Green Approaches to Catalytic Epoxidation of Olefins

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by

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Declaration

I hereby declare that the thesis summarizes my own work carried out since my registration for the Degree of Doctor of Philosophy in October, 2000, and that it has not been previously included in a thesis, dissertation or report submitted to this or any other institution for a degree, diploma or other qualification.

Tong Kit Ho

May, 2004

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Abstract

Epoxides are useful intermediates for the synthesis of a range of chemicals with a variety of commercial applications. Epoxidation of olefins is an important reaction in organic chemistry. Many studies have shown that high yield and selectivity of epoxide can be obtained efficiently by different catalyzed reaction systems. Nevertheless, most of the reported studies needed to use organic solvents and/or toxic catalyst. The work presented in this thesis aims to develop some simple, inexpensive, environmentally friendly and scalable methods for olefin epoxidation

Chapter 2 shows a chemoenzymatic approach for the *in situ* generation of hydrogen peroxide in the epoxidation of olefins. In this system, hydrogen peroxide can be simply produced by enzymatic oxidation of glucose in aqueous medium. Water-soluble olefins were oxidized with oxygen/glucose/glucose oxidase and Mn^{II}/HCO_3^- to afford excellent yields of epoxides. By using sodium dodecylsulfate (SDS), lipophilic olefins could be effectively epoxidized with similar conditions without the need for an organic co-solvent. The use of immobilized GOx was explored and it was found that chemically immobilized GOx on silica gel was stable and could be reused up to ten cycles.

Ionic liquids are considered as "green" or "clean" solvents as they are non-volatile and potentially easily recycled. In Chapter 3, a simple catalytic system, manganese sulfate/bicarbonate, was developed to epoxidize olefins with hydrogen peroxide in the room temperature ionic liquid, 1-butyl-3-methylimidazolium. The ionic liquid itself can be easily recovered and re-used.

Epoxidation of terminal olefins remains a challenging task in organic chemistry. In Chapter 4, a useful method for the epoxidation of unactivated olefins using a modified bis-phenanthroline iron dimer as catalyst in ionic liquids as the reaction medium was developed. By using this catalytic system, a wide range of terminal olefins could be simply oxidized to epoxides by peracetic acid in minutes. The ionic liquid could be easily recycled and re-used. The mechanism of the reaction was discussed.

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1.1 Green Chemistry

"Sustainable development meets the needs of the present without compromising the ability of future generations to meet their own needs."

(Brundtland Commission)

Population growth and rising living standards in industrial countries, as well as an expansion of the market economies, necessitate an increase in production and consumption. Natural resources for the production of goods are taken from the environment. Wastes and contaminants from production processes are discharged into the environment and as a result the environment is exposed to a global impact and endangered.

"Sustainability in the economic sense means the efficient allocation of scarce goods and resources. Sustainability in the environmental sense means not to exceed the limits of environmental impact and to maintain the natural basis of life. Sustainability in social sense means a maximum of equality of opportunity, social justice and freedom. All these three elements must be in equilibrium with each

other."

(Ondruschka, B., Nüchter, M., Müller U., Jungnickel, A. and Struppe, C., The 3rd Annual Green Chemistry and Enginerring Conference)

"Green Chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products"

(P. C. Anastas and J. C. Warner, "Green Chemistry Theory and Practice", Oxford University Press (1998))

In the area of chemical research and manufacturing, there has been a growing movement towards the practice of "Green chemistry". The term green chemistry was first coined by Paul Anastas who formulated a number of principles which are considered the basic tenets of green chemistry. [1] The twelve principles are:

1. *Prevention*- It is better to prevent waste than to treat or clean up waste after it has

been created.

2. *Atom economy-* Synthetic methods should be designed to maximize the incorporation of all materials used into the final product.
3. *Less hazardous chemical synthesis-* Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.
4. *Designing safer chemicals-* Chemical products should be designed to effect their desired function while minimizing their toxicity.
5. *Safer solvents and auxiliaries-* The use of auxiliary substances (*e.g.*, solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.
6. *Design for energy efficiency-* Energy requirements of chemical processes should be recognized for their environment and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. *Use of renewable feedstocks-* A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable
8. *Reduce derivatives-* Unnecessary derivatization (use of blocking groups, protection/de-protection process) should be minimized or avoided if possible,

because such steps require additional reagents and can generate waste.

9. *Catalysis*- Catalytic reagents (selective as possible) are superior to stoichiometric reagents.
10. *Design for degradation*- Chemical products should be designed so that at the end of their function they break down into innocuous degradation products which do not persist in the environment.
11. *Real-time analysis for pollution prevention*- Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. *Inherently safer chemistry for accident prevention*- Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.

Besides, environmental disasters have often resulted in new and specific laws being enacted. In the 1980s, as the nature of the impact of chlorofluorocarbons (CFCs) on the stratospheric ozone layer became clearer through the use of satellite photographs. In addition, through the work of Nobel laureate chemists Rowland and Molina, the Montreal Protocol which first called for CFCs to be phased out, was adopted. In 2001, the Stockholm Convention was signed by more than 100 countries. It is a global treaty to protect human health and the environment from persistent organic pollutants (POPs). POPs are chemicals that remain intact in the environment for long periods, becoming widely distributed geographically, accumulating in the fatty tissue of living organisms and are toxic to humans and wildlife. POPs circulate globally and can cause damage wherever they travel. In implementing the Stockholm Convention, Governments will take measures to eliminate or reduce the release of POPs into the environment.

Hong Kong is an international city, and the Government attempted to implement pollutant prevention schemes and environmental protection. For example, enforcing environmental legislation; monitoring environmental quality; providing collection, transfer, treatment and disposal facilities for many types of waste; advising on the environmental implications of town planning and new policies; handling pollution complaints and incidents; and raising awareness and support in the community for environmental initiatives.

One of the active areas of chemical research in Hong Kong is to develop new chemistry involving the use of environmentally benign solvents, catalysis and synthetic methodologies. This may be viewed as the first step towards creating a framework for a win-win situation in which economic growth goes hand in hand with environmental protection.

The use of benign solvents is of vital importance to the development of green chemistry. The use of organic solvents in industry or research is widespread and, although, they play a valuable 'enabling' role, they are responsible for significant amounts of pollution. For example, in Hong Kong alone, there were about 2702 tonnes of halogenated, non-halogenated and flammable solvents collected by the Chemical Waste Treatment Center in 2002. Many organic solvents are also toxic, needing the use of personal protective equipment. In order to replace these solvents in chemical processes, the solution is to use no solvent or an environmentally benign solvent, for example water, supercritical carbon dioxide or an ionic liquid.

Industrially, waste minimization is very important. For economic and environmental reasons, reactions should be designed to be atom efficient, *i.e.* as many of the reacting atoms as possible should end up in the final products.[2] In the example shown in Figure 1.1, the atom efficiency of the reaction is defined as the ratio of the molecular weights of desired product to the sum of the molecular weights of all materials produced in the process. In the above example the atom efficiency would be 44.6%

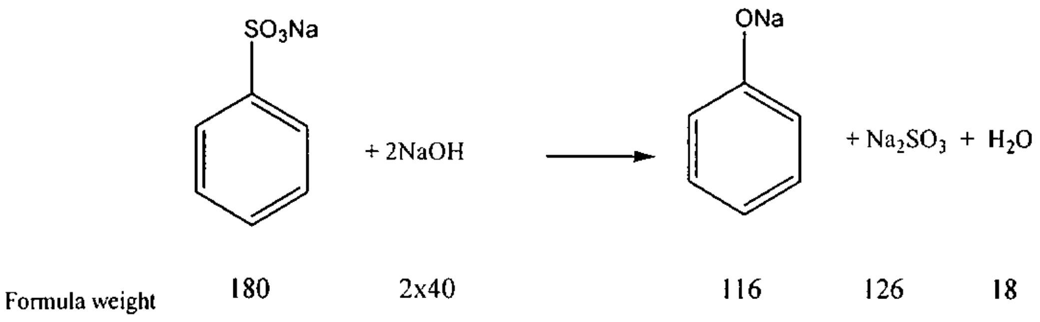


Figure 1.1 Benzenesulfonate route to phenol.

Catalysts play a ‘vital’ role, not only in shortening the reaction time, but also in improving the selectivity of the reaction, *i.e.* more useful products are generated. Therefore, the cost and pollution can be reduced. Today it is estimated that 90% of the chemicals used have, at some stage in their manufacture, come into contact with a catalyst.[3] The range is truly broad from bulk chemicals such as acetic acid and ammonia to consumer products such as detergents and vitamins. Virtually all major bulk chemical and refining processes employ catalysts.

Investigation of new synthetic methodologies is also needed for our future industry. Thus, more efforts should be placed on studying some new, efficient and green reactions. The potential benefits of successfully ‘greening the chemical industry’ are enormous and of benefit to all society and future generations.

1.2 Epoxides

The oxirane functional group is a strained three membered ring containing an oxygen atom. It is an essential component of many industrial products and processes and is a common functional group introduced during the metabolism of many compounds.[4]

The more commonly recognized name of epoxide is formed by adding ‘oxide’ to the name of the olefin that is oxidized. For example, epoxidation of ethylene proceeds to give ethylene oxide as the product. Epoxides are much more reactive than common dialkyl ethers because of the large strain energy (about 25 kcal/mol, *i.e.* 105 kJ/mol) associated with the three membered ring. The resulting strain on the bonds activates the carbon-oxygen bond, allowing the epoxide to undergo a variety of ring opening reactions (Figure 1.2).

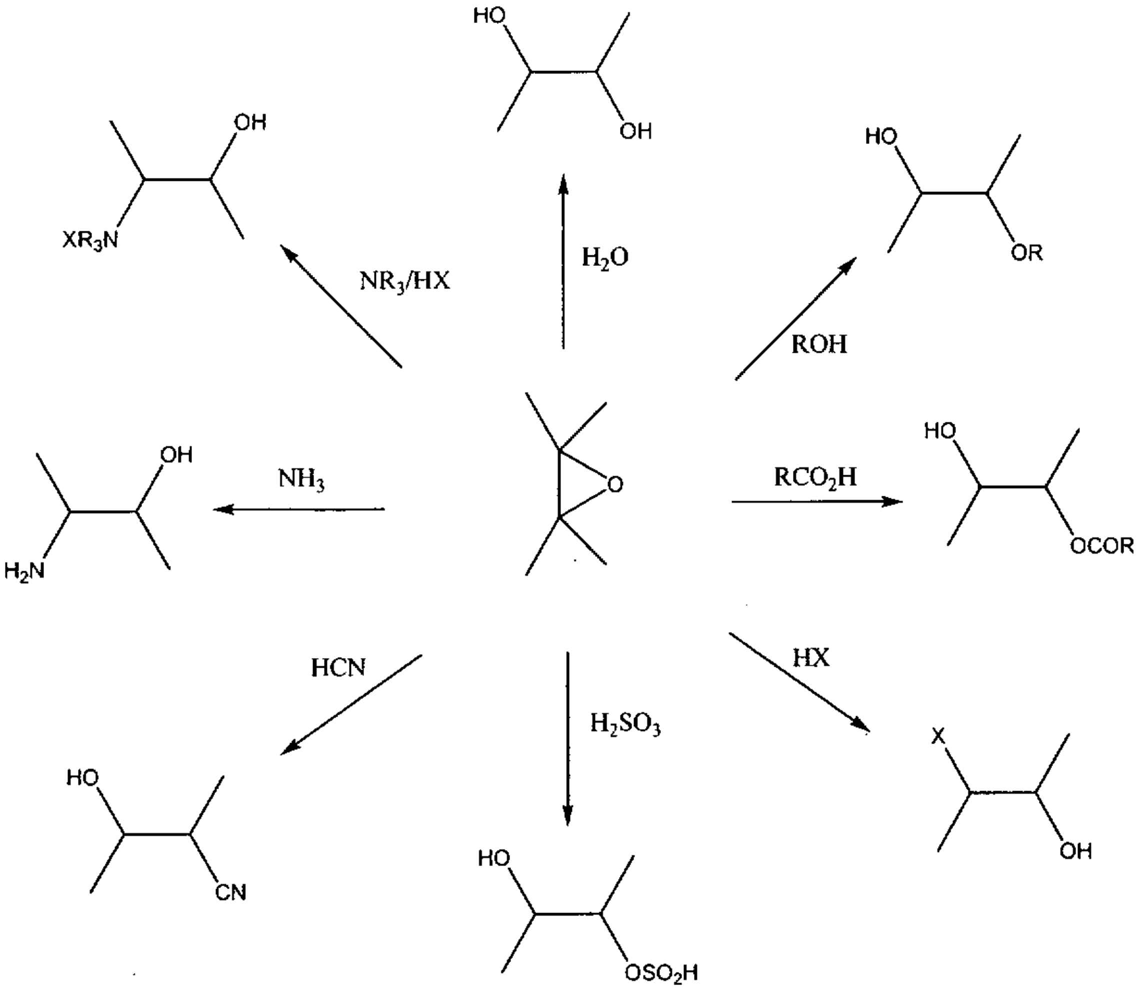
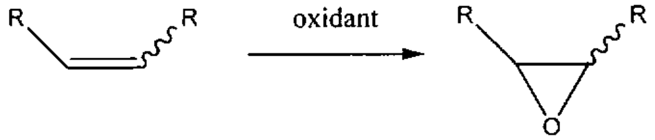
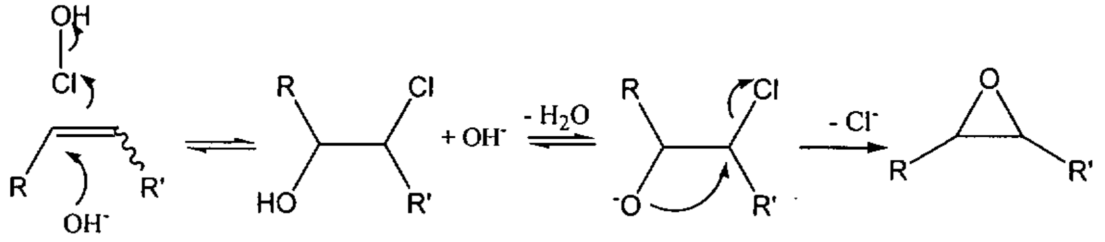


Figure 1.2 Ring opening reactions of epoxides.

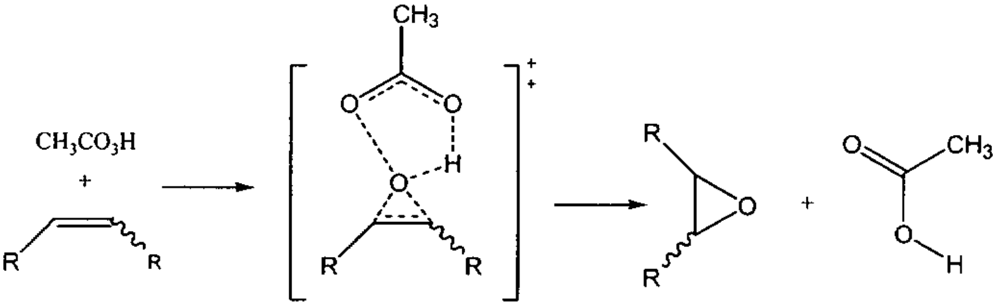


Scheme 1.1

Epoxidation (Scheme 1.1) is the conversion of an olefin to an epoxide through oxidation of the double bond. Commonly this oxidation is carried out by reagents such as halogen with alkali hydroxide, *i.e.* hypochlorous acid (Scheme 1.2), hydrogen peroxide, peracids (Scheme 1.3), or molecular oxygen. Epoxides find applications as detergents, paints, soaps, additives to lubricating oils, textiles and cosmetics (Table 1.1). One of the main commercial uses of epoxides is in the manufacture of epoxy resins. These high-strength polymers are created by the reaction of less-rigid, one-dimensional polymers with epoxides to produce a much more rigid three-dimensional polymer (Scheme 1.4).[4]



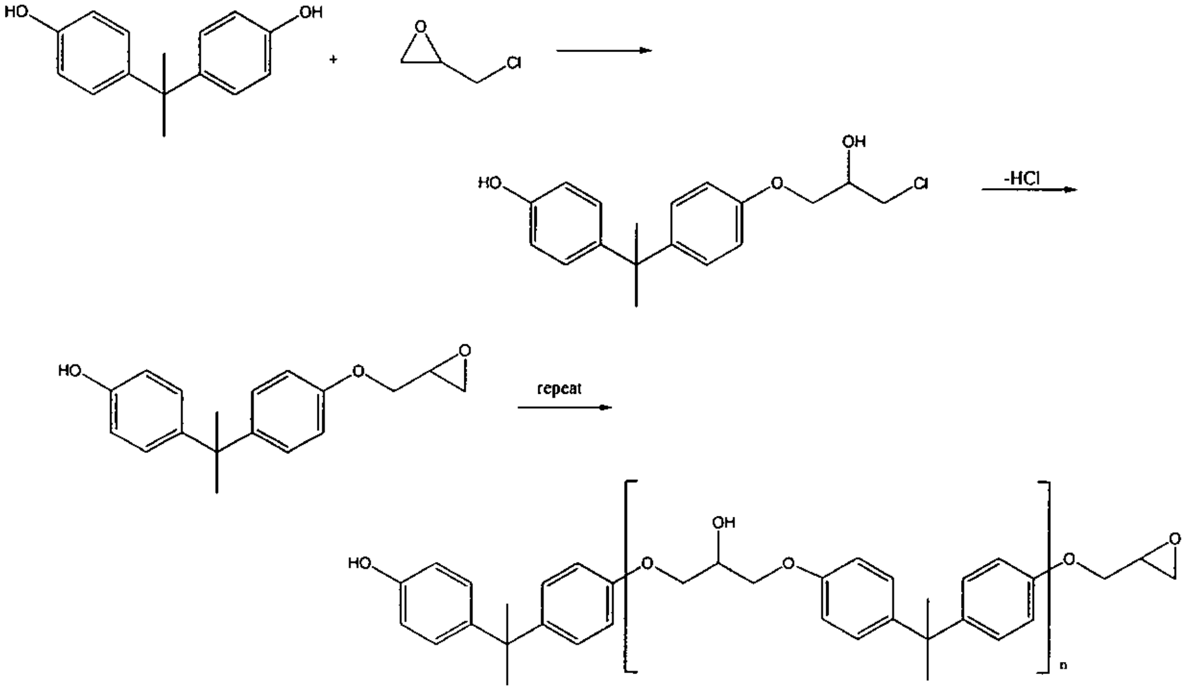
Scheme 1.2



Scheme 1.3

Epoxide	**Applications**
Ethylene oxide	Disinfectant and sterilizer
Ethylene oxide	Cosmetics, lubricants, paints
Styrene oxide	Epoxy resins
Epichlorohydrin	Epoxy resins
1-Octene oxide	Soap
1-decene oxide	Cosmetics

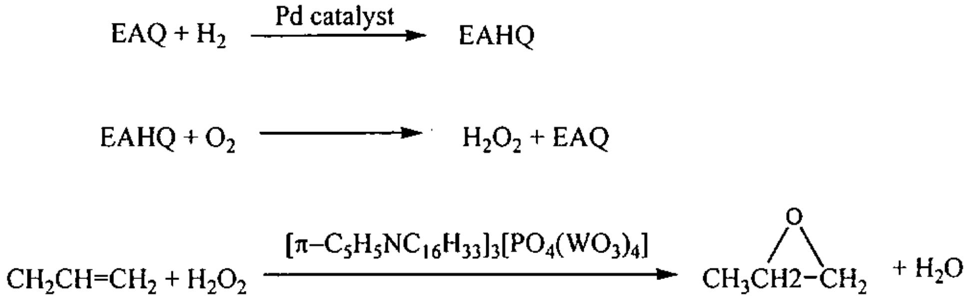
Table 1.1 Applications of epoxides



Scheme 1.4 Preparation of bisphenol A based epoxy resins

Due to the wide commercial applicability of epoxides in general, olefin epoxidation is an important industrial reaction. Industrially, ethylene oxide is produced by direct oxidation of ethylene with air or oxygen using silver salt as catalyst. However, this system is not suitable for the production of epoxides from olefins with allylic hydrogen atoms (e.g. propene) as further oxidation (oxidized to aldehyde and then acid) is the prevailing reaction. Thus, another widely used epoxide, propylene oxide, is produced by the chlorine/alkaline process. This process is carried out in two main steps: synthesis of propylene chlorohydrin, and subsequent dehydrochlorination of propylene chlorohydrin to afford propylene oxide. Since chlorine in aqueous solution, as well as the hydrochloric acid by-product, are corrosive, the construction materials must be selected very carefully. The reactor and all related piping need to be made of corrosion-resistant materials. Besides, the brine effluents from the propylene oxide plants contain several kinds of pollutants, such as total organic carbon, adsorbable organic halides and excess alkaline wastewater. Therefore, a waste treatment system is needed to remove the pollutants.[4] To circumvent these problems, a simple and green system for the epoxidation of propylene has recently been developed.[5] The system coupled the catalytic epoxidation of propylene with hydrogen peroxide (H_2O_2) to the 2-ethylanthraquinone (EAQ)/2-ethylanthrahydroquinone (EAHQ) redox process for H_2O_2 production. Thus, oxygen can be used for epoxidation of propylene (Scheme

1.5).



$$EAQ + H_2 \xrightarrow{\text{Pd catalyst}} EAHQ$$

$$EAHQ + O_2 \longrightarrow H_2O_2 + EAQ$$

$$CH_2CH{=}CH_2 + H_2O_2 \xrightarrow{[\pi{-}C_5H_5NC_{16}H_{33}]_3[PO_4(WO_3)_4]} CH_3CH2{-}CH_2 + H_2O$$

Scheme 1.5

Hydrogen peroxide and peracetic acid are two other common oxidants used in the epoxidation of olefins. Many different catalytic systems for the epoxidation of olefins with peracids and hydrogen peroxide have been described which utilize metals such as tungsten, manganese, rhenium and iron.[6-9] These systems are simple and inexpensive and can be applied for the production of epoxides on both a laboratory and an industrial scale.

1.3 Epoxidation of Olefins with Hydrogen Peroxide

Hydrogen peroxide is a high oxygen content, environmentally friendly oxidant as water is the only by-product created in the oxidation. Hydrogen peroxide is a chemical that is becoming increasingly fashionable as an oxidant both in industry and in academia, and whose production is expected to increase significantly in the next few years. Figure 1.3 shows the trend in publications in this field. This growth in popularity is largely due to the fact that at the present time the environmental impact of many chemical processes is under severe scrutiny and chemical companies are facing increasing restrictions to reduce environmental pollution. From this point of view hydrogen peroxide is unique as an oxidant as its by-product is water. However, reactions of hydrogen peroxide are often slow and non-selective (due to free-radical side reactions) and a catalyst is therefore needed to activate the epoxidation and make it more selective.

