Catalytic asymmetric synthesis of epoxides mediated by chiral iminium salts

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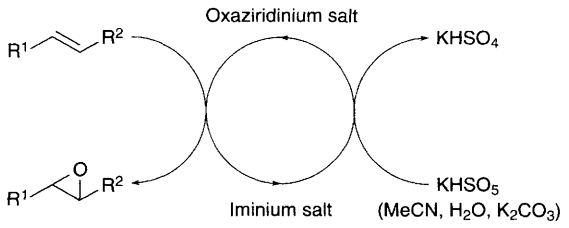
The catalytic asymmetric oxidation of unfunctionalised alkenes is achieved by a non-transition metal catalysed process; just 5 mol% of the binaphthyl-based iminium salt 1 is sufficient to catalyse the oxidation of alkenes to epoxides with moderate to good enantioselectivity.

The catalytic asymmetric synthesis of epoxides[1,2] from unfunctionalised alkenes is a significant problem in organic synthesis. A breakthrough has recently been made using chiral Mn–salen complexes and good enantioselectivities are beginning to emerge for increasing classes of alkenes.[3-9] However, in this process manganese salts contaminate the aqueous effluent due to catalyst instability and therefore need to be removed before discharge. To obviate this problem we have considered the possibility of using non-transition metal mediated epoxidations. We were particularly attracted to the possibility of using catalytic amounts of iminium salts as oxidant relays (Scheme 1). It had been previously shown that iminium salts could be converted to oxaziridinium salts using nucleophilic oxidants[10] and that oxaziridinium salts were strong electrophilic oxidants[11,12] (they are more electrophilic than the Davis oxaziridines[13]). Nucleophilic oxidants should not react directly with nucleophilic alkenes but in the presence of iminium salts, rapid oxidation should occur *via* oxaziridinium salts (Scheme 1). The use of chiral iminium salts should therefore result in catalytic asymmetric epoxidation. During the course of this work, Hanquet demonstrated the workings of this catalytic cycle using oxone with Na_2CO_3 in MeCN–H_2O and obtained non-racemic epoxides with a chiral iminium salt.[14] After trying many different combinations of oxidant and base we also arrived at the same set of conditions. Here we report a new, enantiomerically pure iminium salt for use in this novel catalytic cycle for asymmetric epoxidation.

Binaphthyl based systems have emerged as some of the best ligands in asymmetric synthesis[15,16] and we therefore designed a chiral iminium salt based on this motif, (*S*)-(+)-**1**. The known binaphthylamine[17,18] (*S*)-(+)-**2** was oxidised using $KMnO_4$,[19] and alkylated using Meerwein's reagent (Scheme 2). This enantiomerically pure iminium salt† was tested with a range of alkenes in the catalytic cycle for asymmetric epoxidation (Scheme 3) and the results are summarised in Table 1.

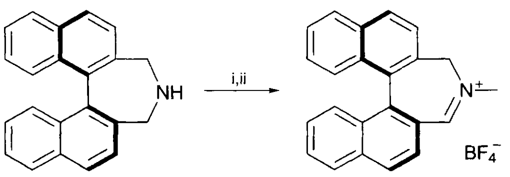
During the course of these studies several critical observations were made. Reactions with trisubstituted alkenes were considerably faster than disubstituted alkenes which were themselves faster than monosubstituted alkenes; a result consistent with the electrophilic nature of the oxaziridinium salt. The oxidations were geometrically specific: *cis* and *trans* stilbenes gave *cis* and *trans* stilbene oxides respectively with no contamination of the alternative epoxide in either reaction suggesting that concerted formation of both C–O bonds occurred. In contrast, oxidation with Mn–salen complexes gave mixtures of *cis*- and *trans*-epoxides from (*Z*)-alkenes.



Scheme 1

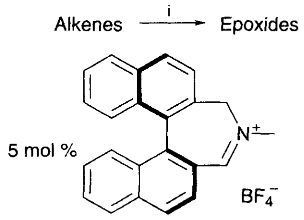
Whilst the levels of enantioselectivity were low to moderate with mono- and di-substituted alkenes, much higher enantioselectivities were obtained with trisubstituted alkenes, particularly 1-phenylcyclohexene.

The oxidation process involves two stereoselective steps. Oxidation of the iminium salt, which can give rise to two possible diastereoisomers followed by oxidation of the alkene, which can give either enantiomer. To obtain high enantioselectivity in the epoxidation process, high diastereoselectivity should be obtained in the formation of the oxaziridinium salt followed by high enantioselectivity in transfer of oxidant to the alkene. We were not able to characterise the intermediate



2 (*S*)-(+)-**1**

Scheme 2 *Reagents and conditions*: i, $KMnO_4$, THF, 80%; ii, $Me_3O^+BF_4^-$, CH_2Cl_2, 96%



