# Catalysis in Environmentally Friendly Solvents

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**By**


***Sukhvinder Kaur Kandola***

**Department of Chemistry**

**University of Leicester**



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Author: Sukhvinder Kaur Kandola

**Abstract**

Room temperature ionic liquids (RTILs) are attracting increasing interest as environmentally benign reaction media for chemical synthesis and catalysis. This thesis describes the use of the RTILs (BMIM[OTf], BMIM[$PF_6$], BMIM[$NTf_2$], BMIM[$BF_4$]) as solvents for a variety of non-catalysed and metal-catalysed reactions, and some copper-catalysed asymmetric reactions.

Chapter one provides an overview of the principles of Green Chemistry, biphasic catalysis, the physiochemical properties of RTILs and an introduction to chemistry in RTILs. Chapter two describes nucleophilic aromatic substitution reactions of dinitrochlorobenzene and explores the potential to reuse the IL. The employment of RTILs in alkylation reactions and the Biginelli condensation is also discussed.

Chapter three reports the synthesis and use of BMIM[Cl]-$ZnCl_2$ as a catalyst and reaction medium for Diels-Alder reactions and the Fisher-Indole synthesis. The effect of the composition of the IL on yield and selectivity is examined. Further applications of BMIM[Cl]-$ZnCl_2$ in the synthesis of coumarins by the Pechmann reaction, and as a catalyst for the one pot Pictet-Spengler reaction are described.

Chapter four concerns the use of chiral copper oxazoline complexes as catalysts for several reactions including Diels-Alder, cyclopropanation, aziridination, and allylic oxidation. These reactions have been investigated in RTILs, and the affect of anion on yield and enantioselectivity is discussed. In all cases a comparison is made to conventional organic solvents and attempts are made to correlate the results against known solvent parameters. The possibility of recovery and reuse of the catalyst ionic liquid solution is discussed in selected cases, as is the effect of impurities in the RTILs on the reactions.

## *Acknowledgements*

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*To all my family & friends…a special 'thank you' for all your love, support and encouragement, always…*

# Abbreviations and Symbols

## *General and Physical*

| | | |
|---|---|---|
| br s | = | broad singlet |
| d | = | doublet |
| dd | = | doublet of doublets |
| dt | = | doublet of triplets |
| δ | = | chemical shift |
| $^0$ | = | degrees |
| EI | = | electron ionisation |
| FAB-MS | = | fast atom bombardment mass spectrometry |
| FBS | = | fluorous biphase system |
| GC | = | gas chromatography |
| GCMS | = | gas chromatography mass spectrometry |
| h | = | hour |
| HOMO | = | highest occupied molecular orbital |
| HPLC | = | high performance liquid chromatography |
| *J* | = | coupling constant |
| LUMO | = | lowest occupied molecular orbital |
| m | = | multiplet |
| min | = | minute |
| MTBE | = | methyl *tert*-butyl ether |
| MW | = | microwave |
| NMR | = | nuclear magnetic resonance |
| ppm | = | parts per million |
| RT | = | room temperature |
| s | = | singlet |
| t | = | triplet |
| $t_r$ | = | retention time |
| tlc | = | thin layer chromatography |
| UV | = | ultraviolet |

***Chemical***

| | | |
|---|---|---|
| Ac | = | acetyl |
| acac | = | anion of pentane-2,4-dione |
| $BMIM^+$ | = | 1-butyl-3-methylimidazolium cation |
| $BMMIM^+$ | = | 1-butyl-2,3-dimethylimidazolium cation |
| Bn | = | benzyl |
| Bz | = | benzoyl |
| $^tBu$ | = | t-Butyl |
| CFC | = | chlorofluorocarbon |
| Cp | = | cyclopentadiene |
| *de* | = | diastereomeric excess |
| DMF | = | dimethylformamide |
| $DMIM^+$ | = | 1-decyl-3-methylimidazolium cation |
| DMSO | = | dimethylsulphoxide |
| *ee* | = | enantiomeric excess |
| EMIM | = | 1-ethyl-3-methylimidazolium cation |
| FBS | = | fluorous biphase system |
| HDA | = | hetero-Diels Alder |
| HMIM | = | 1-hexyl-3-methylimidazolium cation |
| IL | = | ionic liquid |
| LDA | = | lithium diisopropylamide |
| MCRs | = | multicomponent reactions |
| Me | = | methyl |
| mes | = | 1,3,5-trimethylbenzene (mesitylene) |
| *mim* | = | 1-methylimidazole |
| $MMIM^+$ | = | 1,3-dimethylimidazolium cation |
| Ms | = | methanesulphonyl |
| *N*-$Rpy^+$ | = | *N*-alkylpyridinium cation |
| NOBA | = | 3-nitrobenzyl alcohol (matrix) |
| OAc | = | acetate |
| OMIM | = | 1-octyl-3-methylimidazolium cation |
| OTf | = | triflate |
| Oxaz | = | oxazoline |
| PMIM | = | 1-pentyl-3-methylimidazolium cation |

| | | |
|---|---|---|
| $^{i}Pr$ | = | isopropyl |
| PTC | = | phase transfer catalyst |
| $NTf_2$ | = | Bis(trifluoromethylsulphonyl)imide |
| $RMIM^{+}$ | = | 1-alkyl-3-methylimidazolium cation |
| RTILs | = | room temperature ionic liquids |
| SCF | = | supercritical fluids |
| TBAF | = | tetrabutylammonium fluoride |
| THF | = | tetrahydrofuran |
| TOF | = | turnover frequency |
| Ts | = | *para*-toluenesulphonyl |
| VOC | = | volatile organic solvent |

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# Chapter One

# Introduction

# Chapter One - Introduction

## 1.1 GREEN SUSTAINABLE CHEMISTRY

The increasing knowledge in natural sciences and the application of this knowledge are the driving forces for the development and welfare of mankind. Chemistry plays a central role in this development by providing molecular understanding of living systems leading not only to better medical care, agricultural production, but also more efficient telecommunications and informatics. The driving forces for development in chemistry (especially synthetic chemistry which produces tailor-made materials and compounds for specific purposes) have been strong, due to a demand for new and efficient processes and chemicals. However, certain chemicals produced and used in large quantities cause various hazards in the environment, hence there is a need for research in sustainable or 'Green' chemistry. Many people associate Nature with the word 'green', and therefore the reconsideration of how nature and chemistry can coexist and how the environment can be protected while still manufacturing products necessary for human life is brought together in 'Green Chemistry'.

Green chemistry is defined as: "The invention and application of chemical products and processes which are designed to reduce or eliminate the use and generation of hazardous substances".[1] Hazards encompass local effects *e.g.* explosion and fire, and global effects *e.g.* global warming, stratospheric ozone depletion, resource depletion and bioaccumulation. Since environmental protection has become a global concern, the chemical industry is increasingly obliged to re-examine conventional methodologies, and to seek ways of developing and applying more efficient and environmentally benign strategies for future sustainable growth. This will involve increasing energy efficiency in chemical transformations and waste minimisation, leading not only to a cleaner environment but also a more cost effective use of the starting materials. The 12 Principles of Green Chemistry help show how this can be achieved.[1]

1. Prevention

It is better to prevent waste than to treat or clean up waste after it has been created.

2. Atom Economy

Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.

3. Less Hazardous Chemical Synthesis

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.

4. Designing Safer Chemicals

Chemical products should be designed to effect their desired function while minimising their toxicity.

5. Safer Solvents and Auxiliaries

The use of auxiliary substances (*e.g.* solvents or separation agents) should be made unnecessary wherever possible and innocuous when used.

6. Design for Energy Efficiency

Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce Derivatives

Unnecessary derivatisation (use of blocking groups, protection/de-protection, and temporary modification of physical/chemical processes) should be avoided if possible, because such steps require additional reagents and can generate waste.

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 break down into innocuous products and do not persist in the environment.

11. Real-time Analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions, and fires.

Some of the approaches to Green chemistry, such as atom economy, the replacement of stoichiometric reactions with catalytic ones, and the replacement of solvents, are discussed overleaf.

### 1.1.1 Waste minimisation & Atom Economy

Legislation has an important role in setting the framework for waste minimisation. Apart from making the emission and disposal of certain noxious substances illegal, legislation encourages cleaner technology through environmental taxes and regulations. The problems posed by waste, including the inefficient use of resources and capital, together with the risks to welfare and the environment are widely recognised by most sectors of society. Many countries now have active programmes to reduce the amount of waste disposed of to land, air and water through increased recycling and deploying waste minimisation initiatives. An accepted hierarchy for waste management has been developed with the most preferred solution being reduction of waste at source. Lower down the hierarchy comes re-use, followed by recycling to recover materials and / or energy. Disposal of treated or untreated waste should only be considered as a last resort. Clean technology for an industrial chemical process should minimise waste *i.e.* everything produced in the process except the desired product. The best strategy is to apply this philosophy to the entire process *e.g.* maximise the incorporation of all materials used in the process into the final product. In order to assess the waste produced by a process, Sheldon has used the "E factor" of a process, which is the ratio (by weight) of the by-products to the desired product(s).[2,3]

**Table 1. 1 The Sheldon E-Factor for various sectors of the chemical industry[3]**

| Industry | Production /tons p.a. | E-Factor |
|---|---|---|
| Oil refining | $10^6 - 10^8$ | 0.1 |
| Bulk chemicals | $10^4 - 10^6$ | 1 – 5 |
| Fine chemicals | $10^2 - 10^4$ | 5 – 50 |
| Pharmaceuticals | $10^1 - 10^3$ | 25 – 100 |

Sheldon undertook one of the most quoted studies comparing waste produced by various sectors of the chemical industry. The table illustrates that by this definition, the 'dirty' end of the chemical industry, oil refining and bulk chemicals is remarkably waste efficient *i.e.* has high selectivity for the desired product and thus a low E-factor, whereas the fine chemicals and pharmaceuticals, usually viewed as "high tech" and clean, are using very inefficient, dirty processes. It should be born in mind that production of fine chemicals involves multi-step synthesis, however it is inefficient largely due to the use of stoichiometric reagents rather than catalytic methodologies. The process of getting a new pharmaceutical approved for use is long and costly. Past experience has shown that small

amounts of by-products present in the final drug formulation may have a profound effect on the efficacy and side effects produced. As a result, many countries now not only require the drug to be approved but also the process by which it is manufactured. The aim of this action is to ensure a totally consistent drug composition. Once this approval process has been started it is expensive and time consuming to change. Since, for patented drugs, there is effectively no competition there is no effective driver for changing the process, as production costs are generally relatively insignificant compared to the selling price. Therefore new and cleaner technologies are needed, especially in the pharmaceutical sector, ideally at the research stage.

Reaction conditions should be designed such that product selectivity is optimum and product separation processes can be avoided. Reaction efficiency is just as important as product selectivity, because when the overall yield of a process is increased by 10 or 20 %, less material ends up in waste streams and more is converted into product. Unnecessary derivatisation (blocking group, protection / deprotection, etc) should be avoided whenever possible and 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.

Yield alone isn't the only measure of reaction efficiency and needs to be considered in conjunction with the concept of 'atom economy'. A synthetic transformation can achieve 100 % yield of product and still generate a substantial amount of waste if the transformation is not atom economical. Atom economy is the ratio of the molecular weight of the target molecule to the sum total of the molecular weights of all the substances produced in the stoichiometric equation for the reaction involved. The comparison is made on a theoretical basis (*i.e.* 100 % chemical yield).[4] Reactions that have an atom economy of 1.0 are easily recognisable and preferred since no by-products are formed. By taking the atom economy of various synthetic routes into account at the planning stages the chosen strategy is likely to produce a greater weight of products per unit weight of reactants than might otherwise have been the case. Addition reactions, for example, completely incorporate the starting material into the final product and therefore do not produce waste that needs to be treated and disposed of. Rearrangement reactions and concerted processes are also examples of atom economic reactions. Substitution reactions, on the other hand, generate stoichiometric quantities of substances as by-products and waste. Elimination reactions are also among the least atom-economical transformations, generating stoichiometric quantities of substances that are not part of the final target molecule. Overall, we now see a change in the traditional concept of process

efficiency that focussed exclusively on chemical yield, to one that assigns economic value to eliminating waste.

The design of chemical transformations can also reduce the required mechanical and thermal energy input, and thereby the associated environmental and economic impacts of excessive energy usage. For instance, when using new solvents such as supercritical carbon dioxide or ionic liquids, ease of product separation means that a significant energy input will not be required. Also, if a synthetic transformation is developed using a catalytic system rather than a stoichiometric process, then the catalyst lowers the activation energy required for the conversion.

### 1.1.2 Catalysis

One of the most important factors in minimising waste in fine chemicals manufacture is the widespread substitution of classical organic synthesis employing stoichiometric amounts of inorganic reagents with cleaner catalytic alternatives. A catalyst is defined as a material which changes (usually increases) the rate of attainment of chemical equilibrium without itself being changed or consumed in the process. By increasing the rate of attainment of equilibrium through lowering the activation energy, catalysts reduce the energy requirements of a process and therefore can be considered to be inherently green. Many catalysts are also highly selective, either enhancing one synthetic pathway over an alternative, or preferring one reagent in a mixture over another.

#### *1.1.2.1 Homogeneous catalysis versus heterogeneous catalysis*

Catalysts are commonly divided into two basic types, homogeneous and heterogeneous, depending on their state relative to the reaction medium. A system is homogeneous when all reactants are present in the same physical state and phase as the catalyst. In heterogeneous catalysis, at least one of the components (reactants, catalyst or solvent) is present in a different physical state or phase than the other components. Homogeneous catalysis in the liquid state often leads to problems in separation of the catalyst from the product, and therefore the heterogenisation of the system is often used as a tool to facilitate the recycling or reuse of the catalyst, *e.g.* by confining reactants, products and catalyst to different phases. This can be achieved in a multitude of ways: liquid-gas, solid-gas, liquid-liquid or solid-liquid. The last two systems are considered in

detail in the following section (1.1.2.2). The advantages and disadvantages of homogeneous and liquid-solid biphasic catalysis are shown in the table below.

**Table 1.2 Comparison between homogeneous and heterogeneous catalysis[5,6]**

| Homogeneous catalysis | Heterogeneous catalysis |
|---|---|
| Same phase as reaction medium | Usually distinct solid phase |
| Often difficult to separate | Readily separated |
| Expensive / difficult to recycle | Readily regenerated and recycled |
| Often very high rates | Rates are usually as fast as homogeneous |
| Not diffusion controlled | May be diffusion limited |
| Usually robust to poisons | Quite sensitive to poisons |
| High selectivity | Lower selectivity |
| Short service life | Long service life |
| Often takes place under mild conditions | Often high-energy process |
| Often mechanism well understood | Poor mechanistic understanding |

In a homogeneous system, all metal centres can become involved in catalysis, which often results in higher activity than heterogeneous catalysis. In heterogeneous catalysis only those atoms accessible to the substrate participate in the process, resulting in lower activity. Many of the green benefits of homogeneous catalysis, especially that of high selectivity, arise from 'designer' catalysts made from transition metals and tailor-made ligands, having optimal steric and electronic properties. A definitive advantage in homogeneous catalysis is the ease with which catalyst structures as well as their interactions with the substrate within the catalytic cycle can be studied, *e.g.* by spectroscopic means. An understanding of the mechanism allows for specific changes in *e.g.* reaction conditions or ligand structure.

The choice of catalyst is dependent on the application and the reaction conditions needed. Homogeneous catalysts are often fragile and can be used only under relatively mild conditions; otherwise decomposition occurs. Recycling of homogeneous catalysts is expensive. The most widely used homogeneous catalysts are simple acids and bases as a large number of industrial processes are based on the use of mineral ($H_2SO_4$, $H_3PO_4$, etc) and Lewis acids ($AlCl_3$, $ZnCl_2$, etc). While many of these processes are catalytic, some (*e.g.* acylation using $AlCl_3$) require stoichiometric amounts of Lewis acid, which cannot be easily recovered and recycled. Final isolation of the product necessitates neutralisation

steps to remove the acid, resulting in enormous quantities of hazardous waste and the cost of disposal associated with it. On the other hand, heterogeneous catalysts can generally be used directly after separation by filtration or centrifugation, and very often under more corrosive reaction conditions. Biphasic catalysis offers a means by which we may combine the advantages of both homo- and heterogeneous catalysis. (See below).

### *1.1.2.2 Biphasic catalysis*

While the use of solid reagents and catalysts with gaseous or liquid feeds and products provides easy separation, the presence of various surface species with different activity and selectivity frequently limits yields.[7] In contrast, homogeneous liquid phase reactions are generally characterised by high product yields but the separation of the products is a major obstacle for industrial applications. There is a continuing interest in developing new methods for biphasic catalysis where a homogeneous catalyst is immobilised in one liquid phase and the products reside largely in another liquid phase.[8] The formation of a liquid-liquid biphase system is due to the sufficiently different intermolecular forces of two different liquids resulting in limited or negligible solubility in each other. There are three main types of biphase system; the aqueous / organic biphase, the fluorous biphase, and the ionic liquid biphase. A short discussion on each of these is given in sections 1.1.3.2, 1.1.3.4 and 1.1.3.5. In these cases, the selection of a catalyst for a given reaction depends primarily on the solubility properties of the product. For example, if the product is apolar then the catalyst phase should be polar, and vice versa, if the product is polar then the catalyst should be apolar. The success of any biphasic system depends on whether the catalyst can be designed to dissolve preferentially in a single phase. This is usually achieved by attaching appropriate solubilising groups to the catalyst.

### *1.1.2.3 Asymmetric catalysis*

The active component of many pharmaceuticals, pesticides and biochemicals are chiral. It is often the case that when drugs interact with enzymes / cell receptors only one enantiomer will have the desired effect; this can be rationalised since nature has evolved using amino acids with only L-configuration and sugars with only D-configuration about their chiral centre(s). The other enantiomer may be inactive or even have a deleterious affect, as in the well documented case of Thalidomide (the *R*-isomer helps prevent morning sickness and the *S*-isomer is a teratogen). In conjunction with reduced side effects and increased activity of a single enantiomer drug, legislation passed by the US Food and

Drugs Administration (FDA) and the European Committee for Proprietary Medicinal Products requires that for drugs that are to be sold as a racemate, each enantiomer must be fully characterised. These factors have resulted in single-isomer drugs being the most commercially viable alternative.

In nature, enzymes are the catalysts used to carry out highly efficient and stereoselective transformations on a wide range of organic substrates. However, enzymes have some drawbacks for industrial use, they are difficult to extract and purify and in the majority of cases are rather reagent specific. Theses obstacles have led to research into alternative methods for obtaining enantiopure compounds. There are three main routes to obtaining single-enantiomers, these are: stoichiometric synthesis by using the desired configuration of starting material; resolution of enantiomers which has a maximum possible yield of 50 %; and asymmetric catalysis which is often the most efficient method since one molecule of chiral catalyst can produce thousands of enantiopure product molecules by introducing asymmetry directly into achiral starting reagents, eradicating the need for resolution methods. These inherent advantages have brought asymmetric catalysis to the forefront of modern industrial chemistry and, in some cases, the stereoselectivity and efficiency is now approaching that of enzymes. In this thesis, the expression "asymmetric catalysis" is restricted to the specific case of an enantioselective reaction controlled by a chiral catalyst.

The period 1980-1990 was a decade of impressive achievements in asymmetric catalysis, giving birth to new synthetic methods. Most of the progress came from organometallic catalysts. For example, Sharpless described a very general method for the asymmetric epoxidation of allylic alcohols.[9] This method soon became a routine reaction in synthesis, because of its generality, broad scope, high *ee*'s and the ability to predict the configuration of the product. Asymmetric hydrogenation was boosted towards synthetic applications with the preparation of Binap by Noyori *et al.*[10] Another important development was the isomerisation of allylamines into enamines catalysed by cationic rhodium/ binap complexes,[11] which has been applied commercially since 1985 (in Japan at the Takasago Company) for the synthesis of (-)-menthol.

To facilitate industrial applications of asymmetric catalysis, high activity and high *ee* are necessary. In addition, protocols for the separation, and preferably reuse of the catalyst are necessary. Chapter 4 investigates the immobilisation of chiral Lewis acids in BMIM-based ionic liquids and the capacity to reuse the ionic liquid.

### 1.1.3 Alternative Solvents

Developing environmentally benign technologies that provide economical routes to chemical products is an area of research that is being vigorously pursued. Volatile organic compounds (VOCs), including chlorinated hydrocarbons are the normal media for the industrial synthesis of organic chemicals, with a current world-wide usage of approximately £4,000,000,000 per annum.[12] In chemical manufacture, a key role of organic solvents is to provide a homogeneous reaction mixture and speed up reactions through improved mixing, and to enable the exact dosing of reactants, and to ease transfer from one reactor to another. Solvents also contribute to safety by acting as a heat sink for exothermic reactions.

Usually, organic solvents are used in much larger quantities than the solutes they carry and a proportion is lost to the environment through evaporation and leakage leading to possible environmental problems. For example, the use of chlorofluorocarbons (CFCs) has been restricted due to their role in stratospheric ozone depletion, whereas the use of certain VOCs as solvents has caused concern due to their ability to elevate atmospheric ozone levels, affect global warming and contribute to the overall greenhouse gas loading in the environment.

As clean technology is becoming a major concern throughout industry and academia, the search for alternatives to the most damaging solvents has become a high priority. Curzons and coworkers,[13] for example, recently noted that rigorous management of solvent use is likely to result in the greatest improvement towards greener processes for the manufacture of pharmaceutical intermediates. There is a great deal of current interest in developing alternative green solvent systems and their application, with the long term goal of implementing these strategies in the chemical industry. There are in principle two approaches to avoid emission of the compounds mentioned above: reactions can be performed solvent-free, or the solvent can be substituted by an environmentally benign replacement. The most prevalent of these new solvent systems are: using water as a solvent, supercritical fluids, perfluorinated solvents, and ionic liquids.

Using green solvents isn't usually as convenient as simply substituting the solvent in an existing process with a greener one. Changing solvent systems can have a drastic effect on a reaction, effecting rates, chemo-, regio-, and stereo-selectivity. The alternative approaches are discussed further.

### *1.1.3.1 Solvent-free Synthesis*

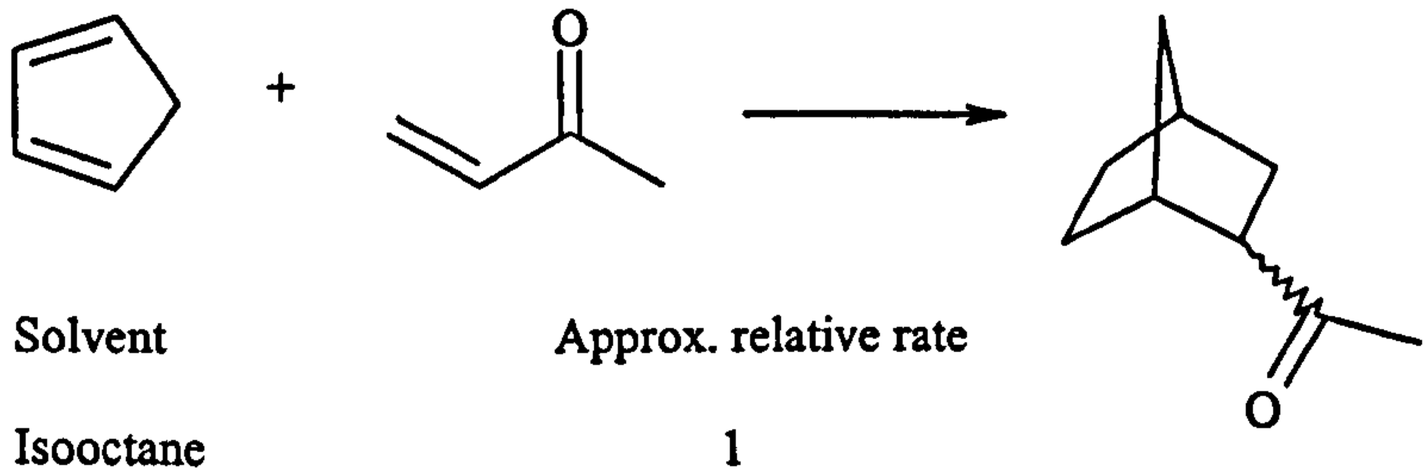
The ideal situation for a chemical process would be to use no solvent. Most high-volume bulk chemicals are actually produced in solvent-free processes, or at least ones in which one of the reactants also acts as a solvent. Typical examples of such large-scale processes include the manufacture of benzene, methanol, MTBE, phenol and polypropylene. There are numerous stoichiometric solid-solid reactions and gas-solid reactions without auxillaries that do not require solvents after the reaction for extraction, chromatography, or recrystallisation, because they yield pure products in the absence of auxillaries. Reactions are shown to proceed with the same, and in many cases even higher, yield and / or higher selectivity, because of the higher concentration of the reactants, with greater rapidity.[14] In some cases auxillaries such as catalysts or solid supports may be required.

The potential for solvent-free synthesis is relatively large, with examples of many well-known reaction types proceeding quite well under this type of regime; these include transesterification, condensation, rearrangement, oxidation and reduction reactions.[15,16] The challenge now being addressed by many researchers is the solvent-free synthesis of more complex fine chemicals that are solids, and that involve the use of some solid reagents with high melting points. Solvent-free reactions can also produce improvements in yield or selectivity. For example, Raston's synthesis of complex pyridines involves sequential solvent-free aldol and Michael addition reactions, which both proceed in higher yield than in conventional solution phase synthesis.[17] Whilst more commercial applications for solvent-free processes will be developed, the use of solvents will continue to be required for the foreseeable future hence there is a need to find more suitable, environmentally benign solvents.

### *1.1.3.2 Using water as a solvent*

Water has many desirable properties as a solvent. It is non-toxic, non-flammable, inexpensive and readily available, it possesses a relatively high dielectric constant ($\varepsilon$ = 78.4), and evaporation into the environment would not cause harmful emission. For some reactions selectivity improvements and / or rate enhancements can be obtained by conducting the reaction in water. For example, Breslow found that the Diels-Alder reaction between cyclopentadiene and butanone was 700 times faster in water than in many organic solvents.[18] This increased rate has been attributed to the hydrophobic effect. A further increase in rate is observed on addition of LiCl.[19] In this case water molecules are

attracted to the polar ions increasing the internal pressure and reducing the volume. This has the effect of further excluding the organic reagents.



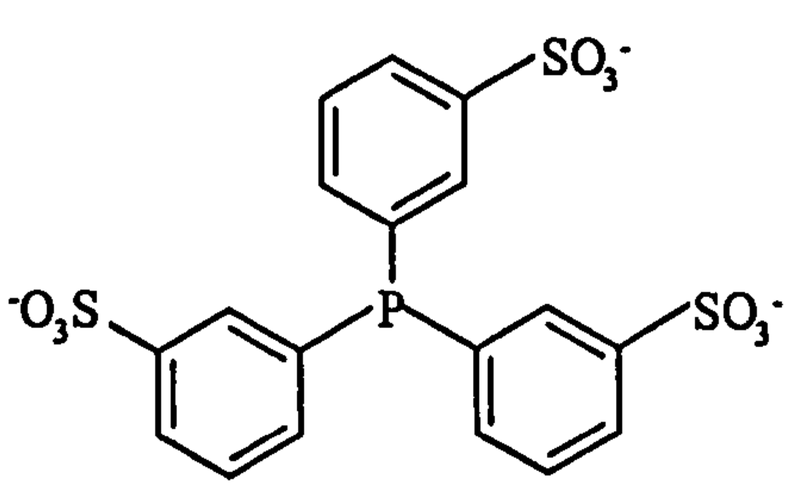
| Solvent | Approx. relative rate |
|---|---|
| Isooctane | 1 |
| Methanol | 12.5 |
| Water | 700 |
| Water / LiCl | 1800 |

**Scheme 1.1 Enhancement of Diels-Alder reaction rates in water**

However, there a number of drawbacks to using water as a solvent for organic reactions. These include, the limited solubility of many organic substrates, a variety of functional groups and conventionally used catalyst-ligand systems are hydrolytically unstable, and water may co-ordinate to the catalytically active metal centre reducing activity. Notwithstanding these drawbacks, a number of important organic reactions give high yields in water including Diels-Alder,[20] epoxidations,[21,22] aldol-style condensations[23] and oxidation reactions.[24] Organic chemistry in water has been reviewed.[25,26,27]

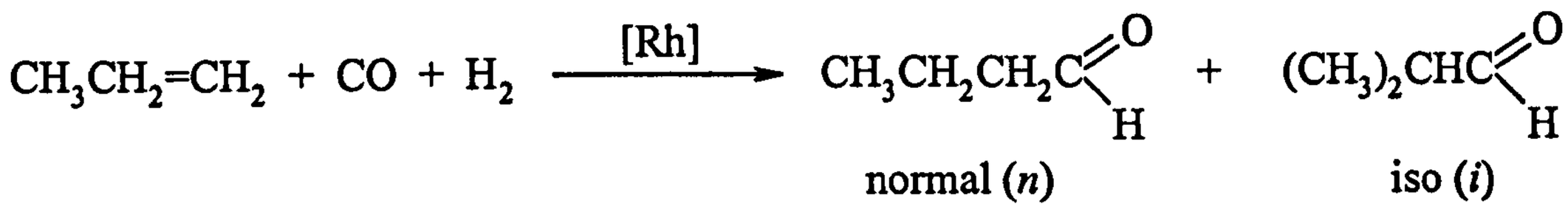
*Aqueous / organic biphase*

One of the most commonly used biphase systems is the aqueous / organic biphase formed by water and hydrocarbons or other low polarity organic liquids. The low water solubility of many organic compounds provides the potential for easy and complete recovery of products. Catalysts can be functionalised by adding polar groups such as $SO_3^-$, $CO_2^-$, $-NR_3^+$, $-PR_3^+$, -OH, $-PO_3^{2-}$ to the ligands attached to the metal centre to increase their solubility in the aqueous phase. For example, one of the most commonly used ligands is triphenylphosphine. To make this soluble in water, the aryl groups are sulphonated. The solubility of the monosulphonated ligand in water is 80 g/l at 20 $^0$C, whilst the trisulphonated triphenylphosphine has a solubility of 1100 g/l.



**(Fig. 1.1)**

One industrial application of this aqueous / organic biphasic system is the hydroformylation of propene (Scheme 1.2), developed by Rhône-Poulenc and commercialised by Ruhrchemie.[28]




**Scheme 1.2 The hydroformylation of propylene**

One of the problems associated with the conventional $HRh(CO)(PPh_3)_3/PPh_3$ catalyst system, is the separation of products from the catalyst by distillation. Using the water soluble $HRh(CO)[P(m\text{-}C_6H_4SO_3Na)_3]_3/[P(m\text{-}C_6H_4SO_3Na)_3]$ catalyst system means that the catalytic reaction occurs in the aqueous phase and the organic phase contains the products. The catalyst can be easily removed from the products by phase separation. In this way, losses of rhodium are kept below $10^{-6}$ mg $kg^{-1}$ of product produced. However, as mentioned above, the low solubility of many organic substrates in water is a limitation. Thus, the aqueous biphase hydroformylation is limited by the solubility of the olefins in the water phase hence it is not efficient for production of $C_n$-aldehydes where $n > 8$.

### *1.1.3.3 Supercritical fluids*

A supercritical fluid (SCF) is a substance which is above its critical pressure, and above its critical temperature. At this point the material is in a single condensed state with properties intermediate between those of liquids and gases that are tuneable simply by changing the temperature and pressure. As the temperature of a liquid rises it becomes less dense and as the pressure of a gas rises it becomes more dense; at the critical point the densities become equivalent. In general, SCFs have densities nearer to liquids and viscosities similar to gases, leading to high diffusion rates which improves heat and mass

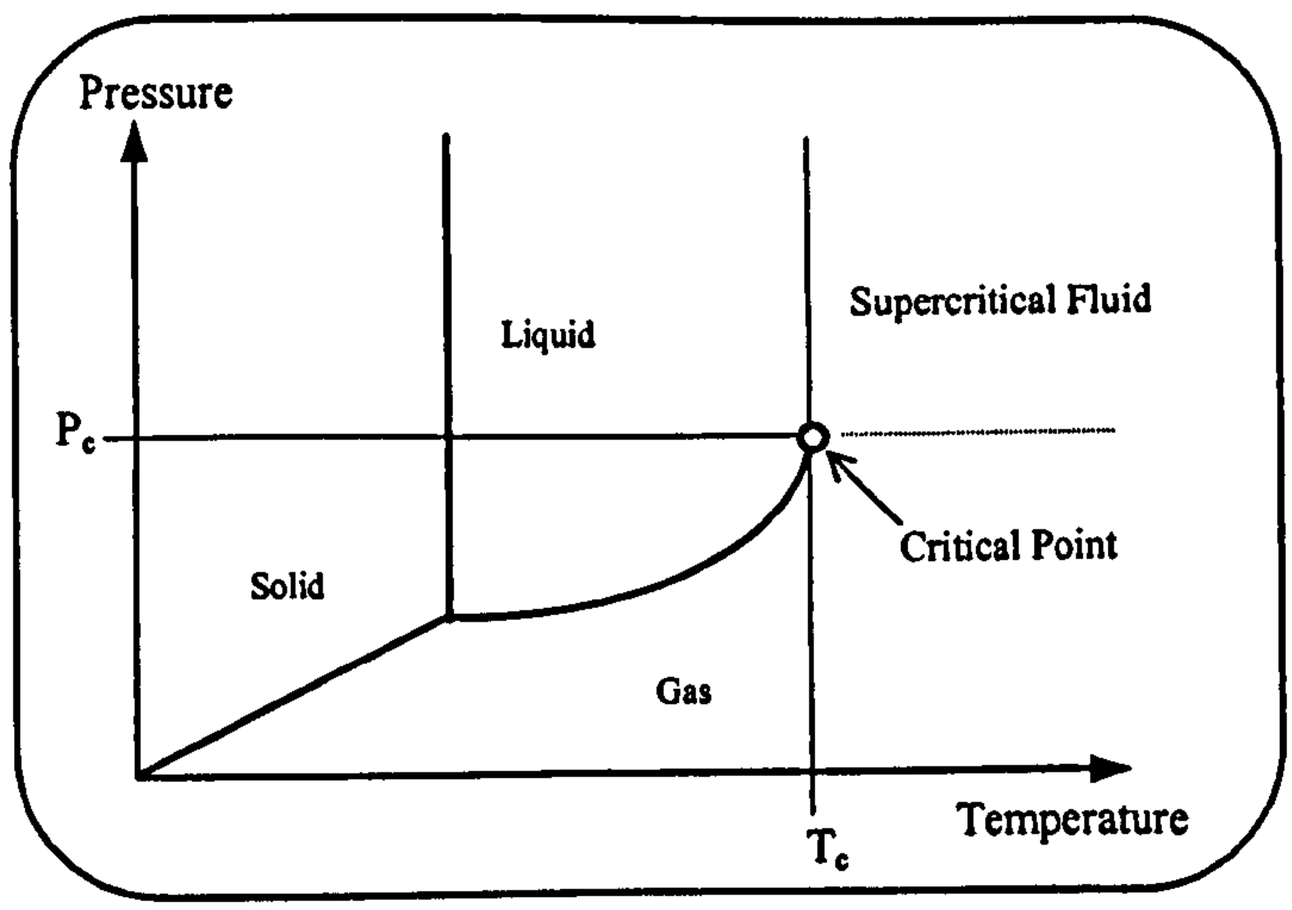



**Figure 1.2 A substance becomes a supercritical fluid above its critical point of temperature and pressure**

transfer. The properties of the fluid can be adjusted by altering the temperature and pressure, as long as they remain above their critical points.[29] At higher liquid densities it can also act as an alternative solvent for extracting products from other reaction media (such as ionic liquids).[30]

Supercritical $CO_2$ is the second most abundant and second least expensive solvent on earth.[31] While $CO_2$ is a gas at ambient conditions, its liquid and supercritical states are easily attained by compression and heat. Many small molecules are soluble in $scCO_2$, including high-vapour pressure solvents such as methanol, acetone, tetrahydrofuran, which increase the polarity and therefore the solubility of polar solutes in $scCO_2$. The high miscibility of gases in SCFs compared to the very limited solubility of gases in liquid solvents means an increase in rate for those reactions that are first order in the concentration of gaseous reagent because the SCF forms a single phase with the gaseous reactants, sometimes avoiding a rate-limiting mass-transfer step and thus enhancing reaction rates.[32] This advantage of enhanced solubilities in SCFs has been known since the 1800s and for decades it has been used in food processing industries to extract compounds such as caffeine and hop oil.[31] The high solubility of fatty acid triglycerides in $scCO_2$ allows the fat content of potato crisps to be reduced by 50 % without, it is claimed, any loss of flavour. Recently high-pressure $CO_2$ technology is being adopted in the dry cleaning industry to extract stains from clothes, thereby replacing perchloroethene as a solvent.[33]

The use of $scCO_2$ can also allow facile separation of reactants, catalysts and products, and it is now being used as a substitute for less environmentally acceptable solvents. For example, naphthalene can be precipitated from a $scCO_2$ solution of naphthalene and phenanthrene by lowering the temperature at a constant pressure between 120 and 230 atmospheres, whilst raising the temperature would precipitate the phenanthrene.[34] This separation technique known as retrograde crystallisation[35] is only possible for mixtures of solids which differ significantly in volatility. Controlled pressure reduction could in principle be used to selectively precipitate a metal-containing catalyst precursor, assuming that these species have significantly lower solubility than the products in the SCF at lower densities.

Continuing work by several research groups has demonstrated that $scCO_2$ can be effectively used as a green reaction medium for organic synthesis, sometimes having profound effects on the outcome of the reaction. Chemistry and catalysis in $scCO_2$[36,37] and $scH_2O$[38,39] has been reviewed. In particular, issues of chemo-, regio-, and stereo-selectivity

are of considerable interest in SCFs. For example, the diastereoselective sulphoxidation of chiral sulphides shows a pressure-dependent increase in diastereoselectivity (up to 95 % *de*) in $scCO_2$ compared to conventional solvents (such as toluene or dichloromethane), where no diastereoselectivity is observed.[40]

However, despite a variety of attractive features, SCFs do not always behave as inert reaction media. While supercritical alkanes are generally unreactive, stoichiometric C-H bond activation reactions of $scCH_4$ and $scC_2H_6$ have been reported.[41] Even $scCO_2$ can be quite reactive; it inserts readily into M-H, M-R, M-OR, or M-$NR_2$ bonds in transition metal complexes[42] and reacts with secondary or primary amines to form carbamate salts.[43] Partially fluorinated methanes and ethanes such as $scCHF_3$ are acidic enough to be deprotonated by strong bases,[44] hence these SCFs are not suitable as media for reactions involving reagents such as LiR, NaH or KOH.

Another notable drawback to the use of SCF's is the sizeable initial costs for specialised equipment that is required. Although the temperature and pressures required for $scCO_2$ are readily obtainable with commercially available apparatus (303 K, 74 bar), the conditions required for other SCF's such as water (647 K, 221 bar) are less practical (and are likely to raise serious safety issues if implemented on an industrial scale).

### *1.1.3.4 Fluorous Solvents*

Fluorous (perfluorinated) solvents such as perfluoroalkanes, perfluoroalkyl ethers and perfluoroalkylamines, are extremely stable, non-polar, inert solvents for organic reactions,[45,46,47] that have unusual properties, such as high density and high stability, low solvent strength, and extremely low solubility in water and organic materials.[48] The fluorous medium is especially suitable for oxidation reactions as the solubility of dioxygen is very high in fluorous solvents[49] and perfluororalkanes are extremely resistant to oxidation. In addition, most oxidation reactions lead to highly polar products, which are inherently less soluble in fluorous solvents, thus resulting in easy separation. Their hydrophobicity and lack of hydrogen bonding capability which renders them relatively insoluble in their hydrocarbon analogues (as all the H atoms are replaced with F atoms in the fluorocarbon) has led to their use as a non-aqueous phase for biphasic catalysis (as detailed in section 1.1.2.2).

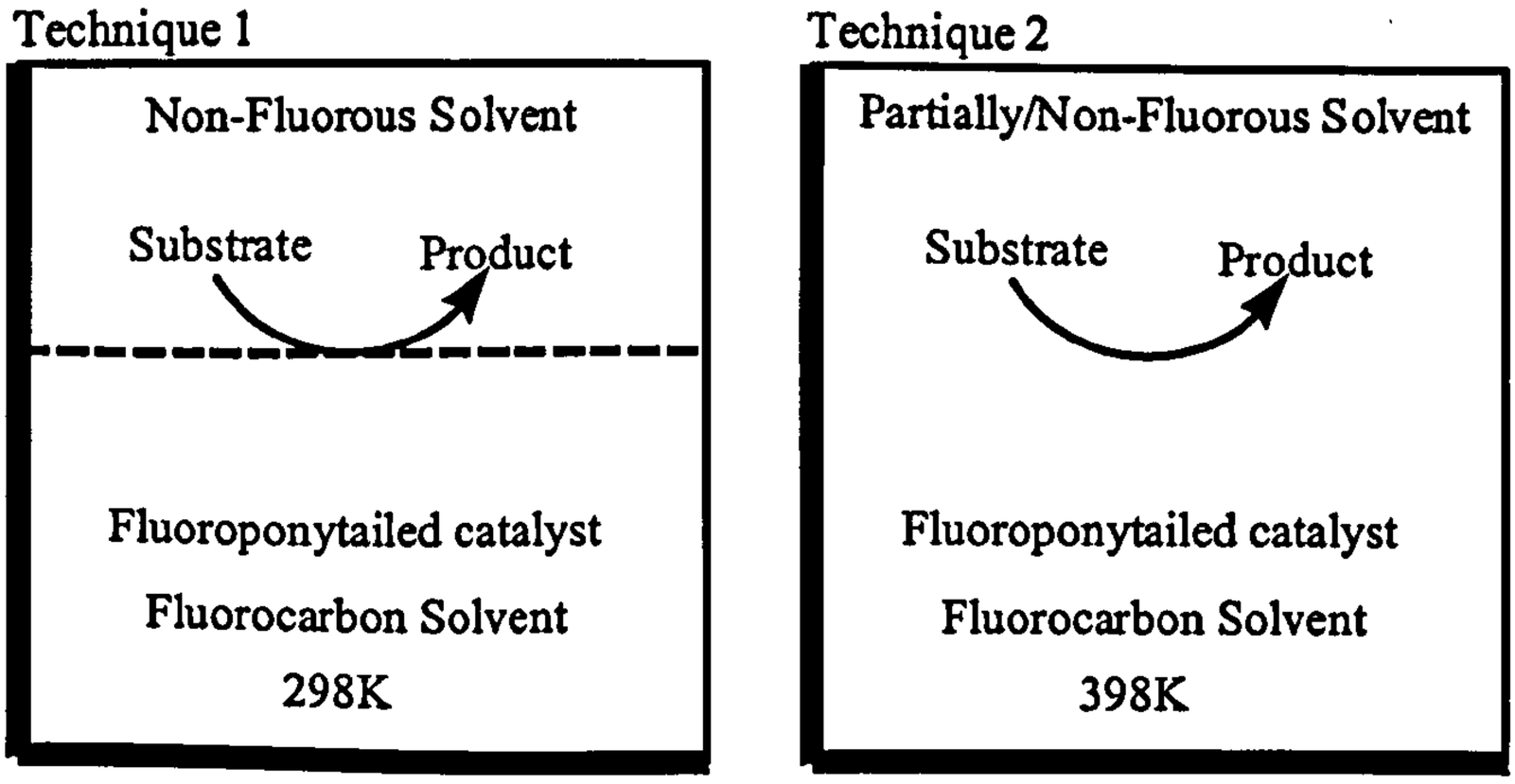
Perfluorocarbon solvents can be expensive and there are some serious environmental concerns. The $C_1$- and $C_2$-fluorocarbons (freons), are greenhouse gases, and contribute to the depletion of the stratospheric ozone layer. A famous example of this is CFC's. There

is some evidence to suggest that the products of breakdown of these perfluorcarbons can be environmentally damaging in the long term.[50] A particular area of concern is the manufacture of these fluorous solvents which currently require extensive use of volatile organic solvents and often employ the use of highly hazardous / toxic and reactive reagents such as molecular fluorine / HF.[51] Other methods include the use of metal-fluorine complexes (such as $CoF_3$) in large quantities at high temperatures.[52,53] The hazardous chemical processes and the safety considerations involved here are certainly less than desirable and may require specialist, expensive equipment.

*Fluorous Biphase*

The 'fluorous biphase system' (FBS) developed by Horvath and Rabai,[54] is based on the limited miscibility of partially or fully fluorinated compounds with nonfluorinated compounds. The catalyst is dissolved in a perfluorocarbon solvent (fluorous phase) while the substrate resides in a second organic or aqueous phase *i.e.* any solvent with limited or no solubility in the fluorous phase. The term fluorous is introduced, as the analogue to the term aqueous, to emphasise the fact that the chemical transformation is primarily controlled by a reagent or a catalyst designed to dissolve in the fluorous phase. The physical properties of fluorinated solvents offer a means of separation of product and catalyst. This occurs by retention of the catalyst in the fluorous phase by derivatisation with highly fluorinated backbones, *i.e.* by appending long–chain fluoroponytails to the ligands of the catalyst to provide a greater than 60 % fluorine content (by weight).[54] Insertion of two or three methylene spacer groups before the fluorous ponytail is often necessary to decrease the strong electron-withdrawing effect of the fluorous ponytails which reduce the ligand binding to the metal.

In the FBS, the chemical transformation may occur either at the interface of the two phases (as in the aqueous / organic biphase system) or in the fluorous phase. In the former case, the reaction is carried out at room temperature in the biphasic mode since hydrocarbon-hydrocarbon interactions and perfluorinated-perfluorinated interactions are stronger than hydrocarbon-perfluoroalkyl interaction, so the phases remain separate. See Figure 1.3, technique 1. In the second instance, two solvents such as trifluoromethylcyclohexane and toluene are used, which become completely miscible at elevated temperatures allowing reactions to proceed homogeneously. This is shown in Figure 1.3, technique 2. On cooling, the phases separate allowing facile catalyst / product separation.




**(Fig. 1.3)**[55]

The potential of the FBS approach has been demonstrated for the rhodium catalysed hydroformylation of olefins, by Horvàth *et al.*[54] The conventional hydroformylation of higher alkenes such as 1-decene is limited by catalyst degradation during distillation of the aldehyde from the catalysts, whilst the use of water soluble catalysts is limited due to the low solubility of the higher alkenes in water. In contrast, Horvàth used toluene and trifluoromethylcyclohexane that are homogeneous at 100 $^{0}$C (*i.e.* technique 2), but separate into two phases at room temperature. The alkene substrate and product aldehyde are soluble in toluene and the catalyst, $[HRh(CO)[\{CF_3(CF_2)_5CH_2CH_2P)_3\}_3]$, is soluble in the fluorous solvent ($CF_3C_6F_{11}$). This system is the first that can be used for the hydroformylation of both low and high molecular weight alkenes and provides facile catalyst / product separation.

Since 1994, FBC has been demonstrated for hydroformylation,[54,56] hydrogenation,[57] hydride reduction,[58] hydroboration,[59] alkene epoxidation,[60] and alkane and alkene functionalisation,[61] while new fluorocarbon-soluble catalysts are being discovered at a rapid pace for these applications and others. However, such 'fluorous catalysts' are not commercially available and their synthesis often requires tedious steps and expensive starting materials. In some cases, leaching is problematic,[62,63] or the strong electron-withdrawing properties of the ligand alter the activity of the catalytically active centre compared to the non-fluorinated catalyst.[64]

### *1.1.3.5 Ionic Liquids*

Ionic liquids are liquids that are comprised entirely of ions. Thus, molten sodium chloride is an ionic liquid, and a solution of NaCl in water (a molecular solvent), is an ionic solution. All ionic liquids have a very wide liquidus range *i.e.* the temperature range between the melting point and boiling point. No molecular solvent, except perhaps some

liquid polymers, can match the liquidus range of ionic liquids or molten salts. In this thesis, ionic liquids will be divided into "molten salts", those melting significantly above room temperature, and room temperature ionic liquids (RTILs) as those melting near or below room temperature. This division, though somewhat arbitrary, has become widely accepted.

## 1.2 MOLTEN SALTS

The melting points of some group 1 chlorides are given below (Table 1.3). The high temperature and often corrosive nature of these liquids rules them out as solvents for the majority of conventional organic chemistry and catalytic chemistry due to decomposition of the reactants.

**Table 1.3 Melting points of group 1 and selected tetrachloroaluminate (III) salts[65]**

| System | Mole % | Melting Point/ °C |
|---|---|---|
| LiCl | 100 | 610 |
| NaCl | 100 | 803 |
| KCl | 100 | 772 |
| LiCl – CsCl | 60 – 40 | 355 |
| $AlCl_3$ | 100 | 192 |
| LiCl – $AlCl_3$ | 50 – 50 | 144 |
| NaCl - $AlCl_3$ | 50 – 50 | 151 |
| KCl – $AlCl_3$ | 50 – 50 | 256 |

Molten salts are potentially useful as electrolytes in batteries, photoelectrochemical cells, and electroplating. Even though the LiCl / KCl eutectic mixture has a low melting temperature for an inorganic salt (355 $^0$C), the temperature causes materials problems inside the battery, and incompatibilities with nearby devices. In 1963, in efforts to find a replacement for the LiCl / KCl molten salt electrolyte used in thermal batteries, King *et al.* found that compositions of mixed ternary systems melt at significantly lower temperatures than either binary component as there are more types of ionic species present.[66] Varying the size of the ions introduces further disorder into the structure of these salts, reducing the lattice energy of the crystalline form of the salt, and hence lowering the melting point.[67] This is illustrated in the bottom part of Table 1.3, where increasing the anion size by adding $AlCl_3$ (which causes conversion of $Cl^-$ to $AlCl_4^-$), causes a decrease in the melting

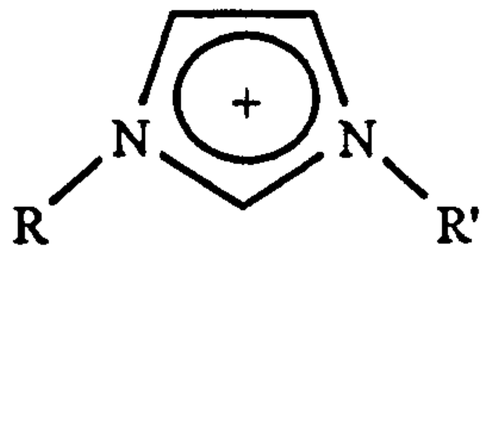
point of these salts. In fact the NaCl / $AlCl_3$ eutectic has a melting point of 151 $^0$C. Although the melting points of these tetrachloroaluminate salts are still in the liquidus range of high boiling organic solvents, further depression of the melting point can be achieved by replacing inorganic cations with much larger, unsymmetrical organic cations thereby giving rise to room temperature ionic liquids.

## 1.3 ROOM TEMPERATURE IONIC LIQUIDS (RTILs)

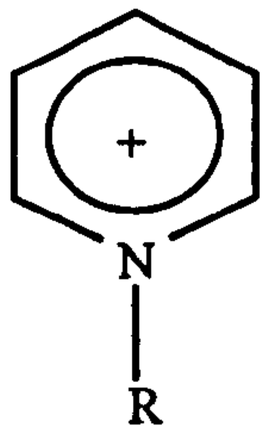
The first ionic liquids with chloroaluminate ions were developed in 1948 by Hurley and Wier (as solutions) for electroplating aluminium.[68] However, further interest didn't develop until the discovery of binary ionic liquids made from mixtures of $AlCl_3$ and *N*-alkylpyridinium (*N*-Rpy)[69] or 1-alkyl-3-methylimidazolium (RMIM) chlorides[70] which were investigated for their use in electrodeposition of metals and thermal batteries. The pyridinium derivatives were too easily reduced to be useful for this application, but the imidazolium derivatives, with their large electrochemical potential window, were good candidates for battery applications.[70]

The first reports of the use of ionic liquids as solvents for homogeneous transition metal catalysts were published in 1990 independently by Chauvin *et al.* and by Wilkes *et al.* Chauvin's group dissolved nickel catalysts in weakly acidic chloroaluminate melts and investigated the resulting solutions for the dimerisation of propene,[71] and Wilkes *et al.* studied ethylene polymerisation with Ziegler-Natta catalysis in weakly acidic chloroaluminate melts.[72] Since then, ionic liquids have expanded to encompass a whole range of cation / anion combinations, the most important types of which are shown in Figure 1.4.

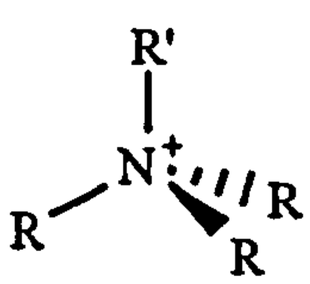
**Figure 1.4 Cations and anions in common RTILs**



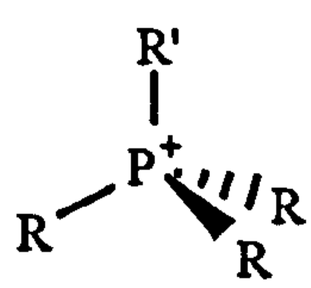

1,3-dialkylimidazolium Ion




Pyridinium Ion




Ammonium Ion




Phosphonium Ion

Alkyl chains are usually: ethyl, butyl, hexyl, octyl, decyl.

Anions include: $Br^-$, $Cl^-$, $I^-$, $[NO_3]^-$, $[PF_6]^-$, $[BF_4]^-$, $[CH_3CO_2]^-$, $[CF_3CO_2]^-$, $[CF_3SO_3]^-$, $[(CF_3SO_2)_2N]^-$, $[Al_2Cl_7]^-$, $[AlCl_4]^-$.

Ionic liquids have several advantages over conventional solvents, they are non-flammable; thermally stable up to 300 $^{0}$C offering a wide operating temperature range; have no measurable vapour pressure and hence emit no VOCs, making them particularly attractive for green synthesis. The high thermal stability is also an advantage in terms of product isolation as distillation from the reaction mixture becomes a possible option. Ionic liquids are also good solvents for a range of organic and inorganic materials. Being highly polar, they have been reported to dissolve transition metal catalysts to a higher degree than conventional solvents in homogeneous catalysis,[73] as well as a wide range of organic, inorganic, and polymeric compounds,[74] meaning much lower volumes of solvent and hence process intensification. Smaller reactor volumes imply less energy for heating to reaction temperature or cooling, and therefore saving energy.[75] Their immiscibility with a wide range of organic solvents allows organic / ionic liquid biphase, as well as aqueous / ionic liquid biphase to provide facile catalyst and product separation and recycling (see sections 1.5.2 and 1.5.3). The physical and chemical properties of ionic liquids can be varied over a wide range by the selection of suitable cations and anions, providing a means to optimise the solvent properties of an ionic liquid for a specific application. For this reason, ionic liquids are often referred to as 'designer solvents'.

### 1.3.1 Physicochemical Properties

The typical RTILs are *N*-alkylpyridinium or *N,N'*-dialkyimidazolium salts, the properties of which can be controlled to a large degree by variation in the substituents on the cation and the nature of the anion providing a potentially vast number of different solvents. In the following section, a few selected examples are used to illustrate the relationships between the structural features of an ionic liquid and its chemical and physical properties.

#### *1.3.1.1 Melting points / Glass transition points*

The melting point is the temperature (at a certain pressure) at which the solid and the liquid state of a compound are in equilibrium. Cooling of melts of such compounds to a temperature below their melting points results in the formation of a solid. For crystalline solids, the compounds adapt a highly ordered state with both short-range and long-range order.[76] Other substances are not able to attain such order, and thus are not able to crystallise. Instead of forming a crystalline solid, these substances form glasses at

temperatures below their glass transition point. The reason for the inability to form a crystal can in some cases be explained with the increase in viscosity upon cooling of a melt: if the viscosity is too high, the molecules cannot achieve their optimal position necessary for crystallisation, and thus supercool into a glass. The low melting / glass transition points of RTILs is due to the presence of either bulky cations or anions, or both, so that ions are not able to form a closely packed lattice structure.[77] Besides, the bulkiness of the ions, the low melting / glass transition points of ionic liquids are due to the delocalised positive charge and the low symmetry of the cation, which reduce the lattice energy of the ordered, *i.e.* crystalline form. Small variations on the nature of the alkyl group attached to the imidazolium moiety lead to huge differences in melting / glass transition points within a series, as shown with RMIM[$PF_6$] and RMIM[$BF_4$] in Figure 1.5 below.

Figure 1.5 also shows that [$C_2$-$C_9$MIM][$BF_4$] possess glass transition points, whereas [$C_{10}$-$C_{17}$MIM][$BF_4$] possess melting points. With increasing alkyl chain length ([$C_{10}$-$C_{18}$MIM][$BF_4$]), the melting point increases, which can be attributed to increased van der Waals forces between the alkyl chains.

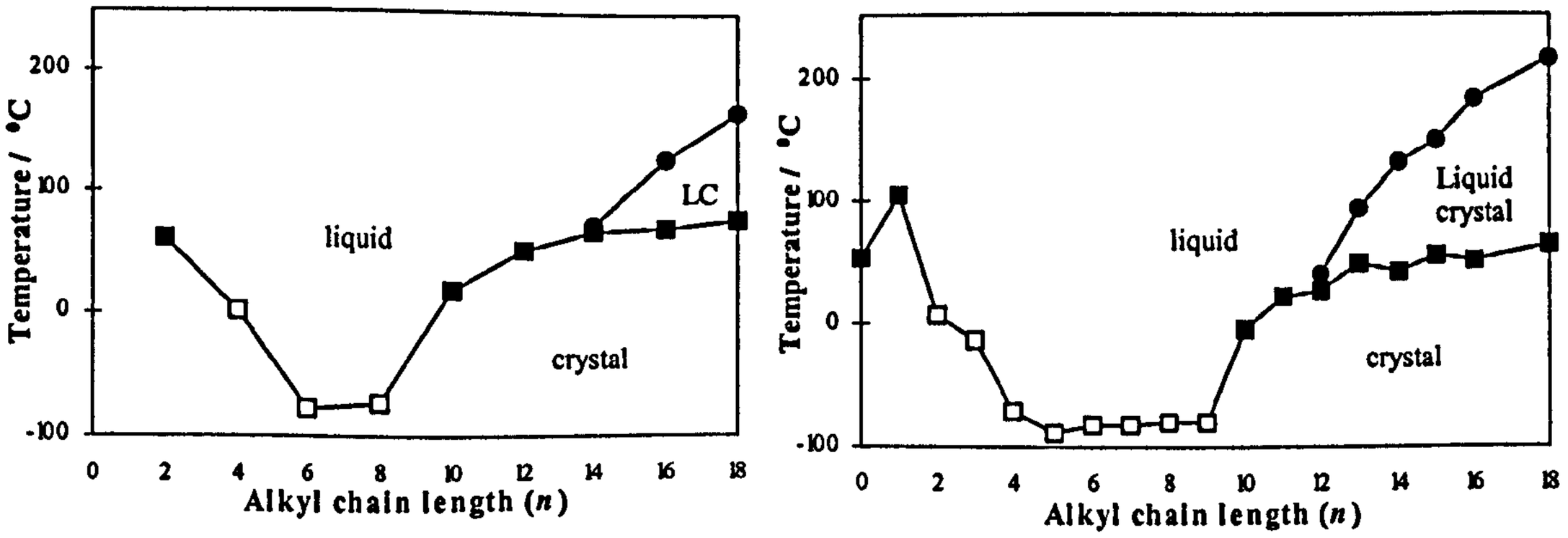
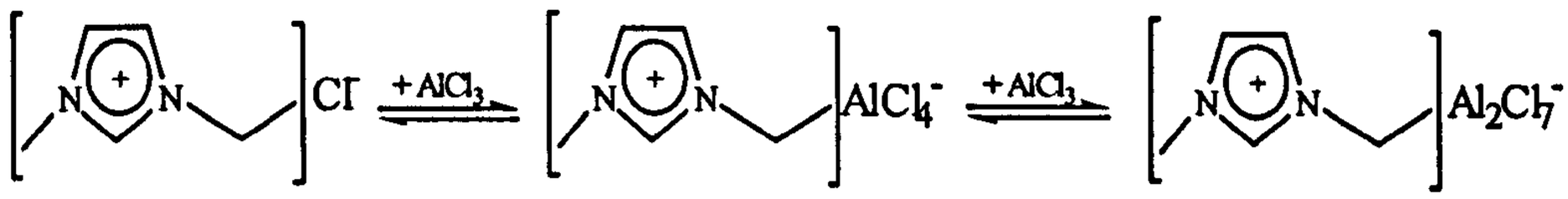



**Figure 1.5 Melting point phase diagram for RMIM[$PF_6$] (left) and RMIM[$BF_4$] (right) ionic liquids as a function of alkyl chain length *n* showing the melting transitions from crystalline (closed square) and glassy (open square) materials and the clearing transition (closed circle) of the liquid.[2]**

The influence of the anion on properties of RTILs can be illustrated by some EMIM salts *e.g.* EMIM[Cl] melts at 87 $^0$C,[71] EMIM[$AlCl_4$] at 7 $^0$C[66] and EMIM[OTf] at –9 $^0$C.[78] The anion also effects chemical properties, *e.g.* salts based on $AlCl_3$ may be prepared which are Lewis-acidic or Lewis-basic depending on the mole fraction of $AlCl_3$. The effect of the mole fraction of $AlCl_3$ on the properties of EMIM[Cl]-$AlCl_3$ is shown in Figure 1.6. When the molar proportions are equal, the system is neutral with a melting point of approximately 6 $^0$C. The lowest melting point (-96 $^0$C) is achieved when the molar ratio is 1: 1.9, EMIM[Cl]-$AlCl_3$.[78]

**Figure 1.6 Controlling the acidity of [EMIM]Cl-$AlCl_3$ by varying the ratio of halide to Lewis acid**




| **Acidity of melt:** | **Basic** | **Neutral** | **Acidic** |
|---|---|---|---|
| Co-ordination ability of anion: | Strong | Weak | Non co-ordinating |
| Mole fraction of $AlCl_3$ | < 0.5 | 0.5 | > 0.5 |
| Melting point / $^0$C | -70 | 6 | -96 |

As might be expected, chloroaluminate ionic liquids promote reactions that are conventionally promoted by $AlCl_3$, without the disadvantage of low solubility of $AlCl_3$ in many solvents.

### *1.3.1.1 Viscosity*

The viscosity of a liquid arises from the internal friction of the liquid, and it manifests itself externally as the resistance of the liquid to flow. As a group, ionic liquids are more viscous than most common molecular solvents. Ionic liquid viscosities at room temperature range from a low of around 10 cP to values in excess of 500 cP; compared to those of water, ethylene glycol, and glycerol at room temperature of 0.890, 16.1, and 934 cP, respectively.[79] The viscosity of ionic liquids is influenced by their tendency to hydrogen bond and by the strength of their van der Waals interactions. The increase in viscosity of more than a factor of ten in basic chloroaluminate melts ($(x)AlCl_3 < 0.5$), is a result of formation of hydrogen bonds between the hydrogen atoms of the imidazolium cation and the basic chloride ion.[80,81] In acidic mixtures, the negative charge is much better distributed over the anions $AlCl_4^-$ and $Al_2Cl_7^-$, leading to weaker hydrogen bonds and a much lower viscosity.

The interplay between van der Waals interactions and hydrogen bonding is highlighted in Table 1.4. The viscosity increases from BMIM[OTf] to BMIM[$C_4F_9SO_3$] and BMIM[$CF_3CO_2$] to BMIM[$C_3F_7CO_2$] due to an increase in van der Waals interactions between the alkyl chain of the cation and fluorinated anion,[82] which outweighs the decrease in H-bonding and better charge delocalisation.

**Table 1.4 Dynamic viscosites of various BMIM salts at 20 $^0$C.[78]**

| Ionic Liquid | Viscosity / cP |
|---|---|
| BMIM[$NTf_2$] | 52 |
| BMIM[$CF_3COO$] | 73 |
| BMIM[OTf] | 90 |
| BMIM[n-$C_3F_7COO$] | 182 |
| BMIM[n-$C_4F_9SO_3$] | 373 |

On the other hand, BMIM[$NTf_2$] has a lower viscosity than BMIM[OTf] despite stronger van der Waals interactions for ionic liquids with the $[NTf_2]^-$ ion. (See Table 1.4) In this case, the almost complete suppression of hydrogen bonding more than compensates for the increased van der Waals interactions.[82] BMIM[$CF_3CO_2$] and BMIM[$NTf_2$] have the lowest viscosities as they combine minimal van der Waals interactions (anion weight) with moderate basicity for the former, and minimal basicity with moderate van der Waals interactions (anion weight) for the latter.

The structure of the cation also influences the viscosity of the ionic liquid. The lowest viscosities are usually obtained for melts with the EMIM ion, in which a side chain with sufficient mobility is combined with a low molar mass. For example, at 20 $^0$C, EMIM[Cl]-$AlCl_3$ has a viscosity of 1.4 cP, whereas BMIM[Cl]-$AlCl_3$ has a slightly higher viscosity of 1.50 cP. Longer or fluorinated alkyl chains result in higher viscosities because of stronger van der Waals interactions.[82] The viscosity of ionic liquids can be lowered, drastically in some cases, by only slight increases in temperature[83] or by the addition of small amounts of organic cosolvents.[84,85]

### *1.3.1.3 Density*

The density of RMIM-based ionic liquids is, in general, higher than that of water, *i.e.* if an ionic liquid is immiscible with water, it will form the heavier, lower phase. Within a homologous series, *e.g.* [$C_2$-$C_{10}$MIM][$BF_4$], the ionic liquids with a shorter alkyl chain have higher density than the ones with longer chains. This can be explained by the ability of the shorter alkyl chain analogues to close-pack and therefore achieve a higher density, whereas the bulkiness of the longer chain derivatives impedes close-packing.

### *1.3.1.4 Miscibility*

The miscibility with water is strongly affected by the composition of the ionic liquid, in particular by the nature of the anion. Hydrophobic ionic liquids are usually based on fluorinated anions, most commonly $[PF_6]^-$ and $[BF_4]^-$. The hydrophobicity of a homologous series, for example $[C_nMIM][BF_4]$, increases with increasing alkyl chain length, so that $EMIM[BF_4]$ and $BMIM[BF_4]$ are fully miscible at room temperature, but higher derivatives are not. On the other hand, all $[C_nMIM][PF_6]$ ionic liquids are hydrophobic and form biphasic systems with water.[86,87]

Figure 1.7 shows the amount of water that is soluble in $[BF_4]^-$ and $[PF_6]^-$ ionic liquids, all of which (shown) form biphasic systems with an excess of water.[88] The amount of water soluble in the $[PF_6]^-$ series is notably smaller than in the $[BF_4]^-$ series.

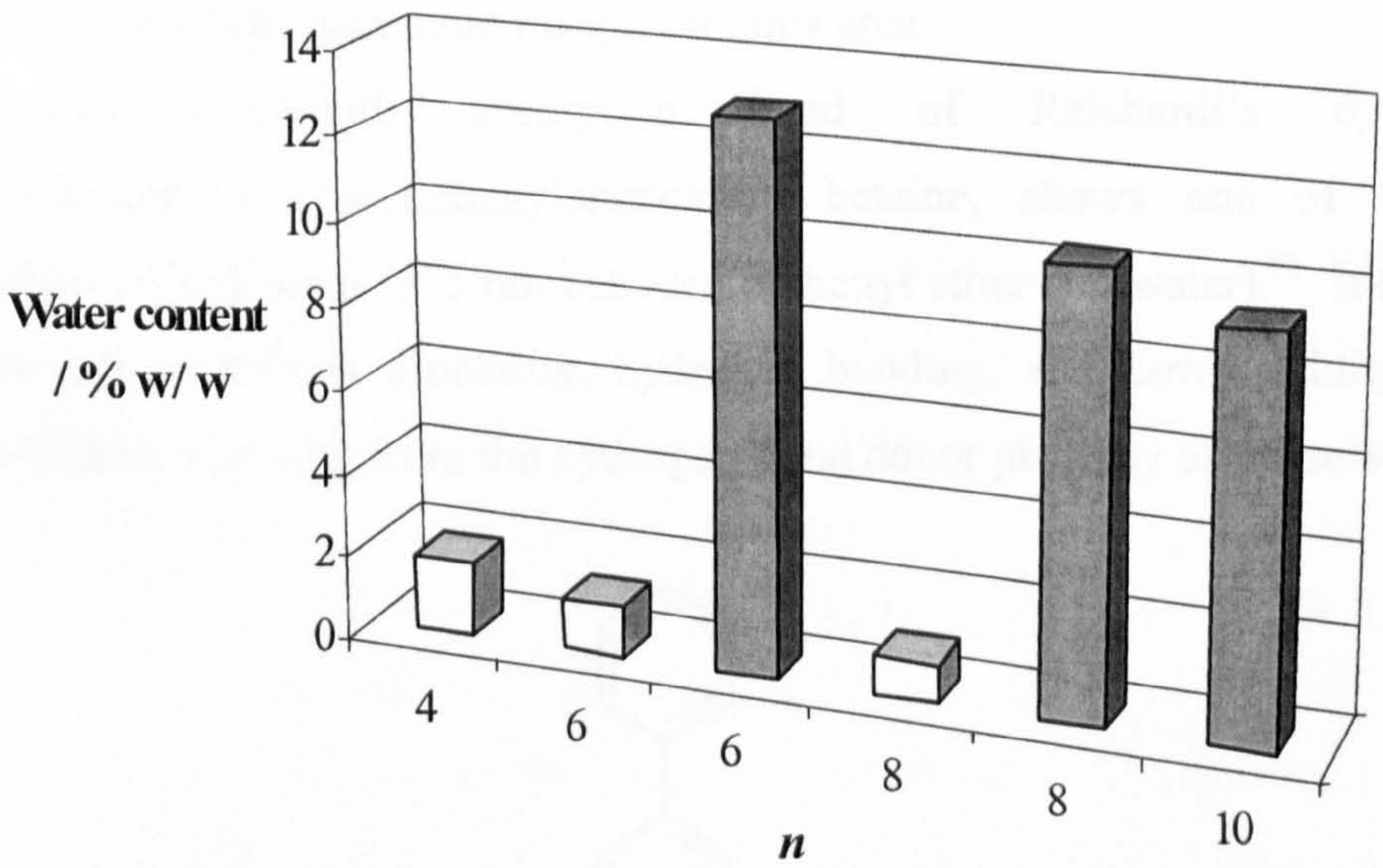



**Figure 1.7 Solubility of water in $[C_4\text{-}C_8MIM][PF_6]$ (white) and $[C_6\text{-}C_{10}MIM][BF_4]$ (grey).[88]**

The amount of water soluble in the ionic liquid decreases with the increasing length of the alkyl chain, *i.e.* with increasing lipophilicity.

Besides the $[PF_6]^-$ and $[BF_4]^-$ based ionic liquids, other anions such as [OTf] with $[C_nMIM]$ ($n > 4$)[89] or $[NTf_2]^-$,[90] also give water-immiscible ionic liquids. Water-immiscible ionic liquids are attractive since their preparation is much easier than that of their water miscible counterparts, because the work-up can include an aqueous extraction (see section 1.3.2.1). Similarly, aqueous extraction of a hydrophilic product at the end of a reaction is feasible. However, it should be noted, that even ionic liquids that form biphasic systems with water do dissolve water to some extent, and are even hygroscopic.

### *1.3.1.5 Polarity*

Until recently, little quantitative information existed regarding the nature of interactions between ionic liquids and different types of solute. Such information is obviously of great importance if we are to understand why certain types of reaction occur particularly favourably in these media. One of the major differences between ionic liquids and a typical organic solvent is that the former is a binary mixture of two different species, and thus is likely to engage in a much wider range of solute-solvent interactions. Since polarity and polarisability are the simplest indicators of solvent strength, organic solvents are frequently classified on their ability to dissolve and stabilise dipolar or charged species. The most common measure of polarity is that of dielectric constant. However, direct measurement, which requires a non-conducting medium, is not available for ionic liquids. Therefore a number of research groups have carried out investigations using solvatochromic probes to gain more insight into this area.

The longest-wavelength absorption band of Reichardt's dye (2,4,6-triphenylpyridinium-*N*-4-(2,6-diphenylphenoxide) betaine, shows one of the largest solvatochromic shifts known (375 nm between diphenyl ether and water).[91] It can register effects arising from solvent dipolarity, hydrogen bonding, and Lewis acidity, with the greatest contribution coming from the hydrogen bond donor property of the solvent.[92]

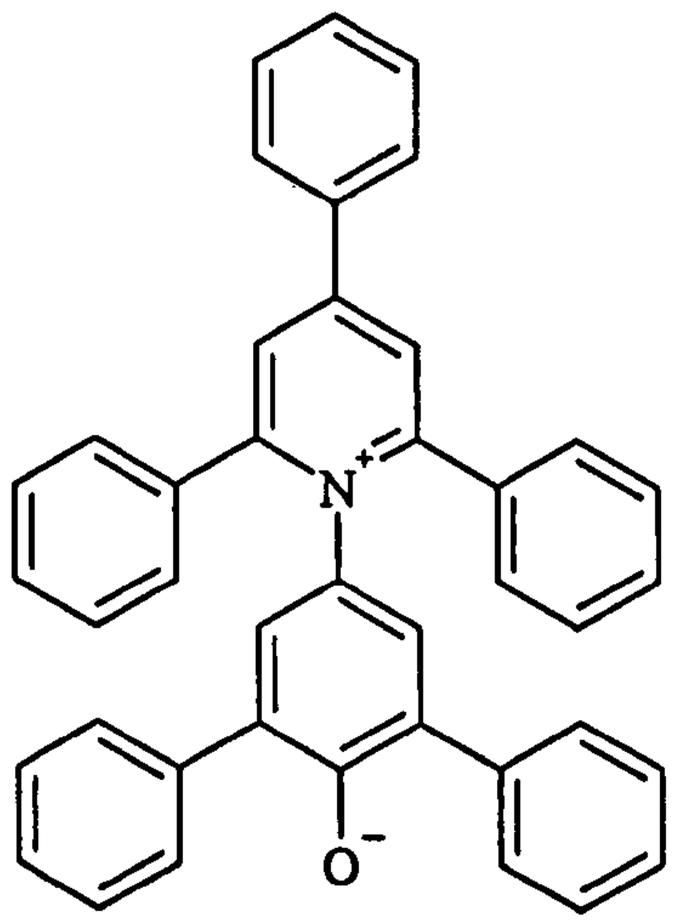



**Figure 1.8 Reichardt's Dye**

On Reichardt's normalised polarity scale, $E_T^N$, ranging from 0 for tetramethylsilane to 1 for water, ionic liquids have polarities around 0.6. Table 1.5 shows polarity measurements for selected solvents.[93]

**Table 1.5 Solvent polarity measurements ($E_T^N$) based on Reichardt's dye for selected ionic liquids. Adapted from ref. 93 and 94**

| Solvent | $E_T^N$ |
|---|---|
| Water | 1.000 |
| $EtNH_3[NO_3]$ | 0.954 |
| $BMIM[BF_4]$ | 0.670 |
| BMIM[OTf] | 0.656 |
| $BMIM[PF_6]$ | 0.669 |
| Ethanol | 0.654 |
| $BMIM[NTf_2]$ | 0.644 |
| $EtNH_3Cl$ | 0.636 |
| $OMIM[PF_6]$ | 0.633 |
| $Et_4NCl$ | 0.454 |
| Diethyl ether | 0.117 |
| Cyclohexane | 0.009 |

Carmichael *et al.* used the solvatochromic dye Nile Red in a UV-study to probe the polarity of ionic liquids such as $[C_{4\text{-}8}][NO_3]$, $[C_{4\text{-}8}][PF_6]$ and $[C_{4\text{-}10}][BF_4]$, and found that they ranged between *N,N*-dimethylformamide and water, thus exhibiting similar polarities to ethanol, methanol, dimethyl sulphoxide and 2-aminoethanol.[95] Use of the fluorescent probes 4-aminophthalimide and 4-(*N,N*-dimethylamino)phthalimide supported the measurements with Reichardt's dye, indicating that the polarity of 1-alkyl-3-methylimidazolium based ILs was similar to that of short chain alcohols, and that the polarity decreased somewhat as the alkyl chain increased (due to a more hydrophobic environment).[96]

However, polarity encompasses many different interactions, for example, hydrogen bonding, π-interactions, van der Waals forces. Therefore an alternative solvatochromic system has been used to determine the hydrogen acceptor ability or nucleophilicity of RTILs *i.e.* the role of the anion in solvation. The square planar salt [Cu(acac)(tmen)][X] (Figure 1.9), X = $[BPh_4]^-$ or $[ClO_4]^-$, can be used to estimate the donor numbers of anions in solution.[97] The solvatochromism arises from changes in the splitting of the d-orbitals as

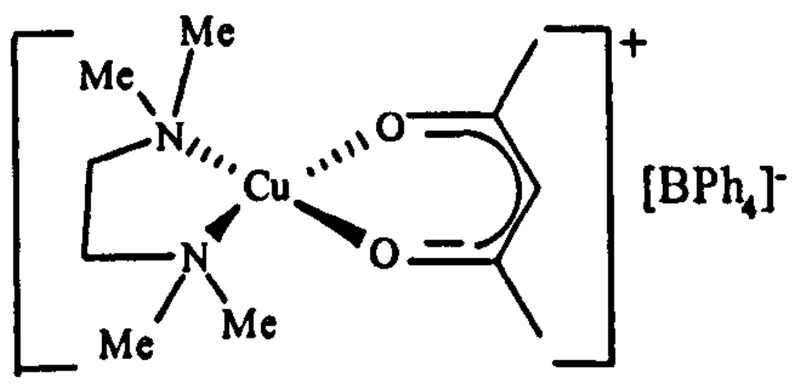


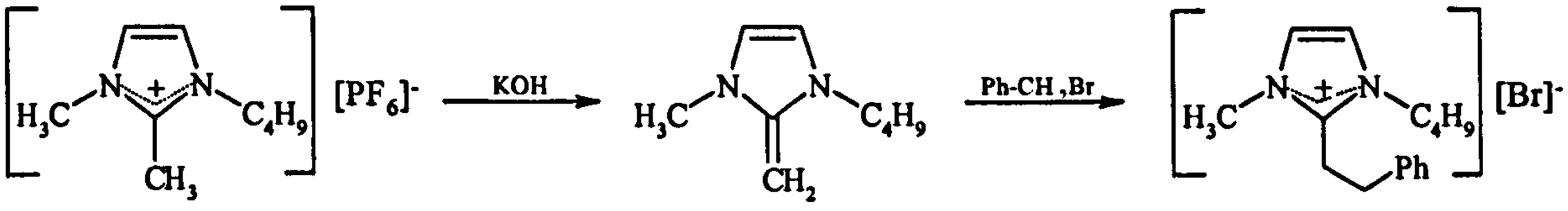

**Fig. 1.9**

the $Cu^{2+}$ salt becomes five- or six-coordinate. Using this probe, the position of $\lambda_{max}$ has been recorded for a range of ILs based on the $[OTf]^-$, $[PF_6]^-$, $[BF_4]^-$ and $[NTf_2]^-$ anions, and the results indicate that the strength of coordination at the Cu(II) centre is entirely anion-dependent.[98] The order of nucleophilicity was determined as $[PF_6]^- < [NTf_2]^- < [BF_4]^- < [OTf]^-$.[94] The low nucleophilicity of the $[PF_6]^-$ ILs is not unexpected, given the symmetrical shape and low charge density of this anion, and these may be thought of as effectively non-coordinating solvents. The $[NTf_2]^-$ ILs appear to be more strongly coordinating, a result that is supported by a crystal structure of an imidazolium $[NTf_2]^-$ ionic liquid,[99] which suggested that the negative charge is localised across the *S-N-S* moiety. The $[OTf]^-$ anion has the greatest nucleophilicity as it coordinates to the Cu(II) centre much more strongly than the other two anions. Furthermore, the colour of [Cu(acac)(tmen)][$BPh_4$] in BMIM[OTf] faded rapidly unless an excess of tmen was present; this behaviour has been noted previously for more strongly donating solvents, and has been ascribed to ligand displacement.[100] The varying co-ordination strengths of the IL anions to the copper centre is of particular interest as Chapter 4 is concerned with asymmetric synthesis using a cationic copper catalyst whose efficiency is affected by the nature of the counterion.

