Nitration of simple aromatics and epoxidation of alkenes in ionic liquids.

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Nitration of Simple Aromatics and Epoxidation of Alkenes in Ionic Liquids

by

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ABBREVIATIONS

1.	IL	Ionic liquids
2.	$scCO_2$	Supercritical carbon dioxide
3.	$[Emim]^+$	1-Ethyl-3-methylimidazolium
4.	$[C_3\text{-mim}]^+$	1-Propyl-3-methylimidazolium
5.	$[C_4\text{-mim}]^+$ or $[bmim]^+$	1-Butyl-3-methylimidazolium
6.	$[C_6\text{-mim}]^+$	1-Hexyl-3-methylimidazolium
7.	$[C_{10}\text{-mim}]^+$	1-Decyl-3-methylimidazolium
8.	$[C_6H_5CH_2\text{-mim}]^+$	1-Benzoyl-3-methylimidazolium
9.	$[N\text{-bupy}]^+$	*N*-Butylpyridinium
10.	$[CH_3O(CH_2)_2\text{-mim}]^+$	1-(2-Methoxyethyl)-3-methylimidazolium
11.	$[HO(CH_2)_2\text{-mim}]^+$	1-(2-Hydroxylethyl)-3-methylimidazolium
12.	$[RR'im]^+$	Dialkylimidazolim
13.	BPC	1-Butylpyridinium chloride
14.	EtDBU	8-Ethyl-1,8-diazobicyclo[5,4,0]-7-undecenium
15.	TMHC	Trimethylaminehydrochloride
16.	$[Capemim]^+$	3-(5-Carboxyphenyl)-1-methylimdazolium)
17.	MeDBU	8-Methyl-1,8-diazobicyclo[5,4,0]-7-undecenium
18.	$[N_{6444}]^+$	*N*-Hexyl-*N*,*N*,*N*-tributyl ammonium
19.	$[Ppmim]^+$	1-(3′-Phenylpropyl)-3-methylimidazolim
20.	$[CF_3CH_2mim]^+$	1-(2,2,2-Trifluoroethyl)-3-methylimidazolium
21.	$[bdmim]^+$	1-Butyl-2,3-dimethylimidazolium
22.	$[Hydemim]^+$	2-Hydroxyethylimidazolium
23.	NTf_2^-	Bis(trifluoromethylsulfonyl)amide
24.	NfO^-	Nonafluorobutanesulfonate
25.	TA^-	Trifluoroacetate
26.	[Lactate]	(*S*)-2-hydroxypropinate
27.	SEt_3NTf_2	Triethylsulfonium bis(trifluoromethylsulfonyl)amide
28.	DC18C6	Dicyclohexano-18-crown-6
29.	Nbd	Norbornadiene
30.	Cod	Cyclooct-1,5-diene
31.	CAS	Camphorsufonic acid
32.	MTO	Methyltrioxorhenium
33.	MTBE	Methyl-*tert*-butyl ether
34.	NBS	*N*-Bromosuccinimide
35.	*m*-CPBA	*m*-Chloroperbenzoic acid
36.	MMPP	Magnesium monoperoxyphathlate
37.	NMO	*N*-Methylmorpholine *N*-oxide

38. 4-PPNO	4-Phenylpyridine *N*-oxide
39. DMF	*N,N*-dimethylformamide
40. THF	Tetrahydrofuran
41. Salen	*N,N'*-ethylenebis(salicyldeneaminato)
42. $Eu(hfc)_3$	Europium tris[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorate
43. TLC	Thin layer chromatography

SUMMARY

The purpose of this study is to develop new green approaches for some organic reactions by using ionic liquids as solvents or co-solvents.

The thesis is composed of six chapters. The principle of green chemistry and three green solvents reported in the literature are introduced in **Chapter 1**.

Chapter 2 introduces the development of ionic liquids, the compositions and properties of ionic liquids and some applications of ionic liquids in chemistry.

Chapter 3 reviews the methods to synthesise various ionic liquids. In addition, syntheses of seven ionic liquids, based on organic cations, including 1-butyl-3-methyl-imidazolium, 1-butyl-2,3-dimethylimidazolium and 1-(2-hydroxyl)-3-methylimidazolium cations, and simple anions, including bromide, tetrafluoroborate, hexafluorophosphate and acetate, are described.

Chapter 4 describes attempts to use ionic liquids as solvents or co-solvents in several nitration systems, including fuming nitric acid–zeolite–IL, fuming nitric acid–IL, fuming nitric acid–acetic anhydride–IL, cupric nitrate–IL and concentrated nitric acid–$Yb(OTf)_3 \cdot nH_2O$–IL. The fuming nitric acid–acetic anhydride–IL system has proved to be the best one from the point of view of both the reaction rate and the selectivity for formation of the products. Furthermore, in this system, a biphasic system (when IL **b** or IL **c** was used) or a triphasic system (when IL **a** was used) formed when the extraction solvent, hexane, was added. Thus, the separation of products from IL solvents is easy. Several simple aromatics have been successfully nitrated in such a system.

Chapter 5 describes attempts to use ionic liquids as solvents or co-solvents in the chiral epoxidation of alkenes. Aqueous NaOCl, aqueous H_2O_2, anhydrous urea-H_2O_2 adduct and molecular oxygen have all been tested as oxidants in this procedure. NaOCl is considered as the best choice in view of both of the reaction rate and the ee of the epoxide. Furthermore, when NaOCl was used, a biphasic system formed in each of the systems IL **a**–CH_2Cl_2 (2 : 3, v/v)–aqueous NaOCl, pure IL **a**–aqueous NaOCl, and pure IL **b**–aqueous NaOCl on addition of hexane. A triphasic system formed when IL **a**–EtOAc (4 : 1, v/v) was used as the solvent. Therefore, it is very easy to separate the product from the IL–catalyst mixture and recover both the catalyst and IL solvent.

Chapter 6 describes the modification of Jacobsen-type complex **5.3** by introducing methyl groups at the C7 and C7′ positions to form complex **6.10**. Unfortunately, complex **6.10** decomposes when it is tested to catalyse the epoxidation of 1,2-dihydronaphthalene using aqueous NaOCl, which is basic, as the oxidant in CH_2Cl_2. Although it might be stable under dry neutral conditions when molecular oxygen instead of NaOCl is used as the oxidant, in a mixture of [bmim]PF_6–CH_2Cl_2 (2 : 1, v/v), it provides only a low yield of the desired product.

CONTENTS

Chapter 3 Synthesis of Ionic Liquids

Chapter 4 Nitration of Simple Aromatics in Ionic liquids

Chapter 5 Epoxidation of Alkenes in Ionic Liquids

Chapter 6 Modifications of a Jacobsen-type complex

Chapter 1

Green Chemistry

1.1 Green Chemistry

The challenge in chemistry is to develop new products, processes and services that are required now and in the future. Unfortunately, millions of tons of waste are produced and released each year, and cause a great burden to the environment. Therefore, 'Green Chemistry' is urgently being sought throughout the world in order to develop new or improve existing chemical products and processes to make them less hazardous to both human beings and the environment. These advances are not confined only to the academic arena, but are clearly being introduced in industrial processes.

What is ***Green Chemistry***? Green Chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances;[1] Green chemistry is environmentally benign, linking the design of chemical products and processes with their impacts on human health and the environment.[2] Anastas and Warner[2] have developed the Twelve Principles of Green Chemistry to aid people in assessing how green a chemical, a reaction or a process is. They are cited as follows:

1. Prevention: it is better to prevent waste than to treat or clean up waste after it is formed.
2. Atom Economy: synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Less Hazardous Chemical Syntheses: wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Designing Safer Chemicals: chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. Safer Solvents and Auxiliaries: the use of auxiliary substances (*e.g.*, solvents, separation agents, *etc.*) should be made unnecessary whenever possible and, innocuous when used.
6. Design for Energy Efficiency: energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks: a raw material feedstock should be renewable rather than depleting whenever technically and economically practical.

8. Reduce Derivatives: unnecessary derivation (blocking group, protection/deprotection, temporary modification of physical/chemical process) should be avoided whenever possible.

9. Catalysis: catalytic reagents (as 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 do not persist in the environment and break down into innocuous degradation products.

11. Real-time Analysis for Pollution Prevention: analytical methodologies need to be further developed to allow for hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention: substances and the form of a substance used in a chemical should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

In order to encourage people to comply with these principles and/or to recognize achievements in applied green chemistry/technology, some actions have been taken. For example, the Royal Society of Chemistry (RSC) journal 'Green Chemistry' made its debut in 1999, and the Presidential Green Chemistry Awards were announced in 1995 by the Clinton administration and the first awards were presented in 1996.

1.2 Green solvents

Chemistry is dominated by the study of species in solution. Volatile organic solvents have a detrimental impact on the environment, and there is a compelling need for synthetic techniques that could reduce the environmental burden. Solvents are high on the list of damaging chemicals for two simple reasons: (i) they are used in huge amounts, and (ii) they are volatile and easily lost to the environment. Based on these reasons, the search for alternatives to the most damaging solvents has become very important. The ideal solvent should have a very low volatility, it should be chemically and physically stable, recyclable and reusable and eventually

easy to handle. In addition, solvents that allow more selective and rapid transformations will have a significant impact.

Fortunately, as the introduction of cleaner technologies has become a major concern throughout both industry and academia, chemists and related researchers have been continuously making some achievements in this respect. The first breakthrough was that water has emerged as a new useful reaction medium and been successfully used in biphasic industrial metal-catalysed reactions during the last 20 years.[3] However, the limitation is the low solubility of organic substrates in water, which causes low reaction rates. Moreover, water is a protic coordinating solvent and it reacts easily with organometallic complexes. In order to overcome these obstacles, another three kinds of fluids have been developed and have been used as alternative greener solvents in organic synthesis, catalytic and separation processes. These are: 1) perfluorinated fluids; 2) supercritical fluids; 3) ionic liquids.

1.2.1 Perfluorinated fluids

Perfluorinated fluids (PFFs), such as perfluoroalkanes, perfluoroalkyl ethers and perfluoroalkylamines, have been recognized generally to have unusual properties, such as high density, high stability, non-polar/inert characteristics in organic reactions, low strength and extremely low solubility in water and some organic chemicals.[4] Because of these properties, they are drawing attention as new solvents for many organic and catalytic reactions, especially for reactions involving unstable reagents, or a requirement for separating low boiling components.[5,6] However, it is still not very clear what kinds of reactions to run in these solvents and how to run them. Furthermore, some catalysts cannot dissolve in fluorous fluids and thus the ligands have to be modified in order to give the catalyst the desired solubility. Moreover, the synthesis of this type 'fluorous catalyst' often requires tedious steps and expensive starting materials.[7,8] In addition, decomposition of such solvents at high temperature yields toxic compounds and fluorous derivatives which are difficult to remove from the organic phases completely.[9,10]

1.2.2 Supercritical fluids

Supercritical fluids (SCFs), such as supercritical water, supercritical carbon dioxide, supercritical propane or supercritical ammonia, *etc.*, are described as fluids that possess a combination of properties associated with either a liquid or a gas. Since SCFs are highly compressible, it is possible to tune their properties, from gas-like through to liquid-like. It is this tunability that renders SCFs as highly unusual solvents for a wide range of common compounds.[11] Performing chemical reactions in such fluids offers some advantages, such as providing easier product separation because solubility of chemical compounds can be a function of pressure and temperature in the critical region, and providing higher diffusivities than liquids and better heat transfer than gases. It is worthy to mention, however, that the ideal fluid for a supercritical process is non-toxic, non-combustible, commercially available in high purity, environmentally benign and has readily attainable critical parameters. Of the fluids commonly studied only CO_2 exhibits all of these properties (critical constant; Tc = 304.2 K, Pc = 72.8 bar). The main problem associated with the widespread uses of supercritical CO_2 ($scCO_2$) is attributed to its low polarity and hence a low solvation ability for polar solutes. Therefore, in some cases it is necessary to add a polar co-solvent to increase the solvent polarity. Such co-solvents, however, have limited solubility in $scCO_2$ and often leave residues in the product when the system is depressurised. In addition, the critical conditions needed for use of SCFs are significant limitations. For example, the elevated pressures and temperatures, which consequently add to the energy cost, have to be associated with chemical reactions that require such conditions.[12,13,14]

1.2.3 Ionic liquids

The third class of green solvents comprises ionic liquids (ILs). The link between ionic liquids and green solvents is also related to the properties of such liquids. Being composed entirely of ions, ILs posses negligible vapour pressure. Also, the wide range of possible cations and anions means that other solvent properties may be controlled. Thus, ILs display a wide liquid ranges (typically from 40 °C to 200 °C), controlled miscibility with organic compounds, good thermal stability, low coordination tendency, high ionic conductivity and a large

electrochemical window. These properties make such liquids attractive for use as solvents in electrochemistry, liquid-liquid separation process and organic reactions. Particularly in the last decade, there has been great interest in the use of this kind of solvents for a wide range of organic reactions.[15,16,17,18,19,20] Many reactions show advantages when conducted in such solvents, with regard to enhanced reaction rate, improved selectivity, or easier reuse of catalysts. The next chapter is reviews of the background and development of uses for this type of liquid.

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Chapter 2

Ionic liquids

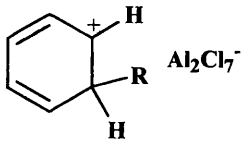
2.1 Introduction to Ionic Liquids

2.1.1 Historical development

What are ionic liquids? Quite simply, they are liquids that are composed entirely of ions (cations and anions) without any neutral molecules. In contrast to most molten salts, which, in general, are thought to be high-melting, highly viscous and very corrosive media, ionic liquids are salts that melt at ambient temperature.[1,2] Synonyms used for ionic liquids include 'room temperature molten salts', 'low temperature molten salts', 'ambient temperature molten salts' and 'liquid organic salts'. Clearly, the roots of ionic liquids are firmly planted in traditional high temperature molten salts. Another term, which is used quite recently to represent a new kind of solvent including ionic liquids,[1,2] is 'neoteric solvent'. More precisely speaking, 'neoteric solvent' particularly means a new type of solvent, or old material that is finding new application as solvent. For example, supercritical fluids are also good neoteric solvents. Among those synonyms, the very common and widely used one is ionic liquids or room temperature ionic liquids (abbreviated as ILs hereafter). ILs are already liquid at low temperatures (<100 °C, sometimes as low as –96 °C) and have relatively low viscosities, are non-corrosive and easily handled like ordinary solvents.

ILs are not new. It is generally acknowledged that ethylammonium nitrate, $[EtNH_3]NO_3$, which has a recorded melting point of 12 °C but usually contains 200–600 ppm water, was the first described ionic liquid in 1914.[3] This material is formed simply by the reaction of ethylamine with concentrated nitric acid. However, its discovery did not prompt a great amount of interest at that time. Furthermore, according to a review by Wilkes,[4] the 'embryo' of ionic liquid had been discovered a long time before the discovery of $[EtNH_3]NO_3$. This review states: ''the first documented observation of ionic liquids by chemists was the so-called 'red oil' formed during Friedel–Crafts reactions. The prototypical Friedel–Crafts reaction is the reaction of the aromatic substrate benzene with the incipient electrophile chloromethane to form toluene. A Lewis acid, such as $AlCl_3$, catalyzes the reaction. Often during the course of this reaction a separate red-coloured phase

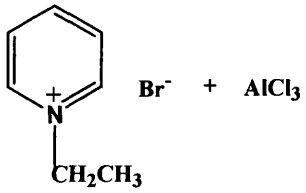
appears, but the composition of the red oil was not known when this was first observed in the mid–19th century. When NMR spectroscopy became widely used by chemists, the structure of the red oil was identified as a salt having a cation that was the long-presumed stable intermediate in a Friedel–Crafts reaction called the sigma complex''.[4] For $AlCl_3$-catalysed reactions, the structure, reported in Wilkes' review, proposed for the liquid was the heptachlorodialuminate salt shown as formula **I**. Wilkes wrote: ''This red oil ionic liquid and more complicated variations were patented as a useful material, but I know of no major industrial use''.[4]



I

CAS Registry Number: 78041-07-3

The first ionic liquid with a chloroaluminate ion was developed in 1948 by Hurley and Wier[5,6,7,8] at the Rice Institute in Texas, and was used as the bath solution for electroplating aluminium. Its structure is formula **II**. However, these systems were not studied further until the late 1970s when the group of Osteryoung rediscovered them.[9,10]



II

It is worthy to mention that another ionic liquid was found during the time between the investigations of Hurley–Wier and Osteryoung–Wilkes. One was a mixture of copper (I) chloride and alkylammonium chloride, which was found to be liquid at room temperature by Yoke in the 1960s.[11] Nevertheless, this ionic liquid proved somewhat to be useful for spectroscopy, but was not widely used for other purposes. Another one, called clathrate, was discovered by Atwood and his colleagues in the 1970s.[12] The structure for that ionic portion is **III**. IL **III** was patented for use in cool liquefaction and petroleum recovery from tar sand by

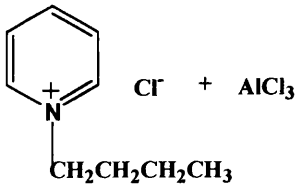
forming a liquid clathrate of the mixture with a given multidentate macromolecular compound containing complex salt.

$$\mathbf{M[Al_2(CH_3)_6X] \cdot n\ Aromatics}$$

M: *mono-* or *di-* or trivalent cation;
X: *mono-* or *di-* or trivalent anion;
n = 2~4.

III

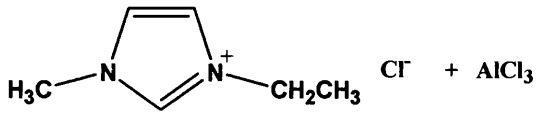
Let us go back to the development of low temperature liquid chloroaluminate melts investigated by the Osteryoung group, whose interests were mainly in searching for an ideal material for an electrochemical electrolyte. The first useful liquid they discovered was 1-butylpyridinium chloride–aluminium chloride mixture **IV**, abbreviated as BPC–$AlCl_3$.[13,14] However, it suffered from a



IV

somewhat high melting point, 40 °C. In addition, the cation readily underwent electrochemical reduction in basic compositions when the $AlCl_3$ mole fraction was less than 0.5 and this resulted in a much narrower available electrochemical window. Both of these two factors are not favourable for use as an electrochemical electrolyte. Therefore, a new challenge in front of Osteryoung's group was to search for a new material with a lower melting point and more stable electrochemical properties. Coincidently, other groups were also searching for new lower melting point ionic materials for electrochemistry at the same time. Eventually, 1-ethyl-3-methylimidazolium chloride-aluminium chloride, [emim]Cl–$AlCl_3$, **V**, was synthesized by Wilkes *et al.*[15] in 1982. It was found that the new ionic liquid had a freezing point below room temperature for all molar compositions of [emim]Cl : $AlCl_3$ between 1 : 0.33 and 1 : 0.67. The cation in such salts was more stable towards electrochemical reduction than the alkylpyridinium

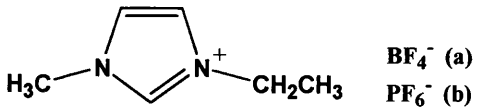
cation in formula **IV**. At the same time, the author also synthesized another series of dialkylimidazolium chloride-chloroaluminate ionic salts and measured their phase transitions, densities, viscosities and conductivities.[15] It was found that this type of ionic salts had good physical, chemical and electrochemical properties. The discovery of [emim]Cl–$AlCl_3$ was a milestone in the history of application of room temperature ionic liquids in electrochemical electrolytes.



V

Not too long after the achievement of synthesis and characterization of [emim]Cl, the groups of Seddon and Hussey began to use chloroaluminate melts as non-aqueous, polar solvents for the study of transition metal complexes.[16] However, at this stage, the applications of chloroaluminate ionic liquids were still limited due to their chemical instability, mainly against moisture. Furthermore, corrosive HCl was produced when such ionic salts reacted with water. Therefore, the materials had to be handled in a glove box.

After another period of investigation, the air and moisture stable IL 1-ethyl-3-methylimidazolium tetrafluoroborate, [emim]BF_4 (**VI a**), was prepared by Wilkes *et al.* in 1992.[17] Shortly after the discovery of [emim]BF_4, another air and moisture stable ionic liquid 1-ethyl-3-methylimidazolium hexafluorophsophate, [emim]PF_6 (**VI b**), was prepared in 1994.[18,19] Those two ir and moisture stable, easy-to-handle ionic liquids simplified the process of using ionic liquids as reaction media.



VI

Since the discovery of both [emim]BF_4 and [emim]PF_6, more and more new

ionic liquids were not only synthesized in the laboratory, but also applied in both academic and industrial areas. To some extent, the discovery of [emim]BF_4 and [emim]PF_6 is another milestone to the use of ionic liquids in the field of chemistry, especially in organic synthesis. Up to now, a number of excellent reviews have been published.[20,21,22,23,24,25,26]

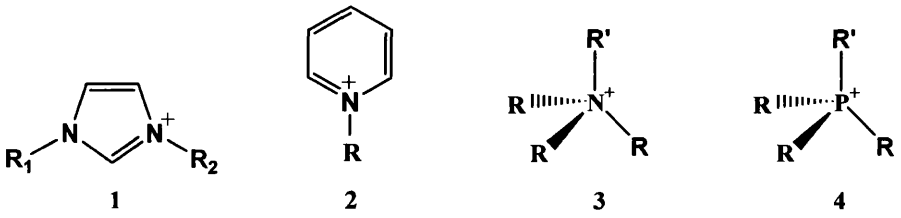
All together, it took one hundred years or so to develop the ionic liquids we use today. The process can be divided roughly into three stages: from unknown 'red oil' to moisture sensitive 'pyridinium or imidazolium chloroaluminates' and then to air and moisture stable 'imidazolium tetrafluoroborate and hexafluorophosphate'.

2.1.2 Compositions

ILs are composed entirely of ions, organic cations and organic or inorganic anions. The organic cations, which are relatively large, mainly account for the melting points and viscosity of the salts. The anions, whether organic or inorganic, determine, to a large extent, the chemical properties of the liquids.[27,28]

2.1.2.1 Cations

The most important cations in use are given in Fig. 2.1 (R/R′/R_n = alkyl).[20~26]



1 2 3 4

Fig. 2.1 Important types of cations in ionic liquids: (1) *N*, *N*′-dialkylimidazolium; (2) *N*-alkylpyridinum; (3) alkylammonium; (4) alkylphosphonium.

Some other organic cations, which have been synthesized, but not used very widely, are described in Fig. 2.2 (structures **5~24**).[4,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45]

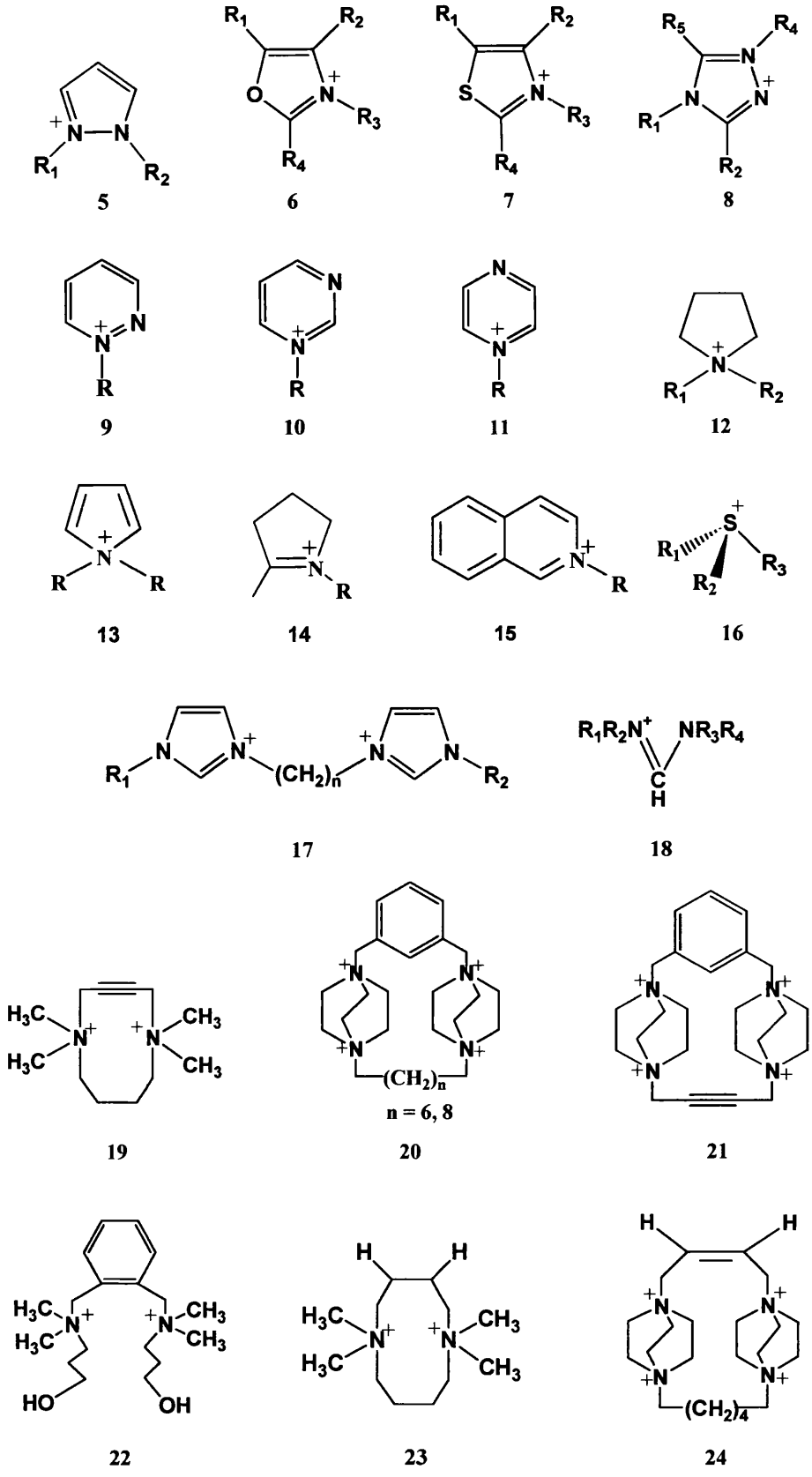


Fig. 2.2 Structures of organic cations which are not used widely in ionic liquids.

(R, R_n = alkyl, n = 1, 2, 3, 4, 5)

Additionally, some cations are derived from cations given in Fig. 2.1 by some modification. A few examples are listed in Fig. 2.3.[46,47,48]

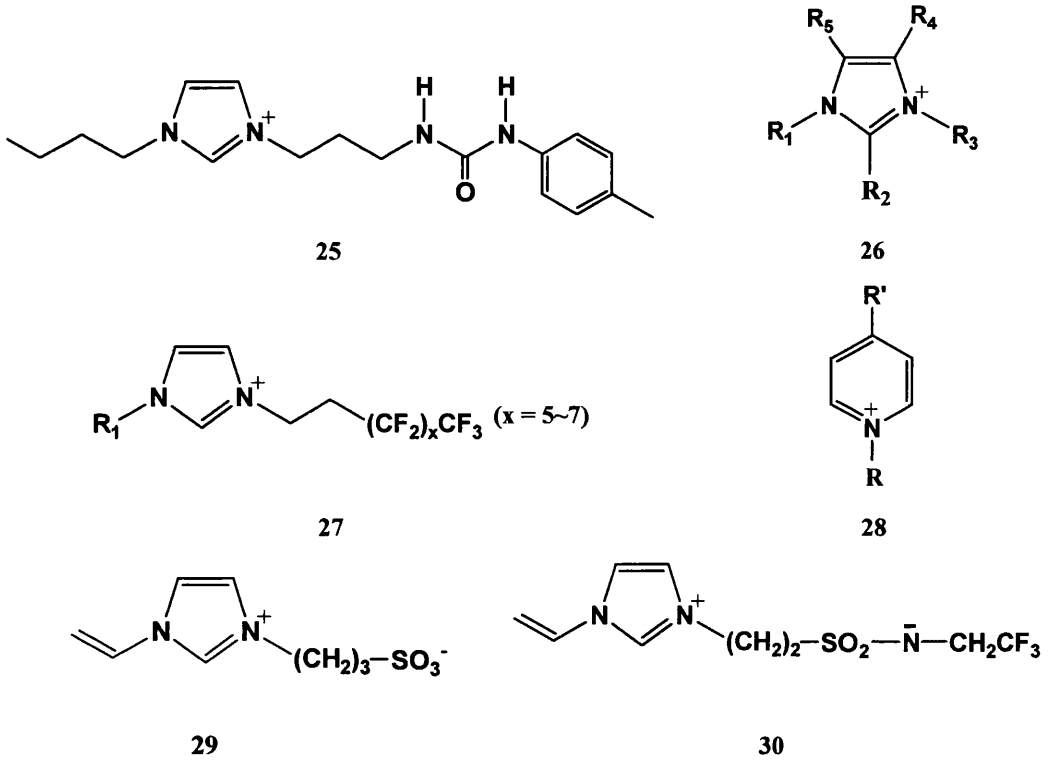


Fig. 2.3 Some cations derived from the cations given in Fig. 2.1(R, R′, R_n = alkyl, n = 1, 2, 3, 4, 5).

Generally, the cations should preferably be bulky, organic with low symmetry, in order to confer the appropriate properties, such as melting point and viscosity, on the ionic liquids. For example, R_1 and R_2 should be different alkyl groups in the *N,N′*-dialkylimidazolium cation (structure **1** in Fig. 2.1).

As for the structures in Fig. 2.1, the family of *N,N′*-dialkylimidazolium cations is of particular interest because of the wide physico-chemical properties available in salts containing this type of cations. The salts containing such cations have lower melting points than most other salts having the same anion. For example, some melting points are: 1-ethyl-3-methylimidazolium chloride ([emim]Cl), m.p., 65 °C;[49] tetraethylammonium chloride ([Et_4N]Cl), m.p., 110 °C;[49] triethylmethylphosphonium chloride ([Et_3MeP]Cl), m.p., 276 °C.[50] In addition, it has been assumed that non-symmetrical cations of structure **1** have lower melting points than symmetrical ones. However, surprisingly, 1,3-dialkylimidazolium

hexafluorophosphates with dibutyl, dipentyl, dioctyl, dinonyl and didecyl substitutents are found to be liquid at room temperature.[51]

N-Alkylpyridinium salts (structure **2**) have also been studied widely, *e.g.*, as solvents for organic reactions,[20~26] even though the salts containing this kind of cations have a higher melting point.

Molten salts based on quaternary ammonium salts of structure **3** have also been known for a long time.[52] However, the melting points of such salts are much higher, only approaching room temperature when the size of the quaternary ammonium cation is larger, for example, where the total number of carbon atoms in the structure is >20. Some attention has also been paid to phosphonium salts (structure **4**), which are solid at room temperature.[53,54] Nevertheless, due to the higher melting points of both ammonium and phosphonium salts, they can offer some advantages over room temperature ionic liquids in certain circumstances. For example, if they are used in a reaction at elevated temperature, simple separation can be accomplished by cooling the mixture to solidify the ILs and decantation of the products.

As for structures in Fig. 2.2, most of them were only studied for an exploratory purpose. Pyrazolium cations **5**,[32] oxazolium cations **6**,[33] triazolium cations **8**,[34] pyrrolidinium cations **12**,[35,36] 1-alkyl-2-methylpyrrolinium cation **14**,[40] pyridazinium cations **9**, pyrimidinium cations **10**, pyrazinium cations **11**[37] and formamidinium cation **18**[39] were found to exhibit interesting ionic conductivity when combined with anions such as BF_4^-, $AlCl_4^-$ and bis(trifluoromethylsulfonyl)-amide anion, $(CF_3SO_2)_2N^-$ or NTf_2^-, *etc.*. Therefore, they have been found to be useful as electrolytes in the field of electrochemistry. 1,1′-Alkylpyrrolinium cation **13**[38] and *N*-alkylisoquinolinium cation **15**[38] were also developed and considered to be suitable medium in liquid/liquid separations.

Interestingly, a novel ionic liquid based on thiazolium ion **7**, *i.e.*, 3-butyl-4-methylthiazolium tetrafluoroborate, was synthesized and used as a reaction medium to promote the coupling of benzaldehyde to benzoin, successfully.[41]

Trialkylsulfonium cations **16** were found to form low melting salts with high conductivity and very low viscosity when combined with the NTf_2^- anion. For example, triethylsulfonium bis(trifluoromethylsulfonyl)amide (SEt_3NTf_2) melts at -35 °C and has a viscosity of 30 mPa at 25 °C.[42] In addition, the preparation of ionic liquids bearing polycations has also received attention recently. Several salts of diimidazolium cations **17** associated with halide anions were synthesized successfully by using a microwave technique.[43] Also, various polyammonium (structures **19~24**) halide salts (solid) were converted into an unique category of non-aqueous ionic phosphates that were considered to have potential applications for electrochemical storage cells.[44,45]

It is worth noting that some interesting cations bearing task-specific functional groups have been studied.[46,47,48] Some examples are given in Fig. 2.3. It was reported that the salts based on those cations showed some special characteristics. For example, the salt composed of imidazolium cation bearing a urea or thiourea derivative functional group (structure **25**) and PF_6^- turned out to be able to be used as an extractant for Hg^{2+} and Cd^{2+} when mixed in equal mass ratios with 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6).[46] A series of novel ionic liquids, composed of imidazolium cations, modified by appending fluorous tails (structure **27**), and PF_6^-, proved to function as surfactants and facilitated emulsification of fluoroalkanes with IL phases when added to conventional ionic liquids.[25] Series of zwitterionic imidazolium salts containing covalently-bound anionic sites (*e.g.*, **29** or sulfonamide **30**) have been synthesized.[48] It was found that such zwitterionic-type salts showed some unique characteristics, such as high ion density but with immobile ions. In addition, these zwitterionic-type salts bearing a vinyl group were polymerised to form rubber-like polymers.

2.1.2.2 Anions

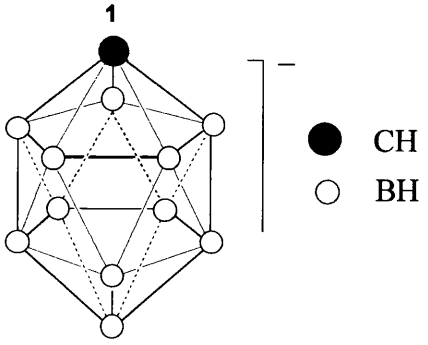
As for anions, the most frequently described [20~26,55,56] are:

Cl^-, Br^-, I^-, BF_4^-, SbF_6^-, PF_6^-, PO_4^{3-}, NO_3^-, $CF_3SO_3^-$, $CF_3CO_2^-$, $CH_3CO_2^-$, TfO^-, *n*-$C_4F_9SO_3^-$, *n*-$C_3F_7CO_2^-$, $(CF_3SO_2)_2N^-$ (NTf_2^-), $N(CN)_2^-$, BR_4^-, $AlCl_4^-$, $Al_2Cl_7^-$, $Al_3Cl_{10}^-$, $AlBr_4^-$, AlI_4^-, $AlCl_3Et^-$, $CuCl_2^-$, $Cu_2Cl_3^-$, $Cu_3Cl_4^-$, $SnCl_3^-$, $Sn_2Cl_5^-$, $Au_2Cl_7^-$, $Fe_2Cl_7^-$, $Sb_2F_{11}^-$, $CB_{11}H_{12}^-$, $CB_{11}H_6Br_6^-$, $CH_3CB_{11}H_{11}^-$, and so on.

Like cations, anions also play important roles in determining the physico-chemical properties of ionic salts. Some salts with some anions (for example, PF_6^-, NTf_2^- or tetraalkylborides BR_4^-), are water-immiscible while salts with other anions (for example, BF_4^- or trifluoromethanesulfonates, $CF_3SO_3^-$) are water-miscible; and salts with yet other anions (for example, $CH_3CO_2^-$, $CF_3CO_2^-$, Br^-, Cl^- or $AlCl_4^-$) are completely water-soluble.

An anion, of particular interest is the bis(trifluoromethylsufonyl)amide anion, NTf_2^-, which gives salts with particularly high thermal stability, low melting point, low viscosity, and high conductivity.[55] In addition, dicyanamide anion ($N(CN)_2^-$) was also reported to form low melting point and low viscosity ionic salt. For example, 1-ethyl-3-methylimidazolium dicyanamide has a low melting point, -21 °C, and a low viscosity, 21 cP.[35,36]

Another type of anion which is also worth noting is the carborane anion (*e.g.*, $CB_{11}H_{12}^-$, structure **31**).[56] Carborane anions are among the most inert anions in modern chemistry, but can lead to new derivatives by being alkylated at position 1 (carbon) or by substituting B–H bonding with strong electrophiles. This allows a systematic variation of the properties of anions. Moreover, their very weak nucleophilicity and redox intertness would favour exploration of new extremes of cation reactivity and the isolation of new superacids.



31

Carborane anions, $CB_{11}H_{12}^-$

2.1.3 Preparations

Welton[20] and Wasserscheid[22] have reviewed the methods for the preparation of ionic liquids, respectively. Ionic salts are prepared starting from the corresponding amine or phosphane or others in a two-step procedure. Such procedure would be described pictorially in Chapter 3. In the first step, alkylation leads to quaternization of the nitrogen or the phosphorus atom, respectively, to form a quaternary salt (which are usually halide salts and here we call them 'precursory halide salts'). This process is usually followed by anion exchange with an alkali or ammonium salt of the desired anion.

In the latter step, there are two basic methods: the first one is exchange of precursory halide salts with silver salts of desired anions in methanol or methanol-water with precipitation of silver halides,[17] or treatment of precursory halide salts with ammonium or sodium salts of desired anions in acetone, giving insoluble ammonium or sodium salts as by-products.[27,57] The second method is an acid-base neutralization reaction in water[18,58,59,60,61] or organic solvent,[20] giving volatile acids as by products. However, the first method is quite expensive and has no potential for preparation on an industrial scale when the silver salt was used, even though a halide free ionic liquid can be obtained. Therefore, the silver-free method has received a great deal of attention. Also, in the second method, some volatile acids were produced as by products and caused some environmentally unfriendly waste. So this method has attracted relatively little interest.

In addition to the above two methods, another one involves a direct combination of a precursory halide salt with a metal halide. However, this method is only used to prepare ionic liquids containing halogenoaluminate (III) salts.[62]

It is worth noting that purity is an important factor to some properties of ionic liquids. For example, the melting point of [emim]BF_4 has been reported as: 15 °C,[17] 5.8 °C,[27] 12 to 12.5 °C,[57] 11 °C,[63] and 14.6 °C.[64] That was probably caused by the residual impurities. However, the purity of ionic liquid seems to be neglected in some cases.

There are two kinds of impurities that easily remain in ionic liquids. The first is halide anion, which comes from the unreacted starting material. Halides are known to coordinate to transition-metal ions easily, and thus influence the rates of reactions catalysed by a transition metal complex. The second one is water, which is usually present in ionic liquids either due to an ineffective drying after preparation or due to absorption of moisture from the air. Similarly, water may also coordinate to transition metal catalysts and thus affects the reaction rate. Furthermore, impurity of both halide and water could also influence the viscosity and density of the ionic liquids.[59~61]

2.1.4 Properties

Some simple properties of ionic liquids that can result in 'greener' qualities when compared to other solvents are listed below:

- low melting points with liquid ranges up to about 300 °C;
- very low vapour pressures, allowing easy separations of products by distillation or sublimation and potential recycling of the ionic liquid;
- high thermal conductivities and large electrochemical windows, allowing electrochemical synthesis;
- stablility toward various organic chemicals;
- controlled miscibilities with organic compounds, providing easy separation of the ionic liquids from a large range of organic products;
- abilities to dissolve a wide range of ionic complexes, organic, inorganic, or organometallic compounds, allowing some moisture sensitive compounds to be involved in the reactions;
- tuneable parameters (*e.g.*, length of alkyl chain changes their properties);
- tuneable Lewis acidity, offering potential as non-volatile replacements for hazardous acids such as HF in Lewis acid catalysed reactions;
- adjustable coordinating abilities, *e.g.*, weakly coordinating anions BF_4^-, PF_6^-, hence, have the potential to be highly polar yet non-coordinating solvents.

Specifically, dialkylimidazolium-based (structure **1** in Fig. 2.1) ionic liquids are much more interesting and more commonly used than others. Therefore, such

ionic liquids are used to illustrate some specific physico-chemical properties in the sections below.

2.1.4.1 Melting points of dialkylimdazolium salts

Usually, melting points of ionic liquids are measured by thermal analysis, particularly by differential scanning calorimetry (DSC). The melting points are difficult to correlate with chemical composition of the salts. Both cations and anions in ionic liquids could influence the melting points of the whole salts. As for cations, the following features are the key to the low-melting salts: low symmetry, weak intermolecular interaction and a good distribution of charge in the cation. It has been pointed out that the compounds containing symmetrical cations exhibit higher melting points than those containing non-symmetrical cations.[27] For example, the melting point of [emim]BF_4 is 15 °C,[17] whereas [bmim]BF_4 exhibits a glass transition temperature of -81 °C.[65] In addition, incooperation of a methyl group at C-2 increases the melting point by 50 to 120 °C and methylation at C-4 or C-5 also augments the melting point, although to a lesser extent.[55] As for anions, in most cases, increasing the size of the anion with the same charge leads to a further decrease on the melting point. For example, the melting points of some different salts with 1-ethyl-3-methylimidazolium ($[emim]^+$) cation are: [emim]Cl, 87 °C;[66,67] [emim]NO_3, 55 °C;[66,67] [emim]$AlCl_4$, 7 °C; [59~61] [emim]CF_3SO_3, -9 °C[55] and [emim]CF_3CO_2, -14 °C.[55]

2.1.4.2 Densities of dialkylimidazolium salts

Both the cations and the anions can affect the density of ionic liquids. The dependence on the type of cation can be illustrated by the densities of a series of 1,3-dialkylimidazolium chloroaluminates [RR′im]$AlCl_4$ in Fig. 2.4.[68] It is clear that the densities of the ionic liquids decrease as the bulkiness of the organic cations increase.

As for the anions, bulky and weakly coordinating anions usually confer relatively high densities regardless of the counter cations. For example,[69] the

density of [emim]$AlCl_4$, 1.26 g cm^{-3}, whilst [emim]$AlBr_4$ is 1.90 g cm^{-3}.

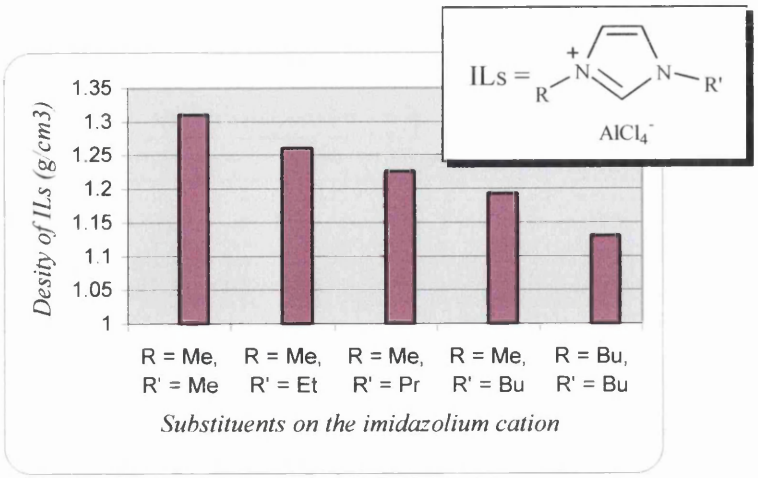


Fig 2.4 Dependence of the density (at 60 °C) of ILs on the type of alkyl groups.[68]

2.1.4.3 Viscosity of dialkylimidazolium salts

The viscosity of ionic liquids is generally much higher than that of water at room temperature. It has been pointed out that the viscosity of an ionic salt is governed by van der Waals interaction and electrostatic attraction, including hydrogen bonding.[55] Therefore, the structures of cation and anion affect the viscosity. The cation strongly influences the viscosity. Generally, lengthening of the alkyl chain in the cation makes the liquid more viscous, due to the increased van der Waals interactions. Branching of the alkyl chains has the same effect, due to reduced rotational freedom. Concerning the anions, the effects of hydrogen bonding and van der Waals interactions can compensate each other in some cases. For instance, decreasing the size of the anion can decrease the van der Waals interactions, and therefore leads to lower viscosity. However, the smaller anion has greater electrostatic interactions, which tends to confer a higher viscosity on the ionic liquid. In addition to the structure of the ionic salt itself, temperature also affects the viscosity of an ionic liquid. Lower temperatures can increase viscosity drastically in some cases.[57]

In addition, impurities, such as water and/or halides, or co-solvents, also influence the viscosity of the ionic liquid. Usually, the presence of halide contamination increases the viscosity of the ionic liquid, whereas the presence of

water or other co-solvents reduces the viscosity.

2.1.4.4 Conductivity of dialkylimidazolium salts

It has been reported that the conductivity of ionic liquids is related to their viscosity, formula weights, density and the radii of their ions as well.[55] However, it is rather difficult to estimate the contribution of each parameter to the conductivity.

2.1.4.5 Stability of dialkylimidazolium salts

Salts based on 1,3-dialkylimidazolium cations are more thermally stable than other quaternary ammonium cations. Ngo *et al.*[70] have investigated systematically the thermal stability of this type of ionic liquids. It was found that salts containing halide anions are less stable and will decompose when the temperature is above 300 °C, while salts containing larger size anions such as BF_4^-, PF_6^- or $(CF_3SO_2)_2N^-$, are more stable and do not decompose until the temperature is up to 400 °C. Statistically, the thermal stabilities of imidazolium based salts increase with the increased alkyl substituents, as long as linear alkyl groups are used.

As for chemical stabilities, ionic salts containing halide or tetrahaloaluminate anions, are moisture sensitive. Typically, ionic salts containing BF_4^- or PF_6^- anions are stable towards moisture and oxygen.

The stabilities against strong reducing metals such as lithium and sodium have also been reported.[66,67] Such characteristics favour the use of the ionic salts for battery application.[66,67]

2.1.4.6 Polarity of dialkylimidazolium salts

Because they are composed entirely of ions, ionic liquids are generally highly polar. For example, the solvent strength and polarity of imidazolium based ionic salts are higher than those of acetonitrile and lower than those methanol.[59] However, unlike other physical properties of ILs, such as phase transition

temperatures, viscosity, *etc.*, which vary over wide ranges, only small polarity difference have been reported.[60] The dielectric constants of some ionic liquids are given in Table 2.1.[60,61]

Table 2.1 Dielectric constants of some ionic liquids.