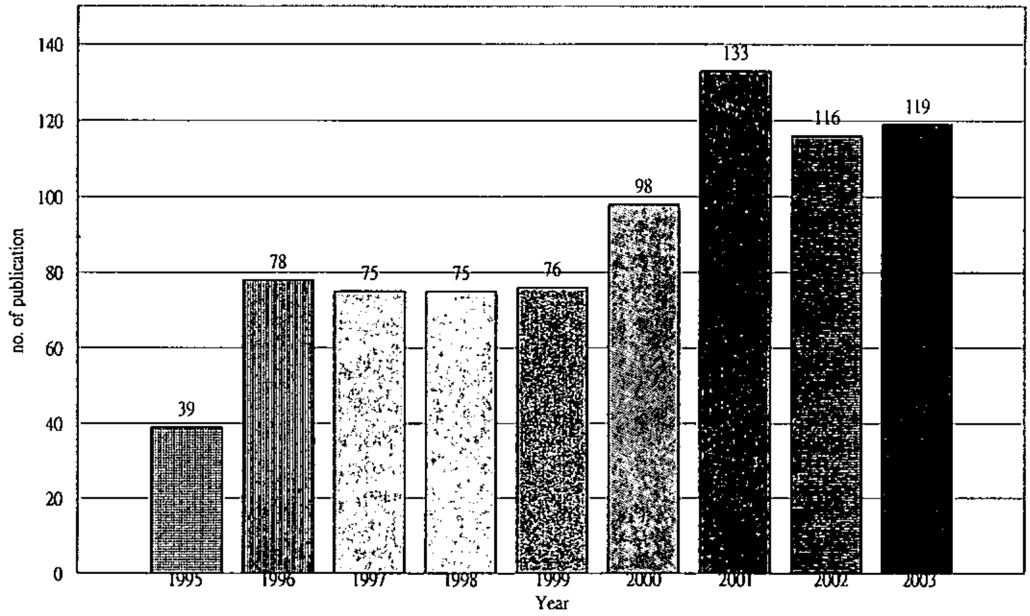
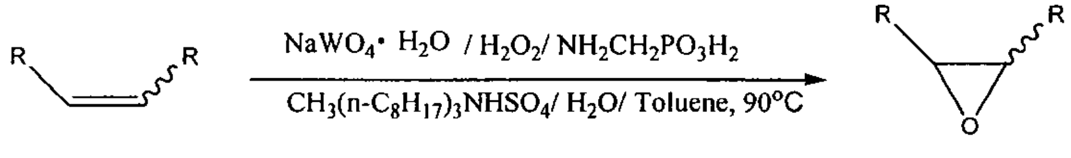
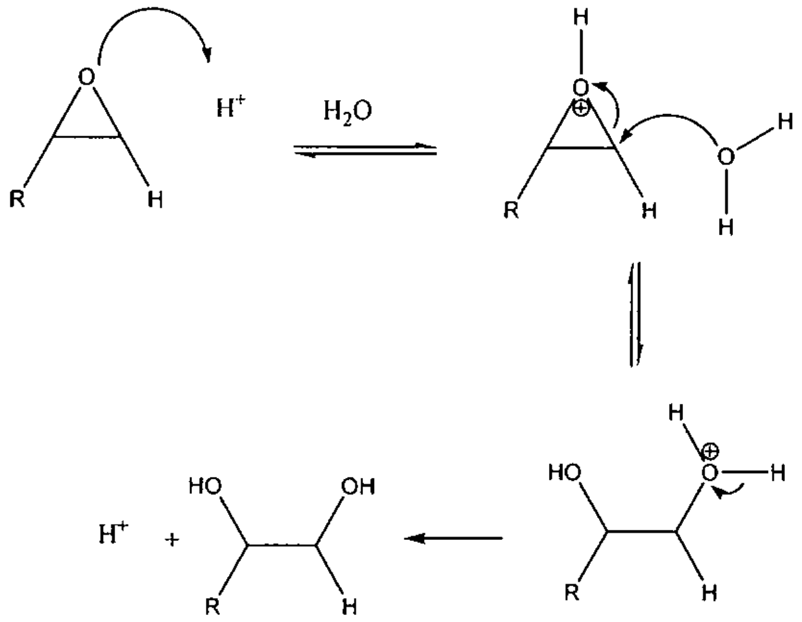


Figure 1.3 Publication of papers on oxidation and hydrogen peroxide (from Scifinder Scholar).

An efficient transition metal catalyzed epoxidation system using aqueous hydrogen peroxide as the oxidant was described by Venturello, who employed a tungstate catalyst under phase transfer conditions.[10] However, chlorinated solvents are normally required in order to obtain high reaction rates and yields of epoxides. An improved catalytic system, developed by Noyori and co-workers,[9] used sodium tungstate dihydrate, amino-methylphosphonic acid and a quaternary ammonium hydrogen sulfate with 30% hydrogen peroxide in toluene (Scheme 1.6). The presence of the lipophilic quaternary ammonium hydrogen sulfate as a phase transfer catalyst significantly enhanced the yield of epoxide. This catalytic system was found to be effective for the epoxidation of terminal and cyclic olefins, but failed to produce acid sensitive epoxides due to their hydrolytic cleavage under the acidic conditions (Scheme 1.7).

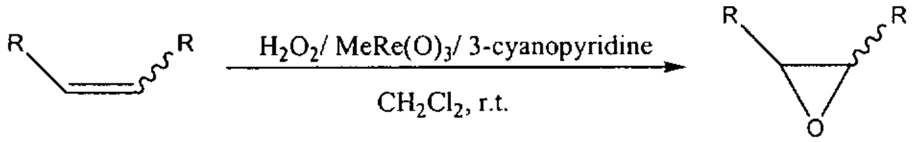


Scheme 1.6



Scheme 1.7

Methyltrioxorhenium (MTO) is an active catalyst for the epoxidation of olefins using hydrogen peroxide as an oxidant. Initially, anhydrous hydrogen peroxide in *tert*-butanol was used as the oxidant but low selectivities were reported for acid sensitive epoxides due to the high acidity of the MTO-H_2O_2 system.[11] The addition of a base, such as pyridine,[12] in large excess relative to MTO (>10:1) enhances the rate and selectivity of the epoxidation of di-, tri-, and tetra-substituted olefins, as it protects the epoxide from ring opening (Scheme 1.8). Although MTO is a very active epoxidation catalyst, it is difficult, hazardous and environmentally unfriendly to prepare. In particular, the presence of organotin reagents[13] in the preparation of MTO makes it an unattractive option as an industrial catalyst for epoxidation reactions.



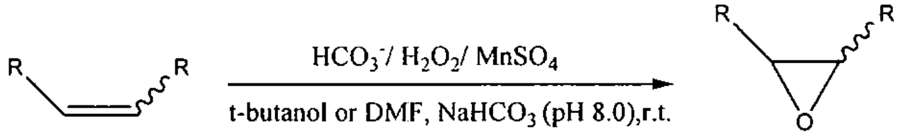
Scheme 1.8

An alternative, mild and low environmental impact oxidation method has recently been developed by Richardson and co-workers.[14,15] It was found that the peroxymonocarbonate, HCO_4^-, formed by the reaction of hydrogen peroxide and bicarbonate can be used as an active oxidant (Scheme 1.9) to epoxidize the olefins in aqueous or co-solvent (acetonitrile) medium. However, the rate of epoxidation in metal-free system is slow and the yield of the epoxide is moderate.

$$H_2O_2 + HCO_3^- \rightleftharpoons H_2O + HCO_4^-$$

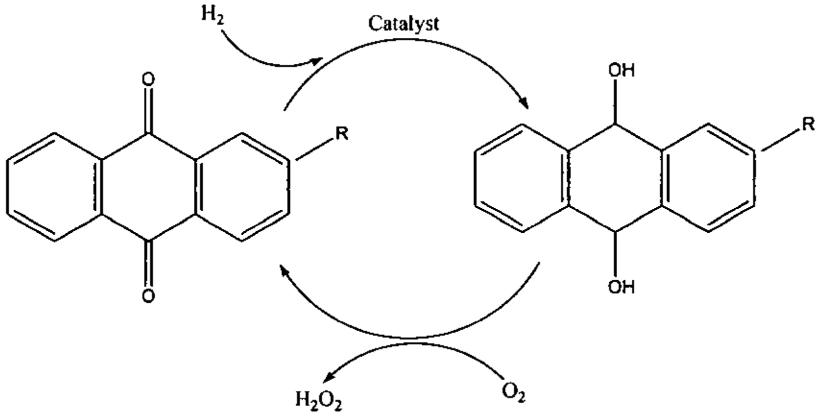
Scheme 1.9

More recently, an improved catalytic epoxidation system has been reported by Burgess and co-workers.[6,16] The system described uses simple manganese salts, such as manganese sulfate, to catalyze the epoxidation of a range of disubstitued olefins in good yield using a hydrogen peroxide bicarbonate buffer solution. Peroxymonocarbonate is formed *in situ* and combines with manganese to give the active intermediate, reducing the reactions times (Scheme 1.10). However, the method suffers from the use of *tert*-butanol or DMF as a solvent.



Scheme 1.10

As the concern over worldwide pollution increases, there is a strong need for the development of new epoxidation methods which employ safer oxidants and solvents and produce less waste. Hydrogen peroxide, as a green oxidant, may play a very important role in the future oxidation industry. Currently, it is produced commercially by the anthraquinone (AQ) process (Scheme 1.11)



Scheme 1.11

However, this process itself can hardly be considered to be 'green'. It involves the sequential hydrogenation and oxidation of an alkyl-anthraquinone dissolved in a mixture of organic solvents (usually a mixture of an aromatic hydrocarbon and a polar organic compound),[17] followed by liquid-liquid extraction in the recovery of product.[18] Each process cycle requires replacement of solvents and anthraquinone. Aromatic hydrocarbon solvents are generally to be avoided because they contribute to volatile organic contaminants (VOC) and are potentially toxic. Another concern in the use of hydrogen peroxide is the danger of transportation because of the hazardous nature of neat hydrogen peroxide. It is usually handled as a 30% aqueous solution, adding to the bulk and weight of transportation. Methods for the alternative production of hydrogen peroxide are being actively explored. These include the use of membrane catalysts,[19] liquid carbon dioxide as the solvent in the AQ process[20] and electrochemical reduction of oxygen.[21-23]

One way to circumvent the commercial production and transportation of hydrogen peroxide is to use microbial/enzymatic generation. In theory, such a method could be employed for the epoxidation of olefins. Microbial epoxidation of olefins has been reported previously, but the yields of epoxides tended to be low, and were often accompanied by hydrolysis side products.[24] The use of peroxidases and hydrogen peroxide for the epoxidation of olefins has also been reported, but suffers from the easy degradation of the peroxidases.[25] More recently, the combined co-immobilization of glucose oxidase and peroxidases has been explored to alleviate the operational instability of the peroxidases.[26] A general problem in using purely enzymatic system is the limitation of substrate specificity and product inhibition of the enzymes.

1.4 Epoxidaiton of Olefins with Peracetic Acid

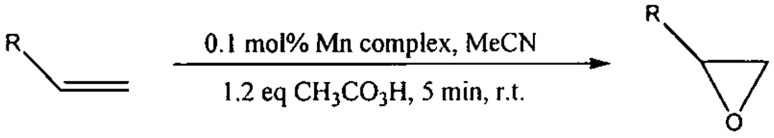
Uncatalyzed epoxidation of olefins with peroxycarboxylic acids is a fundamental reaction in organic chemistry. Compounds with an isolated double bond that cannot be oxidized with hydroperoxides or hydrogen peroxide in the absence of a catalyst are epoxidized smoothly and sterospecifically by peroxycarboxylic acids. Cyclic ketones, such as cyclohexanone, are converted to lactones; the production of ε -caprolactone, an important intermediate for the production of polyesters and polyurethanes, is carried out on a large scale by this method. Peracetic acid is a simple and inexpensive commercial oxidant. Generally, it is produced by the reaction of acetic acid, hydrogen peroxide and catalytic amount of sulfuric or phosphoric acid (Scheme 1.12).

$$RCO_2H \quad + \quad H_2O_2 \quad \xrightleftharpoons{H^+} \quad RCO_3H \quad + \quad H_2O$$

Scheme 1.12

Peracetic acid is capable of epoxidizing electron-deficient terminal olefins, albeit at elevated reaction temperatures (>60 °C) and with extended reaction times. Such conditions significantly reduce the selectivity of the reaction as the epoxide-ring can be opened easily (e.g. hydroxylation). Metal-catalyzed variants of this reaction can circumvent such limitations by enhancing the reaction rates and lowering the reaction temperatures.

One such method for the efficient epoxidation of electron-deficient olefins was developed by Stack and co-workers.[27] In this study, a highly selective and efficient cationic manganese complex, $[\mathrm{Mn}^{\mathrm{II}}\text{-(R,R-mcp)}]^{2+}$, was employed that can rapidly (<5 min) epoxidize a wide range of olefins at room temperature with low catalyst loadings using 1.2 equiv of commercially available peracetic acid (Scheme 1.13).



Scheme 1.13

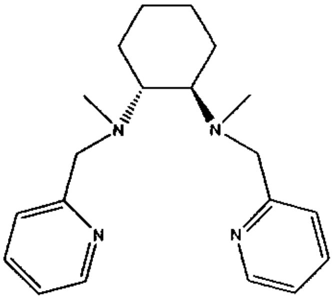
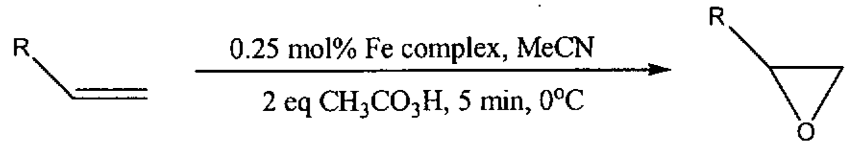


Figure 1.4 R,R-mcp:

N,N'-dimethyl-N,N'-bis(2-pyridylmethyl)cyclohexane-1R,2R-diamine

In the same year, Stack reported another metal-catalyzed system for the epoxidation of terminal olefins.[7] This system utilizes a ferric phenanthroline catalyst that is prepared *in situ*. The ferric species prefer to dimerize in the presence of water, leading to a ferric μ-oxo dimer such as $[((phen)_2(H_2O)Fe^{III})_2(\mu\text{-}O)](ClO_4)_4$. This catalytic species can efficiently epoxidize terminal and trans olefins within 5 min using peracetic acid as the oxidant (Scheme 1.14).



Scheme 1.14

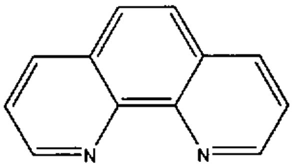
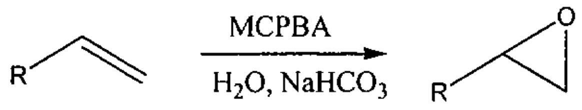


Figure 1.5 Phenanthroline

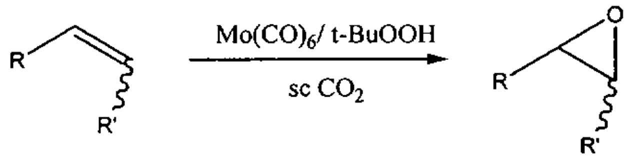
Both the two epoxidation systems described are very effective in achieving their aims. The catalyst loading is low, the amount of peracetic acid is small and a wide range of electron-deficient olefins can be epoxidized in a short time. However, such systems still require the use of organic solvents, which defeats the aim of reducing the environmental burden of volatile organic contaminants. An alternative solvent which is relatively non-toxic, environmentally-friendly and recyclable should be used.

Savelli has found that epoxidation of olefins with m-chloroperoxybenzoic acid (MCPBA) in water at room temperature gives epoxides in high yields (Scheme 1.15),[28] however the reaction is very slow for the epoxidation of terminal olefins.



Scheme 1.15

Supercritical carbon dioxide (sc CO_2) is also a suitable solvent for epoxidation of olefins. Hass has shown that molybdenum hexacarbonyl ($Mo(CO)_6$) can act as catalyst and soluble in sc CO_2, olefins are easily oxidized to epoxides by using tert-butyl hydroperoxide (Scheme 1.16).[29]



Scheme 1.16

1.5 Ionic Liquids

"Ionic liquids? Neoteric solvents? Molten salts for clean technology and catalysis?

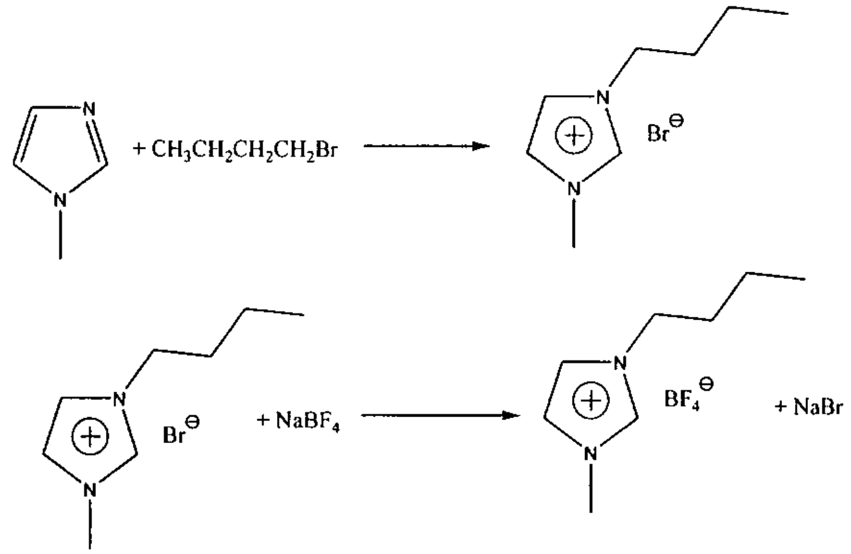
Are you serious?? Well, yes, I am serious......"

(Seddon, K. R., "Molten Salt Forum", Trans Tech, (1998).)

The chemical industry is under considerable pressure to replace many of the volatile organic compounds that are currently used as solvents in organic synthesis. The toxic and/or hazardous properties of many solvents, notably chlorinated hydrocarbons, combined with serious environmental issues, such as atmospheric emissions and contamination of aqueous effluents is making their use prohibitive. This is an important driving force in the quest for novel reaction media. Also, the current emphasis on novel reaction media is also motivated by the need for efficient methods for recycling homogeneous catalysts. Therefore, the use of ionic liquids as novel reaction media may offer a convenient solution to both the solvent emission and the catalyst recycling problem.

Ionic liquids are liquids that are composed entirely of ions. Molten sodium chloride, for example, is an ionic liquid whereas a solution of sodium chloride in water is an ionic solution. The term molten salts, which was previously used to describe such materials, evokes an image of high-temperature, viscous and highly corrosive media. The term ionic liquid, in contrast, implies a material that is fluid at, or close to, ambient temperature, has a low viscosity and is easily handled, such that it is a material with attractive properties for a solvent. Room temperature ionic liquids are generally salts of organic cations, e.g. N-alkylpyridinium and 1,3-dialkylimidazolium cations and organic or inorganic anions, e.g. bromide, tetrafluoroborate and trifluoromethanesulfonyl anions (Figure 1.6).

Ionic liquid can be prepared by direct quaternization of the appropriate amine or phosphine, most commonly with a haloalkane and different anions can subsequently be introduced by anion exchange (Scheme 1.17). The hydrophilicity/lipophilicity of an ionic liquid can also be modified by a suitable choice of anion, e.g. 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) is completely miscible with water while the PF_6 salt is largely immiscible with water. The lipophilicity of dialkylimidazolium salts, or other ionic liquids, can also be increased by increasing the chain length of the alkyl groups.[30-33]



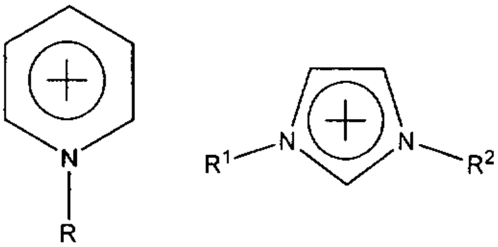
Scheme 1.17

Organic reactions in ionic liquids is an exciting and burgeoning area of research which holds considerable potential for industrial application (Figure 1.7). Numerous catalytic reactions, including biocatalytic reactions, have been carried out in ionic liquid. For example, Sheldon has shown that the *Candida antaractica* Lipase can catalyze alcoholysis and perhydrolysis reactions using ionic liquids as reaction media.[34,35]

Reaction rates in ionic liquids have been found to be generally comparable with, or better than, those observed in organic media. Epoxidation reactions in ionic liquids have also been explored. Owens has reported[36] that olefins can be epoxidized by methyltroxorhenium (MTO)/urea hydrogen peroxide in an ambient-temperature ionic liquid (Scheme 1.18a). Besides, Maietti has found that sodium hydroxide can catalyze the oxidation of electrophilic olefins with hydrogen peroxide in ionic liquids (Scheme 1.18b).[37] Srinivas has shown that water-soluble iron(III) porphyrins are also a good catalysts in the epoxidation of olefins with hydrogen peroxide in ionic liquid (Scheme 1.18c).[38] In this report, catalyst and ionic liquid can also be recycled efficiently.

Although many ionic liquids have important industrial and commercial applications [31] (*i.e.* as surfactants, phase transfer catalysts, and electrolytes), the environmental fate and any potential toxicity issue for most ionic liquids are still not known. Rogers has mentioned that 1-butyl-3-methylimidazolium hexafluorophosphate, one of the most widely used of ionic liquids, can decompose under the conditions used for its preparation, to give the fluoride hydrate[39,40]. The decomposition reaction is thus likely to lead to the toxic product HF, as well as to the potential for release of HF during acidic reactions. Besides, as potential full-scale commercial applications of ionic liquids come to fruition, their ultimate disposal has to be considered. From this perspective, environmentally acceptable disposal of ionic liquids requires that they contain only elements and functionalities that can be rendered benign either by biodegradation or by incineration.

Cations:



Anions: BF_4^-, $CF_3SO_3^-$

Figure 1.6 Cations and anions of ionic liquid.

