Highly regioselective and diastereoselective epoxidation of allylic amines with Oxone†

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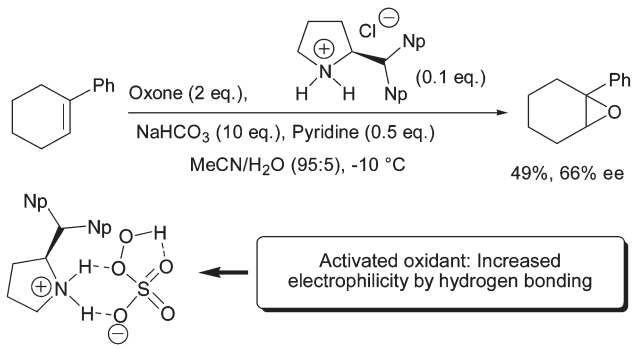
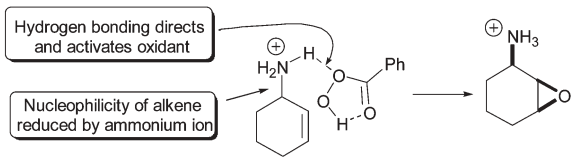
Allylic amines (as their protonated ammonium salts) can be epoxidised with high *syn* diastereoselectivity and regioselectivity at the proximal alkene in substrates with several double bonds using Oxone. The protonated ammonium cation activates the Oxone by hydrogen bonding, thus promoting the oxidation of groups within the vicinity of the complex.

We recently reported a novel amine-catalysed epoxidation of alkenes using Oxone.[1,2] Using chiral amines, up to 66% ee was achieved, demonstrating that the amine was intimately involved in the epoxidation process. We proposed that the ammonium salt (the active catalyst rather than the amine) had two distinct roles: (i) it acted as a phase transfer catalyst bringing the Oxone into solution and (ii) it activated Oxone as an electrophilic oxidant by hydrogen bonding (Scheme 1).[2] Our mechanism has now been generally accepted by the scientific community.[3]

It occurred to us that this process could be applied to the controlled epoxidation of protonated allylic ammonium salts where issues of regioselectivity and stereoselectivity remain. Protonated allylic ammonium salts are the simplest protected forms of allylic amines that are compatible with strong oxidative reagents. Unfortunately the ammonium salt strongly deactivates the proximal alkene towards electrophilic attack and reaction times can be very long.[4a] However, oxidants capable of hydrogen bonding to the protonated ammonium salt like *meta*-chloroperoxybenzoic acid (*m*-CPBA) or even dimethyldioxirane (DMDO) are rendered more electrophilic and so are activated, resulting in diastereoselective epoxidation *syn* to the ammonium ion[4–6] in a manner akin to the classical Henbest hydroxy-directed epoxidation (Scheme 2).[7]

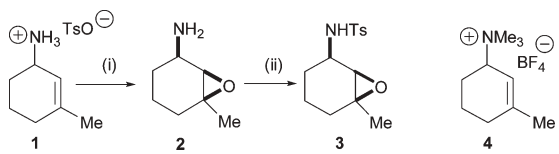


Scheme 1 The ammonium salt catalysed epoxidation of 1-phenylcyclohexene and proposed working model.



Scheme 2 Model for epoxidation of a protonated allylic ammonium salt with *m*-CPBA.

We believed that if our proposed mechanism is correct, Oxone should also be directed and activated by a protonated ammonium ion, leading to high diastereoselectivity. We therefore tested the ammonium salt **1**[8] in our epoxidation process using Oxone and observed complete diastereoselectivity (>95 : 5) in favour of the *syn* isomer **2**. The stereochemistry was proved by X-ray analysis‡ of the corresponding tosylamide **3** (Scheme 3).



