperature pyrrolidine was oxidized by Oxone.[12,13] However, this observation can also be rationalized. At −10 °C, the concentration of the free base **1** is significantly lower than that at room temperature so that the rate of amine oxidation is reduced further. Interestingly, even β-hydroxyamine **3** could be reisolated in >90% yield. Following alkene oxidation at *room temperature*, this amine subsequently decomposed, and benzophenone was generated, a process which either occurs from the amine radical cation[14] or from the *N*-oxide of the hydroxylamine.[15] Our early observations on the formation of benzophenone provided additional circumstantial evidence for the intermediacy of radical cations. However, the fact that we can reisolate even amine **3** at low temperature shows that the irreversible oxidation of **3** to the corresponding amine radical cation cannot be an intermediate in the catalytic epoxidation process. We now believe that after alkene oxidation at room temperature with amine **3**, the amine is oxidized to the *N*-oxide of the hydroxylamine and then fragments.[15]

Scheme 7. Reaction of Oxone with (*S*)-2-(Diphenylmethyl)pyrrolidine 1 and Pyridine at −10 °C

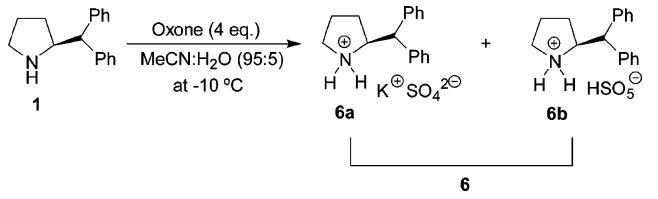


Further evidence that the basic amine is protonated and protected from oxidation came from reacting a mixture of amine and pyridine with Oxone at −10 °C in the presence of sodium bicarbonate (Scheme 7). The reaction resulted in complete conversion of pyridine to the *N*-oxide and, after basic workup, >90% reisolation of the amine. These results can be rationalized by assuming that the less basic amine (pyridine) remains largely unprotonated and so is oxidized,[16] whereas the more basic amine is protonated and effectively protected from oxidation.

Note that the low yield obtained with the hydrochloride salt of amine **3** at −10 °C (Table 1, entry 9) is probably due to the low solubility of the salt at this temperature.

Isolation of Actual Oxidizing Species. In attempting to gain further insights into the mechanism of the process, we discovered that a complex, **6**, was formed between Oxone and the amine at −10 °C (Scheme 8). Through a combination of IR, ^{1}H NMR, ^{13}C NMR and elemental analysis of the complex and comparison with an authentic sample of **1**·H_2SO_4, we concluded that complex **6** was a mixture of the potassium sulfate **6a**[17] and peroxymonosulfate anions **6b** (see Supporting Information for data).[18] Attempts to grow suitable crystals of the complex for X-ray analysis were unsuccessful. The complex titrated to a value of 57−62 wt % of active oxidizing agent **6b**[19] and is relatively stable: a sample left for 6 weeks at 0 °C lost approximately 10% of activity.

Scheme 8. Reaction of Oxone ($2KHSO_5$, $KHSO_4$, K_2SO_4) with (*S*)-2-(Diphenylmethyl)pyrrolidine at −10 °C

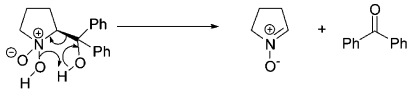


This isolated complex **6** was tested in the epoxidation of four different alkenes (Table 2, method **A**) and compared with the catalytic process using 10% of the corresponding hydrochloride salt (Table 2, method **B**). In every case identical enantioselectivities were obtained (Table 2). As it is highly unlikely that the ammonium salt **6b** reacts with pyridine to return the neutral

(13) For examples of oxidation of amines with Oxone/acetone system see: (a) Brik, M. E. *Tetrahedron Lett.* **1995**, *36*, 5519−5522. (b) Webb, K. S.; Seneviratne, V. *Tetrahedron Lett.* **1995**, *36*, 2377−2378. (c) Crandall, J. K.; Reix, T. *J. Org. Chem.* **1992**, *57*, 6759−6764.

(14) Su, Z.; Mariano, P. K.; Falvey, D. E.; Yoon, U. C.; Oh, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 10676−10686.

(15) Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170−6172. In the case of **3**, the mechanism below could account for the formation of benzophenone and nitrone.