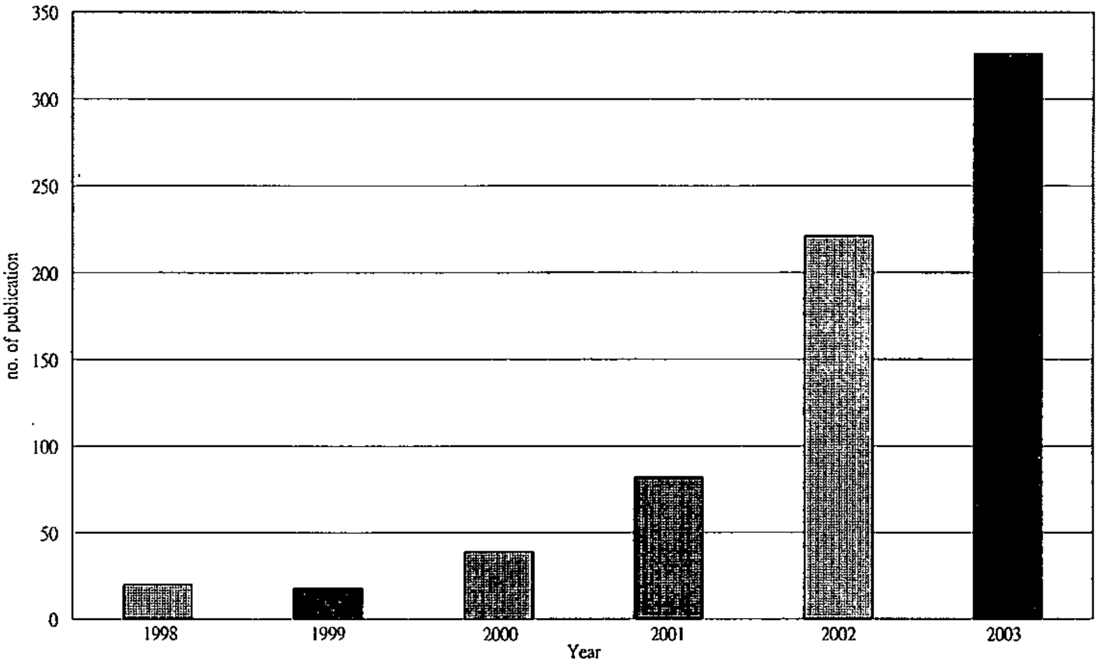
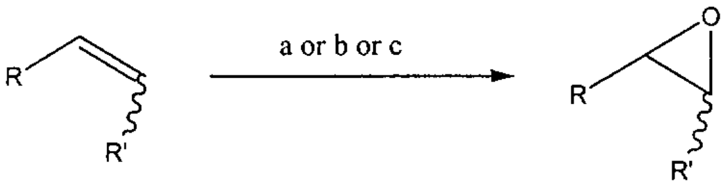


Figure 1.7 Publication of papers on ionic liquids (from Scifinder Scholar)



a= MTO/ urea-H_2O_2/ [emim][BF_4]
b=NaOH/ H_2O_2/ [bmim]PF_6] or [bmim][BF_4]
c=Iron(III) porphyrins/ H_2O_2/ [bmim][Br]

Scheme 1.18

In the majority of cases studied, the ionic liquid containing the catalyst could be readily recycled.[38,41] Therefore, ionic liquids provide a medium for performing clean reactions with minimum waste generation. As was remarked by Seddon[42] they could, quite literally, revolutionize the methodology of synthetic organic chemistry.

1.6 Aims of this Project

From the discussion summarized in the preceding sections, it can be seen that epoxides are useful intermediates for the synthesis of a range of chemicals with a variety of commercial applications. It therefore follows that epoxidation of olefins is an important reaction. Many investigations have found that high yield and selectivity of epoxide can be produced in a short time by different catalyzed reaction system.

However, most of reported studies needed to use organic solvents and/or toxic catalysts and therefore the development of environmentally friendly, inexpensive, simple and scalable methods for olefin epoxidation is highly desirable.

Whilst hydrogen peroxide is considered to be a green oxidant, the process of generation of hydrogen peroxide can be considered to be environmentally unfriendly. For example, anthraquinone (AQ) process is a method to generate hydrogen peroxide. However, it is a non-green one as this process needs to use organic solvents, such as. Benzene and trimethyl benzene. Methods for the alternative production of hydrogen peroxide are being actively explored. These include the use of membrane catalysts,[19] and electrochemical reduction of oxygen.[21-23] In our studies, we have probed an alternative method for the generation of hydrogen peroxide by using glucose and glucose oxidase combined with the system described by Burgess[16] to develop a chemoenzymatic approach to the epoxidation of olefins in aqueous media (Chapter 2).

In the case of manganese/bicarbonate-catalyzed epoxidation of lipophilic olefins,[16,43] both manganese and bicarbonate salts are inexpensive and relatively non-toxic. A common drawback is the fact that volatile organic solvents, such as acetonitrile, are required as reaction media. In section 1.5, reference was made to the advantages of using ionic liquids as reaction media in organic reactions. We have aimed to use ionic liquid as the only solvent and manganese and bicarbonate salts as catalysts to develop a simple, green and effective catalytic epoxidation system (Chapter 3).

The selective catalytic epoxidation of terminal and electron-deficient olefins remains a challenging task.[6] Recently, metal-catalyzed epoxidation of such olefins in ionic liquids have been reported.[36,38] However, these methods all suffer from certain limitations such as: the use of copious quantities of organic co-solvents or environmentally unfriendly synthesis of the catalyst. In this part, we have aimed to develop an effective terminal olefins epoxidation system in ionic liquids using a simple iron complex (Chapter 4).

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Chapter 2: A Green Chemoenzymatic Approach to the Epoxidation of Olefins in Aqueous Media

2.1 Introduction

2.2 Preliminary studies

2.3 The Epoxidation of Olefins by the Chemoenzymatic System

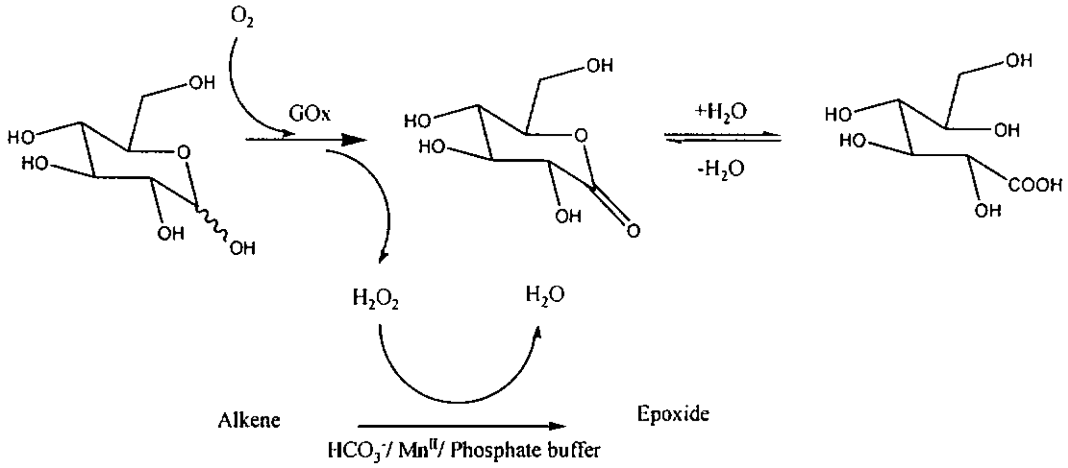
2.4 The Epoxidation of Olefins by the Chemoenzymatic System using Immobilized Enzyme

2.5 Conclusion

2.1 Introduction

Recently, the manganese/carbonate-catalyzed epoxidation of olefins with hydrogen peroxide has been investigated and found to be a facile and scalable process.[1,2] Some possible limitations of the manganese/carbonate-catalyzed reaction are that the hydrogen peroxide solution must be added slowly (1.2-4.1 mL/h) to the reaction *via* a syringe pump in order to obtain synthetically useful yields of epoxides and that organic co-solvents are required for the epoxidation of lipophilic olefins.[1,2]

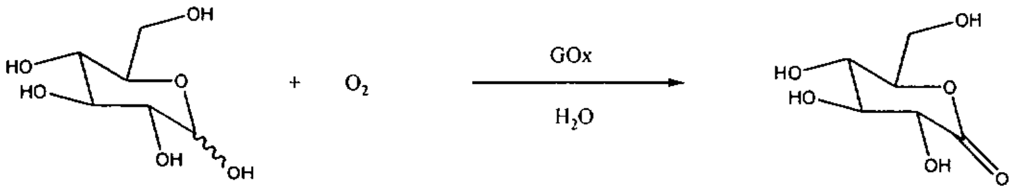
As mentioned in Chapter 1, hydrogen peroxide is a high oxygen content, environmentally friendly oxidant as water is the only by-product created in the oxidation. However, the anthraquinone (AQ) process for the production of hydrogen peroxide involves organic solvents and it can hardly be considered to be green. One way to circumvent the commercial production and transportation of hydrogen peroxide is to use microbial/enzymatic generation. In this chapter, we attempt to combine the enzymatic production of hydrogen peroxide by glucose oxidase with the epoxidation of olefins in aqueous medium to design a chemoenzymatic approach for olefins epoxidation. The olefins can be oxidized by hydrogen peroxide generated by glucose oxidase (GOx) in phosphate buffer with sodium hydrogen carbonate and manganese (II) sulfate as catalysts. (Scheme 2.1)



Scheme 2.1

2.2 Preliminary studies

Glucose oxidase (GOx, EC: 1.1.3.4) is a flavoenzyme which catalyzes the oxidation reaction between β-D-gluconolactone and hydrogen peroxide (Scheme 2.2).



Scheme 2.2

GOx is readily available from commercial sources owing to its wide application in food industry and in biosensors for the detection of glucose. In most preparations of GOx, catalase, which catalyzes the decomposition of hydrogen peroxide, is also present in low concentration and therefore is not suitable for the generation of hydrogen peroxide. Recently, a catalase-free preparation of GOx with high activity (>300 unit/mg) has become available and is therefore now suitable for use in hydrogen peroxide generation involving glucose as the substrate. Because glucose is likely to be present in excess in the enzymatic generation of hydrogen peroxide, the potential effect of glucose on the chemical catalytic system for epoxidation was first examined. Using the sodium salt of 4-styrenesulfonic acid (**1a**) as the olefin and sodium bicarbonate (1 M) as the catalyst in a pH 7.0 buffer solution, hydrogen peroxide (0.15 M) epoxidation of the olefin was examined as a function of glucose concentration. It was found that glucose did not retard the bicarbonate catalyzed epoxidation reaction (Figure 2.1) at a concentration of 0.1 M and 0.2 M. However, when the concentration of glucose was increased to 0.3 M or higher, the retardation effect became significant. This suggests that a reasonable concentration of glucose should not exceed 0.2 M for the chemoenzymatic epoxidation.

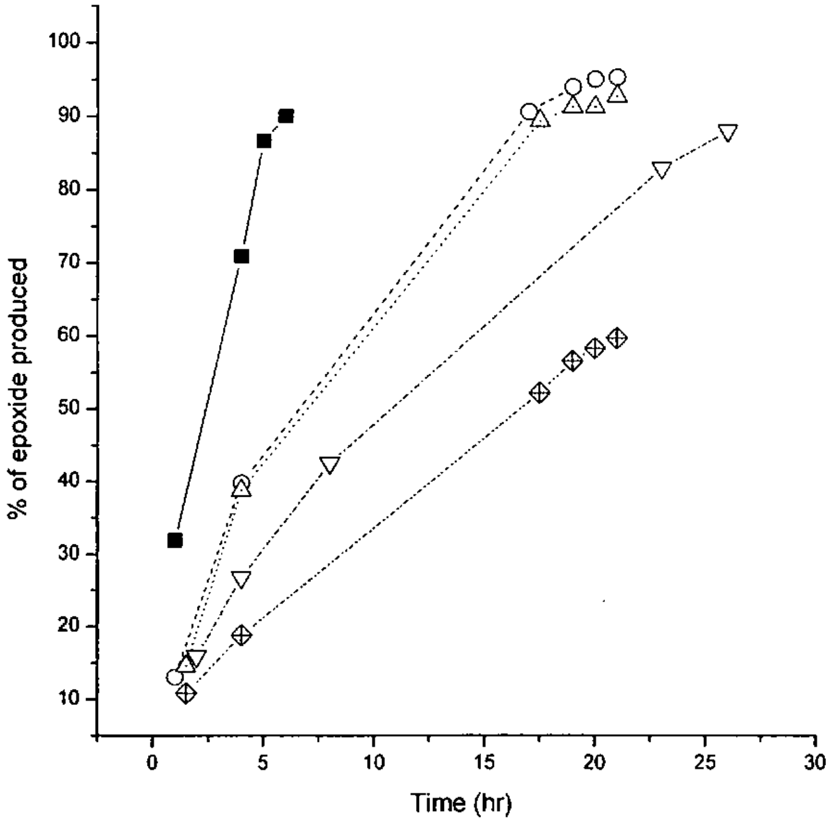


Figure 2.1 The effect of glucose on the bicarbonate catalyzed epoxidation of **1a** with hydrogen peroxide. The reaction was monitored by ^{1}H NMR spectroscopy and the percentage yield was determined by ^{1}H NMR spectroscopy using internal standard. (—■— without Glucose, --○-- 0.1M Glucose, ···△··· 0.2M Glucose, ---▽--- 0.3M Glucose and ---⊕--- 0.5M Glucose)

A method to monitor the optimal conditions for hydrogen peroxide formation by the glucose oxidase was carried out by electrochemical analyzer. From these studies, it was found that hydrogen peroxide was produced to an optimal concentration of 0.025 M in 6.5 hours (Figure 2.2). The concentration of hydrogen peroxide started to plateau after that time even though the glucose was not depleted. This result suggests that product inhibition of the enzyme was beginning to occur and that is therefore preferable that the epoxidation be completed within that timeframe.

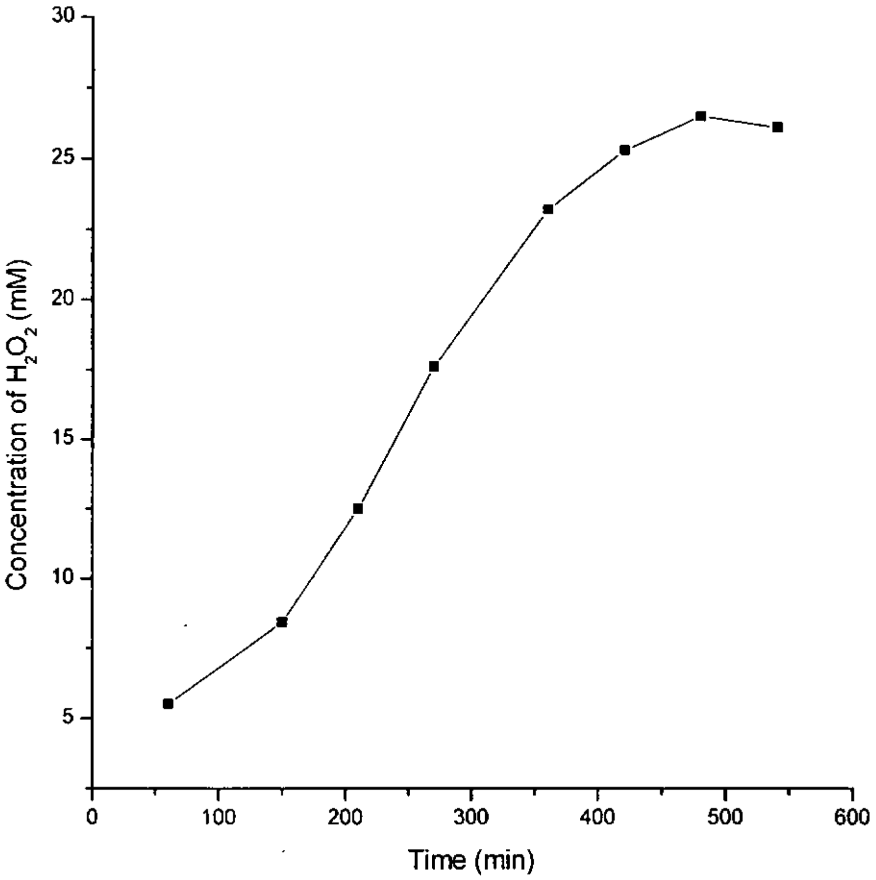
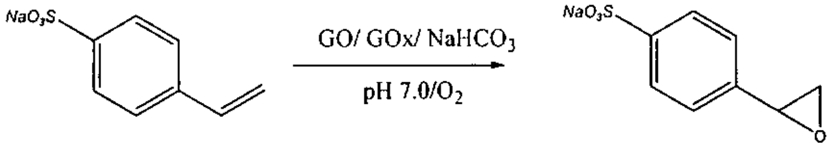


Figure 2.2 The generation of hydrogen peroxide by glucose oxidase (175 uint/mL) and 0.2M glucose in 10ml pH 7.0 phosphate buffer solution with an oxygen flow of 0.1 mL/min

2.3 The Epoxidation of Olefins by the Chemoenzymatic System

A chemoenzymatic system for epoxidation of olefins can therefore be set up by using 0.2 M glucose, 0.5 M $NaHCO_3$ and 0.05 M **1a** as the substrate in pH 7.0 phosphate buffer solution and GOx (175 unit/mL) as the standard condition, with oxygen bubbling at a flow rate of 0.1 mL/min (Scheme 2.3). In our studies, the epoxidation was followed by ^{1}H NMR spectroscopy. From these studies, the yield of epoxide was found to be poor, at about 15% even after prolonged reaction times. Increasing the amount of glucose in the reaction mixture did not improve the yield significantly and therefore other means of optimizing the reaction were pursued.



1a

Scheme 2.3

More recently, it has been reported that catalytic amount of manganese sulfate greatly accelerates epoxidation of olefins in the hydrogen peroxide/aqueous sodium bicarbonate process.[1,2] With the addition of manganese sulfate (0.1 mol%) to our chemoenzymatic systems, as described above, it was found that epoxidation of **1a** was completed in a relatively short time (less than 3 hours) and in excellent yields (>90%, entry 1, table 1). Other water-soluble olefins, such as 4-vinylbenzonic acid (**1b**, entry 2) and 3-methyl-2-buten-1-ol (**1c**, entry 3) were also epoxidized in high yields under similar conditions.

Having optimized the epoxidation of water soluble olefins under chemoenzymatic conditions, efforts were then focused on extending the methodology for the epoxidation of lipophilic olefins. As it is known that glucose oxidase is quite a robust enzyme and is not deactivated in the presence of tert-butanol,[3] we examined the effect of using tert-butanol as a co-solvent in the epoxidation of **1a** (Figure 2.3). It was found that both the rates of conversion of the olefin to the epoxide were substantially lower as the concentration of tert-butanol was increased,[3] but only moderately affected in 10% solution (Figure 2.3, curve B-D; entries 4-6, table 2.1). Thus, using an aqueous 10% tert-butanol solution as the reaction medium and the same reaction conditions as previously described, styrene (**1d**) was epoxidized with oxygen/glucose/GOx and manganese/sodium bicarbonate to give 45% conversion of the corresponding epoxide after three hours, in 90% yield (Entry 7).

In developing a green approach to the epoxidation of olefins, it would be preferable to be able to avoid the use of organic co-solvent completely. It is known that the integrity of glucose oxidase is not compromised in the presence of sodium dodecyl sulfate (SDS) at 10 mM concentration at pH 6-7, even after prolonged incubation.[4] Therefore the effect of 5 mM SDS on the epoxidation of **1a** in aqueous media under identical conditions was examined (Figure 2.3, curve E). It is clear that the presence

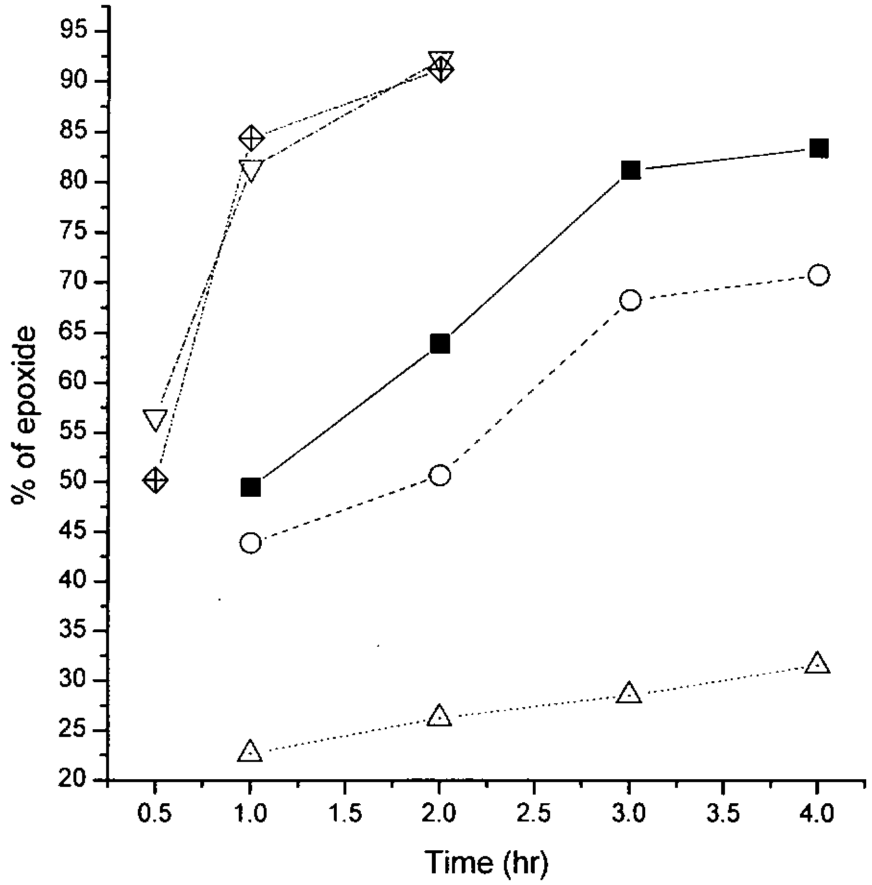
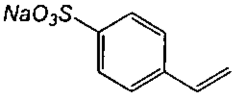
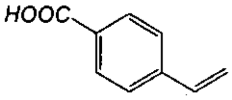
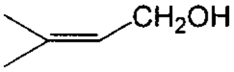
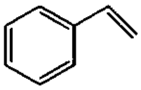
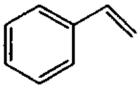


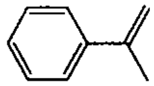
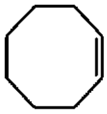
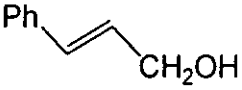
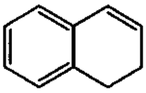
Figure 2.3 The effect of tert-butanol and SDS on the chemenzymatic epoxidation of 4-styrenesulfonic acid, sodium salt (**1a**). The reaction was monitored by ^{1}H NMR and the percentage yield was determined by ^{1}H NMR spectroscopy. (--▽-- Curve A: without SDS and tert-butanol, —■— Curve B: 10% tert-butanol, --○-- Curve C: 20% tert-butanol, ···△··· Curve D: 30% tert-butanol --⊕-- and Curve E: 5mM SDS)

of SDS did not affect the rate or yield of the epoxidation reaction under the chemoenzymatic conditions. Therefore, the SDS (5 mM) conditions was applied to the epoxidation of the more insoluble styrene (**1d**) to give 65% conversion to styrene oxide after three hours and styrene oxide was obtained in 91% (Entry 8). Similar results were obtained when 8 mM SDS, the critical micelle concentration, was used. Operationally, the SDS conditions are quite simple to handle and can be used readily for the preparative scale epoxidation of olefins.