Scheme 3 Epoxidation of ammonium salt **1** with Oxone. *Reagents and conditions*: (i) 2 equiv. Oxone, 10 equiv. $NaHCO_3$, 0.5 equiv. pyridine, $MeCN/H_2O$ (95:5), −8 °C, 73%, >95:5 dr; (ii) TsCl/TEA, DMAP, 87%.

We also examined the quaternary ammonium salt **4**,[8] but this failed to give any epoxide. This clearly demonstrates that the ionic interaction between the peroxymonosulfate anion and the ammonium cation is not sufficient alone to promote epoxidation; epoxidation clearly requiring a protonated ammonium ion. This is

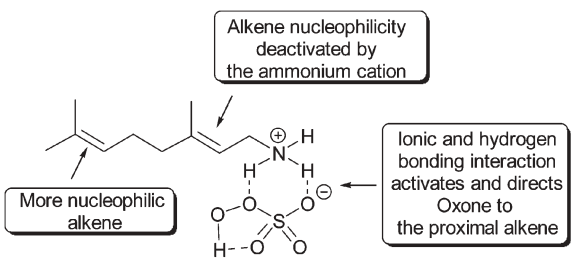


Fig. 1 Factors affecting regioselective epoxidation of geranylammonium tosylate **5** with Oxone.

† Electronic Supplementary Information (ESI) available: Experimental details and spectral data for synthesis and characterisation of compounds **1–8**. See http://www.rsc.org/suppdata/cc/b5/b503516c/

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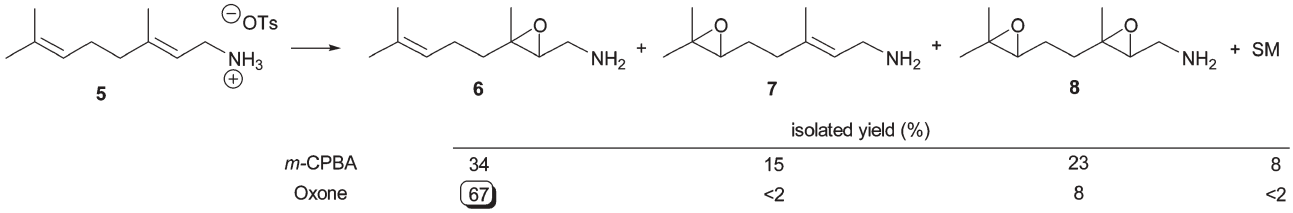

Scheme 4 Epoxidation of geranylammonium tosylate **5** with *m*-CPBA and Oxone.

in keeping with our mechanism in which a protonated amine activates by hydrogen bonding the peroxymonosulfate anion (it is now a better electrophile) towards nucleophilic attack by the alkene.

We then tested a more challenging substrate, geranylammonium tosylate **5**.[9] This substrate has two alkenes: a remote trisubstituted, electron rich alkene, and an alkene that is strongly deactivated by the ammonium cation. We questioned whether the directing/activating effects of the protonated ammonium ion with Oxone could overcome the inherent reduced nucleophilicity of the alkene, and so control the regiochemistry of epoxidation (Fig. 1).

We tested both *m*-CPBA[10] and Oxone in the epoxidation process. Epoxidation of the geranylammonium salt with *m*-CPBA gave a mixture of monoepoxides **6** and **7**, diepoxide **8**, and starting material. This indicates that the directing effect of the ammonium cation, which promotes epoxidation of the proximal alkene, was effectively cancelled out by the deactivation caused by the strong electron withdrawing group, resulting in similar rates of epoxidation for the two alkenes (Scheme 4). In contrast using Oxone, a much cleaner reaction was observed, and the only monoepoxidation product isolated was the epoxyamine **6**. This clearly demonstrates that the protonated ammonium ion both activated and directed Oxone epoxidation to take place at the alkene proximal to it. The degree of activation of the oxidant by the ammonium ion (relative to the power of the free oxidant) is clearly greater for Oxone than *m*-CPBA as it completely outweighed the reduced nucleophilicity of the alkene (Scheme 4).