### *1.3.1.6 Interactions of cations and anions*

There are two main differences between analogues of the *N*-Rpy and RMIM series: the symmetry of the cation and the acidity of the ring-protons. The *N*-Rpy cation has higher symmetry ($C_{2v}$) than the RMIM cation ($C_S$). The higher symmetry is at least partly responsible for the fact that the *N*-Rpy derivatives melt considerably higher than the imidazolium derivatives,[74] *e.g.* the melting point of *N*-$^n$Bupy[$BF_4$] is 15.3 $^0$C,[101] whereas the analogous BMIM[$BF_4$] melts at –71$^0$C (glass transition).[102] Secondly, *N*-Rpy-based ionic liquids do not possess any acidic protons, whereas RMIM-based ionic liquids have an acidic proton on C-2 which may be removed by a base to give (stable) carbenes. The ability to form carbenes (1-alkyl-3-methylimidazoline-2-ylidenes), even in the presence of weak bases,[103] is an important feature of imidazolium-based ionic liquids, since carbenes can act as ligands for transition metal catalysts, this is discussed further in Chapter 3, section 3.1. In order to exclude participation of the 1-alkyl-3-methylimidazoline-2-ylidene in a catalytic cycle, the C-2 position of the 1-alkyl-3-methylimidazolium-based ionic liquid may be 'blocked' by methylation. The resulting 1-alkyl-2,3-dimethylimidazolium is still acidic to some extent (for example, see Scheme 1.3), but is not able to form a carbene and

thus participate as a ligand in the catalytic cycle.[104] The reaction in Scheme 1.3 also shows that the protons of the C-2 methyl are more acidic than the ones on C-4 and C-5 of the imidazolium moiety.




**Scheme 1.3 Proton abstraction from C-2 methylated ionic liquids**

In addition to the ability of the RMIM cation to form carbenes, and thus co-ordinate to a metal catalyst, anions such as halides are also able to act as ligands. Thus ionic liquids possessing different anions can affect the yields of reactions. For example, Xu *et al.* showed that in Heck reactions, stable, soluble 1-butyl-3-methylimidazol-2-ylidene palladium bromide complexes were obtained in BMIM[Br] (Figure 1.10), whereas in BMIM[$BF_4$], no stabilising effect of the ionic liquid was observed, but palladium black slowly precipitated.[105] See Chapter 3, section 3.1 for a more detailed discussion on the role of ionic liquids for the Heck reaction.

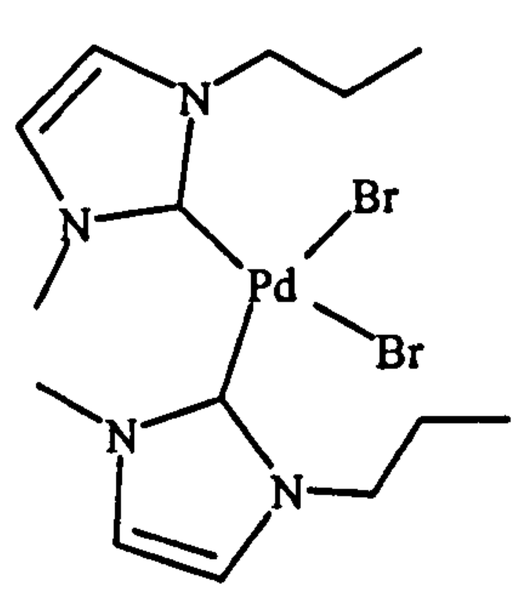



**Figure 1.10 Palladium carbene complex formed in BMIM[Br][105]**

### *1.3.1.7 Conductivity*

The conductivity of an electrolyte is a measure of the available charge carriers and their mobility. The conductivity of some commonly used ILs are given below.

**Table 1.6 Conductivity data for selected imidazolium-based ILs**

| Ionic Liquid | Conductivity / mS $cm^{-1}$ | Temperature / K | Reference |
|---|---|---|---|
| BMIM[Cl]-($x$)$AlCl_3$ ($x = 0.67$) | 9.2 | 298 | 70 |
| MMIM[$NTf_2$] | 8.4 | 293 | 82 |
| EMIM[$BF_4$] | 12 | 295 | 106 |
| BMIM[OTf] | 3.7 | 293 | 82 |
| BMIM[$NTf_2$] | 3.9 | 293 | 82 |
| BMIM[$PF_6$] | 1.8 | 295 | 107 |
| BMMIM[$BF_4$] | 0.23 | 295 | 106 |

The overall trend in conductivity with respect to cation type follows the order: imidazolium ≥ sulphonium > ammonium ≥ pyridinium. Interestingly, the correlation between the anion type or size and the ionic liquid conductivity is very limited. Other than the higher conductivities observed for ionic liquids with the $[BF_4]^-$ anion, there appears to be no clear relationship between anion size and conductivity. Ionic liquids with large anions such as $[NTf_2]^-$ for example, often exhibit higher conductivities than those with smaller anions.

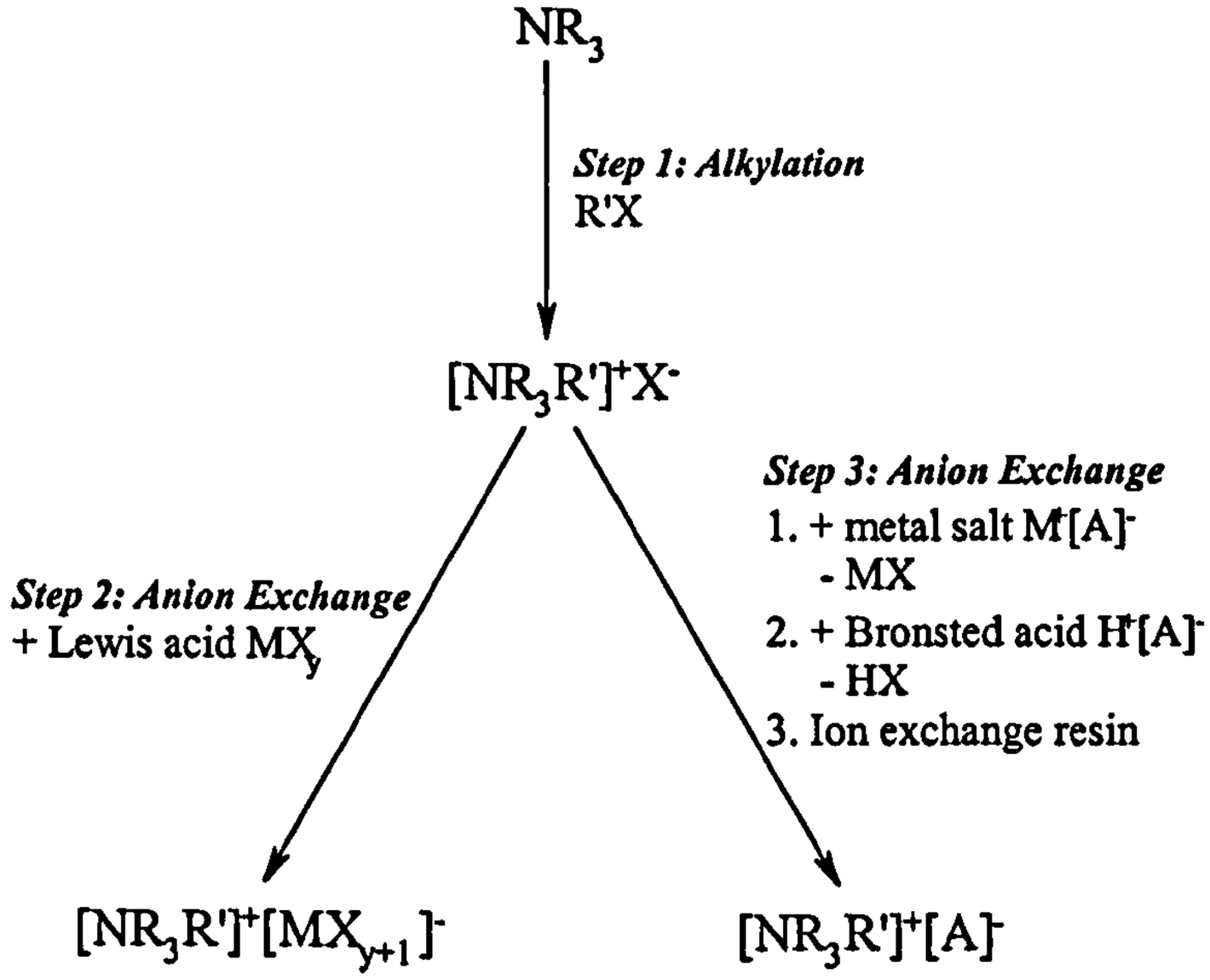
Superficially, one would expect ionic liquids to possess very high conductivities because they are composed entirely of ions. However, this is not the case; ionic liquids possess reasonably good conductivities, but they are significantly less conductive than concentrated aqueous electrolytes. The smaller than expected conductivity of ionic liquids can be attributed to the reduction of available charge carriers due to ion pairing and / or aggregation, and to the reduced ion mobility resulting from the large ions present in many ionic liquids.

## 1.3.2 Preparation of Ionic Liquids

### *1.3.2.1 Synthesis*

The synthesis of ionic liquids can generally be split into two parts: formation of a salt of the desired cation, and anion exchange where necessary to form the desired product.

**Scheme 1.4 Typical synthesis paths for the preparation of ionic liquids** (adapted from ref. 78)




For the alkylation process (step 1), a wide range of cheap haloalkanes are available, and the substitution reactions generally occur smoothly at reasonable temperatures. Furthermore, the resultant halide salts can easily be converted into salts with other anions (steps 2 and 3). By far the most common starting material is 1-methylimidazole. Typically, it is necessary to heat 1-methylimidazole with chloroalkanes to 80 $^{0}$C for 2-3 days to ensure complete reaction. The equivalent reaction with bromoalkanes is usually complete within 24 h, and can be carried out at lower temperatures (ca. 50 – 60 $^{0}$C). In the case of iodoalkanes, the reaction can be carried out at room temperature. Fluoride salts cannot be formed in this manner.

The most important requirement is that the reaction mixture be kept free of moisture as the products are often extremely hygroscopic. The reaction may be carried out without the use of a solvent, as the reagents are generally liquids, and mutually miscible, whereas the halide salt products are usually immiscible in the starting materials. Often, solvents are employed and these include: 1,1,1-trichloroethane, ethyl ethanoate, or toluene. Although no particular advantage appears to accrue with any specific one of these, they are all immiscible with the halide salt product, hence excess solvent and starting material can be removed simply by decantation. Following this, it is necessary to remove all excess

solvent and starting material by heating the salt under vacuum. The halide salts are generally solids at room temperature and purification is best achieved by recrystallisation from a mixture of dry acetonitrile and ethylethanoate.

The thermal reaction has been used in almost all reports of ionic liquids, being easily adaptable to large-scale processes, and providing high yields of products of acceptable purity. An alternative approach involving the use of microwave irradiation has been reported, giving high yields with very short reaction times (minutes rather than hours),[108] however, the reaction was only carried out on a small scale.

*Anion-exchange Reactions*

In cases where it is not possible to form the desired anion by the quaternisation reaction, the halide ion can either be exchanged by direct treatment of the halide salt with a Lewis acid, or subjected to anion metathesis. The former is usually achieved by simply mixing the two together, with the ionic liquid forming on contact of the two materials. This results in the formation of more than one anion species, depending on the relative ratio of the two components. Such behaviour is displayed by chloroaluminate ionic liquids, for example [Eq. (1) - (3)].[109]

$$[R'R_3N]^+Cl^- + AlCl_3 \rightleftharpoons [R'R_3N]^+[AlCl_4]^- \quad (1)$$

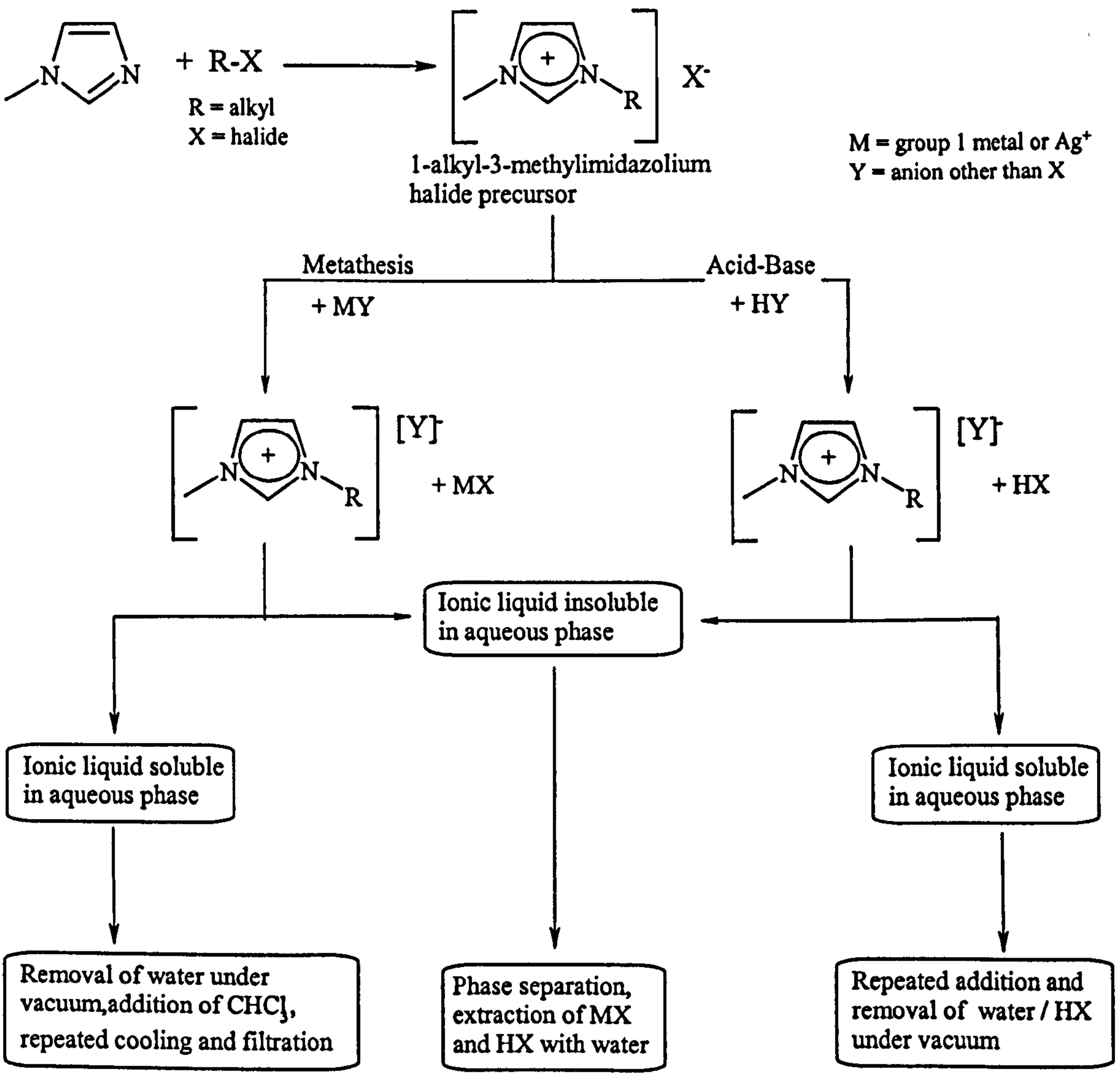
$$[R'R_3N]^+[AlCl_4]^- + AlCl_3 \rightleftharpoons [R'R_3N]^+[Al_2Cl_7]^- \quad (2)$$

$$[R'R_3N]^+[Al_2Cl_7]^- + AlCl_3 \rightleftharpoons [R'R_3N]^+[Al_3Cl_{10}]^- \quad (3)$$

Other Lewis acids used in the preparation of ionic liquids, include $AlEtCl_2$,[110] $BCl_3$,[111] CuCl,[112] and $SnCl_2$.[113] The preparative methods employed for all these salts are similar to those indicated for $AlCl_3$-based ionic liquids.

The preparation of relatively air- and water-stable ionic liquids based on RMIM cations involves a metathesis reaction between the RMIM halide (mostly chloride) and a silver salt of the desired anion, or a group 1 metal salt (eg. $NaBF_4$), or in an acid-base neutralisation reaction, see Scheme 1.5. This reaction is stoichiometric and therefore equimolar amounts of waste MX or HX are produced. Both methods are usually carried out in water at room temperature, although some authors report using organic solvents.[82] The main goal of all anion exchange reactions is the formation of the ionic liquid uncontaminated with unwanted cations and anions, a task that is easier for water-immiscible ionic liquids because aqueous extraction removes the chloride (MX or HX, or the unreacted starting material). For water-miscible ionic liquids, the work-up of the metathesis reaction

involves the removal of water under reduced pressure, addition of trichloromethane and repeated cooling to 5 $^{0}$C to precipitate MX,[114] followed by several filtration steps. The work-up of the water-miscible ionic liquids prepared by the acid-base method includes repetitive addition of water and removal of water / HX under reduced pressure and elevated temperatures. In both cases, this is a very cumbersome process and the effectiveness of the removal of the chloride is mediocre. The most efficient method for the synthesis of water-miscible ionic liquids is to use silver salts in an organic solvent, as the low solubility of the AgX by-product in the organic solvent means that it can be separated simply by filtration and any residual silver ions can removed electrochemically[115] to yield ionic liquids of high purity, although this method is limited by the relatively high costs of silver salts. A procedure involving lead (II) salts[116] has been shown not to be viable.[117]




**Scheme 1.5 Preparation and work-up procedures used in the synthesis of imidazolium-based ILs[118]**

### *1.3.2.2 Purification*

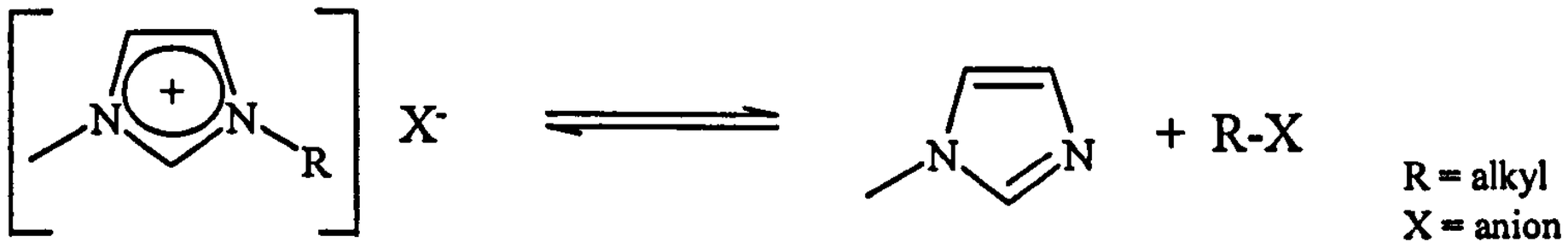
The presence of small amounts of unreacted 1-methylimidazole (a coordinating base) in the ionic liquids from incomplete alkylation poses potential downstream problems from catalyst poisoning and introduction of protic impurities. Furthermore, its high boiling point (198 $^0$C) means that it can prove difficult to remove from ionic liquids. Holbrey *et al.* reported a simple colorimetric method to determine the levels of unreacted 1-methylimidazole contamination, based on the formation of the blue $[Cu(MIM)_4]^{2+}$ ion, which is sensitive to 1-methylimidazole in the 0 – 3 mol % concentration range.[119] Although this doesn't solve the problem, it provides a rapid means of checking the purity of an imidazolium ionic liquid. The presence of halide ions (due to inefficient separation from the IL) can also be extremely detrimental to the performance of ionic liquids, particularly in applications involving transition metal-based catalysts, which are often deactivated by halide ions. The concentration of halide ions can be monitored by the use an ion-selective electrode, or alternatively by use of a chemical method such as the Vollhard procedure for chloride ions.[120] Water present in ionic liquids may also coordinate to the transition metal catalyst thus affecting the rate of a reaction, or significantly influencing the physiochemical properties and stability of the ionic liquid (some wet ionic liquids may undergo hydrolysis with formation of protic impurities). If the amount of water present is of importance, it may be determined by Karl-Fischer titration, however heating to at least 60 $^0$C under vacuum, for several hours with stirring provides an acceptably low degree of water contamination.

## 1.3.3 Stability of Ionic Liquids

Although the recent 'second generation' ionic liquids can be used on the bench, being both air and water stable, most ammonium and imidazolium salts are hygroscopic and if used in open vessels, hydration will almost certainly occur over time. The consequences of water contamination depend on the use to which the ionic liquid is being put and what solutes are being used. Regarding stability, ionic liquids based on the $PF_6^-$ anion have been found, in the presence of 10 M $HNO_3$[121]or at high temperatures, to liberate HF which is extremely toxic and corrosive, and etches glass. Although no problems have been reported, organic nitrates and perchlorates (used in $EtNH_3[NO_3]$, $EMIM[NO_3]$, and $EMIM[ClO_4]$), are potentially explosive, especially when rigorously dried.

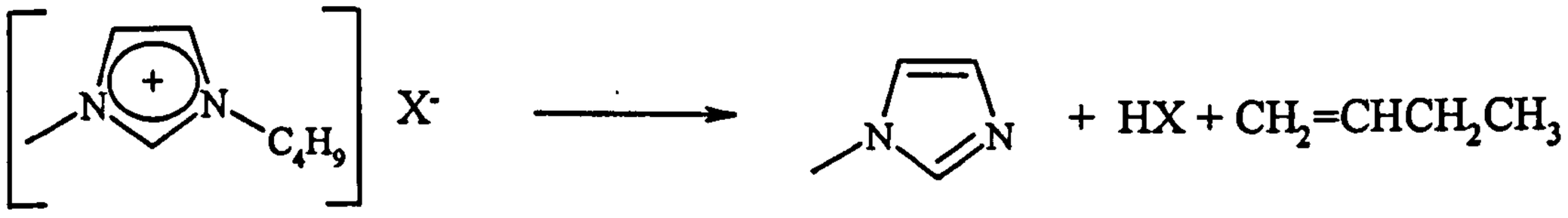
The ionic liquids may be slightly coloured, depending on the method of preparation. For instance, when a nitrate-based ionic liquid is heated above 80 $^0$C at reduced pressure to remove water, it will turn dark-brown, whereas it stays almost colourless when heated gently. Similar observations have been made, *e.g.* by Gale and Osteryoung, who attributed this to the formation of impurities by degradative side-reactions.[122] The nature of these coloured impurities is, as yet, unknown, and they are not detectable by NMR spectroscopy.

In theory, imidazolium based ionic liquids can decompose by two pathways, as found for tetraalkylammonium[123] and *N*-alkylpyridinium salts.[122] These are, the reverse of the Menschutkin reaction used for the preparation (Scheme 1.6) and the Hofmann reaction (Scheme 1.7).




**Scheme 1.6 The reversed Menschutkin reaction**

The latter is dependent on the nucleophilicity of the anion $X^-$: the rate of alkene formation increases in the order $[NO_3]^- < [SCN]^- < I^- < Br^-$ in tetraalkylammonium salts.[123] The reaction was shown to be dependent on the extent of the reversed Menschutkin reaction; the olefin is formed by a dehydrohalogenation of RX by $R_3N$, a known side-reaction in the Menschutkin reaction.[123]




**Scheme 1.7 The Hofmann reaction**

There are two uses of ionic liquids; namely, as solvents for extraction, and as a reaction medium for chemical reactions. Chemistry in ionic liquids has been reviewed[78,124,125] and more recently a book has been published,[93] selected examples are discussed overleaf.

## 1.4 APPLICATIONS OF IONIC LIQUIDS

### 1.4.1 Ionic liquids as solvents in separation technology

The design of safe and environmentally benign separation processes has an increasingly important role in the development of clean manufacturing processes. Liquid-liquid extractions are a favoured choice for (the development of) separation processes.[126] These usually employ an organic solvent (*i.e.* a VOC) and an aqueous solution as the two immiscible phases.[127] The desire to reduce the use of VOCs, the cost of containing them safely, and their safe disposable due to environmental protection regulations, therefore becomes highly significant. Ionic liquids are able to solvate a wide range of species, including organic, inorganic, organometallic compounds, whilst being immiscible with a number of non-polar organic solvents *e.g.* benzene and toluene, hence they are favourable media for product recovery in liquid-liquid extraction systems.

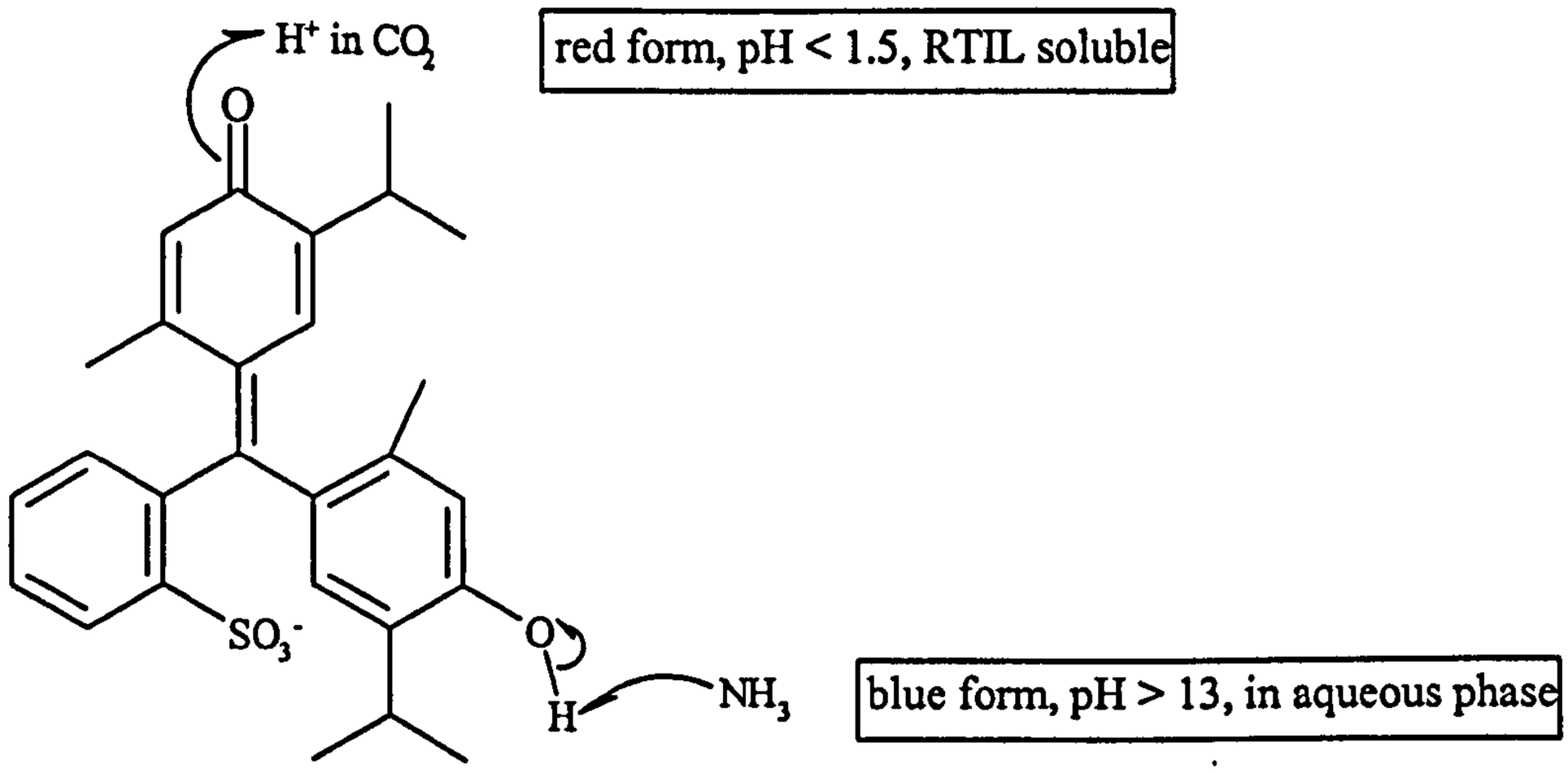
### 1.4.2 Extraction from water with Ionic Liquids

The partitioning of a number of charged and uncharged aryl organic moieties in a biphasic extraction system comprising BMIM[$PF_6$] and water was found to be similar to their partitioning in traditional organic solvent-water systems.[128] Equal volumes of the ionic liquid and distilled deionised water were contacted in the presence of $^{14}C$-labelled tracers of several ionisable and nonionisable substituted aryl molecules. The distribution of these molecules between the heavy, ionic liquid phase and the light, water phase was determined radiochemically. Although the partitioning of these solutes in octan-1-ol / water systems was found to be slightly better than that observed in BMIM[$PF_6$]-water system, both types of media are equally adequate for practical applications.[127] In both cases, neutral or apolar species have greater preference for the non-aqueous phase, compared to the corresponding species having charged groups or strong hydrogen bonding moieties.

For acids (*e.g.* benzoic acid) as well as for bases (*e.g.* aniline) it was found that the partition coefficient can be controlled via alternation of the pH by addition of acids or bases to the aqueous phase, as it is classically accomplished in extraction technology. Thus, benzoic acid favours the ionic liquid BMIM[$PF_6$] over the aqueous phase, if the latter is acidic. However, if the aqueous phase is basic, the molecule dissociates and then tends to dissolve better in the aqueous phase.[129]

Another environmentally benign alternative for the adjustment of pH was demonstrated to be the use of recyclable gases, such as $CO_2$ and $NH_3$, in the distribution of thymol blue (Scheme 1.8), between the ionic liquid phase and water.[130] At low pH, the zwitterionic red form could be found uniquely in the ionic liquid phase, whereas when the pH of the medium was increased beyond 12, the now blue, dianion form was quantitatively partitioned in the aqueous phase. An additional advantage of ionic liquids in separation technology is the possibility to fine-tune the solubility of a substrate by alternation of the alkyl chain length, *e.g.* from butyl (BMIM[$PF_6$]) to octyl (OMIM[$PF_6$]). For example, thymol blue, which is distributed between BMIM[$PF_6$] and the aqueous phase, enriches in the aqueous phase at pH 12. However, if OMIM[$PF_6$] is used under the same conditions, the dye possesses a higher solubility in the ionic liquid phase than in water. Phase separation can be facilitated by choosing an ionic liquid with a melting point above room-temperature (*e.g.* 1-decyl-3-methylimidazolium derivative, mp = 38 $^0$C), and performing the extraction at slightly elevated temperatures, which upon cooling to room temperature crystallises enabling removal of the dye by an alkaline wash.

**Scheme 1.8 A proton switch in a RTIL / water mixture**




Water-immiscible imidazolium-based ionic liquids have also been used to extract Sr(II) from aqueous medium with the help of a crown ether .[131] The affinity of crown ethers to certain metal cations can be fine-tuned by changing the ring size and rigidity, the type of donor atoms, or its lipophilicity. In typical liquid-liquid extractions, the crown ether resides in the hydrophobic extracting phase and serves to dehydrate and complex metal ions while removing them from the aqueous phase. To enhance the efficiency of such a

process, an organic solvent is selected to sustain the biphasic system while maximising the hydrophobic and complexing properties of the extracting phase. Conventionally, volatile organic solvents such as chloroform or toluene are used with crown ethers, but the distribution coefficient for these solvents is much smaller than when ionic liquids are used, due to the limited solubilites of ionic species, such as $Sr^{2+}$, in non-ionic organic solvents. In particular, the distribution coefficient is low if the cation, which is to be extracted, coexists with a hydrophillic anion, such as nitrate.[131]

This enhanced extraction efficiency was shown to have its origin in differences in the mechanism of strontium ion transfer from an aqueous phase into the IL.[132,133] Specifically, for PMIM[$NTf_2$], exchange of the cationic strontium-crown ether complex for the cation of the IL, was found to represent an important mode of strontium ion transfer from the aqueous nitrate solution. In contrast, strontium ion partitioning in conventional solvents has been found to proceed *via* extraction of a strontium nitrato-crown ether complex.[134] The poor co-ordinating ability of the $[NTf_2]^-$ anion toward alkaline earth cations[135] and the large amount of water dissolved in PMIM[$NTf_2$] make it likely that the co-ordination sites left vacant by the nitrate are occupied by water molecules in a 1 $H_2O$ : 1 $NO_3^-$ ratio.[133] This means that increased metal ion partitioning in ILs will be accompanied by increased solubilisation of the IL in the aqueous phase,[132] a clearly undesirable result. However, as the hydrophobicity of the IL cation is increased, cation exchange becomes increasingly more difficult, and the ion-exchange mechanism is no longer viable.[136] Using DMIM[$NTf_2$], the neutral strontium nitrato-crown ether complex was extracted, showing that the predominant mode of metal ion partitioning reverts to that observed for conventional organic diluents. Thus, just as relatively minor variations in the nature of the cation or anion comprising an IL can lead to dramatic changes in its physiochemical properties, so too can such variations lead to a significant change in the mechanism of ion transfer into these solvents.

Visser *et al.* conducted an extensive study of the behaviour of $[C_{4\text{-}8}][PF_6]$ as hydrophobic extractants of $Sr^{2+}$, $Cs^+$ and $Na^+$ from water, using crown ethers of different lipophilicities.[121] Their results showed that factors such as aqueous phase composition and water content of the ionic liquid have a dramatic effect on the metal ion extraction and the stability of the IL. It was found that the affinity of the crown ether complex is dependent on the chain length of the ionic liquid; although on first sight it would be expected that the hydrophobic crown ether complex has a higher affinity for the more hydrophobic OMIM[$PF_6$] than for BMIM[$PF_6$], it was found that the amount of water present in the

ionic liquid is relevant as well. The increased solubility of the crown ether complex in the less hydrophobic ionic liquid, BMIM[$PF_6$], was attributed to the fact that it dissolves more water. The amount of water present in BMIM[$PF_6$] is also strongly dependent on the concentration of additives such as sodium citrate, HCl and $NaNO_3$, all of which decrease the amount of water in the ionic liquid phase, and thus the distribution ratio of $Sr^{2+}$. On the other hand, high concentrations of $HNO_3$ (>1 M) increase the water content of BMIM[$PF_6$], and even higher concentrations of $HNO_3$ (10 M) increase the water solubility of BMIM[$PF_6$] causing a monophasic system to be generated, due to decomposition of the ionic liquid. Although a more fundamental understanding is required, it can be concluded that some ionic liquids such as OMIM[$PF_6$], follow similar trends to commonly used solvents in the extraction of $Sr^{2+}$, $Cs^+$ and $Na^+$ from an aqueous phase.[121]

Imidazolium-based hexafluorophosphate ionic liquids with thiourea-, thioether and urea-side chains have been used to extract $Hg^{2+}$ and $Cd^{2+}$ from aqueous solutions. It was found that successful extraction of these metals into the ionic liquid phase was dependent on the pH of the aqueous phase. Additionally, doping the much cheaper BMIM[$PF_6$] with the thioether-derived ionic liquid led to comparable results as if the thioether-based extractant was used in pure form.[137]

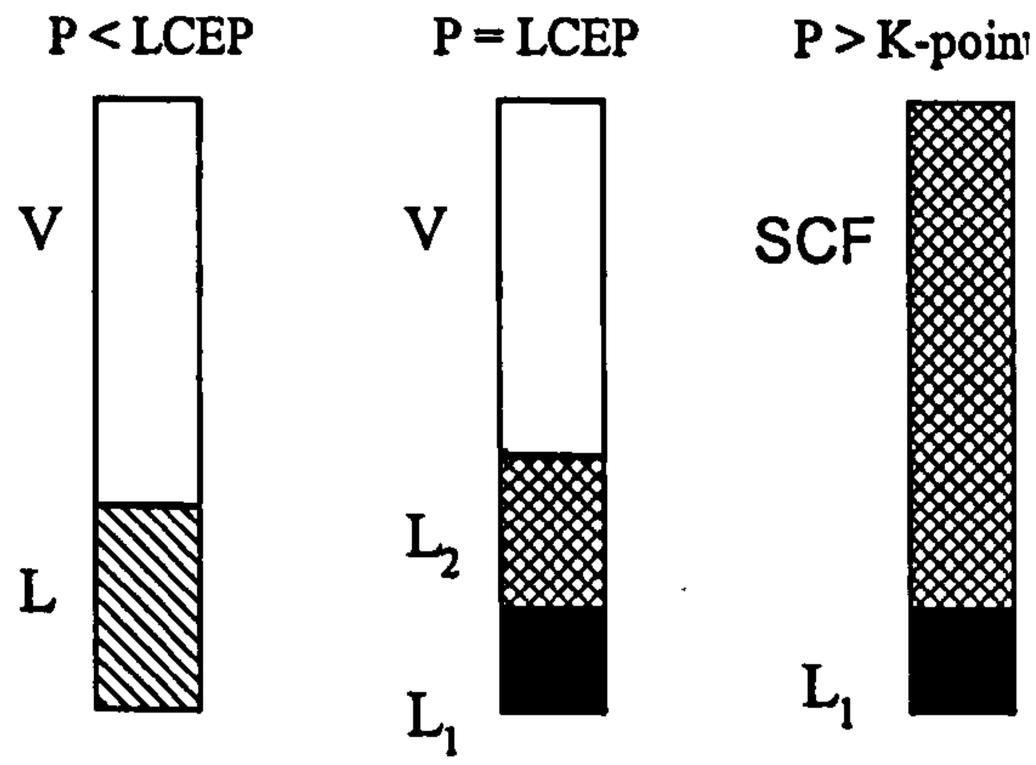
RTILs have been reported to have potential as extractants in recovery of butyl alcohol from fermentation broth.[138] Ethanol is currently recovered by distillation but distillative recovery of BuOH is not economical, as the amount of energy required is approximately 3 times higher[139] since ABE (acetone-butyl alcohol-ethanol) fermentation broth contains only 2 wt% of BuOH *vs.* 6 wt% of EtOH in yeast fermentation broth. Most of the solvents suitable as extraction media are flammable, *e.g.* diethyl ether, or hazardous and toxic to humans and microorganisms[140] *e.g.* tri-*n*-butyl phosphate, octan-1-ol. Although the solubility of BuOH in BMIM[$PF_6$] and OMIM[$PF_6$] was small, it was still within the range of solubilities in octanol, and even this small partitioning of BuOH into the ionic liquid phase could still result in an economical recovery process due to the non-volatility of the extractant.[138] The toxicity of ionic liquids on microorganisms is now being investigated as well as further applications in clean, separation technologies.

### 1.4.3. Extraction from Ionic Liquids with Supercritical Fluids

Extraction with a supercritical fluid is the ultimate method for 'green' partitioning of phases, since commonly used volatile organic solvents will cause harmful emission. Brennecke and co-workers reported that supercritical carbon dioxide partly dissolves at 8 MPa in BMIM[$PF_6$], but the two phases are not completely immiscible. Although $CO_2$ can dissolve significantly (up to 0.6 mole fraction) into the lower IL phase, no IL was detectable in the upper $scCO_2$ phase. An advantage of using $scCO_2$ to extract products from ILs is that cross-contamination and leaching are not encountered. Extraction with $scCO_2$ is particularly suitable for substances that are hydrophilic or water-sensitive, and therefore do not permit aqueous extraction from ionic liquid media, or for poorly volatile or thermally labile products, for which distillation as a method of separation is not applicable. As an example of a low-volatility solute, the authors chose napthalene, which was easily extracted from the ionic liquid phase at 13.8 MPa at 40 $^0$C.[141]

The $scCO_2$ / IL biphasic system has been demonstrated for the hydrogenation of dec-1-ene using Wilkinson's catalyst $RhCl(PPh_3)_3$, which is soluble in BMIM[$PF_6$], but insoluble in $scCO_2$.[142] The hydrogenation of dec-1-ene proceeded in 98 % conversion to *n*-decane in 1 h at 48 bar $H_2$ and a total pressure of 207 bar, in a biphasic reaction mixture with a colourless $CO_2$ phase above a yellow ionic liquid phase. The product was recovered by separating the $scCO_2$ phase to a receiver vessel under high pressure after the reaction, and recharging the reaction vessel with dec-1-ene, $H_2$ and $CO_2$. The process was repeated up to four times and the reaction proceeded to *ca.* 98 % conversion each time, thereby demonstrating efficient catalyst recycling through immobilisation of the rhodium catalyst in the ionic liquid. The reaction was also repeated in an organic / IL system by using *n*-hexane in place of carbon dioxide, and 99 % conversion of dec-1-ene to *n*-decane after 1 h at 50 $^0$C confirmed that there is no reactivity advantage for $CO_2$ over *n*-hexane for simple hydrogenation reactions.

Brennecke and co-workers have shown that solutions of methanol and the ionic liquid, BMIM[$PF_6$], can be induced to from three phases in the presence of $CO_2$. Methanol and BMIM[$PF_6$] are completely immiscible in all proportions at ambient conditions. At a given temperature and initial loading of methanol and IL, the applied $CO_2$ pressure at which the second liquid phase appears is called the lower critical endpoint (LCEP). The most-dense liquid is rich in IL (labelled $L_1$), the next phase is rich in methanol ($L_2$), and the third vapour phase (V) is mostly $CO_2$ with some methanol. At pressures above the LCEP, the methanol-rich phase expands significantly whilst the IL-rich phase expands relatively




**Scheme 1.9 BMIM[$PF_6$] phase behaviour with increasing $CO_2$ pressure**

little. Eventually the increased $CO_2$ pressure induces another critical point, the K point, at which the methanol-rich phases merges with the vapour phase, and the last traces of IL that had remained in the methanol-rich liquid are expelled. The resulting sc$CO_2$ / methanol phase (SCF) contains no detectable IL. It was concluded that dissolution of $CO_2$ in a methanol / IL mixture reduces the solvent strength of the methanol to such an extent that it is no longer able to dissolve the ionic species. This was based on dielectric constant measurements of Roskar *et al.*[143] which reduce from 37.5 for pure methanol to 4.9 at a $CO_2$ mole fraction of 0.733.

Brennecke *et al.* has also demonstrated that gaseous or liquid $CO_2$ can cause the separation of both hydrophobic and hydrophilic ILs from aqueous solutions at ambient temperatures and pressure below 5.2 MPa.[144] This is below the saturation (vapour) pressure of pure $CO_2$ (6.41 MPa) at room temperature and as $CO_2$ is usually sold in cylinders at its vapour pressure, practical laboratory separations can be performed with no special heating or pumping systems to induce phase separation. Since aqueous waste streams are the most likely avenue for ILs to enter the environment, IL contamination of aqueous waste streams is a major issue. Removing water from aqueous solutions dilute in IL using distillation would be a very energy intensive process, so low pressure $CO_2$ may have practical implications for designing processes with ILs. However, the study also reveals that hydrophilic ILs at very low concentrations cannot be removed from water under these conditions. Specifically, BMIM[$BF_4$] can be separated from water at ambient temperatures when the concentration of the IL is between 1.58 and 9.3 mole %, but no separation is observed for lower concentrations, even when the pressure is increased to 6.41 MPa.

### 1.4.4. Ionic Liquids as Stationary Phases in Gas Chromatography

BMIM[$PF_6$] can solubilise complex polar molecules such as cyclodextrins and glycopeptides, and due to its wetting ability and viscosity it can be coated onto fused silica capillaries. Its use as a stationary phase for reverse phase GC with a wide variety of organic compounds has been examined.[145] This ionic liquid displays dual behaviour: it acts a low polarity stationary phase to non-polar compounds or polar compounds that do not contain good proton-donating or accepting groups, whereas molecules with strong proton donor groups are tenaciously retained. Thus molecules with proton-donor or –acceptor characteristics tend to be spatially resolved, as a group, from non-polar analytes. Low melting ionic liquids, in particular tetraalkylammonium nitrate and thiocyanate, can also be used as mobile phases. In cases where the viscosity is too high or when the melting point is too low, solvents such as dichloromethane, water, ethanonitrile, methanol or tetrahydrofuran are added to achieve suitable flow properties.[146,147]

## 1.4 APPLICATIONS OF IONIC LIQUIDS IN PREPARATIVE CHEMISTRY

This rapidly expanding area of research can be categorised into three main types: i) the use of ionic liquid solely as solvent; ii) use as catalytically active solvents; iii) use as solvents with a dissolved catalyst for homogeneous or biphase catalysis.

### 1.5.1 As 'Innocent' Solvents (for Stoichiometric Reactions)

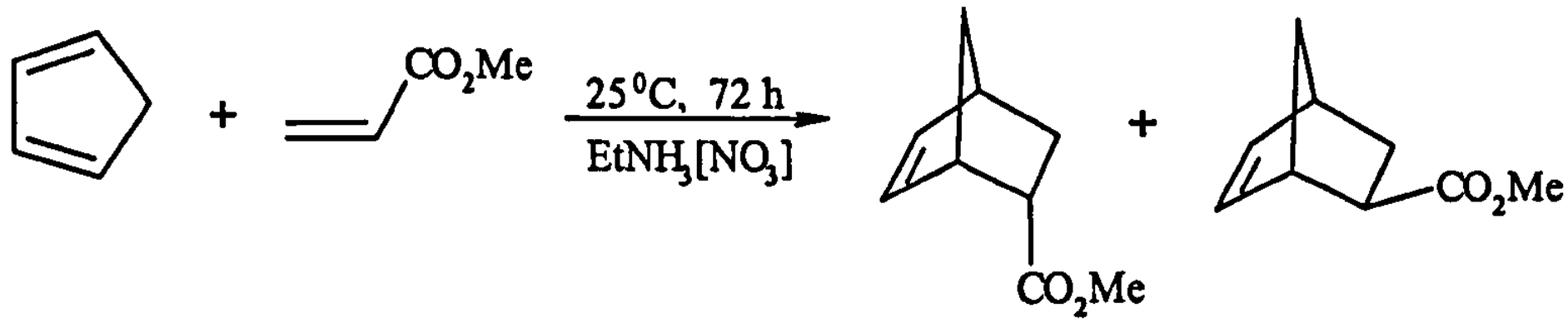
In the majority of cases ionic liquids can be considered as polar phases with their solvent properties being mainly determined by the ability of the salt to act as a hydrogen-bond donor and/or acceptor, and the degree of localisation of the charge on the anion.[124]

***Diels-Alder reactions***

The Diels Alder reaction is one of the most useful carbon-carbon bond-forming reactions in organic synthesis. It is a common method for forming cyclic structures and is widely used in the synthesis of natural products. Hence there is increasing interest in the development of special physical and catalytic methods for the purpose of improving the rate and selectivity of [$4\pi + 2\pi$] cycloaddition reactions. Usually, Lewis acids such as $AlCl_3$[148] and $SnCl_4$[149] are employed but among other methods are the use of $scCO_2$ as

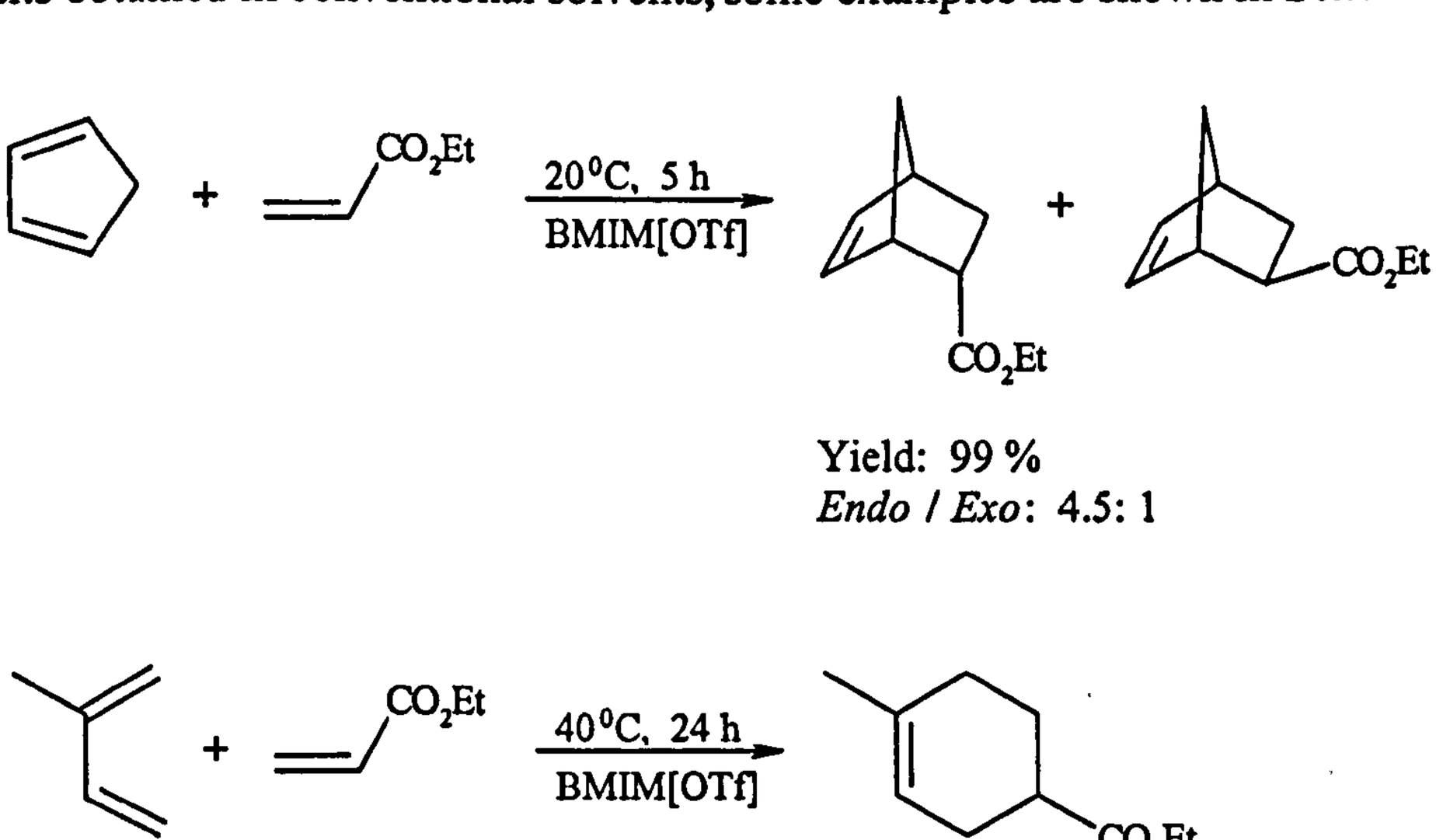
solvent,[150] transition metal-catalysts,[151] and the use of lithium perchlorate-diethyl mixtures.[152]

The first instance of a pure ionic liquid being used as a solvent for Diels-Alder reactions was the demonstration of strong *endo* selectivity for the addition of cyclopentadiene (Cp) to methyl acrylate in $EtNH_3[NO_3]$ (Scheme 1.10), which was also associated with an acceleration of the rate.[153]




**Scheme 1.10**

BMIM[OTf] and BMIM[$PF_6$] are also effective solvents for Diels Alder reactions, showing significant rate enhancements, high yields and selectivity, comparable with the best results obtained in conventional solvents, some examples are shown in Scheme 1.11.




**Scheme 1.11 Diels-Alder reactions in BMIM[OTf][154]**

Welton *et al.* studied the Diels Alder reaction of Cp with methyl acrylate in BMIM-based ILs and attributed the *endo*-selectivity and rate enhancement to a hydrogen bond formed between the IL cation and methyl acrylate.[155] The selectivity for the *endo*-adduct was reduced when changing the ionic liquid from BMIM[$BF_4$] (*endo*: *exo* = 4.6) to

BMMIM[$BF_4$] (*endo*: *exo* = 3.3). The principle difference between $BMIM^+$ and $BMMIM^+$ is that the ability of the latter to hydrogen bond through the proton on the C-2 position of the imidazolium ring has been blocked, although weaker hydrogen bonds can still be formed with the protons at the C-4 and C-5 positions.[156] The selectivity of the reaction was even greater in [$HO(CH_2)_2$MIM][$NTf_2$] (*endo*: *exo* = 6.7),[157] which is an O-H hydrogen bond donor, and $EtNH_3[NO_3]$ (*endo*: *exo* = 6.7),[153] which is an N-H hydrogen bond donor. This shows that the ability of the cation to act as a hydrogen bond donor is important in controlling the *endo* selectivity of the reaction.

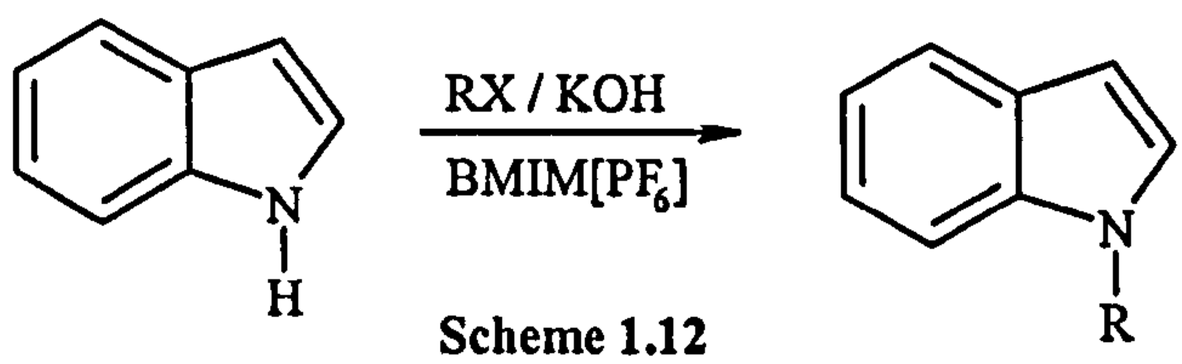
The selectivity for the *endo* isomer was also affected by the anion used. The lowest selectivity was observed in BMIM[$CF_3CO_2$] (*endo*: *exo* = 4.0) whilst the highest was observed in BMIM[$PF_6$] (*endo*: *exo* = 4.8).[155] It was found that the *endo* selectivity increases with the increasing $E_T^N$ value of the IL. When a solvent is capable of acting as a hydrogen bond donor, this property dominates its $E_T^N$ value,[92] giving a measurement of the liquid's ability to hydrogen bond to a *solute*. The ability of the ionic liquid to hydrogen bond to methyl acrylate arises from the hydrogen bond donor ability of the cation, moderated by the hydrogen bond acceptor ability of the anion.[158] There are two competing equilibria in this reaction: the cation can hydrogen bond to the anion of the ionic liquid or to the methyl acrylate. As the anion becomes more basic (*i.e.* a better hydrogen acceptor), the concentration of free non-hydrogen bonded $BMIM^+$ decreases, hence the concentration of the $BMIM^+$...methyl acrylate complex falls, leading to reduced selectivity. This was demonstrated by adding BMIM[Cl] to BMIM[$BF_4$], to form an IL which is less able to coordinate to the methyl acrylate (as the chloride anion is a better hydrogen bond acceptor than tetrafluoroborate), thus reducing the *endo*: *exo* ratio.[155] The authors concluded that the greatest selectivities will be observed in ILs with the strongest hydrogen-bond donor cation coupled with the weakest hydrogen-bond accepting anion. In the case of BMIM-based ILs, the *endo* selectivity was shown to decrease in the order BMIM[$PF_6$] > BMIM[$BF_4$] > BMIM[OTf] > BMIM[$NTf_2$]. The effect of the anion on *endo* selectivity and enantioselectivity for the Diels-Alder reaction is discussed further in Chapter 4, section 4.2. Furthermore, the effect of increasing Lewis acidity of the ionic liquid on *endo* selectivity is examined in Chapter 3, section 3.3.

Dialkylimidazolium salts have been shown to act as homogeneous and heterogeneous Lewis acid catalysts in the Diels Alder reaction between crotonaldehyde / methacrolein and Cp at low temperatures.[159] Using 20 mol% diethylimidazolium bromide or trifluoroacetate in $CH_2Cl_2$ gave 35 – 40 % yield of desired products after 48 h at –25 $^0$C, whereas the

control reaction (without any dialkylimidazolium salt added) gave no product under these conditions. Additionally, $CH_2Cl_2$ could be substituted with ether to form a heterogeneous system (due to the immiscibility of diethylimidazolium bromide in ether) which allowed the products to be decanted off with the ether at the end of the reaction, and the salt to be reused as a catalyst four times with no loss in activity. The authors attempt to carry out an asymmetric Diels-Alder reaction using homochiral *N,N*-di(2'*S*-2'-methylbutane)imidazolium bromide as catalyst was unsuccessful as enantiomeric excesses achieved in the reactions were less than 5 %.[159] The immobilisation of a chiral copper bisoxazoline catalyst in RTILs for the asymmetric Diels Alder reaction between 3-but-2-enoyl-oxazolidin-2-one and Cp has been successful in providing excellent levels of enantioselectivity[160] and is discussed further in Chapter 4, section 4.2.

***Regioselective Alkylation***

Ionic liquids have been used as solvents for regioselective alkylation reactions. Indole undergoes alkylation on the nitrogen atoms, when treated with a haloalkane and base (usually NaOH or KOH) in BMIM[$PF_6$] (Scheme 1.12).[161]



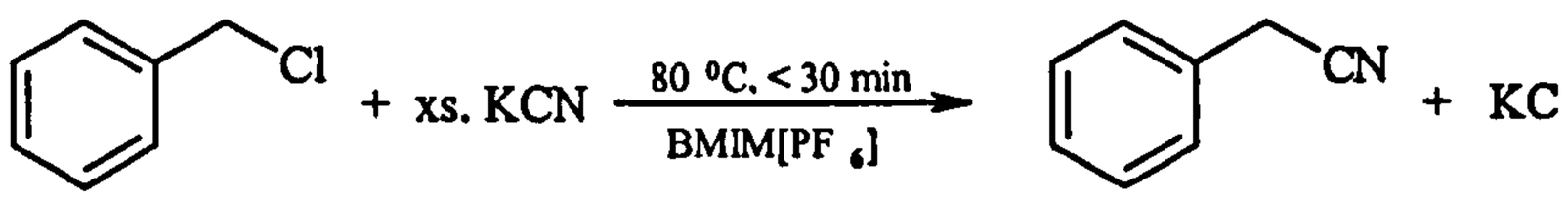

**Scheme 1.12**

The reaction occurs with similar selectivity to those carried out in dipolar aprotic solvents such as DMF or DMSO, but with the added advantage that the products can be extracted from the ionic liquid using diethyl ether. The by-product, sodium or potassium halide, can then be removed by extraction into water, and the ionic liquid recycled many times without any noticeable decrease in yield or regioselectivity. The influence of ionic liquids on regioselectivity for other substrates is discussed further in Chapter 2.

***Nucleophilic Substitution / Addition***

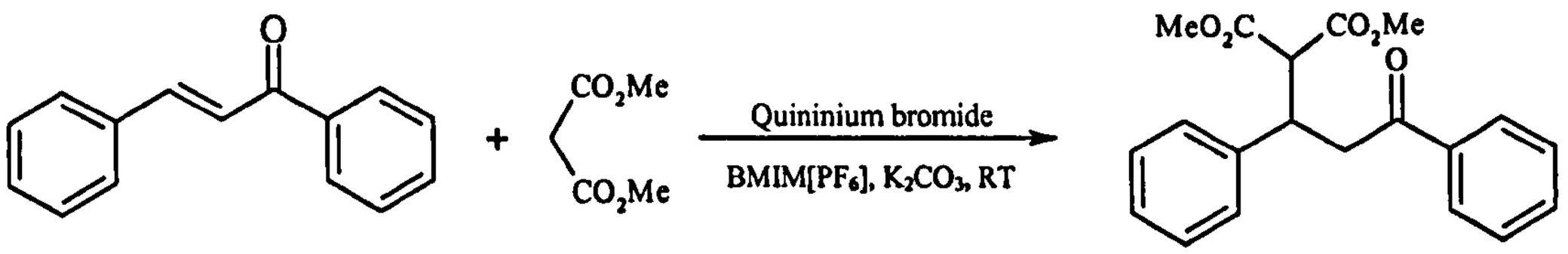
RTILs have also gained recognition as possible alternative reaction media for phase-transfer catalysed (PTC) biphasic systems, such as those used for nucleophilic displacement reactions.[162] Nucleophilic displacement reactions are often carried out using PTC to facilitate the reaction between the organic reactants and the inorganic salts that provide the nucleophiles.[163] The phase-transfer catalyst, often a tetraalkylammonium salt,

acts as a shuttle for the reactant anion between a polar phase that contains the salt reactant and a non-polar phase that contains the organic reactant. This technique overcomes the problem of contacting the reactants. Because ionic liquids are comprised of bulky organic cations, they seem well suited for the types of reaction for which PTC is effective. This was demonstrated for the reaction of cyanide with benzyl chloride to yield phenylacetonitrile, in BMIM[$PF_6$] (Scheme 1.13)[162] The reaction proceeds to give almost quantitative yield in less than half an hour at 80 $^0$C.




**Scheme 1.13 Nucleophilic substitution of benzyl chloride in BMIM[$PF_6$]**

More recently, ionic liquids have been investigated for the asymmetric conjugate addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one using quininium bromide, a quaternary ammonium salt of quinine, as a chiral PTC.[164] (See Scheme 1.14). The ILs employed in this study were 1-butyl-3-methylpyridinium[$BF_4$], BMIM[$BF_4$] and BMIM[$PF_6$].




**Scheme 1.14 Catalytic enantioselective Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one in ILs**

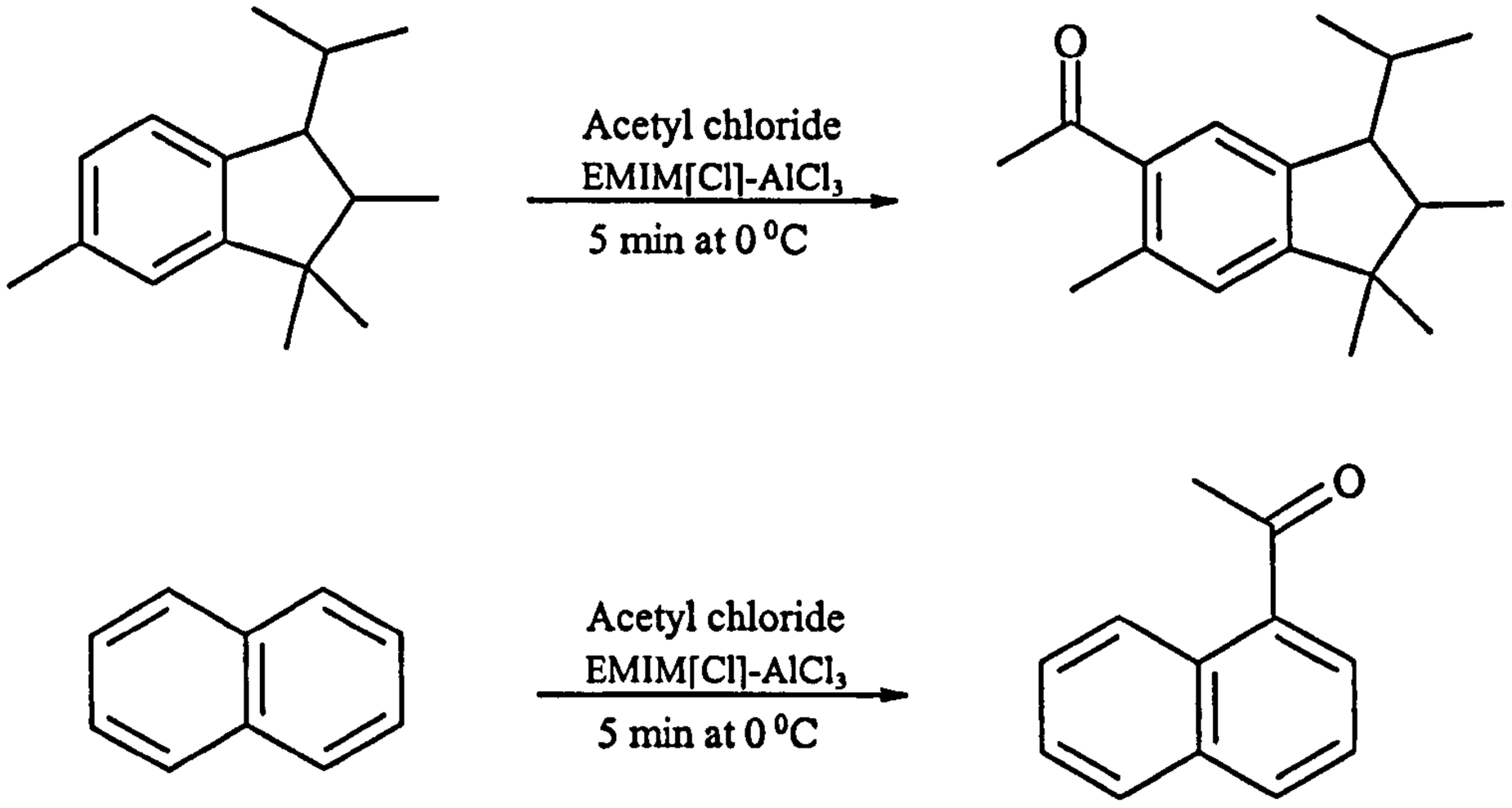
The reactions in ILs afforded the Michael adduct in excellent yields in relatively short periods of time but more interestingly, it was found that the enantioselectivity in BMIM[$BF_4$] and BMIM[$PF_6$] was opposite to that in 1-butyl-3-methylpyridinium[$BF_4$], which was the same as that found in conventional organic solvents under investigation ($CH_2Cl_2$, toluene, DMSO). The recyclability of BMIM[$PF_6$] containing the quininium bromide was studied for three consecutive runs and gave high yields (> 90 %) in all cases, demonstrating that ILs can be used as media for phase transfer catalysed asymmetric synthesis.[164] (Previously, other groups have investigated lipase-catalysed transesterification of chiral substrates in ILs and shown that the rates and enantioselectivity were dependent on both the anion and the alkyl group in the RMIM cation).[165]

## 1.5.2. As Catalytic Solvents

Chloroaluminate ionic liquids are excellent catalysts and solvents in many processes, including Friedel-Crafts acylations,[166,167] alkylations,[168,169] acetylations,[170] sulphonylation,[171] isomerisation of alkanes,[172] and Diels Alder reactions (see Chapter 3, section 3.3.1).[173] Because Lewis acidic ionic liquids behave as simultaneous solvent and catalyst, no other solvent may be necessary.

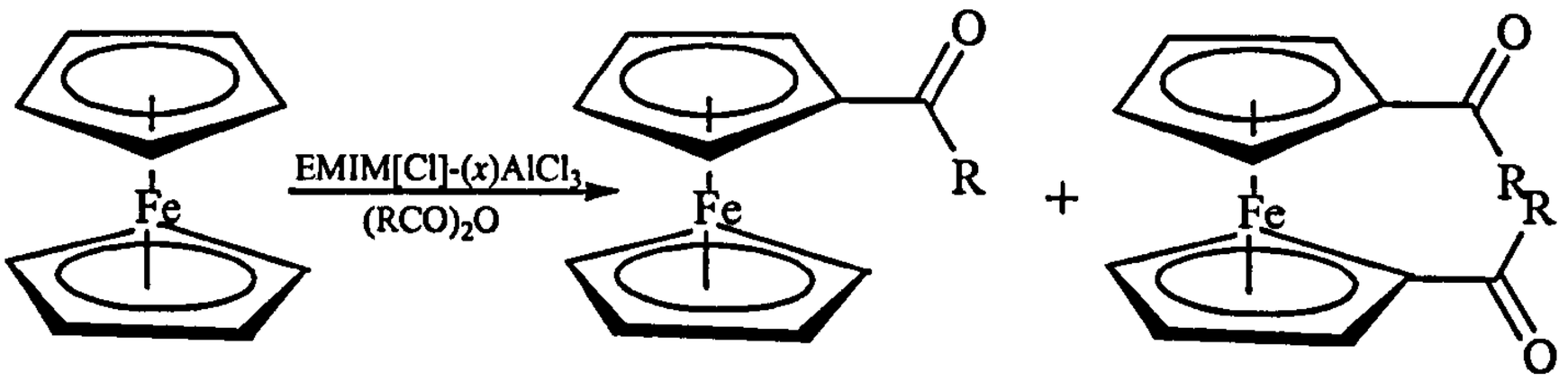
***Friedel-Crafts Acylation***

A number of commercially important fragrance molecules have been synthesised by Friedel-Crafts acylation reactions in EMIM[Cl]-$AlCl_3$[174] (Scheme 1.15). Molecules such as toluene, chlorobenzene and anisole are also acylated in the 4-position with 98% specificity.[174] The acylation of naphthalene in EMIM[Cl]-$AlCl_3$ gives the highest known selectivity for the 1-position over the 2-position, the thermodynamically favoured product under conventional Friedel-Crafts acylation conditions (see Scheme 1.15).




**Scheme 1.15 The acetylation of 1,1,2,6-tetramethyl-3-isopropylindane (upper) and naphthalene (lower) in EMIM[Cl]-$AlCl_3$[174]**

Organometallic compounds, such as ferrocenes, are also easily acetylated by anhydrides or acid chlorides and the selectivity to mono or bis(acetylated) ferrocene is a function of the Lewis acidity of the IL (Scheme 1.16).[175]




**Scheme 1.16 Acetylation of ferrocene**

| EMIM[Cl]-($x$)$AlCl_3$ | Yield /% | Yield /% |
|---|---|---|
| $x = 0.5$ | 0 | 0 |
| $x = 0.55$ | 89 | 0 |
| $x = 0.75$ | 16 | 40 |

### 1.5.3. As solvents for added catalysts

Biphasic catalysis in ionic liquids is attracting increasing interest because transition metal catalyst precursors are often soluble and stable in room temperature ionic liquids. Two types of biphase systems can be used: an ionic liquid / water biphase or an ionic liquid / organic biphase. In some special cases, the second phase is exclusively product, due to insolubility of the organic products in the ionic liquid, and is easily separated by decantation, allowing the recovered ionic catalytic solution to be reused.[176] The application of ionic liquids in biphasic catalysis is discussed below.

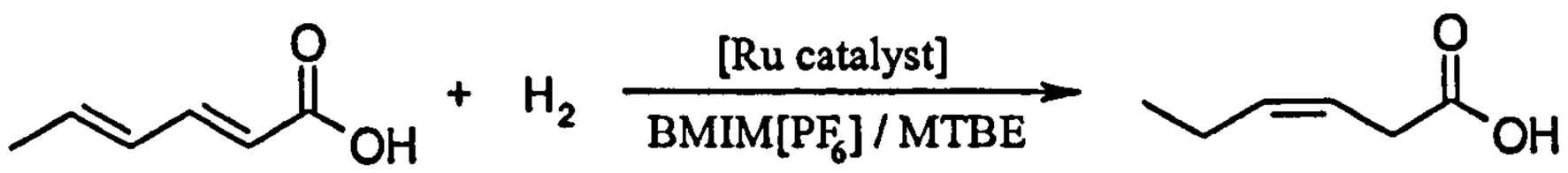
Many catalytically-active transition metal complexes can be immobilised in ionic liquid solvents without the need for specially modified ligands. This is a rapidly expanding field with reports of catalysis in ionic liquids including hydrogenations,[177,185] hydrodimerisations,[178] epoxidations,[179] alkoxycarbonylations,[180] oligomerisations,[181] Trost-Tsuji couplings,[182] and Heck reactions.[183] The reaction rates and selectivities depend on the relative solubilities of the reactants and products in the ionic liquid phase. BMIM[$PF_6$] seems by far the most popular choice of RTIL for this application as it is immiscible with water but readily dissolves many organic molecules, forming triphasic mixtures with alkanes and water. This multiphasic behaviour has important implications for clean synthesis. A particularly useful reaction is the palladium-catalysed coupling of aryl halides with alkenes *i.e.* the Heck reaction. The palladium complex catalyst $BMIM_2[PdCl_4]$ dissolves exclusively in the ionic liquid, thus allowing the inorganic by-products and product alkene to be separated from the catalyst, by solvent extraction with water and alkane solvents respectively.[184] Alternatively, some volatile products can be separated from the ionic liquid and catalyst by distillation, as the ionic liquid has effectively no vapour pressure and therefore cannot be lost. This facile product separation is of greater

significance when using precious metals, enabling both the ionic liquid and catalyst to be recycled and re-used.

### *Hydrogenation*

The first example of catalytic hydrogenation in an ionic liquid was reported by Chauvin *et al.* in 1995.[185] A solution of $[Rh(nbd)(PPh_3)_2][PF_6]$ 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 than in acetone as solvent which was attributed to the formation of an unsolvated cationic rhodium (III) dihydride complex with two free co-ordination sites in the nonsolvating ionic liquid. However, when ionic liquids with strongly co-ordinating anions, such as chloride, were used in the hydrogenation experiments, the rate of hydrogenation dropped while the selectivity to the isomerisation product pent-2-ene increased. The ionic liquid clearly plays not only the part of the solvent here, but the choice of the anion determines whether hydrogenation or isomerisation takes place.

In the field of hydrogenation almost all of the classical Ru, Rh, Co, Pd catalytic systems have been successfully transposed to biphasic conditions. For example, Dupont and coworkers[177] performed the biphasic hydrogenation of cyclohexene with $[Rh(cod)_2][BF_4]$ in BMIM$[BF_4]$ and BMIM$[PF_6]$ (TOF of *ca* 50 $h^{-1}$), and have shown that $RuCl_2(PPh_3)_3$ in BMIM$[BF_4]$ is an effective catalyst for the biphasic stereoselective hydrogenation of olefins (with TOF up to 540 $h^{-1}$).[186] The ruthenium-catalysed hydrogenation of sorbic acid to *cis*-hex-3-enoic acid (Scheme 1.17) was achieved in a biphasic BMIM$[PF_6]$-methyl *tert*-butyl ether system.[187] Compared to conventional ether biphasic systems the hydrogenation proceeds with enhanced activity in BMIM$[PF_6]$ (with TOF up to 1100 $h^{-1}$).

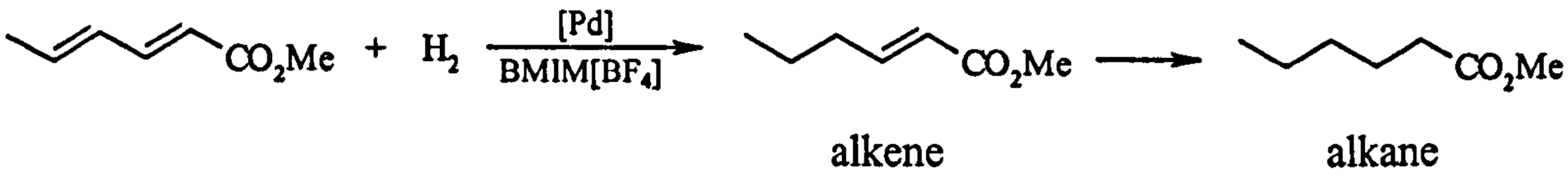



**Scheme 1.17** 85 % selectivity

The hydrogenation of arenes such as benzene, toluene, and cumene to cycloalkanes can also be performed by the ruthenium cluster, $[H_4Ru_4(\eta^6\text{-}C_6H_6)_4][BF_4]_2$ dissolved in BMIM$[BF_4]$ in a typical biphasic reaction with similar turnovers to those obtained by the same catalyst dissolved in water under the same reaction conditions.[188] The starting material / product stream is easily separated from the IL allowing the same batch of IL to be used repeatedly for the catalytic hydrogenation of several different arenes.[188]

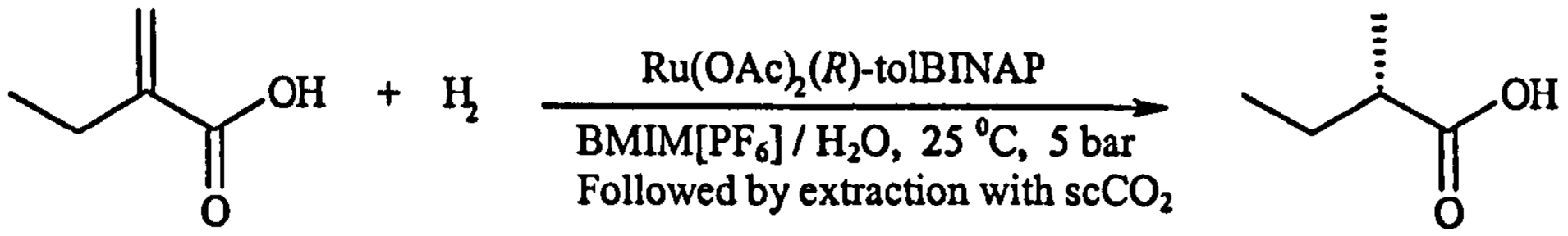
More interestingly, it was found that $RuHCl(CO)(PCy_3)_2$ dissolved in $BMIM[BF_4]$, is able to selectively reduce NBR (acrylonitrile–butadiene rubber) to HNBR (hydrogenated acrylonitrile–butadiene rubber) under mild reaction conditions.[189] The selectivity and catalytic activity achieved in molten salts were clearly superior to those obtained under homogeneous and heterogeneous conditions.

Another interesting property of IL biphase systems is the possibility of extracting the primary products formed during the course of the reaction (due to the different miscibility of the products) and thus enabling the modulation of the product selectivity. In ionic liquids this property has been used to modulate the selectivity in the mono-hydrogenation of alkenes from the hydrogenation of dienes promoted by transition metal complexes.[190] For example, the hydrogenation of methyl sorbate by Pd(II) compounds dissolved in $BMIM[BF_4]$ produces, as the primary product, the alkene (Scheme 1.18) which can be recovered almost quantitatively before further hydrogenation can take place.




**Scheme 1.18 Selective hydrogenation of methyl sorbate**

An example of a transition metal-catalysed hydrogenation in which the ionic liquid used does not provide a permanent biphasic reaction system should also be mentioned here. The hydrogenation of 2-butyne-1,4-diol, reported by Dyson *et al.*, made use of an ionic liquid / water system that underwent a reversible two-phase / single phase transformation upon a temperature switch (Scheme 1.19).[191]




**Scheme 1.19 Ru-catalysed asymmetric hydrogenation of tiglic acid, followed by product extraction with $scCO_2$**

At room temperature, the ionic liquid $OMIM[BF_4]$ containing the cationic Rh catalyst formed a separate layer with water containing the substrate; at 80 $^0$C however, a homogeneous single-phase reaction was formed. Temperature-dependent phase behaviour was first applied to separate products from an ionic liquid / catalyst solution by de Souza

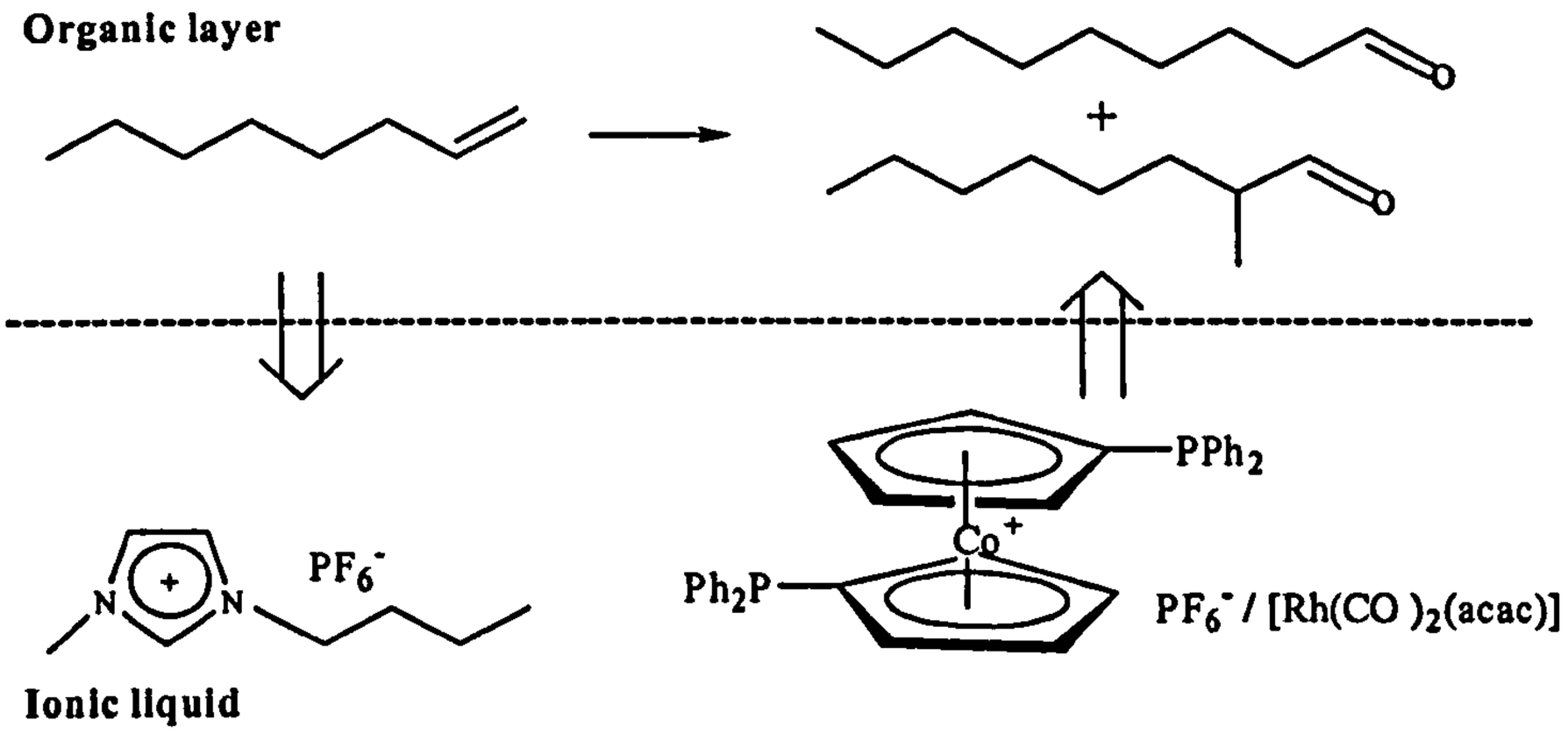
and Dupont in the telomerisation of butadiene and water.[178] This concept is especially attractive if one of the substrates shows limited solubility in the ionic liquid.