The conditions above were also successfully applied to the epoxidation of α-methylstyrene (**1e**), cyclooctene (**1f**) and cinnamyl alcohol (**1g**), although in the latter case, oxidation of the allylic alcohol to the corresponding aldehyde was observed as a competing side-reaction. It should be noted that in the epoxidation of lipophilic olefins, the oxygen was not bubbled through the reaction because the volatile olefins would be carried away by the oxygen with subsequent reduction of yield. Thus the reaction was simply carried out under an oxygen atmosphere which may have contributed to the lower observed conversion of some of the olefins to epoxide within the reaction time studied

Table 2.1 Chemoenzymatic Epoxidation of Olefins

Entry	Olefin (**1**)	Time (hrs)	Additive	Conversion of **1** (%)	Yield of epoxide (%)[a]
1	 **1a**	3	-	>99	93
2	 **1b**	3	-	>99	91
3	 **1c**	8	-	>99	81
4	**1a**	3	10% tert-BuOH	80	90
5	**1a**	3	20% tert-BuOH	68	91
6	**1a**	3	30% tert-BuOH	30	90
7	 **1d**	3	10% tert-BuOH	45	90
8	 **1d**	3	5mM SDS	65	91

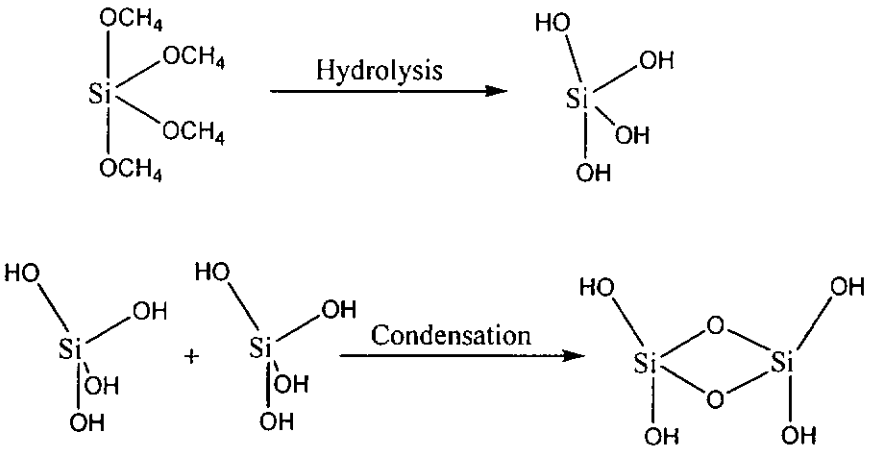
9	 **1e**	3	5mM SDS	>90	71
10	 **1f**	8	5mM SDS	20	99
11	 **1g**	6	5mM SDS	95	60[b]
12	 **1h**	8	5mM SDS	32	90

[a] Yields were calculated based on converted olefin and were determined by ^{1}H NMR spectroscopy or by GC using an internal standard. [b] Trans-3-phenylpropenal was observed in 35% yield.

2.4 The Epoxidation of Olefins by the Chemoenzymatic System using Immobilized Enzyme

In this project, glucose oxidase is likely to be the most expensive component in the system. The use of immobilized glucose oxidase for the reaction and the possible recovery and recycling of the enzyme was therefore explored. Two methods of immobilization were examined: (a) sol-gel formation[5-7] and (b) immobilized glucose oxidase on silica gel surface using the approach outlined in Scheme 4.[8-10]

In the first approach, the enzyme was physically dispersed in the sol-gel. The sol-gel was made up by two processes: hydrolysis and condensation (Scheme 2.4). The enzyme is then trapped into the sol-gel network and affectively immobilized (Figure 2.4). The advantage here is that enzyme is readily accessible to the substrate in the aqueous reaction mixture. This method of enzyme immobilization was found to be effective in the epoxidation of **1a**, giving 82% conversion to epoxide after 3 hours (Figure 2.5). The sol-gel was recovered from the aqueous phase by simple filtration and followed by washing with pH 7.0 phosphate buffer solution. However, it was evident that on recycling of the sol-gel immobilized enzyme, the activity dropped dramatically and by the third cycle, the system was no longer active (Figure 2.5). We attributed the loss of the enzymatic activity to the removal of the enzyme from the sol-gel during washing process.



Scheme2.4

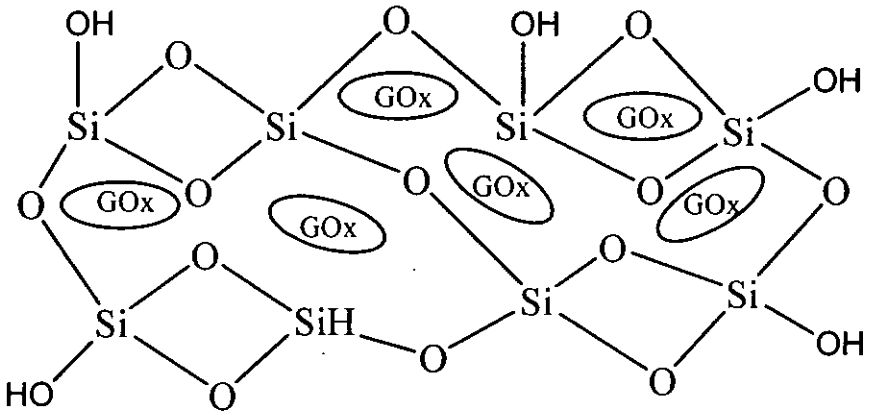


Figure 2.4 The enzyme is trapped into the sol-gel network.

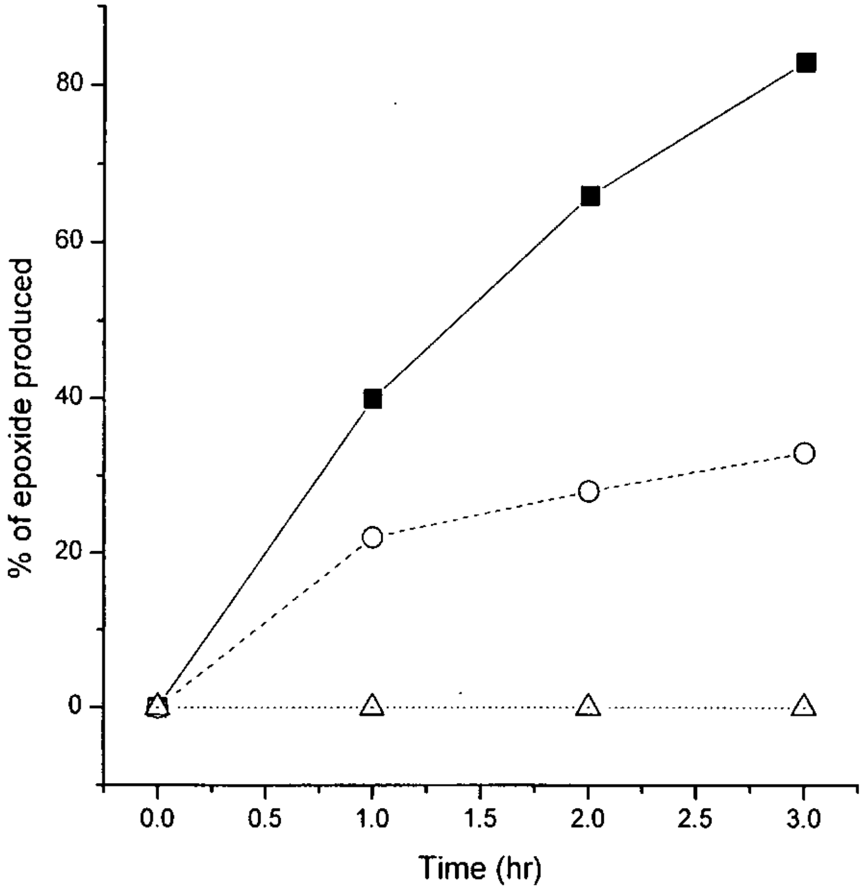
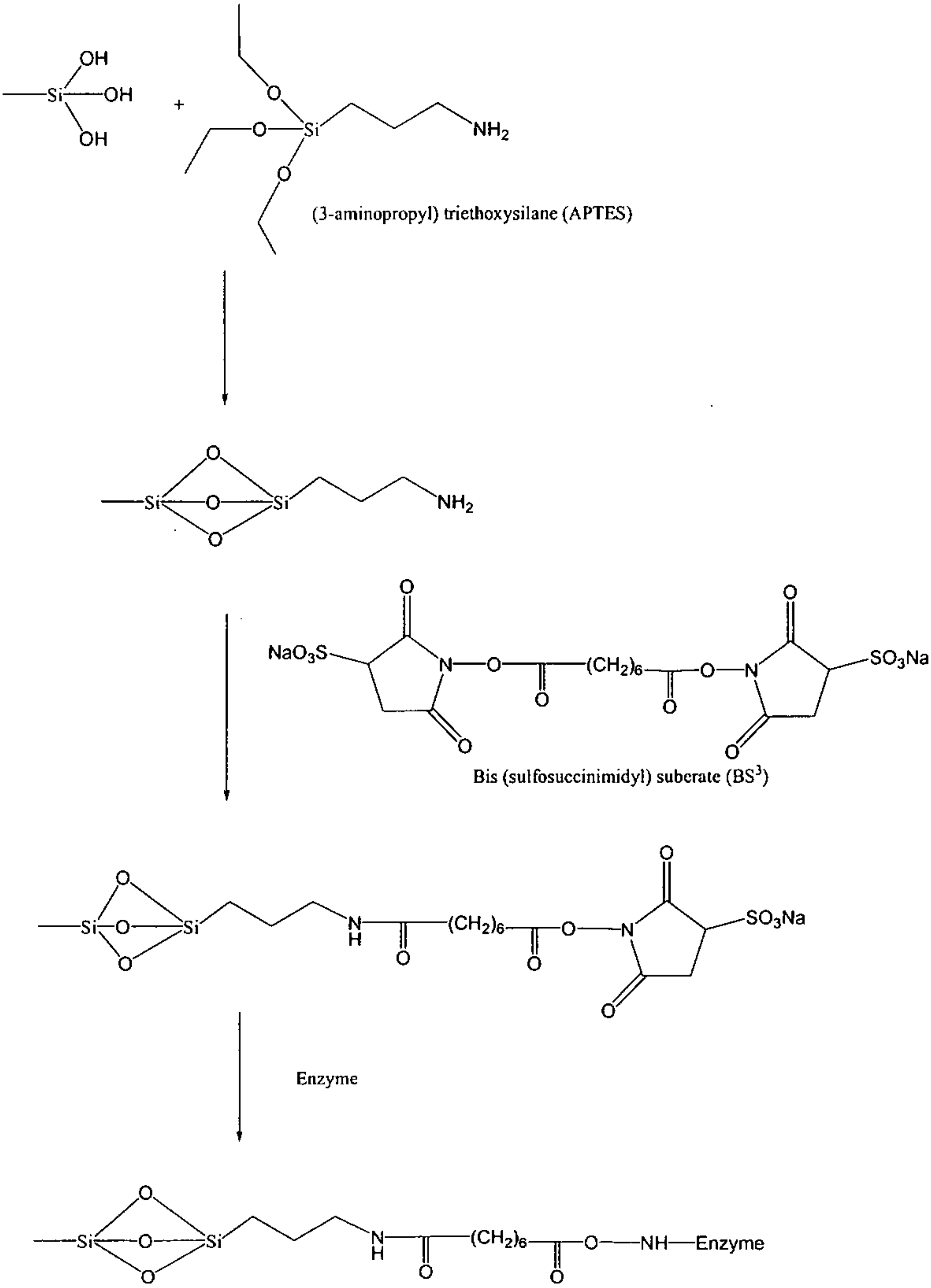


Figure 2.5 Epoxidation of **1a** by chemoenzymatic system using enzyme immobilized in sol-gel. Yield was determined by HPLC versus an internal standard. (—■— 1st cycle, --○-- 2nd cycle and ···△··· 3rd cycle)

In view of the difficulties encountered with recycling the immobilized enzyme in the sol-gel system, we then turned our attention to another immobilization method where the glucose oxidase is convalently anchored onto silica gel. We first used (3-aminopropyl) triethoxysilane (APTES) to modify the surface of the silica surface. Bis(sulfosuccinimidyl) suberate (BS^3) was used as a linker to coordinate the APTES and the enzyme (Scheme 2.5). In this method of immobilization, the enzyme is less accessible, and thus larger amount of enzyme (4500 units) was required in order to achieve the epoxidation of **1a** in three hours. In order to avoid the enzyme only physically trapped among the silica-gel, the immobilized-enzyme-silica gel was washed with pH 7.0 phosphate buffer solution. The filtrate was monitored by UV to ensure that no more enzyme was washed out.

The immobilized enzyme could be easily recovered by simple filtration, and unlike the sol-gel case discussed previously, covalently immobilized GOx can be re-used up to 8 times without significant loss of activity, resulting in excellent yields of the epoxide (Figure 2.6). In addition, the covalently immobilized GOx was very stable and can be stored for 4 weeks at -4°C without loss of activity.


OH
Si
OH
OH
+
O
O
Si
O
NH2
(3-aminopropyl) triethoxysilane (APTES)
O
Si
O
Si
O
NH2
O
NaO3S
N
O
(CH2)6
O
N
SO3Na
O
O
O
O
O
Bis (sulfosuccinimidyl) suberate (BS3)
O
Si
O
Si
O
N
H
(CH2)6
O
N
SO3Na
O
O
O
O
Enzyme
O
Si
O
Si
O
N
H
(CH2)6
O
NH
Enzyme
O
O

Scheme 2.5

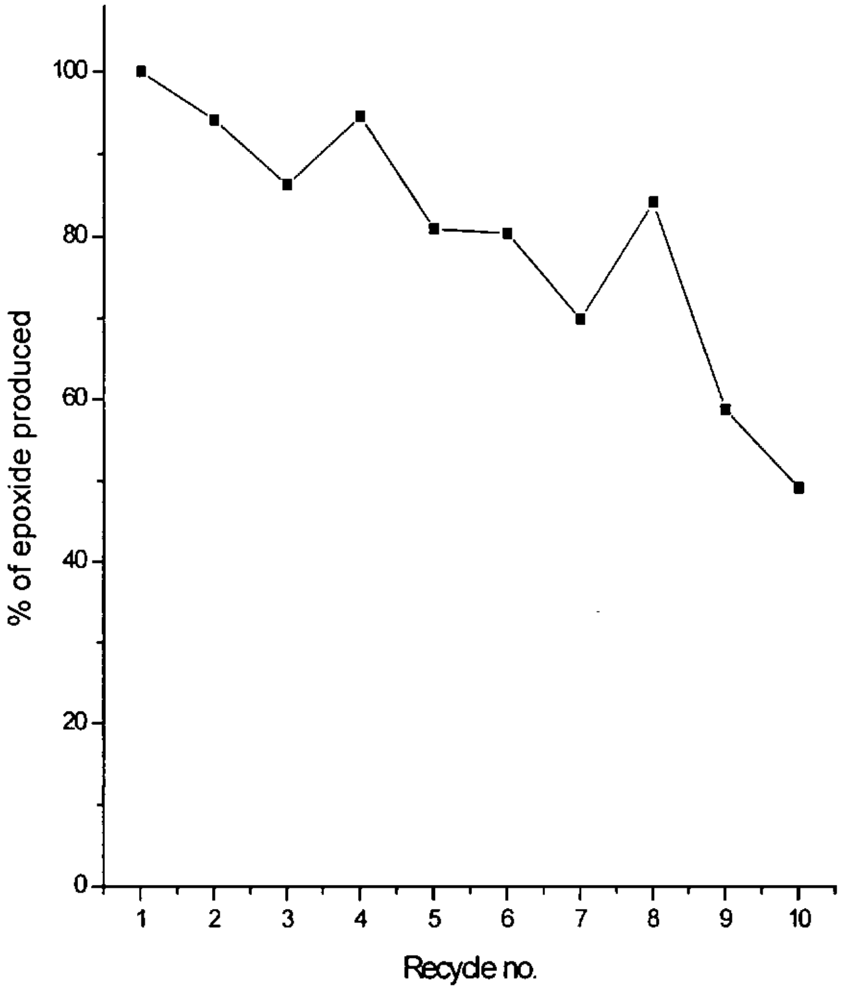


Figure 2.6 Recycling of enzyme in the epoxidation of **1a** by chemoenzymatic system using enzyme immobilized on silica gel. Yield was determined by HPLC versus an internal standard.

2.5 Conclusion

A chemoenzymatic approach for the *in situ* generation of hydrogen peroxide in the epoxidation of olefins has been investigated. In this system, hydrogen peroxide can be simply produced by enzymatic oxidation of glucose, a renewable resource, in aqueous medium. Many environmentally hazardous solvents or products normally associated with the AQ process can be avoided. Water-soluble olefins were oxidized with oxygen/glucose/GOx and Mn^{II}/HCO_3^- to afford excellent yields of epoxides (~90%). The effect of tert-butanol or SDS on the chemoenzymatic oxidation system was also studied. By using SDS, lipophilic olefins could be effectively epoxidized with oxygen/glucose/GOx and Mn^{II}/HCO_3^- without the need for an organic co-solvent. Moreover, the use immobilized GOx was explored and it was found that chemically immobilized GOx on silica gel was stable and could be re-used 8 times with no significant loss of activity. By combined use of enzymatic generation of hydrogen peroxide with a chemical catalyst, one can take advantage of the easy modifications of the chemical system and the broad substrate generality as demonstrated in the present study for the epoxidation of olefins.

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biochemical sensing", *Trac-Trends in Analytical Chemistry*, Vol.16, pp. 200-211 (1997).

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10 Rhee, W. M., Eur. Pat. Appl. Patent EP 96-102366, (1996)

Chapter 3: Manganese/Bicarbonate-Catalyzed Epoxidation of Olefins with Hydrogen Peroxide in Ionic Liquid

3.1 Introduction

3.2 The Mechanism of the Catalytic Epoxidation System

3.3 The Formation of Peroxymoncarbonate Ion in Ionic Liquid

3.4 The Catalytic Epoxidation of Olefins using Manganese/Bicarbonate with Hydrogen Peroxide in Ionic Liquid

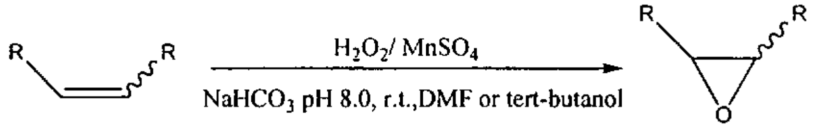
3.5 Conclusion

3.1 Introduction

The use of ionic liquids as environmentally benign solvents for a broad range of chemical processes has been strongly advocated in recent years.[1,2] This is due to a number of beneficial properties of ionic liquids, such as: high thermal and chemical stability, non-flammability and no measurable vapor pressure. Recently, olefin epoxidation in ionic liquids has been explored,[3-5] however the reported studies all suffer from certain limitations which render them impractical for use in industrial scale preparations. For example, some methods of olefin epoxidation in ionic liquids require the use of copious quantities of organic co-solvents such as dichloromethane,[3,4] whilst others utilize catalysts which are highly toxic and rely on environmentally unfriendly synthesis of the catalyst itself.[5] There is therefore impetus for the development of a more environmentally friendly system for the epoxidation of olefins in ionic liquids. The work described in this chapter discusses our attempts to develop a simple manganese sulfate/bicarbonate catalytic system for lipophilic olefins epoxidation with hydrogen peroxide in ionic liquid at room temperature.

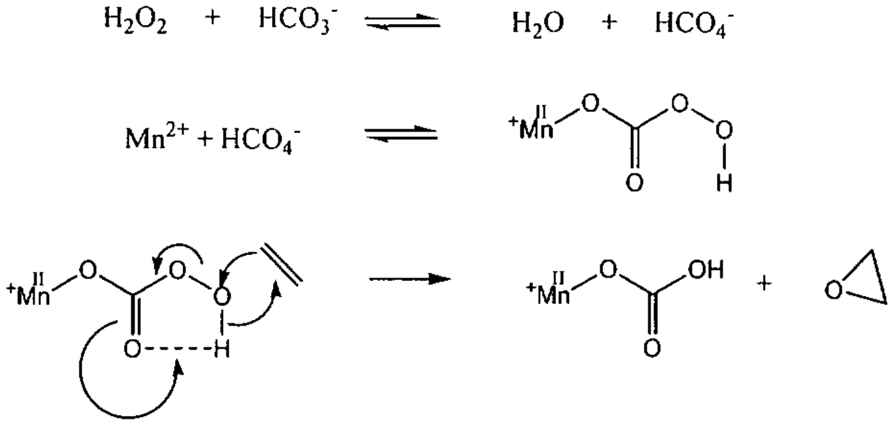
3.2 The Mechanism of the Catalytic Epoxidation System

The manganese sulfate/bicarbonate/hydrogen peroxide catalytic system is a very efficiency system (Scheme 3.1).



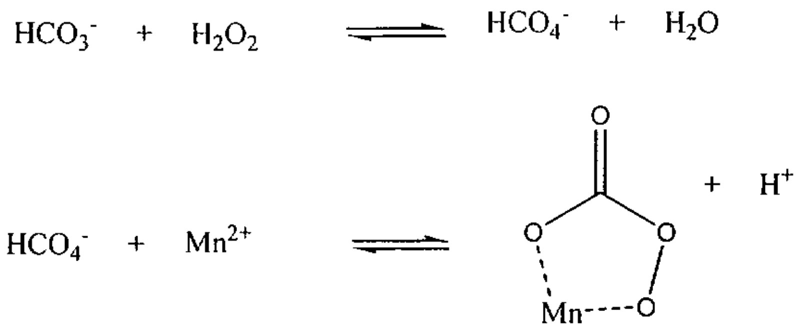
Scheme 3.1

But, the mechanism is still unknown. Lane has proposed that after the formation of the peroxymonocarbonate ion, the manganese acts as a Lewis acid to facilitate cleavage of the O-O bond by stabilizing the carbonate leaving group (Scheme 3.2). However, they believe it is not the predominant pathway since they found EPR-active species were generated as the reaction proceeded, which they assume is due to the metal undergoing redox processes.[6] Moreover, it is surprising that most of the metal salts that were screened did not have similar activities,[6] because many of them would have comparable Lewis acidities.

