Green Chemical Reactions

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Green Chemical Reactions

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PREFACE

The Advanced Study Institute (ASI) "New Organic Chemistry Reactions and Methodologies for Green Production" represents the evolution of the preceding series of "Summer School on Green Chemistry" that were held in Venice, Italy for eight consecutive years.

Main focus was "Green Chemistry", i.e. fundamental research towards the development of new sustainable chemical processes, starting from the idea that pollution and hazards have to be eliminated at the source, thus reducing environmental impact and costs, as opposed to end-of-pipe remeiation. Green Chemistry incorporates all aspects of chemistry that reduce impact on human health and on the environment. Its goal is to improve the quality of life and the competitiveness of industry, by developing safer and more eco-friendly chemistry.

The scope of the ASI fits the definition of NATO "Priority Research Topics" as "Environmental Security" that can be defined as *the relative public safety from environmental dangers caused by natural or human processes due to ignorance, accident, mismanagement or design and originating within or across national borders*. From this standpoint, the objectives of Green Chemistry are indeed aimed to minimize the environmental concerns caused, inter alia, by many human activities.

There are five focus areas, whereby Green Chemistry can be achieved, and that are currently the main focus themes of this area of research in Europe:

1. Alternative synthetic pathways based on atom (and mass) economy, achievable through catalysis and biocatalysis, natural processes, such as photochemistry, electrochemistry and biomimetic synthesis.
2. Alternative reaction conditions, based on the use of solvents that have a reduced impact on human health and the environment, increased selectivity and reduced wastes and emissions.
3. The design, use, and production of chemicals that are less toxic than their current alternatives and inherently safer with regard to accident potential.
4. Alternative feedstocks and safe reagents to reduce the dependency on fossil fuels and the potential for accidents.
5. The evaluation of the risk connected to chemical processes, to chemical products and reagents, to by-products.

To this end, significant challenges are available for chemists to design new syntheses that are less polluting, and to gain detailed understanding of the scientific facts and of the technical base needed to support sustainable development and environmental protection.

Green Chemistry is an inventive science, since it is not necessarily connected to the profit, but it involves fundamental aspects and does not aim automatically to an industrial process. There is a great need to create a new type of chemistry focused on a new production system, in order to prepare the younger generation to get to a greener future. Following this scenario, this book has been planned with the aim to extend the knowledge on green chemistry not disregarding, however, the industrial interest.

Nowadays the globalization, induced by many factors, pushes the chemistry community to adopt ethical issues. In this prospect Green Chemistry can achieve the approval of the society by teaching students to be confident in science and at the same time by convincing people that it is now possible, thanks to technological improvement, to attain technological development respecting and having care of the environment in which we live. In this respect it is important that education and fundamental research are strictly connected, so that democracy and development can also grow and progress side by side.

The NATO ASI was intended as a contribution to the dissemination of knowledge and the establishment of international scientific contacts. The teaching was aimed at scientists at the postdoctoral level or senior PhD students and young researchers in industry with an appropriate scientific background. It provided a unique opportunity to bring together a number of experts in the field of Green Chemistry and young researchers interested in this topic. This synergy of competencies will certainly be a valuable occasion to promote diffusion of the knowledge in this emerging field.

The teaching was divided in basic themes i.e Atom economy, Industrial Processes, Alternative Solvents, New Feedstocks and Products, New Reactions and New Synthetic Methods. In addition topics related to current research in Green Chemistry were addressed with the aim to familiarize the students with the strategies behind the planning and designing of efficient and “greener” synthetic routes.

The ASI provided high level training and understanding in the five focus areas outlined above. As an added value it will give rise to new research projects and collaborations. These will be effectively carried out by the exchange of young researchers, particularly students from developing nations.

Participants have become part of the network of European green chemists. All the students are now ambassadors of (Green) Chemistry in their institutions, in their countries, and to their peers. In this they will be aided by the present volume and by the lectures of the schools disseminated on the internet, and through the network of practitioners of which they will effectively become part of.

The ASI had duration of 10 working days in order to give adequate time for the development of a topic and allow for sufficient interaction between scientists. The presentation of contributed papers from applicants is limited to the submission of posters.

The course was split in two subsequent weeks and took place in two different locations. The first week was held in the city of Lecce (southern Italy) in a 19th century neo-Renaissance theatre surrounded by the Baroque old city centre. For the second week students and teachers moved about 30 km south-east in the city of Otranto, a splendid location on the Adriatic Sea.

The format will balance lectures with ample free time for one-to-one discussion between instructors and students and socialization. Approximately 50% of the ASI has covered fundamental principles, while the rest has focused on specific aspects.

The organization was taken care of by the Inter University Consortium “Chemistry for the Environment”, INCA, and in particular by the research unit based in Lecce, coordinated by Vittorio Esposito. All events were made possible by the efforts of Michele Pellegrino, Annamaria Maffei and Luisella De Vitis whose invaluable contribution is gratefully acknowledged.

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AN INTRODUCTION TO GREEN CHEMISTRY

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Abstract: The fundamental principles and concepts of Green Chemistry are outlined, together with selected examples illustrating the identified areas for development.

Keywords: Green chemistry; alternative feedstocks; benign reagents; catalytic synthetic pathways; natural processes; biocatalysis; alternative solvents; safer chemicals; alternative reaction conditions; minimization of energy consumption

1. General Principles

A general definition of Green Chemistry is the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances. In relation to organic synthesis, this definition can be modified as follows – the design of new synthetic pathways to perform chemical processes in a very controlled way, so as to reduce drastically, or to eliminate completely, all the environmental impact. Several important ideas lie behind the concept of Green Chemistry. One is a consideration of all materials used in a process, not just those most central to product formation. Another is the desire to achieve a minimization of negative impacts and the optimization of the efficiency of a process. There also needs to be a consideration of intrinsic hazards of all the substances involved. Bearing in mind that

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

it is important to recognize that Green Chemistry focuses on limiting hazards. This represents a change from previous practise that focused on reducing risk by limiting exposure.

P. Tundo and V. Esposito (eds.), *Green Chemical Reactions.*

The chemical industry is concerned with regulation and control of processes, and is also required to clean up any waste materials, and remediate polluted areas. Green chemistry addresses all these issues, and in doing so, avoids the need for clean up and remediation, and avoids extensive regulation: thus it has a major impact on the economics of the process.

Twelve general principles of Green Chemistry have been enunciated[1] and are listed below:

- It is better to prevent waste rather than treat or clean up waste after it is formed
- Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product
- Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment
- Chemical products should be designed to preserve efficacy of function while reducing toxicity
- The use of auxiliary substances (e.g. solvents, separation agents etc.) should be made unnecessary wherever possible and innocuous when used
- Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure
- A raw material or feedstock should be renewable, rather than depleting, wherever technically and economically practical
- Unnecessary derivatization (blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible
- Catalytic reagents (as selective as possible) are superior to stoichiometric reagents
- 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
- Analytical methodologies need to be further developed to allow for real time in-process monitoring and control prior to the formation of hazardous substances
- Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Within the context of chemical reactions, these twelve principles can be simplified to the following:

- Prevention is better than treatment
- Maximize the incorporation of all materials into the final product
- Use and generate substances that possess little or no toxicity
- Products should preserve efficacy of function with reduced toxicity
- Avoid use of auxiliary substances (e.g. solvents, separation agents etc.)
- Energy requirements should be minimized: use ambient temperature and pressure
- Use renewable raw materials or feedstocks
- Avoid derivatization (blocking groups, protection/deprotection etc.)
- Catalytic reagents are superior to stoichiometric reagents
- Chemical products should not persist in the environment at the end of their function
- Analytical methodologies should allow in-process monitoring and control
- Processes should minimize the potential for chemical accidents.

2. Some Concepts in Green Chemistry

2.1. THE E FACTOR

This is defined[2] as the number of kilograms of waste per kilogram of product.

2.2. ATOM ECONOMY

This is defined[3] as the ratio of molecular weight of the target molecule to the sum total of molecular weights of all the substances produced in the stoichiometric equation for the reaction involved.

2.3. THE ENVIRONMENTAL QUOTIENT

This is defined[2] as the E factor multiplied by an arbitrarily assigned unfriendliness quotient.

2.4. LIFE CYCLE ASSESSMENT

This is the consideration of all stages along the life cycle of a chemical, as well as the consideration of environmental impacts caused by by-products and auxiliaries.[4]

3. Identified Areas for Development of Green Chemistry

There are seven major areas that will be elaborated upon throughout the remainder of this chapter. These are:

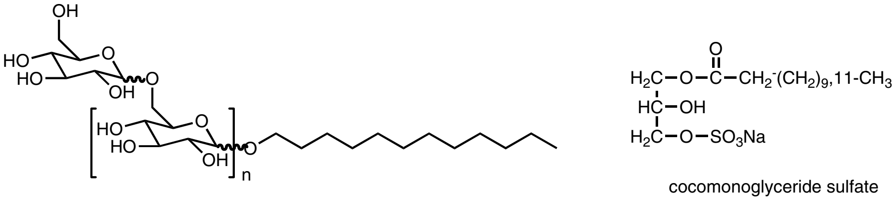
- Use of alternative feedstocks (renewable and less toxic)
- Use of innocuous or benign reagents
- Employment of natural processes for efficiency and selectivity
- Use of alternative solvents
- Design of safer chemicals
- Alternative reaction conditions for efficiency and selectivity
- Minimization of energy consumption.

3.1. ALTERNATIVE FEEDSTOCKS

In a consideration of alternative feedstocks the following points[5] are important:

- The use of feedstocks that are both renewable rather than depleting and less toxic to human health and the environment.
- Selection of starting material is crucial: this considers not only the characteristics of the material, but also its origins and mode of use.
- Is the material hazardous?
- Is it obtained from a hazardous material or a hazardous source?
- Does its use require the involvement of hazardous substances or processes?
- Is the source renewable or depleting, e.g. carbohydrates, proteins, fatty oils etc., as opposed to fossil and mineral raw materials?
- Does the source make use of waste material, e.g. Biomass.

An excellent source of alternative feedstocks can be exemplified by a range of natural products, such as carbohydrates, proteins, fatty acids, vegetable oils and fats. For example, alkyl polyglycosides, made from glucose



alkyl polyglycosides

from glucose and palm or coconut oil

cocomonoglyceride sulfate

from coconut oil and glycerol

Figure 1. Some natural surfactants for shampoos.

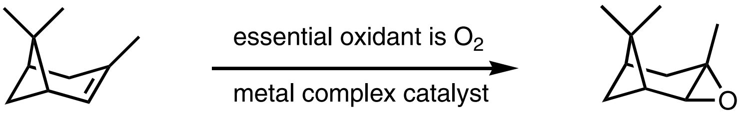
and palm or coconut oil, and cocomonoglyceride sulfate, made from coconut oil and glycerol, are surfactants that can be used as shampoos (Figure 1).[6]

3.2. INNOCUOUS OR BENIGN REAGENTS

The fundamental issues are the following:

- The use of reagents that are inherently less hazardous and are catalytic wherever feasible
- Selection of a reagent requires a similar full analysis
- Is the reagent hazardous?
- Can an alternative more innocuous one be used?
- Does the reagent give a high conversion and high selectivity?
- Can a catalyst be used?
- Can UV light or sunlight be used?
- Can a clean free radical reaction be used?
- Can a natural process be used, e.g. biocatalysis?.

One of the most important aspects of those listed above is catalysis. A great deal of research has been carried out in the investigation of catalysts for the epoxidation of alkenes. The oxidation of α-pinene to α-pinene epoxide (Equation 1) is one of the standard trial reactions for catalyst identification. The Jacobsen manganese complex catalyst,[7] based on a salen derivative, shows brilliant enantioselectivity, whereas the use of related indole derivatives provides greater structural variety and powerful catalysis, but so far shows poorer enantioselectivity (Figure 2).[8] Such catalysts can sometimes be effectively embedded in zeolites.[9]



Equation 1. Epoxidation of α-pinene

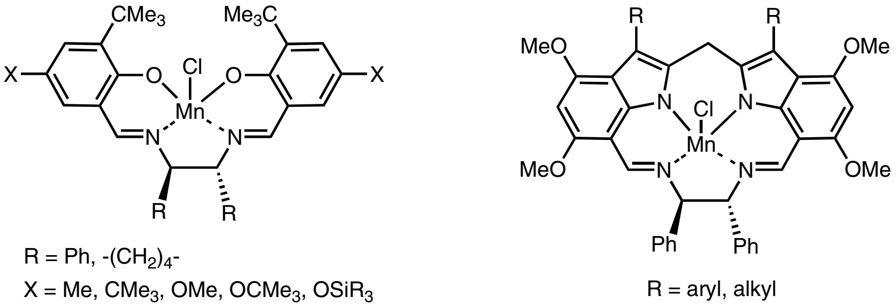
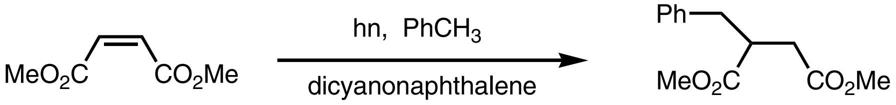


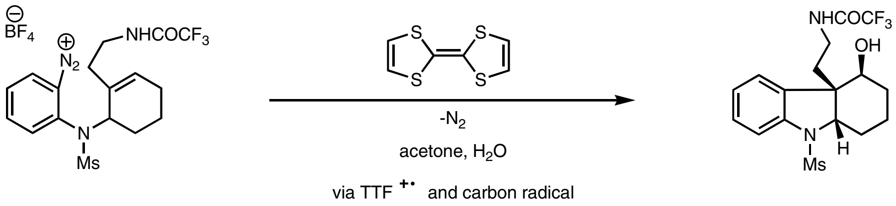
Figure 2. Manganese catalysts for epoxidation.

Photochemical processes provide very benign reaction conditions and can be exemplified by the conjugate alkylation of electophilic alkenes (Equation 2).[10]



Equation 2. Conjugate alkylation of electrophilic alkenes

Free radical processes have also come to the fore in recent years, as clean and effective reactions in many cases. The example shown in Equation 3



Equation 3. Radical cyclization

involves a tetrathiafulvalene-mediated radical-polar crossover reaction that has been used in a total synthesis of aspidospermidine.[11]

3.3. EMPLOYMENT OF NATURAL PROCESSES

It is very desirable if natural processes can be used for synthetic reactions, because they are usually catalytic and also renewable. Enzymic processes are also highly specific.[5] The main features for consideration of natural processes are as follows:

- Use of biosynthesis, and biotechnology-based chemical transformations for efficiency and selectivity
- Use of enzymic reactions
- Biocatalysis
- Usually give extremely high efficiency and selectivity
- Usually carried out in water at ambient temperature and pressure
- No tedious protection and deprotection of functional groups
- Often shorter reaction sequences with fewer steps
- Removes the need for organic solvents such as dichloromethane.

Some important fermentation and biotransformation products are shown in Figure 3.[12]

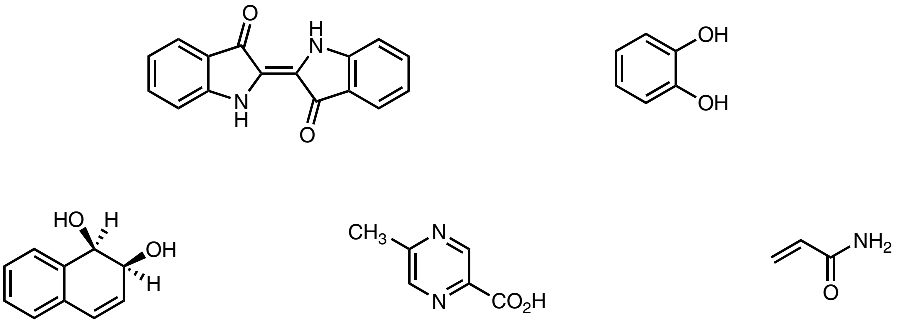
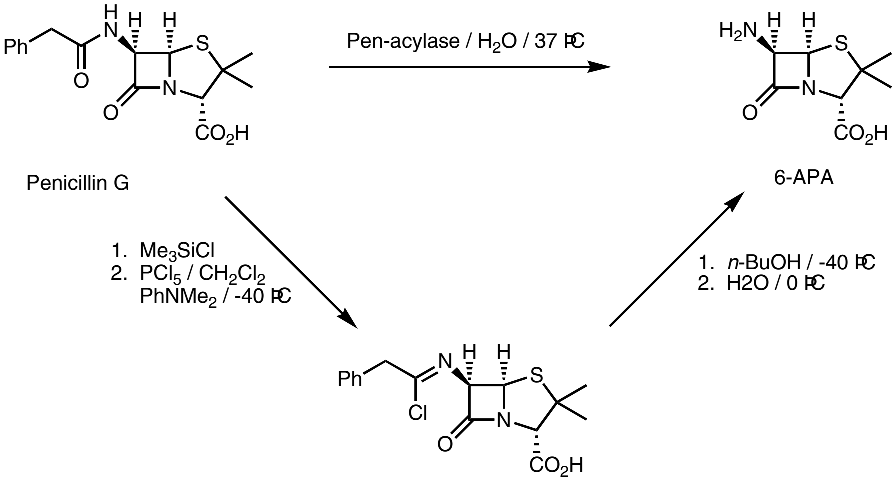


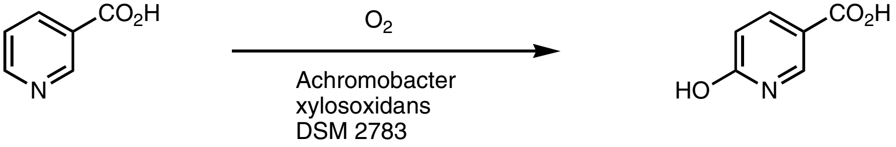
Figure 3. Some fermentation and biotransformation products.

Biocatalysis has been very useful in many penicillin transformations, and an interesting comparison between an enzymic process and the corresponding synthetic chemical process is shown in Scheme 1.[2]

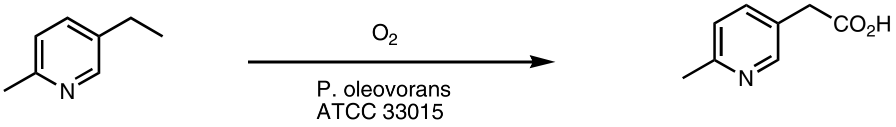


Scheme 1. Selective amide hydrolysis in penicillins

Two simple but very effective oxidations of pyridine derivatives are shown in Equations 4 and 5.[2]



Equation 4. Oxidation of nicotinic acid



Equation 5. Oxidation of 5-ethyl-2-methylpyridine

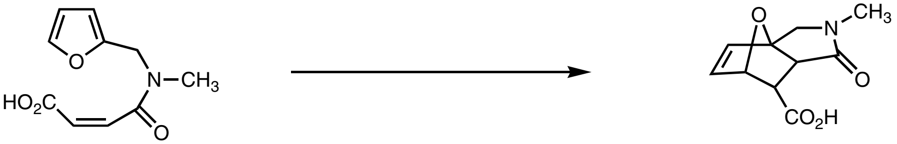
3.4. ALTERNATIVE SOLVENTS

A major source of waste in chemical processes relates to the use of solvents. Therefore improvements in reaction conditions that minimize the deleterious effects are urgently sought.[5] The essential points relating to solvents are summarized as follows:

- The design and utilization of solvents that have reduced potential for detriment to the environment and serve as alternatives to currently used volatile organic solvents, chlorinated solvents, and solvents that damage the natural environment

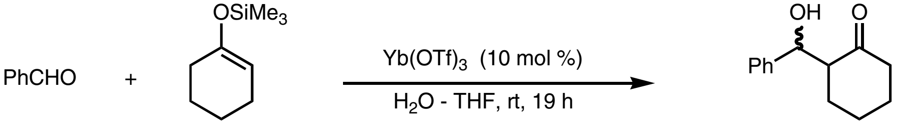
- Minimization of toxic organic solvents with high vapour pressure, and reduction in typically large volumes
- Often flammable, explosive, carcinogenic
- Phase transfer catalysis
- Reactions in water are desirable
- Solventless reactions desirable but limited
- Use of ionic liquids with low volatility
- Use of supercritical carbon dioxide.

A dramatic example of an alternative solvent is use of water for the Diels-Alder reaction of a furanyl acrylic acid: the rate was found to be 153 times faster than the corresponding reaction in hexane (Equation 6).[13] It was proposed that enforced hydrophobic and hydrogen bonding interactions are responsible.



Equation 6. Diels-Alder cyclization

Lewis acid catalysed aldol addition reactions can also be carried out very effectively in water. In the addition of the silyl enolate of cyclohexanone to benzaldehyde 50 equivalents of water gave an 80% yield of the product (Equation 7).[14]



Equation 7. Aldol reaction in water

3.5. DESIGN OF SAFER CHEMICALS

This area is one of the most dificult to achieve, and requires many different approaches.[5] The key considerations are summarized below:

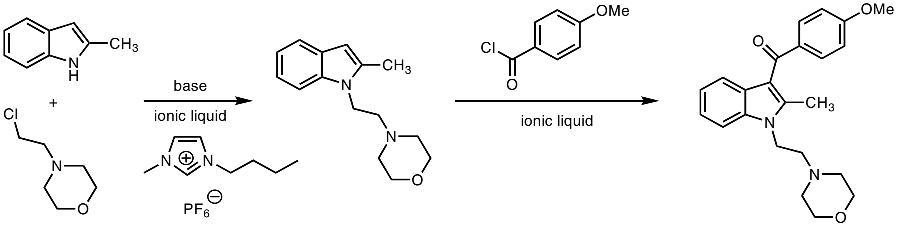
- Use of molecular structure design – and consideration of the principles of toxicity and mechanism of action – to minimize the intrinsic toxicity of the product while maintaining its efficacy of function
- Need to understand the mechanism of action
- Structure-activity relationships
- Elimination of 'toxic' functional groups
- Innovative and ingeneous molecular design
- Need for innocuous fate.

3.6. ALTERNATIVE REACTION CONDITIONS

This aspect overlaps with some previous ones, in that the various effects of solvent, waste prevention, selectivity etc., cannot be separated out into discrete categories.[5] The three main points are listed below:

- The design of reaction conditions that increase the selectivity of the product and allow for dematerialization of the product separation process
- Designed for efficiency and selectivity
- Usually associated with innovative solvents, e.g. SC CO_2 or ionic liquids.

Just a single example is given here, in Scheme 2, showing the synthesis of pravadoline, making use of an ionic liquid solvent.[15]



Scheme 2. Synthesis of pravadoline using ionic liquids

3.7. MINIMIZATION OF ENERGY CONSUMPTION

This is a fairly obvious area for investigation, and the main points are listed as follows:

- Reduction in mechanical, thermal, and other energy inputs
- Intrinsically linked to other "green" techniques, e.g. lower temperatures used with alternative solvents
- Catalytic processes operate with lower energy.

4. Conclusion

Green Chemistry has a major role to play in the chemical industry, to provide greater efficiency. Ideally chemical reactions should proceed with quantitative yield, low costs, and generating no waste. This is a great intellectual challenge, which will drive Green Chemistry forward. Any improvements will impact greatly on protection of the environment, and sustainable development, which in turn will result in improved quality of life for the benefit of human welfare in general.

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THE POSSIBILITY TO OBTAIN A NEW GENERATION OF IONIC LIQUIDS STARTING FROM NATURAL COMPOUNDS

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Abstract: Room temperature ionic liquids (ILs) have attracted considerable attention as novel reaction media over the last decade. By virtue of their unique properties, ILs have been proposed as alternative solvents. Structurally, most of the ILs that have been investigated to date are based on imidazolium, pyridinium and ammonium cations, associated with polyatomic anions such as chloroaluminates, tetrafluoroborate, hexafluorophoshate and bis-triflimide. Although these salts have positive properties, imidazole, pyridine and halogenoalkanes come from petroleum feedstocks that are neither green nor sustainable. Renewable resources may represent a valid alternative to synthesized new ILs; an alternative able to take into accounts both the ecological and economic requirements.

Keywords: Ionic liquids, renewable resources, natural materials

1. Introduction

Room temperatures ionic liquids (ILs)- salts with melting points below 100°C- have attracted considerable attention as novel reaction media over the last decade.[1] By virtue of their nonflammability, thermal stability and non-volatility ionic liquids have been proposed as alternative solvents receiving serious consideration with the promise of both environmental and technological benefits.[2] Really, recent data showing that commonly used ILs have very low but not null vapour pressures (they can distilled at low pressure),[3] that a large group of ILs is combustible[4] and some commercially available ionic compounds are toxic for some aquatic species,[5] have cast a shadow on the "green" character of ILs. The instinctive skepticism toward

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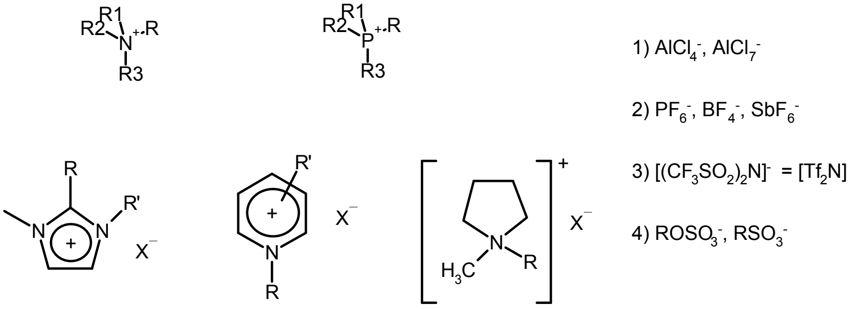
novelty has found therefore a re-enforcement in these latter data. Doubts and diffidence arise essentially from the unjustified attribution to all ionic liquids in general of features which have been observed for selected classes of ILs. The term “ionic liquids” defines an extremely large class of salts (the number of possible ionic liquids has been evaluated higher than 10^{14}) and the properties (positive or negative), characterising a group of ILs cannot be extended to all low-melting ionic compounds. Probably, the most attractive feature of ILs is just the fact that the extremely high variability of ions can give rise to specific properties and behaviours. These properties have favoured their application as solvents in chemical reactions and in catalysis, in electrochemistry, in analytic chemistry and as “engineering fluids” in batteries and fuel cells and, now, they are favouring the development for applications in new, and sometimes, surprising areas of chemistry and technology; as biosensors, in lubrification, as rocket propulsions, in textile and so on.

All the physico-chemical properties strictly dependent upon the precise nature of the cation and anion constituting the IL and they can be changed or modulated by changing the anion or cation or modifying the nature of substituents on cation. Structurally, most of the ILs that have been investigated to date are based on imidazolium, ammonium and pyridinium cations, bearing alkyl chains, associated with polyatomic anions such as chloroaluminates, tetrafluoroborate, hexafluorophosphate and bis-triflimide. In Scheme 1 are reported the above mentioned cations and anions whose combination gives the most commonly employed ionic liquids.



Scheme 1. Cations and anions of common ionic liquids

Recently, also ILs bearing functional groups on the cation or anion have received attention as designer media in catalysis and material sciences. The presence of specific groups on the cation (alcohols, ethers, amines, amides, acids, thiols, alkenes, alkynes, nitriles, ferrocenyl groups) or on anion is able to impart highly specific properties to the ionic liquid.[6] These salts, which are generally named as "task-specific ionic liquids", may show an increased hydrogen bond ability, increased basicity or acidity, specific ability to complex metals or to bind simple molecules, such as CO_2. Consequently, design of new ionic liquids has become one of the most active areas of research. However, for a rational design it is necessary to correlate the key physico-chemical properties of the already investigated ILs to their chemical structure; an ability this latter not completely developed. However, bulk properties such as melting point, viscosity, density, refraction index have been determined[7] for many ionic liquids and several attempts have been made to correlate these properties to structural features.[8]

Also the question "How polar are ionic liquids" has been addressed by many methods that previously have been used to characterize the polarity of common molecular solvents. The macroscopic constant, generally used by the chemists to evaluate the solvent power of a molecular liquid, the dielectric constant, has been evaluated in the case of ILs initially using indirect methods,[9] and more recently by microwave dielectric spectroscopy.[10] Generally, the values found for the investigated ILs are moderate and, at least those obtained by microwave dielectric spectroscopy, insignificantly affected by the IL structure.

Ionic liquids are however more just than a bulk medium and the dielectric constant may be not the best parameter to define ILs polarity. They are constituted by positive and negative ions which can exert various effects. Recently, the microscopic properties of ILs, i.e. the ability of these media to interact with specific dissolved species (reagents, transition states, intermediates and products), have been measured and several polarity scales, previously developed for common molecular solvents, have been extended to ILs.[11] At variance with molecular solvents, ILs are characterized by complex interaction forces between anion and cation and these interactions are competitive with the ability of both anion and cation to interact with dissolved species; thus, multiparameters solvatochromic correlations, better than single point measurements, resulted useful to understand the solvent polarity.[12]

Kamlet-Abbaud-Taft parameters have been determined for several ILs showing that dipolarity- polarizability, expressed by π^* parameter, is relatively high and depends on both the anion and cation; hydrogen bond donating ability (α) is moderately high for a variety of ILs and depends on cation, although it is affect also by the anion; hydrogen bond acceptor ability (β) is moderate for many imidazolium, pyridinium and ammonium salts but depends on the anion. Although the polarity scales of the investigated ILs, obtained using different probes are not exactly the same, the values reported to date in literature show that ILs can be consider polar (but not super polar) solvents, with generally low nucleophilicities. A combination this latter, thought to be responsible for some of the peculiar properties of ILs.

It is however noteworthy that care is needed while estimating polarity of ILs using solvatochromic dyes, and more in particular from the measured fluorescence maxima of dipolar systems.[13] As evidenced by Samanta *et al.*, salvation is a slow process in ILs, only those systems having fluorescence times longer than the solvation time can ensure that the frequency corresponding to the maximum represents the solvation equilibrium energy. The mechanism of solvation in ILs is fundamentally different from that in polar molecular solvents. In these latter media the net force acting on the solvent molecules due to the change in the electric field of the dipolar molecules can be taken to be zero. Consequently, the dipolar solvent molecules undergo reorientation around the photoexcited species without moving from their original positions. At variance, due to the charge, the ionic moiety of the ILs experiences a net force when the dipole moment of the solute changes on photoexcitation. As a result, the ions move from their initial position and, hence, the translation motion of the constituent ions mainly contributes to solvation in the case of ILs. Moreover, the fluorescence response of a dipolar system in ILs can be dependent on the excitation wavelength.[14] This unusual behaviour has been rationalized[14] considering the presence of various energetically different associated forms of the constituting ions and the inefficiency of the energy transfer process between the photoexcited species and other species having low-lying excited states. The most peculiar property of ILs is indeed the pronounced supramolecular self-organization both in the condensed[15] and gas phase.[16]

The strong ion-ion interactions present in the ILs lead to high ordered three-dimensional supermolecular polymeric networks of anions and cations linked by hydrogen bonds and/or Coulombic interactions, producing a completely different environment with respect molecular solvents. ILs can be therefore considered nanostructurally organized materials, with ionic networks permeated by non-polar region.[17] ILs exhibit medium-range ordering and simulation studies points out their slow dynamic and the persistence of local environments, typical of the glassy state.[18] Generally, these salts are composed by charged head-groups, with nearly net charges, and nonpolar tails (generally, alkyl chains), with little charge. Electrostatic interactions dominate the head groups and anions, while the non polar part interacts through collective short-range interactions. These latter inter-actions may be important in ILs characterized by cations bearing long chains: tail groups can aggregate forming spatially heterogeneous domains. The existence of microphase aggregation between polar and unpolar regions changes the way in which salvation can be understood.[19]

It is noteworthy that the nature of anion and cation determines the structural organization of ILs, the dimension and localization of polar and unpolar regions, and therefore their macro- and microscopic properties.

In conclusion ionic liquids can be considered a mixing of general salt effects and ion-specific effects, often only partially investigated and understood, which make them fascinating media having new and improved properties.

From the application point of view, there are many reasons to favour the development of the IL chemistry and many reasons for considering new "non-imidazolium" and "non-pyridinium" ILs. Although these salts have positive properties, imidazole, pyridine and halogenoalkanes come from petroleum feed-stocks that are neither green nor sustainable.

Renewable resources represent a valid alternative able to take into accounts both the ecological and economic requirements and several groups are developing new classes of ILs starting from natural compounds. It is noteworthy, that many of these compounds contain one or two chiral centres and their use to obtain ILs has contributed to the development of the interest in chiral ionic solvents (CILs).[20]

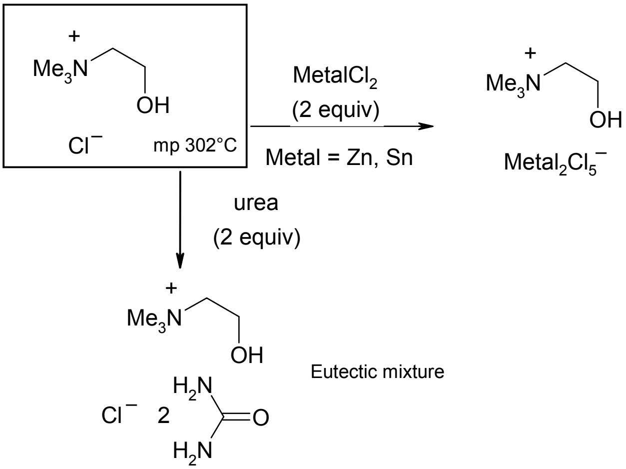
2. Organic Cations from Natural Sources

2.1. NATURAL COMPOUNDS CONTAINING NITROGEN

Natural nitrogen containing compounds (amines, aminoalcohols and amino acids) have been the first substrates used to obtain cations (ofetn asymmetric cations), although more recently also other classes of natural compounds have been employed.

The simplest approach to obtain ILs from natural sources is surely the direct use of quaternary ammonium salts. Choline chloride, a salt melting at 302 °C, has been transformed recently by Davies and co-workers[21] in a fluid at room temperature by mixing the organic salt with metal chlorides or other simple organic compounds (such as, urea or polyalcohols), which depress the melting point producing liquids with significant ionic character (Scheme 2).[22] These liquids systems are known as eutectic mixtures.

Following the approach previously applied to imidazolium and pyridinum chlorides, which were transformed in ionic liquids by addition of $AlCl_3$, chloline was initially combined in a 1:2 ratio with tin(II)chloride or zinc(II)chloride. The resulting eutectic mixtures, arising from the formation of complex anions, e.g. $Zn_2Cl_5^-$ or $Sn_2Cl_5^-$, are liquid at room temperature, not moisture-sensitive and characterized by interesting catalytic properties.



Scheme 2. Transformation of choline in fluids at room temperature

Unfortunately, both these liquids are highly viscous and this feature has limited their application.

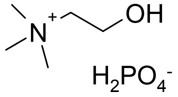
Subsequently, to circumvent the use of metal in ionic fluids a larger variety of eutectic solvents were prepared by complexing the choline chloride with a range of hydrogen donors, such amides[22] and carboxylic acids.[23] The complexing agent interacts with the chloride anion, increasing its effective size. This in turn decreases the interaction with the cation and consequently decreases the freezing point of the mixture. The major advantage of this approach is that common, non-toxic components can be used and the properties of the resulting liquids can be tuned, changing the hydrogen bond donor. These liquids are similar to the metal-containing ionic liquids, but to differentiate them from the wide range of ionic liquids that are available, they have been given the name deep eutectic solvents (DES). The deep eutectic phenomenon was first described in 2003 for a 2 to 1 by mole mixture of choline chloride and urea. Choline chloride, as reported above, has a melting point of 302°C, that of urea is 133°C but the eutectic mixture melts as low as 12°C. Eutectic solvents, analogously to common ILs, have a very low volatility and are non-flammable. Moreover, they are unreactive with water, many are biodegradable and the toxicological properties of components are generally well known. Compared to ILs, which share many characteristics but are ionic compounds and not ionic mixtures, deep eutectic solvents are cheaper and easier to make; simply, it is necessary to take the two solids, mix them together with gentle heating until they melt, and when they cool they remain liquid.

Several deep eutectic solvents of choline chloride have been therefore formed with a wide variety of other hydrogen bond donors such as acids, amines and alcohols. Generally, the physical properties are significantly affected by the structure of the hydrogen bond donor but the phase behavior can be modeled considering the mole fraction of the components in the mixture. The physical properties such as viscosity, conductivity and surface tension of these DES are similar to room temperature ILs. Moreover, the DES are shown to be good solvents for some metal oxides. The dissolution of metal oxides is fundamental for a range of important processes such as metal winning, catalyst preparation and corrosion remediation. Furthermore, these solvents are applied for electroplatining and should have potential application in electropolishing.[24]

It is noteworthy that the different solubilities and reduction potentials, evidenced for a variety of metal oxides using choline based DES, provided a new strategy for separating selected metal oxides from mixed oxide matrices.[25]

Moreover, recently DES of choline chloride/urea (or malonic acid) have been used as solvents in the synthesis of new coordination polymers, $Zn(O_30PCH_2CO_2)NH_4$, of open-framework iron oxaphosphates and aluminophospate zeolite analogues.[26] Generally, the ionic medium not only acts as a solvent but also provides the template cations around which the inorganic frameworks order.

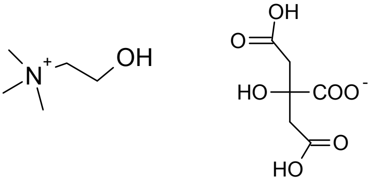
Finally, it is to mention that DES are good solvents also for strong hydrogen-bonding compounds, such as unprotected sugars and cellulose, whereas simple choline salts having as counteranion acetate, citrate, dihydrogenphosphate (Scheme 3) and saccharinate have been proposed as unique solvents for important biomolecules, such as proteins.[27] It has been shown that some proteins are soluble, stable and remain active in these ILs.



Scheme 3. Choline dihydrogenphosphate

More in particular, cytochrome c can be dissolved in choline dihydrogenphosphate, containing 10–20% of water, up to final concentration of 37 mg/ml. Very significantly, the secondary structure of the enzyme is retained in the IL solubilized protein, and the thermal stability increases. The nature of the anion seems to be fundamental for the application in biocatalysis; the dihydrogenphosphate anion provides both a proton activity similar to that of neutral water and, contemporaneously, it is able to hydrogen bond donor and acceptor sites.

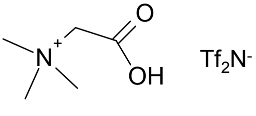
Choline dihydrogenphosphate, choline acetate and choline citrate (Scheme 4) show improved properties, with respect common molecular solvents and imidazolium based ILs, also in the chloroperoxidase-catalyzed reactions.[28] In the presence of these cosolvents (up to 70%) the conversion of methyl phenyl sulfide to the corresponding sulfoxide, leads to satisfactory yields and very good enantioselectivities. In addition, over-oxidation of the sulfoxide to the sulfone is not observed.



Scheme 4. Choline citrate

Although many ionic liquids and deep eutectic mixtures based on choline have the advantages to be cheap and no-toxic, they are all hydrophilic and miscible with aqueous solvents. This may be a problem for applications such as the extraction of metal ions from an aqueous phase or the electro-deposition of reactive metals (aluminium, magnesium, tantalum..).

Recently, a protonated betaine bis(trifluoromethylsulfonyl)imide (Scheme 5) has been proposed as a versatile hydrophobic alternative to choline salts.[29]

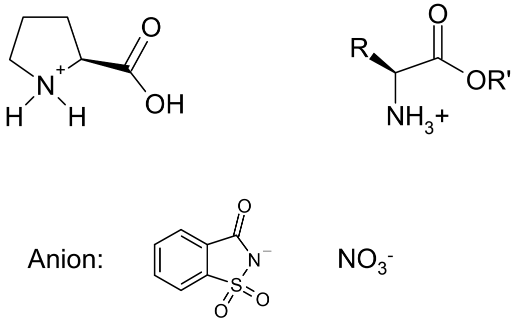


Scheme 5. *N,N,N*-trimethylglycine bis(trifluoromethylsulfonyl)imide.

This ionic liquid, having *N,N,N*-trimethylglycine as cation and being practically the oxidized form of choline, is able to dissolve large amounts of metal oxides. This metal solubilizing power is selective, making possible separation of metals. Moreover, the metals can be stripped from the ionic liquid by treatment with an acidic aqueous solution. Protonated betaine bis(trifluoromethylsulfonyl)imide can be switched from a hydrophobic IL to a hydrophilic one by temperature or pH control. At high temperature, or under basic condition (pH > 8), this IL and water form a sole phase whereas at room temperature, for acidic and neutral conditions, a two-phase system is obtained.

In the last year also other natural compounds, containing a non-quaternary nitrogen atom (and frequently a chiral carbon) have been used to synthesize chiral ILs (Scheme 6).[30] It is noteworthy, that although amino acids and their derivatives are the most abundant source of nitrogen containing compounds, their use to prepare ILs is relatively recent.[30]

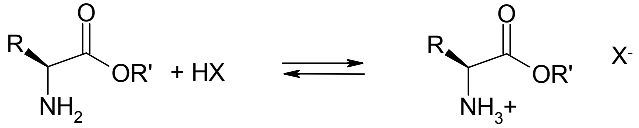
In particular, a family of novel ionic liquids with amino acids, or their ester derivatives as cations, and environmentally benign materials as anions have been synthesized using easy preparation techniques. The ionic liquids obtained have practically the same characteristics (thermal stability, phase behaviour and miscibilities) as conventional imidazolium ionic liquids and the same chiralities as natural amino acids. Most of the salts obtained by simple acidification of the aminoacids have however high melting points, whereas those arising from the corresponding ester derived salts are viscous oils at room temperature. Despite the high viscosity, these ILs have been used as catalysts and solvents in the cycloaddition of cyclopentadiene to methyl acrylate, a typical Diels–Alder reaction, showing that amino acids and their derivatives can serve as an alternative to traditional ionic liquids having synthetic chemical components.



Scheme 6. Amino acids based ionic liquids

It is noteworthy that all these salts behave to the class of protic ILs, formed *via* neutralization.

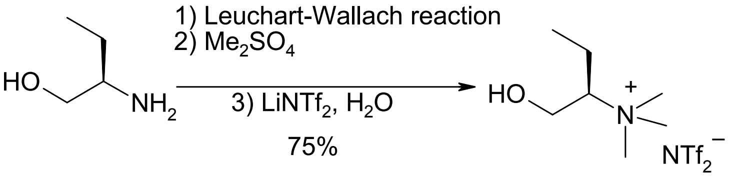
Angell *et al.* have discussed the general properties of such ionic liquids[31] evidencing that all the neutralization reactions are really equilibria, which may not lie completely towards the ionized form, unless the relative acidity of the acid and protonated base are such that there is strong tendency towards the ionized forms (Scheme 7).



Scheme 7. Protonation of amino acids and ester derivatives

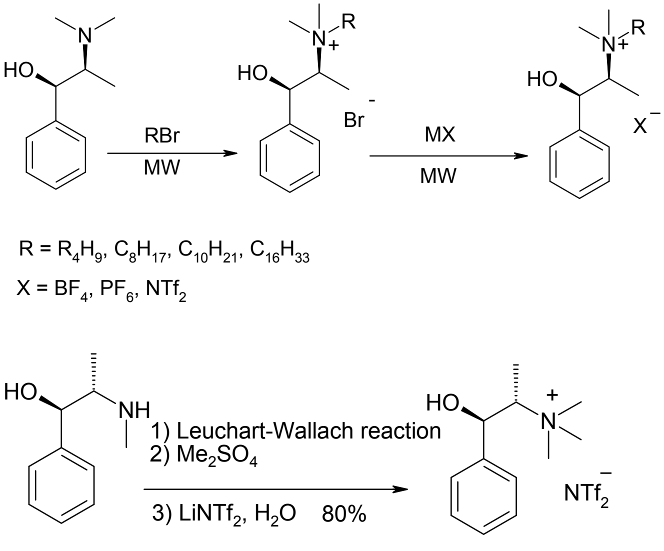
In other words, like many other lower-melting point salts, ionic liquids arising from protonation of amino acids and their ester derivatives may not be “ionic liquids” in a strict sense. The situations where the neutral acid and base represent some tens of mol% of the ionic liquid should be described as liquid mixtures, containing the ionic liquid and neutral species, whereas the term ionic liquid should be used for situation in which the percent of ionization is higher than 99%.[32] Unfortunately, values for equilibrium constants for such reactions are unknown under these (non-aqueous) conditions and they are not easy to measure, therefore this distinction may be made at the moment only on the basis of the data in aqueous solution.