Ionic liquid	Dielectric constant (ε)[a]
$[C_3\text{-mim}]NTf_2$	52.0[59]
$[C_{10}\text{-mim}]NTf_2$	52.1[59]
$[C_6H_5CH_2\text{-mim}]NTf_2$	52.5[59]
$[CH_3O(CH_2)_2\text{-mim}]NTf_2$	54.1[59]
$[HO(CH_2)_2\text{-mim}]NTf_2$	61.4[59]
$[C_4\text{-mim}]BF_4$	52.5[60]
$[C_4\text{-mim}]PF_6$	52.4[60]
[*N*-Bupy]BF_4	44.9[60]
$[Et_3NH]NO_3$	61.6[61]

[a] The figures were estimated using $E_T(30)$ values.[59,60,61]

The figures in Table 2.1 indicate that the dielectric constants of ionic liquids are not much influenced by changes of cations or anions.

2.1.4.7 Miscibility of dialkylimidazolium salts with other liquids

The miscibility behaviour of ionic liquids and organic solvents is not well documented. According to the principle of 'like dissolves like', the miscibility between two liquids is dependent upon their polarity. Due to their high polarities, ionic liquids are miscible with liquid media of high dielectric constant (ε), including water ((ε = 78.0), simple alcohols, such as methanol (ε = 32.66), ketones, such as acetone (ε = 20.56), dichloromethane (ε = 8.93) and THF (ε = 7.58). They are usually immiscible with alkanes, *e.g.*, hexane (ε = 1.89), toluene (ε = 2.38) and diethyl ether (ε = 4.33). Ethyl acetate (ε = 6.02) appears to constitute the borderline.[55,59-61]

As for the miscibility with water, anions in the salts primarily control the water miscibility of the resulting ionic liquids. Usually, the salts containing anions, such as BF_4^-, $CF_3SO_3^-$, $CF_3CO_2^-$, NO_3^- and halides, display complete miscibilities with water at room temperature. By contrast, salts containing anions, such as PF_6^-, SbF_6^-, NTf_2^- and BR_4^-, show very low miscibility with water. However, there is no absolute borderline. It also depends upon the structure of the cation in the salt. For example, $[C_n mim]BF_4$ salts are fully miscible with water when $n<4$ and form biphasic systems when $n>4$.[27] Even $[bmim]BF_4$ is fully water-miscible at room temperature, while a water-rich phase separates when the mixture is cooled to 4 °C.[71] Another example is that $[bmim]PF_6$ is water immiscible, whereas $[mmim]PF_6$ is water soluble, although they have the same anion.

Some ionic liquids are miscible with a mixture of molecular solvents even though they cannot dissolve in either of them individually. For instance, $[bmim]PF_6$, which was regarded as a hydrophobic ionic liquid, has been found to be totally miscible with aqueous ethanol between 0.5 and 0.9 mol fraction of ethanol, whereas it is hardly miscible with either pure water or absolute ethanol.[71]

Table 2.2 Some physical characteristics of commonly used ionic liquids.[55,28,59~61,66,67]

Ionic liquid	Melting point (°C)	Density ($g\ cm^{-3}$)	Viscosity (cP)	Conductivity ($S\ m^{-1}$)	Solubility in water[a]
$[Emim]BF_4$	15	1.24 (22 °C)	38 (22 °C)	1.4 (25 °C)	s
$[Emim]CF_3CO_2$	-14	1.29 (22 °C)	35 (20 °C)	0.96 (20 °C)	s
$[Emim]NTf_2$	-3	1.52 (22 °C)	34 (20 °C)	0.88 (20 °C)	i
$[Bmim]BF_4$	-82 to -83	1.17 (30 °C)	233 (30 °C)	0.17 (25 °C)	s
$[Bmim]PF_6$	-61	1.37 (30 °C)	312 (30 °C)	0.15 (25 °C)	i
$[Bmim]CF_3SO_2$	16	1.29 (20 °C)	90 (20 °C)	0.37 (20 °C)	s
$[Bmim]NTf_2$	-4	1.43 (19 °C)	52 (20 °C)	0.39 (20 °C)	i
$[Bmim]CF_3CO_2$	-50 to -30	1.21 (21 °C)	73 (20 °C)	0.32 (20 °C)	s
$[Emim]AlCl_4$	7	1.42 (20 °C)	--	--	r

[a] s: soluble; i: insoluble; r: reacts.

Some typical physical characteristics of the more commonly used salts are given in Table 2.2.

2.2 Applications of ionic liquids

Because of their unique physico-chemical properties, ILs have been applied in a wide range of fields, in both academia and industry, from electrochemistry and photochemistry, to separation processes and organic synthesis. This can be illustrated by the rise in number of publications concerning ionic liquids over the past twelve years (these papers are just related to the term 'ionic liquids or ionic liquid' in the title only determined from Web of Science)(WOS)(see Fig. 2.5). A similar trend is found in the patent literature.

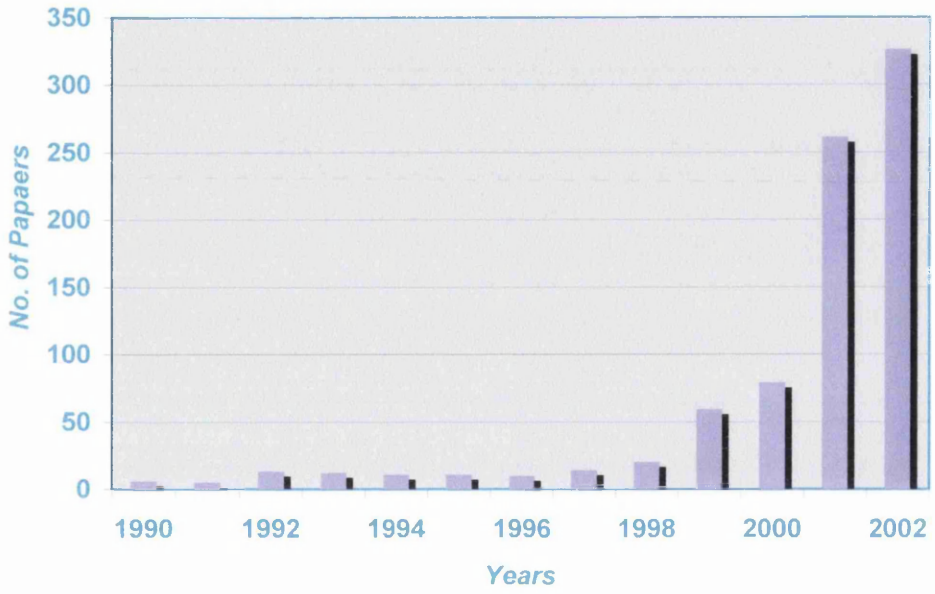


Fig. 2.5 Publications on ionic liquids as a function of time, as determined using WOS.

2.2.1 Uses of ionic liquids in electrochemistry

Molten salts and ionic liquids were primarily developed by electrochemists for the use in power systems. Since ionic liquids are characterised by rather large window of electrochemical stabilities, high conductivities and wide thermal stabilities, they proved to be excellent candidates for use in electrochemistry including in supercapacitors, fuel cells, electroplating, *etc.*.

As mentioned in Sections 2.1.1 and 2.1.2, ionic liquids containing such cations as pyrazolium (structure **5**), oxazolium (structure **6**), triazolium (structure **8**), pyrrolidiniums (structures **12** and **14**), pyridazinium (structure **9**), pyrimidinium (structure **10**), pyrazinium (structure **11**), and formamidium cation (structure **18**) were found to exhibit interesting ionic conductivities when combined with some anions, such as BF_4^-, $AlCl_4^-$ and NTf_2^-, *etc.*, and have been paid attention for use as electrolytes in the field of electrochemistry.

Apart from those ionic salts, imidazolium-based salts have also been investigated by electrochemists.[57] Such salts were considered to have great potential as electrolytes because of their special physico-chemical properties, such as low melting point and good stability to moisture and oxygen, in addition to some properties common to many other salts, such as a high ionic conductivity, negligible vapour pressure at elevated temperature, a wide electrochemical window, thermal stability and non-flammability.

Polymerisation of molten salts has been investigated in order to prepare solid, polymer electrolytes. An all-solid-state polymer electrolyte has advantages that include safety, stability, and mechanical properties. Batteries and other conductive devices could be made much smaller and lighter by using such polymerised conductive materials. Some efforts have been made to develop such type ion-conductive polymers[72,73,74,75] and some achievements have been obtained. For example, the complex composed of a butylpyrimidinium chloride, $AlCl_3$ and poly(butylpyridinium chloride) showed a high ionic conductivity of about 10^{-3} S cm^{-1} at room temperature in spite of its film-like properties.[72] Ionic liquid-polymer gels, prepared by incorporating hydrophilic [emim]BF_4, [emim]OTf or hydrophobic [bmim]PF_6 into a poly(vinylidene fluoride)-hexafluoropropylene copolymer (PVdF(HFP)) matrix with a mass ratio of ionic liquid : PVdF(HFP) = 2 : 1, exhibited ionic conductivities of $>10^{-3}$ S cm^{-1} at room temperature and $>10^{-2}$ S cm^{-1} at 100 °C.[73] In addition, it was reported that the imidazolium molten salt having a vinyl group exhibited excellent ionic conductivity, but the conductivity dropped greatly after polymerisation. However, it was very interesting that the ionic conductivity of a co-polymer, in which the vinyl group and molten salts unit were

tethered with ethylene oxide, increased by a factor of 100 compared to that without the oligo spacer.[74,75]

Apart from the above investigations, lithium polyelectrolyte ionic liquid systems were also studied widely somehow. The challenge for a Li-ion rechargeable battery is to identify a highly conductive electrolyte that is electrochemically stable and allows multiple recharging. Although lithium-based polymers are regarded as important electrolyte materials in this field, they still suffer from a relatively low conductivity. Recently the investigation of lithium polyelectrolyte ionic liquid systems enabled the improvement in this respect. For instance, in spite of its rubber-like property, the polymer obtained by polymerisation of zwitterionic vinylimidazolium sulfonate showed excellent ionic conductivity of around 10^{-5} S cm^{-1} at 50 °C by addition of an equimolar amount of lithium bis(trifluoromethanesulfonyl)imide.[48] Another interesting report is that a polyelectrolyte–ionic liquid system composed of co-polymer of poly(lithium 2-acrylamino-2-methylpropanesulfonate) with *N*-vinylformamide and ionic liquid *N*-hexyl-*N*,*N*,*N*-tributylammonium methanesulfonate (solvating medium) exhibits two to three times higher conductivity than those of the co-polymer alone.[76]

2.2.2 Uses of ionic liquids in liquid-liquid separations

In a traditional liquid-liquid separation process, a volatile organic solvent is commonly employed as one of the two solvents in the two immiscible phases. These solvents can have detrimental effects on the environment and human health as a result of inflammability, volatility or toxicity. In addition, some other problems are associated with the usage of volatile organic solvents. For instance, the costs of solvents are high and their safe engineering attracts significant capital costs over and above simple containment; disposal of spent extractants and diluents will also attract increasing costs through the impact of environmental protection. Therefore, the design of a safe and environmentally benign separation process is very important in the development of clean manufacturing processes.

Very recent efforts by several investigators have been focused on the

application of ionic liquids in separation,[48,49,58] in particular, on the utility of such liquids as replacements for the organic diluents employed in traditional liquid-liquid separation processes. Dai *et al.*[77] have demonstrated that a highly efficient extraction of strontium nitrate from aqueous solution could be achieved when dicyclohexano-18-crown-6 (DC18C6) was combined with various water-immiscible 1-alkyl-3-methyl-imidazolium hexafluorophosphates and bis[(trifluoromethane)-sulfonyl]amides. Subsequently, Rogers and co-workers[78] reported the extraction of sodium, cesium and strontium nitrates from aqueous solution into 18-crown-6, DC18C6 and 4,4′ (5′)-di-(*tert*-butylcyclohexano)-18-crown-6 in 1-butyl, 1-hexyl- and 1-octyl-3-methyl-imidazolium hexafluorophosphates. Very recently, Visser *et al.*[46] explored new task-specific ionic liquids containing metal ion chelating units (urea or thiourea derivatives) and made use of them as valuable alternative solvents to remove some toxic, easily transported metal ions (*e.g.*, Hg^{2+} and Cd^{2+}) from the environment. It was found that, for example, the distribution ratios of Hg^{2+} between a thiourea derivative IL and the aqueous phase at *ca.* pH = 7.2 was as high as 710.[46]

In addition, another novel separation approach has been explored by combining supercritical carbon dioxide ($scCO_2$) with ionic liquids.[79,80] This method was used especially in a biphasic reaction system (a simple separation principle is depicted pictorially in Fig. 2.6).

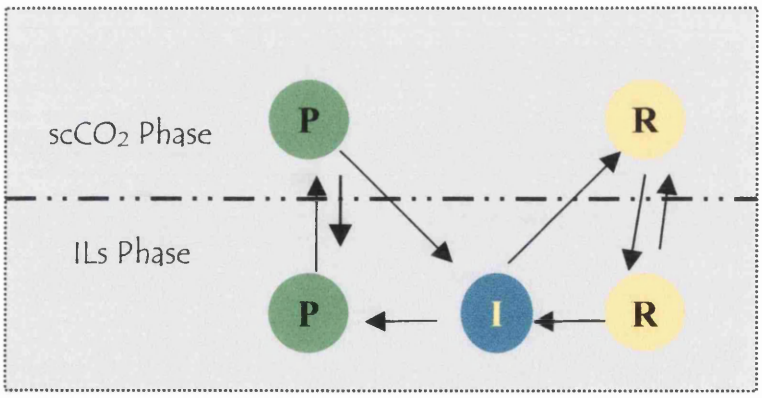


Fig 2.6 Principle of a simple work-up procedure in a $scCO_2$/IL biphasic system.
R: reactant; P: product; I: polar intermediate

It has been reported that $scCO_2$ is extremely soluble in ionic liquids, while the reverse is not the case, with no appreciable ionic liquid solublisation in the CO_2

phase. That observation suggested $scCO_2$ could possibly extract some organic compounds from the IL phase without any contamination caused by ionic liquids. However, it was reported that the solubility of CO_2 in the IL was very dependant on the water content.[80] For example, only 0.13 mol fraction of CO_2 could dissolve into water saturated [bmim]PF_6 (2.3 wt% water contained) at 57 bar and 40 °C, while 0.54 mol fraction of CO_2 could dissolve into dried [bmim]PF_6 under identical conditions. Therefore, it was suggested that effective use of $scCO_2$ as an extractant may have a great value only in a water-free system, though not absolutely of course.

2.2.3 Uses of ionic liquids in organic reactions

The applications of ionic liquids in organic reactions can be roughly categorized into three classes: solvents for organic reactions (including acid-catalysed reactions), solvents for transition-metal-mediated catalysis, and solvents for reactions catalysed by enzymes.

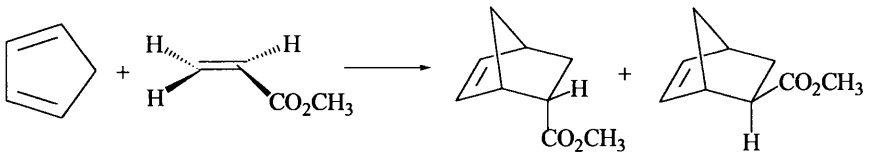
From a chemical standpoint, the main potential benefits of using ionic liquids as reaction media are about enhancement of reaction rates and improvement in chemo- and regio-selectivities in most cases, compared to those in other organic solvents. From an economic and practical point of view, the use of ionic liquids as reaction media, especially in metal complex catalysed processes, can of course be beneficial if separation of the products and recovery of the catalyst are simple enough.

2.2.3.1 Solvents for organic reactions (including reactions catalysed by Lewis acids)

2.2.3.1.1 Diels–Alder reactions

The great usefulness of the Diels–Alder reaction lies in its high yield and high stereospecificity. When ionic liquids are used in such reactions, significantly enhanced rates, high yields and improved selectivities have been observed.

At first, the possibility of using ILs as a substitute for water, which has become a popular solvent for Diels–Alder cycloaddition reactions, was studied. The Diels–Alder cycloaddition of cyclopentadiene and methyl acrylate according to



endo *exo*

Eq. (2.1)

endo : *exo* = 6.7 in $[EtNH_3]NO_3$
endo : *exo* = 5.9 in water

Equation (2.1) was firstly carried out in $[EtNH_3]NO_3$.[81] After that report, similar reactions were carried out in [emim]BF_4, [emim]ClO_4, [emim]CF_3SO_3, [emim]NO_3, [emim]PF_6, [bmim]OTf, [bmim]BF_4, [bmim]PF_6, [bmim]lactate, [1-BuPy]Cl/$AlCl_3$ and [emim]Cl/$AlCl_3$, successively[82,83,84](see Table 2.3). Nevertheless, $[EtNH_3]NO_3$ was the best one among all of the solvents above, because the reactions showed a strong preference for *endo* product and an acceleration of the reaction rate in comparison to non-polar organic solvents. That was probably due to stronger N–H hydrogen bonding.

In addition, the Diels–Alder reactions of isoprene with methyl acrylate, but-3-en-2-one and acrylonitrile were carried out in the IL $[R_3PR']OTs$ with 5% $ZnCl_2$ as catalyst.[54] The reaction with oxygen-containing dienophiles showed high regioselectivities. The authors explained that the outstanding regioselectivities were due to the formation of an adduct between the phosphorus atom of the phosphonium tosylates and the carbonyl oxygen, which resulted in a large increase in steric bulk causing the isoprene to approach the methyl group from as far away as possible from the coordinated carbonyl group.

Another impressive study on Diels–Alder reactions, in which a number of different dienophiles were treated with a series of dienes in [bmim]X (X = PF_6, SbF_6 and OTf) in the presence of 0.2 mol% $Sc(OTf)_3$ as a catalyst was reported recently.[85] The reaction proceeded with high yields with PF_6^-, SbF_6^- and OTf^- counter ions. For example, the reaction of 1,4-naphthoquine with 2,3-dimethylbuta-1,3-diene

proceeded smoothly to completion within 2 h in a [bmim]PF_6–CD_2Cl_2 mixture, while it was extremely sluggish in CD_2Cl_2 alone under the same conditions. Moreover, the type of anion had only little effect on the catalytic activity. Furthermore, it was very interesting that the yield was increased, from 46% to 99%, with the increase of the molar proportion of ionic liquid in the solvent mixture, from 0.1 to 1.0. Recycling of the IL was also demonstrated. After completion of the reaction and extraction of the product with diethyl ether, the ionic liquid phase containing the $Sc(OTf)_3$ was recovered. The catalyst-ionic liquid was recycled very effectively for another ten times without any drop in activity.

Table 2.3 Diels–Alder reactions conducted in various ionic solvents.

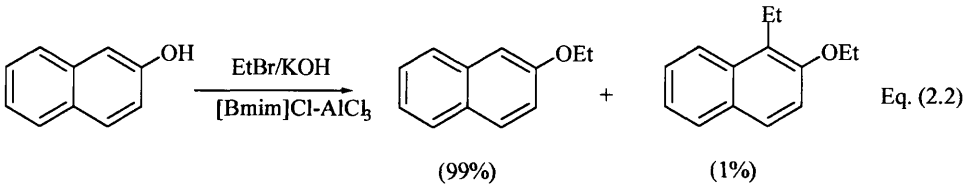
ILs	Catalysts	Advantages	Refs.
$[EtNH_3]NO_3$	--	Enhanced reaction rate, preference for *endo* product	81
$[Bmim]BF_4$, $[bmim]PF_6$, [bmim][lactate], [Bmim]OTf	--	Moisture sensitive reagents can be used	82
[Emim]OTf, $[bmim]ClO_4$, $[bmim]BF_4$, $[emim]NO_3$, $[Emim]PF_6$, $[EtNH_3]NO_3$,	--	Biphasic with easy separation	83
[1-BuPy]Cl/$AlCl_3$, $[R_3PR']OTs$, [emim]Cl/$AlCl_3$,	ILs or $ZnCl_2$	Excellent reactivities and selectivities	84, 54
$[Bmim]PF_6$, $[bmim]SbF_6$, [bmim]OTf	$Sc(OTf)_3$	Enhanced reaction rates, improved selectivities and easy recovery of catalyst	85
[EtDBU]OTf [a]	$Sc(OTf)_3$	Low waste Lewis acid and recoverable catalyst	86

[a] EtDBU = 8-ethyl-1,8-diazobicyclo[5,4,0]-7-undecenium.

2.2.3.1.2 Friedel–Crafts reactions

Friedel–Crafts alkylation and acylation are of great commercial importance, and are also among the earliest reported investigations of using ionic liquid as solvents or both solvents and catalysts. As early as in 1986, the first Friedel–Crafts alkylation and acylation reactions of aromatics using acidic [emim]Cl–$AlCl_3$ as both a solvent and a catalyst was studied by the group of Wilkes.[62] In that report, the nature of the catalyst that promoted the reactions was established and a series of alkylating agents were tested, but both the monoalkylated and the polyalkylated products were observed. Acylation proved to be simpler than alkylation and only monosubstitution was observed when benzene and acetyl chloride were reacted in acidic IL [emim]Cl–$AlCl_3$. That might be because the first substitution product deactivates the aromatic nucleus towards further ring substitution.

In 1998, Seddon investigated the regioselective alkylation and acylation of polyaromatics (*e.g.*, anthracene, phenanthrene),[87] indole and 2-naphthol[88] (Eq. (2.2)) in [emim]Cl–$AlCl_3$ and [bmim]PF_6. It was found that in ILs, the reactions gave high regioselectivity for *O*- or *N*-alkylation products in the latter cases. The NMR spectra (^1H, ^{13}C and ^{31}P NMR) of recovered solvent indicated no evidence of degradation of the ILs during the course of the reactions. Furthermore, the recovered solvents were recycled several times with no appreciable decrease in yield or regioselectivity of the products, with only small mechanical losses of ILs.



Eq. (2.2)

Recently, Song *et al.*[89] reported that Friedel–Crafts alkylation of aromatic compounds catalysed by $Sc(OTf)_3$ were carried out in neutral hydrophobic ILs of 1,3-dialkylimidazolium associated with PF_6^- and SbF_6^- anions. In such ILs, conversions were reported to be effectively quantitative and the catalyst/solvent were recycled easily. However, the reactions did not occur in water or in hydrophilic ILs with BF_4^- anion under the same reaction conditions.

Other Friedel–Crafts reactions reported up to now are listed in Table 2.4.

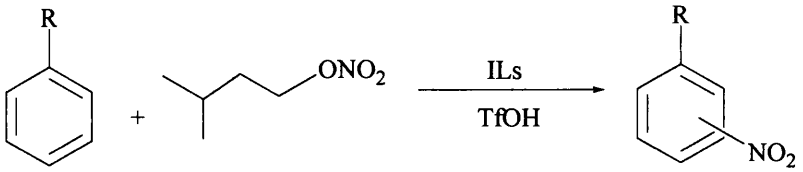
Table 2.4 Friedel–Crafts reactions carried out in ionic liquids.

Reaction	ILs	Catalyst	Advantages	Refs.
Alkylation	[Emim]Cl–$AlCl_3$	--	IL acts as both solvent and catalyst	62,90
	[Emim]Cl–$AlCl_3$, [bmim]PF_6	--	Improved regioselectivites and reaction rates	87,91
	[Rmim]PF_6/SbF_6/BF_4/OTf (R = Et, Bu, Pr, Hex)	$Sc(OTf)_3$	Easy recovery of catalyst	89,92
	[Bmim]Cl/$AlCl_3$–supported on silica	IL	Improved activity and selectivity	93
	[Emim]Cl–$AlCl_3$, [1-BuPy]Cl–$AlCl_3$, MHC–$AlCl_3$[a]	ILs	Better regioselectivities	94
Acylation	[Emim]Cl–$AlCl_3$	IL	IL acts as both solvent and catalyst	[b]
	Silica or charcoal supported [bmim]Cl–$FeCl_3$ / $AlCl_3$/$SnCl_2$	Fe–IL	--	95
	[Bmim]BF_4	$Cu(OTf)_2$, $Zn(OTf)_2$ $Sn(OTf)_2$, $Sc(OTf)_3$	$Cu(OTf)_2$ was the best catalyst; improved regioselectivity and enhanced reaction rate with recoverable catalyst-IL solvent system	90

[a] BPC: 1-butylpyridinium chloride; TMHC: trimethylamine hydrochloride. [b] Refs 62, 87 and 91.

2.2.3.1.3 Nitrations

Up to now, three reports about nitration of aromatic compounds in IL media were published. The first, by Boon *et al.* in 1987,[96] described the nitration of benzene with KNO_3 in acidic [emim]Cl/$AlCl_3$ to give 55% nitrobenzene. In the second report, by Laali and Gerrwert in 2001,[97] a series of ionic salts ([emim]X with X^- = TfO^-, CF_3COO^- and NO_3^- as well as [$HNEtPr_2^i$]CF_3COO were explored as solvents for nitration of aromatics using a variety of nitrating systems (see Eq. (2.3)). It was found that [$HNEtPr^i$]CF_3COO–isoamyl nitrate/TfOH was the best system for high yield and selectivity, for example, nitration of fluorobenzene gave a 97% yield and *para-/ortho-* ratio of 21 : 1. The authors concluded that ionic liquid nitration was a useful alternative to the classical nitration route due to easier product isolation and recovery of the solvent.



Eq. (2.3)

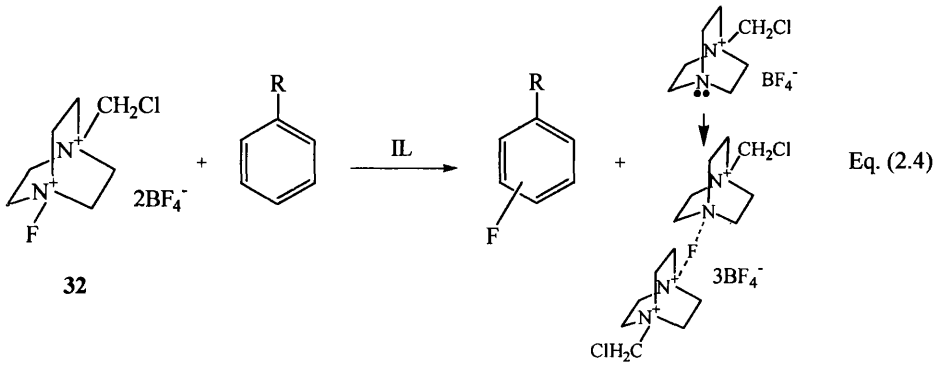
R = OMe, *t*-Bu, F, Me, CF_3, *etc.*

The third one, by Rajagopal and Srinivasan,[98] described that ultrasound promoted nitration of phenol and substituted phenols using ferric nitrate and Clayfen, respectively, in ionic liquid ethyl ammonium nitrate. Enhanced reaction rates and high *para*-selectivities for product formation were obtained in IL with ultrasound as compared to the corresponding reactions performed without ultrasound. For example, phenol was nitrated in IL with ultrasound, giving 85% *para*-nitrophenol and 2% *ortho*-nitrophenol after 0.75 h, whereas 75% *para*-nitrophenol and 12% *ortho*-nitrophenol was provided after 12 h, in the same IL, but without ultrasound.

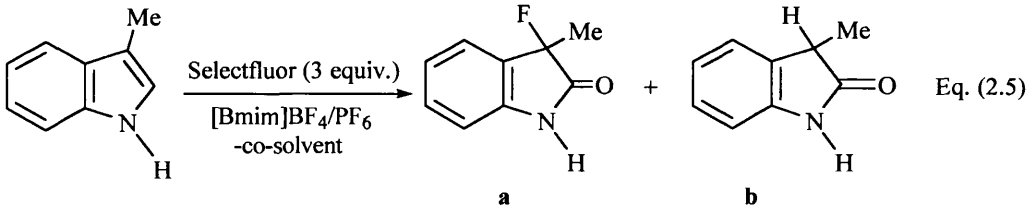
2.2.3.1.4 Fluorinations

Little attention has yet been focused on fluorination in ionic liquids. Up to now, there are only three published reports about fluorination using ionic liquids as solvents. The first two are electrophilic fluorination. One, by Laali and Borodkin,[99]

described a 'green' electrophilic fluorination of arenes by using selectfluor™ (**32**) in ionic liquids [emim]OTf, [emim]BF_4, [bmim]PF_6 and [bmim]BF_4 (see Eq. (2.4)). The ILs provided convenient media for fluorination of arenes under essentially acid-free conditions in a simple work-up (no volatile solvent, simple extraction of the aromatics without aqueous work-up). Further, the ionic liquid can be easily recycled and reused. The second report, by Baudoux *et al.*,[100] described an electrophilic fluorination of indole in [bmim]PF_6 and [bmim]BF_4 (see Eq. (2.5)). Both high yields and good chemoselectivities were observed.



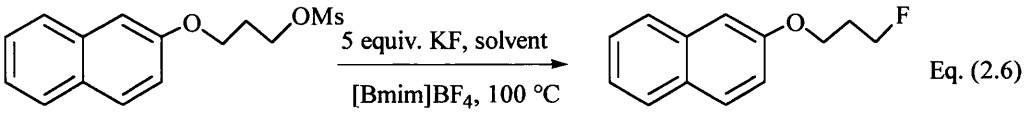
Eq. (2.4)



Eq. (2.5)

a : b > 99, when [bmim]BF_4-MeOH used

Quite recently, Song *et el.*[101] reported an interesting method of nucleophilic fluorination by using potassium fluoride in ionic liquids [bmim]BF_4, [bmim]PF_6, [bmim]SbF_6, [bmim]OTf and [bmim]NTf_2. The reactions proceeded effectively in ILs. For instance, the fluorination of (methanesulfonyloxypropoxy)naphthalene with KF in [bmim]BF_4 (see Eq. (2.6)) was complete within 1.5 h at 100 °C, affording 85% of the desired product 2-(3-fluoropropoxy)naphthalene together with 2% of the by-product alkene, whereas the same reaction in CH_3CN under identical reaction conditions occurred hardly at all even after 24 h. Very interestingly, the addition of water (5 equiv.) in ionic liquids completely eliminated the formation of the undesired alkene.



Eq. (2.6)

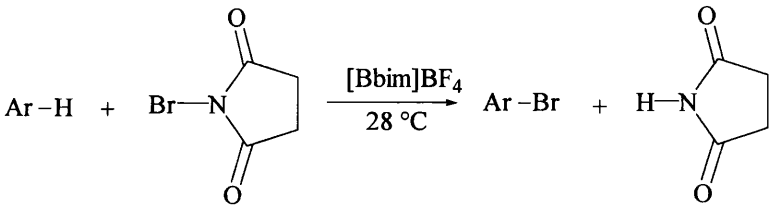
2.2.3.1.5 Chlorinations

Only one report about chlorination in ionic liquids has so far appeared in the literature.[96] It was reported that benzene was chlorinated by chlorine in an ionic liquid [emim]Cl/$AlCl_3$ and the reaction was considered to involve electrophilic mechanism.

2.2.3.1.6 Brominations

As for bromination, Chiappe *et al.*[102,103] have investigated stereoselective halogenations of alkenes and alkynes in ionic liquids including bromination by Br_2 in [bmim]Br, [bmim]BF_4 and [bmim]PF_6. For some alkenes, *e.g.*, diphenylethene, high *anti*-stereoselectivity was observed, but for others alkenes, *e.g.*, cyclohexadiene, a complicated reaction mixture was produced.

Quite recently, by Rajagopal *et al.*,[104] described that aromatic substrates were monobrominated regioselectively with NBS in the ionic liquid 1,3-di-*n*-butylimidazolium tetrafluoroborate [bbim]BF_4 in 5 min at 28 °C in excellent isolated yields (80%~98%) in the absence of catalyst (see Eq. (2.7)). For example, anisole was brominated to give 4-bromoanisole in 98% yield in [bbim]BF_4.



Eq. (2.7)

The remarkable enhancement in the reaction rate observed have been explained to be probably due to the enhancement of the reactivity of NBS as a result of increased polarization of the N–Br bond in the polar IL [bbim]BF_4, which was considered to have acidic protons H2, H4 and H5 in its imidazolium cation. In order to confirm such a hypothesis, the authors also conducted the bromination of anisole with NBS in the IL

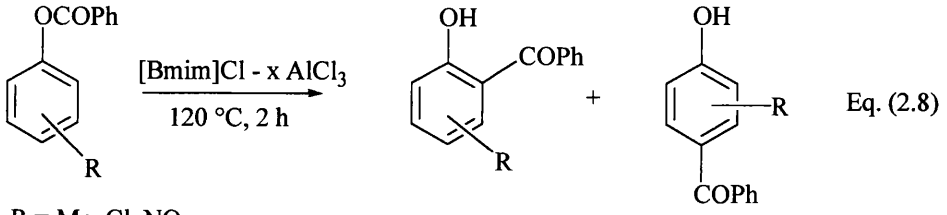
N-*n*-octylpyridinium tetrafluoroborate which does not exhibit such acidity characteristics, and found that the reaction was indeed sluggish, taking 5 h at 30 °C as compared to 5 min in [bbim]BF_4 with a comarable conversion.

2.2.3.1.7 Fischer indole synthesis

The Fischer indole synthesis of different ketones using IL 1-butylpyridinium chloroaluminate ([1-BuPy]Cl/$AlCl_3$, [1-BuPy]Cl : $AlCl_3$ = 1 : 2) as both a solvent and a catalyst has been described.[105] The amount of the ionic liquid taken for the reactions was such that the $AlCl_3$ content was equimolar to the substrate in most cases. With different ketones and indoles, the yields of purified products varied from 41% to 92%. The advantages of using such IL solvents was that the amount of $AlCl_3$ required was much less than that required for other reported catalysts such as PPA (polyphosphoric acid), which is usually needed in 8 to 9 fold excess by weight, or $ZnCl_2$, which is used in as large as three fold excess.

2.2.3.1.8 Fries rearrangement

1-Butyl-3-methylimidazolium chloroaluminate, [bmim]Cl/$AlCl_3$, has been used as both a solvent and a Lewis acid catalyst in Fries rearrangement reactions of phenyl benzoates (Eq. (2.8)).[106] Positive results were obtained only in the case of an acidic ionic melt as expected. Moreover, it was observed that, at low Lewis acidity, more *ortho*-hydroxybenzophenone was formed (at [bmim]Cl : $AlCl_3$ = 1.53, *ortho-/para-* = 61/39), while at high Lewis acidity the proportion of *para*-hydroxybenzophenone increased (*e.g.*, at [bmim]Cl : $AlCl_3$ = 2.00, *ortho-/para-* = 18/82).



Eq. (2.8)

R = Me, Cl, NO_2

Apart from the above reactions, several other reactions catalysed by Lewis acids have also been reported, for instance, esterification,[107,108] Beckman rearrangement,[109,110] and so on (see Table 2.5).

Table 2.5 Some other reactions, catalysed by Lewis acids, have been studied in ionic liquids.

Reaction	ILs	Catalysts	Advantages	Refs.
Esterification	[1-BuPy]Cl/$AlCl_3$[107] [bmim]PF_6, [bmim]BF_4[108]	IL acts as both catalyst and reaction medium	Easy separation of products	107,108
Beckman rearrangement	[Bmim]BF_4, [bmim]CF_3CO_2, [1-BuPy]Cl/$AlCl_3$	PCl_5 or P_2O_5 or $POCl_3$	Excellent conversion and selectivity	109,110
Claisen rearrangement	[EtDBU]OTf	$Sc(OTf)_3$	Reusable catalyst and solvent	111
Biginelli reaction	Solvent free	[Bmim]PF_6/BF_4 (0.2~0.4 mol%)	0.2~0.4 mol% ionic liquids as catalysts; enhanced reaction rates and high yields.	112
Wittig reaction	[Bmim]BF_4	--	Reusable green solvent	113

Knoevenagel condensation	$[C_6\text{-Mim}]PF_6$ (6 = 1-hexyl)[114] [bmim]$Cl/AlCl_3$, [1-BuPy]$Cl/AlCl_3$[115]	NaOH[114] Acidic IL[115]	Reusable green solvent	114,115
Reduction of aldehyde	$[Emim]PF_6/BF_4$ $[bmim]PF_6/BF_4$	BR_3	Easy product separation and solvent recycling	116
1,3-dipolar cycloaddition	$[Emim]BF_4$/NfO, $[bmim]BF_4$, $[capemim]BF_4$	AcOH	Easy product separation and solvent recycling	117
Aromatic benzoylation	[1-BuPy]$Cl/AlCl_3$	--	--	118
Condensation of alcohol	$[NR_4]NTf_2$	H_3PO_4, TsOH	--	119
Allylation of alcohol	$[Bmim]PF_6/BF_4$	R_4Sn	Easy product separation and solvent recycling	120
Alkylation of isobutene with alkenes	[Bmim]$Cl/AlCl_3$	IL	--	121
Reformatsky reaction with Zn reagent	$[Bmim]PF_6/BF_4$, [emim]OTf, [EtDBU]OTf, [MeDBU]OTf	Zn or $Zn(OTf)_2$	Recyclable ionic liquids	122
One pot synthesis of heterocyclic compounds	$[Bmim]PF_6/BF_4$, [emim]OTf, [EtDBU]OTf, [MeDBU]OTf	--	Green, recoverable IL solvent	123

Steroselective synthesis of spirocyclopropane	$[NBu_4]Br$	NaOAc, $NaHCO_3$	One-step reaction, high selectivity	124
Nucleophilic displacement: Cl→CN	$[Bmim]PF_6$		Green solvent	125
Acylative cleavage of ether	$[Emim]I/AlCl_3/Al_2Cl_7$	--	--	126
Catalytic cracking of polyethylene	$[Emim]Cl/AlCl_3$, $[bmim]Cl/AlCl_3$, $[1\text{-}BuPy]Cl/AlCl_3$	--	Easy product separation and solvent recycling	127
Synthesis of cyclotriveratrylene (CTV)	$[N_{6444}]NTf_2$	--	High yield and recycling of IL	119
Cycloaddition of CO_2 to propylene oxide	$[1\text{-}BuPy]Cl$, $[bmim]PF_6$, $[bmim]BF_4$	--	Excellent selectivity and recycling ILs	128

2.2.3.2 Solvents for transition-metal-mediated catalysis

Biphasic solvent systems have been effectively used in reactions catalysed by transition metal complexes in recent years. In a homogeneous catalysis process, such systems typically consist of a bottom solvent phase that can dissolve the catalyst and an upper solvent phase that can carry the substrate into and/or the product out of the reaction vessel.

ILs are highly polar and able to dissolve organometallic compounds. Therefore, they are alternative solvents for reactions catalysed by transition metal complexes. Depending on the coordinative properties of the anions, they could be regarded as an 'innocent' solvent which provides a polar, weakly coordinating medium for a transition–metal–mediated reaction. Due to their tunable ability to dissolve some organic or inorganic compounds, ionic liquids have been recognised as suitable solvents for some biphasic reactions. In such biphasic systems, an easy product separation and catalyst recovery can be achieved in the most cases. In an ideal IL–organic system, the catalyst would be in the bottom IL phase, and the substrate would reside in the upper organic phase. Thus, separation of the product could be carried out by simple decantation, and in principle, the catalyst solution could be reused (see Fig. 2.7). Based on these advantages, some reactions had been carried out in such ionic liquid media.

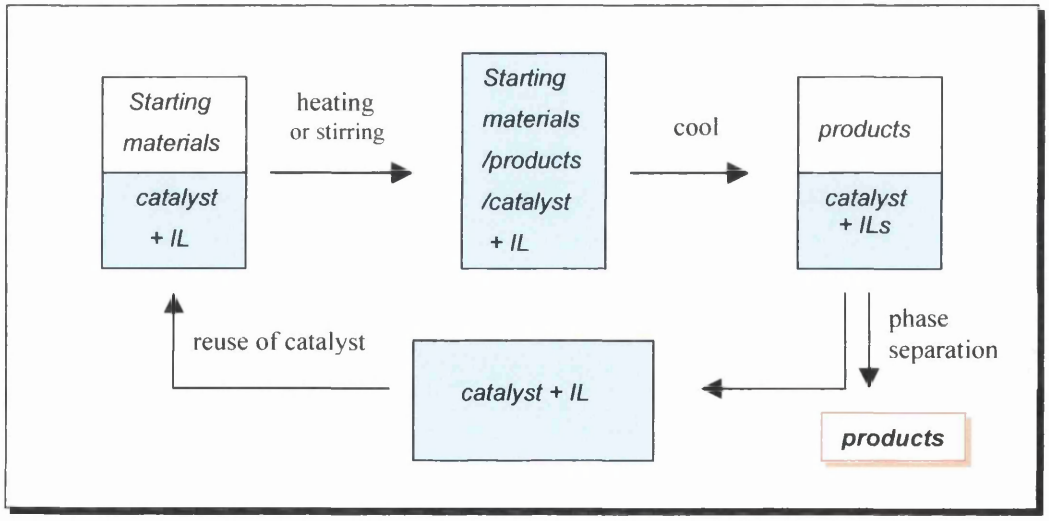
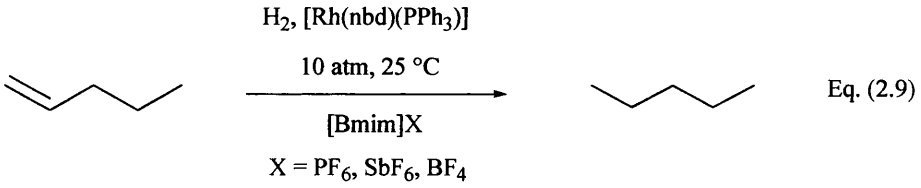


Fig 2.7 Principle of a simple work-up procedure when ILs are used as solvents in a biphasic system

2.2.3.2.1 Hydrogenations

The first successful rhodium-catalysed hydrogenation of 1-pentene in ILs [bmim]BF_4/PF_6/SbF_6 (Eq. (2.9)) was studied by the group of Chauvin *et al.*[128] in 1995. A solution of the cationic $[Rh(nbd)(Ph_3P)_2]PF_6$ in [bmim]PF_6 or [bmim]SbF_6 was shown to be an effective catalyst for the biphasic hydrogenation of pent-1-ene. Reaction rates were up to five times higher in ILs than those in acetone. The catalyst-ionic liquids solution could be reused with rhodium losses below the detection limit of 0.02%. However, poor results were obtained in [bmim]BF_4, which was ascribed to the presence of trace amounts of strongly coordinating chloride ions as an impurity in the sample of IL [bmim]BF_4. The reuse of the solvent with minimal less of Rh was also possible in the selective hydrogenation of cyclohexadiene to cyclohexene in [bmim]PF_6/BF_4/SbF_6 by making use of a biphasic reaction system. It was found that the solubility of cyclohexadiene in [bmim]PF_6 is about five times that of cyclohexene and hence, the latter was produced with 98% selectivity at 96% conversion. From the results obtained, the authors concluded that the rhodium catalyst could be immobilized in ILs without the use of a specially designed ligand.

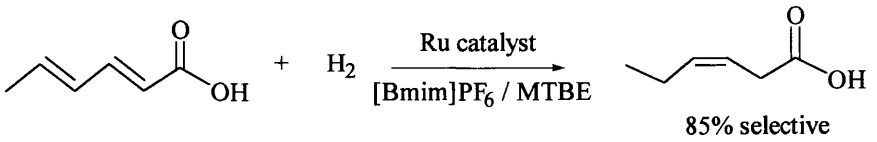


Eq. (2.9)

In the following year de Souza *et al.*[65] reported the biphasic hydrogenation of cyclohexene to cyclohexane with $Rh(cod)_2BF_4$ (cod = cycloocta-1,5-diene) in ionic liquids [bmim]PF_6 and [bmim]BF_4. Roughly, equal reaction rates were observed in the two ILs. If de Souza's system was assumed to be chloride-free, the observations may confirmed that chloride impurity could affect the reaction rate strongly.[128]

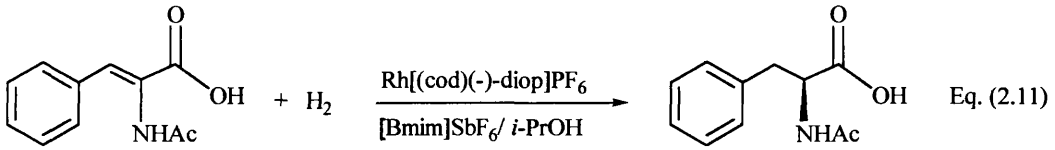
Steroselective hydrogenation is also possible. For instance, the ruthenium-catalysed hydrogenation of sorbic acid in a biphasic [bmim]PF_6–MTBE (MTBE =

methyl *tert*-butyl ether) system gave an 85% yield of *cis*-3-hexenoic acid (Eq. (2.10)).[129]

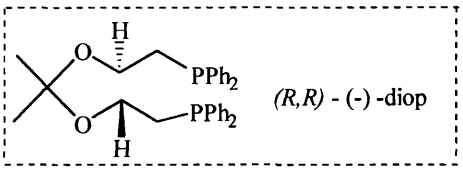


Eq. (2.10)

Asymmetric hydrogenation in ILs is also feasible. This kind of reaction (including other asymmetric reactions) in ionic liquids is of particular interest as it could provide potential to recycle the expensive chiral metal complexes. The first example of such hygrogenation was again reported by Chauvin *et al.*[128] The authors described a [Rh(cod)(-)-(diop)]PF_6 catalysed enatioselective hydrogenation of α-acetamidocinnamic acid to give (*S*)-phenylalanine with 64% ee (Eq. (2.11)), which proceeded successfully in a biphasic [bmim]SbF_6–isopropyl alcohol solvent system. The product, residing in the isopropyl alcohol, could be separated quantitatively and the recovered ionic liquid containing the catalyst could be reused.



Eq. (2.11)



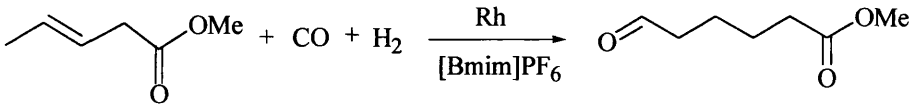
Recently, a novel approach using an ionic liquid–supercritical CO_2 ($scCO_2$) biphasic system has been reported for catalytic hydrogenation.[129,130] However, how many advantages in such systems over other biphasic system would be taken depends on the chosen substrates. For example, Brown *et al.*[129] reported asymmetric hydrogenation of tiglic acid catalysed by Ru(CH_3CO_2)$_2$((R)-tolBINAP) in [bmim]PF_6 with addition of some water as co-solvent, gave 2-methylbutanoic acid with 85% ee and 99% conversion. The product was separated by $scCO_2$ extraction without contamination from either the ionic liquid or the Ru complex when the reaction was complete. Furthermore, the ionic liquid phase containing catalyst was recovered and recycled another four times with consistently high ees (87~91%) and yields (97~98%)

of the products. However, in contrast to Brown's report, Liu *et al.*[130] reported there was no advantages on reactivity by using $scCO_2$ in place of hexane in the process of hydrogenation of dec-1-ene and cyclohexene using Wilkinson's catalyst $RhCl(PPh_3)_3$.