More recently, Dupont *et al.* reported the use of RTILs for the formation and stabilisation of iridinium nanoparticles that are recyclable catalysts for biphasic hydrogenation reactions.[192] It is believed that nanoparticles (near monodispersed particles that are usually less than 100 Å in diameter) will have properties intermediate between those of bulk and single particles. However, nanoparticles are solely kinetically stable and therefore require stabilisation against aggregation into larger particles and bulk material. The main methods used for stabilisation of nanoparticles in solution involves electrostatic or steric protection by, for example, the use of water-soluble polymers, quaternary ammonium salts, surfactants, or polyoxoanions.[193,194] In this example, the nanoparticles were generated in the ionic liquid which was then used to hydrogenate various alkenes under mild reaction conditions, allowing the products to be isolated almost quantitatively by simple decantation. Moreover, the Ir nanoparticles could be isolated by centrifugation to be used directly for heterogeneous processes or re-immobilised in BMIM[$PF_6$] and reused for the hydrogenation reactions showing the same catalytic performance to those that have been freshly prepared. The Ir particles in BMIM[$PF_6$] maintain their efficiency for up to seven cycles. (The presence of water in the system causes the decomposition of BMIM[$PF_6$], however, without affecting the catalytic performance of the ionic liquid catalyst "solution").

***Hydroformylation***

As described in section 1.1.3.2, the hydroformylation of propene in an aqueous biphasic system using a water-soluble rhodium complex of the sodium salt of trisulphonated triphenylphosphine is limited to $C_2$ to $C_7$ olefins due to the very low solubility of higher olefins in water. Hence, one can envisage that the use of an appropriate ionic liquid could provide the basis for biphasic hydroformylation of higher olefins. Chauvin *et al.* investigated the biphasic hydroformylation of pent-1-ene with the neutral [$Rh(CO)_2acac$]/ triarylphosphine as the catalyst precursor in BMIM[$PF_6$].[185] Although high activities were observed, slight leaching of the catalyst into the organic phase occurred. Although the use of a monosulphonated triphenylphosphane (tppms) ligand was able to suppress this completely by making the catalyst more soluble in the ionic liquid, the activity of the system was significantly reduced.

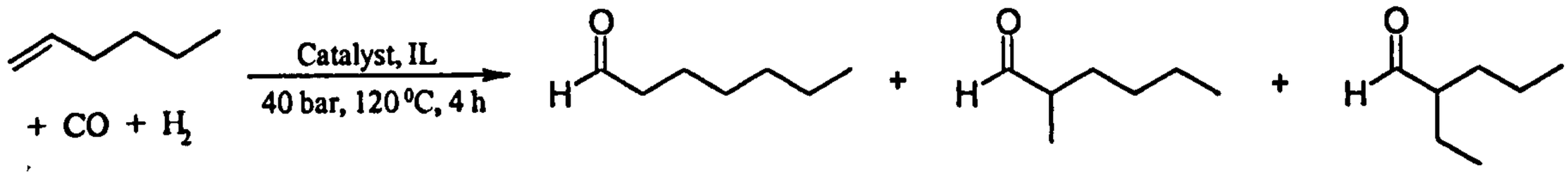
**Scheme 1.20 Biphasic, Rh-catalysed hydroformylation of 1-octene in BMIM[$PF_6$] using a cationic cobaltoceniumdiphosphane ligand.**




Salzer and Brasse then developed and synthesised a cobaltocenium ligand[195] and showed that the reaction benefits from the use of ligand systems that are specifically designed for this application (Scheme 1.20).[196] Not only did they observe high activity for longer chain α-olefins such as 1-octene and good regioselectivity for the linear aldehyde, but the Rh-leaching into the organic layer was less than 0.5%.

The hydroformylation of hex-1-ene to heptanal, 2-methylhexanal and 2-ethylpentanal (Scheme 1.21) catalysed by $[Rh_2(OAc)_4]$, both in the presence and absence of phosphine ligands was also carried out in various phosphonium *p*-toluenesulphonates.[197]

**Scheme 1.21 Hydroformylation of hex-1-ene**




It was found that without additional triphenylphosphine, conversions lay between 80 and 96 %. The product distribution of the isomers was strongly dependent on the ionic liquid used; a ratio of 1: 4 (unbranched: branched) was obtained in *butyltriphenyl*phosphonium *p*-toluenesulphonate, whereas the unbranched isomer formed preferably in *ethyltributyl*phosphonium *p*-toluenesulphonate (2.5: 1). Therefore, the reaction outcome can be controlled by the choice of solvent. Advantage was taken of the higher melting points of these molten salts ($Bu_3PEt$[OTs] and $Ph_3PEt$[OTs] have melting points of 81 - 83 $^0$C and 94 - 95 $^0$C respectively), to decant the product from the solid catalyst medium at room temperature. The authors reported that the catalyst containing phase was reused several times without loss of catalytic activitiy.[197] It should be noted that ionic liquids

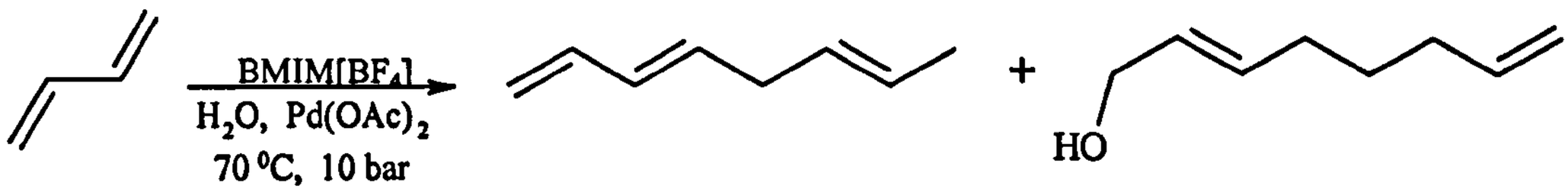
containing very bulky phosphonium cations, such as butyl- and octyltriphenylphosphonium *p*-toluenesulphonate were not stable towards hydroformylation. The alkyl groups were eliminated from the phosphorus to give the corresponding alkene (butene and octene), which were then hydroformylated.

### *Olefin dimerisation*

The Dimersol X process is a liquid-phase dimerisation process that produces nearly 200,000 tonnes of isooctenes per year from *n*-butenes using a Ziegler-Natta-type homogeneous catalyst based on a nickel component activated by an organoaluminium reduction compound.[198] Isooctenes are used as a raw material for the production of $C_9$-plasticisers. The dimerisation process is commonly operated solvent-free, even though the catalyst shows greater activity in solution. Separation of products from the catalyst is a major problem and leads to increased operational costs and environmental impact. As mentioned earlier, organo-aluminate molten salts derived from RMIM or *N*-Rpy cations, were amongst the first to be used in biphasic catalysis. The immobilisation and activation of nickel catalyst precursors in these type of ILs, which were then applied to the oligermerisation of α-olefins, was developed by Chauvin *et al.*[199,200,201] Chauvin and coworkers[199,200] discovered that by using a ternary ionic liquid system (BMIM[Cl]-$AlCl_3$-$EtAlCl_2$), it is possible to form the active catalyst from a $NiCl_2L_2$ precursor and that most importantly, the ionic liquid solvent stabilises the active nickel species. Alkenes are dimerised with activities well in excess of that found in both solvent-free and conventional solvent systems. The Ni-catalysed oligomerisation in a chloroaluminate melt has been commercialised under the name 'Difasol process,' by the Institut Francais du Pètrole (IFP),[181] and is the first industrial application of ionic liquids.

### *Hydrodimerisation*

Palladium complexes have been used to catalyse organic reactions for several decades, and are very versatile in the synthesis of highly functionalised, complex organic molecules, with the added advantage that they are among the most readily available, easily prepared and easily handled of transition metal complexes.[202] Dullius *et al.* investigated the Pd catalysed dimerisation and hydrodimerisation of buta-1,3-diene to octa-1,3,6-triene and octa-2,7-dien-1-ol, in BMIM[$BF_4$], as depicted in Scheme 1.22.[178]

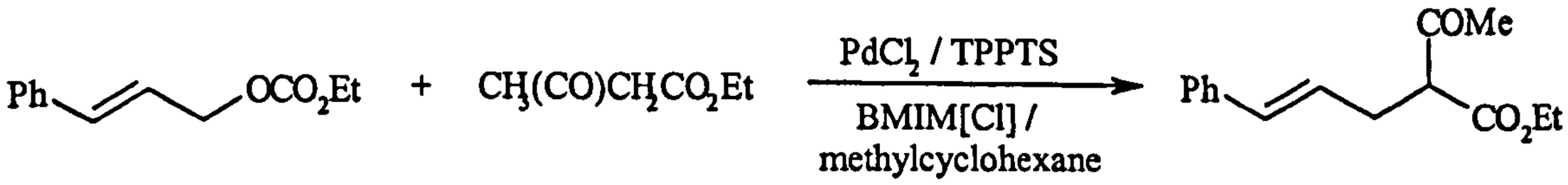



**Scheme 1.22 Dimerisation and hydrodimerisation of buta-1,3-diene**

Different palladium(II)-ligand systems were tested, but simple $Pd(OAc)_2$ gave similar results with respect to selectivity and conversion, leading to the suggestion that an imidazol-2-ylidene complex may be formed *in situ* by all catalytic systems used. More than 97 % of the palladium could be retained in the IL and the products were phase separated upon cooling to 5 $^0$C. This facilitated catalyst recycling and thus the ionic liquid-catalyst solution could be reused for several runs without significant loss of catalytic efficiency.[203]

***Trost-Tsuji couplings***

Ionic liquids improve the activity, selectivity, and stability of palladium-catalysed Trost-Tsuji couplings in biphasic media. In an elegant study, C. de Bellefon and coworkers showed that $PdCl_2$ associated with P(*m*-$C_6H_4SO_3Na)_3$, dissolved in BMIM[Cl], promoted the selective coupling between ethyl cinnamyl carbonate and ethyl acetoacetate (Scheme 1.23)[204]




**Scheme 1.23 Allylic alkylation catalysed by Pd dissolved in BMIM[Cl]**

The molten salt catalytic system has faster reaction rates (due to increased solubility of the organic reagents) and better selectivity, than the corresponding aqueous biphasic system and common organic solvents can be used for product extraction without catalyst deactivation. The formation of cinnamyl alcohol and tri(*m*-phenylsulphonate)cinnamylphosphonium compound (Figure 1.11) are problematic, when the reaction is performed in water. (Using BMIM[Cl], avoids the formation of both by-products).

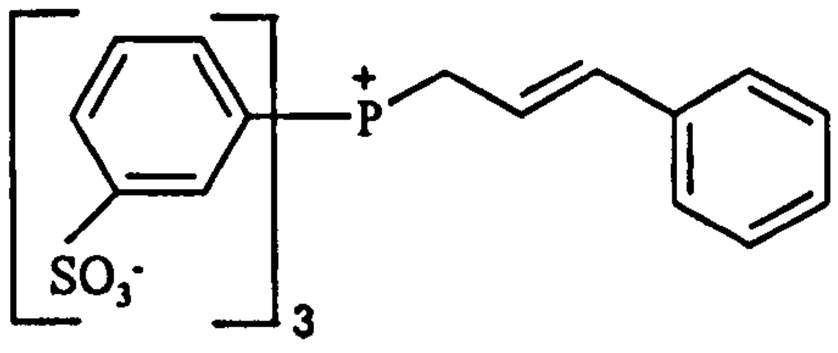
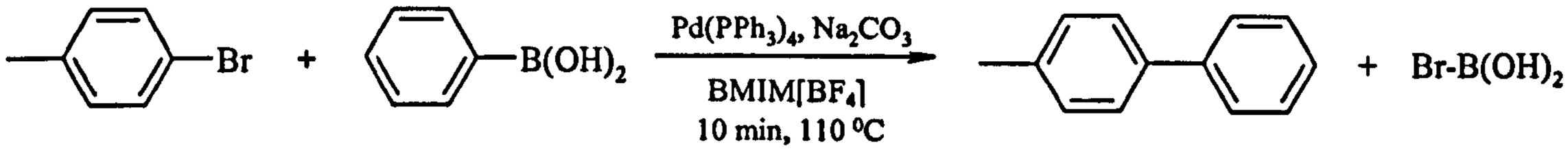



**Fig. 1.11**

### *Suzuki cross-coupling*

The coupling of 4-bromotoluene with phenylboronic acid using the conventional catalyst, $Pd(PPh_3)_4$, was investigated in $BMIM[BF_4]$. (Scheme 1.24).

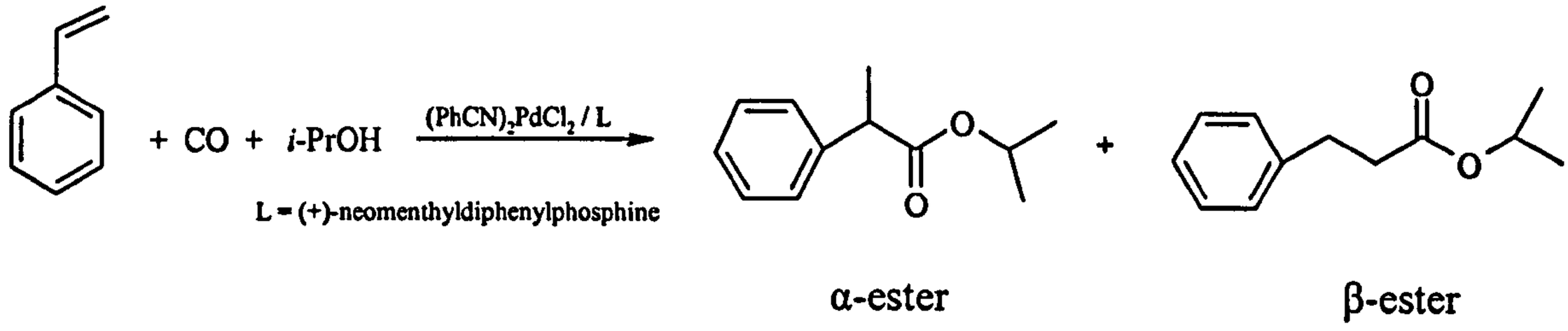



**Scheme 1.24 Suzuki cross-coupling of 4-bromotoluene with phenylboronic acid**

The best results were achieved by preheating the aryl halide to 110 $^0$C in the ionic liquid with the Pd-complex. The arylboronic acid and $Na_2CO_3$ were then added to start the reaction. The use of $BMIM[BF_4]$ has several advantages over toluene as a solvent, namely a significant increase in reactivity (TOF = 455 $h^{-1}$ in $BMIM[BF_4]$, in comparison to 5 $h^{-1}$ under conventional Suzuki conditions); the formation of homocoupling aryl by-products is eliminated; the reaction can be performed in air; and the catalyst can be reused three times without loss of catalyst activity.[205] In these cases the products were extracted with diethyl ether and the by-products ($NaHCO_3$ and $Na[XB(OH)_2]$) were removed by washing with water leaving the clean ionic liquid catalyst solution. (The by-products ($NaHCO_3$ and $Na[XB(OH)_2]$) generated in the reaction modify the miscibility of water with $BMIM[BF_4]$ such that two phases are formed at ambient temperature, with the by-products being preferentially soluble in the large excess of added water). Alternatively, the product could be isolated from the $BMIM[BF_4]$ reaction mixture by sublimation or precipitation by addition of water, all without any apparent leaching of palladium species into the product.[205]

### *Alkoxycarbonylation / Hydroesterification*

Zim *et al.* demonstrated that styrene derivatives are hydroesterificated by carbon monoxide and propan-2-ol in a liquid-liquid biphasic system, consisting of $BMIM[BF_4]$ - cyclohexane, under mild conditions (70 $^0$C and 10 bar). The catalyst (derived from $[PdCl_2(PhCN)_2]$, (+)-neomenthyldiphenylphosphine and 4-toluenesulphonic acid) was soluble in the ionic liquid phase, whereas propan-2-ol dissolved in the upper cyclohexane phase. Using this method, styrene gave the α-ester in 89 % yield and very high selectivity ($\alpha : \beta = 99.5 : 0.5$), (Scheme 1.25).[206]



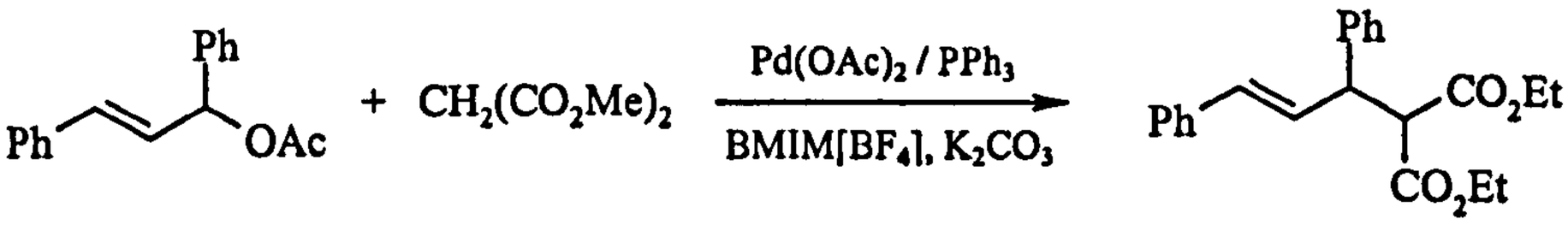

**Scheme 1.25 Alkoxycarbonylation of styrene with CO and propan-2-ol**

Similar results are obtained in the ionic liquid and in a homogeneous system (solvent), and unfortunately attempts to separate the products from the catalyst failed because the catalyst leached into the cyclohexane phase.

Following this, the palladium-catalysed alkoxycarbonylation and amidocarbonylation of aryl bromides and iodides in BMIM[$BF_4$] and BMIM[$PF_6$] has been described.[207] Enhanced reactivities were observed compared to conventional media and the activity of the catalyst species was more sustainable in the ionic liquid media, allowing the ionic liquid-catalyst to be recycled without a significant decrease in yield, as was the case with the organic solvent.

***Alkylation Reactions***

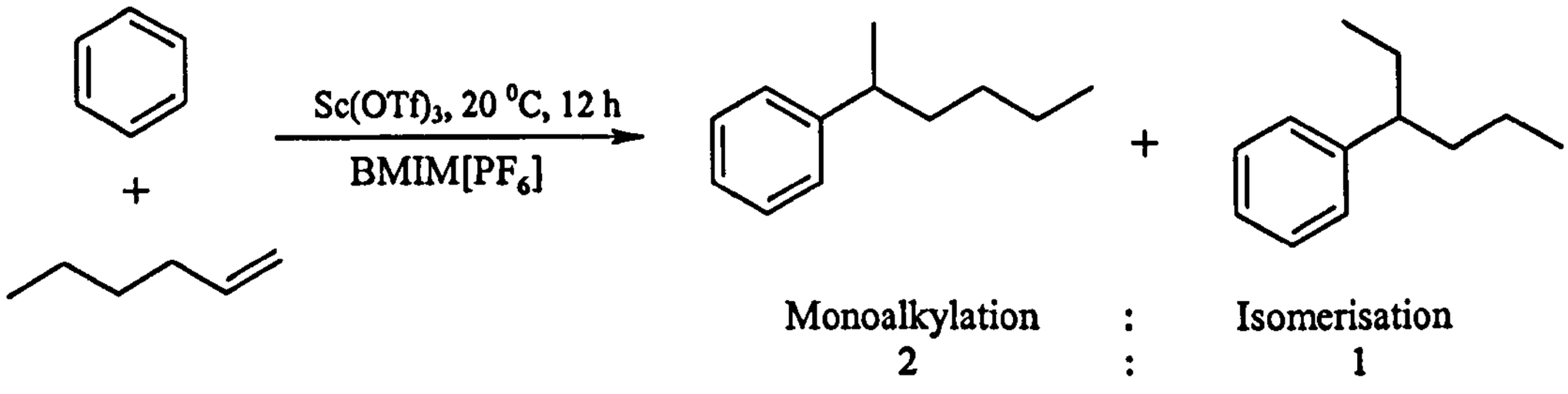
Palladium-catalysed allylic substitution by carbon nucleophiles constitutes a synthetically useful method for the generation of C-C bonds. 1,3-diphenylallyl acetate was alkylated with dimethyl malonate using $Pd(OAc)_2$ / $PPh_3$ (with $K_2CO_3$ as base) in BMIM[$BF_4$] (Scheme 1.26). It was found that the presence of triphenylphosphine is a prerequisite for the reaction to occur, and the rate increases with the $Pd(OAc)_2$: $PPh_3$ ratio.[182] Since this is a monophasic reaction in BMIM[$BF_4$], product separation is only feasible by extraction with an organic solvent. However, the authors found that the catalyst leached into the organic phase when extraction with various organic solvents was attempted. This can be circumvented by replacing triphenylphosphine with P(*m*-$C_6H_4SO_3Na)_3$,[182] and the resulting catalyst was reused three times without losing activity in the alkylation of dimethyl malonate, by extracting the product with toluene.




**Scheme 1.26 Alkylation of 3-acetoxy-1,3-diphenylprop-1-ene with dimethyl malonate**

The same reaction has also been conducted using chiral ferrocenylphosphine complexes of palladium, in BMIM[$PF_6$].[208] Using (*rac*)-(E)-1,3-diphenylallyl acetate as substrate, high enantiomeric excesses of both, the *R*- and the *S*-enantiomer were obtained, (68 % *ee* and 74 % *ee*, respectively) depending on the choice of the ligand, in yields up to 81 %. However, the ligands were prone to leaching into the toluene phase when the product was extracted from the BMIM[$PF_6$], which led to decreased selectivity as well as yield in subsequent runs.

The Friedel-Crafts alkylation of aromatic compounds with alkenes catalysed by $Sc(OTf)_3$ was demonstrated to proceed readily in hydrophobic ILs (BMIM[$PF_6$] and BMIM[$SbF_6$]) to give a quantitative yield of product, whereas the reactions didn't occur in common organic solvents, water or hydrophilic ILs at all.[209] (Scheme 1.27).




**Scheme 1.27 Friedel-Crafts alkylation of benzene with hex-1-ene**

The ionic liquid catalyst solution was recovered by simple decantation of the organic layer after the reaction, and reused a couple of times again to afford a quantitative yield of product. Interestingly, in the hydrophilic ILs, EMIM[OTf], EMIM[$BF_4$], BMIM[OTf], and BMIM[$BF_4$], no reaction occurred even though the catalyst was highly soluble and thus totally immobilised in these ILs.[209] This demonstrates that the catalytic efficiency can be significantly affected by choice of anion.

### *Epoxidation and epoxide ring-opening reactions*

The epoxidation of an array of alkenes and allylic alcohols has been achieved with urea hydrogen peroxide in EMIM[$BF_4$], with methyltrioxorhenium as catalyst, at room temperature.[210] The medium remains homogeneous however, this did not lead to any significant improvements to the rate of reaction. Following this, the asymmetric epoxidation of diverse alkenes by Jacobsen's catalyst in BMIM[$PF_6$]: $CH_2Cl_2$ (1: 4 v/v) with aqueous NaOCl as oxidant at 0 $^0$C was reported by Song *et al.*[211] Since BMIM[$PF_6$] solidifies at 0 $^0$C, dichloromethane was required as a cosolvent. Although the conversion of alkenes to epoxides and enantioselectivity were satisfactory and comparable to those obtained without an IL present, the reaction proceeded faster when an IL was employed.

For example, the epoxidation of 2,2-dimethylchromene in the presence of BMIM[$PF_6$] was complete in 2 h whereas in a control experiment, the same reaction without BMIM[$PF_6$] required 6 h to achieve the same conversion. Furthermore, the ionic liquid containing the catalyst, could be recovered (by washing the reaction mixture with water and extracting the product with hexane) and recycled 5 times, albeit with significant reductions in yield but only slight decreases in *ee*.

The same group used a chromium salen complex in the asymmetric ring opening of epoxides with trimethylsilylazide.[212] It was found that both reactivity and enantioselectivity were strongly influenced by the nature of the anion. When BMIM[$PF_6$] was used, the product was obtained with the same degree of yield and enantiomeric excess (94 % *ee*) as those obtained in conventional solvents, and using a different hydrophobic IL, BMIM[$SbF_6$] gave similar conversion in slightly lower *ee*. In sharp contrast, using the hydrophilic ILs, BMIM[$BF_4$] and BMIM[OTf], the reaction hardly occurred (< 5 % yield) and the product was obtained in nearly racemic form. However, as the catalyst appeared to better immobilised in the hydrophilic ILs, the authors used a combination of BMIM[$PF_6$]: BMIM[OTf] with a volume ratio of 5: 1, to combine the beneficial effects of catalytic activity with immobilisation. In this case, the product was obtained in high *ee* and the catalyst-containing ionic liquid phase was recyclable after extraction of the product with hexane.[212] This example demonstrates how a combination of two ionic liquids (with different physical properties) may be able to provide the optimal reaction medium for a given reaction.

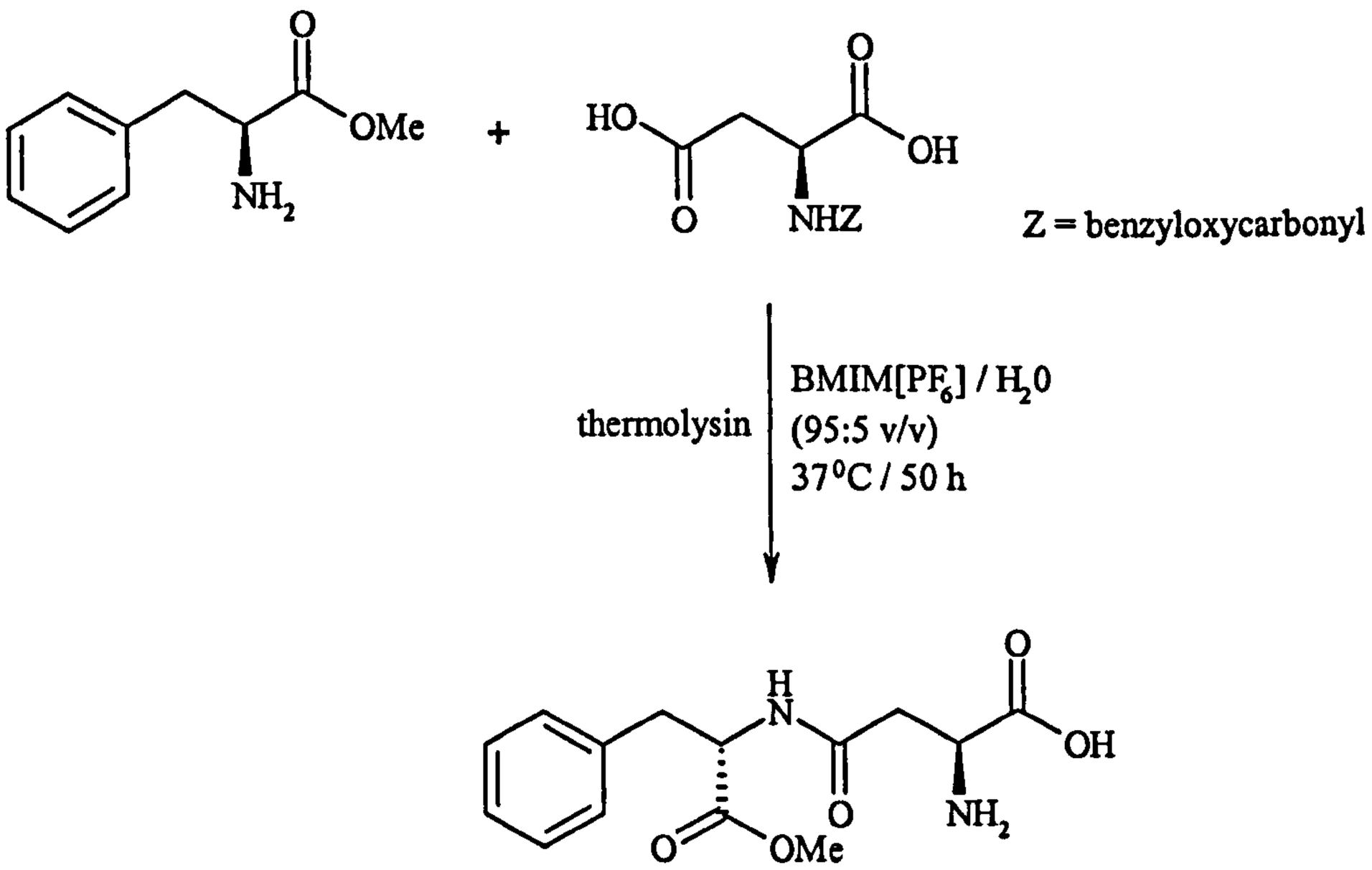
### 1.5.4 Biocatalysis

The term 'biocatalysis' is used for processes in which a starting material is converted into the desired product by using whole cells or (partially) purified enzymes. Products made this way range from bulk chemicals (such as acrylamide) to fine chemicals and chiral synthons (chiral amines or alcohols, for example). Enzymes and whole cells are often inhibited by products or substrates and this is commonly overcome by the use of reactors with *in situ* product removal. The addition of organic solvents to increase the solubility of substrates and / or products is a common practice.[213] Biphasic reaction conditions are also used if the substrate is toxic to the biocatalysts' cell membrane in high concentrations. The organic solvent acts as a substrate reservoir, which constantly release substrate to the

biocatalyst. Ionic liquids have been used as substitutes for organic solvents in organic-aqueous biphasic biotransformations.

It was already known in 1984[214] that the enzyme alkaline phosphatase is relatively stable in a 4: 1 (v/v) mixture of triethylammonium nitrate and water. More recently, Lye and co-workers[215] compared BMIM[$PF_6$] to toluene as reservoirs for 1,3-dicyanobenzene, which is converted to 3-cyanobenzamide and 3-cyanobenzoic acid by *rhodococcus* bacteria in aqueous buffer solution. They found that the ionic liquid is compatible with the cells, and the transformation profiles were similar in both systems. The authors observed aggregation of the cells at the interphase between water and toluene, whereas they were finely dispersed in both phases in the ionic liquid-water system; this is of advantage in the down-stream work-up.[215]

Erbeldinger *et al.* reported the use of the protease thermolysin for the synthesis of the dipeptide Z-aspartame (Scheme 1.28), in BMIM[$PF_6$] containing 5 % (v/v) water.[216] When either an organic solvent or the ionic liquid is used, proper control over the water content, or rather the water activity, is of crucial importance, as a minimum amount is necessary to maintain the enzyme's activity. The reaction rates were comparable to those found in conventional organic solvents such as ethyl acetate. However, the enzyme stability was

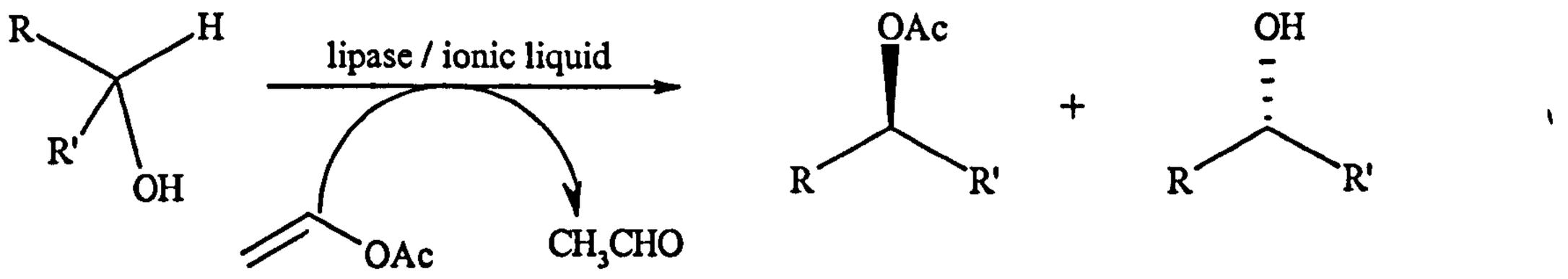



**Scheme 1.28 The thermolysin-catalysed reaction of *L*-phenylalanine methyl ester and carbobenzoxy-*L*-aspartate to Z-aspartame**

increased in the ionic liquid. The ionic liquid was recycled several times after the removal of non-converted substrates by extraction with water and product precipitation. Recycling of an enzyme had not been reported prior to this.

The majority of enzymes reported so far to be active in ionic liquids belong to a class of lipases which are designed in nature to work at aqueous / organic interfaces for the cleavage of fats and oils, making the cleavage products accessible as nutrients. Sheldon and co-workers were the first to demonstrate that *Candida Antarctica* lipase is able to catalyse a variety of transformations: transesterification, ammoniolysis and perhydrolysis, in BMIM[$BF_4$] or BMIM[$PF_6$] in the absence of water.[217] Reaction rates were comparable with or better than those observed in conventional organic media. For example, the reaction of octanoic acid with ammonia, in BMIM[$BF_4$] at 40 $^0$C, gave complete conversion to octanamide in 4 days compared to 17 days for the same conversion using ammonium carbamate in methyl isobutyl ketone.[218]

Subsequently, other groups have reported lipase-catalysed enantioselective transesterification of chiral alcohols (Scheme 1.29) in ionic liquids.[219,220] Kragl and coworkers investigated the kinetic resolution of 1-phenylethanol with nine different lipases in ten different ionic liquids.[221] Good activities and, in many cases, improved enantioselectivities were observed compared with the same reaction in MTBE. Rates and / or enantioselectivities were dependent on the anion as was also observed by Itoh and co-workers.[219] In addition, the products could be extracted with ether and the ionic liquid (BMIM[$PF_6$]), containing the suspended enzyme, could be recycled.[219]




**Scheme 1.29 Resolution of a secondary alcohol by esterification with vinyl acetate**

Similarly, Kim and co-workers observed markedly enhanced enantioselectivities in *Candida Antarctica* and *Pseudomonas cepacia* lipase-catalysed transesterifications of chiral alcohols in BMIM[$BF_4$] and BMIM[$PF_6$].[220]

## 1.6 GREEN TECHNOLOGY IN INDUSTRY

A growing environmental awareness and increasingly stringent legislation have focussed the attention of the chemical industry to reduce the detrimental impact it has on the environment. In a limited number of cases greener chemistry methodology is being applied in industry. Examples include the use of $scCO_2$ in the dry cleaning of clothes as a replacement for perchloroethylene.[33] The use of ionic liquids in commercial olefin oligomerisation has also been adopted.[181] Potential applications for green solvent processes in industry and every day services (such as dry cleaning) are rapidly expanding. However, chemical companies will not pay millions to completely revolutionise the processes they use for production simply because it is environmentally friendly. A further economic benefit must be apparent to promote the adoption of green technology. A good first approach to satisfy both the public and economic needs is to substitute existing parts of processes with high environmental impacts by new technology (retrofit). This phase is relatively cheap to achieve because plants will be kept in use while changes to the process may decrease dramatically the environmental impact. This has been shown in the case of the Dimersol® process, which can be retrofitted with the Difasol® unit.

Ionic liquids are expensive, however, they can be recycled. There are a number of newer ILs that are becoming available that are cheaper, but are still considerably more costly than traditional volatile organic solvents, (Acros Organics 'Ionic Liquids' Handbook). The production of ILs is possible in high yields (over 80%) but this requires extensive use of volatile organic solvents. Generally, production of 100g IL requires approximately 400 ml of volatile solvent, including dichloromethane. Acetone, methanol, hexane, mineral acids, alkyllithium reagents and other hazardous reagents are also used in the preparation of these ILs.[124] However, changing solvent systems can have a drastic effect on a reaction, effecting rates, chemo-, regio-, and stereo-selectivity. Among the many unique properties of ILs is an extraordinary degree of tunability, with relatively minor changes in the structure of the constituent cation and anion, thereby providing a means to optimise the solvent properties of an ionic liquid for a specific application. If employing an IL optimises product selectivity, then product separation processes can be avoided. And if catalytic efficiency improves the overall yield of a process by 10 or 20 %, waste is reduced as more starting material is converted into product.

There have also been concerns with extracting products from ILs. In the case where the product(s) are volatile, they can simply be distilled off. However, if the products are non-volatile, then use of volatile organic solvents becomes necessary to extract the

product(s). Considering that most of the solvent waste currently produced is as a result of extraction, as opposed to solvent being used as a reaction medium, this seems to undermine one of the reasons for using ILs to cut solvent waste in the first place. Fortunately, recent research has shown that $scCO_2$ can be employed to extract products from ILs, hence drastically reducing solvent waste.[30] Thus these green technologies are not mutually exclusive, but can be used in conjunction to produce synergistic improvements on current methods. By further developing these technologies it should be possible to make them even more attractive. The green alternatives briefly discussed in section 1.1.3 are likely to gain more and more momentum as chemists become familiar with the ideas, benefits and strategies involved in their applications. The potential economical, ecological and chemical advantages offered by such systems should assure their adoption on a wider scale in industry and discovery establishments. This does not mean that these novel green solvents will render traditional organic solvents obsolete or completely replace them, as this is not always practical, but are more likely to act as a complimentary methodology offering alternative strategies to today's modern synthetic chemist. New synthetic methodologies which provide reduced energy costs, improved safety, reduced environmental emissions, easier product separation and catalyst recycling, are essential for the continuing competitiveness of the UK in synthetic chemistry for the pharmaceutical industry.

## 1.7 MY RESEARCH

Ionic liquid research is currently undergoing an unprecedented explosion of interest (as outlined in sections 1.4 and 1.5); the number of papers and patents currently being published reflects both academic and industrial interest in using ILs in diverse areas ranging from synthetic and catalytic chemistry to biotechnology, electrochemistry, and material science. Their immediate advantage is their negligible vapour pressure, which considerably facilitates solvent recycling. Additionally, ionic liquids are immiscible with some organic solvents such as diethyl ether, and thus conventional extraction technology may be applied; alternatively thermally robust products may be distilled from the ionic liquids. Their polar character may have a positive effect on the reaction rate, selectivity and enantioselectivity. This project seeks to further establish the scope for the use of ionic liquids as solvents for non-catalysed and metal-catalysed organic chemistry. The content of the thesis is outlined overleaf.

***Chapter 2: Non-catalysed reactions***

There have only been two reports of nucleophilic aromatic substitution reactions in RTILs. Therefore we have investigated the reactivity of aryl halides in ionic liquid media, with potassium fluoride (aiming to improve the halex reaction) and aniline (to synthesis aromatic heterocycles). In all cases, the rate and selectivity are compared to the reaction in a conventional organic solvent. Alkylation reactions where yield is limited by the selectivity for the desired product are also considered here.

***Chapter 3: Metal-catalysed reactions***

Ionic liquids have been reported to dissolve transition metal catalysts to a higher degree than conventional solvents so the Heck reaction has been examined using a cyclopalladated complex and the capacity to reuse the catalyst in the ionic liquid assessed.

The use of Lewis acidic ionic liquid, BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.5 – 0.71), as catalyst and reaction medium for C-C bond forming reactions such as Diels-Alder reactions and particularly the synthesis of heterocycles such as the indoles, coumarins, and tetrahydro-β-carbolines has been investigated. The effect of the composition of the IL on yield and selectivity will be described in selected cases.

***Chapter 4: Copper catalysed asymmetric reactions***

Copper triflate complexed with a bisoxazoline will catalyse a number of reactions *e.g.* Diels-Alder, cyclopropanation, allylic oxidation with good *ee* and in some cases asymmetric induction is dependent on anion. Therefore, we have investigated some of these reactions in BMIM[OTf], BMIM[$PF_6$], BMIM[$NTf_2$], BMIM[$BF_4$] and examined the affect of anion on yield and enantioselectivity. The possibility of recovery and reuse of the catalyst ionic liquid solution has also been assessed in selected cases. When this work commenced, there were no reports of copper-bisoxazoline catalysed reactions in ionic liquids.

# Chapter Two

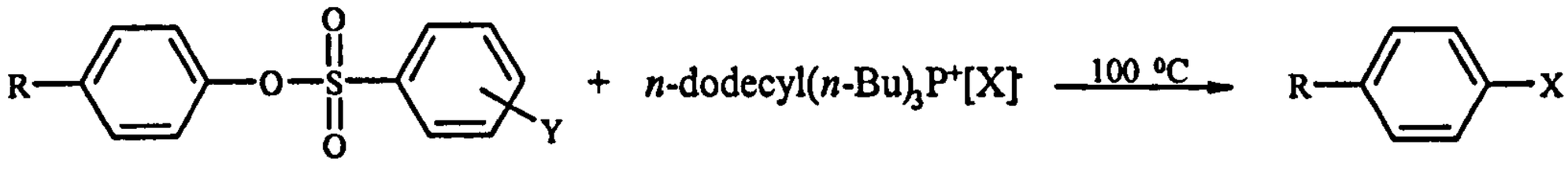
# Non-Catalysed Reactions

# Chapter Two - Non-Catalysed Reactions

## 2.1 NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS

### 2.1.1 Introduction

To date, there have been two reports of nucleophilic aromatic substitution reactions in ILs. The first uses dodecyltributylphosphonium halide RTILs[222] whereby the anion of the IL acts as the nucleophile. Rate constants were measured for the reaction in Scheme 2.1 and the reactivity of aromatic substrates with different substituents investigated in order to determine the transition state for the reaction.



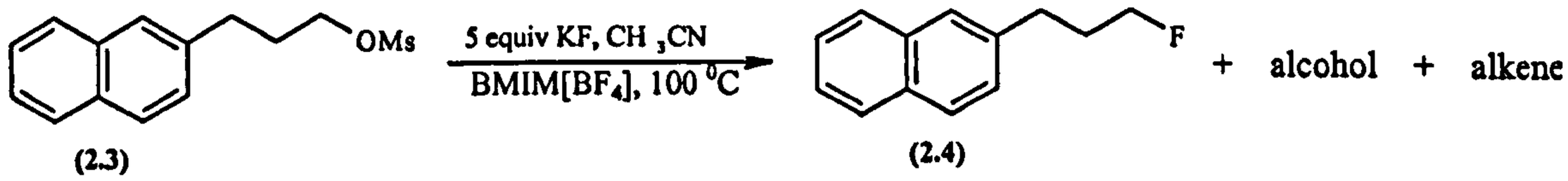

**(2.1)** **(2.2)**

R = H, $NO_2$, $CO_2Et$, $OCH_3$ X = Cl, Br, I
Y = *p*-Me, *p*-Br, *m*-$NO_2$

**Scheme 2.1 Nucleophillic Aromatic Substitution in Dodecyltributylphosphonium Salts**

It was found that ILs containing different halides were virtually identical in reactivity. The second example involves aromatic amination and is described in section 2.1.2.2.

There have also been a few reports of nucleophilic substitution reactions in RTILs. The nucleophilic fluorination of alkyl mesylates or alkyl halides to generate fluoroalkanes using KF in the presence of BMIM-ILs has been described.[223] In this method, ILs not only enhanced significantly the reactivity of KF but reduced the formation of byproducts such as alkenes and / or alcohol. Whereas the fluorination (2.3) with KF in an organic solvent such as $CH_3CN$ at 100 $^0$C occurred hardly at all, even after 24 h, the same reaction in BMIM[$BF_4$] as a reaction solvent was completed within 2 h, affording (2.4) (Scheme 2.2). Moreover the addition of 5 equivalents of water or using $CH_3CN$ as a cosolvent did not affect the outcome of the fluorination. This means that anhydrous conditions are not required for the reaction and catalytic amounts of BMIM[$BF_4$] can be used for the reaction.



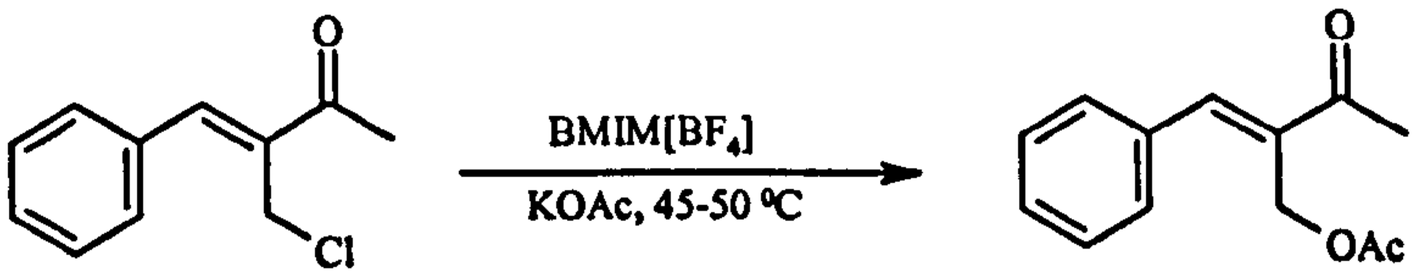

**(2.3)** **(2.4)**

**Scheme 2.2 Nucleophillic fluorination in BMIM[$BF_4$]**

In fact, using 0.1 equiv BMIM[$BF_4$], the fluorination proceeded much faster than using 2 equivalents of the 18-crown-6 PTC. Although BMIM[$PF_6$] and BMIM[$SbF_6$] displayed similar results to those obtained in BMIM[$BF_4$], the fluorination using BMIM[OTf] or BMIM[$NTf_2$] gave lower yields.[223] The reactivity of various metal fluorides, especially alkali, alkali earth, and transition-metal fluorides in the presence of various ILs for nucleophilic fluorination was described more recently.[224] The same fluorination of (2.3) using CsF in BMIM[$BF_4$] gave complete conversion to (2.4) without any byproducts in 20 mins, whereas using LiF, NaF, $CaF_2$, and AgF under the same conditions gave no product. The order of reactivity was found to be CsF > RbF > KF, since the reactivities of alkali metal fluorides depend on the tightness of ion pairs and the size of alkali metals.[225] Again, the reaction does not occur in an organic solvent such as acetonitrile and using 18-crown-6, the reaction is much slower and still gives traces of the alkene and alcohol byproducts.[224]

Wheeler *et al.* reported the reaction of benzyl chloride with cyanide to yield phenylacetonitrile quantitatively, using BMIM[$PF_6$] as solvent. (see Chapter 1, section 1.5.1).[162] This method avoids the need to employ a separate PTC to facilitate the reaction between the insoluble KCN and benzyl chloride, presumably this role is done by the imidazolium cation. These reactions were carried out at different temperatures. The reactions at 60 $^0$C and 80 $^0$C show expected pseudo-first-order kinetic behaviour in benzyl chloride (since the amount of cyanide available for reaction should be constant), however, the reaction at 40 $^0$C appeared to be zero order. This behaviour indicates that mass transfer of KCN into the solvent is probably the rate-limiting step at the lower temperature, which is consistent with the fact that the viscosity of the ionic liquid is observed to decrease steeply with an increase in temperature.

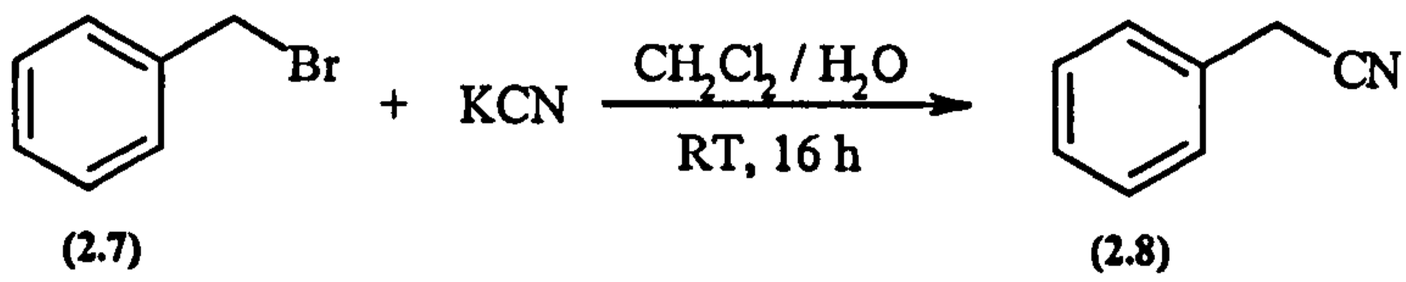
The $S_N2$ nucleophilic substitution of (Z)-keto allyl substrates with three anions $N_3^-$, $AcO^-$, and $PhSO_2^-$ was investigated in organic solvents and BMIM[$BF_4$]; the reaction was faster and gave higher yields in BMIM[$BF_4$].[226] For example, reaction of (Z)-keto allyl chloride (2.5) with KOAc gave 77 % yield of (2.6) in DMF after 24 h, compared to 92 % yield in BMIM[$BF_4$] after 2 h. (Scheme 2.3). The reaction did not proceed at all in THF, $CH_2Cl_2$, or dioxane.




(2.5) (2.6)

**Scheme 2.3 Nucleophillic substitution in BMIM[$BF_4$]**

More recently, BMIM[$PF_6$] was found to be an effective PTC for several representative nucleophilic substitution reactions under aqueous-RTIL phase transfer conditions.[227] In a biphasic blank experiment using a system consisting of sodium phenoxide in water and benzyl bromide in $CH_2Cl_2$, without BMIM[$PF_6$] only 3 % of phenyl benzyl ether was observed. On the other hand, the addition of BMIM[$PF_6$] to the biphasic aqueous / $CH_2Cl_2$ system gave 80 % conversion to product. Similar effects were also observed for the substitution on benzyl bromide with cyanide (5 % versus 47 %) and azide (37 % versus 90 %) in BMIM[$PF_6$].




(2.7) (2.8)

Without BMIM[$PF_6$] = 5 %
With 0.5 eq BMIM[$PF_6$] = 47 %

**Scheme 2.4 Nucleophilic displacement of benzyl bromide with KCN**

Substituting $CH_2Cl_2$ with BMIM[$PF_6$] for the nucleophilic substitution of benzyl bromide with KCN gave a 92 % yield of (2.8). This compares well to the 92 % yield reported using LiCN in refluxing THF[228] and quantitative yield reported using an 18-crown-6 PTC in $CH_3CN$ at ambient temperature,[229] but better than the 40 % yield reported using NaCN and methyl 2-pyridyl sulphoxide as a PTC in a benzene / aqueous biphase system after 30 h at 70 $^0$C.[230] For azide formation it was demonstrated that BMIM[$PF_6$] could be recycled 15 times to give a quantitative yield of product: after each cycle the aqueous phase was removed by decantation and the BMIM[$PF_6$] was extracted using diethyl ether.[227] More substrate and an aqueous phase containing $NaN_3$ were then added to the BMIM[$PF_6$] and the reaction repeated. Generally, ILs have been found to enhance rate and reactivity of nucleophiles in nucleophilic substitution reactions and therefore we focussed our attention on nucleophilic aromatic substitution (NAS) reactions with fluoride and aniline in RTILs.

Organic compounds with low fluorine content have received much attention because of their physiological properties.[231] Many efforts have been made to increase the potency of biologically active compounds by replacing an hydrogen atom with a fluorine. The synthesis of carbon fluorine bonds may be accomplished by functional group interconversion of carbon-hydrogen or carbon-halogen bonds, using either an electrophilic fluorinating agent such as Selectfluor(TM)[232] or elemental fluorine,[233] or a source of fluoride ion, using an alkali metal fluoride, hydrogen fluoride or amine hydrofluoride.[234,235] In particular, halogen exchange (Halex) processes involving nucleophilic substitution of

halogens by fluorine, upon reaction of a suitably activated halogenated substrate with an alkali metal fluoride, have been used extensively for the synthesis of various fluorinated aliphatic[236] and aromatic systems.[237]

Alkali metal salts are generally stable, economical, and easy to obtain and are traditional nucleophile sources in nucleophilic substitution processes. However, their limited solubility and low nucleophilicity in organic solvents can make the process of nucleophilic substitution difficult.[238] In the case of the use of tight ion pair salts, such as KF, as a nucleophile, this reaction still requires generally vigorous conditions. Thus, a number of metal fluoride reagents such as KF/18-crown-6,[239] polymer supported fluoride,[240] "spray-dried" KF,[241] and calcium fluoride supported on alkali metal fluoride[242] have been reported to solve these problems. 18-Crown-6 derivatives have been largely used to enhance the solubility and nucleophilicity of KF in organic media.[239] However, these procedures are still less effective than using tetraalkylammonium fluorides as the nucleophile. Tetrabutylammonium fluoride (TBAF) is the most commonly used reagent for the nucleophilic fluorination.[243,244] Despite their good solubility and reactivity, tetraalkylammonium fluorides have some drawbacks; they can cause the hydroysis of the starting halide to the corresponding alcohol (due to traces of moisture in the reagent) and elimination of alkyl halides because "naked" fluoride can act not only as a nucleophile but also as a base.[243] DeShong *et al.* recently developed the fluorinating agent, tetrabutylammonium triphenyldifluorosilicate (TBAT), which is soluble in a wide range of organic solvents, non-hygroscopic and less nucleophilic.[245] However, TBAT requires long reaction times due to its relative low reactivity. Moreover, it is relatively expensive and causes more chemical waste considering its large molecular weight compared with that of KF.

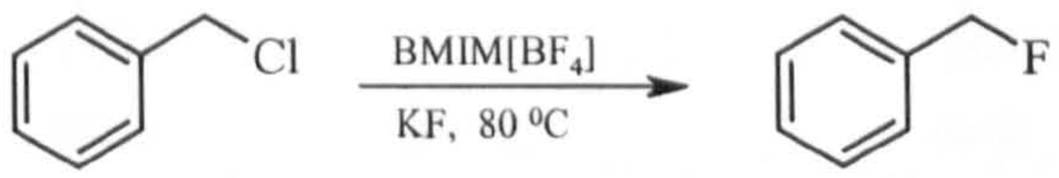
Generally, polar aprotic solvents,[246] particularly dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide (HMPA), and *N*-methylpyrrolidinone (NMP) are good solvents for nucleophilic substitution using metal salts. DMSO is the most commonly used solvent for this reaction despite the fact that it is a relatively poor solvent for KF (ca. 0.6 mmolar at 82 $^{0}$C).[247,248] Since the nucleophilicity of the fluoride ion is sufficiently high only in non hydrogen-bond donor solvents, where the solubility of KF is relatively low, these systems are heterogeneous (solid-liquid) in nature. It is generally accepted that dipolar aprotic solvents do not solvate $F^-$ to any significant extent and this characteristic along with their high boiling points and good thermal stabilities make them obvious choices as solvents in reactions using alkali metal fluorides. However, the high boiling

points and high water solubility of these solvents can create problems in the separation and purification of organic products from these solvents. Also, these reactions in polar aprotic solvents are generally less efficient in the absence of crown ether derivatives[249] or phase-transfer catalysts.[250]

## 2.1.2 Results and discussion

### *2.1.2.1 Nucleophilic aromatic substitution with fluoride*

Before proceeding to investigate NAS with fluoride, the nucleophilic substitution of benzyl chloride with KF was investigated in BMIM[$BF_4$] under the same conditions as those used by Wheeler *et al.* in the nucleophilic displacement of benzyl chloride with KCN. (Scheme 2.5)




**(2.9)** **(2.10)**

**Scheme 2.5 Nucleophilic substitution in BMIM[$BF_4$]**

A three fold excess of KF was reacted with benzyl chloride (1 Molar) in the IL. Before introduction of benzyl chloride, KF was stirred overnight in the IL so that uniform particles would form and the salt would reach an equilibrium concentration. However, solid KF was still observed throughout the reaction. The reaction mixture was then stirred at 80 $^0$C for 12 h, after which time $^1$H NMR spectroscopy showed complete conversion of the starting material so the product was isolated by extraction with ether. An isolated yield of 94 % was attained which was pure by NMR and GC analysis. To test the generality of this result for the other ILs, the reaction was repeated in BMIM[$PF_6$], BMIM[OTf] and BMIM[$NTf_2$]. For comparison, the reaction was also performed in $CH_3CN$. The results are shown in Figure 2.1.

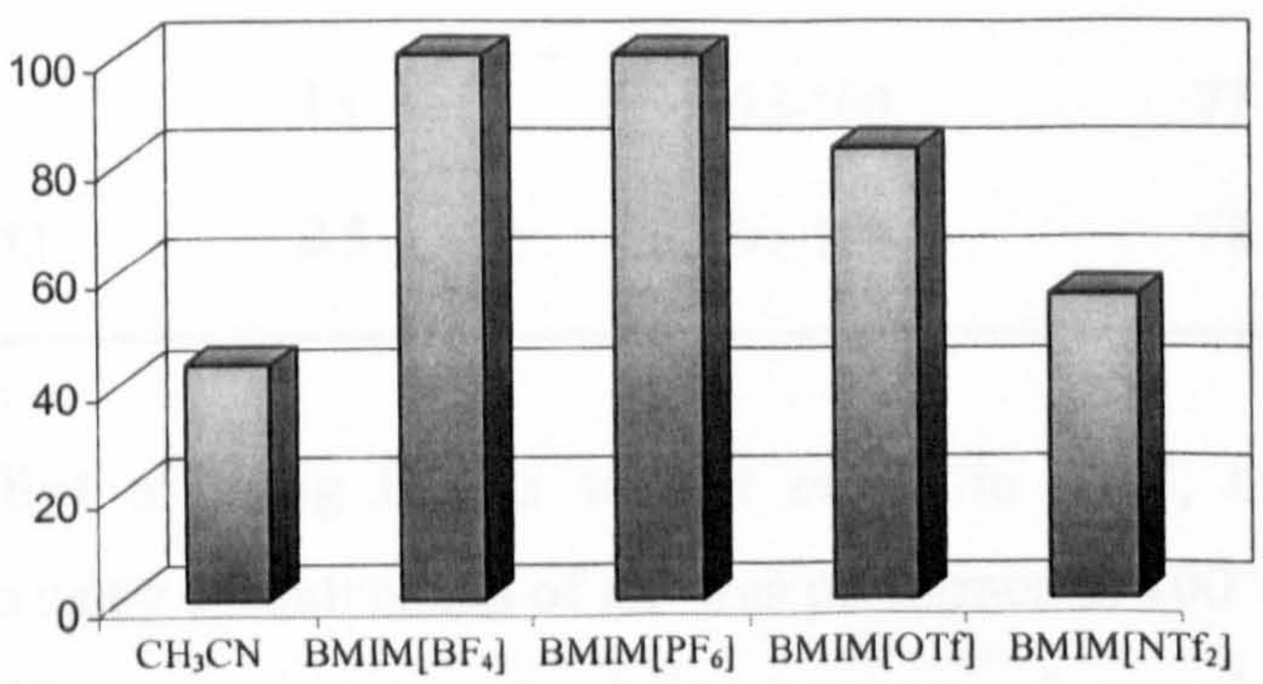
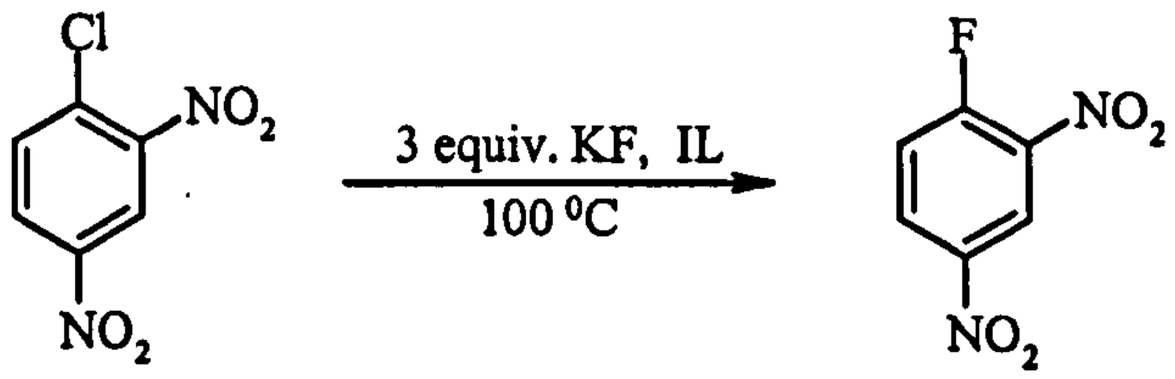



**Figure 2.1 Yields from the nucleophilic substitution of benzyl chloride with KF in RTILs**

Figure 2.1 shows that indeed the reactivity of KF is enhanced in ILs compared to organic media. Only a 43 % conversion of benzyl chloride was observed in $CH_3CN$ after 12 h, whereas BMIM[$BF_4$] and BMIM[$PF_6$] showed complete conversion in the same time. The conversion was slightly less in BMIM[OTf] (83 %) and only 56 % in BMIM[$NTf_2$] *i.e.* not much better than in MeCN. This order of reactivity for fluorination reactions using KF, BMIM[$BF_4$] ≈ BMIM[$PF_6$] > BMIM[OTf] > BMIM[$NTf_2$], is consistent with that reported previously for the fluorination of (2.3) using KF (Scheme 2.2).[223]

Having established that BMIM[$BF_4$] and BMIM[$PF_6$] can enhance the reactivity of KF, the nucleophilic aromatic substitution (NAS) reaction of 2,4-dinitrochlorobenzene with KF in RTILs (Scheme 2.6) was investigated.




**(2.11)** **(2.12)**

**Scheme 2.6 NAS of dinitrochlorobenzene with KF**

To date, there have been no reports on NAS in RTILs. This reaction is reported to proceed without a solvent at 200-230 $^0$C, however the use of a solvent has shown a significant increase in the rate of reaction and proceeds smoothly at 100 $^0$C in DMF or DMSO.[251] The accelerating effect of various solvents in NAS of chloride for fluoride is shown in Table 2.1.

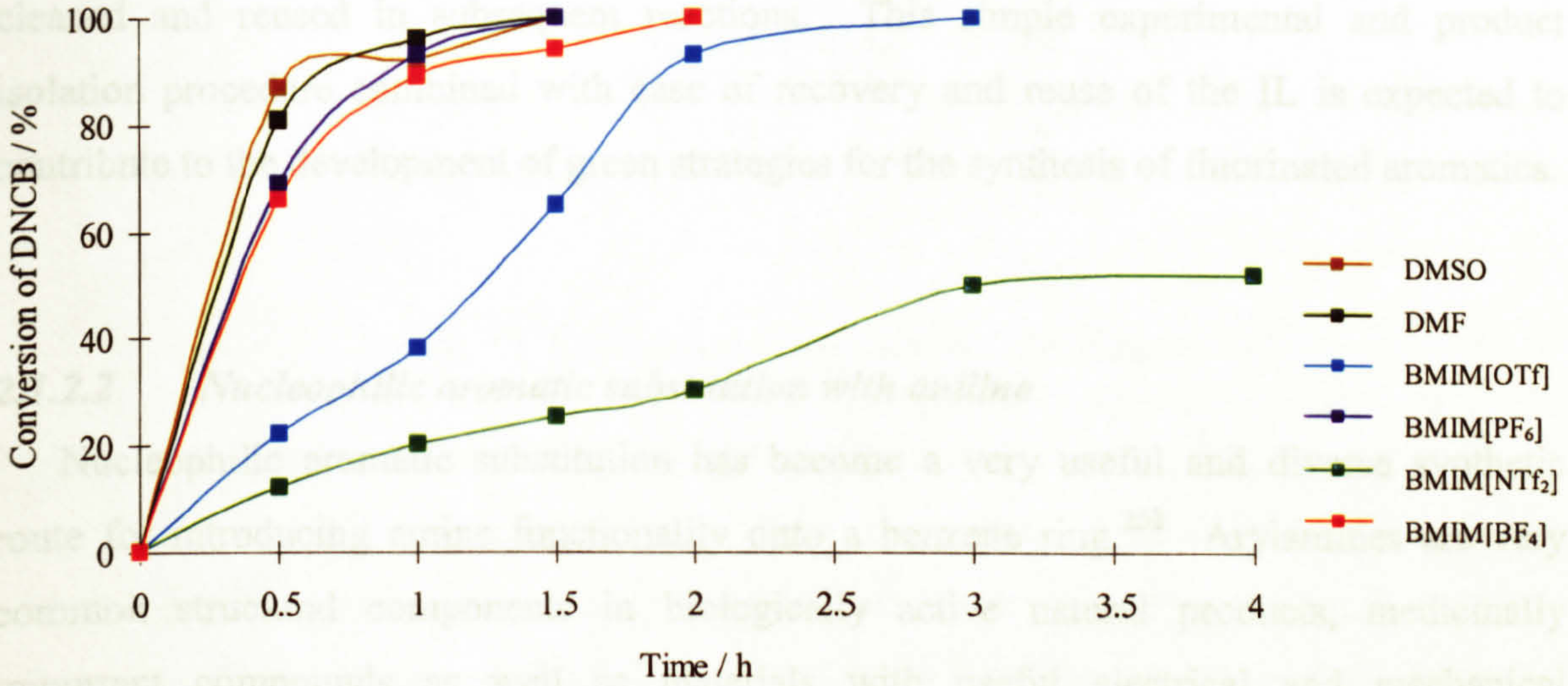
**Table 2.1. The effect of solvent on the NAS of 2,4-dinitrochlorobenzene with KF[251]**

| Solvent | Time / h | Temperature/ $^0$C | Yield / % |
|---|---|---|---|
| No solvent | 0.5 | 200-230 | 62 |
| Nitrobenzene | 4 | 195-210 | 76 |
| Benzonitrile | 2 | 150-170 | 57 |
| DMF | 0.5 | 140-150 | 77 |
| DMF | 13 | 95-100 | 77 |
| DMSO | 2.5 | 95-100 | 78 |

To compare the effect of using ILs as solvent media in NAS, the reaction of 2,4-dinitrochlorobenzene using 3 equivalents of KF was performed at 100 $^0$C, in parallel in the different solvents. These systems are also heterogeneous. A sample was withdrawn at

regular time intervals and analysed by $^1$H NMR spectroscopy and GCMS to check the conversion of the starting material. Only starting material and product were observed in all cases. The results are shown in Figure 2.2.

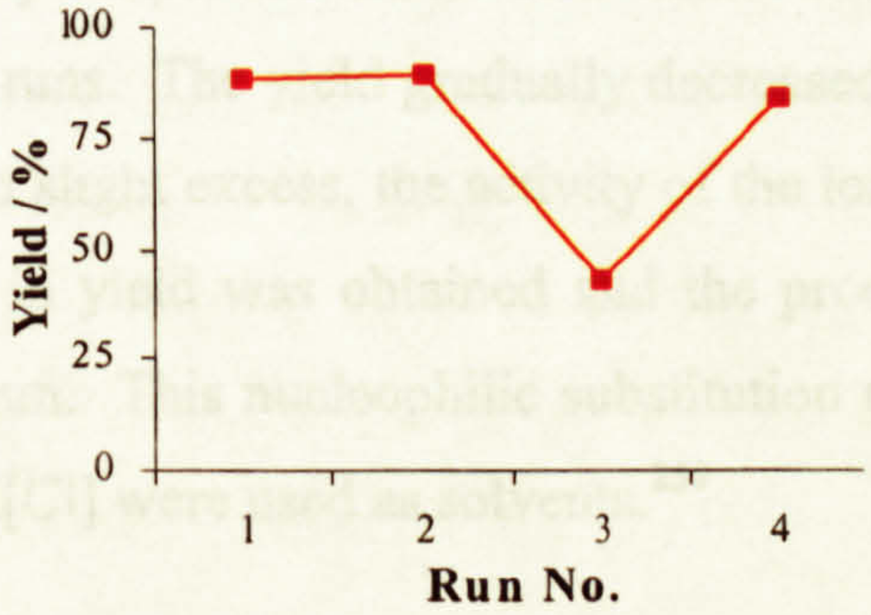
**Figure 2.2 The affect of IL anion on the rate of substitution with $F^-$**




DMSO, DMF and BMIM[$PF_6$] showed complete conversion of 2,4-dinitrochlorobenzene to 2,4-dinitrofluorobenzene after 1.5 h, under these conditions which shows that there is little difference in the reactivity of KF in these solvents. However, complete conversion took 2 h in BMIM[$BF_4$], 3 h in BMIM[OTf], and only a 52 % conversion was observed after 4 h in BMIM[$NTf_2$]. Thus the rate decreases in the order BMIM[$PF_6$] > BMIM[$BF_4$] > BMIM[OTf] > BMIM[$NTf_2$] as found for the substitution of benzyl chloride.

The recyclability of the IL was then examined. At the end of the reaction, the product was vacuum distilled from BMIM[$PF_6$] using a Kugelrohl oven. 2,4-dinitrofluorobenzene had limited solubility in organic solvents which are immiscible with BMIM[$PF_6$] so a liquid-liquid extraction wasn't feasible. An isolated yield of 88 % was obtained. 2,4-dinitrochlorobenzene and another 1 equivalent of KF was then added to the same batch of IL and the reaction mixture stirred at 100 $^0$C for 16 h. Figure 2.3 shows the yields obtained over 4 runs.

**Figure 2.3 Repeated NAS in BMIM[$PF_6$]**



A significant drop in yield was noted after the second run presumably due to the build-up of KCl by-product and lower concentration of KF in the IL. Therefore, the IL was washed with water to remove traces of all salts after the third run, dried under vacuum overnight and replenished with 3 equivalents of KF. The reaction was repeated under the same conditions to yield 84 % product. This demonstrates the ease with which the IL can be cleaned and reused in subsequent reactions. This simple experimental and product isolation procedure combined with ease of recovery and reuse of the IL is expected to contribute to the development of green strategies for the synthesis of fluorinated aromatics.

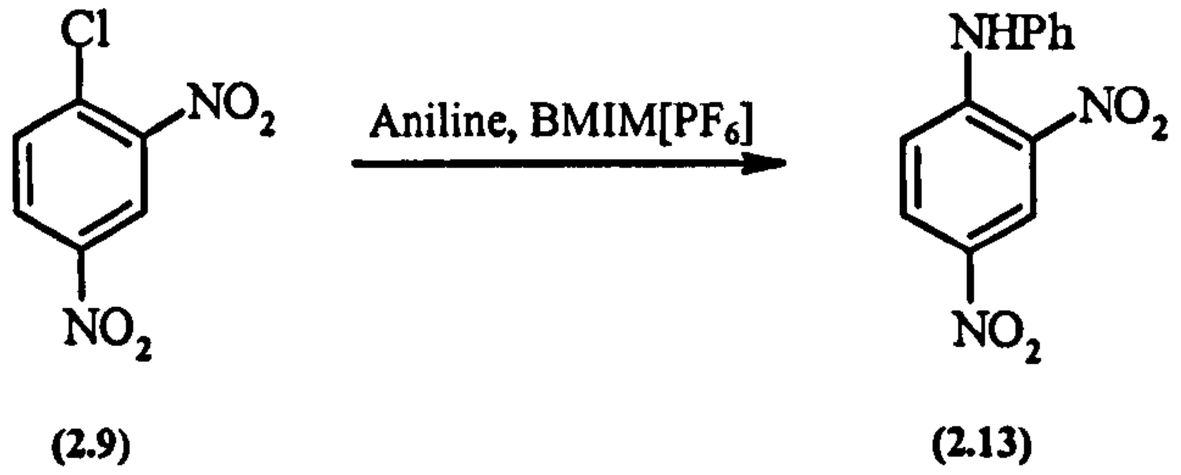
### *2.1.2.2 Nucleophilic aromatic substitution with aniline*

Nucleophilic aromatic substitution has become a very useful and diverse synthetic route for introducing amine functionality onto a benzene ring.[252] Arylamines are very common structural components in biologically active natural products, medicinally important compounds as well as materials with useful electrical and mechanical properties.[253] Substituted arylamines are widely used clinically as antihistamine, anti-hypertensive, and anti-inflammatory drugs. They are also an important class of compounds in neuropharmaceuticals.[254]

Classical methods for the synthesis of arylamines typically require a large excess of base, highly polar solvents such as DMF or DMSO at high temperatures with highly activated aryl halides[255] and under high pressure conditions.[256] Hartwig[257] and Buchwald[258] have recently reported the amination of both activated and unactivated aryl halides with amines using Pd and Ni as catalysts under mild conditions.

During the course of our work, RTILs have been described as recyclable solvent systems for the synthesis of arylamines. Reaction of a variety of aryl halides with a range of secondary amines at room temperature in BMIM[$PF_6$] and BMIM[$BF_4$] gave arylamines in excellent yields.[259] This method was shown to be effective with sterically hindered and highly functionalised aryl halides. Since the products were only weakly soluble in the ILs, they were easily separated by simple extraction with ether. The IL was washed with ether and recycled in subsequent runs. The yield gradually decreased over four runs. However, when the amine was used in slight excess, the activity of the ionic liquid was consistent in the runs, thus no decrease in yield was obtained and the products obtained were of the same purity as in the first run. This nucleophilic substitution reaction was not successful when *n*-$Bu_4N$[Cl] or BMIM[Cl] were used as solvents.[259]

We decided to test the generality of the results obtained for NAS with fluoride to other substrates and as there had been no reports of NAS reaction with amines in ILs when this work commenced, we investigated the NAS of 2,4-dinitrochlorobenzene with aniline to give (2,4-dinitrophenyl)-phenylamine (Scheme 2.7).




(2.9) (2.13)

**Scheme 2.7 NAS of dinitrochlorobenzene with aniline**

The reaction was carried out using a slight excess of aniline at 80 $^0$C. In this case, the reaction mixture was homogeneous leading to a much faster reaction which was complete within 1 h. The product was precipitated out of the IL by adding saturated $NaHCO_3$ solution to afford a bright red solid. The red solid was then filtered off, washed with water and recrystallised from ethanol. The yields are given in Table 2.2.

**Table 2.2. NAS of 2,4-dinitrochlorobenzene with aniline in RTILs**

| Solvent | Yield /% |
|---|---|
| DMSO | 91 |
| BMIM[$PF_6$] | 89 |
| BMIM[OTf] | 88 |
| BMIM[$NTf_2$] | 90 |
| BMIM[$BF_4$] | 92 |

All the reactions resulted in a high yield of product and there appears to be no significant affect of the IL anion. However, we wished to examine whether the IL could be reused after the aqueous work-up. In the case of BMIM[$PF_6$] and BMIM[$NTf_2$], this was relatively straightforward as the filtrate was biphasic so the aqueous layer could be decanted to leave the IL which was then dried under vacuum. However, a repeated reaction in the same batch of either IL gave yields of less than 60 % after an 8 h reaction period, indicating that the IL may not be a pure as the first run. In attempting to reuse the water-miscible ILs, BMIM[OTf] and BMIM[$BF_4$], a continuous batch extraction using ether was set-up over three days to extract all the (2.13) from the IL as the product has

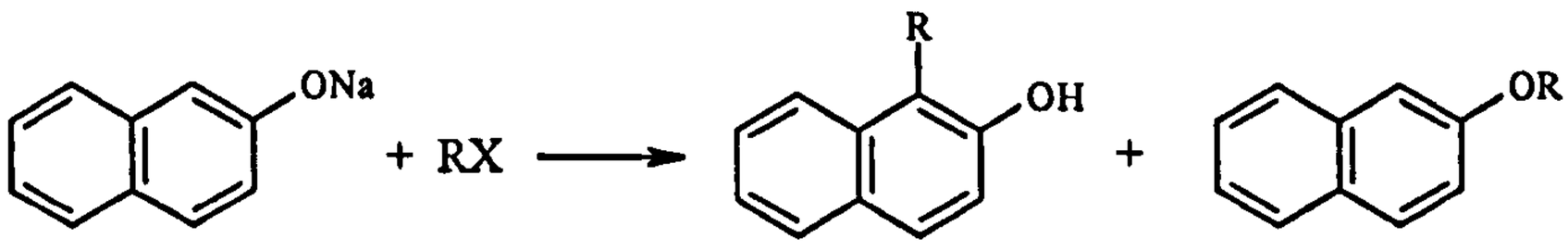
limited solubility in ether. Using this method it was found that some IL was extracted with the product, and in the case of BMIM[OTf] this resulted in the formation of an oil rather than the desired solid. Therefore, the continuous batch extraction was applied after adding saturated $NaHCO_3$ solution to the IL at the end of the reaction. As the IL is preferentially soluble in water, minimal IL leaching into the product phase was observed and the product was isolated quantitatively. A small amount of IL was still extracted into the product phase which meant that the product still had to be purified by recrystallisation. The IL was dried under vacuum and the reaction repeated by adding fresh substrates, but in this case < 40 % yield was obtained, possibly due to the build-up of the salt by-product after the first reaction.

Although in this case we have been unable to recycle the IL to perform optimally, we have demonstrated that NAS reactions can be successfully performed in RTILs with amines to provide a high yield of product. A method to recover and reuse the IL would need to be developed before such a procedure can become economically viable.

## 2.2 ALKYLATION REACTIONS

### 2.2.1 Introduction

Chapter one (section 1.5.1) described the regioselective alkylation of indole in BMIM[$PF_6$]. Other examples of regioselective alkylation reactions in ILs have also been described. For example, molten phosphonium and ammonium halides were investigated as solvents for *C vs. O*-alkylation of sodium β-naphthoxide with benzyl halides and lead to highly regioselective *O*-alkylation.[260] (See Scheme 2.8).




(2.14) (2.15) (2.16)

**Scheme 2.8 *C vs. O*-alkylation in high temperature ILs**

It is well known that the regioselectivity of the alkylation of β-naphthol salts with benzyl bromide strongly depends upon the nature of both the counter ion and the solvent.[261] Broadly speaking, the freer the nucleophile, the higher the *O / C* alkylation ratio. For instance, in the reaction of sodium β-naphthoxide with benzyl bromide in protic solvents, the distribution varies with the acidity of the solvent (the more acidic the alcohol, the lower the *O/C* alkylation ratio). In aprotic solvents, *O*-alkylation is favoured (*e.g. O / C*

alkylation = 60 / 36 in THF), and in dipolar aprotic solvents, *O*-alkylation occurs with high selectivity (> 95 %). *n*-$Bu_4PBr$, *n*-$Bu_4NBr$, *n*-$Bu_4PCl$ and EMIM[Br] induced high regioselectivity for the *O*-alkylation product, thus indicating similar behaviour to classical dipolar aprotic solvents.[260]

More recently, the alkylation of phenol with *tert*-butyl alcohol was reported to be catalysed by BMIM[$PF_6$].[262] This acid-catalysed reaction can lead to the *C*-alkylated product (*tert*-butyl phenol, TBP) and / or the oxygen alkylated product (phenyl alkyl ether, *t*-BPE). The product selectivities are largely dependent on the acidity and the reaction temperature. Weakly acidic catalysts lead to mainly *t*-BPE, whereas strong acid catalysts or high reaction temperatures produce TBP. Alkyation of phenol in BMIM[$PF_6$] gave a mixture of TBP and 2,4-DTBP, and no phenyl ethers were detected. 2,4-DTBP was isolated as the major product with selectivity greater than 75 %. The phenol conversion was also higher than that reported in organic solvents such as tetrachloromethane. We investigated a few examples of alkylation in RTILs to examine the effect of counterion on the regioselectivity.