At variance, alkylation of natural nitrogen containing compounds gives always ILs in strict sense. Chiral quaternary ammonium salts have been synthesized recently from (-)ephedrine and (R)-2-aminobutan-1-ol, unfortunately using no-green conditions (dimethyl sulfate in dichloromethane), followed by anion exchange (Scheme 8).[33a] The ammonium salt arising from and (R)-2-aminobutan-1-ol, and having Tf_2N^- as counterion, is liquid at room temperature (mp –18 °C) whereas that synthesize from ephedrine has a mp of 54 °C. This latter was used as chiral shift reagent in NMR investigation, showing a resolution ability towards the sodium salt of the Mosher acid. Moreover, the same class of chiral ILs has been used as stationary phase in gas chromatography, confirming the ability to discriminate between enantiomers.[34]



Scheme 8. Transformation of amino alcohols in quaternary ammonium salts.

More recently, ephedrinium salts have been synthesized under solvent free and microwave activation (Scheme 9).[33b] Their application as sole source of chirality in the Baylis-Hillman reaction has represented the first example of significant asymmetric induction by a chiral ionic solvent (ee 20-44%).

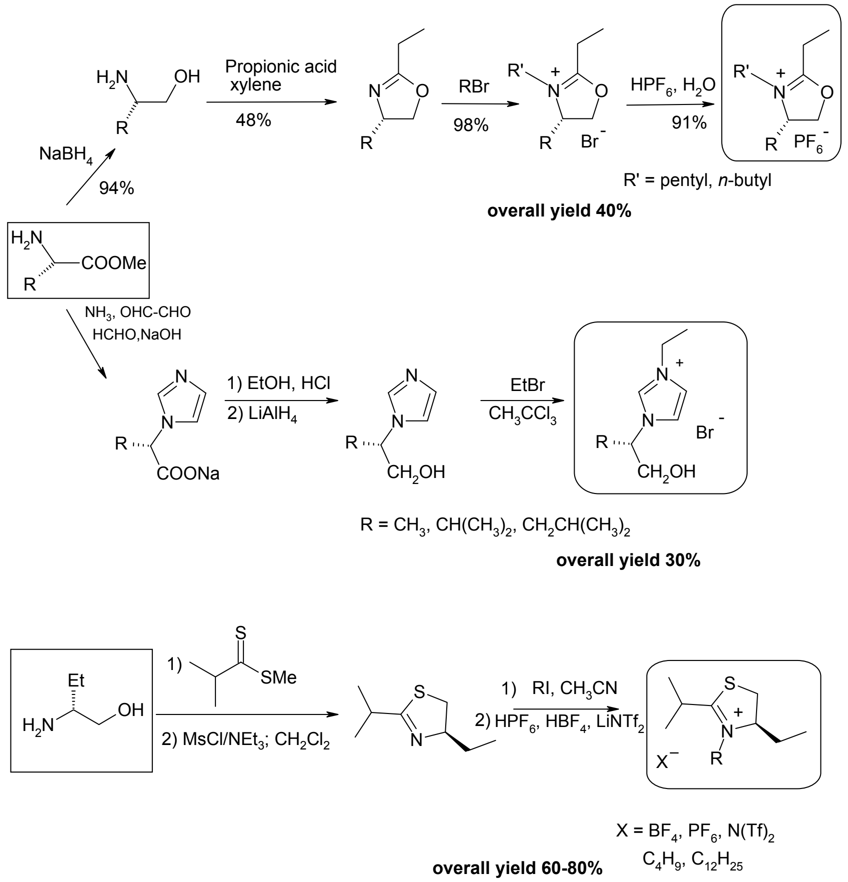


Scheme 9. Transformation of ephedrine in quaternary ammonium salts

Amino alcohols and amino acids have also been transformed in heterocyclic systems, generally through a more complex sequence of reactions. Chiral oxazolium and imidazolium[35] ionic liquids have been obtained starting from natural amino acids, whereas amino alcohols have been transformed in thiazolium based ILs (Scheme 10).[36]

Although the oxazolium ILs can be prepared on multigram scale, the relative low overall yield and the low stability under acidic conditions have limited their use as solvents.

More promising results have been obtained in the case of thiazolium ILs, which can be prepared in higher overall yield and are stable under basic and even acidic conditions.[36]



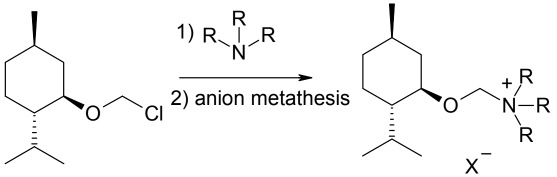
Scheme 10. Oxazolium, imidazolium and thiazolium ionic liquids from natural amino acids and amino alcohols.

2.2. NATURAL COMPOUNDS NOT CONTAINING NITROGEN

The presence of a nitrogen atom is not essential to transform natural compounds in ionic liquids. Recently, ionic liquids have been synthesized from alcohols and polyhydroxylated compounds (sugars) after transformation of the hydroxyl group on the primary carbon(s) in a more efficient leaving group (halogen, tosylate, triflate, and so on).

Feder-Kubis and coworkers have proposed[37] the synthesis of an ionic liquid based on (*1R,2S,5R*)-(-)-menthol, starting from the corresponding chloromethyl

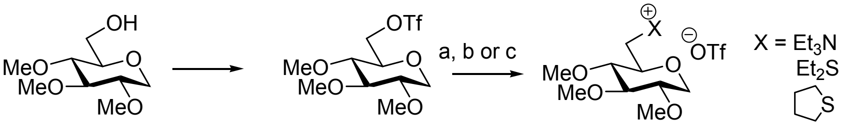
chloromethyl derivative through a simple Menschunkin reaction (Scheme 11).[37] Since these chloride salts generally exhibit rather high melting points (the sole exception being the trimethyl derivative, mp = 31-33 °C), the initially formed salts were converted in the corresponding bis(triflimide) derivatives by anion metathesis, obtaining a new family of viscous liquids. The same starting material and its enantiomer were used by Armstrong[38] for the synthesis of chiral imidazolium salts.



X = PF_6, NTf_2, CF_3CO_2, NTf_2

Scheme 11. Transformation of (*1R,2S,5R*)-(-)-menthol in ionic liquids

Since the primary hydroxyl site of carbohydrates can be easily and selectively functionalized to the corresponding triflates or tosylates, this approach has been followed to synthesize chiral ammonium and sulfonium triflates starting from selectively protected 1-deoxy sugars (Scheme 12).[39] The absence of any substituent at the anomeric position increases the chemical stability of these ILs.

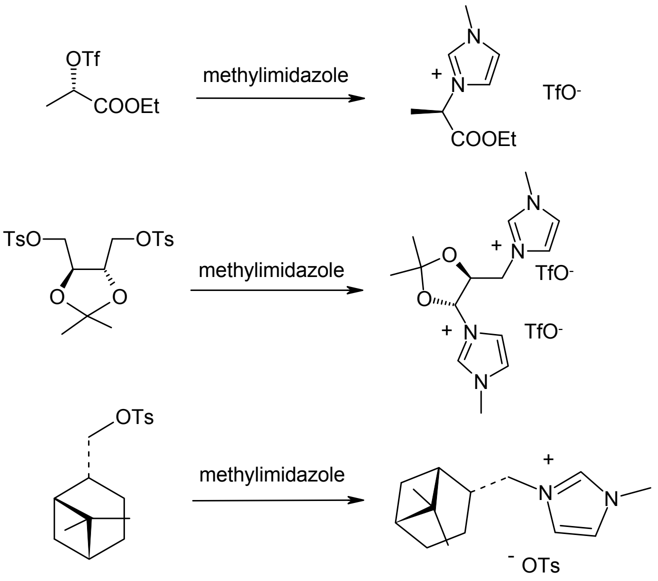


a) THF, TEA, -20 °C; b) Et_2S, 60 °C; c) tetrahydrothiophene, 60°C

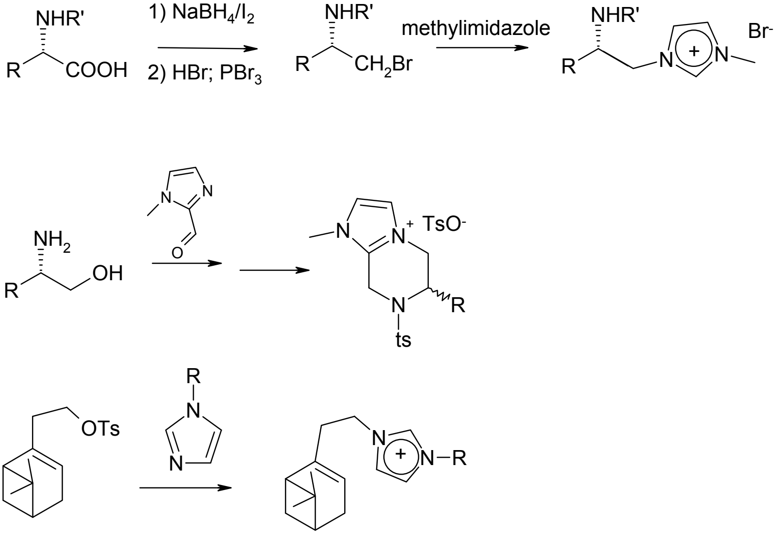
Scheme 12. Trasformation of 1-deoxy sugars in ionic liquids

However, also simple carbohydrates have been transformed in ILs. D-Mannitol and methyl D-glucopyranoside have been used to obtain chiral ionic liquids starting from the corresponding tosyl derivatives by reaction with 4-(dimethylamino)pyridine. A modified tosylation procedure was used in both cases.[40]

The strategy to use chiral compounds, arising from biological sources and available at reasonable cost, to synthesize functionalized imidazolium and pyridinium ILs has been really followed more times and several classes of chiral ILs have been obtained (Scheme 13).[41]



Scheme 13. Functionalized imidazolium ionic liquids from natural compounds.

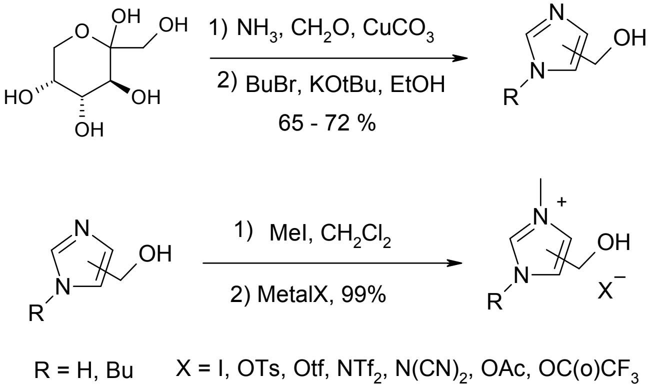


Scheme 14. Other functionalized imidazolium ionic liquids from natural com-pounds.

Recently, also chiral ILs bearing an amino group on the alkyl chain or including fused ring systems has been designed and synthesized using the same approach (Scheme 14).[42]

It is however noteworthy that the synthesis of all the latter salts implies the use of imidazole which, as previously evidenced, arises from petroleum. Really, imidazolium cations can be obtained also from natural compounds, as evidenced by Handy *et al* (Scheme 15).[43] Fructose has been converted into hydro-methylimidazium based ILs after two sequential alkylations and an anion metathesis step.

This class of protic ionic liquids resulted miscible with polar molecular solvents such as acetonitrile, acetone, methylene chloride and ethyl acetate, remaining immiscible with hydrocarbon solvents. Two different applications have been reported by the same authors: as solvents in the Heck reaction and as supports for homogeneous supported-phase synthesis.



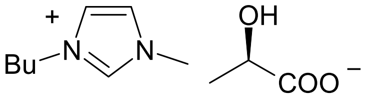
Scheme 15. Imidazoliun ionic liquids from fructose.

3. Ionic Liquids Anions from Natural Sources

The possibility to use anions arising from natural or renewable materials to prepare ILs has been marginally investigated. Chloride, the most ubiquitous naturally occurring anion, typically forms high melting salts whereas other simple anions, such as sulfate and phosphate, have likewise been largely avoided, although a report by Engel and coworkers shows that phosphate based room temperature ionic liquids are readily achievable with a wide variety of quaternary ammonium salts.[44]

Moreover, the popularity of tetrafluoroborate and hexafluorophosphate imidazolium salts and the improved properties evidenced more recently by ILs having bis(triflimide) as anion have probably discouraged the research of new anions, although several common natural carboxylates (acetate, lactate, tartrate and citrate) have jerkily been used.

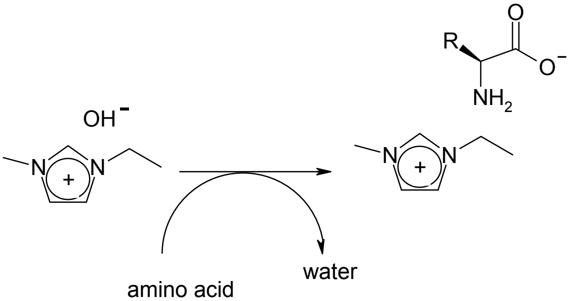
In 1999, R.K. Seddon and coworkers reported the use of [bmim][lactate] (Scheme 16) as solvent in the Diels-Alder reaction between cyclopentadiene and acrylonitrile or ethyl acrylate.[45]



Scheme 16. Ionic liquids having amino acids as anions

The lactate salt provided a slightly lower *endo/exo* selectivity than the corresponding triflate or tetrafluoroborate salts whereas the reaction rate, determined in [bmim][lactate], was between those characterizing the other two salts. Unfortunately, no enantioselectivity was observed for this cycloaddition process when performed in the chiral lactate salt. Lactates have been no more synthesized for long time.

More recently, natural amino acids have been used to develop room temperature ionic liquids in which the anion is the natural compound. In the first paper, published in 2005 by Ohno and coworkers,[46] a new class of chiral ionic liquids was prepared starting from 1-ethyl-3-methylimidazolium hydroxide and 20 different natural amino acids (Scheme 17). All of the resulting salts are transparent and nearly colorless liquids, showing a glass transition temperature ranging from -57 °C to 6 °C. Unfortunately, they are high viscous liquids characterized by a moderate thermal stability.

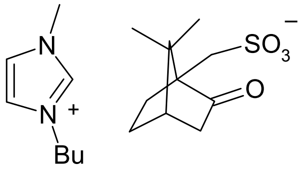


Scheme 17. Transformation of 1-ethyl-3-methylimidazolium hydroxide in ionic liquids having amino acids as anions

It is to note that, although ammonium and pyrrolidium based amino-acid ionic liquids, subsequently prepared by the same authors, do not show improved properties compared to the corresponding imidazolium based salts, positive results have been obtained introducing the tetrabutyl-phosphonium cation.[47]

In particular, these ILs when supported on silica gel effect fast and reversible CO_2 absorption. The CO_2 absorption capacity at equilibrium is 50 mol% of the ionic liquid but in the presence of water (1 wt%), the ionic liquids can absorb equimolar amounts of CO_2.[48]

In the same year (2005), it has been reported also the synthesis of camphor based imidazolium ionic liquids (Scheme 18).[49] It is noteworthy that, despite the high molecular weight, the imidazolium camphor salt [bmim][CS] is a viscous liquid even on a salted ice bath, while [bmim][CH_3SO_3] is solid at room temperature.

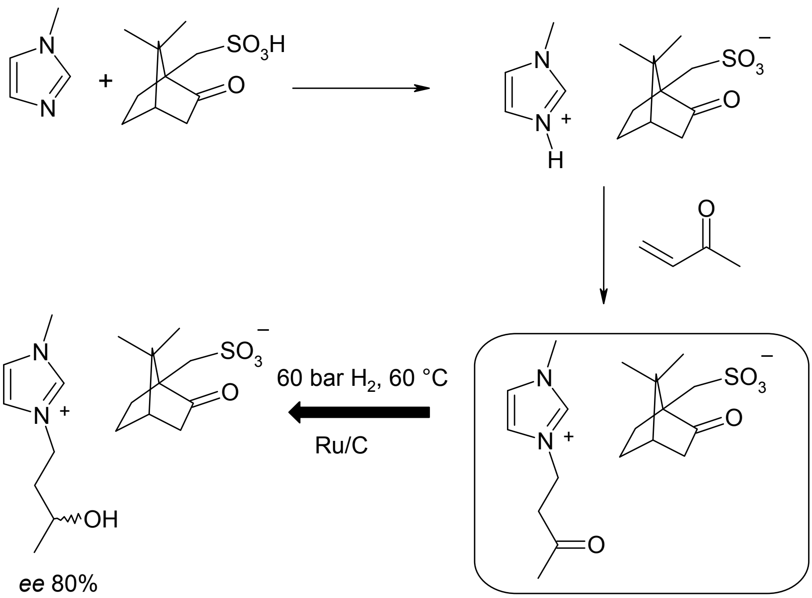


[bmim][CS]

Scheme 18. Camphor based ionic liquids

The bulk camphorsulfonate anion seems therefore to have a reduced packing ability. Furthermore, it is a chiral anion. The ability of the (R)-camphorsulfonate anion to transfer the chiral information has been recently evidenced by Wasserscheid and co-workers through an elegant experiment (Scheme 19).[50] To demonstrate the great potential of the ion-pairing effects in chirality transfer, the asymmetric hydrogenation of a keto group present on the imidazolium counterion was investigated using [N-(3'-oxobutyl)-*N*-methylimidazolium][(R)- camphorsulfonate] as the model substrate. This functionalized cation was prepared using an alternative and far more efficient method: by protonation of methylimidazole with (R)- camphorsulfonic acid followed by Michael-type addition of methyl vinyl ketone, in an overall yield of over 95%.

The hydrogenation reaction proceeds up to 80% *ee* to give the expected product, a doubly chiral ionic liquid bearing the enantiomeric pure (R)-camphorsulfonate anion. Ethanol has been used as diluting solvents in these reactions since the IL was too viscous for the reaction to be run under solvent free conditions. The concentration dependence of the chiral induction



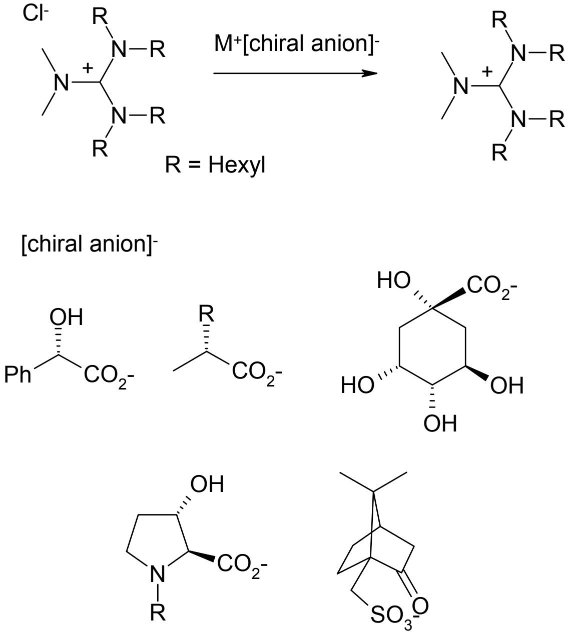
Scheme 19. Synthesis of camphor based ionic liquids by Michael addition and asymmetric hydrogenation. An example of transfer of the chiral infor-mation through ion-pairing effects.

has been therefore considered evidence able to support the hypothesis that the chiral induction is based on ion-pair interactions.

At the same time, the degree of chiral induction has been taken as a probe of the intimacy of cation-anion interaction in the transition state of the hydrogenation reaction.

Recently, also a guanidinium camphor salt has been prepared by Afonso *et al.* (together with other chiral salts), simply combining the tetra-*n*-hexyl-dimethylguanidinium cation with readily available chiral crystalline anions. Noticeably, the IL with lactate as anion has low viscosity and a lower T_g value (Scheme 20).[51]

Moreover, using the chiral IL [(di-h)$_2$-dmg]quinic] as sole source of chirality in the Sharpless dihydroxylation of 1-hexene and styrene it was possible to isolate the corresponding diols in high yields (>92%) and high

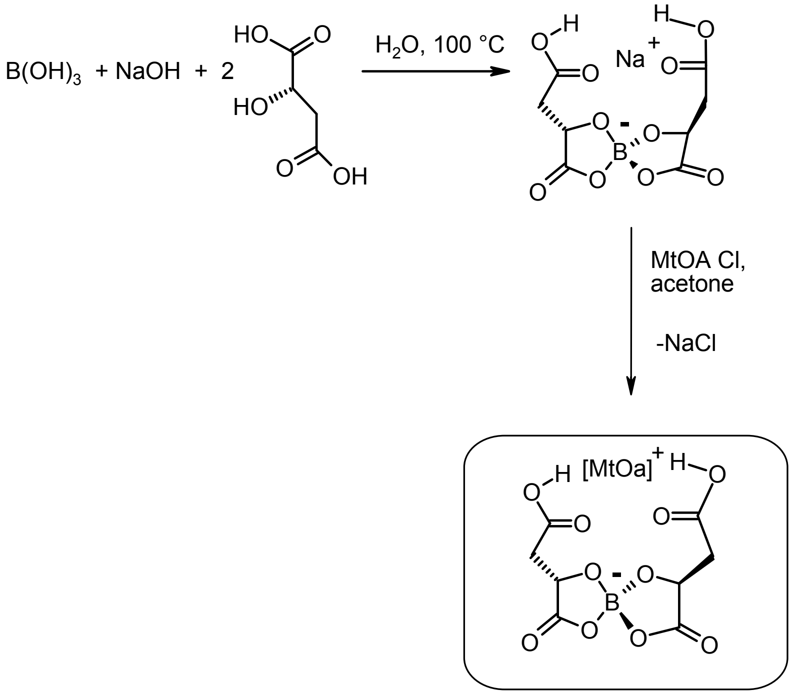


Scheme 20. Ionic liquids based on guanidinium cation and natural chiral anions.

enantiomeric excesses (85 and 72%, respectively). These results can be mentioned among the highest values of enantioselectivity induced to date by a solvent.

Finally, liquids bearing chiral boronate anions have been synthesized starting from boric acid, sodium hydroxide and chiral hydroxyl acids (l-malic acid, mandelic acid and diethyl tartrate) followed by the exchange of the sodium ions with methyltrioctylammonium (Scheme 21).[52]

The obtained ionic liquid, methyltrioctylammonium dimaloborate, has been used as the only source of chirality in the aza-Baylis-Hillman reaction between methyl vinyl ketone and N-(4-bromobenzylidene)-4-toluenesulfonamide using PPh3 as catalyst, obtaining enantioselectivities up to 84% *ee*.



Scheme 21. Ionic liquids bearing chiral boronate anions.

4. Conclusions

In conclusion, nature provides a vast new vista of opportunities for the preparation of new recyclable, biodegradable, chiral and/or functionalized ionic liquids, having improved biocompatibility. These solvents, which can be obtained often through simple derivatization procedures, have potential to find applications as media in organic synthesis and catalyzed processes, in the separation sciences (GC, HPLC) and probably as materials in more specific applications. Moreover, considering that many natural products contain chiral carbons, these ILs can be used as inductors of chirality in organic synthesis. Therefore, a new generation of ionic liquids having improved properties can arise from natural sources.

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CATALYSIS IN IONIC LIQUIDS: A KEY TO SUSTAINABLE CHEMISTRY

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Abstract: a key to the development of innovative sustainable technology platforms is represented by the combination of different green strategies. The access to new synthetic processes deriving from the merging of heterogeneous catalysis with intrinsically safer solvents such as ionic liquids, and possibly using flow through techniques, is discussed in this chapter. Examples taken from the very recent literature are analysed and classified according to four different strategic approaches to generate catalysis in ionic liquid media; (i) the ionic liquid is the solvent for the catalytic reaction, (ii) the ionic liquid is both the solvent and the catalyst (or pre-catalyst), (iii) the ionic liquid is simply used as the catalyst, easily removable from the reaction mixture, (iv) the ionic liquid is supported in the form of a thin layer on a solid support. In the last case, the solid material is exploitable in fixed bed reactors, thus rendering possible the application of continuous flow technologies.

Keywords: Heterogeneous catalysis, biphasic catalysis, ionic liquids, task-specific ionic liquids, supported ionic liquid phases

P. Tundo and V. Esposito (eds.), *Green Chemical Reactions.*

1. Introduction

The last decade has endorsed an ever increasing focus on Green Chemistry issues owing to the ever spreading awareness of the urgent need to devise sustainable chemical processes in the face of a rapidly growing consumer population. A number of tenets have been elaborated in the twelve rules of Green Chemistry; here we wish to demonstrate the power of cooperativity when two green technologies are coupled in a chemical process, for example "catalysis" with its apparent impact on the process mass balance, and innovative solvents such as ionic liquids (ILs), a virtually infinite class of solvents with tunable properties and with no significant vapor pressure.

Homogeneous catalysis provides one of the most efficient and environmentally sustainable routes to high added-value chemicals and is of central importance to modern synthetic and pharmaceutical chemistry. Homogeneous catalysis has the advantage over heterogeneous catalysis that all of the catalytic centres metal are available to the reagents, and so it is inherently more efficient in terms of catalytic activity and of selectivity[1] However, the high catalyst loadings (usually 1–10 mol% and even more, in the case of organocatalysis) and the difficulties associated with recovery and reuse of expensive chiral catalysts severely hampers its practical applications. In addition, metal contaminants can leach from the homogeneous catalysts into the products (this contamination is particularly unacceptable in pharmaceutical productions) or into the environment. One of the most promising solutions to these problems is represented by the heterogenisation of homogeneous catalysts.[2] The most widely used heterogenisation procedure involves the anchoring of the catalytically active species onto the surface of a solid support. In principle, it is possible to prepare heterogeneous analogues of most, if not all, of the most commonly used soluble and homogeneous catalysts. Recently an alternative "self-supporting" approach to the heterogenisation of homogeneous chiral catalysts has been developed, which exploits the self-assembly of chiral multitopic ligands with metal ions to deliver solid metal-organic coordination polymers.[3]

Thanks to the extensive studies in the last years on ionic liquids as alternative solvents for homogeneous catalysis, the recourse to liquid-liquid biphasic catalysis is now a common way to heterogenisation. The result is that the catalyst and the product are confined into two separate and immiscible liquid phases, for example an aqueous phase[4] or a molecular organic solvent,[5] and an ionic liquid.[6] The catalyst is dissolved in the IL phase, and the substrate resides in the other phase. During reactions, the two layers are vigorously stirred, thus allowing suitable interaction of catalyst and substrate. Eventually, the mixture of phases separates into two layers, one containing the product and the other containing the catalyst. Separation is carried out by simple decantation or phase separation, and in principle, the catalyst solution is available for immediate reuse.

Despite the chemistry of ionic liquids is still in its infancy, an exponential growth of work in this field was recorded over the last 7 years, as witnessed by a number of recent review articles on ILs.[7]

Details about ILs properties are covered in this book in the contributions by Seddon, Chiappe and Scott. However, two features deserve a comment for their possible consequences on reactivity and catalysis. First, depending on a delicate balance of entropic and enthalpic factors, including the polarity of the transition state structures with respect to regents, a reaction can be either speeded up or decelerated when carried out in an ionic liquid medium compared to a molecular solvent. An elegant study by Welton shows that in S_N2 reactions, primary, secondary and tertiary amines are more reactive as nucleophiles in ionic liquids,[8] while halides react faster in conventional molecular solvents such as CH_2Cl_2. In particular in a series of [Bmim] salts the order of nucleophilicity of halides is determined by the anion partner.[9] To the same direction moves a kinetic study by Dyson on a cationic Ru(II) complex-catalysed hydrogenation of styrene in ILs, where it is clearly demonstrated that both the cation and the anion of the IL can inhibit or accelerate the formation of the active catalytic species.[10]

The second opportunity is offered by the almost unlimited combination of cations and anions which makes possible for a reactants pair to follow different reaction channels in different ILs. A beautiful example was reported by Earle and Seddon, who discovered that the reaction of toluene with nitric acid affords three different products when conducted in three different [bmim] salts.[11]

This chapter overviews the current state of the art of the application of ionic liquids in catalysis by selecting examples mainly from the 2006–2007 literature, and providing information on the different strategies in which ionic liquids are applied in catalysis.

In particular we identify four general strategies, **A**–**D**.

- **Strategy A**. A classic homogeneous catalyst is used in an ionic liquid.
- **Strategy B**. A task-specific IL is used, namely a tailored IL capable to play the double role of reaction medium and of catalyst or pre-catalyst or ligand for a catalytically active metal centre.
- **Strategy C**. A catalytically active quaternary onium salt is used either under solvent-free conditions or in solution. The value of the catalyst

mp is not relevant in these applications, solid catalysts being even preferred for their more facile separation from the reaction products.

- **Strategy D.** A solid-phase supported IL phase is used under biphasic conditions.

2. Organocatalysis

2.1. ENAMINE-BASED ORGANOCATALYTIC CROSS-ALDOL REACTIONS USING PROLINE DERIVATIVES

A leading process in organocatalysis is the direct asymmetric cross aldol reaction of a prochiral aldehyde **1** with an enolisable ketone **2** promoted by proline (Figure 1). The proposed catalytic cycle is shown in Figure 2. Reactions are generally carried out in DMSO or, alternatively in the ketone itself as the solvent. Aldols **3** are produced with good regioselectivity in the case of unsimmetrically substituted ketones (the more substituted enamine is favoured) and good diastereoselectivity, the *anti*-adduct **3** being the major product. As refers to the enantioselectivity, the carboxylic group of proline ensures the enantioface discriminating control element by binding the carbonyl oxygen of the aldehyde via hydrogen-bond in the rate-determining nucleophilic addition step.[12]

Even though proline displays a very poor efficiency as catalyst (TONs generally range in the interval 2–5), its performance is partially mitigated by its low cost and low molecular weight.

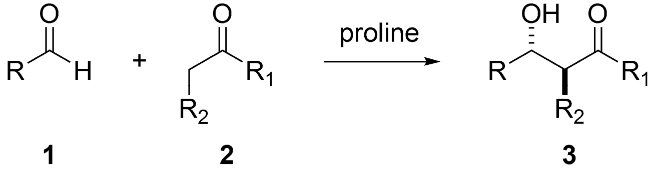


Figure 1. Model proline-catalyzed asymmetric cross aldol reaction.

A few variants of the proline-catalyzed cross-aldolization reactions have been proposed in ILs, by adopting strategy **A**. The reaction depicted in Figure 1 has been carried out in [bmim][PF_6] or [bmim][BF_4] by Loh and

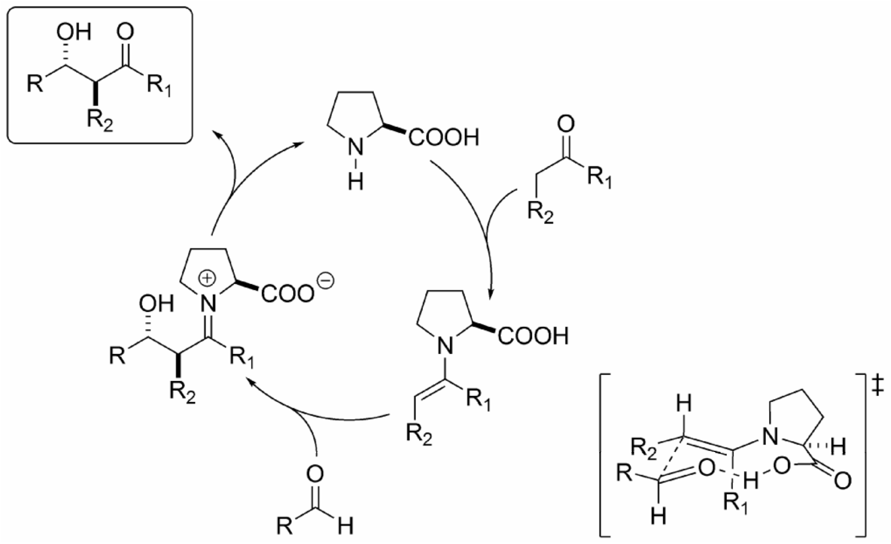
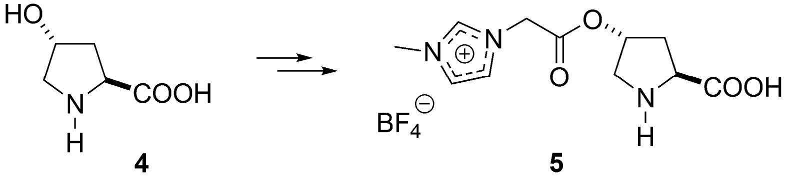


Figure 2. Mechanism of the proline-catalyzed asymmetric cross aldol reaction.

coworkers[13] and Toma and coworkers,[14] independently. However, comparing the original organocatalysed aldol protocol in DMSO using acetone and aromatic aldehydes,[8] with the same reaction carried out in [bmim][PF_6] under the same experimental conditions (RT, 24 h, 30% catalyst loading, 30 equivalents of acetone with respect to the limiting aldehyde),[9,10] yields and ee's do not benefit from appreciable improvements.

The advantage ensured by the IL consists of facilitating product separation and recycling of the catalyst, which is reused at least 4–5 times without appreciable loss of catalytic activity and enantioselectivity.

Following strategy **C**, Miao and Chan used 3-hydroxyproline **4** as starting material for the reparation of catalyst **5**, containing a methyl imidazolium tag on the side chain and tetrafluoroborate as the counter ion (Figure 3).[15]



4 **5**

Figure 3. Synthesis of a proline-containing task-specific ionic liquid.

Compound **5** was checked as catalyst (30% loading) for the reaction shown in Figure 1, in DMSO or in acetone itself as the solvent. With respect to the use of 3-hydroxyproline itself in DMSO,12a the reaction of acetone with *p*-nitrobenzaldehyde gave an about 20% poorer yield, but an improved enantioselectivity, which passed from 78% to 87%. When acetone was the solvent, after an extractive separation of **5** from the aldol, it was possible to recycle the catalyst for three more times without any appreciable loss of activity and selectivity.

Considering that a kinetic benefit can arise from the use of ILs when charge separation is present in the TS or in intermediate of a polar reaction 8 as the result of tight stabilizing interactions with the highly ordered domains of the IL phase,[16] we considered that onium ion-tagged prolines such as **7** and **8** should perform much better than proline as catalyst in IL media. Thus, we prepared onium ion-tagged prolines **7** and **8** via a flexible synthetic approach amenable for an easy creation of diversity *via* the common intermediate **6**, and investigated their activity as catalysts for cross-aldolization reactions in commercial ionic liquids (Figure 4).[17]

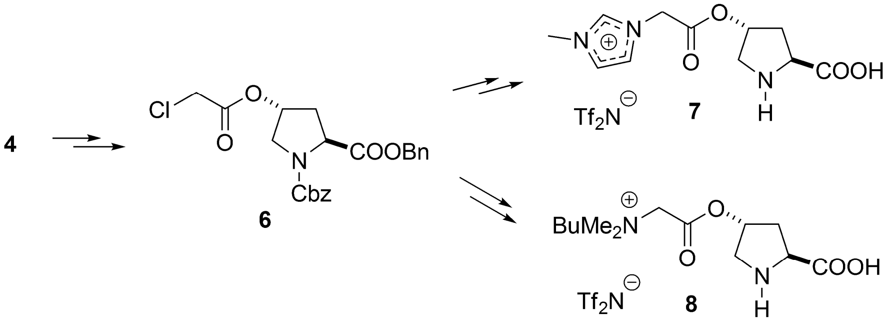


Figure 4. Straightforward synthesis of onium ion-tagged prolines.

TABLE 1. Asymmetric cross aldol reactions of acetone (10 equivs.) and RCHO (**1**) catalyzed by **7** or **8** (5 mol%) in [bmim][Tf_2N] for 24 h at rt.17.

Entry	R in RCHO (1)	Catalyst	2 Y%	2 ee%
1	*p*-NO_2-Ph-	**7**	79	84
2	*p*-NO_2-Ph-	**8**	75	85
3	Ph-	**7**	50	80
4	2-Naphthyl-	**8**	57	84
5	*p*-Cl-Ph-	**8**	80	84

Onium ion-tagged proline catalysts **7** and **8** in [bmim][Tf_2N] proved to be an excellent catalytic system for the direct asymmetric aldol reaction. The catalytic protocol developed makes use of use of a 6-fold lower amount of catalyst with respect to the preceeding reports based on the use of proline 12 and affords greater chemical yields and higher enantioselectivity. In particular, **8** in [bmim][Tf_2N] gave better results compared both to the use of proline in the same IL and of **7** in DMSO.[15]

2.2. ENAMINE-BASED ORGANOCATALYTIC MICHAEL REACTIONS USING A CHIRAL ONIUM ION-TAGGED PYRROLIDINE

Strategy C. A chiral pyrrolidine tagged with an imidazolium ion, combined to to the use of one equivalent of trifluoroacetic acid (TFA), was proposed as organocatalyst for a highly enantioselective Michael addition of carbonyl compounds to nitroolefins.[18] In catalyst **9** the imidazolium moiety not only ensures the opportunity to recover and recycle the catalyst by exploiting its facile separation from the product mixture *via* precipitation from ether, but also furnishes an acidic proton which can actively participate to the formation of diastereomorphic transition states, in analogy to the role played by the carboxylic acid group in Figure 2. The filtered catalyst is directly recycled and demonstrated identical activity and slightly decreased enantioselectivity. When the reaction shown in Figure 5 is catalysed by proline, 40% of catalyst is necessary to get a 75% conversion only after 60 h.

Enamine-based organocatalytic α-aminoxylation of carbonyl compounds using proline in ionic liquids.

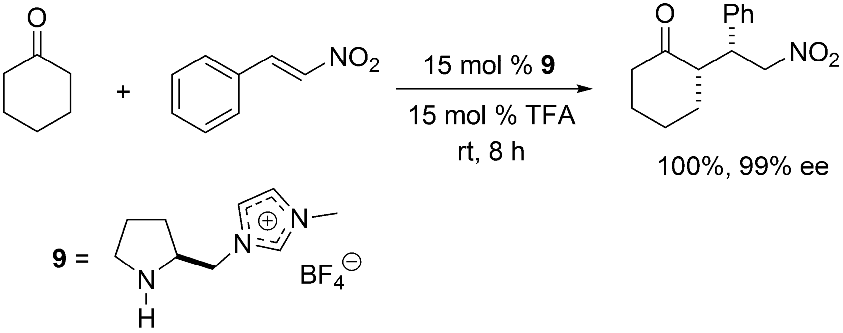


Figure 5. Asymmetric Michael addition to nitroolefins catalysed by onium ion-tagged pyrrolidine **9**.

Strategy A. The enamine strategy to asymmetric transformations of carbonyl compounds is also exploited for the construction of carbon-hetero-atom bonds using proline as catalyst, dissolved in ionic liquid media. Thus, a highly enantioselective α-aminoxylation of aldehydes and ketones has been reported based on the use of nitrosobenzene as the aminoxylating agent and catalysed by proline in [bmim] and [pmim] [BF_4] and [PF_6].[19,15] The reaction reported in Figure 6 affords poorer values in terms of yield and reaction rate when carried out in molecular solvents. Conversely, proline dissolved in the IL is recovered up to 6 times without appreciable loss of activity.

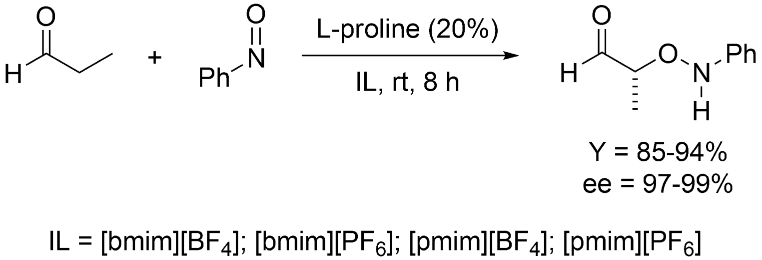


Figure 6. Asymmetric aminoxylation of carbonyl compounds catalysed by proline in ILs.

2.3. ORGANOCATALYTIC BAYLIS-HILLMANN REACTION IN IONIC LIQUIDS

The Baylis-Hillmann reaction is another bench-mark reaction in which ionic liquids have been successfully tested. The catalytic cycle of the Baylis-Hillmann reaction is reported in Figure 7. The catalyst is a highly nucleophilic tertiary amine, generally DABCO, or a tertiary phosphine, which adds to the α,β-unsaturated electrophile in a 1,4 fashion to deliver an enolate which, in turn, adds to the aldehyde. The critical step is now a proton transfer from the enolisable position to the oxygen atom; this process is catalysed by an alcohol which plays the role of a proton shuttle between the two foregoing positions. Once a β-ammonium enolate is formed, a rapid β-elimination takes place, delivering the Baylis-Hillmann condensation product.

Strategy A. The first investigation here discussed refers to the use of [epy][BF_4] as solvent for the DABCO-catalysed condensation of aromatic or aliphatic aldehydes with acrylonitrile (Figure 8).[20] With respect to the use of THF or acetonitrile, the IL-based protocol offers several advantages, i.e.

milder reaction conditions, shorter reaction times, higher yields, a simple work-up procedure which allows to reuse the solvent and DABCO dissolved in it. A direct comparison between the use of [epy][BF_4] and other solvents or ILs is reported in Table 2.

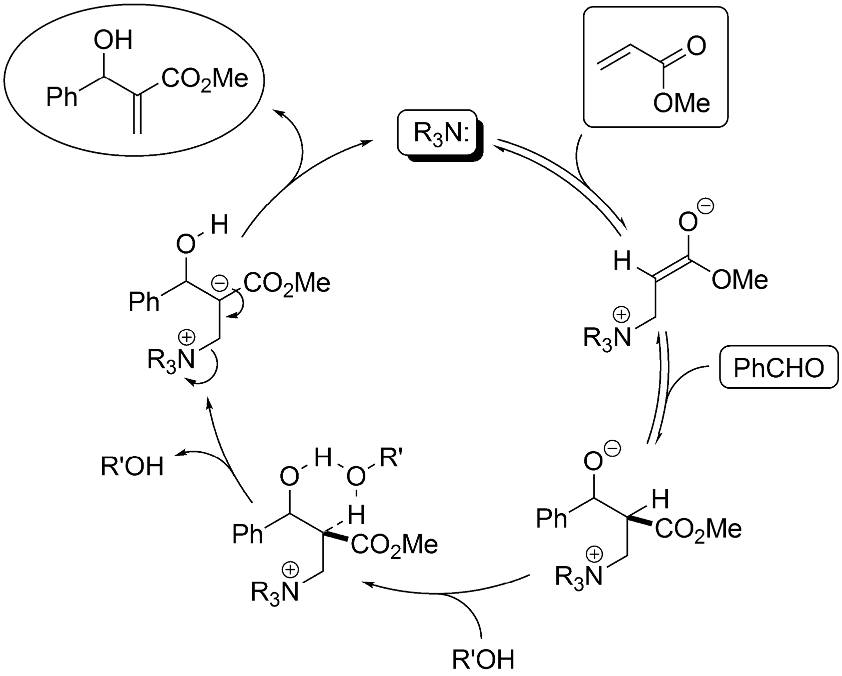


Figure 7. The Baylis-Hillmann catalytic cycle.