2.2.3.2.2 Hydroformylations

The first Pt-catalysed hydroformylation of ethane in tetraethylammonium trichlorostannate melts was described by Parshall in 1972,[131] but there were no detailed reports about catalytic activity. Then in 1987, Knifton[132] reported the ruthenium- and cobalt-catalysed hydroformylation of internal and terminal alkenes in molten tetra-*n*-butylphosphonium bromide (m.p., 100 °C). Similar reactions have been conducted recently in molten phosphonium tosylates, *e.g.*, $[Ph_3PEt]OTs$ (m.p., 94~95 °C).[54] An advantage of using a higher melting salt was that the product could be decanted from the solid catalyst–IL mixture at room temperature.

Considering the separation of the product, several other systems were also developed for the process of hydroformylation. The monophasic hydroformylation of methylpent-3-enoate in $[bmim]PF_6$ has been reported (Eq. (2.12)).[133] The product was removed by distillation (0.2 mbar/110 °C) and the ionic liquid was recycled ten times without significant loss in activity.



Eq. (2.12)

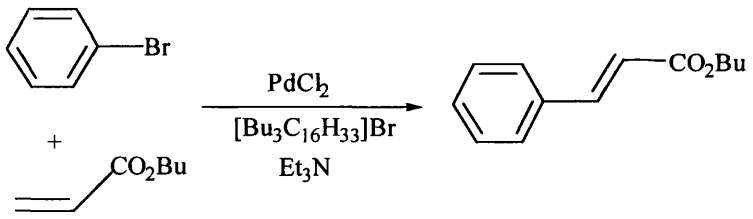
Biphasic hydroformylation was investigated by Chauvin.[128] The Ru-catalysed hydroformylation of pent-1-ene was conducted in $[bmim]PF_6$. It was found that the leaching of catalyst into the organic phase occurred to some extent.

In order to minimise catalyst leaching, the group of Oliver-Bourbignou[134] has attempted to modify the ligand in the catalyst with a cationic or anionic group. The modified catalyst was used to catalyse hydroformylation of 1-hexene in an ionic liquid solvent.

Similar to that in the process of hydrogenation, an IL–$scCO_2$ biphasic system has also been applied in hydroformylation processes and helped avoid leaching of the catalyst into the non-IL phase. For example, hydroformylation of oct-1-ene in [bmim]PF_6–$scCO_2$ was conducted successfully and analysis of recovered products revealed that <1 ppm Rh is leached into the organic phase.[135]

2.2.3.2.3 Heck reactions

Heck reactions carried out in both alkylammonium-[136,137,138]and imidazolium-based[139] ionic liquids have been studied. The first palladium-catalysed Heck reaction in an IL media was described by Kaufmann *et al.* in 1996.[136] The reaction of bromobenzene with butyl acrylate to give butyl *trans*-cinnamate (Eq. (2.13)) proceeded successfully in high yield and the product was separated just by distillation from the IL. Surprisingly, no Pd loss by formation of palladium black, which was easily produced when such a reaction was conducted in a molecular solvent,[136] was observed after reaction.

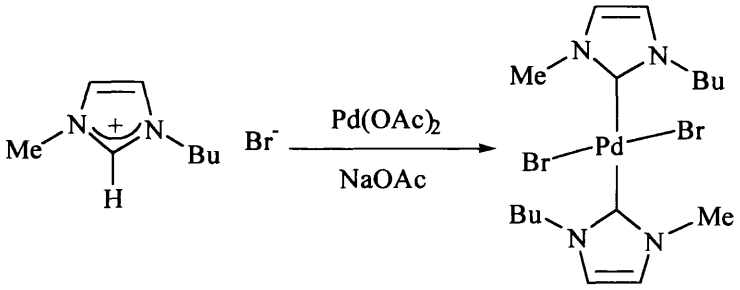


Eq. (2.13)

Extensive studies on Heck reactions in ILs have been presented by Hermann's group[137,138] and Seddon's group,[139] respectively. Herrmann *et al.* showed that the molten salt Bu_4NBr (m.p. 103 °C) is a particularly suitable reaction medium for the Heck reaction, affording superior results compared with commonly used organic solvents such as DMF. For example, in the reaction of bromobenzene with styrene, using diiodobis(1,3-dimethylimidazolin-2-ylidene)palladium(II) as the catalyst, the yield of stilbene was increased from 20% in DMF to 99% in Bu_4NBr under identical reaction conditions. The product was separated by distillation and the catalyst contained in the ionic liquid was recycled up to 13 times without significant loss of activity.

Interestingly, Seddon *et al.*[139] described a triphasic system ([bmim]PF_6 /water/hexane) for the Heck reaction, where the catalyst remained in the IL phase, the products dissolved in the organic layer and the by-product salts were extracted in the aqueous phase.

In a recent publication, it was noted that Pd complexes of imidazolinylidene carbenes formed by deprotonation at C-2 during some Heck reactions, especially when a strong nucleophilic anion is associated with the imidazolium salt. For example, complex **33** formed when $Pd(OAc)_2$ is heated in the presence of [bmim]Br (Scheme 2.1).[140] Those Pd carbene complexes have been shown to be active and stable catalysts for Heck (and other C–C coupling) reactions. The activity of those Pd carbene complexes was confirmed by Xiao and co-workers,[140] who observed a significantly enhanced rate of the Heck coupling in [bmim]Br compared to the same reaction in [bmim]BF_4. The isolated carbene complexes were shown to be active catalysts when they were redissolved in [bmim]Br.



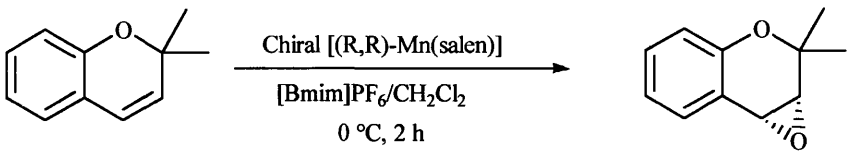
33

Scheme 2.1

2.2.3.2.4 Oxidations

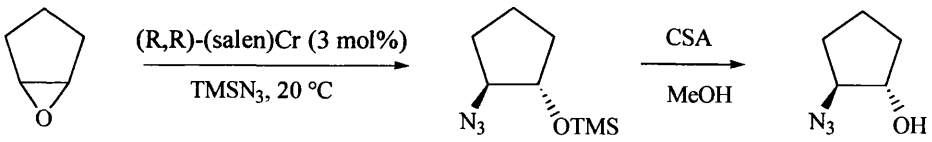
Relatively few transition metal catalysed oxidation reactions have been reported in ionic liquids. Song and Roh investigated[141] the epoxidation of, for example, 2,2-dimethylchromene with a chiral Mn^{III}(salen) complex (see Eq. (2.14)) in a mixture of [bmim]PF_6 and CH_2Cl_2 (1:4, v/v). The reaction rate was enhanced in [bmim]PF_6–CH_2Cl_2, in which an 86% yield was achieved after 2 h, while in CH_2Cl_2 alone, the same yield was obtained only after 6 h. In both cases, the enantiomeric excess was as high as 96%. Moreover, the ionic liquid–catalyst solution could be

recovered and reused further. However, although the enantiomeric excess was only a little decreased (90%~88%) after five recycles, the conversions of the reactions dropped by a greater amount, from 83% to 53%, during the recycling runs. The problem may have been caused by a slow degradation of the Mn^{III}(salen) complex.



Eq. (2.14)

Another published report by Song and Roh[142] described the Cr(salen) catalysed symmetric ring opening reaction of epoxides in a range of $[bmim]^+$ based ionic liquids. The reactions were effective in some ionic liquids. For example, excellent yields and ees were obtained in a hydrophobic ionic liquid $[bmim]PF_6$ or $[bmim]SbF_6$, while there was little or no product in a water miscible ionic liquid $[bmim]BF_4$ or [bmim]OTf under the same reactions. However, when the reaction was conducted in a mixture of $[bmim]PF_6$–[bmim]OTf (5:1, v/v) (Eq. (2.15)), cyclopentene epoxide was converted into the corresponding ring-opened product with 68% yield and 94% ee. Moreover, it was interesting that the enantioselectivities did not change, though the yield was increased from 68% to 75%, after five recycles of the ionic liquid–catalyst solution. The authors concluded that the yield and ee were strongly dependent on the nature of the anion in the ionic liquid.



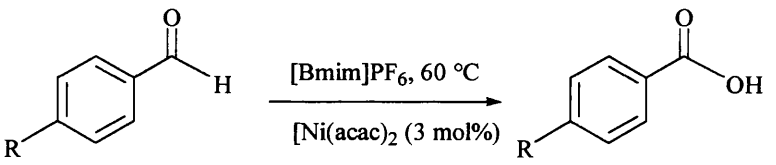
Eq. (2.15)

CSA = camphorsulfonic acid

Owens and Abu-Omar[143] reported the epoxidation of alkenes and allylic alcohols using methyltrioxorhenium (MTO) and urea hydrogen peroxide (UHP) in $[bmim]BF_4$. It was found that both UHP and MTO were completely soluble in $[bmim]BF_4$ and that the reaction mixture remained homogeneous throughout the reaction. Moreover, the system was nearly water-free, which resulted in only epoxides being produced and no diols being formed. Quite recently, Conte *et al.*[144] reported that

epoxidation of electrophilic alkenes was conducted in ionic liquids [bmim]BF_4 and [bmim]PF_6 by using an aqueous basic solution of hydrogen peroxide as oxidant. Yields of epoxides ranging from very good to almost quantitative were observed for all substrate. A similar system, [bmim]BF_4 or [bmim]PF_6–H_2O_2, was chosen by Namboodiri *et al.*[145] to use for a Pd-catalyzed oxidation of styrene to acetophenone.

Howarth[146] reported another clean procedure for oxidation of aromatic aldehydes using [Ni(acac)$_2$] as catalyst and dioxygen as oxidant at atmospheric pressure in [bmim]PF_6 (Eq. (2.16)). That was the first example of combining an IL with molecular oxygen as a clean oxidation system. The system appeared to be effective. The catalyst–IL solution could be recycled for another three cycles without leaching of the catalyst and the yields of the products for these subsequent runs were similar to those obtained in the initial run.



Eq. (2.16)

R = H, Me, Cl, Br, OMe, OH, CHO

After Howarth's report, some other reports on oxidation using molecular oxygen as oxidants in ionic liquids have also been published,[147,148] including oxidation of alcohols catalysed by a ruthenium catalyst,[147] and selective oxidation of benzyl alcohol catalysed by Pd(AcO)$_2$.[148]

In addition to the reactions listed above, some other reactions catalysed by transition metal complexes have also been investigated in ionic liquid media, such as dimerization of olefins,[149,150] polymerization[151] and oligomerizations[152] and so on. Some examples are listed in Table 2.6.

Table 2.6 Some other examples of reactions catalysed by transition metal complexes.

Reaction	Ionic liquids	Catalyst	Advantages	Refs
Olefin dimerization	[Bmim]Cl/$AlCl_3$	Ni catalyst	Easy catalyst recycling	149, 150
Olefin polymerization	[Bmim]BF_4 [BuPy]BF_4	Ru-catalyst	Enhanced reaction rate and recoverable IL	151
Olefin oligomerization	[Bmim]/[hmim]BF_4	Ni-catalyst	Better reactivity and selectivity	152
Trost-Tsuji coupling	[Bmim]Cl/$AlCl_3$	Pd-catalyst	Enhanced reaction rate	153
Suzuki cross-coupling	[Bbim]BF_4, [bbim]Br	Pd-catalyst	Enhanced reaction rate	154
Negishi cross-coupling	[Bdmim] BF_4	Pa-catalyst	Recoverable IL	155
Stille coupling	[Bmim] BF_4	Pd-catalyst	IL solvent recycling	156
Carbonylation of aryl halides	[Bmim]/BF_4/PF_6	Pd-catalyst	Reusable IL–catalyst	157
Esterification	[Bmim]BF_4	Pd-catalyst	Enhanced reaction rate	158
Radical reactions (*e.g.*, manganese (III)-mediated reaction	[Bmim] BF_4/$CHCl_3$	$Mn(OAc)_3$	High yield, recoverable $Mn(OAc)_3$ and IL	159

2.2.3.3 Enzyme catalysed reactions

Although more than 13000 enzyme-catalysed reactions have been described, there are still some problems with the solubilities of the substrates, the yields or enantioselectivities of the products. Since ILs have good miscibility with most

chemicals, they have been recently discovered to be possible replacements for the organic solvents in bioprocess operations, such as enzyme catalysed reactions.

Several enzyme-catalysed reactions have been carried out in ionic liquids. The first was reported by the group of Seddon in 2000.[160] In their report, the authors described that the hydration of 1,3-dicyanobenzene to 3-cyanobenzamide and 3-cyanobenzoic acid catalysed by *Rhodococcus* 312 was carried out in both a [bmim]PF_6–H_2O biphasic system and a comparable toluene–H_2O biphasic system. The results showed a lower initial reaction rate in [bmim]PF_6–H_2O system than in toluene–H_2O system, but a slightly higher final yield was obtained in the former system. The author concluded that: enzymes were present in the aqueous phase, where the reaction took place, and that the ionic liquid effectively acted only as a reservoir for the organic substrate, which was then partitioned into the aqueous phase. Although the results were not as good as the authors expected, they still indicated an improved catalytic stability in an ionic liquid medium compared to that in an organic solvent.

Although Seddon *et al.*[160] considered that ILs acted only as a reservoir for organic substrates, Madeira[161] attempted the use of *candida aritica* lipase B (Novozym 435) (CaLB (Nov 435)) for transesterification, ammoniolysis and epoxidation in pure ionic liquids [bmim]BF_4 and [bmim]PF_6 under anhydrous conditions. The reactions still took place, although at different rates. For example, the transesterification of ethyl butanoate with butan-1-ol was slightly faster in either [bmim]BF_4 or [bmim]PF_6 (in both ILs, 81% conversion was observed after 4 h) than in *tert*-butanol (74% conversion after 4 h) or in *n*-butanol (66% conversion after 4 h). However, when the transesterfication of ethyl octanoate with propan-2-ol was conducted in the presence of CaLB (Nov 435) as a catalyst, the conversion was higher in *tert*-butyl alcohol, 81% after 24 h, than in ionic liquid [bmim]PF_6, 56% after 24 h.

Similarly, Schöfer *et al.*[162] reported the screening of nine lipases systems against ten different ionic liquids for the kinetic resolution of *rac*-1-phenylethanol by transesterification with vinyl acetate. The results showed that reactions were faster in some ionic liquids, and that there was no reaction at all in others, even when similar ionic liquids were used.

In addition, Kim *et al.*[163] reported that ionic liquids could favour selective esterification. For example, transesterification of some chiral alcohols catalysed by *pseudomonas cepacia* (PCL) or CaLB in ionic liquids [bmim]BF_4 and [bmim]PF_6 were found to proceed with higher enantioselectivites than in THF or toluene. Moreover, recycling studies on the CaLB-catalysed reaction showed that the ionic liquid–enzyme could be recycled twice without loss of enantioselectivity or reactivity.

Clearly, the results were not consistent in some cases, even though they were observed in the same biocatalysis reaction and in similar ionic liquids.[162] Park and Kazalauskas[164] explained that this might have been caused by some impurities in the ionic liquids. The impurities might inhibit the lipase-catalysed reaction. To identify the effect from such impurities, the authors made a series of test reactions by using some further purified ionic liquids and others without further purified ionic liquids or by addition of some impurity to the purified ionic liquids. They found that some lipase-catalysed reactions that previously did not occur in untreated ionic liquids, took place in the purified ionic liquids at rates comparable to those in organic solvents. That confirmed that the impurities did affect the biocatalysis reactions.

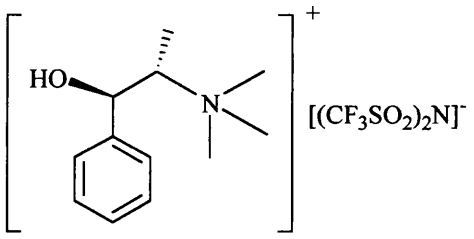
Quite recently, Lee *et al.*[165] reported that an ionic liquid-coated enzyme (ILCE) was used as a useful catalyst for biocatalysis in an organic solvent. The authors described that a lipase from *Pseudomonas cepacia* coated by the ionic liquid [ppmim]PF_6 ([ppmim] = 1-(3′-phenylpropyl)-3-methylimidazolium) (m.p. 53 °C) was used to catalyse the transesterification of some secondary alcohols in the presence of vinyl acetate in toluene at 25 °C and offered markedly improved enantioselectivity without losing any significant activity. Furthermore, the coated lipase was easy to reuse and retained its full activities even after several runs.

2.3 Chiral ionic liquids

The number of published examples related to chiral ILs has been very limited so far. Howarth *et al.*[166] described the use of chiral imidazloium cations, which was synthesised with an expensive chiral alkylating agent, such as *S*-(+)-1-bromo-2-methylbutane, in Diels–Alder reactions. Seddon *et al.*[82] prepared chiral IL

[bmim][lactate] with a readily available sodium (*S*)-2-hydroxypropionate and also used in a Diels–Alders reaction. However, no enantioselectivity was observed.

Recently, Wasserscheid *et al.*[167] synthesized some ILs with chiral cations, such as (*S*)-2-ethyl-3-pentyl-4-isopropyloxazolium hexafluorophosphate, (–)-*N,N'*-dimethylephedrinium bis(trifluoromethanesulfonyl)imidate (**34**), and so on. The initial chiral moiety was directly derived in enantiopure form from the 'chiral pool'. Such chiral moiety were used to evaluate their usefulness for enantioselective reactions and separation techniques. For example, chiral IL **34** was used as a chemical shift reagent to separate a racemic mixture of Mosher's acid sodium. Interestingly, two isomers peaks were separated clearly and can be observed from ^{19}F NMR spectroscopy. The authors suggested that these chiral ILs might be good alternative solvents in enationselective reactions and separation processes. Further investigations in this respect are still ongoing in their group.



34

2.4 Modified organic salts

In the preceding sections, the application of liquid organic salts as solvents and catalysts haven been reviewed. However, in recent time, many modifications of the common IL organic salts have been made. Some of these modifications render the salts as solids rather than liquids, but they nevertheless retain some of the properties of ILs. Examples include: (i) immobilization of catalytic salts containing $[Al_nCl_{3n+1}]^-$ anions onto solid supports (*e.g.*, a charcoal,[93,95] zeolite or other supporter having a silanol group[168,169]), thereby providing easily recoverable solid Lewis acids; (ii) in co-operation of an organic salt into a polymer membrane capable of carrying a heterogeneous Pd catalyst useful in hydrogenation reactions;[170] (iii) grafting a phosphine units onto organic cations so that they became good complexes of transition

metal ions, while retaining good solubility in ILs;[171,172,173,174] and (iv) attachment of chemical substrates for combinatorial synthesis, to allow ready removal of unwanted by-products.[175,176]

It is clear that many new applications of such modified organic salts will emerge over the next decade.

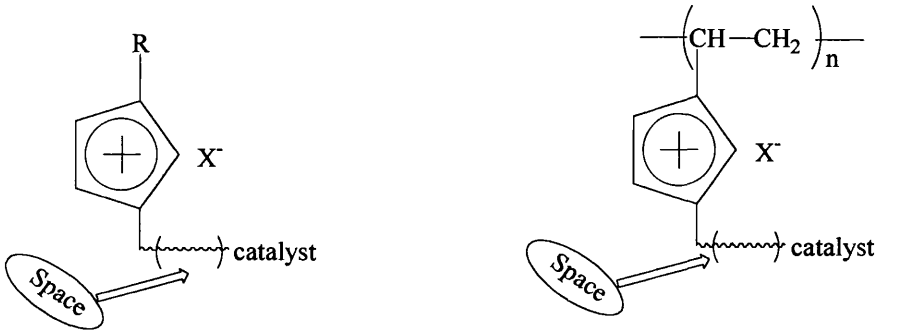
2.5 Summary and outlook

Ionic liquids have recently been regarded as an eco-friendly alternative to replace volatile organic solvents in current chemical processing, due to their unique physical and chemical properties. Their non-volatile natures enable easy separation from volatile products by distillation. Their controllable miscibilities with organic and/or inorganic chemicals make them ideal candidates as solvents in the applications in biphasic catalysis to minimize solvent and catalyst consumption. Acidic ionic liquids with tuneable acidities enable them to be used as effective catalysts in place of some Lewis acids in some cases. In addition, ILs also have high ionic conductivities and large electrochemical windows (> 3 V), and thus it is possible to use these electrochemical properties to maintain transition metal catalysts in certain oxidation states, which should be of great significance for some oxidation reactions in the field of chemistry and biochemistry.

However, although ionic liquids display many advantages, especially improvements in reaction rate and product selectivity, over traditional molecular solvents, the investigation of ionic liquids is still in its infancy. Many possible ionic liquids have not yet been synthesized. Most importantly, the chemical and physical properties of such materials are not known. The lack of some physical data for ionic liquids renders it is difficult to arrive at a clear consensus in the explanation of some advantages (*e.g.*, the influence of ionic liquids upon the improved reaction rates and product selectivities) observed between different researching groups. Therefore, more investigations are needed to answer these queries.

In the applications of ionic liquids to organic reactions catalysed by transition metal complexes, it may be possible to attach a preformed catalyst on a organic salt

monomer having an imidazoilum moiety (*e.g.*, Scheme **2.2** a)) or to a polymerised one (*e.g.*, Scheme **2.2** b)). This strategy might lead to soluble polymer-bound catalysts due to the tuneable solubility of ionic liquids in organic solvents. If so, materials that have advantages over common homogeneous or heterogeneous catalysts may emerge. It is clear that these and other potential application will continue to encourage research into ionic liquids for some time to come.



a) Monomeric ionic liquid support.

b) Polymerized ionic liquid support.

Scheme 2.2

2.6 References for Chapter 2

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Chapter 3

Synthesis of Ionic Liquids

3.1 Introduction

As mentioned in Section 2.1.3 in Chapter 2, ionic liquids can be prepared starting from the corresponding amines or other compounds, *e.g.*, phosphanes, in a two-step procedure. Alkylation leads to quaternization of the nitrogen atom in an amine or a phosphorus atom in a phosphane. The following step involves anion exchange by one of three methods: metathesis of an ionic liquid halide salt precursor with a silver salt or ammonium or group 1 metal salt of a desired anion; acid-base neutralization between a halide salt and an acid having the desired anion; or direct combination of a halide salt with a metal halide such as $AlCl_3$.

The most common salts in use are those having alkylammonium, alkylphosphonium, *N*-alkylpyridinium, or *N,N'*-dialkylimidazolium cations, as mentioned in Chapter 2. Many alkylammonium halides are commercially available. In some cases, such halide salts can be made simply by a standard preparative approach involving the reaction of the appropriate halogenoalkane and amine.[1] Phosphonium salts can be prepared in a similar way from the appropriate halogenoalkane and the corresponding trialkylphosphane.[2] Pyridinium and imidazolium halides can be prepared similarly.[3,4]

High purity of the ionic liquids is of prime importance for achieving reliable uses, especially use as a reaction medium. Therefore, all the steps involved in the preparation have to proceed with high efficiency, since purification after synthesis is extremely tedious.

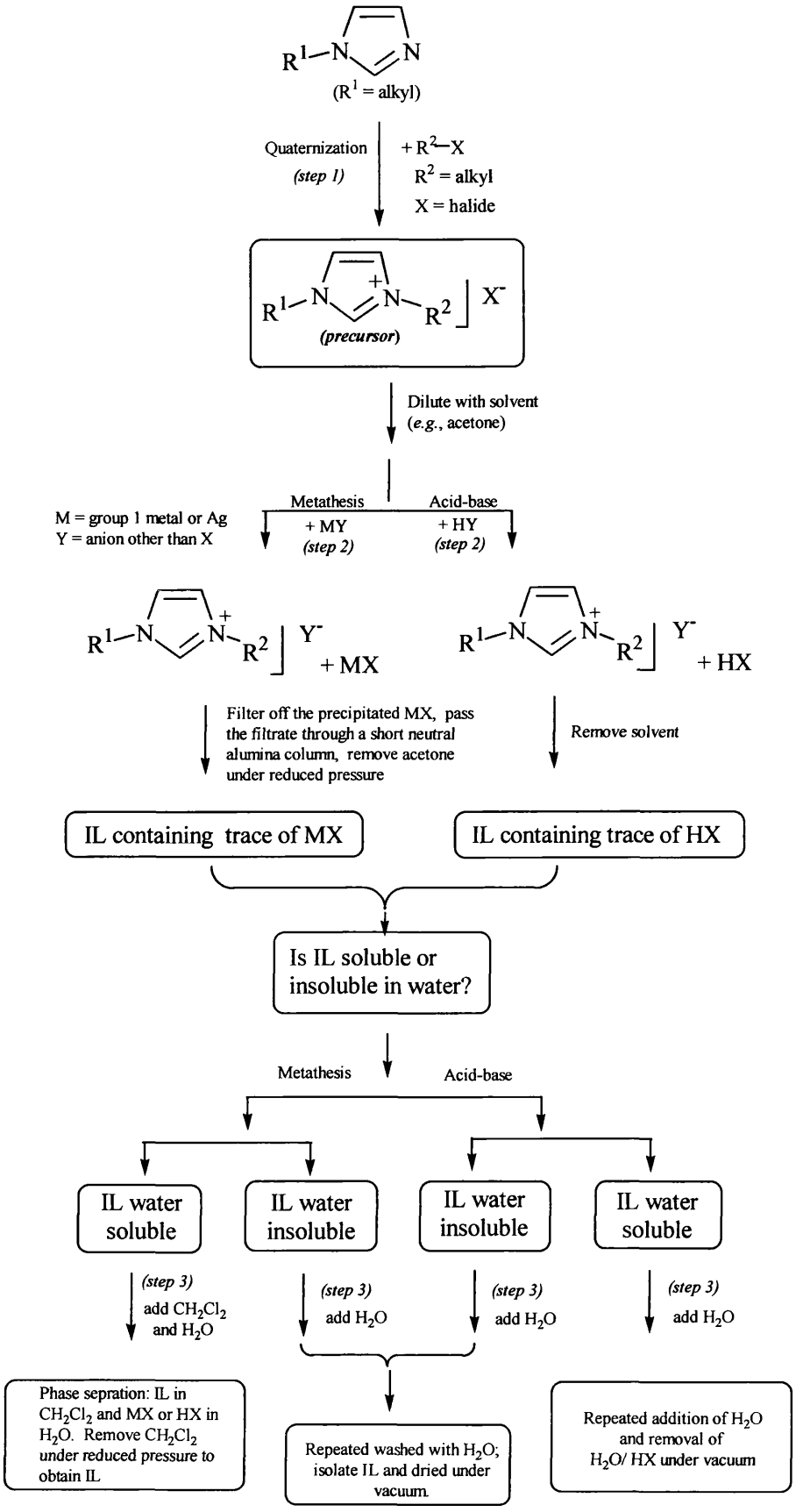
Since dialkylimidazolium-based ionic liquids are attracting significant attention as novel solvents due to their particular characteristics, the typical methods for the preparation of such liquids are discussed in this chapter. The preparation procedures are given in Scheme 3.1.

As depicted in Scheme 3.1, the imidazolium-based ionic liquids are usually derived from a common precursor, the dialkylimidazolium halide. The precursor is prepared by alkylation of *N*-alkylimidazole (RIm) with an equimolar quantity of

appropriate halogenoalkane (R–X) (step 1) in an appropriate organic solvent.[5] For volatile halogenoalkanes, the low boiling points lead to preparations requiring a sealed tube, for example, in the synthesis of [emim]Cl.[6] For longer chain substituents, the halogenoalkanes can be used in conventional glassware by heating at reflux temperature.[7] For C_2-symmetrical imidazolium halides, they can also be prepared by alkylation of imidazole with two molar equivalents of halogenoalkane directly.[8]

In step 2, the reaction is also stoichiometric and therefore an equimolar amount of waste MX or HX is produced. The problem in this step is that the by-product solid salts are soluble in the produced ionic liquids and difficult to be removed completely in some cases. Therefore, the choice of cation M is a very critical factor to prepare a pure ionic liquid.[9] Table 3.1 summarizes the synthetic conditions for some commonly used salts containing imidazolium cations.

Depending on the anion chosen, the resulting ionic liquid is either miscible or immicible with water. If it is immiscible with water, *i.e.*, forms a biphasic system with water (*e.g.*, when the anion is PF_6^- or $(CF_3SO_2)_2N^-$)), the removal of halide salt MX or acid HX is simple in the third step, by aqueous extraction. After several washings with water, a halide free ionic liquid is produced. If the ionic liquid formed is water miscible (*e.g.*, if the anion is BF_4^- or $CH_3CO_2^-$), the removal of halide salt MX or acid HX in the third step is tedious. In the case of the metathesis method, the reaction solvent is first removed under reduced pressure; dichloromethane is added and the ammonium halide NH_4X or metal halide MX is removed following precipitation at low temperature (*ca.* 0 °C). In the case of the acid-base method, the work-up of the water-miscible ionic liquid involves repetitive addition of water following by evaporation to remove as much acid as possible under reduced pressure.



Scheme 3.1 Procedures for synthesis of ionic liquids based on imidazolium cations.

As has been pointed out in Chapter 2, purity is an important factor for some properties of ionic liquids. Usually, water and halide salts can easily remain in ionic liquids as major impurities. Residual water in ionic liquids is usually due to either ineffective drying after preparation or absorption of moisture from the air. It is much easier to remove water than to remove halide salts. Water could usually be removed by evaporation in *vacuo* at above 70 °C for a certain time. The halide impurities usually come from two sources: the precursor organic salts and/or by-product inorganic salts. The unreacted starting material can be removed by passing the ionic liquids through a short neutral alumina column.[10] The way to remove inorganic salts depends on whether the ionic liquid is hydrophobic or hydrophilic. For a hydrophobic ionic liquid, the removal procedure is simple, involving mere washing with water. For a hydrophilic ionic liquid, the removal procedure is tedious to some extent. It is first necessary to evaporate the reaction solvent if the salt has a high solubility in that solvent. Then, another solvent, *e.g.*, CH_2Cl_2, in which the inorganic salt has a very low solubility, is added to precipitate the inorganic salt, which is then filtered. Finally, residual salt is extracted with water at low temperature (*e.g.*, 0 °C).

In addition to the general effects from the impurities mentioned above, the purity of the salt MY and the nature of the reaction solvent can also influence the physico-chemical properties of ionic liquids. For example, in one report a high quality ionic liquid [emim]BF_4 was produced when a high purity ammonium tetrafluoroborate (99.99%) was employed as a source of the desired anion, while a discoloured one possessing a pungent odour was obtained in the same reaction when a low purity ammonium salts (*e.g.*, 98% and 99.5% purity grades) were used.[10] Interestingly, the colour of the ionic liquid was also affected by the reaction solvent. For example, in the preparation of ionic liquid [emim]BF_4 using a 99.5% purity ammonium tetrafluoroborate, a discoloured product was obtained in when acetone was used as the solvent, while a clear, odourless liquid was provided when acetonitrile was used as the solvent.[10] Therefore, it was recommended that acetonitrile should be used if only lower purity ammonium salts are available.

Table 3.1 Preparative methods of some alkylimidazolium-based room temperature ionic liquids.

Ionic liquids	Reactions	Solvents	Ref.
[Mmim]/[bmim]Tf_2N[a]	[Mmim]/[bmim]I + Li Tf_2N[a]	H_2O	5
[Bmim]/[emmim]NfO[a]	[Bmim]/[emmim]Br + NaONf[a]	H_2O	5
[Mmim]/[emim]TA[a]	[Mmim]/[emim]Br + AgTA[a]	H_2O	5
[Bmim]/[emmim]OTf[a]	Bim/Eim + MeOTf[a]	$CHCl_3$	5
[Emim]BF_4	[Emim]I + $AgBF_4$	MeOH or MeOH + H_2O	10
"	[Emim]Cl + Ag_2O +HBF_4	H_2O	11
"	[Emim]Cl + NH_4BF_4	Me_2CO	9
"	[Emim]Cl + $AgBF_4$	MeCN	12
[Emim]PF_6	[Emim]Cl + HPF_6	HF	13
"	[Emim]Cl + HPF_6	H_2O	14
[Emim]Cl	Mim + EtCl	Solvent free	15
[Emim]Cl/$AlCl_3$	[Emim]Cl + $AlCl_3$	Solvent free	15
[Bmim][lactate][a]	[Bmim]Cl + Na[lactate][a]	Me_2CO	16
[MeOemim]Tf_2N[a]	[MeOemim]TfO + LiTf_2N[a]	H_2O	5
[CF_3CH_2mim]Tf_2N[a]	[CF_3CH_2mim]Br + LiTf_2N[a]	H_2O	5
[Bmim]SbF_6	[Bmim]Cl + $HSbF_6$	H_2O	17
[Bmim]NO_3	[Bmim]Cl + $AgNO_3$	H_2O	18
"	[Bmim]Cl + $NaNO_3$	H_2O	18
"	[bmim]Cl + HNO_3	H_2O	18
[Emim]$N(CN)_2$	[Emim]I + $AgN(CN)_2$	H_2O	19

[a] TA: Trifluoroacetate; [lactate]: (*S*)-2-hydroxypropionate; NfO: nonafluorobutanesulfonate; Tf_2N^-: bis(trifluoromethyl)sulfonyl)amide; [MeOemim]: 1-(2-methoxyethyl)-3-methylimidazolium; [CF_3CH_2mim]: 1-(2,2,2-trifluorethyl)-3-methylimidazolium.

3.2 Reagents and apparatus

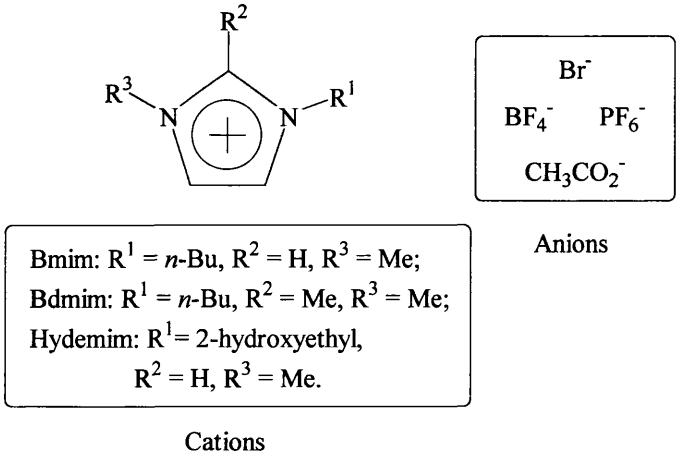
Unless otherwise stated, all reactions were conducted in an atmosphere of argon. Glassware was usually dried in an oven at 120 °C and cooled to room temperature under a flow of argon. All chemicals were obtained from Aldrich Chemical Company or Lancaster Synthesis Ltd. Solvents were distilled from the relevant drying agent prior to use: ethyl acetate and acetonitrile were distilled from CaH_2 twice, and kept under argon in the presence of 4Å molecular sieves; toluene was distilled from CaH_2 and kept over Na wires. 1,2-Dimethylimidazole (98%), *N*-methylimidazole (anhydrous, 99.99%) and 1-bromobutane (99.99%) were used directly without any treatment; 2-bromoethanol (99%) was distilled at 56~57 °C /20 mmHg under the protection of argon before use.

Nuclear magnetic resonance (NMR) instrumentation: ^{1}H and ^{13}C NMR spectra were recorded on a AV400 Bruker spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C measurements. ^{11}B, ^{19}F and ^{31}P NMR were recorded on a AC250 Bruker spectrometer operating at 128 MHz for ^{11}B NMR, 376 MHz for ^{19}F NMR and 162 MHz for ^{31}P NMR measurements. Chemical shifts are reported in parts per million relative to tetramethylsilane ($Si(CH_3)_4$) for ^{1}H and ^{13}CNMR spectra and relative to boron trifluoride etherate (BF_3OEt_2) for ^{11}BNMR spectra, phosphoric acid (H_3PO_4) for ^{31}P NMR spectra and 1-fluoro-1,1,1-trichloromethane ($CFCl_3$) for ^{19}F NMR spectra. Coupling constants J are in Hz. Assignments of signals are based on coupling patterns and some expected chemical shift values have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Electrospray mass spectra were recorded on a Quattro II spectrometer. IR spectra were recorded on a Satellite FTIR instrument.

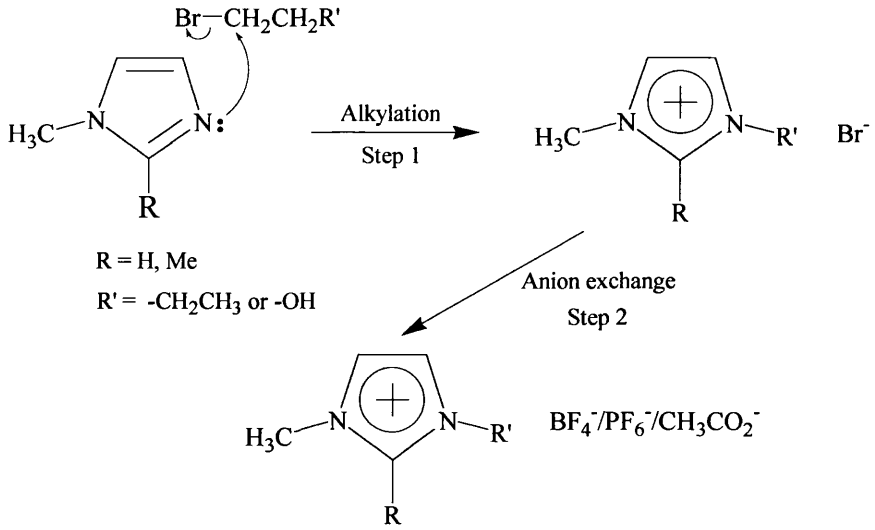
3.3 Syntheses of ionic liquids

Synthesis of seven salts are reported in this chapter: [bmim]Br, [bmim]BF_4, [bmim]PF_6, [bdmim]Br, [bdmim]BF_4, [hydemim]Br and [hydemim]PF_6, as were shown in Scheme 3.1. They can be prepared by alkylation of appropriate

N-methylimidazole precusor followed by anion exchange with a salt containing the desired anion, as shown in Scheme 3.2.



Scheme 3.1 Cations and anions in the synthesised ionic salts.

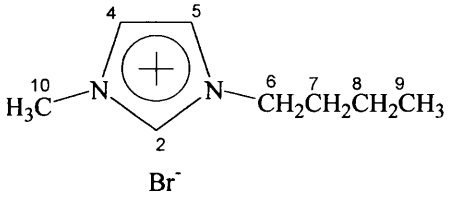


Scheme 3.2 Route for synthesis of imidazolium salts.

3.3.1 Synthesis of 1-butyl-3-methylimidazolium bromide ([bmim]Br) (Structure 3.1)

[Bmim]Br was synthesized according to a literature procedure,[19] with the following modifications: under vigorous stirring, bromobutane (17.72 ml, 0.165 mol) was added dropwise over 15 min by a syringe to *N*-methylimidazole

(neat liquid, 11.96 ml, 0.150 mol) in a three-necked, 250-ml round-bottomed flask equipped with a reflux condenser and a side arm under dry argon. The mixture was maintained for 4 h at reflux temperature and then left to cool in a freezer at *ca.* -13 °C overnight. The product solidified as a waxy solid, leaving no residual liquid to be removal. The solid was dissolved in hot acetonitrile (15 ml) and the solution was filtered by the Schlenk technique under the protection of dry argon, in case there were solid particles suspended in the dark coloured liquid. Pre-dried ethyl acetate (25 ml) was added to the filtrate and the mixture was placed in the freezer at *ca.* –13 °C again, this time to give a white needle-like crystalline solid, which was isolated by Schlenk filtration and dried in *vacuo* for 2 h at room temperature. Yield: 19.25 g, 59%. The product was characterized by using NMR and mass spectrometry.



3.1

^{1}H NMR (in $CDCl_3$, δ_{ppm}): 10.24 (1H, s, H_2), 7.63 (1H, d, J = 1.7 Hz, H_4), 7.50 (1H, d, J = 1.7 Hz, H_5), 4.29 (2H, t, J = 7.4 Hz, H_6), 4.05 (3H, s, H_{10}), 1.83 (2H, quint, J = 7.4 Hz, H_7), 1.31 (2H, sext, J = 7.4 Hz, H_8), 0.87 (3H, t, J = 7.4 Hz, H_9).

^{13}CNMR (in $CDCl_3$, δ_{ppm}): 137.1 (C_2), 123.7 (C_4), 122.2 (C_5), 49.7 (C_6), 36.6 (C_{10}), 32.1 (C_7), 19.4 (C_8), 13.4 (C_9).

Electrospray MS: ES^+, m/z (%), 139.0 ($[bmim]^+$, 100%); ES^-, m/z (%), 78.9/80.9 (Br^-, 100%).

3.3.2 Synthesis of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) (the same structure as 3.1 except anion of BF_4^-)

3.3.2.1 Use of water as a reaction solvent[20]

To a cooled (ice-bath, 0 °C), rapidly stirred solution of 1-butyl-3-methyl-midazolium bromide (7.09 g, 32.34 mmol) in water (100 ml) (note: [bmim]Br was

weighed under argon because it is very hygroscopic), a solution of $NaBF_4$ (3.39 g, 32.34 mmol) in water (20 ml) was added slowly. The reaction was maintained in an ice-bath for 1.0 h, allowed to warm up to room temperature and maintained for an additional 3.0 h afterwards. The final solution was extracted with dichloromethane (3 x 50 ml). The organic layer was dried over anhydrous $MgSO_4$. Solid $MgSO_4$ was filtered and the solvent in the filtrate was removed by rotary evaporation to yield a pale yellow liquid product. The yield of the product in the organic layer was very low because the ionic salt was highly soluble in water. Therefore, the water layer was concentrated nearly to dryness under vacuum and the residue was washed with ethyl acetate (3 x 15 ml). After removing the solvent from the combined organic fraction, the colourless liquid product was obtained: 3.09 g, 42% yield.

3.3.2.2 Use of acetone as a reaction solvent[21]

An aliquot of [bmim]Br (14.86 g, 67.86 mmol) was weighed under argon and added to a 250-ml round-bottomed flask containing dried acetone (100 ml) and a magnetic stirring, equipped with side arm under dry argon. Next, ammonium tetrafluoroborate (7.12 g, 67.86 mmol) was added. Both solid reactants were only slightly soluble in acetone. The reaction mixture was stirred vigorously at room temperature for 60 h under the protection of argon. Such a long reaction time was used in order to ensure a complete reaction. After this time, the insoluble by-product NH_4Br was removed by filtration in the air. To remove trace organic impurities, neutral alumina (2.0 g) was added to the acetone filtrate containing the produced soluble $[bmim]BF_4$. After stirring for 2.0 h, the alumina was filtered from the solution. The acetone was removed by rotary evaporation to give the product $[bmim]BF_4$ as a colourless liquid. The $[bmim]BF_4$ was subsequently dried in vacuum at 70 °C for 5.0 h, giving a final yield of 14.99 g, 97%.

Nevertheless, there was still a very small amount of residual NH_4Br in $[bmim]BF_4$. This NH_4Br could be observed as transparent needle-like crystals suspended in the far bottom part of the $[bmim]BF_4$ after a certain time. Therefore, further purification was taken by dissolving the ionic liquid in dichloromethane (*ca.*1 : 1 by weight). The solution was repeatedly stirred with small amounts of

distilled water at 0 °C and then separated. It was found that the loss of the hydrophilic ionic liquid [bmim]BF_4 into the aqueous phase could be minimised at this temperature. When both phases were free of bromide (test with silver nitrate), the solvent was removed from the IL phase and the resultant IL was dried under reduced pressure. The IL was kept under argon for further use.

^{1}H NMR (in acetone-d_6, δ_{ppm}): 8.91 (1H, s, H_2), 7.71 (1H, d, J = 1.8 Hz, H_4), 7.65 (1H, d, J = 1.8 Hz, H_5), 4.30 (2H, t, J = 7.3 Hz, H_6), 3.99 (3H, s, H_{10}), 1.88 (2H, quint, J = 7.4 Hz, H_7), 1.34 (2H, sext, J = 7.4 Hz, H_8), 0.91 (3H, t, J = 7.4 Hz, H_9).

^{13}C NMR (in acetone-d_6, δ_{ppm}): 137.4 (C_2), 124.5 (C_4), 123.2 (C_5), 49.9 (C_6), 36.4 (C_{10}), 32.6 (C_7), 19.8 (C_8), 13.7 (C_9).

^{19}F NMR (in acetone-d_6 δ_{ppm}): -150 (two peaks, ratio, 4:1).

^{11}B NMR (in acetone-d_6 δ_{ppm}): -0.26.

Electrospray MS: ES^+, m/z (%), 139.0 ($[bmim]^+$, 100%); ES^-, m/z (%), 86.9 (BF_4^-, 100%).

IR (liquid film, NaCl window, ν, cm^{-1}): 3640, 3566 (ν_{O-H}, free H_2O, absorbed from air), 3167 and 3130 (ν_{C-H}, aromatic), 2968, 2937 and 2875 (ν_{C-H}, aliphatic), 1574 ($\nu_{C=C}$) and 1468 (ν_{C-H}), 1058 (ν_{B-F}).

3.3.3 Synthesis of 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) (the same structure as 3.1 except the anion of PF_6^-)[22]

The procedure was similar to that for the synthesis of [bmim]BF_4 in acetone, with the exception of using a different way to remove the by-product NaBr from [bmim]PF_6 as follows: the crude ionic liquid [bmim]PF_6, which is immiscible with water, was repeatedly washed with small volumes of distilled water directly until no precipitation of AgBr occurred in both the aqueous and organic phases on addition of a concentrated $AgNO_3$ solution. After decanting the water phase away, the ionic liquid phase containing some residual water was dried in vacuum at 70 °C for 12 h, giving a colourless liquid product. The final liquid was flushed with argon and kept for further use. The IL obtained was characterized by NMR, MS and IR.

Yield: from [bmim]Br (10.95 g, 50.0 mmol) and $NaPF_6$ (8.40 g, 50.0 mmol), there was obtained [bmim]PF_6 (12.64 g, 44.5 mmol, 89% yield).

^1H NMR (in acetone-d_6, δ_{ppm}): 8.89 (1H, s, H_2), 7.70 (1H, d, J = 1.7 Hz, H_4), 7.65 (1H, d, J = 1.7 Hz, H_5), 4.33 (2H, t, J = 7.3 Hz, H_6), 4.02 (3H, s, H_{10}), 1.90 (2H, quint, J = 7.4 Hz, H_7), 1.36 (2H, sixtet, J = 7.4 Hz, H_8), 0.93 (3H, t, J = 7.4 Hz, H_9).

^{13}C NMR (in acetone-d_6 δ_{ppm}): 137.3 (C_2), 124.7 (C_4), 123.3 (C_5), 50.1 (C_6), 36.5 (C_{10}), 32.6 (C_7), 19.9 (C_8), 13.6 (C_9).