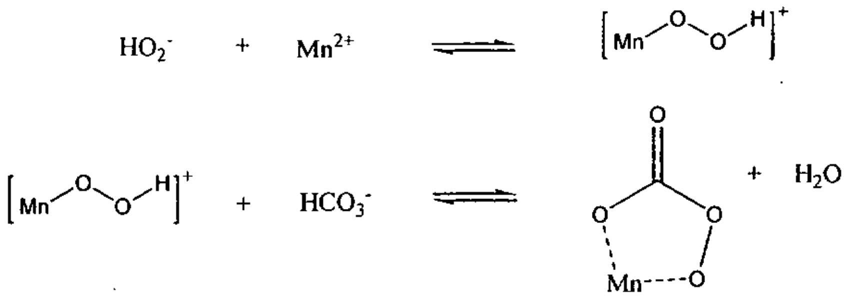


Scheme 3.2

The mechanistic pathways that they regard as most likely all involve manganese η^2-peroxycarbonate complexes. Scheme 3.3 outlines routes by which a manganese peroxymonocarbonate complex could form. One possibility involves the generation of an equilibrium concentration of peroxymonocarbonate, and then coordination of this to Mn^{II}. Alternatively, the coordination of peroxide anion to Mn^{II}, deprotonation, and reaction of this with bicarbonate would lead to the same intermediate, as indicated in Scheme 3.3b. Both routes seem plausible, and both might be operative simultaneously.

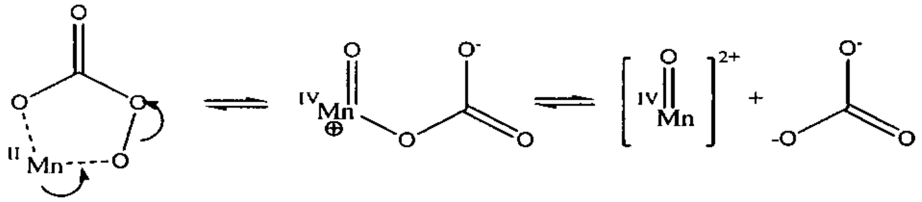


Scheme 3.3a

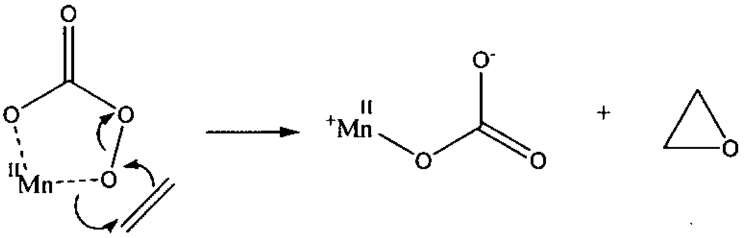


Scheme 3.3b

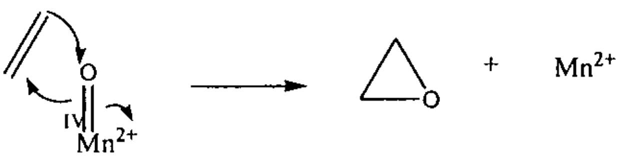
Lane has suggested that the manganese η^2-peroxycarbonate complexes may epoxidize olefins as shown in Scheme 3.4a. Besides, this species might be in equilibrium with a Mn^{IV} complex that could potentially deliver oxygen to the olefin (Scheme 3.4a). Alternatively, oxygen-transfer from the free Mn^{IV} oxo-species might take place, as shown in Scheme 3.4c. Mn^{IV} complexes have been proposed as viable epoxidation intermediates, and an interpretation of the mechanism of these reactions is that a Mn^{IV} oxo-complex gives the epoxidation reaction.[7-9] They may be presumed to act *via* the direct addition of the olefin substrate to the oxo-ligand with the concerted or sequential formation of the C-O bonds. The latter is similar to the Mn^{III}/ Mn^{IV} catalytic cycles widely accepted for epoxidations reactions catalyzed by Mn-porphyrin[10,11] and salen[12,13] complexes.



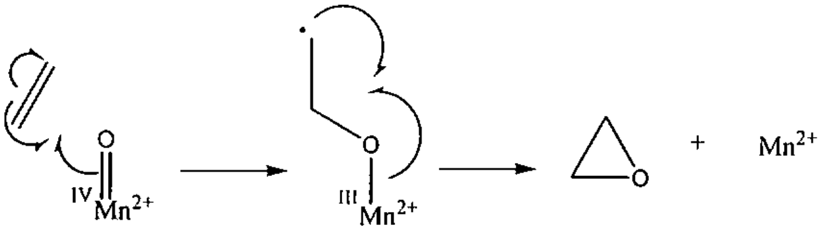
Scheme 3.4a



Scheme 3.4b



Scheme 3.4c



Scheme 3.4d

All proposed mechanisms shown are plausible and none of them can be eliminated at this time. Besides, the acquisition of more data to exclude some of these possibilities is a difficult task. The system is hard to study because the active catalyst forms *in situ* and it is not stabilized by organic ligands. Kinetic investigations are complicated by the disproportionation of hydrogen peroxide and the possibility of competing pathways, and the paramagnetic properties of some of the compounds in the reaction mixture preclude NMR analyses. However, a stepwise oxygen delivery via intermediates Mn^{4+} oxo-species as implied in Scheme 3.4c seems the least speculative mechanistic proposal based on similarities with Mn-porphyrin[10,11] and salen.[12,13] complexes.

3.3 The Formation of Peroxymonocarbonate Ion in Ionic Liquid

Richardson and co-workers reported that, in the aqueous reaction, the reactive oxidizing species in the manganese salt/bicarbonate/hydronge peroxide catalytic system is believed to be the peroxymonocarbonate HCO_4^-, which is formed by the reaction of hydrogen peroxide with the bicarbonate ion according to Scheme 3.5.[14]

$$H_2O_{2(solv)} + HCO_3^-{}_{(solv)} \rightleftharpoons H_2O_{(solv)} + HCO_4^-{}_{(solv)}$$

Scheme 3.5

The peroxymonocarbonate species is then thought to combine with the Mn^{II} ion in a yet to be defined manner to effect the epoxidation.[6,15] In ionic liquids, we proposed a similar mechanism based on the following experimental observations. Due to the low solutility of sodium hydrogen carbonate in 1-butyl-3-methylimidazolium ([bmim][BF_4]), tetramethylammonium hydrogen carbonate (TMAHC) was used in our systems. The ionic liquid [bmim][BF_4] was chosen on the basis of its ease of preparation and stability in the presence of oxygen and water.[16] Figure 3.1 shows the ^{13}C NMR spectra of the formation of HCO_4^- from TMAHC and hydrogen peroxide in [bmim][BF_4]. When TMAHC was dissolved in [bmim][BF_4], the bicarbonate anion HCO_3^- could be readily observed at 160.9 ppm (Figure 3.1a). When hydrogen peroxide was added to the solution, the peroxymonocarbonate HCO_4^- , at 157.9 ppm, was formed as the major species (Figure 3.1b). From the relative peak ratios of ^{13}C NMR spectra (delay time = 10s) and the concentration of hydrogen peroxide, the equilibrium constant (K_1) for the scheme 3.5 in ionic liquid can be estimated (Calculation will be shown in Appendix).

$$H_2O_{2(solv)} + HCO_3^-{}_{(solv)} \overset{K_1}{\rightleftharpoons} H_2O_{(solv)} + HCO_4^-{}_{(solv)}$$

$$K_1 = \frac{[H_2O][HCO_4^-]}{[H_2O_2][HCO_3^-]} \tag{7.5}$$

When 0.15 mmol styrene and 0.15 mmol TMAHC were reacted with 10 equiv of hydrogen peroxide in 300 μL [bmim][BF_4], the peroxymonocarbonate species persisted more or less unchanged overnight according to ^{13}C NMR. Furthermore, little formation of the product styrene oxide was detected. However, when a catalytic amount of $MnSO_4$ was added to the mixture, the peroxymonocarbonate species quickly declined in intensity, with the concomitant formation of styrene oxide. This is consistent with the mechanism that Mn^{2+} reacts with peroxymonocarbonate ion and forms an intermediate which is similar or the same specie as the case in aqueous media. This intermediate will then oxidize the olefins and form epoxides.

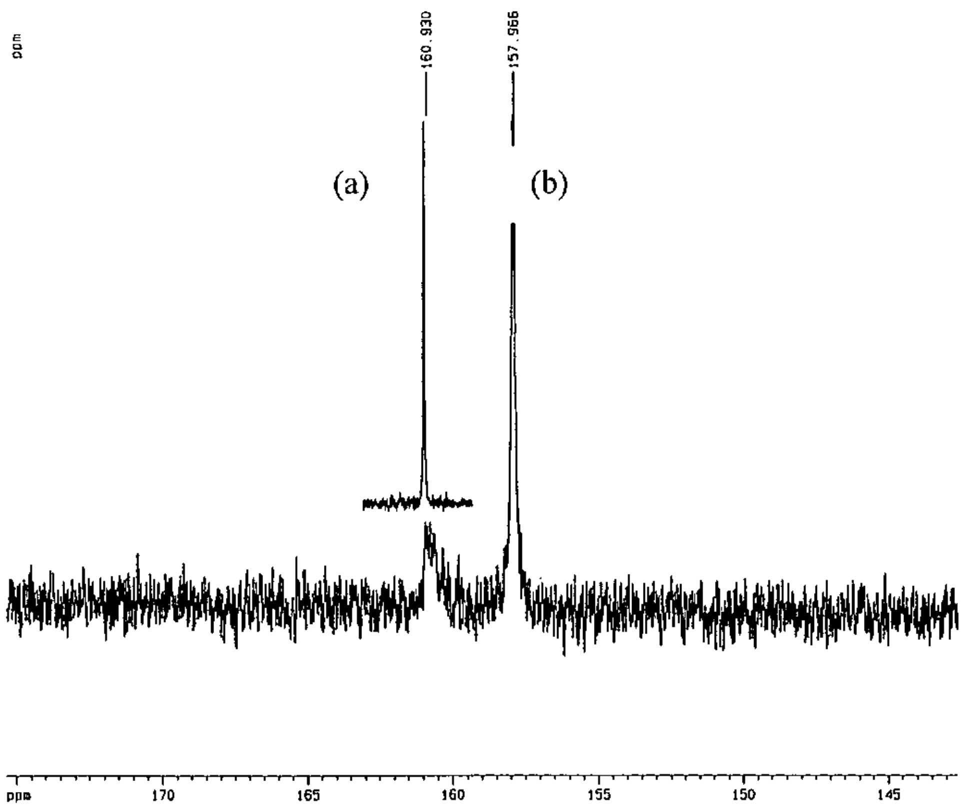


Figure 3.1 ^{13}C NMR spectrum for a solution at 25°C of (a) 0.49 M TMAHC in 300μL of [bmim][BF_4] and (b) 0.42 M TMAHC and 1.6 M H_2O_2 in 300 μL [bmim][BF_4].

3.4 The Catalytic Epoxidation of Olefins using Manganese/Bicarbonate with Hydrogen Peroxide in Ionic Liquid

Having demonstrated the successful formation of the peroxomonocarbonate ion and its subsequent decomposition in the presence of Mn^{II} in the ionic liquid, the system was utilized for olefin epoxidation at room temperature using 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) as the solvent. Styrene (**1a**, 0.15 mmol) was used as the standard substrate with 10 equiv of H_2O_2 in [bmim][BF_4] at room temperature. Manganese sulfate (0.2 mol%) and sodium bicarbonate (0.15 mmol) were added as the catalyst. Under these conditions, no epoxidation was observed (Table3.1, entry 1). The failure of the reaction was assumed to be due to the poor solubility of sodium bicarbonate in the ionic liquid. Indeed, when tetramethylammonium hydrogen carbonate (TMAHC, 0.15 mmol) was used in its place, the reaction proceeded readily to give styrene oxide in excellent yield after 2h at room temperature (Table 3.1, entry 2).

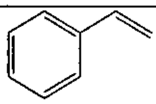
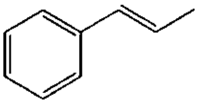
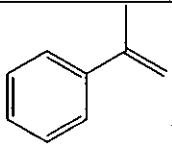
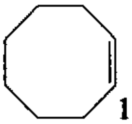
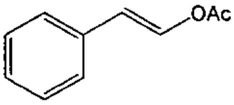
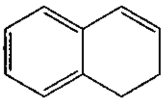
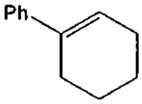
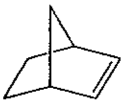
Manganese sulfate was found to be essential for the reaction to proceed, as the reaction gave little or no product in the absence of the manganese salt (entry 3). The ionic liquid itself was also an essential requirement for useful conversion to the desired epoxides as in its absence (*i.e.* aquous media); the reaction gave very low conversion to styrene oxide (Table 3.1, entry 4).

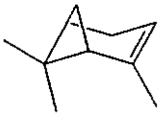
When only 4.5 equiv of H_2O_2 was used, the conversion of styrene to epoxide was still very effective, but the reaction took slightly longer to proceed to completion (Table 1, entry 5). However, when the amount of H_2O_2 was reduced to 1 or 2 equiv, only low conversion of the styrene was observed even after prolonged reaction times (entries 6 and 7). We presumed that it was because Mn^{2+} enhanced the rate of decomposition of hydrogen peroxide.[18,19,20] This, in turn, resulted in a lower amount of hydrogen peroxide in the epoxidation process.

Burgess and co-workers have reported that co-additives, such as salicylic acid, can enhance the rate of the epoxidation reaction relative to a competing disproportionation of hydrogen peroxide. However, in our hands the addition of salicylic acid did not improve the rate of reaction in ionic liquid (Table 3.1, entry 8), unlike the corresponding reaction conducted in aqueous media.[6]

Having optimized the catalytic system for styrene oxide, a number of representative lipophilic olefins were epoxidized under the same reaction conditions (Table 3.1, entries 9-16). In general, good to excellent yields of the epoxides could be obtained without further attenuation of the catalytic system. For olefins conjugated with aromatic ring, they were easily oxidized and gave good yields. However, it should be noted that terminal olefins were not epoxidized (entry 17) under these conditions, consistent with the observations by Burgress in the aqueous reaction.[6,15] Generally, the alkyl substituents olefins (*e.g.* cyclooctene) and terminal olefins (*e.g.* 1-decene) are less reactive than olefins with aromatic ring. [17]

Table 3.1. Epoxidation of Olefins

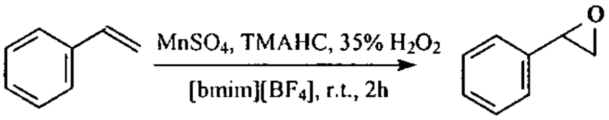
Entry	Substrate (0.15 mmol)	35 % H_2O_2 (equiv)	Time (hr)	Conversion (%)	Yield (%)[a]
1[b]	 **1a**	10	8	0	0
2	**1a**	10	2	>99	98
3[c]	**1a**	10	8	10	>99
4[d]	**1a**	10	8	7	>99
5	**1a**	4.5	4	97	96
6	**1a**	2	24	20	99
7	**1a**	1	24	12	99
8[e]	**1a**	2	24	25	97
9	 **1b**	10	5	>99	99(93)
10	 **1c**	10	5	>99	99(92)
11	 **1d**	10	2	53	99
12	 **1e**	10	4	>99	(95)
13	 **1f**	10	3	>99	99(95)
14	 **1g**	10	5	>99	80[f]
15	 **1h**	10	4	82	>99

16	 1i	20	3	53	>99
17	 1j	20	23	0	0

[a] Conditions: 0.15 mmol of olefin, 0.15 mmol of TMAHC, 0.2 mol% $MnSO_4$, and 300 μL of [bmim][BF_4]. Yields were calculated on the basis of converted olefins and determined by NMR spectroscopy or GC-MS versus an internal standard. [b] Performed with 0.15 mmol of $NaHCO_3$. [c] Without $MnSO_4$. [d] Without [bmim][BF_4]. [e] Salicylic acid (4 mol%) was added. [f] 3-Phenyl-2-cyclohexene-1-one was observed in 20% yield. Isolated yield was given in parenthesis.

With [bmim][BF_4] as the solvent, the lipophilic product epoxide was easily extracted by pentane. Since the ionic liquid is likely to be the most expensive among all the components in the reaction system, the capacity to recycle [bmim][BF_4] was investigated and the results are summarized in Table 3.2. After pentane extraction in the first cycle, the recovered yellowish liquid containing $MnSO_4$ and TMAHC could be re-used for the same reaction by adding the alkene and more hydrogen peroxide to give 92% yield of the epoxide. However, the yield was diminished on the third and fourth cycles. This could be easily rectified, however, simply by adding a catalytic amount of $MnSO_4$ to return the same high yield of epoxide. By the seventh or eighth cycle, addition of TMAHC together with $MnSO_4$ was found to be necessary. However, it is clear that the ionic liquid itself can be re-used up to at least 10 cycles without any diminished capacity to act as the medium for the reaction.

Table 3.2. Recovery and Re-use of [bmim][BF_4] for the Epoxidation of Styrene[a]



Cycle	1	2	3	4	5[b]	6	7[b]	8	9[c]	10
Yield (%)[d]	95	92	45	10	96	93	30	10	95	97

[a] 0.6 mmol Styrene was used. [b] Addition of 0.2 mol% $MnSO_4$. [c] Addition of 0.6 mmol of TMAHC. [d] Yields were determined by GC-MS.

3.4 Conclusion

Ionic liquids are considered as "green" or "clean" solvents as they are non-volatile and potentially easily recycled. In this chapter, a simple catalytic system, manganese sulfate/bicarbonate, was developed to epoxidize olefins with hydrogen peroxide in room temperature ionic liquid, 1-butyl-3-methylimidazolium ([bmim][BF_4]). From the ^{13}C NMR spectra, it could be determined that the peroxymonocarbonate ion, HCO_4^-, was formed by the reaction of bicarbonate ion with hydrogen peroxide in [bmim][BF_4]. The equilibrium constant for the formation of peroxymonocarbonate in ionic liquid is estimated to be 7.5. A wide range of olefins have been studied and good to excellent yields of epoxides were obtained. Moreover, the ionic liquid itself can be easily re-used up to at least 10 cycles without any diminished capacity to act as the media for the reaction. With the recycling of the ionic liquid, the reaction can be considered as a cheap, catalytic, scalable, and environmentally benign method for olefin epoxidations. The potential limitation of this catalytic system is that terminal olefins (1-decene) cannot be epoxidized and this is the subject of investigation in the next chapter.

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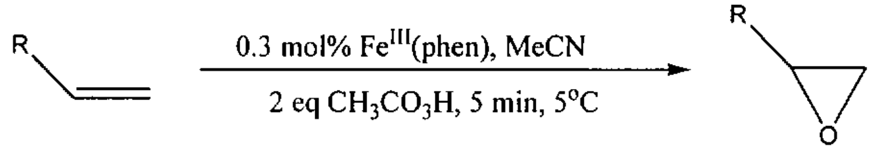
Chapter 4: The Epoxidation of Terminal Olefins with Iron Catalyst in Ionic Liquids

4.1 Introduction

Epoxidation of terminal and certain classes of electron-deficient olefins remains a challenging task in organic chemistry. Few catalytic methods exist that are operationally efficient and readily scaled using simple oxidants. Recent reports have detailed several impressive catalytic systems for such olefins, but each system has limitations that include expensive or toxic catalysts, long reaction time, high catalyst loadings, or limited substrate scope.[1-8] Recently, Stack and co-workers[9] have performed a simple and efficient catalytic epoxidation system for terminal olefins. They used a ferric phenanthroline catalyst, prepared *in situ*, that epoxidized terminal olefins using peracetic acid as oxidant. However, a drawback is that this system requires the use of acetonitrile as solvent. In this chapter, we describe our efforts to use a modified iron catalyst for the epoxidation of unactivated olefins in 'green' ionic liquids which can be used as solvents.

4.2 The Mechanism of the Catalytic Epoxidation System

The iron catalytic epoxidation system is a very efficient system (Scheme 4.1). Stack suggested that a μ-oxo bridge was formed between the dimer iron complex (Complex **1**, figure 4.1). The μ-oxo diiron(III) complexes have been studied for three decades.[10] Different μ-oxo diiron(III) complexes have been used as catalysts for olefin epoxidation systems.[9,11] However, despite the established use of such catalysts, the mechanism of oxidation is still unknown.



Scheme 4.1

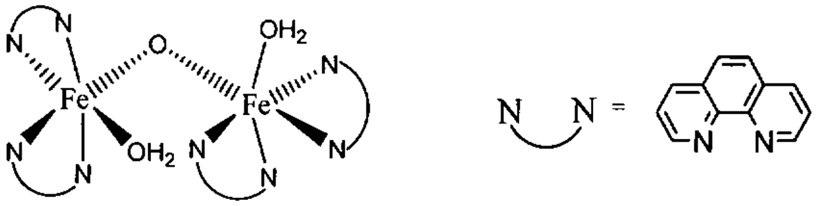
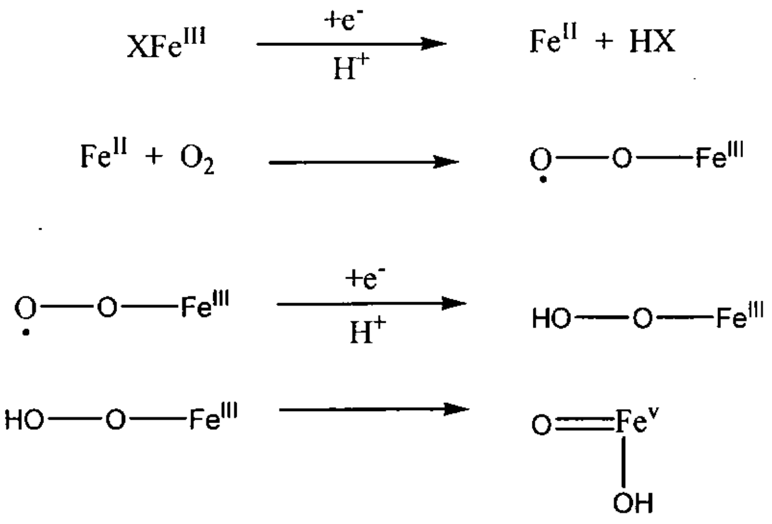


Figure 4.1 Purposed structure of $[((phen)_2(H_2O)Fe^{III})_2(\mu\text{-}O)](ClO_4)_4$ (complex **1**)

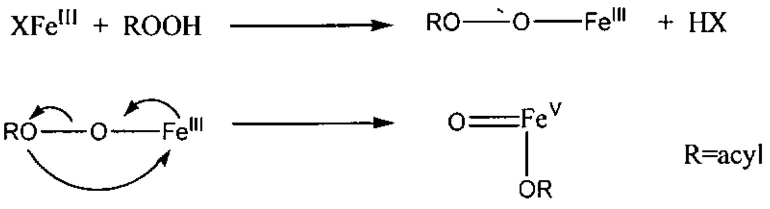
The μ-oxo diiron complex **1** contains accessible coordination sites (water). Such loosely coordinated ligand sites probably allows the iron ions to interact with and to activate the peracetic acid. If strongly coordinating ligands (*e.g.* chloride) are coordinated to the irons, the catalyst becomes inactive as it has been shown in the literature.[9]

Many studies have proposed that the mechanistic pathways most likely involve oxoiron(V) complex.[12-14] In biochemical oxidations mediated by the cytochrome P-450 monooxygenases, the active oxidant is thought to be an oxoiron(V) species formed by the reductive activation of dioxygen by iron(II) (Scheme 4.2)[12].