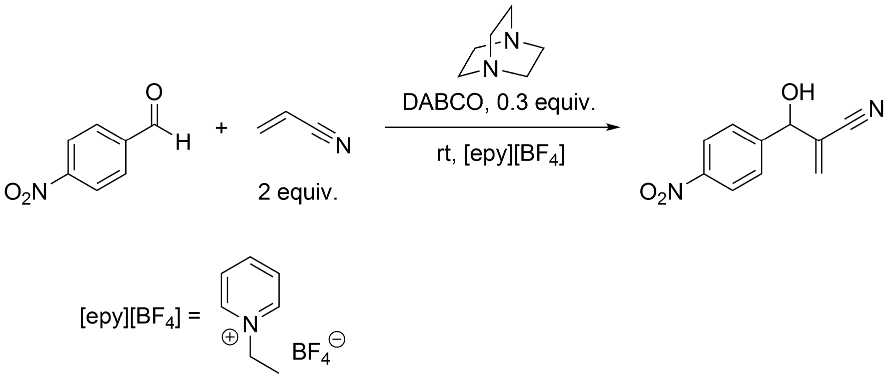
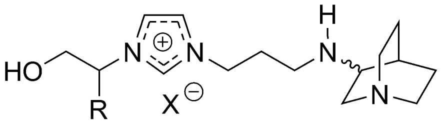


Figure 8. DABCO-catalysed Baylis-Hillmann reaction in an ionic liquid.

TABLE 2. The DABCO-catalysed Baylis-Hillmann reaction in different reaction media.

Entry	Solvent	Time (h)	Yield (%)
1	CH_3CN	48	32
2	THF	48	40
3	[bmim][BF_4]	12	48
4	[bupy][NO_3]	5	72
5	[epy][BF_4]	2	92

Strategy C, solvent-less conditions. An example of catalyst design by tailoring a task specific ionic liquid in such a way to fulfill all the mechanistic requests of the Baylis-Hillmann reaction is offered by imidazolium derivative **10** (Figure 9).



10: R = H, CH_3; X = Br, BF_4, PF_6

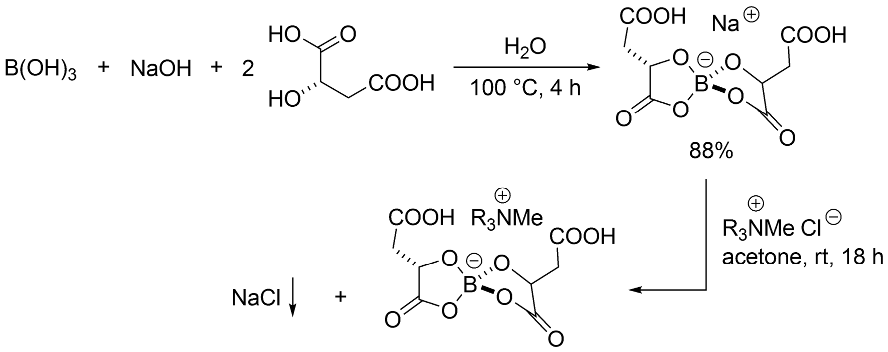
Figure 9. Structure of the rationally designed Baylis-Hillmann catalyst **10**.

One arm of the imidazolium scaffold contains the catalytic centre, a bridgehead nitrogen atom possessing the required nucleophilicity, the second arm contains a Broensted acidic primary alcohol capable to speed up the critical proton transfer step which leads to the β-ammonium enolate intermediate, direct precursor of the final Baylis-Hillmann product.[21] The reaction of R_1CHO and $CH_2=CH\text{-}R_2$ is carried out under solvent free conditions at room temperature, catalyst **10** can be readily recovered from the reaction mixture and reused for at least 6 times without significant loss of catalytic activity. A few results are reported in Table 3.

TABLE 3. Baylis-Hillmann reactions catalysed by **10** under solvent-free conditions.

Entry	R_1	R_2	Time (h)	Yield (%)
1	$n\text{-}C_3H_7$	$COOCH_3$	12	79
2	$i\text{-}C_4H_9$	$COOCH_3$	12	74
3	$n\text{-}C_6H_{13}$	$COOCH_3$	12	80
4	Ph	$COOCH_3$	8	94
5	p-Cl-Ph	$COOC_2H_5$	8	88
6	p-Cl-Ph	$COOC_4H_9$	8	86
7	2-Pyridyl	$COOCH_3$	0.5	95

Strategy A. An unprecedented highly enantioselective aza-Baylis-Hillmann reaction has been carried out in a chiral reaction medium, represented by the ionic liquid **11**.[22] The synthesis of the chiral anion is shown in Figure 10. Using chiral molecular solvents, there are not examples on the literature of ee's in the order of magnitude of 85%. The observation that **11** promotes such a chiral induction suggests that the highly ordered domains of the IL amplify the chiral information on the anion, thus acting as an effective stereocontrol element. The reaction is shown in Figure 11. The imine and the catalyst (10%) are dissolved in the IL, then methyl vinyl ketone is added and the reaction is stirred at room temperature for 24 h.



11, R = 1-octyl

Figure 10. Preparation of the chiral ionic liquid **11**.

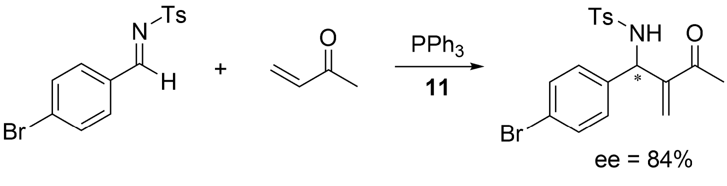


Figure 11. Enantioselective aza-Baylis-Hillmann reaction in the chiral ionic liquid 11.

2.4. ORGANOCATALYSIS BY CINCHONA-DERIVED AMMONIUM SALTS.

In 2005 two groups, Ricci and coworkers[23] and Palomo and coworkers,[24] independently, reported an enantioselective aza-Henry reaction catalysed by cinchona quaternary ammonium salts, e.g. **12** (Figure 12). Following

Strategy C, a preformed carbamoyl imine **13** or a carbamoyl imine formed *in situ* from an α-amidosulphone **14**, is treated with an excess of nitromethane and a 10–40% of catalyst. The solvent is toluene and a base is necessary in order to generate the nitronate ion. When **13** is used as starting material, KF is used as the base at room temperature. When **14** is used as the imine precursor, KOH, CsOH and Cs_2CO_3 are the bases of choice, and reactions are carried out at –40°C for 40–44 h. A typical experiment, as reported by Ricci, is presented in Figure 12.[23] When nitroethane is used, the *syn*-adducts are formed in 90% de and in 91–99% e.e.[24]

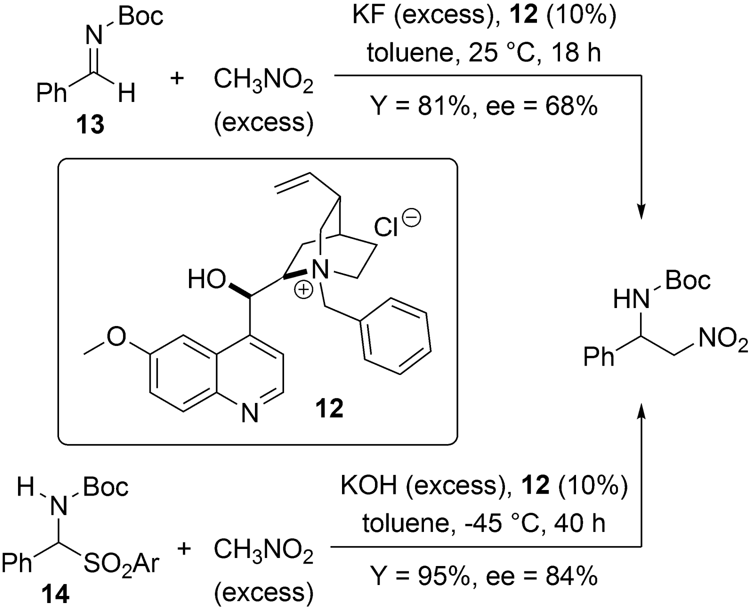


Figure 12. N-Benzyl quininium chloride catalysed aza-Henry reaction.

The foregoing approach to the aza-Henry reaction can be also classified as an example of chiral phase transfer catalysis. A more recent example of chiral phase transfer catalysis in water was made possible by a careful molecular design aiming at incorporating into the same species both a water soluble frame in the form of a long PEG chain and two catalytically active quininium salt moieties. The synthetic plan is shown in Figure 13.[25] The dimeric species **15** is *N*-anchored to a long linear PEG chain, by the reaction of diacetamido-PEG2000 chloride with 2 equivalents of the cinchona alkaloid in refluxing $CHCl_3$.

Using a 1M KOH aq solution, it is possible to perform the asymmetric alkylation of the benzophenone glycine Schiff base with benzyl bromide using 10 mol% of **15** at room temperature, as shown in Figure 14.

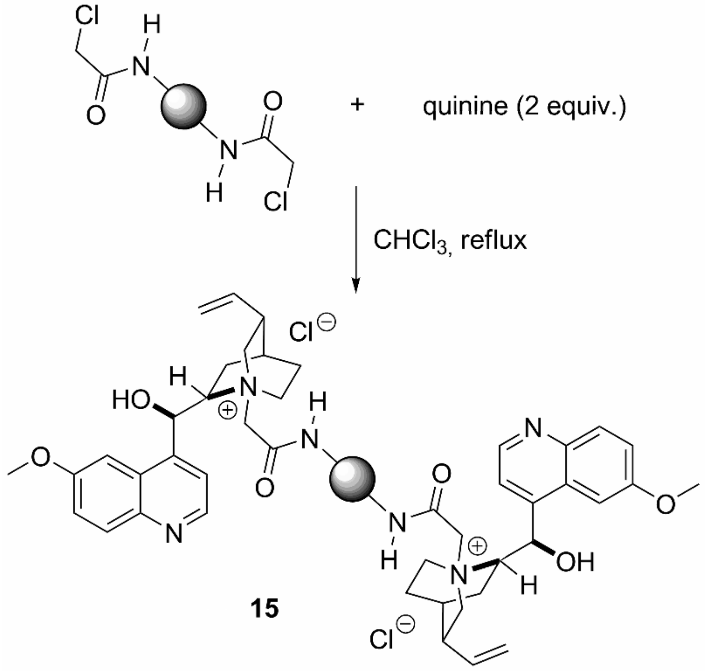


Figure 13. A preparation of a water soluble PEG-supported bis quininium chloride.

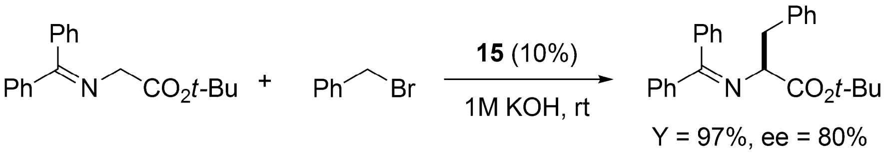


Figure 14. Catalytic asymmetric alkylation of a Shiff base promoted by 15.

3. Broensted-Acid Catalysed Reactions

3.1. MANNICH REACTIONS UNDER SOLVENT-FREE CONDITIONS

Strategy C. The Broensted acid **16** smoothly catalyses the Mannich reaction shown in Figure 15, affording the corresponding β-amino carbonyl compounds in excellent yield and short reaction times.[26]

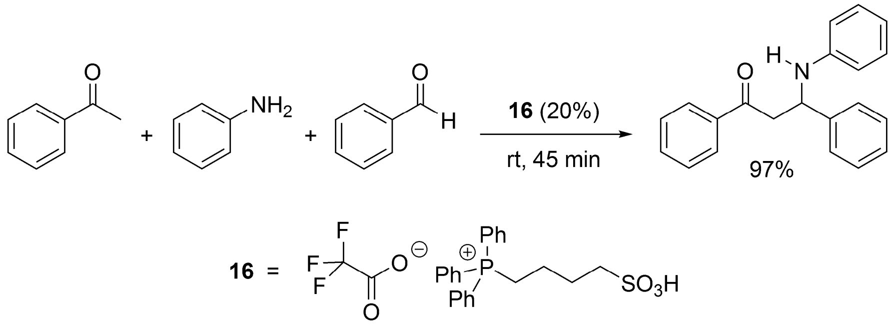


Figure 15. Mannich reaction catalysed by the acidic ionic liquid 16 under solvent-free conditions.

In an extremely simple one-pot reaction protocol, an aldehyde, an amine and a ketone are mixed together in a 1:1:1 molar ratio, then **16** is added together with two drops of water to allow a proper mixing. Catalyst **16** is recycled 4 times delivering the product in similar yield and purity.

3.2. REGIOCONTROLLED HECK ARYLATION OF ELECTRON-RICH OLEFINS

Compared to the Heck arylation of electron-poor olefins, the analogous arylation of their electron-rich counterparts has been much less widely investigated.[27] The problem of controlling regiochemistry has been solved by using aryl triflates instead of the more thermally stable halides, or by adding stoichiometric amounts of silver or thallium salts. However, low TON (<40) and TOF (<2 h^{-1}) values have been documented.

Mo and Xiao recently reported an upgraded reaction protocol (Figure 16) which is based on the use of $Pd(OAc)_2$, dppp, and a Broensted acid, namely $[Et_3NH][BF_4]$. Both [bmim]$[BF_4]$ and DMF can be used as solvents. Author hypothesis is that Et_3NH^+ favours the dissociation of the Pd-Br bond, thus allowing the olefin to bind to the vacant coordination site.[28] Using this modified procedure, TON and TOF increased to 1000 and 80 h^{-1}, respectively.

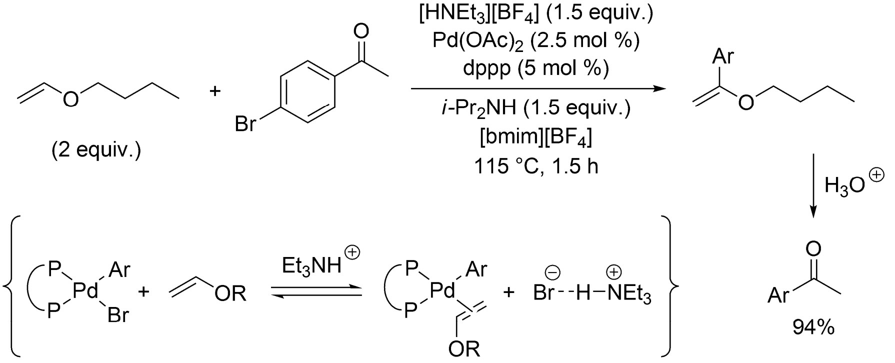


Figure 16. Pd-catalysed Heck reaction of electron-rich olefins.

4. Oxidation Reactions in Ionic Liquids

4.1. CHEMOSELECTIVE OXIDATION OF SECONDARY ALCOHOLS IN IONIC LIQUIDS

N-Hydroxyphthalimide in conjunction with a Co(II) salt is known to be a selective oxidation catalyst of secondary alcohols, using molecular oxygen as the stoichiometric oxidant. For a discussion on the mechanism, shortly depicted in Figure 17, the reader is redirected to the excellent review article by Ishii *et al.*[29]

N-Hydroxyphthalimide **17**, containing an onium-tag anchored on the aromatic ring, was designed in order to confer the catalyst solubility in ionic liquids. The preparation of **13** is outlined in Figure 18.[30]

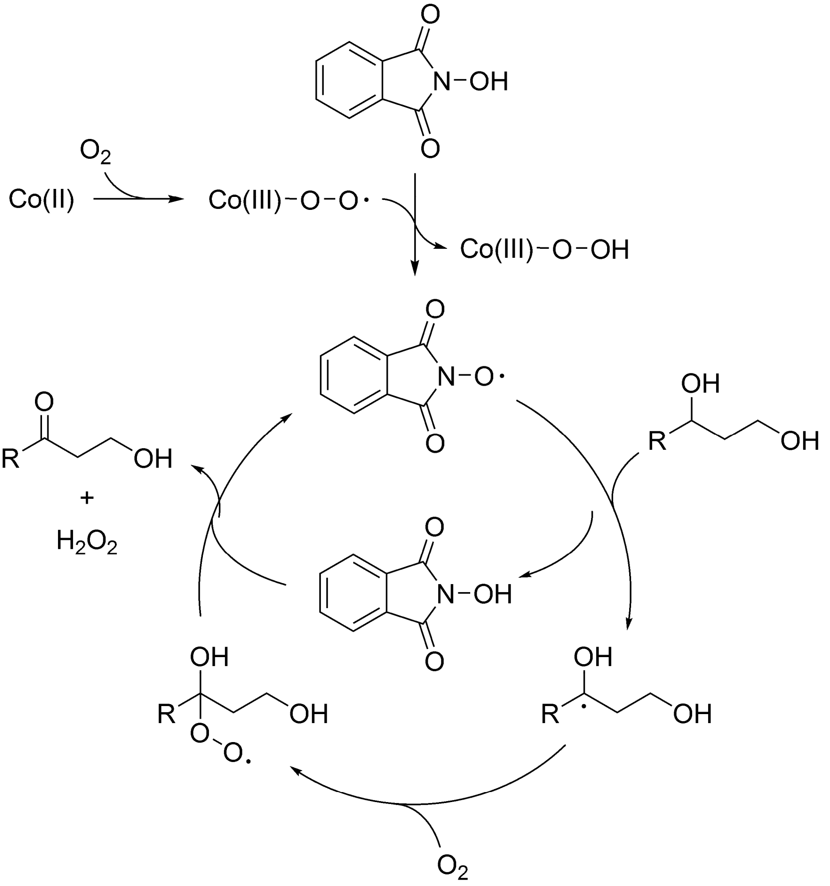
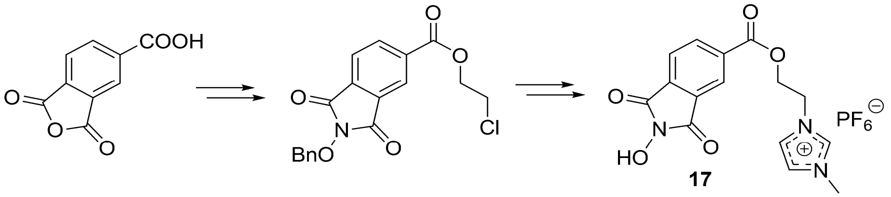


Figure 17. N-Hydroxyphthalimide/Co(II)-catalysed chemoselective oxidation of a secondary alcohol.



17

Figure 18. Preparation of the task-specific ionic liquid **17**.

Following **Strategy C**, The chemoselective oxidation shown in Figure 19 is simply carried out by dissolving the substrate, **17** and $Co(OAc)_2$ in [bmim][PF_6], followed by stirring under O_2 at 80°C in a pressure steel vessel. The product is extracted with $scCO_2$ at 35°C and the recovered catalyst **17** is reused three times for the same raction with almost identical results.

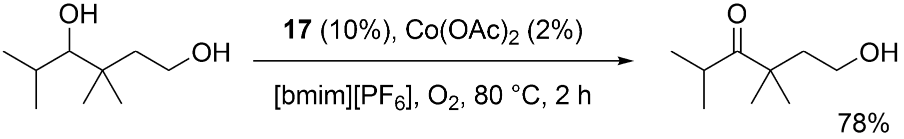
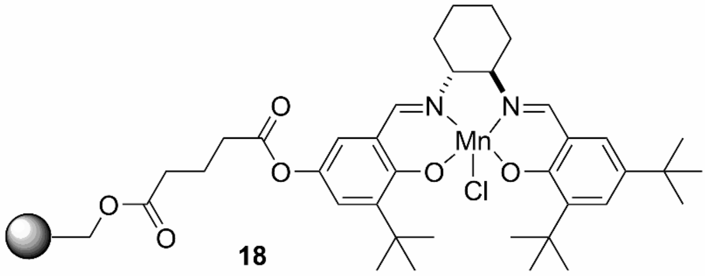


Figure 19. Chemoselective oxidation of a secondary alcohol in the presence of a primary alcohol catalysed by 17 in an IL.

4.2. ENANTIOSELECTIVE EPOXIDATION OF NONFUNCTIONALISED ALKENES

The strategy of tagging a known catalyst with an onium ion, beside to improve the solubility in an ionic liquid medium, may also serve to trap the catalyst in an ionic exchanger solid support. The resulting material can join the efficiency of the reference homogeneous catalyst to the advantages of heterogeneous catalysis in terms of separation and recyclability.

Among the so called privileged ligands, an important position is occupied by Jacobsen's Salen ligand. Reger and Janda in 2000[31] generated the first solid-supported versions **18** of the standard Jacobsen epoxidation catalyst, which could afford equal levels of enantioselectivity as the commercial catalyst, with the additional benefit of heterogeneous catalysis, namely the reuse in a few cycles (Figure 20). The solid phase consists either of soluble polymers such as poly(ethyleneglycol) monomethyl ether (MeO-PEG,



18

Figure 20. Structure of the solid-supported Mn-Salen complex 18.

MW = 5000), or insoluble polymers such as the hydroxymethyl Merrifield resin. Reactions are carried out in the temperature range –78 – 0°C, depending on the substrate, using *N*-methylmorpholine-*N*-oxide (5 equiv) as stoichiometric oxidant and the (salen)Mn catalyst (4 mol%) in CH_2Cl_2.

Starting from the chloromethylated salicylaldehyde **19**, Kureshy *et al.* proposed an alternative strategy to bind the Jacobsen epoxidation catalyst to a solid support.[32] Through a series of standard reactions they converted **19** into the di-cation **20** which was exchanged with a montmorillonite type of clay (Figure 21). Thus, **20** was supported into the interstitial space of this clay through robust ionic interactions. The insertion of **20** into the interlayer space was confirmed by the increase in basal spacing of TOT layers of the Salen-Mn containing clay **21** (Figure 21). According to **Strategy C**, epoxidation reactions are carried out in CH_2Cl_2 using 2 mol% of **21**, a catalytic amount of pyridine *N*-oxide and NaOCl as the stoichiometric oxidant. Quantitative yields are obtained with styrene, indene and 2,2-dimethyl-6-nitrochromene after less than 5 h, the e.e.s ranging from 50 to 99%. The catalyst was recycled 4 times in the epoxidation of styrene, with no loss in catalytic activity and enantioselectivity.

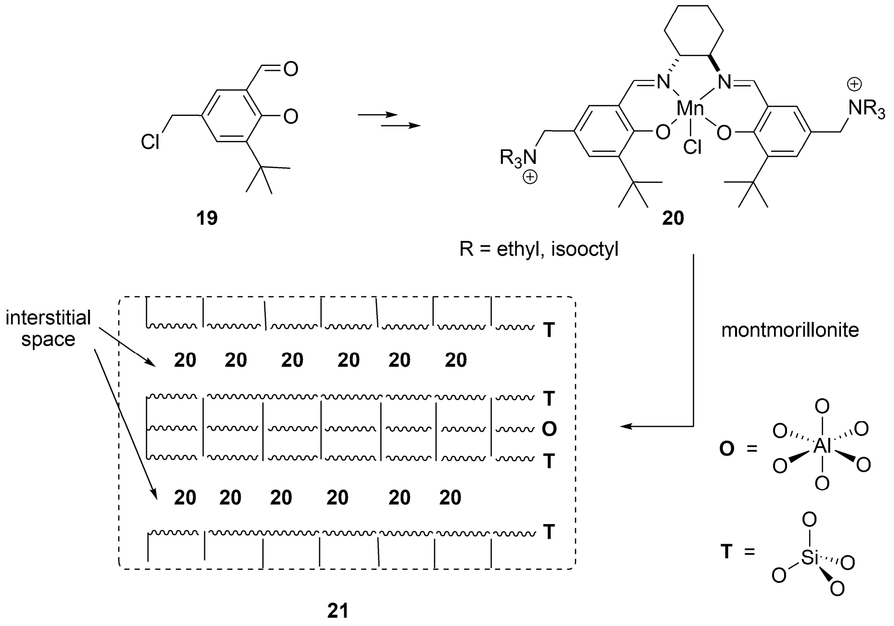


Figure 21. Preparation of a Salen/Mn complex ionically bound into the TOT layers of montmorillonite.

5. Metal-Catalysed Reactions in Ionic Liquids

The room-temperature chloroaluminate(III) ionic liquids are the most important members of the first generation of ionic liquids, developed in the second half of the last century.[33] The room-temperature halogenoaluminate(III) ionic liquids are extremely sensitive to moisture and must be handled under an inert atmosphere. Preparation of the halogeno-aluminate(III) ionic liquids is simple: a quaternary ammonium (QUAT) halide, e.g. an imidazolium or pyridinium halide, is directly mixed with $AlCl_3$ in the ratio necessary to generate the composition required. Upon mixing, an exothermic reaction occurs and the two solids melt into a liquid. The first report on the formation of a room temperature liquid salt, based on the combination of 1-butylpyridinium with $AlCl_3$ in the relative molar proportions 1:2 ($X = 0.66$) dates back to 1951.[34] Depending on the ammonium chloride/$AlCl_3$ molar ratio, more than one anion species are formed, as shown by equations 1–3. The Lewis acid/base behaviour is controlled by the proportion of the two, ionic liquids with an excess of [bmim][Cl] are basic, containing Cl^- and $[AlCl_4]^-$, ionic liquids with an excess of $AlCl_3$ are acidic, containing $[AlCl_4]^-$ and $[Al_2Cl_7]^-$.[35]

$$[QUAT]^+Cl^- + AlCl_3 \rightarrow [QUAT]^+[AlCl_4]^- \quad (1)$$

$$[QUAT]^+[AlCl_4]^- + AlCl_3 \rightarrow [QUAT]^+[Al_2Cl_7]^- \quad (2)$$

$$[QUAT]^+[Al_2Cl_7]^- + AlCl_3 \rightarrow [QUAT]^+ [Al_3Cl_{10}]^- \quad (3)$$

It is not surprising that electrophilic aromatic substitutions were the first organic reactions investigated using acidic room-temperature chloroaluminate(III) ionic liquids. Indeed, chloroaluminate(III) species combine their properties of good solvents for simple arenes to their role as Lewis acid catalysts. In Friedel-Craft alkylations, polyalkylation is common as well as the isomerisation of primary halides to secondary carbonium ions.

Wasserscheid and coworkers considerably renovated the original processes catalysed by $[QUAT]^+[AlCl_4]^-$ ionic liquids.[36] The catalyst used is a mixture of $AlCl_3$/[bmim][Tf_2N] in ratios higher than 1.5. The target reaction is the isopropylation of toluene with propene, which is carried out in a liquid-liquid biphasic reaction using a continuous loop reactor. The catalyst containing IL is placed into the reactor loop, propene and toluene are fed in continuous and, after passing an internal phase separator, the products are continuously discharged. Under the operation conditions adopted, a 1:1.6:1.8 ratio for *m*-cymene/*p*-cymene/*o*-cymene is obtained.

Friedel-Crafts acylations of aromatic compounds have also been carried out in chloroaluminate(III) ionic liquids.[37]

For the reaction of acetyl chloride with benzene, it was determined that the rate at which acetophenone was produced was dependent on the Lewis acidity of the ionic liquid, which in turn depends on the ionic liquid composition. For example, in the acidic composition described by equation 2, $[Al_2Cl_7]^-$ reacts with the reagent to generate the electrophile according to equation 4.[38]

$$CH_3COCl + [Al_2Cl_7]^- \rightarrow [CH_3CO]^+ + 2[AlCl_4]^- \qquad (4)$$

For more details readers are directed to a recent excellent book, where other room temperature halometallate ionic liquids are reported.[39]

An example is offered by the room temperature cholinium chlorozincate ionic liquid **22**, an efficient catalyst for the protection of carbonyl groups with diols under solvent-free conditions (**Strategy C**). An equimolar mixture of a diol (1,2- to 1,5-diol) and a carbonyl compound is stirred at room temperature for 10–20 h in the presence of **22**. Very high yields of acetals are reported and the catalyst is easily recovered and recycled. A typical reaction is reported in Figure 22.

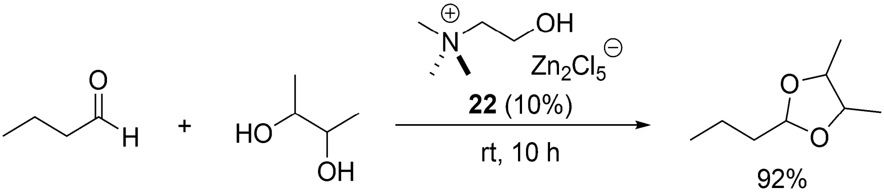
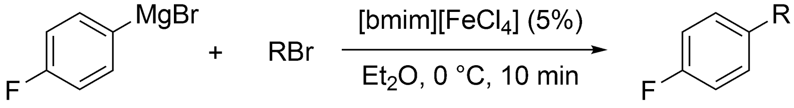


Figure 22. A cholinium chlorozincate-catalysed acetalisation reaction.

[Bmim][FeCl$_4$] is a further example of a transition metal halometallate ionic liquid; it is easily prepared in a solid state reaction by mixing solid [bmim][Cl] and $FeCl_3 \cdot 6H_2O$. A hydrophobic ionic liquid is formed from which water is easily separated.[37b] The tetrachloroferrate ionic liquid proved to behave as an exceptional cross coupling catalyst of aryl Grignard reagents with primary and secondary alkyl halides. The reactions are run in the biphasic system[bmim][FeCl$_4$]/diethyl ether, the IL is air and moisture stable, and reactions proceed so fast to give within 10 min the coupling product in high yield and no more than traces of classic by-products deriving from β-elimination or reductive elimination. A few typical examples are reported in Figure 23.[40]



R = n-$C_{12}H_{25}$ Y = 86% (1st cycle)
R = n-$C_{12}H_{25}$ Y = 76% (4th cycle)
R = cyclohexyl Y = 89%
R = 2-octyl Y = 84%

Figure 23. [Bmim][FeCl4] catalysed cross coupling of aryl Grignard reagents and alkyl halides.

The IL phase upon reaction with the Grignard reagent immediately turns black for the formation of the catalytically active low valent iron species. The product is extracted by washing the [bmim][$FeCl_4$] phase with ether, then the IL is charged with fresh reagents. It is interesting to notice that the whole catalytic process is so fast to render negligible the expected acid-base reaction between the acidic imidazolium ion[41] and the Grignard reagent. Exactly to prevent acid-base chemistry, [2-isopropyl bmim][Tf_2N] had been previously proposed as an efficient ionic surrogate of ethereal solvents for classical Grignard additions to carbonyl compounds.[42] In this example the room temperature ionic liquid (RTIL) provides the pre-catalyst Fe(III) and ensures the development of a biphasic reaction where reagents and products are stored in the ether phase while the catalytic cycle takes place in the RTIL phase. In a first approximation, the catalytic cycle involves reduction of Fe(III) by the Grignard reagent to a low valent species which oxidatively adds to the alkyl halide. Then, in analogy to the classic cross coupling reactions promoted by low valent metals, a transmetallation process leads to an alkyl aryl iron which eventually undergoes reductive elimination to restore the catalytically active iron species and deliver the coupling product. In this example, the nature of the catalytically active iron species was not investigated, however formation of NCH carbenes, which are known to be excellent ligands for transition metals in low oxidation states, can not be ruled out. Indeed, formation of *N*-heterocyclic carbene is conceivable in the interaction of the acidic imidazolium ion[43] and the strongly basic Grignard reagent.

Imidazolylidene ligands are enjoying a rapidly increasing use in catalysis.[44] For example, formation of Pd-carbene complexes from the interaction of [bmim][Br] with $Pd(OAc)_2$ has been reported in the literature. The observation that the Heck reaction proceeded markedly more efficiently in the ionic liquid [bmim][Br] (Figure 24) than in the analogous tetrafluoroborate salt, led Xiao and coworkers to isolate 1-butyl-3-methylimidazol-2-ylidene (bmiy) complexes of palladium [PdBr(μ-Br)(bmiy)]$_2$ (**23**) and [PdBr$_2$(bmiy)$_2$] (**24**) from a mixture of Pd(OAc)$_2$, NaOAc and [bmim][Br] stirred at 100°C for 4 h, but not in [bmim][BF$_4$] (Figure 25).[45]

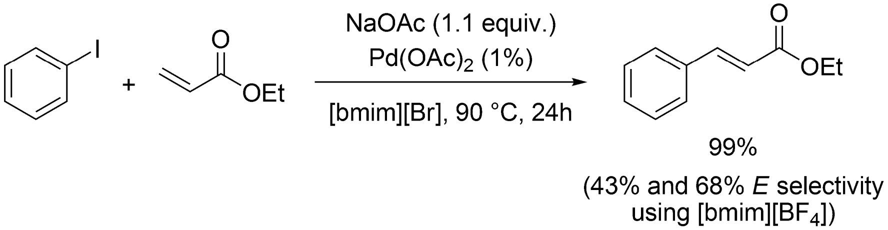


Figure 24. Pd-catalysed Heck raction in ionic liquids.

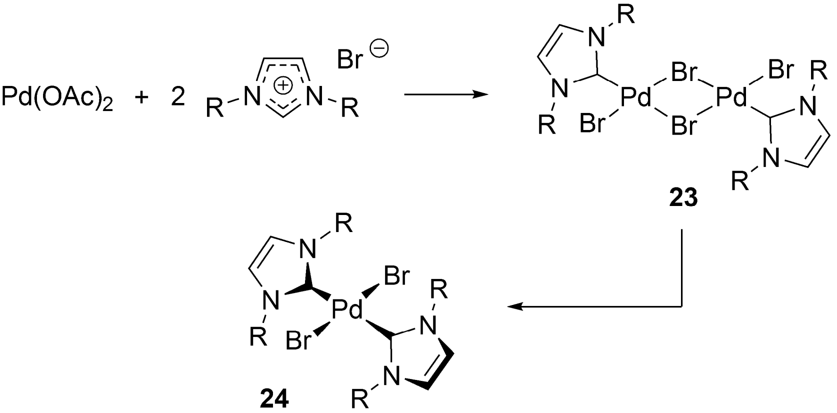


Figure 25. N-Heterocyclic Carbene Complexes of Palladium in the Heck Reaction in Ionic Liquids.

The coulombic environment produced by [bmim][BF$_4$] displayed a beneficial effect on the reaction rate of the Suzuki reaction. When the Suzuki reaction shown in Figure 26 was carried out in the traditional solvent mixture (toluene/water/EtOH in 4:2:1 v/v ratio) using 3% of catalyst, 84% of product and 7% of homocoupling product were obtained in 6 h, corresponding to a TOF of 5 h^{-1}. When the same reaction was carried out in [bmim][BF$_4$] with a lower catalyst loading (1.2%), 92% yield was obtained

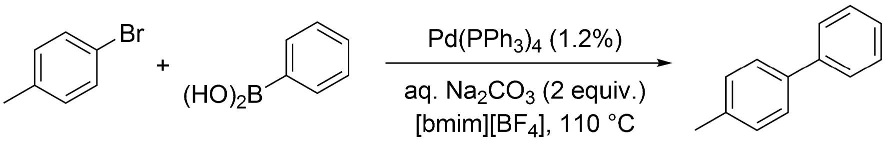


Figure 26. Pd-Catalysed Suzuki reaction in [Bmim][BF4].

in 3 hrs (2% homocoupling), and 68% of product was formed after 10 min, corresponding to a 34-fold higher TOF (TOF = 170 h^{-1}).[46]

The process is carried out in two steps; the first step involves the dissolution of $Pd(PPh_3)_4$ in thoroughly degassed and dried [bmim][BF_4] at 110°C under N_2 in the presence of 4-bromotoluene and NaCl, until a yellow-orange solution results. In the second step the solution is cooled to room temperature, and a solution of Na_2CO_3 in water and phenylboronic acid are added. The cross coupling was achieved by stirring at 110°C under N_2. The *in situ* formation of mixed phosphine/imidazolylidene palladium complexes in the catalytically active solutions has been demonstrated.[46]

A further evidence on the acceleration enjoyed by a typical Pd-catalysed reaction, the Heck reaction, in an ionic phase (*N*-methyl-*N,N,N*,-trioctylammonium chloride or Aliquat 336) is found in a triphasic protocol developed by Tundo and coworkers.7b,[47] The arylation of electron poor olefins is catalysed by palladium supported on charcoal (Pd/C) and is carried out in the heterogeneous isooctane/Aliquat 336/water system (Figure 27). Under this multiphasic condition, Aliquat 336 forms a third liquid phase between the organic and the aqueous phase that traps the catalyst. The use of phosphines is not necessary. As a matter of fact, Aliquat 336 incorporates the solid-supported catalyst and ensures an efficient mass transfer between the bulk phases resulting in an increase of the reaction rate of an order of magnitude compared to the reaction in the absence of the ionic liquid. A determing role is played by the base: while Et_3N drives the reaction towards the formation of ethyl cinnamate, reaction carried out in the presence of KOH lead to formation of Ullmann dimerisation products.

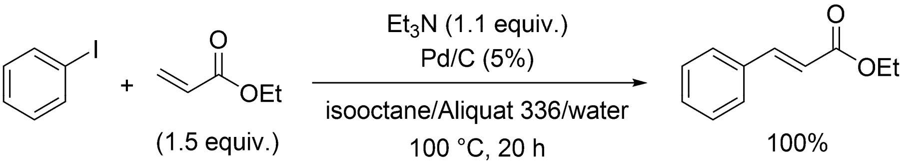


Figure 27. The Pd/C-catalysed Heck reaction in a triphasic reaction system.

6. Metal-Catalysed Reactions in Task-Specific Ionic Liquids

Task-specific ionic liquids (TSILs) represent a more advanced approach to the design of ionic liquids to be exploited in catalytic applications. Indeed, the structure of one partner of the ion pair is tailored in such a way to incorporate a functional group able to stabilise the catalytically active metal. A range of different functional groups have been installed on the cation moiety of onium salts, for example nitrile,[48] thiol,[49] alcohol,[50] acid,[51] amide,[52] urea,[53] *etc.* Thus, the ionic liquid plays a double role, acting both as the reaction medium and as a stabilising ligand for the catalytically active species. Such a stabilisation, hopefully, should improve the catalyst half-life and afford better results compared to unfunctionalised ionic liquids.

In this context, a functionalized ionic liquid, 1-(2-hydroxyethyl)-3-methyl imidazolium tetrafluoroborate [hemim][BF_4], is reported as an efficient and recyclable reaction medium for the palladium catalyzed Heck reaction. The olefination of iodoarenes and bromoarenes with olefins generates the corresponding products in good to excellent yields under phosphine-free reaction conditions. After separation of the product, fresh starting materials are charged into the recovered ionic liquid which entraps the palladium catalyst. The reactions still proceed quantitatively for six cycles, without significant loss of catalytic activity.[54] The effect of both the cation and the anion on the chemical yield is shown in Figure 28.

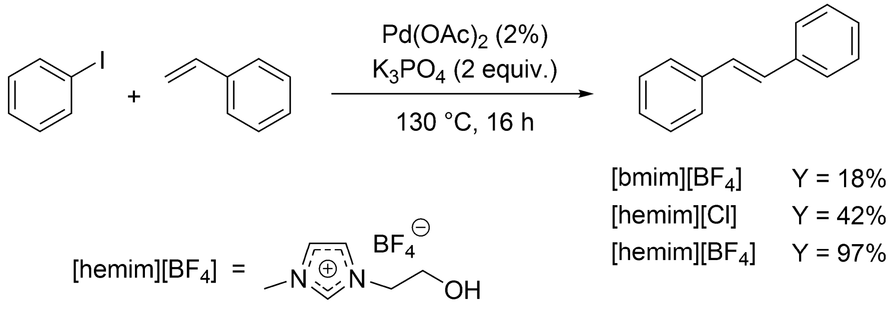


Figure 28. Pd-Catalysed Heck reaction in task-specific ionic liquid [hemim][BF4].

No investigation was carried out aimed at establishing which interaction between [hemim] and palladium occurred, however, as a matter of fact, an astonishing improvement is recorded passing from [bmim] to the hydroxyllated imidazolium.

In an important effort to the development of new TSILs, Dyson and coworkers prepared a family of nitrile-functionalised pyridinium[55] and imidazolium salts[48] and investigated their reactions with $PdCl_2$.[56] When nitrile-functionalised imidazolium chlorides, e.g. **25a**, are used, a tetrachloropalladate dianion salt **26** results; in contrast, when the counterion is PF_6^-, BF_4^-, or Tf_2N^- as in **25b–d**, the reaction of nitrile-functionalised imidazolium salts and $PdCl_2$ in a 2:1 ratio gives complexes **27** in which two nitrile groups are coordinated to a metal centre (Figure 29).

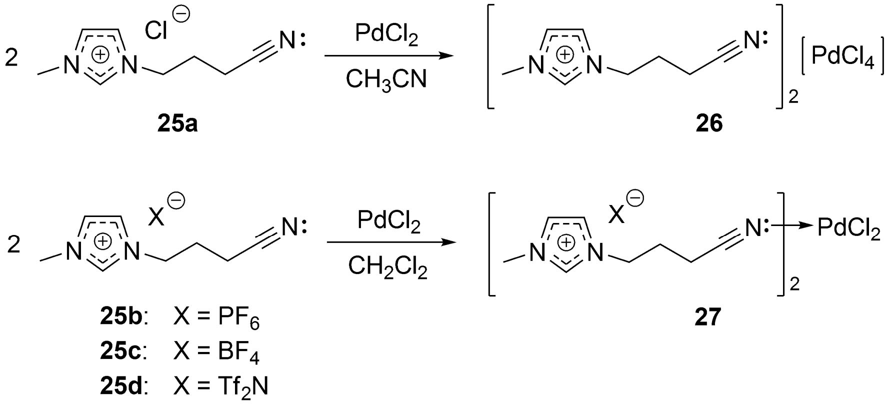
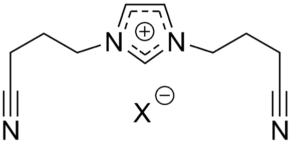


Figure 29. Preparation of Pd complexes with nitrile functionalized imidazolium salts.

A number of nitrile functionalised ILs Pd-complexes, including **26** and **27**, were found to be active as catalysts for carbon-carbon bond forming reactions such as Suzuki and Stille cross-coupling and the Heck reaction. For the Suzuki reaction, the Pd complex, e.g. **26**, is added to a mixture of phenyl iodide and phenyl boronic acid in [bmim][BF_4] or [bmim][PF_6] and aqueous sodium carbonate and heated at 110°C for 12 h. A virtually quantitative conversion to biphenyl is achieved. Comparing the catalytic performance of $PdCl_2$ in [bmim][BF_4] and $PdCl_2$ in **25c**, the catalyst stability is increased by **25c**, preventing the formation of palladium black as observed in the $PdCl_2$/[bmim][BF_4] system. Moreover, using a nitrile functionalised IL, metal leaching during the extractive work-up is greatly reduced, passing from ~100 ppm using $PdCl_2$/[bmim][BF_4] to ~5 ppm using **25c**.[56]

The same Authors reported the superior activity of $PdCl_2$ dissolved in **28** (Figure 30),[56] in both the Heck and the Stille reaction.