^{19}F NMR (in acetone-d_6 δ_{ppm}): -71.4 (doublet).

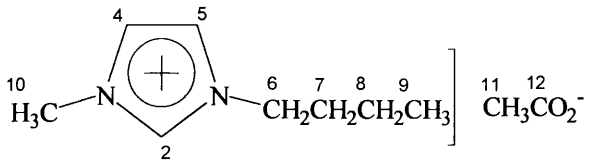
^{31}P NMR (in acetone-d_6 δ_{ppm}): -90.2 (septet).

Electrospray MS: ES^+, m/z (%), 139.0 ($[bmim]^+$, 100%); ES^-, m/z (%), 145.0 (PF_6^-, 100%).

IR (liquid film, NaCl window, ν, cm^{-1}): 3672, 3594 (ν_{O-H}, free H_2O, small, absorbed from air); 3171 and 3125 (ν_{C-H}, aromatic), 2966, 2939 and 2882 (ν_{C-H}, aliphatic); 1574 ($\nu_{C=C}$), 1467 (ν_{C-H}), 851 (ν_{P-F}).

3.3.4 Synthesis of 1-butyl-3-methylimidazolium acetate ([bmim]OAc) (the structure 3.2)[21]

The procedure was similar to that for the synthesis of [bmim]BF_4 in acetone. However, it is rather difficult to remove NH_4Br completely because of a higher partition coefficient of [bmim]OAc in water than that in CH_2Cl_2. In the end, mass spectral analysis indicated that there was still a mixture of [bmim]OAc and NH_4Br in the final liquid. Therefore, use of AgOAc instead of NH_4OAc is recommended.



3.2

From [bdmim]Br (1.52 g, 7.0 mmol) and $NH_4CH_3CO_2$ (0.55 g, 7.0 mmol), there was obtained [bdmim]BF_4 (1.22 g, 6.1 mmol, 88% yield).

^{1}H NMR (in acetone-d_6, δ_{ppm}): 10.2 (1H, s, H_2), 7.55 (1H, d, J = 1.6 Hz, H_4), 7.44 (1H, d, J = 1.6 Hz, H_5), 4.29 (2H, t, J = 7.4 Hz, H_6), 4.07 (3H, s, H_{10}), 1.96 (3H, s, H_{11}), 1.86 (2H, m, H_7), 1.34 (2H, m, H_8), 0.92 (3H, t, J = 7.4 Hz, H_9).

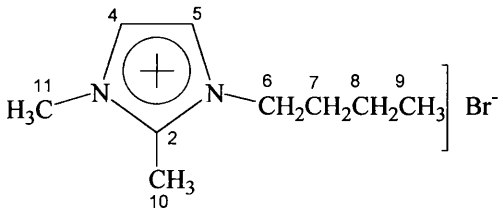
^{13}C NMR (in acetone-d_6 δ_{ppm}): 176.3(C_{12}), 137.8 (C_2), 124.0 (C_4), 122.4 (C_5), 50.2 (C_6), 37.1 (C_{10}), 32.5 (C_7), 23.0 (C_{11}), 19.8 (C_8), 13.8 (C_9).

Electrospray MS: ES^+, m/z (%), 139.0 ($[bmim]^+$, 100%); ES^-, m/z (%), 59.0 (CH_3CO_2, 100%), 79.8/80.9 (Br^-, 80%).

IR (liquid film, NaCl window, ν, cm^{-1}): 3427 (ν_{O-H}, free H_2O, absorbed from air), 3074 (ν_{C-H}, aromatic), 2956 and 2877 (ν_{C-H}, aliphatic), 1706 ($\nu_{C=O}$), 1569 ($\nu_{C=C}$), 1444, 1386, 1254, 1163 (ν_{C-H}).

3.3.5 Synthesis of 1-butyl-2,3-dimethylimidazolium bromide ([bdmim]Br) (Structure 3.3)[22]

A similar procedure was used as that for the synthesis of [bmim]Br, but with some modifications: to a vigorously stirred solution of 1,2-dimethylimidazole (7.87 g, 80.23 mol) in toluene (10 ml) at 0 °C under the protection of argon, 1-bromobutane (9.48 ml, 88.25 mmol, 1.1 molar equiv.) was added dropwise through a syringe. The solution was heated to reflux at *ca.* 115 °C for 12 h. After the mixture had cooled to room temperature, two phases formed. The upper layer, toluene, was separated by decantation, and the bottom semi-solid layer of [bdmim]Br was recystallized twice from a mixture of acetonitrile (5.0 ml) and ethyl acetate (10 ml) to give a white crystalline solid, which was dried in vacuum to give pure [bdmim]Br (15.01 g, 64.18 mmol, 80% yield).



3.3

^{1}H NMR (in DMSO-d_6, δ_{ppm}): 7.83 (1H, s, H_4), 7.82 (1H, s, H_5), 4.26 (2H, t, J = 7.0 Hz, H_6), 3.91 (3H, s, H_{11}), 2.73 (3H, s, H_{10}), 1.79 (2H, m, H_7), 1.40 (2H, m, H_8), 1.04 (3H, t, J = 1.8 Hz, H_9).

^{13}C NMR (in DMSO-d_6 δ_{ppm}): 144.7 (C_2), 122.8 (C_4), 121.4 (C_5), 47.7 (C_6), 35.2 (C_{11}), 31.7 (C_7), 19.3 (C_8), 13.9 (C_{10}), 9.86 (C_9).

Electrospray MS: ES^+, m/z (%), 153.0 ($[bmim]^+$, 100%); ES^-, m/z (%), 78.8/80.8 (Br^-, 100%)

3.3.6 Synthesis of 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim]BF_4, the same structure as 3.3 other than BF_4^- anion)[21]

The procedure was the same as that used for the synthesis of [bmim]BF_4 in acetone. From [bdmim]Br (6.99 g, 30.0 mmol) and NH_4BF_4 (3.57 g, 33.0 mmol), there was obtained of [bdmim]BF_4 (6.40 g, 26.7 mmol) in 87% yield.

^{1}H NMR (in acetone-d_6, δ_{ppm}): 7.64 (1H, s, H_4), 7.62 (1H, s, H_5), 4.28 (2H, t, J = 7.0 Hz, H_6), 3.92 (3H, s, H_{11}), 2.76 (3H, s, H_{10}), 1.84 (2H, m, H_7), 1.42 (2H, m, H_8), 0.94 (3H, t, J = 1.8 Hz, H_9).

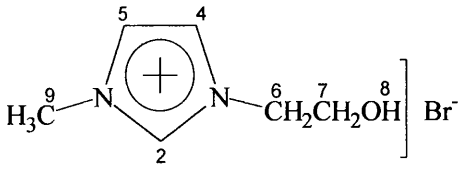
^{13}C NMR (in DMSO-d_6, δ_{ppm}): 146.0 (C_2), 123.8 (C_4), 122.3 (C_5), 49.2 (C_6), 35.8 (C_{11}), 32.9 (C_7), 20.5 (C_8), 14.2 (C_{10}), 10.1 (C_9).

Electrospray MS: ES^+, m/z (%), 153.0 ($[bdmim]^+$, 100%); ES^-, m/z (%), 87.0 (BF_4^-, 100%).

IR (liquid film, NaCl window, ν, cm^{-1}): 3641, 3569 (ν_{O-H}, free H_2O, absorbed from air), 3149 (ν_{C-H}, aromatic); 2965, 2941 and 2877 (ν_{C-H}, aliphatic), 1590 and 1544 ($\nu_{C=C}$), 1465 and 1429 (ν_{C-H}), 1058 (ν_{B-F}).

3.3.7 Synthesis of 1-(2-hydroxyethyl)-3-methylimidazolium bromide ([hydemim]Br, structure 3.4)[23]

[Hydemim]Br was synthesized according to the procedure in the literature,[24] with the following modifications: under vigorous stirring, *N*-methylimidazole (11.96 ml, 0.15 mol) was added dropwise over 15 min by syringe to 2-bromoethanol (neat liquid, 10.63 ml, 0.15 mol) in a three-necked, 100-ml round-bottomed flask equipped with a reflux condenser and a side arm under dry argon at room temperature. The mixture was heated up to 80 °C slowly, then maintained at this temperature for 1.0 h with vigorous stirring (note: when the temperature was up to



3.4

ca. 80 °C, the reaction became so violent that the reaction mixture became brown). After removal of the heating bath, dry acetonitrile (20 ml) was added into the hot reaction mixture and some white precipitate formed quickly with the decrease of the temperature. The mother liquor was filtered away by means of the Schlenk technique under the protection of dry argon. The solid was redissolved into hot dry acetonitrile (20 ml) and the mother liquor was filtered again. The same precipitation procedure was repeated five times in order to remove the brown colour. Finally, a pure, snow-like solid (11.65 g, 38% yield) was obtained. The product was characterized by NMR and mass spectrometry.

^{1}H NMR (in acetone-d_6, δ_{ppm}): 8.79 (1H, s, H_2), 7.49 (1H, d, J = 1.9 Hz, H_5), 7.44 (1H, d, J = 1.9 Hz, H_4), 4.15 (2H, t, J = 4.9 Hz, H_6), 3.79 (3H, s, H_9), 3.72 (2H, t, J = 4.9 Hz, H_7), 3.16 (1H, s, H_8).

^{13}C NMR (in acetone-d_6, δ_{ppm}): 38.8 (C_2), 125.2 (C_4), 124.5 (C_5), 61.5 (C_6), 53.7 (C_7), 36.9 (C_9).

Electrospray MS: ES^+, m/z (%), 127.1 ([dyhemim]$^+$, 100%); ES^-, m/z (%), 78.8/80.8 (Br^-, 100%)

3.3.8 Synthesis of 1-(2-hydroxyethyl)-3-methylimidazolium hexafluorophosphate ([hydemim]PF_6, the same structure as 3.3 other than PF_6^- anion)

The procedure used was the same as that in Section 3.3.2.2, with the exception of using $NaPF_6$ in place of NH_4BF_4.

Yield: from [hydemim]Br (3.10 g, 15.0 mmol) and $NaPF_6$ (2.77 g, 16.5 mmol), there was obtained [hydemim]PF_6 (3.29 g, 12.1 mmol, 80% yield).

^{1}H NMR (in acetone-d_6, δ_{ppm}): 8.97(1H, s, H_2), 7.73 (1H, d, J = 1.6 Hz, H_5), 7.68 (1H, d, J = 1.6 Hz, H_4), 4.45 (2H, t, J = 5.0 Hz, H_6), 4.06 (3H, s, H_9), 3.97 (2H, t, J = 5.0 Hz, H_7), 2.10 (1H, s, H_8).

^{13}C NMR (in acetone-d_6, δ_{ppm}): 139.2 (C_2), 124.8 (C_4), 124.3 (C_5), 61.2 (C_6), 53.4 (C_7), 37.0 (C_9).

Electrospray MS: ES^+, m/z (%), 127.0 ($[dhyemim]^+$, 100%); ES^-, m/z (%), 145.0 (PF_6^-, 100%)

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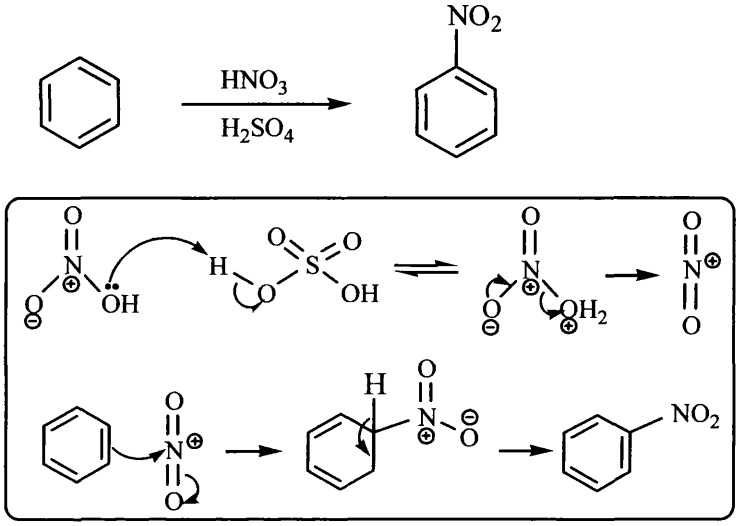
Chapter 4

Nitration of Simple Aromatics in Ionic Liquids

4.1 Introduction

Nitration of aromatic substrates is a widely studied reaction of great industrial significance as many nitro-aromatics are extensively utilised and act as chemical feedstocks for a wide range of useful materials such as dyes, pharmaceuticals, agrochemicals, perfumes, plastics and explosives. Traditionally, nitration has been performed with a mixture of nitric and sulfuric acids (mixed acid method). As an example, nitration of benzene is shown in Scheme 4.1.[1,2,3]



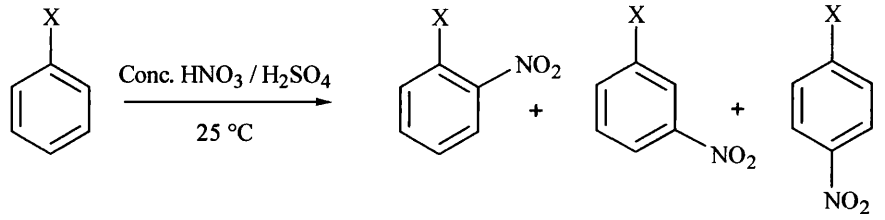
Scheme 4.1

However, a major problem associated with the classical method is the use of large quantities of sulfuric and nitric acids, which are both corrosive and responsible for the generation of a large amount of acidic waste water, which is costly to treat. In addition, overnitration and oxidation of by-products are also associated problems. Moreover, the reaction is usually not selective. The distributions of some nitrated products obtained by using the traditional nitration method are given in Table 4.1.[1,2]

In order to address these problems, several alternative methods for the nitration of aromatics have been developed recently. Some are based on homogeneous procedures in solution. These include, for example, a nitration process using metal nitrate as a direct nitrating reagent,[4,5,6] and a nitration process using nitric acid as a nitrating reagent, but employing Lewis acids (*e.g.*, lanthanide triflate[7,8,9,10,11,12]) or other acids (*e.g.*, triflic acid[13]) as catalysts to replace sulfuric acid.

Others depend upon reactions involving heterogeneous conditions, such as supported solid acidic catalysts,[14,15,16,17,18,19] zeolites[20,21,22,23] and so on. It is not appropriate to introduce each of them in depth here. Just some of them are discussed below.

Table 4.1 The distribution of nitrated products obtained by using the classical nitration method.



X	*Ortho-*	*Meta-*	*Para-*
F	13	0.6	86
Cl	35	0.9	64
Br	43	0.9	56
I	45	1.3	54
CH_3	60	3	37

4.1.1 Nitration with nitric acid

Nitric acid can be used without additional acid activators in some aromatic nitration reactions. Many studies have been carried out to evaluate the rate and the mechanism of such aromatic nitration reactions.[24] These studies indicate that a nitronium ion attacks the aromatic ring directly in an electrophilc manner (Eq. (4.1)). The nitronium species can be produced according to Equations (4.2) through (4.4).

$$ArH + HNO_3 \longrightarrow ArNO_2 + H_2O \quad (4.1)$$

$$2HNO_3 \rightleftharpoons H_2NO_3^+ + NO_3^- \quad (4.2)$$

$$H_2NO_3^+ \rightleftharpoons H_2O + NO_2^+ \quad (4.3)$$

$$NO_2^+ + NO_3^- + H_2O \rightleftharpoons 2HNO_3 \quad (4.4)$$

In addition, dilute nitric acid contains a very small concentration of nitrous acid, which gives rise to the nitrosonium ion, NO^+, in principle. The nitrosonium ion can nitrosate the aromatic ring, and the nitroso- compound can be oxidized by nitric acid to the nitro compound, which generates more nitrous acid to continue the chain reaction (Equations (4.5) and (4.6)):[24]

$$ArH + HNO_2 \longrightarrow ArNO + H_2O \quad (4.5)$$

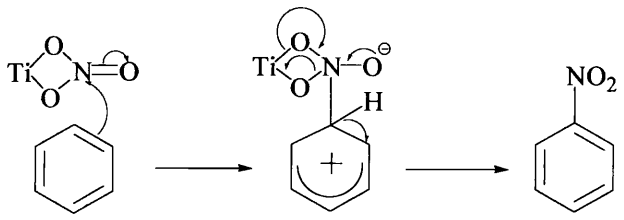
$$ArNO + HNO_3 \longrightarrow ArNO_2 + HNO_2 \quad (4.6)$$

Consequently, some highly reactive compounds (*e.g.*, phenols), which undergo nitrosation, can be nitrated with dilute nitric acid.

4.1.2 Nitration with metal nitrates

Metal nitrates, such as transition metal nitrates, have been used to nitrate aromatic compounds in organic solvents. For example, titanium(IV) nitrate had been used to nitrate benzene, nitrobenzene, toluene and chlorobenzene quantitatively in tetrachloromethane.[4,5] It was reported that the relative ratios of the various nitroaromatic isomers produced were fully consistent with electrophilic attack by NO_2^+. In addition, it was found that one mole of benzene reacted with one mole of titanium(IV) nitrate to give one mole of nitrobenzene and a solid by-product that has a Ti : NO_3^- ratio of 1:3 (see Eq. (4.7)). Therefore, it was suggested that a bidentate nitrate directly attacked the aromatic rings through a metal bound nitrate species. A possible mechanism is shown in Scheme 4.2, taking nitration of benzene as an example.

$$C_6H_6 + Ti(NO_3)_4 \longrightarrow PhNO_2 + (OH)Ti(NO_3)_3 \quad (4.7)$$



Scheme 4.2

However, a limitation associated with this nitration method is the solubility of titanium(IV) nitrate in organic solvents, which is quite low.

Recently, Pattenden and co-workers[6] reported that vanadium(V) oxytrinitrate, $VO(NO_3)_3$, can be used as a powerful reagent for the nitration of aromatic compounds at room temperature under non-acidic conditions. Nitrations of most mono-substituted benzene derivatives with one equivalent of $VO(NO_3)_3$ were complete within 3~20 min. However, a disadvantage is that dichloromethane was used as a reaction solvent.

4.1.3 Nitration with clay-supported metal nitrates

Laszlo[14~17] had developed a one-pot procedure for the mono- or polynitration of aromatic compounds by using 'claycop', a reagent consisting of an acidic montmorillonite clay (K10) impregnated with anhydrous cupric nitrate. Toluene was nitrated quantitatively by 'claycop' in the presence of acetic anhydride, called claycop–acetic anhydride system, in tetrachloromethane. The reaction could produce high *para*-selectivity (o/m/p = 20/1/79) under conditions of high dilution, provide that the addition of toluene was very slow and a long reaction time (120 h) was used.[15] However, when the concentration of the solution was higher, the amount of the *para*-product was less.

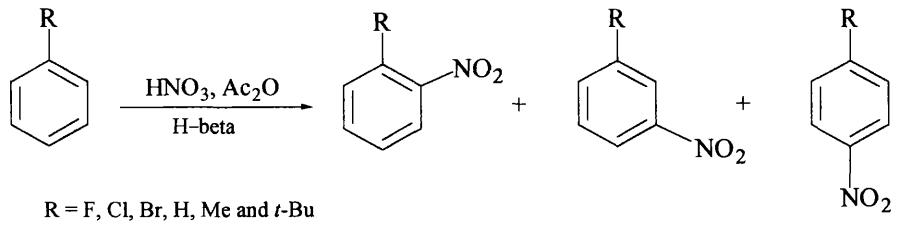
As well as cupric nitrate, other nitrates, including aluminium nitrate, bismuth nitrate and so on, were also impregnated onto K10 montmorillonite and used as supported reagents for the nitration of aromatic compounds.[17]

In the light of their results, Laszlo and co-workers improved the 'claycop' nitration system further by including fuming nitric acid and acetic anhydride, called claycop–nitric acid–acetic anhydride system.[18] The reaction was driven to go faster in the claycop–nitric acid–acetic anhydride system than that in the claycop–acetic anhydride system. Moreover, the claycop–nitric acid–acetic anhydride system is applicable not only to activated aromatics but also to a wide range of unactivated and deactivated substrates. However, the reaction is susceptible to over-nitration.

4.1.4 Zeolite-assisted nitrations

Zeolites, with their well-defined cages and channels, have been applied extensively to organic reactions, either as active participants or inert supports.[20~23] Zeolite-based solid acid catalysts are potentially attractive due to the easy removal of substrate or product, easy catalyst recycling and possible regioselectivity. Zeolite-assisted nitrations of aromatic compounds have been studied successfully by a number of researchers. Smith *et al.*[20] reported that toluene and other alkylbenzenes can be mononitrated in essentially quantitative yield and highly *para*-selectivities by benzoyl nitrate in the presence of aluminium/proton exchanged large port mordenite. For example, toluene was nitrated by benzoyl nitrate over the zeolite in tetrachloromethane to give 67% of the *para*-isomer in 10 min. However, tetrachloromethane is environmentally unfriendly. Nagy *et al.*[21] have used ZSM-11 in hexane, with the external acids sites of the zeolite selectively poisoned by treatment with tributylamine, to nitrate toluene with benzoyl nitrate. In their work, excellent *para*-selectivity (98%) was achieved, but in low yield. Kwok and his coworkers[22] used alkyl nitrate as a nitrating reagent in conjunction with a highly dealuminated ZSM-5 zeolite (Si/Al = 1000) to nitrate toluene, with toluene as its own solvent. Mononitrotoluene was successfully produced in 54% yield, based on the alkyl nitrate, with a product distribution of o/m/p = 5/0/95. However, when a less dealuminated sample of ZSM-5 (Si/Al < 300) was used in place of ZSM-5 (Si/Al = 1000) under the same reaction conditions, much poorer selectivity was obtained, o/m/p = 32/1/67.

Since water could cause the poisoning of the acidic sites in zeolites, industrially preferred nitrating reagent nitric acid present water is limited to use when it alone is in conjunction with zeolite. However, zeolites can be used if the water in nitric acid can be removed by some dehydrating reagents, such as acetic anhydride. More recently, in Smith's group the highly acidic zeolite Hβ has been used to catalyse the nitration of simple aromatics by a mixture of acetic anhydride and nitric acid at room temperature, according to Equations (4.8) and (4.9). Both improved selectivities towards the *para* position and very good yields were provided in this nitration system.[23] Some results are cited in Table 4.2.



$$Ac_2O + HNO_3 \longrightarrow AcONO_2 + AcOH \qquad (4.9)$$

Table 4.2 Nitration of PhR according to Eqs (4.8) and (4.9) in Ref. 23.

R	Yield (%)	Isomers of the products		
		Ortho-	*Meta-*	*Para-*
F	>99	6	0	94
Cl	>99	7	0	93
Br	>99	13	0	87
H	>99	--	--	--
Me	>99	18	3	79
t-Bu	92	8	Trace	92

Following Smith's[23] reports, Choudary and co-workers[25] developed another nitration system in which various solid acidic catalysts, such as K10 montmorillonite, zeolite β and ZSM-5, and so on, in conjunction with nitric acid (60~90%) alone were used as nitrating reagents. This system was effective and gave only water as a by-product, but offered a lower selectivity than that of Smith's system. For example, nitration of chlorobeneze using one equivalent of 60% HNO_3 over a sample of zeolite β (Si/Al = 22) provided nitrochlorobenzene in 51% yield with distribution of 18% *ortho*-isomer and 82% *para*-isomer.

4.1.5 Nitration in a nitrogen dioxide–ozone/oxygen system

Recently, a nitrogen dioxide–ozone (NO_2/O_3) system has been used to nitrate a variety of aromatic compounds.[26,27] Very good conversions were obtained but the selectivities were similar to those in the classical mixed acid nitrating system.[26] The

active nitrating agent was thought to be N_2O_5, which was formed in *situ* from NO_2 and O_3. However, some drawbacks to this method still exist, including the use of ozone, which may make the reaction mixture susceptible to explosion on the one hand and can cause the degradation of some sensitive compounds on the other hand.

The direct use of N_2O_5 as a nitrating reagent, instead of material generated *in situ*, has also been investigated and proved to be efficient for activated aromatic rings.[28] For example, nitration of toluene at 0 °C gave a virtually quantitative yield after only 10 min. However, it was not suitable for nitration of less activated aromatic rings. For example, when it was applied to acetophenone, the intact starting material was recovered.

Due to these limitations in the nitration system involving NO_2/O_3 or N_2O_5 as nitrating reagent, Suzuki *et al.*[29,30] developed further alternative nitration approaches on the basis of their previous reports.[26,27] In the new method, dinitrogen tetroxide was used as the nitrating reagent, oxygen was used as an oxidant and $Fe(acac)_3$ was used as a catalyst. By using this nitration methodology, not only activated aromatics, such as toluene, but also deactivated aromatics, such as chlorobenzene or acetophenone could be nitrated successfully. However, the selectivity was similar to that obtained with the mixed acid system.[30]

As in Suzuki's method, Bak and Smallridge[28] used N_2O_5 and $Fe(acac)_3$ as a nitrating reagent to nitrate a range of deactivated aromatic compounds. Most of the substrates were nitrated in near quantitative yields within 4 min. For example, the yields were 93% for benzaldehyde and 98% for acetophenone at 0 °C, 99% for bromobenzene at 20 °C, and 94% for nitrobenzene at 40 °C. The reaction conditions were extremely mild, as exemplified by the ready formation of nitrobenzaldehyde from benzaldehyde, with no evidence of oxidation of the aldehyde functionality. However, the regioselectivities were also similar to those observed for reactions conducted under standard nitrating conditions with HNO_3/H_2SO_4, except in the cases of nitration of benzaldehyde and acetophenone, which produced increased amounts of the *ortho*-isomers.[28]

Based on the results obtained by Suzuki[26~27,29~30] and Bak,[28] the groups of Smith[31,32] and Suzuki[33] made some additional investigations, respectively, in order to improve the *para*-selectivity of nitrated aromatic compounds using the NO_2–O_2 system. Smith *et al.*[31] reported that the nitration of halogenobenzenes using zeolite Hβ or zeolite HY as a solid catalyst, with a combination of liquid nitrogen dioxide and gaseous oxygen as the nitrating reagent, led to high yields and significant *para*-selectivites. For example, nitration of toluene using excess NO_2–O_2 in the presence of zeolite Hβ in 1,2-dichloroethane resulted in 100% conversion to give an 85% yield of mononitro products with a ratio o/m/p = 53/2/45 after 24 h. Also, nitration of chlorobenzene under the same conditions gave rise to 98% conversion to give a 95% yield of mononitro products with a ratio o/m/p = 14/1/85 after 48 h. With those exciting results in hand, the authors developed a milder nitrating system using air in place of gaseous oxygen.[32] The new procedure was also efficient and much cleaner than the previous one. By using the new nitrating system, toluene and halogenobenzene were nitrated successfully under clean, solvent free conditions, to offer high yields and similar selectivities as those in the previous report (*e.g.*, after 14 h reaction time, for toluene, a 76% yield of mononitro products with a ratio *para* to *ortho* of 0.9 was obtained; for chlorobenzene, a 97% yield with a ratio *para* to *ortho* of 5.6 was obtained).

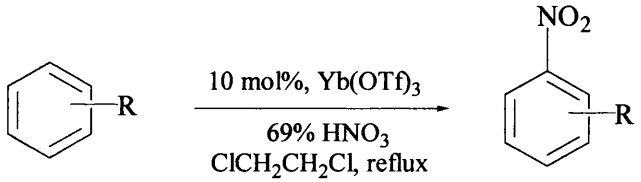
Suzuki and co-workers made some similar investigations.[33] After making a series of experiments of nitration of toluene using NO_2–O_2 in the presence of various zeolites, the authors reported that NO_2–O_2–HZSM-5 was the optimal system. Nitration of toluene with toluene as its own solvent at room temperature after 22 h yielded mononitrotoluenes as the main products, with the *para*-isomer up to 90% and the ratio of *para* to *ortho* up to 13. Similarly, chlorobenzene also reacted in a *para*-selective manner with the isomer ratio of o/m/p = 8/2/90 (*p/o* up to 11).

4.1.6 Nitrations catalysed by lanthanide triflates

As mentioned above, the classical method for nitration of aromatic compounds, involving mixed acids, leads to excessive waste acid streams and added expense. Fortunately, sulphuric acid may be replaced by strong Lewis acids such as

organic acids,[13] lanthanide triflate or triflide,[7~12] or indium triflamide,[34] and so on.

Lanthanide triflates have been used as recoverable catalysts to activate nitric acid.[7~12] A suitable method was reported a few years ago by Barrett and co-workers.[7] In their communication, they reported the use of ytterbium trifluoromethanesulfonate (triflate) (Scheme 4.3) as a catalyst for the nitration of aromatic substrates using a stoichimetric amount of 69% nitric acid as the nitrating agent. Water was the only by-product. By using this method, a number of substrates could be effectively nitrated, including a modestly deactivated system such as bromobenzene. Furthermore, the catalyst could be recovered from the water layer following aqueous work-up. After drying, the resulting solid could be used to catalyse further nitrations. However, the selectivity of nitrated product was still similar to that obtained in traditional nitration processes.[7] Also, 1,2-dichloroethane, which is environmentally unfriendly, was used as a solvent.



Scheme 4.3

Nitronium ion was considered to be the nitrating species in this system. However, due to the poor solubility of the lanthanide triflates in 1,2-dichloroethane, it was supposed that NO_2^+ was produced in the aqueous layer initially, and then subsequently diffused into the organic phase, where the nitration occurred.[9]

4.1.7 Nitration with alkyl nitrates

Alkyl nitrates, R–O–NO_2, can also be used to nitrate aromatics, since they are inherently stable. However, they are not usually capable of an effective nitration when used independently of other reagents. Instead, highly electron attracting compounds such as Lewis acids are necessary as activators in combination with the alkyl nitrates to effect the nitration process.[35] For example, in the nitration of toluene, an intact starting material was observed when methyl nitrate, CH_3–O–NO_2, alone was

used as the nitrating reagent, whereas toluene was nitrated with a ratio of o/m/p = 64/3/33 when boron trifluoride, BF_3, was used as a catalyst.[36]

4.1.8 Nitration in ionic liquids

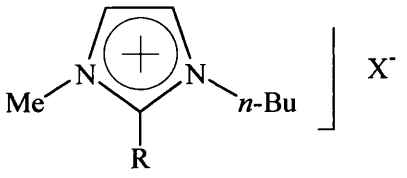
Boon *et al.* reported the first example of nitration in an ionic liquid in 1987.[37] Benzene was treated with KNO_3 in [emim]Cl/$AlCl_3$ to give a 55% yield of nitrobenzene. The ionic liquid acted as both solvent and catalyst in the process. Recently, after the initiation of our own project, Laali *et al.*[38] investigated the electrophilic nitration of aromatics in a series of ILs, such as [emim]X with X = OTf, CF_3COO, NO_3 and [$HNEtPr_2^i$][CF_3COO], by using a variety of nitrating systems, namely NH_4NO_3/TFAA, isoamyl nitrate/$BF_3{\cdot}Et_2O$, isoamyl nitrate/TfOH, $Cu(NO_3)_2$/TFAA, and $AgNO_3/Tf_2O$. For example, NH_4NO_3/TFAA in [emim]CF_3COO or [emim]NO_3, and isoamyl nitrate/$BF_3{\cdot}Et_2O$ or isoamyl nitrate/TfOH in [emim]OTf provided effective overall systems both in terms of nitration efficiency and recycling/reuse of the ionic liquids. Other systems are not so useful. For instance, the commonly used ionic liquids [emim]$AlCl_4$ and [emim]Al_2Cl_7 are unsuitable when [NO_2]BF_4 is used as the nitrating reagent. Quite recently, Rajagopal and Srinivasan[39] reported that ultrasound promoted nitration of phenol and substituted phenols using ferric nitrate and Clayfen, respectively, in the ionic liquid, ethyl ammonium nitrate, and offered significant enhancement in rates of reaction as well as high *para*-selectivity of the products as compared to the corresponding reactions performed without ultrasound.

In summary, various nitration approaches have been explored in order to avoid the traditional mixed acid method, ranging from homogeneous catalysts, such as lanthanide triflates,[7~12] to heterogeneous catalysts, such as solid acid catalysts,[7-9] including zeolites.[20~23] Although much success has been achieved, some problems still exist. For example, the use of lanthanide triflates as catalysts does not improve the selectivity, and furthermore, chlorinated solvents are required; the use of zeolites as catalysts can result in by-products, such as water or other small molecules, which form during the course of reaction and can block the entrances of the zeolite pores and

deactivate the catalyst. Therefore, there is a need to develop other alternative approaches to improve the nitration of aromatics.

4.2 Proposal in this chapter

As was reviewed in Chapter 2, ionic liquids have received attention for their promise as alternative reaction media, because of their convenient physical properties, which make them useful as potential 'clean and green' solvents. However, the application of ionic liquids in organic reactions is still in its initial stage. To our knowledge, very little attention has been paid to the nitration of aromatics in ionic liquids up to now.[37,38] On the basis of work reported in the literature and the results obtained in the previous work in Prof. Keith Smith's research group,[23] we were interested in developing a greener nitration process by making use of ionic liquids, hydrophilic [bmim]BF_4 or [bdmim]BF_4, or hydrophobic [bmim]PF_6 (see Fig. 4.1), as solvents for such a process.



IL **a** R = H, X = PF_6, [bmim]PF_6
IL **b** R = H, X = BF_4, [bmim]BF_4
IL **c** R = Me, X = BF_4, [bdmim]BF_4

Figure 4.1 The structures of IL **a**, IL **b** and IL **c**.

We initially intended to use fuming nitric acid as the nitrating reagent, zeolite Hβ as the catalyst and a water miscible ionic liquid, [bmim]BF_4, as the solvent to nitrate simple aromatic compounds. We expected that water, which would be liberated as the only by-product from the reaction, could go into the ionic liquid phase rather than inside of the zeolite pores. Thus, the deactivation of zeolite by water was expected to be reduced. Subsequently, we also aimed to use metal nitrate as nitrating reagents for nitration in an ionic liquid, either a hydrophilic one or a hydrophobic one. We expected ionic liquids to enhance the reaction rate compared to the molecular solvents in the light of their higher polarities, which would favour the solubilities of

the metal salt in such ionic solvents. Finally, we also intended to try using an ionic liquid as a solvent in a lanthanide triflate-catalysed nitration process. The results are reported in the following section.

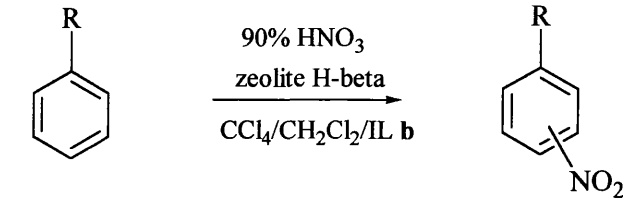
4.3 Results and Discussion

The systems chosen for use in the nitration of simple aromatic compounds in this chapter are:

- fuming nitric acid–zeolite–IL;
- fuming nitric acid–IL;
- fuming nitric acid–acetic anhydride–IL;
- cupric nitrate–IL;
- concentrated nitric acid–$Yb(OTf)_3 \cdot nH_2O$–IL.

4.3.1 Fuming nitric acid (90%)–zeolite Hβ–ionic liquid system

We chose the nitration of fluorobenzene, chlorobenzene and toluene as the test reactions, as described in Scheme 4.4. Zeolite Hβ was used as catalyst because preliminary screening suggested that it was quite active.[23] Ionic liquid $[bmim]BF_4$ (IL **b**, Fig. 4.1) was chosen as the solvent because it is water-miscible. Two equivalents of fuming nitric acid was used to ensure enough nitrating reagent. The results are given in Table 4.3.



Scheme 4.4

As can be seen from Table 4.3, in the presence of zeolite Hβ, reactions carried out either in IL **b** alone or IL **b**–co-solvent were slower than those carried out in a simple molecular solvent such as CCl_4 or in CH_2Cl_2. However, the *para*-selectivities

of the nitrated products, except in the case of toluene, were improved slightly. For example, the ratio of *para* to *ortho* was increased from 7.3 in CCl_4 to 11 in IL **b** for fluorobenzene and from 1.8 in CH_2Cl_2 to 3.0 in IL **b** for chlorobenzene. For toluene, the ratio of *para* to *ortho* remained the same, 0.7, in both CCl_4 and IL **b**.

Table 4.3 Nitration of simple aromatic compounds according to the reaction in Scheme 4.4.[a]

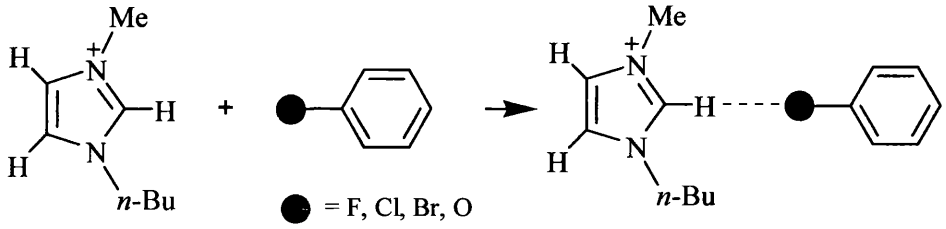
R	Solvent	Reaction time (h)	Yield[b] (%)	Yields of isomers (%)[b]			*Para-/ortho-*[c]
				Ortho-	*Meta-*	*Para-*	
F	CCl_4	6	>99	12	<1	88	7.3
	IL **b**	5	9.0	0.7	--	7.5	11
		24	33	2.7	--	30	11
	IL **b**–CCl_4[d]	15	56	5.3	--	51	9.6
Cl	CH_2Cl_2	5	74	27	<1	46	1.8
	IL **b**	5	8	2.1	--	6.0	3.0
CH_3	CCl_4	6	64	35	2.3	26	0.7
	IL **b**	6	33	19	0.8	13	0.7

[a] Reactions were carried out using Hβ (Si/Al = 25, 0.5 g), HNO_3 (20 mmol, 90%), CCl_4/ IL **b** (2.5 ml), fluorobenzene (10 mmol, 99%), at 25 °C over stated reaction times. [b] By quantitative GC. [c] Ratio of *para-/ortho-* calculated from GC data. [d] IL **b** (1.25 ml) + CCl_4 (1.25 ml).

One reason for the slow reaction rate might be due to the pores of the zeolite becoming blocked by the IL **b**, and therefore the substrate and nitric acid could have been prevented from diffusing into the pores. Thus, the reactants could not get to the acidic sites and catalysis by the zeolite would be decreased.

It was thought that the reasons for the improved selectivities in the cases of halogenobenzenes probably depended on hydrogen bonding between the halogen atoms in halogenobenzenes and the C-2 hydrogen atom in the imidazolium cation of the ionic liquid (Scheme 4.5),[40,41,42,43,44] as was proposed in the literature.[40] Hydrogen

bonding between the C-2 hydrogen and the fluorine atoms in PF_6^- anions has also been shown in an X-ray crystal structure (Fig. 4.2).[44] We speculated that the H-bonding produced a bulky effect at the *ortho* position in the halogenobenzene. Due to hindrance at the *ortho* positions, the *para* positions become preferred for attack by the nitronium ion, and thus the *para*-selectivities were increased correspondingly. For toluene, no similar hydrogen bonding is formed, so the selectivity obtained in both ionic and molecular solvents is similar.



Scheme 4.5

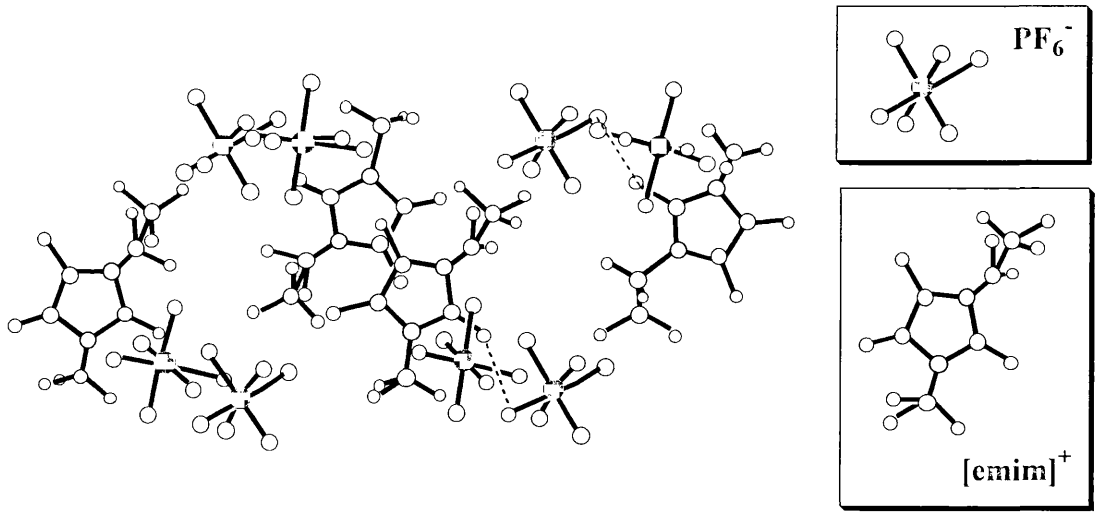


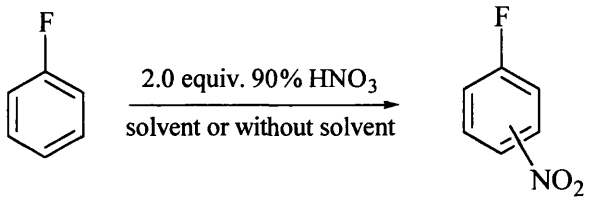
Fig. 4.2 Hydrogen bonding between the C-2 hydrogen and a fluorine atom in the ionic liquid [emim]PF_6.[44]

Another possible explanation for the lower rates of reaction in ILs could be the higher viscosity of the solvent IL **b** (density 1.17 g· cm^{-3}; viscosity 233 cP at 303 K[45]). In order to prove the reason for the slow reaction rate, some molecular solvent was added to reduce the viscosity of the ionic liquid and therefore to improve the reaction rate. It was found, as expected, on nitration of fluorobenzene, that the yield of the product was increased from 33% in pure solvent IL **b** (2.5 ml) after 24 h to 56% in the

mixed solvent, IL **b** (1.25 ml)–CCl_4 (1.25 ml), after 15 h. However, the selectivity for the *para*-product decreased (*p/o* ratio 11 in pure IL **b**; 9.6 in IL **b**–CCl_4 mixture). The results implied that the viscosity of the ionic liquid might indeed have affected the reaction rate. As for the decreased selectivity, it might be due to the decreased amount of IL, so that a smaller proportion of the solvent was involved in hydrogen bonding to the substrate.

4.3.2 Fuming nitric acid (90%)–ionic liquid systems

Since the zeolite might have been deactivated by the ionic liquid, we attempted to use a new system, nitric acid–IL (without zeolite) instead. Nitration of fluorobenzene was chosen as an example (Scheme 4.6). Both water immiscible IL **a** and water miscible IL **b** were used as reaction solvents. In addition, the reactions were also carried out under similar conditions in a molecular solvent (CCl_4) or without solvent for comparison. The results are shown in Table 4.4.



Scheme 4.6

Table 4.4 Nitration of PhF using 90% HNO_3 in CCl_4, IL **a** or IL **b** or no solvent.[a]

Entry	Solvent	Reaction time (h)	Yield (%)[b]	Yield of isomers (%)[b]		*Para-/ortho*[c]
				Ortho-	*Para-*	
1	no	1.5	100	14	86	6.1
2	CCl_4	1.5	96	13	83	6.3
3	IL **a**	6	33	2.3	30	13
4	IL **b**	3	3.8	0.3	3.5	12
		20	17	1.3	16	13

[a] Reactions were carried out using IL **a**, IL **b** or CCl_4 (0.5 ml) or no solvent, HNO_3 (4.2 mmol, 90%), PhF (2.1 mmol), at 25 °C over the stated reaction times. [b] By quantitative GC. [c] Calculated from GC results.

As can be seen from Table 4.4, the yields obtained in ILs, even with two equivalents of 90% nitric acid, were poorer than those in molecular solvent, since the reaction occurred very slowly. For example, in the nitration of fluorobenzene the yield was 33%, with a *para* to *ortho* ratio of 13, after 6 h in IL **a** (entry 3) and 17%, with a *para* to *ortho* ratio of 13, after 20 h in IL **b** (entry 4), whereas the reaction was complete, with a *para* to *ortho* ratio of 6.1, after 1.5 h without solvent (entry 1) or nearly complete, with a *para* to *ortho* ratio of 6.4, after 1.5 h in CCl_4 (entry 2). Although the yields were quite low, it was exciting to note that the *para*-selectivities were significantly higher in both ILs (*p/o* = 13) than that in CCl_4 (*p/o* = 6.4) or in the absence of solvent (*p/o* = 6.1). In addition, it was found that the reaction proceeded faster in IL **a** than in IL **b**.

4.3.3 Fuming nitric acid (90%)–acetic anhydride–ionic liquids system

From the results we obtained in Section 4.3.1, it could be concluded that there was no advantage on reaction rate, but a little improvement in selectivity in the nitration of aromatic compounds when ionic liquids were used as the solvents in combination with zeolite, compared to those when molecular solvent was used instead of IL in the same reaction. It also could be concluded, from the results in Section 4.3.2, that the system nitric acid–IL offered little improvement on the reaction rates, but gave an even greater improvement in the regioselectivity in the absence of zeolite than in its presence. This inspired us to focus on the contribution to selectivity of ILs. In order to overcome the problem of low reactivity in such systems involving an IL as the solvent, we intended to use nitric acid–acetic anhydride as a nitrating reagent, based on the method developed in the literature.[23]

Before using nitric acid–acetic anhydride in conjunction with ILs in a nitration reaction process, we conducted a series of preliminary experiments under various conditions in order to choose an optimal reaction procedure that would provide a satisfactory rate of reaction. The variations investigated included the presence or absence of zeolite Hβ, the presence or absence of acetic anhydride, and the use of a solvent (both ionic and molecular solvents) or solvent free conditions. The reactions were carried out on small scale. Fluorobenzene was chosen as the substrate. The

amount of acetic anhydride was calculated to be enough to destroy the water in the nitric acid and to convert the nitric acid into acetyl nitrate. The results are shown in Table 4.5.