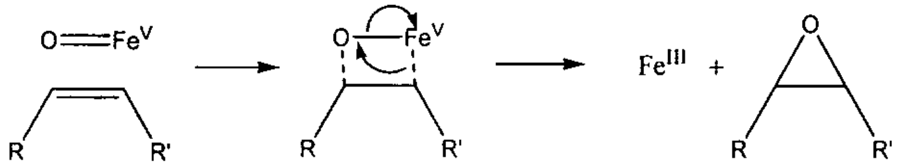
Scheme 4.2 (X=halogen)

The active oxidant can also be generated by directly treating iron(III) enzyme with active oxygen donors such as peroxy acids (Scheme 4.3)[12].



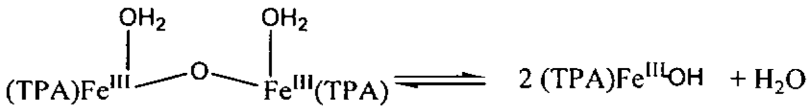
Scheme 4.3

Que found that a high-valent oxoiron(V) could be formed by the reaction of a non-porphyrin iron complex with peroxy acid (Scheme 4.5)[13] and considered such a species as an active intermediate in the oxidation of olefins (Scheme 4.4).[12]



Scheme 4.4

Que has proposed a mechanism for the formation of oxoiron(V) species. By using the mass spectrometer, he found that (L)Fe^{III}-OH could form from a diiron (III) complex[14] (Scheme 4.5) followed by oxidation by peracetic acid to form the oxoiron(V) complex[12] according to Scheme 4.6.

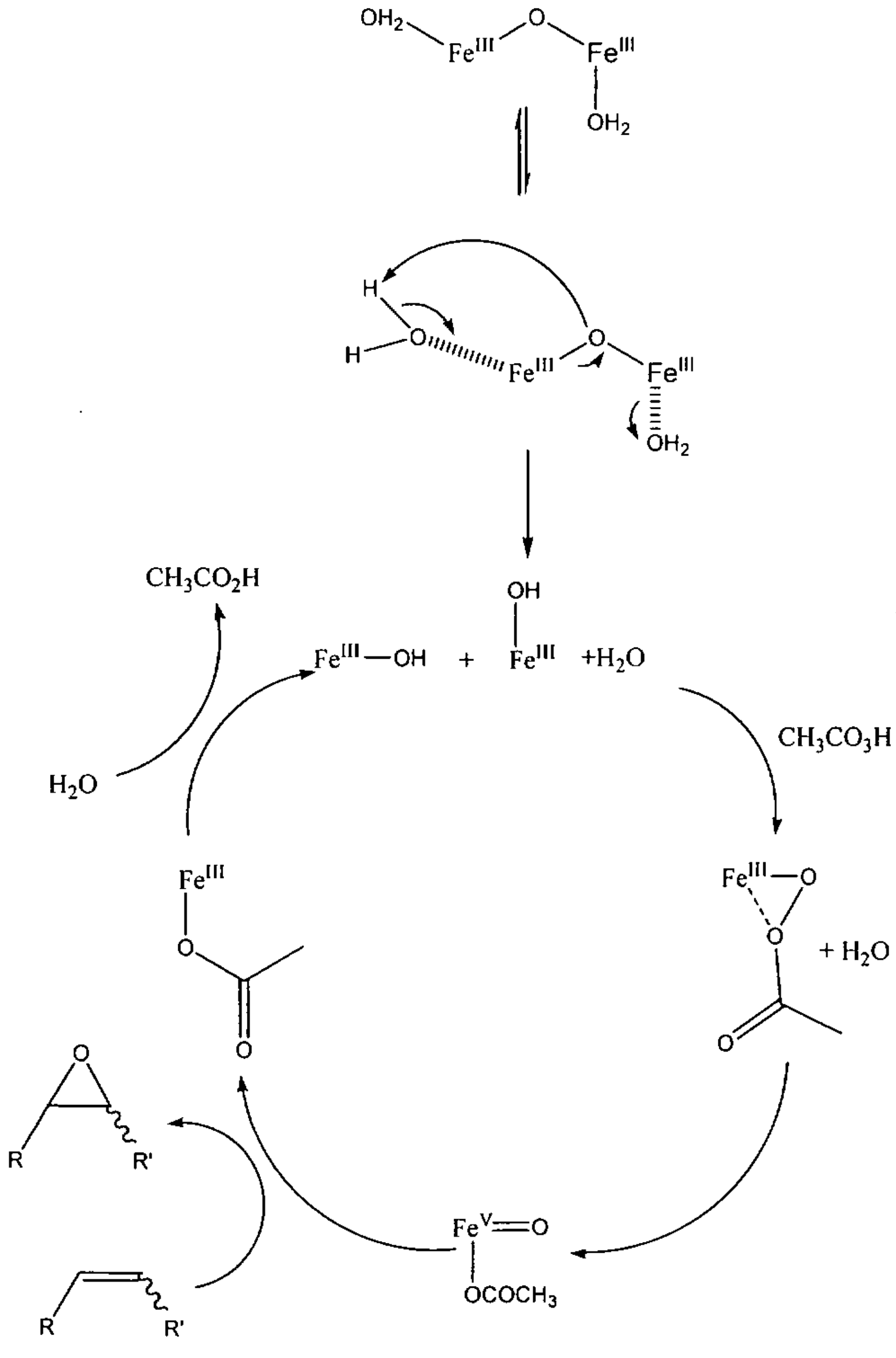


$$(TPA)\overset{OH_2}{\overset{|}{Fe^{III}}}-O-\overset{OH_2}{\overset{|}{Fe^{III}}}(TPA) \rightleftharpoons 2\,(TPA)Fe^{III}-OH + H_2O$$

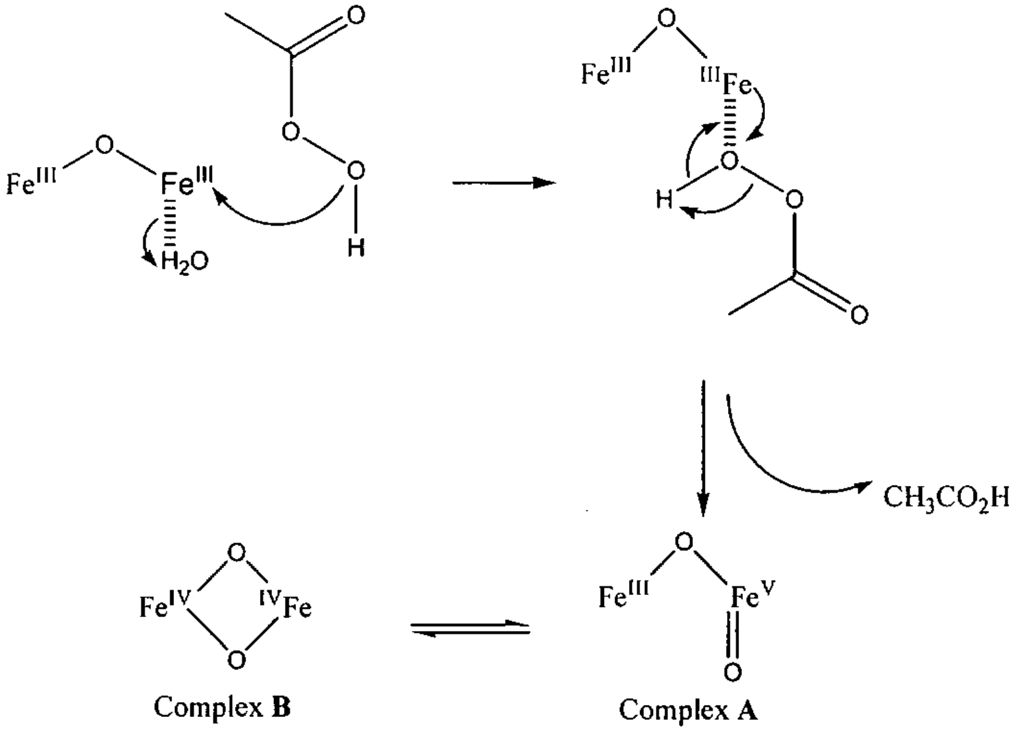
TPA=tris(2-pyridylmethyl)amine

Scheme 4.5

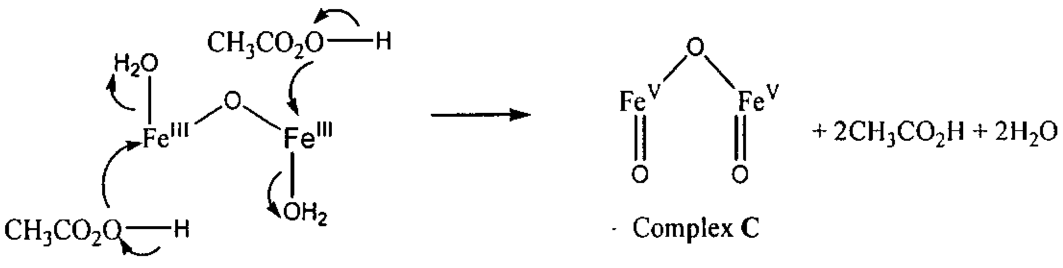
Alternatively, Sheldon suggested that the oxoiron(V) species could be formed by the oxidation of iron(III) complex with peroxy acid according to Scheme 4.7.[12] The oxoiron(V) complex (complex A) could then form an equilibrium with complex **B**. Similarly, diiron (V) oxo complex **C** could form when two molecules of peracetic acid attack the same μ-oxo diiron(III) complex (Scheme 4.8). Olefins are then epoxidized by these active species (Schemes 4.9 & 4.10).



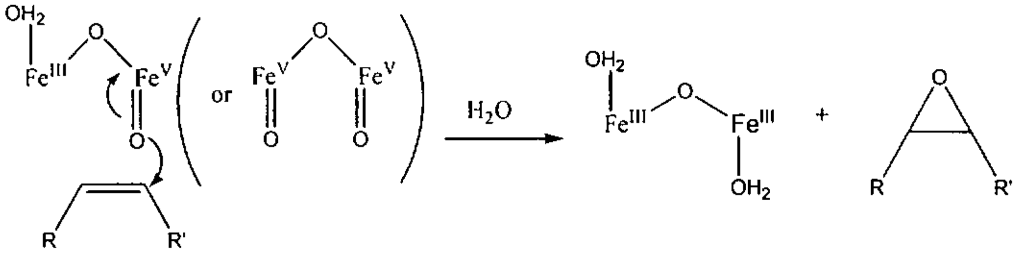
Scheme 4.6 (for clarity, the ligands are omitted)



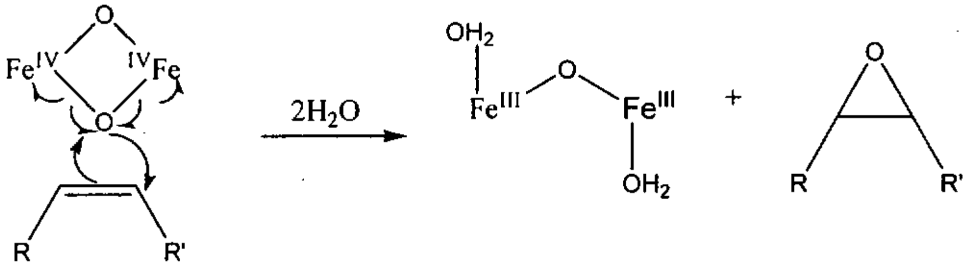
Scheme 4.7 (for clarity, the ligands are omitted)



Scheme 4.8 (for clarity, the ligands are omitted)

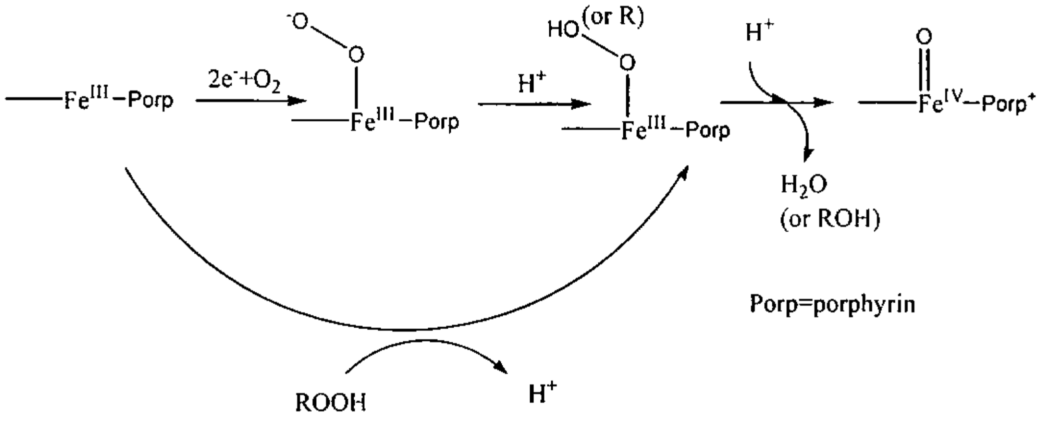


Scheme 4.9 (for clarity, the ligands are omitted)



Scheme 4.10 (for clarity, the ligands are omitted)

On the other hand, high-valent oxoiron(IV) may also be plausible species for this system. High-valent oxoiron(IV) porphyrins have been suggested to be the reactive species responsible for the oelfin epoxdiation (Scheme 4.11).[15,16] Que has also reported the crystal and spectroscopic characterization of an oxoiron(IV) species prepared from $Fe^{II}(TMC)(CF_3SO_3)_2$ (Scheme 4.12).[17] Besides, Morishima has found that *meso*-substituted (acylperoxo) iron(III) porphyrin complexes could form oxoiron(IV) porphyrin cation radicals (Scheme 4.13).[18]

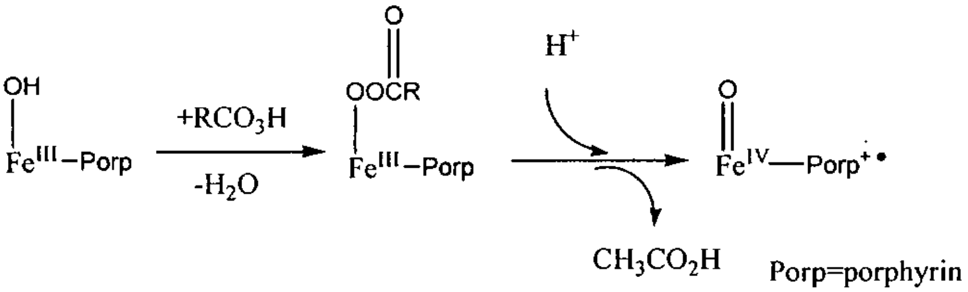


Scheme 4.11

$$Fe^{II}(TMC)(CF_3SO_3)_2 \xrightarrow[\text{AeCN/ -40°C}]{\text{iodosylbenzene (PhIO)}} [Fe^{IV}(O)(TMC)(NCCH_3)](CF_3SO_3)_2$$

TMC=1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecne

Scheme 4.12



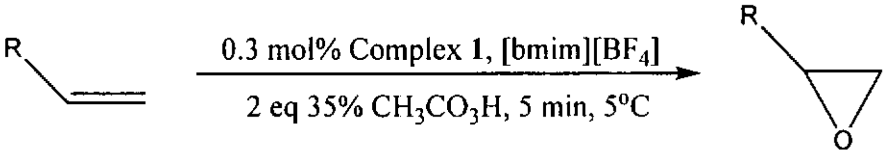
Scheme 4.13

All the mechanisms above seem plausible and both oxoiron(IV) and oxoiron(V) complexes are the possible active species in the reaction. More experimental data are needed to understand the nature of the oxidative species and the mechanism of the reaction.

4.3 The Catalytic Epoxidation of Terminal Olefins with Iron Catalysts in Ionic Liquids

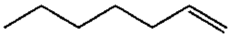
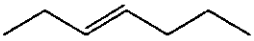
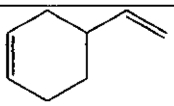
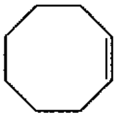
4.3.1 Using ferric phenanthroline as catalyst in ionic liquid

Stack and co-workers[9] have reported that when the ferric phenanthroline catalyst, complex **1** (Figure 4.1), is combined with commercial peracetic acid, efficient and rapid epoxidation occurs with a wide range of electron-rich and electron-poor olefins at 0°C. Low loadings of catalyst (0.25 mol%) are sufficient for high conversions, and comparable product yields are found. We have developed a similar epoxidation system (Scheme 4.14) but with the ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate,([bmim][BF_4]), used as the reaction medium. In general, good to excellent yields of epoxides could be obtained in a short period of time (Table 4.1). Terminal (1-heptene), internal (trans-3-heptene) and cyclic (cylclooctene) olefins were epoxidized by using 2 equiv. 32% peracetic acid within 5 min. For 4-vinyl-1-cyclohexene (entry 4), both 1,2-monoepoxide (60%) and diepoxide (40%) were obtained when the reaction was stopped at 5 min. However, there was only diepoxide as a product when the reaction was allowed to proceed for 10 min.



Scheme 4.14

Table 4.1 Epoxidation of Olefins

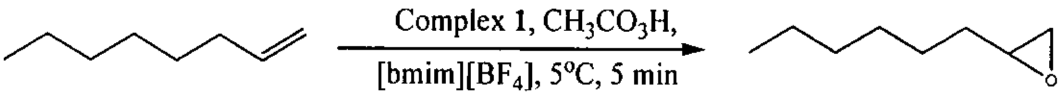
Entry	Substrate (0.18 mmol)	32% peracetic acid (equiv)	Time (min)	Conversion (%)	Yield (%)[a]
1		2	5	>99	99
2		2	5	>99	99
3		2	5	97	99
4[b]		2.5	10	>99	98(92)
5		2	5	>99	99(93)

[a] Condition: 0.18 mmol alkene, 0.3 mol% complex 1 and 200 μL [bmim][BF$_4$] at 5°C. Yields were calculated on the basis of converted olefins and determined by GC-MS versus an internal standard. [b]

Diepoxide product only. Isolated yields were given in parenthesis.

With ionic liquid as the reaction medium, the lipophilic product epoxides were easily extracted using pentane. As the ionic liquid is likely to be the most expensive among all components of the reaction system, we examined the recycling of [bmim][BF_4] for the epoxidation reaction. Also, we investigated the stability of the complex **1** in [bmim][BF_4] (Table 4.2).

Table 4.2 Recovery and reuse of [bmim][BF_4] for the epoxidation of 1-octene



Cycle	1	2	3	4[b]	5	6
Yield (%)[a]	98	38	12	95	25	10

[a] Yields were calculated on the basis on converted olefins and determined by GC-MS. [b] Addition of 0.3 mol% complex **1** .

It is clear from the results in Table 4.2 that the ionic liquid, [bmim][BF_4], could be re-used up to 6 times without loss of its capacity as a solvent. However, the yield of the epoxide diminished on the second and third cycles. This could be rectified by addition of a further catalytic amount of complex **1** to return to the same high yield of epoxide (cycle 4) but the yield declined again subsequently (cycles 5 and 6). We presumed that the loss of catalytic activity in cycles 2 and 3 was due to the removal of free phenanthroline from the ionic liquid during the extraction process. This, in turn, resulted in a lower amount of catalyst in the recycled system.

4.3.2 Using the ferric bathophenanthrolinedisulfonic acid, disodium salt (2) as catalyst in ionic liquids

In order to minimize the loss of ligand during the extraction process, another similar ligand, bathophenanthrolinedisulfonic acid, disodium salt (dpps), insoluble in pentane, was used. As in the case for complex **1**, the iron complex formed with this ligand is assumed to have the ferric μ-oxo dimeric structure $[((dpps)_2(H_2O)Fe^{III})_2\ ]_2(\mu\text{-}O)](Na)_2$ (Complex **2**, figure 4.2) analogous to the known iron(III) phenanthroline complexes.[9,19]

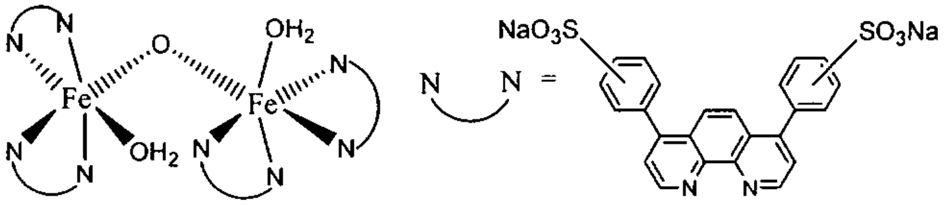
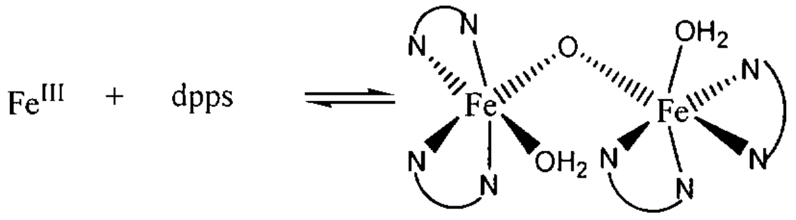


Figure 4.2 Proposed structure of complex **2**



Scheme 4.15

From the analysis of the complex by negative electrospray ionization (ESI) mass spectrometry, it showed that complex **2** was formed (Scheme 4.15) after mixing with Fe^{3+} and dpps in aqueous medium (Figure 4.3a). The evidence showed that free dpps was present in the aqueous medium [(*m/z*=245, [dpps]$^{2-}$), (*m/z*=491, [dpps+H]$^{-}$) and (*m/z*=513,[dpps+Na]$^{-}$)]. Mono-iron complex was also present in the medium [*m/z*=518, $(Fe(dpps)_2)^{2-}$] (Figure 4.3a). Besides, we found evidence for diiron complex in the reaction medium [(*m/z*=561, $(Fe_2O(H_2O)(dpps)_2)^{2-}$), (*m/z*=807, $(Fe_2O(H_2O)(dpps)_3)^{2-}$) and (*m/z*=1063, $((Fe_2O(H_2O)_2(dpps)_4)^{2-}$)] (Figure 4.3 b and c). From the results, we believed that the structure of complex **2** (Figure 4.2) is similar to that of complex **1**.