28a: $X = BF_4$
28b: $X = Tf_2N$

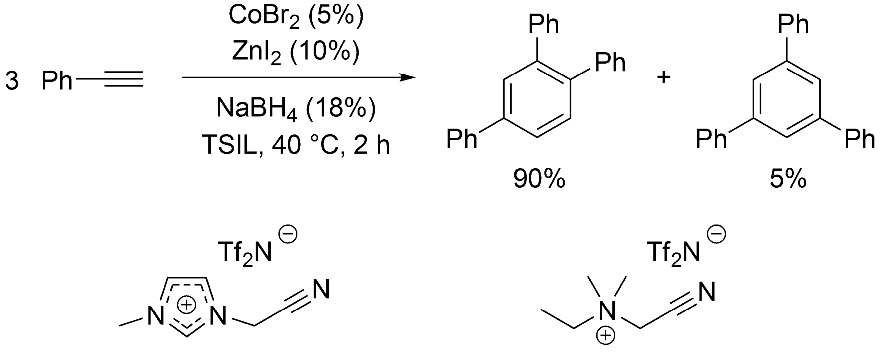
Figure 30. A bis nitrile functionalised IL proposed by Dyson.

Thus, the Heck reaction between iodobenzene and ethyl acrylate proceeds efficiently using $PdCl_2$ dissolved in **28b**, cholinium acetate as the base and ammonium formate as reducing agent. *Trans*-ethyl cinnamate is produced in 60% after heating at 80°C for 1 h.

The Stille coupling of tributylvinyl stannane with iodobenzene has been also investigated using a variety of preformed Pd-TSIL complexes or combinations of $PdCl_2$ and TSILs. The highest conversion in styrene (96%) is obtained using $PdCl_2$ dissolved in **28a**. In this last reaction, transmission electron microscopy (TEM) has been used to study the catalyst phase after a catalytic cycle. It has been confirmed that Pd nanoparticles with a diameter of ~5 nm are formed and that their morphology depends on the nature of the ionic liquid. For example, nanoparticles grown in TSIL **25c** are perfectly separated, while nanoparticles formed in $[bmim][BF_4]$ are aggregated, forming nanoclusters of ~30 nm. These observations are considered an evidence of the stabilising effect exerted by the nitrile groups in TSILs; in particular nitrile groups coordinate the nanoparticle surface and prevent their aggregation. A major benefit is enjoyed by catalyst recovery and reuse; indeed the ionic liquid phase containing Pd-particles can be recycled up to ten times maintaining almost the same activity (~90% yield of styrene).[56,57]

In general terms, the interest in metal nanoparticles as catalysts is increasing dramatically, as reflected by the large number of publications in the last five years. This field, defined as "semi-heterogeneous catalysis", is recording a substantial progress in terms of efficiency and selectivity of reactions on one hand, and recovery and recyclability of the catalytic materials, on the other. As far as nanoparticles in catalysis are concerned, the reader is directed to the excellent review article by Astruc *et al.* [58]

TSILs **29** and **30** containing a nitrile functionality also found an interesting application in a Co(I)-catalysed reaction, namely the cyclotrimerisation of arylethynes (Figure 31).[59] The generation of Co(I) species by reduction of a Co(II) salt is critical. Indeed, stabiliser agents are required in order to avoid full reduction to stable Co(0) and to confer an acceptable half-life to the catalyst, whose fate is that of disproportionating to Co(II) and Co(0). Phosphines, diimines, acetonitrile and Lewis acids such as ZnI_2 have been found to play the role of Co(I) stabilisers. The reaction protocol involves dissolution of a mixture of $CoBr_2$ and ZnI_2 in the 1:2 molar ratio in the selected cyano containing TSIL at 130°C. The interaction of $CoBr_2$ with ZnI_2 is known to give ion pairs such as $[Co][ZnI_2Br_2]$. A greenish-grey solution is obtained at 130°C which, on cooling to 40°C turns pink. The solution is charged with an arylethyne and finally with $NaBH_4$ as the reducing agent. The solution turns immediately dark brown and after 2 h at 40°C the crude reaction mixture is directly poured on the top of a short chromatographic column. Essential is to add the reducing agent to the Co(II) salt in the presence of the alkyne; this condition led authors to assume that the catalytically active species does contain an alkyne in its coordination sphere.



29

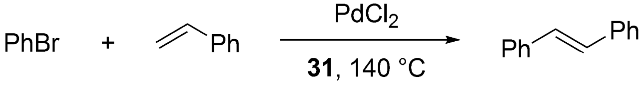
30

Figure 31. Co(I)-catalysed cyclotrimerisation of arylethynes in TSILs 29 and 30.

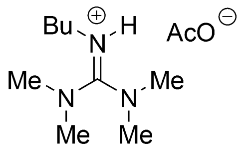
To make a direct comparison, when reaction shown in Figure 31 is carried out in $[bmim][Tf_2N]$ or in acetonitrile, the overall yields are 35 and 50%, respectively. These results confirm the stabilising role of the cyano groups and the reaction rate enhancement obtained in this reaction by using TSILs **29** or **30**, compared to acetonitrile. Unfortunately, the consequence of a low catalyst stability makes recyclability impossible. Indeed, the recovered Co-containing ionic liquid phase does not promote a second cyclotrimerisation process, unless new $NaBH_4$ is added: in this case a halved yield in the second run is obtained.[59]

The classic Heck reaction, which shares with the Suzuki reaction the top positions in the hit parade of Pd-catalysed bench-mark reactions, was the object of a bright investigation by Li and coworkers.[60] They summed up in the same ionic liquid structure three missions; it has to work as the solvent, it must play the role of the base and, finally, it has to stabilise the catalytically active Pd species. These three tasks are simultaneously fulfilled by a few guanidinium ILs, e.g. **31** (Figure 32).

Results shown in Figure 32 are impressive, particularly in terms of TON values. Moreover, after extraction of products with toluene/hexanes (1:1), the IL phase was recycled 5 times without loss of catalytic activity.



31 =



cat. (mol %)	t (h)	Y (%)	TON
0.16	0.25	96	620
0.01	20	96	9800
0.0001	48	34	340000

Figure 32. Pd-catalyse Heck reaction in guanidinium ion liquid 31.

As apparent from the examples discussed in this section, catalysis using TSILs may either (i) involve the use of a limited amount of TSIL or of a preformed TSIL-catalyst complex in an unfunctionalised IL, or (ii) may use the TSIL itself as the solvent. An example of the former approach has been reported by Kou and coworkers. With the aim to develop an alternative catalytic system for the hydrogenation of benzene, copolymer **31** (Figure 33), functionalised with imidazolium salts and strong coordinating pyrrolidone groups, was used as stabiliser of Rh(0) nanoparticles in [bmim][BF_4].[61] Copolymer **31** displays a high solubility both in [bmim][BF_4] and in ethanol.

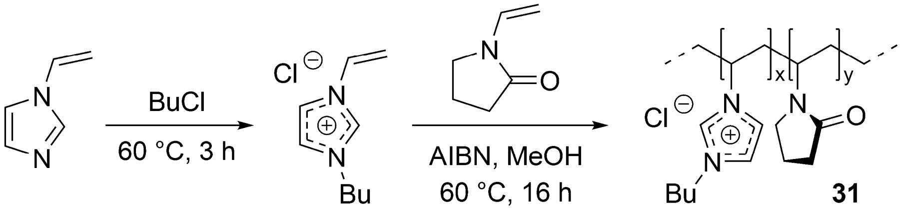


Figure 33. Preparation of poly[(N-vinyl-2-pyrrolidone)-co-(1-vinyl-3-butylimidazolium chloride)] copolymer.

Rhodium nanoparticles are produced by reducing $RhCl_3{\cdot}3H_2O$ with hydrogen in a solution of **31** in [bmim][BF_4]. TEM micrographs of Rh nanoparticles in the IL present a narrow unimodal size distribution with a diameter of ~3 nm. Even more interesting is that the particle size distribution undergoes negligible variations after four recycles in benzene hydrogenation reactions. Hydrogenations are carried out at 75°C under 40 bar of H_2, using Rh nanoparticles (0.25 mol% of Rh with respect to benzene) immobilised in the [bmim][BF_4]/**31** system. After separation of cyclohexane by decantation or reduced pressure distillation, the lower ionic liquid phase can be directly used in a following run without additional purification. Over five consecutive runs, a total TON of 20,000 was achieved. Authors demonstrated with blank experiments that neither [bmim][BF_4] alone or **31** alone possess the same catalytic activity of their mixture, thus suggesting that a high synergistic, even though unidentified, effect between **31** and the IL has to be responsible of the great stability and activity of the Rh nanoparticles.

In noble metal catalysis pressing claims dictated by quality and economy concerns urge chemists to (i) reduce catalyst use by reducing the loading or by recycling it, (ii) avoid product contamination by the metal, (iii) reclaim the catalyst as much as possible. Both catalyst recovery and recycling are made easier by adopting heterogeneous conditions, such as solid-liquid or liquid-liquid conditions. An industrially relevant process based on the use of Pt-catalysts is the hydrosilylation of olefins (Figure 34) which provides organomodified siloxanes, an important sector of the silicone market.

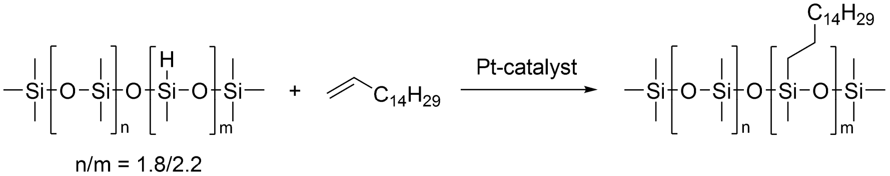
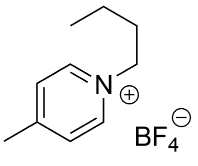


Figure 34. Synthesis of organomodified siloxanes via hydrosilylation of olefins.

Dyson carried out a careful optimisation of this reaction by adopting a sort of combinatorial approach where a number of Pt-precatalysts where tested dissolved in ionic liquids.[62] Among Pt-precatalysts K_2PtCl_4, $Pt(Ph_3P)_4$, $PtCl_2(cod)$ and $[PtCl_2(C_6H_{10})]_2$ have been checked in a series of pyridinium, picolinium and imidazolium salts combined with different anions, in particular [Tf_2N], [BF_4], [$N(CN)_2$], [$MeSO_4$]. The role of both the cation and the anion as well as that of the Pt species used has been investigated. In a typical experiment, the ionic liquid **32** (0.4 ml) containing1.2 10^{-6} mol of Pt-catalyst is added at 90°C to hydrosiloxane (22 ml). Then 1-hexadecene (32 ml) is added and the reaction mixture is stirred at 90°C for 45 min. When the reaction mixture is cooled to room temperature, two liquid phases separate. The ionic liquid phase can be directly recharged with fresh siloxane for the next catalytic run.

In Figure 35 results on catalytic activities and recycling data for the best catalyst/IL pairs are reported.



32

	K_2PtCl_4 5 ppm	$Pt(Ph_3P)_4$ 5 ppm	$Pt(Ph_3P)_4$ 15 ppm
Run 1	97%	89%	88%
Run 5	90%	84%	86%
Run 10	71%	74%	84%

Figure 35. Conversions in organomodified siloxanes using two Pt-precatalysts in IL **32**. Reactions are carried out at 90°C for 1 h.

A number of observations have been collected on the *in situ* formation of Pt-nanoparticles under the reported reaction conditions. After a few cycles, TEM micrographs reveal the presence of Pt-nanoparticles; moreover the observation of an induction time prior to the reaction, resulting in a sigmoidal kinetics curve, and the inhibition exerted by elemental mercury, a known selective poison for nanoparticles, are indicative of the formation of Pt-nanoparticles. Their role in the catalytic process is not clear, since they could act either as the true active catalyst or as a reservoir of Pt atoms for the generation of a mononuclear molecular Pt catalyst. With the aim to better control reproducibility, the use of preformed nanoparticles under well-defined conditions could be advantageous. Among several attempts, the best results were obtained by reducing H_2PtCl_6 with $NaBH_4$ in the presence of the thiol-functionalised IL **33**,[63] as shown in Figure 36. The resulting sulphur-stabilised Pt nanoparticles **34** precipitated; after centrifugation they were redispersed in IL **32** and their catalytic efficiency was evaluated in the usual hydrosilylation reaction. After 5 h a 94% conversion is observed; the catalyst is stable for four runs, then its activity markedly decreases in the fifth run (<50% conversion).[62]

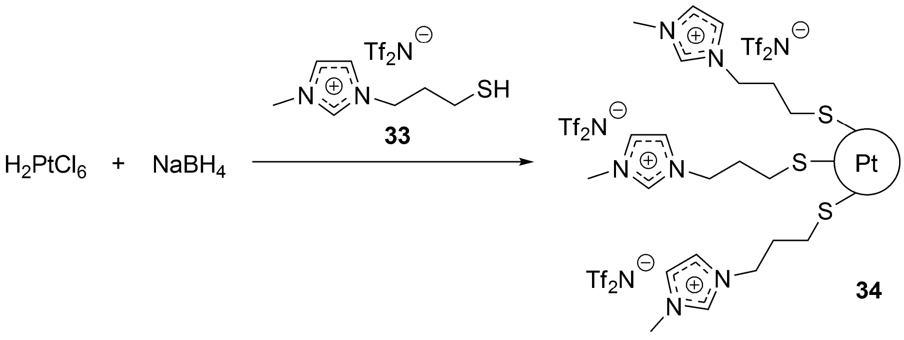
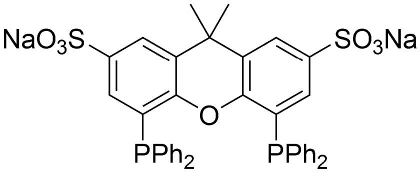


Figure 36. Preparation of Pt-nanoparticles 34 stabilized by the thiol-functionalised IL **33**.

7. Supported Ionic Liquids Phases for Catalytic Applications

In the previous sections the use of catalysts dissolved in ionic liquids has been documented with a variety of examples from the most recent literature. They were classified are catalytic systems based on the adoption of **Strategies A, B** and **C**, when solvent-less conditions were not adopted. In an ideal liquid-liquid biphasic system, the IL must dissolve the catalytic intermediates and, in part, the substrate to avoid that mass transfer limits reaction rates. Moreover, products should have a limited solubility in the IL to allow a facile product removal or extraction, and, possibly, the recycle of the ionic liquid-trapped catalyst. The separation of the catalyst from the products is made easier if solid support-immobilised ILs are used. The preference for a solid catalyst is dictated not only by the easier separation but also, as outlined by Mehnert in an excellent review article,[64] by (i) the possible use of fixed bed reactors, and (ii) the use of a limited amount of IL, a generally expensive chemical which can limit the economic viability of the process. In this section attention will be focused only on the most recent examples of solid-phase assisted catalysis using ionic liquids, following **Strategy D**. Examples prior to 2006 are covered in recent reviews and will not be discussed here.[64, 65]

Discussion starts by examining the Supported Ionic Liquid Phase (SILP) approach to catalysis, particularly advantageous for gas-phase applications using flow reactor technologies.[66] For SILP-catalyst generation, a support material (SiO_2, Al_2O_3, TiO_2, ZrO_2, *etc.*) is added to a methanolic solution of a catalyst precursor, for example $Rh(acac)(CO)_2$, a ligand, for example **35**, and an IL, for example **36** (Figure 37). After methanol is removed *in vacuo*, the resulting solid material is characterised. A SILP is defined by (i) its ionic liquid loading α, defined as the IL volume/support pore volume ratio and correlated to the film thickness, (ii) the metal content, i.e. the Rh/support mass ratio, and (iii) the ligand/metal molar ratio.



35

[bmim][n-$C_8H_{17}OSO_3$]

36

Figure 37. Structure of a Rh ligand and an IL used by Wasserscheid for the preparation of a SILP-hydroformylation catalyst.

Magnifying the section of a SILP surface, we should obtained a picture similar to that hypothesized in Figure 38. The IL film is physically adsorbed on the surface of the solid support and contains the dissolved catalyst. Since the film has the size of the diffusion layer, all metal complexes are involved in the catalytic reaction. When SILP particles are used as the fixed bed of a flow reactor, reagents enter the IL film, they react under homogeneous conditions (the thin IL film) and products, eventually, are desorbed into the carrier gas stream.

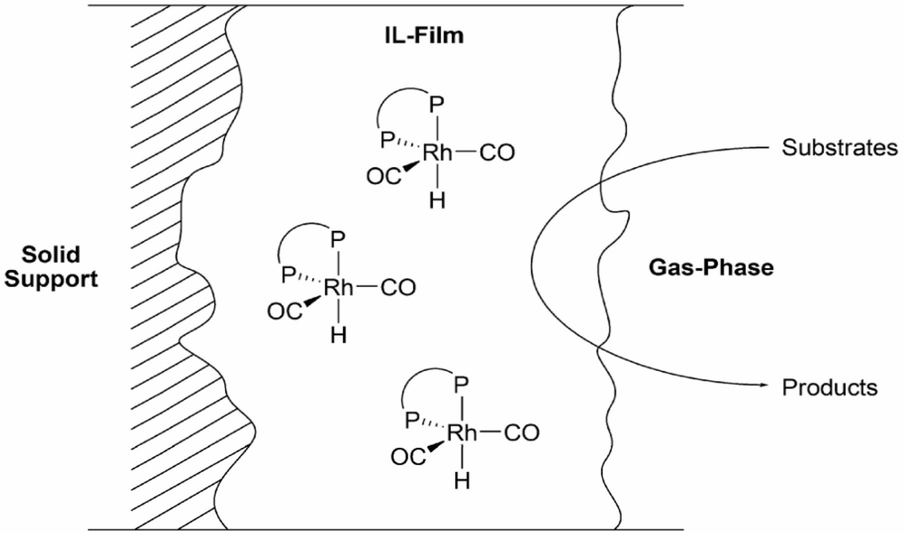


Figure 38. Schematic representation of the surface cross section of a SILP catalyst in a fixed-bed.

Reactions are run for a time which depends on catalyst half-life. A benchmark process for SILP catalysis is the hydroformylation of alkenes. Wasserscheid and coworkers reported the hydroformylation of propene catalysed by a silica-supported phosphane **35**-Rh complex in [bmim] [*n*-$C_8H_{17}O–SO_3$] (Figure 39). TOF values range from 16 to 46 h^{-1} under different reaction conditions (reagent partial pressures, support pre-treatment, *etc.*), while selectivity in favour of the linear aldehyde was constantly around 94–95%.

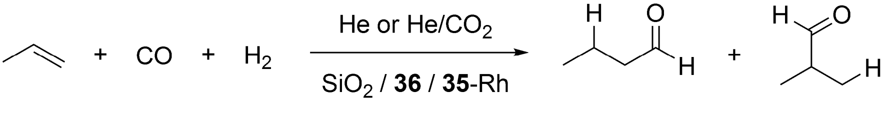
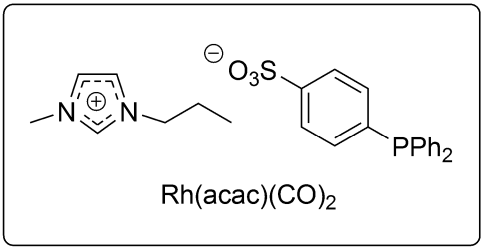


Figure 39. The SILP-catalysed hydroformylation reaction of propene.

Using silica 100 (particle size 63 to 200 μm) or porous glass, both treated at 450°C for 24 h, coated with the previously reported [bmim] [*n*-$C_8H_{17}O–SO_3$] containing Rh-**35** complex with the **35**/Rh ratio of 10, a continuous gas-phase hydroformylation of 1-butene has been also successfully performed.[67] Compared to the hydroformylation of propene, the SILP catalyst exhibits a higher activity and selectivity with 1-butene. Among various conditions examined in a continuous fixed bed reactor, when 0.1 weight% of Rh is used, TOF is 17 and 324 h^{-1} at 80°C and at 120°C, respectively, while the % of linear aldehyde decreases from 99.9 to 97.7%. From the determination of the full rate law, a first order with respect to Rh is found, meaning that mass transport from the gas to the IL phase is not limiting the reaction rate; moreover, the overall kinetics picture is consistent with a homogeneous Rh-catalysed reaction. This observation confirms the potentiality of SILP-catalysis, which joins the kinetic advantages of homogeneous conditions (the reaction takes place in the IL liquid film confined on the support surface with high specific area) with the practicality of solid heterogeneous catalysis. Indeed recyclability and the reduced amount of IL needed with respect to liquid-liquid processes, provide the SILP strategy important economic and environmental benefits.

Higher alkenes too, liquid at room temperature, can be hydroformylated over a fixed bed SILP catalyst. In this case the carrier gas is $scCO_2$, which is soluble in ILs but does not dissolve ionic compounds.[68] For example, 1-octene, CO and H_2 are mixed in $scCO_2$ and flowed through a tubular reactor containing the catalytic system **37** (Figure 40) dissolved in [omim][Tf_2N] which, in turn, is supported on silica gel.

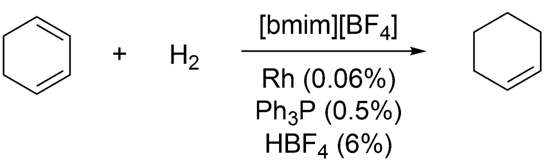


37

Figure 40. Rhodium catalyst dissolved in ionic medium.

Under optimised conditions, rates corresponding to 800 mol substrate·mol catalyst^{-1} · h^{-1} are observed, with a selectivity in favour of the linear aldehyde = ~3. The catalyst remains stable over a 40 h reaction time with less than 0.5 ppm of rhodium leaching.[68]

It is easy to predict that the tremendous progress recorded in the last two decades in material chemistry, for example thanks to the expansion of soft inorganic chemistry processes, will reflect in an analogous breakthrough in the generation of solid supported ionic liquid phases. As an innovative solid support Kiwi-Minsker and coworkers recently proposed sintered metal fibers (SMFs), that consist of micrometer-size metal filaments sintered into a homogeneous three-dimensional structure in the form of thin plates.[69] To favor the formation of a homogeneous layer of IL, the SMFs are coated by a layer of carbon nanofibers (CNFs). The resulting CNF/SMF material displays high thermoconductivity, resulting in the suppression of hot spots during exothermic reactions. After an appropriate thermal activation, the CNF/SMF support is loaded with the IL [bmim][BF_4], the hydrogenation pre-catalyst **38**, PPh_3 as catalyst stabilizer and a protic acid (HBF_4). The acid too is essential in the gas-phase selective monohydrogenation of 1,3-cyclohexadiene (Figure 41). In particular, the excess of phosphine and the presence of the protic acid are essential to maintain catalyst activity (TOF up to 250 h^{-1}) and selectivity (>96%) during 6 h on stream.

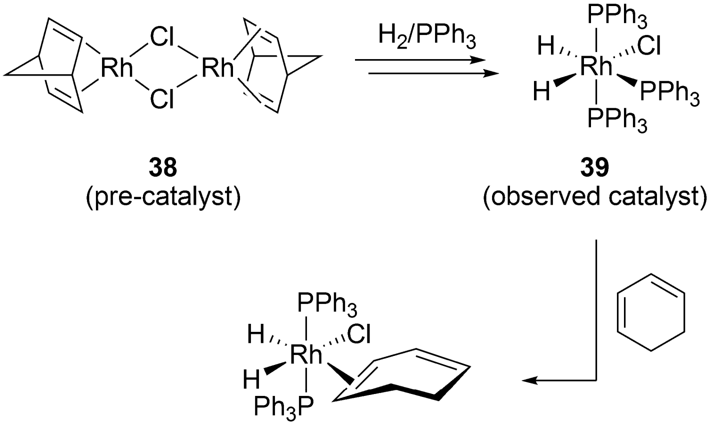


observed reaction rate: 285 h^{-1}
selectivity > 96%

Figure 41. The CNF/SMF/IL-catalysed semihydrogenation of 1,3-cyclohexadiene.

High-pressure NMR spectroscopy made possible to observe the true catalyst **39**, which is conceivable to produce **40** as catalytic intermediate (Figure 42).

The drawback of SILP strategy to heterogeneous catalysis lies in the weak interactions (physical adsorption) between the IL and the solid support which limit applications to gas-solid phase reactions, only. Indeed, in biphasic liquid phase conditions both mechanical forces and partitioning processes could slowly remove the IL film from the solid support. To circumvent this problem, stronger interactions must be created between the IL phase and the support.



38
(pre-catalyst)

39
(observed catalyst)

40
(proposed intermediate)

Figure 42. Rh species involved in the CNF/SMF/IL-catalysed semihydrogenation of 1,3-cyclohexadiene.

On the basis of biphasic catalysis concepts, Kobayashi and coworkers recently developed a heterogeneous catalyst consisting of a silica-supported scandium loaded with a hydrophobic IL, for organic reactions in water.[70]

Using sol-gel procedures, scandium triflate, a known water-tolerant Lewis acid, has been immobilised on a silica gel which had previously covalently functionalised with a sulphonic acid linker. The formation of the silica-gel supported species **41** and **42** is shown in Figure 43.

A hydrophobic IL, 1-butyl-3-decylimidazolium hexafluoroantimonate [dbim][SbF_6], was then chosen for particle impregnation, thus creating a lipophilic environment around the particle where reactions can take place. Thus, **42** is added to a solution of [dbim][SbF_6] in ethyl acetate to give, after solvent removal under reduced pressure, a fine powder of SiO_2-Sc-IL (**43**).

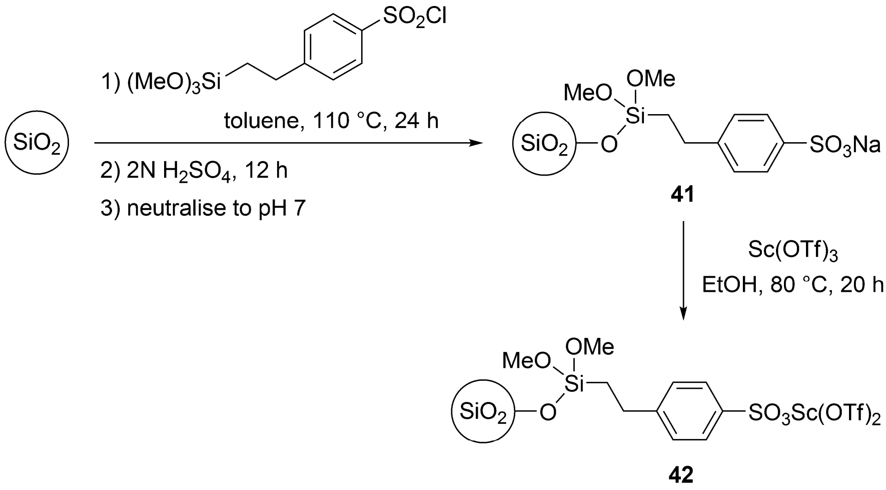


Figure 43. Preparation of the silica-gel supported scandium catalyst.

Different versions of **43** are available, differing in the ion exchange capacity. These materials were tested in a few carbon-carbon bond forming reactions, which traditionally involve the use of anhydrous solvents, using water as medium. As an example, the Mukayama reaction of benzaldehyde with 1-ethylthio-1-trimethylsiloxy-2-methyl-1-propene **44** proceeds in the **43**/water biphasic system much faster than in organic solvents, and the presence of both water and the IL is demonstrated to be essential to achieve good results. An example is presented in Figure 44.[70]

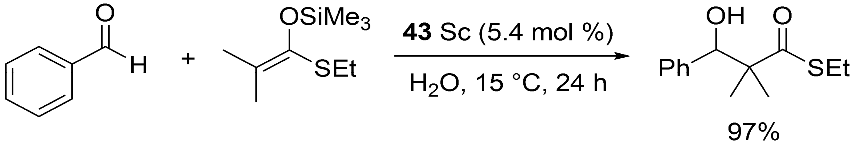


Figure 44. SiO_2-Sc-IL catalysed Mukayama reaction in water.

The same **43**/water biphasic system efficiently works for the Michael addition of indoles to α,β-unsaturated enones, the Mannich reaction in its one-pot three-component version, the allyl stannylation of carbonyl compounds and the asymmetric hydroxymethylation of silylenolethers. The last reaction (Figure 45) is carried out in the presence of the chiral bipyridine **45**.[70]

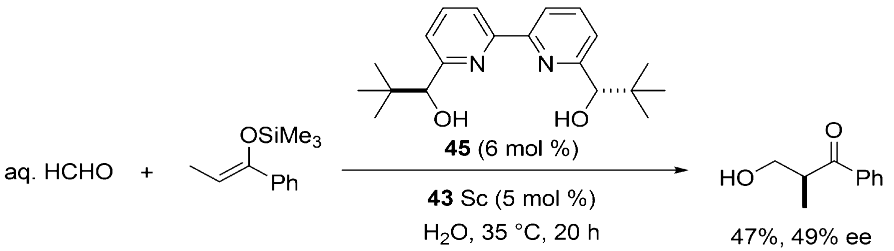


Figure 45. Asymmetric SiO_2-Sc-IL catalysed aldol condensation in water.

Solid sodium sulphonate species **41** (Figure 43) impregnated with [dbim][SbF_6] (25% wt) is itself capable to catalyse the 1,4-addition of several indole derivatives to methyl vinyl ketone (MVK) and other Michael acceptors in water (Figure 46).[71]

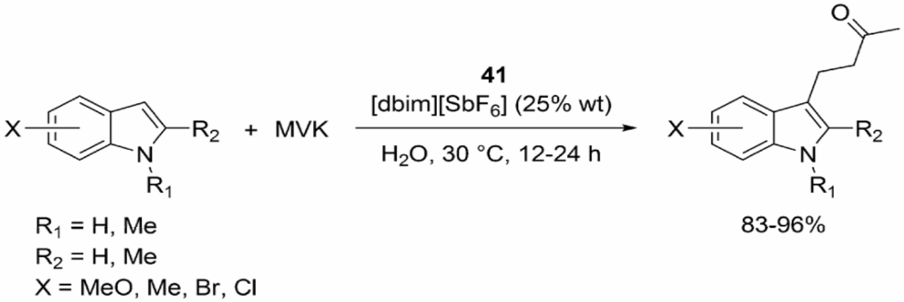


Figure 46. Asymmetric SiO_2-Sc-IL catalysed aldol condensation in water.

In summary, the Kobayashi solution to the development of a SILP for catalytic applications in liquid biphasic conditions implies the adoption of a more robust anchoring technique of the catalytically active species to the solid support and of a IL/solvent pair as far as possible in terms of mutual solubility, namely water and [dbim][SbF_6]. The role of the IL impregnated on the solid support is that of creating a hydrophobic environment on the surface of the silica material where the catalyst, ionically bound to the organic spacer, exerts its role promoting the desired reaction. Since the catalyst is easily separated from water, the system could be easily optimised for recycle.

8. Conclusions

Although catalysis, in particular asymmetric catalysis, has emerged for the last century as the most innovative and efficient tool for stereoselective transformations, its contribution to the expected discoveries of this century will be even more profound. The development of catalytic processes in ionic liquids is part of the today efforts to transform conventional homogeneous catalysis into green biphasic catalytic processes under the everyday increasing pressure of sustainability and economy issues. Efforts in these directions also include the great field of enzymes; for example lipases, have been successfully used in bulk ILs and in IL-based membranes.[72,73]

The choice of ILs to generate heterogeneous phases is dictated by a few major merits:

I. the availability of a virtually unlimited number of congeners, which excites the creativity of synthetic chemists as molecular designers in the challenge to tailor ILs on the basis of specific physical and chemical requirements;

II. when switching from water or molecular solvents to ILs, catalyst activity and selectivity often results significantly modified; they can either deteriorate or improve, or even change the mechanistic path leading to new products;

III. by supporting ionic liquids (**Strategy D**), the required amount of the ionic phase can be significantly reduced with respect to their use as a bulk liquid phase (**Strategies A–B**), thus circumventing their cost limitations;

IV. the SILP concept opens the possibility to use fixed-bed reactor technologies which are supposed to heavily replace the current batch technologies in the next decades, combining the advantages of homogeneous and heterogeneous catalysis. In this case the combination of three enabling techniques,[65] heterogeneous catalysis, innovative solvents, continuous flow processes, looks highly promising for the development of new sustainable technology platforms.

V. the low risk associated to their use in terms both of safety at work and accidental environmental contamination (negligible vapour pressure).

This Chapter analyses a few examples from the very recent literature on different strategic approaches to generate catalysis in ionic liquid media; four main concepts were identified and classified as **Strategies A–D**. The IL is the solvent for the catalytic reaction (**A**), the IL is both the solvent and the catalyst (or pre-catalyst) (**B**), the IL is simply used as the catalyst, easily removable from the reaction mixture (**C**), the IL is supported in the form of a thin (diffusion) layer on a solid support (**D**).

One of the horizons in catalysis research is to combine the efficiency of homogeneous catalysis to the technological advantages of heterogeneous catalysis (simple reaction monitoring, reduced overall cost, lower catalyst leaching to the environment or to the final product, simple separation, recycling, reuse and possibly regeneration of the catalyst, etc.). Essential to cope with such a cutting-edge task is to gather into the same team a multifaceted expertise in (i) organic and inorganic synthesis for the preparation of both organic and inorganic phases, (ii) homogeneous catalysis, (iii) material chemistry which should provide new nanostructured surfaces as solid supports, (iv) heterogeneous catalysis, immobilization techniques, etc., up to (v) chemical engineering, as far as new reactor design for flow-through processes, technological questions addressing process intensification, use of alternative energy sources, and process development between different scaled reactions are concerned.

Abbreviations

[bmim]	Butyl methyl imidazolium
Boc	t-Butyloxycarbonyl
CNF	Carbon nanofibers
DABCO	1,4-Diazabicyclo[2.2.2.]octane
[dbim]	1-Butyl-3-decylimidazolium
DMSO	Dimethylsulfoxide
Dppp	1,3-bis(diphenylphosphino)propane
[epy]	N-Ethyl pyridinium
[hemim]	1-(2-Hydroxyethyl)-3-methyl imidazolium
IL	Ionic liquid
MVK	Methyl vinyl ketone.
[omim]	1-Methyl-3-octyl-imidazolium
[pmim]	1-Methy-3-pentyl-imidazolium
QUAT	Quaternary onium ion
RTIL	Room temperature ionic liquid
Salen	N,N'-Bis(3,5-di-t-butylsalicylidene)-1,2-trans-cyclohexanediamine
scCO2	Supercritical carbon dioxide
SMF	Sintered metal fibers
TEM	Transmission electron microscopy
Tf2N-	Bis(trifluoromethane)sulfonimide anion
TOF	Turn over frequency
TON	Turn-over number
TSIL	Task-specific ionic liquid

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IONIC LIQUIDS FOR SPECTROSCOPY; SPECTROSCOPY FOR IONIC LIQUIDS

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Abstract: In this paper we address two aspects of ionic liquids (ILs) that to date have either no or limited studies. They are (1) exploitation of unique features of ILs to develop novel spectroscopic methods which otherwise is not possible and (2) development of novel spectroscopic methods for the sensitive and accurate determination of thermal physical properties of ILs. In the first category, we have successfully developed a novel, highly sensitive and accurate method for the determination of enantiomeric compositions of chiral compounds with different sizes, shape and functional groups including pharmaceutical products. This method is based on the use of a chiral IL which serves both as a solvent and also as a chiral selector. We have also demonstrated that ILs can be used to substantially enhance the sensitivity of thermal lens measurements. In the second category, we have demonstrated that transient grating technique and thermal lens technique can be used for the sensitive, accurate, nondestructive determination of thermal physical properties of ILs.

Keywords: Ionic liquid; near-infrared; fluorescence; chiral; enantiomeric excess; thermal lens; transient grating

1. Introduction

Ionic liquids (ILs) are a group of organic salts that are liquid at room temperature. They have unique chemical and physical properties, including being air and moisture stable, a high solubility power, and virtually no vapor pressure.[1–5] Because of these properties, they can serve as a "green" recyclable alternative to the volatile organic compounds that are traditionally

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used as industrial solvents.[1–5] The ILs have, in fact, been successfully used in many applications, including replacing traditional organic solvents in (1) organic and inorganic syntheses,[2] (2) solvent extractions,[6] (3) liquid-liquid extractions,[7–9] (4) electrochemical reactions[10,11] and (5) as a medium for enzymatic reaction[12].

A large number of scientists from many disciplines have been engaged on study of ILs. However, to date, majority of research on ILs has focused on synthesizing novel ILs with either new anions and/or cations and determining their chemical properties. Because of the efforts, substantial advances have been made, and it has been estimated that the number of novel and task-specific ILs which can be readily synthesized can be as large as 10^6. In spite of availability of a rather large number of newly synthesized ILs, information on their spectroscopic and thermal properties is not widely available. This is rather unfortunate because with their superior spectroscopic and physical properties, the ILs can potentially be used not only as a green but also as superior solvent in term of enhancing sensitivity and selectivity of spectroscopic measurements, as well as high performance fluids for use of a wide range of engineering and materials science applications, such as high pressure and high temperature lubricants. It is probable that laboratory and industrial applications of ILs in spectroscopy, engineering and material processing are limited because of lack of studies and the paucity of data on their spectroscopic and physical properties.

This overview addresses these shortcomings. Specifically, its focus is not on the synthesis of novel ILs or the investigations of their chemical properties but rather on what ILs can uniquely do, as solvents for spectroscopy, and what spectroscopic techniques can do for ILs. That is, it will summarize studies which focus on (1) the exploitation of unique properties of ILs as solvents to enhance sensitivity and selectivity of spectroscopic measurements, and (2) the development of novel spectroscopic methods which are nondestructive, require only a small amount of samples and have high sensitivity, accuracy for the determination of thermal physical properties of ILs.

2. Ionic Liquids for Spectroscopy

2.1. CHIRAL IONIC LIQUID THAT FUNCTIONS AS BOTH SOLVENT AND CHIRAL SELECTOR FOR THE DETERMINATION OF ENANTIOMERIC COMPOSITIONS OF PHARMACEUTICAL PRODUCTS

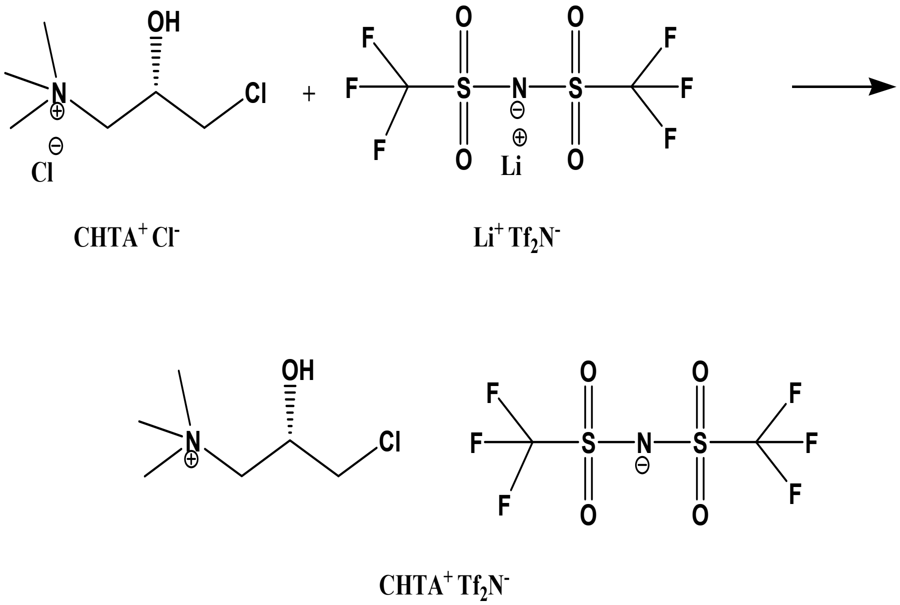
Chiral analysis is an important subject in science as well as in technology. Enantiomeric forms of many compounds are known to have different physiological and therapeutic effects.[13–16] Very often, only one form of enantiomeric pair is pharmacologically active.[13–16] The other or others can reverse or otherwise limit the effect of the desired enantiomer. Recognizing the importance of chiral effects, the FDA in 1992 has issued a mandate requiring pharmaceutical companies to verify the enantiomeric purity of chiral drugs that are produced.[13–16] It is thus hardy surprising that pharmaceutical industry needs effective methods to determine enantiomeric purity.

Methods currently available for the determination of enantiomeric purity are based either on separation (HPLC, GC, CE) or spectroscopy (CD, NMR, MS).[17–22] While these methods have proven to be effective, they all have some drawbacks including time consuming, low sensitivity and destructive.[17–22] More importantly, none of them is truly universal; namely, they cannot be used for all types of compounds. Contrary to the general belief, we have demonstrated recently that it is possible to develop a novel method which is not only universal but also has relatively higher sensitivity and accuracy.[23,24] The method is based on the use of the NIR technique to measure diastereomeric interactions between an added carbohydrate compounds (e.g., α-, β-, γ-cyclodextrin or sucrose) with both enantiomeric forms of an analyte followed by partial least square analysis of the data.[23,24] Compared to other existing methods this method not only has relatively higher sensitivity and accuracy but also is universal.[23,24] Specifically, it can be used to determine enantiomeric compositions of all types of compounds including amino acids and pharmaceutical products (propranolol, atenolol, ibuprofen) with only microgram concentration and enantiomeric excess as low as 1.5%.[23,24] It is noteworthy to add that while this method has proven to be very effective, it still has some limitations such as the need to add a carbohydrate compound (to induce the diastereomeric interactions) and the fact that the analysis must be performed in a solvent which can dissolve both analyte and the carbohydrate compound. Because of the latter requirement (and because of the different solubility of various types of analytes), it may be necessary to perform the analysis in a variety of solvents including water or a mixture of water and organic solvents. As a consequence, a separated calibration curve must be constructed for each set of carbohydrate – analyte in each specific solvent system. This cumbersome and time consuming task somewhat limits the application of the method. It is, therefore, desirable to modify this method by eliminating the added carbohydrate and using only one solvent system for the analysis of all types of compounds. Chiral ionic liquid with its unique properties offers a solution for this problem.

Advances in ILs have made synthesis of chiral ILs a subject of intense study in recent years.[25–37] The popularity stems from the fact that it is possible to use chiral ILs as chiral solvents for optical resolutions, for asymmetric induction in synthesis and as chiral stationary phase in chromatography.[25–37] It may also be possible to use chiral IL to replace the solvent as well as the added carbohydrate compound for the enantiomeric purity determination method. Specifically, the chiral IL with its high solubility power should dissolve many different types of analytes. Its chirality may produce the needed diastereomeric interactions with both enantiomeric forms of an analyte. Unfortunately, in spite of their potentials, chiral ILs are not commercially available. Only a few chiral ILs have been synthesized, and the synthesis of reported chiral ILs required rather expensive reagents and elaborated synthetic schemes.[25–37] Because of these limitations, in spite of extensive efforts made by various groups, to date, the study and applications of chiral ILs have been severely hindered. Therefore, it is of particular importance to develop a novel synthesis method by which chiral ILs can be simply and easily prepared from commercially available reagents by chemists from various disciplines, not just by those with expertise in synthesis.

We have demonstrated recently that both enantiomeric forms of a novel chiral ionic liquid, R- and S-(3-chloro-2-hydroxypropyl) trimethylammonium Tf_2N^- ((R)- and S-$[CHTA]^+$ $[Tf_2N]^-$) can be readily synthesized in enantiomerically pure form by a simple ion exchange reaction from corresponding (R)- and (S)-chloro-2-hydroxypropyl)trimethylammonium chloride salts which are commercially available (Scheme 1).[38,39]

(R)- and S-$[CHTA]^+$ $[Tf_2N]^-$ are liquid at room temperature, and results from differential scanning calorimetric (DSC) measurements indicate that they have glass transition temperature of –58.4°C. Results from thermal



Scheme 1. Preparation of a chiral ionic liquid through an ion-exchange reaction

gravimetric analysis (TGA) indicate that this chiral IL has high thermal stability, namely it remains stable at 300°C and loses only 1% of its weight at 326°C.[38] Even at temperature as high as 437°C, it still retains 50% of its mass. ^{19}F NMR study of the interactions between optically active S- CHTA$^+$ Tf$_2$N$^-$ ionic liquid and racemic Mosher's salt shows that that chiral S-CHTA$^+$ Tf$_2$N$^-$ readily differentiates R-Mosher salt from S-Mosher's salt, and this disastereomeric interaction resulted in the shift of the Mosher's salt fluorine signal. The difference in the chemical shifts was found to be 24.6 Hz.[38] These results clearly indicate that optically active R- and S- CHTA$^+$ Tf$_2$N$^-$ ionic liquid do exhibit relatively strong enantiomeric recognition and that their chiral recognition is relatively stronger than those for other reported chiral ILs.[26,27] The high solubility power and enantiomeric recognition ability of the IL make it possible to use this chiral IL to solubilize an analyte and to induce diastereomeric interactions for the determination of enantiomeric purity.

