

Epoxidation of alkenes by OxoneTM using 2-alkyl-3,4-dihydroisoquinolinium salts as catalysts in ionic liquids

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Abstract

A number of ionic liquids have been used as co-solvents for the *N*-alkyl-3,4-dihydroisoquinolinium catalyzed epoxidation of alkenes. Water miscible ionic liquids gave systems with similar reactivities to the conventional acetonitrile based systems. Attempts to produce an aqueous/ionic liquid biphasic system that could be used to recycle the catalyst failed due to a lack of phase transfer between the aqueous and ionic liquid phases. © 2007 Elsevier B.V. All rights reserved.

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1. Introduction

Interest in the use of ionic liquids as solvents for synthesis continues unabated [1]. Ionic liquids have various useful properties, often being non-flammable, non-corrosive and non-volatile under atmospheric conditions. Consequently, they have been used as solvents for a wide range of organic reactions. A great deal of the work in the area has been based on the possibility that they might offer an environmentally benign alternative to conventional VOC solvents. However, it should be noted that this is a matter of some current contention [2].

The use of ionic liquids as solvents for catalysis has been a particular focus [3]. Although catalysis is dominated by the use of transition metal compounds, there has been a great deal of recent interest in catalysis by organic compounds [4]. Organocatalysis offers the possibility of eliminating toxic metal residues that have to be removed from product streams and the need to deal with the metal wastes. One area where organocatalysis has been applied is in homogeneous oxidations [5]. Since ionic liquids have been used for a wide variety of oxidation reactions [6], it is surprising that these two technologies have yet to be combined. Hence, we report here the first organocatalytic oxidation in an ionic liquid.

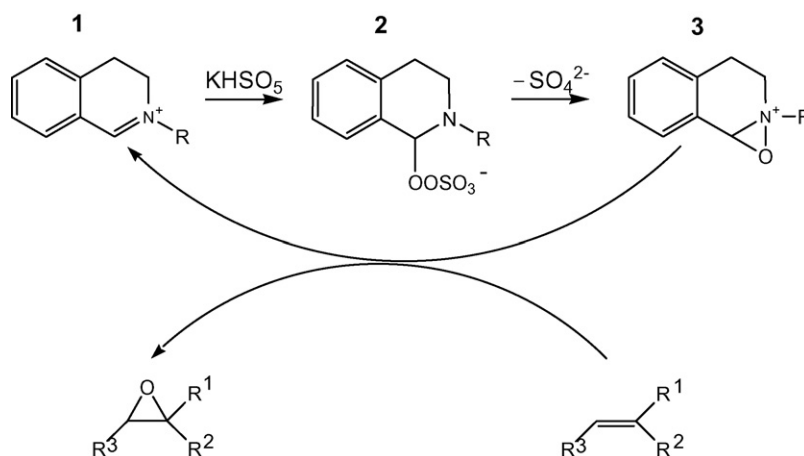
Epoxides are important synthetic building blocks. They are highly reactive and can be ring opened with different regioselectivity

by choice of suitable reagents, making them a useful and versatile synthons. Catalytic methods by which alkenes, and particularly unfunctionalized alkenes, can be epoxidized are therefore an ongoing area of research. Lusinchi and co-workers reported that an oxaziridinium salt, derived from tetrahydroisoquinoline, could stoichiometrically epoxidize olefins [7]. Further work elaborated the range of alkenes that could be epoxidized [8]. They also described the first syntheses of enantiomerically pure oxaziridinium salts for the asymmetric epoxidation of unfunctionalized alkenes, achieving ee's of 33% for the epoxidation of *trans*-stilbene with (1*S*,2*R*,3*R*,4*S*)-2-methyl-1,2-oxido-3-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolinium tetrafluoroborate [9,10]. Importantly, they also found that OxoneTM functioned as a stoichiometric oxidant for iminium salts, forming the oxaziridinium *in situ*, if the solution was buffered with sodium hydrogen carbonate. Therefore, iminium salts could be used catalytically (Scheme 1) [10].