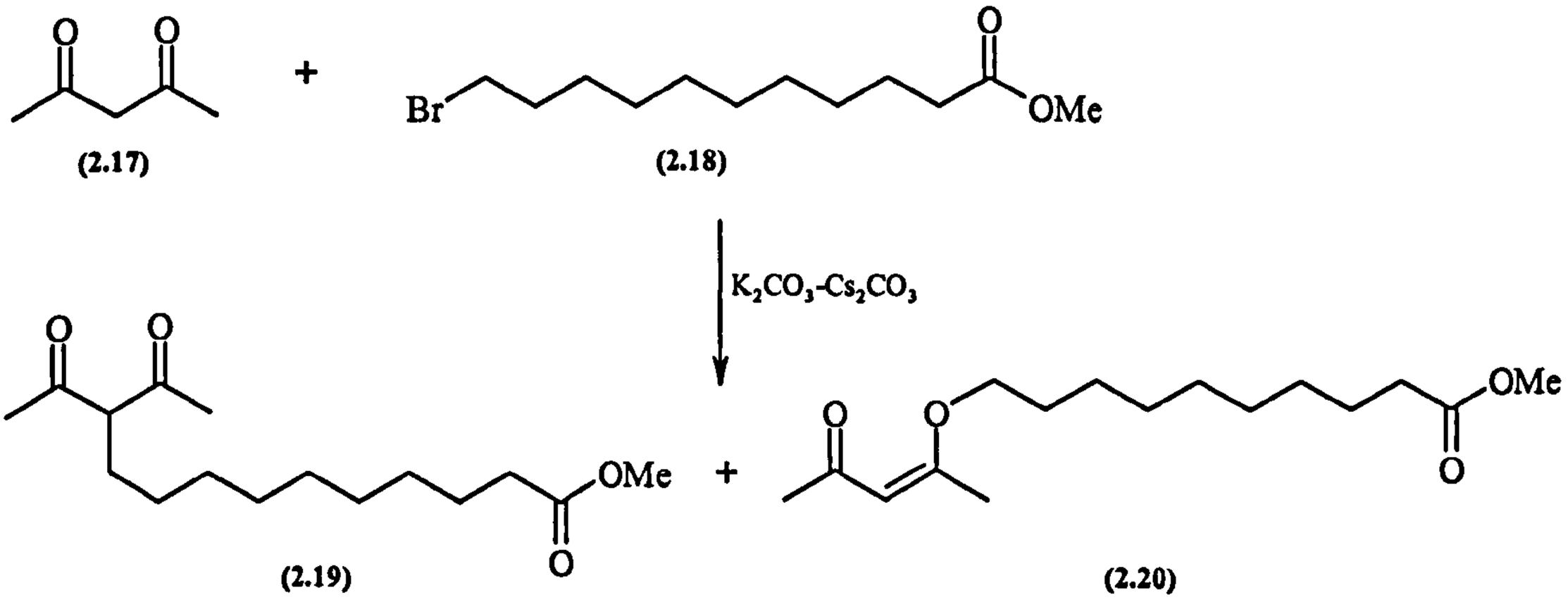
## 2.2.2 Results and discussion

### *2.2.2.1 Alkylation of Pentane-2,4-dione with ω-Bromoacid esters*

A difficulty that frequently arises in the alkylation of β-dicarbonyl compounds is the concurrent formation of both *C*- and *O*-alkylated products as well as in some cases, products from competing Claisen condensations, β-diketone cleavage, and coupling of the air oxidised enol salts of both starting material and its monoalkylated product. *O*-alkylation presents a serious competitive reaction when the enol content of the *β*-diketone or *β*-ketoester is high, but attempts to limit this and other side reactions have usually met with limited success.[263,264] It is reported that *O*-alkylation may be inhibited by preventing the existence of large amounts of free enolate anion, which may be achieved by careful control of conditions or by shielding the oxygen atom by association with a metal cation or with a hydrogen-bonding solvent.[265] The most successful of the synthetic procedures involves either the use of tetraalkylammonium fluorides as bases in reactions of pentane-2,4-dione and other acyclic *β*-dicarbonyl compounds with low molecular weight alkyl iodides,[266] or the reaction of crystalline thallium(I) enolates with short chain alkyl iodides.[267] The use of low molecular weight iodides appears to be essential with methyl

iodide working best.[264-267] However it is more difficult to achieve mono-*C*-alkylation of *β*-dicarbonyl compounds using high molecular weight ω-bromoesters.

Lightner *et al.* found that pentane-2,4-dione could be mono-alkylated with ethyl bromoacetate in $CH_2Cl_2$ using 9:1, $K_2CO_3$: $Cs_2CO_3$ as base to give a high yield of the *C*-alkylated product.[268] $Cs_2CO_3$ is more soluble than $K_2CO_3$ and $Cs^+$ apparently serves as a phase transfer agent to draw the $CO_3^{2-}$ base into solution. However, the procedure was not adequate for the alkylation of pentane-2,4-dione with longer chain ω-bromo esters and it led to unacceptably high levels of *O*-alkylation. In this case, the use of a 5:1 (v/v) mixture of $CH_3CN$-DMSO was found to increase selectivity for the *C*-alkylated product. The alkylation of pentane-2,4-dione by methyl 11-bromoundecanoate in 5: 1 $CH_3CN$-DMSO is reported to give a 63: 37 % ratio of the *C*- and *O*-alkylated products[269] (2.19 and 2.20 in Scheme 2.9).




**Scheme 2.9 Alkylation of Pentane-2,4-dione with methyl 11-bromoundecanoate**

We examined the same reaction in RTILs in an attempt to improve the 63 % yield of the *C*-alkylated product (2.19). (2.17) and (2.18) were both soluble in the ILs but due to the presence of a solid base, the reactions were heterogeneous. The reactions were stirred at 65 $^0$C for 24 h, and then a sample of the reaction mixture withdrawn for GCMS analysis to analyse the *C* / *O* product ratio. The reactions were carried out in parallel in acetone, DMSO, $CH_3CN$ and the RTILs, and the results are shown in Table 2.3 overleaf.

Using acetone, DMSO or $CH_3CN$ with $K_2CO_3$ as base (entries 1-3) gave the lowest levels of selectivity, as documented in the literature for high molecular weight bromo esters.[268] Interestingly, (2.18) gave a best *C*: *O* alkylation ratio of 72: 28 in BMIM[OTf], BMIM[$PF_6$], BMIM[$NTf_2$] and BMIM[$BF_4$] using $K_2CO_3$ as base. This is the same as the best reported ratio which uses 5:1 $CH_3CN$: DMSO as solvent with 9:1 $K_2CO_3$: $Cs_2CO_3$ as base,[268] (compare entries 4, 5, 6, 7 and 10). This demonstrates that using ILs as solvent

can circumvent the need to use a more expensive base and mixtures of solvents for this reaction. Using just $K_2CO_3$ in 5:1 $CH_3CN$: DMSO led to a lower selectivity of 56: 44 for the *C*: *O* alkylated products (entry 8), similar to that observed in the other organic solvents. It would seem that the although the solubility of $Cs_2CO_3$ may account for the increased *C*-alkylated product in the $CH_3CN$: DMSO mixture, it is unlikely that $Cs_2CO_3$ is any more soluble in the ILs than $K_2CO_3$, as using a 9: 1 ratio of $K_2CO_3$: $Cs_2CO_3$ as base gave a slightly lower selectivity of 68: 32 for the *C*: *O* –alkylated products (entry 12).

**Table 2.3. The alkylation of 2,4-pentanedione with methyl 11-bromoundecanoate**

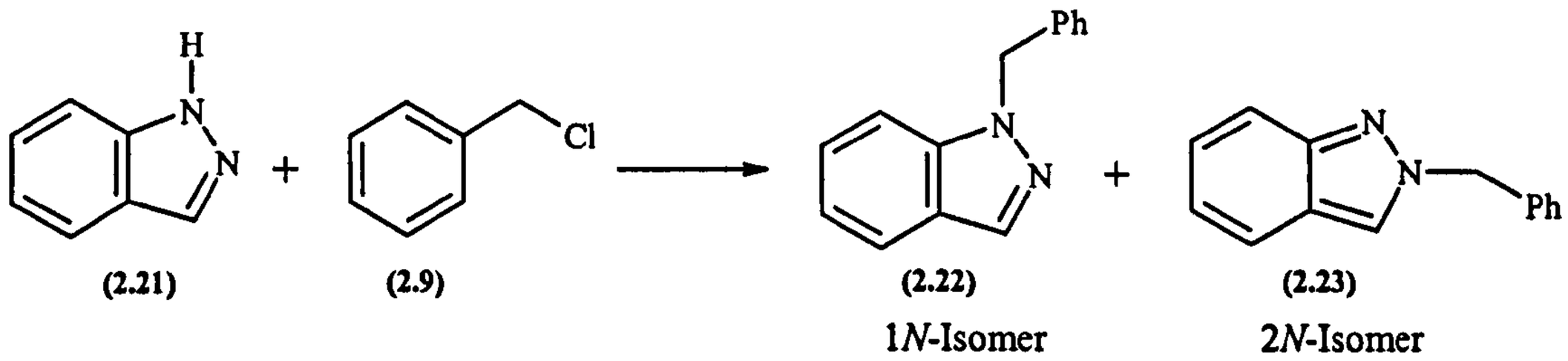
| Entry | Solvent | Base | *C*-alkylation[a] | *O*-alkylation[a] |
|---|---|---|---|---|
| 1 | Acetone | $K_2CO_3$ | 60 | 40 |
| 2 | DMSO | $K_2CO_3$ | 57 | 43 |
| 3 | $CH_3CN$ | $K_2CO_3$ | 65 | 35 |
| 4 | BMIM[OTf] | $K_2CO_3$ | 72 | 28 |
| 5 | BMIM[$PF_6$] | $K_2CO_3$ | 72 | 28 |
| 6 | BMIM[$NTf_2$] | $K_2CO_3$ | 72 | 28 |
| 7[b] | BMIM[$BF_4$] | $K_2CO_3$ | 72 | 28 |
| 8 | 5: 1, $CH_3CN$: DMSO | $K_2CO_3$ | 56 | 44 |
| 9[c] | 5: 1, $CH_3CN$: DMSO | 9:1, $K_2CO_3$: $Cs_2CO_3$ | 65 | 35 |
| 10 | 5: 1, $CH_3CN$: DMSO | 9:1, $K_2CO_3$: $Cs_2CO_3$ | 72 | 28 |
| 11[d] | BMIM[$PF_6$] | 9:1, $K_2CO_3$: $Cs_2CO_3$ | 66 | 34 |
| 12 | BMIM[$PF_6$] | 9:1, $K_2CO_3$: $Cs_2CO_3$ | 68 | 32 |

Reactions performed using 2 mmol of reagents in 1 ml solvent at 65 $^0$C for 24 h [a]Determined by GCMS [b]Isolated yield of 72 % on 10 mmol scale [c]Reaction performed at RT only gave 10 % conversion [d]Reaction performed at RT only gave 12 % conversion.

The reaction was also carried out at room temperature to see whether the solvent has an affect on the reactivity of the bromo ester. However, after 24 h, a conversion of 10 % and 12 % in the $CH_3CN$: DMSO mixture and BMIM[$PF_6$], respectively (entries 9 and 11), showed that the solvent didn't influence the reactivity of the substrates significantly and a temperature of 65 $^0$C was necessary for the reaction to proceed in 24 h. Overall, we have demonstrated that ILs give the highest level of selectivity for (2.19) using $K_2CO_3$ as base, and the IL anion does not affect this selectivity.

### *2.2.2.2 Selective alkylation of indazole*

Indazole is well known as an aza analogue of indole, and a number of indazole derivatives have powerful pharmacological activities, for example, anti-inflammatory, anti-tumor, anti-HIV, anti-depressant, and contraceptive activities, etc.[270] *N*-alkylation of secondary amines with alkyl halides is an important synthetic method to obtain tertiary amines. The alkylation of indazole with benzyl chloride (Scheme 2.10) is reported using equimolar amounts of reactants, tetrabutylammonium bromide or bisulphate as catalyst, and xylene as solvent to give an 80 % yield of the 1*N*: 2*N* isomers in a 60: 40 ratio.[271]




(2.21) (2.9) (2.22) 1*N*-Isomer (2.23) 2*N*-Isomer

**Scheme 2.10 *N*-Alkylation of indazole**

The preparation of 1-benzylindazole was examined in ionic liquid media using benzyl chloride as alkylating agent, in order to improve selectivity for the 1*N*-isomer. The reaction was carried out under the previously reported conditions.[271] A mixture of indazole, benzyl chloride, one equivalent of $K_2CO_3$ and one equivalent KOH was heated to 140 $^0$C for 16 h. A sample was withdrawn from the reaction mixture and analysed by GCMS to determine the ratio of 1*N*- and 2*N* isomers. The products were then extracted with ether and separated by preparative TLC using 95: 5, chloroform / acetonitrile as eluent. The results are shown below.

**Table 2.4. The alkylation of indazole with benzyl chloride**

| Entry | Solvent | PTC | Ratio of 1*N*: 2*N*-Isomers[a] |
|---|---|---|---|
| 1 | Xylene | $^n$Bu$_4$N[Br] | 58 : 42 |
| 2 | BMIM[NTf$_2$] | - | 64 : 36 |
| 3 | BMIM[NTf$_2$][b] | - | 67 : 33 |
| 4 | BMIM[NTf$_2$][c] | - | 70 : 30 |
| 5 | BMIM[OTf] | - | 66 : 34 |
| 6 | BMIM[PF$_6$] | - | 65 : 35 |

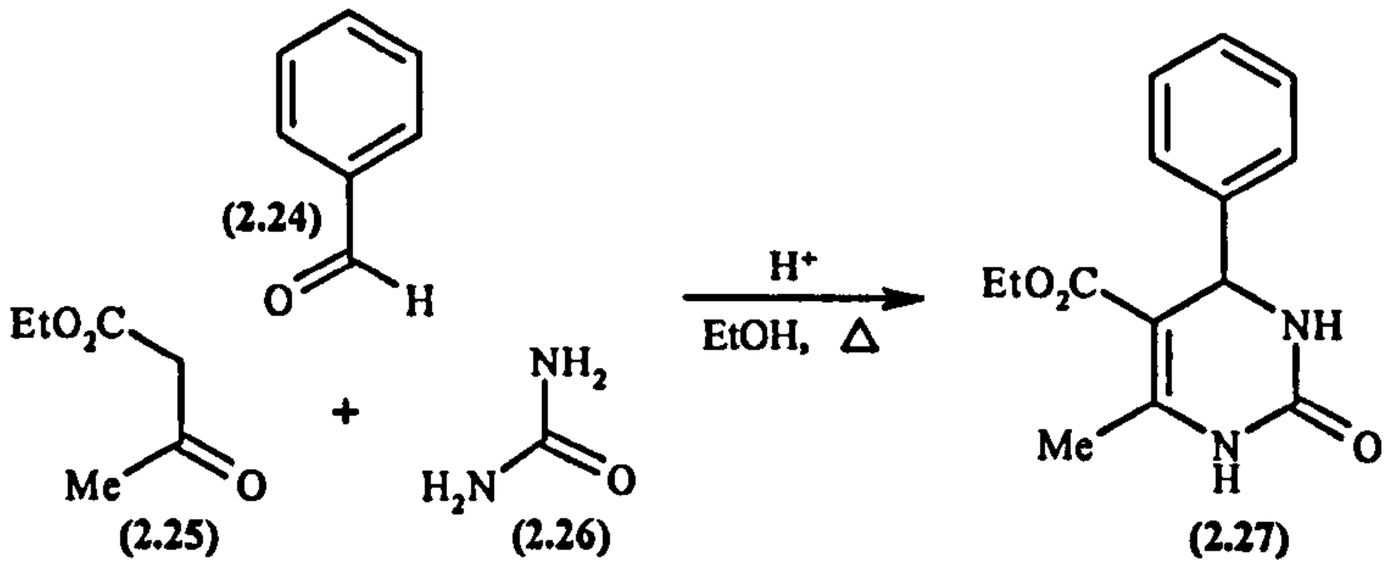
Reaction performed using 1 mmol indazole,1 mmol benzyl chloride, 1 mmol $K_2CO_3$, 1 mmol KOH in 2 ml solvent at 140 $^0$C for 16 h. [a]Ratio of isomers integrated by GCMS and $^1$H NMR.[271] [b]Using 1 mmol benzyl bromide. [c]Using 1 mmol benzyl bromide and 2 mmol $K_2CO_3$.

We found that using xylene as a solvent for the alkylation of indazole, the presence of 5 % tetrabutylammonium bromide was necessary to achieve complete conversion of the starting materials within the reaction time. A selectivity of 58: 42 for the 1*N*: 2*N* isomers was found (entry 1). Using BMIM[OTf], BMIM[$PF_6$] or BMIM[$NTf_2$] as solvent gave a moderate improvement in selectivity, averaging a 65: 35 ratio for the 1*N*: 2*N* isomers (see entries 2, 5, and 6) and no PTC was needed in these reactions. The effect of the alkylating agent on selectivity was investigated by using benzyl bromide rather than benzyl chloride. In this case a small improvement for the 1*N*-isomer was noted (entry 3). Using two equivalents of $K_2CO_3$ (instead of KOH) proved to be the most effective method to improve selectivity giving a 70: 30 ratio of isomers, 1*N*: 2*N* respectively, (entry 4). Substituting KOH for $K_2CO_3$ may minimise formation of the imidazolium carbene that is known to form from BMIM-ILs in the presence of such strong base.[104] This could be tested using the 2-methyl substituted imidazolium salt. Overall, we have shown that ILs behave as PTCs in the alkylation of indazole and provide moderate improvements in selectivity for the 1*N*-isomer, compared to conventional solvents. The IL anion had no effect on the selectivity for this reaction, as previously noted for the alkylation of pentane-2,4-dione.

## 2.3 BIGINELLI CONDENSATION

### 2.3.1 Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry,[272,273] offering significant advantages over conventional linear-type syntheses in the drug discovery process where a premium is put on speed, diversity, and efficiency.[274] In such MCRs, three or more reactants come together in a single reaction to form new products that contain portions of all the components. One such MCRs is the Biginelli dihydropyrimidine synthesis. In 1893, Pietro Biginelli reported on the acid-catalysed cyclocondensation of benzaldehyde (2.24), ethyl acetoacetate (2.25) and urea (2.26), to afford 3,4-dihydropyrimidin-2(1H)-one (2.27), (Scheme 2.11).[275] The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product precipitated on cooling of the reaction mixture.




**Scheme 2.11 Biginelli Dihydropyrimidine Synthesis**

Over the past decade, dihydropyrimidinones, an important class of compounds,[276,277,278] have become increasingly significant due to their therapeutic and pharmacological properties.[279] They have emerged as integral backbones of several calcium channel blockers, antihypertensive agents and antagonists. A broad range of biological effects, including antiviral, antitumour, antibacterial, anti-inflammatory activities, has been ascribed to these partly reduced pyrimidine derivatives.[280] Synthetic strategies for the synthesis of the dihydropyrimidinone nucleus involve both one-pot and multi-step approaches. Thus, Biginelli's reaction for the synthesis of dihydropyrimidinones has received renewed interest and several improved procedures have now been reported.[281,282]

The simple and straightforward procedure illustrated in Scheme 2.11 often suffers from low yields, especially in the case of aliphatic and substituted aromatic aldehydes. This has led to the development of complex multi-step synthetic strategies that produce somewhat better yields, but lack the simplicity of the original, one-pot, Biginelli protocol.[283,284,285,286] The $BF_3{\cdot}OEt_2$ or polyphosphate ester-mediated Biginelli reactions[287,288] require long reaction times (~18 h) to achieve moderate to high yields of the products. The acidic clay montmorillonite KSF has also been employed for this transformation but involves a longer reaction time (10-48 h) to obtain good yields.[289]

Our interest developed when the use of BMIM[$PF_6$] and BMIM[$BF_4$] as catalysts for the Biginelli condensation reaction under solvent-free conditions was reported.[290] Thus, the reaction of benzaldehyde, ethyl acetoacetate and urea in the presence of different amounts of BMIM[$BF_4$] (0.2 to 0.8 mol% relative to benzaldehyde) at 100 $^0$C gave yields of greater than 85 % after only 30 min, and the conversion increased slightly with increasing amounts of IL. BMIM[$PF_6$] gave slightly higher yields (94 % using 0.4 mol%) under the same conditions. Interestingly, BMIM[Cl] gave a much lower yield of 56 % and Peng reported that no reaction occurred when *n*-$Bu_4NCl$ was employed as catalyst.[290] This led us to believe that both the cation and anion in the IL played a role as the catalyst of the Biginelli condensation. We decided to investigate the effect of the IL anion on this

reaction and whether non-racemic dihydropyrimidinones could be synthesised in this manner, by employing a chiral IL as the catalyst.

Since our work was carried out there have been numerous publications reporting modifications to the Biginelli condensation emphasising the great deal of current interest in this reaction. These include the use of metal catalysts,[291] metal catalysts under solvent-free conditions,[292] the application of microwave irradiation as the heat source,[293] and the use of other organic reagents to promote the reaction.[294]

### 2.3.2 Results and discussion

To begin with, we investigated the one-pot condensation of benzaldehyde, ethyl acetoacetate and urea at 100 $^0$C, using 0.5 mol % BMIM[$PF_6$], BMIM[$BF_4$], BMIM[OTf], or BMIM[$NTf_2$] as catalyst. In all cases, a pale yellow solid was formed after 40 min which was crushed, washed with water, filtered and dried in vacuo. We then decided to test the background non-catalysed reaction by performing a blank reaction *i.e.* no IL added, under the same conditions. To our surprise, we observed similar results for all the reactions with or without IL, as shown in Table 2.5.

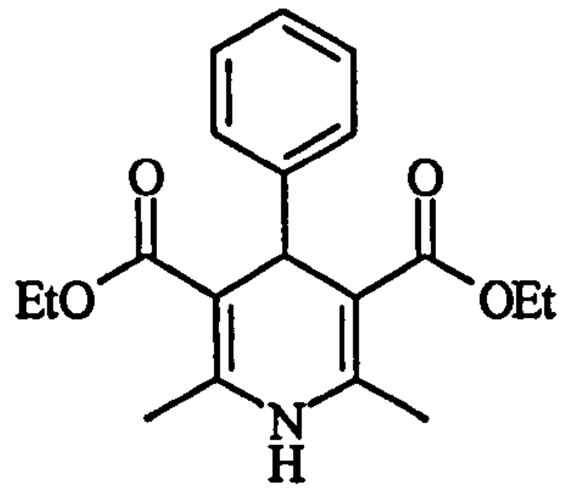
**Table 2.5. The Biginelli dihydropyrimidinone synthesis in RTILs**

| Entry | Catalyst | Yield /%[a] |
|---|---|---|
| 1 | - | 86 |
| 2 | BMIM[$PF_6$] | 88 |
| 3 | BMIM[OTf] | 87 |
| 4 | BMIM[$NTf_2$] | 88 |
| 5 | BMIM[$BF_4$] | 89 |
| 6 | BMIM[Cl] | 85 |

Reaction performed using 10 mmol benzaldehyde, 10 mmol ethyl acetoacetate, 12 mmol urea, 0.5 mol% IL at 100 $^0$C for 40 min.
[a]Isolated yield after recrystallisation from isopropanol.

It is apparent that the reaction proceeds to give a high yield of product using thermal heating under solvent-free conditions. Contrary to the results observed by Peng *et al.*,[290] the presence of 0.5 mol% BMIM[Cl] did not lead to a lower yield of product (see entry 6).

In all cases, a small amount (< 5 %) of the Hantzsch product, 1,4-dihydropyrimidine (2.28), was observed to form. The Hantzsch synthesis of 1,4-dihydropyridines involves the condensation of two moles of ethyl acetoacetate with one mole of aldehyde and $NH_3$.[295] The synthesis of Hantzsch 1,4-dihydropyridines under Biginelli reaction conditions has previously been reported.[296]



**(2.28)**

The reaction was repeated at a lower temperature of 60 $^0$C, to see whether a bigger difference in reactivity could be observed between the non-catalysed and IL-catalysed reaction. This time the reaction was monitored by GCMS. Although the reaction took longer to reach completion (*ca.* ~ 4 h), at 60 $^0$C there was virtually no difference in the rate of the reaction with or without any IL present. In order to be able to successfully carry out a catalytic asymmetric version of this reaction, there needs to be a greater difference in rate between the non-catalysed background reaction and the IL catalysed reaction so this idea was abandoned. However, we did investigate whether the reaction time could be shortened using microwave irradiation.

Microwave irradiation has been used for the rapid synthesis of a variety of compounds,[297,298,299] including Biginelli. Solvents possessing high dielectric constants are usually used for reactions in the microwave oven since they get superheated rapidly.[300] As ionic liquids consisting entirely of ions absorb microwave energy efficiently, the application of microwave chemistry to reactions using ILs is now being exploited.[301,302,303] Ley *et al.* showed that addition of a small quantity of an IL to a toluene solution can greatly increase the rate and yields of a reaction.[304,305] Non-polar solvents with low dielectric constants can be heated way above their boiling point in sealed vessels using a small quantity of IL, thereby allowing them to be used as media for microwave-assisted chemistry. For example, hexane can be heated to 228 $^0$C, THF to 268 $^0$C, dioxane to 264 $^0$C and toluene to 234 $^0$C.[306] (For comparison purposes, the boiling points of these solvents are 69 $^0$C, 66 $^0$C, 101 $^0$C, and 111 $^0$C, respectively).

The Biginelli condensation was performed in sealed vessels in a CEM microwave. The reaction mixture was irradiated with 100 W (100-110 $^0$C), for 5 min and then the solid product isolated by filtration. The yields are shown in Table 2.6

**Table 2.6. The Biginelli dihydropyrimidinone synthesis in RTILs under MW irradation**

| Entry | Catalyst | Yield /%[a] |
|---|---|---|
| 1 | - | 90 |
| 2 | BMIM[$PF_6$] | 91 |
| 3 | BMIM[OTf] | 90 |
| 4 | BMIM[$NTf_2$] | 88 |
| 5 | BMIM[$BF_4$] | 92 |
| 6 | BMIM[Cl] | 90 |

Reaction performed using 5 mmol benzaldehyde, 5 mmol ethyl acetoacetate, 6 mmol urea, 0.5 mol% IL at 100-110 $^0$C (100 W MW) for 5 min. [a]Isolated yield after recrystallisation from isopropanol.

As can be seen, the reaction with no added IL (entry 1) was as successful as the reactions with a catalytic amount of IL employed (entries 2-6). Interestingly, in this case, the reaction was more selective as no 1,4-dihydropyrimidine formed. However, as our results showed that the reaction proceeds without a catalyst under solvent-free conditions, our studies of the Biginelli condensation were abandoned at this stage. We cannot ascertain why Peng *et al.* observed no reaction in the absence of an IL after 30 min at 100 $^0$C. As their ILs were synthesised by metathesis of BMIM[Cl] with $NaPF_6$ / $NaBF_4$, the possibility of residual acid from the IL synthesis catalysing the reaction can be disregarded. However, to support our results, the catalyst-free Biginelli condensation using microwave radiation has since been reported.[307] Equimolar amounts of neat reactants, benzaldehyde, ethyl acetoacetate and thiourea, gave 90 % yield of product after 2.5 min of microwave heating (800 W, 110-120 $^0$C). Under our conditions, the IL does not act as a catalyst.

## 2.4 CONCLUSION

In this Chapter we have investigated the use of RTILs as 'innocent' solvents in organic synthesis: for nucleophilic aromatic substitution reactions, alkylation reactions, and the Biginelli condensation. We have found in some cases the use of an IL may be beneficial whereas in others, there are no significant advantages of substituting conventional solvents for an IL. For example, in the NAS of 2,4-dinitrochlorobenzene using KF, it was demonstrated that after isolation of the product by distillation, the IL could easily be cleaned and reused in subsequent reactions, thus contributing to the development of green strategies for the synthesis of fluorinated aromatics. However, using aniline as a nucleophile gave similar results to those obtained in conventional solvents and the IL proved difficult to recycle. Also, in the Biginelli condensation we found the reaction to proceed smoothly under solvent-free conditions with or without a catalytic amount of IL hence there appear to be no advantages in using an IL in this case.

We also considered the effect of the IL anion in these reactions. In general, the IL anion had little or no effect on the reactions investigated, except the NAS using KF where the rate of substitution was found to decrease in the order BMIM[$BF_4$] ≈ BMIM[$PF_6$] > BMIM[OTf] > BMIM[$NTf_2$] and is consistent with previous fluorination reports using KF in RTILs. For the alkylation of indazole, we found that the ILs play a dual role of solvent and PTC, making the reaction more 'atom-economical.' Overall, the substitution of an organic solvent with an IL for a given reaction will depend upon many factors: the effect of the IL on the course of the reaction, the substrates involved, the ease with which the product can be isolated, the capacity to recycle the IL. An economic benefit must be apparent to promote the adoption of this green technology.

## 2.5 EXPERIMENTAL

Chemicals and solvents were purchased from commercial suppliers except the ionic liquids which were synthesised and dried under vacuum at 60 °C prior to use. For thin layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualised by irradiation with UV light and / or by treatment with a solution of phosphomolybdic acid (25g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concentrated $H_2SO_4$ (60 mL), and $H_2O$ (940 mL) followed by heating. Flash Chromatography was performed by using silica gel Merck 60 (particle size 0.040-0.063 mm). GC was performed on a Perkin Elmer XL gas chromatograph, using BP10 (SGE) capillary columns (30 m x 0.25 mm) with hydrogen as

carrier. GCMS analysis was performed on a Perkin-Elmer TurboMass GCMS autosystem using a PE5 column (30 m x 0.25 mm). $^{1}$H NMR and $^{13}$C NMR spectra were recorded either on a Bruker AMX 400, AMX 300 and AMX 250. Chemical shifts are given in $\delta$ relative to tetramethylsilane (TMS); the coupling constants $J$ are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature; TMS served as internal standard ($\delta = 0$ ppm) for $^{1}$H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for $^{13}$C NMR.

### 2.5.1 Preparation of the Ionic liquids

***1-butyl-3-methylimidazolium chloride, BMIM[Cl]***

This was prepared by method of Wilkes.[70] Freshly distilled 1-methylimidazole (40.0 g, 0.49 mol) and chlorobutane (89.0 g, 0.98 mol) were heated at 75 $^{0}$C for 2 days with magnetic stirring. The excess chlorobutane was removed on the rotary evaporator, resulting in a slightly off-white solid product that showed no starting material by $^{1}$H NMR spectroscopy. The product was recrystallised from acetonitrile/ethyl acetate. Yield: 62.1 g (75 %). $^{1}$H NMR (400 MHz, $d_6$-acetone): δ 10.95 (s, 1H, NC*H*N), 7.64 (s, 1H, NCHC*H*N), 7.47 (s, 1H, NC*H*CHN), 4.24 (t, 2H, $J = 7.41$, N$CH_2$), 4.15 (s, 3H, N*Me*), 1.80 (m, 2H,$CH_2CH_2$Me), 1.28 (m, 2H,$CH_2CH_2$Me), 0.86 (t, 3H, $J = 7.41$, $CH_2$*Me*); $^{13}$C NMR (75 MHz, $d_6$-acetone): δ 137.8 (NCHN), 124.4 and 123.1 (NCHCHN), 49.8 ($NCH_2$), 36.8 (N*Me*), 32.9 ($CH_2CH_2$Me), 20.0 ($CH_2CH_2$Me), 13.8 ($CH_2$*Me*).

***1-butyl-3-methylimidazolium trifluoromethanesulphonate, BMIM[OTf]***

This was also prepared by a method reported in the literature.[308] BMIM[Cl] (20.0 g, 0.11 mol) and potassium trifluoromethanesulphonate (43.1 g , 0.22 mol) were stirred in reagent grade acetone (150 ml) for 72 h at room temperature. The salt by-product was separated by filteration through celite. On removal of the acetone, some salt was observed to be insoluble and present in the BMIM[OTf], so the product was redissolved in dichloromethane and refiltered over celite. Removal of the $CH_2Cl_2$ by rotary evaporater gave BMIM[OTf]. Yield: 31.2 g (96 %). $^{1}$H NMR (400 MHz, $d_6$-acetone): δ 9.11 (s, 1H, NC*H*N), 7.64 (t, 1H, $J = 1.76$, NCHC*H*N), 7.74 (t, 1H, $J = 1.76$, NC*H*CHN), 4.38 (t, 2H, $J = 7.32$, N$CH_2$), 4.00 (s, 3H, N*Me*), 1.92 (m, 2H,$CH_2CH_2$Me), 1.37 (m, 2H,$CH_2CH_2$Me), 0.96 (t, 3H, $J = 7.43$, $CH_2$*Me*); $^{13}$C NMR (75 MHz, $d_6$-acetone): δ 137.7 (NCHN), 124.7 and 123.4 (NCHCHN), 50.0 ($NCH_2$), 36.6 (N*Me*), 32.8 ($CH_2CH_2$Me), 19.9 ($CH_2CH_2$Me), 13.8 ($CH_2$*Me*).

***1-butyl-3-methylimidazolium hexafluorophosphate, BMIM[$PF_6$]***[308]

The metathesis procedure used is the same as that described for BMIM[OTf], using potassium hexafluorophosphate (40.5 g, 0.22 mol) in place of potassium trifluoromethanesulphonate. Yield: 29.6 g (91 %). $^1$H NMR (400 MHz, $d_6$-acetone): δ 8.65 (s, 1H, NC*H*N), 7.74 (t, 1H, *J* = 1.79, NCHC*H*N), 7.68 (t, 1H, *J* = 1.79, NC*H*CHN), 4.35 (t, 2H, *J* = 7.32, NC*H*$_2$), 4.20 (s, 3H, N*Me*), 1.95 (m, 2H,*CH*$_2$CH$_2$Me), 1.39 (m, 2H,CH$_2$*CH*$_2$Me), 0.96 (t, 3H, *J* = 7.41, CH$_2$*Me*); $^{13}$C NMR (75 MHz, $d_6$-acetone): δ 137.7 (NCHN), 125.0 and 123.7 (NCHCHN), 50.6 (NCH$_2$), 36.9 (N*Me*), 33.0 (*C*H$_2$CH$_2$Me), 20.3 (CH$_2$*C*H$_2$Me), 14.1 (CH$_2$*Me*).

***1-butyl-3-methylimidazolium bis((trifluoromethyl)sulphonyl)amide, BMIM[$NTf_2$]***[82]

The metathesis procedure used is the same as that described for BMIM[OTf], using lithium bis((trifluoromethyl)sulphonyl)amide (65.4 g 0.22 mol), in place of potassium trifluoromethanesulphonate. Yield: 47.7 g (90 %). $^1$H NMR (400 MHz, $d_6$-acetone): δ 8.55 (s, 1H, NC*H*N), 7.794 (t, 1H, *J* = 1.79, NCHC*H*N), 7.74 (t, 1H, *J* = 1.79, NC*H*CHN), 4.39 (t, 2H, *J*=7.32, NC*H*$_2$), 4.05 (s, 3H, N*Me*), 1.95 (m, 2H,*CH*$_2$CH$_2$Me), 1.40 (m, 2H,CH$_2$*CH*$_2$Me), 0.96 (t, 3H, *J* = 7.41, CH$_2$*Me*); $^{13}$C NMR (75 MHz, $d_6$-acetone): δ 137.2 (NCHN), 124.7 and 123.3 (NCHCHN), 50.3 (NCH$_2$), 36.6 (N*Me*), 32.6 (*C*H$_2$CH$_2$Me), 19.9 (CH$_2$*C*H$_2$Me), 13.6 (CH$_2$*Me*).

***1-butyl-3-methylimidazolium tetrafluoroborate, BMIM[$BF_4$]***[308]

The metathesis procedure used is the same as that described for BMIM[OTf], using sodium tetrafluoroborate (25.1 g, 0.22 mol) in place of potassium trifluoromethanesulphonate. Yield: 23.8 g (92 %). $^1$H NMR (400 MHz, $d_6$-acetone): δ 8.98 (s, 1H, NC*H*N), 7.76 (t, 1H, *J* = 1.77, NCHC*H*N), 7.70 (t, 1H, *J* = 1.77, NC*H*CHN), 4.36 (t, 2H, *J* = 7.32, NC*H*$_2$), 4.05 (s, 3H, N*Me*), 1.93 (m, 2H,*CH*$_2$CH$_2$Me), 1.37 (m, 2H,CH$_2$*CH*$_2$Me), 0.96 (t, 3H, *J* = 7.41, CH$_2$*Me*); $^{13}$C NMR (75 MHz, $d_6$-acetone): δ 137.5 (NCHN), 124.2 and 123.2 (NCHCHN), 50.0 (NCH$_2$), 36.3 (N*Me*), 32.1 (*C*H$_2$CH$_2$Me), 19.5 (CH$_2$*C*H$_2$Me), 13.4 (CH$_2$*Me*).

## 2.5.2 Nucleophilic aromatic substitution reactions

***Benzyl fluoride (2.10)***

Potassium fluoride (174 mg, 3 mmol) was added to BMIM[$BF_4$] (1 ml) in a 25 ml round bottom flask. The salt was allowed to stir for overnight allowing uniform particle sizes to form. Benzyl chloride (115 µl, 126 mg, 1 mmol) was then added and the reaction mixture stirred for 12 h at 80 $^0$C. The product was extracted using diethyl ether (3 x 2 ml). Isolated yield: 103 mg (94 %). $^1$H NMR (300 MHz, $CDCl_3$): δ 7.46-7.30 (m, 5H), 5.36 (d, 2H, J = 48.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 136.3, 128.8, 128.7, 128.6, 127.5, 127.4, 84.6; $^{19}$F NMR (282 MHz, $CDCl_3$): δ –207.2 (t, $J_{H-F}$ = 48.2 Hz);[309] EI *m/z* 110.

***2,4-Dinitrofluorobenzene (2.12)***

Potassium fluoride (0.348 g, 6 mmol) was added to BMIM[$PF_6$] (1 ml) in a 25 ml round bottom flask. The salt was allowed to stir for 1 h allowing uniform particle sizes to form. 2,4-dinitrochlorobenzene (0.4 g, 2 mmol) was then added and the reaction mixture was magnetically stirred for at 100 $^0$C for 16 h. The products was isolated by distillation using a Kogelrohl oven at > 150 $^0$C. Isolated yield: 164 mg (88 %). $^1$H NMR (300 MHz, $CDCl_3$): δ 8.84 (m, 1H), 8.56 (m, 1H), 7.64 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 160.6, 156.9, 143.6, 137.0, 130.6, 130.5; $^{19}$F NMR (282 MHz, $CDCl_3$): δ -106.54; GCMS *m/z* 186.

***(2,4-Dinitrophenyl)-phenylamine (2.13)***

2,4-dinitrochlorobenzene (2.0 g, 10 mmol) was added to BMIM[$NTf_2$] (3 ml). Aniline (1.1 ml, 1.12 g) was added and the reaction mixture stirred at 80 $^0$C for 16 h. Saturated $NaHCO_3$ solution (10 ml) was then added to precipitate the product, which was filtered, and washed with hot water (5 x 3 ml). After drying in air, the product was crystallised from ethanol and dried in a vacuum oven at 40 $^0$C to afford a bright red solid. Alternatively, the product could be purified by column chromatography on silica-gel using ether: acetone (2: 5 v/v). The product was observed visually as a red-yellow band. Isolated yield: 2.38 g (92 %). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.17 (s, br), 8.89 (d, 1H, *J* = 2.7 Hz), 8.24 (dd, 1H, *J* = 9.6, 2.7 Hz), 7.20-7.50 (m, 5H), 7.10 (d, 1H, *J* = 9.6 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$,): δ 146.1, 136.4, 135.7, 134.7, 129.3, 128.9, 126.7, 124.5, 123.0, 122.6, 121.3, 120.9; EI *m/z* 259; Mp 158-159 $^0$C. (Lit.[310] Mp 158 $^0$C).

### 2.5.3 Alkylation Reactions

***Methyl 12-Acetyl-13-oxotetradecanoate (2.19)***

A mixture of 11-bromo-undecanoic acid (5g, 18.9 mmol), *p*-toluenesulphonic acid (*ca.* 10 mg), methanol (4 ml) and chloroform (40 ml) was heated at reflux for 16 h on apparatus equipped with a Soxhlet extractor containing dry 4 Å molecular sieves in a thimble. The cooled solution was washed with 10 % sodium carbonate solution (10 ml), and the dried ($Na_2SO_4$) organic phase was evaporated (in vacuo) to afford a yellow oil. The methyl ester was obtained in its pure form upon distillation, bp 125-126 $^0$C/ 0.26 mm (4.5 g, 89 %) with $^1$H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.39 (t, 2H, $J$ = 7.0 Hz), 2.29 (t, 2H, $J$ = 7.0 Hz), 1.83 (quint, 2H, $J$ = 7 Hz), 1.57-1.65 (m, 2H), 1.37-1.45 (m, 2H), 1.27-1.65 (s, br, 10H). It was used directly in the next step. A mixture of pentanedione (1.07 g, 10.7 mmol), methyl 11-bromo-undecanoate (2.98 g, 10.7 mmol), anhydrous potassium carbonate (1.8g, 12.9 mmol), anhydrous cesium carbonate (0.18 g, 10 wt% of $K_2CO_3$), in 12 ml IL was heated at 65 $^0$C for 24 h. A sample of the reaction mixture was analysed by GCMS to analyse the *C/O* product ratio. The hot reaction mixture was added to ice-cold water (15 ml) and the aqueous phase extracted with diethyl ether (3 x 10 ml). The combined organic extracts were washed with water (3 x 10 ml), dried ($Na_2SO_4$) and evaporated (in vacuo) to give an oily residue (3.10 g, 97 %). To remove the *O*-alkylated product, the crude oil was dissolved in glacial acetic acid (10 ml) and heated at reflux in the presence of anhydrous sodium acetate (2.2 g, 2.6 mmol). After 12 h, the hot solution was poured into ice-cold water (15 ml) and extracted with $CH_2Cl_2$ (2 x 10 ml). The combined organic extracts were washed with 10 % sodium carbonate (3 x 10 ml) and dried ($Na_2SO_4$). Evaporation of $CH_2Cl_2$ gave an oil (3.06 g), which was distilled (154-156 $^0$C, 0.04 mm) to afford the title compound as a white waxy solid (2.3 g, 72 %). $^1$H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.58 (t, 1H, $J$ = 7.0 Hz), 2.27 (t, 2H, $J$ = 7.0 Hz), 2.15 (s, 6H), 1.75-1.85 (m, 2H), 1.52-1.65 (m, 2H), 1.23 (s, br, 14H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 204.3, 174.1, 68.8, 51.2, 33.9, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.8, 28.1, 27.4, 24.8; GCMS $t_r$ = 17.94 min, *mz* 298.

The *O*-alkylated product was observed at GCMS $t_r$ = 18.74 min, *mz* 298.

***1-Benzyl-1H-indazole (1N-Isomer) (2.22)***

A mixture of indazole (118 mg, 1 mmol), benzyl chloride (115 µl, 126 mg, 1 mmol), anhydrous potassium carbonate (138 mg, 1 mmol), and anhydrous potassium hydroxide (56 mg, 1 mmol) in IL (2 ml) was heated at 140 $^0$C for 16 h. A sample was taken into $CH_2Cl_2$ after this time for GCMS analysis. The products were extracted using diethyl ether (5 x 2 ml) and the combined extracts were then evaporated to afford a pale yellow oil. The oil was purified by preparative TLC using 95: 5, chloroform: acetonitrile as eluent to afford the solid products.

$R_f$ = 0.48 ($CHCl_3$: $CH_3CN$, 95:5); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, br, 1H), 7.70 (d, 1H, *J* = 8.1 Hz), 7.08-7.32 (m, 8H), 5.55 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ139.6, 136.8, 133.3, 128.9, 128.8, 127.8, 127.3, 127.2, 126.6, 124.4, 121.3, 120.8, 109.4, 53.0; EI MS *m/z* 208; GCMS $t_r$ = 13.18 min; Mp 90–91 $^0$C. (Lit.[311] M.p 91–93 $^0$C).

***1-Benzyl-2H-indazole (2N-Isomer) (2.23)***

$R_f$ = 0.36 ($CHCl_3$: $CH_3CN$, 95:5); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.80 (s, br, 1H), 7.72 (d, 1H, *J* = 8.7 Hz), 7.58 (d, 1H, *J* = 8.3 Hz), 7.19-7.-32 (m, 6H), 7.04 (m, 1H), 5.51 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 139.8, 136.9, 133.2, 128.9, 128.7, 127.8, 127.3, 127.2, 126.6, 124.5, 121.3, 120.6, 109.4, 53.1;. EI MS *m/z* 208; GCMS $t_r$ = 14.41 min; Mp 69–71 $^0$C. (Lit.[312] M.p 71 $^0$C).

The isomers are easily differentiated by proton NMR spectroscopy from the PhC*H*NH and benzylic protons, and GCMS retention times.

## 2.5.3 Biginelli Condensation

A mixture of stoichiometric amounts of benzaldehyde (1.0 ml, 1.0 g, 10 mmol), ethyl acetoacetate (1.3 ml, 1.35 g, 10 mmol) urea (0.72 g, 12 mmol) and a catalytic amount of IL was stirred at 100 $^0$C for h. After completion of the reaction as indicated by TLC and GCMS analysis, the resulting solid was filtered under suction and recrystallised from isopropanol to afford the pure product. Yield: 2.29 g (88 %).

***5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (2.27)***

$^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 9.22 (s, br, 1H), 7.78 (dr, 1H, $J$ = 2.5 Hz), 7.22-7.41 (m, 5H), 5.17 (d, 1H, $J$ = 3.0 Hz), 4.03 (q, 2H, $J$ = 7.5 Hz), 2.28 (s, 3H), 1.12 (t, 3H, $J$ = 7.5 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 165.2, 152.0, 148.2, 144.7, 128.3, 127.1, 126.1, 99.2, 59.1, 53.9, 17.7, 13.9; GCMS *m/z* 261; GCMS $t_r$ = 23.24 min; Mp 203–205 $^{0}$C. (Lit.[276] Mp 202 $^{0}$C).

***2,6-Dimethyl-4-phenyl-1,4-dihydropyrimidin-3,5-dicarboxylic acid ethyl ester (Hantzsch product) (2.28)***

$^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.80 (s, br, 1H), 7.25-7.35 (m, 5H), 5.05 (s, 1H), 4.10 (q, 4H, $J$ = 8.2 Hz), 2.55 (s, 6H), 1.30 (t, 6H, $J$ = 8.2 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 168.1 (2C), 148.2, 144.4 (2C), 128.4, 128.3, 127.5, 127.1, 126.5, 104.4 (2C), 60.1 (2C), 40.0, 19.8 (2C), 14.6 (2C); GCMS *m/z* 329; GCMS $t_r$ = 23.90 min.

# Chapter Three

# Metal Catalysed Reactions

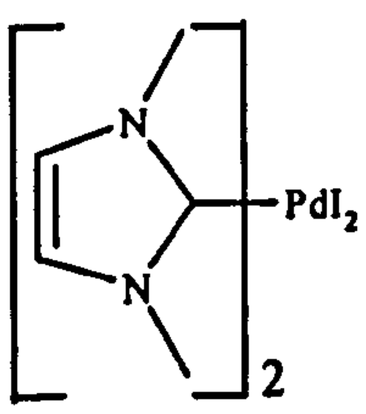
# Chapter Three – Metal-Catalysed Reactions

## 3.1 HECK REACTIONS

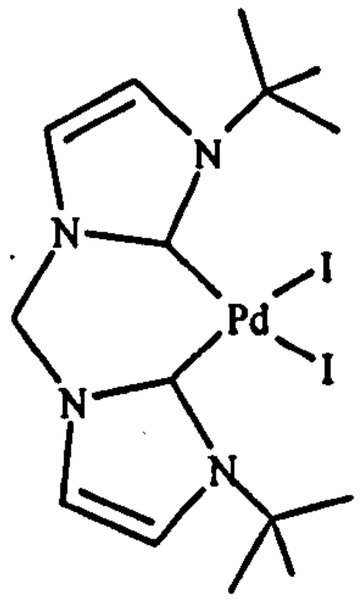
### 3.1.1 Introduction

Palladium catalysis has been investigated in RTILs for several different types of reactions, as discussed in Chapter 1, section 1.5.3. The Heck reaction,[313] the palladium-catalysed arylation of alkenes with aryl halides, has received considerable attention, primarily due to the enormous synthetic potential to generate $sp^2$-$sp^2$ carbon-carbon bonds. However, industrial applications are rare.[314] This is because a large amount of catalyst (>1 mol%) is needed for reasonable conversions and the reactivity of aryl halides decreases drastically in the order ArI > ArBr > ArCl, hence the cheaper chlorides and even some bromides do not react with sufficiently high yields, turnover numbers (TON), and selectivities. Also, a major problem with the Heck reaction is that the palladium catalyst is often lost at the end of the reaction. Hence, a process for recycling the catalyst is of

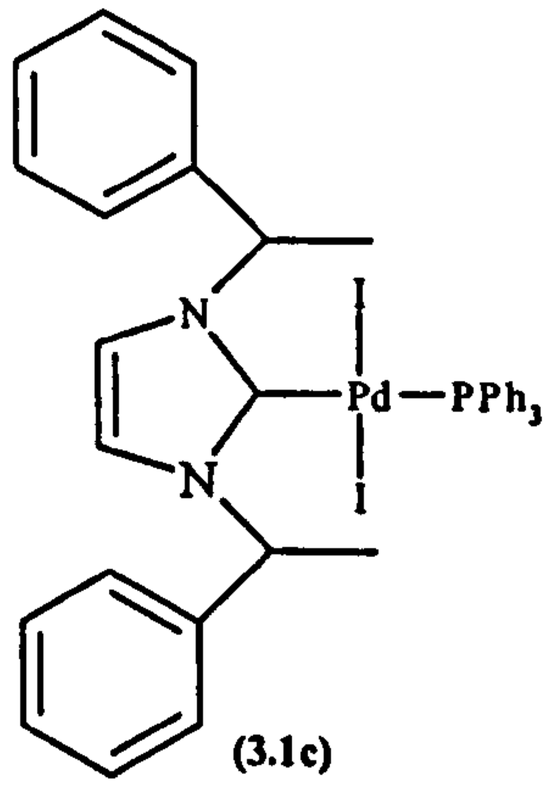
**Carbene complexes:**




(3.1a)

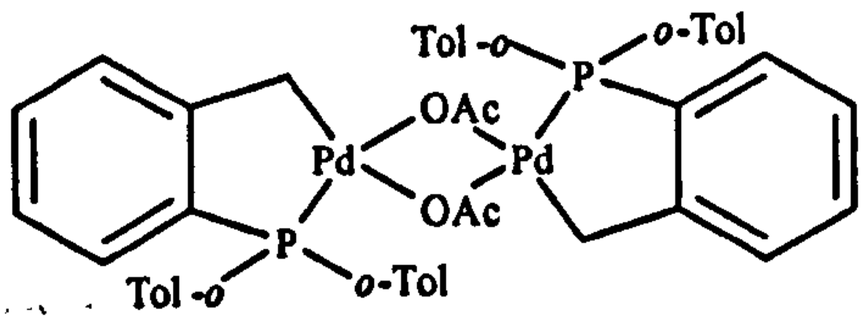



(3.1b)



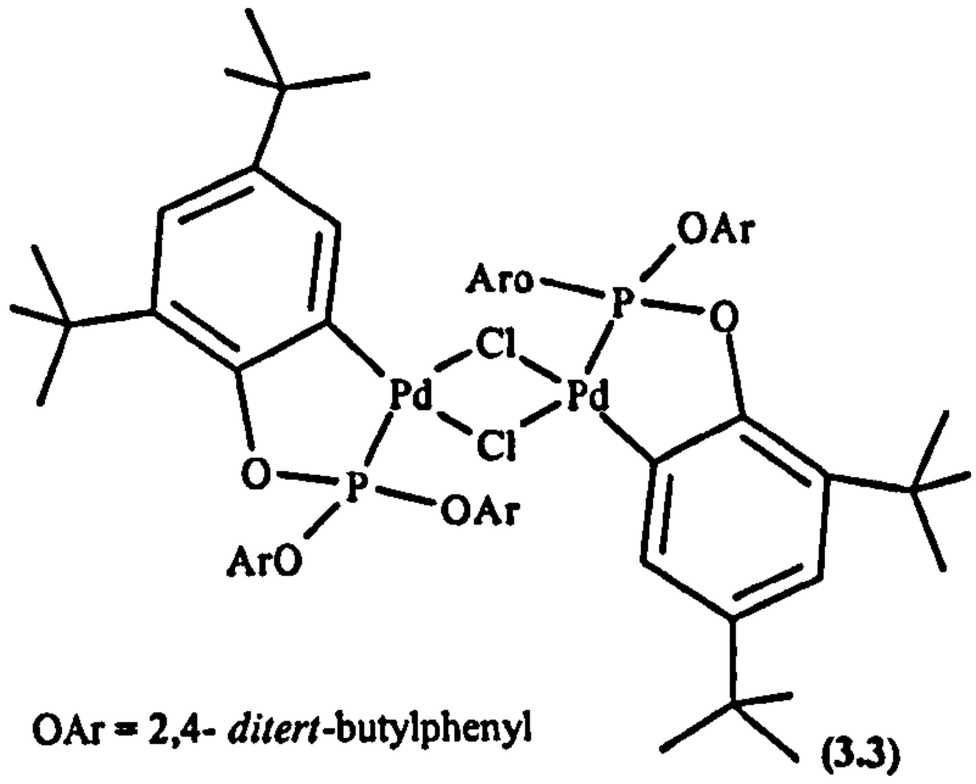

(3.1c)

**Phospha-Palladacycle:**




(3.2)

**Aryloxy-Phospha-Palladacycle:**



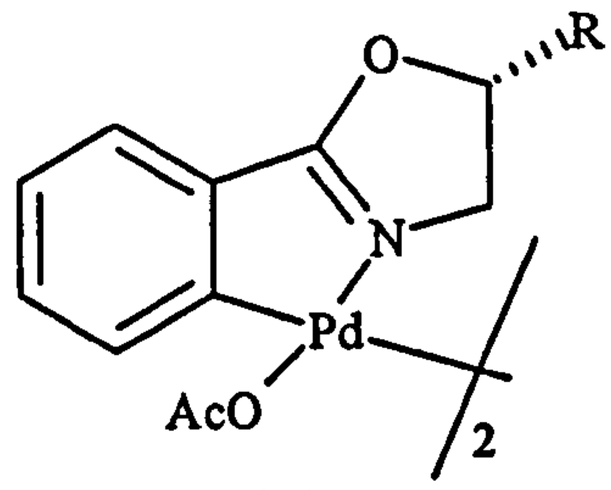

OAr = 2,4- *ditert*-butylphenyl

(3.3)

**Figure 3.1 Structurally defined palladium (II) catalysts for the Heck reaction**

importance. Many catalytic systems are known, including the use of highly basic, sterically hindered phosphines,[315] N-heterocyclic carbenes (NHC) (see 3.1a-e in Figure 3.1),[316] palladacycles (see 3.2 & 3.3 in Figure 3.1),[317,318] the use of a large excess of coordinating ligands, for example triphenylphosphine[319] or tris(2,4-di-*tert*-butylphenyl)phosphite,[320] the use of heterogeneous Pd/C[321] or Pd/MgO,[322] or the use of nanostructured palladium clusters.[323]

Although phosphines are employed as ligands in many palladium catalysed coupling reactions, it is highly desirable to develop phosphine-free catalysts and hence avoid the need for expensive and air-sensitive basic phosphines. More recently, nitrogen-, oxygen-, and sulphur-containing palladacycles have been shown to be excellent catalysts for the Heck reaction.[324] Milstein reported the application of palladacycles obtained by cyclopalladation of imines or oxazolines (*e.g.* 3.4), and showed that such compounds can be used in the Heck reaction of iodoarenes with simple olefins to achieve high TON values.[325]

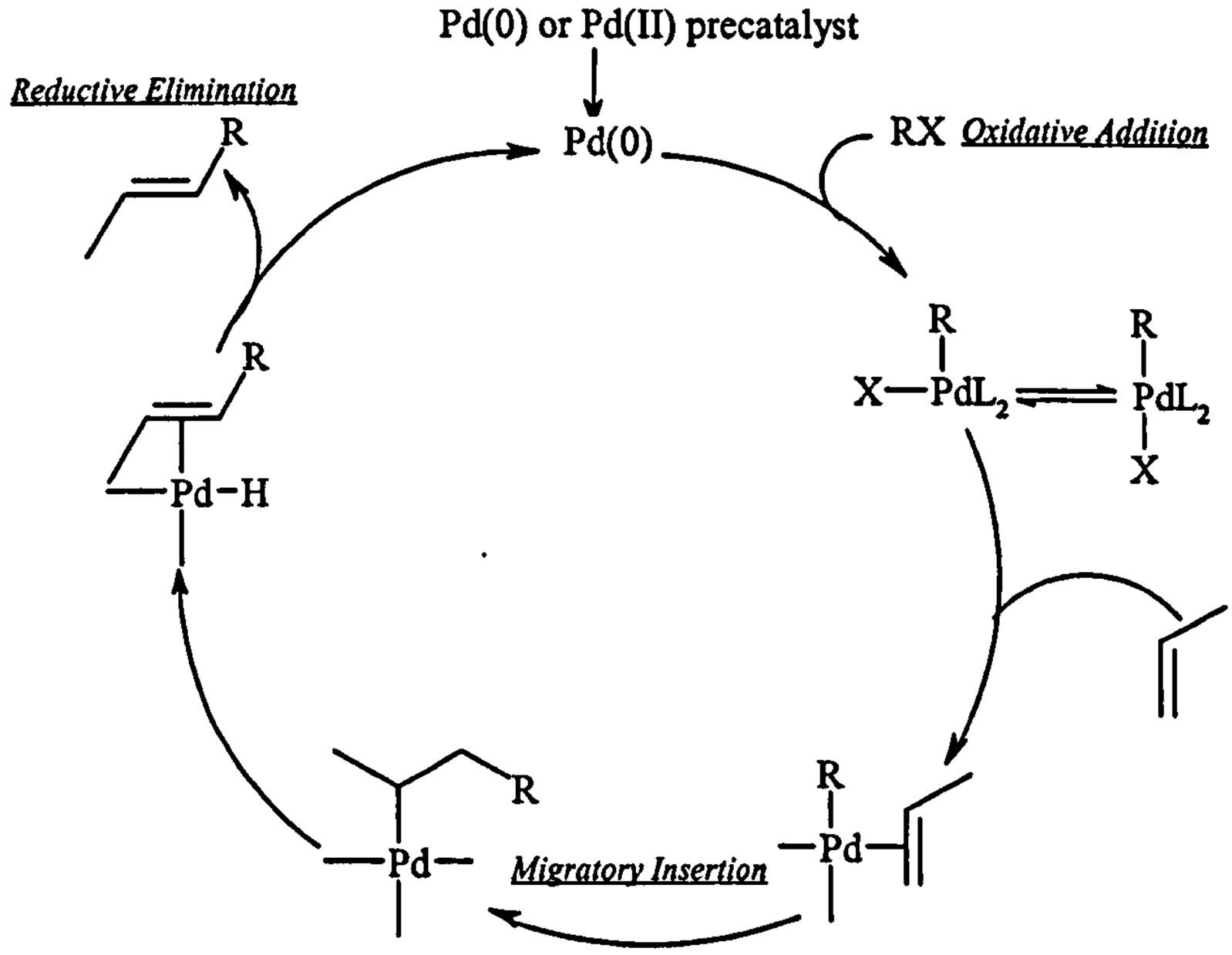



**(3.4)**

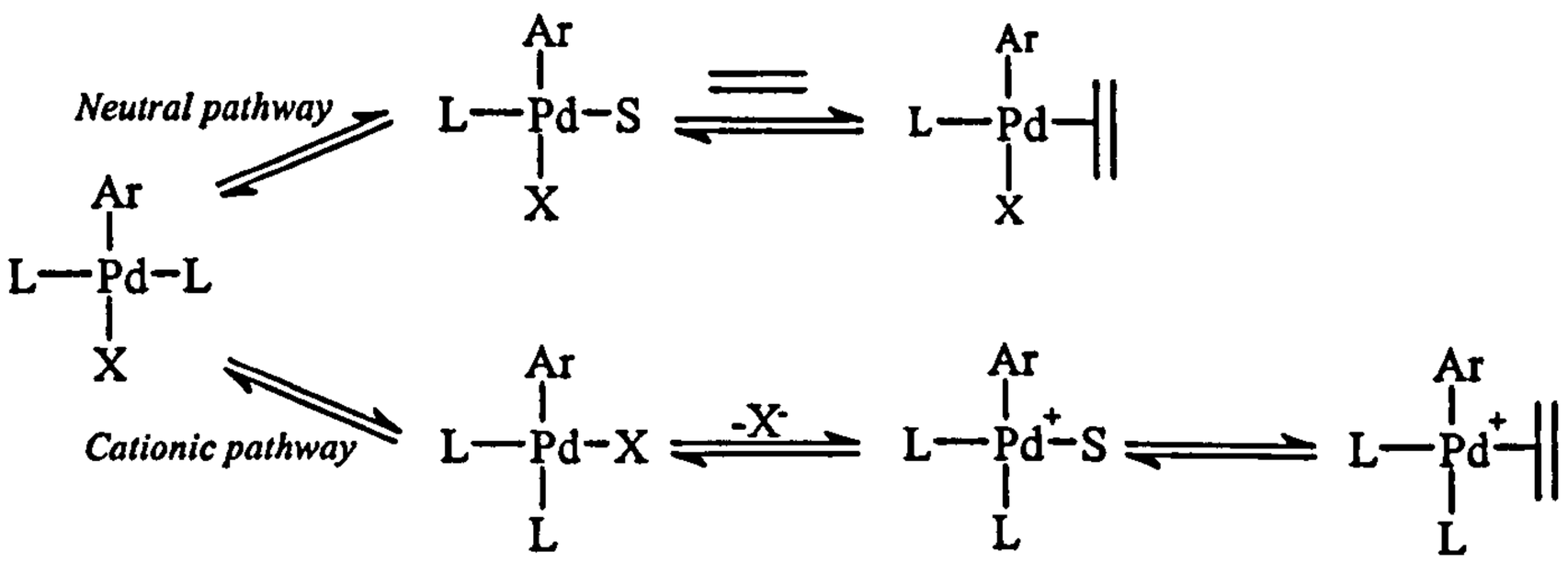
These complexes are also not sensitive to oxygen and moisture, so reactions can be carried out in air with no change in efficiencies or yield.

The Heck reaction is performed best in polar solvents possibly because they facilitate the cationic mechanism (see Scheme 3.1). Firstly, Pd(II) complexes are reduced to Pd(0) to generate the active catalytic species. The reduction is assisted by hard nucleophiles, of which the most common are hydroxide ions, alkoxide ions, water, or acetate ions.[314] The oxidative addition is much less sensitive to the substituents on the unsaturated system but much more sensitive to the strength of the C-X and M-X bonds. The order of reactivity is X = I >> OTf > Br >> Cl.[326] After oxidative addition reaction, loss of a ligand from palladium generates a vacant site for coordination of the alkene. Two different routes have been proven for this process (Scheme 3.2): the nonpolar route initiated by loss of a neutral ligand (phosphine in most cases) and the cationic route, initiated by loss of an anionic ligand.[327]

**Scheme 3.1 The major steps of the Heck catalytic cycle[328]**




**Scheme 3.2 The two possible pathways for the co-ordination of the alkene substrate[328]**



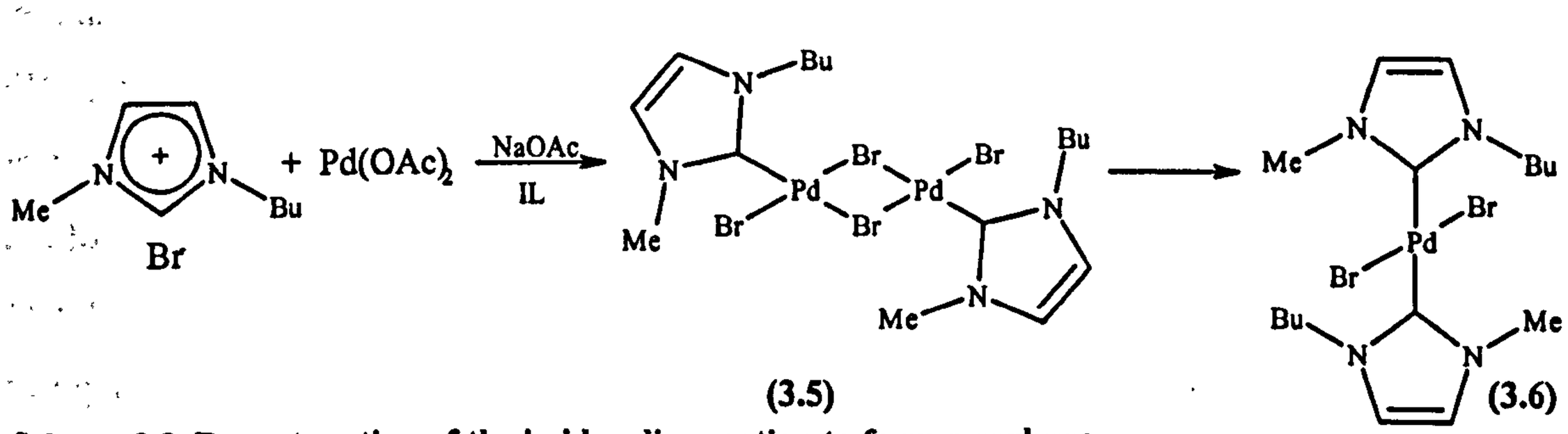

A majority of phosphine-free reactions are performed in polar media such as DMF, DMAc, *N*-methyl-2-pyrrolidinone, or in the presence of additives, which assist in the exchange of anionic ligands. Additives such as ammonium or phosphonium chlorides or bromides stabilise the palladium catalyst, probably via formation of a zerovalent palladium halide species and accelerate the olefination with or without phosphines.[329,330]

The Heck reaction has now been investigated using a number of different catalysts in different ionic liquids. The results can be summarised in terms of the anions involved, halide-containing or not, and the type of cation, dialkylimidazolium, ammonium or phosphonium. The most commonly investigated ammonium or phosphonium halides are *n*-$Bu_4N[Br]$,[331,332,333] $Ph_3MeP[Cl]$,[334] $Ph_3MeP[Br]$,[334] and *n*-$Bu_3$-*n*-$C_{16}H_{33}P[Br]$.[183,334] Molten $Bu_4N[Br]$ proved to be a particularly suitable reaction medium among the ionic solvents under investigation. In the reaction of bromobenzene with styrene using Herrmann's palladacycle (3.2) as catalyst, the yield of stilbene could be increased from 20

% in DMF to over 99 % in $Bu_4N[Br]$, under otherwise identical conditions. Distillation of the product from the non-volatile ionic catalyst solution was possible and the latter could be reused up to thirteen times without significant drop in activity.[335] This means that this catalyst is more stable in ionic media than in conventional homogeneous media. Also, using molten *n*-$Bu_4N[Br]$ as solvent provided the first example of the Heck reaction of chlorobenzene with a phosphine-free system giving 26 % yield of *trans*-stilbene after 16 h of heating in the presence of 1 mol % $Pd(OAc)_2$.[334] If chloroarenes can be made to react under reasonable conditions without any expensive and non-recoverable additives, then this would be a great economical advantage over using bromo- and iodoarenes. However, the best TONs and yields are still obtained if (3.2) is used with $Ph_4PCl$ or $Ph_4AsCl$ in 6-20 mol% amounts *i.e.* an equimolar amount with respect to the catalyst. Activated chloroarenes give quantitative conversions under these conditions.[334] Note, using $Ph_4AsCl$ in *n*-$Bu_4N[Br]$, a darkening of the IL was observed and the authors concluded that the dark solution could indicate the formation of palladium(0) aggregates implying that the reaction took place at the surface of palladium clusters. However, colloidal palladium is not capable of efficiently coupling chlorobenzene,[323a,b] thus suggesting that at least with chlorobenzene the reaction is not mediated by palladium clusters.

Although $Ph_3MeP[Cl]$, $Ph_3MeP[Br]$, and *n*-$Bu_3$-*n*-$C_{16}H_{33}P[Br]$ gave less than 25 % conversion of chlorobenzene using (3.2),[335] quantitative conversions of bromobenzene have been reported for the Heck reaction using $Pd(OAc)_2$ in *n*-$Bu_3$-*n*-$C_{16}H_{33}P[Br]$.[183] It was noted that when $PdCl_2$ was employed as catalyst in *n*-$Bu_3$-*n*-$C_{16}H_{33}P[Br]$, a dark brown solution developed and the palladium cluster slowly precipitated after some hours.

The Heck reaction has been found to proceed much more efficiently in the ionic liquid BMIM[Br] than in $BMIM[BF_4]$.[336] Imidazolium RTILs were inefficient in the absence of phosphine ligands at temperatures below 100 $^0$C, possibly due to the formation of carbene complexes, which release catalytically active palladium only at higher temperatures. Xiao confirmed that BMIM[Br], reacts readily with $Pd(OAc)_2$ under conditions similar to those used for the Heck reaction, to give *N*-heterocyclic carbene complexes of palladium




**Scheme 3.3 Deprotonation of the imidazolium cation to form a carbene**

(Scheme 3.3).[336] The $C_2$-H proton of the imidazolium ring is acidic and is deprotonated to give 1-butyl-3-methylimidazol-2-ylidene (bmimy) complexes of palladium (3.5) and (3.6). In contrast, no carbene species were detected on heating palladium salts in BMIM[$BF_4$] in the presence of NaOAc. Since N-heterocyclic carbene complexes of palladium, have strong Pd-C bonds and are catalytically active for C-C bond forming reactions, the easy formation of the carbene species in BMIM[Br] but not in BMIM[$BF_4$] explains, at least partly, the different activity and stability of palladium in the two ionic liquids. The isolated complexes proved to be active catalysts in the Heck reaction when redissolved in BMIM[Br].

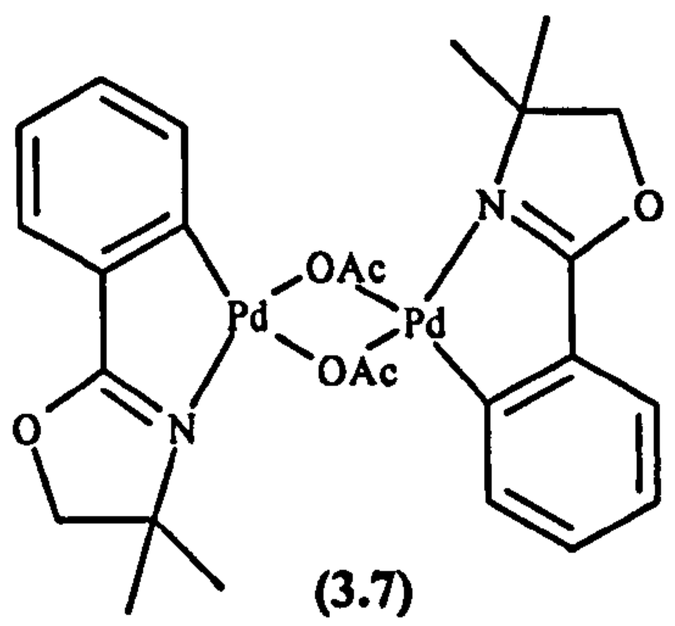
More recently, the *in situ* formation of a mixed phosphine-imidazolylidene palladium complex $[(PPh_3)_2Pd(bmimy)X]^+$ (X = Br, Cl), was also reported in BMIM[$BF_4$] using NaX as the halide source, under conditions employed in many palladium-catalysed reactions.[337] It was noted that addition of 4 equivalents of halide ions (with respect to the Pd) was necessary to stabilise the catalyst and prevent decomposition.[338] The beneficial effects of halide ions for the Heck reaction (under phosphine-free conditions) is also apparent from the report that adding catalytic amounts of *n*-$Bu_4NX$ to $Pd(OAc)_2$ in BMIM[$BF_4$] accelerated the reaction rate giving a quantitative yield of product for the reaction between methyl acrylate and iodobenzene under mild conditions.[339]

The Heck reaction has been studied by *in situ* X-ray absorption fine structure (XAFS), to examine the palladium species formed when $Pd(OAc)_2$ is dissolved in various ILs, both in the presence and absence of $PPh_3$ as well as reagents, and indicates that palladium clusters of 0.8 – 1.6 nm diameter are the main species present during the reaction.[340] On dissolution of $Pd(OAc)_2$ at 80 $^0$C in BMIM[$PF_6$] and BMIM[$BF_4$], the gradual change formation of palladium metal was observed, whereas using BMIM[Cl] prevented formation of palladium clusters. In HMIM[Cl], the XAFS was consistent with the formation of a bis-carbene complex and no palladium metal formed, with or without $PPh_3$. The XAFS following dissolution of $Pd(OAc)_2$ in BMIM[$PF_6$] and BMIM[$BF_4$] at 80 $^0$C for 20 min in the presence of $PPh_3$, showed formation of 20 % palladium metal, and the remaining to be coordinated to acetate (25 %) and $PPh_3$ (55 %). In comparison, without $PPh_3$, dissolution resulted in 80 % palladium metal and only 20 % coordinated to acetate. In the presence of reagents, little change was observed in the species generated although the formation of palladium was found to be quicker.[340] The formation of stabilised clusters of Pd nanoparticles has also been reported for the ultrasound assisted $Pd(OAc)_2$ / $PdCl_2$ catalysed Heck reaction in 1,3-dibutylimidazolium [Br] and [$BF_4$] ionic liquids; the 20 nm

clusters of $Pd^0$ nanoparticles were found to be stable even after a week in the ILs.[341] No reaction under similar sonication conditions was observed when the IL was replaced by DMF or NMP even in the presence of a ligand such as $PPh_3$. More recently, the reaction of $Pd(OAc)_2$ or a Pd-benzothiazole catalyst with *n*-$Bu_4N$[OAc] dissolved in *n*-$Bu_4N$[Br], was reported to lead to the fast formation of Pd nanoparticles which efficiently catalyse the stereospecific reaction of cinnamates with aryl halides to give β-aryl-substituted cinnamic esters.[342]

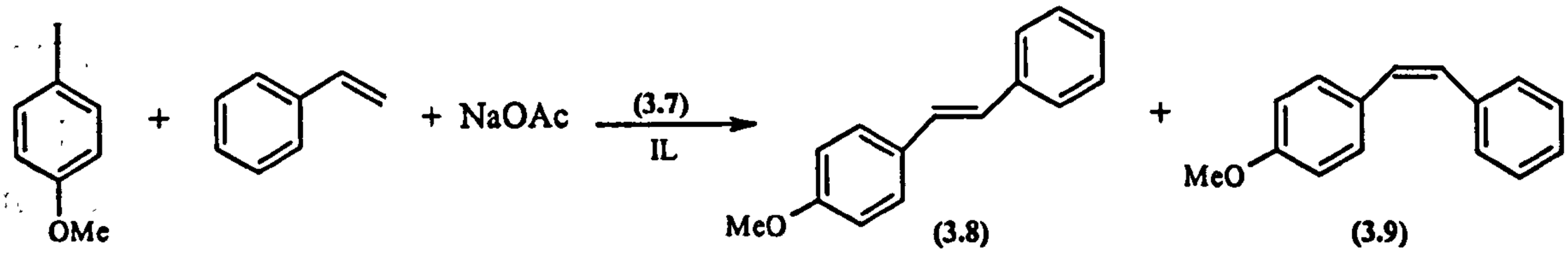
### 3.1.2 Results and Discussion

We chose to investigate the (C-N) bonded palladacycles (3.7), which have not yet been investigated in ionic liquids. The Heck reaction between 4-iodoanisole and styrene was performed using 0.5 mol% (3.7); comparisons were made with $Pd(OAc)_2$. The reaction was heated at 140 $^0$C for 16 h in BMIM[$PF_6$] and NaOAc was employed as base.




(3.7)

Although there are three isomeric products possible in this reaction, $^1$H NMR spectroscopy showed trans-4-methoxystilbene (3.8) to be the only product and GCMS showed negligible amounts of the *cis*-isomer (3.9) and 1-methoxybenzene-l,1-phenylethylene (3.10) irrespective of whether the reaction was performed in an IL or an organic solvent. The results are summarised in Table 3.1.




**Scheme 3.4 The Heck reaction between Iodoanisole and Styrene**

**Table 3.1 Results of the Heck reaction of Iodoanisole and Styrene in various solvents using $Pd(OAc)_2$ and (3.7) as catalysts.**

| Entry | Solvent | Catalyst | Amount of catalyst / mol % | Additive | Conversion / % |
|---|---|---|---|---|---|
| 1 | Mesitylene | $Pd(OAc)_2$ | 2 | - | 19 |
| 2 | DMF | $Pd(OAc)_2$ | 2 | - | 89 |
| 3 | BMIM[$PF_6$] | $Pd(OAc)_2$ | 2 | - | 46 |
| 4 | BMIM[$PF_6$] | $Pd(OAc)_2$ | 2 | 4% $PPh_3$ | 38 |
| 5 | BMIM[$PF_6$] | $Pd(OAc)_2$ | 2 | 4% DPPP | 39 |
| 6 | DMF | (3.7) | 0.5 | - | 100 |
| 7 | BMIM[$PF_6$] | (3.7) | 0.5 | - | 45 |
| 8 | BMIM[$PF_6$] | (3.7) | 0.5 | ($NEt_3$)[a] | 44 |
| 9 | BMIM[OTf] | (3.7) | 0.5 | - | 46 |
| 10 | BMIM[Cl] | (3.7) | 0.5 | - | 25 |

All reactions were performed in 1ml solvent with 1 mmol iodoanisole, 1.5 mmol styrene, and 1.2 mmol sodium acetate as base. The external oil temperature was maintained at 140 $^0$C for 16 h. Yield of *trans*-4-methoxystilbene was determined by GCMS. [a]Instead of NaOAc.

Clearly, the highest conversions are seen in DMF regardless of the catalyst employed (see entries 2 and 6), with the cyclopalladated catalyst giving slightly higher yield than $Pd(OAc)_2$ (100 % versus 89 %). Since the main role of the solvent in this reaction is probably to stabilise the polar intermediates formed, we might expect similar results in ionic liquid media which are also polar media. However under our conditions, the reactions in the ionic liquids are much less efficient giving less than 50 % yield (entries 3,7,9), though large amounts of unreacted iodoanisole and styrene were detected by GC. It is possible that polar solvents *e.g.* DMF stabilise the cationic palladium species by coordination which is not likely with "non-coordinating" anions $[PF_6]^-$ or $[OTf]^-$. Low yields for the Heck reaction in imidazolium-based ILs have been reported previously.[334,343] For example, Herrmann reported a 51 % yield of *trans*-stilbene for the Heck arylation of chlorobenzene with styrene in $NBu_4$[Br] at 150 $^0$C, using (3.3) (0.5%) as catalyst, with 6 % $PPh_4$[Cl], but the yields obtained in approximately the same length of time in 1-butyl-3-propylimidazolium salts BPIM[Br] and BPIM[$PF_6$] were only 11 % and 5 % respectively.[335] They concluded that co-ordinating halides were necessary for a beneficial solvent effect as the reaction proceeds further in BPIM[Br] than BPIM[$PF_6$]. However, this contradicts our results where only 25 % conversion occured in BMIM[Cl] compared to 45 % in BMIM[$PF_6$]. (Compare entries 7 and 10). It is possible that the carbene complex $[PdCl_2(bmimy)_2]$ is formed under our experimental conditions but probably to a small

extent, as the greater activity reported for these carbene catalysts would otherwise be reflected in an increased yield. It is interesting to note that recent publications reporting better yields for the Heck reaction in BMIM-ILs compared to organic solvents, employ excess base or high temperatures for the reaction, as most catalysts are more stable at higher temperatures in ILs.[343,344,345] For example, it has been demonstrated that Heck reactions can be performed in 5 - 45 min with controlled microwave heating in BMIM[$PF_6$] and several catalysts were stable despite the high reaction temperature (180-220 $^0$C), whereas massive formation of "palladium black" was observed in DMF.[343] These reports were published since our study was carried out so the affect of using excess base under our conditions was never examined, although we found substituting $NEt_3$ for NaOAc made no difference to the yield of product obtained (compare entries 7 and 8).