Initially, atenolol, a beta blocker drug, was used to evaluate chiral recognition of S-CHTA$^+$ Tf$_2$N$^-$ ionic liquid. Ten solutions of atenolol in S-CHTA$^+$ Tf$_2$N$^-$ ionic liquid having the same total concentration of 60 mM with relatively different enantiomeric compositions (see Table 1) were prepared, and their NIR spectra were taken. If the chiral ionic liquid has enantiomeric recognition toward R- and S-atenolol, the distereomeric interacntios will lead to changes in the NIR spectra. Figure 1 shows eighteen NIR spectra: a spectrum of the pure S-CHTA$^+$ Tf$_2$N$^-$, spectra of the ten standard solutions of atenolol and spectra of seven solutions of atenolol whose compoions are to be calculated. It is evident from the figure that adding atenolol to the S-CHTA$^+$ Tf$_2$N$^-$ solution leads to changes in the spectra. Of interest are the differences among the spectra of atenolol solutions. Since these atenolol solutions have the same total concentration (60 mM) but different enantiomeric compositions, the observed differences clearly indicate that, similar to cyclodextrins and sucrose[23,24], the chiral S-CHTA$^+$ Tf$_2$N$^-$ ionic liquid can differentiate R-atenolol from S-atenolol, and, as expected, the diastereomeric interactions lead to changes in the NIR spectra. Similar to the procedures used in our previous studies[23,24], multivariate method of analysis (i.e., partial least squares method (PLS)) was used to develop cali-bration models for subsequent determination of enantiomeric purity of unknown samples. Results from the PLS cross-validation show that calibration for 10 models require a relatively small number of factors for optimal performance (12 for R- atenolol and 9 for S-atenolol). The root mean standard error of prediction (RMSEP) values are 0.122 and 0.109 for R- and S-atenolol, while the standard error of prediction (SEP) values are 0.120 and 0.110 for R- and S-atenolol, respectively.

TABLE 1. Compositions of Atenolol Solutions Used for Calibration.

Sample	Mole fraction of R-atenolol	Mole fraction of S-atenolol
1	0.30	0.70
2	0.40	0.60
3	0.45	0.55
4	0.50	0.50
5	0.55	0.45
6	0.60	0.40
7	0.65	0.35
8	0.70	0.30
9	0.75	0.25
10	0.85	0.15

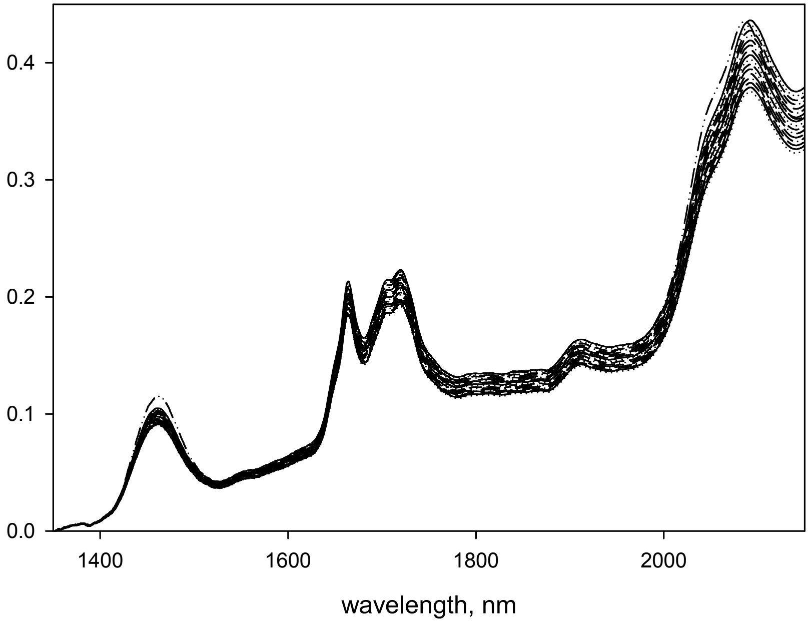


Figure 1. NIR spectra of the pure S-CHTA$^+$ Tf$_2$N$^-$ and of 17 solutions of atenolol with the same total concentration of 60 mM but different enantiomeric compositions.

To evaluate the effectiveness of this method, seven samples of atenolol with the same total concentration of 60 mM but different enantiomeric compositions were prepared, and the concentrations of R- and S-atenolol in each sample were calculated using the calibration models developed above. Results obtained are shown in Figure 2, where the calculated concentrations of R- and S-atenolol in seven samples were plotted against actual concentrations. To illustrate the accuracy of the method, calculated concentrations of R-atenolol (in seven samples) were plotted separately from those of S-atenolol (of the same sample). As expected, the calculated concentrations for both R-and S-atenolol are linearly related to actual concentrations. Furthermore, the linear relationship obtained for R-atenolol (y = (0.97 ± 0.09)x + (0.01 ± 0.03)) is, within experimental error, the same as that for S-atenolol (y = (1.04 ± 0.13)x + (0.01 ± 0.09)). In fact, both concentra-tions of R- and S-propranolol fit well into a single equation with y = (1.03 ± 0.04)x + (0.00 ± 0.02) with correlation coefficient of 0.99999.

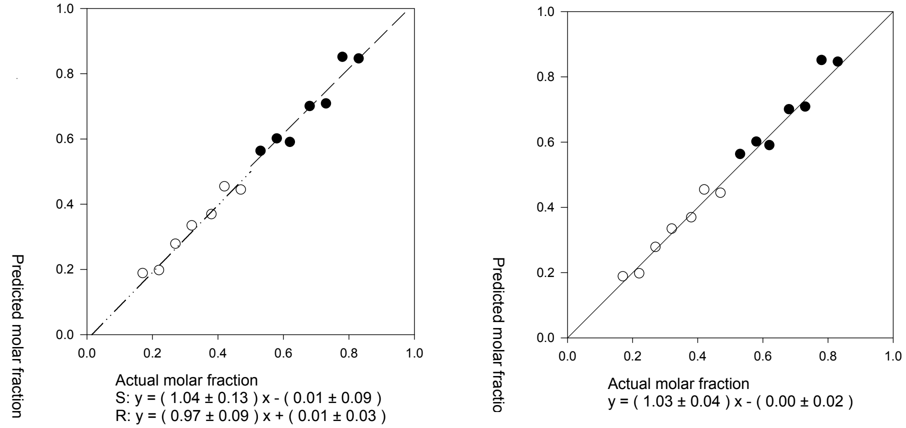


Figure 2. Predicted enantiomeric composition versus actual composition for 60 mM Atenolol in S-CHTA$^+$ Tf$_2$N$^-$ ionic liquid. Filled circles, S-atenolol; open circles, R-atenolol. **Left:** Predicted R-atenolol values were plotted separately from S-atenolol; **Right:** R-atenolol and S-atenolol were plotted together.

It is expected that the method is not specific to atenolol but is effective for other compounds as well. This possibility was investigated by studying its effectiveness on other types of compounds including two drugs (ibuprofen and propranolol) and two amino acids (alanine and phenylalanine). Figure 3 A–D show the results obtained where the calculated concentrations are plotted against actual concentrations. As illustrated, enantiomeric compositions for ibuprofen, propranolol, alanine and phenylalanine can be accurately determined by this method. It is important to add that the five compounds studied here (atenolol, ibuprofen, propranolol, alanine and phenylalanine) are different not only on their structures but also on their sizes, shapes and solubility as well. Specifically, propranolol is probably the largest among them as it has a naphthalene ring. There is a phenyl ring in atenolol, ibuprofen and phenylalanine, and alanine is the smallest as it does not have any aromatic ring at all. Except ibuprofen, all other four compounds are soluble in water. The solubility of ibuprofen in water is so poor that in our previous work (with cyclodextrins and sucrose as chiral selector[12]), instead of water we had to use a mixture of 30:70 ethanol:water mixture. It was not necessary to change the solvent in this case because $CHTA^+$ Tf_2N^- ionic liquid has so high solubility power that it dissolves ibuprofen as well as it does for propranolol and atenolol.

It is expected that similar to method reported previously based on the use of cyclodextrins and sucrose[23,24], the present method should have high sensitivity. Its sensitivity can be evaluated from two values: the lowest enantiomeric excess (EE% which is defined as EE% = [(R-enantiomer – S-enantiomer)/(R-enantiomer + S-enantiomer)]) that can be determined at the lowest concentration of a sample. It should be noted that these two terms are interdependent to each other, namely, the limit of detection (LOD) on ee% can be improved by increasing sample concentration or vice versa. In an attempt to estimate the sensitivity of the method, we performed measurements on 10 samples of 10.0 mM or 2.66 mg/mL of atenolol with different ee%'s in S- $CHTA^+$ Tf_2N^-. Results obtained are listed in Table 2 . It is evident from the table that the method is not only effective but also very sensitive. It can accurately determine samples with concentration as low as micrograms having ee value as high as –90.00% (or +97.00%) and as low as 0.6%. Furthermore, even at ee as low as 0.6%, the relative error was only 3.33%.

Collectively, the results presented clearly demonstrate that both enantiomeric forms of a novel chiral ionic liquid, R- and S-$[CHTA]^+$ $[Tf_2N]^-$ can be readily synthesized in enantiomerically pure form by a simple ion exchange reaction from corresponding chloride salts which are commercially available. In addition to the ease of preparation, this chiral IL has relatively high thermal stability (up to 300°C), is liquid at room temperature (glass transition temperature of –58.4°C) and exhibits strong enantiomeric recognition. The high

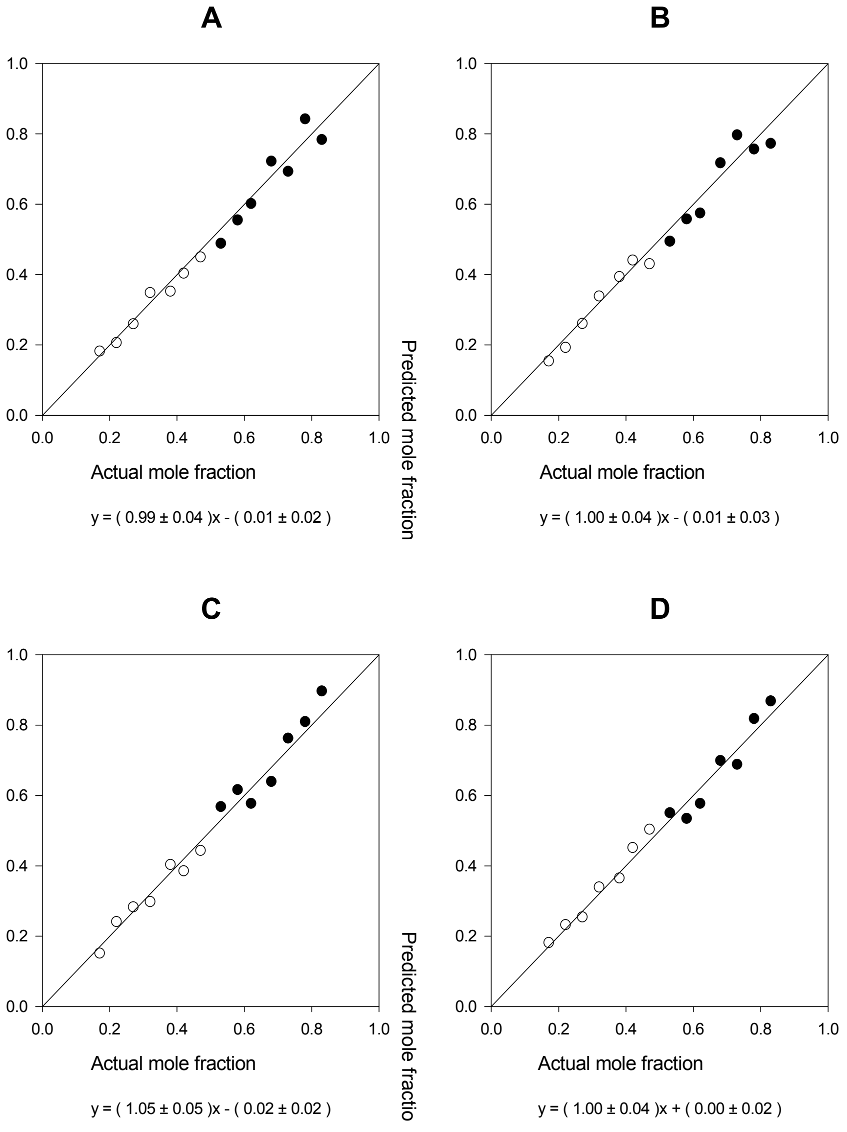


Figure 3. Predicted enantiomeric composition versus actual composition for 60 mM of: (A) ibuprofen; (B) atenolol; (C) phenylalanine and (D) alanine in S-CHTA$^+$ Tf$_2$N$^-$ ionic liquid. Filled circles, S-enantiomers for ibuprofen and propranolol and L-enantiomers for phenylalanine and alanine; Open circles, R-enantiomers for propranolol and D-enantiomers for phenylalanine and alanine.

TABLE 2. Actual and Calculated Enantiomeric Excess of Solution of 10 mM Atenolol in (S) CHTA$^+$ Tf$_2$N$^-$ Ionic Liquid.

Sample	**R-atenolol (mole fraction)**	**S-atenolol (mole fraction)**	**Actual ee (%)[a]**	**Calcd. ee (%)[a]**	**Rel. error[b]**
1	0.050	0.950	–90.00	–82.17	8.70
2	0.150	0.850	–70.00	–72.95	4.21
3	0.300	0.700	–40.00	–39.34	1.65
4	0.365	0.350	–27.00	–27.69	2.55
5	0.480	0.520	–4.00	–4.25	6.25
6	0.496	0.504	–0.80	–0.74	7.50
7	0.503	0.497	0.60	0.58	3.33
8	0.510	0.490	2.00	2.10	5.00
9	0.800	0.200	60.00	61.86	3.10
10	0.985	0.015	97.00	101.06	4.19

[a] Defined as ee (%) = [(R-atenolol – S-atenolol)/(R-atenolol + S-atenolol)] × 100

[b] Defined as relative error = [(actual value – calculated value)/(actual value)] 100

solubility power and enantiomeric recognition ability of the IL make it possible to use this chiral IL to solubilize an analyte and to induce diastereomeric interactions for the determination of enantiomeric purity. In fact, a new method based on the near-infrared technique with this chiral IL serves both as a solvent and also as a chiral selector for the determination of enantiomeric purity has been developed. Enantiomeric compositions of a variety of pharmaceutical products and amino acids with different shape, size and functional groups can be sensitively (microgram concentration) and accurately (enantiomeric excess as low as 0.60%) deter-mined by use of this method. Because in this method, the chiral IL serves both as solvent and chiral selector, it is not necessary to add a carbohydrate compound or to perform the analysis in a variety of solvents. Relatively fewer and simpler calibration models are needed. As a consequence, the method will have wider applications and universal utility as it can be used for the analysis of all type of compounds with relatively shorter analysis time and easier procedure.

It is noteworthy to add that the enantiomeric composition determination method based on chiral IL is not specific to near-infrared spectroscopic technique but is rather general as it can be used with other spectroscopic techniques as well. In fact, we have successfully demonstrated that fluorescence technique can also be used with this method.[39] Furthermore, the fluorescence based method has relatively higher sensitivity and lower limit of detection compared to the method based on the near-infrared technique.[39] Specifically, we have demonstrated that enantiomeric compositions of a variety of pharmaceutical products with different shapes, sizes and functional groups can be determined sensitively (microgram concentration) and accurately (enantiomeric excess as low as 0.30% and enantiomeric impurity as low as 0.08%) by use of the fluorescence based method[39]. The high sensitivity obtained by this method is based on the inherent high sensitivity of the fluorescence technique. However, it is important to add in spite of its high sensitivity, the fluorescence based method has relatively limited application compared to the near-infrared based method which has much wider applications as the latter can be used for all types of compounds while the former can only be used for analytes which are fluorescent; e.g., propranolol, naproxen and warfarin.[39]

2.2. IONIC LIQUIDS AS SUPERIOR SOLVENT FOR THERMAL LENS MEASUREMENTS

Thermal lens techniques have been demonstrated to be a sensitive method for low-absorbance measurements.[40,41] Absorptivities as low as $10.^{7}$ have been measured using these techniques[40,41]. The utility of the techniques has increased substantially because it has been demonstrated recently that, in addition to the ultrasensitivity, the techniques are particularly suited for small volume samples.[42] In fact, the combined ultrasensitivity and small volume capability make it possible to successfully use the techniques as a detector for microfluidic devices. The technique is based on the nonuniform temperature rise that is produced in an illuminated sample by nonradiative relaxation of the energy absorbed from a TEM_{00} laser beam. For weak absorbing species, the thermal lens signal, which was measured using the thermal lens instrument shown figure 4, as the relative changes in the laser beam center intensity in the far field, $\Delta I_{bc}/I_{bc}$, is related to the excitation laser power P and sample absorbance A by

$$\frac{\Delta I_{bc}}{I_{bc}} = \frac{1.21P(dn/dT)A}{\lambda k} \qquad (1)$$

where λ is the wavelength, and dn/dT and k are the temperature coefficient of the refractive index and thermal conductivity of the solvent, respectively.[40,41]

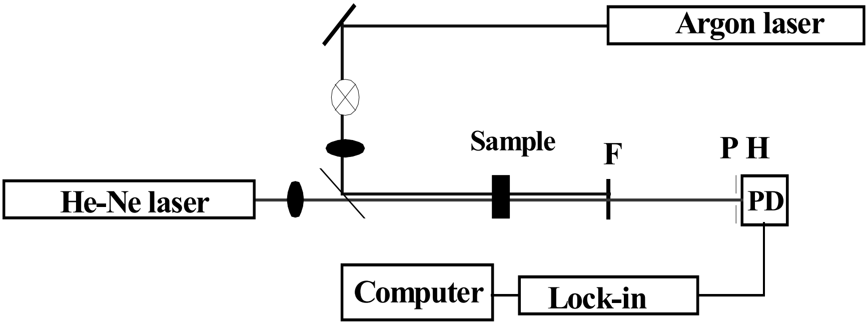


Figure 4. Schematic diagram of the thermal lens instrument: F, filter; PH, pinhole; PD, PIN photodiode.

It is thus clear that in addition to the sample absorbance and excitation laser power, the thermal lens signal is directly proportional to dn/dT and inversely proportional to the k value of the solvent.[40,41] Nonpolar, volative organic solvents such as benzene, carbon tetrachloride and hexane, should provide good media for thermal lens measurements owing to their high dn/dT and low k values. Conversely, water, which is the most powerful and widely used solvent in spectrochemical analysis is considered to be the worst medium for thermooptical techniques because it has very low dn/dT and high k values.[40,41] In fact, we have successfully demonstrated that for the same sample concentration and excitation laser power, the sensitivity of thermal lens measurements in volatile solvent such as carbon tetrachloride and benzene are about 40 and 26 times higher than that in water, respectively.[43–47] This is very unfortunate because it severely limits the scope of these techniques. As a consequence, considerable efforts have been made either to develop novel solvents that have better thermo-optical properties than water but do not produce pollution like traditional volatile organic solvents. Ionic liquids with their unique properties may provide the answer for this problem.

Initial investigation was on the effect of the anion on the thermo-optical properties of the ILs. Butyl-methyl imidazolium ($BMIm^+$) was used as the cation as it is one of the most widely studied and used ILs[1–12]. Three different

TABLE 3. List of Ionic Liquids Used.

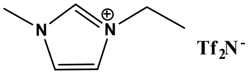
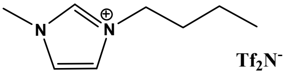
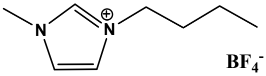
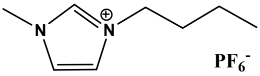
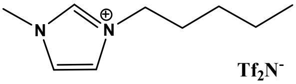
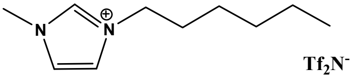
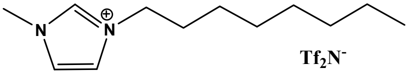
	**1-ethyl-3-methylimidazolium Tf_2N^- or $[EMIm]^+$ $[Tf_2N]^-$**
	**1-butyl-3-methylimidazolium Tf_2N^- or $[BMIm]^+$ $[Tf_2N]^-$**
	**1-butyl-3-methylimidazolium BF_4^- or $[BMIm]^+$ $[BF_4]^-$**
	**1-butyl-3-methylimidazolium PF_6^- or $[BMIm]^+$ $[PF_6]^-$**
	**1-pentyl-3-methylimidazolium Tf_2N^- or $[PMIm]^+$ $[Tf_2N]^-$**
	**1-hexyl-3-methylimidazolium Tf_2N^- or $[HMIm]^+$ $[Tf_2N]^-$**
	**1-octyl-3-methylimidazolium Tf_2N^-or $[OMIm]^+$ $[Tf_2N]^-$**

TABLE 4. Relative Thermal Lens Sensitivity in Different Media.

Solvent	Relative Thermal Lens Sensitivity
Water	1
Benzene	26 ± 1
$[BMIm]^+$ $[Tf_2N]^-$	26 ± 1
$[BMIm]^+$ $[BF_4]^-$	29 ± 2
$[BMIm]^+$ $[PF_6]^-$	31 ± 1
$[EMIm]^+$ $[Tf_2N]^-$	18.0 ± 0.8
$[PMIm]^+$ $[Tf_2N]^-$	30 ± 1
$[HMIm]^+$ $[Tf_2N]^-$	32 ± 1
$[OMIm]^+$ $[Tf_2N]^-$	35 ± 1

anions were selected: Tf_2N^-, tetraborate (BF_4^-) and hexafluoro phosphate (PF_6^-) (see Table 3 for structures of ILs used). Figure 5 shows the calibration curves in water as well as in three ILs. As illustrated, the slopes for all three ILs are much larger than that for water. Actual sensitivity values are listed in Table 4 where the sensitivity for water is normalized to be 1. It is interesting to observe that the sensitivity in all three ILs are at least 20 to 30 times higher than that in water. Interestingly, changing the anion of the ILs also produce significant changes in the sensitivity. Specifically, replacing Tf_2N^- in $BMIm^+$ $Tf_2N^-$with BF_4^- increases the sensitivity from 26 folds to 29 folds (relative to water) or an increase of 11.5%. PF_6^- seems to produce stronger effect as it increases the sensitivity up to 31 folds or 19% increase compared to Tf_2N^-.

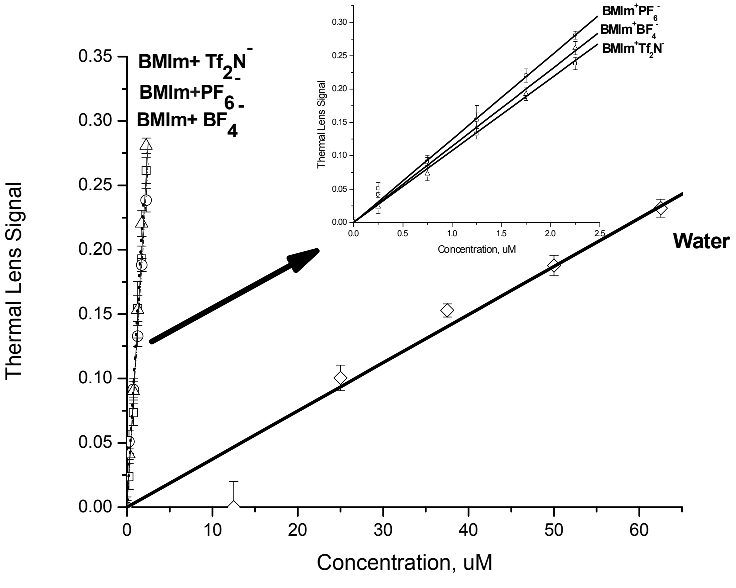


Figure 5. Calibration curves for thermal lens in water and in three different ionic liquids: $BMIm]^+$ $[Tf_2N]^-$, $[BMIm]^+$ $[BF_4]^-$ and $[BMIm]^+$ $[PF_6]$.

Subsequent investigation was on the effect of the cation. Four different ILs with the same anion (Tf_2N^-) but different cations (C_2MIm^+, C_4MIm^+, C_5MIm^+, C_6MIm^+ and C_8MIm^+) were used. Figure 6 shows the calibration curves in these five ILs. As illustrated, increasing the chain length of the alkyl group on the imidazolium cation led to an increase in the sensitivity.

As listed in Table 4, the sensitivity increase from 18 folds by C_2MIm^+ to 26, 30, 32 and 35 folds by C_4MIm^+, C_5MIm^+, C_6MIm^+ and C_8MIm^+, respectively. Interestingly, as shown in figure 6B, the relative sensitivities seems to be linearly related to the number of carbons in the alkyl group of the imidazolium cation.

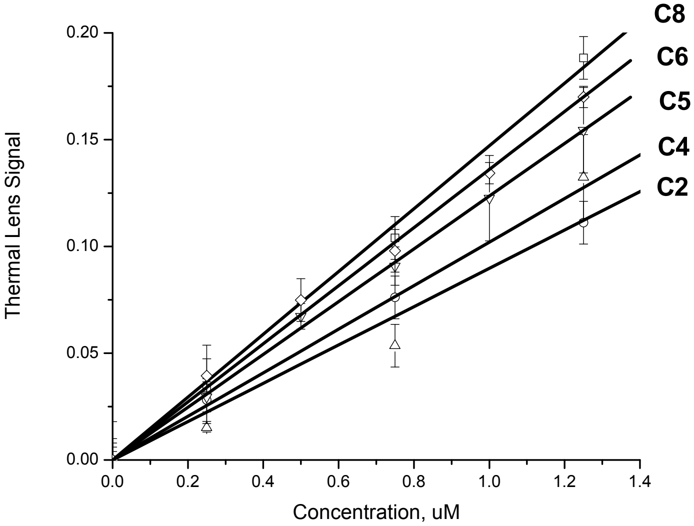


Figure 6. Calibration curves for thermal lens in ionic liquids having alkyl group with different length.

The origin of this linear relationship is unclear at this time, and may be just a coincidence. However, the results clearly indicate that increasing the chain length of the alkyl group or increasing the hydrophobicity of the ILs leads to an increase in the sensitivity of thermal lens measurements. In fact, the results observed here are in agreement with those obtained in our previous studies, namely, we found that the sensitivity of thermal lens is higher in hydrocarbon with longer carbon chain (e.g., n-heptane) than those of relatively shorter chain (e.g., pentane).[4–8]

Collectively, it is evidently clear that ILs can be used as an attractive and superior solvent for thermal lens measurements. The ILs are superior to water as they have relatively high solubility power, and by judicious selecting either the cation and/or anion, they can be made to dissolve many different types of compounds including polar as well as non polar compounds. More importantly, they provide a better medium for thermal lens measurements than water. Specifically, not only the ILs offer at least 20 times higher sensitivity than water but that the enhancement can be appropriately adjusted by changing either the cation and/or the anion of the ILs. For example, the sensitivity in $[BMIm]^+$ $[Tf_2N]^-$ is about 26 times higher than in water. It can be increased up to 31 times by changing the anion to $[PF_6]^-$ (i.e., $[BMIm]^+$ $[PF_6]^-$) or to 35 times by changing the cation to $[OMIm]^+$ (i.e., $[OMIm]^+$ $[Tf_2N]^-$). In fact, the sensitivity of thermal lens measurements in ILs is comparable to those in volatile organic solvents such as benzene, carbon tetrachloride, hexane, but ILs are more desirable as they have virtually no vapor pressure. Results obtained for the two analytes used in this study, ferroin and C_{60}, illustrate some of potential applications of this enhancement method. Ferroin which is insoluble in non polar solvent, can be dissolved in ILs instead of water to substantially enhance its thermal lens detection. Fullerenes such as C_{60} are soluble only in highly nonpolar solvent (e.g., benzene). Instead of using volatile organic compounds (VOC) such as benzene as solvent, its detection can be readily and sensitively achieved by using solutions of surfactants in ILs. As described previously in the introduction, the thermal lens technique is particularly suited as detection method for microfluic devices because of its ultrasensitivity and small volume capability (conventional spectrophotometric technique cannot be used for such devices because not only that it has much lower sensitivity but that its sensitivity is proportional to the pathlength of the sample). The ILs induced thermal lens enhancement reported here can, therefore, be synergistically used in microfluic devices by simply replacing either water (to enhance detection sensitivity) or VOC solvent (to prevent pollution and also to enhance the sensitivity) with ILs.

3. Spectroscopy for Ionic Liquids

As described in the introduction, the majority of studies on ILs have focused on synthesizing ILs with new anions and cations, and determining their chemical properties.[48–55] Unfortunately, information on the ILs including their physical properties and the relationships between structure and physical properties is not widely available despite their superior physical properties which make them suitable, not only as green solvents, but also as high performance fluids for use in a wide range of engineering and materials science applications, such as high pressure and high temperature[48–55] lubricants. It is probable that industrial applications of ILs in chemistry, engineering, and material processing are limited because of the paucity of data on their physical properties. To hasten the implementation of such applications as well as to guide the development of novel ILs that have desired properties, it is particularly important to perform study which aims not only to measure physical properties of the ILs but also to determine the relationship between their structure and properties. Differential scanning calorimery (DSC) is usually the instrument of choice for such study as it can determine phase transition temperatures and heat capacities of various substances. Thermal conductivity values can also be determined by use of the DSC but such measurement requires instrumental modification. While the DSC is effective for thermal characterization of the ILs, the instrument is relatively expensive and measurements are often time consuming and tedious. Furthermore, relatively large amount of samples is required for DSC measurement especially high sensitivity is required. As a consequence, it is important that new techniques which are capable of sensitively and accurately determine thermal physical properties of ILs be developed. We have recently demonstrated that techniques based on photothermal and photoacoustic effect, including transient thermal grating and thermal lens, are particularly well suited for the determination of thermal physical properties of ILs.

3.1. DETERMINATION OF THERMAL PHYSICAL PROPERTIES OF IONIC LIQUIDS BY TRANSIENT GRATING TECHNIQUE

Transient grating technique is one form of photothermal techniques.[48–54] It is based on the transient grating formed by intersecting two pulsed laser beams (pump beam) in the sample.[48–54] If the sample absorbs the laser light, the heat generated as the consequence of the nonradiative relaxation will produce photoacoustic wave and sinusoidal temperature elevation. The acoustic wave and thermal wave undergo decay as the sample slowly returns to ambient temperature. Since the decay of the acoustic wave and thermal wave are dependent on the thermal physical properties of the sample, by monitoring these decays with a probe laser beam, thermal physical properties of the sample including its thermal diffusivity and thermal conductivity value can be determined.[48–54] In fact, transient grating technique has been successfully used for the sensitive and accurate determination of thermal physical properties of various substances.[48–54] As can be seen in following sections, by use of the transient grating method[51–55] we were able not only to determine the physical properties of ILs, but also to gain insight into relationship between IL structure and their thermophysical properties.

Theoretical treatment of photoacoustics and its application to the transient grating technique have been reported previously.[49–55] The photoacoustic

acoustic effect occurs because of thermoelastic expansion of the absorbing media. For a point source, the density change, δ can be written as:

$$\delta = \frac{\alpha E_0 \beta}{Cp}\left[-e^{-K^2 \chi t} + e^{-K^2 \sigma t} Cos(cKt)\right] \tag{2}$$

where the damping parameter **σ**, and the viscous and heat conduction lengths[17] ***l*$_v$'** and ***l*$_h$** respectively, are given by

$$\sigma = \frac{1}{2}c\left[\ell_v{}' - (\gamma - 1)\ell_h\right]$$

$$\ell_v{}' = \frac{\eta + \frac{4}{3}\mu}{\rho c} \tag{3}$$

$$\ell_h = \frac{\chi}{c}$$

The quantities **α**, ***c***, ***γ***, μ, η, and ρ are the thermal diffusivity, sound speed, heat capacity ratio, bulk viscosity coefficient, shear viscosity coefficient, and density of the sample, respectively; and **E$_0$**, **a**, **β** and **Cp** are the energy fluence of the laser beam, the optical absorption coefficient, the volume expansion coefficient, and the isobaric heat capacity, respectively, of the fluid. The first and second terms in Eq. 2 describe the time dependences of the thermal and acoustic modes of wave motion, respectively. Since the decays of the acoustic and thermal mode densities back to their ambient values take place on such different time scales (microsecond time scale for acoustic mode and millisecond time scale for thermal mode), they were recorded on the oscilloscope using different time bases.

$$Signal_{acoustic}(t) = \left(F(-A + e^{-E(t+C)} Cos[\frac{2\pi(t+C)}{B}]\right)^2 + D \tag{4}$$

$$Signal_{thermal}(t) = \left(-Ge^{-H(t+C)}\right)^2 + D \tag{5}$$

The quantities denoted by capital letters are adjustable parameters used in the least-square fitting procedure. Therefore, by fitting measured transient grating signals to equations 2, 4 and 5, thermal diffusivity, sound speed, heat capacity ratio, bulk viscosity coefficient, shear viscosity coefficient, and density of the sample can be obtained.

TABLE 5. Thermal Diffusivities (α), Sounds Speeds (c) and Damping Parameter (σ) Determined by Transient Grating Technique Together with Some Reported Values.

10^{-7} α/m^2 s^{-1}	c/m s^{-1}	$c_{Ref.}$/m s^{-1}	10^{-4} σ/m^2 s^{-1}	η/mPa s
0.86±0.01	1564±8	1570±3[59]	3.7±0.4	119.78±1.28[61]
0.75±0.02	1441±4	1433±3[59]	4.2±0.4	207.00±11.12[56]
0.60±0.01	1227±6	1238.06±62[60]	2.4±0.6	52±3[56]
0.601±0.004	1240±4	–	2.6±0.7	31[56]
0.58±0.02	1227±2	–	3.0±0.8	–
0.606±0.009	1232±11	–	2.3±0.3	–
0.61±0.01	1232±5	–	3.1±0.7	–

The results listed in Table 5 show that the properties of the anion of the ILs have a strong effect on the sound speed. Specifically, changing the anion from BF$_4$ to either PF$_6$ or Tf$_2$N leads to 7.9% and 21.5% decrease in the sound velocity (from (1564 ± 8) ms^{-1} for BMIm$^+$ BF$_4^-$ to (1441 ± 4) ms^{-1} for BMIm$^+$ PF$_6^-$ and to (1227 ± 6) ms^{-1} for BMIm$^+$ Tf$_2$N$^-$). Interestingly, the size of the cation does not seem to have observable effect on the sound velocity of the ILs: the sound velocity of the IL with C$_2$ cation (i.e., EMIm$^+$ Tf$_2$N$^-$) is 1240 ± 4 ms^{-1} which is similar to that of the IL with C$_4$ or BMIm$^+$ Tf$_2$N$^-$ (1227 ± 6 ms^{-1}), C$_5$ or PMIm$^+$ Tf$_2$N$^-$ (1227 ± 2 ms^{-1}), C$_6$ or HMIm$^+$ Tf$_2$N$^-$ (1232 ± 11 ms^{-1}) and C$_8$ or OMIm$^+$ Tf$_2$N$^-$ (1232 ± 5 ms^{-1}). It is pleasing to see that the results obtained by this method for BMIm$^+$ BF$_4^-$ and BMIm$^+$ PF$_6^-$ agree very well (within 1% error) with reported values determined using other methods[56,57] (1564 ± 8 ms^{1} and 1441 ± 4 ms^{-1} for BMIm$^+$ BF$_4^-$ and BMIm$^+$ PF$_6^-$,determined by this method compared with 1570 ± 23 ms^{-1} and 1431 ± 59 ms^{-1} by other workers).[56,57] It is noteworthy to add that the reported sound velocity values were determined by other workers using a different technique (non-intrusive acoustic microcell that used an acoustic transducer at 0.5 MHz).[56,57] The fact that their values agree well with the values determined by this method lends further credence to our method and clearly demonstrates that our method is effective for the determination of sound velocity of ILs, in particular, and of all liquids, in general.

As can be seen by inspection of Figure 7, the damping constant for [BMIM]$^+$ [PF$_6$]$^-$ is similar to that of [BMIM]$^+$ [BF$_4$]$^-$, but is approximately double that of [BMIM]$^+$ [Tf$_2$N]$^-$. As Table 6 shows, the character of the anion of the IL has a strong effect on the damping parameter $\boldsymbol{\sigma}$, while that of the cation exerts no significant effect, a trend that parallels the relative influence of the anion and cation on the sound speed, as noted above. Since **σ** is a decay parameter that includes energy losses primarily due to viscosity with typically only a small contribution from heat conduction, the data suggest that for identical densities that [BMIM]$^+$ [PF$_6$]$^-$ is the most viscous of the ILs studied here, and that varying the number of carbons on the cation has little influence on the overall viscosity. Furthermore, if the bulk viscosity can be taken as negligible to the shear viscosity, then the experimental quantity **σ** is related to the bulk and shear viscosities through **$\sigma = (2/3)\mu\rho$**. As listed in Table 6, viscosities for [BMIM]$^+$ [PF$_6$]$^-$, [BMIM]$^+$ [Tf$_2$N]$^-$, [EMIM]$^+$ [TF$_2$N]$^-$, and [BMIM]$^+$ [BF$_4$]$^-$ at 298°K were previously reported[56,57] to be 207cP, 52cP, 31cP, and, 119.78 ± 1.28cP respectively. These values are in very good agreement with values obtained by the transient grating technique reported here.

TABLE 6. Thermal Conductivity (λ) of BMIm$^+$ BF$_4^-$, BMIm$^+$ PF$_6^-$, BMIm$^+$ Tf$_2$N$_4^-$ and EMIm$^+$ BF$_4^-$ Determined by Transient Grating Technique Together with Some Reported Values.

ρ/kg m^{-3}	Cp/J kg^{-1} K^{-1}	λ/W m^{-1} K^{-1}	λ_{Ref}/W m^{-1} K^{-1}
1205.0±0.2[59]	1613±81[59]	0.162±0.006	0.186±0.001[61]
1205±2[62]	1555±58[62]		
1201.8[61]	1614[62]		
1366.0±0.3[59]	1438±72[59]	0.109±0.005	–
1363[56]	1399±62[60]		
1437.04[60]	1293[60]	0.108±0.004	–
1429[56]	1279±46[60]		
1438.6±0.3[62]			
1520[56]	1340±52[62]	0.120±0.005	–

In addition to acoustic properties, the transient grating measurements also provide information on the thermal diffusivity of the ILs. In this study, various ILs with different anions and cations were used in order to elucidate the effect of the anon and the cation on their thermal diffusivities and

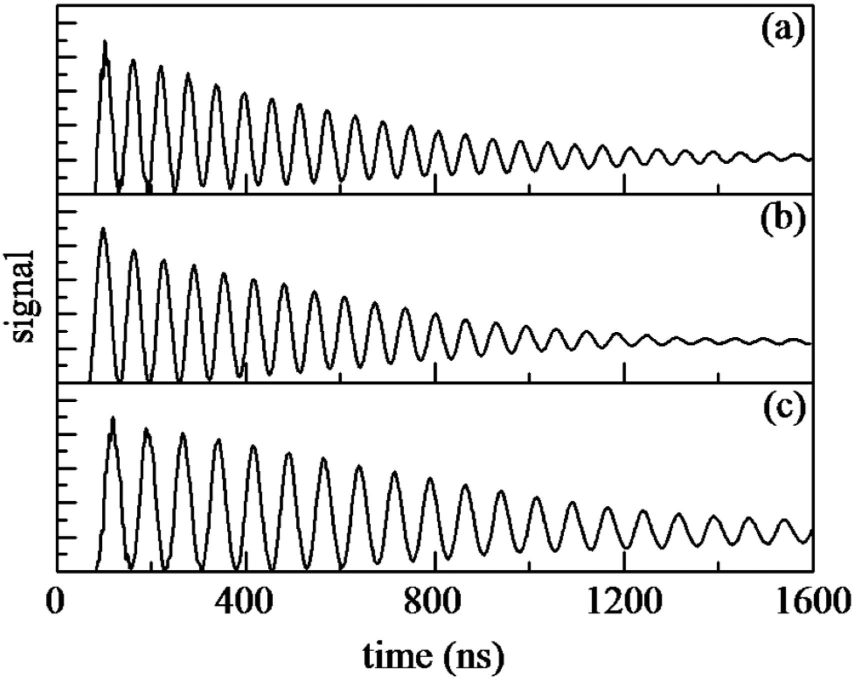


Figure 7. Plots of the damping parameter (σ) in Ed 3 as a function of time for three ILs: (a) BMIm$^+$ BF_4^-; (b) BMIm$^+$ PF_6^- and (c) BMIm$^+$ Tf_2N.

thermal physical properties. It seems that similar to the effect on the sound velocity, the anions of the ILs exert strong influence on their thermal diffusivities. This can be seen in Figure 8 which plots the decays of the thermal mode in eq 5 for the three ILs which the same cation but different anion: BMIm$^+$ BF_4^-, BMIm$^+$ PF_6^- and BMIm$^+$ Tf_2N.

It is evident from the figure that the damping of the thermal mode becomes less profound as the anion becomes more bulky. More detailed information can be found in the calculated thermal diffusivity values that are listed in Table 5 As listed in the table, changing the anion from BF_4^- to either PF_6^- or Tf_2N^- leads to 12 and 30% decrease in the thermal diffusivity (from (0.86 ± 0.01) 10^{-7} m^2 s^{-1} for BMIm$^+$ BF_4^- to (0.756±0.02) 10^{-7} m^2 s^{-1} for BMIm$^+$ PF_6^- and to (0.60 ± 0.01)10^{-7} m^2 s^{-1} for BMIm$^+$ Tf_2N^-). Again, similar to the effect on the sound velocity, the size of the cation does not seem to have observable effect on the thermal diffusivity of the ILs: the

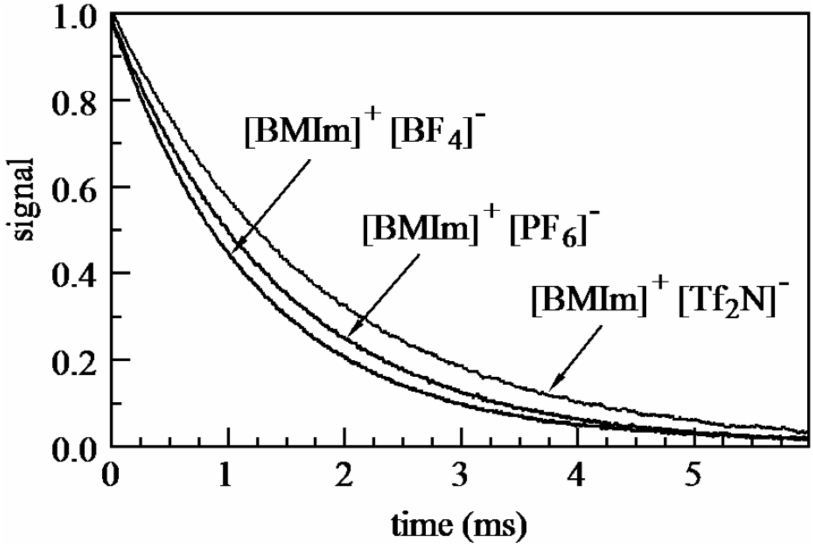


Figure 8. Plots of the decay of thermal mode for three ILs.

thermal diffusivity of the IL with C_2 cation (i.e., $EMIm^+$ Tf_2N^- is (0.601± 0.004) 10^{-7} m^2 s^{-1} which is similar to that of the IL with C_4 or $BMIm^+$ Tf_2N^- (0.60 ± 0.01) 10^{-7} m^2 s^{-1}), C_5 or $PMIm^+$ Tf_2N^- (0.58 ± 0.02) $10^{-7}m^2s^{-1}$), C_6 or $HMIm^+$ Tf_2N^- (0.606 ± 009) 10^{-7} m^2 s^{-1}) and C_8 OMIm Tf_2N (0.61 ± 0.01) 10^{-7} m^2 s^{-1}). Taken together, the results seem to indicate that heat diffusion is controlled not by the cation but rather by the anion.