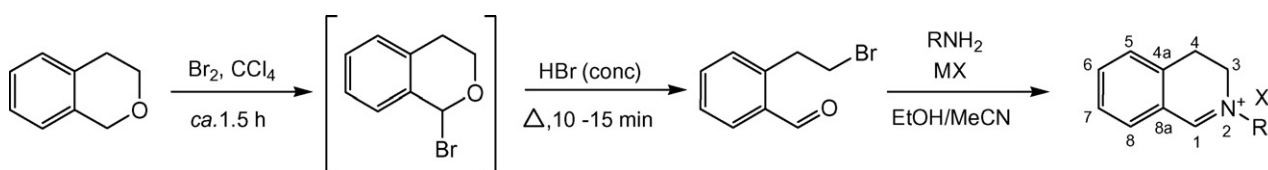
In 1996 Aggarwal and Wang demonstrated that a related system, incorporating a binaphthalene-derived iminium salt, could also be used for the asymmetric epoxidation of simple alkenes with complete retention of stereochemistry [11]. Armstrong et al. subsequently showed that an acyclic iminium salt could also epoxidize alkenes with OxoneTM, although it was susceptible to hydrolysis [12]. More recently, Page et al. have published a number of papers documenting the use of dihydroisoquinolinium salts for asymmetric epoxidations and have, in some instances, achieved ee's of up to *ca.* 60% [13].

OxoneTM is an ionic oxidant, is cheap and readily available. 2-Alkyl-3,4-dihydroisoquinolinium salts are also both soluble

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Scheme 1.



Scheme 2.

and stable in ionic liquids. Analysis of the catalytic cycle itself (Scheme 1) involves nucleophilic attack of caroate (potassium hydrogen persulfate, KHSO_5) on the iminium salt **1**, a step potentially retarded by ionic liquids, followed by formation of the oxaziridinium salt **3** via the irreversible expulsion of sulfate, which would be expected to be accelerated by ionic liquids, and subsequent epoxidation of the alkene [13]. Consequently, we decided to investigate if this could provide a useful catalytic epoxidation system.

2. Results and discussion

The catalysts were prepared using the synthetic route reported by Page et al. (Scheme 2) [13]. It was found that the tetraphenylborate and tetrafluoroborate salts of the 3,4-dihydroisoquinolinium derivatives precipitated readily and were easily recrystallized. The $[\text{N}(\text{Tf}_2)]^-$ derivatives proved to be more difficult to isolate by recrystallisation.

The 2-methyl-3,4-dihydroisoquinolinium tetrafluoroborate and *bis*(trifluoromethylsulfonyl)imide salts $\{[\text{mdhqm}][\text{BF}_4]$ and $[\text{mdhqm}][\text{Tf}_2\text{N}]\}$ have melting points of 86 and 58 °C, respectively; hence they meet the usual definition of being ionic liquids. 2-Methyl-3,4-dihydroisoquinolinium tetraphenylborate $\{[\text{mdhqm}][\text{BPh}_4]\}$ has a higher melting point of 175 °C. This trend of melting points is in agreement with the melting point trends of other similar salts [1].

It is well documented that 2-methyl-3,4-dihydroisoquinolinium salts will catalytically epoxidize alkenes in the presence of OxoneTM and sodium carbonate when the solvent system is water/acetonitrile [13]. We first substituted a variety of ionic liquids for the acetonitrile in this system. We selected 1-phenyl-cyclohexene as the ini-

tial substrate because it is a liquid at room temperature and could be thoroughly and quickly mixed in the reaction system.

A range of ionic liquids was used as co-solvent with the standard reaction conditions of 1-phenyl-cyclohexene as substrate and 5-mol% of the catalyst, $[\text{mdhqm}][\text{Tf}_2\text{N}]$ (Table 1). It is immediately apparent that no conversion to the epoxide occurred for the water immiscible ionic liquids, whereas the water miscible ionic liquids gave good conversions (entries 1 and 2). The reactions were selective to the epoxide; in no case was there any evidence of the formation of other oxidation products in the GC-MS.

For oxidation to occur the *in situ* formation of an oxaziridinium ion by nucleophilic attack of $[\text{HSO}_5]^-$ upon the iminium ion is first required (Scheme 1). It is possible that in the biphasic systems there is no phase transfer of the $[\text{HSO}_5]^-$ from


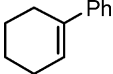
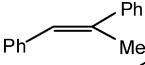

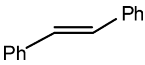
Table 1

Epoxidation of 1-phenyl-cyclohexene with $[\text{mdhqm}][\text{Tf}_2\text{N}]$ as catalyst in different co-solvent/water solvent systems

Entry	Co-solvent	Conversion (%) [TON]
1	$[\text{bmim}][\text{BF}_4]$	53 [11]
2	$[\text{bmim}][\text{OTf}]$	63 [13]
3	$[\text{bmim}][\text{SbF}_6]$	0
4	$[\text{bmim}][\text{Tf}_2\text{N}]$	Trace
5	$[\text{bmpy}][\text{Tf}_2\text{N}]$	0
6	MeCN	75 [15]

Conditions: 5 mol% catalyst, 2 equiv. OxoneTM, 4 equiv. Na_2CO_3 , solvent: H_2O 1:1, 0 °C attaining ambient temperature, reaction time 18 h. Conversion measured by GC. Only product and unreacted starting material were observed in the G.C. traces. No reaction was observed in the absence of catalyst. All results are the average of at least three runs.