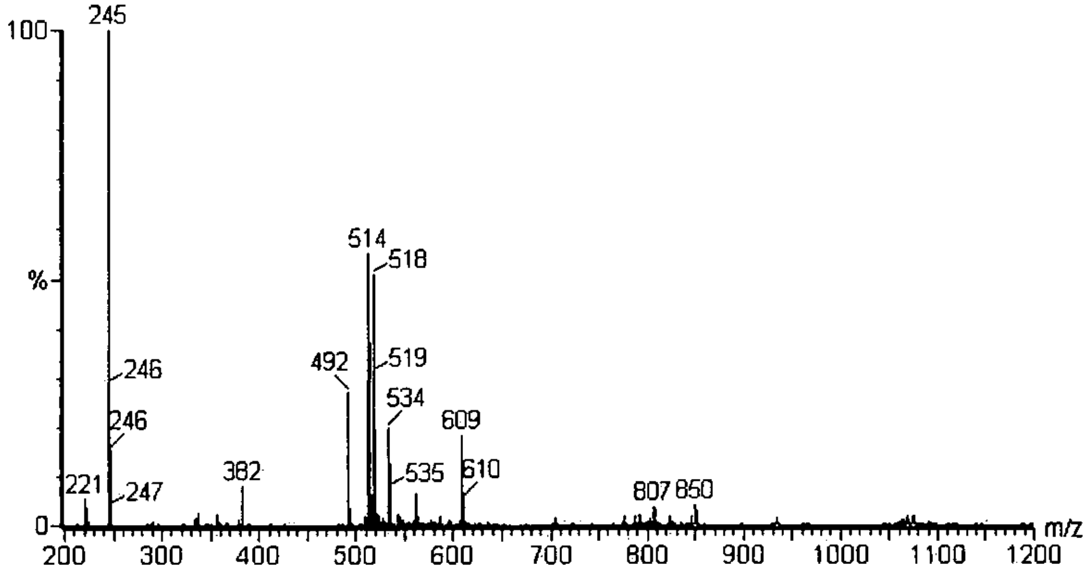


Figure 4.3a Negative electrospray ionization mass spectrum of a solution of Fe^{3+} and dpps in water.

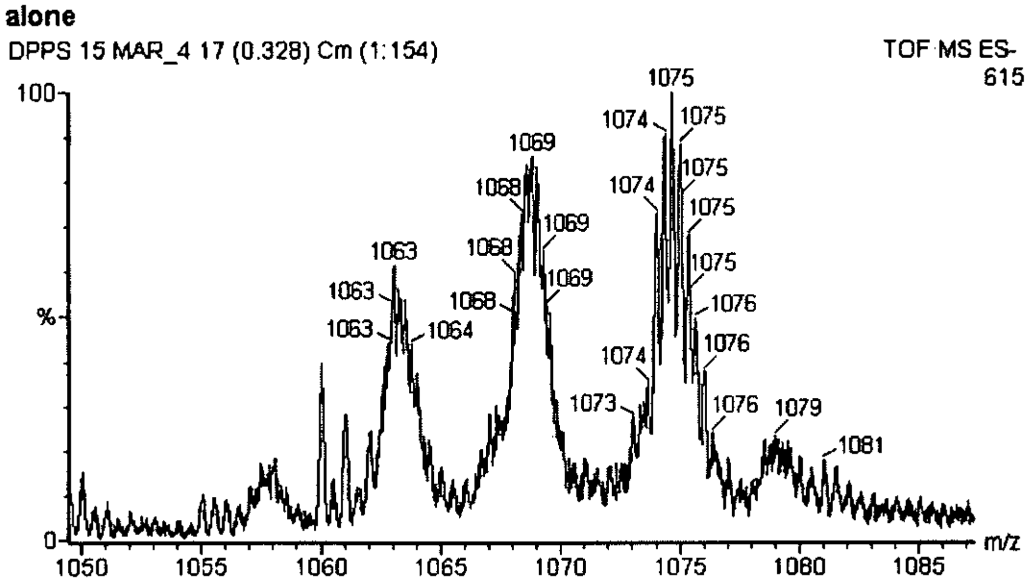


Figure 4.3b Expansion of *m/z*=1050-1090 showing *m/2* at 1063.

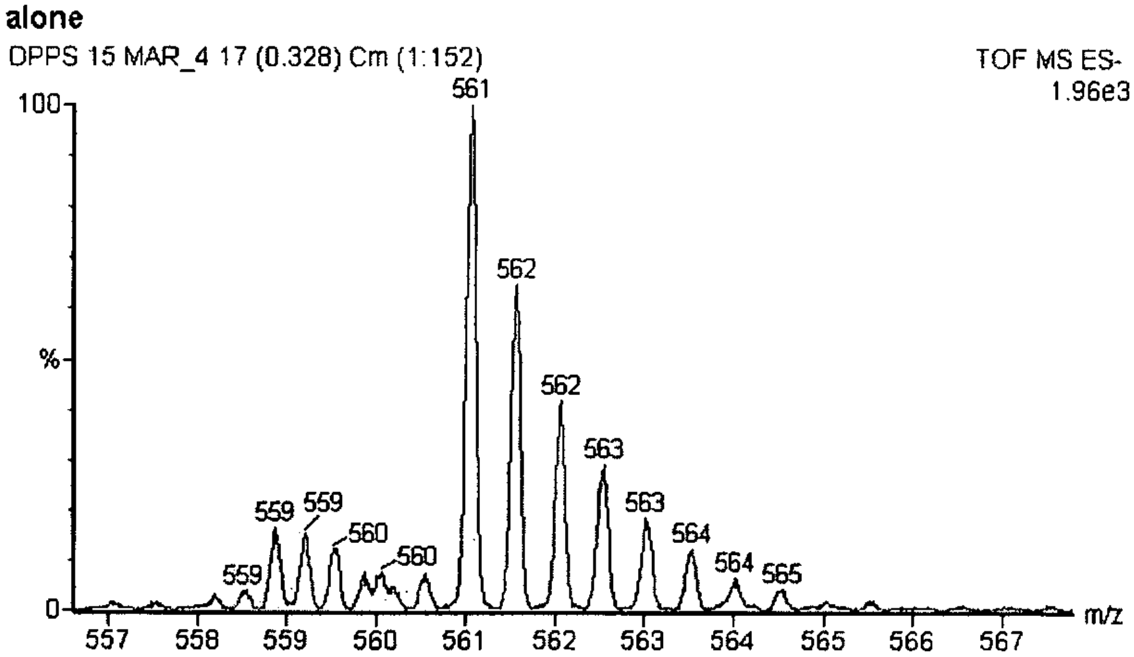


Figure 4.3c Expansion of *m/z*=555-570 showing *m/2* at 561.

The structure was corroborated by UV-vis spectroscopic studies. For a solution of Fe^{3+} in water, there was a peak near 300 nm which is assigned to the d-d transition of iron (Figure 4.4b).[19] There was a strong absorption band between 200 nm and 370 nm when dpps alone was dissolved with water. It is assigned to the absorption from dpps ligand (Figure 4.4c). As [bmim][BF_4] has very strong absorption band between 200 nm and 320 nm, the absorption either from iron or dpps (Figure 4.4a) could not be observed when [bmim][BF_4] was used as solvent. The presence of the characteristic absorbance in the UV-vis spectrum of Fe^{3+} and dpps in water suggested that the binuclear structure of complex **2** was formed in water (near 485 nm, figure 4.5a) in analogy with complex

1[19]. In ionic liquid, a similar UV-vis absorption was found but at a longer wavelength (near 545 nm, figure 4.5b). These absorptions are assigned to oxo-to-iron charge-transfer transition.[10,11,19] As the solvent changed from water to ionic liquid, the electronic ground state or excited state was changed and it led to a shift in the relative position of the energy levels and to a change in polarizability. Therefore, the band was shifted and this general phenomenon is called bathochromic effect. Similar UV-vis absorptions were found when complex **1** was formed in water and in ionic liquid (Figure 4.6). Also, we believed that the presence of two sulfonate groups of the ligand should make the catalyst more ionic which may help to stabilize the catalyst in [bmim][BF_4]. This is demonstrated by the results in Table 4.3 which examined the recovery and reuse of the catalyst-containing ionic liquid.

1-Octene was epoxidized when it mixed with complex **2** and peracetic acid in [bmim][BF_4]. After pentane extraction following the first cycle, the recovered reddish-brown [bmim][BF_4] containing complex **2** could be reused for the same reaction in the next cycle by adding the olefin and more peracetic acid to give 91% yield of epoxide. The yield of the epoxide was still quite high in the third cycle (80%). However, the yield was diminished by the fourth cycle (52%), but this could be easily rectified by adding a further catalytic amount of complex **2** to give again high yields of epoxide. From these studies, we concluded that the stability of complex **2** is much higher than that of complex **1** in the ionic liquid [bmim][BF_4].

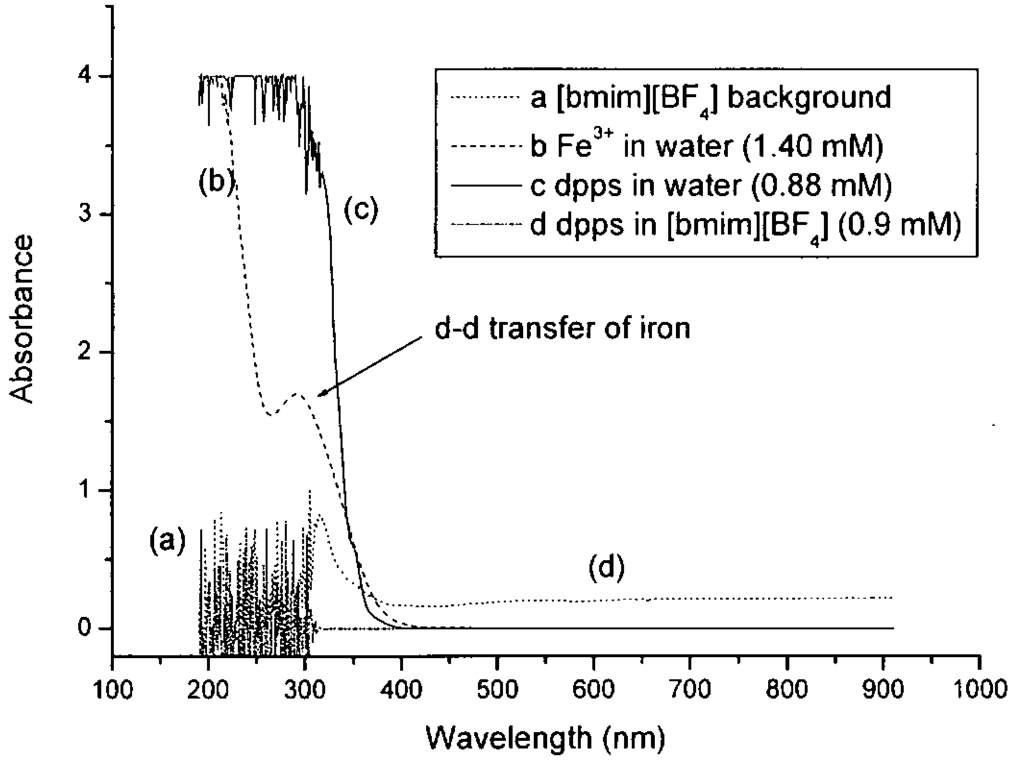


Figure 4.4 UV-vis spectra of Fe^{3+} and dpps in water and [bmim][BF_4].

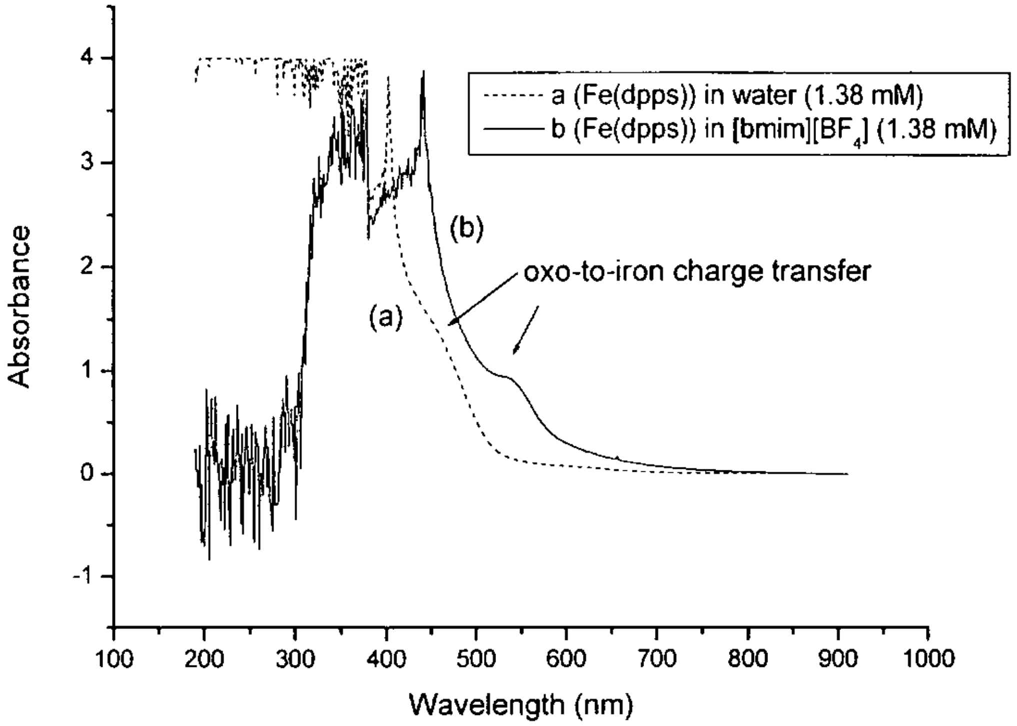


Figure 4.5 UV-vis spectra of (Fe(dpps)) in water and [bmim][BF$_4$].

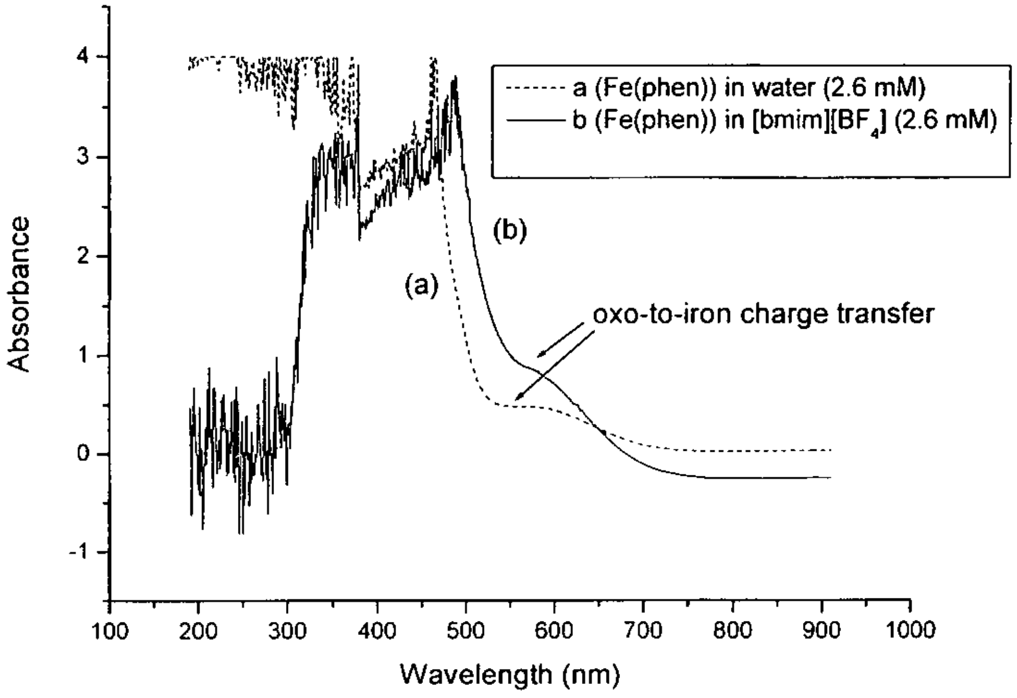
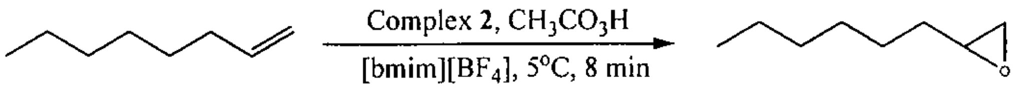


Figure 4.6 UV-vis spectra of Fe((phen)) in water and [bmim][BF$_4$].

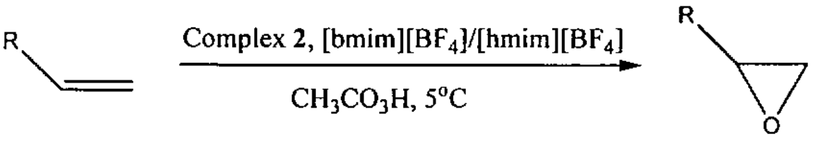
Table 4.3 Recovery and reuse of [bmim][BF$_4$] for the epoxidation of 1-octene



Cycle	1	2	3	4	5[b]	6	7
Yield (%)[a]	98(90)	96(91)	91(80)	60(52)	92(81)	95(87)	86(80)

[a] Yields were calculated on the basis on converted olefins and determined by GC-MS. Isolated yields were given in parenthesis. [b] Addition of 0.3 mol% complex **2**.

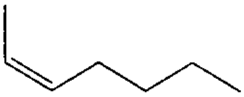
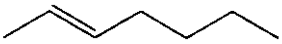
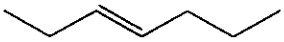
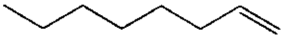
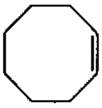
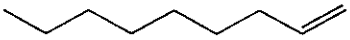
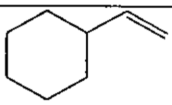
Other unactivated olefins were epoxidized in good to excellent yields (Scheme 4.16) and the results are summarized in Table 4.4.

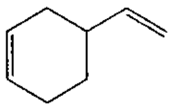
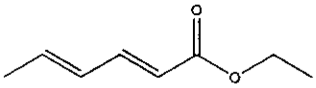
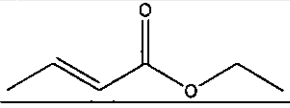


Scheme 4.16

The lower conversions observed for 1-nonene and 1-decene (entries 8 and 11) are attributed to their lower solubility in the chosen ionic liquid. As mentioned in Chapter 1.5, the hydrophobicity of ionic liquids can be easily adjusted by changing the chain length of alkyl groups. Thus, by using the ionic liquid 1-hexyl-3-methylimidazolium tetrafluorobrate ([hmim][BF_4]) instead of [bmim][BF_4] as the reaction medium, the epoxidation gave improved yields for 1-nonene and 1-decene (entries 9 and 12). This is presumably due to the increased solubilities of these olefins in [hmim][BF_4]. For 4-vinyl-1-cyclohexene (entry 14), only 1,2-epoxide was obtained, unlike the corresponding reaction conducted with complex **1** (Table 4.1, entry 4). We believed that complex **2** is more bulky than complex **1** such that 1,2-epoxide can approach the complex **1** more easily and thus oxidized to the diepoxide. For unconjugated diene substrates such as ethyl sorbate (entry 15), the more electron-rich C=C moiety was epoxidized to give the corresponding monoepoxide without the successive epoxidation of the other C=C fragment (*i.e.* no diepoxide was formed). On the other hand, double bond which was conjugated with a carbonyl function was not epoxidized (entry 16).

Table 4.4 Epoxidation of olefins

Entry	Substrate	Peracetic acid (eqiv.)	Time (min)	Conversion (%)	Yield (%)[a]
1		2.5	8	>99	99(90)
2		2.5	8	>99	99
3		2.5	8	>99	99
4		2.5	8	>99	99
5		2.5	8	98	99(93)
6		2.5	20	>99	99
7		2.5	10	>99	99(95)
8[b]		2.5	30	80	99
9[b,c]		2.5	25	95	99
10[b]		2.5	30	96	99(86)
11[b]		2.5	30	52	99
12[b,c]		2.5	30	92	99
13		5	10	>99	99(88)

14[d]		5	30	>99	99(92)
15[e]		2.5	10	>99	99(93)
16		2.5	10	1	99

[a] Yields were calculated on the basis on converted olefins and determined by GC-MS versus and internal standard. Isolated yield was given in parenthesis. [b] 0.6 mol% catalyst was used. [c] [hmim][BF_4] was used instead of [bmim][BF_4]. [d] only 4-vinyl-1-cyclohexene 1,2-epoxide was obtained. [e] only 4,5-monoepoixde was obtained.

4.4 Conclusion

A useful method for the epoxidation of unactivated olefins using a modified bis phenanthroline iron dimer complex as a catalyst in ionic liquids as the reaction medium has been developed. By using this catalytic system, a wide range of terminal olefins could be simply oxidized to epoxides in a short time. Since the ionic liquid could be easily recycled and reused, the cost and the pollution from the organic solvents could be reduced. Moreover, by using UV-vis spectrometry and ESI-MS, we have found that the structure of complex **2** is similar to that of complex **1**. Moreover, the binuclear structure of the catalyst remained unchanged both in water and ionic liquid. The mechanism of the system has been discussed. It is important to emphasize that complex **2** may not be the active catalytic species in the reaction. Indeed it may be the case that complex **2** is one of a number of possible catalytic species in the reaction. Further, mechanistic studies will need to be conducted in order to elucidate the mechanism of the epoxidation of olefins by complex **2**. Also, we proposed that either oxoiron(V) complex or oxoiron(IV) complex could be the active oxidants in the system.

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Chapter 5: Experimental Section

5.1 General Protocols

5.2 Experimental-Chapter 2

5.3 Experimental-Chapter 3

5.4 Experimental-Chapter 4

5.1 General Protocols

Materials

All Chemicals were purchased from Aldrich, Acros or Sigma and used as received. Glucose oxidase (catalase free) was purchased from Biocatalyst Limited.