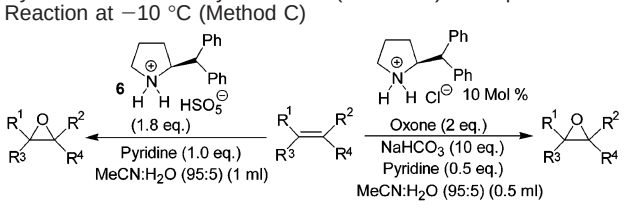
(16) In the absence of amine **1**, pyridine is not oxidised at −10 °C with Oxone in MeCN/H_2O.

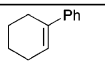
(17) (a) pK_a of pyrrolidine = 11.31: Crampton, M. R.; Robotham, I. A. *J. Chem. Res. (S)* **1997**, 22−23. (b) pK_a of $KHSO_4$ = 1.9: Zhu, W.; Ford, W. T. *J. Org. Chem.* **1991**, *56*, 7022−7026.

(18) For spectroscopic analysis of Oxone, see: (a) Flanagan, J.; Griffith, W. P.; Skapski, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 1574−1575. (b) Arnau, J. L.; Giguere, P. A. *Can. J. Chem.* **1970**, *48*, 3903−3910.

(19) We used the method employed by Trost for the determination of active oxidant in tetrabutylammonium Oxone (TBO) to determine the amount of active oxidant in complex **6**. See: Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532−537. Complex **6** is a mixture of ∼40% **6a** and ∼60% **6b** by weight; 100 mg of complex **6** provides ∼0.17 mmol of oxidant (HSO_5^-).

Table 2. Epoxidation Reaction with Peroxymonosulfate Ammonium **6b** (Method A) or Using the Corresponding Hydrochloride in Catalytic Amount (Method B) and Epoxidation Reaction at −10 °C (Method C)



Entry	Alkenes	Method[a]	Time	Yield (%)[b]	Ee (%)[d]
1		A	30 min.	70 (21[c])	46 (*S*,*S*)[e]
2		B	20 min.	93 (5[c])	46 (*S*,*S*)[e]
3		C	4 h 30	91	52 (*S*,*S*)[e]
4		A	25 min.	57	27 (1*R*,2*S*)[f]
5		B	30 min.	64	27 (1*R*,2*S*)[f]
6		C	4 h 30	48	31 (1*R*,2*S*)[f]
7		A	2 h.	74	0
8		B	4 h.	60	0
9		C	4 h 30	21	0
10		A	2 h.	72	21 (*S*,*S*)[g]
11		B	4 h.	3	21 (*S*,*S*)[g]

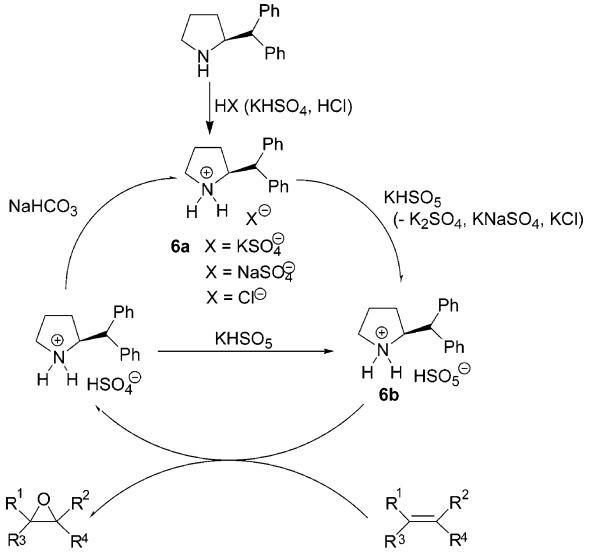
[a] **Method A** (rt): 1-phenylcyclohexene (0.212 mmol), complex **6** (223 mg, 0.38 mmol oxidant), pyridine (0.212 mmol), MeCN:H_2O (95:5) (1 mL). **Method B** (rt): 1-phenylcyclohexene (0.424 mmol), Oxone (0.848 mmol), $NaHCO_3$ (4.24 mmol), pyridine (0.212 mmol), MeCN:H_2O (95:5) (0.5 mL), **1**·HCl (0.042 mmol). **Method C** (−10 °C): 1-phenylcyclohexene (0.424 mmol), Oxone (1.272 mmol, added in three portions over 4 h 30 min), $NaHCO_3$ (2.12 mmol), pyridine (0.212 mmol), MeCN:H_2O (95:5) (0.5 mL), **1**·HCl (0.042 mmol). [b] Yields determined by ^{1}H NMR relative to an internal standard (*p*-dimethoxybenzene). [c] Yield of diol. [d] Enantioselectivities determined by chiral GC using a α-CD column. [e] The absolute configuration was determined by comparison of the optical rotation with literature data. [f] The absolute configuration was determined by chiral GC (Chiraldex γ-TA column). [g] The absolute configuration was determined by chiral HPLC using an OD column. See Supporting Information.