Table 2
Epoxidation of alkenes catalyzed by [mdhqm][Tf₂N]

Entry	Substrate	MeCN/H ₂ O (1:1) % Conversion [TON]	[bmim][triflate]/H ₂ O (1:1) %Conversion [TON]
1		92 [19]	100 [20]
2		75 [15]	63 [13]
3 ^c		66 [13]	6 [1]
4		18 [4]	14 [3]
5		0	0

Conditions: 5 mol% catalyst, 2 equiv. OxoneTM, 4 equiv. Na₂CO₃, H₂O:solvent 1:1, 0 °C attaining ambient temperature, reaction time 18 h. Conversion measured by GC. Only product and unreacted starting material were observed in the G.C. traces. No reaction was observed in the absence of catalyst. All results are the average of at least three runs.

the aqueous phase to the ionic liquid phase, nor of the 2-methyl-3,4-dihydroisoquinolinium ion from the ionic liquid to the aqueous phase. This would lead to no oxaziridinium ion being formed and, consequently, no catalysis. An ESI–MS of a [bmpy][N(Tf)₂] ionic liquid that had been contacted, with stirring, with the aqueous OxoneTM solution overnight showed no signal for [HSO₅][−] in the ionic liquid layer, suggesting that this is indeed the case.

Lacour et al. have used TRISPHAT salts of chiral dibenzazepinium derived iminium cations in combination with 18-C-6 under biphasic conditions (dichloromethane:H₂O, 3:2) and OxoneTM for the oxidation of 1-phenyl-cyclohexene [14]. However, when we added 18-C-6 (2.5–12.5 mol%) to reactions in the aqueous/ionic liquid biphasic system we found no significant increase in conversion. Negative ion ESI–MS of a [bmpy][Tf₂N] ionic liquid containing 10 mol% of 18-C-6 that had been contacted with the OxoneTM solution overnight showed no evidence of [HSO₅][−] in the ionic liquid phase. However, the positive ion spectrum did show the presence of [K.18-C-6]⁺ in the ionic liquid layer. This is best described as a cation exchange of [bmim]⁺ from the ionic liquid for K⁺ from the aqueous layer.

Although both [bmim][BF₄] and [bmim][OTf] gave good conversions, only marginally lower than for the water/acetonitrile system, [bmim][OTf] gave the higher ones and was selected for subsequent investigations. It was found that the counter ion of the catalyst had no significant effect on the measured conversions in [bmim][OTf]. This is probably due to total fast exchange of the catalyst counter anion with the anion of the ionic liquid leading to the iminium cation being only associated with the triflate anion. This ion scrambling has been previously noted in polymerisation catalysis [15], and in our own work on the reactivity of anionic nucleophiles, where it was found that the counter cation of the nucleophile had no significant effect upon its reactivity and that cation of the ionic liquid determined its reactivity [16].

To further test the scope of the catalytic system a number of alkenes were reacted under the standard conditions. The trends

observed (Table 2) may be rationalized in terms of the reactivity and solubility of the respective alkenes. In those examples where different solubility of the alkenes was not an issue, similar reactivities were found. The considerable difference in conversion observed for the epoxidation of *trans*-α methylstilbene in the two different solvent systems is certainly a consequence of solubilities. While *trans*-α methylstilbene was partially soluble in the acetonitrile/water system it was clearly observed to be insoluble in the [bmim][OTf]/water system. *Trans*-stilbene itself was insoluble in both systems and no conversion was seen in either case.

A general rule for the epoxidation of alkenes is that the more substituted the alkene is with alkyl substituents the more reactive it will be, due to a decrease in the reaction activation barrier [17]. It has also been proposed that while both alkyl and phenyl groups stabilize the partial positive charge that develops during epoxidation, the former do so more effectively [18]. Therefore, it is expected that cyclohexene is converted more readily than 1-hexene, as is observed (Table 2, entries 1 and 4). In the case of 1-phenylcyclohexene, since it is more substituted than cyclohexene one might expect a higher conversion of 1-phenylcyclohexene to the epoxide. However, in both the acetonitrile and ionic liquid systems lower conversions were observed. This is presumably due to it being less soluble under these reaction conditions.