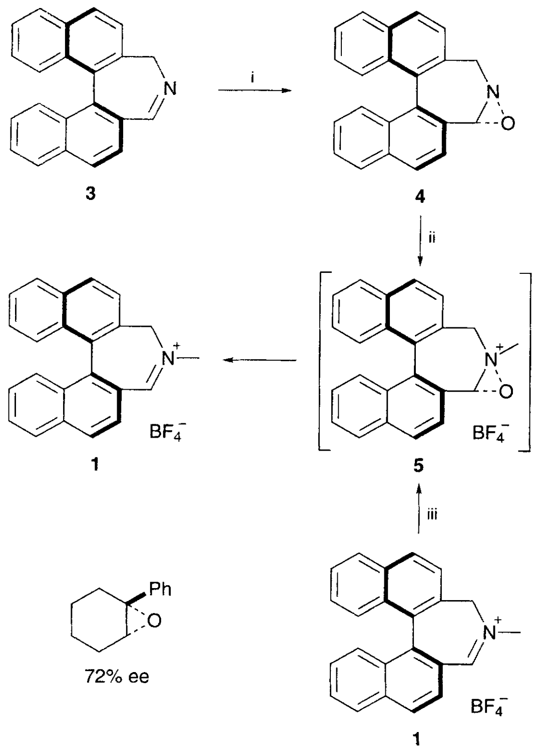
(*S*)-(+)-**1**

Scheme 3 *Reagents and conditions*: i, Oxone (1 equiv.), $NaHCO_3$ (4 equiv.), MeCN, H_2O

Table 1 The expoxidation of alkenes using iminium salt **1**

Alkene	Reaction time/h	Yield (%)	ee (%)[a]
trans-Stilbene	3	71	31 (*R*,*R*)[b]
trans-α-Methylstilbene	2	60	45 (*R*,*R*)[b]
1-Phenylcyclohexene	2	80	71 (*R*,*R*)[c]
1-Methylcyclohexene	1	80	39 (1*S*,2*R*)[c]
Styrene	12	66[d]	8 (—)[c,e]

[a] Absolute configuration was determined by comparison of the optical rotation with literature values.[5,20] [b] Determined by HPLC using Chiralcel OD column. [c] Determined by GC using chiral G-TA column. [d] Yield determined by GC integration against an internal quantitative standard (dodecane). All others are isolated yield. [e] Optical rotation was too low to give an accurate measurement.



Scheme 4 *Reagents and conditions*: i, MCPBA, $NaHCO_3$, CH_2Cl_2–H_2O, phase transfer catalyst; ii, $Me_3O^+BF_4^-$, $NaHCO_3$, MeCN, phenylcyclohexene; iii, oxone, $NaHCO_3$, MeCN, H_2O, phenylcyclohexane

oxaziridinium salt due to its instability but we do have indirect evidence that shows that the first step is completely selective. Oxidation of the imine using MCPBA under basic conditions gave a single diastereoisomeric oxaziridine (Scheme 4).[14] The oxaziridine was alkylated with Meerwein's reagent[14] in the presence of 1-phenylcyclohexene and the epoxide was obtained with the same absolute configuration and essentially the same enantiomeric excess (72%) as before. A control experiment without Meerwein's reagent did not give any epoxide. Thus, the same oxaziridinium salt intermediate must be involved as the oxidant in the two processes. As the oxidation route *via* the oxaziridine involved a single diastereoisomer, a single diastereoisomeric oxaziridinium salt must also be produced from oxidation of the imine/iminium salt. From inspection of molecular models it is clear that one face of the iminium salt is much more accessible than the other (Scheme 5) and the relative stereochemistry of the oxaziridine **4** and oxaziridinium salt **5** are tentatively assigned upon this basis.

From practical considerations, whilst the levels of enantioselectivity are only moderate at present (but encouraging) the process described is particularly amenable to being scaled up as it requires the use of cheap reagents (oxone, $NaHCO_3$) and environmentally friendly solvents. Further structural variations of the iminium salts are being explored to improve the enantioselectivity obtained.

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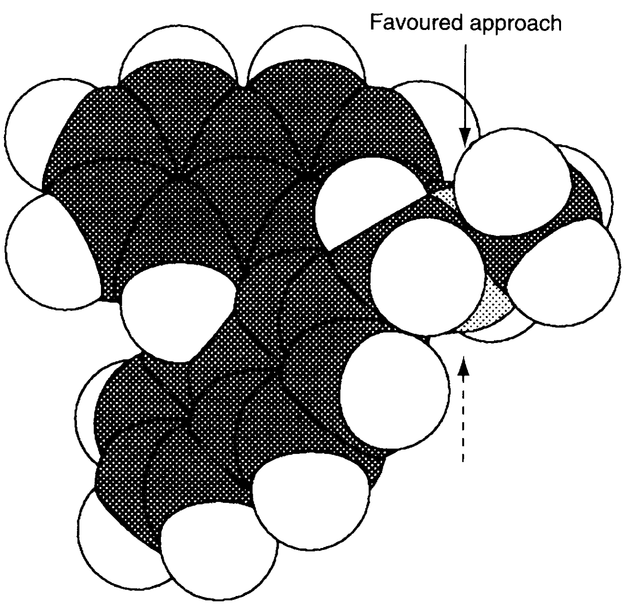

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Scheme 5 Favoured approach of oxidant to iminium salt **1**

Footnote

† Only 5 mol% of the iminium salt was used in the catalytic process. No attempt was made to recover and recycle the catalyst.

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