Table 4.5 Nitration of fluorobenzene under various conditions.[a]

Solvent	Ac_2O (mmol)	Hβ zeolite (mg)	Reaction time (h)	Yield (%) [b]	Yields of isomers (%) [b]		*Para-/ortho-* [c]
					Ortho-	*Para-*	
no	no	no	0.5	50	8.7	42	4.8
no	no	60	0.5	57	7.0	50	7.0
no	2.9[d]	no	0.5	50	3.6	46	12
no	2.9[d]	60	0.25	>99	6.0	93	16[e]
CCl_4	2.9[d]	no	0.25	9	0.6	8.3	14
CCl_4	2.9[d]	60	0.25	>99	5.7	94	17
IL b	2.9[d]	no	0.25	94	5.3	89	17
IL b	2.9[d]	60	0.5	79	5.1	74	15

[a] Reactions were carried out using the appropriate solvent (0.5 ml) or no solvent with HNO_3 (90%, 2.1 mmol), acetic anhydride (2.9 mmol) or no acetic anhydride, zeolite Hβ (60 mg) or no zeolite, and fluorobenzene (2.1 mmol), at 25 °C over 30 min. [b] By quantitative GC. [c] Ratio of *para-/ortho-* calculated from GC data. [d] Enough to be completely react with the water in the nitric acid and to convert the nitric acid itself into acetyl nitrate. [e] This result is very similar to that reported in ref. 23.

From the results shown in Table 4.5, several conclusions could be drawn.

1) Both the reaction rate and the *para*-selectivity of the reaction could be improved by the addition of zeolite Hβ, in the presence or absence of acetic anhydride, when either a molecular solvent or no solvent was used in the reaction mixture.

2) Acetic anhydride alone in the absence of zeolite Hβ could improve the *para*-selectivity of the reaction with no obvious effect on the reaction rate, when the reaction was conducted in solvent-free conditions.

3) Acetic anhydride in conjunction with zeolite Hβ could improve both the rate and the *para*-selectivity of the reaction in a molecular solvent or in the absence of any solvent.

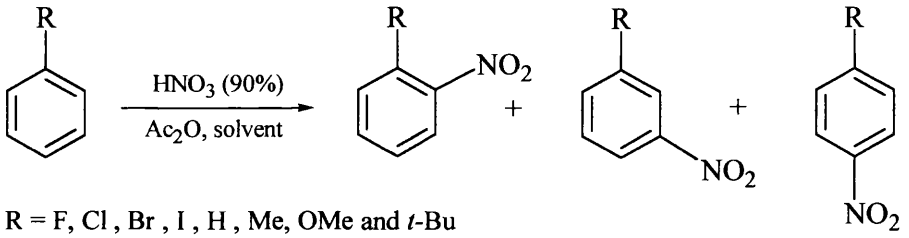
4) In the presence of zeolite Hβ, the reaction was slower in CCl_4, but offered better selectivity, than in solvent-free conditions.

5) In the presence of zeolite Hβ and acetic anhydride, both the rate and selectivity of the reaction in CCl_4 were comparable to reactions without solvent.

6) In the presence of both zeolite Hβ and acetic anhydride, the reaction was slower in IL **b** than in CCl_4 or in solvent-free conditions.

7) In the presence of acetic anhydride, but without zeolite Hβ, the reaction in IL **b** was effective and both the rate and *para*-selectivity of the reaction were comparable to those in the acetic anhydride–nitric acid–Hβ zeolite system.

As a result of those observations, we were interested in IL **b**–90% nitric acid–acetic anhydride system. Further investigation was made to optimise the specific reaction conditions according to the reactions in Equations (4.10) and (4.11) (R = F)(Scheme 4.7).



$$Ac_2O + HNO_3 \longrightarrow AcNO_2 + AcOH \qquad (4.11)$$

Scheme 4.7

The effect of the reaction temperature on nitration of fluorobenzene was investigated. The results are presented in Table 4.6.

As can be seen from Table 4.6, there was no obvious difference in the yield of nitration product in reactions carried out at different temperatures for a reaction period of 15 minutes. This suggested that the reactions were so fast for fluorobenzene under those

conditions that it was difficult to distinguish them. The proportions of the *ortho-* and *para*-products also varied little over the temperature range.

Table 4.6 Effect of temperature on the reactions in Eqs. (4.10) and (4.11)(R = F, solvent: IL **b**).[a]

T (°C)	Yield[b] (%)	Yield of isomers (%)[b]		*Para-/ortho-*[c]
		Ortho-	*Para-*	
-15	94	5.5	88	15
25	94	5.3	89	17
40	93	5.0	88	18

[a] Reactions were carried out using IL **b** (0.5 ml), HNO_3 (2.1 mmol, 90%), acetic anhydride (2.9 mmol), and PhF (2.1 mmol), at the stated temperature, over 15 min. [b] By quantitative GC. [c] Ratio of *para-/ortho-* calculated from GC data.

The effect of the concentration of the reaction mixture was also investigated. The results are given in Table 4.7.

Table 4.7 Effect of concentration on the reactions in Eqs. (4.10) and (4.11) (R = F, solvent: IL **b**) at 25 °C.

Entry[a]	Concentration of fluorobenzene (mmol/ml)	Time (min)	Yield[b] (%)	Yield of isomers (%)[b]		*Para-/ortho-*[c]
				Ortho-	*Para-*	
1	4.2	15	95	5.3	90	17
2	2.1	10	21	1.3	20	16
		30	70	4.0	66	17

[a] In entry 1, IL **b** (0.5 ml), HNO_3 (2.1 mmol, 90%), acetic anhydride (2.9 mmol), PhF (2.1 mmol), in entry 2, IL **b** (0.5 ml), HNO_3 (1.05 mmol, 90%), acetic anhydride (1.45 mmol), PhF (1.05 mmol). [b] By quantitative GC. [c] Ratio *para-/ortho-* calculated from GC data.

As the results in Table 4.7 show, the reaction was significantly slower in the more dilute solution, but the selectivity was similar in each case.

So far, it was clear from the above results that the IL **b**–90% HNO_3–acetic anhydride system was suitable for the nitration of fluorobenzene at 25 °C when the scale of the reaction was the use of 2.1 mmol substrate with one equivalent of nitric acid and one equivalent of acetic anhydride in 0.5 ml solvent.

Clearly, the use of IL **b** was advantageous from the points of view of the reaction rate and selectivity. In order to gauge the importance of the counter-ion of the IL, a nitration reaction of fluorobenzene was conducted in the hydrophobic IL **a**, [bmim]PF_6, under the conditions that had previously been used with IL **b**. The yield and the isomer proportions were very similar in the two ILs, indicating that the anion had relatively little effect on the reaction rate or selectivity. A similar reaction was also conducted using IL **c**, [bdmim]BF_4 (see Fig. 4.1), which has a methyl group at C-2 of the imidazolium cation structure, rendering it incapable of taking part in hydrogen bonding at that position. In this case the reaction was much slower, giving a yield of only 55% even after 30 minutes. The isomer proportions, however, were very similar to those obtained in IL **a** and IL **b**. The results are given in Table 4.8 (the results for IL **b** and CCl_4 were also listed in Table 4.8).

Table 4.8 Nitration of fluorobenzene in IL **a**, IL **b** and IL **c**.[a]

Solvents	Yield (%)[b]	Yields of isomers (%)[b]			*Para-/ortho-*[c]
		Ortho-	*Meta-*	*Para-*	
CCl_4	9	0.6	0	8.3	14
IL **b**	94	5.3	0	89	17
IL **a**	96	5.0	0	91	17
IL **c**[d]	55	3.0	0	52	17

[a] Reactions were carried out using the appropriate solvent (0.5 ml) with HNO_3 (90%, 2.1 mmol), acetic anhydride (2.9 mmol), and fluorobenzene (2.1 mmol), at 25 °C, for 15 min. [b] By quantitative GC. [c] Ratio of *para-/ortho-* calculated from GC data. [d] Reaction allowed to continue for 30 min.

In view of the success of the new reaction system for the nitration of fluorobenzene, it was decided to apply it to a range of simple substrates. For comparison,

all reactions were conducted under similar conditions (25 °C, 30 min) in CCl_4, IL **a**, IL **b** and IL **c**. The results are shown in Table 4.9.

As shown in Table 4.9, reactions carried out in ILs, either in hydrophilic IL **b** or IL **c** or in hydrophobic IL **a**, almost invariably proceeded faster than those in the molecular solvent, CCl_4. This could possibly be because of better solubility of the nitrating reagent, or a good solvation of the charged intermediate electrophilic species, NO_2^+, in the charged, higher polarity ILs.[46,47] The effect was most noticeable for the less reactive substrates, which gave very low yields in tetrachloromethane. In some cases (*e.g.*, for benzene) the substrate was not miscible with the ILs, which may also have affected the reaction rate. Reactions conducted in IL **a** were generally somewhat faster than those in IL **b** or IL **c**, which may be a result of greater solubility of acetic anhydride in ILs having PF_6^- anions than those having BF_4^- anions.[48]

The reactions were also generally more *para*-selective in ILs than in tetrachloromethane. However, this trend was less apparent for toluene, *tert*-butylbenzene and iodobenzene than for fluorobenzene, chlorobenzene or bromobenzene. A correlation between the degree of *para*-selectivity and the ability of appropriate substituents to from a hydrogen bond, between the substrate and the hydrogen at C-2 of the IL, has been interpreted as resulting from greater hindrance at positions *ortho* to such substituents.[40] However, the results in Tables 4.8 and 4.9 show that there is no significant difference between the results in IL **b** and IL **c**. IL **c** has a methyl group at C-2 and could therefore not take part in such hydrogen bonding. Consequently, it would appear that such hydrogen bonding is not important in the reaction. In addition, for anisole the effects were more subtle, perhaps because of the high reactivity of this substrate in all solvents. The fact that selectivities were very similar in IL **b** and IL **c** suggests that specific hydrogen bonding between the substrate and the hydrogen atom at C-2 of the cation of IL **b** is not particularly important, while the fact that the selectivity was significantly more in favour of the *para*-isomer in IL **a** than in IL **b** may suggest that the anion has some significance in this respect.

Table 4.9. Nitrations of PhR in CCl_4 and ionic liquids **a**, **b** and **c** according to Eqs. (4.10) and (4.11).[a]

PhR	Solvent	Yield (%)[b]	Yields of isomers (%)[b]			*Para-/ortho-*[c]
			Ortho-	*Meta-*	*Para-*	
Cl	CCl_4[d]	3	0.6	0	2.1	3.5
	IL **b**	60	9.8	0	50	5.2
	IL **a**	81	15	0	66	4.4
	IL **c**	60	11	0	49	4.5
Br	CCl_4[e]	4	1.1	0	3.0	2.8
	IL **b**	39	8.3	0	31	3.7
	IL **a**	70	15	0	55	3.7
	IL **c**	43	9.0	0.4	33	3.7
I	CCl_4[f]	5	1.8	0	3.6	2.0
	IL **b**	2	0.7	0	1.6	2.3
	IL **a**	14	4.3	0	9.4	2.2
	IL **c**	2	0.6	0	1.2	2.0
H	CCl_4	2	---	---	---	---
	IL **b**	18	---	---	---	---
Me	CCl_4	78	46	1.9	30	0.65
	IL **b**	88	53	3.2	32	0.60
	IL **a**	95	56	3.1	36	0.64
	IL **c**	64	39	1.7	23	0.59
OMe	CCl_4	99	68	0	31	0.46
	IL **b**	87	60	0	27	0.45
	IL **a**	63	36	0	27	0.75
	IL **c**	57	40	0	17	0.43
t-Bu	CCl_4	59	5.2	4.4	49	9.4
	IL **b**	91	8.3	9.5	72	8.7
	IL **a**	96	9.8	9.1	77	7.9
	IL **c**	62	5.7	7.6	49	8.6

[a] Reactions were carried out using IL / CCl_4 (0.5 ml), HNO_3 (90%, 2.1 mmol), acetic anhydride (2.9 mmol), and PhR (2.1 mmol) at 25 °C over 30 min. [b] By quantitative GC. [c] Ratio of *para-/ortho-* calculated from GC data. [d] 1 h reaction. [e] 2 h reaction. [f] 24 h reaction.

Although the nitration of fluorobenzene has been conducted at different concentrations in IL **a** (Table 4.7), there were no obvious differences in selectivity. That might be because fluorobenzene is rather active and its reactions are generally *para*-selective. Therefore, in order to test whether the selectivity would be affected by the concentration at which the reaction was run for another substrate, reactions of chlorobenzene were also performed in different amounts of IL **b** and IL **a**. The results are shown in Table 4.10.

Table 4.10 Nitration of PhCl in various amounts of IL **b** and IL **a** according to Eqs. (4.10) and (4.11).[a]

Solvent	Amount of solvent (ml)	Yield (%)[b]	Yields of isomers (%)[b]			*Para-/ortho-*[c]
			Ortho-	*Meta-*	*Para-*	
IL **b**	1.00	25	3.5	0	21	6.1
	0.50	60	9.8	0	50	5.2
	0.25	70	13	0	57	4.4
IL **a**	1.00	83	15	0	68	4.6
	0.50	81	15	0	66	4.4
	0.25	70	14	0	56	4.0

[a] Reactions were carried out using various amounts of ILs (as shown in Table), HNO_3 (90%, 2.1 mmol), acetic anhydride (2.9 mmol) and PhCl (2.1 mmol), for 30 min, at 25 °C. [b] By quantitative GC. [c] Ratio of *para-/ortho-* calculated from GC data.

It can be seen from the results in Table 4.10 that the reaction became a little more selective at higher dilution. In the case of IL **b**, the reaction was clearly more rapid at higher concentration, but for IL **a** the yield was high at all dilutions.

In addition, we attempted to recycle the ionic liquid, taking nitration of chlorobenzene in IL **a** as an example. The results are listed in Table 4.11.

As can be seen from Table 4.11, the IL could be recovered in high yield with loss of about 0.3 g during each cycle. After reuse it still offered the nitro-products with a good yield and the same selectivity as it did initially (note: the ratio of ionic

liquid to chlorobenzene was the same in each run). Moreover, the finally recovered IL was unchanged in structure, which was shown by NMR, MS and IR.[49] In order to compare to the results in the recycled IL, an identical experiment was performed under the same conditions except without any solvent. After 30 min, the starting material was intact.

Table 4.11 Recycle of ionic liquid IL **a** according to Eqs (4.10) and (4.11)(R = Cl)[a].

Run	Yield[b] (%)	Yields of isomers (%)[b]			*Para-/ortho-*[c]	Recovery of IL **a** (%)
		Ortho-	*Meta-*	*Para-*		
1[d]	82	15	0	67	4.5	fresh
2[e]	86	17	0	69	4.2	81
3[f]	88	17	0	71	4.2	77
4[g]	68	13	0	55	4.2	70

[a] The reactions were for 30 min, at 25 °C. [b] By quantitative GC. [c] Ratio of *para-/ortho-* calculated from GC data. [d] Reactions were carried out using IL **a** (1.6 g, fresh), HNO_3 (90%, 4.2 mmol), acetic anhydride (5.8 mmol), and PhCl (4.2 mmol). [e] 1.3 g IL **a** used, recovered from run 1, PhCl (3.4 mmol). [f] 1.0 g IL **a** used, recovered from run 2, PhCl (2.6 mmol). [g] 0.65 g IL **a** used, PhCl (1.6 mmol), recovered from run 3.

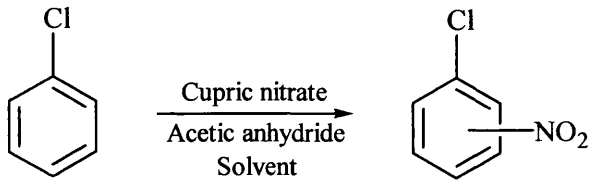
In short, nitration of simple aromatics using fuming nitric acid and acetic anhydride in ILs proceeds successfully with good yields, faster rates and better *para*-selectivites (for halogenbenzenes only) than in tetrachloromethane. Both the nature of the substituent on the aromatic ring and the structure of the IL can influence the *para*-selectivity. Furthermore, the ILs could be recovered easily by simple procedures and reused successfully.

In view of the success on the nitration of aromatics in ILs by using nitric acid–acetic anhydride as a nitrating reagent, we decided to attempt similar nitration with other nitrating reagents.

4.3.4 Copper (II) nitrate–acetic anhydride–ionic liquid system

As reviewed in Section 4.1.3, titanium(IV) nitrate has been used to nitrate

benzene, nitrobenzene, toluene and chlorobenzene in tetrachloromethane, quantitatively,[4,5] but it suffers from a low solubility in organic solvents. Cupric nitrate, analogous to titanium(IV) nitrate, might be also an appropriate nitrating reagent. Cupric nitrate has been supported on K10 montmorillonite to form a solid catalyst, which has been used to nitrate aromatics effectively in the presence of acetic anhydride.[8] In the light of these successful investigations,[7~12] we decided to attempt to use cupric nitrate only, without clay, to nitrate chlorobenzene in the presence of acetic anhydride in an ionic liquid, according to the reaction in Scheme 4.8. For comparison, the reactions were also performed in polar molecular solvents under identical conditions. The results were provided in Table 4.12.



Scheme 4.8

Table 4.12 Nitration of chlorobenzene with $Cu(NO_3)_2 \cdot 3H_2O$ in both molecular solvents and IL **b**.[a]

Entry	Solvents	Yield (%)[b]	Yields of isomers (%)[b]			*Para-/ortho-*[c]
			Ortho-	*Meta-*	*Para-*	
1	DMF	--	--	--	--	--
2	THF	--	--	--	--	--
3[d]	CCl_4	20	3.7	0.8	15	4.1
4[d]	IL **b**	42	8.0	0.3	33	4.1
5[e]	IL **b**	18	3.4	0.3	14	4.1

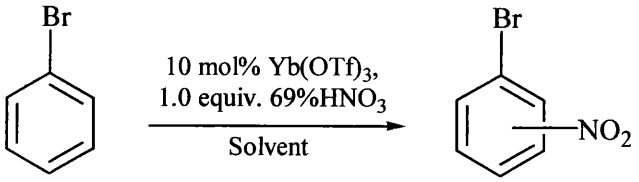
[a] Reactions were carried out using PhCl (6.0 mmol, 99%), $Cu(NO_3)_2 \cdot 3H_2O$ (3.0 mmol, 99.5%), Ac_2O (12 mmol) and CCl_4 / IL **b** (2.0 ml) at 30 °C over 20 h. [b] By quantitative GC. [c] Ratio of *para-/ortho-* calculated from GC data. [d] Addition order was: $Cu(NO_3)_2 \cdot 3H_2O$–CCl_4/IL **b**–PhCl–Ac_2O. [e] Addition order was: $Cu(NO_3)_2 \cdot 3H_2O$–IL **b**–Ac_2O–PhCl.

It can be seen from Table 4.12, no reaction occurred after 20 h when THF or DMF was used as a solvent, although such solvents are highly polar. The reaction took place when CCl_4 or IL **b** was used as solvent, but it was rather slow, just 18%~42% overall yields obtained after 20 h reaction time. As expected on grounds of solubility, the reaction in IL **b** was somewhat faster than that in CCl_4 (entry 3 and entry 4), but the selectivities for formation of the nitrochlorobenzenes were the same in both solvents. In addition, the order of addition of the materials had a significant effect on the reaction rate. The better order involved premixing the IL with cupric nitrate, followed by addition of chlorobenzene and lastly the acetic anhydride (see entry 4 and entry 5).

4.3.5 Ytterbium (III) triflate–69% HNO_3–ILs system

As was reviewed in Section 4.1.6, lanthanide triflates have been used as recoverable catalysts to activate the nitration of arenes with nitric acid.[12] However, two practical issues limit the application of this method. First, the catalyst must be separated and dried before it can be reused. In particular, the drying phase of this recycling is time and energy intensive. Second, the reaction solvent, $(CH_2Cl)_2$, is an environmental and safety hazard. Furthermore, the catalyst has low solubility in such solvents.

In order to address those issues in the nitration process involving lanthanide triflates as catalysts, we wanted to develop a better method on the basis of the method in the literature but using a more polar but low vapour pressure ionic liquid to replace the molecular organic solvent. We expected that the reaction could proceed under mild conditions in ionic liquids, rather than under reflux conditions in 1,2-dichloroethane.[12] Nitration of bromobenzene was chosen as a model reaction, as shown in Scheme 4.9. The results are given in Table 4.13.



Scheme 4.9

Table 4.13 Nitration of bromobenzene with 69% HNO_3, catalysed by $Yb(OTf)_3 \cdot 3H_2O$ in both molecular and ionic solvents.[a]

Entry	Solvent	Yield (%)[b]	Product distribution (%)[b]			*Para-/ortho-*[c]
			Ortho-	*Meta-*	*Para-*	
1[d]	$(CH_2Cl)_2$	92	44	trace	56	1.3
2[e]	$(CH_2Cl)_2$	43	43	trace	57	1.3
3[f]	IL **a**	9.1	2.2	--	6.7	3.0
4[f]	IL **b**	0	--	--	--	--

[a] Reactions were carried out using PhBr (1.2 mmol, 99%), $Yb(OTf)_3 \cdot nH_2O$ (0.12 mmol, 99.5%), HNO_3 (1.2 mmol, 69%), 1,2-dichloroethane/IL (1.0 ml), 6 h. [b] By quantitative GC; [c] Ratio of *para-/ortho-* calculated from GC data. [d] Ref. 11, reflux for 12 h. [e] At reflux temperature. [f] Reaction temperature was 50 °C.

As the results in Table 4.13 show, the reaction conducted in hydrophobic IL **a** was sluggish, only giving a 9.1% yield after 6 h at 50 °C. However, the selectivity was improved slightly, the *para/ortho* ratio increasing from 1.3 in $(CH_2Cl)_2$ to 3.0 in IL **a**. The substrate was intact when the reaction was performed in a hydrophilic IL **b**. The reaction proceeded successfully in dichloroethane at reflux temperature, though the selectivity was a little poorer than that in IL **a**.

4.4 Conclusions

In summary, various nitrating systems have been used to nitrate aromatic compounds in ionic liquids. Several conclusions can be drawn, as indicated below.

1) The use of nitric acid or nitric acid–acetic anhydride as a nitrating reagent in conjunction with zeolite Hβ as catalyst in an IL solvent has no advantage on the reaction rate, but gives improved *para*-selectivities for halogenobenzenes compared to those in molecular solvents.

2) When nitric acid alone was used to nitrate aromatic compound in ILs, the reactions were rather slow, but the selectivities were also improved slightly compared to those in CCl_4 or under solvent-free conditions.

3) When fuming nitric acid in combination with acetic anhydride was used to nitrate simple aromatics in ILs, the reactions proceeded successfully, giving somewhat faster rates and better *para*-selectivites than in tetrachloromethane. Furthermore, the ILs could be recycled for further use.

4) When half an equivalent of cupric nitrate, *i.e.*, one equivalent of nitronium ion, was used to nitrate chlorobenzene, the overall reaction rate was rather low although the reaction was slightly faster in an ionic liquid than in CCl_4. Nevertheless, the selectivities were the same in both molecular and ionic solvents.

5) Nitration of bromobenzene using 69%HNO_3 as the nitrating reagent and with yetterbium (III) triflate as catalyst was slow in ILs, although some improvement in selectivity for the *para*-isomer was achievedin IL **a**.

4.5 Experimental section

4.5.1 Reagents and apparatus

Ionic liquids **a, b** and **c** were synthesized as reported in Chapter 3. Acetic anhydride (98%), fuming nitric acid (90%), cupric nitrate (99.5%) and all substrates employed here were purchased from Aldrich Chemical Company or Lancaster Synthesis Ltd. All were used as received, except for acetic anhydride, which was distilled from phosphorous pentoxide. *N*,*N*-dimethylformamide (DMF)(99.99%) was anhydrous. Tetrachloromethane was dried over 4Å molecular sieves prior to use. Tetrahydrofuran (THF) was dried over sodium by using benzophenone as an indicator.

The analysis of the products was carried out using a Phillips PU 4400 Gas Chromatograph using an ALTECH ECONO-CAP Carbowax column (15 m x 530 μm x 1.2 μm).

4.5.2 Procedures for the reactions

All the reactions were carried out under a nitrogen atmosphere unless stated otherwise. All ILs used here were dried *in vacuo* at 70 °C for 5 h prior to use.

4.5.2.1 Nitration of aromatics in a nitric acid (90%)–zeolite Hβ–IL b system

Nitration of fluorobenzene is a typical example: to a cooled (0 °C, ice-water bath), vigorously stirred mixture of IL **b** (2.5 ml) and zeolite Hβ (Si/Al = 25)(0.5 g), nitric acid (90%, 20 mmol, 1.0 ml) was added, followed by addition of fluorobenzene (10 mmol, 0.95 ml), dropwise under a flow of nitrogen. The ice-water bath was removed and the reaction mixture was heated to 25 °C. After a certain time, the nitrogen inlet was removed and the reaction was quenched by addition of 0.5 M $NaHCO_3$ (*ca.* 1.0 ml). Tetradecane (100.2 mg) was added as an internal GC standard, followed by dilution with acetone (10 ml). Zeolite was filtered off and washed with acetone (3 x 15 ml) again. The filtrates were combined and acetone was evaporated to leave a mixture containing IL **b**, the nitrated products and some remaining starting material. The products were extracted with hexane (3 x 15 ml). The extract was combined, dried over anhydrous $MgSO_4$ and monitored by GC.

The procedure used in the nitration of fluorobenzene, chlorobenzene and toluene in CCl_4, CH_2Cl_2 or IL **b**–CCl_4/CH_2Cl_2 mixture was the same as that in IL **b** alone.

4.5.2.2 Nitration of aromatics in a nitric acid (90%)–IL b system

To a cooled (0 °C, ice-water bath), vigorously stirred mixture of IL **b** (0.5 ml) and nitric acid (90%, 4.2 mmol, 0.2 ml), fluorobenzene (2.1 mmol, 0.2 ml) was added, dropwise under a flow of nitrogen. The ice-water bath was removed and the reaction mixture was heated to 25 °C. After a certain time, the nitrogen inlet was removed and the reaction was quenched by addition of water (*ca.* 2 ml), followed by addition of tetradecane (109.4 mg). The resulting mixture was extracted with hexane (3 x 10 ml). The extracts were combined, washed with distilled water (5 x 10 ml), and dried over anhydrous $MgSO_4$. The conversion of the reaction, the yields of the products and the distribution of the isomers were monitored by GC using tetradecane as an internal standard. The residue containing IL **b** and water was extracted with CH_2Cl_2, in which IL **b** was collected. The dichloromethane extracts were combined and the solvent was evaporated under reduced pressure to leave the recovering IL **b**. The recovered IL **b**

was dried further at 70 °C *in vacuco* for 5 h in order to remove water accumulated during the wok-up, then flushed with N_2 and employed for further reactions.

A similar procedure to that in IL **b** was used when IL **a** or CCl_4 was employed as a solvent. Moreover, when IL **a** was employed as a solvent, three phases formed after addition of some water and hexane. Thus, it was easier to remove the ionic liquid solvent by a simple separation. Details are given in Section 4.5.2.3.

4.5.2.3 Nitration of aromatics in nitric acid–acetic anhydride–IL systems

The procedure for the reaction of fluorobenzene in IL **a** is illustrated as an example. To a cooled (0 °C, ice-water bath), vigorously stirred mixture of IL **a** (0.5 ml) and nitric acid (90%, 2.1 mmol, 0.1 ml), acetic anhydride (2.9 mmol, 0.28 ml) was added, followed by addition of fluorobenzene (2.1 mmol, 0.2 ml), dropwise under a flow of nitrogen. The ice-water bath was removed and the reaction mixture was heated to 25 °C. After a certain time, the nitrogen inlet was removed and the reaction was quenched by addition of water (*ca.* 10 ml). Tetradecane (110.0 mg) was added, followed by hexane. The resulting mixture was briefly stirred. Three phases formed. The bottom one was IL **a**, the middle one was an aqueous phase and the upper one was an organic phase. The upper two phases were decanted from the viscous IL phase into a separating funnel and the aqueous phase was run off. The IL phase was washed twice more, each time with a mixture of water (10 ml) and hexane (10 ml) and the upper two layers were decanted into the same separating funnel, mixed with the preceding hexane extract. The aqueous phase was run off each time. The final organic layer was washed with additional water (5 x 10 ml), then dried over anhydrous $MgSO_4$ and monitored by GC as described in Section 4.5.2.1. The recovered IL **a** was dried at 70 °C *in vacuco* for 5 h, then flushed with N_2 and employed for further reactions.

Procedures for nitrations of other substrates in IL **b**, IL **c** or CCl_4 (Table 4.9) were the same as used for nitration of fluorobenzene in IL **a**.

4.5.2.4 Nitration of chlorobenzene in a cupric nitrate–acetic anhydride–IL b system

To a cooled (0 °C, ice-water bath), vigorously stirred mixture of IL **b** (2.0 ml) and cupric nitrate ($Cu(NO_3)_2 \cdot 3H_2O$) (0.56 g, 3.0 mmol), chlorobenzene (6.0 mmol, 0.6 ml) was added dropwise, followed by addition of acetic anhydride (12 mmol, 1.2 ml) slowly under a flow of nitrogen. The ice-bath was removed and the reaction mixture was heated to 30 °C, then maintained at the same temperature for 20 h with continuous stirring. After 20 h, hexadecane (360.5 mg, as GC standard) was added and the reaction was quenched by addition of acetone (*ca.* 15 ml), then filtered quickly to remove the blue precipitate. The acetone in the filter was evaporated under reduced pressure to leave the residual containing IL **b**, nitrated products and some unreacted starting material. The product was extracted from the residue using hexane (3 x 10 ml). The hexane extracts were combined, dried over anhydrous $MgSO_4$ and monitored by GC.

It is worth noting that $Cu(NO_3)_2 \cdot 3H_2O$ dissolved in IL **b** to form a blue solution. When acetic anhydride was added, the blue solution gradually changed into violet. At the same time, some brown gas was liberated. During the course of the reaction, the colour of the reaction mixture became light blue from violet and some blue precipitate gradually formed.

The same procedure as that in IL **b** was also used when CCl_4 was employed as the solvent. It was observed clearly in this case that some $Cu(NO_3)_2 \cdot 3H_2O$ was not in solution, but formed a suspension.

4.5.2.5 Nitration of bromobenzene using 69%HNO_3, catalysed by ytterbium (III) triflate in ILs

Nitric acid (69%, 80 μl, 1.2 mmol) was added to a stirred suspension of ytterbium(III) triflate (74.5 mg, 0.12 mmol) in ionic liquid IL **a** or IL **b** (1.0 ml) at room temperature, followed by addition of bromobenzene (128 μl, 1.2 mmol). The reaction mixture was heated to 50 °C and stirred at the same temperature for 6 h. The

ytterbium(III) triflate dissolved within the first few minutes. After 6 h, the reaction mixture was allowed to cool and quenched by addition of water (5 ml), then hexadecane (209.0 mg) was added. The mixture was extracted with hexane (3 x 5 ml), and the hexane extract were combined and dried over anhydrous $MgSO_4$. The yields of products were measured by GC.

The same procedure as that in ILs was used for the reaction conducted in 1,2-dichloroethane, with the exception that the reaction mixture was maintained at reflux rather than at 50 °C for 6 h.

4.5.3 Analysis of products

The reaction conversion, the yields of products and the distributions of product isomers were determined by gas chromatography.

4.5.3.1 GC conditions

The analysis of the products was carried out using a Phillips PU 4400 Gas Chromatograph using an ALTECH ECONO-CAP Carbowax column (15 m x 530 μm x 1.2 μm). The GC conditions used for analysis were: 40 °C for 0.2 min, ramped to 150 °C at 15 °C/min and held for 2 min, then to 180 °C at 10 °C/min and held for 5 min. Both the injection temperature and the detection temperature were 300 °C. The flow rates of gases were: helium, 2 ml/min; nitrogen, 28 ml/min; hydrogen, 25 ml/min; air, 400 ml/min. Tetradecane, hexadecane or dodecane were used as internal standard depending on the substrate. Tetradecane was used for fluorobenzene and toluene; hexadecane was used in the cases of chlorobenzene, bromobenzene, *tert*-butylbenzene, benzene and anisole; and dodecane was used for iodobenzene.

4.5.3.2 Calculation of response factors

A calibration solution, comprising known amounts of substrate, products (*para*, *ortho* and *meta*) and a non-reactive internal GC standard, was prepared. The solvent was that used to extract the products in the corresponding reaction.

The solution was injected into GC and the areas of the peaks of each component were recorded. The response factor (R_f) for each component was calculated from the chromatograms according to Equation (4.12).

$$R_f = \frac{M_c}{A_c} \times \frac{A_s}{M_s} \qquad (4.12)$$

Where, M_c is the amount (in moles) of the compound that was measured;

M_s is the amount of internal standard;

A_c is the GC peak area for the compound that was measured;

A_s is the GC peak area for the standard;

R_f is the GC response factor of the compound that was measured.

Typically, three GC injections would be made for each solution to be measured and the mean figure would be taken.

4.5.3.3 Calculation of the conversion of the reaction and yield of the product

The residual starting material or the yield of the product were calculated according to Equation (4.13).

$$M_c\% = R_f \times M_s \times \frac{A_c}{A_s} \times \frac{1}{M_0} \times 100\% \qquad (4.13)$$

Where M_0 is the total amount (in moles) of starting material used in the experiment.

The conversion was calculated according to Equation (4.14).

$$\text{Conversion } \% = 100 - Mc\ \% \qquad (4.14)$$

Where Mc is the amount of the starting material remaining at the end of the reaction.

4.6 References for Chapter 4

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49. After four times use, IL [bmim]PF_6 was characterized by NMR, MS and IR:

^{1}H NMR (in acetone-d_6, δ_{ppm}): 8.86 (1H, s, H_2), 7.65 (1H, d, J = 1.7 Hz, H_4), 7.58 (1H, d, J = 1.7 Hz, H_5), 4.24 (2H, t, J = 7.3 Hz, H_6), 4.03 (3H, s, H_{10}), 1.81 (2H, quint, J = 7.6 Hz, H_7), 1.36 (2H, sextet, J = 7.4 Hz, H_8), 0.93 (3H, t, J = 7.4 Hz, H_9).

^{13}C NMR (in acetone-d_6 δ_{ppm}): 137.8 (C_2), 125.2 (C_4), 123.8 (C_5), 50.6 (C_6), 37.0 (C_{10}), 33.1 (C_7), 20.4 (C_8), 14.0 (C_9).

Electrospray MS: ES^+, m/z (%), 139.0 ($[bmim]^+$, 100%); ES^-, m/z (%), 145.0 (PF_6^-, 100%)

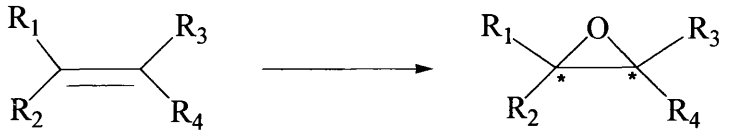
IR (liquid film, NaCl window, ν, cm^{-1}): 851 (ν_{P-F}).

Chapter 5

Epoxidation of Alkenes in Ionic Liquids

5.1 Introduction to epoxidation

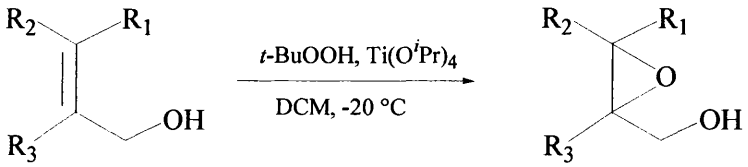
Epoxidation of alkenes (Scheme 5.1) is a very important reaction in organic synthesis. The predominant reason is that the resulting epoxides constitute versatile synthetic intermediates, as they can be readily transformed into a large variety of useful functional groups by means of regioselective ring opening reactions.[1,2] Hence, asymmetric alkene epoxidation is considered as one of the most useful strategies for the synthesis of enantiomerically enriched compounds, especially for the synthesis of biologically active compounds or natural products.



*: chirality centres
(sterogenenic centres)

Scheme 5.1

Sharpless asymmetric epoxidation proved to be highly effective with allylic alcohols by using Ti(IV) alkoxide and a chiral tartrate as catalyst together with *t*-butyl hydroperoxide (Scheme 5.2).[3] By the use of this catalyst, most allylic alcohols can be converted to the corresponding epoxy alcohols with high enantioselectivity.

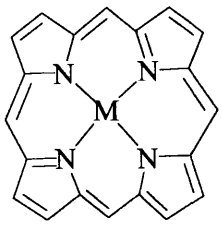


Scheme 5.2

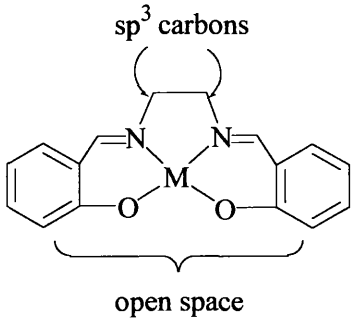
However, asymmetric epoxidation of simple alkenes is still a major challenge in organic synthesis. Metalloporphyrins, based on structure **5.1** and its derivatives, have been widely used for various oxo transfer reactions, including the epoxidation of alkenes.[4]

In recent years, enantioselective epoxidation catalysed by chiral (salen)Mn complexes (structure **5.2**) [salen = *N,N'*-ethylenebis(salicylideneaminato)] has become

a useful preparative method for chiral epoxides in organic synthesis.[5,6] Jacobsen,[5] Katsuki[6] and others[7,8] have explored, respectively, various valuable types of epoxidation catalysts in this field.



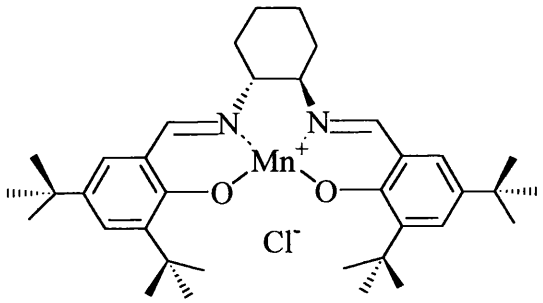
5.1 Metalloporphyrin



5.2 Metallosalen

5.1.1 Jacobsen-type catalysts

In the early 1990s, Jacobsen and his colleagues designed some chiral (salen)Mn(III) complexes based on metallosalen **5.2**. Those included complex **5.3**, which is currently the most efficient and commercially available catalyst for the enantioselective epoxidation of unfunctionalised alkenes.[9]

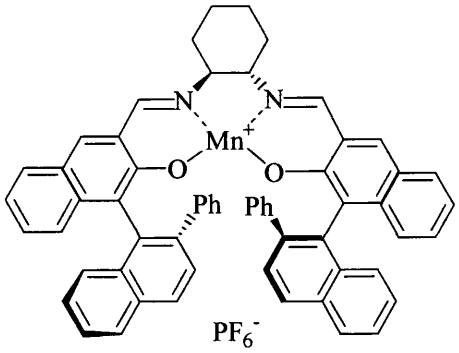


5.3

5.1.2 Katsuki-type catalysts

Shortly before Jacobsen's group published their key findings, Katsuki and his colleagues had developed another series of complexes, also based on metallosalen **5.2**. An example is complex **5.4**. The main difference in the ligand design between Katsuki's complex **5.4** and Jacobsen's complex **5.3** is the introduction of two extra chirality centres (stereogenic centres) in **5.4** in place of the bulky tertiary alkyl groups at the C-3 and C-3′ positions of the aryl groups in **5.3**.[6] Due to the introduction of two

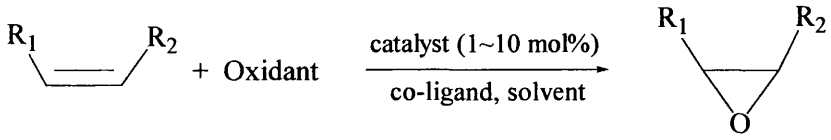
extra stereogenic centres, Katsuki's complex was reported to generate greater enantioselectivity than Jacobsen's complex.[4,5,6]



5.4

5.2 Application of both Jacobsen-type and Katsuki-type complexes in the epoxidation reaction

Both Jacobsen-type and Katsuki-type catalysts have been widely used in epoxidation processes by using a homogeneous system, a heterogeneous system or a biphasic system (Scheme 5.3).



Scheme 5.3

A number of oxidants have been used as oxygen atom sources in such enantioselective epoxidations, including sodium hypochlorite,[10] *m*-chloroperoxy-benzoic acid (*m*-CPBA),[11] tetra-*n*-butylammonium periodate (Bu_4NIO_4),[12] hydrogen peroxide (H_2O_2),[13] O_2/aldehyde,[14,15] iodosylbenzene (PhIO),[16,17,18] and magnesium monoperoxyphthalate (MMPP).[19] Among these, different oxidants exhibited different characteristics under specific reaction conditions. For example, *m*-CPBA is widely used, and is effective for a wide range of alkenes particularly when the reactions are conducted at –78 °C in combination with excess of *N*-methylmorpholine *N*-oxide (NMO) as an additive.[11] However, *m*-CPBA itself in a pure form is both shock-sensitive and potentially explosive. Hydrogen peroxide is an attractive oxidant as it is

cheap, readily available and gives only water as a by-product. However, problems are the homolytic cleavage of its weak O–O bond (formation of radicals), and its relative ease of dismutation. Furthermore, hydrogen peroxide easily causes the oxidative destruction of Mn(salen) catalysts.[10] MMPP is considered to be a stable and mild oxidant, but it suffers from low solubility in normal organic solvents.[6,11] NaOCl is an inexpensive, reasonably stable, commercially available oxidant. Furthermore, mild reaction conditions are possible when such an oxidant is used. However, excess NaOCl is usually used in order to accelerate the reaction.[6]

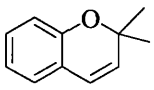
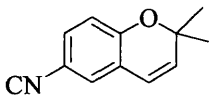
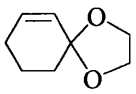
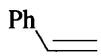
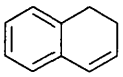
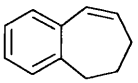
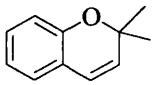
Usually acetonitrile, dichloromethane and dichloroethane are used as solvents for the epoxidation of alkenes, but the use of fluorobenzene has been recommended when molecular oxygen is used as an oxidant.

It has also been found that 4-phenylpyridine *N*-oxide is a useful additive under aqueous conditions, whereas *N*-methylmorpholine *N*-oxide appears to be more effective in a non-aqueous system.

5.2.1 Homogeneous catalysis

In homogeneous systems, either for Jacobsen-type complexes or for Katsuki-type complexes, reactions are usually carried out under mild conditions in the presence of a certain amount of the catalyst (1~10 mol%) and an excess of the terminal oxidant at the appropriate temperature in various solvents.[10~19] Yields of the epoxides up to 96% and enantiomeric excess as high as 98% have been achieved, depending on the substrate, oxidant and co-ligand used.[10~19] Some recorded yields and ees in epoxidation reactions using Jacobsen's complex **5.3** are listed in Table 5.1.

Table 5.1 Asymmetric epoxidation of some alkenes catalysed by Jacobsen's complex **5.3** under various reaction conditions.

Alkene	Oxidant	Co-ligand	Yield (%)	Ee (%)	Refs
	NaOCl	4-PPNO[a]	84	92	10
	NaOCl	4-PPNO[a]	72	98	10
	NaOCl	4-PPNO[a]	96	97	10
	NaOCl	4-PPNO[a]	63	94	10
	*m*-CPBA [a]	NMO[a]	59	94	11
	Bu_4NIO_4	*N*-methylimidazole	55	64	12
	H_2O_2	UHP/MA[a]	71	87	13
	O_2	*N*-octylimidazole /pivaladehyde	37	92	14,15

[a] 4-PPNO, 4-phenylpyridine-*N*-oxide; *m*-CPBA, *m*-chloroperbenzoic acid; NMO, *N*-methyl-morpholine-*N*-oxide; UHP/MA, urea-H_2O_2/maleic anhydride.

Clearly, homogeneous catalysis generally provides high activities and selectivities under relatively mild conditions. Furthermore, few by-products are given. However, an obvious shortcoming associated with this system is that the catalysts are not easily separated from the reaction mixture and this is usually critical for an industrial-scale process. Therefore, in order to avoid this limitation, in recent years more and more efforts have been focused on developing a heterogeneous system by immobilizing a catalyst onto a solid support.

5.2.2 Heterogeneous catalytic processes

A number of approaches have been developed to incorporate the salen ligand into a heterogeneous support in order to recycle the chiral catalyst. These approaches

can be roughly classified into four categories: a) non-covalent immobilization on a zeolite,[20,21] clay[22,] or polydimethylsiloxane (PDMS) membrane;[23,24] b) grafting onto silica[25] or MCM-41;[26,27] c) co-polymerization of a functionalised salen ligand or catalyst with other organic monomers;[28,29,30,31,32] and d) attachment of a salen ligand or catalyst to a preformed polymer,[33,34,35,36,37]or dendrimer.[38] However, there are drawbacks with all of those strategies, probably because of the nature of heterogeneous reactions (no linear kinetic behaviour, unequal distribution of and/or access to the reactive centres, solvation problems, *etc.*). For example, use of a zeolite 'ship-in-a-bottle' catalyst was limited to a narrow range of substrates and gave poor enantioselectivity in some cases;[20,21] use of a clay supported catalyst resulted in a unavoidable decomposition of the ligand;[22] use of a PDMS membrane led to an unavoidable leaching of catalyst from the membrane;[23,24] co-plymerization of a salen complex monomer containing a pendant vinyl group with styrene and divinylbenzene resulted in a cross-linked catalyst which offered a promising yield and recycled catalyst, but showed very poor enantioselectivity.[28~32] Although use of polymer-supported catalysts can be effective and the catalysts can be recycled, synthesis of such catalysts, either by direct attachment or stepwise build-up of the salen ligand or complex on a preformed polymer, is tedious.[33~37] Moreover, the bond between the polymer and the salen complex cleaves in some cases.[33~36]

The limitations in both homogeneous and heterogeneous catalysis have led us to explore systems in which the catalyst could display the advantages of both homogeneous catalysis, such as high reactivity and enantioselectivity, and heterogeneous catalysis, such as easy recovery of catalyst. Such studies are reported in this Chapter (see Section 5.3 onwards).

5.2.3 Fluorous biphasic systems

Pozzi and co-workers[39,40] have described another interesting approach to a recoverable, though not polymer-supported, epoxidation catalyst by using a fluorous biphasic system, known as FBS. They reported that salen catalysts containing perfluorinated alkyl chains were used as epoxidation catalysts in fluorous-organic biphasic systems. The perfluoroalkylated salen complexes were found to be efficient and the immiscibility of the perfluorocarbons with regular organic solvents allowed a

quick and effective separation of the catalyst from the products. However, enantioselectivities were generally poor, good ees (70~92%) being obtained for only one substrate, indene. Moreover, it was necessary to use salen ligands incorporating perfluorinated alkyl chains in order to help the catalysts to dissolve in the FBS solvent.

5.3 Proposal in this chapter

As described above, although some successes have been achieved with both homogeneous and heterogeneous catalysis, or a FBS system, some limitations still exist. Therefore, we decided to develop other alternative approaches.