It has been suggested that ionic liquid may provide ideal solvents for enantioselective reactions [19]. Finally, in an attempt to perform enantioselective epoxidations, we prepared 2-isopinocampheyl-3,4-dihydroisoquinolinium tetraphenylborate and used it as a catalyst for the epoxidation of 1-phenylcyclohexene (Table 3). Page et al. had previously identified this catalyst as giving a good combination of both reactivity and selectivity [13].

While this catalyst led to good conversions, in no case were high ee's achieved in this reaction. However, use of the ionic liquid system led to much lower selectivities than found with either acetonitrile or dichloromethane co-solvents for the reaction. Page et al. found ee's of 20–40%, depending on the

Table 3

The epoxidation of 1-phenyl-cyclohexene catalyzed by *N*-isopinocampheyl-3,4-dihydroisoquinolinium tetraphenylborate

Entry	Solvent system	% Conversion [TON]	Ee %
1	CH ₂ Cl ₂ /H ₂ O 1:1	25 [5]	26
2	MeCN/H ₂ O 1:1	70 [14]	16
3	[bmim][OTf]/H ₂ O 1:1	68 [14]	6
4	[bmim][BF ₄]/H ₂ O 1:1	73 [15]	7

Conditions: 5 mol% catalyst, 2 equiv. Oxone™, 4 equiv. Na₂CO₃, H₂O:solvent 1:1, 0 °C attaining ambient temperature, reaction time 18 h. Conversion measured by GC, ee's were measured by GC with a chiral 'chrompack' capillary column. Only product and unreacted starting material were observed in the G.C. traces. No reaction was observed in the absence of catalyst. All results are the average of at least three runs.

anion (28% for [BF₄]⁻) for this substrate in a 1:1 acetonitrile/water system [13]. Their results suggested that the better selectivities could be achieved by using more hydrophobic anions ([ClO₄]⁻ < [BF₄]⁻ = [PF₆]⁻ < [BPh₄]⁻). However, for ionic liquids this would lead to biphasic systems that would have minimal reactivity (see above). Hence this was not pursued any further.

When conducting control experiments in the absence of catalyst it, an oxidation product of the 1-butyl-3-methylimidazolium cation of the ionic liquid, 1-butyl-3-methylimidazolidine-2,4,5-trione, was found to have formed. This was found to increase at higher temperatures. Inspection of the GC–MS results of reactions conducted under the standard conditions revealed only two instances with evidence for the formation of trace amounts of 1-butyl-3-methylimidazolidine-2,4,5-trione. Notably, no evidence for its formation was found when the concentration of the catalyst in the reactions was increased from 5 to 15 mol% and 50 mol%. Finally, Oxone™ (0.012 mol of [HSO₅]⁻) was added to the [bmim][BF₄] (2 cm³, 0.012 mol) ionic liquid and stirred at 75 °C for 24 h in the absence of both catalyst and alkene. The GC–MS of this product mixture showed the formation of a considerable amount of 1-butyl-3-methylimidazolidine-2,4,5-trione. This suggests that Oxone™ can act as a stoichiometric oxidant for the 1-butyl-3-methylimidazolium cation, but that this reaction is slower than the catalyzed epoxidation of the alkenes.

We have noted the formation of 1-butyl-3-methylimidazolidine-2,4,5-trione while conducting oxidation reactions previously [20]. This result suggests that imidazolium salts are unsuitable solvents for oxidation reactions and that other ionic liquids should be used. Certainly, the formation of oxidation products should be investigated whenever they are used.

3. Conclusions

A number of ionic liquids have been used as replacement co-solvents for the *N*-alkyl-3,4-dihydroisoquinolinium catalyzed epoxidation of alkenes. [bmpy]⁺ ionic liquids were preferred due to the potential for oxidation of the imidazolium based ionic liquids. The effectiveness of the reaction systems depended on the miscibilities of the various reagents with the ionic liquids. For oxidation to occur it was required that the ethane was soluble in the ionic liquid. It was also required that the Oxone™

was dissolved in the ionic liquid layer. Consequently, water miscible ionic liquids gave systems with similar reactivities to the conventional acetonitrile based systems. However, attempts to produce a aqueous/ionic liquid biphasic system that could be used to recycle the catalyst failed do to a lack of phase transfer of the [HSO₅]⁻ from the aqueous to the ionic liquid phase.