Using $Pd(OAc)_2$ the effect of additives such as triphenylphosphine and 1,2-bis(diphenylphosphino)ethane (DPPP) was also investigated. These gave a reduced yield (see entries 4 and 5). The adverse effect of both these ligands has since been reported in the $Pd(OAc)_2$ catalysed Heck reaction between bromoanisole and butyl acrylate in BMIM[$PF_6$] at 180 $^0$C; the reaction gave a 53 % yield with no additives, a 43 % yield with 4 mol% $PPh_3$ added, and only a 21 % yield when 4 mol% DPPP was added.[343] Howarth also used $PPh_3$ as an additive in $Pd(OAc)_2$ catalysed Heck reactions at 140 $^0$C, and interestingly the yields reported in BMIM[$PF_6$] were lower than those found in DMF.[346] Note, the presence of $PPh_3$ in BMIM[$PF_6$] for the Heck reaction of iodobenzene and butyl acrylate has since been reported to increase the induction period of the reaction and decrease the reaction rate.[340] Seddon *et al.*. also investigated the effect of additives and reported that ligands such as triphenylstilbene and 1,2-bis(diphenylphosphino)ethane have an adverse effect when employed in the Heck reaction, but in their case, $PPh_3$ provided moderate improvements to the yield.[347]

The observation of large amounts of unreacted starting material for our reactions in ILs suggests that longer times or higher temperatures may be beneficial, alternatively more reactive substrates could be used. Hence the reaction between styrene and iodobenzene, which is a more reactive than iodoanisole,[313] was studied and the results are shown in Table 3.2. The reaction in BMIM[$PF_6$] gave a 53 % yield of product compared to 45 % using iodoanisole. (Compare entry 1 in Table 3.2 to entry 7 in Table 3.1). The same yield was also obtained in BMIM[$BF_4$] (entry 2).

**Table 3.2 Results of the Heck reaction of Iodobenzene and Styrene in ILs using $Pd(OAc)_2$ and (3.7) as catalysts.**

| Entry | Solvent | Catalyst | Amount of catalyst / mol % | Additive | Conversion / % |
|---|---|---|---|---|---|
| 1 | BMIM[$PF_6$] | (3.7) | 0.5 | - | 53 |
| 2 | BMIM[$BF_4$] | (3.7) | 0.5 | - | 53 |
| 3[a] | BMIM[$PF_6$] | (3.7) | 0.5 | - | 61 |
| 4[b] | BMIM[$PF_6$] | (3.7) | 0.5 | - | 68 |
| 5 | BMIM[$PF_6$] | $Pd(OAc)_2$ | 2 | - | 50 |
| 6 | BMIM[$PF_6$] | $Pd(OAc)_2$ | 2 | 4% $PPh_3$ | 41 |
| 7 | BMIM[$PF_6$] | $Pd(OAc)_2$ | 2 | 6% $Ph_4PBr$ | 56 |
| 8 | BMIM[$PF_6$] | (3.7) | 0.5 | $Et_4NBr$ | 35 |

All reactions were performed in 1 ml solvent with 1 mmol iodobenzene, 1.5 mmol styrene, and 1.2 mmol sodium acetate as base. The external oil bath temperature was maintained at 140 $^0$C for 16 h. Yield of *trans*-stilbene was determined by GCMS. [a]Reaction period of 60 h, [b]120 h.

Doubling the reaction time to 120 h gave a slight increase in yield (see entries 3 and 4). As before, $Pd(OAc)_2$ with or without $PPh_3$ was also tested as catalyst, giving 50 % and 41 % yield respectively (entries 5 and 6). Addition of $Ph_4PX$ (X = Cl, Br, I) to $Pd(OAc)_2$ is reported to give high catalytic activities,[348] the active catalyst is believed to be $(Ph_4P)_2[Pd(OAc)_2Cl_2]$. Hence, a reaction was attempted using $Ph_4PBr$ as additive and a slight increase in yield was noted (compare entries 5 and 7). Although adding catalytic amounts of $Bu_4N[Br]$ to $Pd(OAc)_2$ in BMIM[$BF_4$] leads to a rate enhancement,[339] halide counterions appear not to stabilise the cyclopalladated catalyst in the same way, as a reduced yield was observed (entry 8). Overall, (3.7) displays better activity in organic media compared to imidazolium based ILs (even in the presence of additives). As Herrmann has demonstrated that palladacycles are more active in molten $Bu_4N[Br]$ than RTILs,[334] and Vallin *et al.* found a palladacycle catalyst to be less active than $PdCl_2$ in BMIM[$PF_6$],[343] and there are now numerous reports describing simple Pd salts as effective catalysts for the Heck reaction,[335,347,349] which can be successfully immobilised in ILs providing a means of recycling both the catalyst and solvent, this study was abandoned.

## 3.2 BMIM[Cl]-$ZnCl_2$

Many reactions have been shown to proceed smoothly in the chloroaluminate ionic liquids, (see Chapter 1, section 1.5.2), however these ionic liquids react with water to give hydrated aluminium(III) ionic species and HCl, hence they must be handled under dry conditions. Furthermore, these ionic liquids often have to be quenched (usually in water) destroying the ionic liquid and generating acidic aqueous waste. Research is, therefore shifting to the investigation of ionic liquids that are more stable to water to allow for straightforward product separation and ease of handling.

Therefore we synthesised and investigated organic synthesis in organo-zincate ILs, BMIM[Cl]-($x$)$ZnCl_2$ where $x$ is the molar fraction of $ZnCl_2$ and in our case is equivalent to 0.5, 0.6, 0.67, 0.71. Dupont *et al.* has previously reported the synthesis of BMIM[Cl]-($x$)$ZnCl_2$ for $x$ = 0.33, 0.50, 0.64, and 0.75 and determined the melting points as 60 $^0$C, 96 $^0$C, 78 $^0$C, 105 $^0$C, respectively.[350] They used BMIM[Cl]-$ZnCl_2$ to immobilise $RuCl_2(PPh_3)_3$ for the biphasic hydrogenation of 1-hexene. Thus dissolving $RuCl_2(PPh_3)_3$ in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.33) gave a stable brown-red solution from which the transition metal complex could not be removed by organic solvents, and therefore the catalyst ionic liquid solution could be reused seven times with no loss of catalyst activity. The activity of this catalyst was of the same magnitude in BMIM[Cl]-$ZnCl_2$ as in BMIM[$BF_4$] which means that the presence of Zn does not influence the catalytic properties of $RuCl_2(PPh_3)_3$ in this case.[350] To our knowledge there have been no reports on using BMIM[Cl]-$ZnCl_2$ as solvent and catalyst in organic synthesis.

Other examples of ionic liquids made from metal chlorides other than aluminium include BMIM[Cl]-$FeCl_3$[351] and those synthesised from quaternary ammonium salts *e.g.* $Me_3NC_2H_4Y$[Cl] (Y = OH, Cl, OC(O)Me, OC(O)Ph) and $MCl_2$ (M = Zn and / or Sn).[352] The latter form moisture-stable ionic liquids and the influence of the substituent Y and metal M on the physical properties of the ILs were investigated. Choline chloride, $Me_3NC_2H_4OH$[Cl], mixed with two equivalents of $ZnCl_2$ gave the lowest freezing point (23-25 $^0$C), and unlike analogous aluminium systems, ratios with a molar excess of choline chloride, *i.e.* basic melts, did not form RTILs, implying that complex zinc anions in which the charge can be delocalised are necessary in these ILs.[352] Organic chemistry has been investigated in choline chloride-$ZnCl_2$, and results obtained for two important reactions: the Diels Alder cycloaddition[353] and the Fischer indole synthesis[354] are described in sections 3.3 and 3.4, respectively.

### 3.3.1 Results and Discussion

The organo-zincate ILs were prepared by mixing appropriate amounts of solid BMIM[Cl] and $ZnCl_2$ and heating to 100 $^0$C with efficient stirring until complete dissolution of the solid reagents occured, to give pale-yellow viscous ionic liquids. The melting points and viscosity were measured on cooling. The physical-chemical properties of these ILs depend upon their composition, as can be seen in Table 3.4.

**Table 3.4 The physicochemical properties of BMIM[Cl]-($x$)$ZnCl_2$**

| $X$ | Melting Point / $^0$C | Viscosity at 25 $^0$C/ cP | $H^2$ chemical shift (ppm relative to HOD) |
|---|---|---|---|
| 0.0 | 65 | - | 9.11 |
| 0.50 | 0.5 | 3 524 | 8.90 |
| 0.60 | 3.0 | 6 440 | 8.66 |
| 0.67 | 12.5 | 18 040 | 8.45 |
| 0.71 | 18.0 | 61 040 | 8.30 |

The FAB mass spectrum of BMIM[Cl]-$ZnCl_2$ shows the presence of $ZnCl_3^-$ (m/z 171), $Zn_2Cl_5^-$ (m/z 307), and $Zn_3Cl_7^-$ (m/z 445). The different observed melting points can be attributed to the formation of different amounts of the chlorozincate anions, similar to the well-known chloroaluminate imidazolium ILs.[355] It is also apparent that these anions interact through hydrogen bonds with the aromatic imidazolium hydrogens. The chemical shift of the $H^2$ proton of the $BMIM^+$ cation is a sensitive indicator of the degree of positive charge situated on the imidazole ring between the two nitrogen atoms, which should be affected by cation-anion interactions. A large decrease in chemical shift (from 9.11 to 8.30 ppm) is observed as a 1: 2.5 mole ratio of mixture of BMIM[Cl]-$ZnCl_2$ is approached as increasing amounts of $Zn_2Cl_5^-$and $Zn_3Cl_7^-$ anions interact with the $H^2$ proton, reducing the positive charge on the $BMIM^+$ cation, compared to lower values of $x$ where there are more $Cl^-$ anions present in the ILs. As can be seen, the minimum melting point occurs at $x = 0.5$. In this case delocalisation of the negative charge causes a reduction in lattice energy and hydrogen bonding compared to BMIM[Cl], hence a reduced melting point. As $x$ increases, the viscosity and melting point increase due to an increase in the amounts of $Zn_2Cl_5^-$ and $Zn_3Cl_7^-$, the increased size of these anions reduces their mobility.

It is important to note that Dupont *et al.* reported BMIM[Cl]-($x$)$ZnCl_2$ to have a melting point > 50 $^0$C for all values of $x$.[350] They prepared BMIM[Cl]-$ZnCl_2$ by mixing appropriate amounts of BMIM[Cl] and $ZnCl_2$ at 100 $^0$C, with and without an organic

solvent (acetone or acetonitrile). If a solvent was used then organic solvent distillation under vacuum followed at the end of the reaction, to yield pale-yellow viscous ILs that solidified on standing. Although their solvent-free method of preparation is the same as that employed by us, we did not find BMIM[Cl]-$ZnCl_2$ to solidify on standing. We cannot account for the observed differences in melting point, only to suggest that there may be traces of water present in our ILs. Although Schlenk techniques were used during the preparation of BMIM[Cl]-$ZnCl_2$, a glovebox was not used during the transfer of BMIM[Cl] and $ZnCl_2$ into the Schlenk tube. However, the ILs were thoroughly dried under vacuum (at 65 $^0$C) after preparation. We cannot offer any other explanation for the discrepancies in the results.

In 1960, Yates and Eaton demonstrated that Lewis acids can dramatically accelerate the Diels-Alder reaction by a factor of up to $10^5$ times.[356] Indeed, numerous important carbon-carbon bond-forming organic transformations have been shown to be menable to rate acceleration by a Lewis acid. The rest of this Chapter focuses on using BMIM[Cl]-$ZnCl_2$ as solvent and catalyst in C-C bond forming reactions and examines the rate, selectivity, and scope to reuse the IL for selected reactions.

## 3.3 DIELS-ALDER REACTIONS IN BMIM[Cl]-$ZnCl_2$

### 3.3.1 Introduction

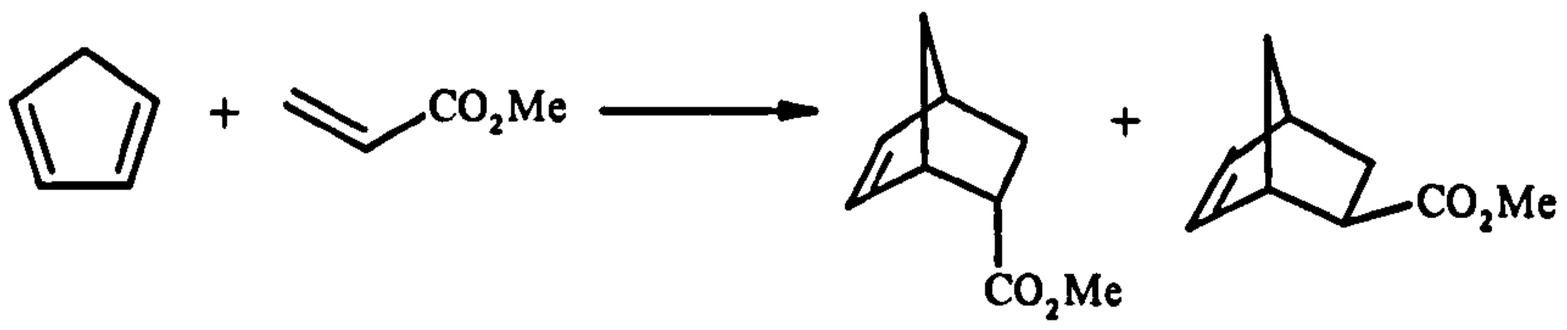
As mentioned in Chapter 1, section 1.5.1, there is an interest in finding methodologies by which Diels-Alder reactions may be performed to give one product. It is an addition reaction and so potentially highly 'atom efficient', but the reaction is often not selective, giving a mixture of isomers. The first report of a imidazolium-based IL being used as reaction medium / catalyst for the Diels-Alder reaction utilised EMIM[Cl]-$AlCl_3$ for the cycloaddition of methyl acrylate to Cp, and a four-fold increase in selectivity was reported in going from a basic melt ($x$ = 0.48) to an acidic melt ($x$ = 0.51).[173] *Endo / exo* ratios increased from 5/1 to 19/1. The use of BMIM[$BF_4$], EMIM[$CF_3SO_3$] and BMIM[$ClO_4$] as solvents for this reaction has been reported to give *endo / exo* ratios of 4.3, 4.9 and 5.3 respectively, under the same conditions.[357] As described in Chapter 1, section 1.5.1, the increased *endo* selectivity in BMIM-based ILs has been attributed to a hydrogen bond formed between the IL cation and methyl acrylate. Similarly, dialkylimidazolium bromides and trifluoracetates have been used as catalysts, in dichloromethane solution, for

the addition of Cp and either crotonaldehyde or methacrolein.[358] Here the effect was attributed to the Lewis acidity of the salts.

Choline chloride-$ZnCl_2$ proved to be an effective medium for a number of Diels-Alder reactions, providing isolated yields of 90 % or greater in all cases.[353] As the reactions were biphasic, the products were separated from the ionic liquid by decantation and washing with hexane, allowing the IL to be reused at least five times. Interestingly, the ILs were insensitive to moisture as addition of an equivalent amount of water to the metal, did not affect the yield obtained in the Diels-Alder reactions. The most noticeable effect of adding water, was the reduction in viscosity of the IL allowing more efficient stirring. The less Lewis acidic tin-containing liquid, choline chloride-$SnCl_2$, displayed lower catalytic activity but was also stable to moisture.[353]

There have been no reports on Diels Alder reactions in room temperature BMIM-zincate ILs. Selectivity and reactivity of Diels-Alder reactions are strongly influenced by the Lewis acidity of the medium and unlike most reaction media, the composition of zincate ILs can be easily varied. Literature data on the effect of solvent on the rate and selectivity of the Cp / methyl acrylate Diels-Alder reaction (Scheme 3.5) are shown in the Table 3.3.[359]

**Scheme 3.5 The Diels Alder reaction between methyl acrylate and Cp**




*Endo* *Exo*

**Table 3.3 The effect of solvent on selectivity in the Diels-Alder reaction of Cp and methyl acrylate[359]**

| Solvent | Temperature / $^0$C | Ratio of *Endo / Exo* |
|---|---|---|
| Benzene | 35 | 2.8 |
| Ethanol | 30 | 5.2 |
| Methanol | 26 | 7.0 |
| Water | 20 | 9.3 |
| Ethyl ammonium nitrate | 25 | 6.7 |

The rate and *endo* selectivity enhancements for Diels-Alder reactions in water have been attributed largely to hydrophobic association of reactants and hydrogen bonding to the activating group of the dienophile.[360,361] Ethylammonium nitrate (EAN) is a low-melting

fused salt that resembles water in those properties associated with the hydrophobic effect, since it, like water, has a high cohesive energy.[362] We investigated the influence of BMIM[Cl]-(*x*)$ZnCl_2$ ($x$ = 0.5, 0.6, 0.67, 0.71) on the selectivity for the Diels-Alder reaction between Cp and methyl acrylate.

### 3.3.2 Results and Discussion

In a typical Diels- Alder reaction, the methyl acrylate was added to 1 molar equivalent BMIM[Cl]-$ZnCl_2$ and stirred at 25 $^0$C to form a homogeneous solution. Freshly cracked Cp was then added and the resultant biphasic mixture was stirred for 24 h. The organic layer was then separated by decantation from the viscous IL and any residual product was extracted from the IL with diethyl ether. The results are shown in Table 3.5.

**Table 3.5 The effect of BMIM[Cl]-(*x*)$ZnCl_2$ on selectivity in the Diels-Alder reaction of methyl acrylate and Cp**

| *X* | *Endo* / *Exo* ratio[a] | Yield / %[b] |
|---|---|---|
| 0.50 | 7.2 | 84 |
| 0.60 | 11.1 | 82 |
| 0.67 | 14.9 | 84 |
| 0.70 | 15.6 | 89 |

[a] Measured by $^1$H NMR integration [b] Measured by $^1$H NMR integration using ferrocene as an internal standard

**Figure 3.2 The effect of solvent on selectivity in the Diels-Alder reaction of methyl acrylate and Cp**

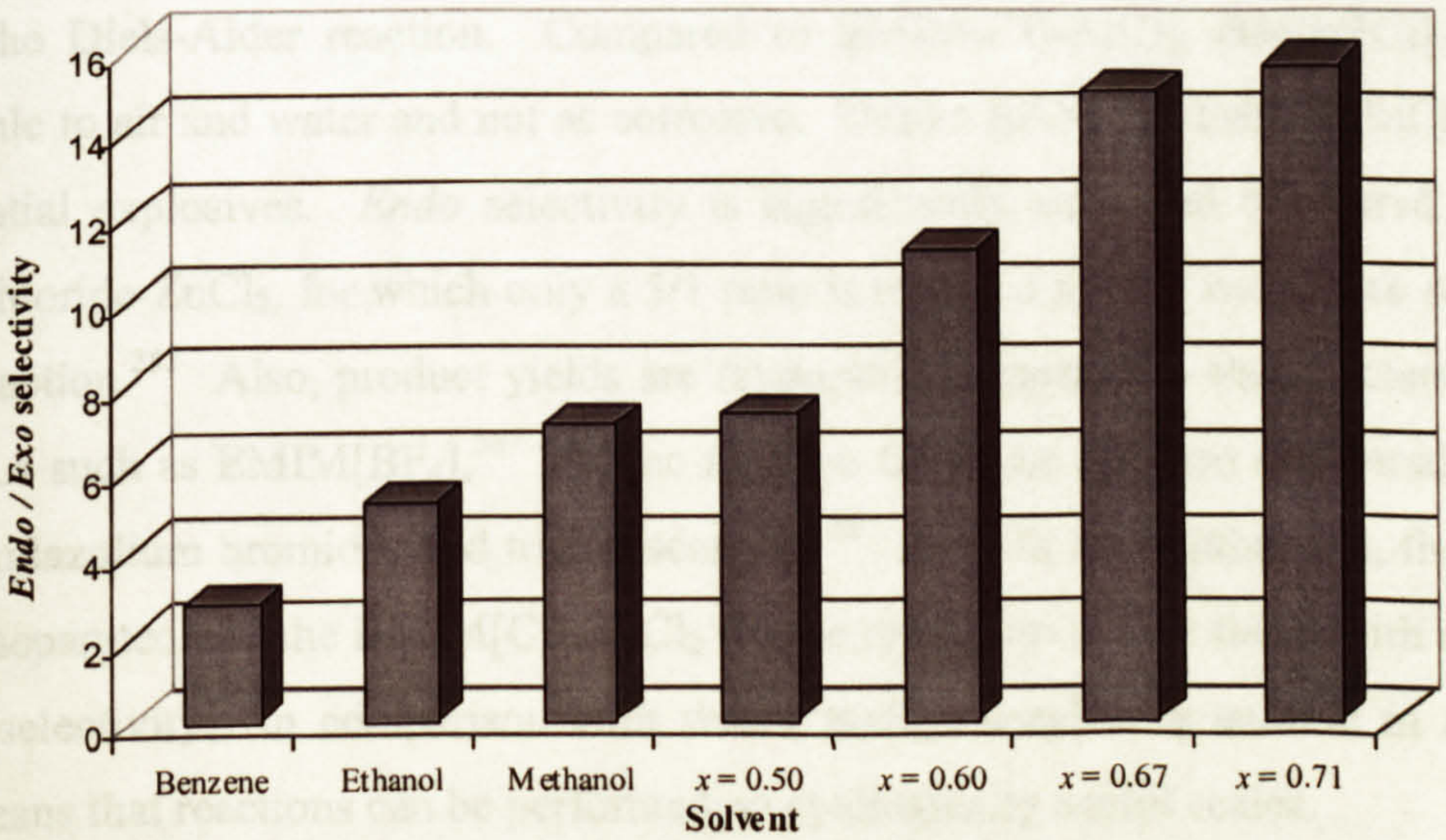
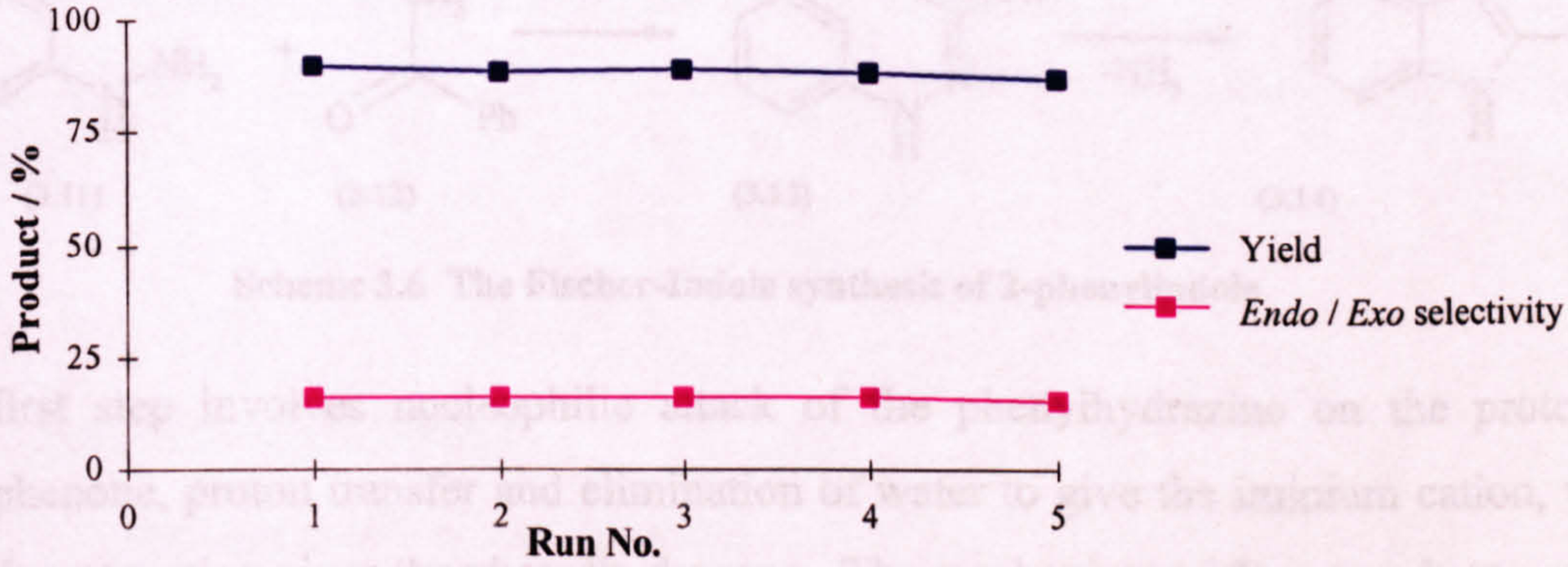


Figure 3.2 shows that increasing ($x$), has a profound effect on selectivity for the *endo*-isomer. The observed 7/1 *endo*/*exo* product in the neutral melt is a reflection of the polarity of the medium, this is deduced by the similar selectivities noted for methanol and BMIM[Cl]-($x$)$ZnCl_2$ where $x = 0.5$. (See Figure 3.2). A two fold increase in selectivity is observed when $x = 0.71$ probably due to the increase in the Lewis acidity of the medium (*i.e.* the amount of "free" $ZnCl_2$ in the IL has increased). Similar results were found using 5 mol% $ZnI_2$ in BMIM[$PF_6$],[154] emphasising that the increased rate and selectivity are primarily due to the Lewis acidic zinc.

The capacity to reuse the IL was then examined. The IL was dried under vacuum at 80 $^0$C for 16 h before adding fresh substrates. The results are illustrated in Figure 3.3. The IL was reused five times with negligible decrease in yield or selectivity, demonstrating that the reaction is catalytic and there is no significant leaching of the IL into the organic phase during decantation and extraction of the product.

**Figure 3.3 Repeated Diels-Alder reactions in BMIM-($x$)$ZnCl_2$, ($x$ = 0.71)**

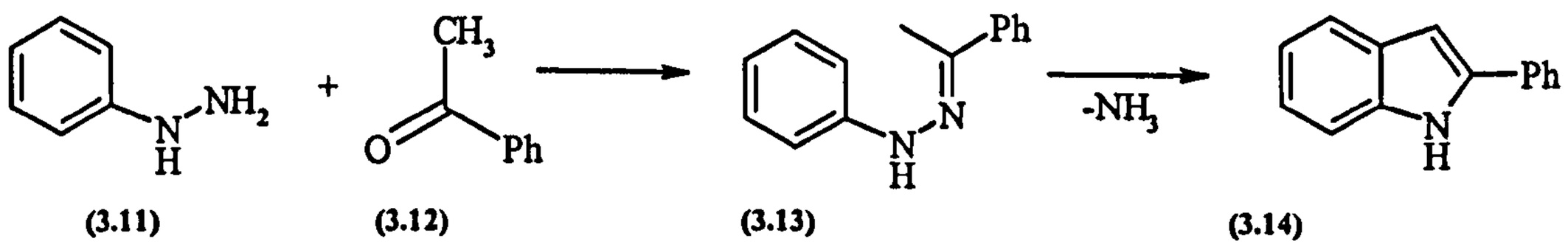



Overall, there are significant advantages of using BMIM[Cl]-$ZnCl_2$ rather than other ILs for the Diels-Alder reaction. Compared to EMIM[Cl]-$AlCl_3$, BMIM[Cl]-$ZnCl_2$ is more stable to air and water and not as corrosive. Unlike EAN, BMIM[Cl]-$ZnCl_2$ ILs are not potential explosives. *Endo* selectivity is significantly enhanced compared to using choline chloride-$ZnCl_2$, for which only a 5/1 ratio is reported for the *endo* / *exo* selectivity of this reaction.[353] Also, product yields are favourable compared to those obtained using neutral ILs such as EMIM[$BF_4$],[357] and the reaction times are reduced compared to using dialkylimidazolium bromides and trifluoracetates.[358] As with some other ILs, the product is easily separated and the BMIM[Cl]-$ZnCl_2$ can be reused up to five times with no loss in yield or selectivity. In comparison with water, methyl acrylate is soluble in these ILs which means that reactions can be performed on synthetically useful scales.

## 3.4 THE FISCHER-INDOLE SYNTHESIS IN BMIM[Cl]-$ZnCl_2$

### 3.4.1 Introduction

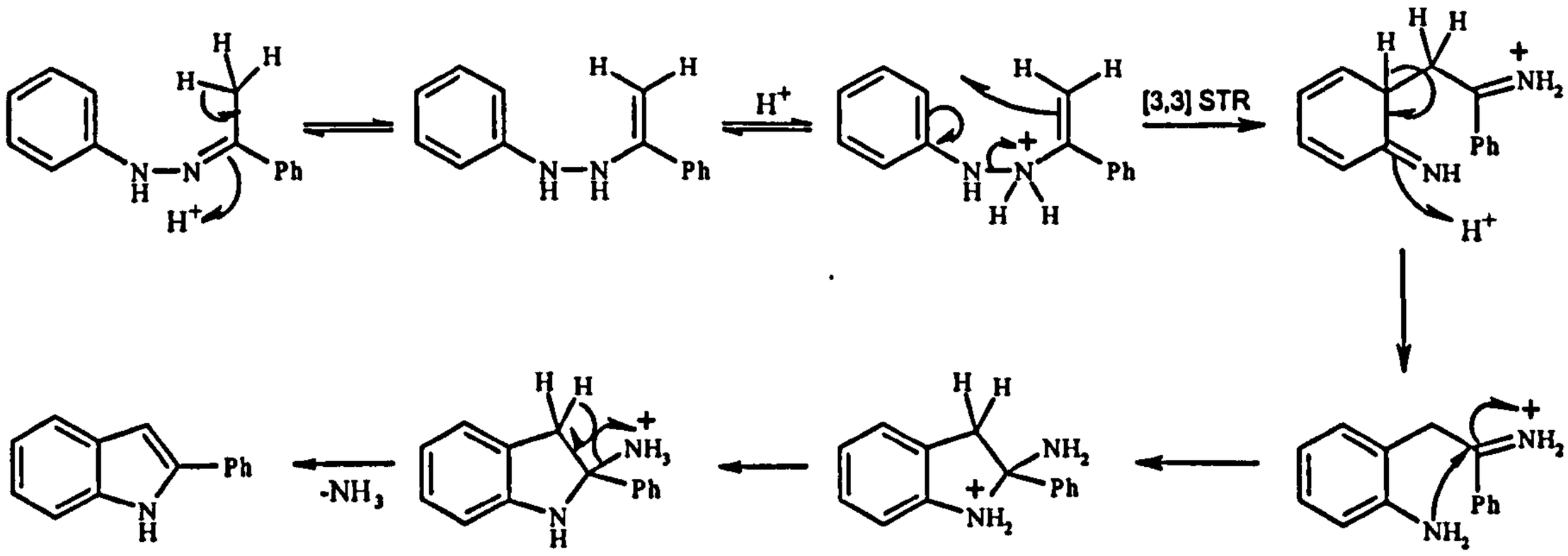
In 1883, while studying the reactivity of arylhydrazines and arylhydrazones, Emil Fischer found that, under acidic conditions, enolisable arylhydrazones undergo rearrangement and loss of ammonia to provide indole products.[363,364,365] The Fischer indole synthesis has since been studied in great detail[366] due its versatility and broad applicability in the synthesis of a number of biologically active natural and synthetic products, as well as in the synthesis of essential amino acid tryptamine,[367] photoconductors,[368] and antioxidants.[369] It is by far the most widely used indole synthesis. It consists of heating a phenylhydrazone, most often with an acid (though sometimes in an inert solvent). The reaction can be carried out in one pot by mixing a ketone with one mole equivalent of phenylhydrazine in acetic acid, and heating to reflux *i.e.* there is no need to isolate the intermediate phenylhydrazone. Scheme 3.6 illustrates the Fischer indole synthesis of 2-phenylindole.




(3.11) (3.12) (3.13) (3.14)

**Scheme 3.6 The Fischer-Indole synthesis of 2-phenylindole**

The first step involves nucleophilic attack of the phenylhydrazine on the protonated acetophenone, proton transfer and elimination of water to give the iminium cation, which after deprotonation gives the phenylhydrazone. The mechanism of the second step and the formation of a new carbon-carbon bond in a [3,3] sigmatropic rearrangement is shown in Scheme 3.7.




**Scheme 3.7 Mechanism of the synthesis of 2-phenylindole from the hydrazone**

In some cases the Fischer synthesis may be achieved simply by heating a phenylhydrazone to 200 $^0$C in the absence of acid.[370] However, the reaction occurs much more rapidly by weak acid catalysis. A wide variety of catalysts have been reported to catalyse the cyclisation of arylhydrazones of ketones: AcOH,[371] $ZnCl_2$,[372] refluxing polyphosphoric acid,[373] $PCl_3$.[374] Noncatalytic indolisation has also been reported in high temperature aqueous media[375] as well as in different solvents[376] like ethylene glycol, diethylene glycol, and tetralin.

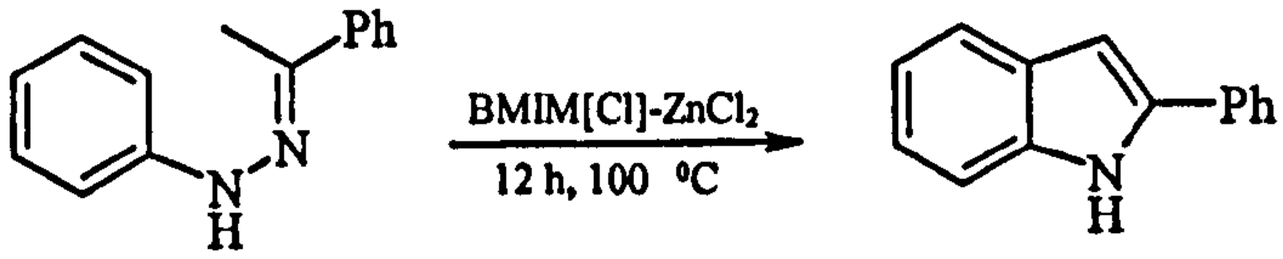
Further improvements look possible as $PCl_3$ and polyphosphoric acid are environmentally unfriendly, hazardous or difficult to handle; $PCl_3$ is needed in equimolar quantity; PPA in 8 to 9 fold excess by weight; and $ZnCl_2$ is used in three fold excess. To our knowledge there are only two reports of the Fischer indole synthesis in ILs, both published recently. The first example used 1-butylpyridinium chloride-($x$)$AlCl_3$ ($x$ = 0.67), and demonstrated that indoles could be synthesised in high yield in a relatively short time.[377] The second example which utilises choline chloride-($x$)$ZnCl_2$ ($x$ = 0.67) demonstrates that milder reaction conditions can be employed for the reaction and that the IL can be recycled by extracting the product by sublimation.[354] We report here that the Fischer-indole synthesis can also proceed under relatively mild conditions in BMIM[Cl]-($x$)$ZnCl_2$.

## 3.4.2 Results and Discussion

### *3.4.2.1 One pot and two-step synthesis*

To begin with, the reaction between phenylhydrazine (3.11) and acetophenone (3.12) was carried out in acetic acid to give phenylhydrazone of acetophenone (3.13). (See Scheme 3.6). Phenylhydrazone was then heated in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67) for 12 h at 100 $^0$C. Product extraction with ether gave 2-phenylindole (3.14) as yellow crystals in 98 % isolated yield. The product was purified by vacuum sublimation. Alternatively, the indole product could be isolated by direct vacuum sublimation from the ionic liquid reaction mixture to give a 95 % isolated yield of 2-phenylindole. A key factor in

**Scheme 3.8 The Fischer-Indole synthesis of 2-phenylindole in BMIM[Cl]-$ZnCl_2$**

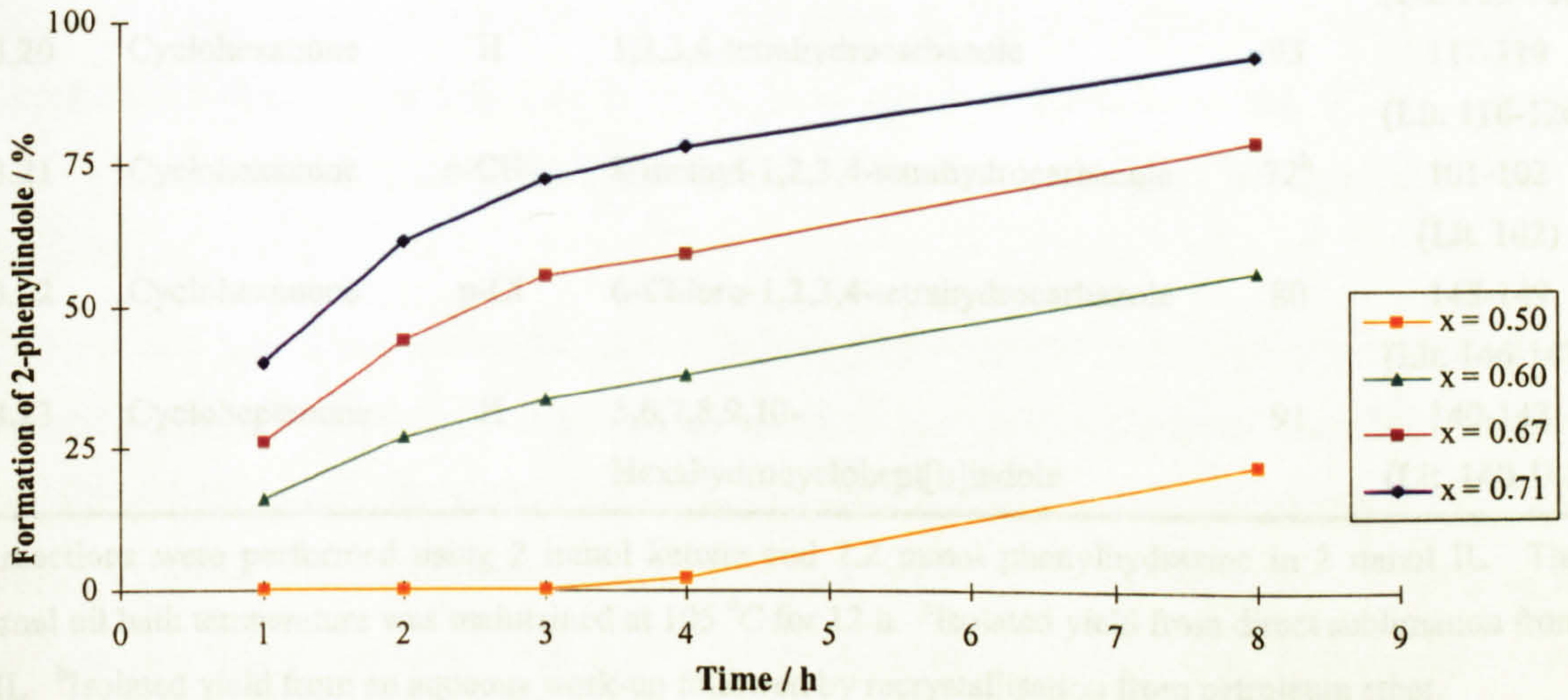



**(3.13)** **(3.14)**

determining the efficiency of the product sublimation is that a basic hydrazone is converted to indole which is a weaker base as the lone pair on the nitrogen in indole is part of the aromatic system and not available for coordination to the $ZnCl_2$.

The one-pot Fischer-indole synthesis of 2-phenylindole was then investigated in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.5, 0.6, 0.67, 0.71). Acetophenone and phenylhydrazine were added to 1 molar equivalent of the IL and the reaction mixture was stirred at 100 $^0$C for 12 h. A sample was withdrawn from the reaction mixture at regular intervals and analysed by GC; the results are displayed in Figure 3.4.

**Figure 3.4 Investigating the progress of the Fischer-indole synthesis in BMIM[Cl]-($x$)$ZnCl_2$**



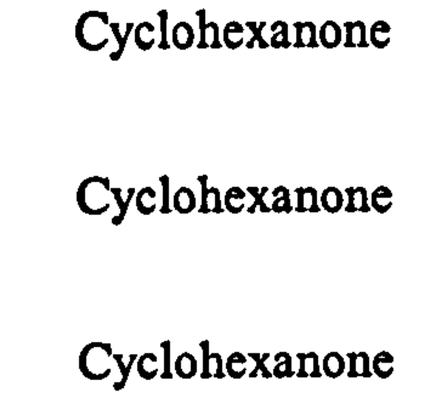

The Figure shows the formation of 2-phenylindole *i.e.* the second step of the reaction shown in Scheme 3.6, as the intermediate phenylhydrazone (3.13) is formed after 1 h in all the ILs. As shown the reaction is fastest in BMIM[Cl]-($x$)$ZnCl_2$ where $x$ = 0.71 due to the increased amount of $ZnCl_2$ present in this IL, the reaction being complete after 8 h. Even though the reaction is considerably slower for lower values of $x$, quantitative conversion of the hydrazone to 2-phenylindole was still achieved with longer reaction periods in all cases.

We investigated the one-pot version in which the hydrazone is formed in situ for other substrates as these consistently gave higher yields and cleaner product mixtures than those with preformed hydrazones. Table 3.6 shows the results achieved using phenylhydrazine, *o*-tolyhydrazine hydrochloride, 4-chlorophenylhydrazine hydrochloride or 2,5-dichlorophenylhydrazine with a variety of cyclic and acyclic ketones.

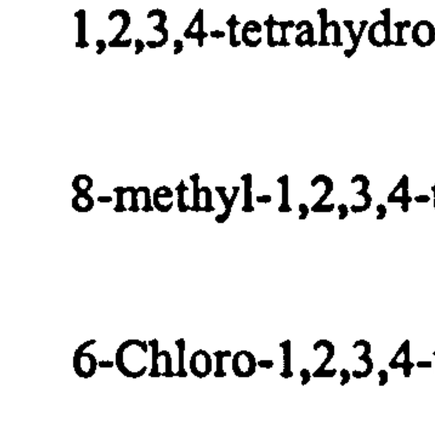
**Table 3.6 Fischer-indole synthesis in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.71)**

| Product | Ketone | Phenyl-hydrazine | Indole | Yield / %[a] | MP / $^0$C |
|---|---|---|---|---|---|
| 3.14 | Acetophenone | H | 2-Phenylindole | 95 | 186-187 (Lit. 188-189) |
| 3.15 | Butanone | H | 2,3-dimethylindole | 94 | 107-109 (Lit.111-112) |
| 3.16 | Butanone | o-$CH_3$ | 2,3,7-Trimethylindole | 90[b] | 76 (Lit. 76-77) |
| 3.17 | Butanone | p-Cl | 5-Chloro-2,3-dimethylindole | 88 | 142-143 (Lit. 141-142) |
| 3.18 | Butanone | 2,5-$Cl_2$ | 4,7-Dichloro-2,3-dimethylindole | 73 | 89-90 (Lit. 90-91) |
| 3.19 | Cyclopentanone | H | 1,2,3,4-tetrahydro-cyclopenta[b]indole | 90 | 106-107 (Lit. 105-106) |
| 3.20 | Cyclohexanone | H | 1,2,3,4-tetrahydrocarbazole | 93 | 117-119 (Lit. 118-120) |
| 3.21 | Cyclohexanone | o-$CH_3$ | 8-methyl-1,2,3,4-tetrahydrocarbazole | 72[b] | 101-102 (Lit. 102) |
| 3.22 | Cyclohexanone | p-Cl | 6-Chloro-1,2,3,4-tetrahydrocarbazole | 80 | 148-149 (Lit. 146-147) |
| 3.23 | Cycloheptanone | H | 5,6,7,8,9,10-Hexahydrocyclohept[b]indole | 91 | 140-142 (Lit. 140-141) |

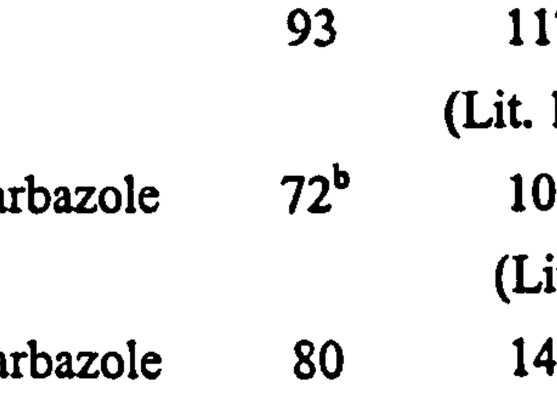
All reactions were performed using 2 mmol ketone and 2.2 mmol phenylhydrazine in 2 mmol IL. The external oil bath temperature was maintained at 105 $^0$C for 12 h. [a]Isolated yield from direct sublimation from the IL. [b]Isolated yield from an aqueous work-up followed by recrystallisation from petroleum ether.



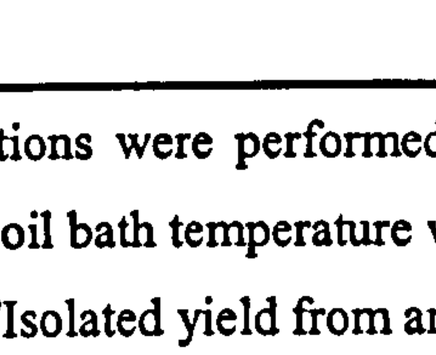
(3.15)



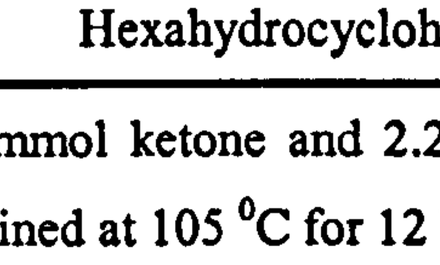
(3.16)



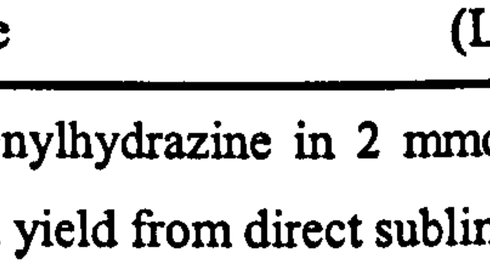
(3.17)



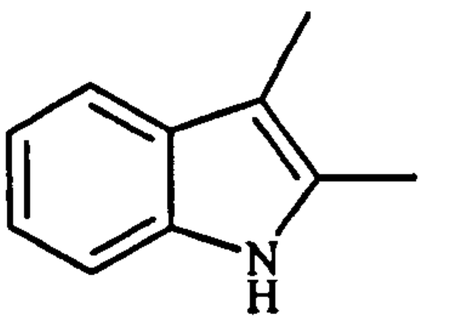
(3.18)



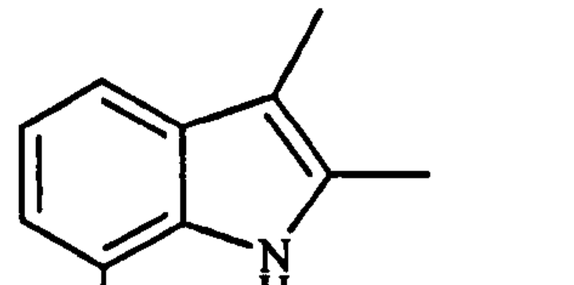
(3.19)



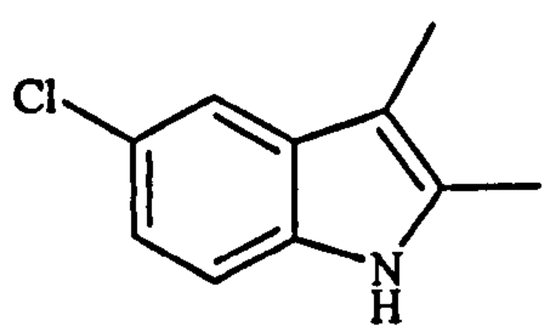
(3.20)



(3.21)



(3.22)



(3.23)

In all cases, good yields of product were obtained and in most cases the product could easily be isolated by vacuum sublimation. Interestingly, using butanone led to the formation of only one isomer (entries 3.15, 3.16, 3.17 and 3.18) and this observed level of high regioselectivity is discussed further in section 3.4.2.2. The yields are comparable to those reported for the one-pot Fischer-indole synthesis in 1-butylpyridnium chloride-($x$)$AlCl_3$ ($x = 0.67$),[377] and choline chloride-($x$)$ZnCl_2$ ($x = 0.67$).[354] In the latter case, it was found necessary to use three molar equivalents of IL (*i.e.* 6 equivalents of $ZnCl_2$) for the synthesis of (3.15), (3.18), and (3.20) to give yields of 80 %, 72 % and 82 % respectively, whereas we found using 1 molar equivalent of BMIM[Cl]-($x$)$ZnCl_2$ ($x = 0.71$) (*i.e.* 2.5 equivalents of $ZnCl_2$) and a longer reaction period gave improved yields (94 %, 73 % and 93 %, respectively). Using *o*-tolyhydrazine hydrochloride gave indoles that proved difficult to sublime but an aqueous work-up followed by recrystallisation from petroleum ether afforded the pure indole products in good yield (entries 3.16 and 3.21). Cyclic ketones also react readily in BMIM[Cl]-$ZnCl_2$ to give a high yield of product (see entries 3.19 - 3.23).

To reduce the time taken for the reaction, the reaction was also performed with microwave promotion. The Fischer indole reaction has previously been described to give good to moderate yields of product under microwave conditions. Previous reports involve heating of the preformed hydrazone in a microwave for 2 min at full power (with a brief cooling period after 1 min of heating);[378] or using montmorillonite clay in the microwave for 5 min at 160 W[379] or 300 $^0$C.[380] The use of montmorillonite clay and $ZnCl_2$ under microwave conditions is reported to afford 2-(2-pyridyl)indoles (in 60 % yield) at much lower temperatures (143 $^0$C).[381] Microwave irradiation in a pressurised reactor with water as solvent (220 $^0$C, 30 min) gives 2,3-dimethylindole in 67 % yield from phenylhydrazine and 2-butanone.[382] Interestingly, the one-pot reaction of acetophenone and phenylhydrazine hydrochloride is reported to give a 65 % yield of 2-phenylindole, in 28 s using acetic acid as solvent and 700 W microwave irradiation.[383]

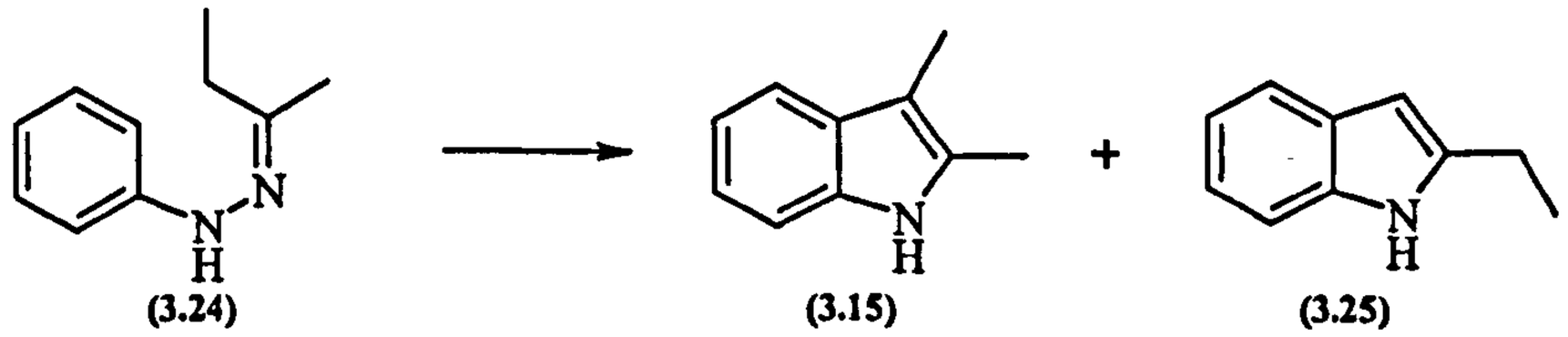
We found that to maintain a temperature of 100 $^0$C for the one-pot reaction of acetophenone and phenylhydrazine in BMIM[Cl]-$ZnCl_2$ ($x = 0.71$), 40 W microwave irradiation was sufficient and the reaction was complete in 40 min. As mentioned in Chapter 2, section 2.3.2, ILs absorb microwave irradiation extremely well, thus we found that setting a power higher than 40 W meant that the IL temperature increased well above that required (at the start of the experiment) just from the initial burst of power. Therefore the microwave irradiation was set at 40 W, but this meant that after the initial burst of

power, very little power (< 10 W) was used to maintain the temperature at 100 $^0$C and therefore the reaction takes 40 min to reach completion. An aqueous work-up gave 92 % yield of 2-phenylindole. Although a longer reaction period proved necessary for complete conversion of the starting materials, we obtained a yield higher than that previously reported for this reaction in the microwave.[383] However, an aqueous work-up was required to isolate the product at the end of the reaction as the reaction mixture had solidified, which meant that the IL could not be reused immediately afterwards as it had to be recovered and vigorously dried to remove the water. Therefore the reaction was attempted using toluene as a cosolvent with BMIM[Cl]-$ZnCl_2$, so that the product could be decanted off in the organic layer, making recyclability of the IL more feasible. As expected, the reaction rate was reduced with the reaction taking 90 mins for completion. In addition, the formation of unidentified side-products was observed by GCMS, thus a reduced yield of 68 % was isolated.

### *3.4.2.2 Regioselectivity*

Another important issue in the Fischer indole synthesis is the regioselectivity when an unsymmetrical dialkyl ketone is used. The direction of the cyclisation in a Fischer reaction may be highly dependent on the identity of the catalyst used and on the concentration of the catalyst. For example, the cyclisation of the phenylhydrazone of butanone (3.24) can occur to give 2,3-dimethylindole (3.15) or 2-ethylindole (3.25). See Scheme 3.9.

**Scheme 3.9 The direction of cyclisation of unsymmetrical phenyhydrazone**

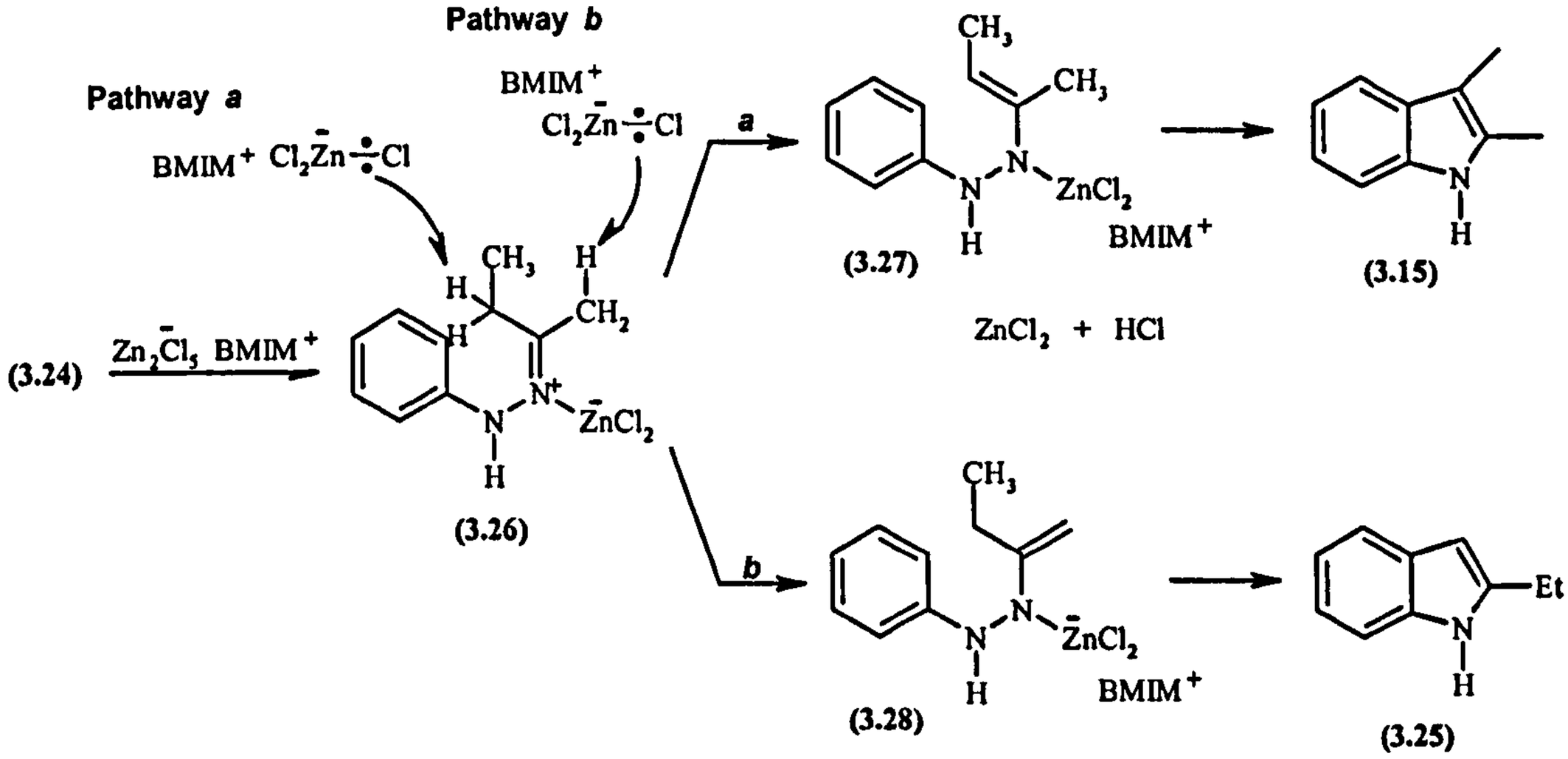


(3.24) (3.15) (3.25)

| | | | |
|---|---|---|---|
| Polyphosphoric acid[384] | 50 | : | 50 |
| $H_2SO_4$ / EtOH[384] | 50 | : | 50 |
| $P_2O_5$ / $MeSO_3H$[385] | 22 | : | 78 |
| $ZnCl_2$ / EtOH[386] | 20 | : | 80 |
| BMIM[Cl]-$ZnCl_2$ | 100 | : | 0 |

To investigate regioselectivity for the Fischer indole synthesis in BMIM[Cl]-$ZnCl_2$, the reaction between butanone and phenylhydrazine was studied. In previous studies of this reaction, a 4:1 mixture of (3.15) and (3.25) was obtained with $ZnCl_2$ as catalyst.[386] In our case, exclusive formation of 2,3-dimethylindole was observed in 94 % yield. (Entry 3.15,

Table 3.6). The exclusive formation of (3.15) was also observed by our colleagues who investigated the Fischer-indole synthesis in the related ionic liquid choline chloride-$ZnCl_2$. They proposed an explanation as shown in Scheme 3.10.[354]



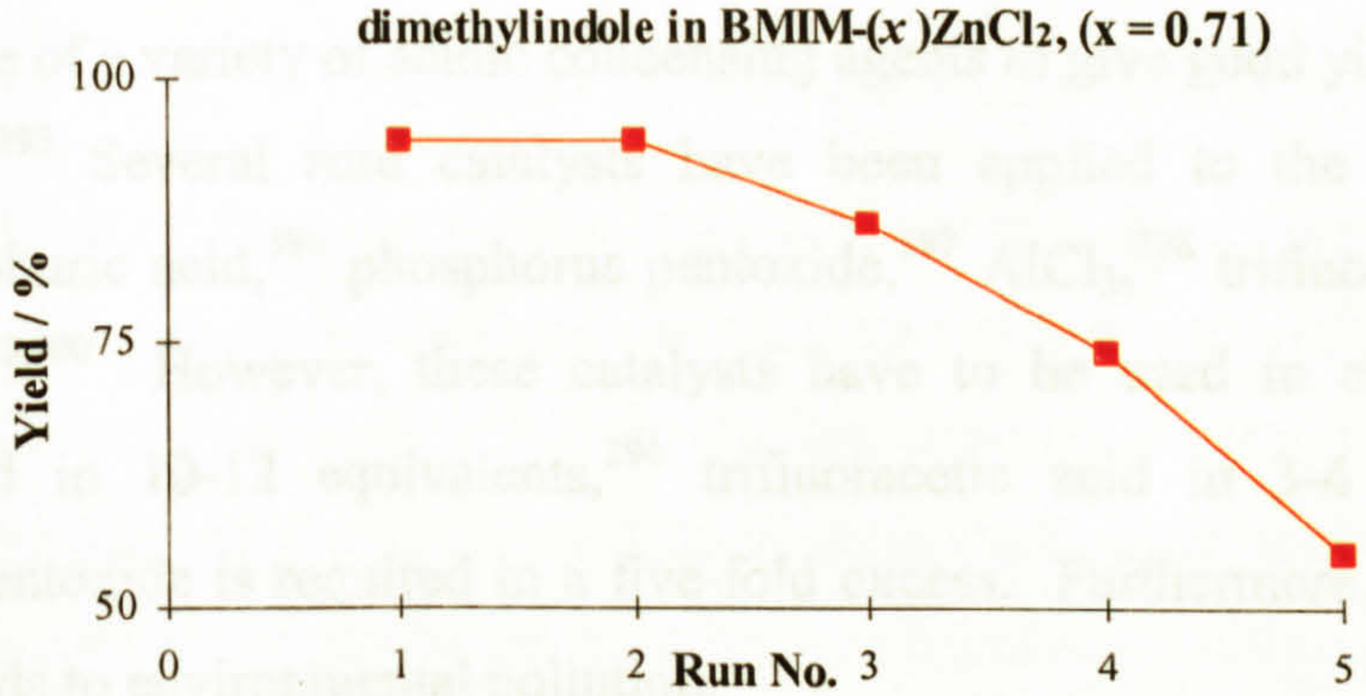

**Scheme 3.10 Proposed mechanism for the Fischer-indole synthesis in BMIM[Cl]-$ZnCl_2$ Adapted from ref 354**

$ZnCl_3^-$ can act as a base and remove a proton in one of two ways. In pathway *a*, the proton is removed by $ZnCl_3^-$ to produce the zinc enamine (3.27), which is the thermodynamic product, $ZnCl_2$ and HCl. Under the published reaction conditions pathway *b* is also observed in which a proton is lost from the methyl group to give the less substituted zinc enamine (3.28), which is the kinetic product. The reaction is under kinetic control as there is no special stability of the iminium cation (3.26) and pathways *a* and *b* are irreversible processes leading to two products (3.15) and (3.25). In BMIM[Cl]-$ZnCl_2$ the iminium cation is stabilised and pathway *b* becomes a reversible reaction hence the less substituted zinc enamine can reprotonate, return to the iminium cation (3.26) and follow pathway *a* to the more stable zinc enamine (3.27) and hence form exclusively 2,3-dimethylindole (3.15). This explanation is supported by three other examples using butanone, in all cases a single indole arising from the more substituted enamine intermediate is observed (see entries 3.16, 3.17 and 3.18 in Table 3.6).

### *3.4.2.3 Recyclability*

The recyclability of the IL from the reaction between butanone and phenylhydrazine was then assessed. Having isolated the product by vacuum sublimation, another one molar equivalent of butanone and phenylhydrazone was added and the reaction repeated. This time the yield was 94 % and a third repetition gave 86 % yield. The yields obtained over five runs are shown in Figure 3.5.

**Figure 3.5 Repeated Fischer-indole synthesis of 2,3-dimethylindole in BMIM-($x$)$ZnCl_2$, (x = 0.71)**




During the Fischer indole reaction, one molar equivalent of ammonia is produced which would be expected to coordinate to the $ZnCl_2$. In the repeated use of BMIM[Cl]-$ZnCl_2$ for a series of reactions (as shown by the mechanism in Scheme 3.10), $NH_3$ is produced which would be expected to accumulate by coordination to zinc and hence reduce the efficiency of the reaction as observed by the fall in yield.

Overall, we have shown that the one pot Fisher indole synthesis can be carried out using 1 equivalent BMIM[Cl]-$ZnCl_2$ to give good to excellent yields of product, with direct product isolation in most cases by vacuum sublimation from the IL, preventing the need for further recrystallisation steps. In unsymmetrical cases regiospecific formation of a single product arising from the formation of the more substituted enamine intermediate is observed. The IL can be reused at least three times with negligible drop in activity.

## 3.5 THE PECHMANN REACTION IN BMIM[Cl]-$ZnCl_2$

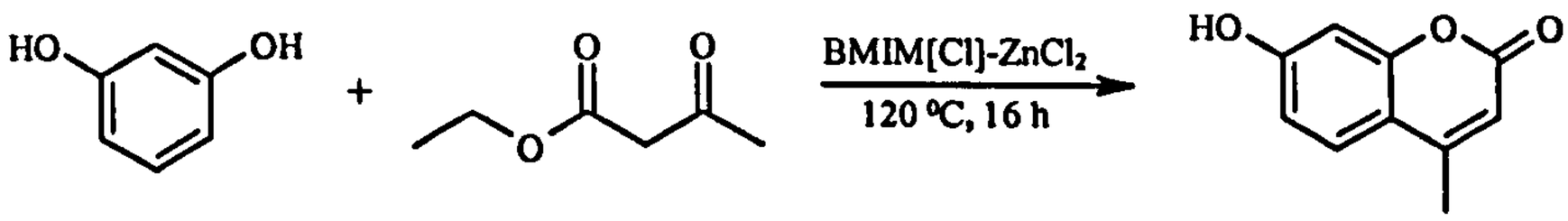
### 3.5.1 Introduction

Coumarin and its derivatives find their main application as fragrances, cosmetics, pharmaceuticals and agrochemicals.[387,388] There have been many synthetic routes to coumarins, including the Pechmann,[389] Perkin,[390] Knoevenagel,[391] Reformatsky[392] and Wittig[393] reactions. However, the Pechmann reaction has been the most widely applied method for preparing coumarins, involving condensation of phenols with β-ketonic esters in the presence of a variety of acidic condensing agents to give good yields of 4-substituted coumarins.[394,395] Several acid catalysts have been applied to the Pechmann reaction including sulphuric acid,[396] phosphorus pentoxide,[397] $AlCl_3$,[398] trifluoroacetic acid,[399] and many more.[395,400] However, these catalysts have to be used in excess; for example, sulphuric acid in 10-12 equivalents,[394] trifluoracetic acid in 3-4 equivalents,[399] and phosphorus pentoxide is required in a five-fold excess. Furthermore, the disposal of this acid waste leads to environmental pollution.

More recently, alternative syntheses of coumarins have been described, namely solvent-free synthesis using *p*-TsOH,[401] using cation exchange resins, using solid supported catalysts and by a combination of solid acid catalysts and microwave irradiation.[402,403] Some of these methods require high temperatures, longer reaction times and in some cases gave lower yields. BMIM[Cl]-$AlCl_3$ ($x$ = 0.67) has been successfully applied as solvent and catalyst in the Pechmann condensation and was found to reduce the reaction time drastically at ambient conditions and in most cases, gave excellent yields of coumarin derivatives.[404] The same results were also observed in *N*Bpy-$AlCl_3$, although in this case, the authors used a higher reaction temperature (130 $^0$C).[405] However, there is still the problem of disposal of the aluminium catalyst after the aqueous work-up. We therefore investigated the Pechmann reaction in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67) to see whether we could provide a recyclable medium (solvent and catalyst) for this reaction, as we had previously done for the Fischer-indole synthesis.

### 3.5.2 Results and Discussion

The reaction between resorcinol and ethyl acetoacetate (Scheme 3.11) was studied in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67) under different experimental conditions. We found that at temperatures below 80 $^0$C, the reaction was very slow and remained incomplete after a day, hence the reaction was repeated at 120 $^0$C.

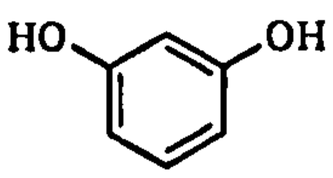
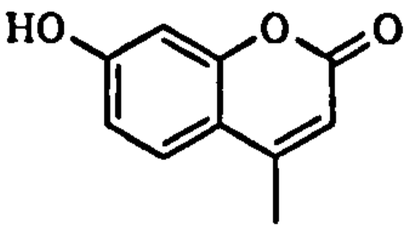
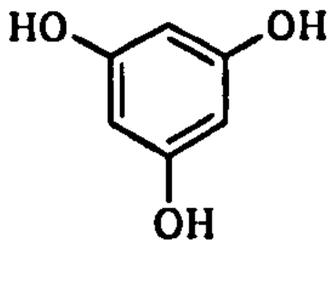
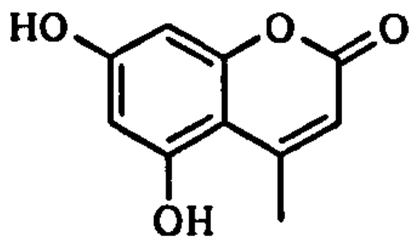
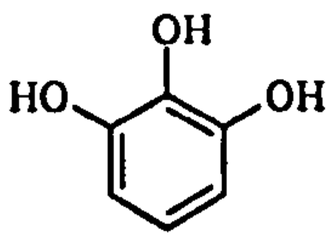
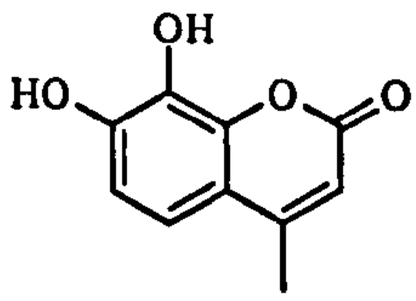
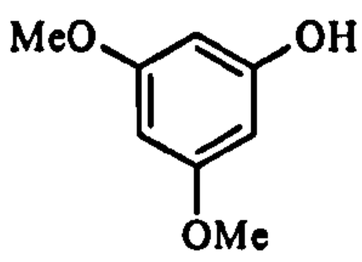
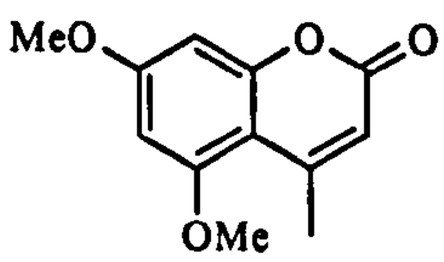
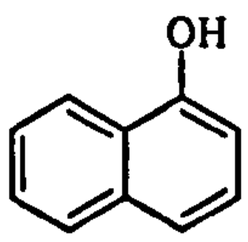
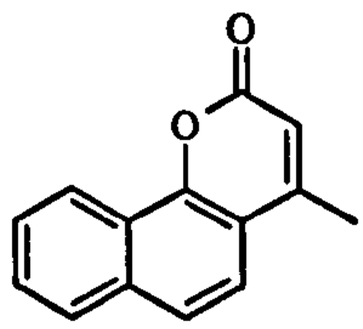
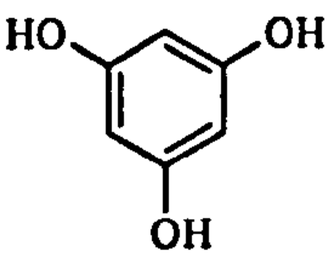
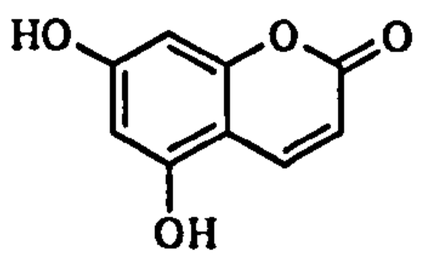
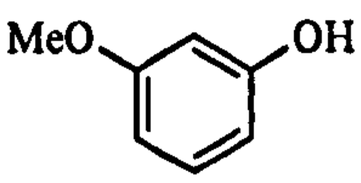
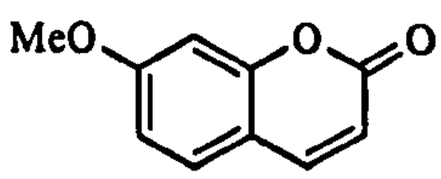
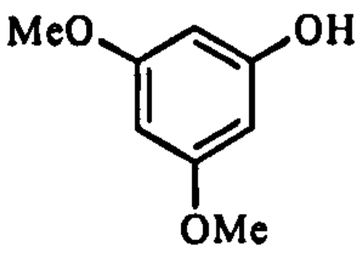
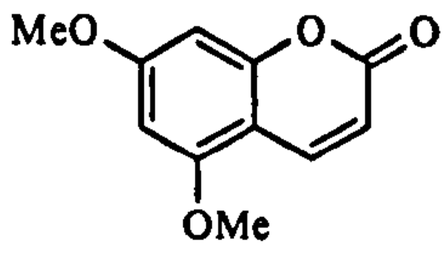
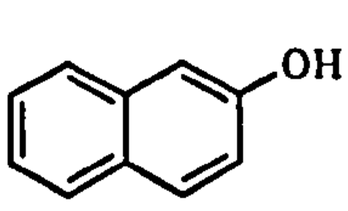
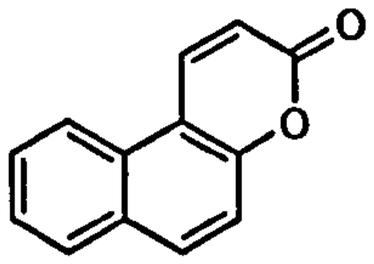
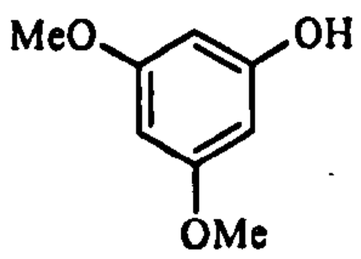
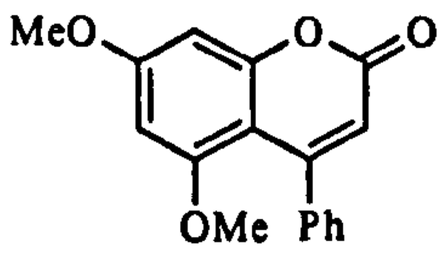



**Scheme 3.11. The Pechmann reaction to synthesise 7-Hydroxy-4 methylcoumarin**

At the end of the reaction, vacuum sublimation of the product directly from the IL was attempted but this proved difficult and virtually no product could be isolated in this way. As the product has limited solubility in all the organic solvents which would form a biphase with BMIM[Cl]-$ZnCl_2$, a liquid-liquid-separation could not be used to extract the product and therefore an aqueous work-up became necessary. Addition of water dissolved the BMIM[Cl]-$ZnCl_2$, and caused precipitation of the product which was separated by filtration. Recrystallisation of the filtered solid from ethyl acetate / heptane gave 95 % yield of product. The aqueous extract was transferred to a Schlenk tube and placed under vacuum at 60 $^0$C to remove the water and recover the IL. Removal of water gave a pale brown IL (no impurities could be detected by $^1$H NMR), to which resorcinol and ethyl acetoacetate were added in order to investigate the capacity to which the IL could be reused. After 16 h, the aqueous work-up was repeated, but in this case, there was very little precipitate and a thick tar resulted. Amongst unreacted starting material, there were unidentifiable side-products and less than 10 % yield of product. We cannot ascertain what factors are causing the low yield in the repeated reaction.

To test the generality of the result, the reaction was extended to other substrates under the same conditions and the results are shown in Table 3.7. In all cases, excellent yields of coumarins were achieved. We have shown that BMIM[Cl]-$ZnCl_2$ can be used as solvent and catalyst for this condensation reaction and that one molar equivalent of BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67) is sufficient to achieve high yields. Using a lower value of $x$ gave a lower yield of product. For example, the reaction between resorcinol and ethyl acetoacetate in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67) gave a 95 % yield of (3.29), whereas BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.60) gave a 73 % yield under the same conditions. Unfortunately, attempts to recycle the IL were unsuccessful.

**Table 3.7 The Pechmann reaction of various phenols in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67)**

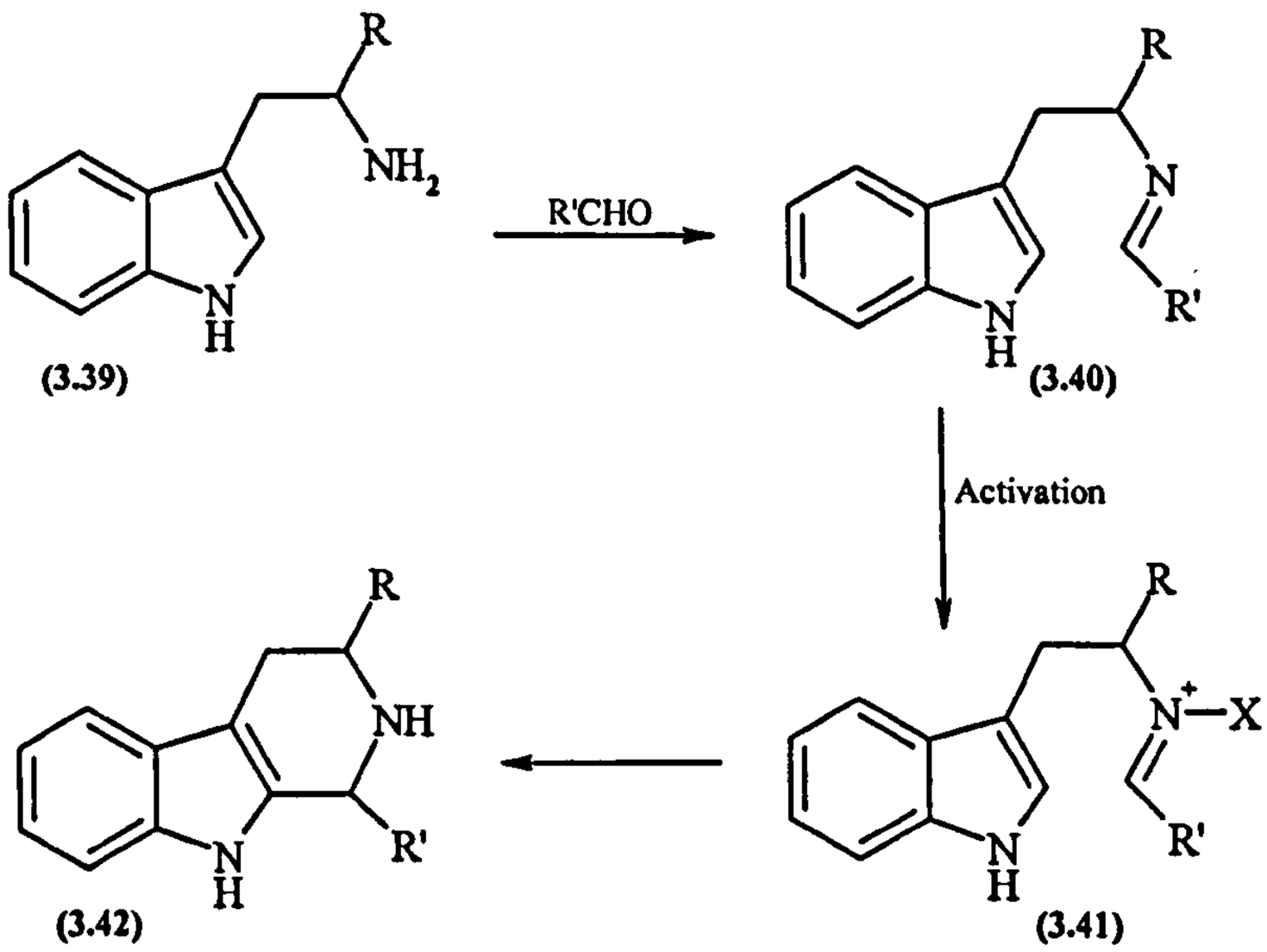
| Entry | Phenol | Ester | Product | Yield / % | M. P. / $^0$C |
|---|---|---|---|---|---|
| 3.29 |  | Ethyl acetoacetate |  | 95 | 193-194 (Lit. 194-195) |
| 3.30 |  | Ethyl acetoacetate |  | 90 | 282-284 (Lit. 284-285) |
| 3.31 |  | Ethyl acetoacetate |  | 88 | 242-243 (Lit. 243) |
| 3.32 |  | Ethyl acetoacetate |  | 91 | 169-170 (Lit. 169) |
| 3.33 |  | Ethyl acetoacetate |  | 80 | 153-154 (Lit. 155) |
| 3.34 |  | Ethyl propynoate |  | 93 | 274-276 (Lit. 270-272) |
| 3.35 |  | Ethyl propynoate |  | 94 | 120 (Lit. 119-120) |
| 3.36 |  | Ethyl propynoate |  | 96 | 145-146 (Lit. 146-147) |
| 3.37 |  | Ethyl propynoate |  | 82 | 114-115 (Lit. 116-117) |
| 3.38 |  | Ethyl benzoylacetate |  | 81 | 164-166 (Lit. 165-166) |

All reactions were performed using 1 mmol phenol and 1.1 mmol ester in 1 mmol IL. The external oil bath temperature was maintained at 120 $^0$C for 16 h. [a]Isolated yield after recrystallisation.