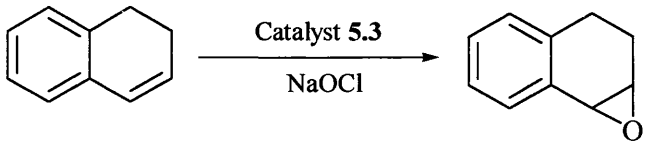
Over the past few years, as were reviewed in Chapter 2, ionic liquids have generated much excitement in the field of organic synthesis, particularly for metal complex catalysis, because of their potential as green solvents. A number of reactions have been conducted in such IL media. To our knowledge, the study of the oxidation reactions in IL solvents is still at an initial stage. Up to now, there are only a few published reports in this area, as were reviewed in Chapter 2. Song *et al.*[41] have investigated the epoxidation of 2,2-dimethylchromene with a Jacobsen-type chiral Mn^{III}(salen) complex (**5.3**) in 4 mol% proportion in a mixture of an IL, [bmim]PF_6, and CH_2Cl_2 (1:4 v/v), providing a good yield, high enantiomeric excess and a recoverable catalyst. Unfortunately, the yield and enantioselectivity became progressive lower with each recovery.

Since Katsuki-type complexes have been reported to be more stable than Jacobsen-type complexes under the basic reaction conditions prevailing in reactions involving NaOCl, and have also been reported to give higher enantiomeric excesses,[4,5,6] we decided to investigate epoxidation reactions using a Katsuki complex in ILs. The air- and moisture-stable ionic liquids 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6, called IL **a** hereafter, see Fig. 4.1 in Chapter 4) and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4, called IL **b** hereafter, also see Fig. 4.1 in Chapter 4) and the Katsuki's complex **5.4** were chosen for the study. The Jacobsen's complex **5.3** was also used in some cases.

We decided to use sodium hypochlorite, hydrogen peroxide and molecular oxygen as the terminal oxidants. The results are reported in the following section.

5.4 Results and discussion

In order to gain experience of salen complex catalysed epoxidation reactions in both molecular solvent and IL media, 1,2-dihydronaphthalene was treated with sodium hypochlorite in the presence of Jacobsen's catalyst **5.3** (Scheme 5.4) with and without the presence of 4-PPNO using a literature method with some modification.[41] After reaction, the IL containing the catalyst was recovered and reused. The results of this study are reported in Tables 5.2 and 5.3.



Scheme 5.4

Table 5.2 Asymmetric epoxidation of 1,2-dihydronaphthalene catalysed by catalyst **5.3** in both CH_2Cl_2 and IL **a**–CH_2Cl_2 (1:4, v/v) in the absence of 4-PPNO.[a]

Solvent (ml)	Run	Time (h)	Conversion (%)[c]	Yield (%)[c]	Ee (%)[d]
CH_2Cl_2		2.0	100	57	84
IL **a**–CH_2Cl_2 (1:4, v/v)	1st	1.5	100	63	78
"	2nd	2.5	100	57	71
"	3rd	16	93	55	59
"	4th	24	64	22	41

[a] Reaction conditions: 1,2-dihydronaphthalene (111.6 mg, 0.84 mmol), catalyst **5.3** (2.5 mol% of substrate, 13.4 mg, 0.021 mmol), solvent (3.75 ml), NaOCl (0.55 M, 7.0 ml, 3.85 mmol, pH = 11.3), 0 °C. [c] Calculated from GC using hexadecane as an internal standard. [d] Determined by ^{1}H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent.

Table 5.3 Asymmetric epoxidation of 1,2-dihydronaphthalene catalysed by catalyst **5.3** in IL **a**–CH_2Cl_2 (2:3, v/v) in the presence of 4-PPNO.[a]

Solvent (ml)	Run	Time (h)	Conversion (%)[c]	Yield (%)[c]	Ee (%)[d]
IL a–CH_2Cl_2 (2:3, v/v)	1st	1.5	100	68	75
"	2nd	1.5	72	35	59
"	3rd	2.0	83	46	67
"	4th	2.0	85	41	74
"	5th	2.0	78	25	67

[a] Reaction conditions: 1,2-dihydronaphthalene (38 mg, 0.28 mmol), catalyst **5.3** (2.5 mol% of substrate, 4.5 mg, 0.007 mmol), solvent (1.58 ml), NaOCl (0.588 M, 2.43 ml, 1.43 mmol, pH = 11.3), 0 °C. [c] Calculated from GC using hexadecane as an internal standard. [d] Determined by ^{1}H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent.

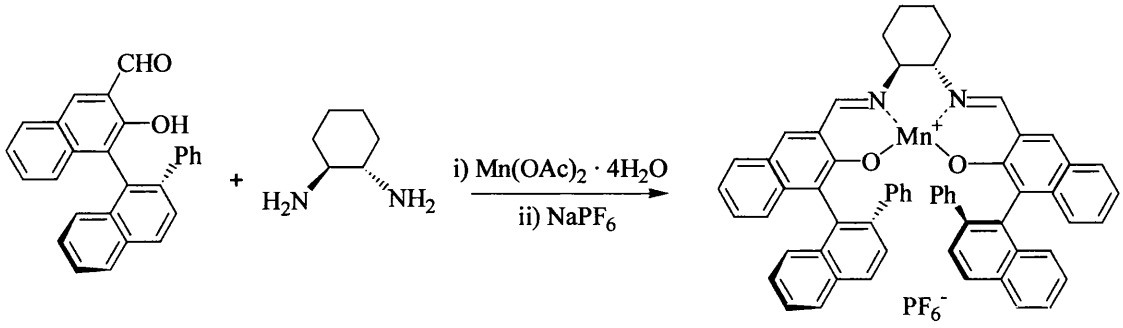
As can be seen from Tables 5.2 and 5.3, the yields and enantioselectivities decrease after several recoveries. In the presence of 4-PPNO, the reduction in ee is much less than when 4-PPNO is absent. However, neither case is very satisfactory for recovery of intact catalyst having the original activity.

At this point, therefore, it was of interest to prepare a suitable Katsuki-type catalyst for testing.

5.4.1 Preparation of Katsuki-type complex 5.4

Generally, preparation of (salen)Mn(III)PF_6 complexes is achieved by a multistage reaction sequence. First, two equivalents of a salicylaldehyde derivative are reacted with one equivalent of a diamine, followed by treatment with hydrated manganese diacetate ($Mn(OAc)_2{\cdot}4H_2O$) in an ethanolic solution in air to give the corresponding (salen)Mn(III)OAc complex. This complex is then treated with sodium hexafluorophosphate ($NaPF_6$) to give the (salen)Mn(III)PF_6 complex as a dark brown, air- and moisture-stable powder.[6,42,43,44,45]

The complex **5.4** was prepared from a preformed homochiral ligand (*R*)-3-formyl-2-hydroxy-2′-phenyl-1,1′-binaphthalene (**5.5**), which was prepared by Dr. C.–H. Liu in Prof. Keith Smith's laboratory at the University of Wales Swansea,[46] and a commercially available (1*S*,2*S*)-(-)-1,2-diaminocyclohexane (**5.6**) in a one-pot precedure according to the reaction in Scheme 5.5.[42,45] The reaction was successful and gave **5.4** in 38% yield after recrystallization.



5.5 (2.0 equivs.) **5.6** (1.0 equiv.) **5.4**

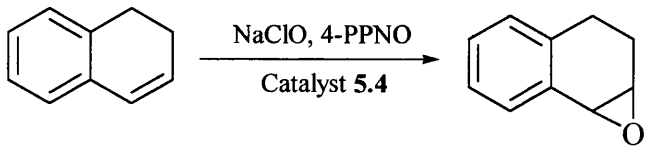
Scheme 5.5

The structure **5.4** was confirmed by FAB-MS, accurate mass determination of its molecular cation, electrospray MS of its cation and anion, and by comparison of its IR spectrum with that reported by Dr. C.–H. Liu.[46]

5.4.2 Epoxidation of alkenes

5.4.2.1 Use of aqueous sodium hypochlorite (NaOCl) as the terminal oxidant

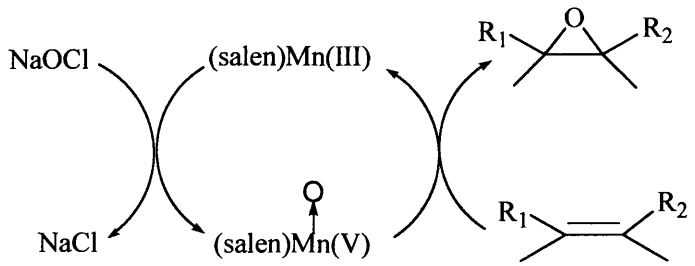
Epoxidation of 1,2-dihydronaphthalene (Scheme 5.6) was chosen as a model reaction.



Scheme 5.6

A possible mechanism is shown in Scheme 5.7. Conversion of an alkene into an epoxide involves the formation of a Mn(V)=O intermediate, which actually

releases oxygen as the terminal oxidant. In between, a (salen)Mn(III) complex is oxidized to the oxo-manganese(V) species by the hypochlorite, which is the consumable oxidant.



Scheme 5.7

Initially, it was decided that excess NaOCl should be used.

5.4.2.1.1 Use of excess aqueous sodium hypochlorite

In order to establish a baseline for comparison, a series of reactions was initially conducted using CH_2Cl_2 as solvent under various conditions. The results are given in Table 5.4.

Table 5.4 Asymmetric epoxidation of 1,2-dihydronaphthalene in a molecular solvent, CH_2Cl_2.[a]

Amount of solvent (ml)	Amount of catalyst (mol% of substrate)	Time (h)	Conversion (%)[c]	Yield (%)[c]	Ee (%)[d]
1.0	2.5	8.0	100	87	96
1.0	0.25	30	98	78	100
0.5	2.5	6.0	100	84	96
0.5[b]	0.25	18	100	81	100

[a] Reaction conditions: 1,2-dihydronaphthalene (21.6 mg, 0.16 mmol), 4-phenylpyridine *N*-oxide (6.8 mg, 0.04 mmol), catalyst **5.4** (as shown in the Table), solvent (as shown in the Table), NaOCl (0.588 M, 1.4 ml, 0.82 mmol, pH = 11.3), 0 °C. [b] Reaction conditions: 1,2-dihydronaphthalene (108 mg, 0.80 mmol), 4-phenylpyridine *N*-oxide (34 mg, 0.20 mmol), catalyst **5.4** (as shown in the Table), solvent (as shown in the Table), NaOCl (0.588 M, 7.0 ml, 4.1 mmol, pH = 11.3), 0 °C. [c] Calculated from GC using hexadecane as an internal standard. [d] Determined by ^{1}H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent.

It was found that the reaction was effective and provided good yields and high enantioselectivities. Larger quantities of catalyst or higher concentrations of reactants resulted in shorter reaction times, as would be expected.

Similar experiments were then carried out in a mixed solvent, IL **a**–CH_2Cl_2 (2:3, v/v) or IL **b**–CH_2Cl_2 (2:3, v/v), or in pure IL **b**. The results are listed in Table 5.5.

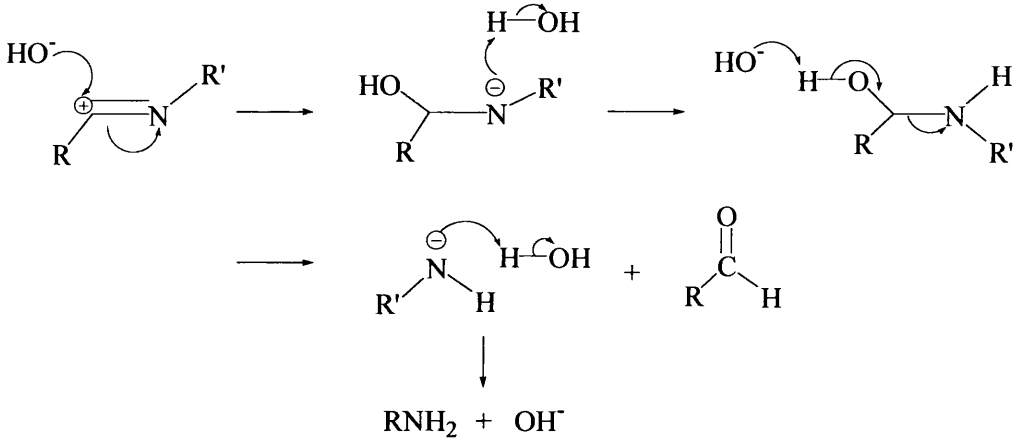
Table 5.5 Asymmetric epoxidation of 1,2-dihydronaphthalene in an IL or IL–CH_2Cl_2 mixture.[a]

Solvents	Amount of catalyst (mol % of substrate)	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
IL **a**–CH_2Cl_2 (2:3, v/v)	2.5	2.0	100	100	95
IL **b**–CH_2Cl_2 (2:3, v/v)	2.5	2.0	91	64	33
IL **b**	2.5	2.0	100	83	90
IL **a**–CH_2Cl_2 (2:3, v/v)	0.25	20	100	77	96
IL **a**–CH_2Cl_2 (2:3, v/v)	0.025	108	93	35	68

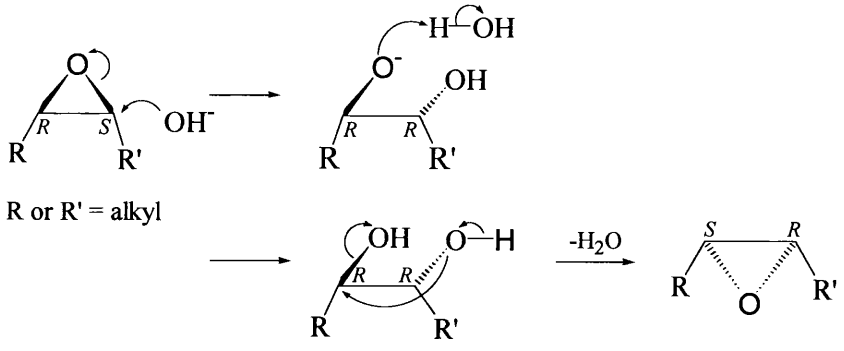
[a] Reaction conditions: 1,2-dihydronaphthalene (21.6 mg, 0.16 mmol), 4-phenylpyridine *N*-oxide (6.8 mg, 0.04 mmol), catalyst **5.4** (as indicated in the Table), solvent (1.0 ml), NaOCl (0.588 M, 1.4 ml, 0.82 mmol, pH = 11.3), 0 °C. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^{1}H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent.

As shown in Table 5.5, reactions performed in IL **a**–CH_2Cl_2 (2:3, v/v) provided good conversions, yields and enantioselectivites, comparable to those in CH_2Cl_2 alone (Table 5.4), but over much shorter reaction times. For instance, the reaction catalysed by 2.5 mol% of catalyst was complete in 2 h in IL **a**–CH_2Cl_2 (2:3, v/v), while it required 8 h to go to completion in CH_2Cl_2 alone. Similarly, the reaction catalysed by 0.25 mol% of catalyst was complete in 20 h in IL **a**–CH_2Cl_2 (2:3, v/v), while it required 30 h to go to completion in CH_2Cl_2 alone. It is noteworthy that both the enantioselectivity (33%) and the yield (64%) were much

lower in IL **b**–CH_2Cl_2 (2:3, v/v) than those in IL **a**–CH_2Cl_2 (2:3, v/v). That might be because IL **b** is water miscible, which leads to a higher proportion of the catalyst or the epoxide in the basic aqueous phase, in which the catalyst (Scheme 5.8) or epoxide (Scheme 5.9) might be unstable. Therefore, in order to avoid such drawbacks, we decided to conduct a reaction in pure IL **b**. Surprisingly, when the reaction was conducted in pure IL **b** (no CH_2Cl_2 present), the yield was improved to 83% and the enantioselectivity was improved to 90%. Furthermore, the catalyst could be recycled more easily by simple decantation or washing with hexane (see experimental section). Nevertheless, both the yield and enantioselectivity were still lower in pure IL **b** than those in IL **a**–CH_2Cl_2 (2:3, v/v). Therefore, IL **a** was chosen for further study with a smaller quantity of catalyst. The results are also given in Table 5.5.



Scheme 5.8



Scheme 5.9

As also indicated in Table 5.5, it needed a longer reaction time, 108 h, to convert all of the alkene into the corresponding epoxide when the quantity of catalyst was reduced to 0.025 mol%. Furthermore, a low yield, 35%, and a poor enantioselectivity, 68%, were achieved. We suspected that over the longer reaction time, the greater opportunity for decomposition of the catalyst or epoxide accounts for the poor results. Therefore, we decided to increase the concentrations of components, such as alkene, catalyst and other related starting materials in the organic phase and expected the reactions would proceed well.

Initially, we kept the catalyst amount at 2.5 mol% of the substrate, but doubled the concentration by utilising only half the volume of solvent. The result, 92% yield and 98% ee, was very similar to that in the more dilute concentration, but the reaction time was reduced from 2 h to 1.25 h. It therefore appeared likely that if the concentration was increased even more, the amount of catalyst could be reduced significantly while retaining a convenient reaction period.

The results of reactions conducted at ten times the initial concentration (see footnote in the Table 5.6) in 0.5 ml IL **a**–CH_2Cl_2 (2:3, v/v) are given in Table 5.6.

Table 5.6 Asymmetric epoxidation of 1,2-dihydronaphthalene in an IL **a**–CH_2Cl_2 mixture under concentrated conditions.[a]

Amount of catalyst (mmol% of substrate)	Time (h)	Conversion[b] (%)	Yield[b] (%)	Ee[c] (%)
0.25	10	100	82	100
0.025	54	99	58	95
0.0125	100	99	47	66
0.0100	65	99	41	43

[a] Reaction conditions: 1,2-dihydronaphthalene (108.0 mg, 0.80 mmol), 4-phenylpyridine *N*-oxide (34 mg, 0.20 mmol), catalyst **5.4** (as indicated in the Table), IL **a**–CH_2Cl_2 (2:3, v/v) (0.5 ml), NaOCl (0.588 M, 7.0 ml, 4.1 mmol, pH = 11.3), 0 °C. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^1H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent.

As shown in Table 5.6, the reaction catalysed by 0.25 mol% of catalyst was complete within 10 h at the higher concentration whereas it needed 20 h (see Table 5.5) at the initial concentration. Similarly the reaction catalysed by 0.025 mol% of catalyst was complete in 54 h at the higher concentration while it took 108 h to complete at the initial concentration (see Table 5.5). Furthermore, improved results were also obtained for a reaction conducted at the higher concentration when a lower quantity of catalyst was used. For example, 58% yield and 95% enantiomeric excess were attained in a reaction performed at the higher concentration in the presence of 0.025 mol% of catalyst, while only 35% yield and 68% enantiomeric excess (see Table 5.5) were attained in a reaction carried out under identical reaction conditions except at the initial concentration. Based on the results, the quantity of catalyst was reduced further, to 0.0125 mol% and 0.0100 mol%. The results obtained were 47% yield and 66% ee in the experiment involving 0.0125% catalyst and 41% yield and 43% ee in the experiment involving 0.010% catalyst respectively.

In the light of the enhanced reaction rates, yields and enantioselectivities resulting from reactions conducted in solvents containing ILs, we also attempted recycling of both the catalyst and the ionic liquids. At first, the lower concentration reaction mixtures were studied (see Table 5.7).

As shown in the entries 1~5 in Table 5.7, when 2.5 mol% of catalyst was used, the IL **a**–catalyst mixture could be recycled up to four times with promising enantioselectivities (95%~89%), even though the yield of epoxide progressively decreased. However, as shown in the entries 6~8 in Table 5.7, with a lower amount of catalyst (0.25 mol%), the IL **a**–catalyst mixture could be recycled only once while retaining promising enantioselectivity (94%) and even then the yield of epoxide decreased, from 77% to 55%. When the system was recovered a second time, only 23% yield and 38% ee were obtained.

In the case of IL **b**, the IL **b**–catalyst system could be recycled only once with reasonable yield and enantioselectivity even at the higher catalyst proportion (2.5 mol%) (see entries 9 and 10 in Table 5.7). By the third run (entry 11), the

IL **b**–catalyst mixture became gummy and difficult to stir and thus gave rise to a poor result.

Table 5.7 Recycle of both catalyst and ionic liquid solvent under low concentration conditions.[a]

Entry	Solvent	Amount of catalyst (mol%)	Run	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
1	IL **a**–CH_2Cl_2 (2:3, v/v)	2.5	1st	2.0	100	100	95
2	"	recycled	2nd	3.0	93	87	94
3	"	"	3rd	4.0	90	68	95
4	"	"	4th	4.0	72	47	94
5	"	"	5th	4.0	--	30[d]	89
6	"	0.25	1st	20	100	77	96
7	"	recycled	2nd	20	88	55	94
8	"	"	3rd	20	58	23	38
9	IL **b**	2.5	1st	2.0	100	83	90
10	"	recycled	2nd	3.0	100	82	79
11	"	"	3rd	3.0	44	5.2	50

[a] Reaction conditions: 1,2-dihydronaphthalene (21.6 mg, 0.16 mmol), 4-phenylpyridine *N*-oxide (6.8 mg, 0.04 mmol), catalyst **5.4** (as shown in Table), solvent (1.0 ml), NaOCl (0.588 M, 1.4 ml, 0.82 mmol, pH = 11.3), 0 °C. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^{1}H NMR analysis using Eu(hfc) as a chiral shift reagent. [d] Isolated yields.

It is likely that the decreased yields during successive runs with the recovered solvent-catalyst system is due to the decreased amount of residual catalyst, following loss of catalyst during work-up or by decomposition under the basic conditions.

In an attempt to gauge the effect of reactant concentration on the ability to recycle the catalyst–IL mixture, a double concentration, IL **a**–2.5 mol% catalyst system was recycled several times. The results are shown in Table 5.8.

Table 5.8 Recycle of both catalyst and ionic liquid solvent under double the initial concentration conditions.[a]

Solvent	Run	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
IL **a**–CH_2Cl_2 (2:3, v/v)	1st	1.25	100	92	96
Recycled	2nd	2.0	100	91	95
"	3rd	2.5	87	76	95
"	4th	3.0	78	57	91
"	5th	4.0	60	40	90
"	6th	5.0	--	38[d]	84
"	7th	24	98	67	33

[a] Reaction conditions: 1,2-dihydronaphthalene (43.2 mg, 0.32 mmol), 4-phenylpyridine *N*-oxide (13.6 mg, 0.08 mmol), catalyst **5.4** (2.5 mol% of alkene originally), solvent (1.0 ml), NaOCl (0.588 M, 2.8 ml, 1.64 mmol, pH = 11.3), 0 °C. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^{1}H NMR analysis using Eu(hfc) as a chiral shift reagent. [d] Isolated yields.

As the results in Table 5.8 show, the IL **a**–catalyst system could be recycled up to five times with promising enantioselecitivities, though the reaction time had to be increased and the yield of epoxide progressively decreased. When the system was used for a seventh run, a significant yield, 67%, could be achieved after 24 h, but the ee dropped dramatically, to only 33%.

From the results obtained so far, it is clear that ionic liquids [bmim]PF_6 (IL **a**) and [bmim]BF_4 (IL **b**) can be used successfully as a solvent or part solvent in the epoxidation of 1,2-dihydronaphathalene catalysed by Katsuki's catalyst **5.4** and oxidised by a five times excess of aqueous sodium hypochlorite. Indeed, enhanced reactivities and enantioselectivities comparable to those in a molecular solvent

(CH_2Cl_2) could be achieved and the ionic liquids–catalyst system could be recovered successfully several times.

However, for atom economy, the use of excess oxidant would still be a disadvantage, especially for reactions on an industial scale. Therefore, we attempted to reduce the amount of oxidant to the stoichiometric level. Such investigations are reported in the following section.

5.4.2.1.2 Use of a stoichiometric amount of aqueous sodium hypochlorite

For a prevailing investigation, 1,2-dihydronaphthalene was initially treated with a stoichiometric amount of aqueous NaOCl in CH_2Cl_2, pure IL **a** or IL **a**–CH_2Cl_2 (2:3, v/v) mixture, respectively, in the presence of 4-PPNO, or in pure IL **a** or IL **a**-CH_2Cl_2 mixture, respectively, in the absence of 4-PPNO. The results are given in Table 5.9.

Table 5.9 Asymmetric epoxidation of 1,2-dihydronaphthalene using one equivalent NaOCl as an oxidant under various conditions.[a]

Entry	Solvent / co-ligand	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
1	CH_2Cl_2 / 4-PPNO	3.0	100	83	95
2	IL **a** / 4-PPNO[d]	3.0	84	47	82
3	IL **a**–CH_2Cl_2 (2:3, v/v) / 4-PPNO	1.0	100	81	93
4	IL **a** / no[d]	3.5	80	48[e]	68
5	IL **a**–CH_2Cl_2 (2:3, v/v) / no	2.0	46	41	82

[a] Reaction conditions: 1,2-dihydronaphthalene (54 mg, 0.40 mmol), 4-phenylpyridine *N*-oxide (17 mg, 0.10 mmol), catalyst **5.4** (10.24 mg, 10 μmol, 2.5 mol%), solvent (0.25 ml), NaOCl (0.588 M, 0.7 ml, 0.40 mmol, pH = 11.3), 0 °C. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^1H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent. [d] CH_3CH_2OH was used as solvent in order to make good solubility of catalyst in IL **a** and then being evaporated off under vacuum; the reaction is conducted at 22 °C. [e] Isolated yield

As the results in Table 5.9 show, 4-PPNO is a crucial additive in this reaction system, even when IL **a** is involved as solvent or part solvent. For example, 81% yield and 93% ee of epoxide were provided over 1.0 h reaction time (entry 3) when the reaction was conducted in IL **a**–CH_2Cl_2 (2:3, v/v) mixture in the presence of 4-PPNO, whereas only 41% yield and 82% ee were obtained over 2.0 h reaction time (entry 5) when the reaction was conducted under identical conditions except for the absence of 4-PPNO. In addition, CH_2Cl_2 was considered as a necessary co-solvent in such two phase systems, based on comparison of both the yield and ee (47% yield and 82% ee after 3.0 h reaction time) obtained from the reaction conducted in pure IL **a** (entry 2) with those (81% yield and 93% ee after 1.0 h reaction time) from the reaction conducted in IL **a**–CH_2Cl_2 mixture (entry 3). Therefore, the IL **a**–CH_2Cl_2 (2:3, v/v)–4-PPNO system proved to be the best choice.

In view of the enhanced reaction rate, the comparable yield and the comparable enantioselectivity resulting from a reaction conducted in IL **a**–CH_2Cl_2–4-PPNO mixture, we decided to recover the catalyst–ionic liquid–4-PPNO mixture following an epoxidation reaction involving 2.5 mol% catalyst in the first run (entry 3 in Table 5.9) for recycling uses. The results are listed in Table 5.10.

As the results in Table 5.10 show, the catalyst **5.4**–IL **a**–4-PPNO mixture could be recycled at least seven times with quite exciting ees in the range of 79~93%, even with a progressive drop in yield of epoxide (81%~53%). In the eighth recycled run, 83% conversion with 50% yield and 79% enantiomeric excess was obtained over a 5 h reaction time. That might suggest the catalyst was lost or decomposed during each work up as we have previously concluded. However, it was found that the use of a stoichiometric amount of NaOCl has advantage over the use of excess NaOCl on the recovery of catalyst, seen by comparison of the results in Table 5.10 and the results in Table 5.8. This implies that the salen complex may be more stable under less basic reaction conditions.

Table 5.10 Recycles of IL **a**–catalyst **5.4**–4-PPNO mixture in the epoxidation procedure involving a stoichiometric amount of NaOCl.

Solvent / co-ligand	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
IL **a**–CH_2Cl_2 (2:3, v/v) / 4-PPNO (1st use)	1.0	100	81	93
" (2nd use)	1.5	88	81	94
" (3rd use)	2.0	93	79	91
" (4th use)	2.5	86	75	91
" (5th use)	2.5	69	63	90
" (6th use)	3.0	83	67	91
" (7th use)	3.0	71	59	90
" (8th use)	3.0	71	53	87
" (9th use)	5.0	83	50	79

[a] Reaction conditions: 1,2-dihydronaphthalene (54 mg, 0.40 mmol), 4-phenylpyridine *N*-oxide (17 mg, 0.10 mmol), catalyst **5.4** (10.24 mg, 10 μmol, 2.5 mol%), solvent (0.25 ml), NaOCl (0.588 M, 0.7 ml, 0.40 mmol, pH = 11.3), 0 °C. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^{1}H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent.

Up to now, we have successfully conducted the epoxidation in IL **a**–CH_2Cl_2 mixture, or IL **b** alone. However, although IL **a**–CH_2Cl_2–4-PPNO turned out to be the most ideal system for the epoxidation of 1,2-dihydronaphthalene up to now, shortcomings still existed due to the use of a halogen-containing molecular solvent (CH_2Cl_2) that is generally concerned to be unfriendly to the environment. Therefore, we decided to attempt to use a non-halogen solvent instead. A series of solvents, such as diethyl ether, hexane, cyclohexane and ethyl acetate, was tested. In the end, ethyl acetate was chosen as the best alternative because of its moderate polarity. In other words, ethyl acetate could be miscible with high polarity ionic liquids to some extent.

In addition, in order to build up a suitable two phase system when an IL **a**–ethyl acetate mixture was mixed with an aqueous phase, aqueous NaOCl (0.588 M, pH = 11.3), it was also necessary to choose an appropriate proportion of IL **a** *vs.* EtOAc. In order to obtain a simple product separation after the reaction when

the mixed solvent was to be used as a reaction medium for an epoxidation, it would be preferable if the IL **a**–EtOAc mixture would stay in the bottom layer in IL **a**–EtOAc–NaOCl mixture. Mixtures of different proportions of an IL **a** *vs.* EtOAc were made and further mixed with aqueous NaOCl. The phenomena observed after mixing are shown in Fig. 5.1. For comparison, an (IL **a**–CH_2Cl_2 (2:3,v/v))–aqueous NaOCl mixture was also prepared (see case **d** in Fig. 5.1).

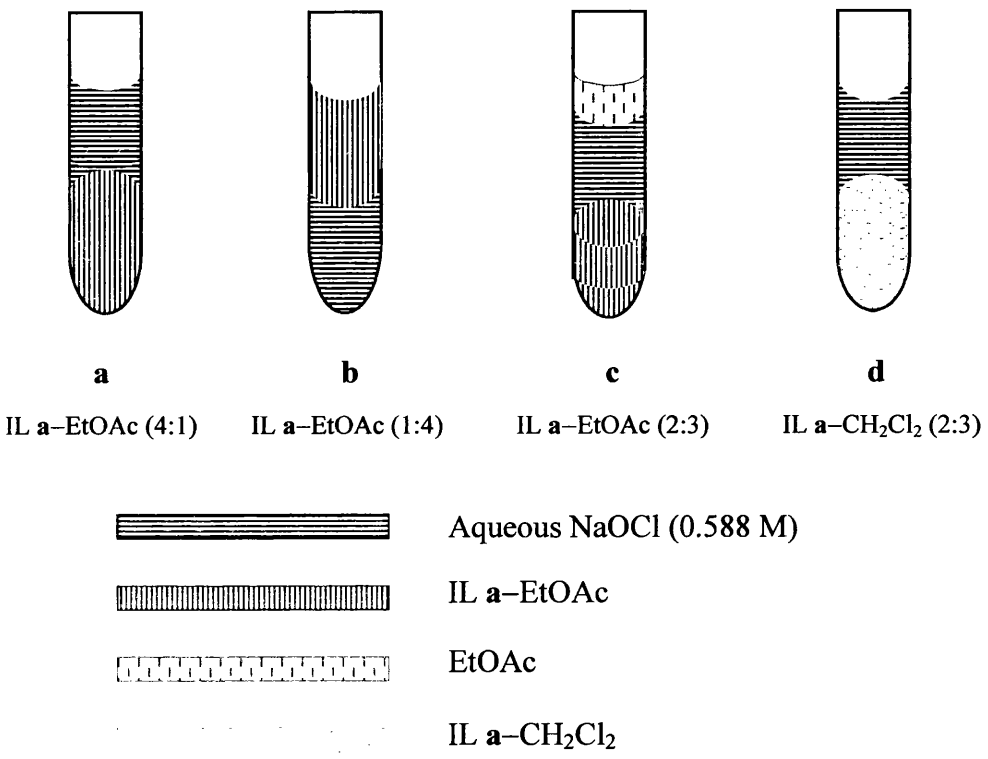


Fig. 5.1 Mixture solvents of different proportions of IL **a** *vs.* EtOAc or IL **a**–CH_2Cl_2.

As shown in Fig 5.1, when the organic phase was comprised of IL **a** and EtOAc in the proportion of 4:1(v/v) (case **a**), the IL **a**–EtOAc mixture was the bottom layer and the aqueous phase was the upper layer in the static mixture. The mixture of IL **a**–CH_2Cl_2 (case **d**) exhibited the same observation. By contrast, when the organic phase was composed of IL **a** and EtOAc in the proportion of 1:4 (v/v) (case **b**), the IL **a**–EtOAc mixture was the upper layer and the aqueous phase was the bottom layer in the static mixture. When the organic phase was mixed with IL **a** and EtOAc in the proportion of 2:3 (v/v)(case **c**), some heavy organic phase (it might be IL **a**–EtOAc mixture) was the bottom layer, the aqueous phase was the middle layer and the EtOAc

phase was the upper layer (case **c** indicates that IL **a** is not miscible with EtOAc in all proportions).

Since IL **a**–EtOAc (4:1, v/v) was the most suitable system, it was chosen as a solvent for the epoxidation of 1,2-dihydronaphthalene catalysed by Katsuki's catalyst **5.4**. The results obtained from the reactions conducted in such a solvent are given in Table 5.11.

Table 5.11 The epoxidation of 1,2-dihydronaphthalene in a IL **a**–EtOAc mixture solvent using a stoichiometric amount of aqueous NaOCl.[a]

Solvent / co-ligand	Amount of catalyst (mmol% of substrate)	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
IL **a**–EtOAc (4:1, v/v) / 4-PPNO	2.5	1.0	96	72	92
IL **a**–EtOAc (4:1, v/v) / 4-PPNO (1^{st} use)	1.25	2.0	98	77	90
" (2^{nd} use)	recycled	2.5	100	71	91
" (3^{rd} use)	"	2.5	90	62	81
" (4^{th} use)	"	2.5	81	57	85

[a] Reaction conditions: 1,2-dihydronaphthalene (54 mg, 0.40 mmol), 4-phenylpyridine *N*-oxide (17 mg, 0.10 mmol), catalyst **5.4** (as shown in Table), solvent (0.25 ml), NaOCl (0.588 M, 0.7 ml, 0.40 mmol, pH = 11.3), 0 °C. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^{1}H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent.

As the results in Table 5.11 show, the alkene was converted into the corresponding epoxide with 96% conversion in 72% yield and 92% ee within 1.0 h when 2.5% mmol of catalyst was used and 98% conversion in 77% yield and 90% ee within 2.0 h when 1.25 mol% catalyst was used. The results are comparable with those from the reactions conducted in IL **a**–CH_2Cl_2 (2:3, v/v) in the presence of 2.5 mol% catalyst (see Table 5.9).

We were pleased to obtain such results in a much greener and more economic reaction system. On the basis of those results, we attempted to recycle catalyst–IL **a**–4-PPNO following a reaction involving 1.25 mol% catalyst, as we previously did in the IL **a**–CH_2Cl_2–4-PPNO system. The results are also listed in Table 5.11. It can be seen that catalyst–IL **a**–4-PPNO could be effectively recycled with considerable enantioselectivities, in the range of 91%~85%. Similarly to the results from other systems, the yield decreased in each further recycled run, from 77% in the first run to 57% in the fourth run. It is worth noting that a very simple procedure was offered when ethyl acetate was used as co-solvent (see experimental section).

Although ionic liquids could enhance the reaction rate of epoxidation of alkene when NaOCl was used as a terminal oxidant, the reason is still not clear up to now. With these results in hand, we decided to test some other oxidants in order to try to develop an even more environmentally friendly epoxidation procedure.

5.4.2.2 Use of hydrogen peroxide as the terminal oxidant

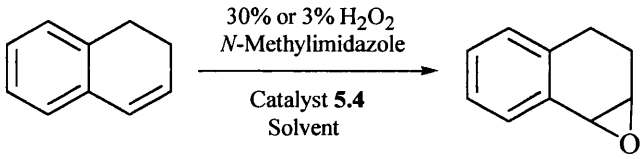
Hydrogen peroxide is a particularly attractive oxidant as it is cheap, reasonable stable, readily available, and gives only water as a by-product. Some problems still exist in transition metal complex-catalysed (including salen-based catalyst) epoxidations with hydrogen peroxide as oxidant, such as the homolytic cleavage of its weak O–O bond and so on as reviewed in Section 5.2. The heterolytic bond cleavage, which can result in the formation of reactive metal-oxo species, (salen)Mn(V)=O for example, can be favoured by using a nitrogen heterocycle co-ligand, which acts as a base or an axial ligand. Typical nitrogeneous bases used are imidazoles, pyridines, and tertiary amine *N*-oxides.[13,47] In some cases, an ammonium salt has been used, together with the co-ligand mentioned above as a co-catalyst to favour the enantiomeric selectivity.[47]

Abu-Omar[48] has reported epoxidation of alkenes and allylic alcohols in IL [bmim]BF_4, using methyltrioxorhenium as a catalyst and urea hydrogen peroxide as an oxidant. Excellent yields were obtained for many substrates. Recently, Conte[49]

reported epoxidation of electrophilic alkenes in ionic liquids [bmim]BF_4 and [bmim]PF_6 using aqueous hydrogen peroxide as the oxidant. However, up to now no asymmetric epoxidation involving H_2O_2 has yet been reported. Therefore, we decided to attempt to use such a type of oxidant in an asymmetric epoxidation reaction catalysed by Katsuki's chiral complex **5.4**. Our original purpose was to build up a clean and economic epoxidation process, in which the costly catalyst could be recycled easily by using an ionic liquid as solvent.

5.4.2.2.1 Use of aqueous 30% or 3% H_2O_2 as the oxidant

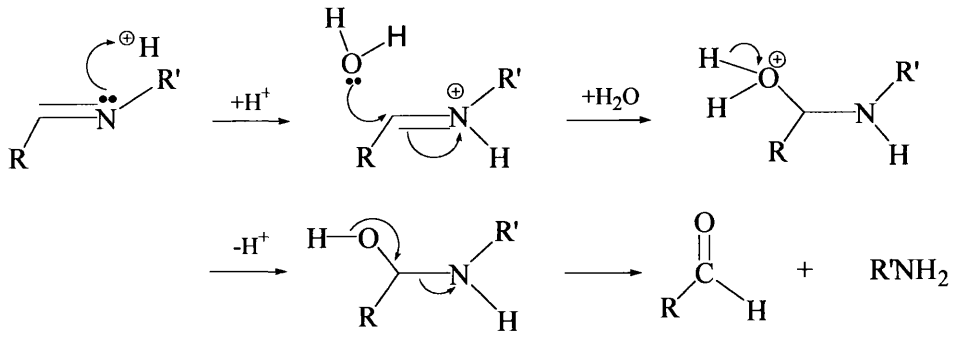
Initially, we attempted to use aqueous hydrogen peroxide as oxidant and the hydrophobic ionic liquid [bmim]PF_6 (IL **a**) as solvent in order to build up a biphasic system. Epoxidation of 1,2-dihydronaphthalene was chosen as the model reaction in such a system, as shown in Scheme 5.10. The results from a series of experiments involving aqueous H_2O_2 as oxidant are provided in Table 5.12.



Scheme 5.10

As the results in Table 5.12 show, when 1,2-dihydronaphthalene was oxidized with 30% H_2O_2 catalysed by 2.5 mol% of Katsuki's complex **5.4** in the presence of *N*-methylimidazole in either CH_3CN–CH_2Cl_2 (1.0 ml, entry 1) or IL **a**–CH_2Cl_2 (1.0 ml, entry 2), moderate yields (47%~56%) and high ees (90%~93%) were achieved. Moreover, the reaction proceeded much faster in IL **a**–CH_2Cl_2 than in CH_3CN–CH_2Cl_2. Unfortunately, the decomposition of the catalyst was suggested by decolouration of the reaction mixture, from dark brown to colourless. The reaction was also conducted in pure IL **a** (0.5 ml, entry 3), using 30% H_2O_2. It was found that the reaction was worse in pure IL **a** (0.5 ml) than in IL **a**–CH_2Cl_2 (1.0 ml) in respect of either yield or ee. We suspected that this might be caused by the acidic reaction conditions caused by 30% H_2O_2 (measured pH = 2.62, which is less than a value

presumed from the pK_a of H_2O_2 and the reason is unknown), because the imine group in catalyst is acid labile (Scheme 5.11).



Scheme 5.11

Table 5.12 Epoxidation of 1,2-dihydronaphthalene using aqueous H_2O_2 as oxidant (Scheme 5.10).[a]

Entry	Solvent (ml)	Oxidant	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
1	CH_3CN–CH_2Cl_2 (2:3, v/v, 1.0 ml)	30% H_2O_2	2.0	100	47[e]	94
2	IL **a**–CH_2Cl_2 (2:3, v/v, 1.0 ml)	30% H_2O_2	1.0	100	56[e]	90
3	IL **a** (0.5 ml)[d]	30% H_2O_2	1.0	67	41	86
4	IL **a**–CH_2Cl_2 (2:3, v/v, 1.0 ml)	3% H_2O_2	1.5	80	56[e]	89
5	IL **a**–CH_2Cl_2 (2:3, v/v, 0.5 ml, 1st run)	3% H_2O_2	0.5	100	63	92
6	"(2nd run)	30% H_2O_2	1.0	32	8.3	
			10	63	37	63
7[f]	IL **a**–CH_2Cl_2 (2:3, v/v)(0.5 ml)	3% H_2O_2	0.5	70	50	95

[a] Reaction conditions: 1,2-dihydronaphthalene (21.6 mg, 0.16 mmol), *N*-methylimdazole (7.8 µl, 0.08 mmol), catalyst **5.4** (4.2 mg, 0.004 mol, 2.5 mol%), solvent (as shown in the Table), 30% or 3% H_2O_2 (1.6 mmol), 0 °C. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^1H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent. [d] 0.2 ml CH_3CN was used to aid dissolution of the catalyst, and was then evaporated under vacuum. [e] Isolated yield. [f] Using $NH_4CH_3CO_2$ (0.08 mmol) as a co-catalyst.

In order to minimise the negative effect from the acidic reaction conditions, we decided to use 3% H_2O_2, which had a measured pH value of 4.00. We expected the catalyst to be stable under such weakly acidic conditions, involving 3% H_2O_2. When the reaction was conducted under such conditions (entry 4), the reaction became slow, giving only 80% conversion with 56% yield after a 1.5 h reaction time, compared to that using 30% H_2O_2 (entry 2). However, the enantiomeric excesses were almost the same under both conditions. In order to shorten the reaction time, we decided to double the concentrations of the reaction mixture by using half the volume of solvent (0.5 ml). The reaction was complete within 1.0 h in 63% yield and 92% ee, when it was carried out in the concentrated reaction solution (entry 5). Although the reaction rate was enhanced, the decomposition of the catalyst still happened. That could be confirmed by the results from the recycled run (2^{nd} run) (entry 6), only 32% conversion with 8.3% yield after 1.0 h and 63% conversion with 37% yield and 63% ee even after 10 h.

Finally, $NH_4CH_3CO_2$ (50 mol% of alkene) was added as a co-catalyst (entry 7), according to Katsuki's report.[47] We expected that $NH_4CH_3CO_2$ could have buffered the reaction mixture to some extent. It was found that the reaction became sluggish, giving only 70% conversion and 50% yield after 30 minutes, but the enantioselectivity was improved to 95% under such conditions compared to that of 89% the reaction (entry 4) in which there was no co-catalyst. Nevertheless, the degradation of (salen)Mn complex could still be implied by the decolouration of the reaction mixture.

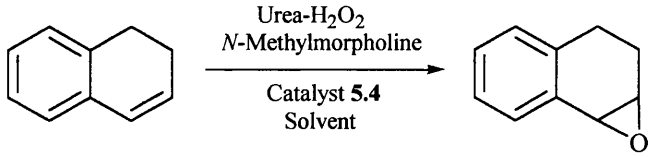
It was concluded that alkene could be converted into the corresponding epoxide successfully when it was oxidised by 30% H_2O_2 or 3% H_2O_2, catalysed by Katsuki's complex **5.4**. An enhanced reaction rate was achieved when ionic liquid [bmim]PF_6 was used as solvent or co-solvent instead of a molecular solvent, CH_3CN, but aqueous H_2O_2 does not favour recycling the catalyst.

5.4.2.2.2 Use of anhydrous urea–H_2O_2 adduct as the oxidant

As was described above, for reuse of the catalyst, aqueous 3% or 30% H_2O_2

was not a suitable oxidant for an epoxidation either in a molecular solvent or an ionic liquid probably due to the acidic conditions that might cause the degradation of the catalyst. Therefore, we attempted to use a mild oxidant, urea hydrogen peroxide adduct, instead.

Urea hydrogen peroxide (UHP) is an easy-to-handle solid and has been shown to be a water-free peroxide source for methyltrioxohenium (MTO)-catalysed epoxidation.[48] The disadvantage, thus far, for UHP is that it is insoluble in organic solvents, even in highly polar solvents such as acetonitrile. Hence, the MTO–UHP system in organic media is heterogeneous. In view of the high polarities of ionic liquids, we decided to use an IL as a solvent or co-solvent in the procedure for epoxidation of an alkene using urea-H_2O_2 adduct as an oxidant. A homogeneous reaction system was expected. Furthermore, it was assumed that the urea released as a by-product during the reaction might have neutralized the reaction system more or less and thus neutral or less acidic reaction conditions under which the catalyst was probably stable might have been conferred. If so, recycling of the catalyst in such a system might be achieved. With those ideals in mind, we decided to conduct the epoxidation of 1,2-dihydronaphthalene in such system according to the reaction in Scheme 5.12. The results are provided in Table 5.13.



Scheme 5.12

When a hydrophobic IL **a** ([bmim]PF_6) was used, DMF was chosen as a co-solvent. As the results in Table 5.13 show, when the alkene was epoxidised by a two fold excess of UHP in IL **a**–DMF (4:1, v/v) mixture, the reaction proceeded very slowly, giving only *ca.* 10% product after 20 h (entry 1). When the amount of UHP was increased to ten times that of the alkene, the reaction took place more rapidly and 57% conversion with 44% yield and 70% ee were obtained after 0.5 h (entry 2). However, it suffered not only the poor solubility of such an amount of UHP in such an amount of solvent, which was indicated by the presence of undissolved solid UHP,

but also the degradation of the catalyst, which can be implied by the decolouration of the reaction mixture.