4. Experimental

Reagents were purchased from Avocado Research Chemicals Ltd., Lancaster Synthesis Ltd. and Aldrich. Solvents were freshly distilled and dried by standard procedures. Ionic liquids were prepared as previously described [20]. General procedures for the formation of the 2-alkyl-3,4-dihydroisoquinolinium salts are given below. Detailed experimental methods and analytical data for the 2-alkyl-3,4-dihydroisoquinolinium salts are given in the Supplementary data.

4.1. Preparation of 2-(2-Bromoethyl)benzaldehyde [13]

Isochroman (C₉H₁₀O, 25 g, 0.19 mol, 1.0 eq) was placed in a three neck round bottom flask (250 cm³) attached to a reflux condenser. Under a dry nitrogen atmosphere and connected to a pyridine scrubber, carbon tetrachloride (100 cm³) was added to the isochroman, with stirring, and then thoroughly chilled in an ice-bath. Over a period of 10 min bromine (30 g, 0.19 mol, 1.0 eq) was added using a dropping funnel. When the exothermic reaction had finished and the fuming ceased, the ice-bath was removed. The dark brown reaction mixture was then cautiously heated to reflux until the mixture became yellow and had stopped evolving HBr (g) (*ca.* 1.5 h). The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*, to give a yellow oil (1-bromoisochroman). HBr (48% aq, 37.5 cm³, 0.33 mol, 1.7 eq) was added to the oil to form a dark green solution, which was heated under reflux for *ca.* 20 min, by which time the solution was green/yellow. The reaction mixture was allowed to cool to room temperature and extracted with dichloromethane (4 cm × 50 cm), washed with water (2 cm × 50 cm) and dilute aqueous sodium bicarbonate (3 cm × 50 cm) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give crude 2-(2-bromoethyl)benzaldehyde *ca.* 75% pure as a brown/red oil (39.6 g, 0.14 mol).

ν_{\max} (neat)/cm⁻¹; 1695 (C=O str., vs).

¹H NMR δ_{H} (270 MHz; CDCl₃); 3.01 (2H, t, *J* 5.9 Hz (PhCH₂CH₂O-), 3.52–3.61 (4H, m, PhCH₂CH₂Br), 4.74 (2H, s, PhCH₂O-), 10.12 (1H, s, PhCHO).

m/z (EI); 133 (C₉H₉O⁺, 100%), 213 (C₉H₉BrO⁺, 27%).

4.2. General procedure for the synthesis of dihydroisoquinolinium salts from 2-(2-bromoethyl)benzaldehyde and primary amines [13]

A solution of the desired amine (1.0 eq) in ethanol (10 ml per g of amine) was added dropwise to stirred, crude 2-(2-bromoethyl)benzaldehyde (1.8 eq of crude), that had been cooled in an ice-bath. The reaction was stirred for a few hours (or overnight, depending on the amine) and then allowed to warm

to ambient temperature. A solution of the anion exchanging salt (MX, 1.1 eq), dissolved in the minimum amount of acetonitrile, was then added in one portion. After stirring for *ca.* 5 min the organic solvents were removed *in vacuo*, and the resulting solid recrystallized.

4.3. General procedure for the catalytic epoxidation of alkenes catalyzed by iminium salts [13]

Sodium carbonate (4.0 eq) was dissolved in water (12 cm³ per 1.20 g of sodium carbonate) and chilled in an ice-bath. OxoneTM (2.0 eq) was added in one portion to this vigorously stirring solution, forming a suspension. The foaming suspension was stirred for precisely 5 min upon which most of the effervescence subsided. The iminium salt (5 mol% with respect to the substrate) was added as a solution in the co-solvent to be used (7 cm³ per 100 mg of catalyst), followed by the alkene substrate (1.0 eq) also as a solution in the co-solvent (5 cm³ per 400 mg of alkene). The mixture was stirred at 0 °C until there was no further reaction as indicated by TLC. Water was added to the reaction mixture until most of the inorganic material dissolved, and extracted four times with diethyl ether. The organic fractions were washed with water and brine, and dried over sodium sulfate. The product mixture was isolated by filtration and the solvents removed *in vacuo*. The epoxide was then analyzed by GC to determine conversion.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2007.06.004.

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