## 3.6 THE PICTET-SPENGLER REACTION IN BMIM[Cl]-$ZnCl_2$

### 3.6.1 Introduction

The Pictet-Spengler reaction generally refers to condensations of tryptamines or tryptophans with aldehydes or ketones to give the corresponding $\beta$-carboline derivatives and has for decades been the method of choice for the preparation of these compounds.[406] The tetrahydro-$\beta$-carboline ring system is present in numerous biologically active indole alkaloids, as well as synthetic compounds. Activation of imine (3.40) is most commonly achieved via Brønsted acid catalysis (X = H) (see Scheme 3.12) as Lewis-acid catalysed Pictet-Spengler reactions yielding tetrahydro-$\beta$-carbolines are rare.[407,408,409]




**Scheme 3.12 The Pictet-Spengler reaction**

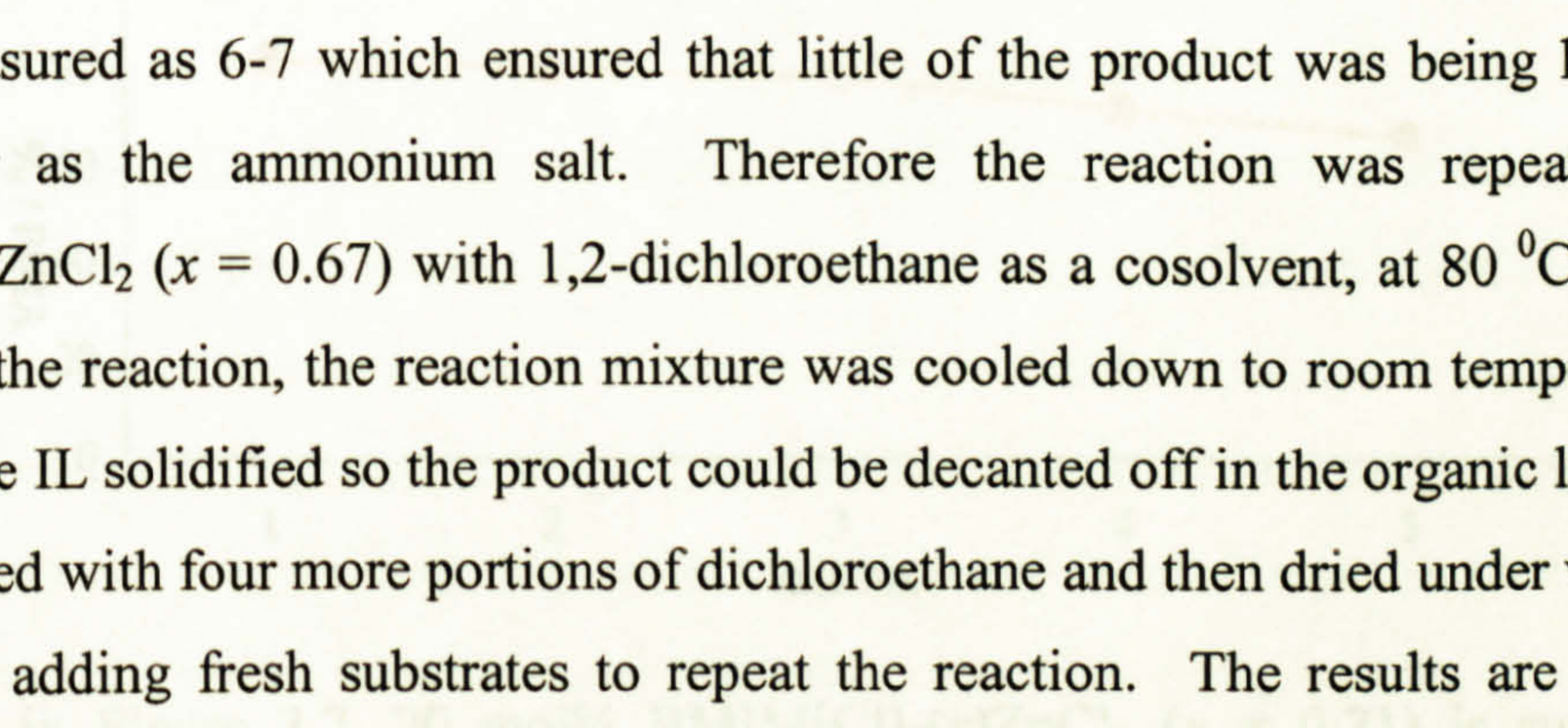
Only recently has the use of Lewis acids been described for this transformation and it was found that BMIM[Cl]-($x$)$AlCl_3$ ($x$ = 0.5) is a highly active catalyst for the Pictet-Spengler reaction of tryptophan methyl ester (R = $CO_2Me$) with benzaldehyde ($R^1$ = Ph).[410] Using 20 mol% BMIM[Cl]-$AlCl_3$, an 80 % yield of product (3.42) was obtained under ambient temperature conditions, after 24 h. On the other hand, using $AlCl_3$ in BMIM[$BF_4$] was only moderately effective and the reaction needed 2.5 days for complete conversion of starting material. Extending these results to tryptamine (R = H) was less straightforward as in the absence of the inductively electron-withdrawing carbonyl group in tryptophan, tryptamine imines are significantly less reactive. In the literature,[411,412] protic acid catalysed tryptamine Pictet-Spengler reactions often feature harsher conditions and poorer yields than their tryptophan counterparts. Indeed those Lewis acids successful in the tryptophan cyclisations were unable to promote the analogous conversion of tryptamine under a number of different experimental conditions. Various additives were

tested to boost the reactivity of these Lewis acids and it was found that a combination of 10 % $Yb(OTf)_3$ and 50 mol% BMIM[Cl]-($x$)$AlCl_3$ ($x$ = 0.5), resulted in a very active catalyst which gave uniformly high yields, either with preformed imines or in one-pot condensations with the aldehydes. The ionic liquid was integral to the additive effect, as substitution by 50 mol% $AlCl_3$ alone resulted in lower yields.[410]

### 3.6.2 Results and Discussion

The Pictet-Spengler reaction of tryptamine and benzaldehyde was investigated using BMIM[Cl]-$ZnCl_2$ to see whether the IL would provide high catalytic activity (thus circumventing the need for additional Lewis acid catalysts) for this cyclisation reaction and whether it could be used as a recyclable solvent / catalyst. Tryptamine was added to an equimolar amount of BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67), and stirred at 60 $^0$C for 10 min before addition of 1.2 equivalent benzaldehyde. The reaction mixture was stirred at 100 $^0$C for 16 h, after which time TLC and GCMS analysis showed complete conversion of the tryptamine, so $CH_2Cl_2$ was added to extract the product. However this proved extremely difficult as the reaction mixture had solidified. Addition of water to solubilise the IL facilitated extraction, but gave a modest yield of product (55 %). The pH of the aqueous layer was measured as 6-7 which ensured that little of the product was being lost in the aqueous layer as the ammonium salt. Therefore the reaction was repeated using BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67) with 1,2-dichloroethane as a cosolvent, at 80 $^0$C for 24 h. At the end of the reaction, the reaction mixture was cooled down to room temperature, at which point the IL solidified so the product could be decanted off in the organic layer. The IL was extracted with four more portions of dichloroethane and then dried under vacuum at 80 $^0$C, before adding fresh substrates to repeat the reaction. The results are shown in Figure 3.6.

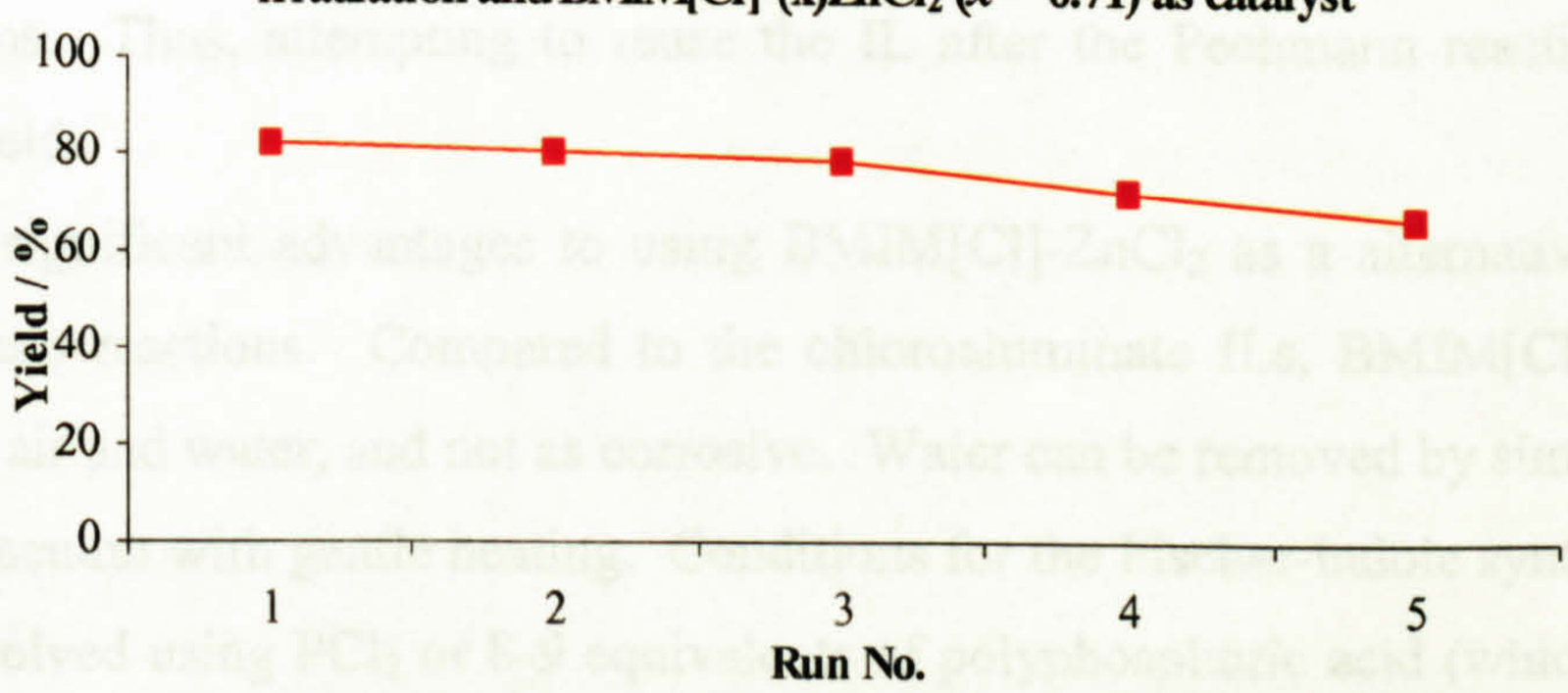
**Figure 3.6 Repeated Pictet-Spengler reactions in BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67)**



An isolated yield of approximately 70 % was obtained (after purification by preparative tlc) from each of the five runs, demonstrating that the IL is stable to the reaction conditions.

We then investigated whether BMIM[Cl]-$ZnCl_2$ could be used in catalytic amount in dichloroethane and the results maintained. The reaction was repeated using 20 mol% BMIM[Cl]-$ZnCl_2$ ($x$ = 0.71) under the same conditions, but an isolated yield of 62 % suggested that a longer reaction period may be necessary to convert all the tryptamine into product. Microwave irradiation was described for this reaction by the group utilising $Yb(OTf)_3$ and BMIM[Cl]-$AlCl_3$ as catalyst,[410] hence we attempted microwave promotion. Performing the reaction at 120 $^0$C for 2 h in the microwave gave an increased yield of 82 %. Furthermore, the dichloroethane was decanted to leave behind the BMIM[Cl]-$ZnCl_2$ as a pale yellow gel at the bottom of the microwave vial. The reaction was repeated in the same vial by adding fresh substrates and dichloroethane and the following results observed.

**Figure 3.7 Repeated Pictet-Spengler reactions using microwave irradiation and BMIM[Cl]-(x)$ZnCl_2$ ($x$ = 0.71) as catalyst**




As shown in Figure 3.7, 20 mol% BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.71) is sufficient to catalyse the Pictet Spengler reaction between tryptamine and benzaldehyde. Although the IL appeared unchanged by $^1$H NMR, a colour change from pale yellow to pale brown was noted after the third run. On the whole, the yields are generally quite high and demonstrate that an additional Lewis acid catalyst is not necessary to increase catalytic activity. Also, this is the first example of a catalyst that can be recycled for the Pictet-Spengler reaction.

## 3.7 CONCLUSIONS TO ORGANIC SYNTHESIS IN BMIM[Cl]-$ZnCl_2$

Overall, we have demonstrated that BMIM[Cl]-$ZnCl_2$ is an effective solvent / catalyst medium for the Diels Alder, Fischer-indole, Pechmann and Pictet-Spengler reactions. Good to excellent yields have been obtained in all cases. In addition, the stereoselectivity of the Diels-Alder reaction of methyl acrylate and Cp, and the regioselectivity in the Fischer-indole synthesis using unsymmetrical ketones *e.g.* butanone are both better in BMIM[Cl]-$ZnCl_2$ than in conventional organic solvents.

In all these reactions we have demonstrated that the IL can be recovered and recycled. Products can be extracted by sublimation, liquid-liquid extraction or from an aqueous work-up. In the former case, we found that the IL could be reused five times in the Fischer-indole synthesis of 2,3-dimethylindole with a slight drop in yield being observed after the third run, probably due to a build-up of by-product. For the Diels-Alder reaction, a liquid-liquid extraction meant that the IL could be reused five times with negligible drop in yield and in the case of the Picet-Spengler reaction, the product could simply be decanted off with the organic solvent. However, in cases where an aqueous work-up was necessary to isolate the product, it was noted that the activity of the IL was reduced in subsequent runs. Thus, attempting to reuse the IL after the Pechmann reaction gave a much lower yield.

There are significant advantages to using BMIM[Cl]-$ZnCl_2$ as a alternative to other solvents in these reactions. Compared to the chloroaluminate ILs, BMIM[Cl]-$ZnCl_2$ is more stable to air and water, and not as corrosive. Water can be removed by simply drying the IL under vacuum with gentle heating. Conditions for the Fischer-indole synthesis have in the past involved using $PCl_3$ or 8-9 equivalents of polyphosphoric acid (which are both environmentally unfriendly, hazardous or difficult to handle); using a three fold excess of $ZnCl_2$; or using high temperatures with ethylene glycol or tetralin as solvent. Under our conditions, one molar equivalent of BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.71) is sufficient to catalyse the reaction in high yield under relatively mild conditions. For selected indoles, this is an improvement over the three fold excess of choline chloride-($x$)$ZnCl_2$ ($x$ = 0.67) needed to obtain similar yields. For the Pictet-Spengler reaction, a combination of 10 mol% $Yb(OTf)_3$ and 50 mol% BMIM[Cl]-($x$)$AlCl_3$ ($x$ = 0.5) is reported to give the best results for the synthesis of 1-Phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline (3.42). Although 20 mol% BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.71) gave a somewhat reduced yield (82 % compared to 92 % with $Yb(OTf)_3$ / BMIM[Cl]-$AlCl_3$), we have been able recover the IL and reuse it five times with negligible drop in yield. This demonstrates that BMIM[Cl]-$ZnCl_2$ can also be

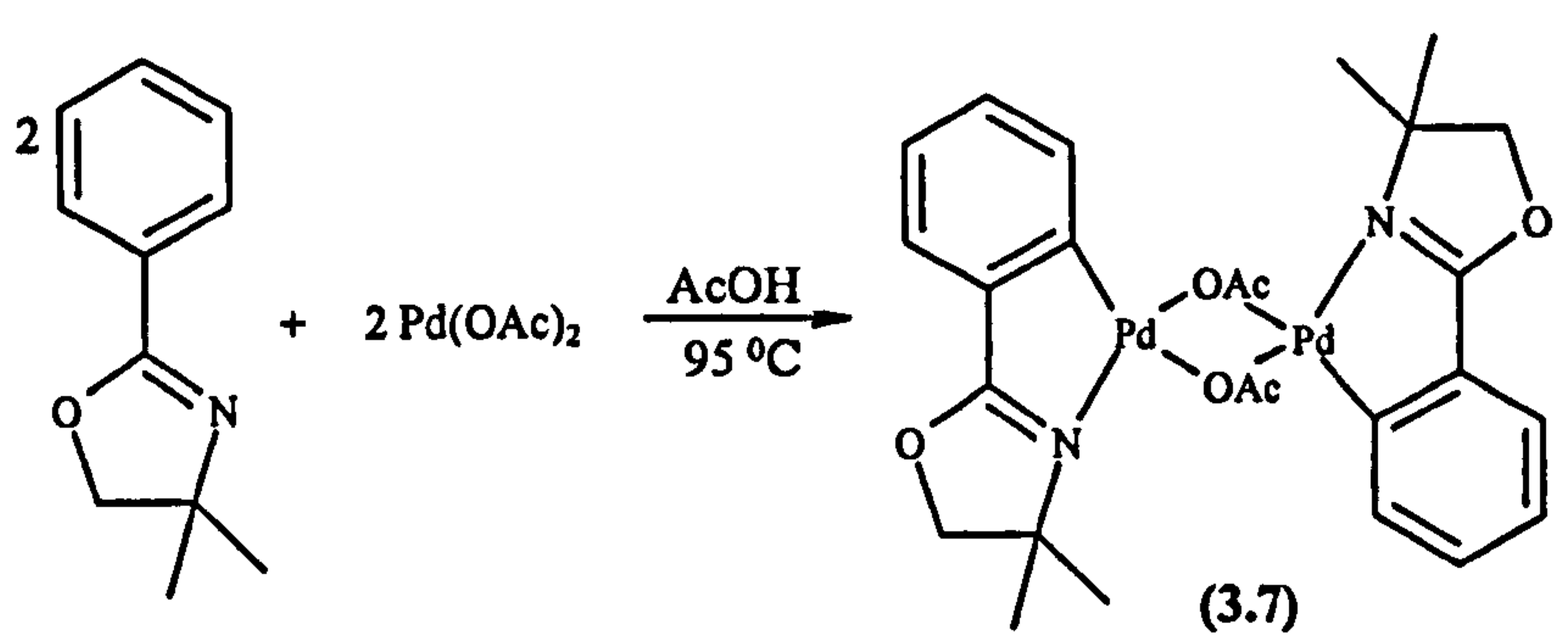
used as a recyclable catalyst, and the potential of this solvent in organic synthesis needs further investigation.

## 3.8 EXPERIMENTAL

The ionic liquids were synthesised by anion exchange from BMIM[Cl][70] according to literature procedures (see Chapter 2),[308] and dried under vacuum at 60 °C prior to use. For thin layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualised by irradiation with UV light and / or by treatment with a solution of phosphomolybdic acid (25g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concentrated $H_2SO_4$ (60 mL), and $H_2O$ (940 mL) followed by heating. Flash Chromatography was performed by using silica gel Merck 60 (particle size 0.040-0.063 mm). GC was performed on a Perkin Elmer XL gas chromatograph, using BP10 (SGE) capillary columns (30 m x 0.25 mm) with hydrogen as carrier. GCMS analysis was performed on a Perkin-Elmer TurboMass GCMS autosystem using a PE5 column (30 m x 0.25 mm). $^1$H NMR and $^{13}$C NMR spectra were recorded either on a Bruker AMX 400, AMX 300 and AMX 250. Chemical shifts are given in $\delta$ relative to tetramethylsilane (TMS); the coupling constants $J$ are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature; TMS served as internal standard ($\delta = 0$ ppm) for $^1$H NMR, and $CDCl_3$ was used as internal standard ($\delta =$ 77.0 ppm) for $^{13}$C NMR.

### 3.8.1 The Heck Reaction

***Preparation of di-μ-aceto-bis [2-(4',4-dimethyl)-2'-oxazolinyl) phenyl, 1-C,3'-N] dipalladium (II), (3.7).***




(3.7)

2-phenyl-4,4-dimethyl-2-oxazoline was previously prepared by A.J.Davenport using a literature method.[413] To a solution of palladium acetate (0.650g, 2.90 mmol) in acetic acid (15 ml) was added 2-phenyl-4,4-dimethyl-2-oxazoline (0.560g, 3.18 mmol) in acetic acid

(15 ml) at room temperature. After refluxing for 2 h, the solvent was evaporated under reduced pressure to a solid, then dissolved in $CH_2Cl_2$. After filtration through celite, recrystallisation from pentane gave the product as a very dark yellow powder (0.89g, 1.31 mmol): yield 90 % based on the palladium acetate. The spectroscopic data are in agreement with literature values.[414] $^1$H NMR (300 MHZ, $CDCl_3$): δ 1.60 (s, 12H, $CH_3$C), 2.05 (s, 6H, O*Ac*), 4.45 (dd, 4H, $CH_2$ on oxazoline), 6.96-7.23 (m, 8H, Ar*H*); calculated mass for $C_{26}H_{30}N_2O_6Pd_2$: 679 m/z; FAB MS: 680 ($MH^+$).

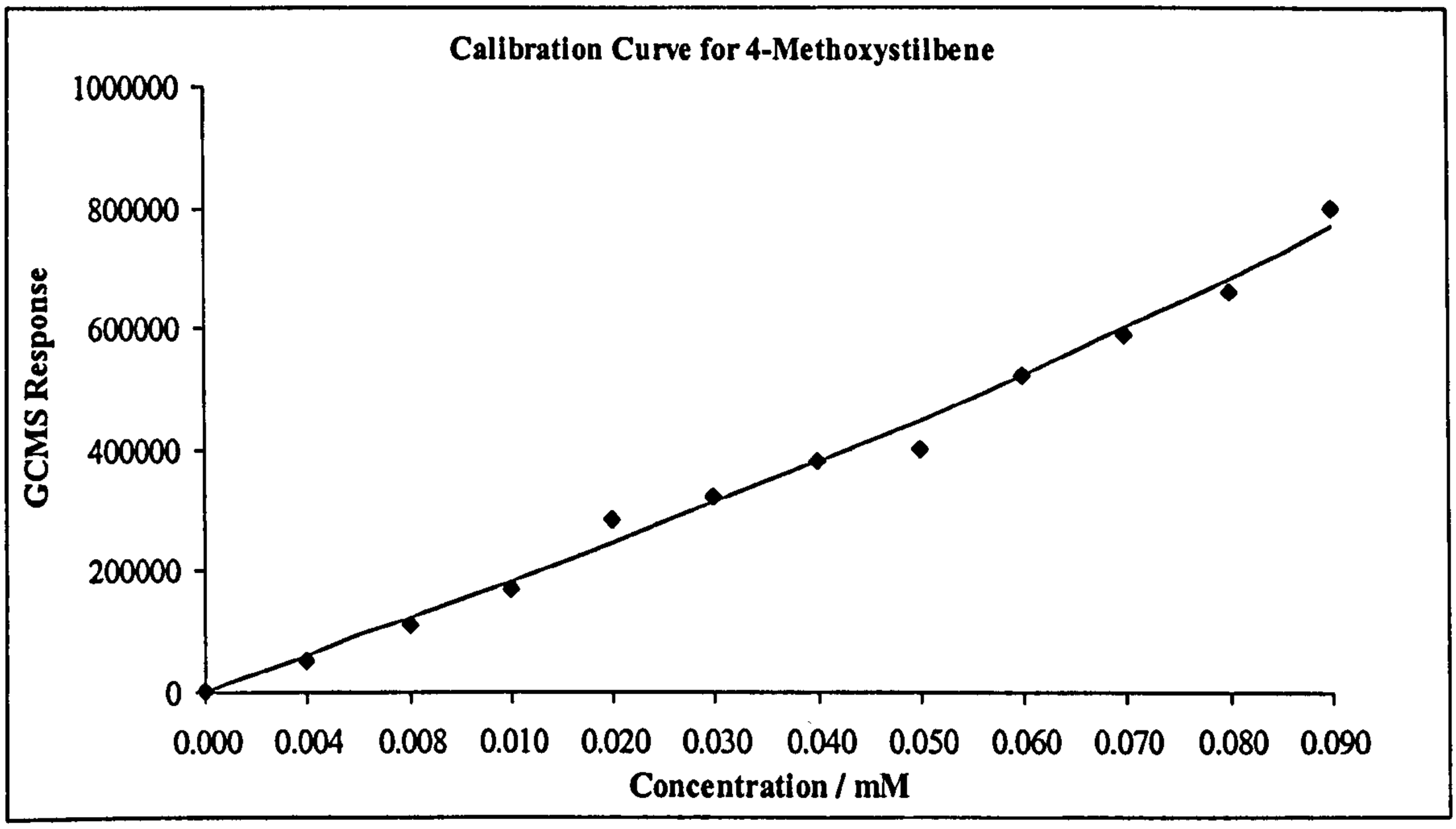
**Procedure for the Heck reaction of 4-iodoanisole with styrene**

All reactions were carried out under an atmosphere of nitrogen. The (3.7) catalyst was used in 0.5 % (0.0036g, 0.02 mmol) amount for each reaction.

*General procedure:* $Pd(OAc)_2$ (0.0045 g) was dissolved in $CH_2Cl_2$ and transferred to a wide-based schlenk tube by syringe. 4-iodoanisole (0.234g, 1 mmol) was transferred in the same way and sodium acetate (0.100 g, 1.2 mmol) added. The reaction mixture was placed under vacuum to remove the $CH_2Cl_2$. The appropriate solvent (1 ml) was added and the reaction mixture stirred magnetically for 5 minutes to dissolve the catalyst. Finally the styrene (0.156g, 1.5 mmol) was added and the Schlenk tube placed in an oil bath at 165 $^0$C. The reaction was stirred at this temperature for 16 h and then removed from the hot oil bath. Once cooled to room temperature, $CH_2Cl_2$ (2 ml) was added. The reaction mixture was filtered through silica and the filtrate transferred to a 50 ml volumetric flask and made up to the mark with $CH_2Cl_2$. This was diluted by a factor of 10 for GCMS quantification.

*Calibration Curve for 4-methoxystilbene*

Pure 4-methoxystilbene was obtained by performing flash chromatography on the crude product from one of the above reactions using petroleum ether / ethyl acetate 4 : 1, $R_f$ = 0.53. The spectroscopic data are in agreement with literature.[415] $^1$H NMR (300 MHZ, $CDCl_3$) : δ 7.44-7.52 (m, 4H), 7.35 (t, 2H, *J*=7.3 Hz), 7.21-7.26 (m, 1H), 7.07 (d, 1H, *J*=16.5 Hz), 6.98 (d, 1H, *J*=16.5 Hz), 6.90 (d, 2H, *J*=8.8 Hz), 3.81 (s, 3H); $^{13}$C NMR (69.5 MHZ, $CDCl_3$): δ 159.4, 137.8, 130.3, 128.7, 128.3, 127.8, 127.3, 126.7, 126.3, 114.2, 55.4; EI *m/z* 210; Mp 134-136 $^0$C. (Lit.[416] Mp 135 $^0$C). The white solid (0.0210g, 0.1 mmol) was dissolved in $CH_2Cl_2$ (50 ml), to make up the stock solution for the calibration. The response of the peak was monitored over a range of concentrations and a graph of peak response *vs*. concentration plotted.

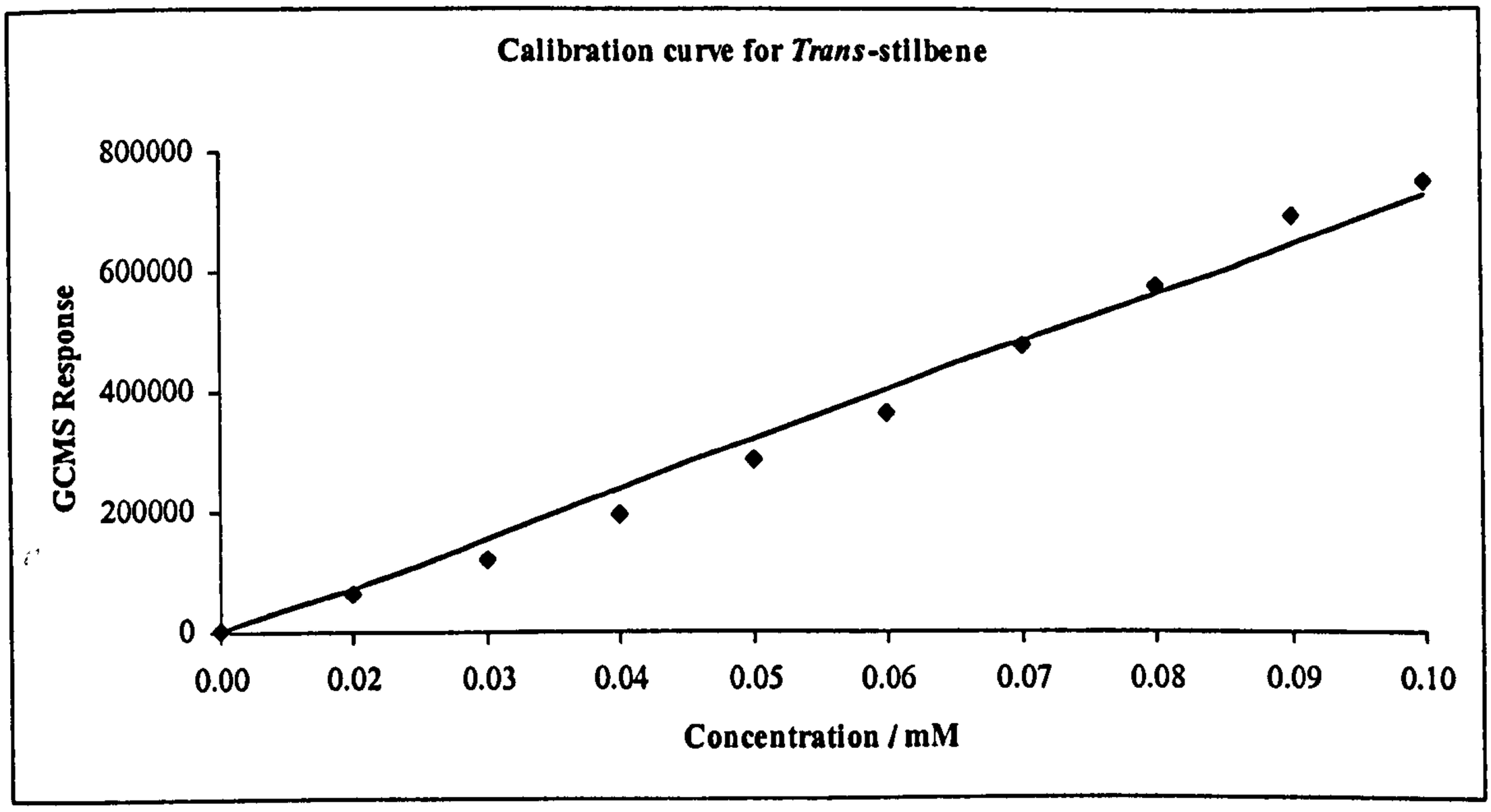



**Procedure for the Heck reaction of iodobenzene with styrene**

The same procedure as that described for the reaction between 4-iodoanisole and styrene was followed, using iodobenzene (112 μl, 0.204g, 1 mmol).

*Calibration Curve for Trans-stilbene*

A calibration curve for *trans*-stilbene (Aldrich) was measured similarly. The white solid (0.0180g, 0.1 mmol) was dissolved in $CH_2Cl_2$ (50 ml), to make up the stock solution for the calibration. The calibration curve is shown below.



### 3.8.2 Synthesis of BMIM[Cl]-($x$)$ZnCl_2$

BMIM[Cl] was synthesised as described in Chapter 2 (section 2.5.1) and zinc dichloride was used as purchased from Aldrich. NMR chemical shifts are reported using neat ILs with an external $D_2O$ lock at 353K. FAB mass spectra were obtained on a Kratos concept mass spectrometer using no matrix.

BMIM[Cl] (7.0 g, 0.04 mol) was weighed into a Schlenk tube and $ZnCl_2$ (5.46 g, 0.04 mol) added. The two white solids were stirred on a vortex mixture for 5 min which gave a white gel and then heated to 90 $^0$C and stirred for a further 16 h to give a clear-yellow viscous liquid. On cooling, the freezing point was determined using an electrical thermometer and the viscosity using a Brookfield DV-E viscometer at 25 $^0$C. Synthesis of BMIM[Cl]-($x$)$ZnCl_2$ where $x$ = 0.60 used 8.19 g $ZnCl_2$ (0.06 mol, 1.5 equiv), $x$ = 0.67 used 10.92 g $ZnCl_2$ (0.08 mol, 2 equiv), $x$ = 0.71 used 13.65 g $ZnCl_2$ (0.1 mol, 2.5 equiv).

**$x$ = 0.50**

$^1$H NMR (400 MHz): δ 8.90 (s, 1H, NC*H*N), 7.57 (d, 2H, NC*H*C*H*N, $J$ = 7.4 Hz), 4.23 (m, 2H, NC$H_2$), 3.97 (s, 3H, N*Me*), 1.82 (m, 2H,C$H_2$CH$_2$Me), 1.25 (m, 2H,CH$_2$C$H_2$Me), 0.80 (m, 3H,CH$_2$*Me*); $^{13}$C NMR (75 MHZ): δ 136.6, 124.3, 123.2, 50.3, 37.6, 32.3, 19.7, 13.9; FAB MS (no matrix): *m/z* 139 $BMIM^+$, 171 $[ZnCl_3]^-$, 307 $[Zn_2Cl_5]^-$

**$x$ = 0.60**

$^1$H NMR (400 MHz): δ 8.66 (s, 1H, NC*H*N), 7.42 (d, 2H, NC*H*C*H*N, J = 7.4 Hz), 4.13 (m, 2H, NC$H_2$), 3.86 (s, 3H, N*Me*), 1.73 (m, 2H,C$H_2$CH$_2$Me), 1.18 (m, 2H,CH$_2$C$H_2$Me), 0.73 (m, 3H,CH$_2$*Me*); $^{13}$C NMR (75 MHZ): δ 136.2, 124.9, 123.1, 50.3, 37.5, 32.1, 19.7, 13.9; FAB MS (no matrix): *m/z* 139 $BMIM^+$, 171 $[ZnCl_3]^-$, 307 $[Zn_2Cl_5]^-$, 445 $[Zn_3Cl_7]^-$

**$x$ = 0.67**

$^1$H NMR (400 MHz): δ 8.45 (s, 1H, NC*H*N), 7.27 (d, 2H, NC*H*C*H*N, $J$ = 7.4 Hz), 4.00 (m, 2H, NC$H_2$), 3.74 (s, 3H, N*Me*), 1.63 (m, 2H,C$H_2$CH$_2$Me), 1.10 (m, 2H,CH$_2$C$H_2$Me), 0.63 (m, 3H,CH$_2$*Me*); $^{13}$C NMR (75 MHZ): δ 135.8, 124.3, 123.0, 50.3, 37.4, 32.0, 19.6, 13.8; FAB MS (no matrix): *m/z* 139 $BMIM^+$, 171 $[ZnCl_3]^-$, 307 $[Zn_2Cl_5]^-$, 445 $[Zn_3Cl_7]^-$

**$x$ = 0.71**

$^1$H NMR (400 MHz): δ 8.30 (s, 1H, NC*H*N), 7.14 (d, 2H, NC*H*C*H*N, $J$ = 7.4 Hz), 3.90 (m, 2H, NC$H_2$), 3.65 (s, 3H, N*Me*), 1.55 (m, 2H,C$H_2$CH$_2$Me), 1.02 (m, 2H,CH$_2$C$H_2$Me), 0.56 (m, 3H,CH$_2$*Me*); $^{13}$C NMR (75 MHZ): δ 136.6, 124.2, 122.9, 50.3, 37.4, 31.9, 19.5, 13.8; FAB MS (no matrix): *m/z* 139 BMIM$^+$, 171 [ZnCl$_3$]$^-$, 307 [Zn$_2$Cl$_5$]$^-$, 445 [Zn$_3$Cl$_7$]$^-$

### 3.8.3 Diels-Alder reaction of Cp and methyl acrylate

Methyl acrylate (360 µl, 4 mmol) was added to BMIM[Cl]-($x$)ZnCl$_2$ ($x$ = 0.50) (1.244 g, 4 mmol) and stirred for 5 min to give a homogenous solution. Freshly cracked Cp (282 µl, 4.2 mmol) was added to give a biphasic reaction mixture which was stirred at 25 $^0$C for 64 h. After this time, deionised water (1 ml) was added to the reaction mixture and the product extracted with 5 x 2 ml diethyl ether. A solution of ferrocene (0.372 g, 2 mmol) in ether was made in a 5 ml volumetric flask. The stock solution (500 µl, 0.0372g, 0.2 mmol) was added to the combined ether extracts of product. The ether was removed in *vacuo* to give a yellow oil. Yield and selectivity was determined by $^1$H NMR integration.

***Endo- Methyl-bicyclo[2.2.1]hept-2-ene-4-carboxylate***

$^1$H NMR (250MHz, CDCl$_3$): δ 6.16 (dd, 1H, $J$ = 5.7, 3.1 Hz), 5.90 (dd, 1H, $J$ = 5.6, 2.8 Hz), 3.6 (s, 3H), 3.17 (m, 1H), 2.92 (ddd, 1H, $J$ = 9.5 Hz, 7.9 Hz, 4.0 Hz), 2.88 (m, 1H), 1.88 (ddd, 1H, $J$ = 12.1 Hz, 9.4 Hz, 3.7 Hz), 1.42-1.37 (m, 2H), 1.26-1.23 (m, 1H); $^{13}$C NMR (69.5 MHz, CDCl$_3$): δ 175.0, 137.7, 132.4, 51.3, 49.6, 45.7, 43.2, 42.6, 29.3; GCMS *m/z* 152. The spectroscopic data are in agreement with literature.[417]

### 3.8.4 The Fischer-Indole Synthesis

***Acetophenone phenylhydrazone (3.13)***

A solution of phenylhydrazine (2.0 ml, 2.20 g, 20 mmol) in glacial acetic acid (5 ml) was added to a solution of acetophenone (2.30 ml, 2.40 g, 20 mmol) in glacial acetic acid (5 ml) in a flask. The mixture was stirred at 0 $^0$C for 30 min, whilst the hydrazone product precipitated out of solution. The product was filtered, washed with dilute acetic acid and water to yield the acetophenone phenylhydrazone as colourless crystals. Yield: 2.52 g (60 %). $^1$H NMR (250 MHz, CDCl$_3$): δ 8.0 (m, 1H), 7.4 –7.7 (m, 9H), 7.1 (m, 1H), 2.4 (s, 3H); GCMS *m/z* 210.

***2-Phenylindole (3.14)***

Acetophenone (1.20 ml, 1.20 g, 10 mmol) and phenylhydrazine (1.10 ml, 1.19 g, 11 mmol) was added to BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.71) (5.15 g, 10 mmol). The reaction mixture was heated to 100 $^0$C and stirred for 12 h. Then direct sublimation of the product from the ionic liquid gave 2-phenylindole as yellow crystals. Yield: 1.83 g (95 %). $^1$H NMR (250 MHz, $CDCl_3$): δ 8.26 (s, br, 1H), 7.64-7.61 (m, 3H), 7.44-7.27 (m, 4H), 7.00-7.09 (m, 2H), 6.82 (s, 1H); $^{13}$C NMR (69.5 MHz, $CDCl_3$): δ 137.9, 136.8, 132.3, 129.2, 129.0, 127.7, 125.1, 122.3, 120.6, 120.2, 110.9, 100.0; EI *m/z* 193; Mp 186-187 $^0$C. (Lit.[373] Mp 188–189 $^0$C).

***2,3-Dimethylindole (3.15)***

As for the preparation of 2-phenylindole, using butanone (180 µl, 144 mg, 2 mmol) and phenylhydrazine (216 µl, 238 mg, 2.2 mmol) gave 2,3-dimethylindole as yellow crystals. Yield: 273 mg (94 %). $^1$H NMR (250 MHz, $CDCl_3$): δ 7.50 (s, br, 1H), 7.38 (m, 1H), 7.15 (m, 1H), 7.05 (m, 2H), 2.26 (s, 3H), 2.18 (s, 3H); $^{13}$C NMR (69.5 MHz, $CDCl_3$): δ 135.6, 131.1, 129.9, 121.3, 119.4, 118.4, 110.4, 107.6, 11.9, 8.9; EI *m/z* 145; Mp 107-109 $^0$C. (Lit.[418] Mp 111–112 $^0$C).

***2,3,7-Trimethylindole (3.16)***

As for the preparation of 2-phenylindole, using butanone (180 µl, 144 mg, 2 mmol) and *o*-tolylhydrazine hydrochloride (350 mg, 2.2 mmol) gave 2,3,7-trimethylindole as yellow crystals after an aqueous work-up and recrystallisation from petroleum ether. Yield: 286 mg (90 %). $^1$H NMR (250 MHz, $CDCl_3$): δ 7.24 (d, 1H, $J$ = 7.80 Hz), 6.91 (t, 1H, $J$ = 7.58 Hz), 6.81 (d, 1H, $J$ = 7.10 Hz)), 2.30 (s, 3H), 2.26 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 133.6, 129.2, 127.9, 120.6, 118.2, 118.1, 114.7, 106.6, 15.5, 10.5, 7.5; EI *m/z* 159; Mp 76 $^0$C. (Lit.[419] Mp 76-77 $^0$C).

***5-Dichloro-2,3-dimethylindole (3.17)***

As for the preparation of 2-phenylindole, using butanone (180 µl, 144 mg, 2 mmol) and 4-chlorophenylhydrazine hydrochloride (400 mg, 2.2 mmol) gave 5-chloro-2,3-dimethylindole as white crystals. Yield: 315 mg (88 %). $^1$H NMR (250MHz, $CDCl_3$): δ 7.40 (d, 1H, $J$ = 1.8 Hz), 7.08 (d, 1H, $J$ = 8.5 Hz), 7.01 (dd, 1H, $J$ = 8.5, 1.8 Hz), 2.30 (s, 3H), 2.18 (s, 3H); $^{13}$C NMR (250 MHz, $CDCl_3$): δ 140.0, 132.8, 131.0, 125.1, 121.4, 118.0, 111.4, 107.5, 12.0, 8.8; EI *m/z* 179. Mp 142 – 143 $^0$C. (Lit.[420] Mp 141–142 $^0$C).

***4,7-Dichloro-2,3-dimethylindole (3.18)***

As for the preparation of 2-phenylindole, using butanone (180 µl, 144 mg, mmol) and 2,5-dichlorophenylhydrazine (392 mg, 2.2 mmol) gave 4,7-dichloro-2,3-dimethylindole as white crystals. Yield: 3.11 mg (73 %). $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, br, 1H), 6.96 (d, 1H, $J$ = 8.2 Hz), 6.90 (d, 1H, $J$ = 8.2 Hz), 2.40 (s, 3H), 2.30 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 133.6, 133.1, 127.5, 124.7, 120.8, 120.7, 114.6, 109.4, 11.8, 10.8; EI *m/z* 213; Mp 89–90 $^{0}$C. (Lit.[421] Mp 90–91 $^{0}$C).

***1,2,3,4-Tetrahydrocyclopent[b]indole (3.19)***

As for the preparation of 2-phenylindole, using cyclopentanone (177µl, 168 mg, 2 mmol) and phenylhydrazine (216 µl, 238 mg, 2.2 mmol) gave 1,2,3,4-tetrahydro-cyclopenta[*b*]indole as colourless crystals. Yield: 283 mg (90 %). $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.73 (s, br, 1H), 7.52 (m, 1H), 7.30 (m, 1H), 7.17 (m, 2H), 2.94-2.84 (m, 4H), 2.61 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 143.5, 140.8, 124.5, 120.3, 119.5, 119.3, 118.3, 111.2, 28.7, 25.8, 24.4; EI *m/z* 157; Mp 106 – 107 $^{0}$C. (Lit.[422] Mp 105–106 $^{0}$C).

***1,2,3,4-Tetrahydrocarbazole (3.20)***

As for the preparation of 2-phenylindole, using cyclohexanone (207 µl, 196 mg, 2 mmol) and phenylhydrazine (216 µl, 238 mg, 2.2 mmol) gave 1,2,3,4-tetrahydrocarbazole as white crystals. Yield: 318 mg (93 %). $^{1}$H NMR (250 MHz, $CDCl_3$): δ 7.52 (d, 1H, $J$ = 7.89), 7.3 (d, 1H, $J$ = 7.6 Hz), 7.15 (dt, 2H, $J$ = 7.03, 13.5 Hz), 2.90 (m, 4H), 2.10 (m, 4H); $^{13}$C NMR (69.5 MHz, $CDCl_3$): δ 136.1, 134.6, 128.3, 121.4, 119.5, 118.2, 110.9, 110.6, 23.8, 23.7, 21.4; GCMS *m/z* 171; Mp 117 – 119 $^{0}$C. (Lit.[423] Mp 118–120 $^{0}$C).

***8-methyl-1,2,3,4-tetrahydrocarbazole (3.21)***

As for the preparation of 2-phenylindole, using cyclohexanone (207 µl, 196 mg, 2 mmol) and *o*-tolylhydrazine hydrochloride (350 mg, 2.2 mmol) gave 8-methyl-1,2,3,4-tetrahydrocarbazole as yellow crystals after an aqueous work-up and recrystallisation from petroleum ether. Yield: 266 mg (72 %). $^{1}$H NMR (250 MHz, $CDCl_3$): δ 7.50 (s, br, 1H), 7.20 (d, 1H, $J$ = 7.6 Hz), 6.90 (t, 1H, $J$ = 7.3 Hz), 6.80 (d, 1H, $J$ = 7.3 Hz), 2.75 (m, 4H), 2.45 (s, 3H), 1.90 (m, 4H); $^{13}$C NMR (69.5 MHz, $CDCl_3$): δ 135.6, 134.2, 127.8, 122.2, 119.9, 119.8, 116.0, 111.2, 23.8, 23.7, 23.6, 21.5, 17.0; EI *m/z* 185; Mp 101-102 $^{0}$C. (Lit.[424] Mp 102 $^{0}$C).

***6-Chloro-1,2,3,4-tetrahydrocarbazole (3.22)***

As for the preparation of 2-phenylindole, using cyclohexanone (207 µl, 196 mg, 2 mmol) and 4-chlorophenylhydrazine hydrochloride (400 mg, 2.2 mmol) gave 6-chloro-1,2,3,4-tetrahydrocarbazole as white crystals. Yield: 328 mg (80 %). $^{1}$H NMR (250 MHz, $CDCl_3$): δ 7.65 (s, br, 1H), 7.40 (d, 1H, $J$ = 2.1 Hz), 7.15 (d, 1H, $J$ = 8.5 Hz), 7.0 (dd, 1H, $J$ = 2.1, 8.5 Hz), 2.67 (m, 4H), 1.90 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 136.2, 134.4, 129.4, 125.2, 121.4, 117.7, 111.6, 110.5, 23.6, 23.5, 23.4, 21.2; EI *m/z* 205; Mp 148-149 $^{0}$C. (Lit.[425] Mp 146-147 $^{0}$C).

***5,6,7,8,9,10-Hexahydrocyclohept[b]indole (3.23)***

As for the preparation of 2-phenylindole, using cycloheptanone (235 µl, 224 mg, 2 mmol) and phenylhydrazine (216 µl, 238 mg, 2.2 mmol) gave 5,6,7,8,9,10-hexahydrocyclohept[*b*]indole as white crystals. Yield: 337 mg (91 %). $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.70 (s, br, 1H), 7.47 (m, 1H), 7.25 (m, 1H), 7.08 (m, 2H), 2.81 (m, 4H), 2.00-1.50 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 137.4, 134.2, 129.2, 120.6, 119.0, 117.6, 113.7, 110.1, 31.8, 29.6, 28.7, 27.5, 24.6; EI *m/z* 185; Mp 140 – 142 $^{0}$C. (Lit.[426] Mp 140–141 $^{0}$C).

## 3.8.5 Procedure for the Pechmann Condensation

***4-Methyl-7-hydroxycoumarin (3.29)***

Resorcinol (110 mg, 1 mmol) was added to BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.67) (450 mg, 1 mmol) in a Schlenk tube and the hetereogeneous mixture stirred at 50 $^{0}$C for 10 min. Ethyl acetoacetate (140 µl, 143 mg, 1.1 mmol) was then added and the reaction mixture stirred at 120 $^{0}$C for 16 h. The reaction mixture was cooled to 40 $^{0}$C and water (2 ml) added to precipitate the product. The solid was filtered, washed with water (3 x 2 ml), recrystallised from ethyl acetate / heptane and dried in a vacuum oven at 40 $^{0}$C to give a pale grey fine powdered solid. Yield: 167 mg (95 %). $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.52 (d, 1H, $J$ = 1.7 Hz), 6.70-6.85 (m, 2H), 6.11 (s, 1H), 3.36 (s, br, 1H), 2.38 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 161.2, 160.3, 154.8, 153.5, 126.5, 112.9, 111.9, 110.2, 102.2, 18.1; EI *m/z* 176; Mp 193–194 $^{0}$C. (Lit.[399] Mp 194-195 $^{0}$C).

***4-Methyl-5,7-dihydroxycoumarin (3.30)***

In the same way phloroglucinol dihydrate (163 mg, 1 mmol) and ethyl acetoacetate (140 µl, 143 mg, 1.1 mmol) gave 173 mg white solid (90 % yield), following a recrystallisation from ethanol. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 6.25 (d, 1H, $J$ = 1.8 Hz), 6.16 (d, 1H, $J$ = 1.8 Hz), 5.83 (s, 1H), 4.2-3.8 (s, br, 2H), 2.48 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 161.7, 160.7, 158.5, 157.0, 155.6, 109.4, 102.7, 98.6, 95.1, 24.0; EI *m/z* 192; Mp 282–284 $^{0}$C. (Lit.[395] Mp 284-285 $^{0}$C).

***4-Methyl-7,8-dihydroxycoumarin (3.31)***

In the same way pyrogallol (126 mg, 1 mmol) and ethyl acetoacetate (140 µl, 143 mg, 1.1 mmol) gave 169 mg white solid (88 % yield), following a recrystallisation from ethanol. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.08 (d, 1H, $J$ = 1.9 Hz), 6.82 (d, 1H, $J$ = 1.9 Hz), 6.11 (s, 1H), 4.23-3.81 (s, br, 2H), 2.36 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 161.7, 160.7, 158.5, 157.0, 155.6, 109.4, 102.7, 98.6, 95.1, 24.0; EI *m/z* 192; Mp 242–243 $^{0}$C. (Lit.[427] Mp 243 $^{0}$C).

***5,7-Dimethoxy-4-methylcoumarin (3.32)***

In the same way 3,5-dimethoxyphenol (154 mg, 1 mmol) and ethyl acetoacetate (140 µl, 143 mg, 1.1 mmol) gave 200 mg white solid (91 % yield), following a recrystallisation from ethyl acetate / heptane. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 6.33 (d, 1H, $J$ = 2.5 Hz), 6.18 (d, 1H, $J$ = 2.5 Hz), 5.96 (s, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 163.1, 161.3, 159.5, 157.2, 154.7, 111.5, 105.1, 95.5, 93.7, 56.0, 55.9, 24.7; EI *m/z* 220; Mp 169–170 $^{0}$C. (Lit.[428] Mp 169 $^{0}$C).

***4-Methyl-benzocoumarin (3.33)***

In the same way 1-napthol (144 mg, 1 mmol) and ethyl acetoacetate (140 µl, 143 mg, 1.1 mmol) gave 168 mg yellow crystals (80 % yield), following a recrystallisation from ethanol. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.33-8.38 (m, 1H), 8.01-8.07 (m, 1H), 7.70-7.88 (m, 4H), 6.48 (s, 1H), 2.50 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 159.6, 154.2, 149.6, 134.3, 128.6, 127.9, 127.3, 123.9, 122.2, 121.6, 121.2, 115.1, 113.9, 18.6; EI *m/z* 210; Mp 153–154 $^{0}$C. (Lit.[429] Mp 155 $^{0}$C).

***4-Methyl-5,7-dihydroxycoumarin (3.34)***

In the same way phloroglucinol dihydrate (163 mg, 1 mmol) and ethyl propynoate (115 µl, 108 mg, 1.1 mmol) gave 166 mg pale yellow solid (93 % yield), following a recrystallisation from ethanol. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 6.25 (d, 1H, $J$ = 1.8 Hz), 6.16 (d, 1H, $J$ = 1.8 Hz), 5.83 (s, 1H), 4.2-3.8 (s, br, 2H), 2.48 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 161.7, 160.7, 158.5, 157.0, 155.6, 109.4, 102.7, 98.6, 95.1, 24.0; EI *m/z* 178; Mp 274-276 $^{0}$C. (Lit.[430] Mp 270-272 $^{0}$C).

***7-Methoxycoumarin (3.35)***

In the same way 3-methoxyphenol (124 mg, 1 mmol) and ethyl propynoate (115 µl, 108 mg, 1.1 mmol) gave 165 mg pale brown solid (94 % yield), following a recrystallisation from ethanol. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, 1H, J = 9.6 Hz), 7.38 (d, 1H, J = 8.5 Hz), 6.84 (m, 2H), 6.25 (d, 1H, J = 9.6 Hz), 3.88 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 163.2, 161.4, 156.5, 143.4, 128.8, 113.6, 112.7, 112.6, 101.1, 55.9; EI *m/z* 176; Mp 120 $^{0}$C. (Lit.[430] Mp 119-120 $^{0}$C).

***5,7-Dimethoxycoumarin (3.36)***

In the same way 3,5-dimethoxyphenol (154 mg, 1 mmol) and ethyl propynoate (115 µl, 108 mg, 1.1 mmol) gave 198 mg pale yellow solid (96 % yield), following a recrystallisation from ethanol. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 1H, $J$ = 9.6 Hz), 6.41 (d, 1H, $J$ = 2.2 Hz), 6.27 (d, 1H, $J$ = 2.2 Hz), 6.15 (d, 1H, $J$ = 9.6 Hz), 3.88 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 164.1, 161.8, 157.3, 157.1, 139.0, 111.0, 104.2, 94.9, 93.1, 56.1, 55.9; EI *m/z* 206; Mp 145-146 $^{0}$C. (Lit.[431] Mp 146-147 $^{0}$C).

***5,6-Benzocoumarin (3.37)***

In the same way β-naphthol (144 mg, 1 mmol) and ethyl propynoate (115 µl, 108 mg, 1.1 mmol) gave 161 mg yellow solid (82 % yield), following a recrystallisation from ethyl acetate / heptane. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, 1H, $J$ = 10.1 Hz), 8.21 (d, 1H, $J$ = 8.5 Hz), 8.00 (d, 1H, $J$ = 9.1 Hz), 7.93 (d, 1H, $J$ = 8.0 Hz), 7.73 (dd, 1H, $J$ = 8.5, 7.0 Hz), 7.56 (dd, 1H, $J$ = 8.0, 7.0 Hz), 7.47 (d, 1H, $J$ = 9.1 Hz), 6.61 (d, 1H, $J$ = 10.1 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 160.3, 153.5, 138.5, 133.5, 130.8, 128.9, 128.1, 127.9, 125.6, 120.9, 116.5, 114.9, 111.9; EI *m/z* 196; Mp 114-115 $^{0}$C. (Lit.[432] Mp 116-117 $^{0}$C).

***5,7-Dimethoxy-4-phenyl-coumarin (3.38)***

In the same way 3,5-dimethoxyphenol (154 mg, 1 mmol) and ethyl benzoylacetate (210 µl, 230 mg, 1.1 mmol) gave 228 mg white solid (81 % yield), following a recrystallisation from ethyl acetate / heptane. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.39 (m, 3H), 7.29 (m, 2H), 6.55 (d, 1H, $J$ = 2.0 Hz), 6.25 (d, 1H, $J$ = 2.0 Hz), 6.02 (s, 1H), 3.89 (s, 3H), 3.44 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 163.3, 160.9, 158.2, 157.2, 155.7, 139.7, 127.9, 127.3, 127.1, 112.7, 103.5, 95.7, 93.5, 55.8, 55.4; EI *m/z* 282; Mp 164–166 $^0$C. (Lit.[428] Mp 165-166 $^0$C).

## 3.8.6 Procedure for the Pictet-Spengler Reaction

***1-Phenyl-2,3,4,9-tetrahydro-1H-β-carboline (3.42)***

Tryptamine (0.160 g, 1 mmol) was added to BMIM[Cl]-($x$)$ZnCl_2$ ($x$ = 0.71) (0.103 g, 0.2 mmol, 20 mol%) in dichloroethane (2 ml), followed by benzaldehyde (122 µl, 1.2 mmol). The reaction mixture was stirred at 80 $^0$C for 24 h, after which time the reaction mixture was allowed to cool to 35 $^0$C and diluted with water (1 ml). The dichloroethane was separated by decantation and any remaining product extracted with more dichloroethane (5 x 2 ml). The combined extracts were concentrated and subjected to preparative tlc (hexane: EtOAc: $NEt_3$, 6: 4: 1). The product was isolated ($R_f$ = 0.40) and dried in the vacuum oven at 40 $^0$C. The IL was dried under vacuum at 80 $^0$C overnight before reusing it in the next reaction.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.45 (s, br, 1H), 6.90-7.50 (m, 9H), 5.13 (s, br, 1H), 3.10-3.22 (m, 2H) , 2.95-3.08 (m, 2H), 2.65-3.85 (m, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 143.18, 135.94, 135.30, 128.43, 128.07, 127.15, 126.86, 120.47, 118.16, 117.50, 111.04, 108.28, 56.85, 41.18, 40.04, 39.48, 38.93; GCMS *m/z* 248; Mp 170–171 $^0$C. (Lit.[433] Mp 168-169 $^0$C).

# Chapter Four

# Asymmetric Copper Catalysis

# Chapter Four – Asymmetric Copper Catalysis

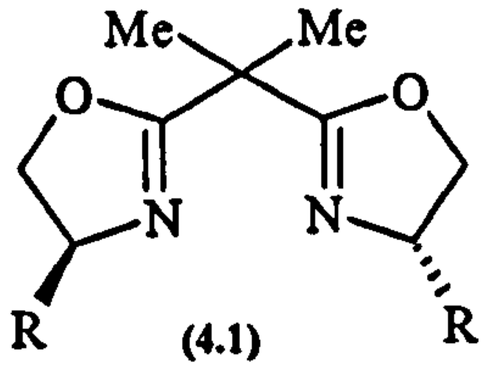
## 4.1 COPPER-BISOXAZOLINE COMPLEXES

Considerable effort has been expended in the discovery of chiral metal complexes that serve as Lewis acids to facilitate the efficient asymmetric synthesis of organic compounds. Chiral oxazolines have been used in stoichiometric synthesis for many decades, but it is only since the late 1980's that their potential as ligands in asymmetric catalysis was recognised. Many research groups have independently investigated the application of catalysts derived from $C_2$-symmetric bis(oxazoline) (box) ligands with various metal salts.[434,435] In general, bis(oxazoline) ligands with a one carbon spacer between the oxazoline rings are most frequently utilised. These ligands form a six membered metal chelate and the substituents on the ring are close to the metal centre. In a particular asymmetric process, both the choice of substituents on the ligand and the metal are critical to optimum enantioselectivity.

The general utility of $C_2$-symmetric bis(oxazoline) ligands in copper-catalysed asymmetric transformations has been demonstrated in a number of processes,[436] including cyclopropanation,[437] aziridination,[438] Diels-Alder,[439,440,441,442] hetero-Diels Alder,[443] 1,3-dipolar cycloadditions,[444] carbonyl-ene reactions,[445] Michael additions,[446] aldol condensations,[447] Henry (nitroaldol) reaction,[448,449] allylic oxidation reactions,[450] Claisen rearrangements,[451] [2,3]-sigmatropic rearrangements,[452,453] Mannich reactions,[454] Nazarov cyclisations,[455,456] Friedel-crafts reactions,[457] and electrophilic fluorinations.[458] As a consequence, the immobilisation of such complexes could provide an easy means of separation and even recovery and reuse of the catalysts. Different strategies for the immobilisation of bis(oxazoline)-copper catalysts have been studied, namely by covalent grafting onto an organic polymer,[459,460,461] covalent anchoring on silica,[462] or by ion-pairing with an anionic support.[460,463] The immobilisation of an aza-bis(oxazoline) by attachment to a soluble organic polymer has also been described.[464] Recently, perfluoroalkyl-substituted box ligands have been synthesised and their Cu complexes investigated as catalysts for the cyclopropanation and ene reaction in a fluorous biphasic system.[465] In all cases, the immobilisation exerts a significant influence on the outcome of the reaction, particularly the enantioselectivity. The changes observed after the grafting process could be due to modification of the chiral ligand, which is now bonded to a large polymeric 'substituent' whose presence would be expected to modify the conformational preferences

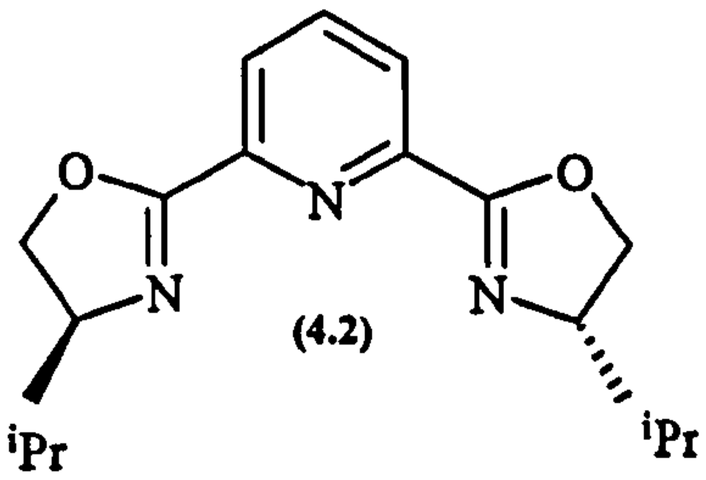
and as a consequence, the relative energies of the different transition states. Hence there is a need for immobilisation methods that are able to reduce the influence of the support.

Evans has reported that copper bisoxazolines can provide excellent *ee* in asymmetric catalysis, however the counterion dramatically affects catalyst efficiency. The "non-coordinating" counterions $[SbF_6]^-$, $[PF_6]^-$, $[BF_4]^-$, $[OTf]^-$, differ strongly in the degree of interaction with the Lewis acidic copper centre, with $[SbF_6]^-$ giving improved results compared to $[OTf]^-$.[466,467] For an example, see section 4.2.1.




(4.1)

a R = $^t$Bu
b R = CH$^i$Pr
c R = Ph




(4.2)

The accelerating effect is probably caused by a higher degree of ligand dissociation from the metal. Jørgensen *et al.* showed that the nature of the solvent also affects the catalytic properties of $[Cu((S,S)^tBu\text{-box})](OTf)_2$, for example, using $[Cu((S,S)^tBu\text{-box})](OTf)_2$ in $CH_3NO_2$ for the Diels Alder reaction between cyclohexadiene and 3-acryloyloxazolidine-2-one increases the rate of reaction twelve-fold, compared to $CH_2Cl_2$.[468] They also found that for the hetero-Diels Alder reaction between cyclohexadiene and ethyl glyoxylate, a combination of $SbF_6^-$ counterion and $CH_3NO_2$ solvent gave the highest reaction rate, but lowest *ee*, thus indicating that the catalytic properties of copper bisoxazoline complexes can be improved further by a careful tuning of the anion and the solvent.

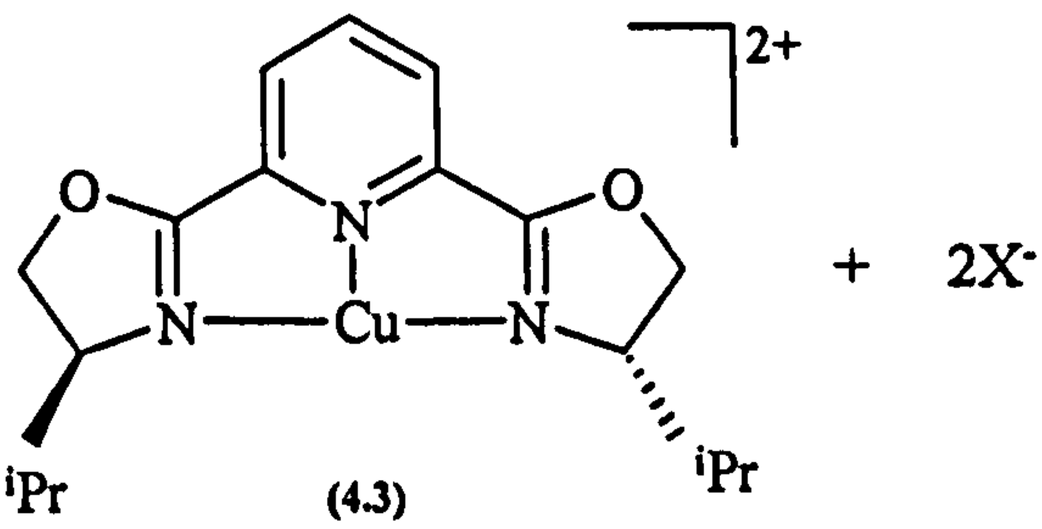
Use of an ionic liquid to immobilise copper bisoxazolines may eliminate the drawbacks associated with other immobilisation strategies since the chiral ligand is not modified; thus selected reactions have been investigated in BMIM$[PF_6]$, BMIM[OTf], BMIM$[BF_4]$ and BMIM$[NTf]_2$, using either Cu(OTf) or $Cu(OTf)_2$ and 2,2-isopropylidenebis[4(*S*)-4-disubstituted–2-oxazoline], (box) (4.1) or 2,6-bis[4(*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine, (pybox) (4.2) as the chiral ligand. The primary objective was to deduce whether immobilisation of the copper catalyst in ILs would provide an effective means of recovering and recycling the catalyst, whilst maintaining catalytic efficiency. We also anticipated that use of a polar environment, ionic liquid as solvent, may promote anion dissociation and hence give faster rates than in organic solvents.

It is reasonable to expect that ionic liquids could play a significant role in asymmetric catalysis, one of the prime concerns for industry and academia. Their polar and non-coordinating properties hold considerable potential for enantioselective reactions since profound effects on reactivities and selectivities can be expected. Surprisingly, it is only very recently that attention has been focussed on the application of ILs as reaction media for enantioselective processes. The first example of asymmetric synthesis in ionic liquids was proposed by Chauvin in 1995,[185] however most subsequent studies were published after 2000. When this project was started, none of the reactions investigated had been examined in ILs, excepting the Diels Alder reaction. To date, there are still no reports of any asymmetric hetero-Diels Alder, aziridinations, allylic oxidations or Friedel-Crafts additions reactions in ILs in the literature.

## 4.2 ASYMMETRIC DIELS ALDER REACTION

### *4.2.1* Introduction

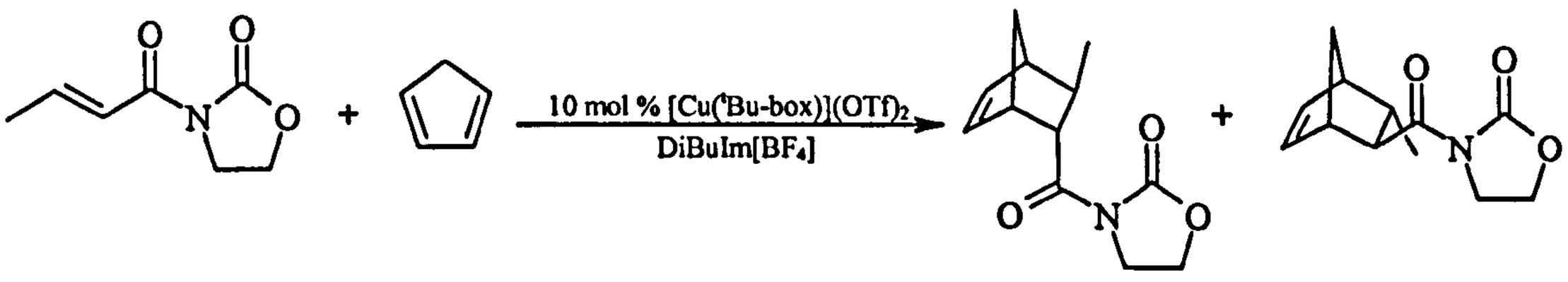
One of the fundamental reactions in organic chemistry is the Diels-Alder reaction to obtain carbo- and heterocycles in a highly regio- and stereospecific way.[469,470] Therefore, considerable attention has been focused on the development of metal-catalysed asymmetric variants of the Diels-Alder reaction. Evans *et al.*[471] showed that $[Cu(pybox)]^{2+}$ (4.3), is an efficient system for catalysing Diels-Alder reactions with a range of dienes and dienophiles. The $[Cu(pybox)]^{2+}$ species has a vacant site, ready for coordination by the dienophile. The choice of counter-ion strongly influences the reactivity of the Lewis acid.




(4.3)

For example, the cycloaddition of methacrolein with Cp that required 120 h catalysed by $[Cu(pybox)](OTf)_2$ at –20 $^0$C, was complete in 8 h with $[Cu(pybox)](SbF_6)_2$.[466] The best ligands for the reaction are (*S,S*)-$^t$Bu-pybox and (*S,S*)-benzylpybox, giving *exo*: *endo* ratios of up to 98: 2 and *ee*'s of up to 96 %.

Although Diels Alder reactions in ionic liquids lead to significant rate enhancement and high yield and selectivity (see Chapter 1, section 1.5.1), there have been few reports of asymmetric Diels Alder reactions in ILs. Seddon *et al.* attempted to induce chirality into bicyclic molecules by using a chiral IL based on the lactate anion, BMIM[lactate], as solvent for the Diels Alder reaction between methyl acrylate and Cp.[154] However, no enantioselectivity was observed. To date, there are only two groups that have reported asymmetric Diels-Alder reactions performed in ionic liquids, both of which were published during the course of this work. Meracz and Oh observed an *ee* of 96 % and a yield of 65 % for the [Cu($^t$Bu-box)](OTf)$_2$ catalysed Diels-Alder reaction (Scheme 4.1) in 1,3-dibutylimidazolium tetrafluoroborate, compared with only 76 % *ee* and a yield of only 4 % in $CH_2Cl_2$.[472]




*endo* *exo*

| | | |
|---|---|---|
| In $CH_2Cl_2$: | 79 (76 % *ee*) | 21 (24 % *ee*) |
| In DiBuIm[$BF_4$]: | 93 (96 % *ee*) | 7 (4 % *ee*) |

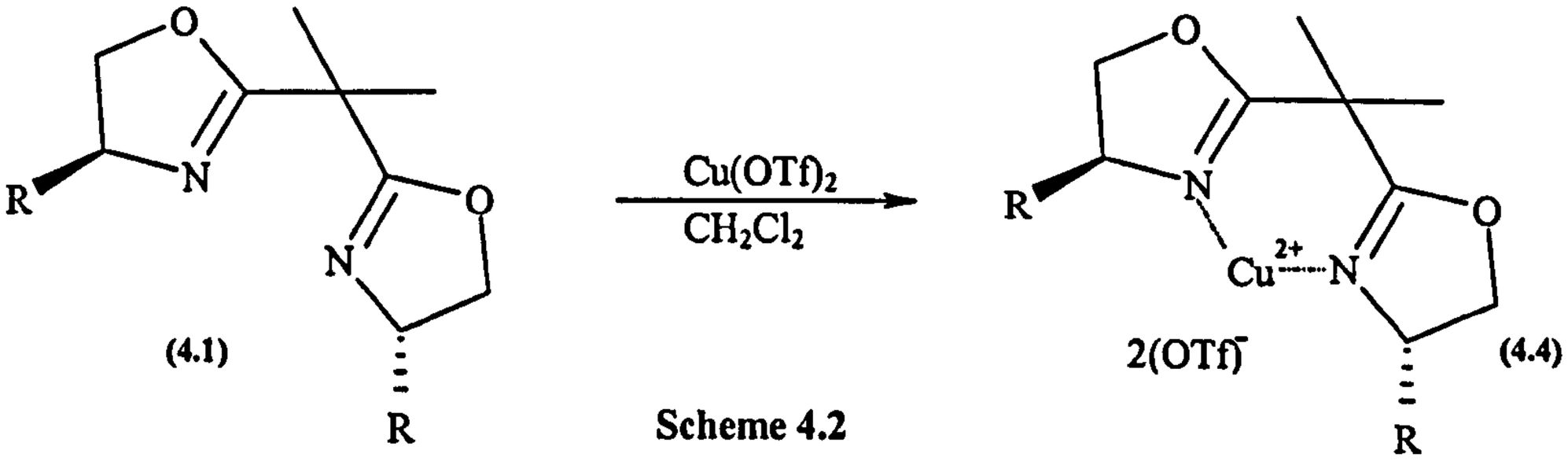
**Scheme 4.1**

More recently, the same reaction was compared in dichloromethane and selected ionic liquids using platinum complexes of BINAP, or of conformationally flexible NUPHOS-type diphosphines.[473] Significant enhancements in the enantioselectivity ($\Delta ee \approx 20$ %), as well as reaction rate, were achieved in ionic liquids compared with the organic media. Typically, high conversions were achieved in only 1 h at 20 °C in ionic liquids compared to more than 20 h to achieve similar conversion in $CH_2Cl_2$. To achieve high enantioselectivities in $CH_2Cl_2$, low temperatures and long reaction times were required, *e.g.* 88 % *ee* at -20 °C, whilst 93 % *ee* was obtained in ionic liquids at room temperature, which highlights the beneficial influence of ionic liquids over $CH_2Cl_2$ in this case.[473]

### *4.2.2* Results and Discussion

The Diels Alder reaction between methacrolein and Cp was selected as a model reaction to investigate the effect of the IL anion on the rate and selectivity of the [Cu-pybox](OTf)$_2$ catalysed reaction. The ligand-copper complexes were prepared *in situ* by mixing Cu(OTf)$_2$ and the bis(oxazoline) ligand in $CH_2Cl_2$ for an hour at ambient temperature. The formation of monomeric or dimeric-complexes depends upon reaction

conditions, reactivity of the metal ions and the ligand structure.[436] As shown in Scheme 4.2, a 1:1 mixture of bis(oxazoline) ligand (4.1) and $Cu(OTf)_2$ is assumed to form a chelated complex (4.4). The ionic liquid is then added and allowed to stir for half an hour before removal of the $CH_2Cl_2$ under vacuum. In all cases, a blue-green homogeneous solution resulted which was then used for the catalysis.




**Scheme 4.2**

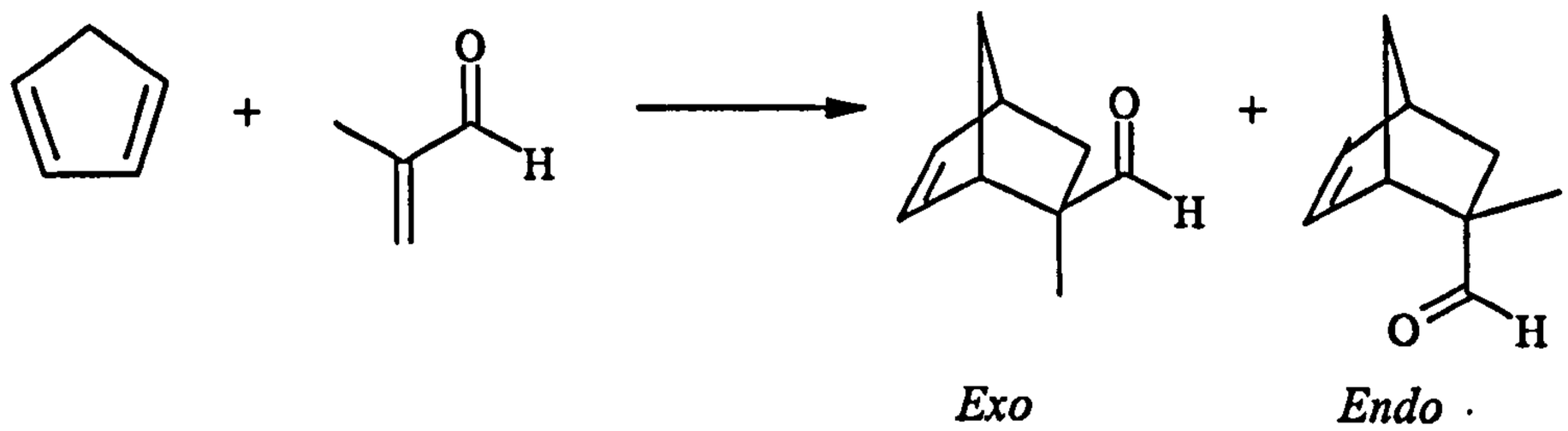
The catalytic solution was cooled to 2.5 $^0$C before addition of methacrolein, followed by 1.5 equivalents of freshly cracked Cp, and then stirred for 12 h. After the reaction the products were extracted from the ionic liquid with ether and filtered through silica. The results are shown in Table 4.1.

**Table 4.1 Reaction of methacrolein and Cp catalysed by [Cu($^i$pr-pybox)](OTf)$_2$ in various ILs**

| Entry | Solvent | Yield / %[a] | Stereoselectivity / %[b] *Exo / Endo* | Enantioselectivity / %[c] *Exo* |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 55 | 93 : 7 | 45 |
| 2 | BMIM[OTf] | 62 | 96 : 4 | 59 |
| 3 | BMIM[$PF_6$] | 68 | 96 : 4 | 60 |
| 4 | BMIM[$NTf_2$] | 60 | 92 : 8 | 49 |
| 5 | BMIM[$BF_4$] | 66 | 95 : 5 | 55 |

All reactions were performed in 1 ml solvent with 2 mmol methacrolein, 3 mmol cyclopentadiene, and 1.0 % $Cu(OTf)_2$. The external temperature was maintained at 2.5 $^0$C for 12 h. [a]Yield of 2-methylbicyclo[2.2.1] hept-5-ene-2-carbaldehyde was determined by $^1$H NMR integration using ferrocene as an internal standard. [b]Determined by $^1$H NMR. [b]Enantioselectivity of the *exo*-isomer was determined by $^1$H NMR after acetalisation with (2*R*,4*R*)-2,4-pentanediol.[466]

**Scheme 4.3 The Diels Alder cycloaddition between methacrolein and Cp**




*Exo* *Endo*

For this particular reaction, the *exo* isomer is favoured. The overall yield and *ee* observed in $CH_2Cl_2$ are lower than those reported by Evans under similar conditions,[466] possibly as a result of a lower catalyst loading (1 % compared to 5 %); a higher temperature (2.5 $^0$C compared to –20 $^0$C); and the different concentrations of methacrolein used (0.2 M compared to 0.1 M), though the ratio of reagents used was approximately the same. It is important to note that Cp is only sparingly soluble in the ILs therefore making the reactions biphasic. With higher catalyst loadings (4 mol%), the reaction proceeded very rapidly (in seconds) and exothermically, and the colour changed from blue-green to dark brown. Therefore the catalyst loading was reduced so that a comparison could be made between the reaction media. The same observation was noted by Song *et al.* who investigated the Diels Alder reaction in BMIM-ILs using 10 mol% $Sc(OTf)_3$, and they found it necessary to reduce the catalyst loading to 0.2 mol%.[474] At temperatures below 0 $^0$C, the ILs are too viscous to stir effectively hence reactions were conducted at 2.5 $^0$C.

As shown in Table 4.1 the reaction occurs moderately well in an ionic liquid using the chiral pybox ligand and provides slightly improved yields, stereoselectivity (except BMIM[$NTf_2$]) and *ee*. It was noted that the enantioselectivity in all the ILs was better than that of the $CH_2Cl_2$ (49 - 60 % compared to 45 %), increasing in the order BMIM[$NTf_2$] < BMIM[$BF_4$] < BMIM[OTf] ≈ BMIM[$PF_6$]. This trend is very similar to that reported by Evans for the rates using different counter-ions with the [Cu-(pybox)] catalyst which increased in the order $BF_4^-$ < $TfO^-$ < $PF_6^-$.[466] It is apparent that the anions interact to a different extent with the Cu catalyst, thus affecting the extent of reaction and selectivity. It appears that the fastest reaction is also the most selective, based on the rates observed by Evans using different counterions. It is interesting to note that for the Diels Alder reaction between methyl acrylate and Cp, Welton *et al.* also observed the fastest rate of reaction in the most viscous ionic liquid, BMIM[$PF_6$], and that the rate of reaction fell as ILs of lower viscosities were employed which means that in a homogeneous system the rate isn't limited by the migration of the reactants through the IL.[155] In our case, the dienes employed for the reactions gave biphasic reaction mixtures except when ethyl acrylate was used as a

dienophile (Table 4.2, entries 16-20). The viscosities of BMIM[$PF_6$],[93] BMIM[$BF_4$],[475] BMIM[OTf],[82] and BMIM[$NTf_2$][82] are 207 cP (at 298K), 233 cP (at 303K), 90 cP (at 293K), and 52 cP (at 293K), respectively. Although the rate wasn't measured, the yield are similar (59 – 64 %) and therefore the viscosity of the IL is unlikely to have a significant effect on the results. The enantioselectivity also doesn't correlate well with viscosity of the IL as BMIM[OTf] gave higher *ee*'s than BMIM[$BF_4$].