amine[17] (which could then catalyze the epoxidation through an alternative pathway), this salt is believed to be the active oxidant in both methods **A** and **B**. *Thus, whether the amine, or hydrochloride salt, or complex **6** is employed, it is believed that the key oxidant in all of these cases is the same and is the ammonium salt **6b**.* The application of the optimized condition at −10 °C (method **C**) with the hydrochloride salt of amine **1** on the series of alkenes is also given in Table 2. Again, slightly higher enantioselectivities were obtained, but more importantly, the amine could be reisolated in >90% yield in every case.

Note, the low yield obtained with *trans*-stilbene under catalytic conditions (Table 2, entry 11) is due to the very low solubility of the alkene in MeCN/H_2O in the presence of the salts (Oxone/bicarbonate). Our previous communication[1] described the broad scope of this epoxidation process: tetra-, tri-, and certain disubstituted alkenes were good substrates, but terminal alkenes (except for styrene) were not.

Discussion of Mechanism. There is now overwhelming evidence that the epoxidation process is the result of the reaction of a nucleophilic alkene with an electrophilic oxidant rather than a one-electron transfer to form an intermediate amine radical cation−alkene complex. The following experiments provide additional support for this mechanism.

Scheme 9. Catalytic Cycle for Alkene Epoxidation



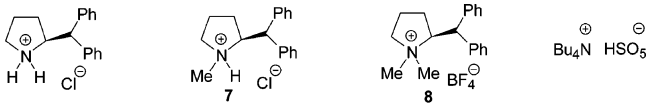
In competition experiments, the relative rates of oxidation of *cis*- and *trans*-β-methyl styrenes was 56:44. A similar ratio (58:42) was observed with *m*CPBA, while in the radical cation mediated cyclopropanation of stilbene reported by Bauld, (*E*)-stilbene is at least 100 times more reactive than (*Z*)-stilbene.[20] Amine radical cation catalyzed cyclopropanations are compared rather than epoxidations because, in both cases, the rate-determining step involves reaction of the triarylaminium cation with the alkene to give the alkene radical cation. Furthermore, the cyclopropanation reactions are more reproducible than the epoxidation reactions. The ρ value for oxidizing a series of 1-arylcyclohexenes was found to be −0.71. This is much closer to the value obtained for electrophilic epoxidation of styrenes with *m*-CPBA ($\rho = -0.93$),[21] whereas the ρ value for radical cation mediated cyclopropanation is −5.17.[20,22]

This evidence, together with the results from the isolated complex, lead us to propose a new catalytic cycle for the epoxidation process (Scheme 9). The amine is initially converted into the ammonium salt **6a** ($X = KSO_4^-$), which upon exchange with peroxymonosulfate gives the active oxidant **6b**. After oxidation, the hydrogen sulfate counterion of the ammonium salt can either be exchanged for one of the other counterions present including persulfate or react with $NaHCO_3$ to give the $NaSO_4^-$ salt.

A series of ammonium salts with different levels of alkylation and therefore different numbers of N−H protons were prepared (**7**, **8**) and tested as catalysts for epoxidation. These amines were chosen with minimal differences to amine **1**·HCl in steric and therefore physical properties (solubility) so that the effect of degree of alkylation could be probed. It was found that tertiary amine **7** was quite effective although both the enantioselectivity and conversion were markedly reduced (Scheme 10). However, the quaternary ammonium salt **8** was essentially ineffective, giving similar amounts of epoxide to tetrabutylammonium Oxone. In the absence of amine, the level of background epoxidation is less than 5%. In fact, we originally considered the possibility of a phase transfer catalyzed process in operation,

(20) Bauld, N. L.; Yueh, W. *J. Am. Chem. Soc.* **1994**, *116*, 8845−8846.
(21) Brook, M. A.; Smith, J. R. L.; Higgins, R.; Lester, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1049−1055.
(22) Yueh, W.; Bauld, N. L. *Res. Chem. Intermed.* **1997**, *23*, 1−16.