Instrumentation

Proton (^{1}H) and carbon (^{13}C) NMR spectral measurements were carried out on a Bruker DPX-400MHz NMR spectrometer.

Differential pulse voltammetry (DPV) was carried out on a Bioanalytical System (BAS) model 100B electrochemical analyzer interfaced to a computer. A conventional two-compartmental electrochemical cell was used.

HPLC was conducted on a Waters Associate model 486 liquid chromatography equipped with a Sigma-Aldrich C18 column. Tetrabutyl ammonium acetate (1g/1L) was used as ion-paired agent. The solvent system was 60:40 (water:acetonitrile). The flow rate was 1mL/min and the absorbance wavelength was 230 nm. The injection volume was 50 μL.

GC-MS was conducted on a Hewlett-Packard model G1800C gas chromatograph equipped with an electron ionization detector. A HP-5MS (30 m X 0.25 mm X 0.25 mm) stainless steel column was employed in the analysis with helium as the carrier gas. The injection volume was 2 μL.

Infrared spectra were recorded on a Perkin Elmer 1800 Fourier Transform Infrared Spectrophotometer. Samples were analyzed as KBr pellets.

UV-visible spectra were recorded on a Milton Roy Spectronic 3000 photo diode array spectrophotometer.

Mass spectra were recorded on a Micromass Q-TOF2 Hybrid Quadrupole-Time of Flight Mass Spectrometer, using negative ion electrospray ionization techniques. Mass spectral data are listed as mass-to-charge ratios (m/z).

5.2 Experimental-Chapter 2

Epoxidation of 4-styrenesulfonic acid (1a) in the presence of varying concentrations of glucose

An aqueous solution of the olefin (0.1 mmol, **1a**), $NaHCO_3$ (1M) and hydrogen peroxide (0.15 M) was mixed with glucose (0.0.1 - 0.5M) in 500 µL of pH 7.0 phosphate buffer made up in D_2O. The reaction was monitored by ^1H NMR spectroscopy for the disappearance of the vinylic proton signals at 6.2 ppm as well as the appearance of the epoxide signals at 2.4 ppm.

Electrochemical determination of hydrogen peroxide concentration[1,2]

Platinum was used as the working electrode. It was first polished with 0.05 µm alumina, followed by ultrasonic cleaning and thorough rinsing with deionised distilled water. The electrode was then inserted into an electrochemical cell with 1.0 M sulfuric acid and the potential was scanned between 1.3 and -0.25 V vs SCE at a scan rate of 100 mV/s. The platinum electrode was considered as being activated if the cyclic voltammogram exhibited the characteristic hydrogen adsorption and desorption fine structure as well as the oxide formation and removal profile.

A solution of glucose was mixed with glucose oxidase (175 unit/mL) in a pH 7.0 phosphate buffer solution (10 mL) to make up a 0.2 M glucose solution. The mixture was bubbled with oxygen gas. DPV was carried out at different time intervals to monitor the hydrogen peroxide generated by the enzyme. A calibration curve was constructed using known concentrations of hydrogen peroxide

Chemoenzymic epoxidation of water-soluble olefins

A mixture of olefin (**1a** - **1c**, 0.1 mmol), $NaHCO_3$ (0.5M), glucose (0.2 M), glucose oxidase (175 units/mL) and $MnSO_4$ (0.1 mol %) was added to a pH 7.0 phosphate buffer solution (2.0 mL) which was prepared using D_2O as solvent. The mixture was bubbled with oxygen gas at a flow rate of 0.1 mL/min. The reaction was monitored by ^1H NMR spectroscopy for: (**1a** & **1b**) the disappearance of the vinylic proton signals at 6.2 ppm as well as the appearance of the epoxide signals at 2.4 ppm, (**1c**) the disappearance of the olefin proton signals at 5.3 ppm as well as the appearance of the epoxide signals at 3.1 ppm. The percentage yield was determined by ^1H NMR spectroscopy.

*Epoxidation of **1a** in the presence of varying concentrations of tert-butanol*

A solution of olefin **1a** (0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol

%) and GOx (175 unit/mL) was mixed with different concentrations of tert-butanol in a pH 7.0 phosphate buffer solution in D_2O (15 mL). The reaction was monitored by ^1H NMR spectroscopy for the disappearance of the vinylic proton signals at 6.2 ppm as well as the appearance of the epoxide signals at 2.4 ppm

*Epoxidation of **1a** in the presence SDS*

A solution of olefin **1a** (0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol %), SDS (5 mM) and GOx (175 unit/mL) was mixed in a pH 7.0 phosphate buffer solution in D_2O (15 mL). The reaction was monitored by ^1H NMR spectroscopy for the disappearance of the vinylic proton signals at 6.2 ppm as well as the appearance of the epoxide signals at 2.4 ppm

Chemoenzymatic epoxidation of water-insoluble olefins

A solution of olefin (**1d-1h**, 0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol %) and GOx (175 unit/mL) was mixed in a pH 7.0 phosphate buffer solution in water (20 mL) containing 10% tert-butyl alcohol or SDS (5 mM). The solution was then saturated with oxygen and the mixture was stirred. When the reaction was completed, water (20 mL) was added and the mixture was extracted with diethyl ether (5 x 20 mL). The organic layer was then washed with brine (2 x 15 mL), dried over sodium sulfate, filtered, and the diethyl ether was removed *in vacuo* to give the desired product. The percentage yields were determined by GC-MS with internal standard (tetradecane) or ^{1}H NMR.

Immobilization of glucose oxidase in sol-gel

A solution of tetramethoxysilane (300 μL) in hydrochloric acid (0.1 M, 10 μL) was mixed vigorously with distilled water (700 μL) for 3 hours. After this time, pH 7.0 phosphate buffer solution (200 μL) was added to the reaction mixture in order to neutralize the excess acid. The enzyme GOx (2900 unit) was then added and the resulting mixture was vigorously stirred. The mixture was then put into refrigerator for 2 days at 4℃ for condensation.

Immobilization of glucose oxidase on silica gel

A quantity of silica gel (1.0 g, 60 mesh, Aldrich) was activated under vacuum at about 80 ℃ for 2 days. After cooling, a solution of 3-(aminopropyl)-triethoxysilane (4 mL) in chloroform (60 mL) was added and the resulting mixture was stirred for 24 hours. The slurry was filtered off and the solid was washed with chloroform (10 mL) and dried in air. The solid was then mixed with *bis*(sulfosuccinimidyl) suberate (1.5 mL, 0.57 mg/mL) in a pH 7.0 phosphate buffer solution (20 mL). After 20 minutes, the solid was filtered off and washed with the buffer solution (5 mL). It was then mixed with GOx (4500 units) in a pH 7.0 phosphate buffer solution (20 mL). After 30 minutes, the yellowish solid was filtered off and washed with the buffer solution. The immobilized GOx was kept under -4℃.

*Epoxidation of **1a** with immobilized enzyme:*

(a.) Sol-gel immobilized glucose oxidase

A solution of olefin **1a** (0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol %) and the sol-gel immobilized GOx (2900 units) was mixed in a pH 7.0 phosphate buffer solution (in D_2O) (2 mL) for 3 hours with stirring under an atmosphere of oxygen. After this time, the immobilized GOx was filtered and washed with pH 7.0 phosphate buffer solution in D_2O. The yield was determined by ^1H NMR spectroscopy.

b.) Silica-gel immobilized glucose oxidase

A solution of alkene **1a** (0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol %) and the silica-gel immobilized GOx (4500 units) was mixed in a pH 7.0 phosphate buffer solution in water (20 mL) and the mixture was allowed to react for 7 hours with stirring under an atmosphere of oxygen. After this time, the immobilized GOx was separated by centrifugation and washed with a pH 7.0 phosphate buffer solution. The yield was determined by HPLC and benzoic acid was used as an internal standard. The recovered silica-gel immobilized GOx could be stored at -4 °C and reused for the epoxidation reaction.

5.3 Experimental-Chapter 3

Preparation of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]

The [bmim][BF_4] was prepared from bromobutane (1.2 mol) and N-methylimidazole (1.0 mol) using the recently reported microwave-assisted procedure.[3] The [bmim][BF_4] was purified using the same procedure reported by Park and Kazlauskas.[4]

Preparation of tetramethylammonium hydrogencarbonate (TMAHC)[5]

A 25% w/w solution of tetramethylammonium hydroxide in water (10 g) was concentrated *in vacuo* and taken up in methanol (40 mL). The resulting solution was then bubbled with carbon dioxide at room temperature for 4 hours. Methanol was distilled off under reduced pressure and pale brown solid was obtained, 3.65g, 99%. IR (KBr, cm^{-1}) 1655, C=O.

Typical procedure for the epoxidation of olefin with TMAHC/Mn^{2+}/H_2O_2 in [bmim][BF_4]

To [bmim][BF_4] (300 μL) was added TMAHC (0.02 g), followed by oelfin (20 μL, 0.15 mmol), $MnSO_4$ (0.2 mol%), and hydrogen peroxide (200 μL, 35%). The reaction mixture was stirred vigorously at room temperature. After this time, the reaction mixture was extracted with pentane (5 x 2 mL), (It is generally assumed that, if necessary, pentane can be replaced by supercritical carbon dioxide for the extraction of lipophilic substrates[6,7]) and the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the desired products. The percentage yields were determined by GC-MS using an internal standard (tetradecane) or by ^1H NMR spectroscopy

Recycling of [bmim][BF_4] in the epoxidation of styrene (1a)

To [bmim][BF_4] (1200 μL) was added TMAHC (0.08 g), followed by **1a** (80 μL, 0.6 mmol), $MnSO_4$ (0.2 mol%), and hydrogen peroxide (800 μL). The reaction mixture was stirred vigorously at room temperature. When the reaction was completed, the mixture was extracted by pentane (5 x 3 mL), and the organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* .to afford the desired product. The percentage yields were determined by GC-MS using an internal standard (tetradecane). The residual pentane in the [bmim][BF_4] was removed by rotary evaporation. The recovered ionic liquid was then reused in further epoxidation reactions of **1a** as described by Table 3.2.

5.4 Experimental-Chapter 4

The preparation of ionic liquids followed a previously reported procedure.[3,4]

Synthesis of $([((phens)_2(H_2O)Fe^{III})_2(u\text{-}O)](ClO_4)_4)$ *(complex 1) stock solutions*[8]

$Fe^{III}(ClO_4)_3$ hydrate (0.197g, 0.56 mmol) was dissolved in 0.5 mL water, then a 4.5 mL acetonitrile solution of phenanthroline (0.2g, 1.1 mmol) was added. The green-brown solution was stirred for 5 minutes at room temperature. The stock solution (0.055 M) was stored at -4°C to ensure that no decomposition of the complex occurred.

Synthesis of $([((dpps)_2(H_2O)Fe^{III})_2(u\text{-}O)](Na)_2)$ *(complex 2) stock solutions*

$Fe^{III}(ClO_4)_3$ hydrate (0.02g, 0.056 mmol) was dissolved in 1 mL water, and bathophenanthrolinedisulfonic acid disodium salt (0.065 g, 0.11 mmol) was added. The reddish-brown solution was stirred for 5 minutes at room temperature. The stock solution (0.055 M) was stored at -4°C to ensure that no decomposition of the complex occurred.

Typical procedure for the epoxidation of olefins using iron catalyst in ionic liquids

Complex **1** (or compelx **2**) (0.3 mol%) and olefin (0.18 mmol) were added to [bmim][BF_4] (200 μL). Peracetic acid (100 μL, 32%) was added via a syringe over the course of 1 minute with stirring. The reaction mixture was stirred vigorously at 5°C. After this time, the mixture was extracted by pentane (5 x 1 mL).[6,7] The organic layer was washed with saturated $NaHCO_3$, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired product. The percentage yields were determined by GC-MS using an internal standard (tetradecane).

Recycling of [bmim][BF₄] in the epoxidation of 1-octene

Complex **1** (0.3 mol%) and olefin (0.93 mmol) were added to [bmim][BF_4] (1000 μL). Peracetic acid (500 μL, 32%) was added via a syringe over the course of 5 minutes with stirring. The reaction mixture was stirred vigorously at 5°C for 5 minutes. After this time, the mixture was extracted by pentane (5 x 2 mL) and the organic layer was washed with saturated $NaHCO_3$, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the desired product. The percentage yields were determined by GC-MS with internal standard ((tetradecane). The recovered ionic liquid was then reused for the repeated epoxidations as described in Table 4.2.

Recycling of [bmim][BF$_4$*] in the epoxidation of 1-octene with complex* ***2*** *as catalyst*

Complex **2** (0.3 mol%) and olefin (0.93 mmol) were added to [bmim][BF_4] (1000 μL). Peracetic acid (500 μL, 32%) was added via a syringe over the course of 5 minutes with stirring. The reaction mixture was stirred vigorously at 5°C for 8 minutes. When the reaction was completed, the mixture was extracted by pentane (5 x 2 mL), washed with saturated $NaHCO_3$, dried over sodium sulfate, filtered, concentrated *in vacuo* to give the desired product. The percentage yields were determined by GC-MS with internal standard. The recovered oily yellowish liquid was then reused for the same epoxidation of olefin as described by Table 4.3. In order to avoid the ionic liquid containing a larger amount of acetic acid, after the 4th cycle, the ionic liquid was diluted with dichloromethane (10 mL) and the resulting mixture was washed with saturated $NaHCO_3$ (3 x 10 mL). Dichloromethane was then removed from the ionic liquid *in vacuo* and the recovered ionic liquid was reused for the 5th cycle reaction after adding of catalyst.

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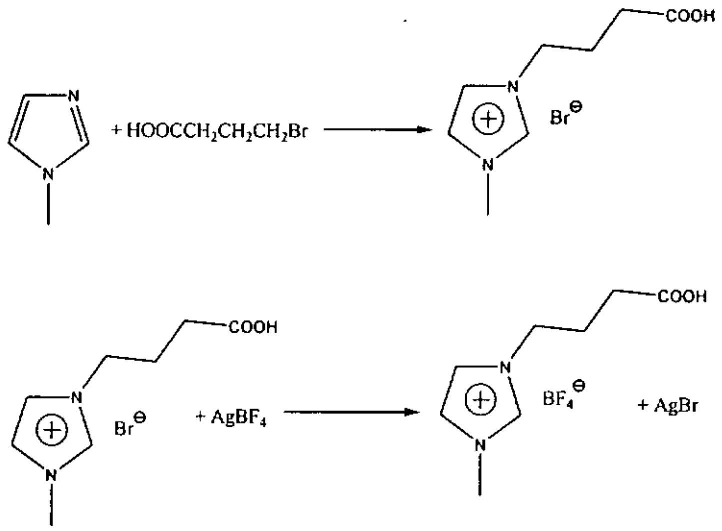
Chapter 6: Future Work

Future work

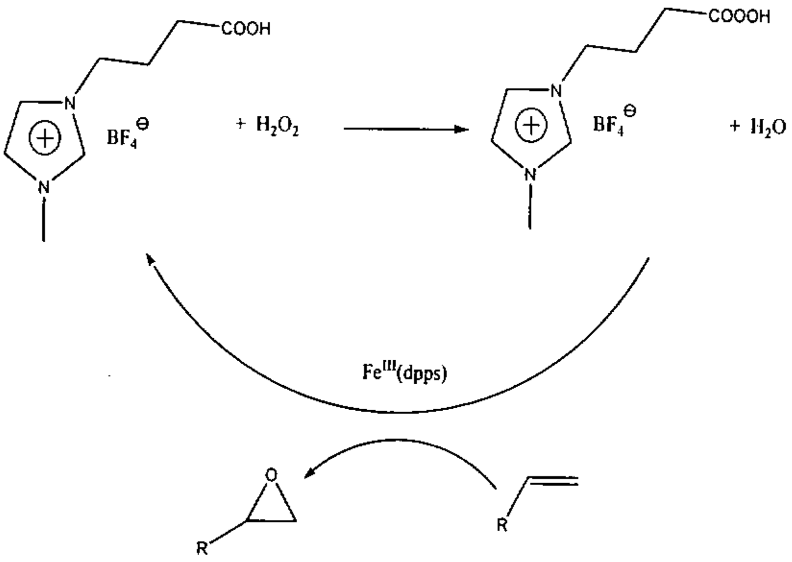
In recent years, the use of soluble polymer supports has received considerable attention because such "liquid phase" synthesis retains many of the advantages of conventional solution phase chemistry. Thus, soluble poly(ethyelene glyol) (PEG) and other polymers have been used for the synthesis of oligopeptides[1] and oligonucleotides.[2] However, there are some limitations when soluble polymer supports are used, e.g. loading capacity and limited solubility.

As mentioned in Chapter 1.5, there has been considerable interest in the use of ionic liquids as an environmentally benign reaction media. Recently, Chan and coworkers[3] have demonstrated that low molecular weight ionic liquids can be used as soluble supports for organic synthesis. Phase separation between the "ionic liquid phase", the organic phase and the aqueous phase can be achieved for product separation and purification.

In Chapter 4, an effective catalytic system for the epoxidation of terminal olefins in ionic liquids was demonstrated. However, acetic acid was always a by-product in this system since peracetic acid was used as the oxidant. In the future, we would like to develop a modified system such that the carboxylic acid group is attached onto the ionic liquid (Scheme 6.1) itself. When we add hydrogen peroxide into the system, it will react with the carboxylic acid to form an ionic liquid-bound peroxy acid which will then function as the oxidant. After the reaction, the carboxylic acid moiety will be regenerated, ready to be re-oxidized with a further equivalent of hydrogen peroxide. In this case, water is the only by-product (Scheme 5.2).



Scheme 6.1



Scheme 6.2

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APPENDIX

The Calculation of Equilibrium Constant for the Formation of Peroxymonocarbonate Ion in Ionic Liquid

$$H_2O_{2(solv)} + HCO_3^-{}_{(solv)} \xrightleftharpoons{K_1} H_2O_{(solv)} + HCO_4^-{}_{(solv)}$$

The initial concentration of hydrogen peroxide (H_2O_2) is 0.6 M.

The initial concentration of tetramethylammonium hydrogen carbonate (HCO_3^-) is 0.3 M

The initial concentration of water (H_2O) and peroxymonocarbonate ion (HCO_4^-) are 0 M

Assumption: One HCO_3^- reacted with one H_2O_2 and formed one H_2O and one HCO_4^-.

According to the area ratio of ^{13}C NMR spectrum (Figure 1),

the final concentration of H_2O_2 is 0.42 M.

The final concentration of HCO_3^- is 0.12 M.

The final concentration of H_2O is 2.09 M

The final concentration of HCO_4^- is 0.18 M

So, the equilibrium constant K_1:

$$K_1 = \frac{[H_2O][HCO_4^-]}{[H_2O_2][HCO_3^-]}$$

$$= \frac{(2.09)(0.18)}{(0.42)(0.12)}$$

$$=7.5$$

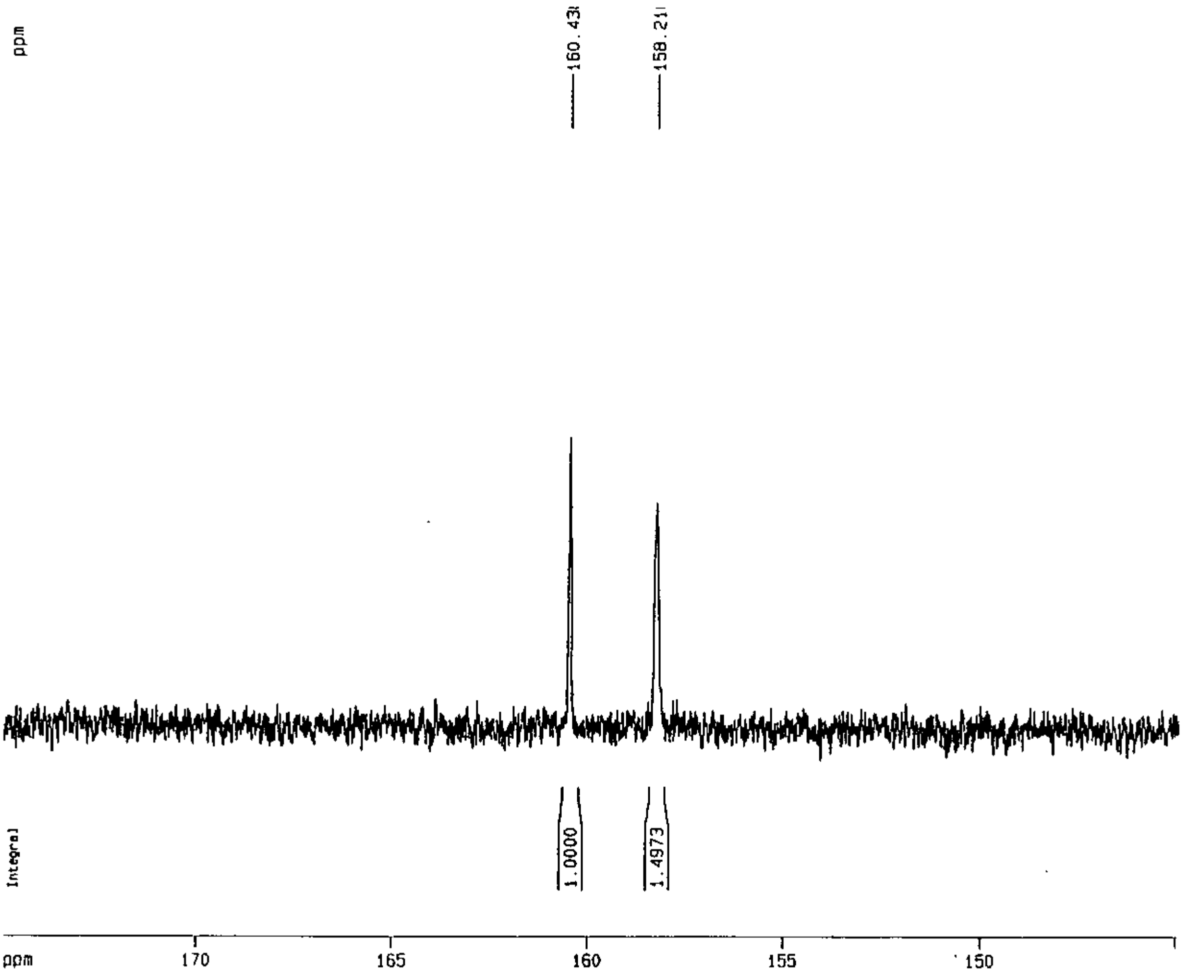

Figure 1. ^{13}C NMR spectrum for a solution at 25°C of 0.3 M TMAHC and 0.6 M H_2O_2 in 500 μL [bmim][BF$_4$].