In an effort to understand the observed enantioselectivities in the ILs, we have considered correlations with some of the solvent polarity parameters that have been measured for ILs. As mentioned in Chapter 1, section 1.3.1.5, BMIM-ILs have different $E_T^N$ values and this measure was used to compare the effect of the polarity of the solvent on enantioselectivity for the Diels-Alder reaction, (see Figure 4.1). The nucleophilicity of ILs have been determined using [Cu(acac)(tmen)][$BPh_4$] (Chapter 1, section 1.3.1.5, Figure 1.9)[162] so the affect of increasing IL nucleophilicity on enantioselectivity was also examined. However, our results show no correlations with either of these two solvent parameters. There is a loose association between the $E_T^N$ values of ILs *i.e. ee* increases with increasing $E_T^N$ of the IL, but this does not correlate with that observed in $CH_2Cl_2$. It must be born in mind that the results reflect not only a change in the solvent used, but perhaps in the catalyst too as [Cu($^i$pr-pybox)]($OTf)_2$ is known to exist as a tight ion-pair in $CH_2Cl_2$ but this may not be the case in ILs. Also the $E_T^N$ value of a hydrogen bond donor solvent is dominated by its ability to hydrogen bond to a *solute*,[92] so doesn't provide an adequate measure of the overall IL polarity. On the other hand, for some of the ILs *ee* is found to increase with increasing nucleophilicity of the solvent: $CH_2Cl_2$ < BMIM[$NTf_2$] < BMIM[$BF_4$] < BMIM[OTf]. However, BMIM[$PF_6$] is a clear exception to this, therefore

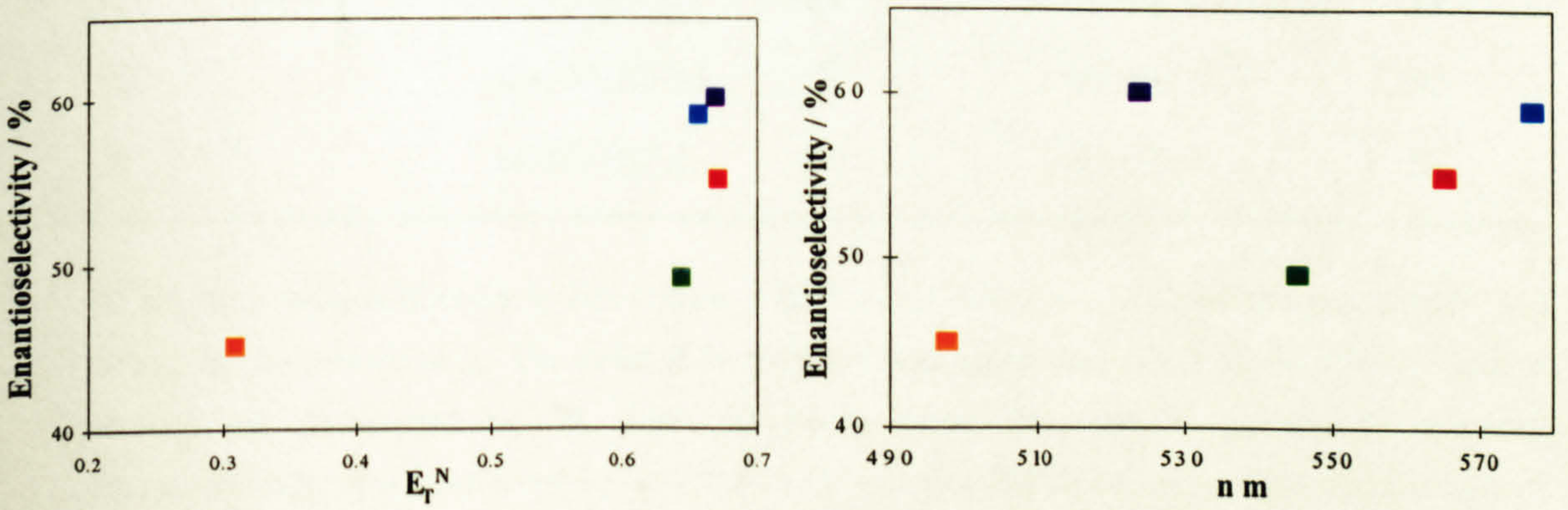
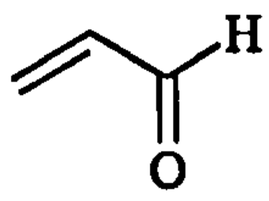
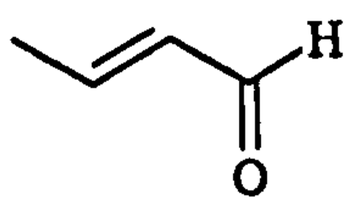
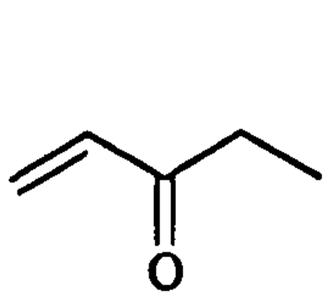
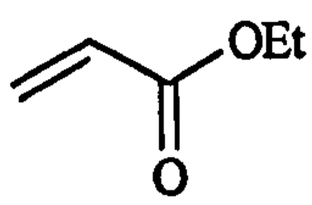



**Figure 4.1 Effect of solvent polarity, $E_T^N$ (left) and nucleophilicity (right) on the enantioselectivity for the [Cu($^i$Pr-pybox)]($OTf)_2$ catalysed Diels-Alder reaction of methacrolein and Cp.**

this association is probably just coincidental. In addition, though $OTf^-$ has the highest nucleophilicity on this scale, Evans concluded that it interacted less with the copper catalyst in $CH_2Cl_2$.

Overall we have demonstrated that the anion of the IL can lead to significant effects on the enantioselectivity for the [Cu($^i$Pr-pybox)](OTf)$_2$ catalysed reaction of methacrolein and Cp. We therefore extended this investigation to include other substrates. (Table 4.2). The reaction between acrolein and Cp in $CH_2Cl_2$ gave a 83 % yield of product and *endo* / *exo* ratio of 90 / 10 with 20 % *ee* for the *endo*-isomer (entry 1). In BMIM-ILs the yields and stereoselectivity were very similar, but with a moderate improvement in *ee*. The best result was in BMIM[$PF_6$] with 28 % *ee* (entry 3). The enantioselectivity was found to increase in the order BMIM[$NTf_2$] < BMIM[$BF_4$] < BMIM[OTf] ≈ BMIM[$PF_6$] *i.e.* equivalent to that found for the reaction of methacrolein and Cp. However, when crotonaldehyde, ethyl vinyl ketone and ethyl acylate were employed as dienophiles, there was little difference in the enantioselectivities found in the different ILs which indicates that the anion doesn't have much effect in other Diels Alder reactions. Although it was noted that BMIM[$NTf_2$] always displayed the lowest level of stereoselectivity and / or enantioselectivity (entries 4, 9, 14 and 19).

**Table 4.2 The effect of ILs containing different anions on enantioselectivity in Diels alder reactions with Cp, using 1 mol% [Cu($^i$pr-pybox)](OTf)$_2$ as catalyst.**

| Entry | Dienophile | Solvent | Yield / %[a] | Stereoselectivity / %[b] *Endo / Exo* | *Ee* / %[c] *Endo* |
|---|---|---|---|---|---|
| 1 |  | $CH_2Cl_2$ | 83 | 90 : 10 | 20 |
| 2 | | BMIM[OTf] | 85 | 91 : 9 | 25 |
| 3 | | BMIM[$PF_6$] | 88 | 91 : 9 | 28 |
| 4 | | BMIM[$NTf_2$] | 81 | 90 : 10 | 22 |
| 5 | | BMIM[$BF_4$] | 86 | 91 : 9 | 24 |
| 6 |  | $CH_2Cl_2$ | 71 | 90 : 10 | 20 |
| 7 | | BMIM[OTf] | 78 | 90 : 10 | 25 |
| 8 | | BMIM[$PF_6$] | 79 | 90 : 10 | 26 |
| 9 | | BMIM[$NTf_2$] | 67 | 90 : 10 | 21 |
| 10 | | BMIM[$BF_4$] | 72 | 90 : 10 | 23 |
| 11 |  | $CH_2Cl_2$ | 50 | 91 : 9 | 34 |
| 12 | | BMIM[OTf] | 57 | 90 : 10 | 36 |
| 13 | | BMIM[$PF_6$] | 59 | 90 : 10 | 35 |
| 14 | | BMIM[$NTf_2$] | 46 | 90 : 10 | 33 |
| 15 | | BMIM[$BF_4$] | 51 | 90 : 10 | 34 |
| 16 |  | $CH_2Cl_2$ | 63 | 90 : 10 | 33 |
| 17 | | BMIM[OTf] | 60 | 90 : 10 | 35 |
| 18 | | BMIM[$PF_6$] | 64 | 91 : 9 | 34 |
| 19 | | BMIM[$NTf_2$] | 59 | 90 : 10 | 30 |
| 20 | | BMIM[$BF_4$] | 62 | 91 : 9 | 34 |

All reactions were performed in 1ml solvent with 2 mmol dienophile, 3 mmol cyclopentadiene, and 1.0% [Cu($^i$pr-pybox)](OTf)$_2$. The external temperature was maintained at 2.5 $^0$C for 12 h. [a]Yield of product was determined by $^1$H NMR integration using ferrocene as an internal standard. [b]Stereoselectivity was determined by $^1$H NMR or GC analysis (BP10 column). [c]Enantioselectivity of the major *endo* product was determined by $^1$H NMR after acetalisation with (2*R*,4*R*)-2,4-pentanediol or by GC analysis using a cydex-ß column.

***Assessing the effect of ionic liquid impurities on yield and enantioselectivity***

A problem that can arise in the use of ionic liquids for immobilisation of transition metal based catalysts is that at low catalyst concentrations impurities in the ionic liquids, particularly halide ions, can have a significant effect by coordinating to the metal and hence blocking an active site. For example, the rate of rhodium catalysed biphasic hydrogenation of pent-1-ene in BMIM[$BF_4$] was significantly lower than in BMIM[$PF_6$] due to the presence of chloride impurity in the BMIM[$BF_4$] ionic liquid.[185] Chloride impurities in BMIM[$BF_4$] also had a marked effect on the metal catalysed Michael addition of acetylacetone to methylvinyl ketone.[476]

The effect of low levels of chloride and 1-methylimidazole (*mim*) in the Diels Alder reaction between methacrolein and Cp was investigated using 2 mol% [Cu($^i$Pr-pybox)](OTf)$_2$ catalyst with varying concentrations of BMIM[Cl] and *mim*. The results are shown in Figures 4.2 and 4.3.

**Figure 4.2 The effect of added BMIM[Cl] on yield and enantioselectivity in the Diels Alder reaction between methacrolein and Cp**

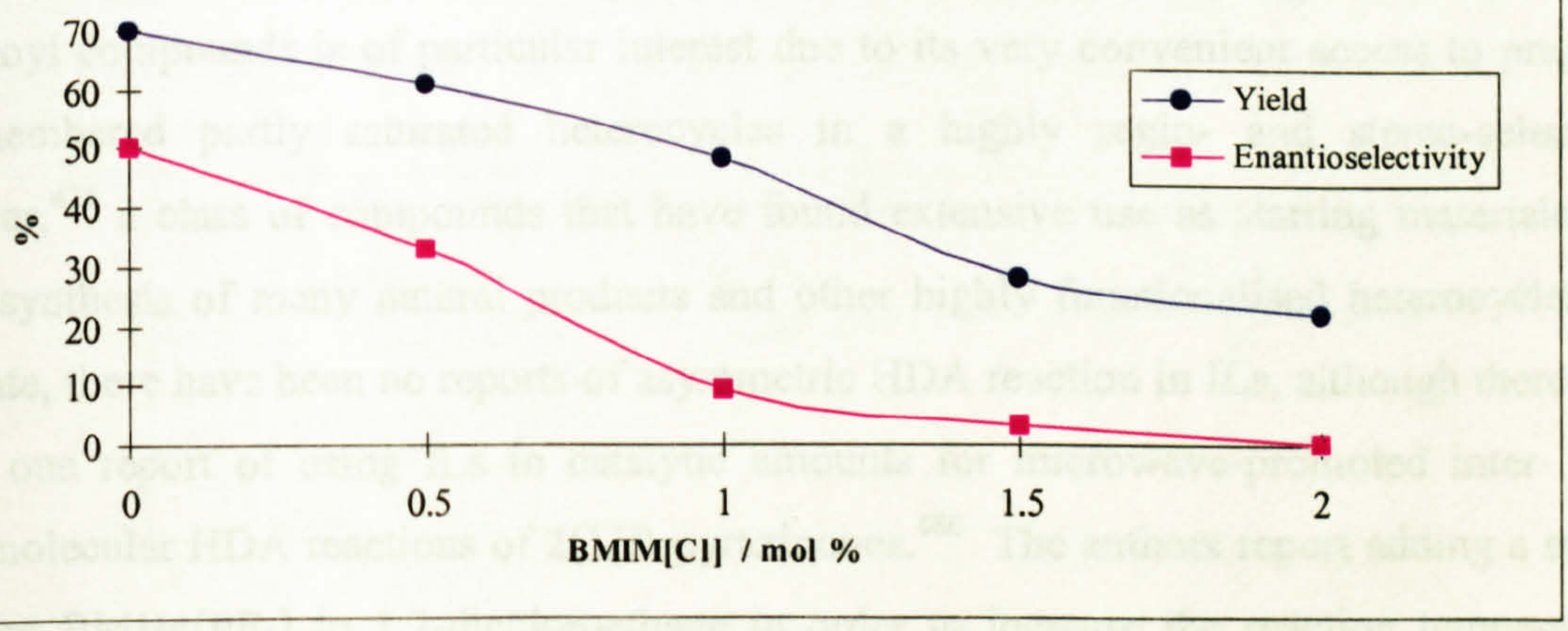
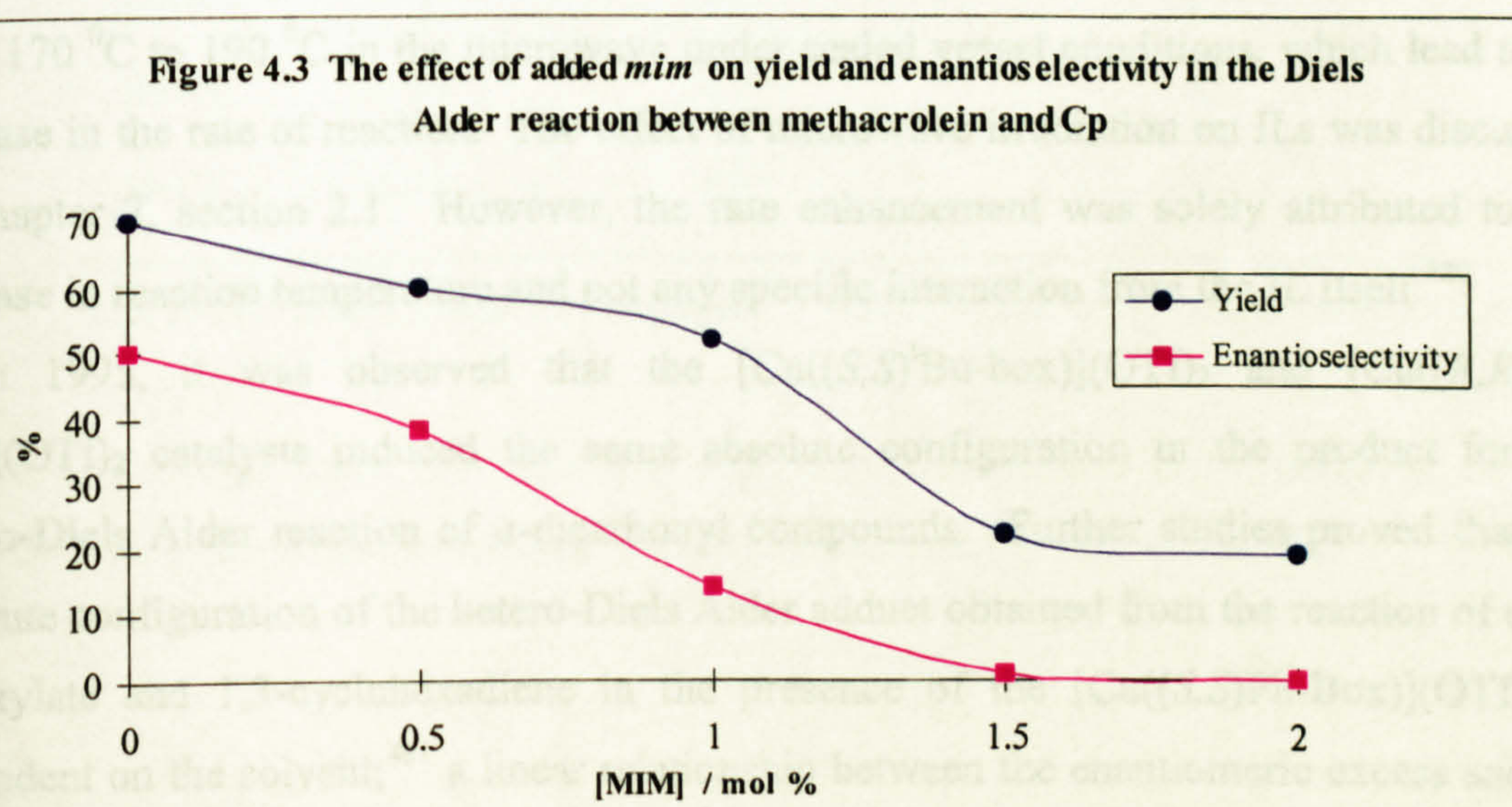



**Figure 4.3 The effect of added *mim* on yield and enantioselectivity in the Diels Alder reaction between methacrolein and Cp**



On addition of small quantities of BMIM[Cl] there is a gradual decrease in yield (from 70 % to 22 %), selectivity (from *exo: endo*, 94: 6 to 85: 15) and enantioselectivity (from 50 to 0 %), as may be expected due to the strong coordinating nature of the chloride ion compared to OTf. The same effects, reduction in yield, stereoselectivity and enantioselectivity, are seen for *mim*, with the reduction in stereoselectivity being even more marked (*exo: endo*, 70: 30). These findings reflect the need for using high quality ILs that are free from impurities and highlight the fact that both $Cl^-$ amd *mim* bind strongly to the copper catalyst. The complexation of *mim* with $CuCl_2$ to form the $[Cu(mim)_4]^{2+}$ ion[477] has been described previously as a method of analysis to detect the level of *mim* impurity in ILs (Chapter 1, section 1.3.2.2).[119]

## 4.3 ASYMMETRIC HETERO-DIELS ALDER REACTION

### *4.3.1* Introduction

The metal-catalysed Hetero-Diels Alder (HDA) reaction of conjugated dienes with carbonyl compounds is of particular interest due to its very convenient access to prepare six-membered partly saturated heterocycles in a highly regio- and stereo-selective manner,[478] a class of compounds that have found extensive use as starting materials for total synthesis of many natural products and other highly functionalised heterocycles.[479] To date, there have been no reports of asymmetric HDA reaction in ILs, although there has been one report of using ILs in catalytic amounts for microwave-promoted inter- and intramolecular HDA reactions of 2(1*H*)-pyrazinones.[480] The authors report adding a small amount BMIM[$PF_6$] to 1,2-dichloroethane in order to increase the reaction temperature from 170 $^0$C to 190 $^0$C in the microwave under sealed vessel conditions, which lead to an increase in the rate of reaction. The effect of microwave irradiation on ILs was discussed in Chapter 2, section 2.1. However, the rate enhancement was solely attributed to the increase in reaction temperature and not any specific interaction from the IL itself.[480]

In 1995, it was observed that the [Cu((*S,S*)$^t$Bu-box)](OTf)$_2$ and [Cu((*R,R*)Ph-box)](OTf)$_2$ catalysts induced the same absolute configuration in the product for the hetero-Diels Alder reaction of α-dicarbonyl compounds. Further studies proved that the absolute configuration of the hetero-Diels Alder adduct obtained from the reaction of ethyl glyoxylate and 1,3-cyclohexadiene in the presence of the [Cu((*S,S*)Ph-Box)](OTf)$_2$ is dependent on the solvent;[481] a linear relationship between the enantiomeric excess and the dielectric constant of the solvent being observed. Thus, solvents with a low dielectric

constant of ~5 ($CHCl_3$ and $CH_2Cl_2$) gave the *endo* adduct in ~75 % *ee* with a (1*S*, 3*R*, 4*R*) configuration, while $EtNO_2$ with a dielectric constant of ~29 gave a nearly racemic mixture of the *endo* adduct. When the reaction was performed in a solvent with a dielectric constant of 36 (MeCN), the absolute configuration of the *endo* adduct was (1*R*, 3*S*, 4*S*) with 60 % *ee*. Although the results indicate that the solvent has an influence on the structure of the intermediates in this reaction induced by [Cu((*S*,*S*)Ph-Box)](OTf)$_2$, currently there is no explanation for this apparent linear relationship observed between the dielectric constant and enantioselectivity. However, simple co-ordination of the solvent is not occurring since addition of co-ordinating molecules such as $H_2O$ / MeCN to both [Cu((*S*,*S*)$^t$Bu-Box)](OTf)$_2$ and [Cu((*S*,*S*)Ph-Box)](OTf)$_2$ complexes which were then applied as catalysts to the HDA reaction of ethyl glyoxylate and cyclohexadiene, had no effect on the enantioselectivity.[481] Interestingly, the solvent only affects the *ee* with the Ph-substituted catalyst, the *ee* for the adduct obtained with the chiral [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ is independent of the solvent.

**Table 4.3 HDA reaction of ethyl glyoxylate with 1,3-cyclohexadiene catalysed by 10 mol% [Cu((*S*,*S*)Ph-Box)](OTf)$_2$ and [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ in different solvents.[481]**

| Solvent | Dielectric constant | [Cu((*S*,*S*)Ph-box)](OTf)$_2$ *Ee* / % | [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ *Ee* / %$^{\Delta}$ |
|---|---|---|---|
| $CDCl_3$ | 4.80 | 79* | 97 |
| $CHCl_3$ | 4.89 | 78* | 97 |
| THF | 7.47 | 47* | 99 |
| $CH_2Cl_2$ | 9.08 | 59* | 97 |
| $EtNO_2$ | 28.96 | 11$^{\Delta}$ | 97 |
| MeCN | 36.00 | 60$^{\Delta}$ | - |

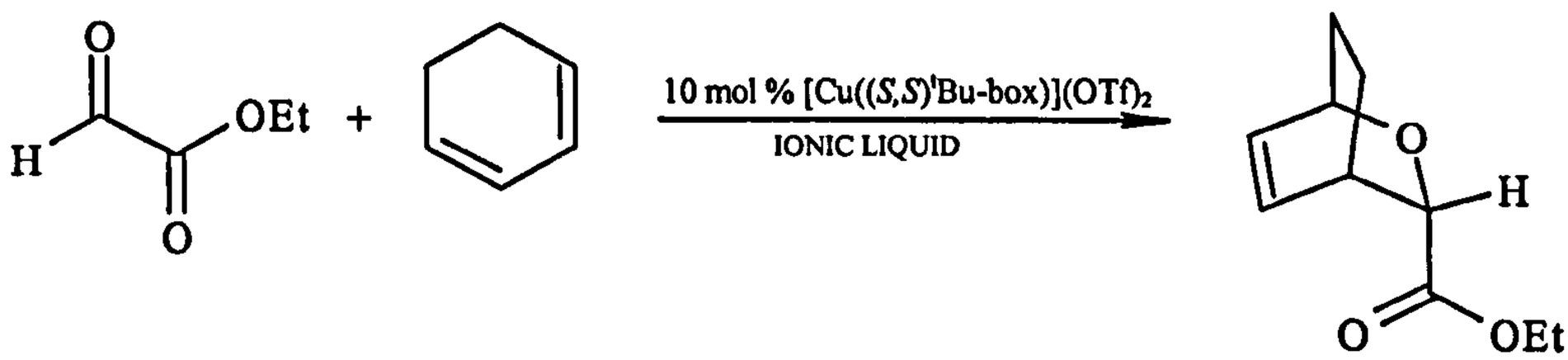
*(1*S*, 3*R*, 4*R*) is the predominant enantiomer $^{\Delta}$(1*R*, 3*S*, 4*S*) is the predominant enantiomer

To our knowledge, there have been no reports of asymmetric HDA reactions in ILs. Therefore the effect of both substituted-box catalysts was investigated in ILs.

### *4.3.2* Results and Discussion

The reaction between ethyl glyoxylate and cyclohexadiene was studied in the presence of 10 mol% [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ as catalyst immobilised in ILs (see Scheme 4.4). High enantioselectivity is typically realised using the bis(oxazoline) Cu(II) system only when the substrate undergoing activation is capable of bidentate co-ordination to the chiral Lewis acid. This criterion of chelation is apparently necessary to provide good catalyst-substrate organisation before and / or during the bond-forming event.[482]

**Scheme 4.4 The HDA reaction between ethyl glyoxylate and cyclohexadiene**




The catalyst solutions were prepared from Cu(OTf)$_2$ / (4.1a) in $CH_2Cl_2$ before dissolution in the ionic liquid and then removal of the $CH_2Cl_2$ under vacuum. The substrates were then added and the reaction mixture stirred at room temperature for 8 h. As cyclohexadiene is not appreciably soluble in the ionic liquids, these reactions are biphasic. After the reaction the cycloadducts were extracted from the ionic liquid with ether and filtered through silica. The yield, stereoselectivity and the enantiomeric excess was determined by GC. The results are shown below.

**Table 4.4 Hetero-Diels Alder reaction of ethyl glyoxylate and cyclohexadiene catalysed by [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$**

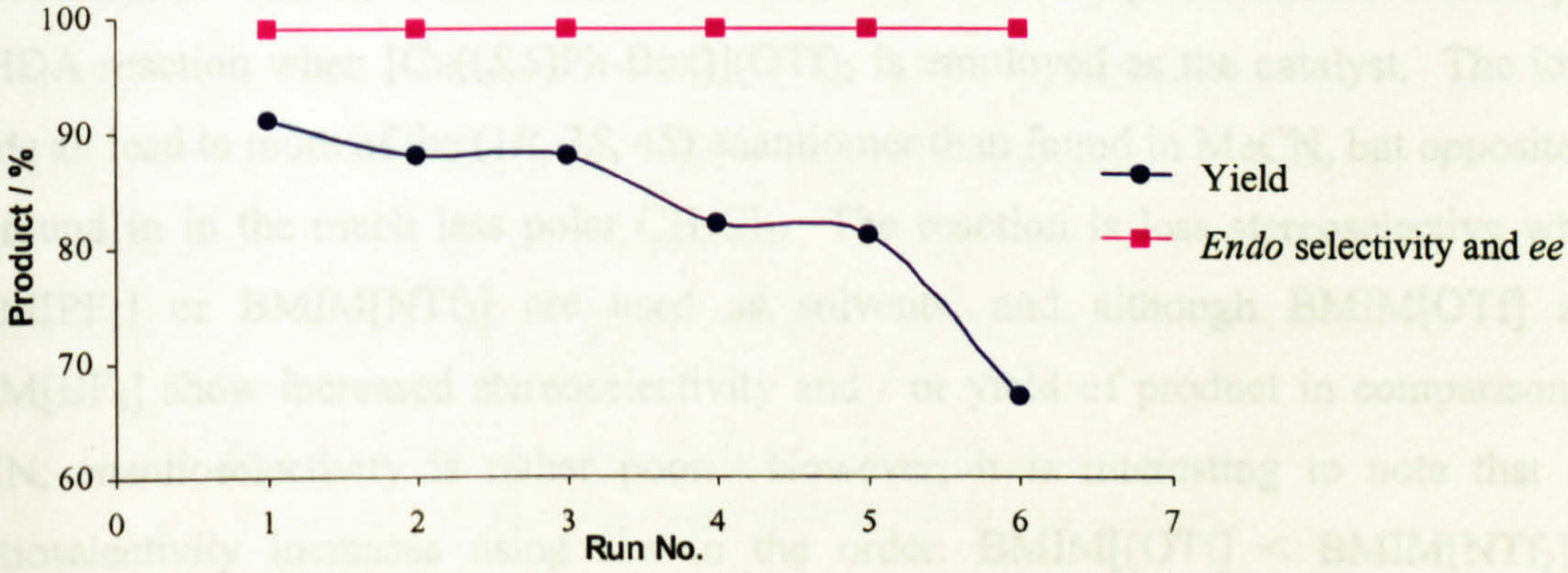
| Solvent | Yield /%[a] | Selectivity /% *Endo* : *Exo* | Enantioselectivity /%[b] Endo |
|---|---|---|---|
| $CH_2Cl_2$ | 47 | 98 : 2 | 99 |
| BMIM[OTf] | 48 | 98 : 2 | 99 |
| BMIM[$PF_6$] | 53 | 98 : 2 | 99 |
| BMIM[$NTf_2$] | 44 | 97 : 3 | 99 |
| BMIM[$BF_4$] | 52 | 99 : 1 | 99 |

[a] Yield determined by GC using decane as an internal standard. [b] Determined by chiral GC (ß-cyclodextrin column), absolute configuration is (1*R*, 3*S*, 4*S*)

As can be seen the yields (44 - 53 %), stereoselectivity and enantioselectivity are broadly similar in all the ionic liquids and in $CH_2Cl_2$, though the yield and stereoselectivity are both somewhat less in the $NTf_2$ liquid. These results are consistent with those reported previously[481] *i.e.* the *ee* of the product with chiral [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ as catalyst is independent of the solvent.

Reuse of the catalyst solution was investigated in BMIM[$BF_4$], since visually BMIM[$BF_4$] and BMIM[$PF_6$] showed minimal leaching of the catalyst into the organic phase when the products were extracted using ether. There is a very small loss of catalyst at the end of each reaction, as judged by the faint blue baseline that remains on the preparative tlc plate, during purification of the products. The yield is highly dependent on the quality of the alkyl glyoxylate used. The polymerisation of alkyl glyoxylates is reversible and sometimes the semipolymerised form can be used in reactions[483] but the yield does not exceed 60 % for these HDA reactions. To ensure a high yield of the HDA-adduct, freshly distilled monomeric alkyl glyoxylate is essential. Hence, in the catalyst recycling experiments, 3 equivalents of ethyl glyoxylate were used and the reaction time was increased from 8 to 20 h. This gave an increased yield of product and the results are shown in Figure 4.4.

**Figure 4.4 Repeated Hetero-Diels Alder reactions of ethyl glyoxylate and cyclohexadiene catalysed by [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ in BMIM[$BF_4$]**




It can be seen that [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ can be reused in BMIM[$BF_4$] up to five times with no loss in stereoselectivity or enantioselectivity, and only a minimal loss of product yield. (Yield is declining each time with a bigger drop in run 6). The gradual decrease could be due to small losses of catalyst into the ether extract (see above). Another possible reason could be increase in impurity level *e.g.* polymerised ethyl glyoxylate which may coordinate to copper and hence reduce activity.

As mentioned previously (Chapter 1, section 1.3.1.5), BMIM-based ILs have different polarity ($E_T^N$ values), acidity, nucleophilicity / basicity and dipolarity.[484] Hence this HDA reaction was repeated using [Cu((*S,S*)Ph-Box)](OTf)$_2$ as catalyst, which is known to exhibit large solvent effects.[481] The results are shown in Table 4.5.

**Table 4.5 Hetero-Diels Alder reaction of ethyl glyoxylate and cyclohexadiene catalysed by [Cu((*S,S*)Ph-Box)](OTf)$_2$**

| Solvent | $E_T^{N(a)}$ | Dipolarity[a] $\pi^*$ | Nucleophilicity[a] $\lambda_{Cu}$ /nm | Basicity[a] $\beta$ | Yield /%[b] | Stereoselectivity /%[c] *Endo* : *Exo* | *Ee* /%[d] *Endo* |
|---|---|---|---|---|---|---|---|
| $CH_2Cl_2$ | 0.309 | 0.791 | 497.5 | -0.014 | 68 | 98 : 2 | -63[e] |
| MeCN | 0.460 | 0.799 | 575[485] | 0.370 | 42 | 96 : 4 | 58 |
| BMIM[OTf] | 0.656 | 1.006 | 577.0 | 0.464 | 59 | 96 : 4 | 9 |
| BMIM[$PF_6$] | 0.669 | 1.032 | 524.0 | 0.207 | 34 | 90 : 10 | 24 |
| BMIM[$NTf_2$] | 0.644 | 0.984 | 545.0 | 0.243 | 33 | 93 : 7 | 15 |
| BMIM[$BF_4$] | 0.670 | 1.047 | 565.0 | 0.376 | 66 | 98 : 2 | 35 |

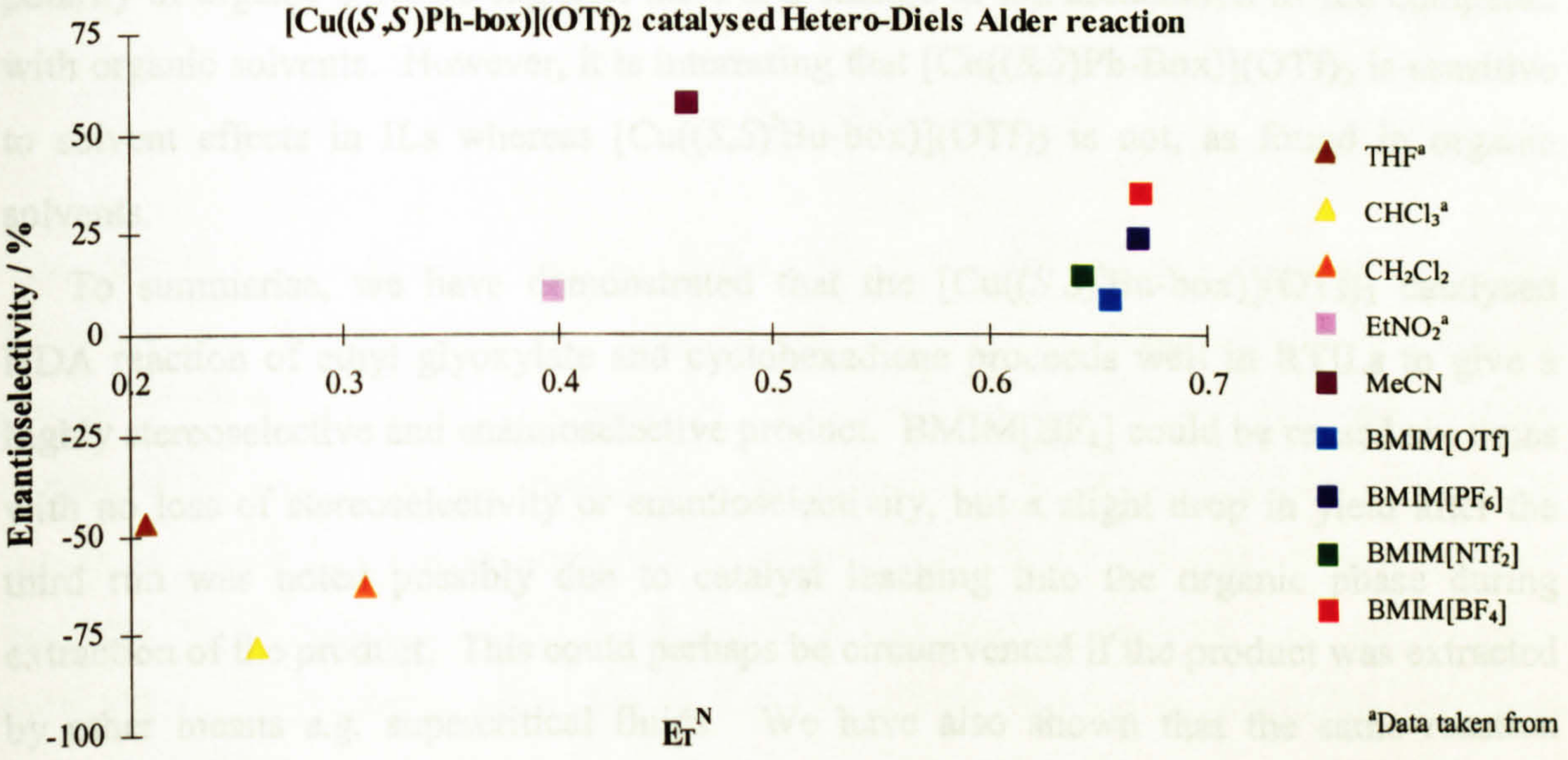
[a]Data taken from ref.484. [b]Yield determined by GC using decane as an internal standard [c]Stereoselectivity was determined by GC analysis (BP10 column). [d]Enantioselectivity of the major *endo*-isomer determined by chiral GC (ß-cyclodextrin column), absolute configuration is (1*R*, 3*S*, 4*S*). [e]Negative sign indicates (1*S*, 3*R*, 4*R*) as the predominant enantiomer in $CH_2Cl_2$.

The results show that the choice of IL affects the stereoselectivity and enantioselectivity of the HDA reaction when [Cu((*S,S*)Ph-Box)](OTf)$_2$ is employed as the catalyst. The ionic liquids all lead to more of the (1*R*, 3*S*, 4*S*) enantiomer than found in MeCN, but opposite to that found in in the much less polar $CH_2Cl_2$. The reaction is less stereoselective when BMIM[$PF_6$] or BMIM[$NTf_2$] are used as solvents, and although BMIM[OTf] and BMIM[$BF_4$] show increased stereoselectivity and / or yield of product in comparison to MeCN, enantioselectivity is rather poor. However, it is interesting to note that the enantioselectivity increases using ILs in the order: BMIM[[OTf] < BMIM[$NTf_2$] < BMIM[$PF_6$] < BMIM[$BF_4$]. To explain these results, we considered some known solvent polarity measures.

To see if there is a correlation between solvent polarity and enantioselectivity for the HDA reaction, $E_T^N$ was plotted against *ee*. Figure 4.5 illustrates that solvents with a low $E_T^N$ give moderate to high *ee* of the (1*S*, 3*R*, 4*R*) enantiomer, solvents with an $E_T^N$ ranging between 0.4 – 0.5 give low to moderate *ee*'s favouring the (1*R*, 3*S*, 4*S*) enantiomer, whilst ILs give fairly low *ee*'s favouring the (1*R*, 3*S*, 4*S*) enantiomer. In organic solvents there is

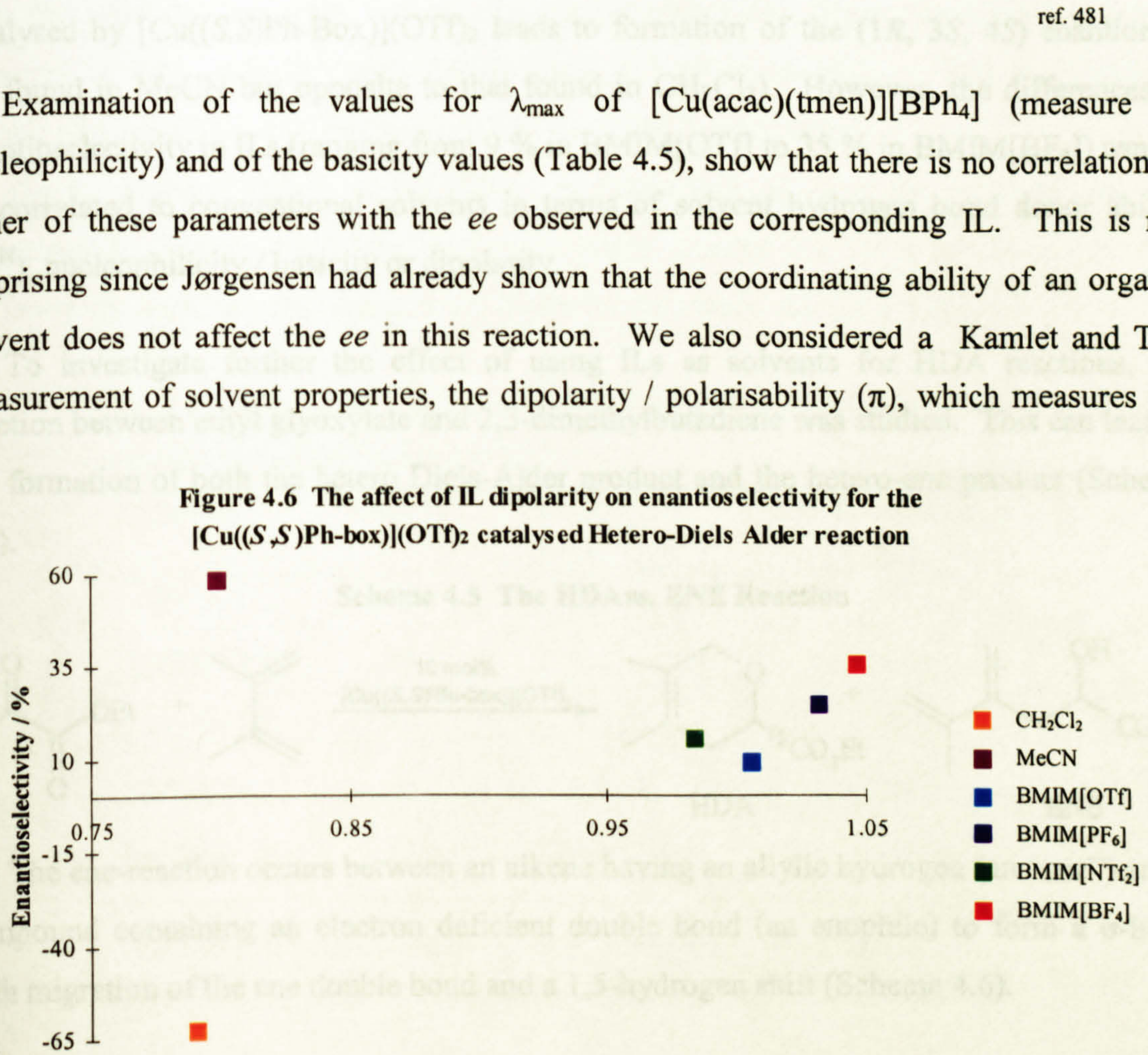
a linear correlation between *ee* and $E_T^N$ of the solvent with favouring formation of the (1*R*, 3*S*, 4*S*) enantiomer.[481] All the ILs favour the (1*R*, 3*S*, 4*S*) enantiomer as expected for polar solvents, however there is no direct correlation with $E_T^N$ and even though their $E_T^N$ values are all higher than that of MeCN, the *ee*'s are all less. However, the affect of the IL anion is apparent as the *ee* ranges from 35 % in BMIM[$BF_4$] to only 9 % in BMIM[OTf].

**Figure 4.5 The affect of solvent polarity ($E_T^N$) on enantioselectivity for the [Cu((*S*,*S*)Ph-box)](OTf)$_2$ catalysed Hetero-Diels Alder reaction**




Examination of the values for $\lambda_{max}$ of [Cu(acac)(tmen)][$BPh_4$] (measure of nucleophilicity) and of the basicity values (Table 4.5), show that there is no correlation of either of these parameters with the *ee* observed in the corresponding IL. This is not surprising since Jørgensen had already shown that the coordinating ability of an organic solvent does not affect the *ee* in this reaction. We also considered a Kamlet and Taft measurement of solvent properties, the dipolarity / polarisability ($\pi$), which measures the

**Figure 4.6 The affect of IL dipolarity on enantioselectivity for the [Cu((*S*,*S*)Ph-box)](OTf)$_2$ catalysed Hetero-Diels Alder reaction**



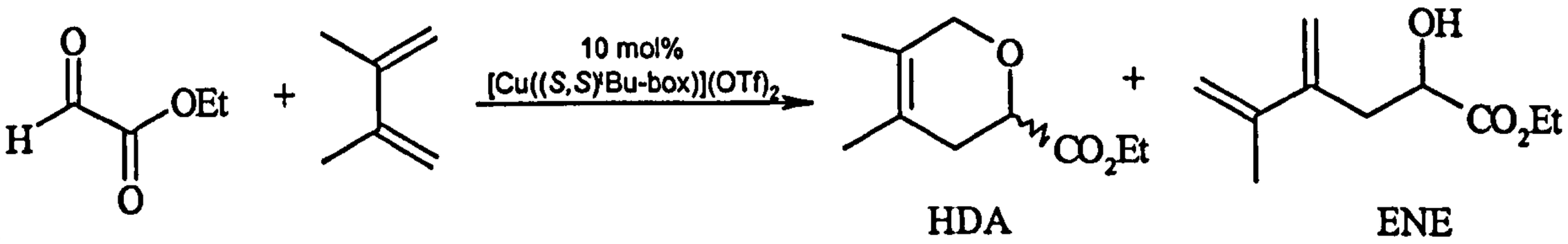
ability of the solvent to stabilise a charge or a dipole due to its dielectric effect. Again, there was no correlation (see Figure 4.6).

The fact that polarity correlates for organic solvents may be due to ion-pairing. However, ILs of broadly similar polarity still show quite a wide variation in *ee* (9 – 35 %). This variation does not correlate well with polarity, nucleophilicity, basicity or dipolarity. The lack of correlation with polarity and that ILs do not fit the same trend based on the polarity of organic solvents suggests there is a change in ion association in ILs compared with organic solvents. However, it is interesting that [Cu((*S*,*S*)Ph-Box)](OTf)$_2$ is sensitive to solvent effects in ILs whereas [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ is not, as found in organic solvents.

To summarise, we have demonstrated that the [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ catalysed HDA reaction of ethyl glyoxylate and cyclohexadiene proceeds well in RTILs to give a highly stereoselective and enantioselective product. BMIM[$BF_4$] could be reused six times with no loss of stereoselectivity or enantioselectivity, but a slight drop in yield after the third run was noted possibly due to catalyst leaching into the organic phase during extraction of the product. This could perhaps be circumvented if the product was extracted by other means *e.g.* supercritical fluids. We have also shown that the same reaction catalysed by [Cu((*S*,*S*)Ph-Box)](OTf)$_2$ leads to formation of the (1*R*, 3*S*, 4*S*) enantiomer (as found in MeCN but opposite to that found in $CH_2Cl_2$). However, the differences in enantioselectivity in ILs (ranging from 9 % in BMIM[OTf] to 35 % in BMIM[$BF_4$]) cannot be correlated to conventional solvents in terms of solvent hydrogen bond donor ability ($E_T^N$), nucleophilicity / basicity or dipolarity.

To investigate further the effect of using ILs as solvents for HDA reactions, the reaction between ethyl glyoxylate and 2,3-dimethylbutadiene was studied. This can lead to the formation of both the hetero Diels-Alder product and the hetero-ene product (Scheme 4.5).

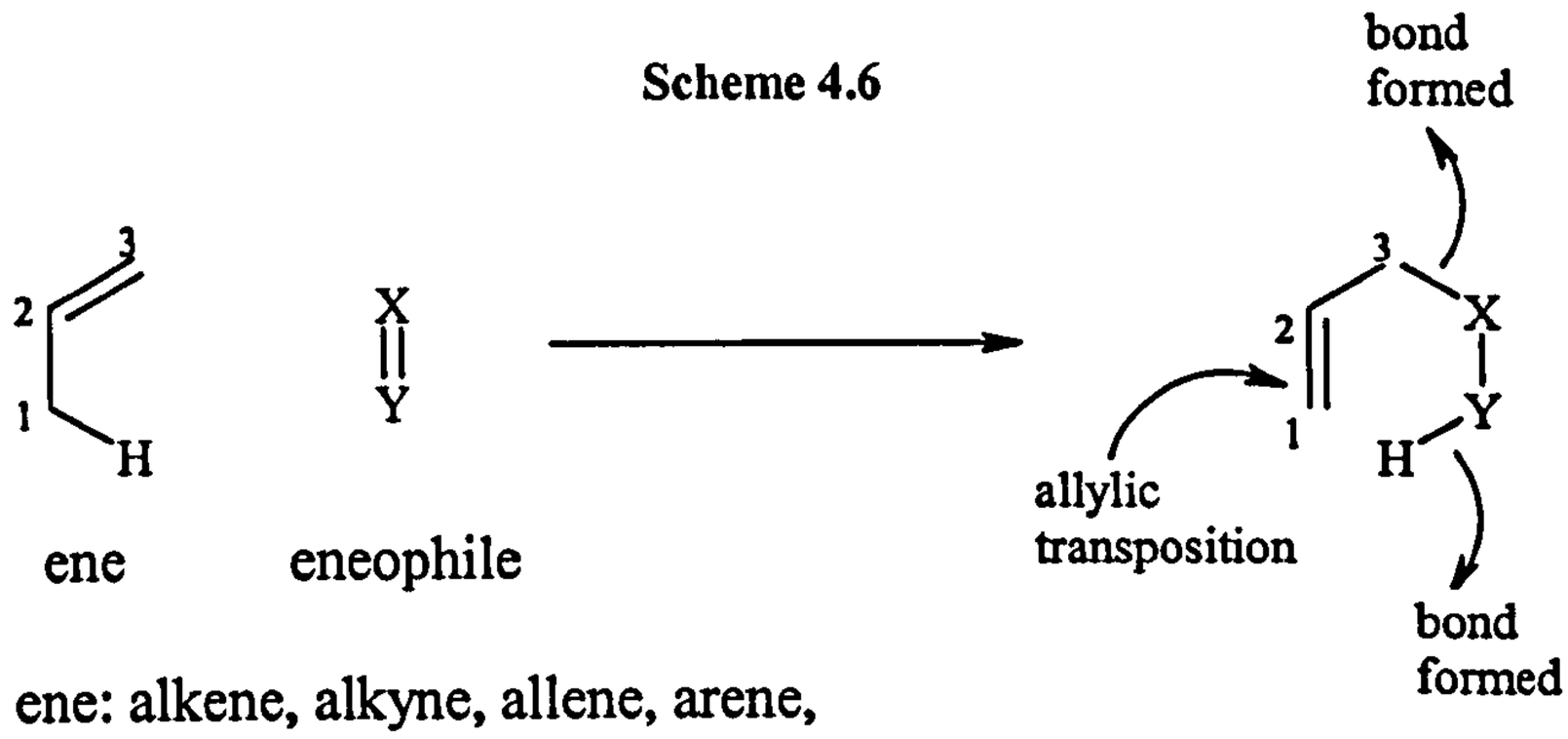
**Scheme 4.5 The HDA*vs.* ENE Reaction**




HDA ENE

The ene-reaction occurs between an alkene having an allylic hydrogen (an "ene") and a compound containing an electron deficient double bond (an enophile) to form a σ-bond with migration of the ene double bond and a 1,5-hydrogen shift (Scheme 4.6).

**Scheme 4.6**




ene: alkene, alkyne, allene, arene, carbon-heteroatom bond

X=Y: C=C, C=O, C=N, C=S, O=O, N=N

The thermal and Lewis acid catalysed glyoxylate ene-reaction was introduced more than 30 years ago by Klimova and Arbuzov *et al.* and has been studied by several groups.[486,487,488] In 1995, Jørgensen *et al.* discovered that [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ catalysed the reaction of glyoxylate ester with a diene to give the HDA and ene products in moderate yields with a high enantiomeric excess. The HDA : ene ratio is dependent on both the chiral ligand attached to the copper, the glyoxylate ester, and the reaction temperature.[489] Further studies showed that the solvent also has a significant impact on both the HDA to ene ratio, and on the enantioselectivity. Thus, the HDA product is favoured in more polar solvents (HDA / ene = 1.25 in $MeNO_2$, = 0.56 in $CH_2Cl_2$; a combined yield of 56 % in $MeNO_2$ and 68 % in $CH_2Cl_2$ is reported).[490]

The influence of the IL on the HDA : ene ratio and the *ee* of the products was also investigated. The reaction was performed under exactly the same conditions as with cyclohexadiene, hence the reactions are biphasic; the results are shown in Table 4.6.

**Table 4.6 HDA / Ene reaction of ethyl glyoxylate and 2,3-dimethylbutadiene catalysed by [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$**

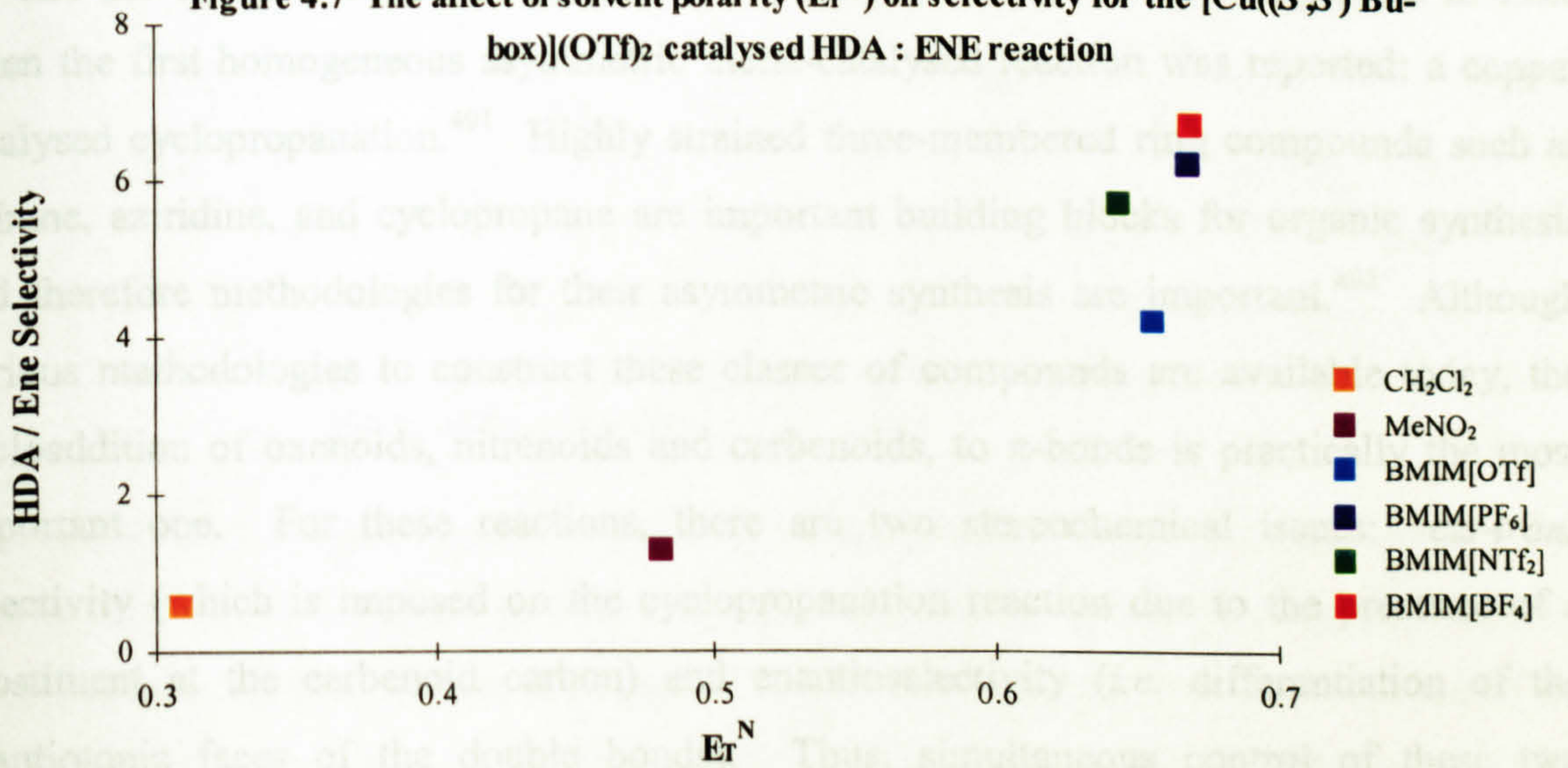
| Solvent | Yield /%[a] | Selectivity /% | Enantioselectivity /%[b] |
|---|---|---|---|
| | | HDA : ENE | ENE |
| $MeNO_2$ | 48 | 1.3 : 1 | 87 |
| BMIM[OTf] | 46 | 4.2 : 1 | 91 |
| BMIM[$NTf_2$] | 45 | 5.7 : 1 | 89 |
| BMIM[$PF_6$] | 46 | 6.2 : 1 | 90 |
| BMIM[$BF_4$] | 47 | 6.7 : 1 | 94 |

[a] Combined yield determined by GC using decane as an internal standard

[b] Determined by chiral GC (ß-cyclodextrin column (average of 2 experiments)

Our combined yield of 48 % in $MeNO_2$ compares reasonably to the 56 % reported for this reaction under similar conditions where a slightly longer reaction time was used (12 h compared to 8 h). Table 4.6 shows that the IL anion has a significant impact on the HDA to ene ratio. In all cases, the HDA was the favoured product, but compared to $MeNO_2$, a four-fold increase in selectivity for the HDA product was found in BMIM[$BF_4$]. The selectivity for the HDA adduct was found to increase in the order BMIM[OTf] < BMIM[$NTf_2$] < BMIM[$PF_6$] < BMIM[$BF_4$]. We found no correlations of this selectivity with the $E_T^N$ (Figure 4.7), or with the nucelophilicity or dipolarity of the ILs.

**Figure 4.7 The affect of solvent polarity ($E_T^N$) on selectivity for the [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ catalysed HDA : ENE reaction**




Excellent levels of enantioselectivity of the ene product were also achieved in all the ILs. Unfortunately, it has not been possible to determine the enantioselectivity of the HDA cycloadducts due to poor resolution of the enantiomers on the chiral column. High levels of selectivity for the HDA adduct were also observed in RTILs in the HDA / ene reaction between 2,3-dimethylbutadiene and cyclohexadiene.

Clearly, a single "polarity" / "solvent strength" / "interaction" parameter will not be sufficient to explain the variation in experimental results in the HDA or HDA / ene copper-catalysed reactions. Most simple molecular solvents (*e.g.*hexane) are limited in the number and types of solvation interactions possible with dissolved molecules. More complex solvents with additional functional groups are capable of having additional interactions with dissolved molecules. Ionic liquids are among the most complex solvents, capable of most types of interaction (*e.g.* dispersive, π-π, n-π, hydrogen bonding, dipolar, ionic / charge-charge), there may be a number of different (in terms of type and strength) and often simultaneous solute-solvent interactions. For any given reaction, there will be

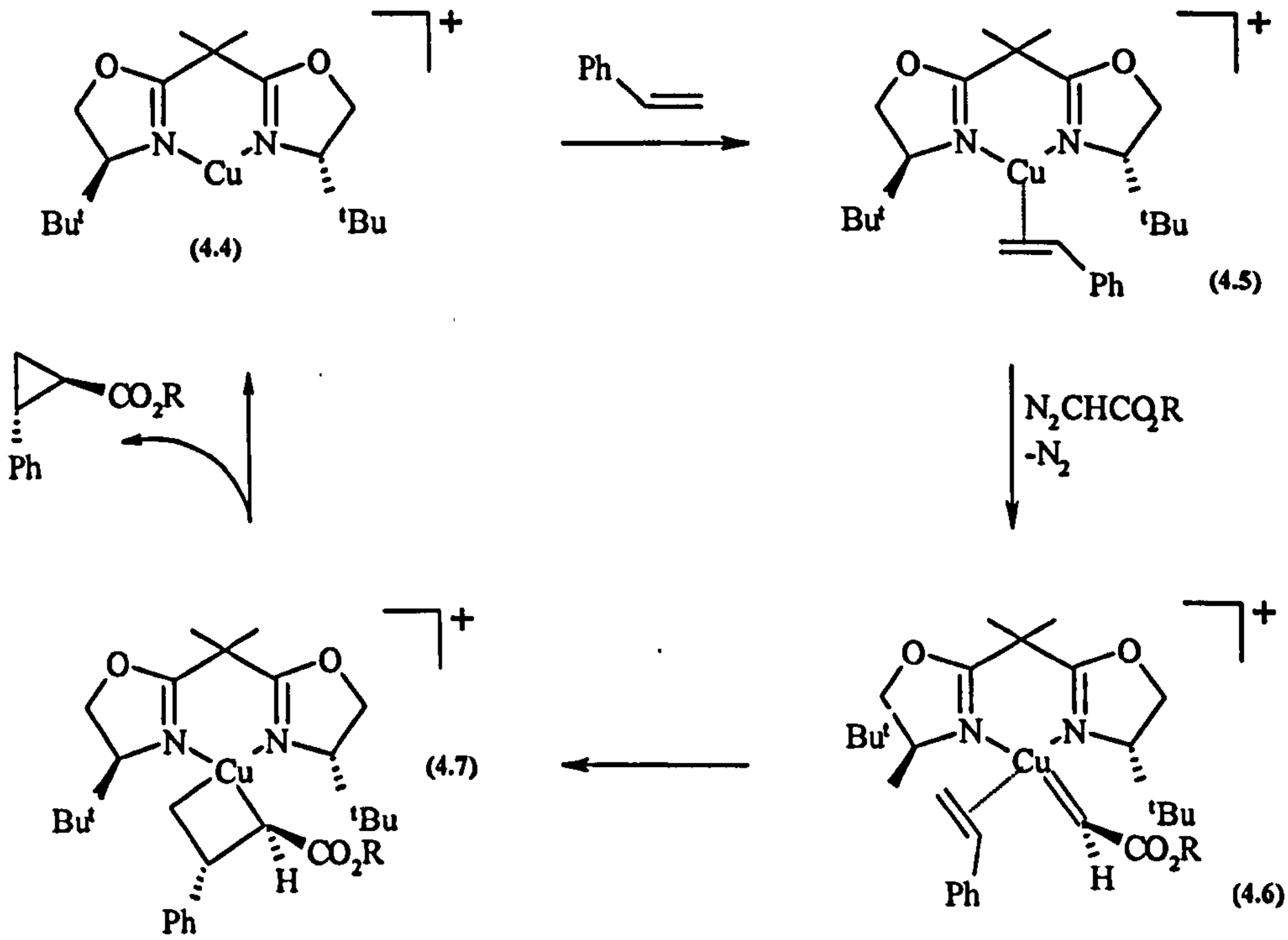
dominant and less-substantial interactions. The various single polarity parameters are essentially weighted averages of all possible solute-solvent interactions and do not adequately explain all experimental observations *i.e.* we cannot treat ILs as just "ordinary" solvents.

## 4.4 Asymmetric Cyclopropanation

### 4.4.1 Introduction

The use of chiral copper complexes in asymmetric catalysis was inaugurated in 1966 when the first homogeneous asymmetric metal-catalysed reaction was reported: a copper catalysed cyclopropanation.[491] Highly strained three-membered ring compounds such as oxirane, aziridine, and cyclopropane are important building blocks for organic synthesis and therefore methodologies for their asymmetric synthesis are important.[492] Although various methodologies to construct these classes of compounds are available today, the cycloaddition of oxenoids, nitrenoids and carbenoids, to π-bonds is practically the most important one. For these reactions, there are two stereochemical issues: *cis-trans* selectivity (which is imposed on the cyclopropanation reaction due to the presence of a substituent at the carbenoid carbon) and enantioselectivity (*i.e.* differentiation of the enantiotopic faces of the double bonds). Thus, simultaneous control of these two stereochemical issues is a prerequisite for achieving highly efficient cyclopropanation.

The mechanism of cyclopropanation is believed to involve the formation of a copper carbenoid as an intermediate, though details of the subsequent C-C bond forming steps are scarce, Scheme 4.7. Evans suggested that the catalyst resting state in this reaction is a Cu alkene complex (4.5).[493] Variable temperature NMR studies indicate that the catalyst complexes one equivalent of styrene which, in the presence of excess alkene, readily undergoes alkene exchange at ambient temperature. Addition of diazoester fails to provide an observable complex. These workers invoke the metallacyclobutane intermediate (4.7) via a formal [2 + 2] cycloaddition from copper carbenoid alkene complex (4.6). Formation of (4.7) is the stereochemistry-determining event in this reaction. In our study, it is anticipated that changing the anion of the IL may stabilise (4.7) to different extents, thus affecting stereoselectivity and enantioselectivity. The square-planar $d^8$ Cu(III) intermediate (4.7) then undergoes a reductive elimination forming the cyclopropane product and complex (4.4), which binds another alkene molecule.




**Scheme 4.7 Mechanism proposed by Evans for the cyclopropanation of alkenes [Adapted from ref 436]**

An important competing process with significant practical consequences is the catalytic dimerisation of diazoacetate to form maleate and fumarate esters. Most catalysts suffer from this side reaction, leading to the use of the alkene as solvent in order to accelerate the productive pathway, and / or the slow addition of diazo compound, in order to minimise dimerisation.

During the course of this research, there have been three reports of cyclopropanations in ionic liquids. The cyclopropanation of styrene with ethyl diazoacetate (Scheme 4.8) has been reported using $Pd(OAc)_2$, $PdCl_2$ and cyclopalladated complexes in OMIM[$BF_4$].[494] The *trans* / *cis* ratio was between 1.6 – 1.8 and all the catalysts could be reused 6 - 7 times in the IL without loss of efficiency. More recently, Chandrasekhar *et al.* described the cyclopropanation of cyclohex-2-enone using trimethyl sulphoxonium iodide and KOH as base in BMIM[$PF_6$]. They reported clean formation of product within two hours at room temperature, and were able to recycle the BMIM[$PF_6$] and gave a high yield of 90 % even on the fourth run.[495]

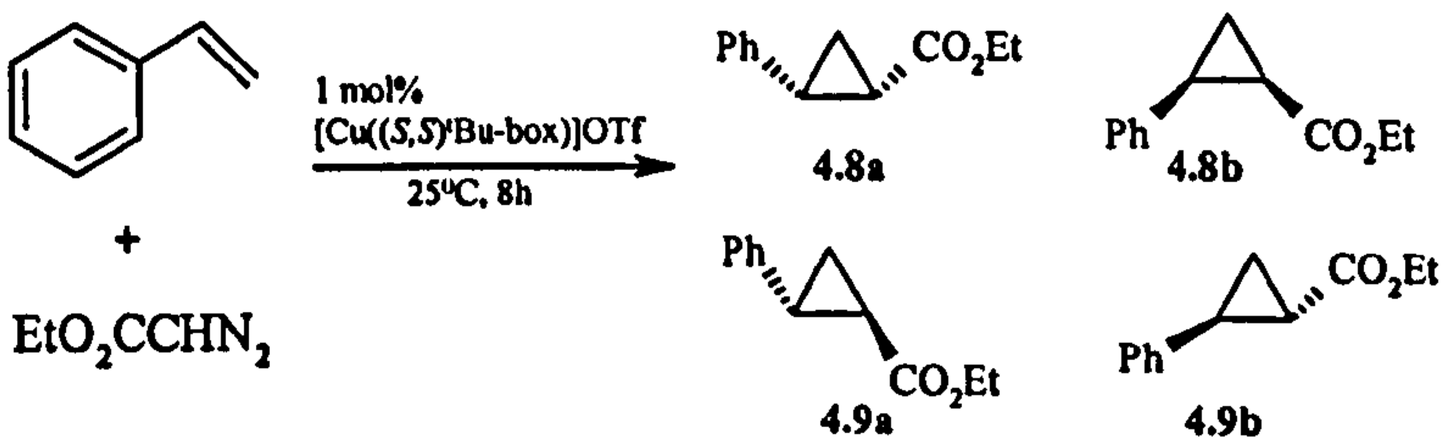
More importantly, the use of imidazolium based ionic liquids for immobilisation of [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ and their use in cyclopropanation of styrene has been reported and it was found that the nature of the cation and anion of the ionic liquid affected the performance of the catalysts.[496] In that case, the ILs used were: EMIM[$NTf_2$], EMIM[$BF_4$], and $Oct_3NMe[NTf_2]$. EMIM[$NTf_2$] displayed the best results in terms of

yield, stereoselectivity and enantioselectivity, (62 %, 61: 39 *trans* / *cis*, 86: 84 *ee*, respectively). Our results in BMIM-based ILs are described below.[497]

### *4.4.2* Results and Discussion

Evans *et al.* reported that cyclopropanation of styrene with ethyl diazoacetate in chloroform catalysed by [Cu((*S*,*S*)$^t$Bu-box)](OTf) (Scheme 4.8) gave the *trans* and *cis* cyclopropanes in a 73: 27 ratio and 99 and 97% *ee* respectively.[527]

**Scheme 4.8. The cyclopropanation of styrene with ethyl diazoacetate**




Under our conditions the *trans* : *cis* selectivity remains the same, though the *ee*'s, 89 and 96 % respectively, are slightly lower. The only variation to the literature conditions has been to add the ethyl diazoacetate to the styrene and catalyst at 10 °C instead of 0 °C before warming to 25 °C and to use a lower excess of styrene (1.5 equivalents with respect to diazoacetate rather than 5 equivalents). These changes were introduced to allow a direct comparison with the reactions carried out in ionic liquids. Styrene is not appreciably soluble in the ionic liquids, hence these reactions are biphasic and at 0 $^0$C the viscosity of the ionic liquids makes magnetic stirring rather inefficient, however, much better mixing occurs at 10 $^0$C. The catalyst solutions were prepared in chloroform before dissolution in the ionic liquid and then removal of the chloroform under vacuum. After the reaction the products were extracted from the ionic liquid with ether and filtered through silica. The yield and regioselectivity were analysed by GC and the enantiomeric excess was determined by GCMS after conversion to the (*R*)-1-phenylethylamides.[527] The results of the cyclopropanation are shown in Table 4.7.

**Table 4.7 Cyclopropanation of styrene with ethyl diazoacetate catalysed by [Cu((*S*,*S*)$^t$Bu-box)](OTf)**

| Solvent | Yield /%[a] | Stereoselectivity /% | Enantioselectivity /%[b] | |
|---|---|---|---|---|
| | | *Trans* : *Cis* | *Trans* | *Cis* |
| $CHCl_3$ | 59 | 73 : 27 | 89 | 96 |
| BMIM[OTf] | 53 | 76 : 24 | 97 | 95 |
| BMIM[$PF_6$] | 47 | 75 : 25 | 95 | 91 |
| BMIM[$NTf_2$] | 45 | 63 : 37 | 94 | 93 |
| BMIM[$BF_4$] | 61 | 75 : 25 | 95 | 89 |
| BMIM[$BF_4$]/[Cl][c] | <1 | - | - | - |
| BMIM[$BF_4$]/[Br][c] | <1 | - | - | - |

[a]Determined by GC using decane as an internal standard. [b]Determined by chiral GC after conversion to the 1-phenylethylamide; 16*S* was the major *trans* enantiomer and 17*S* the major *cis* enantiomer based on retention times of the 1-phenylethylamides. [c]Contains 5 % BMIM[X] (X = Cl, Br) w.r.t. the IL.

As can be seen the yields are broadly similar in all the ionic liquids and in chloroform. The stereoselectivity and enantioselectivity are similar in all the ionic liquids and in chloroform, though the stereoselectivity is somewhat less in the $NTf_2$ liquid. A reduction in the stereoselectivity in EMIM[$NTf_2$] was noted previously.[496] However, the yields and enantioselectivities are significantly higher than those (3-50% yield, 0-85% *ee*) observed previously[496] for the same reaction and catalyst in EMIM[$BF_4$], EMIM[$NTf_2$] and $Oct_3NMe[NTf_2]$. Notably in the previous study the catalyst was prepared from copper(II) triflate rather than copper(I) and was added to the ionic liquid as a solid. Also in the previous study, use of EMIM[$BF_4$] led to very low yields and no enantioselectivity (see below). In that case the authors noted that when bis(oxazoline) copper complexes (chloride or triflate) were added to EMIM[$BF_4$] the solution became a deep red colour and some solid precipitated. In our hands addition of [Cu((*S*,*S*)$^t$Bu-box)](OTf) to BMIM[$BF_4$] gave a clear blue homogeneous solution as with all the other ILs. Halide anions are expected to coordinate more strongly to copper than triflate and hence reduce or even stop catalytic activity. Similar adverse effects of halide impurity on catalysis in ionic liquids have been noted previously.[498,499] To investigate this possibility we examined the effect of added BMIM[X] (X = Cl, Br) on the catalysis. Addition of the catalyst to a solution of BMIM[$BF_4$] containing BMIM[Cl] (5 % with respect to BMIM[$BF_4$]) gave a homogeneous yellow-green solution which was inactive as a cyclopropanation catalyst though it did lead to decomposition of the ethyl diazoacetate. If 5 % BMIM[Br] was used

a deep red / brown solution was formed when the catalyst was added, this was also catalytically inactive for cyclopropanation. Thus, we suggest that the poor results observed previously for copper catalysed cyclopropanation in EMIM[$BF_4$] are due to the presence of EMIM[Br] impurity in the ionic liquid. The EMIM[$BF_4$] used was made from EMIM[Br] and $NaBF_4$ and filtered through celite to remove the NaBr formed.[496] Seddon and coworkers have shown, at least for chloride salts, that this procedure is inefficient at removing all the unreacted dialkylimidazolium halide.[118] We have extracted BMIM[$BF_4$] with chilled water (5 °C) which gives much lower levels of halide impurity.

Another important issue with the use of ionic liquids is the possibility of recycling the catalyst solution. It was noted that using BMIM[OTf] and BMIM[$NTf_2$], some leaching of the catalyst occurred in extraction of the products as judged by the colour transferred to the ether layer, there was also a faint blue spot on the baseline of the tlc plates used in purification. BMIM[$BF_4$] and BMIM[$PF_6$] showed minimal leaching and since the yields were better in the $BF_4$ liquid we chose that for experiments on recycling and reusing the catalyst.

**Table 4.8 Repeated cyclopropanation reactions of styrene with ethyl diazoacetate catalysed by [Cu((*S*,*S*)$^t$Bu-box)](OTf) in BMIM[$BF_4$]**

| Run | Yield /%[a] | Stereoselectivity /% | Enantioselectivity /%[b] | |
|---|---|---|---|---|
| | | *Trans* : *Cis* | *Trans* | *Cis* |
| 1 | 88 | 75 : 25 | 97 | 94 |
| 2 | 88 | 75 : 25 | 95 | 93 |
| 3 | 90 | 73 : 27 | 93 | 91 |
| 4 | 85 | 72 : 28 | 98 | 98 |
| 5 | 69 | 65 : 35 | 76 | 76 |
| 6 | 71 | 66 : 34 | 81 | 78 |
| 7 | 55 | 69 : 31 | 76 | 72 |
| 8 | 51 | 69 : 31 | 77 | 78 |

[a]Determined by GC using decane as an internal standard. [b]Determined by chiral GC after conversion to the 1-phenylethylamide; 16*S* was the major *trans* enantiomer and 17*S* the major *cis* enantiomer based on retention times of the 1-phenylethylamides.

To optimise the yield we wished to minimise the levels of diethyl maleate and fumarate formed by carbene dimerisation. This is often done by increasing the concentration of the styrene. However due to the limited solubility of styrene in the ionic liquids we chose to reduce the rate of addition of the ethyl diazoacetate (5 h) and to keep the reaction mixture at 10 °C throughout this period and lower the concentration of the catalyst by using twice the amount of ionic liquid. Using these conditions gave increased yields of products. The results of performing the reaction eight times in the same batch of ionic liquid are displayed in Table 4.8. As can be seen for the first four runs the yield and enantioselectivity are comparable. After the fourth run, the yield drops with a slight reduction in stereoselectivity and enantioselectivity.

In conclusion we have shown that copper catalysed cyclopropanation can be carried out in ionic liquids with high yield and enantioselectivity. The yields, stereoselectivity and enantioselectivity are comparable to those reported in conventional solvents and better than those previously reported for BMIM-ILs. In this case, there is no marked effect in changing the IL anion. Using BMIM[$BF_4$] the catalyst solution can be recycled at least four times before there is a significant drop in yield. The purity of the ionic liquids has a marked effect on the catalysis. Particular care should be taken in the purification of hydrophilic ionic liquids prepared by metathetical anion exchange to ensure that all the dialkyl imidazolium halide is removed.

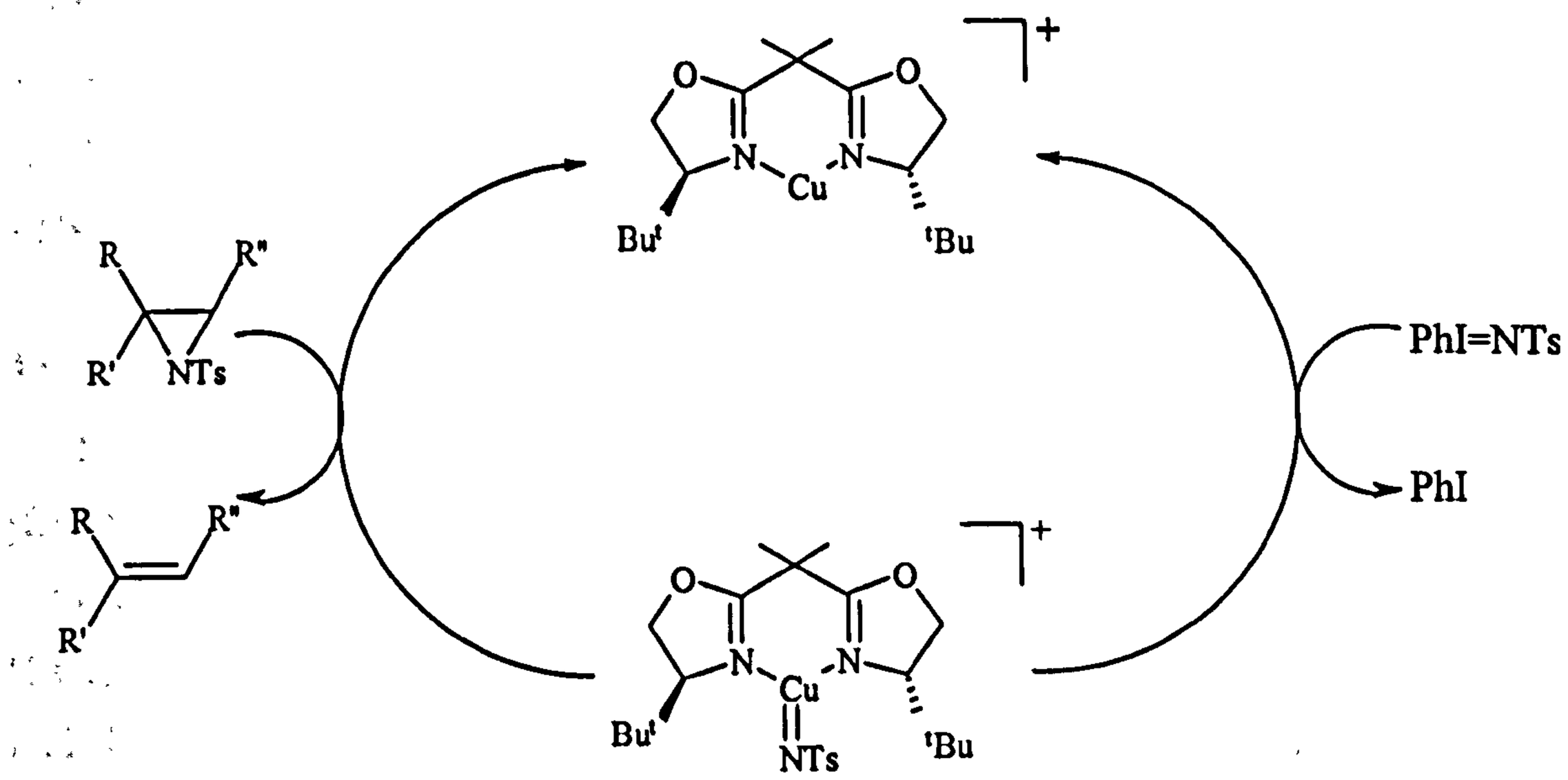
## 4.5 Asymmetric Aziridination

### *4.5.1* Introduction

Another group-transfer reaction that is related to cyclopropanation, is the aziridination of alkenes. Aziridines are highly versatile synthetic precursors and have been used as synthons for chiral amines, amino acids, amino alcohol, alkaloids, and β-lactam antibiotics. A number of routes to chiral nonracemic aziridines have been developed using carbohydrates, hydroxyl acids, epoxides, and 1,2-diols, as well as some enzymatic methods.[500] These include ring-closure reactions of 1,2-amino alcohols or their derivatives, with optically active starting materials derived from amino acids;[501] ring opening of chiral epoxides with sodium azide and subsequent treatment with triphenylphosphine;[502] synthesis from *N*-benzylideneaniline and an anion derived from chiral 1-chloroalkyl toly-*p*-sulphoxides;[503] or by addition of dimethyloxosulphonium iodide to (*S*)-(+)–*N*-tolyl-*p*-sulphonyl phenylimine.[504] However, the use of aziridines as

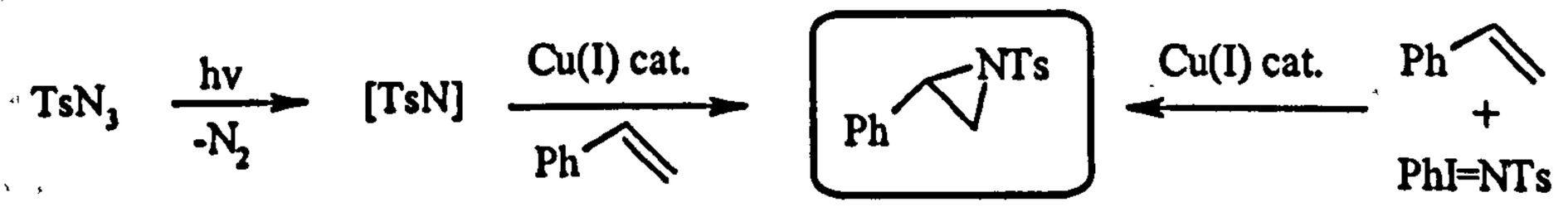
chiral building blocks in synthesis has been restricted because their preparation in optically active form typically requires multiple-step transformation of available starting materials. The development by Evans *et al.*. of the copper catalysed aziridination of a wide range of alkenes using PhI=NTs (N-(p-toluenesulphonyl)iminophenyliodinane) as the nitrene source was a breakthrough in this area.[505,506,507] Further developments led to catalytic enantioselective reactions with the Evans group using chiral nonracemic bis(oxazoline) ligands.[508]

It is assumed that this reaction is mechanistically related to the copper-catalysed diazo-transfer cyclopropanation. As such, the intervention of a metal complexed nitrenoid intermediate has been proposed as the principle mode of action (see Scheme 4.9).