Oxone and *m*-CPBA show similarly high levels of diastereoselectivity in the epoxidation of cyclic, allylic ammonium salts. As Oxone is the safer and less hazardous reagent of the two, especially on a large scale, we would expect it to be the reagent of choice for such substrates. In reactions of allylic ammonium salts containing multiple double bonds it is far superior, delivering high levels of regiocontrol due to its strong activation by hydrogen bonding.

This work reinforces the proposed mechanism of the ammonium salts in that they not only act as directing groups, but also as activators of Oxone by hydrogen bonding. In addition, the work fills a methodology gap by providing a method for controlling the regiochemistry of epoxidation in allylic amines.

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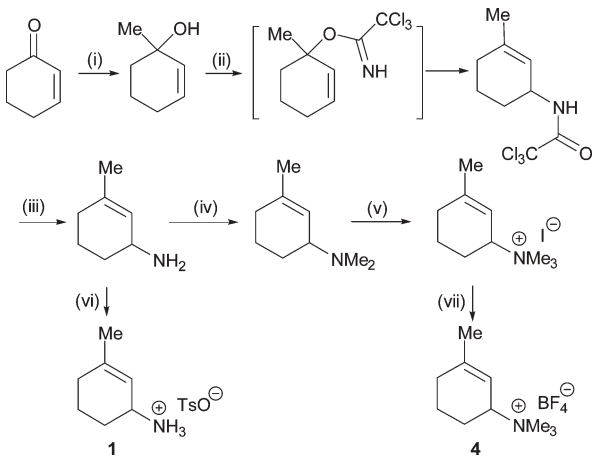

Scheme 5 Synthesis of ammonium salts **1** and **4**. *Reagents and conditions*: (i) MeLi/$CeCl_3$, THF, −78 δC to r.t. 78%; (ii) KH, Et_2O, $NCCCl_3$, −5 δC to r.t, 83%; (iii) 6 N NaOH, EtOH, 81%; (iv) HCHO, $NaBH_3CN$, 95%; (v) MeI/Et_2O, 98%; (vi) TsOH, THF, 89%; (vii) $AgBF_4/H_2O$, 89%.

Notes and references

‡ *Crystal data* for compound **3**: $C_{14}H_{19}NO_3S$, M = 281.1, triclinic, space group $P\bar{1}$, a = 7.1014(6), b = 8.6018(7), c = 12.6772(11) Å, α = 101.5860(10), β = 98.6520(10), γ = 109.5870(10)°, V = 694.53(10) Å^3, Z = 2, T = 173(2), Dc = 1.345 Mg m^{-3}, crystal dimensions 0.25 × 0.10 × 0.10 mm, Mo-Kα radiation, λ = 0.71073 Å. Data were collected on a Bruker Smart CCD area-detector diffractometer and a total of 3146 of the 7277 reflections were unique (R_{int} = 0.0247). Refinement on F^2, wR_2 = 0.1051 (observed reflections), $R1$ = 0.0496 [$I > 2\sigma(I)$]. CCDC 266382. See http://www.rsc.org/suppdata/cc/b5/b503516c/ for crystallographic data in CIF or other electronic format.

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8 The ammonium salts **1** and **4** were made from 2-cyclohexen-1-one (Scheme 5). Experimental details and related analytical data are included in the Electronic Supplementary Information.
9 Geraniol has often been employed to examine the power of hydroxy-promoted epoxidation. The remote 6,7-alkene is more electron rich than the 2,3-alkene and the ratio of regioisomeric products gives a measure of the relative rates of epoxidation. See: W. Adam and A. K. Smerz, *Bull. Soc. Chim. Belg.*, 1996, **105**, 581.
10 According to the proposed mechanism for the epoxidation of protonated allylic amines with *m*-CPBA (see ref. 4 and 5), the hydrogen bonding interaction between *m*-CPBA and protonated amino group should also enhance its reactivity.