Scheme 10. Epoxidation of 1-Phenylcyclohexene Using the Corresponding Secondary, Tertiary, and Quaternary Ammonium Salts as Catalyst

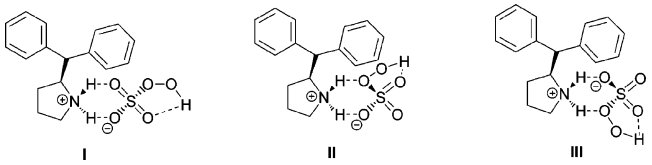


93% yield	58% yield	13% yield	15% yield
46% ee	5% ee	0% ee	-

but discounted this mechanism on the basis of the lack of activity of quaternary ammonium salts. These results show that the protonated ammonium salts are uniquely effective in the epoxidation process and that the more N−H's there are available the more effective is the catalyst in terms of both conversion and enantioselectivity.

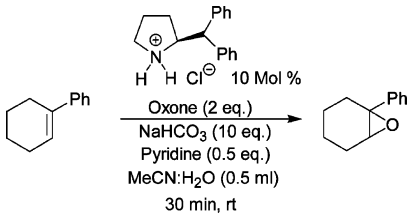
It now seems that the protonated ammonium salts serve a dual role. Not only do they act as PTCs and help bring the oxidant into solution, but we now believe that they also activate the peroxymonosulfate, through hydrogen bonding, generating a more electrophilic species.[23] There are a number of possible peroxymonosulfate−ammonium salt complexes, which can be formed with amine **1** and they all activate the oxidant either directly (**II**, **III)** or indirectly (**I)** (Scheme 11). The different complexes clearly place the peroxy group in a different steric environment, and this is likely to be a factor responsible for the moderate enantioselectivity observed. The key to enhancing the selectivity is to reduce the number of reactive complexes or to engineer complexes so that one complex is considerably more reactive than the others. Nevertheless, the high levels of enantioselectivity observed are remarkable, considering the fact that oxone is complexed to the chiral amine without covalent bonds, especially considering that such levels of selectivity have never been achieved in chiral peracid mediated epoxidations (<15%)[24] where the oxidant is *covalently attached* to the chiral controller.

Scheme 11. Possible Forms of Peroxymonosulfate Ammonium **6b**



If this proposal is correct, increased solvation of the ammonium peroxymonosulfate **6b** should not only result in a reduction in rate of epoxidation but also in the enantioselectivity. To test this, reactions were conducted in MeCN with increasing concentrations of water (Table 3) (for the effect of other solvents on epoxidation, see Supporting Information). Indeed, as the water content was increased, both conversion and enantioselectivity generally decreased.[25] However, the decrease was not as precipitous as we had expected perhaps because of the high salt content of the reaction. Water would no doubt solvate the inorganic ions in preference to the lipophilic complex **6b** reducing its ability to break up this ion pair.

Table 3. Variation of the Amount of Water



entry	CH_3CN/H_2O ratio[a]	yield (%)[b]	ee (%)[d,e]
1	95/5	93	46
2	90/10	90	42
3	75/25	92	38
4	50/50	60[c]	33
5	25/75	20[c]	40
6	5/95	8[c]	31

[a] Standard conditions: 1-phenylcyclohexene (0.424 mmol), Oxone (0.848 mmol), $NaHCO_3$ (4.24 mmol), pyridine (0.212 mmol), MeCN:H_2O (0.5 mL), **1**·HCl (0.042 mmol). [b] Yields determined by ^1H NMR relative to an internal standard (*p*-dimethoxybenzene). [c] Remainder is alkene. [d] Enantioselectivities determined by chiral GC using a α-CD column. [e] The epoxides have the (*S*,*S*) configuration. The absolute configuration was determined by comparison of the optical rotation with literature data.

The difficulty in obtaining consistent and reproducible results starting with the amine can now be understood if the rate of protonation to form the salt **6a** is slow and variable. In this case amine degradation can occur through oxidation, giving rise to different potential catalyst species, which will have different activities. Rate of protonation versus oxidation could vary for different reactions as it will depend on the amount of Oxone and bicarbonate in *solution* which in turn will depend on the particle size of Oxone and $NaHCO_3$ and the rate of stirring (the reaction mixture is heterogeneous). Starting with the protonated amine salt, the amine is effectively protected from oxidation and leads to completely reproducible results.