Although, the transient grating measurements yield values for thermal diffusivity for each IL directly, the thermal conductivity must be found from a knowledge of the density and specific heat capacity through the relation $\boldsymbol{\alpha = \lambda\rho^{-1}C_p^{-1}}$. Only a few values of density and heat capacity have been reported for $BMIm^+$ BF_4^-, $BMIm^+$ PF_6^-, $BMIm^+$ Tf_2N^-, and $EMIm^+$ Tf_2N^- [58–62]. Based on the reported values of these two quantities, thermal conductivities for these four ILs were calculated and the results listed in Table 6. As expected, similar to the effect on the thermal diffusivity, thermal conductivity of the ILs are strongly effect by their anion. The effect of the cation again seems to be very small, if any.

In summary, it has been demonstrated that the transient grating technique can be used to determine thermal physical properties (thermal diffusivity and thermal conductivity) of ILs. The technique has relatively high precision, namely relative errors are about 1%. It also has relatively high accuracy: thermal conductivity values of ILs determined by this method agree, within 1% with values previously determined by other workers. More importantly, the technique is sensitive, non destructive, fast, and requires only small amount of sample.

3.2. DETERMINATION OF THERMAL PHYSICAL PROPERTIES OF IONIC LIQUIDS BY THERMAL LENS TECHNIQUE

Thermal physical properties of a sample can also be determined by the thermal lens technique. As described in Section 1.2, thermal lens signal is recorded as the time-dependent change in the far filed beam center intensity (of the probe beam) after the onset of excitation laser illumination[4–8].

$$I_{bc}(t)=I_{bc}(0)\left[\begin{array}{l} 1-\theta\arctan\left[\dfrac{2\xi}{3+\xi^2+(9+\xi^2)t_c/2t}\right]+ \\ \left\{\dfrac{\theta}{2}\arctan\left[\dfrac{2\xi}{3+\xi^2+(9+\xi^2)t_c/2t}\right]\right\}^2 + \\ \left(\dfrac{\theta}{4}\ln\left\{\dfrac{[(2+t_c/t)(3+\xi^2)+6t_c/t]^2+16\xi^2}{(9+\xi^2)^2(2+t_c/t)^2}\right\}\right)^2 \end{array}\right] \tag{6}$$

where ξ is related to the distance between the sample and the beam waist Z_1 and the confocal distance Z_c by

$$\zeta = Z_1/Z_c \tag{7}$$

The strength of the thermal lens, θ, is related to wavelength (λ) and power of the laser (P), the sample absorbance (A) and dn/dT and thermal conductivity k values of the solvent as (In this section, k, not λ as in the previous 2.1 section, is used for thermal conductivity. This was done in order to differentiate the thermal conductivity from the wavelength of the laser, which is λ in this section.)

$$\theta=\frac{2.303PA(-dn/dT)}{\lambda k} \tag{8}$$

The thermal time constant t_c is given by

$$t_c=\frac{\omega^2\rho C_p}{4k} \tag{9}$$

where c_p is the heat capacity, ρ is the density and ω is the beam spot size. From the recorded time dependence of the beam center intensity, $I_{bc}(t)$, the thermal lens strength, θ and the thermal time constant t_c can be obtained by curve fitting of the data according to Eq. 6. Thermal conductivity of a sample can then be determined from the thermal time constant t_c value using the relationship shown in Eq. 9. As described above, density and heat capacity values are currently available for only a few ILs. Using these values, thermal conductivity values for $[BMIm]^+[BF_4]^-$ and $[BMIm]^+[Tf_2N]^-$ were found to be 0.178 $Wm^{-1}K^{-1}$ and 0.110 $Wm^{-1}K^{-1}$, respectively. These values are in good agreement with values determined by the transient grating technique (0.162 $Wm^{-1}K^{-1}$ and 0.108 $Wm^{-1}K^{-1}$, respectively) as well as the reported value[61] of 0.186 $Wm^{-1}K^{-1}$ for $[BMIm]^+[BF_4]^-$.

4. Conclusions

In summary, in this work, we have successfully addressed two aspects of ILs which to date are not widely studied. They are (1) exploitation of unique features of ILs to develop novel spectroscopic methods which otherwise is not possible and (2) development of novel spectroscopic methods for the sensitive and accurate determination of thermal physical properties of ILs. In the first category, we have successfully demonstrated that ILs are more than just solvents. By fully exploiting their unique properties, they can be used to develop novel methods which otherwise are not possible with other solvents and/or substance. For example, we have successfully developed a novel, highly sensitive (microgram concentration) and accurate (enantiomeric excess as low as 0.30% and enantiomeric impurity as low as 0.08%) for the determination of enantiomeric compositions of chiral compounds with different sizes, shape and functional groups including pharmaceutical products. This method is based on the use of a chiral IL which serves both as a solvent and also as a chiral selector. We have also demonstrated that ILs can be used to substantially enhance the sensitivity of thermal lens measurements. These are just two examples obtained in our preliminary studies. It is expected that a variety of novel methods will be developed in the near future by exploiting unique properties of ILs which are currently available or by using novel ILs which will be synthesized to fit the tasks/methods. In the second category, we have demonstrated that transient grating technique and thermal lens technique can be used for the sensitive, accurate, nondestructive determination of thermal physical properties of ILs. This development will make it possible, for the first time, to easily, quickly and sensitively determination of physical properties of ILs which currently are not available. This, in turn, will hasten and implementation and applications of ILs in industry.

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CHEMICAL REACTIONS AND RELATED PHASE BEHAVIOR IN SUPERCRITICAL CO_2 AND CO_2/IONIC LIQUID MIXTURES

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Abstract: Supercritical (SC) CO_2 and ionic liquids (ILs) are two types of solvents with special properties, which have been used as reaction media for different chemical reactions. In this chapter, some recent work about the effect of phase behavior on chemical reactions in SC CO_2 and SC CO_2/IL biphasic systems are discussed.

Keywords: Supercritical; CO_2 ; ionic liquids; chemical reactions; phase behavior

1. Introduction

In recent years, supercritical (SC) science and technology have received much attention. Supercritical fluids (SCFs) can be used in many chemical processes, such as extraction and fraction,[1] chemical reactions,[2] material processing,[3] and cleaning.[4] Study on the chemical reactions in SC solvents or under SC conditions is a promising area. An important incentive for the use of SCFs in chemical reactions results from the increasing demand for high efficient environmentally benign processes to produce clean and high-value products. There are some unique advantages to conduct chemical reactions in SCFs, especially in the critical region. For example, reaction rates, yields, and selectivity can be adjusted by varying pressure, i.e., the high compressibility of SCFs provides density as an additional adjustable parameter; environmentally benign SCFs (such as CO_2, H_2O) can be used to replace toxic solvents; mass transfer can be improved for heterogeneous reactions; and simultaneous reaction and separation may be accomplished

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for some reactions. Research efforts on the use of SCFs as green solvents have been well documented.[5] It is not surprised that in recent years the use of SCFs, especially SC CO_2 and H_2O, as solvents for chemical reaction media has received much attention. SC CO_2 is the most attractive since it is nontoxic, nonflammable, inexpensive, readily available in large quantity, and has moderate critical temperature and pressure (31.1°C and 7.38 MPa). Solvent-free products can be obtained via simple pressure release and non-toxic CO_2 can be easily recycled.

Ionic liquids (ILs) are another type of solvents, which have attracted much interest as an alternative for volatile organic compounds.[6] ILs are organic salts that are liquid at ambient conditions and have some unique properties, such as extremely low vapor pressure, excellent solvent power for both organic and inorganic compounds, high thermal and chemical stability, etc. In addition, they have designable nature which means that ILs can be designed in structure to afford certain specific properties, and are therefore designated as 'designer' solvents. ILs have wide potential applications in different processes.

Many ILs can be designed as green solvents. Combination of the two environmentally acceptable solvents, CO_2 and ILs, is an interesting area.[7] The very distinct properties of SC CO_2 and ILs make them ideal candidates to offer environmentally benign biphasic solvent systems with special properties. The pioneering work of Brennecke and co-workers[8,9] has exploited a new method to separate organic substances and ILs. They have demonstrated that some low-volatility organic compounds could be extracted from ILs completely using SC CO_2 under mild condition. Furthermore, high-pressure CO_2 was soluble in IL, while solubility of ILs in SC CO_2 was extremely low[8,9,10,11] Therefore, at suitable conditions the organic compounds could be extracted from the ILs without cross-contamination. With these unique properties, CO_2/IL biphasic systems can be used not only in separation, but also in biphasic reactions. In recent years, our laboratory studied some physicochemical properties of the special biphasic systems.[12,13,14,15]

Many elegant researches have been carried out for chemical reactions in SC CO_2 and SC CO_2/IL system, and huge number of papers have been published on this. Study on effect of phase behavior of reaction system on the properties of the reactions in SC CO_2[16] and application of the special phase behavior of SC CO_2/IL system in chemical reactions[17,18] are interesting topics. In this chapter, we discuss some of the related work in our laboratory

2. Chemical Reactions in Supercritical CO_2

Researchers usually use a diagram of pure component to discuss the definition of an SCF. This is reasonable because "supercritical" has clear meaning for a pure substance. A pure SCF has some unique features, especially near its critical point. The solvent properties (e.g. density, dielectric constant, solubility parameter, diffusivity) are sensitive to pressure. Therefore, pressure is an effective variable factor to optimize the operating conditions in the applications. However, a SCF loses most of these features as it is far from the critical point.

The critical parameters of a mixture change with composition and are usually different from those of the components. This can be explained simply by a typical pressure versus composition (P–X) phase diagram of a binary system (Figure 1).[19] X_1 is the mole fraction of the light component; C_1 is the critical point at $T = T_1$. ABC_1 is bubble point curve at this temperature, and C_1DA is the dew point curve. Generally, a mixture above the bubble point curve can be regarded as a homogenous subcritical fluid, and a homogeneous mixture with $X_1 > Xc_1$ is considered as a vapor or a supercritical mixture. The mixture of which both composition and pressure are close to the critical point can be regarded as in the near critical region. The critical pressure and critical composition at T_2 (the dotted line) are different from those at T_1, as qualitatively shown in Figure 1 ($T_2 > T_1$). Many books and papers have discussed similar phase diagrams of mixtures in details. We only emphasize that critical parameters and phase behavior of a mixture depend on the properties of the components and the composition of the mixture.

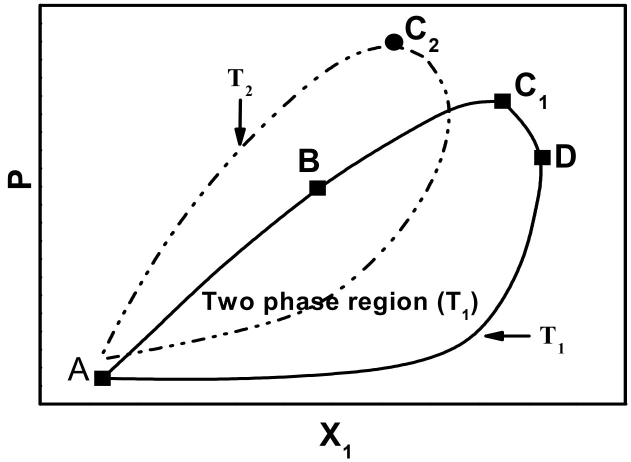


Figure 1. P–X phase diagram of binary mixture ($T_2 > T_1$).

The complexity of phase diagrams increases with the number of components in the mixture. Even the simplest chemical reaction is likely to involve three components (reactant, product, and solvent) and most reactions will involve more. In practice, the concentrations of the reactants and the products are not low during the reaction processes for most reaction systems. In these cases, the critical parameters and phase behavior of a reaction system may differ from those of the solvent significantly because the critical parameters and phase behavior of a mixture depends on the properties of components and its composition.[20] Therefore, any study of reaction chemistry in SCFs will involve the phase behavior of multi-component mixtures. This phase behavior is important because the outcome of a reaction can sometimes be determined by the phase behavior of the reaction system.

Recently, the phase behaviors of some reaction mixtures have been studied.[21] To explore the advantages of the reactions under supercritical condition or in the critical region, the critical parameters and phase behavior of the reaction mixtures should be considered, and reaction properties and the phase behavior of the reaction systems should be combined in the study.[22] In this section, we discuss some work about how pressure and composition of a complex reaction system affect the chemical equilibrium, conversion and selectivity and reaction rate in different phase regions.

2.1. THE SELECTIVE OXIDATION OF CYCLOHEXANE IN SUPERCRITICAL FLUID[23]

The phase behavior and the critical parameters are crucial for selecting the reaction conditions. The phase behavior of the reaction systems of oxidation of cyclohexane (eqn. (1)) was studied. To avoid the reaction during the phase behavior measurement, N_2 was used to replace O_2 for the phase behavior determination, and the results are shown in Figure 2.

$$(n+m)C_6H_{12}+(n+0.5m)\,O_2 \longrightarrow mC_6H_{12}O + nC_6H_{10}O + nH_2O \qquad (1)$$

Figure 2 also shows the density (ρ) *vs* temperature phase diagrams of CO_2-C_6H_{12}-N_2 and CO_2-C_6H_{12}-O_2 systems calculated from PR equation of state.[24] The system is single phase outside the envelopes, and separates into two phases in the envelopes. The results in Figure 2 indicate that the differrence of $\rho \sim T$ curves of the two systems is not considerable. The main reasons are that the physical properties of N_2 and O_2 are similar and their concentrations in the corresponding solutions are low (0.1 mol%). This suggests that N_2 can be used to replace O_2 for the phase behavior measurements.

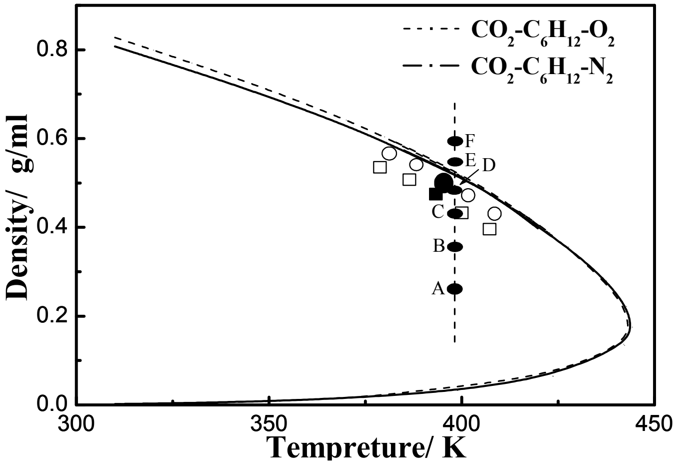


Figure 2. The experimental and calculated phase separation pressure. (—) CO_2:C_6H_{12}:N_2 = 7:2:1 (calculated from PR EOS); (----) CO_2:C_6H_{12}:O_2 = 7:2:1 (calculated from PR EOS); (–□–) CO_2:C_6H_{12}:N_2=7:2:1 (experimental); (–○–) CO_2:C_6H_{12}:N_2:$C_6H_{12}O$:$C_6H_{10}O$ = 7:1.8:0.9:0.1:0.1 (experimental); (–■–) critical point (CO_2:C_6H_{12}:N_2 = 7:2:1); (–●–) critical point (CO_2: C_6H_{12}:N_2:$C_6H_{12}O$:$C_6H_{10}O$ = 7:1.8:0.9:0.1:0.1); Points A, B, C, D, E, F correspond to the selected reaction conditions.

Figure 2 shows the experimental results for the reaction system at $n/m = 1$ (eqn. (1)), and conversion $\alpha = 0$ and 0.1. The value of α has little effect on the critical parameter of the system in the conversion range. The results indicate that the calculated and the experimental phase separation densities show a similar trend with the variation of temperature for the CO_2-C_6H_{12}-N_2 system. However, the calculated data are about 10% larger. The experimental data was used as reference for the selection of reaction conditions.

The reaction experiments were performed in CO_2, liquid butyric acid, CO_2/butyric acid, benzene and CCl_4, and in the absence of any solvent. Results in Table 1 shows that the conversion of the reaction in butyric acid is larger than that in the nonpolar solvents or in the absence of solvent. One of the main reasons may be that butyric acid affects the catalyst surface more significantly because its strong polarity. For the same reaction time, the conversion of cyclohexane in the liquid solvents is higher than that in CO_2, and the amount of byproducts in the liquid solvents is also larger, as can be seen from Table 1. However, it is interesting that at similar conversions (reaction time in CO_2 is longer), the amount of by-products is lower for the reaction carried out in CO_2. One of the reasons is that the diffusion coefficients of cyclohexanol and cyclohexanone in CO_2 are larger than those in the liquid solvents, and thus they can diffuse out of the catalyst quickly, which prevents further reaction of the chemicals. The results of the reaction in CO_2 + butyric acid suggests that addition of small amount of butyric acid as a cosolvent can change the conversion and the selectivity considerably.

TABLE 1. Selective oxidation of cyclohexane with molecular oxygen over MnAPO-5 in different solvents.[a]

Solvents	Conversion (%)	Selectivity (%)		
		$C_6H_{12}O$	$C_6H_{10}O$	Others
No solvent[a]	9.6	40.4	47.2	12.4
Butyric acid[a]	18.2	24.3	46.2	29.5
Benzene[a]	4.2	40.1	56.4	3.5
CCl_4[a]	3.8	50.6	48.1	2.3
CO_2[a]	2.8	56.1	43.4	0.5
CO_2[b]	4.4	42.8	56.3	0.9
CO_2+0.2%butyric acid[a]	7.8	40.1	59.1	0.8

The reactions were carried out at 398.2 K; the weight ratio of cyclohexane to catalyst is 45: 1 in all experiments; the molar ratio of solvent: cyclohexane: oxygen is 7: 2: 1; the apparent density is 0.481 g ml^{-1} as CO_2 is used as solvent; a) Reaction time is 12 h; b) Reaction time is 17 h.

2.2. TRANSESTERIFICATION BETWEEN ETHYL ACETATE AND N-BUTANOL IN COMPRESSED CO_2[19]

The critical parameters of a mixture usually change with composition. Therefore, the phase behavior of a reaction mixture changes with reaction time or conversion. Figure 3 shows the effect of conversion of the transesterification between ethyl acetate and n-butanol in compressed CO_2 on the critical point P_C, bubble point P_B and dew point P_D of the reaction system (Eqn. (2)) at 329.9 K, and the mole fraction of CO_2 changed from 1.0 to 0.88. The curve in the figure is the phase boundary. Above the curves is the single phase region, and below the curves is the two phase region. The curves at different conversions nearly overlap. In other words, the P_C, P_D and P_B do not change considerably with conversion. This is ideal for investigating how the composition and pressure influence the reaction in the critical region of the reaction mixture.

$$CH_3COOC_2H_5 + n\text{-}C_4H_9OH \xrightleftharpoons{\text{Compressed } CO_2} CH_3COOC_4H_9 + C_2H_5OH \quad (2)$$

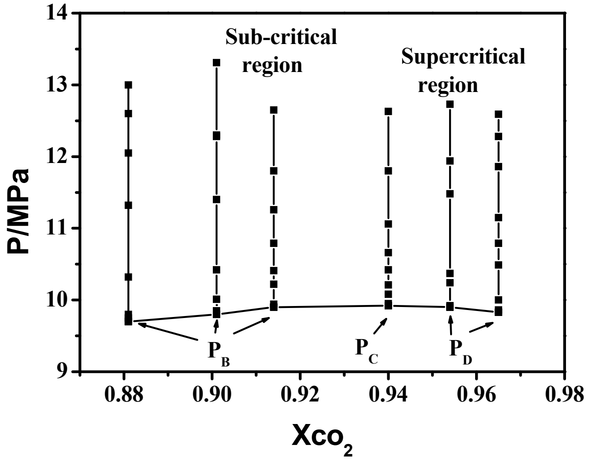


Figure 3. Effect of conversion α on the phase behavior of the reaction system at 329.9 K. The curves at α = 0, 0.2, 0.4, 0.6, 0.8, and 1.0 are nearly overlapped; the vertical lines are experimental conditions for reaction experiments. $CH_3COOC_2H_5$: C_4H_9OH = 1:1.

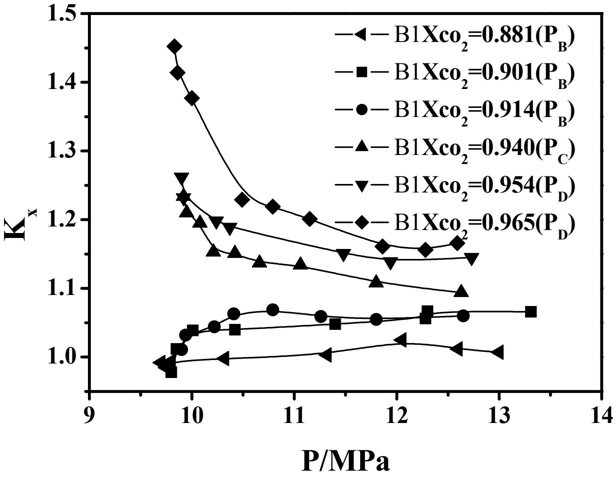


Figure 4. Dependence of equilibrium constant (K_x) on pressure at 329.9 K.

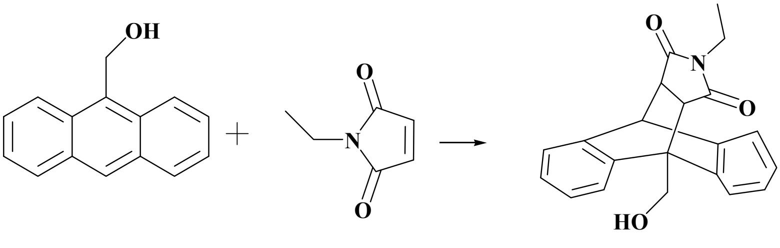
The K_x determined at the conditions shown in Figure 3 are depicted in Figure 4. It is interesting that the K_x is very sensitive to pressure as the reaction mixture approaches the P_C, P_B, and P_D in the critical region, where the mole fractions of CO_2 ($X_{CO2} = 0.965$, 0.954, 0.940, 0.914, 0.901) are equal or close to the critical composition and the pressures are close to critical pressure. In the high pressure region where the reaction mixture is far from the critical point of the reaction system, the effect of pressure on K_x is not significant. It means that the K_x cannot be tuned effectively by changing pressure outside the critical region.

The K_x increases significantly as pressure approaches the P_D and P_C, while it decreases as pressure approaches the P_B, i.e., pressure has opposite effect on the K_x in the sub-critical region and in the supercritical region. To tune the conversion of the reaction by pressure effectively, it is necessary to conduct the reaction in supercritical region.

2.3. EFFECT OF PHASE BEHAVIOUR ON THE RATE OF DIELS-ALDER REACTION USING MIXED SOLVENTS CONTAINING CO_2[25]

Diels-Alder cycloaddition is a type of important synthetic reactions for the construction of six-membered rings, which have been studied extensively in various solvents, including in SC CO_2.[26] Diels-Alder reaction between 9-hydroxymethylanthrance and N-ethylmaleimide (Scheme 1) was carried out in $CO_2(1)$ + hexane(2) and $CO_2(1)$ + ethanol(2) at 318.15 K. The concentration of the reactants was very low.[25] Therefore, the phase behavior of the reaction system could be assumed to be same as that of the mixed solvents.

The phase behavior and the critical point of the mixed solvents are the basis for selecting suitable reaction conditions. The critical parameters at this temperature, the bubble point pressures and dew point pressures of the mixed solvents of different compositions are shown in Figure 5 and Figure 6.



Scheme 1 Diels-Alder reaction between 9-hydroxymethylanthrance and N-ethylmaleimide

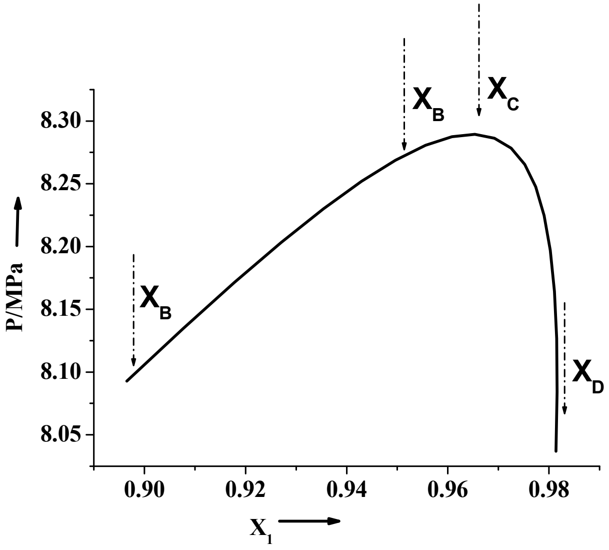


Figure 5. Phase diagram of $CO_2(1)$+hexane(2) system at 318.15 K.

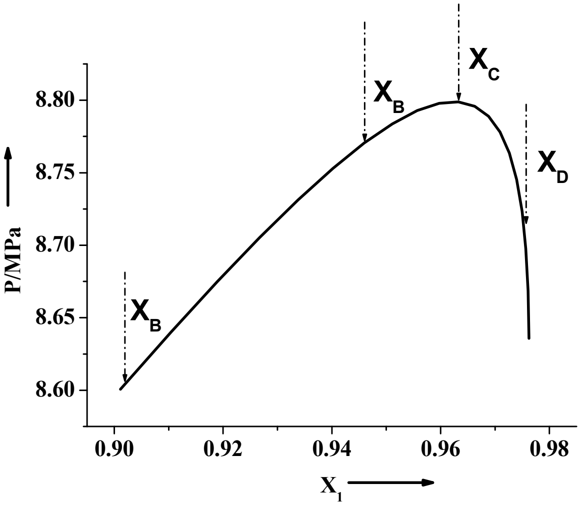


Figure 6. Phase diagram of $CO_2(1)$ + ethanol(2) system at 318.15 K.

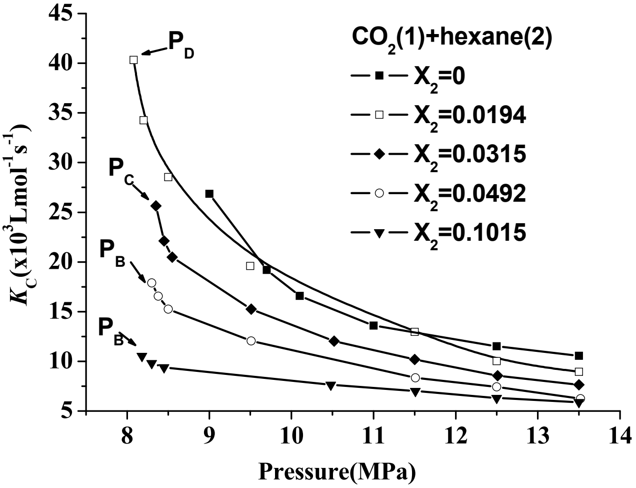


Figure 7. Dependence of the rate constant (k_c) on pressure for the Diels-Alder reaction in $CO_2(1)$ + hexane(2) mixture at 318.15 K. P_D, P_C and P_B denote the dew point, critical point, and bubble point, respectively.

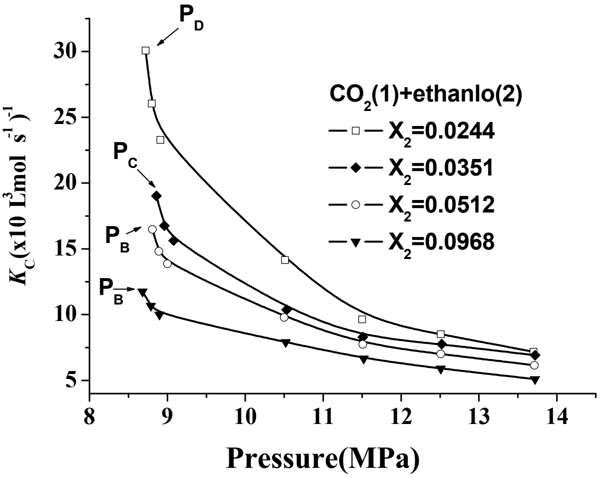


Figure 8. Dependence of the rate constant (k_c) on pressure for the Diels-Alder reaction in $CO_2(1)$ + ethanol(2) mixture at 318.15 K. P_D, P_C and P_B denote the dew point, critical point, and bubble point, respectively.

The dependence of reaction rate constant k_c in CO_2 + hexane and CO_2 + ethanol on pressure is illustrated in Figure 7 and Figure 8, respectively. It is interesting that the k_c is very sensitive to pressure in the critical region of the mixed solvents, and the k_c increases sharply as pressure approaches the dew point, critical point, and bubble point, which is shown by the arrows in the Figures. At suitable solvent compositions the k_c near the phase separation point can be several times larger than that at higher pressure. This indicates that the kinetic properties can be tuned effectively by pressure in the critical region of the mixed solvents. Comparing data of this work and those reported in the literature, the data of k_c in pure CO_2 determined by the two laboratories agree reasonably.[27]

Figures 7 and 8 show that k_c is not sensitive to pressure as the pressure is much higher than the phase separation points of the mixed solvents. The figures also demonstrated that as the composition of the mixed solvents is far from the critical composition, the effect of pressure on the k_c is very limited in entire pressure range. It can be concluded that, to control k_c effectively by pressure, both pressure and composition should be close to the critical point of the mixed solvents at this temperature. The main reason is that the effect of pressure on the density of the mixed solvents is not considerable outside the critical region of the solvents.

2.4. THERMAL DECOMPOSITION OF 2, 2-AZOBIS (ISOBUTYRONITRILE) IN CO_2 + ETHANOL MIXED SOLVENT [28]

The effect of pressure and composition on the kinetics of the decomposition of 2, 2-azobis (isobutyronitrile) (AIBN) in CO_2+ethanol were studied at 333.15 K near the critical region of the mixed solvent.

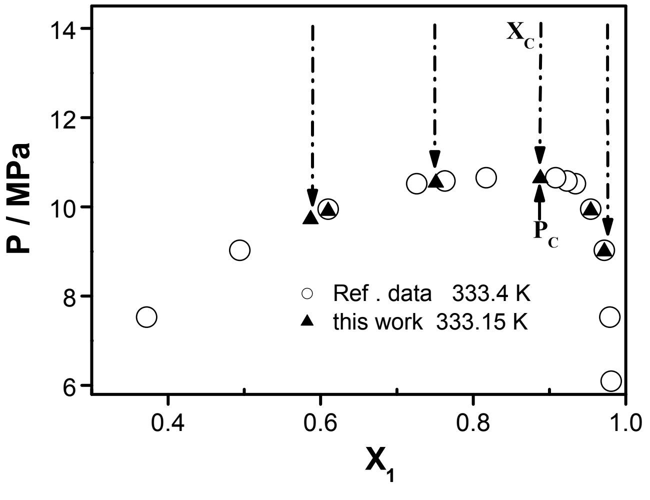


Figure 9. Phase diagram of the CO_2(1) + ethanol(2) system at 333.15 K. X_1 : mole fraction of CO_2.

At the critical point the mole fraction of CO_2 X_1 is 0.888 (Figure 9). In Figure 9 the part of the curve with $X_1 < 0.888$ is the bubble point curve, and a homogenous mixture above the bubble point can be regarded as a subcritical fluid. The part of the curve with $X_1 > 0.888$ is the dew point curve, and a homogeneous mixture above the dew point is a vapor or a supercritical mixture. The mixed solvent near critical region at fixed temperature is defined as the solvent of which the composition and pressure are close to the critical composition and critical pressure of the mixture.

The dependence of k_d on pressure in the solvents of different compositions is illustrated in Figure 10. It is obvious that the k_d is very sensitive to pressure near the critical point of the mixed solvent, and the k_d increases sharply as pressure approaches the critical point and the bubble point of the mixed solvent. This indicates that the kinetic properties can be tuned by pressure in the critical region of the mixed solvent. At $X_2 = 0.112$ and 0.249, the k_d can be increased by about 70% by a small pressure change in the critical region of the mixed solvent, as can be seen from Figure 10. This change is significant considering the fact that the reaction is not very sensitive to solvent.

Figure 10 also shows that k_d is not sensitive to pressure at higher pressures for all the mixed solvents, indicating that k_d cannot be adjusted effecttively by pressure when the solvent is not in the critical region. The main reason is that the isothermal compressibility of the solvent outside

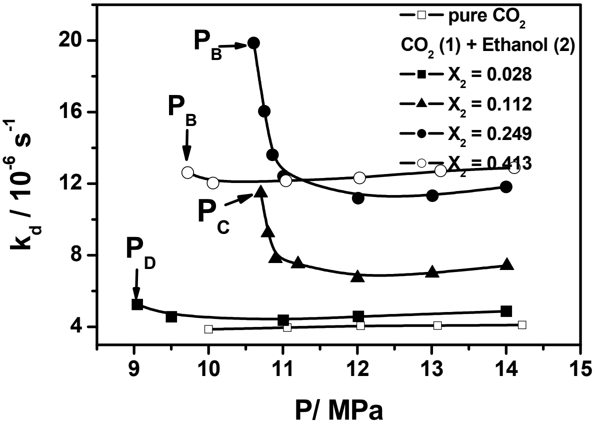


Figure 10. Dependence of the rate constant (k_d) on pressure for the decomposition of AIBN in pure CO_2 and $CO_2(1)$ + ethanol(2) mixture at 333.15 K. P_D, P_C, and P_B denote the dew point, critical point, and bubble point, respectively.

the critical region is small. Thus the properties are not greatly affected by pressure. It can be concluded that, to control k_d effectively by pressure, both pressure and composition should be close to the critical point of the mixed solvent at this temperature. Increasing the concentration of ethanol in the solvent results in an increase in k_d at the higher pressures far from the critical point. This is easy to understand because the k_d increases with the increase in the polarity or dielectric constant of the solvent.[29] This hints that mixed solvents outside the critical region are similar to liquid solvents, and the polarity increases as the concentration of the polar component is increased. The k_d in pure CO_2 could not be studied at pressure below 10 MPa due the limitation of the solubility of AIBN. This suggests that more reactions can be carried out in mixed solvents in critical region, and properties of the reactions may be tuned significantly by pressure.

2.5. ENHANCING THE CONVERSION BY CONTROLLING THE PHASE BEHAVIOR-SYNTHESIS OF DIMETHYL CARBONATE[30]

Development of environmentally benign industrial processes utilizing CO_2, which is a cheap and safe C_1 resource as well as a nontoxic reaction medium, has received much interest. One of the attractive reactions is the synthesis of dimethyl carbonate (DMC) from CO_2 and methanol. The reaction is reversible and can be expressed by eqn. (3):

$$2CH_3OH + CO_2 \Leftrightarrow DMC + H_2O \tag{3}$$

The critical parameters and phase behavior of the multi-component system CO_2-CH_3OH-CH_3I-H_2O-DMC were determined. Based on the determined critical parameters and phase behavior, DMC synthesis using CO_2 and methanol was run at various pressures that corresponded to conditions in the two phase region, the critical region as well as the single phase supercritical region. Figures 11 and 12 indicated that the phase behavior affects the equilibrium conversion of methanol significantly and the conversion reaches a maximum in the critical regions of the reaction system. At 353.2 K, the equilibrium conversion in the critical region is about 7%, and can be about three times as large as those in other phase regions. At 393.15 K, the equilibrium conversion in the critical region is also much higher and can be twice as large as those in other phase regions.

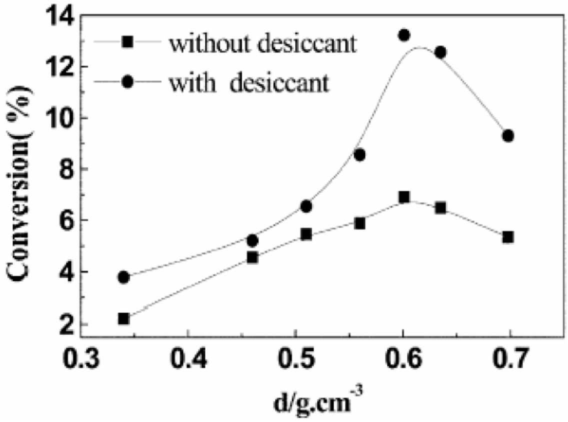


Figure 11. Effect of apparent density (*d*) on equilibrium conversion of methanol at 353.2 K, and the initial ratio CO_2:CH_3OH is 8:2.

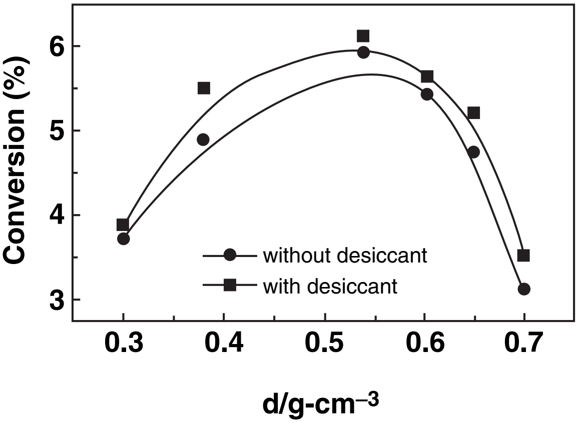


Figure 12. Effect of apparent density (*d*) on equilibrium conversion of methanol at 393.2 K, and initial ratio CO_2:CH_3OH is 7:3.

3. Chemical Reactions In SC CO_2/Il Biphasic Systems

The poor miscibility of SC CO_2 and ILs leads to CO_2/IL biphasic systems that have potential application in chemical reactions. Both batch and continuous-flow processes were developed in which reactants were introduced into the IL directly or with a flow of CO_2 and products were recovered from the compressed or SC CO_2.[CO2/IL]

3.1. TRANSESTERIFICATION IN SC CO_2/IL[31]

Study on the equilibrium conversion of reversible reactions in CO_2/IL mixed solvents is a new and interesting topic. The conversion of some reactions may be tuned effectively by changing operation conditions. The transesterification between isoamyl acetate and ethanol in supercritical SC CO_2, 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), and in CO_2/[bmim]PF_6 mixed solvent was studied at 65.0°C and different pressures.

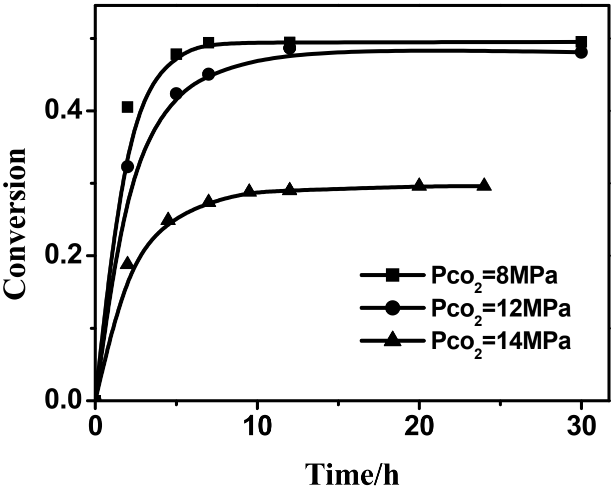


Figure 13. Conversion of the transesterification between isoamyl acetate and ethanol in SC CO_2 at 65.0°C and different pressures.

In the absence of the IL, the reaction system at 65.0°C can be one phase or more than one phase, which depends on the pressure. The phase behavior measurements showed that the reaction system was homogenous at pressures higher than 12.50 MPa, and separated into two phases (vapor and liquid phases) at the lower pressures. Figure 13 is the reaction results at different pressures. At all the pressures the conversion becomes independent of the reaction time after 12 h. The equilibrium conversion varies significantly as reaction system changes from single phase region to two phase region by tuning pressure. Therefore, the equilibrium conversion of the reaction in compressed CO_2 can be tuned to a certain degree by controlling the phase behavior or pressure.

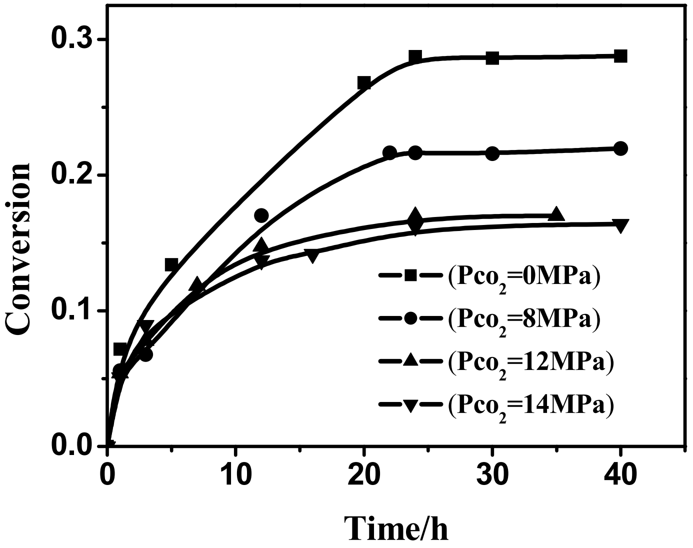


Figure 14. Conversion of the transesterification between isoamyl acetate and ethanol in SC CO_2/IL mixed solvent at 65.0°C and different pressures.

In the presence of the IL, there were three phases in the reaction systems as the pressure was lower than 11.90 MPa, IL-rich phase, CO_2-rich phase, and the liquid chemical (reactants and products)-rich phase. As pressure was higher than 11.90 MPa, the system consisted of two phases, the IL-rich phase and CO_2-rich phase. The experiments also indicated that the phase separation pressure did not change noticeably with the reaction time. Figure 14 shows the conversion as a function of reaction time at 0 (without CO_2), 8.00, 12.00, and 14.00 MPa. The conversion increases with reaction time initially, and equilibrium can be reached after 24 h. At 8.00 MPa, where three phases exist in the reaction system, the equilibrium conversion is higher than that at 12.00 and 14.00 MPa at which there are two phases in the reaction system. Obviously, the change in phase behavior also results in the variation in equilibrium conversion.

Figures 13 and 14 also show that the equilibrium conversion of the reaction in CO_2/IL is different from that in CO_2 or in IL. The reason is that the solvent powers of the two solvents are different. It can also be known from Figures 13 and 14 that the equilibrium conversion in CO_2/IL is lower than that in compressed CO_2 or in IL. This is not desired for this reaction. But it is expected that for some reactions the equilibrium conversion can be enhanced by using this principle.

3.2. OXIDATION OF BENZYL ALCOHOL IN SC CO_2/IL BIPHASIC SYSTEM[32]

Combination of SC CO_2 and IL has also been accomplished in the field of electro-organic synthesis, and electro-oxidation of benzyl alcohol to benzaldehyde was conducted in the CO_2/IL system.