**Scheme 4.9 Mechanism proposed by Jacobsen for the aziridination of alkenes. [Adapted from ref 511]**

The most compelling evidence for the intermediacy of a discrete Cu-nitrenoid intermediate was obtained from studies using tosyl azide ($TsN_3$) as a stoichiometric nitrene source. Under photochemical conditions, $TsN_3$ is known to extrude dinitrogen to generate a reactive intermediate.[509,510] In the presence of catalytic amounts of a copper(I) complex, the photochemical reaction of $TsN_3$ with styrene afforded aziridine with the same enantioselectivity obtained in the catalytic aziridination reaction (Scheme 4.10).[511]



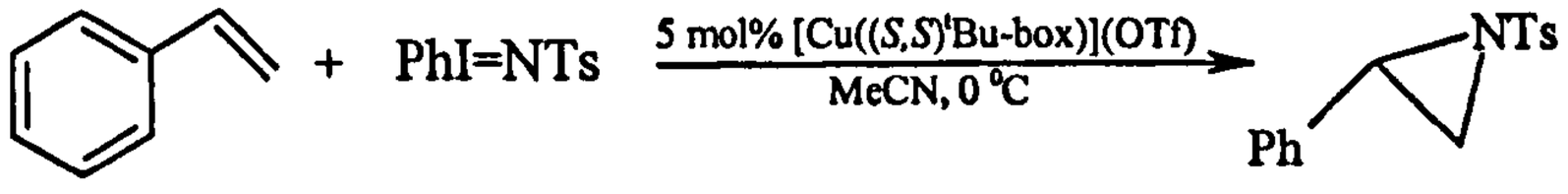

41 % *ee*

**Scheme 4.10**

The aziridination of styrene is inversely dependent on solvent polarity. Excepting styrene, a comprehensive screening of alkene substrates and reaction solvents has indicated that dipolar aprotic solvents such as MeCN and $MeNO_2$ are optimal for this reaction, as reaction rates are much faster than in less polar media (PhMe, $CH_2Cl_2$).[512] Under these latter conditions, the long reaction times necessary to complete the reaction lead to competition between alkene aziridination and decomposition of the nitrene precursor to *p*-toluenesulfonamide. Control experiments in the absence of the alkene substrate indicate that PhI=NTs decomposes rapidly to *p*-toluenesulfonamide (< 5 min, 25 $^0$C) in MeCN using Cu(I) catalysis. It is assumed that the solvent is serving as the proton source.[512] Hence, hydroxylic solvents cannot be used.[513] Also, the oxidation of DMSO by PhI=NTs has been reported,[514] PhI=NTs reacts readily with THF in the absence of metals to afford the α-insertion product.[507] To our knowledge, there have been no reports of aziridine synthesis in ionic liquids. Results of the aziridination of styrene and *trans*-β-methyl styrene in RTILs are discussed below.

### 4.5.2 Results and Discussion

The aziridination of styrene with PhI=NTs was investigated using 5 mol% [Cu((*S*,*S*)$^t$Bu-box)](OTf) as catalyst. Interestingly both Cu(OTf) and $Cu(OTf)_2$ may be used as precatalysts with identical results. (It is known that treatment of a solution of [Cu(*S*,*S*)$^t$Bu-box](OTf) with PhI=NTs in MeCN affords a copper species that is indistinguishable by ultraviolet-visible (UV-vis) spectroscopy to a solution derived from [Cu(*S*,*S*)$^t$Bu-box]$(OTf)_2$).[438]




**Scheme 4.11 The aziridination of styrene**

PhI=NTs was the limiting reagent and styrene was used in excess. From a practical standpoint, this reaction is subject to many of the same limitations as cyclopropanation. Decomposition of the iodinane to toluenesulphonamide is competitive necessitating a high relative concentration of alkene. In all cases the reactions were heterogeneous and biphasic. The reaction mixtures were stirred at 25 $^0$C for 8 h. After the reaction the products were extracted from the ionic liquid with ether and filtered through silica. The yield was determined by $^1$H NMR using ferrocene as an internal standard and the

enantiomeric excess was determined by chiral hplc after purification of the aziridine by preparative tlc. The results are shown in Table 4.9.

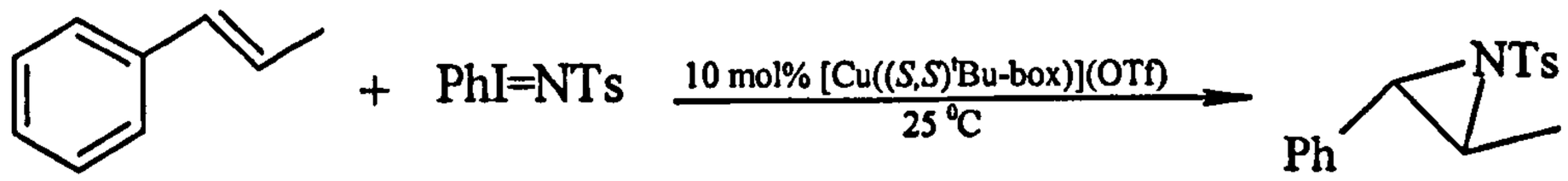
**Table 4.9 [Cu((*S*,*S*)$^t$Bu-box)](OTf) catalysed aziridination of styrene in ILs**

| Solvent | Yield /%[a] | Enantioselectivity /%[b] |
|---|---|---|
| Styrene* | 85 | 60 |
| BMIM[OTf] | 60 | 3 |
| BMIM[$PF_6$] | 60 | 4 |
| BMIM[$NTf_2$] | 65 | 5 |
| BMIM[$BF_4$] | 68 | 3 |

*R enantiomer is predominent[438] [a] Based on $^1$H NMR integration using ferrocene as an internal standard [b] Determined by HPLC on a Chiralcel OJ column (hexane/isopropanol 95:5)

Aziridination of styrene is best performed using a large excess of styrene *i.e.* using it as a solvent for the reaction for which an 89 % yield and 63 % *ee* is reported.[438] Our results for this experiment which was performed as a control are similar (85 % yield, 60 % *ee*). However, the reactions in the ILs showed slightly lower yields and negligible enantioselectivity. The higher yield in styrene could be because the alkene substrate is in large excess whereas when an IL is employed, there is a lower concentration of styrene and the reactions are biphasic. The *ee* is consistent with the finding that the aziridination of styrene with PhI=NTs is inversely dependent on solvent polarity: benzene (57 % *ee*), $CH_2Cl_2$ (36 % *ee*), MeCN (6 % *ee*) and RTILs (~4 % *ee*).

Although the aziridination of styrene requires low polarity media, these conditions cannot be extrapolated back to other alkene substrates. For example, *trans*-β-methyl styrene requires high polarity media for high selectivities with acetonitrile being the solvent of choice, MeCN (53 % *ee*), $CH_2Cl_2$ (33 % *ee*), benzene (15 % *ee*).[438] Mechanistically, these results are intriguing but unexplained. Therefore the aziridination of *trans*-β-methyl styrene was investigated in ILs under the same conditions, to see whether the increasing polarity of the solvent would be reflected in the enantioselectivity observed. The results are given in Table 4.10.




**Scheme 4.12 The aziridination of *trans*-β-methyl styrene**

**Table 4.10 [Cu((*S*,*S*)$^t$Bu-box)](OTf) catalysed aziridination of *trans*-β-methyl styrene in ILs**

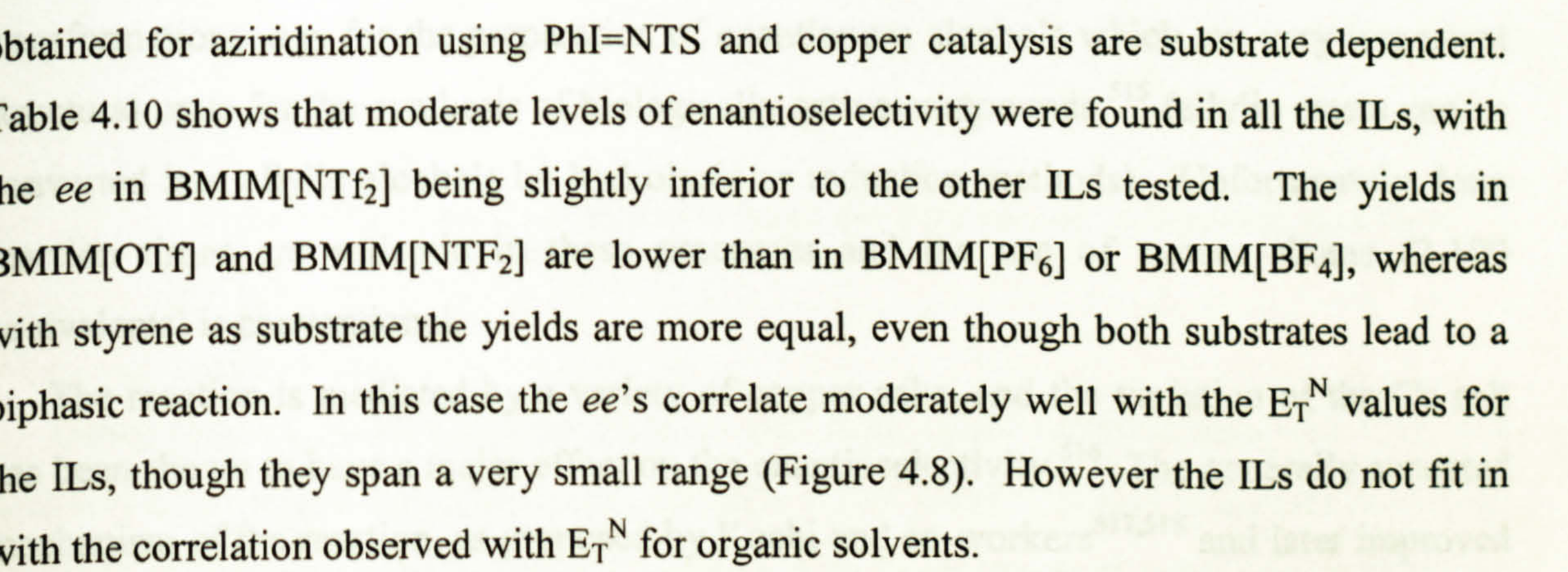
| Solvent | Yield /%[a] | Enantioselectivity /%[b] |
|---|---|---|
| MeCN | 58 | 57 |
| BMIM[OTf] | 43 | 49 |
| BMIM[$PF_6$] | 51 | 48 |
| BMIM[$NTf_2$] | 41 | 45 |
| BMIM[$BF_4$] | 65 | 50 |

[a] Based on $^1$H NMR integration using ferrocene as an internal standard

[b] Determined by HPLC on a Chiralcel AS column (hexane/isopropanol 98:2)

In this case, there was a vast improvement in enantioselectivity confirming that the results obtained for aziridination using PhI=NTS and copper catalysis are substrate dependent. Table 4.10 shows that moderate levels of enantioselectivity were found in all the ILs, with the *ee* in BMIM[$NTf_2$] being slightly inferior to the other ILs tested. The yields in BMIM[OTf] and BMIM[$NTF_2$] are lower than in BMIM[$PF_6$] or BMIM[$BF_4$], whereas with styrene as substrate the yields are more equal, even though both substrates lead to a biphasic reaction. In this case the *ee*'s correlate moderately well with the $E_T^N$ values for the ILs, though they span a very small range (Figure 4.8). However the ILs do not fit in with the correlation observed with $E_T^N$ for organic solvents.

**Figure 4.8 The affect of solvent polarity ($E_T^N$) on enantioselectivity for the [Cu((*S*,*S*)$^t$Bu-box)]OTf catalysed aziridination of *trans*-B-methyl styrene**




Although, using MeCN gave a slightly better *ee*, the yield was slightly lower than that achieved in BMIM[$BF_4$], which shows that either of these two could be considered the optimum solvent for this reaction. Using an IL, the catalyst solution could also be recycled

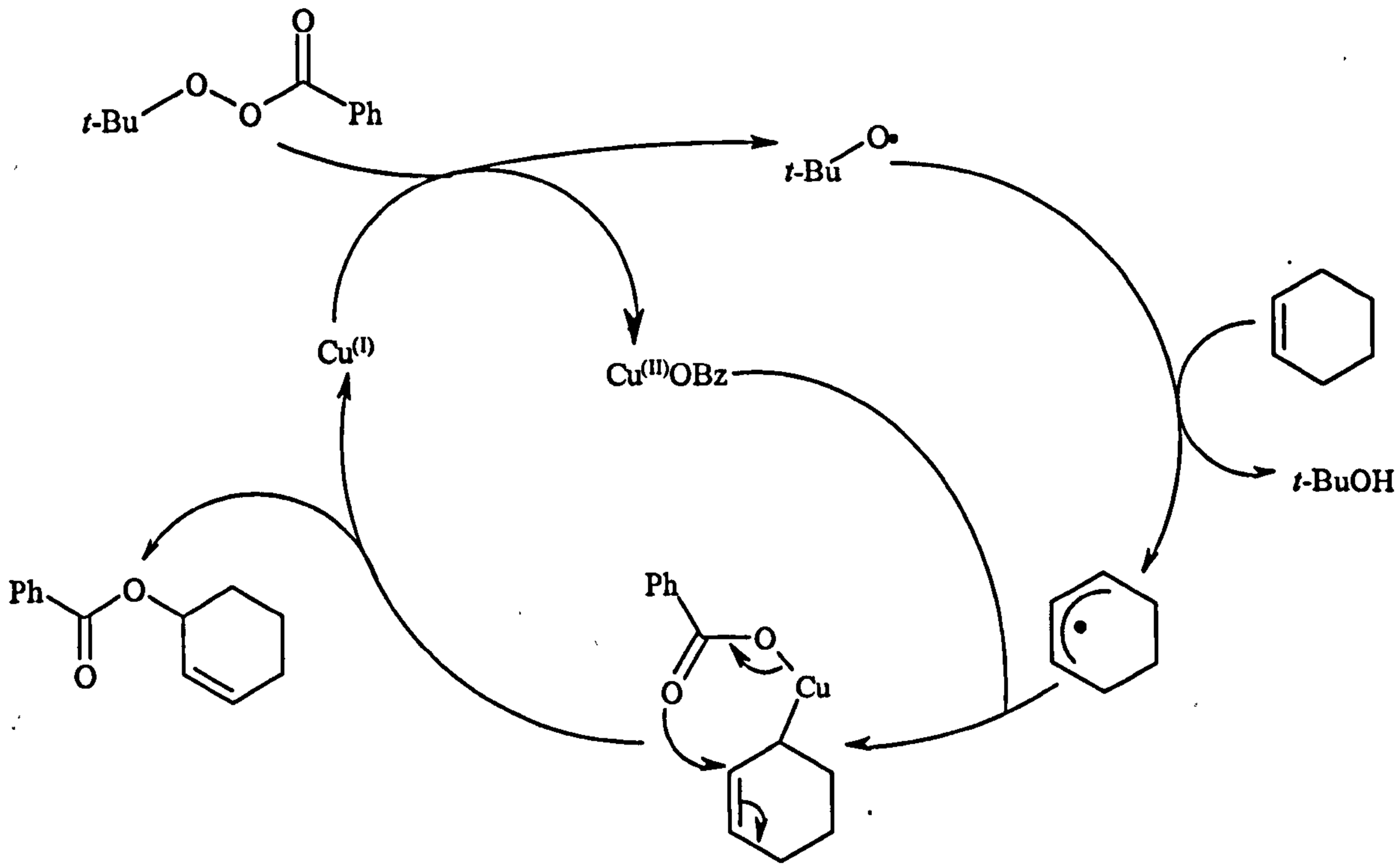
after extraction of product with ether, by dissolving in $CH_2Cl_2$, filtering off the unreacted PhI=NTs, removing the $CH_2Cl_2$ under vacuum and drying. Addition of fresh substrates to BMIM[$BF_4$] gave 64, 64, 63 % yield in subsequent runs.

## 4.6 ASYMMETRIC ALLYLIC OXIDATION

### *4.6.1* Introduction

Asymmetric allylic oxidation using peresters and copper catalysis continues to attract considerable interest. The ability to convert simple alkenes into allylesters is an important transformation with many potential synthetic applications. Allylic oxidation, unlike epoxidations and hydroxylations, maintains the alkene in the product for subsequent transformations; *e.g.* for the preparation of enantiopure alcohols which are very important structural units for the synthesis of biologically active compounds,[515] (allylic esters can be converted into allylic alcohols by hydrolysis or reduction methods). Unfortunately, long reaction times are endemic in these processes and the use of excess alkene (2-100 equivalents) is conventional.

The reaction is mediated by a variety of copper salts, and the variation of the Cu salt has been shown to have a major effect on the enantioselectivity.[516] The generally accepted mechanism of the reaction, as proposed by Kochi and co-workers[517,518] and later improved by Beckwith and Zavitsos[519], is illustrated in Scheme 4.13. Cuprous ion reduces the perbenzoate to a Cu(II) benzoate species and free *t*-BuO radical. The *t*-butoxy radical abstracts an allylic, prochiral hydrogen atom generating an allyl radical that combines with the cupric salts to from an allylcopper(III) species. Reductive elimination with transposition of the allyl moiety generates the allylic ester product (Scheme 4.13).

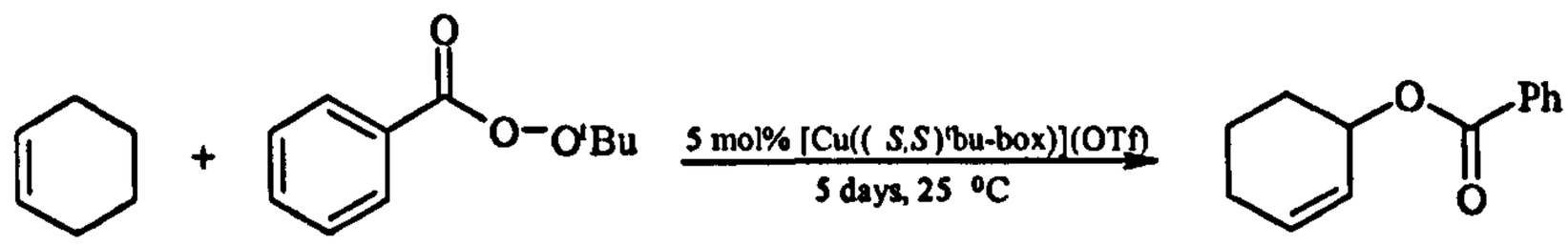



**Scheme 4.13 General mechanism of the copper-catalysed allylic oxidation of alkenes (Kharasch-Sosnovsky reaction)**

Using copper(I) complexes prepared in situ from chiral bisoxazolines and Cu(OTf), with *tert*-butyl perbenzoate as oxidant, optically active 2-cycloalkenyl benzoates have been obtained in moderate to good yields.[520] Electron deficient peresters have been synthesised with the idea that a weaker perester bond would lead to a more rapid bond homolysis, increasing the formation of the copper(II) benzoate species and *tert*-butoxy radical which is assumed to be the rate limiting step.[521] This has had limited success as the reaction still requires up to a week for a moderate yield. The use of copper with other chiral dinucleating ligands has been investigated, and although rate enhancements were observed, low enantioselectivity and the formation of a side product was noted.[522] Previously, there have been no reports of asymmetric allylic oxidations in ILs, and as ILs have shown rate enhancement in many other types of reaction, we investigated whether the ionic environment may provide any beneficial effects.

## 4.6.2 Results and Discussion

The allylic oxidation of cyclohexene with *tert*-butyl perbenzoate was examined using 5 mol% [Cu((*S,S*)$^t$Bu-box)](OTf) as catalyst. (Scheme 4.14)




**Scheme 4.14**

The catalyst solutions were prepared as before. The *tert*-butyl perbenzoate was added, followed by 1.5 equivalents of cyclohexene, and then stirred for 5 days at ambient temperature. After the reaction the products were extracted from the ionic liquid with ether and filtered through silica. It was noted that reactions performed in BMIM[$PF_6$] and BMIM[$BF_4$] were biphasic, whereas the reactions in BMIM[OTf] and BMIM[$NTf_2$] were initially biphasic but became homogeneous as the reaction progressed. The yield was determined by GC and the *ee* was determined by chiral hplc. The results are summarised in the table below.

**Table 4.11 The [Cu((*S,S*)$^t$Bu-box)](OTf) catalysed allylic oxidation of cyclohexene**

| Solvent | Conversion /%[a] | Enantioselectivity /%[b] |
|---|---|---|
| $CH_3CN$ | 52 | 44 |
| BMIM[OTf] | 42 | 43 |
| BMIM[$PF_6$]* | 47 | 33 |
| BMIM[$NTf_2$] | 34 | 55 |
| BMIM[$BF_4$]* | 54 | 23 |

[a]Based on an assay against vinyl 4-tert-butyl benzoate [b]Determined by HPLC on a Chiralcel OJ column (hexane/isopropanol 1000:1) *Biphasic (at the end of the reaction)

Previously this reaction has been reported to give a 68 % yield of product with 60 % *ee* after a week long reaction period at 23 $^0$C, using a four-fold excess of cyclohexene.[520] The 52 % yield obtained under the same conditions is comparable as we used a shorter reaction time (5 days compared to 7 days). The reaction was also performed using 5 mol% [Cu($^i$Pr-pybox)](OTf) for a reaction period of three days, and the following results were found:

**Table 4.12 The [Cu($^i$Pr-pybox)](OTf) catalysed allylic oxidation of cyclohexene**

| Solvent | Conversion /%[a] | Enantioselectivity /%[b] |
|---|---|---|
| $CH_3CN$ | 61 | 67 |
| BMIM[OTf] | 48 | 64 |
| BMIM[$PF_6$]* | 40 | 64 |
| BMIM[$NTf_2$] | 32 | 71 |
| BMIM[$BF_4$]* | 49 | 33 |

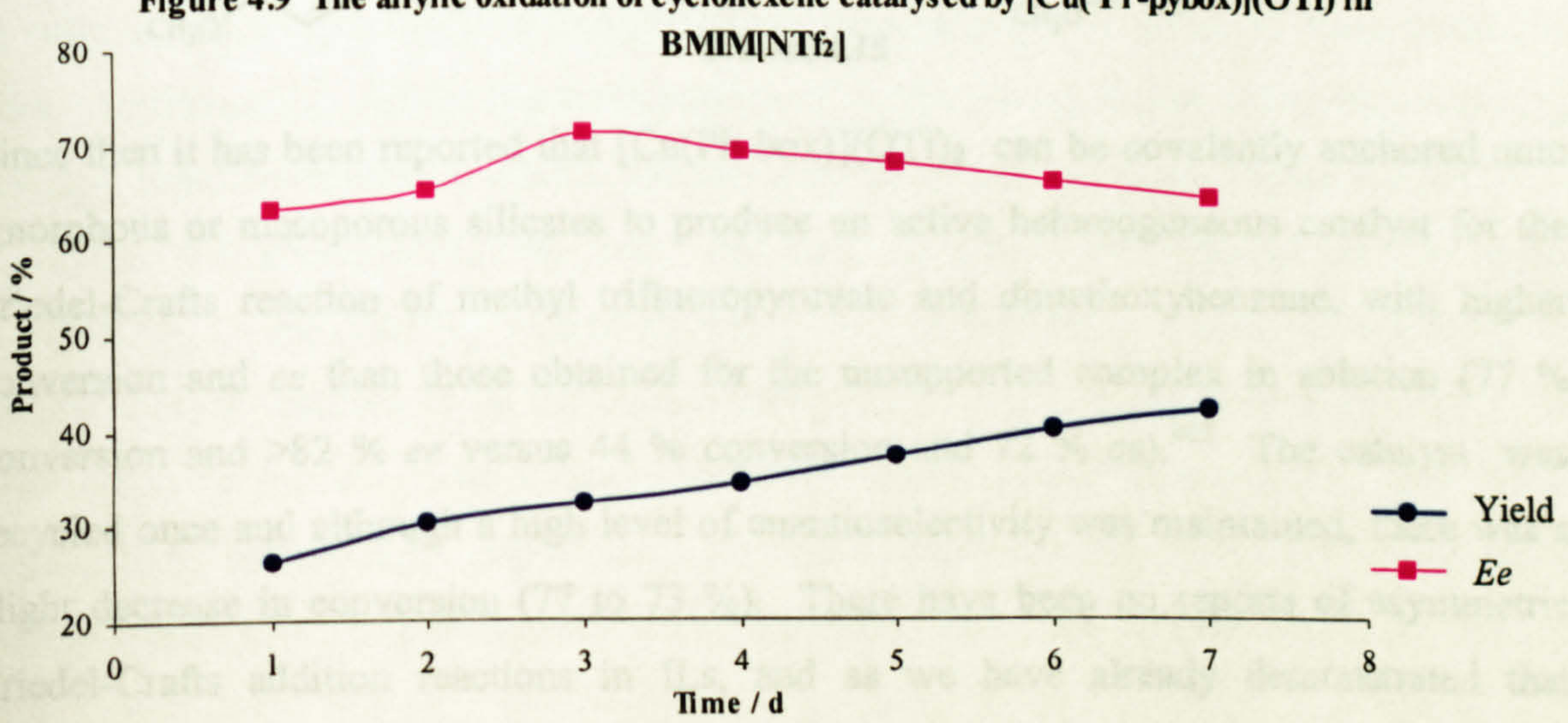
[a] Based on an assay against vinyl 4-tert-butyl benzoate

[b] Determined by HPLC on a Chiralcel OJ column (hexane/isopropanol 1000:1)

Both catalysts display similar results *i.e.* the yield is highest in BMIM[$BF_4$] and lowest in BMIM[$NTf_2$], with the opposite order for enantioselectivity. In general, biphasic reactions (BMIM[$PF_6$] and BMIM[$BF_4$]), gave greater yields but lower enantioselectivity. Clearly BMIM[$NTf_2$] provides the highest enantioselectivity for this Cu(I)-catalysed reaction but the conversion of substrate was quite low. Therefore a longer reaction time was tried to increase the product yield and examine whether enantioselectivity was maintained. The *ee* in BMIM[$NTf_2$] was recorded as the reaction period progressed and it was found that an enantioselectivity of 69 % after 4 days using [Cu($^i$Pr-pybox)](OTf) had dropped to 64 % after 1 week (with only a 10 % increase in yield). (Figure 4.9). This could mean that the product is racemising at longer reaction times, so we observe formation of the second enantiomer.

The effect of temperature was investigated by repeating the reaction at 50 $^0$C, in another attempt to increase the rate of reaction and hence yield of product. However, it was found that the increase in yield was limited by the formation of unidentifiable side

**Figure 4.9 The allylic oxidation of cyclohexene catalysed by [Cu($^i$Pr-pybox)](OTf) in BMIM[$NTf_2$]**

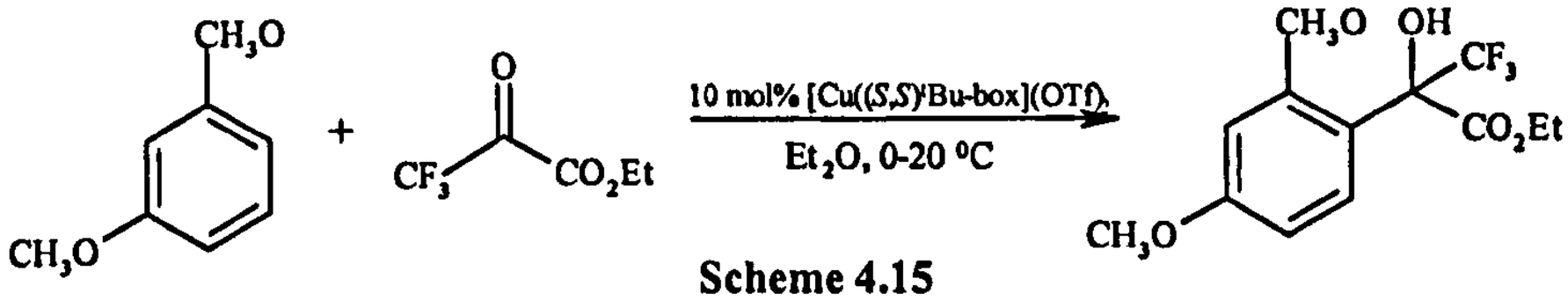


products at higher temperatures. Using BMIM[$NTf_2$], a product yield of 54 % was obtained after 1 day but with a reduced *ee* of 51 % and the yield didn't improve further with time. A low temperature appears necessary to maintain higher levels of enantioselectivity, even though the yield is rather low. In this case ILs didn't provide any benefit over MeCN which gives moderate levels of yield and *ee*.

## 4.7 ASYMMETRIC FRIEDEL-CRAFTS REACTION

### *4.7.1* Introduction

Organofluorine compounds play an important role in several areas and the addition of aromatic compounds to carbonyl compounds, the Friedel-Crafts reaction, leads to products widely used in academia and industry.[523] Such a reaction provides a simple and attractive method for the formation of optically active aryl-substituted compounds from easily available starting materials. These reactions are normally performed in an achiral fashion catalysed by Lewis acids,[524] and only very few catalytic enantioselective versions have been developed.[525] Jϕrgensen recently discovered a copper-catalysed enantioselective method for the formation of aromatic hydroxy-trifluoromethyl ethyl esters and noted that electron-donating substituents on the arene are necessary for the reaction to proceed to give moderate yields.[457] For example, the [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ catalysed Friedel-Crafts reaction of dimethoxybenzene with ethyl trifluoropyruvate proceeds to give a 56 % yield of product, 2-(2,4-Dimethoxyphenyl)-3,3,3-trifluro-2-hydroxypropionic acid ethyl ester, with 86 % *ee* in $Et_2O$.[457] (Scheme 4.15)




**Scheme 4.15**

Since then it has been reported that [Cu(Ph-box)](OTf)$_2$ can be covalently anchored onto amorphous or mesoporous silicates to produce an active hetereogeneous catalyst for the Friedel-Crafts reaction of methyl trifluoropyruvate and dimethoxybenzene, with higher conversion and *ee* than those obtained for the unsupported complex in solution (77 % conversion and >82 % *ee* versus 44 % conversion and 72 % *ee*).[462] The catalyst was recycled once and although a high level of enantioselectivity was maintained, there was a slight decrease in conversion (77 to 73 %). There have been no reports of asymmetric Friedel-Crafts addition reactions in ILs, and as we have already demonstrated that

[Cu((*S,S*)$^t$Bu-box)](OTf)$_2$ can be successfully immobilised in ILs, we were interested to know whether the same / better results could be achieved in ILs and the feasibility of recycling the catalyst. Hence the Friedel-Crafts addition of ethyl trifluoropyruvate to dimethoxybenzene (Scheme 4.15) was examined.

## 4.7.2 Results and Discussion

The catalyst solutions were prepared as before from Cu(OTf)$_2$, the ethyl trifluoropyruvate was added and the reaction mixture cooled to 0 $^0$C; 1.1 equivalents of dimethoxybenzene was added and the homogeneous reaction mixture was allowed to warm to room temperature and stirred for 48 h. The conversion was determined by GC and the *ee* was determined by chiral hplc. The results are shown in the Table 4.13.

**Table 4.13 The [Cu((*S,S*)$^t$Bu-box)](OTf)$_2$ catalysed Friedel-Crafts addition in ILs**

| Solvent | Conversion / %[a] | Enantioselectivity / %[b] |
|---|---|---|
| $Et_2O$ | 52 | 87 |
| BMIM[OTf] | 72 | 74 |
| BMIM[$PF_6$] | 70 | 59 |
| BMIM[$NTf_2$] | 76 | 58 |
| BMIM[$BF_4$] | 69 | 19[*] |

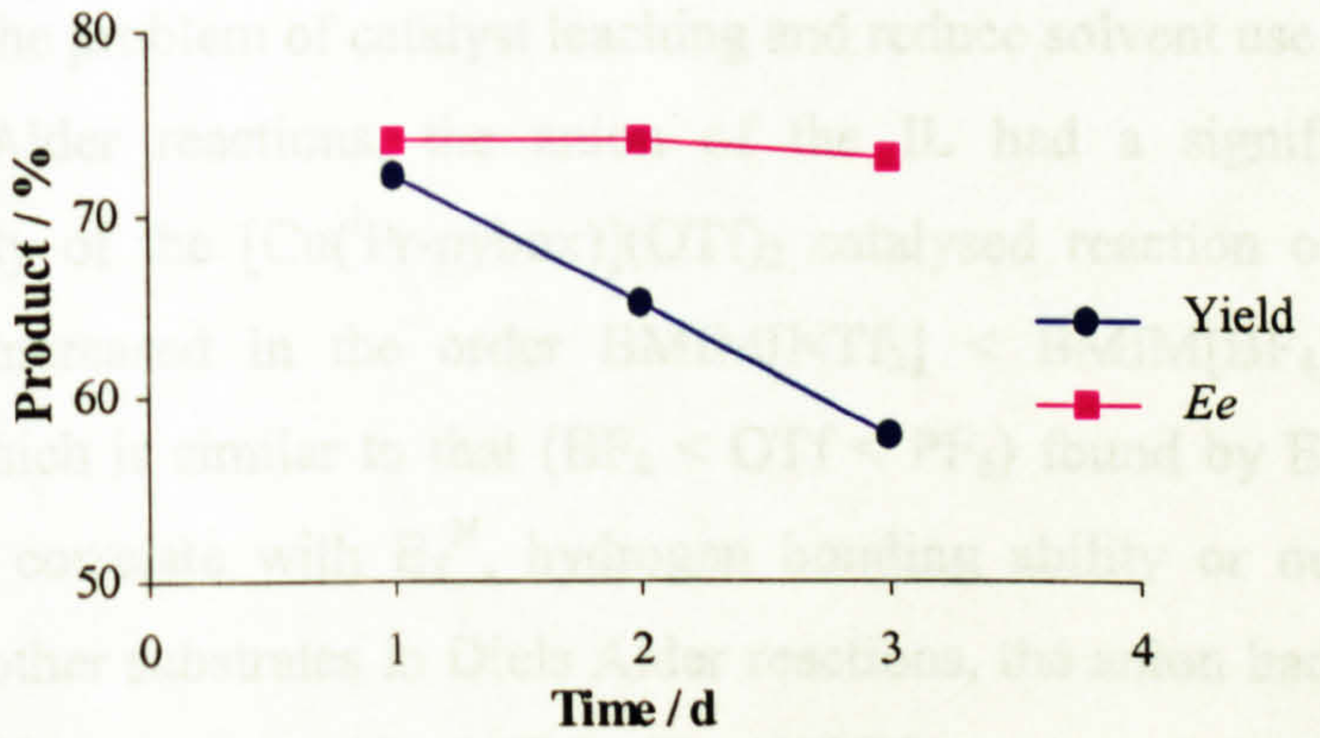
[a] Conversion of ethyl trifluoropyruvate /% [b] Determined by HPLC on a Chiralcel AD column (hexane/isopropanol 95:5) [*]Enantiomer of opposite stereochemistry (average of two runs)

Entry 1 in Table 4.13 shows that 52 % conversion and 87 % *ee* of product were observed in ether which compare well to those reported previously (56 % yield, 86 % *ee* under the same conditions).[457] All the reactions performed in ILs gave a higher conversion showing that the ionic environment affects the catalytic efficiency of [Cu((*S,S*)$^t$Bu-box)](OTf)$_2$. However, the enantioselectivity was less than in ether and reduced in the order BMIM[OTf] > BMIM[$PF_6$] ≈ BMIM[$NTf_2$] >> BMIM[$BF_4$]. This is surprising as BMIM[OTf] is reported to be the most nucleophilic[162] and one may therefore expect the $OTf^-$ anion to interact more strongly with the copper centre than the $PF_6^-$ and $NTf_2^-$ counterions. Interestingly, BMIM[$BF_4$] gave 69 % conversion to product of the opposite stereochemistry. To our knowledge, there have been no reports on ionic liquids

influencing the stereochemical outcome in organic synthesis and we cannot currently offer any explanation for this observation.

As BMIM[OTf] displayed the highest conversion and *ee* of product, this IL was chosen to examine whether the IL catalyst solution could be recycled. At the end of the first reaction, the products were extracted with ether and the IL dried under vacuum to remove any remaining traces of ether. The substrates were then added in the same fashion and the reaction mixture stirred for 48 h. The results for three consecutive runs are shown in Figure 4.10.

**Figure 4.10 Repeated Friedel-Crafts addition reaction of dimethoxybenzene and ethyl trifluoropyruvate catalysed by [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ in BMIM[OTf]**




A moderate decrease in the conversion was observed although the *ee* values remain high. Figure 4.15 illustrates that although the yield decreases by 14 % over three runs, the drop in enantioselectivity is negligible. The fact that the *ee* values of the reused IL catalyst solution are still very high points to the fact that deactivation is probably not caused by degradation of the ligand chirality and is probably due to a small amount of catalyst leaching into the ether during product extractions, which could be circumvented by employing other product extraction methods *e.g.* supercritical fluids. Overall it can be seen that immobilisation of the [Cu((*S*,*S*)$^t$Bu-box)](OTf)$_2$ complex in BMIM[OTf] provides a moderately effective means of being able to recycle the catalyst for the Friedel-Crafts addition reaction with results comparable to the best achieved previously for this reaction.[457] This prevents the need for a multi-step synthesis to heterogenise the catalyst onto a support to give similar results.[462]

## 4.8 CONCLUSION

We have demonstrated that copper bisoxazolines can be successfully immobilised in BMIM-based RTILS to provide high yields, selectivity and enantioselectivity in a number of carbn-carbon bond forming reactions. For example, the copper catalyst could be reused up to five times for the HDA reaction, four times for cyclopropanation, three times for aziridination, and three times for the Friedel Crafts addition with no loss in selectivity or enantioselectivity. However, product extraction using organic solvents lead to a slow decrease in yield over subsequent runs and therefore other methods of product isolation need to be considered in order to make recycling of the IL more efficient. Fortunately, recent research has shown that $scCO_2$ can be employed to extract products from ILs, which may overcome the problem of catalyst leaching and reduce solvent use.[30]

For Diels Alder reactions, the anion of the IL had a significant effect on the enantioselectivity of the $[Cu(^{i}Pr\text{-pybox})](OTf)_2$ catalysed reaction of methacrolein with Cp. The *ee* increased in the order $BMIM[NTf_2] < BMIM[BF_4] < BMIM[OTf] \approx BMIM[PF_6]$, which is similar to that ($BF_4 < OTf < PF_6$) found by Evans. However this order does not correlate with $E_T^N$, hydrogen bonding ability or nucleophilicity of the anions. Using other substrates in Diels Alder reactions, the anion had very little effect on yield or selectivity. For the $[Cu((S,S)Ph\text{-Box})](OTf)_2$ catalysed HDA reaction, we were unable to correlate the observed order of enantioselecivity ($BMIM[OTf] < BMIM[NTf_2] < BMIM[PF_6] < BMIM[BF_4]$) to the $E_T^N$, nucleophilicity/ basicity, or dipolarity of the ILs. Nor are we able to explain (using these measures) why $BMIM[BF_4]$ improves selectivity in the HDA *vs.* ene reaction by six-fold and gives the opposite enantiomer in the Friedel-Crafts addition reaction. In addition, although the *ee*'s observed in the different ILs for the aziridination of *trans*-β-methyl styrene correlated moderately well with the $E_T^N$ value of the IL, they did not fit in with the correlation observed with $E_T^N$ for organic solvents. The lack of correlation with polarity suggests that there may be a change in ion association in ILs compared with organic solvents. Additionally, as ionic liquids are among the most complex solvents, capable of most types of interaction (*e.g.* dispersive, π-π, n-π, hydrogen bonding, dipolar, ionic / charge-charge), there may be a number of different (in terms of type and strength) and often simultaneous solute-solvent interactions. For any given reaction, there will be dominant and less-substantial interactions. Therefore ILs cannot be treated as just "ordinary" solvents to explain these experimental observations. Indeed it is clear that results in ILs do not extrapolate from organic solvents based on any of the individual parameters considered.

We have noted that the purity of the ionic liquid has a marked effect on the yield and enantioselectivity observed in selected reactions. For example, the addition of BMIM[Cl] or *mim* to the Diels-Alder reaction led to a gradual decrease in yield and *ee*; on the other hand, addition of 5 mol% BMIM[Cl] or BMIM[Br] (w.r.t to the IL) led to an inactive catalyst for cyclopropanation. This emphasises that care needs to be taken in the purification of ILs, especially hydrophilic ILs prepared by metathetical anion exchange to ensure that all the dialkyl imidazolium halide is removed.

## 4.9 EXPERIMENTAL

Chemicals and solvents were purchased from commercial suppliers except the ionic liquids which were synthesised by anion exchange from BMIM[Cl][70] according to literature procedures (see Chapter 2)[308] and dried under vacuum at 60 °C prior to use. For thin layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualised by irradiation with UV light and / or by treatment with a solution of phosphomolybdic acid (25g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concentrated $H_2SO_4$ (60 mL), and $H_2O$ (940 mL) followed by heating. Flash Chromatography was performed by using silica gel Merck 60 (particle size 0.040-0.063 mm). GC was performed on a Perkin Elmer XL gas chromatograph, using BP10 (SGE) capillary columns (30 m x 0.25 mm) with hydrogen as carrier. Cydex-β (25m x 0.25mm) was used for determination of enantioselectivity. GCMS analysis was performed on a Perkin-Elmer TurboMass GCMS autosystem using a PE5 column (30 m x 0.25 mm). Chiral HPLC was performed on a Shimadzu SPD-6A chromatograph using chiralcel OD, AD, AS and OJ columns. $^1$H NMR and $^{13}$C NMR spectra were recorded either on a Bruker AMX 400, AMX 300 and AMX 250. Chemical shifts are given in $\delta$ relative to tetramethylsilane (TMS); the coupling constants $J$ are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature; TMS served as internal standard ($\delta$ = 0 ppm) for $^1$H NMR, and $CDCl_3$ was used as internal standard ($\delta$ = 77.0 ppm) for $^{13}$C NMR.

### 4.9.1 [Cu($^i$Pr-pybox)](OTf)$_2$ catalysed Diels Alder reaction of methacrolein and Cp

The methacrolein was distilled (35 $^0$C at normal pressure) and collected in a flask containing 0.5 mol% hydroquinone. The Cp was freshly cracked prior to use. The general procedure for the reaction is as follows.

To a 10 ml round bottom flask was added a solution of $Cu(OTf)_2$ (7.3 mg, 0.022 mmol) in dry $CH_2Cl_2$ (0.5 ml) and a solution of isopropyl[pyridine-bis(oxazoline)] (6.6 mg, 0.022 mmol) in dry $CH_2Cl_2$ (0.5 ml). The blue solution was left to stir at RT for 3 h. 1 ml IL was then added to the flask and the $CH_2Cl_2$ removed under vacuum. The flask was placed in the cold room for an hour to equilibrate at the external temperature of 2.5 $^0$C. This temperature was kept constant for all the reactions. Methacrolein (166 µl, 0.140 g, 2 mmol) was added to the flask followed by Cp (204 µl, 0.198 g, 3 mmol), and the reaction mixture was stirred for 16 h. After this time the reaction was allowed to warm to room temperature. In the case where $CH_2Cl_2$ was employed as solvent, the solution was filtered over celite to remove the catalyst and then excess $CH_2Cl_2$ removed under vacuum to obtain

the product. In the remaining cases where an ionic liquid was used, diethyl ether (2 ml) was added to the flask and the solution stirred vigorously for a couple of minutes. After this the phases were allowed to separate, the top layer of diethyl ether was withdrawn using a pipette and filtered through silica over cotton wool, into another 10ml r.b.flask. This extraction procedure was repeated with a $Et_2O$ (4 x 2 ml) to ensure all the product had been extracted. The solvent was then removed under reduced pressure and ferrocene (0.0272 g, 0.2 mmol) added to the resulting oil. Both components were dissolved in $CDCl_3$ (0.5 ml) and the yield was based on the $^1H$ NMR integration of ferrocene at δ 4.10. *Endo / Exo* selectivity of the cycloadduct was characterised using $^1H$ NMR spectroscopy.

***2-methylbicyclo[2.2.1] hept-5-ene-2-carbaldehyde***

$^1H$ NMR (300 MHZ, $CDCl_3$): δ 9.75 (s, 1H, C*H*O), 6.35 (dd, 1H, $J$ = 5.6, C(6)-*H*), 6.15 (dd, 1H, $J$ = 5.6, C(5)-*H*), 2.90 (br s, 1H, C(1)-*H*), 2.80 (br s, 1H, C(4)-*H*), 2.30 (dd, 1H, $J$ = 11.9, C(3)*HX*HY), 1.35 (m, 2H, C(7)*H2*), 1.0 (s, 3H, *Me*), 0.70 (d, 1H, $J$ = 11.9, C(3)HX*HY*); $^{13}C$ NMR (75 MHZ, $CDCl_3$): δ 205.8, 139.5, 133.1, 53.9, 48.5, 47.6, 43.2, 34.6, 20.0; GCMS *m/z* 136.

*Acetalisation to give (2(1R,2S,4R),9R,11R)-4,6-dimethyl-2-(2-methylbicyclo[2.2.1]hept-5-ene-2-yl)-1,3-dioxane*

The $CDCl_3$ aliquot (0.05 ml) of cycloaddition product (27.2 mg, 0.20 mmol) was diluted with $CDCl_3$ (4 ml) before addition of (2*R*,4*R*)-pentanediol (40 mg, 0.40 mmol) and a few crystals of *p*-TsOH. After stirring at RT for 16 h, the reaction mixture was eluted through a short plug of silica with diethyl ether and analysed by gas chromatography. In this way the enantiomeric excess of the *exo* cycloaddition product was determined.

$^1H$ NMR (300 MHZ, $CDCl_3$): δ 6.07-6.13 (m, 2H, C(5)-*H*, C(6)-*H*), 4.69 (s, 1H,C(8)-*H*), 4.28-4.32 (m, 1H, C(9)-*H*), 3.84-3.91 (m, 1H, C(11)-*H*), 2.73 (br s, 1H, C(1)-*H*), 2.65 (br s, 1H, C(4)-*H*), 1.55-1.76 (m, 3H, C(7)-$CH_2$, C(3)*HX*HY), 1.36 (d, 3H, $J$ = 7.0 Hz, C(9)-$CH_3$), 1.28-1.33 (m, 2H, C(10)-$CH_2$), 1.20 (d, 3H, $J$ = 6.2 Hz, C(11)$CH_3$), 0.86 (s, 3H, C(2)*Me*), 0.74 (dd, 1H, $J$ = 2.7, 12.0 Hz, C(3)HX*HY*); $^{13}C$ NMR (75 MHZ, $CDCl_3$): δ 137.2, 135.7, 99.5, 67.9, 67.7, 47.9, 47.4, 45.5, 37.2, 36.9, 21.9, 18.8, 17.3; GCMS *m/z* 136; GC (PE5 column, oven temperature = 50 $^0$C, flow rate at 1ml /min): $t_r$(minor product) = 18.07, $t_r$(major product) = 20.02 min.

***Endo-Bicyclo[2.2.1]hept-5-ene-2carboxaldehyde (Table 4.2, entries 1 - 5)***

$^1$H NMR (400 MHZ, $CDCl_3$): δ 9.38 (d, 1H, $J$ = 2.8 Hz), 6.17 (dd, 1H, $J$ = 3.1, 5.7 Hz) 5.95 (dd, 1H, $J$ = 2.8, 5.7 Hz), 3.21 (br, 1H), 2.94 (br s, 1H), 2.87 (ddd, 1H, $J$ = 1.3, 2.8, 6.8 Hz), 1.86 (m, 1H), 1.41 (m, 2H), 1.28 (d, 1H, $J$ = 7.6 Hz); $^{13}$C NMR (75 MHZ, $CDCl_3$) δ 201.2, 138.1, 135.3, 52.3, 49.6, 45.0, 42.7, 27.6; GCMS *m/z* 122.

The *endo-exo* ratio was determined by $^1$H NMR analysis of the Diels-Alder adducts and GC analysis after conversion to the chiral acetals by (*2R, 4R*)-2,4-pentanediol: $^1$H NMR (300 MHZ, $CDCl_3$): δ 9.42 (d, 1H, $J$ = 3.0 Hz, C*H*O (*endo*)), 9.79 (d, 1H, $J$ = 3.0 Hz, C*H*O (*exo*)). The *ee* was determined by acetalisation with (*2R, 4R*)-2,4-pentanediol and GC analysis (90 $^0$C): $t_r$ = 35.4 min (*1S,2S,4S*)-isomer, 41.1 min (*1R,2R,4R*)-isomer, 42.6 and 44.6 min (*exo*-isomers).

***Endo-3-Methylbicyclo[2.2.1]hex-5-ene-2carboxaldehyde (Table 4.2, entries 6 - 10)***

$^1$H NMR (400 MHZ, $CDCl_3$): δ 9.37 (d, 1H, $J$ = 3.2 Hz), 6.29 (dd, 1H, $J$ = 3.0, 5.8 Hz) 6.05 (dd, 1H, $J$ = 2.8, 5.6 Hz), 3.13 (br, 1H), 2.56 (br, 1H), 2.34 (dd, 1H, $J$ = 3.2, 4.3 Hz), 1.77-1.87 (m, 1H), 1.55-1.60 (m, 1H), 1.44-1.51 (m, 1H), 1.18 (d, 3H, $J$ = 6.9 Hz). The spectroscopic data are in agreement with literature.[526]

The *endo-exo* ratio was determined by $^1$H NMR analysis of the Diels-Alder adducts and GC analysis after conversion to the chiral acetals by (*2R, 4R*)-2,4-pentanediol: $^1$H NMR ($CDCl_3$, 300 MHZ) δ 9.37 (d, 1H, $J$ = 3.2 Hz, C*H*O (*endo*)), 9.78 (d, 1H, $J$ = 3.2 Hz, C*H*O (*exo*)). The *ee* was determined by acetalisation with (*2R, 4R*)-2,4-pentanediol and GC analysis (90 $^0$C): $t_r$ = 22.9 min (*1S,2S,3S,4R*)-isomer, 25.5 min (*1R,2R,3R,4S*)-isomer, 27.1 and 28.7 min (*exo*-isomers).

***1-[(1R, 2R, 4R)-Bicyclo[2.2.1]hept-5-en-2-yl]-propan-1-one (Table 4.2, entries 11 - 15)***

$^1$H NMR (400 MHZ, $CDCl_3$): δ 6.12 (dd, 1H, $J$ = 2.9, 5.7 Hz), 5.80 (dd, 1H, $J$ = 2.9, 5.7 Hz) 3.20 (bs, 1H), 2.99(dt, 1H, $J$ = 4.4, 8.4 Hz), 2.87 (bs, 1H), 2.45 (dq, 1H, $J$ = 7.3, 17.6 Hz), 2.39 (dq, 1H, $J$ = 7.3, 17.6 Hz), 1.73 (ddd, 1H, $J$ = 3.7, 8.8, 11.7 Hz), 1.48 (ddd, 1H, $J$ = 2.6, 4.4, 11.7 Hz), 1.42 (ddd, 1H, $J$ = 1.8, 4.0, 8.4 Hz), 1.30 (d, 1H, $J$ = 8.8 Hz), 1.00 (t, 3H, $J$ = 7.3 Hz); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 211.5, 137.6, 131.3, 51.2, 49.9, 45.9, 42.6, 34.8, 27.4, 7.8; $R_f$ = 0.43 (Hexane: EtOAC, (9: 1); GCMS *m/z* 150.

The minor *exo* isomer was separated: $^1$H NMR (400 MHZ, $CDCl_3$): δ 6.15 (dd, 1H, $J$ = 2.9, 5.7 Hz), 6.12 (dd, 1H, $J$ = 2.9, 5.3 Hz), 2.94 (bs, 1H), 2.90 (bs, 1H), 2.57 (dq, 1H, $J$ = 7.3, 17.6 Hz), 2.48 (dq, 1H, $J$ = 7.3, 17.6 Hz), 2.37 (ddd, 1H, $J$ = 1.3, 4.6, 8.8 Hz), 1.86

(ddd, 1H, $J$ = 3.7, 4.6, 11.4 Hz), 1.40 (d, 1H, $J$ = 8.4 Hz), 1.31 (m, 1H), 1.25 (ddd, 1H, $J$ = 2.6, 8.8 11.4 Hz), 1.07 (t, 3H, J = 7.3 Hz).

Diastereoselectivity (*endo-exo* ratio) and enantioselectivity was determined by GC analysis using cydex-ß column (30 m x 0.25 mm, 100 $^0$C, 25 psi); $t_r$( major *endo*) = 23.2 min, (minor *endo*) = 24.6 min, (major *exo*) = 18.5 min, (minor *exo*) = 18.2 min.

***Ethyl [(1R, 2R, 4R)-Bicyclo[2.2.1]hept-5-ene-2carboxylate (Table 4.2, entries 16 - 20)***

$^1$H NMR (400 MHZ, $CDCl_3$): δ 6.17 (dd, 1H, $J$ = 3.5, 7.0 Hz), 5.91 (dd, 1H, $J$ = 3.5, 7.5 Hz) 4.02 - 4.10 (m, 2H), 3.18-3.19 (m, 1H), 2.92 (dt, 1H, $J$ = 11.5, 5.0 Hz), 2.88 (brs 1H), 1.85-1.91 (m, 1H), 1.38-1.43 (m, 2H), 1.24-1.27 (m, 1H), 1.21 (t, 3H, $J$ = 8.5 Hz); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 174.7, 137.6, 132.3, 60.0, 49.5, 45.6, 43.3, 42.5, 29.1, 14.2.

Diastereoselectivity (*endo-exo* ratio) and enantioselectivity was determined by GC analysis using cydex-ß column (30 m x 0.25 mm, 100 $^0$C, 25 psi); $t_r$ (*exo*) = 13.8 min, (major *endo*) = 16.1 min, (minor *endo*) = 17.4 min.

*Effect of BMIM[Cl] / mim on the Diels Alder reaction*

For reactions where the effect of impurities was examined, a stock solution of BMIM[Cl] (0.018 g in 0.5 ml $CH_2Cl_2$) was made and aliquots (63 µl, 0.01 mmol, 0.5 %) added to the ionic liquid catalytic solution (0.04 mmol [Cu-pybox]OTf, 2 %) before removal of the $CH_2Cl_2$ under vacuum. The same method was used to examine the effect of *mim*: a stock solution of *mim* (24 µl in 1 ml $CH_2Cl_2$) was made and aliquots (33 µl, 0.01 mmol, 0.5 %) added.

### 4.9.2 Hetero-Diels Alder

The ionic liquid catalyst solutions were prepared from a stock solution of the copper triflate bis(oxazoline). The stock solution was prepared by stirring a mixture of $Cu(OTf)_2$, (0.2534 g, 0.70 mmol) and 2,2'-isopropylidenebis-[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.2471 g, 0.84 mmol) in dichoromethane (700 µl) for 3 h after which time the solution was filtered through glass wool. A measured portion (100 µl) of this solution was added to the ionic liquid (1 ml) and the bluish-green homogeneous solution was stirred for 30 minutes after which time the $CH_2Cl_2$ was removed under vacuum and ethyl glyoxylate (200 µl, 1.2 mmol) added. Ethyl glyoxylate was purchased from Fluka as a 50 % solution in toluene. 10 ml ethyl glyoxylate / toluene solution was distilled to remove most of the toluene (head temperature 110–120 $^0$C). The distillation pot was then warmed to 170–180 $^0$C and the

remaining ethyl glyoxylate / toluene was collected (head temperature 120–130 $^0$C). $^1$H NMR indicates the distilled glyoxylate solution to be typically a 7:3 mixture of ethyl glyoxylate / toluene. After stirring the reaction mixture at room temperature for 10 min, 1,3-cyclohexadiene (98 µl, 1 mmol) was added and the resultant biphasic system was stirred at room temperature for 8 h. The yields and *trans* : *cis* selectivity were determined at this stage by GC using decane as an internal standard. The product was extracted using diethyl ether (5 x 2 ml), the combined extracts were filtered over silica and concentrated in *vacuo* to a pale yellow oil. The cycloadducts was purified by preparative tlc (using diethyl ether-petroleum ether, 1:2, $R_f$ = 0.39 as eluent) and then used to determine the enantioselectivity by chiral GC (ß-cyclodextrin column).

For reversal of *ee* the stock catalyst solution was prepared by stirring a mixture of $Cu(OTf)_2$, (0.217 g, 0.60 mmol) and 2,2'-isopropylidenebis-[(4*S*)-4-phenyl-2-oxazoline] (0.240 g, 0.72 mmol) in dichoromethane (600 µl) for 3 h, of which an aliquot (100 µl) was used for each reaction. In the case where MeCN and $CH_2Cl_2$ were used as solvents, the reactions were homogeneous, whereas using ILs the reactions are biphasic and become homogeneous on stirring.

***(1S, 3R, 4R)-Ethyl 2-oxa-bicyclo[2.2.2]oct-5-ene-3-carboxylate***

$^1$H NMR (300 MHZ, $CDCl_3$): δ 6.54–6.50 (m, 1H, C=CH), 6.28–6.24 (m, 1H, C=CH), 4.59-4.56 (m, 1H, OCH), 4.29 (br s, 1H, OCH), 4.18-4.13 (q, 2H, $J$ = 7.1 Hz, $OCH_2$), 3.10-3.08 (m, 1H, CH), 2.10-2.01 (m, 1H, CH), 1.78-1.70 (m, 1H, CH), 1.43-1.26 (m, 2H, 2 CH), 1.25 (t, 3H, $J$ = 7.1 Hz, $CH_3$); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 172.2, 134.5, 130.4, 74.1, 66.4, 60.7, 33.2, 25.7, 20.9,14.3; GC $t_{exo}$ 11.87 min and $t_{endo}$ 12.17 min (BP10, 30m, 4 min at 50 $^0$C; 50 $^0$C to 150 $^0$C, 30 $^0$C min$^{-1}$, 150 $^0$C to 180 $^0$C, 4 $^0$C min$^{-1}$).

The enantiomers were resolved using ß-cyclodextrin; 130$^0$C; $t_{exo}$ = 19.07 min (major enantiomer) and 19.51 min (minor enantiomer), $t_{endo}$ = 21.24 min (major enantiomer) and 21.57 min (minor enantiomer). GCMS $t_{exo}$ 16.60 min and $t_{endo}$ 16.87 min (PE5, 30m, 1.5 min at 45 $^0$C; 45 $^0$C to 300$^0$C, 10 $^0$C min$^{-1}$; 5 min at 300 $^0$C); GCMS *m/z* 183.

***(S)-Ethyl 4,5-Dimethyl-3,6-dihydro-2H-pyran-2-carboxylate***

$^1$H NMR (300 MHZ, $CDCl_3$): δ 4.28–4.03 (m, 5H, 2 $OCH_2$, OCH), 2.36–2.15 (br m, 2H, $CH_2$), 1.67 (s, 3H, $CH_3$), 1.54 (s, 3H, $CH_3$), 1.33-1.28 (t, 3H, $J$ = 7.1 Hz, $CH_3$); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 171.6, 124.2, 122.5, 72.9, 69.2, 61.0, 33.0, 18.2, 14.2, 13.8; GC $t_r$ = 11.65 min. GCMS $t_r$ = 17.68 min; GCMS *m/z* 184.

**Ethyl 2-Hydroxy-5-methyl-4-methylene-5-hexanoate**

$^1$H NMR (300 MHZ, $CDCl_3$): δ 5.25 (s, 1H, C=CH), 5.14 (s, 1H, C=CH), 5.11 (s, 1H, C=CH), 5.05 (s, 1H, C=CH), 4.37-4.30 (m, 1H, OCH), 4.27-4.19 (m, 2H, $OCH_2$), 2.90-2.84 (dd, 1H, *J* = 3.3, 14.3 Hz, CH), 2.67-2.65 (d, 1H, *J* = 6.6 Hz, OH), 2.59-2.51 (dd, 1H, *J* = 8.2, 14.3 Hz, CH), 1.94 (s, 3H, $CH_3$), 1.33-1.28 (t, 3H, *J* = 7.1 Hz, $CH_3$); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 174.6, 142.7, 142.1, 115.7, 113.4, 69.5, 61.6, 39.2, 21.2, 14.2; GC $t_r$ = 10.72 min. The enantiomers were resolved using ß-cyclodextrin; 120 $^0$C; $t_r$ (minor) = 18.54 min and $t_r$ (major) = 18.95 min; GCMS $t_r$ = 16.23 min; GCMS *m/z* 184.

### 4.9.3 Cyclopropanation

Ethyl diazoacetate and styrene were used as supplied. The ionic liquid catalyst solutions were prepared from a stock solution of the copper triflate bis(oxazoline). The stock solution was prepared by stirring a mixture of $\{Cu(OTf)\}_2$•toluene, (0.0259 g, 0.07 mmol) and 2,2'-isopropylidenebis-[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.0497 g 0.168 mmol) in chloroform (1.4 ml) for 3 h after which time the solution was filtered through glass wool. A measured portion (200 μl) of this solution was added to the ionic liquid (2 ml) and the bluish-green homogeneous solution was stirred for 30 min after which time the chloroform was removed under vacuum. Styrene (344 μl, 3 mmol) was added and the resultant biphasic system was stirred for 10 min before addition of the ethyl diazoacetate (210 μl, 2 mmol) over 2 h. The reaction mixtures were allowed to equilibrate to 25 °C over 4 h and stirred for a further 10 h. The product was extracted using diethyl ether (6 x 3 ml), the combined extracts were filtered over silica and concentrated in *vacuo* to a pale yellow oil. The yields and *trans* : *cis* selectivity were determined at this stage by GC using decane as an internal standard. The esters were converted to the *R*-1-phenylethylamides by the literature method,[527] the amide fraction was separated by preparative tlc and this fraction was used to determine the enantioselectivity.

***Ethyl (1S,2S)-2-phenylcyclopropanecarboxylate***

$^1$H NMR (250 MHZ, $CDCl_3$): δ 7.1-7.4 (m, 5H, Ar-*H*), 4.17 (q, 2H, *J* = 7.1 Hz, C$H_2$O), 2.52 (m, 1H, C*H*CO), 1.90 (ddd, *J* = 4.2, 5.3, 8.4 Hz, C*H* (cyclopropane)), 1.60 (m, 1H, *J* = 4.4, 5.1, 9.4 Hz, C*H* (cyclopropane)), 1.31 (m, 1H, C*H* (cyclopropane)), 1.28 (t, 3H, *J* = 7.1 Hz, C$H_3$CH$_2$); GC $t_r$ 21.43 min (BP10, 30 m, 1 min at 60 $^0$C; 60 $^0$C to 180 $^0$C, 5 $^0$C

$min^{-1}$); GCMS $t_r$ 14.04min (PE5, 30 m, 1.5 min at 45 $^0$C; 45 $^0$C to 300 $^0$C, 10 $^0$C $min^{-1}$; 5 min at 300 $^0$C); GCMS *m/z* 190.

***Ethyl (1S,2R)-2-phenylcyclopropanecarboxylate***

$^1$H NMR (250 MHZ, $CDCl_3$): δ 7.1-7.4 (m, 5H, Ar-*H*), 3.87 (q, 2H, *J* = 7.1 Hz, C$H_2$O), 2.58 (m, 1H, C*H*CO), 2.08 (ddd, 1H, *J* = 5.6, 7.8, 9.3 Hz, C*H*(cyclopropane)), 1.71 (m, 1H, C*H*(cyclopropane)), 1.34 (m, 1H, C*H* (cyclopropane)), 0.97 (t, 3H, *J* = 7.1 Hz, C$H_3$CH$_2$); GC $t_r$ 20.44 min (BP10, 30 m, 1 min at 60 $^0$C; 60 $^0$C to 180 $^0$C, 5 $^0$C $min^{-1}$); GCMS $t_r$ 13.38 min (PE5, 30 m, 1.5 min at 45 $^0$C; 45 $^0$C to 300 $^0$C, 10 $^0$C $min^{-1}$; 5 min at 300 $^0$C); GCMS *m/z* 190.

Determination of enantioselectivity.[527] To a cooled (0 $^0$C) solution of *R*-1-phenylethylamine (0.250 ml, 1.94 mmol) in 1,2-dichloroethane (4 ml) was added trimethylaluminium (1.0 ml, 2.0M in toluene, 2.0 mmol) and the mixture was warmed to 25 $^0$C for 1 h. To this was added a solution of ethyl 2-phenylcyclopropanecarboxylate in dichloroethane (2 ml) and the residual material was rinsed out with dichloroethane (2 ml). The mixture was heated to 80 $^0$C for 16 h. A sample was withdrawn at this point for GCMS analysis to ensure that both esters had completely reacted. The mixture was cooled to 0 $^0$C and and quenched with 15 ml of 1-*N* HCl and this was warmed to 25 $^0$C. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 15 ml). The combined organic phases were washed with 1-*N* HCl (10 ml) and saturated aqueous NaCl (10 ml), filtered through cotton and filtered to give a pale pink oil. GC analysis and GCMS showed four products, *m/z* 265. The diastereoisomers were separated using preparative tlc (40: 60 EtOAc/heptane).

***(1S, 2S, 1'R)-N-(1'-phenylethyl)-2-phenylcyclopropanecarboxamide***

GCMS $t_r$ 20.45 min; TLC $R_f$ = 0.48 (40: 60 EtOAc/heptane); $^1$H NMR (300 MHZ, $CDCl_3$): δ 7.25-7.4 (m, 8H, Ar-*H*), 7.1 (m, 2H, Ar-*H*), 5.90 (bd, 1H, *J* = 7.31 Hz, N-*H*), 5.15 (m, 1H, NC*H*Ph), 2.50 (m, 1H, *CH*CO), 1.59 (m, 2H, C*H*(cyclopropane)), 1.49 (d, 3H, *J* = 7.01 Hz, $H_3$CHPh), 1.21 (m, 1H, C*H*(cyclopropane)); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 169.8, 142.2, 139.9, 127.7, 127.4, 126.4, 126.2, 124.9, 48.0, 27.4, 25.5, 20.8, 16.5.

***(1S, 2S, 1'S)-N-(1'-phenylethyl)-2-phenylcyclopropanecarboxamide***

GCMS $t_r$ 20.27 min; TLC $R_f$ = 0.39 (40: 60 EtOAc/heptane); $^1$H NMR (300 MHZ, $CDCl_3$): δ 7.20-7.4 (m, 8H, Ar-*H*), 7.05 (m, 2H, Ar-*H*), 5.87 (bd, 1H, *J* = 7.31 Hz, N-*H*), 5.16 (m, 1H, NC*H*Ph*)*, 2.45-2.55 (m, 1H, *CH*CO), 1.61 (m, 2H, C*H*(cyclopropane)), 1.51 (d, 3H, *J* = 6.73 Hz, $H_3$CHPh), 1.24 (m, 1H, C*H*(cyclopropane)); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 169.8, 142.1, 139.8, 127.7, 127.4, 126.4, 125.2, 124.9, 48.1, 25.8, 23.9 20.9, 15.08.

***(1S, 2R, 1'R)-N-(1'-phenylethyl)-2-phenylcyclopropanecarboxamide***

GCMS $t_r$ 21.94 min; TLC $R_f$ = 0.25 (40: 60 EtOAc/heptane); $^1$H NMR (300 MHZ, $CDCl_3$): δ 7.25-7.4 (m, 8H, Ar-*H*), 7.1 (m, 2H, Ar-*H*), 5.52 (bd, 1H, *J* = 7.89 Hz, N-*H*), 4.91 (m, 1H, NC*H*Ph*)*, 2.45 (m, 1H, *CH*CO), 1.92 (m, 1H, C*H*(cyclopropane)), 1.70 (m, 1H, C*H*(cyclopropane)), 1.26 (m, 1H, C*H*(cyclopropane)), 1.17 (d, 3H, *J* = 7.02 Hz, $H_3$CHPh); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 168.4, 143.1, 136.9, 128.8, 128.5, 128.1, 127.2, 126.6, 126.2, 48.5, 24.2, 24.1, 21.4, 9.8.

***(1S, 2R, 1'S)-N-(1'-phenylethyl)-2-phenylcyclopropanecarboxamide***

GCMS $t_r$ 21.72 min; TLC $R_f$ = 0.17 (40: 60 EtOAc/heptane); $^1$H NMR (300 MHZ, $CDCl_3$): δ 7.1-7.2 (m, 8H, Ar-*H*), 6.9 (m, 2H, Ar-*H*), 5.39 (bd, 1H, *J* = 7.0 Hz, N-*H*), 4.84 (m, 1H, NC*H*Ph*)*, 2.44 (m, 1H, *J* = 7.6, 9.1 Hz, *CH*CO), 1.92 (m, 1H, C*H*(cyclopropane)), 1.62 (m, 1H, C*H*(cyclopropane)), 1.22 (d and m, 4H, *J* = 6.73 Hz, $H_3$CHPh and C*H*(cyclopropane)); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 168.4, 142.9, 136.7, 128.9, 128.4, 126.9, 126.6, 126.2, 126.0, 48.2, 24.4, 24.1, 21.1, 16.1, 9.9.

Enantioselectivity was determined by integration of the peak area of the diastereoisomers detected by GCMS. An enantiomeric excess of 0 % was obtained for the *cis* and *trans* esters by integration of the peak area of the four diastereoisomers of a racemic mixture.

### 4.9.4 Aziridination

***(N-(p-toluenesulphonyl)imino)phenyliodinane [PhI=NTs]***

The compound was prepared according to the procedure of Yamada *et al.*.[528] To a solution of KOH (8.4 g, 150 mmol) and *p*-toluenesulphonamide (10.2 g, 60 mmol) in MeOH (200 ml) at 0 $^0$C was added diacetoxyiodobenzene[529] (19.2 g, 60.0 mmol). A yellow colour developed within 5 min. The cooling bath was removed and the solution allowed to warm to room temperature as it was stirred for 5 h. Water (200 ml) was added and the solution was refrigerated at 0 $^0$C overnight. The precipitate was collected by filtration and air dried to yield 20.2 g of a light yellow powder. NMR analysis indicated that this material contained residual starting material, so it was triturated with 100 ml $CH_2Cl_2$ to yield 14.2 g (62 %) of desired product. M.p. 103-105 $^0$C (dec); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.78 (d, 2H, $J$ = 8.2 Hz, Ar-*H*), 7.51 (bd, 3H, $J$ = 8.2 Hz, $J$ = 3.1 Hz, Ar-*H*), 7.36 (t, 2H, $J$ = 7.7 Hz, Ar-*H*), 7.13(d, 2H, $J$ = 7.9 Hz, Ar-*H*), 2.34 (s, 3H, C$H_3$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 142.6, 140.5, 133.6, 130.8, 130.5, 129.0, 126.5, 117.6, 21.2.

***(R)-N-p-Toluenesulphonyl-2-phenylaziridine***

The ionic liquid catalyst solutions were prepared from a stock solution of the copper triflate bis(oxazoline). The stock solution was prepared by stirring a mixture of {Cu(OTf)}$_2$•toluene, (0.0460 g, 0.0875 mmol) and 2,2'-isopropylidenebis-[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.0620 g 0.210 mmol) in dichloromethane (0.70 ml) for 3 h after which time the solution was filtered through glass wool. A measured portion (100 μl) of this solution was added to the ionic liquid (1 ml) and the bluish-green homogeneous solution was stirred for 30 min after which time the dichloromethane was removed under vacuum. PhI=NTs (0.187 g, 0.5 mmol) was added and the heterogeneous reaction mixture stirred for 30 minutes before addition of styrene (115 μl, 1 mmol). The resultant heterogeneous system was stirred for 24 h by which time the reaction mixture had become more homogeneous. The reaction mixture was then diluted by addition of dichloromethane (1 ml), and the aziridine product separated by preparative tlc (using hexane: ethyl acetate, 2:1 as eluent, $R_f$ = 0.62). Ferrocene stock solution (9.302 mg , 0.05 mmol) was added to the resulting solid oil and the yield was based on the $^1$H NMR integration of ferrocene at δ 4.10. $^1$H NMR (400 MHZ, $CDCl_3$): δ 7.86 (d, 2H, $J$ = 8.3 Hz, Ar-*H*), 7.27 (m, 7H, Ar-*H*), 3.77 (dd, 1H, $J_{cis}$ = 7.2 Hz, $J_{trans}$ = 4.5 Hz, C*H*Ph), 2.98 (d, 1H, $J$ = 7.8 Hz, *cis*-C*H*-aziridine), 2.43 (s, 3H, Ar-C$H_3$), 2.38 (d, 1H, $J$ = 4.4 Hz, *trans*-C*H*-aziridine); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 144.5, 134.9, 129.6, 128.4, 128.1, 127.8, 126.4, 40.9, 35.7, 21.4; EI

*m/z* 274; White crystalline solid Mp. 88-89 $^0$C; TLC $R_f$ = 0.62 (2: 1, hexane: ethyl acetate). The enantiomers were separated by chiral hplc on a chiralcel OJ column (using hexane: isopropanol, 95 : 5; 1 ml/min flow rate, 254 nm); $t_r$ (*R* enantiomer) = 35.72 min, $t_r$ (*S* enantiomer) = 28.72 min.

***(2S, 3S)-N-p-Toluenesulphonyl-2-phenyl-3-methylaziridine***

As for (*R*)-N-p-Toluenesulphonyl-2-phenylaziridine (above) using PhI=NTs (0.187 g, 0.5 mmol) and *trans*-β-methylstyrene (130 µl, 0.118 g, 1 mmol), with an increased reaction period of 48 h. $^1$H NMR (400 MHZ, $CDCl_3$): δ 7.82 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.26-7.20 (m, 5H, Ar-*H*), 7.13 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 3.79 (d, 1H, *J* = 4.3 Hz, C*H*Ph), 2.9 (dq, 1H, *J* = 6.0, 4.4 Hz, C*H*$CH_3$), 2.37 (s, 3H, Ar-C*H*$_3$), 1.83 (d, 3H, *J* = 6.0 Hz, C*H*$_3$); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 143.8, 137.9, 135.5, 129.5, 128.4, 128.0, 127.1, 126.2, 49.1, 21.5, 14.1; EI: *m/z* 310; Mp. 72-74 $^0$C; TLC $R_f$ = 0.25 (4 : 1, hexane : ethyl acetate).

The enantiomers were separated by chiral hplc on a chiralcel AS column (using hexane: isopropanol, 98 : 2; 1 ml/min flow rate, 254 nm); $t_r$ (minor enantiomer) = 18.01 min, $t_r$ (major enantiomer) = 21.19 min.

### 4.9.5 Allylic oxidation

2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.352 g, 0.168 mmol, 0.12 equiv) was added to Cu(OTf)•toluene complex (0.207 g, 0.8 mmol, 0.10 equiv) and stirred in dry $CH_2Cl_2$ (800 µl) at RT for 3 h. The dark green catalytic solution was then filtered over glass wool in a Pasteur pipette and a measured portion (100 µl) added to the desired solvent (0.9 ml) with 4 Å molecular sieves. The solvent was stirred for an hour at RT before addition of cyclohexene (305 µl, 0.246 g, 3 mmol). $^t$Bu-perbenzoate (380 µl, 0.389 g, 2 mmol) was then added over 10 min. The biphasic reaction mixture was stirred at RT for 12 days. The products were extracted with 5 x 3 ml diethyl ether. The combined extracts were filtered over silica on glass wool in a Pasteur pipette. The solvent was removed on the rotary evaporate to give an yellow oil.

***2-Cyclohexenyl benzoate***

$^1$H NMR (400 MHZ, $CDCl_3$): δ 8.04-8.02 (m, 2H), 7.52 (t, 1H *J* = 7.4), 7.41 (t, 2H *J* = 7.7Hz), 6.01-5.97 (m, 1H), 5.83-5.79 (m, 1H), 5.49 (bs, 1H), 2.12-1.66 (m, 6H); $^{13}$C NMR: δ 166.2, 132.8, 132.7, 130.9, 129.6, 128.3, 125.8, 68.6, 28.4, 25.0, 19.0; GCMS

*m/z* 202. Enantioselectivity was determined by HPLC using a Chiralpak OJ column (hexane: isopropanol, 1000: 1; 0.5 ml/min), $t_r$(*R* enantiomer): 18.9 min, $t_r$(*S* enantiomer): 21.7 min.

### 4.9.6 Friedel-Crafts Addition

0.1239g 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.168 mmol, 0.012 equiv) was added to $Cu(OTf)_2$ (0.1267 g, 0.07 mmol, 0.01 equiv) and stirred in dry dichloromethane (700 µl) at RT for 3 h. The catalytic solution was then filtered over glass wool in a Pasteur pipette and a measured portion (100 µl) added to the desired solvent (0.9 ml). The blue catalytic solution was stirred for an hour before addition of ethyl trifluoropyruvate (85 µl, 0.085 g, 0.5 mmol) and dimethoxybenzene (72 µl, 0.076 g, 0.55 mmol). The reaction mixture was stirred for 48 h at RT. A sample was withdrawn for GC analysis and the products extracted with diethyl ether (5 x 3 ml). The extracts were combined, the solvent removed and the residue oil loaded onto a silica preparative. tlc plate to remove the excess dimethoxybenzene. The enantioselectivity was then determined using chiral hplc on a Chiralpak AD column (hexane: isopropanol, 90: 10).

***2-(2,4-Dimethoxyphenyl)-3,3,3-trifluro-2-hydroxypropionic acid ethyl ester***

$^1$H NMR (400 MHZ, $CDCl_3$): δ 7.36 (dq, *J* = 8.8, 1.6Hz, 1H; *Ar*) 6.44 (dd, *J* = 8.8, 2.4 Hz, 1H; *Ar*); 6.40 (d, *J* = 2.4 Hz, 1H; *Ar*; 4.51 (s, 1H, O*H*); 4.27 (dq, *J* = 10.8, 7.2 Hz, 1H; C$H_2$); 4.20 (dq, *J* = 10.8, 7.2Hz, 1H; C$H_2$); 3.73 (s, 3H, OC$H_3$); 3.69 (s, 3H, OC$H_3$), 1.18 (t, *J* = 7.2Hz, 3H, C$H_3$); $^{13}$C NMR (75 MHZ, $CDCl_3$): δ 168.6, 160.6, 157.4, 128.0, 122.5(q, $J_{C\text{-}F}$ = 286.0 Hz), 114.7, 103.4, 98.5, 76.4 (q, $J_{C\text{-}F}$ = 29.0 Hz), 62.3, 54.6, 54.4, 12.8; GCMS *m/z* 308.

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