Conclusions

In summary, the following evidence supports the intermediacy of pyrrolidinium peroxymonosulfate **6b** as the active oxidizing species in the amine catalyzed epoxidation process: (i) a complex was isolated containing the peroxymonosulfate salt **6b** which showed identical results when used in stoichiometric amounts compared to catalytic amounts of the hydrochloride salt of amine **1** and Oxone, (ii) the amine could be reisolated in essentially quantitative yield, showing that it was protonated (and therefore protected) throughout the oxidation process when the reaction was conducted at −10 °C and not irreversibly oxidized to the corresponding amine radical cation, (iii) the relative rates of oxidation of structurally similar alkenes were closer to those observed in *m*-CPBA oxidations than radical cation mediated processes, (iv) the ρ value for oxidizing a series of arylcyclohexenes was much closer (and smaller) to *m*-CPBA oxidations than radical cation mediated processes, indicating that the process involved an electrophilic oxidant.

(23) Protonated Oxone (i.e. Oxone at low pH) is a powerful electrophilic oxidant. See: Zhu, W.; Ford, W. T. *J. Org. Chem.* **1991**, *56*, 7022−7026.

(24) (a) Ewins, R. C.; Henbest, H. B.; McKervey, M. A. *Chem. Commun.* **1967**, 1085−1086. (b) Bowman, R. M.; Collins, J. F.; Grundon, M. F. *Chem. Commun.* **1967**, 1131−1132. (c) Montarani, F.; Moretti, I.; Torre, G. *Chem. Commun.* **1969**, 135−136. (d) Bowman, R. M.; Collins, J. F.; Grundon, M. F. *J. Chem. Soc., Perkin Trans. I* **1972**, 626−632. (e) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1977**, *42*, 2080−2082. (f) Rebek, J., Jr.; McCready, R. *J. Am. Chem. Soc.* **1980**, *102*, 5602−5605.

(25) We cannot account for the small increase in ee in the 25/75 mixture of MeCN/H_2O (Table 3, entry 5).

(26) There are examples of protonated ammonium salts directing epoxidation through hydrogen bonding with the oxidant (*m*-CPBA or dimethyloxirane) whilst quaternary ammonium salts gave opposite selectivity. See: (a) Asensio, G.; González-Núñez, M. E.; Boix-Bernardini, C.; Mello, R.; Adam, W. *J. Am. Chem. Soc.* **1993**, *115*, 7250−7253. (b) Asensio, G.; Boix-Bernardini, C.; Andreu, C.; González-Núñez, M. E.; Mello, R.; Edwards, J. O.; Carpenter, G. B. *J. Org. Chem.* **1999**, *64*, 4705−4711. These reactions

The remarkable finding that the secondary ammonium salt is considerably more active than the tertiary ammonium salt which in turn is more active than the quaternary ammonium salt shows that the protonated amine is not just acting as a PTC but is also activating Oxone, through hydrogen bonding, toward electrophilic attack. Phase transfer catalyzed processes have a long and well-established history, but as far as we are aware, this is the first example in which a protonated ammonium salt is far superior to a quaternary ammonium salt.[26] As we now have a much better understanding of the mechanism of this unique amine catalyzed epoxidation process, we can begin to improve the levels of asymmetric induction through variations and derivatizations of the bounty of chiral amines bequeathed by nature. Studies in this endeavor are ongoing.

Acknowledgment. We thank GSK (Andy Walker), Pfizer (Clive Mason), Degussa (Ian Grayson), and EPSRC for support of this work. We acknowledge helpful discussions with Dr. Bill Sanderson.

Supporting Information Available: Synthesis and spectroscopic data of all amines/ammonium salts, synthesis and analytical data for complex **6**, titration of **6**, typical procedures (methods A, B, and C), competition experiments and determination of ρ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org or from the author.

JA0289088

are analogous to the seminal work of Henbest[27] on hydroxy-directed epoxidations but do not relate to phase transfer catalysed epoxidations of the type described in this paper. Nevertheless, we appreciate one of the reviewers directing us to this work.

(27) (a) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1959**, 1958−1965. (b) Henbest, H. B. *Proc. Chem. Soc.* **1963**, 159−165.