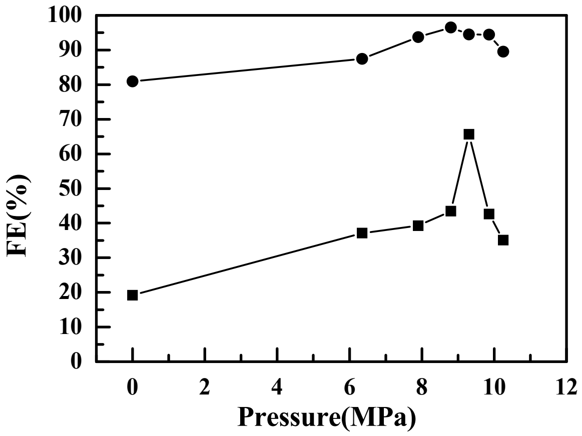


Figure 15. The effect of pressure of CO_2 on the selectivity of the products at 318.2 K ■ FE of benzaldehyde; ● Selectivity for benzaldehyde

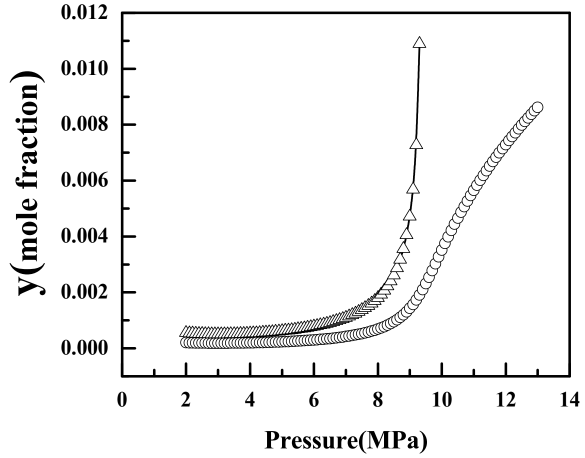


Figure 16. The solubility of benzaldehyde and benzyl alcohol in CO2 at 318.2 K and different pressures calculated from PR equation of state; □ Benzaldehyde, ○ Benzyl alcohol.

The effect of pressure on the selectivity and Faradic efficiency (FE) of the products at 318.2 K are shown in Figure 15. The FE of benzaldehyde increased with pressure at first, and then decreased, and the maximum occurred at about 9.3 MPa.

This phenomenon can be explained from two aspects: one from the actual course and specialty of a heterogeneous electro-organic reaction, and the other from special physico-chemical properties of SCFs. The effect of pressure on the solubility of benzaldehyde and benzyl alcohol in SC CO_2 is shown Figure 16. The significant effect of pressure on the solubility is one of the reasons for the variation of FE and selectivity of benzaldehyde. When the solubility of benzaldehyde in SC CO_2 increased dramatically, more benzaldehyde produced enters SC CO_2 phase, and thus the FE and selectivity of benzaldehyde were enhanced. When the pressure reached a certain value, the solubility of benzyl alcohol (the reactant) in SC CO_2 also increased considerably, which is not favorable to producing benzaldehyde. When the pressure is lower than 9.3 MPa, the first factor is dominant and thus the FE and selectivity of benzaldehyde increased with pressure. However, as pressure was larger than about 9.3 MPa, the second factor became dominant. Therefore a maximum value in FE or selectivity occurred.

There are some unique advantages for this process. For example, the selectivity of the products could be tuned by varying the CO_2 pressure; the amount of by-product benzoic acid in the product was negligible because of the high solubility of benzaldehyde in SC CO_2; the IL can be easily reused after in situ extraction of the product by using SC CO_2. The combination of nonvolatile ILs, non-hazardous SC CO_2 and clean electrochemical technology may be used to produce some other valuable chemicals.

3.3. PHASE SEPARATION OF REACTION SYSTEM AND CONVERSION ENHANCEMENT INDUCED BY CO_2[33]

The effect of compressed CO_2 on the esterification of acetic acid and ethanol in [bmim][HSO_4]) at 60.0°C up to 15 MPa were studied (Figure 17). There was only one phase in the reaction system without CO_2. However, CO_2 can induce phase separation of the reaction system. As the pressure is less than 3.5 MPa, there are two phases in the system and increase in pressure can enhance the equilibrium conversion. In the pressure range of 3.5–9.5 MPa, there are three phases in the system and the equilibrium conversion increases rapidly with increasing pressure. The third phase disappears as the pressure is larger than 9.5 MPa, where the equilibrium conversion remains at high values and is not sensitive to pressure.

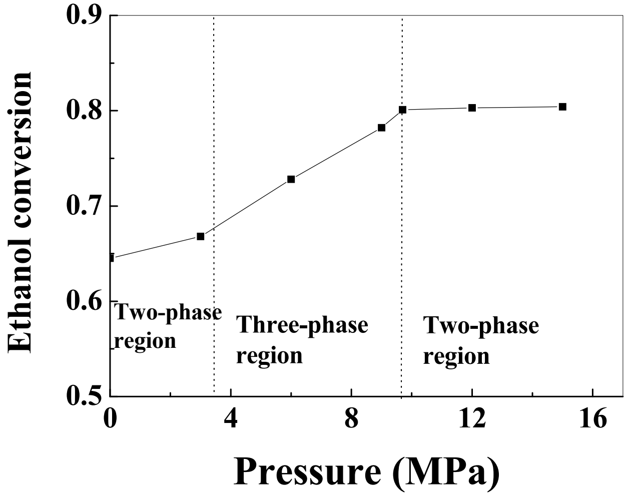


Figure 17. Effect of pressure on ethanol conversion in $[bmim][HSO_4]/CO_2$ system at 60°C.

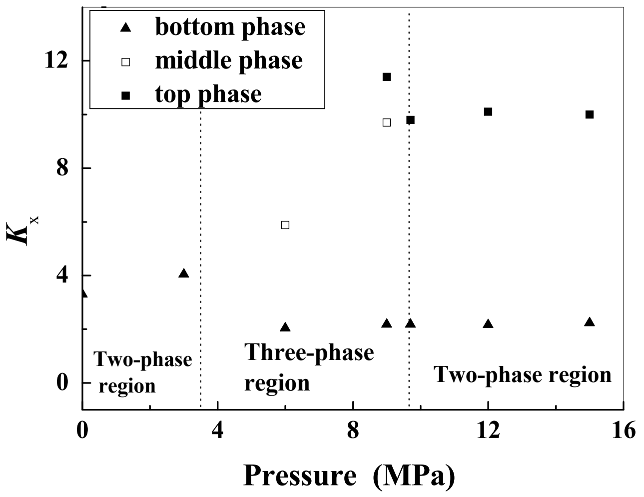


Figure 18. K in different phases at 60 C and different pressures.

Study on the K_x in different phases (Figure 18) indicates that the K_x in the middle phase or top phase is much greater than that in the bottom phase. In the presence of CO_2 the total equilibrium conversion can be considerably larger than that in the absence of CO_2. For example, equilibrium conversion is 64% without CO_2, and can reaches 80% as pressure is higher than 9.0 MPa. The idea to induce phase separation and enhance the reaction efficiency for the reactions in ILs may be applied to some other reactions.

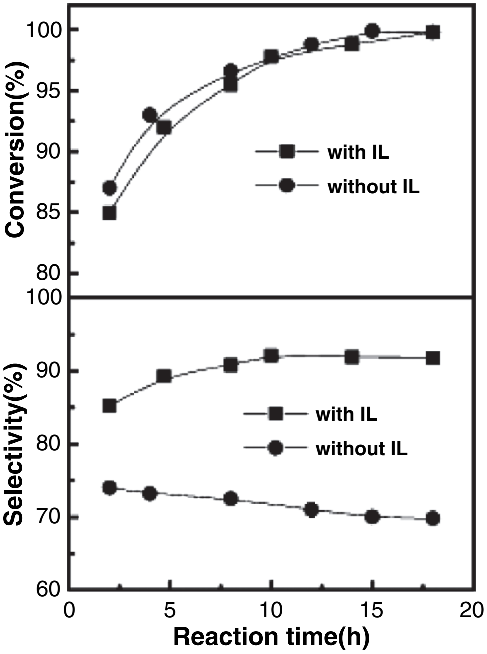


Figure 19. The dependence of conversion and selectivity on reaction time at 333.2 K and 125 bar; IL: ionic liquid $[bmim]PF_6$.

3.4. WACKER OXIDATION OF 1-HEXENE IN SC $CO_2/[BMIM]PF_6$ MIXED SOLVENT[34]

Oxidation of 1-hexene by molecular oxygen has been conducted in 1-n-butyl-3- methylimidazolium hexafluorophosphate $[bmim]PF_6$, SC CO_2, SC $CO_2/[bmim]PF_6$ mixed solvent, and in the absence of solvent. The selectivity to the desired product 2-hexanone is much higher when the reaction is carried out in the mixed solvent, and the catalysts is more stable in SC $CO_2/[bmim]PF_6$ mixed solvent than in SC CO_2.

Figure 19 illustrates that the difference in conversion at various reaction times in SC CO_2 and in the CO_2/IL mixture is not considerable. One of the main reasons may be that the catalysts are well dispersed in the IL-rich phase in the presence of the IL, which favors enhancement of the reaction rate in the CO_2/IL system. On the other hand, the liquid/vapor interface exists in the CO_2/IL system, which does not favor the increase of the reaction rate due to the interface mass transfer. The two opposite factors compensate each other, and thus the conversion is similar. The effect of reaction time on the selectivity in the two solvents is not significant, as can be seen from the figure. However, in the CO_2/IL mixed solvent the selectivity to the desired product is much higher than that in SC CO_2. Moreover, the selectivity in the mixed solvent increases slightly with reaction time, while the selectivity decreases slowly with reaction time in SC CO_2.

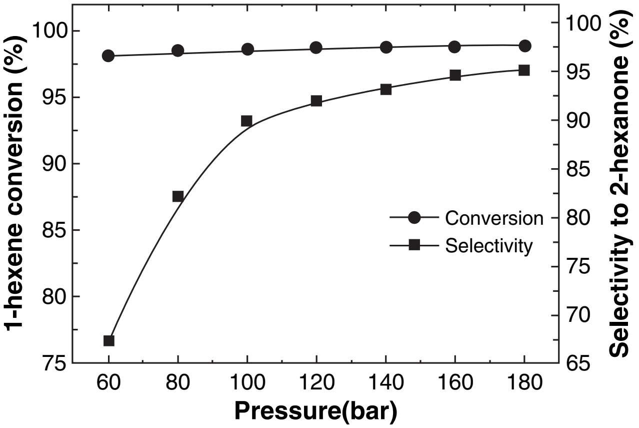


Figure 20. The dependence of conversion and selectivity on pressure in SC CO_2/IL mixed solvent at 333.2 K with a reaction time of 17 h.

It is known that the properties of SCFs are sensitive to pressure, and thus pressure may influence the conversion and selectivity of the reaction. The effect of pressure on the conversion and the selectivity of the reaction in CO_2/IL mixed solvent are shown in Figure 20. In the pressure range studied, the conversion is very high and is nearly independent of pressure. However, the selectivity increases with pressure significantly, especially in the low pressure range. A very rough explanation is that the solvent power of CO_2 increases with increasing pressure. Therefore, less reactant exists in the IL-rich phase at higher pressure, which favors reduction of the isomerization of the reactant. Meanwhile, the solubility of CO_2 in the IL increases with pressure, and so the diffusivity of the solvent is improved more significantly at the higher pressures, which may also enhance the selectivity. This explanation is consistent with the discussion above.

4. Conclusions and Outlook

Study of chemical reactions in SC CO_2 and SC CO_2/IL is a promising area. The phase behavior of the reaction systems can have significant effect on the properties of chemical reactions. Study of chemical reactions should be combined with the phase behavior of the reaction systems, which is interesting and challenging. Many new concepts and new experimental findings need to be investigated in this area. With the accumulation of knowledge on this, significant progress will be achieved on applications of SC CO_2 and SC CO_2/IL in chemical reactions.

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WATER-BASED METAL REMEDIATION PROCESSES: BASICS AND NOVEL DEVELOPMENTS

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Abstract: The fundamentals and novel developments of water-based remediation processes for metals are investigated and assessed. Recent developments in the area of metal remediation in connection with ultrafiltration are the main focus. In addition, the LPR method is explained and highlighted in view of the application in different areas.

Keywords: environment, LPR, metal, polymer, process, remediation, ultrafiltration, water

1. Introduction

Green chemistry has gained considerable attention and importance during the last decades. According to the US Environmental Protection Agency "green chemistry" is defined as follows: "To promote innovative chemical technologies to reduce or eliminate the use or generation of hazardous substances in the design, manufacture and use of chemical product".

Many developments have been made in this area and particularly processes involving water as the solvent have been found advantageous in this context. Among them, water-based metal remediation plays an outstanding role due to the many problems associated with the pollution of the environment with metals.

P. Tundo and V. Esposito (eds.), *Green Chemical Reactions.*

2. Fundamentals

2.1. SOLVENTS

Solvents are widely used throughout the chemical industry and in many research laboratories.[1]

Some typical application areas in chemistry are the following:

- Synthetic chemistry
    - Reaction medium in the laboratory and industry
    - For reaction work-up and purification
- Analytical chemistry
    - Sample extraction and preparation (spectroscopy)
    - Chromatography mobile phase (HPLC, TLC, etc.)
- Crystallography
    - Recrystallization to purify compounds and prepare crystals suitable for analysis

Solvents are not only used in synthetic chemistry, but also in other application areas such as coatings, paints, and adhesives. They are usually removed by evaporation after their application. Nevertheless, they represent a critical source of pollution. For example, the use of perchloroethylene, known as a suspected cancerogenic agent and also a contaminant of groundwater, for dry cleaning, and the extraction of coffee during the decaffeination process with organic solvents (benzene, dichloromethane) raise great concern in both environmental and health respect.

2.2. APPROACHES TO SOLVENT REPLACEMENT

The idea to simply replace one solvent with another is often not possible to realize, especially when considering the solvents used for work-up and purification, and not only as reaction media. In this context, many aspects have to be considered and assessed. One important aspect is the source of the solvent. Other points include the question: is the process for the preparation of the solvent green or sustainable?

Several issues should be here addressed:

- Energy used during the process
- Hazardous processes involved
- Environmental compatibility of the raw material
- By-products formed and their hazard.

2.3. WATER AS A GREEN SOLVENT

Water is an excellent and green solvent for many solutes. It plays an outstanding role for many processes in life and nature. Some of the important and salient features of water as a solvent are listed here:

- The only solvent in nature
- Outstanding solubilizing power for polar compounds (hydration)
- Unique biological solvent (body 70%; cells 80% of weight)
- It is cohesive and adhesive
- No environmental pollution
- Low cost
- Safe
- Accelerating effect: many synthetic organic reactions are accelerated in water.

A molecular model of the water molecule is depicted in Figure 1. The essential effect of hydrogen bonding, responsible for many special and particular properties of water, can be explained by the interaction of the partially negatively charged oxygen with the partially positively charged hydrogen atoms.

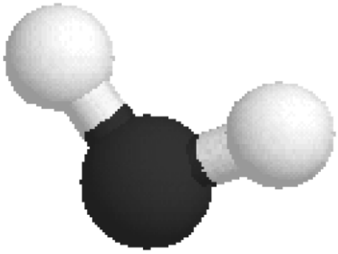


Figure 1. Molecular model of the water molecule.

2.4. SURFACTANTS

2.4.1. *Micelles*

There are several types of surfactants, which are schematically depicted in Figure 2. The power of surfactants in connection with water as the solvent is based on their ability to form micelles.

A simplified micelle structure in an aqueous solution is shown in Figure 3.

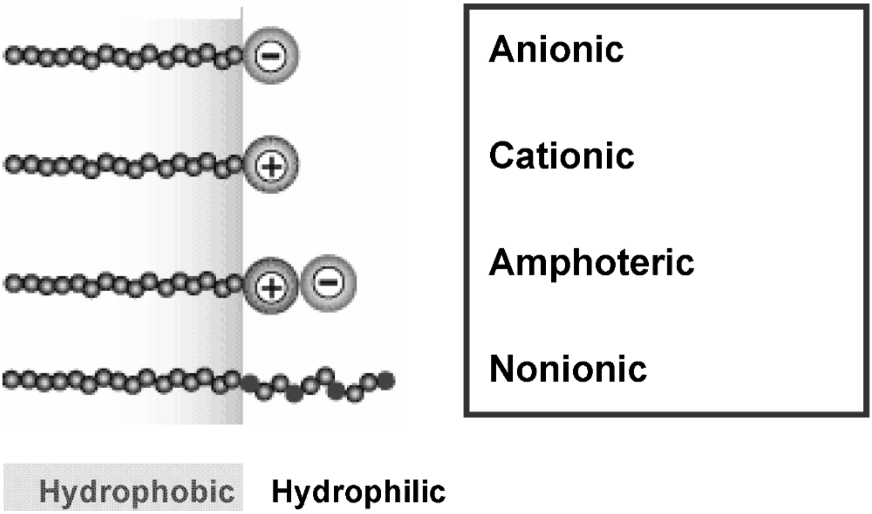


Figure 2. Major classes of surfactants.

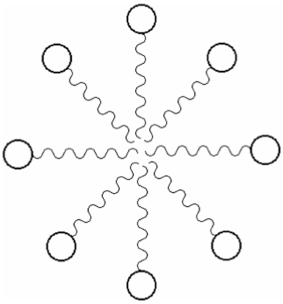


Figure 3. Schematic of a micelle structure in an aqueous solution.

2.4.2. *Surfactants and Metal Nanoparticles*

Surfactants are an important compound class and play a significant role in many areas. Recently, they have been found also very useful for the preparation of metal nanoparticles[2,3] One example is given here, where nonionic surfactants favor the formation and subsequently the stabilization of gold nanoparticles (Figure 4).

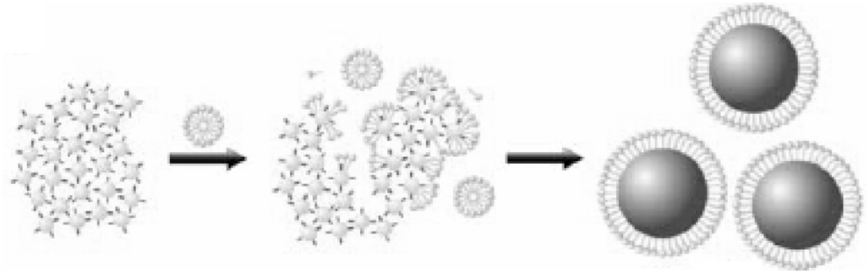


Figure 4. Schematic of the formation of gold nanoparticles from a gold salt in the presence of a surfactant leading to the production of surfactant-wrapped gold nanoparticles.

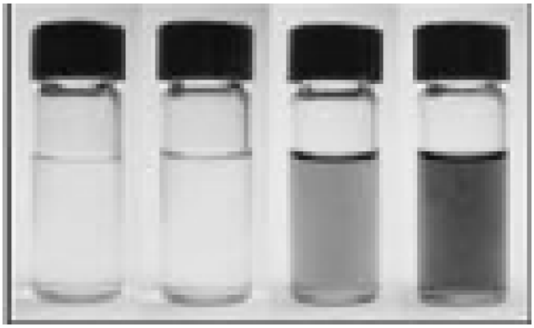
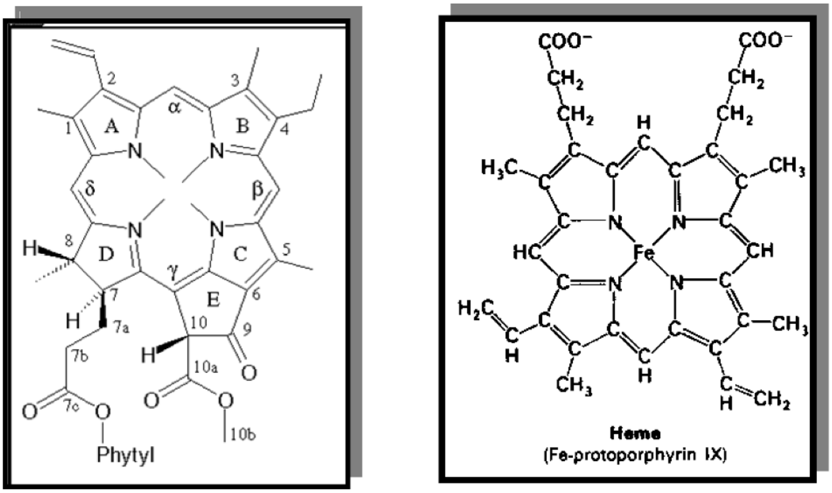


Figure 5. Color changes of the solutions of the gold nanoparticles during the formation process.

The visual appearance of the solutions of the gold nanoparticles during the preparation is shown in Figure 5.

2.5. POLYMER-METAL SYSTEMS IN NATURE

Many important natural substances are metal complexes.[4] Examples of this important class of natural materials include the chlorophyll, which is the base of photosynthesis, and hemoglobin, which is the prerequisite for respiration and the medium for the oxygen transport in the blood (Figure 6).



Photosynthesis (chlorophyll):

$6\ CO_2 + 6\ H_2O \rightarrow C_6H_{12}O_6 + 6\ O_2$

Catalysis of electron transfer

Oxygen transport (blood)

$Hb + O_2 \rightarrow HbO_2$ (Oxyhemoglobin)

Each heme binds one O_2 molecule

Figure 6. Chlorophyll and hemoglobin as examples of naturally occuring polymer-metal complexes.

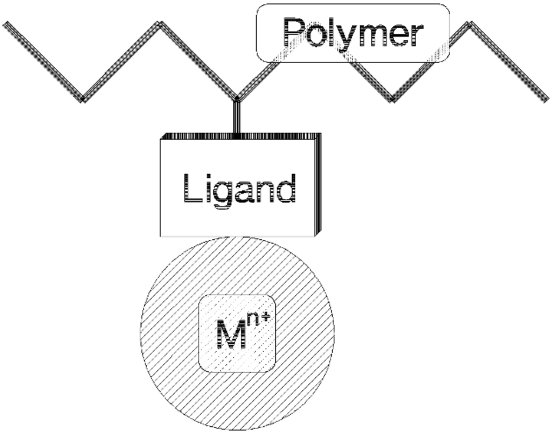


Figure 7. Schematic of the components of a synthetic metal complex. M^{n+}, metal ion.

2.6. SYNTHETIC POLYMER-METAL COMPLEXES

Based on the models of natural metal complexes synthetic metal complexes have been developed for different purposes. They consist of a synthetic polymer, which is the replacement of the biopolymer protein in the natural metal complexes, and a specific synthetic ligand that is able to bind the metal ions. The basic model of synthetic metal complexes is shown in Figure 7.

2.7. ENVIRONMENTAL IMPORTANCE OF METALS AND REMEDIATION

The term remediation refers to the removal of pollution or contaminants from environmental media such as soil, water, or sediment for the general protection of human health and the environment.

The problem of metal contamination is very serious and a few figures can illustrate this:

- 2.4 million tons of metal waste per year from industrial sources.
- 2 million tons per year from agriculture and domestic waste.

The metals Pb(II), Hg(II), and Cd(II) are ranked 2nd, 3rd, and 7th, respectively, on the priority list of the EPA. Due to the importance of metal pollution many processes have been developed to solve or mitigate these environmental problems. The major processes are described shortly in the next section.

2.8. CONVENTIONAL PROCESSES

Many techniques can be used for the treatment of metal-containing solutions, depending on the quality of the water, the cost of the treatment process, and the quality standards targeted.[5] Two main types can be discerned:

- Pyrometallurgy, where the ore is crushed and concentrated by flotation, then roasted and reduced with a chemical reducing agent. Finally, the ore is refined by electrolysis.
- Hydrometallurgy, where the ore is crushed and concentrated by flotation, then roasted and leached with acid. Finally, selectively precipitation is followed and then refining by electrolysis.

2.8.1. *Ion Exchange*

Ion exchange involves the use of polymeric matrices such as polystyrene or acrylic resins, which contain moieties suitable for electrostatical interaction with counter ions. During this process the acid leach is passed through a column containing the resin with the selective ligand, then the metal is stripped from the column with acid, and finally recovered by electrolysis. The advantages of the ion exchange include:

- No use of organic solvents
- Effectiveness at low concentrations
- No shrinking and swelling.

2.8.2. *Solvent Extraction*

The solvent extraction process is based on the treatment of the acid leach with an extractant in an organic solvent. The desired metal is then released back into an aqueous phase with strong acid and the final recovery conducted by electrolysis.

The advantages and disadvantages of solvent extraction are the following:

- High selectivity
- Cost effectiveness for many metals
- Low efficiency at low metal ion concentrations
- Use of toxic and flammable solvents
- Loss of selective ligands.

3. Metal Ion Interaction and Separation

Functional polymers with complex-forming groups (ligands) that are able to interact with the metal ions in a certain manner can be used for metal ion interaction-based separation processes. The principle is shown in Figure 8.

3.1. COMPLEX-FORMING POLYMERS

Many complexing polymers have been shown to be very promising for commercial metal enrichment and separation. Among those, amine polymers such as poly(allylamine) (PAL) and poly(ethylenimine) (PEI) have been found suitable for metal extraction. The main types of the different interaction products of metal ions with functional polymers are shown in Figure 9.

The major types of ligands for the complex formation with metal ions are compiled in Figure 10.

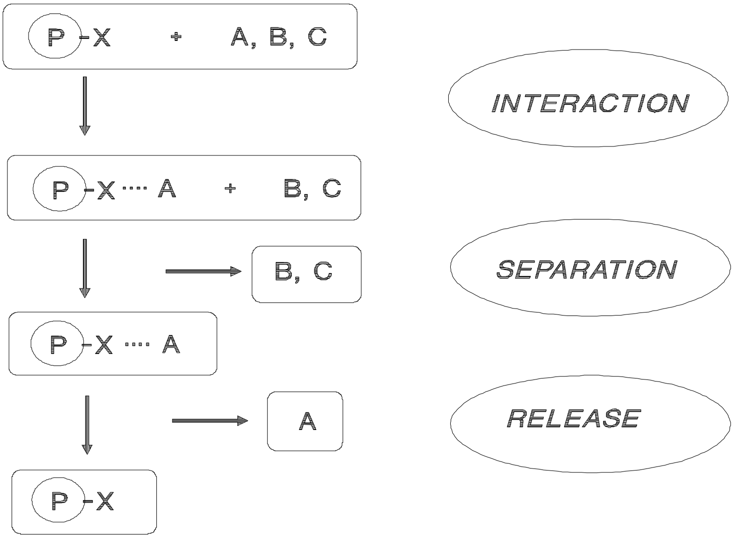


Figure 8. Schematic for the interaction, separation, and release of metal ions with polymeric ligands (functional polymers) in the homogenous phase. P-X, functional polymer; A, B, C, metal ions; A, target metal ion.

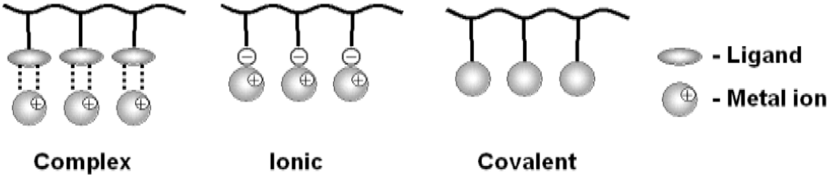


Figure 9. Types of the interaction products between metal ions and the ligands of a polymer.

3.2. POLYAMINES AS LIGANDS

As can be seen from the data given above, polyamines such as poly (allylamine) (PAL) and poly(ethylenimine) (PEI) (Figure 11) show very interesting complexing properties due to the following features:

- High density of amino groups
- Polycationic polyelectrolytes
- Complex strongly with metal ions and anionic polyelectrolytes
- Offer reactive sites for facile addition of ligand molecules.

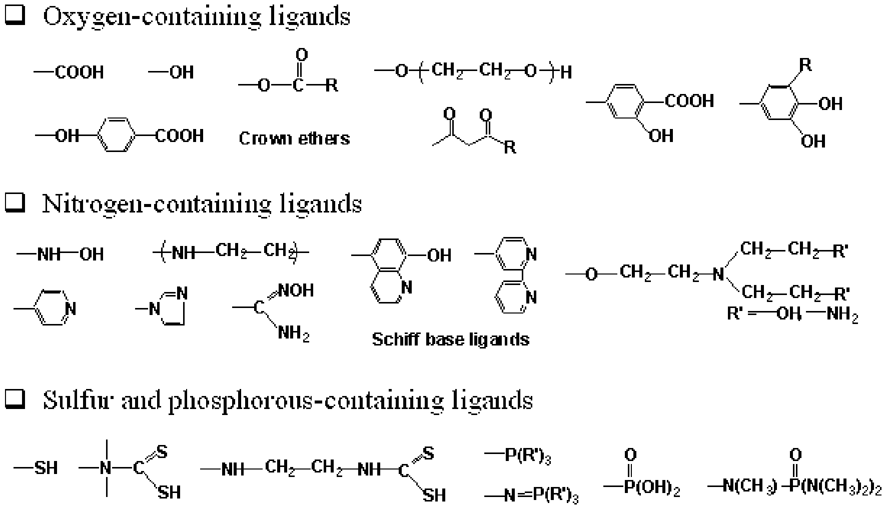


Figure 10. Different ligand types for the complex formation with metal ions.

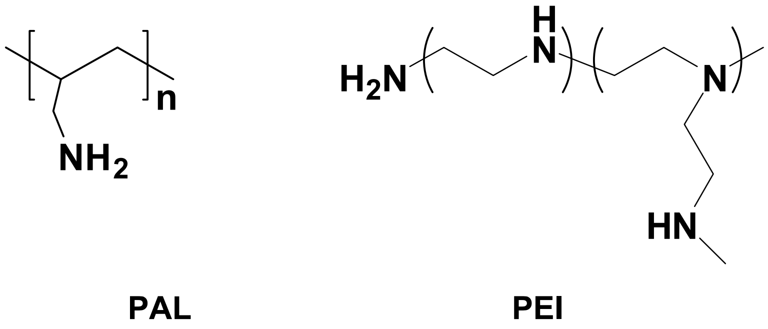


Figure 11. Structural formulae of poly(allylamine) (PAL) and poly(ethylenimine) (PEI).

The polyamines and a series of other polymers can serve as basis polymers and easily derivatized with different ligands. Some examples are given in Table 1.

The polyamines have found many applications such as:

- Chelating agents
- Transparent gels and membranes
- Electrolytes
- Electrolyte complexes.

TABLE 1. Different examples of basis polymers with ligands derived from polyamines.

No.	Basis polymer	Functional Group
1	Poly(acrylic acid)	$-COOH$
2	Poly(ethylenimine)	$-(CH_2)_2-N(CH_2COO$
3	Poly(vinylamine)	$-(CH_2)_2-N(CH_2COO$
4	Poly(vinylpyrrolidone)	$-NH-(CH_2)_3-COOH$
5	Poly(vinylalcohol)	$-PO(OH)_2$
6	Poly(vinylsulfonic acid)	$-SO_3H$
7	Poly(vinylamine)	$-NH_2$
8	Poly(ethylenimine)	$-N^+(CH_3)_3$

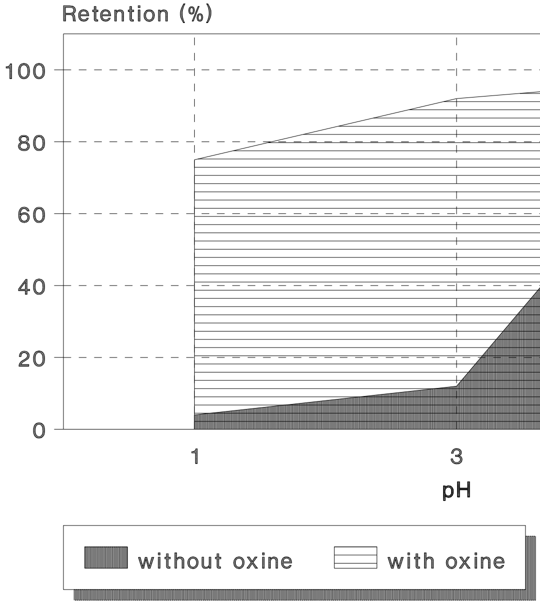


Figure 12. Comparison of the complexation of poly(ethylenimin) and poly(ethylenimin)-oxine with Fe(III) ions as a function of pH.

3.3. OXINE AS A LIGAND

In addition to the usual ligands described above, selective ligands for a series of metal ions can be introduced. An example is the ligand 8-hydroxyquinolin (oxine). Figure 12 shows the retention profiles of the complexation of poly(ethylenimin)-oxine with Fe(III) ions at different pH, when compared to the properties of the precursor poly(ethylenimin).

3.4. SELECTIVITY FOR METAL IONS

Depending on the specific ligand, the metal ions are bound to a different extent to the ligand moieties on the polymer chain. Accordingly, so-called selectivity series can be established for the different polymer ligands. Some examples are given in Table 2.

TABLE 2. Metal selectivity series for some basis polymers. PEI, poly(ethylenimine) (PEI); PTU, thiourea derivative of PEI; PDA, diamino acetic acid derivative of PEI; POX, oxine derivative of PEI.

Polymer	**Selectivity based on complex stability**
PEI	$Au^{3+} > UO_2^{2+} \sim Cu^{2+} > Pt^{4+} > Ni^{2+} \sim Co^{2+}$
PTU	$Au^{3+} \sim Pt^{4+} \sim Cu^{2+} > Ni^{2+} \sim Co^{2+}$
PDA	$UO_2^{2+} > Pt^{4+} > Cu^{2+} > Au^{3+} \sim Ni^{2+} > Co^{2+}$
POX	$UO_2^{2+} > Cu^{2+} \sim Pt^{4+} > Ni^{2+} \sim Co^{2+} > Au^{3+}$

4. Membrane-Based Separation Processes

4.1. MEMBRANES

A membrane is defined as a structured material having lateral dimensions much greater than its thickness (high aspect ratio), through which a mass transfer may occur by different driving forces.[6,8]

The membranes used for ultrafiltration are typically polymer or ceramic membranes with a stability depending on the base material. Depending on the polymer used they are stable over a wide range of pH and resistant to a large number of organic sovlents.[1,8] The permeation of molecules in the solution can be increased by different factors such as linear versus globular molecules, pH and ionic conditions that alter the molecule, e.g., by conformational changes or aggregation. A decrease of molecule permeation can be induced by buffer conditions, which allow an aggregation of the molecules, and the adsorption onto the membrane or walls of the device.

Frequently used polymer materials for the preparation of membranes include the following polymers:

- Polysulfone
- Poly(ethersulfone)
- Regenerated cellulose
- Acetyl cellulose

- Polycarbonate
- Teflon.

4.2. PROCESSES

4.2.1. *Reverse Osmosis*

Reverse osmosis is a process for the removal of particles or ions from a solution for the purification of water and/or removal of salts and other impurities. The solution is allowed to pass through a semipermeable membrane, while the contaminants are rejected. The typical molar mass cut-off (MMCO) is in the range of 150–250 g/mol.

The separation of ions by reverse osmosis is aided by charged particles. Thus, dissolved ions with a charge such as salts are more likely to be rejected by the membrane than non-charged species, e.g., organic molecules. The larger the charge and the larger the particle, the more likely it will be rejected. Membrane fouling is an important issue and a general problem for these processes.[7,8] Practical applications include the improvement of the color, taste, or the properties of the solution. For example, bacteria, salts, sugars, proteins, particles, dyes, and other constituents can be removed from aqueous solutions.

4.2.2. *Ultrafiltration*

Ultrafiltration is a membrane process, in which molecules are separated in solution on the basis of their size.[8] The membrane is a selective barrier that is able to retain species with larger molecular masses and to let permeate small molecules (microsolutes and solvent). A membrane that is partially permeable to perform the separation is used, however, the membrane pores are typically much larger than those used in reverse osmosis. Typically, the size of the molecules to be separated is in the range of ~1 to 500 kg/mol (molecular mass). A typical characteristic of a membrane is its so-called molecular mass cut-off (MMCO), which is the molar mass of the species retained by the membrane. Ultrafiltration does not require the same energy to perform the separation. Generally, it is most commonly used to separate a mixture of components. Thus, the smaller constituents in the solution are allowed to pass through the membrane, while the larger constituents are held back. Larger constituents encompass big molecules such as macrocylces, macromolecules, biopolymers, etc.

The advantages of ultrafiltration comprise the following features:

- For separation, fractionation, metal extraction, desalting, and concentration
- Mild conditions
- Maintenance of ionic and pH milieu
- Low temperature possible
- Relatively fast and inexpensive
- Wide range of applications on a commercial scale.

Typical applications of the ultrafiltration process in different areas are compiled here:.

- Medicine: hemodialysis, acute renal failure treatment and drug detoxification.
- Biotechnology: enzyme harvesting (for concentration and desalting).
- Paper industry: during paper manufacturing (removal of colors and non-biodegradable pollutants)
- Sugar industry: juice clarification and concentration (removal of impurities during the extraction phase)
- Dairy and juice industry: preconcentration of milk (cheese making) and fruit-juice (clarification)
- Textile industry: recovery of polymer agents (starch, carboxymethyl cellulose and poly(vinyl alcohol)).

When ultrafiltration as a separation method is combined with soluble polymers as reagents, the result is a technique that allows to separate solutes, which do bind or not to the polymer, in the homogenous phase. This process was termed “Liquid-phase Polymer-based Retention” (LPR).[10]

4.3. LIQUID-PHASE POLYMER-BASED RETENTION (LPR)

4.3.1. *Separation Principle of the LPR*

The LPR procedure is carried out in the homogenous aqueous phase by using different driving forces such as pressure, vacuum, or gravity.[9] The principle of this separation process is illustrated in Figure 13.

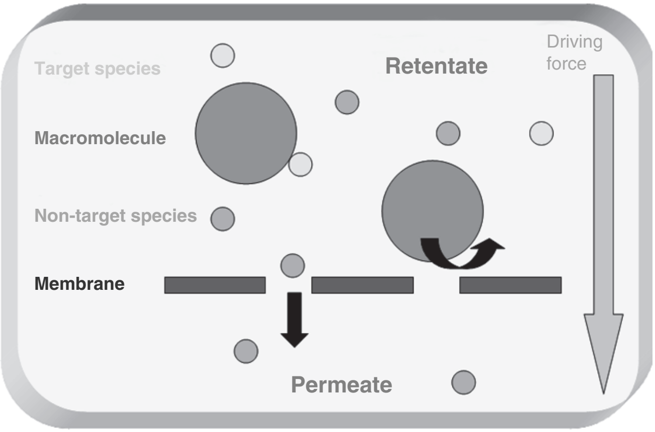


Figure 13. The concept of the Liquid-Phase Retention (LPR) separation.

4.3.2. *Development*

The historical advances of the liquid-phase separation in conjunction with ultrafiltration are compiled in Table 3.

TABLE 3. Historical development of the advances of ultrafiltration in conjunction with soluble polymer reagents.

Advancement	Year	Citation
Polypeptide synthesis	1972	Nature **237**, 512
Soluble polymer supports	1974	Liebigs Ann. Chem. 1671
Water-soluble polymer-metal complexes	1980	Pure Appl. Chem. **52**, 1883
Liquid-phase Polymer-based Retention (LPR)	1985	Nature **315**, 313
Anion exchange	1988	Naturwissenschaften **75**, 198
First review on LPR	1988	Sep. Purif. Methods **17**, 105
Selective polymer ligands	1990	Anal. Chim. Acta **230**, 171
System desing for analysis	1992	Internat. Lab. **17**, 47
Actinide separation	1993	Chem. Tech. **45**, 464
Approval of LPR for analysis by IUPAC	1994	Pure Appl. Chem. **66**, 631
Environmental applications	1996	Env. Sci. Technol. **30**, 725
Mathematical modeling	1996	Macromol. Theory Simul. **5**, 357
Interpolymer complexes	1998	Macromol. Chem. Phys. **199**, 1153
Environmentally degradable polymers	1999	Polym. Internat. **49**, 1519

4.3.3. *Procedure*

As described in Figure 14, the application of the ultrafiltration-assisted separation with soluble polymer reagents involves a series of steps for the separation of species:

- Functionalization by polyreaction or polymer-analogous functionalization
- Interaction with the target species in the homogenous phase (aqueous solution) based on intermolecular forces or bonds
- Formation of the interaction product with the target species
- Separation of the polymer-target product from non-bound species using membrane procedures
- Cleavage and removal of the target compound.

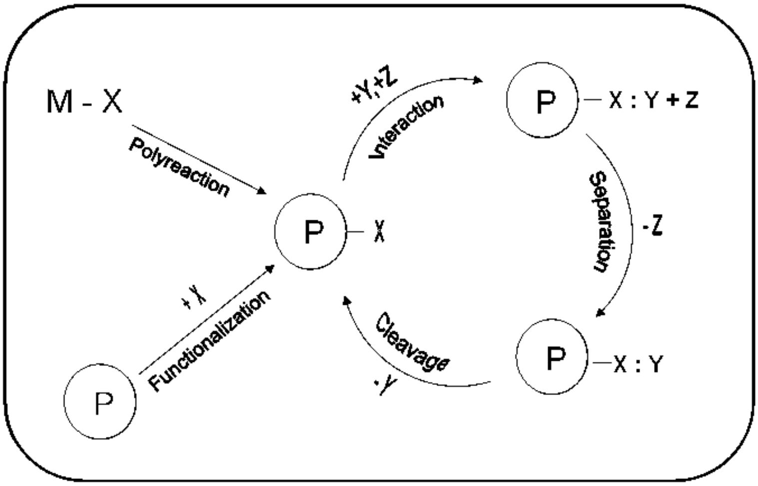


Figure 14. Application scheme of the ultrafiltration-assisted separation with soluble polymer reagents. M-X = Functional monomer, P = Polymer, X = Functional molecule or group, P-X = Functional polymer, Y = Target species, Z = Non-target species, P-X:Y = Polymer interaction product with Y.

4.3.4. *Polymer Reagents*

The polymer reagents for the remediation process in the aqueous phase are called polychelatogens.[10] They consist of water-soluble polymers and have been investigated and reviewed extensively.[11–18] By using different basis polymers and chelating moieties a great variety of polymer reagents with selectivities for many different metal ions can be provided.[19–23]

Recently, a novel class of environmentally degradable polyesters such as carboxy-functional polyesters based on poly(ethylene glycol) and oligo-functional carboxylic acids have been developed.[24] These polyesters are interesting and promising candidates in this class of biodegradable polycondensates. Similarly, a novel type of copolymers, e.g., the poly(ethylenediamine tetra-acetic acid-*co*-lactose), has been found useful for this process.[25] This is a chelate-forming polymer containing lactose in the main-chain that is able to bind many multivalent metals due to the incorporation of acetic acid moieties. These water-soluble carboxy-functional polymers based on poly(ethylene glycol) with an enlarged molar mass and good biodegradability are copolyreacted with EDTA or DPTA and thus incurporated into the polymer backbone.[26] An example of the interesting synthesis of this class of polymer materials through an one-step poly-reaction is described in Figure 15.