Table 5.13 Asymmetric epoxidation of 1,2-dihydronaphthalene using UHP as oxidant (Scheme 5.12).[a]

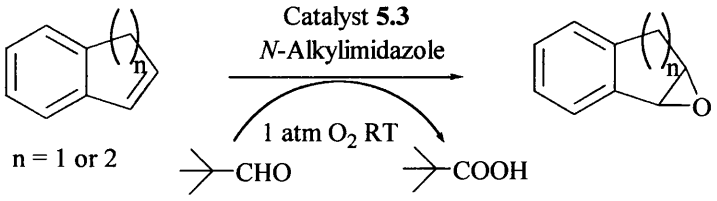
Entry	Solvent (ml)	Amount of oxidant (mmol)	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
1	IL **a**–DMF (4:1, v/v 0.5 ml)	0.32	20	--	10	n.d.[d]
2	IL **a**–DMF (4:1, v/v 0.5 ml)	1.6	0.5	57	44	70
3	IL **b** (1.0 ml) (1^{st} use)[e]	1.6	0.5	81	68	12
4	IL **b** (1.0 ml) (2^{nd} use)[e]	1.6	2.0	73	58	1.2

[a] Reaction conditions: 1,2-dihydronaphthalene (21.6 mg, 0.16 mmol), *N*-methylmorpholine (94 mg, 0.78 mmol), catalyst **5.4** (4.2 mg, 0.004 mol, 2.5 mol%), solvent (as shown in Table), UHP (as shown in Table), 22 °C, under the protection of argon. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^{1}H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent. [d] N.d.: not determined. [e] 0.1 ml of CH_2Cl_2 was added as co-solvent to help to dissolve the catalyst, and was then evaporated under vacuum.

A reaction was also conducted in a pure hydrophilic IL **b** ([bmim]BF_4). It was found that UHP could completely dissolve in IL **b**, thus a homogeneous system was produced. As the results (entry 3) in Table 5.13 show, the reaction proceeded smoothly and 81% alkene was converted into epoxide in 68% yield after 0.5 h. However, poor enantioselectivity, only 12%, was achieved. Recycling of the IL **b**–catalyst–NMO system was also tested (entry 4). In the recycled run, the reaction became rather sluggish and just 73% alkene was converted into the epoxide in 58% yield and 1.2% ee over 2.0 h reaction time. This might indicate that the decomposion of the catalyst might also take place during the process of the reaction.

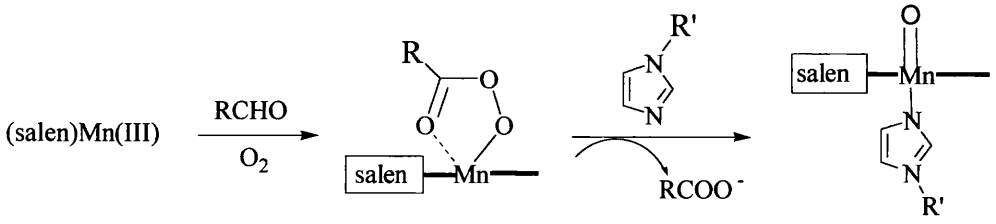
5.4.2.3 Use of molecular oxygen as the terminal oxidant

Enantioselective epoxidation of alkenes by molecular oxygen combined with a Jacobsen (salen)Mn(III) catalyst was reported by Yamada *et. al.* in 1992[14] and 1994.[15] The typical procedure chosen in those reports was using 12% catalyst in combination with molecular oxygen, as an oxidant, pivalaldehyde, as a reductant, and *N*-alkylimidazole, as an additive, to epoxidise various alkenes in fluorobenzene (Scheme 5.13).



Scheme 5.13

Good yields with moderate to good enantioselectivities were obtained. For example, 1,2-dihydronaphthalene was converted into its chiral epoxide in 78% yield and 63% ee within 24 h in the presence of pivalaldehyde and *N*-methylimidazole; 2,2-dimethyl-2*H*-chromene was converted into the corresponding epoxide in 37% yield and 92% ee after 24 h in the presence of pivalaldehyde and *N*-octylimidazole. A reasonable catalytic process was deduced,[14,15] as shown in Scheme 5.14. The oxo-manganese complex II (Scheme 5.14) has been widely accepted as a reactive intermediate for epoxidation using terminal oxidants such as iodosylbenzene or sodium hypochlorite.



I II

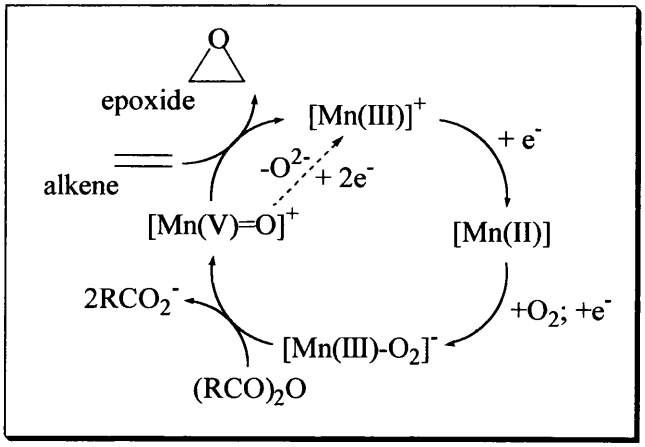
R = $C(CH_3)_3$

R' = Ph, CH_3, C_2H_5, *n*-C_4H_9, *n*-C_8H_{17}

Scheme 5.14

Also as was reviewed in Section 5.2.3, Pozzi *et al.*[39,40] have reported epoxidation of alkenes employing molecular oxygen as an oxidant, pivalaldehyde as a reductant, *N*-methylimidazole as an additive and a modified chiral Jacobsen's Mn(salen) complex as a catalyst in a fluorous–organic biphasic system. A good yield, 83%, and enantiomeric excess, 92%, were obtained for indene. However, for other alkenes, the ees were very poor even with good yields in some cases. For example, 70% yield and 10% ee were obtained for 1,2-dihydronaphthalene using such a system.

More recently, Gaillon and Bedioui1[49] described the electroassisted biomimetic activation of molecular oxygen by a (salen)Mn(III) catalyst in the presence of benzoic anhydride and *N*-methylimidazole in the ionic liquid [bmim]PF_6. It has been suggested that the key step responsible for the formation of a highly reactive oxo-mangnese(V) intermediate that could transfer its oxygen to an alkene is as shown in Scheme 5.15.[49] This offers potential for a clean, electrocatalytic oxidation of alkenes with molecular oxygen in an ionic liquid medium.



Scheme 5.15

Based on these reports in the literature, we decided to try to use molecular oxygen as a terminal oxidant, with *N*-methylimidazole as an additive, pivalaldehyde or benzoic anhydride as a reductant, and Jacobsen's complex **5.3** as a catalyst to epoxidise alkenes in an ionic liquid. Epoxidations of 1,2-dihydronaphthlene and indene were chosen as the model reactions, as shown in Scheme 5.13. The results are reported in Table 5.14.

Table 5.14 Epoxidations of alkenes catalysed by Jacobsen's complex **5.3**, using molecular oxygen as the oxidant (Scheme 5.13).[a]

Entry	Alkene[b]	Solvent	Time (h)	Conversion (%)[c]	Yield (%)[c]	Ee (%)[d]
1	A	PhF	5.0	100	51	61
2	"	IL **a**[e]	24	47	11	n.d.[f]
3	"	IL **b**[e]	24	32	8.0	n.d.[f]
4[g]	"	IL **a**[e]	24	0	0	--
5	"	IL **a**–CH_2Cl_2 (2:1, v/v)	5.0	99	57	8.5
6[g]	"	IL **a**–CH_2Cl_2 (2:1, v/v)	24	0	0	--
7	"	IL **a**–PhF (2:1, v/v)	6.0	99	39[h]	26
8	B	PhF	7.0	85	48	n.d.[f]
9	B	IL **a**–CH_2Cl_2 (2:1, v/v)	1.5	96	79	0
10	B	IL **a**[e]	24	0	0	--

[a] Reaction conditions: alkene (A: 25.6 mg, or B: 23.2 mg, 0.20 mmol), *N*-methylimdazole (7.8 μl, 0.08 mmol), Jacobsen's complex **5.3** (15.2 mg, 0.024 mmol, 12 mol%), solvent (1.5 ml), pivaladehyde (50 μl, 0.60 mmol), oxygen balloon, RT. [b] A: 1,2-dihydronaphthalene; B: indene. [c] Calculated from GC using hexadecane as an internal standard. [d] Determined by ^{1}H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent. [e] CH_2Cl_2 (0.1 ml) was added to aid dissolution of the catalyst, then evaporated under vacuum. [f] N.d.: not determined. [g] Benzoic anhydride was used instead of pivaladehyde. [h] Isolated yield.

In this series of experiments, the epoxidation of 1,2-dihydronaphthalene was initially carried out in pure IL **a** or IL **b** in the presence of *N*-methylimidazole and pivalaldehyde (entries 2 and 3). For comparison, the reaction was also conducted in fluorobenzene under identical conditions (entry 1). The results show that the reaction proceeded rather slowly either in pure IL **a** or IL **b**, 47% conversion in 11% yield in IL **a** and 32% conversion in 8.0% yield in IL **b** after 24 h. By contrast, the reaction occurred successfully in fluorobenzene, giving 100% conversion with 51% yield and

61% ee after a 5 h reaction time. Such results in fluorobenzene corresponded to those in the literature.[14,15] In the light of Caillon and Bedioui's report,[49] we attempted to use benzoic anhydride to replace pivalaldehyde. Unfortunately, no reaction occurred either in pure IL **a** (entry 4) or in an IL **a**–CH_2Cl_2 (2:1, v/v) mixture (entry 6).

However, when a molecular solvent, either dichloromethane or fluorobenzene, was used as a co-solvent, in the presence of pivalaldehyde, the reaction rate was improved significantly compared to that in pure IL **a**. For example, the reaction was complete in 57% yield after 5.0 h in an IL **a**–CH_2Cl_2 (2:1, v/v) mixture (entry 5) and 39% isolated yield after 6.0 h in an IL **a**–PhF (2:1, v/v) mixture (entry 7). Unfortunately, the ees were rather poor in both cases, only 8.5% in the IL **a**–CH_2Cl_2 mixture and 26% in the IL **a**–PhF mixture.

Indene was also used as a substrate (entries 8~10). Surprisingly, the epoxidation of indene proceeded much faster in IL **a**–CH_2Cl_2 (2:1, v/v) than in fluorobenzene. In IL **a**–CH_2Cl_2, it required 1.5 h to achieve 96% conversion with 75% yield, while the same reaction conducted in fluorobenzene required 7.0 h to achieve 85% conversion with 47% yield. Unfortunately, only a racemic epoxide was obtained in IL **a**–CH_2Cl_2.

It was not clear why indene could be epoxidised smoothly in a solvent containing IL **a**. One possibility was that the indene was epoxidised just by molecular oxygen. In order to check on this possibility, a parallel blank reaction without any catalyst was conducted in IL **a** alone (entry 11). It was found that no reaction occurred even after 24 h. This indicated that ionic liquid combined with a (salen)Mn complex was needed in order to accelerate the epoxidation.

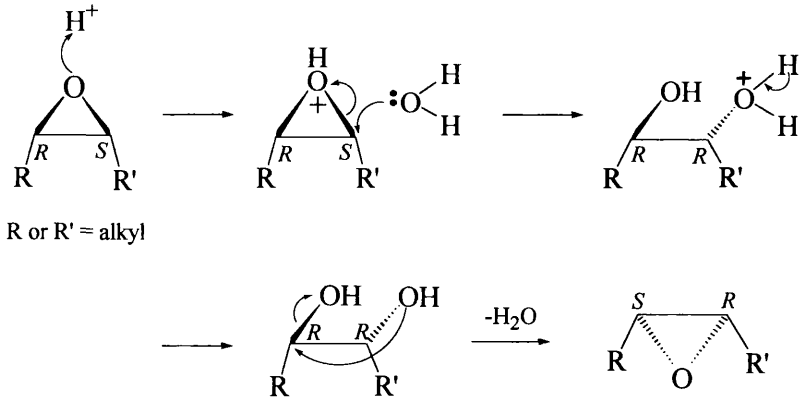
Since an enhanced reaction rate for the epoxidation of indene was conferred in IL **a**–CH_2Cl_2, the IL **a**–catalyst mixture in this system was recovered for further use. The results from the epoxidation of indene catalysed by the recycled catalyst are given in Table 5.15.

Table 5.15 Recycle of Jacobsen's complex **5.3**–IL **a** in the epoxidation of indene using molecular oxygen.[a]

Solvent	Time (h)	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
IL **a**–CH_2Cl_2 (2:1, v/v) (1^{st} run)	1.5	96	79	0
" (2^{nd} run)	2.0	96	76	0
" (3^{rd} run)	2.5	97	48	0

[a] Reaction conditions: indene (23.2 mg, 0.20 mmol), *N*-methylimdazole (7.8 μl, 0.08 mmol), catalyst **5.3** (15.2 mg, 0.024 mol, 12 mol%), solvent (1.5 ml), pivaladehyde (50 μl, 0.60 mmol), oxygen balloon, RT. [b] Calculated from GC using hexadecane as an internal standard. [c] Determined by ^1H NMR analysis using $Eu(hfc)_3$ as a chiral shift reagent.

As the results in Table 5.15 show, the IL **a**–catalyst mixture could recycled at least twice more with a significant yield, although a recemic epoxide was obtained in each case. The poor ee might be due to the instability of the epoxide under the acidic conditions (see Scheme 5.16), which resulted from the carboxylic acid produced (see Scheme 5.15).



Scheme 5.16

In short, ionic liquids were not the ideal solvents for the epoxidation of 1,2-dihydronaphathlene when molecular oxygen was used as a terminal oxidant in the presence of a reductant, either pivalaldehyde or benzoic anhydride, and an additive, *N*-methylimidazole. Quite recently, Talsi *et al.*[50] have also reported similar results.

Even though a good yield was obtained for indene, only a racemic epoxide was produced.

5.5 Conclusions

Epoxidations of alkenes (1,2-dihydronaphathalene and indene) catalysed by Katsuki's catalyst **5.4** or Jacobsen's catalyst **5.3** were carried out in solvent involving an ionic liquid, [bmim]PF_6 or [bmim]BF_4, using aqueous NaOCl, 30% or 3% H_2O_2, or anhydrous urea–H_2O_2 adduct, or molecular oxygen as the terminal oxidant, respectively.

When aqueous NaOCl was used as the oxidant, the reaction proceeded successfully. The chiral salen Katsuki complex **5.4** was effective in an IL **a**–CH_2Cl_2 solvent mixture under the reaction conditions involving either an excess or a stoichiometric amount of NaOCl. Moreover, the IL **a**–catalyst **5.4** or IL **a**–catalyst **5.4**–4-PPNO mixture could be recovered easily and reused effectively (see Tables 5.7 and 5.10). In addition, an IL **a**–catalyst **5.4**–4-PPNO–EtOAc system was also studied and considered as a much greener system than others (see Table 5.11). In short, in such a system involving aqueous NaOCl as an oxidant and an IL as solvent or part solvent, the chiral salen complex displayed not only properties typical of a homogeneous catalyst (high reactivity and a valuable enantioselectivity), but also properties typical of a heterogeneous catalyst (easy recovery of catalyst). Besides, the recovery of catalyst was much simpler in such a system than those methods in the literature,[20~37] because of: a) no need to modify the ligand or catalyst; b) no need to immobilize the catalyst onto a support.

When H_2O_2 (either in an aqueous solution or as an anhydrous adduct) was used as oxidant, bleaching of the catalyst occurred quickly although valuable yields and ees were obtained in some cases (see Tables 5.12 and 5.13).

When molecular oxygen was used as oxidant, the reaction behaved differently under different conditions. In the presence of pivalaldehyde and *N*-methylimidazole, epoxidation of 1,2-dihydronaphthalene was very sluggish in either pure IL **a** or IL **b**.

When CH_2Cl_2 or PhF was used as a co-solvent, the reaction proceeded faster than in IL alone and the conversion of the alkene was comparable to that in the molecular solvent PhF, but the ee was still much poorer than that in PhF alone. When benzoic anhydride was used to replace pivalaldehyde, no reaction occured either in pure IL **a** or in an IL **a**–CH_2Cl_2 mixture. However, when epoxidation of indene was conducted in an IL **a**–CH_2Cl_2 mixture, the reaction occurred much faster than that in PhF alone and the IL **a**–catalyst mixture was easily recovered. Nevertheless, unfortunately only a racemic epoxide was obtained.

5.6 Experimental section

5.6.1 Materials and apparatus

Ionic liquids [bmim]PF_6 (IL **a**) and [bmim]BF_4 (IL **b**) were synthesized as described in Chapter 3. Dichloromethane (A. R. grade), ethyl acetate (A. R. grade), *N*,*N*-dimethylformamide (99.99%, anhydrous), 13% aqueous sodium hypochlorite, 30% hydrogen peroxide, anhydrous urea–hydrogen peroxide (98%), 4-phenypyridine *N*-oxide (98%), *N*-methylimidazole (99+%), *N*-methylmorpholine *N*-oxide (97%), pivalaldehyde (98%), benzoic anhydride (90%) and hexadecane (98%) were purchased from Aldrich Chemical Company or Lancaster Synthesis Ltd. and used as received. Indene (97%) and 1,2-dihydronaphthalene (98%) were also purchased from Aldrich and purified before use by passing through a silica gel column using petroleum ether (40~60°C)/ethyl acetate (5:0.4) as an eluent. Oxygen was from a cylinder purchased from British Oxygen Company.

^{1}H NMR, ^{13}C NMR, IR, and mass spectra were measured by using the same equipment as those mentioned in Chapter 3.

5.6.2 Synthesis of a Katsuki-type complex 5.4

To a solution of (*R*)-3-formyl-2-hydroxy-2′-phenyl-1,1′-binaphthalene (**5.5**) (42.6 mg, 113.9 μmol, 2.0 equiv) in pre-dried CH_2Cl_2 (5 ml) was added (1*S*,2*S*)-(-)-1,2-diaminocyclohexane (**5.6**) (6.56 mg, 56.95 μmol, 1.0 equiv.)(Scheme 5.5). The

resulting mixture was refluxed for 1.0 h under the protection of argon, then cooled to room temperature, followed by addition of $Mn(OAc)_2 \cdot 4H_2O$ (15.35 mg, 62.15 μmol, 1.1 equiv.) in ethanol (5 ml), dropwise, over 15 min. The mixture was further stirred in air for 24 h at room temperature (the reaction was monitored by TLC on silica plate using CH_2Cl_2 : CH_3OH = 5 : 0.6 as eluent until complete ligand disappearance was observed, $R_{f\ (ligand)} = 1.0$, $R_{f\ (complex\ 5.4)} = 0.5$). In order to accomplish anion exchange, $NaPF_6$ (23.91 mg, 143.38 μmol, 2.5 equiv.) in distilled H_2O (0.5 ml) was added and the mixture was stirred for another 10 h at room temperature, after which time the solution was dark brown. The organic solvents (CH_2Cl_2 and EtOH) were evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 5 ml). The organic extract was washed with H_2O (3 x 10 ml), dried over anhydrous $MgSO_4$ and concentrated to dryness to give a crude dark solid **5.4** (29 mg, 26.3 μmol) in 50% yield. The crude solid was recrystallized from CH_2Cl_2–EtOH (1:1) (1.0 ml) to yield a pure crystal-like solid **5.4** (22.2 mg, 21.7 μmol) in 38% yield.

IR (KBr disc, ν, cm^{-1}): 3446 (O–H), 3047, 2936 and 2857(C–H), 1608 (C=N), 1444, 1346, 1326, 1294 (C–H), 842 (P–F).

FAB–MS: m/z (%), 879.3 (100%, $[M-PF_6]^+$).

Electrospray MS (ES^-): m/z (%), 144.9 (100%, PF_6^-).

Acc MS: $C_{60}H_{44}N_2O_2Mn$ ($[M-PF_6]^+$), calculated, 879.2783; found, 879.2784.

5.6.3 Procedures for the epoxidations under various conditions

5.6.3.1 Typical procedure for the epoxidation of 1,2-dihydronaphthalene in IL a–CH_2Cl_2 or IL b–CH_2Cl_2 using excess NaOCl as the oxidant

To a solution of 1,2-dihydronaphthalene (21.6 mg, 0.16 mmol), 4-PPNO (6.8 mg, 0.04 mmol) and hexadecane (10 mg, 0.044 mmol) in IL **a**–CH_2Cl_2 (2:3, v/v, 1.0 ml) or IL **b**–CH_2Cl_2 (2:3, v/v, 1.0 ml), catalyst **5.4** (4.1 mg, 4 μmol) was added and the mixture was cooled to 0 °C, followed by addition of pre-cooled (0 °C) NaOCl solution (1.4 ml, 0.588 M, 0.82 mmol, pH = 11.3, obtained by buffering commercial household bleach using 0.05 M Na_2HPO_4 and 0.5 M NaH_2PO_4) (note: CH_2Cl_2 was necessary to add because ILs are highly viscous and hard to stir at the reaction

temperature). The two-phase solution was stirred at 0 °C and the process of the reaction was monitored by GC. After complete conversion of the substrate, the organic phase was separated from the aqueous NaOCl phase by a separating funnel, washed with distilled water (2 x 5 ml) and the CH_2Cl_2 was then evaporated. The remaining IL phase, containing catalyst, products, hexadecane, and perhaps some 4-PPNO, was washed with hexane (3 x 10 ml). Thus, the residue contained IL, catalyst and some 4-PPNO, and the hexane extract contained the products and hexadecane. The combined hexane extracts were concentrated by rotary evaporation, and the wanted product was purified by column chromatography (SiO_2, petroleum ether 40~60°C/ethyl acetate, 5 : 0.4) to give a pure epoxide 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (**5.7**, $R_{f\,5.7)}$ = 0.45, Scheme 5.17) as a white needle-like solid (23.3 mg, 83%). The enantiomeric excess (96%) was measured by ^1H NMR using $Eu(hfc)_3$ as a chiral shift reagent.

The residue was evaporated under reduced pressure, dried further under vacuum and reused as a both solvent and catalyst for a further reaction, in which the same amount of alkenes, 4-PPNO and CH_2Cl_2 were added.

5.6.3.2 Procedure for epoxidation of 1,2-dihydronaphthalene in IL b alone (without CH_2Cl_2) using excess NaOCl as the oxidant

The procedure was identical to that used in an IL **b**–CH_2Cl_2 (2:3, v/v) mixture, except that the volume of IL **b** used was greater (1.0 ml) and the dichloromethane was removed under reduced pressure after dissolution of the catalyst. The residual viscous mixture of IL **b**–catalyst was employed as a both catalyst and solvent in a further epoxidation process.

5.6.3.3 Procedure for epoxidation of 1,2-dihydronaphthalene in IL a–CH_2Cl_2 using a stoichiometric amount of NaOCl as the oxidant

The procedure was similar to that in Section 5.6.3.1 and 5.6.3.2: to a solution of 1,2-dihydronaphthalene (54 mg, 0.40 mmol), 4-PPNO (17 mg, 0.10 mmol) and hexadecane (20 mg, 0.088 mmol) in IL **a**–CH_2Cl_2 (2:3, v/v, 0.25 ml), catalyst **5.4**

(10.24 mg, 10 μmol) was added and the mixture was cooled to 0 °C, followed by addition of pre-cooled (0 °C) NaOCl solution (0.7 ml, 0.588 M, pH = 11.3, 0.40 mmol). After that, the further treatment was the same as that in Section 5.6.3.1.

After the first use, the residue containing catalyst **5.4**–4-PPNO–IL **a** was reused further in combination with the addition of the same amount of alkene and CH_2Cl_2 as those were in the first epoxidation process.

5.6.3.4 Procedure for epxidation of 1,2-dihydronaphthalene in IL a–EtOAc using a stoichiometric amount of NaOCl as the oxidant

The procedure was the same as that used in Section 5.6.3.3, except that the proportion of IL **a** to EtOAc was 4 : 1. In addition, after the stated reaction time (see Table 5.11), hexane (3 ml) and distilled water (2 ml) were directly added to the reaction mixture and a triphasic system formed afterwards. The upper layer was hexane phase, containing the products, hexadecane and some unreacted starting material. The medium layer was aqueous phase, containing by-product NaCl and perhaps some unreacted NaOCl. The bottom layer was IL **a**, containing catalyst and co-ligand, 4-PPNO. The upper two layers were separated into a separating funnel by a simple decantation. The bottom layer, which is viscous, was washed with hexane (3 ml) and water (2 ml) twice more. The washing was decanted into the same separating funnel each time. After that, the hexane phase was separated by separating funnel from the water phase and dried over anhydrous $MgSO_4$, monitored by GC. The IL **a** phase, containing catalyst and 4-PPNO, was dried in vacuum in order to remove the water accumulated during the work-up before it was reused.

5.6.3.5 Procedure for epoxidation of 1,2-dihydronaphthalene in IL a–CH_2Cl_2 or CH_3CN–CH_2Cl_2 using 30% or 3% H_2O_2 as the oxidant

To a solution of 1,2-dihydronaphthalene (21.6 mg, 0.16 mmol), *N*-methyl-imdazole (7.8 μl, 0.08 mmol), and hexadecane (10 mg, 0.044 mmol) in IL **a**–CH_2Cl_2 or CH_3CN–CH_2Cl_2 (2:3, v/v, 1.0 ml), catalyst **5.4** (4.1 mg, 4 μmol) was added and the mixture was cooled to 0 °C, followed by addition of pre-cooled (0 °C) 30% H_2O_2,

0.18 ml, 1.6 mmol) over 5 min or 3% H_2O_2 (1.8 ml, 1.6 mmol) over 15 min. The two-phase solution was stirred at 0 °C and the process of the reaction was monitored by GC. After the completion of the reaction, hexane (3 ml) and distilled water (2 ml) was added to the reaction mixture to extract the products, by-products, the unreacted alkene and the unreacted H_2O_2. Three phases formed afterwards, as described in Section 5.6.3.4. The further treatment was the same as that in Section 5.6.3.4.

The identical procedure was when pure IL **a** was used except that 0.2 ml CH_3CN was used to aid dissolution of the catalyst, then evaporated off under vacuum.

5.6.3.6 Procedure for epoxidation of 1,2-dihydronaphthalene in IL a–DMF or IL b using urea–H_2O_2 as the oxidant

A solution of 1,2-dihydronaphthalene (21.6 mg, 0.16 mmol), *N*-methyl-morpholine *N*-oxide (94 mg, 0.78 mmol), catalyst **5.4** (4.1 mg, 4 μmol) and hexadecane (10 mg, 0.044 mmol) in IL **a**–DMF (4:1, v/v, 0.5 ml) was stirred at 22 °C under the protection of argon. Then urea–H_2O_2 (32 mg, 0.32 mmol) was added once or urea–H_2O_2 (160 mg, 1.6 mmol) was added in three portions within 30 min. The process of the reaction was monitored by GC. After a certain reaction time, the reaction was quenched by addition of distilled H_2O (2.0 ml), followed by addition of hexane (3 ml). The further treatment was the same as that in Section 5.6.3.5.

Similar procedure was when pure IL **b** was used except that the volume of solvent was increased to 1.0 ml. In addition, 0.1 ml CH_2Cl_2 was added to aid dissolution of the catalyst and then evaporated off under vacuum.

It should be noted that solvents used in this system were dried: IL **a** and IL **b** were dried at 70 °C in vacuum for 5 h before use; dichloromethane was distilled from CaH_2 under argon and stand over 4Å molecular sieve before use; *N*,*N*-dimethylformamide used was anhydrous (99.99%) which was purchased from Aldrich.

5.6.3.7 Procedure for epoxidation of alkenes using molecular oxygen as the oxidant

Typical procedure for epoxidation of 1,2-dihydronaphthalene using molecular oxygen as an oxidant in IL **a**–CH_2Cl_2 (2:1, v/v) mixture was taken as an example. The whole reaction procedure was operated under oxygen atmosphere. IL **a** (1.0 ml) was firstly dried at 70 °C in vacuum and saturated with oxygen. To such an IL **a**, Jacobsen's complex **5.3** (15.22 mg, 0.024 mmol, 12% of the substrates) was added, followed by the addition of 0.5 ml dried CH_2Cl_2 as co-solvent. The mixture was stirred for a few minutes in order to make the complete dissolution of the catalyst. Then, *N*-methylimidazole (8.1 μl, 0.10 mmol), 1,2-dihydronaphthalene (26.3 μl, 0.20 mmol) and pivalaldehyde (50 μl, 0.60 mmol) or benzoic anhydride (150 mg, 0.6 mmol) were added in turn. The mixture was further stirred at room temperature with an oxygen balloon inlet. The process of the reaction was monitored by GC. After the stated reaction time (see Table 5.14), the oxygen balloon was removed and hexadecane (10 mg, 0.044 mmol) was added. The reaction mixture was washed with hexane (5 x 3 ml) and the washings were combined. The conversion of the reaction and the yield of the epoxide were monitored by GC. The procedure for the purification of the product was the same as that in Section 5.6.3.1.

The same procedure was when fluorobenzene was used as co-solvent. Also, the same procedure was when IL **a** or IL **b** alone was used as solvent except that CH_2Cl_2 (0.1 ml) was added in the mixture of IL and catalyst, in order to make a complete dissolution of the catalyst in IL, then evaporated off under vacuum. After which treatment, the mixture of IL **a**–catalyst was saturated with oxygen.

For the epoxidation of indene, the products obtained were separated by passing the mixture of the products through a silica gel column using petroleum ether (40~60°C)/ethyl acetate 5 : 0.4 as eluent to give indene ($R_{f(indene)}$ = 0.86), then using petroleum ether (40~60°C)/ethyl acetate as 3 : 1 as eluent to give 1,2-epoxyindane (**5.10**, Scheme 5.18)($R_{f\,(5.10)}$ = 0.60) and 2-indanone (**5.11**, $R_{f\,(5.11)}$ = 0.43).

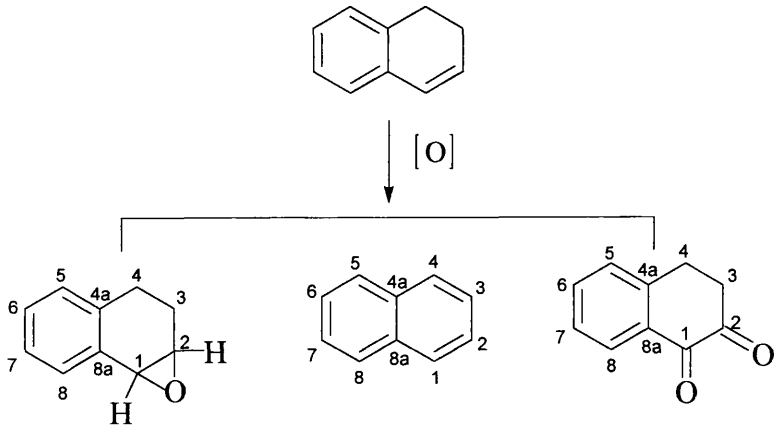
5.6.4 Determination of the concentration of aqueous sodium hypochlorite

The concentration of aqueous sodium hypochlorite (NaOCl) was measured by iodometric titration.[51]

5.6.5 Analysis of products

5.6.5.1 From epoxidation of 1,2-dihydronaphthalene

As was described above in the procedure for epoxidation of 1,2 dihydronaphthalene under various conditions, the final mixture of products was separated by a silica gel column using petroleum ether 40~60°C/ethyl acetate (5 : 0.4) as eluent, to give the main product 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (**5.7**) ($R_{f(5.7)}$ = 0.47) (Scheme 5.17). Besides the main product **5.7**, there were some other by-products contained in different eluate fractions: naphthalene (**5.8**) ($R_{f(5.8)}$ = 0.75), which was identified by GC (retention time was at 11.31 min) and NMR; and a product tentatively assigned as 1,2-dioxo-1,2,3,4-tetrahydronaphthalene (**5.9**)($R_{f(5.9)}$ = 0.45), which was also observed by GC (retention time was at 18.20 min). Since the quantity of the by-product **5.9** produced in a single reaction was not enough to measure by NMR, the material was accumulated from several epoxidations of 1,2-dihydronaphthalene. The combined **5.9**, still containing some **5.7** as an impurity, was further purified by column chromatography (silica gel, petroleum ether 40~60°C/ethyl acetate, 5 : 0.2, ($R_{f\,(5.7)}$ = 0.6 and $R_{f\,(5.9)}$ = 0.4) and was then subjected to NMR and MS analyses. Unfortunately, the amount was very small and the product was still somewhat impure, so it was not suitable for calculation of a GC response factor. Therefore, the yield of compound **5.9** could not be calculated in this way. Furthermore, the data obtained were not clear enough to allow compound **5.9** to be fully characterized. It was presumed to be 1,2-dioxo-1,2,3,4-tetrahydronaphthalene. The yield of compound **5.8** was *ca.* 10% in the first run when 2.5% Katsuki's complex **5.4** and five times aqueous NaOCl were used. However, it increased on decreasing the amount of catalyst.



5.7 **5.8** **5.9**

Scheme 5.17

1,2-Epoxy-1,2,3,4-tetrahydronaphthalene (5.7)

^{1}H NMR (400 MHz, *d*-chloroform, δ_{ppm}): 7.32 (1H, dd, J = 1, 7 Hz, H_5/H_8), 7.19 (2H, dt, J = 1, 7 Hz, H_7/H_6), 7.13 (1H, apparent t, J = 7 Hz, H_6/H_7), 7.03 (1H, d, J = 7 Hz, H_8/H_5), 3.78 (1H, d, J = 4 Hz, H_1), 3.67 (1H, apparent t, J = 3 Hz, H_2), 2.72 (1H, apparent dt, J = 6, 14 Hz, H_{4x}), 2.48 (1H, dd, J = 6, 15 Hz, H_{4y}), 2.35 (1H, dddd, J = 2, 3, 6, 14 H_{3x}), 1.70 (1H, apparent dt, J = 6, 14 Hz, H_{3y}).

^{13}C NMR (400 MHz, *d*-chloroform, δ_{ppm}): 137.1 (C_{4a}), 132.9 (C_{8a}), 129.9 (C_8), 2 x 128.8 (C_6 and C_7), 126.5 (C_5), 55.5 (C_1), 53.2 (C_2), 24.8 (C_4), 22.2 (C_3).

Naphthalene (5.8)

^{1}H NMR (400 MHz, *d*-chloroform, δ_{ppm}): 7.75~7.78 (4H, m, H_1, H_4, H_5 and H_8), 7.38~7.43 (4H, m, H_2, H_3, H_6 and H_7).

^{13}C NMR (400 MHz, *d*-chloroform, δ_{ppm}): 132.1 (2C, C_{4a} and C_{8a}), 127.1 (4C, C_1, C_4, C_5 and C_8), 124.8 (4C, C_2, C_3, C_6 and C_7).

1,2-dioxo-1,2,3,4-tetrahydronaphthalene (5.9)

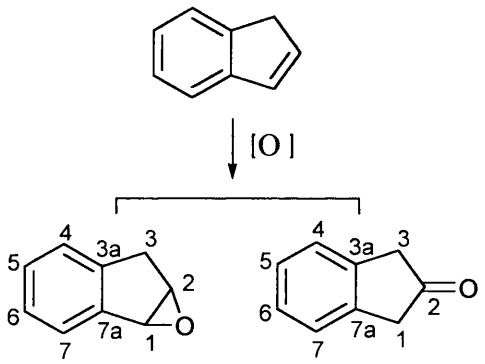
^{1}H NMR (400 MHz, *d*-chloroform, δ_{ppm}): 8.11 (1H, dd, J = 1, 8 Hz, H_8), 7.50 (1H, apparent dt, J = 2, 8 Hz, H_6), 7.33 (1H, apparent t, J = 8 Hz, H_7), 7.21 (1H, d, J = 8 Hz, H_5), 3.14 (2H, t, J = 6 Hz, H_4), 2.90 (2H, t, J = 6 Hz, H_3).

^{13}C NMR (*d*-chloroform, δ_{ppm}): 184.4 (C_1), 142.6 (C_{4a}), 135.0 (C_6), 130.4 (C_8), 129.1 (C_5), 128.8 (C_{8a}), 128.0 (C_7), 43.7 (C_3), 27.9 (C_4). The additional expected signal C_2 could not be clearly identified in the very noisy spectrum.

Mass spectrum: (EI), m/z (%), 160.0 (M^+, 16), 144.0 ([M-O]$^+$, 38), 131.0 (38), 114.9 (100), 103.0 (44), 89.0 (37), 77.0 (66)

5.6.5.2 From epoxidation of indene

Following epoxidation of indene, the products were isolated by passing the final mixture through a silica gel column using petroleum ether (40~60°C)/ethyl acetate (5 : 0.4) as an eluent to obtain indene (R_f = 0.86), then using petroleum ether (40~60°C)/ethyl acetate (3 : 1) as an eluent to obtain the main product 1,2-epoxyindane (**5.10**) (TLC, R_f = 0.60; GC retention time, 11.60 min) (Scheme 5.18) and by-product 2-indanone (**5.11**) (TLC, R_f = 0.43; GC retention time, 11.07 min) which was characterized by NMR. The yield of the main product **5.10** was quantified by GC and the yield of the by-product **5.11,** *ca.* 21% in the first run, was measured by ^{1}H NMR.



5.10 **5.11**

Scheme 5.18

1,2-Epoxyindane (5.10)

^{1}H NMR (400 MHz, *d*-chloroform, δ_{ppm}): 7.43 (1H, d, J = 7 Hz, H_7), 7.10~7.25 (3H, m, H_4, H_5, H_6), 4.20 (1H, dd, J = 1, 3 Hz, H_1), 4.07 (1H, t, J = 3 Hz, H_2), 2.92 (1H, dd, J = 3, 18 Hz, H_3), 3.15 (1H, d, J = 18 Hz, H_3).

^{13}C NMR (*d*-chloroform, δ_{ppm}): 143.9 (C_1), 141.2 (C_{7a}), 138.2 (C_{3a}), 127.8 (C_4), 125.6 (C_6), 125.4 (C_5), 59.5 (C_7), 58.1 (C_2), 35.0 (C_3).

2-Indanone (5.11)

^{1}H NMR (*d*-chloroform, δ_{ppm}): 7.18~7.27 (4H, m, H_4, H_5, H_6 and H_7), 3.51 (4H, s, H_1 and H_3).

^{13}C NMR (*d*-chloroform, δ_{ppm}): 214.2 (C_2), 136.8 (C_{3a} and C_{7a}), 126.4 (C_4 and C_7), 124.0 (C_5 and C_6), 43.1 (C_1 and C_3).

5.6.6 GC conditions

Product mixtures in the epoxidation reaction were subjected to gas chromatography on a Hewlett Packard HP 5890 (series II) gas chromatograph, fitted with an RTX-1 (100% polydimethylsiloxane; 30 m, 0.32 mm ID) column. The GC conditions used for analysis were: 100 °C for 2 min, ramped to 250 °C at 10 °C/min and held for 10 min. The injection temperature was 250 °C and the detection temperature was 300 °C. Hexadecane was used as an internal standard. The calibration solution was prepared using the same method as that in Chapter 4. Responses appeared as follows: 1,2-dihydronaphthalene at 10.89 min, naphthalene at 11.31 min, 1,2-epoxy-1,2,3,4-tetrahydronaphthalene at 13.99 min and hexadecane at 18.25 min; indene at 8.76 min and 1,2-epoxyindeane at 11.60 min.

The GC response factors (R_f) of both the substrates and the products were calculated according to Equation (4.12) in Section 4.5.4 in Chapter 4.

The residual starting material or the yield of epoxide was calculated according to Equations (4.13) through (4.14) in Section 4.5.4 in Chapter 4.

5.6.7 Determination of enantiomeric excess (ee) of the epoxides

The enantiomeric excess was determined by the integration of peak areas in ^{1}H NMR spectra using a chiral shift reagent Eu(hfc)$_3$ according to Equation (5.4).

$$ee\% = \frac{\text{Major enantiomer - minor enantiomer}}{\text{Major enantiomer + minor enantiomer}} \times 100\% \quad (5.4)$$

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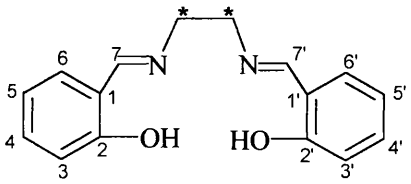
Chapter 6

Modification of a Jacobsen-type complex

6.1 Background of metallosalen complexes

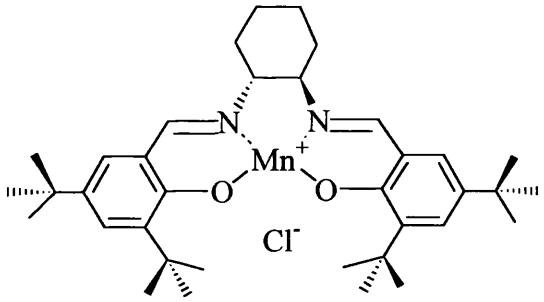
The development of an efficient catalytic asymmetric reaction is one of the most challenging tasks in current synthetic chemistry. Chiral salen ligands based on structure **6.1** have received considerable interest since Jacobsen *et al.* and Katsuki *et al.* reported significant success in asymmetric epoxidation of unfunctionalized alkenes catalysed by chiral manganese(III) complexes of such salen ligands.[1,2]



* Chirality centre (stereogenic centre)

6.1

The Jacobsen-type complex **5.3** has been used widely to catalyse epoxidation of alkenes because of its considerably greater synthetic accessibility than other complexes.



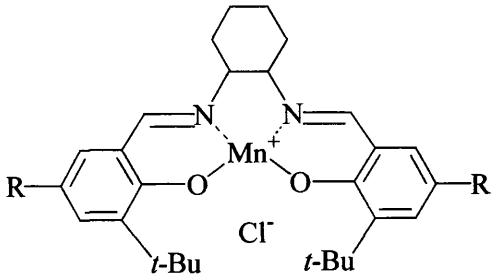
5.3

6.1.1 Ligand design

Generally, steric and electronic properties of salen ligands play important roles in the catalytic properties of their resulting metallosalen complexes.[3]

As for the steric effects, two structural properties of the salen ligand are considered to be important:[4] 1) an asymmetric diamine bridge derived from a

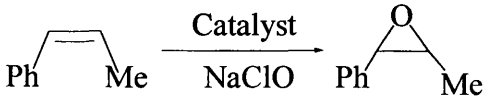
C_2-symmetric 1,2-diamine; 2) bulky substituents at the C-3 and C-3′ positions of the salicylide ligand in the salen structure.



6.2 R = Me
5.3 R = *t*-Bu
6.3 R = OMe
6.4 R = NO_2
6.5 R = OSi(*i*-Pr)$_3$

As for the electronic effects, Jacobsen *et al.* found that the electronic nature of the aromatic substituents in the salen ligand strongly influences the enantioselectivity of formation of the epoxide: complexes with an electron-donating group generally exhibit higher asymmetric induction than those with an electron-withdrawing group.[3] This is illustrated in Table 6.1 by some reported examples for the epoxidation of *cis*-β-methylstyrene, catalysed by various Mn^{III}(salen) complexes (**5.3**, **6.2**~**6.5**).

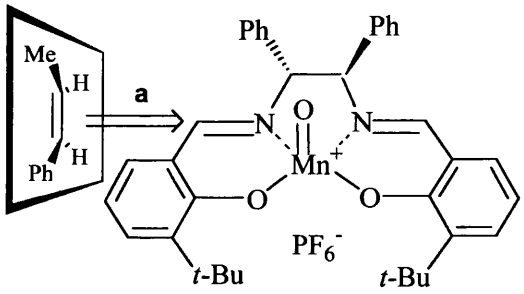
Table 6.1 Epoxidation of *cis*-β-methylstyrene catalysed by various Jacobsen-type complexes.[3,4]



Catalyst	R	Ee (%)
6.2	Me	80
5.3	*t*-Bu	90
6.3	OMe	86
6.4	NO_2	46
6.5	OSi(*i*-Pr)$_3$	92

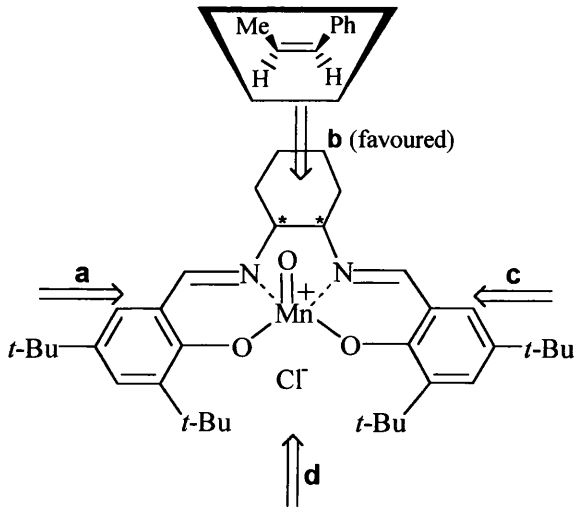
6.1.2 Mechanistic considerations

The direction of approach to the oxo–metal bond by the alkene depends on the structure of the salen complex. Steric repulsion between the substituents on the salen ligand and the approaching alkene is an important factor. For catalyst **6.6**, for example, the alkene was assumed to approach the oxo–metal bond along pathway **a** (from the side) during epoxidation (Fig. 6.1), because of the absence of any substituent at the C-5 and C-5′ positions,[5] while for Jacobsen-type catalyst **5.3**, pathway **b** (from the top) was proposed as the more favoured approach (Fig. 6.2),[6] owing to the presence of bulky *t*-butyl groups at the C-5 and C-5′ positions.



6.6

Fig 6.1 Proposed orientation of alkenes approach to salen complex **6.6**.



* Chirality centre

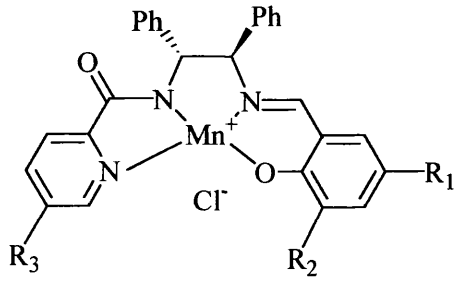
5.3

Fig 6.2 Alternative approaches of alkenes to Jacobsen-type complex **5.3**.

6.1.3 Stability of salen complexes

The stability of the salen ligand itself is very important since the transfer of chiral information is directed by the ligand structure. However, the stability of the ligand (or complex from the coordination of such a ligand to a transition metal ion) under basic reaction conditions is still in dispute. There has been no systematic investigation in this respect, although various authors have alluded to a bleaching or decomposition of the catalyst during the reaction, without providing any further details.[7,8] Nevertheless, the reactive imine and phenoxide moieties in the salen structure have been proposed to be responsible for the oxidative degradation of the catalyst during the epoxidation procedure,[7] under either aqueous basic (see Scheme 5.8) or aqueous acidic conditions (see Scheme 5.11).

In addition to many reported symmetric salen metal complexes, some asymmetric complexes have also been explored. Zhao *et al.*,[7] for example, reported asymmetric complexes **6.7~6.9**. Such manganese complexes have been used to catalyse epoxidation of some *trans* alkenes and provided moderate to good yields of epoxides. However, the enantioselectivities were not very good.



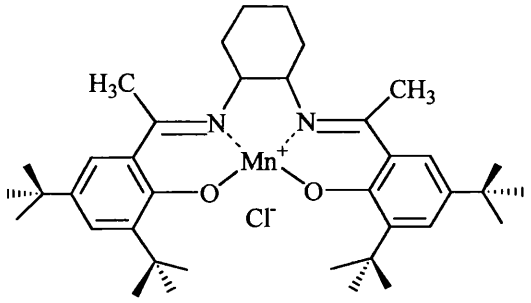
6.7 $R_1 = R_2 = R_3 = H$

6.8 R_1 = *t*-Bu; R_2 = trityl; $R_3 = H$

6.9 R_1 = *t*-Bu; R_2 = 1,1-diethylpropyl; R_3 = *n*-Bu

Although many salen metal complexes, which are almost all based on variation of the substituents on the ligands at the C-3 and C-3′ or C-5 and C-5′ positions, have been investigated, few investigations involving salen ligands modified at the C-7 and C-7′ positions (structure **6.1**) have been studied.[1,2] Therefore, we decided to modify the Jacobsen-type complex **5.3** by methylation at position C-7 and C-7′ in the salen ligand. The methyl groups are expected to donate electron density to the imine double bonds. This should decrease the δ^+ charge on the carbon atom of the imine double bond and make it less susceptible to nucleophilic attack. As reported in

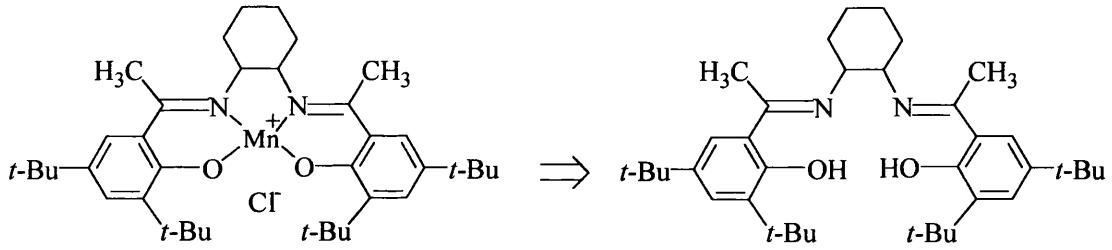
the following sections, we proposed to synthesize complex **6.10** with methyl groups on the C-7 and C-7′ positions, so that we could test its stability under aqueous basic or acidic conditions.



6.10

6.2 Retrosynthetic analysis of [*N,N′*-bis(3,5-di-*tert*-butyl-7-methylsalicylidene) -1,2-cyclohexanediamine]manganese(III) chloride (complex 6.10)

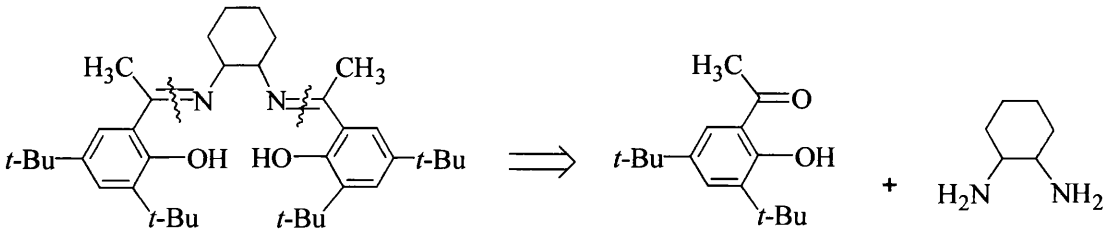
Complex **6.10** should be obtainable from compound **6.11** (Scheme 6.1).



6.10 **6.11**

Scheme 6.1

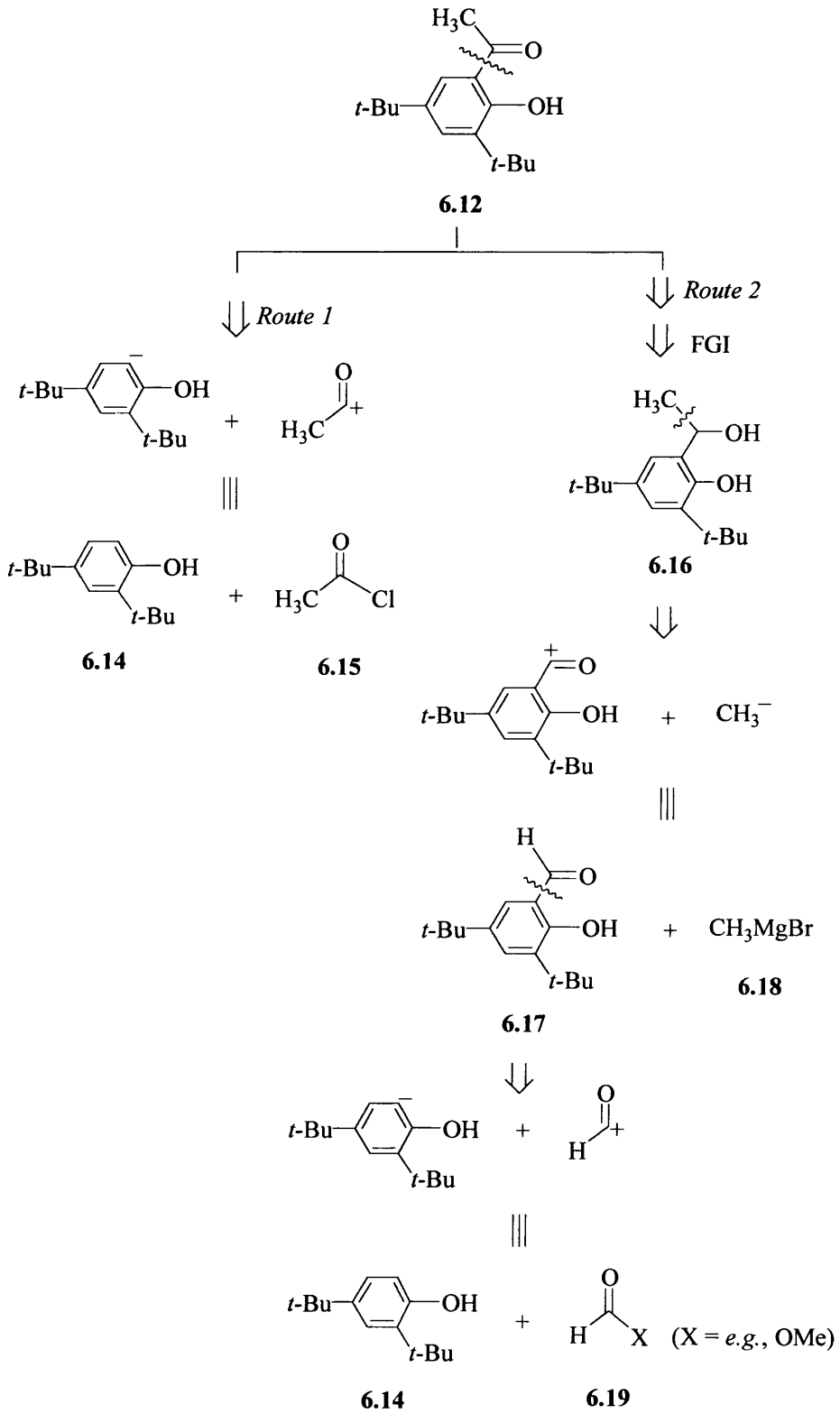
Compound **6.11** in turn should be obtainable from 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)ethanone (**6.12**) and 1,2-diaminocyclohexane (**6.13**) (Scheme 6.2).



6.11 **6.12** **6.13**

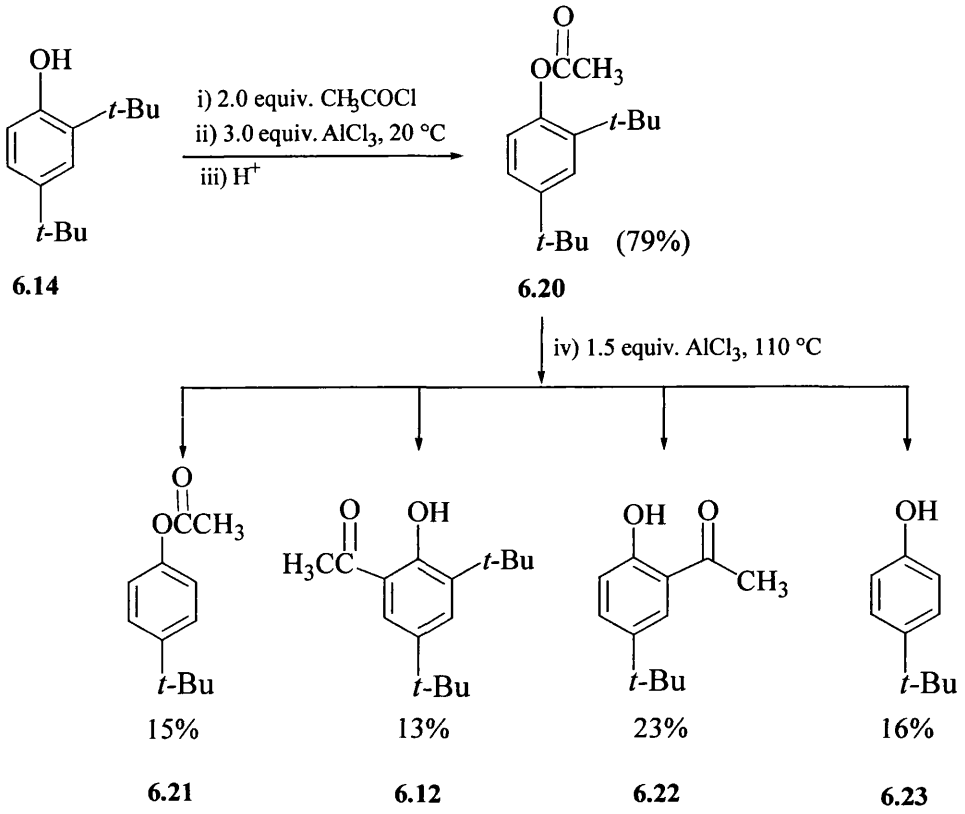
Scheme 6.2

Two possible retrosynthetic disconnections for compound **6.12** are given in Scheme 6.3. In the works reported here, compound **6.12** was synthesized by means of route 1. Details of the work undertaken are given in the following sections.



6.3 Synthesis of [*N,N'*-bis(3,5-di-*tert*-butyl-7-methylsalicylidene)-1,2-cyclohexanediamine]manganese(III) chloride (complex 6.10)

6.3.1 Synthesis of 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)ethanone (6.12)

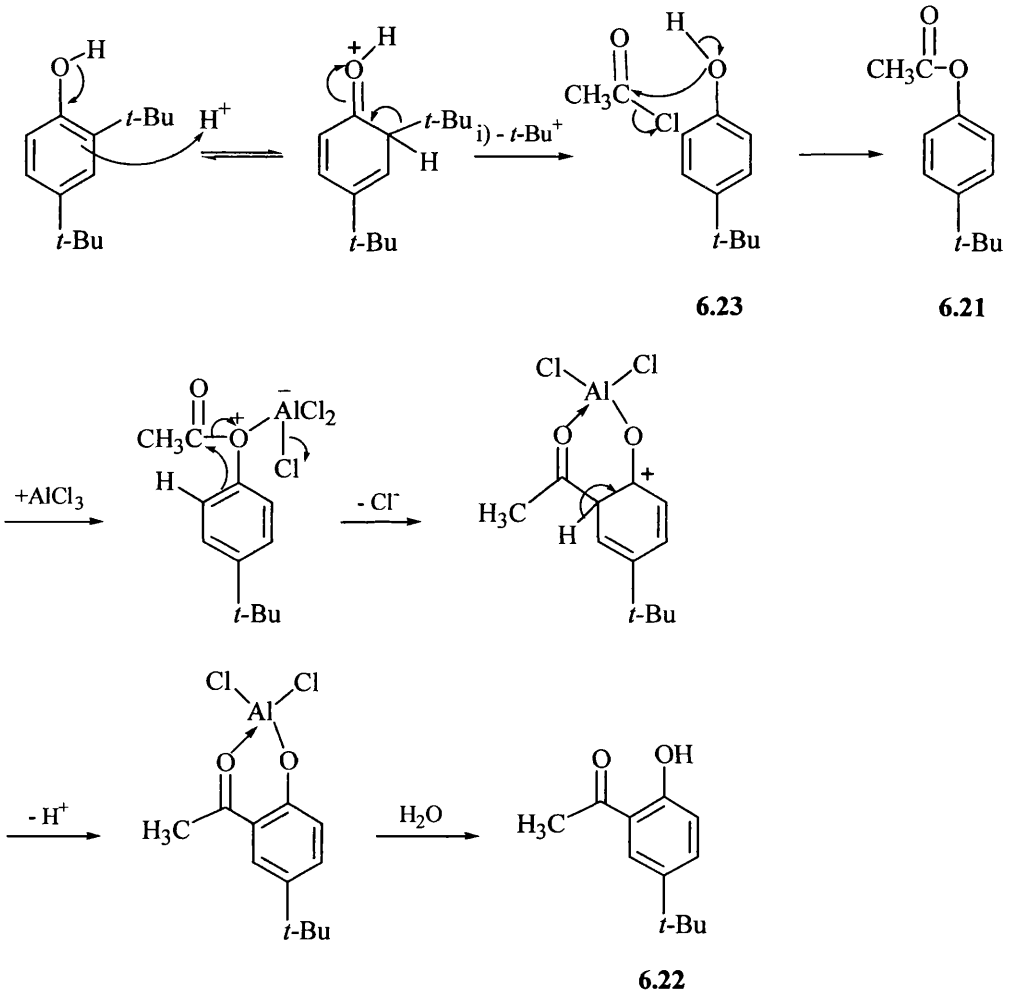


Scheme 6.4

An initial attempt was made to synthesize compound **6.12** from 2,4-di-*tert*-butylphenol (**6.14**) and acetyl chloride (**6.15**), catalysed by a Lewis acid (aluminium chloride, $AlCl_3$), according to a method in the literature, though with some modifications (Scheme 6.4).[9,10] However, the ^1H NMR results indicated that the main product (79%) isolated following column chromatography was 2,4-di-*tert*-butylphenyl acetate (**6.20**). Nevertheless, it should prove possible to convert **6.20** into **6.12** by a Fries rearrangement process. Low temperatures generally favour formation of the *para*-substituted product, while high temperatures generally favour the *ortho*-substituted product in such Fries reactions.[11] Therefore, the ester **6.20** was further treated with Lewis acid ($AlCl_3$) at higher temperature (110 °C)[12] in toluene in order to obtain the desired *ortho*-hydroxyketone. Nonetheless, a mixture of products,

including the desired product **6.12** (13%), the unwanted products 4-*tert*-butylphenyl acetate (**6.21**, 15%), 1-(5-*tert*-butyl-2-hydroxyphenyl)ethanone (**6.22**, 23%), and 4-*tert*-butylphenol (**6.23**, 16%) (Scheme 6.4) were obtained.

A possible mechanism for the formation of the by-products is suggested in Scheme 6.5.



6.23 **6.21**

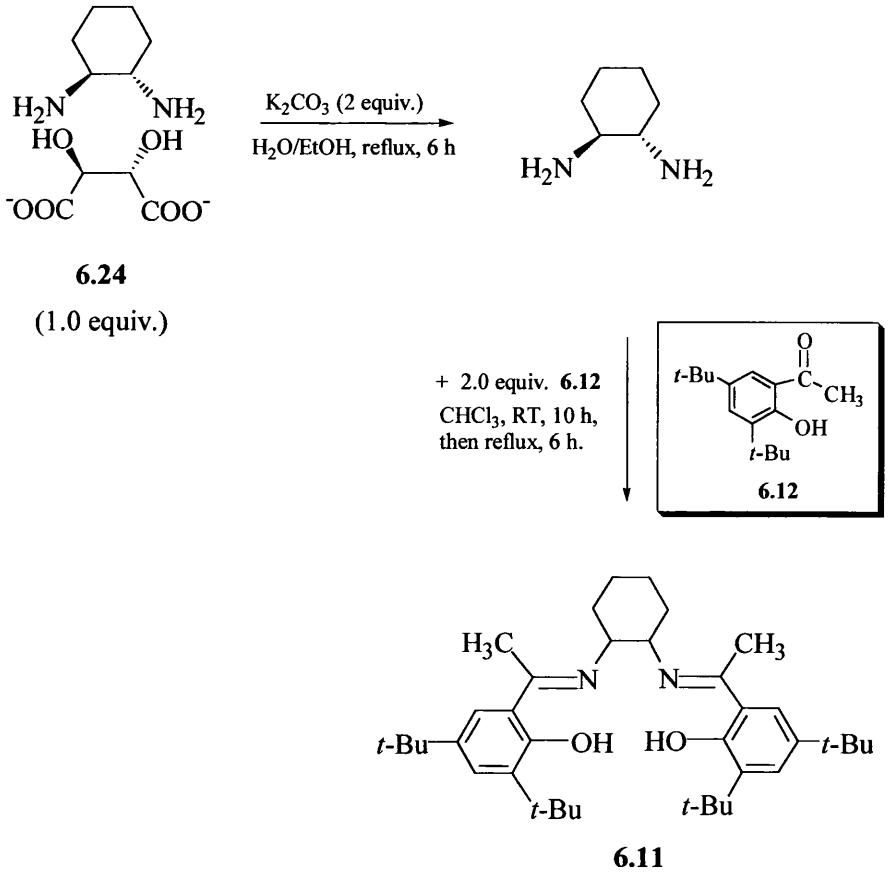
6.22

Scheme 6.5

6.3.2 Synthesis of *N,N'*-bis(3,5-di-*tert*-butyl-7-methylsalicylidene)-1,2-cyclohexanediamine (6.11)

Compound **6.11** was synthesized from two equivalents of compound **6.12** and one equivalent of commercially available (1*S*,2*S*)-(-)-1,2-diaminocyclohexane D-tartrate (**6.24**) in refluxing chloroform (Scheme 6.6). The reaction was monitored by TLC and after 6 h reflux gave a product mixture containing the desired product

6.11 and some residual reactant **6.12** (**6.11** : **6.12** = *ca.* 20% : 80%, which was calculated from ^{1}H NMR by the integration of the peaks H_8 (δ_{ppm} = 2.58) in **6.12** and H_{11} (δ_{ppm} = 2.25) in **6.11**). Attempted column chromatography over silica gel using toluene: petroleum ether (40 °C~60 °C) = 2 : 1 as eluent gave one fraction that was almost pure **6.12** and a second that showed a mixture of **6.11** and **6.12** in a ratio of almost 46% : 54%, although the TLC (silica, toluene: petroleum ether (40 °C~60 °C) = 2 : 1) showed the two spots to be well separated, $R_{f(6.11)}$ = 0.48 and $R_{f(6.12)}$ = 0.84. Despite repeated column chromatography using the same system in attempt to separate the components of the mixture from the first column, a mixture of **6.11** and **6.12** was still obtained, though, in a ratio of 73% : 27%.

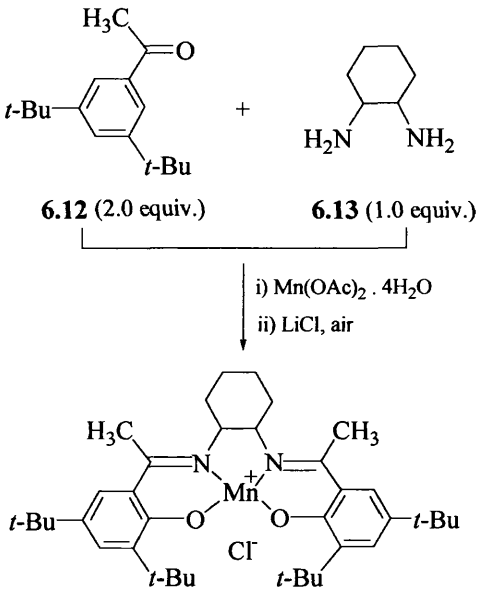


Scheme 6.6

In view of the difficulty in isolation of compound **6.11**, we decided to attempt to convert the crude product directly into its Mn complex without isolation. Attempt to synthesise a Mn complex of ligand **6.11** are reported in Section 6.3.3.

6.3.3 'One pot' synthesis of [*N*,*N*'-bis(3,5-di-*tert*-butyl-7-methylsalicylidene)-1,2-cyclohexanediamine]manganese(III) chloride (complex 6.10)

In principle, complex **6.10** can be directly synthesized in one vessel from two equivalents of ligand **6.12** and one equivalent of 1,2-cyclohexanediamine with excess $Mn(OAc)_2 \cdot 4H_2O$ in ethanolic solution in air to give a [(salen)Mn(III)]OAc complex, followed by a treatment with lithium chloride (Scheme 6.7). Therefore, in view of the difficulty in obtaining a pure sample of the free ligand, it was decided to attempt such a direct synthesis of the complex.

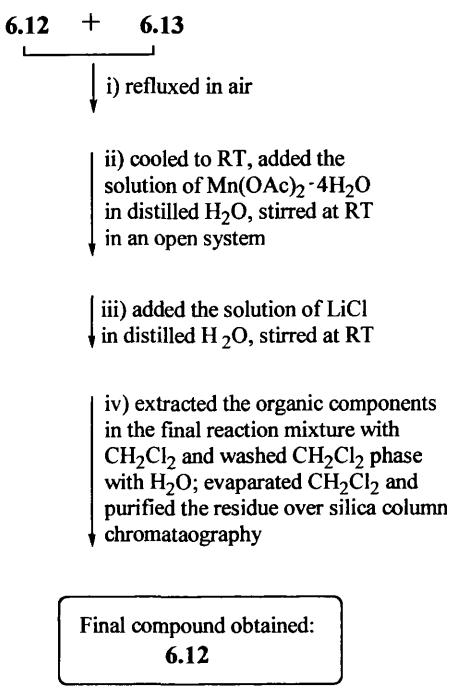


6.10

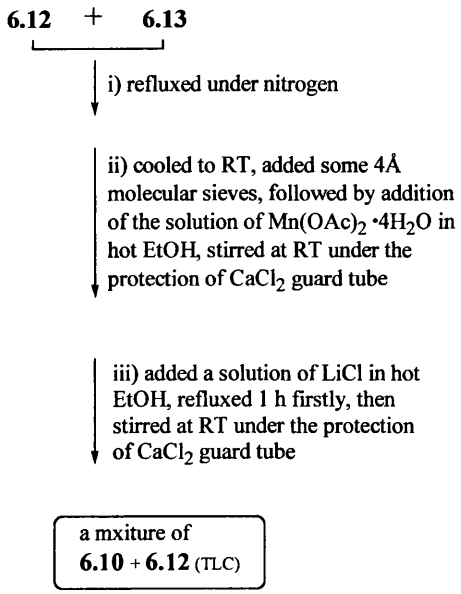
Scheme 6.7

Initially, synthesis of complex **6.10** was attempted by a method reported for the synthesis of complex **5.3** (*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]manganese(III) chloride) (details are in Scheme 6.8).[13] The material obtained from this process was **6.12**, the original starting materials, as shown by ^{1}H NMR and FAB-MS ([M^+], m/z 248). It was noticed that a brown precipitate (it was suspected to be MnO_2 based on its colour and the fact it was able to oxidise potassium iodide to give iodine, see Eqs. (6.1) and (6.2) in Section 6.4.3) formed during washing with water in step (iv) of the procedure (Scheme 6.8). We suspected that the water causing decomposition of complex **6.10**. Therefore, it was decided to

attempt to synthesize complex **6.10** under anhydrous conditions, using an anhydrous $CaCl_2$ guard tube and the aid of 4Å molecular sieves. In order to avoid water being involved, it was decided to dissolve both the $Mn(OAc)_2 \cdot 4H_2O$ and LiCl in the minimum of hot EtOH (the solubilities of both salts in hot EtOH were poor), and hence to reflux the reaction mixture for one hour after addition of the LiCl solution (in Scheme 6.9).



Scheme 6.8

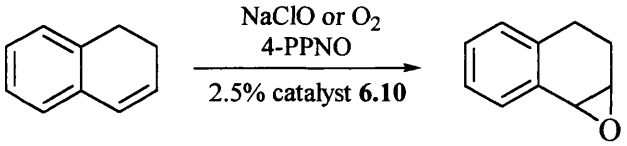


Scheme 6.9

The reaction product following the procedure described in Scheme 6.9 contained a mixture of complex **6.10** and compound **6.12** according to TLC. When this mixture was subjected to silica column chromatography using toluene : petroleum ether (40 °C~60 °C) as eluent, only **6.12** was obtained. This suggested that complex **6.10** might not be very stable to the mildly acidic silica. Therefore, the reaction was repeated to obtain the mixture of **6.12**, **6.10** and some inorganic salts. This mixture was treated as follows: it was firstly washed with hexane to remove **6.12**, then washed with CH_2Cl_2 to obtain a solution of **6.10**, leaving the inorganic salts in the final residue. The solvents were then removed from the two extract. This process gave **6.10** as a dark brown solid in *ca.* 30% yield from the CH_2Cl_2 extract, *ca.* 54% of recovered starting material **6.12** from the hexane extract.

6.4 Catalytic properties of complex 6.10

Complex **6.10** was employed to catalyse the epoxidation of 1,2-dihydronaphthalene using aqueous NaOCl (dichloromethane as organic solvent) or molecular oxygen (in a [bmim]PF_6–CH_2Cl_2 mixture) as a terminal oxidant according to Scheme 6.10.



Scheme 6.10

Unfortunately, the catalyst decomposed quickly to form a brown precipitate when aqueous NaOCl, which is basic, was used as the oxidant. Moreover, the almost intact starting alkene (97%) was recovered even after 8 h reaction time. The brown precipitate was suspected to be MnO_2, also based on its colour and the fact that it enabled to oxidise KI to give I_2 (see Section 6.4.3). Interestingly, however, when molecular oxygen was used as the oxidant, after 10 h in a [bmim]PF_6–CH_2Cl_2 (2 : 1, v/v) mixture solvent, 1,2-dihydronaphthalene was converted into the corresponding epoxide in 76% conversion with a 40% yield of epxide. Nevertheless, it still suffered from a low yield of the desired product, and in view of the difficulty in synthesising the complex, it was not an appropriate catalyst for further study.

6.5 Experimental section

6.5.1 Reagents and apparatus

All chemicals were purchased from Aldrich Chemical Company or Lancaster Synthesis Ltd. and used as received. Some of them were the same as those in Chapters 3~5, others are: 2,4-di-*tert*-butylphenol (99%), anhydrous aluminium chloride (99.9%), (1*S*,2*S*)-(-)-1,2-diaminocyclohexane D-tartrate (99%), trans-1,2-diaminocyclohexane (99%). Diethyl ether and absolute ethanol were distilled from CaH_2 twice and stood over 4Å molecular sieves under nitrogen.

All apparatus used were the same as those in Chapters 3~5.

6.5.2 Procedures for the syntheses of compounds 6.12, 6.11 and 6.10

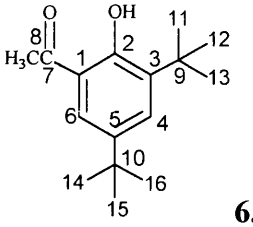
6.5.2.1 Procedure for the synthesis of compound 6.12

To a solution of acetyl chloride (**6.15**) (7.8 g, 7.1 ml, 0.10 mol) and $AlCl_3$ (20.0 g, 0.15 mol) in 100 ml dry diethyl ether was added a solution of 2,4-di-*tert*-butylphenol (**6.14**) (10.5 g, 0.05 mol) in dry diethyl ether (50 ml) at 0 °C under a flow of nitrogen. The resulting mixture was stirred at 0 °C for 3 h, then brought to room temperature (20 °C) and stirred for an additional 5 h. TLC (silica, developed with ethyl acetate/petroleum 40 °C~60 °C (1.0/10) and visualized by UV) showed one dark spot at R_f 0.7, presumed to be **6.20**, and another light spot at the base line, presumed to be **6.14**. The reaction was quenched with diluted HCl (0.5 M, 50 ml) and ice (*ca.* 5 g). The products were extracted with ethyl acetate (4 x 50 ml). The organic extract were combined and dried over anhydrous $MgSO_4$. The solid was filtered off and the organic solvent in the filtrate was evaporated under reduced pressure to obtain a crude product. The crude product was passed through a silica column with ethyl acetate/petroleum 40 °C~60 °C (1.0/10) as eluent to give compound **6.20** (9.7 g, 0.039 mol, 79 % yield).

Compound **6.20** was further treated with $AlCl_3$ (10.0 g, 0.075 mmol) in dried toluene (50 ml) at 100 °C for 3 h. The reaction was quenched by addition of cooled diluted HCl (0.5 M, 10 ml). The organic compounds in the reaction mixture were extracted with ethyl acetate (2 x 20 ml), washed with 0.5 M HCl (2 x 10 ml), 0.5 M $NaHCO_3$ (2 x 10 ml) and distilled water (2 x 20 ml). The organic phase was dried over anhydrous $MgSO_4$, the solid was filtered off and the solvent in the filtrate was evaporated under reduced pressure to give a crude product. TLC (silica, toluene as eluent) indicated that there were four components in the products. The crude products were separated by column chromatography (silica, developed sucessively with toluene : ethyl acetate 1 : 0, 16 : 1, 8 : 1, 4 : 1, 2 : 1 and then 0 : 1) to give compounds **6.21** (by TLC using silica plate and toluene eluent, R_f = 1.00, 1.42 g, 7.4 mmol, 15%), **6.12** (R_f = 0.77, 1.55 g, 6.3 mmol, 13%), **6.22** (R_f = 0.50, 2.23 g, 11.6 mmol, 23%)

and **6.23** (R_f = 0, 1.19 g, 7.9 mmol, 16%). Compound **6.12** was further recystallized from minimum methanol to give light brown crystals, m.p., 38~40 °C (43.0~44.5 °C in the literature[14]). Compounds **6.22** and **6.23** were further recystallized from minimum toluene : ethyl acetate (4 : 1) at below –10 °C to obtain colourless crystals. Melting points were: **6.22**, 30~31 °C, **6.23**, 98~100 °C.

After being purified by column chromatography (**6.12** and **6.20~6.23**) and by subsequently recrystallization (**6.12**, **6.22** and **6.23**), compounds **6.12**, **6.20**, **6.21**, **6.22** and **6.23** were characterized by NMR, MS and IR.

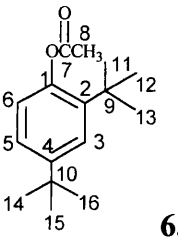


6.12: ^{1}H NMR (400 MHz, *d*-chloroform, δ_{ppm}), 12.90 (1H, s, OH), 7.47 (1H, d, J = 2.3 Hz, H_6), 7.46 (1H, d, J = 2.3 Hz, H_4), 2.58 (3H, s, H_8), 1.33 (9H, s, MeHs in *t*-Bu group), 1.23 (9H, s, MeHs in *t*-Bu group).

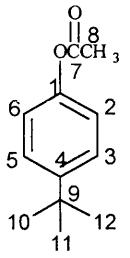
^{13}C NMR (400 MHz, *d*-chloroform, δ_{ppm}), 205.7 (C_7), 160.5 (C_2), 140.5 (C_5), 138.4 (C_3), 131.8 (C_4), 124.8 (C_6), 119.1 (C_3), 35.5 (C_9), 34.7 (C_{10}), 31.8 (C_{14}, C_{15} and C_{16}), 29.8 (C_{11}, C_{12} and C_{13}), 27.5 (C_8).

Mass spectrum: (EI), m/z (%), 248.3 (M^+, 20), 233.3 ($[M\text{-}CH_3]^+$, 100), 86.1 (24), 84.1 (41); (CI), m/z (%), 249.2 ($[M+H]^+$, 100), 182.1 (100).

IR (liquid film, NaCl window, ν, cm^{-1}): 3444 ($\nu_{O\text{-}H}$), 3269 ($\nu_{C\text{-}H}$, aromatic), 2954 ($\nu_{C\text{-}H}$, aliphatic), 1629 ($\nu_{C=O}$), 1437, 1369 and 1249 ($\nu_{C\text{-}H}$), 790, 640 and 518 ($\delta_{C\text{-}H}$, aromatics).

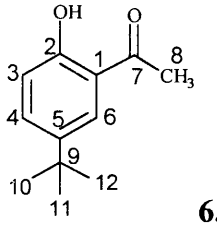


6.20: ^{1}H NMR (250 MHz, *d*-chloroform, δ_{ppm}), 7.30 (1H, d, H_3, J = 2.6 Hz), 7.06 (1H, dd, H_5, J = 2.6, 8.4 Hz), 6.80 (1H, d, H_6, J = 8.4 Hz), 2.21 (3H, H_8), 1.22 (9H, s, MeHs in *t*-Bu), 1.08 (9H, s, MeHs in *t*-Bu).



6.21: ^{1}H NMR (400 MHz, *d*-chloroform, δ_{ppm}), 7.05~7.38 (4H, m, H_2, H_3, H_5, H_6), 2.25 (3H, s, H_8), 1.30 (9H, s, MeHs in *t*-Bu group).

^{13}C NMR (*d*-chloroform, δ_{ppm}), 163.7 (C_7), 148.1 (C_4), 134.8 (C_1), 128.6 (C_3 and C_5), 125.1 (C_2 and C_6), 34.2 (C_9), 31.3 (C_{10}, C_{11} and C_{12}), 20.8 (C_8).

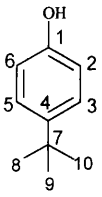


6.22: ^{1}H NMR (400 MHz, *d*-chloroform, δ_{ppm}), 12.10 (1H, s, OH), 7.69 (1H, d, J = 2.4 Hz, H_6), 7.54 (1H, dd, J = 2.4, 8.8 Hz, H_4), 6.93 (1H, d, J = 8.8 Hz, H_3), 2.63 (3H, s, H_8), 1.30 (9H, s, MeHs in *t*-Bu group).

^{13}C NMR (400 MHz, *d*-chloroform, δ_{ppm}), 205.0 (C_7), 160.6 (C_2), 142.0 (C_5), 134.7 (C_4), 126.9 (C_6), 119.4 (C_1), 118.4 (C_3), 34.5 (C_9), 31.7 (C_{10}, C_{11} and C_{12}), 27.0 (C_8).

Mass spectrum: (EI), m/z (%), 192.1 (M^+, 28), 177.1 ([M-CH_3], 100); (CI), m/z (%), 193.1 ($[M+H]^+$, 100).

IR (liquid film, NaCl window, ν, cm^{-1}): 3443 (ν_{O-H}), 2963 and 2872 (ν_{C-H}, aliphatic), 1644 ($\nu_{C=O}$), 1488, 1368 and 1223 (ν_{C-H}), 792, 634 and 550 (δ_{C-H}, aromatics).



6.23: ^{1}H NMR (400 MHz, *d*-chloroform, δ_{ppm}), 7.29 (2H, apparent dt, J = 9, 3 Hz, H_3 and H_5), 6.68 (2H, apparent dt, J = 9, 3 Hz, H_2 and H_6), 4.84 (1H, –OH), 1.33 (9H, s, MeHs in *t*-Bu group).

^{13}C NMR (400 MHz, *d*-chloroform, δ_{ppm}), 153.5 (C_1), 144.0 (C_4), 126.9 (C_3 and C_5), 115.2 (C_2 and C_6), 34.5 (C_9), 31.9 (C_8, C_9 and C_{10}).

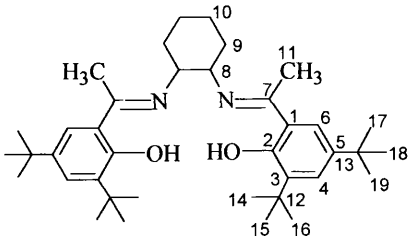
Mass spectrum: (EI), m/z (%), 150.1 (M^+, 18), 135.1 ($[M-CH_3]^+$, 100), 107.1 ($[M-C_3H_7]^+$, 26), 77.2(11); (CI), m/z (%), 167.1($[M+NH_3]^+$, 20), 150.1 ($[M]^+$, 21), 135.0 (100).

IR (liquid film, NaCl window, ν, cm^{-1}): 3227 (ν_{O-H}), 3068, 3026, 1599, 1512 (ν_{C-H}, aromatic), 2960 (ν_{C-H}, aliphatic), 1437 and 1369 (ν_{C-H}), 1236, 1183 (ν_{C-O}), 825, 661, 544 and 507 (δ_{C-H}, aromatics).

6.5.2.2 Procedure for the synthesis of compound 6.11

Compound **6.11** was synthesized (Scheme 6.6) according to the reported procedure.[15] A mixture of (1*S*,2*S*)-(-)-1,2-diaminocyclohexane D-tartrate (**6.24**) (264 mg, 1.0 mmol), and potassium carbonate (276 mg, 2.0 mmol) in 4 ml H_2O-CH_3CH_2OH (1:3) was refluxed for 8 h under the protection of argon. To the resultant mixture, a solution of 1-(3,5-di-*tert*-butyl-2-hydroxy-phenyl)ethanone (**6.12**) (496 mg, 2.0 mmol) in 1.0 ml CH_3Cl was added. The reaction mixture was stirred at room temperature for 10 h and then at reflux for an additional 6 h. The process of the reaction was monitored by TLC (silica, toluene : petroleum ether (40~60 °C) = 2 : 1, $R_{f\,(6.11)}$ = 0.48, $R_{f\,(6.12)}$ = 0.84). However, even after such a long reaction time, there were still two components, **6.12** and **6.11**, in the final resulting mixture. The mole ratio of **6.11** : **6.12** was calculated from the ^1H NMR spectrum to be 20% : 80%. The mixture of **6.12** and **6.11** was chromatographed on a silica column, eluted with toluene : petroleum ether (40~60 °C) = 2 : 1. Compound **6.12** was obtained from the first fraction, and from the remaining fraction, a mixture of **6.11** and **6.12** in the ratio of 46% : 54% (also calculated from ^1H NMR) was obtained. The column chromatography was repeated to give a mixture of **6.11** and **6.12** in the ratio of 73% : 27% (still calculated from ^1H NMR).

Compound **6.11** was characterized by NMR, MS and IR of the final mixture containing *ca.* 73% **6.11** and *ca.* 27% **6.12**.



6.11 ^{1}H NMR: (*d*-chloroform, δ_{ppm}), 7.20 (1H, d, J = 2.4 Hz, H_4), 7.18 (1H, d, J = 2.4 Hz, H_6), 3.83 (1H, m, H_8), 2.25 (3H, s, H_8), 1.77 (2H, m, H_9), 1.32 (9H, s, H_{17}, H_{18} and H_{19} in *t*-Bu group), 1.31 (2H, m, H_{10}), 1.21 (9H, s, H_{14}, H_{15} and H_{16} in *t*-Bu group).

^{13}C NMR (*d*-chloroform, δ_{ppm}), 171.0 (C_7), 160.6 (C_2), 137.6 (C_5), 137.1 (C_3), 126.6 (C_4), 122.3 (C_6), 118.1 (C_1), 63.0 (C_8), 35.0 (C_{12} and C_{13}), 32.4 (C_9) 31.4 (C_{17}, C_{18} and C_{19}), 29.6 (C_{14}, C_{15} and C_{16}), 24.2 (C_{10}), 14.6 (C_{11}).

Mass spectrum: (FAB-MS), m/z (%), 574.3 (M^+, 100), 575.2 ($[M+H]^+$, 95), 559.3 ($[M-CH_3]^+$, 25), 327 (84), 232.1 (28).

IR (KBr disc, ν, cm^{-1}): 3432 (ν_{O-H}), 2954 (ν_{C-H}, aliphatic), 1629 ($\nu_{C=N}$), 1436 and 1375 (ν_{C-H}), 1251 and 1195 (ν_{C-O}), 819 (δ_{C-H}, aromatics).

6.5.2.3 Procedure for the synthesis of complex 6.10

Complex **6.10** was synthesized according to the procedure reported in the literature[13] with some modifications. A 50 ml two-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirrer was charged with 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)ethanone (**6.12**) (164.5 mg, 0.66 mmol, 2.0 equiv.) in pre-dried ethanol (5 ml). *trans*-1,2-Diaminocyclohexane (40 μl, 0.33 mmol, 1.0 equiv.) was added, dropwise by a syringe. The resulting mixture was refluxed for 1 h under the protection of nitrogen (with appearance of the Schiff base as a bright yellow solution[13]), then cooled to room temperature, followed by addition of a solution of 0.5 M KOH in absolute ethanol (1.5 ml, 0.75 mmol). The mixture was further stirred vigorously at reflux and a deep yellow solution was finally obtained. At that time, a $CaCl_2$ guard tube was fitted in place of the nitrogen inlet, followed by addition of a solution of $Mn(OAc)_2{\cdot}4H_2O$ (0.25 g, 0.99 mmol, 3.0 equiv.) in hot ethanol (1.0 ml), dropwise over 15 min. The mixture was stirred for 4 h at room temperature. The reaction was monitored by TLC by using neutral alumina plates (5% EtOH/CH_2Cl_2, **6.12**, R_f = 0.9, salen Mn(III)OAc, R_f = 0) until the observed spot

at R_f = 0.9 was much lighter than the spot at the baseline. Afterwards, LiCl (42 mg, 0.99 mmol, 3.0 equiv.) in hot absolute ethanol (0.5 ml) was added and the reaction mixture was refluxed for 1 h, followed by continuous stirring at RT for an additional 24 h in air for anion exchange. The organic solvent (EtOH) in final dark brown solution was evaporated under reduced pressure. The remaining residue was extracted firstly with hexane (3 x 5 ml) to remove the unconverted starting material **6.12** (89 mg, 0.36 mmol, 54% of its original amount), then with CH_2Cl_2 (3 x 5 ml) to isolate the complex from the inorganic residues (note: no washing with H_2O). The CH_2Cl_2 layer was concentrated to dryness, followed by washing with hexane (2 x 5 ml) to give dark solid **6.10** (60 mg, 0.10 mmol) in 30% yield.

6.10 FAB–MS: m/z (%): 627.3 ($[M-Cl]^+$, 40), 453.4 (37), 435.2 (100), 248.2 (51).

IR (KBr disc, ν, cm^{-1}): 3414 (ν_{O-H}), 3244 (ν_{C-H}, aromatics), 2934, 2862 ($\nu_{C-H,}$), 1574 ($\nu_{C=N}$), 1415 ($\nu_{C-H,}$), 1052, 1024, 658, 616 (δ_{C-H}, aromatics).

6.5.3 Test of the catalytic properties of complex 6.10

Epoxidation of 1,2-dihydronaphthalene catalysed by complex **6.10** was chosen as a model reaction and sodium hypochlorite or molecular oxygen was used as the terminal oxidant, as shown in Scheme 6.10.

6.5.3.1 Procedure for epoxidation of 1,2-dihydronaphthalene catalysed by complex 6.10 using excess aqueous sodium hypochlorite as the oxidant in CH_2Cl_2

To a solution of 1,2-dihydronaphthalene (78.7 mg, 0.60 mmol), 4-PPNO (25.7 mg, 0.15 mmol), hexadecane (71.8 mg, 0.32 mmol) in CH_2Cl_2 (2.1 ml) and complex **6.10** (10 mg, 15 μmol) were added and the mixture was cooled to 0 °C, followed by addition of pre-cooled (0 °C) NaClO solution (5.45 ml, 0.55 M, 3.00 mmol, pH = 11.3, obtained by buffering commercial household bleach using 0.05 M Na_2HPO_4 and 0.5 M NaH_2PO_4). The two-phase solution was stirred at 0 °C. A precipitate formed quickly while the aqueous sodium hypochlorite was added.

After stirring the reaction mixture for 8 h, the organic phase was separated from the aqueous NaClO phase by a separating funnel, washed with distilled water (2 x 5 ml), dried over anhydrous $MgSO_4$, and monitored by GC. 1,2-Dihydronaphthalene (97%) was obtained.

The brown precipitate was filtered, washed with CH_2Cl_2 (3 x 1.0 ml), then with water (3 x 1.0 ml) and left in air at room temperature for a few days to obtain a brown solid powder. It was found that the powder (*ca.* 2.0 mg) would not dissolve in either distilled H_2O, diluted HCl (0.2 M), or diluted NaOH (0.2 M). However, the powder dissolved quickly when solid KI (*ca.* 5.0 mg) was added into the mixture containing it and HCl solution. A red-brown solution was produced. Afterwards, sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$, *ca.* 5 mg) was added. The colour of the solution disappeared quickly on addition of the sodium thiosulfate. The observation suggested that the brown powder is likely to be MnO_2 (see Equations (6.1) and (6.2)).

$$MnO_2 + 2I^- + 4H^+ \longrightarrow Mn^{2+} + I_2 + 2H_2O \qquad (6.1)$$

$$I_2 + 2S_2O_3^{2-} \longrightarrow 2I^- + S_4O_6^{2-} \qquad (6.3)$$

6.4.3.2 Procedure for epoxidation of 1,2-dihydronaphthalene catalysed by complex 6.10 using molecular oxygen as the oxidant in [bmim]PF_6–CH_2Cl_2 (2:1, v/v)

[Bmim]PF_6 (0.5 ml) was dried at 70 °C in vacuum and saturated with oxygen. Complex **6.10** (5.0 mg, 0.007 mmol, 2.5% of the substrate) was added, followed by dried CH_2Cl_2 (0.25 ml) as co-solvent. The mixture was stirred for a few minutes in order to allow a complete dissolution of the catalyst. Then, 1,2-dihydronaphthalene (37.4 μl, 0.28 mmol) and 4-PPNO (34.2 mg, 0.20 mmol) were added in turn. The mixture was further stirred at room temperature with an oxygen balloon inlet. After 10 h, the oxygen balloon was removed and hexadecane (31.3 mg, 0.138 mmol) was added. The further treatment was the same as that in Section 5.6.3.7. Finally, 76% 1,2-dihydronaphthalene was converted, giving 1,2-epoxy-1,2,3,4-tetrahydro-naphthalene in 40 % yield.

6.6 Conclusions

From the observations made during the processes of the syntheses of salen ligand **6.11** and salen complex **6.10**, and the epoxidation of 1,2-dihydronaphthalene catalysed by complex **6.10**, it can be briefly concluded that salen ligand **6.11** or complex **6.10** might not be very stable under aqueous basic conditions. In other words, it is not successful to stabilize C=N bonds in the salen ligand **6.11** or complex **6.10** by introducing of methyl groups at C-7 and C-7′ positions, if such a complex would be used to catalyse a reaction carried out under aqueous basic conditions. Although complex **6.10** was thought to be more stable in the process of epoxidation of alkenes using molecular oxygen as an oxidant in a IL **a**–CH_2Cl_2 (2:1, v/v) mixture under dry neutral reaction conditions, the system was not ideal for the preparation of the epoxide due to its providing a low yield of the desired product.

6.7 References for Chapter 6

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