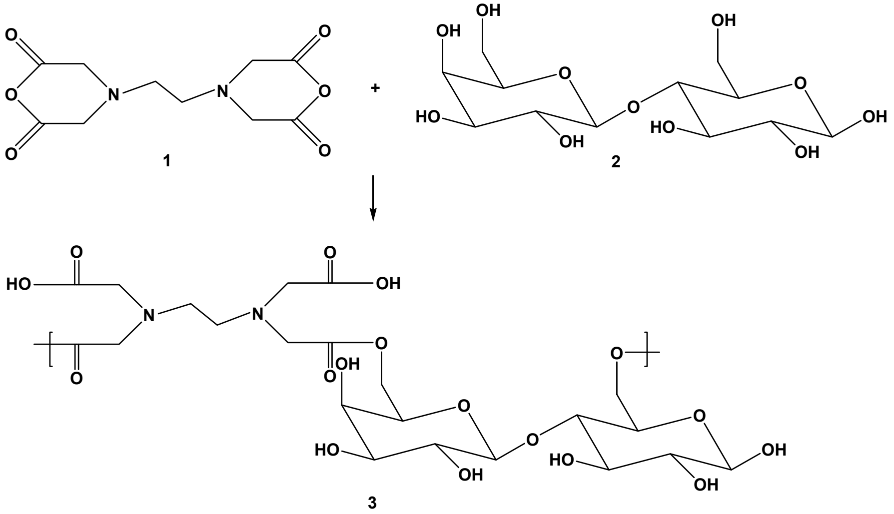


Figure 15. Polyreaction of ethylenediamine tetraacetic acid dianhydride (1) and D-lactose (2), yielding the poly(ethylenediamine tetra-acetic acid-*co*-lactose) (3).

4.3.5. *Metal Complexation Studies*

Metal complexation was conducted by using the LPR method in the aqueous phase under standard conditions (Figure 16).

The retention profiles of the water-soluble polymer the poly (ethylenediamine tetra-acetic acid-*co*-lactose) clearly show that the polymer has a strong binding ability for iron and chromium, as it exhibited a strong metal complexation with Cr(III) and Fe(III) with retention values of 100%. In contrast, Co(II), Ni(II), Cu(II), Zn(II), Sr(III), Cd(II), Pb(II), and Al(III) showed lower retention values (20–80%). Thus, the enrichment of Cr(III) and Fe(III) from the other metal ions can be achieved.

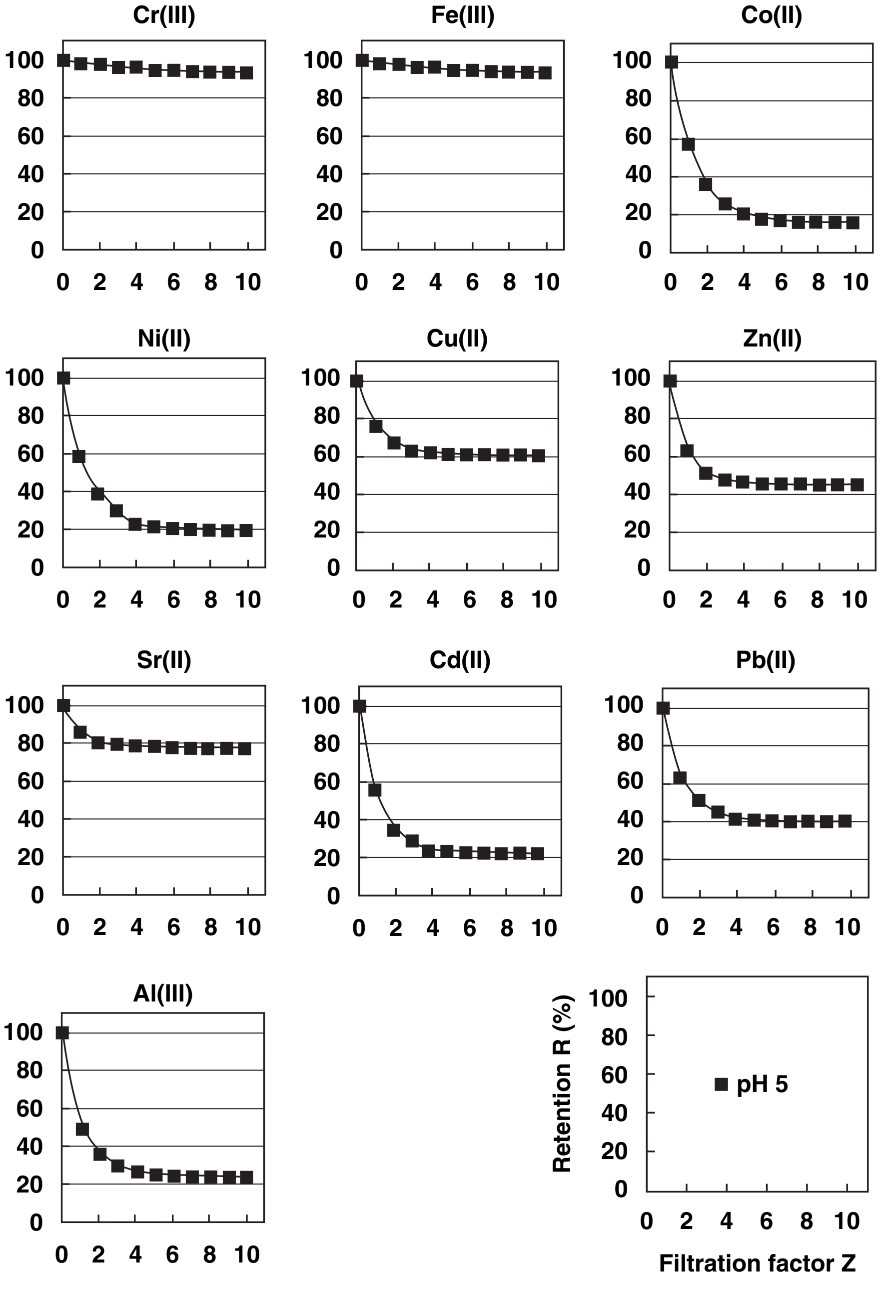


Figure 16. Retention profiles of poly(ethylenediamine tetraacetic acid-*co*-lactose) (1 wt%) for 10 metal ions at pH = 5, obtained by the Liquid-Phase Polymer-Based Retention (LPR) method.

4.3.6. *Biodegradation*

The microbiological degradability can be assessed by several methods including the measurement of the suspension turbidity. To this end, the degradation was performed by a microbiological consortium consisting of a mixture of soil microbes and activated sludge. The difference in turbidity is a measure of the actual degradability. The change of turbidity is due to the enrichment and growth of the mixed culture. In the case of the copolymer poly(ethylenediamine tetra-acetic acid-*co*-lactose) (Figure 17) it is shown that it is microbiologically degradable.

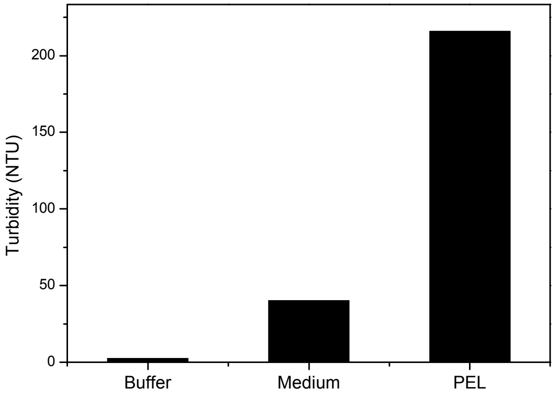


Figure 17. Turbidity of the microbe-enriched solution of poly(ethylenediamine tetraacetic acid-co-lactose) (PEL, 3). Buffer was 0.1 M potassium phosphate buffer (pH 7.2) at 25 □ consisting of 71.7 mL of 1 M K2HPO4 and 28.3 mL of 1 M K2HPO4; Medium was mineral medium solution. (NTU = Nephelometric Turbidity Unit).

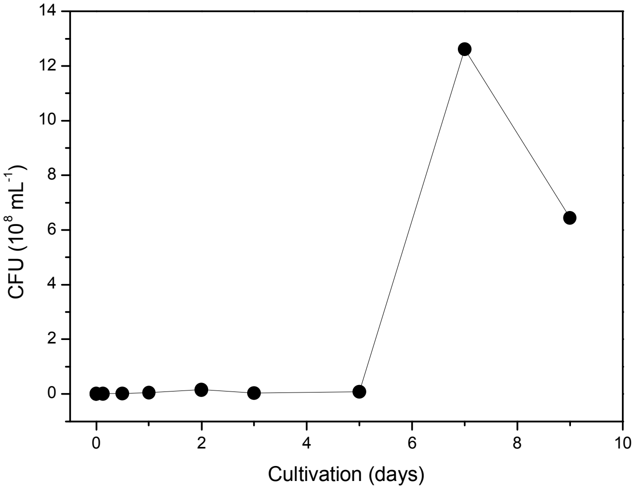


Figure 18. Microbiological degradation of poly(ethylenediamine tetra-acetic acid-*co*-lactose) based on Colony Forming Units (CFU) as a function of the cultivation time.

In terms of the biodegradation of the poly(ethylenediamine tetra-acetic acid-*co*-lactose) it was found that it is microbiologically degradable with an induction phase of 5 days and an exponential phase of two days after induction (Figure 18).

The microorganisms originating from the soil and the activated sludge, acclimated under aerobic conditions and in a mineral medium, may be attributed to the *Pseudomonas* family (Figure 19).

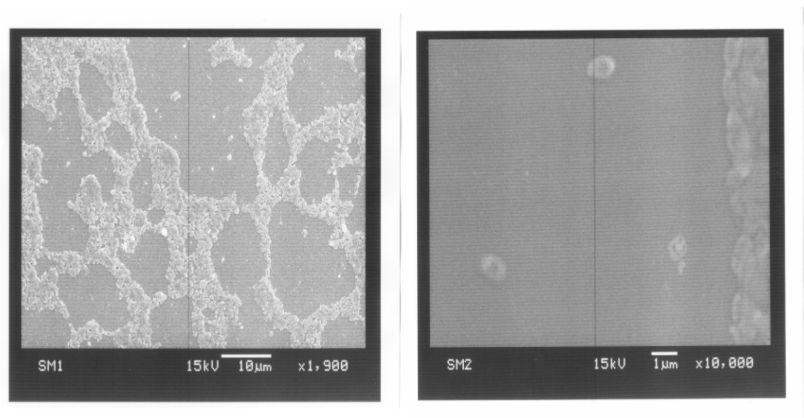


Figure 19. Scanning electron micrographs of the prominent microbial species in culture: (a) egg-shaped and cocci-shaped microbial species of the *Pseudomonas* type (×10,000); (b) morphology of the aggregated network (×1,900).

4.3.7. *Hyphenated Techniques*

The LPR method as a technique for the preconcentration and separation of elements allows generally the development of hyphenated techniques. One example is the combination with the inductively coupled plasma (ICP) emission spectrometry. The general application of the LPR method for the LPR-ICP technique is illustrated in Figure 20.

A hyphenated technique based on the polymer-assisted enrichment of elements was designed and reported.[27] The method has been approved by the IUPAC as an analytical method for the enrichment and separation of elements.[28]

4.3.8. *Analysis of Drinking Water*

The detection of contaminating species in drinking water is essential for the quality control of drinking water. In many cases it is difficult to determine the environmentally relevant elements due to their low concentrations. Conventionally, inorganic matters are determined by inductively coupled plasma spectrometry (ICP). Efficient monitoring of drinking water can be performed by

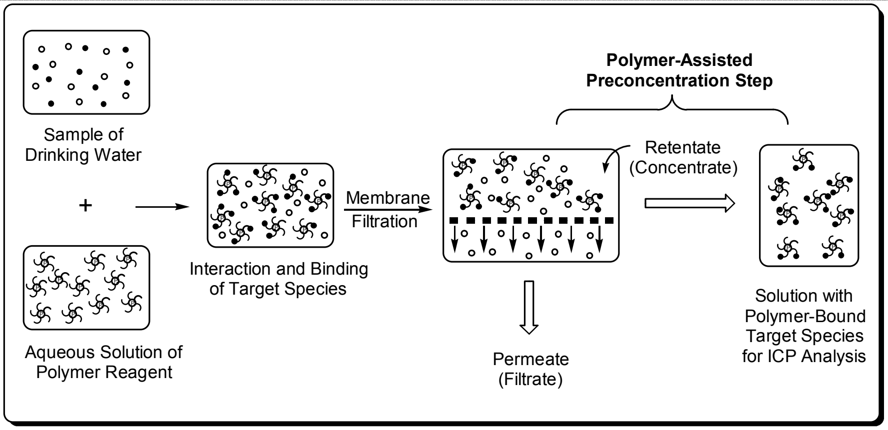


Figure 20. Schematic illustrating the general application principle of the LPR method for the LPR-ICP technique.

using a hyphenated technique, which is based on the Liquid-phase Polymer-based Retention (LPR) method in conjunction with ICP. Thus, the determination of various trace elements is made possible and the analytical accuracy of many other elements is significantly enhanced.

The employment of the hyphenated technique LPR-ICP for the analysis of samples of drinking water is shown in Figure 21.

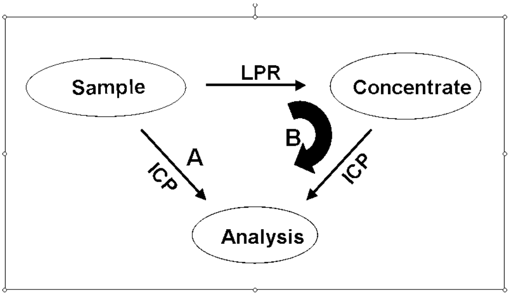


Figure 21. Principle of the polymer-based approach using LPR in conjunction witt the inductively coupled plasma (ICP) emission spectrometry to monitor drinking water.

Many polymer reagents suitable for this technique, e.g., the 2-hydroxyethyl chitin derivative, show a good binding ability for a series of elements, when used for this process under standard conditions. Inter-estingly, some elements, e.g., chromium and zinc, could not be detected by conventional analysis. However, by using this hyphenated method, the determination was made possible.

A comparison of data of drinking water analysis based on the conventional and the LPR-ICP analyses is compiled in Table 4. The data shows clearly the dramatic increase of the detection limits for a series of different elements.

TABLE 4. Comparison of conventional and LPR-ICP analytical data for drinking water analysis.

Metal Ions	Max. Allowed Conc. (mg/L)	Conventional ICP Analysis Conc. in Tap Water (mg/L)	**LPR-ICP Hyphenated Analysis Conc.[a] in Ret. (mg/L)**
Fe(III)	0.3	0.0151	**8.5624**
Al(III)	0.2	0.0236	**8.6128**
Ni(II)	-	0.0341	**0.1669**
Cu(II)	1	0.0207	**1.0646**
Zn(II)	1	0.0	**0.1792**
Cr(III)	-	0.0	**0.0997**
Sr(II)	-	0.0083	**0.1434**

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‘GREENER’ ORGANIC SYNTHESES UNDER NON-TRADITIONAL CONDITIONS USING MICROWAVE AND ULTRASOUND IRRADIATION AND MECHANOCHEMICAL MIXING

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Abstract: Solvent-free mechanochemical methods that involve the use of hypervalent iodine reagents at room temperature are described for the synthesis of heterocyclic entities and conversion of ketones into β-keto sulfones in high yields. A solvent-free approach that involves microwave (MW) exposure of neat reactants (undiluted) catalyzed by the surfaces of less-expensive and recyclable mineral supports such as alumina, silica, clay, or ‘doped’ surfaces is presented; it is applicable to a wide range of cleavage, condensation, cyclization, rearrangement, oxidation, and reduction reactions, including rapid one-pot assembly of heterocyclic compounds from *in situ* generated reactive intermediates. The strategy is adaptable to multi-component reactions, e.g. Ugi and Biginelli reactions, for rapid assembly of a library of compounds. Synthesis of a wide variety of significant precursors and intermediates, namely enones, imines, enamines, nitroalkenes, and oxidized sulfur species, is possible and their value in concise MW synthesis of 2-aroylbenzofurans and thiazole derivatives is illustrated. Ultrasound- and MW-assisted solventless preparation of ionic liquids and their application in alkylation and metal-catalyzed multi-component reactions is described. Efficient reaction of epoxides with carbon dioxide (CO_2) provides ready access to cyclic carbonates using only a catalytic amount of recyclable indium–based ionic liquid. MW heating in aqueous reaction media enables expeditious *N*-alkylation reactions of amines and hydrazines to afford a series of heterocyclic ring systems, such as *N*-azacycloalkanes, 4,5-dihydropyrazoles, and pyrazolidines. A general and expeditious MW-enhanced nucleophilic substitution approach uses easily accessible starting materials, such as halides or tosylates, in reaction with alkali azides, thiocyanates, or sulfinates in the

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absence of any phase transfer catalyst to produce azides, thiocyanates, and sulfones, respectively, wherein a variety of reactive functional groups are tolerated.

Keywords: Green chemistry; Organic synthesis; Solvent-free reactions; Microwave irradiation; Ultrasonic irradiation; Mechanochemical mixing; Aqueous media

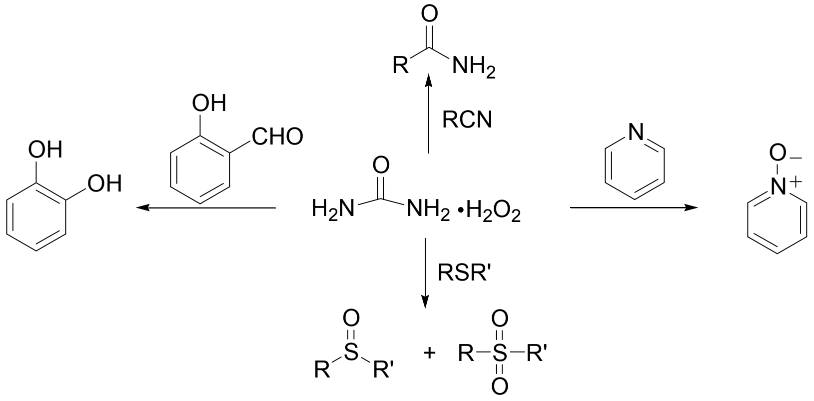
1. Introduction

The diverse nature of the chemical universe requires various green strategic pathways in our quest towards attaining sustainability. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. One of the thrust areas for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimized by-products or waste as well as eliminating the use of conventional organic solvents, wherever possible. Consequently, several newer strategies have appeared, including solvent-free (dry media), solid supported[1–4] and solid/solid reactions (grinding), the use of room temperature ionic liquids,[5] super-critical carbon dioxide, and water[6] as reaction media that can be combined with microwave or ultrasonic irradiation. Indeed, the best solvent is 'no solvent' but in such cases the problem of handling of materials and heat and mass transfer aspects need to be addressed in close cooperation with chemical engineers.

There are different shades of greener processes as we continue exploring several alternatives to conventional chemical transformations. Rather than remediation, which involves cleaning up of waste after it has been produced, the main objective is to avoid waste generation in the first place. That approach will require new environmentally benign syntheses, catalytic methods, and chemical products that are "*benign by design*" and that utilize renewable resources wherever possible.

1.1. OXIDATION REACTIONS

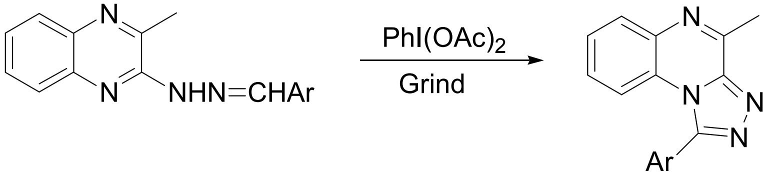
As an example, conventional oxidation processes involve danger in handling of metal complexes, inherent toxicity, and waste disposal problems. A solvent-free oxidation of a variety of organic groups using an inexpensive, safe, and easily handled reagent, urea-hydrogen peroxide (UHP), has been discovered by Varma and Naicker (Scheme 1) and this general solid-state oxidative protocol is applicable in oxidizing hydroxylated aldedydes and



Scheme 1

ketones (to phenols), sulfide (to sulfoxides and sulfones), nitriles (to amides), and *N*-heterocycles (to *N*-oxides).[7]

We have discovered a simple oxidative transformation of arene-carbaldehyde 3-methylquinoxalin-2-yl-hydrazones to 1-aryl-4-methyl-1,2,4-triazolo[4,3-a]quinoxalines (Scheme 2) that is accomplished by simple grinding using a friendlier non-metallic oxidant, iodobenzene diacetate, $PhI(OAc)_2$.[8a]



Ar = C_6H_5, p-$CH_3C_6H_4$, p-ClC_6H_4, p-$OCH_3C_6H_4$, m-$OCH_3C_6H_4$, p-$N(CH_3)_2C_6H_4$,

Scheme 2

The oxidative protocol simply involves grinding of the two solid substrates using a pestle and mortar; a mildly exothermic reaction results in the formation of a yellowish eutectic melt and the reaction gets completed in a few minutes. The work has now been extended to the synthesis of β-ketosulfones[8b] from ketones employing another hypervalent iodine reagent, hydroxytosyloxy iodobenzene, in high yields. This synthesis involves *in situ* generation of α-tosyloxyketones followed by nucleophilic substitution with sodium arene sulfinate in presence of tetrabutylammonium bromide at room temperature. Similarly, novel α-tosyloxy β-ketosulfones, valuable precursors for heterocyclic compounds of therapeutic interests, have been prepared under solvent-free conditions by a simple mechanochemical mixing of β-ketosulfones with [hydroxyl(tosyloxy)iodo]benzene.[8c]

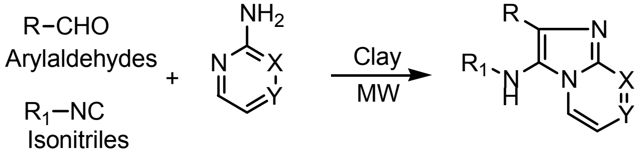
Microwaves, non-ionizing radiation incapable of breaking bonds, are a form of energy that manifest as heat through their interaction with the medium wherein they can be reflected (metals), transmitted (good insulators that will not heat) or absorbed (decreasing the available microwave energy and rapidly heating the sample). This unconventional microwave (MW) energy source has been used for heating food materials for several decades and is now being utilized for a variety of chemical applications including organic synthesis wherein chemical reactions are expedited because of selective absorption of MW radiation by polar molecules, non-polar molecules being inert to the MW dielectric loss. The initial experiments with MW heating exploited the use of high dielectric solvents such as dimethylsulfoxide (DMSO) and dimethylformamide (DMF) in a household kitchen MW oven. The rate enhancements in such reactions are believed to be due to rapid superheating of the polar solvents and pressure effects. However, in these solution-phase reactions, the development of high pressures, and the use of specialized sealed vessels are some of the limitations, although they have been circumvented by the introduction of commercial MW instruments with appropriate temperature and pressure controls.

Heterogeneous reactions facilitated by supported reagents on inorganic oxide surfaces have received much deserved attention in recent years. A related development that had a major impact on heterogeneous reactions is the use of microwave (MW) irradiation procedure for the acceleration of organic reactions. Since the appearance of initial reports on the application of microwaves for chemical synthesis in polar solvents, the approach has matured into a useful technique for a variety of applications in organic synthesis and functional group transformations, as is testified by a large number of publications and review articles on this theme.[1–4,9,10] This solvent-free approach has gained popularity that involves microwave exposure of neat reactants catalyzed by the surfaces of less-expensive and recyclable mineral supports such as alumina, silica, clay, or ‘doped’ surfaces. The strategy is applicable to a wide range of cleavage, condensation, cyclization, rearrangement, oxidation and reduction reactions including rapid one-pot assembly of heterocyclic compounds from *in situ* generated reactive intermediates.[9–11]

1.2. CONDENSATION REACTIONS

1.2.1. *Synthesis of Heterocycles-Applications in Combinatorial Chemistry*

Heterocyclic chemistry has been a major beneficiary of MW-expedited solvent-free chemistry utilizing mineral supported reagents. It has been exploited for parallel synthesis, a strategy that is adaptable for multicomponent reactions, such as Ugi[11a] and Biginelli reactions[11b], for rapid assembly of a library of compounds.[11c] A representative multi-component condensation reaction to create a small-molecule library of imidazo[1,2-a]pyridines, imidazo[1,2-a] pyrazines, and imidazo[1,2-a]pyrimidines is depicted in Scheme 3.

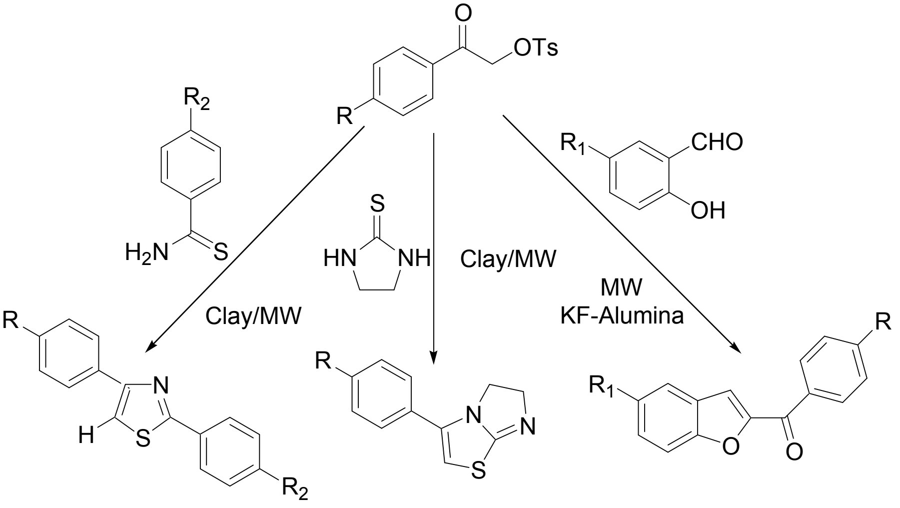


X = Y = C; X= C, Y= N; X= N, Y=C and R, R_1= alkyl, aryl

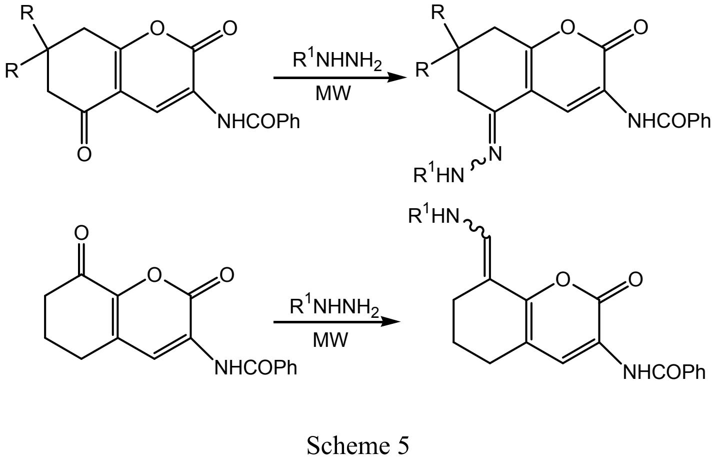
Scheme 3

The conventional preparations of thiazoles and 2-aroylbenzo[*b*]-furans require the use of lachrymatory α-haloketones and thioureas (or thioamides). In a process which eliminates this problem, Varma *et al.* have now synthesized various heterocycles via simple solvent-free reaction of thioamides, ethylenethioureas, and salicylaldehydes with α-tosyloxyketones that are generated *in situ* from arylmethyl ketones and [hydroxy(tosyloxy)iodo] benzene (HTIB) under MW irradiation conditions (Scheme 4).[12]

The only example of a reaction between two solids, under solvent-free and catalyst-free environment, was demonstrated by Varma *et al.* when the reaction of neat 5- or 8-oxobenzopyran-2(1*H*)-ones with a variety of aromatic and heteroaromatic hydrazines provided rapid access to several synthetically useful heterocyclic hydrazones (Scheme 5) via the formation of a eutectic melt below the melting point of either of the reactants.[13]



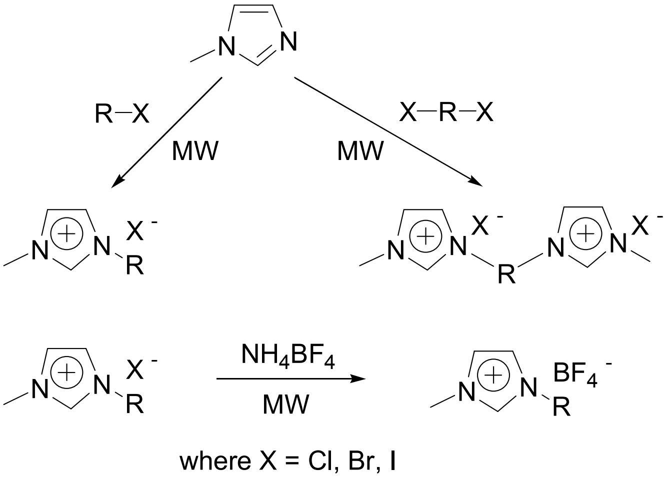
Scheme 4



Scheme 5

1.2.2. *Solvent-free Synthesis of Ionic Liquids*

Ionic liquids, being polar and ionic in character, couple to MW irradiation very efficiently and therefore have been considered MW absorbing candidates for expediting chemical reactions. Unfortunately, most of the initial preparative processes for the preparation of ionic liquids involve several hours of heating in refluxing solvents and use a large excess of alkyl halides/organic solvents, which diminish their true potential as 'greener' solvents.



Scheme 6

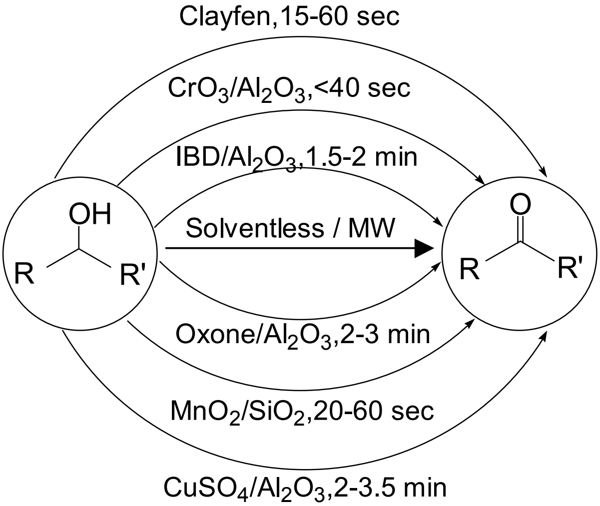
The first solventless preparation of 1,3-dialkylimidazolium halides *via* MW heating has been described by Varma *et al.* (Scheme 6)[5,14] The MW procedure reduces the reaction time from hours to minutes and avoids the use of a large excess of alkyl halides/organic solvents as the reaction medium; the S_N2 alkylations using neutral nucleophiles as amines has been further exploited in the synthesis (*vide supra*). The approach has been extended to other ionic salts bearing tetrafluoroborate anions,[15a] and involves exposing *N, N'*-dialkylimidazolium chloride and ammonium tetrafluoroborate salt to MW irradiation (Scheme 6). Similarly, gallium- and indium-containing ionic liquids[15b,c] have been prepared; a catalytic amount of tetrachloroindate-based ionic liquid efficiently catalyzes the reaction of epoxides with carbon dioxide, affording a greener route to useful cyclic carbonates.[15d] The surge of interest continues in this area and we have explored the use of ultrasonic pathway to prepare these solvents[5b] and their use as catalysts for alkylation of isobutane with 2-butene,[16] for Ruthenium-catalyzed tandem migration,[17] and silver-catalyzed coupling reactions.[18]

1.3. REACTIONS ON SOLID SUPPORTS

1.3.1. *Oxidation Reactions*

The utility of oxidants in oxidation processes is compromised for several reasons, including potential danger in handling of metal complexes, inherent toxicity, cumbersome product isolation, and waste disposal problems. Immobilization of metallic reagents on solid supports has addressed some of these limitations as the containment of metals on the support surface precludes them from leaching into the environment. There are several examples:

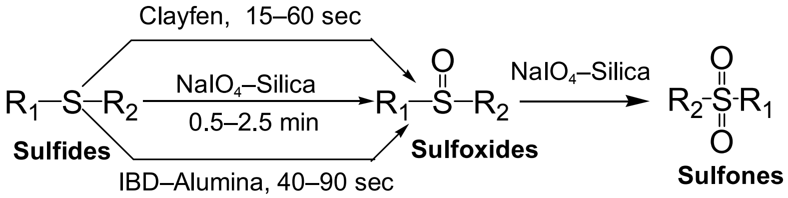
- Silica supported manganese dioxide (MnO_2).[19]
- Chromium trioxide (CrO_3) immobilized on premoistened alumina affords efficient oxidation of benzyl alcohols to carbonyl compounds by simple mixing (Scheme 7). Remarkably, neither the over-oxidation to carboxylic acids nor the formation of tar, a typical occurrence in many CrO_3 oxidations, is observed.[20]
- A rapid MW oxidation protocol for the oxidation of alcohols to carbonyl compounds has been reported by Varma *et al.* using montmorillonite K10 clay-supported iron(III) nitrate (clayfen) (Scheme 7). The simple solvent-free experimental procedure involves mixing of neat substrates



Scheme 7

with clayfen and a brief MW irradiation for 15–60 seconds.[21] The solid state utility of clayfen as an oxidant has afforded higher yields and is more efficient since the amounts used in these protocols are half of that used in solution phase reactions by Laszlo *et al.*[22a,b]

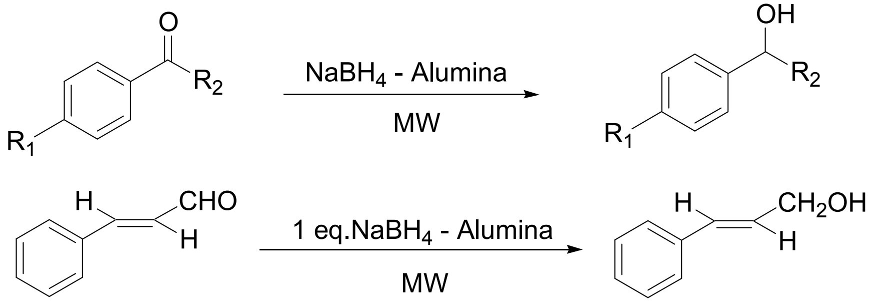
- Varma *et al.* have reported for the first time the use of supported iodobenzene diacetate (IBD) as an oxidant; the use of alumina as a support improved the yields markedly as compared to neat IBD (Scheme 8).[23] The solid IBD-alumina system has also been used for the rapid, high yielding, and selective oxidation of alkyl, aryl, and cyclic sulfides to the corresponding sulfoxides upon MW irradiation.[24]
- The oxidation of sulfides to sulfoxides and sulfones is achieved in a selective manner using MW irradiation under solvent-free conditions with desired selectivity to either sulfoxides or sulfones over sodium periodate ($NaIO_4$) on silica (20%) (Scheme 8).[25] A noteworthy feature of the protocol is its applicability to long chain fatty sulfides that are insoluble in most solvents and are consequently difficult to oxidize. Further, it circumvents the use of oxidants such as nitric acid, hydrogen peroxide, chromic acid, and peracids, which are conventionally used for the oxidation of sulfides to the corresponding sulfoxides and sulfones.



Scheme 8

1.3.2. *Reduction Reactions*

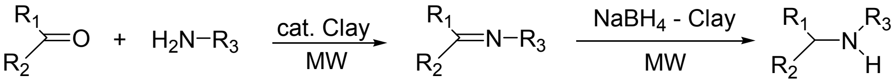
The relatively inexpensive and safe sodium borohydride ($NaBH_4$) has been extensively used as a reducing agent because of its compatibility with protic solvents. Varma and co-workers have reported a simple method for the expeditious reduction of aldehydes and ketones that uses alumina-supported $NaBH_4$ and proceeds in the solid state accelerated by MW irradiation[26] (Scheme 9). The useful chemoselective feature of the reaction is apparent from the reduction of *trans*-cinnamaldehyde.



Scheme 9

The reaction rate improves in the presence of moisture and the reaction does not proceed in the absence of alumina. The alumina support can be recycled and reused for subsequent reduction, repeatedly, by mixing with fresh borohydride without any loss in activity. In terms of safety, the air used for cooling the magnetron ventilates the microwave cavity, thus preventing any ensuing hydrogen from reaching explosive concentrations. The process has been nicely utilized for the MW-enhanced solid-state deuteriation reactions using sodium borodeuteride impregnated alumina.[27] Subsequent extension of these studies to specific labelling has been explored[28], including deuterium exchange reactions for the preparation of reactive intermediates.[29]

Solvent-free reductive amination protocol for carbonyl compounds using sodium borohydride supported on moist montmorillonite K10 clay is facilitated by MW irradiation (Scheme 10).[30] Clay serves the dual purpose of a Lewis acid and also provides water from its interlayers that enhances the reducing ability of $NaBH_4$.



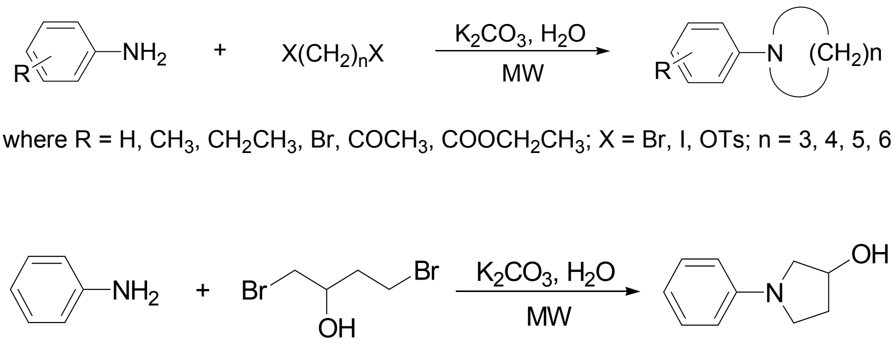
Scheme 10

1.4. REACTIONS IN AQUEOUS MEDIA

Organic synthesis in aqueous media is rapidly gaining importance in organic synthesis in view of the fact that the use of many toxic and volatile organic solvents, particularly chlorinated hydrocarbons, contributes to pollution. Consequently, it is highly desirable to develop environmentally benign processes that can be conducted in aqueous media. Furthermore, using water as a solvent offers many advantages, such as simple operation and high efficiency in many organic reactions that involve water soluble substrates and reagents. Utilization of water as reaction media[31] in conjunction with microwave irradiation is one of the emerging non-conventional methods being recognized as a viable environmentally benign alternative.[1,9,10,32]

We envisioned that the nucleophilic substitution reaction of alkyl halides with amines will be accelerated by microwave energy because of their polar nature. Indeed, a friendlier synthesis of tertiary amines *via* direct *N*-alkylation of primary and secondary amines by alkyl halides under MW irradiation is possible; the reaction proceeds in basic water without any phase transfer reagent.[33]

The same nucleophilic substitution chemistry can be manipulated by means of microwave irradiation to afford a variety of cyclic amines as building blocks in natural product syntheses *via* double *N*-alkylation of primary amines (Scheme 11).[34] The protocol circumvents the difficulty associated with running multi-step reactions to assemble *N*-aryl azacycloalkanes and avoids the use of expensive metal catalysts in building aryl C-N bonds. Further, reactive functional groups, such as carbonyl, ester, and hydroxyl, remain unaffected under these mild reaction conditions. The *N*-alkylation reaction is now extended to hydrazines as well.[34b,c]



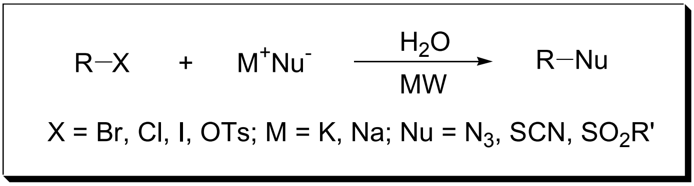
where R = H, CH_3, CH_2CH_3, Br, $COCH_3$, $COOCH_2CH_3$; X = Br, I, OTs; n = 3, 4, 5, 6

Scheme 11

It is noteworthy to mention that this reaction is not a homogeneous single phase system as neither reactant is soluble in aqueous alkaline reaction medium. We believe that the selective absorption of microwaves by polar molecules and intermediates in a multiphase system could substitute as a phase transfer catalyst without using any phase transfer reagent, thereby providing the observed acceleration as has been observed for ultrasonic irradiation.[35]

The experimental observation is consistent with the mechanistic postulation wherein the polar transition state of the reaction is favored by MW irradiation with respect to the dielectric polarization nature of microwave energy transfer.[34,36] In large scale experiments, the phase separation of the desired product in either solid or liquid form from the aqueous media can facilitate product purification by simple filtration or decantation instead of tedious column chromatography, distillation, or extraction processes, which even-tually reduces the usage of volatile organic solvent required for extraction or column chromatography.

A MW-assisted protocol for the synthesis of azides, thiocyanates, and sulfones has been developed (Scheme 12) that has proved to be a useful alternative, as the use of environmentally deterimental volatile chlorinated hydrocarbons is avoided.[37] All the reactions with these readily available halides or tosylates have shown significant increase in reactivity, thus reducing the reaction times with substantial improvement in the yields. Various functional groups such as ester, carboxylic acid, carbonyl, and hydroxyl were unaffected under the mild reaction conditions employed. This method involves simple experimental procedures and product isolation which avoids the use of phase-transfer catalysts, and is expected to contribute to the development of greener strategy for the preparation of various azides, thiocyanates, sulfones, and other useful compounds.



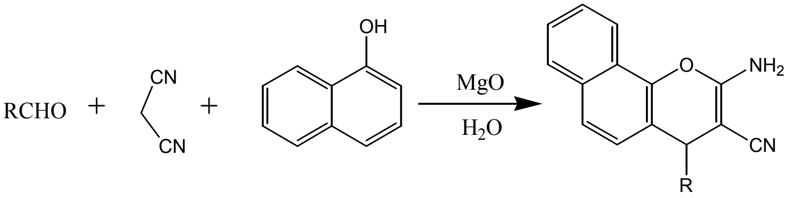
$$R{-}X \quad + \quad M^+Nu^- \xrightarrow[MW]{H_2O} R{-}Nu$$

X = Br, Cl, I, OTs; M = K, Na; Nu = N_3, SCN, SO_2R'

Scheme 12

1.4.1. *Multi-Component Condensation Reaction*

We have recently accomplished and optimized a simple and high yielding protocol for the synthesis of 2-amino-2-chromenes (Scheme 13) involving the three-component, one-pot condensation of aldehyde, malononitrile, and α-naphthol using nanosized magnesium oxide as a novel and eco-friendly heterogeneous catalyst.[38] Mechanistically, the reaction occurs via initial formation of benzylidenemalononitrile in quantitative yield by the Knoevenagel addition of malononitrile to the aldehyde, followed by loss of water molecules. Subsequently, ortho *C*-alkylation of α-naphthol and nucleophilic addition of hydroxyl moiety to the nitrile produces 2-amino-chromenes. The attractive features of this protocol are simple experimentation procedure, use of benign reaction solvents, cost effectiveness, the recyclability of catalysts, and its adaptability for the synthesis of a diverse set of 2-amino-2-chromenes.



Scheme 13

2. Experimental Section

2.1. SOLVENT-FREE MICROWAVE REACTIONS

Most of the neat reactions (undiluted) without solvents or using supported reagents were performed in open glass vessels using a Panasonic household microwave oven (1000 W) equipped with a turntable and operating at 2450 MHz. This MW oven uses inverter technology for realistic modulation of power level operations, which was especially useful for preparation of polar and ionic compounds, such as ionic liquids, that required intermittent heating. An alumina bath (neutral alumina: 125 g, mesh ~150, Aldrich; bath: 5.7 cm diameter) was used as a heat sink inside the MW oven to irradiate the reaction mixtures. The average bulk temperature at the end of the reaction was measured by inserting a thermometer in the alumina bath housing the reaction vessel or using an IR sensor.

2.1.1. *Preparation of ionic liquids using ultrasound irradiation-representative procedure for bromides and iodides*

1-bromobutane (11 mmol) and 1-methylimidazole (MIM) (10 mmol) were placed in a screw-cap test tube and subjected to ultrasound irradiation on a Fisher Scientific ultrasonicator (Model FS 220) for 2 h until a clear single phase of ionic liquid was obtained; temperatures of the bath before and after sonication were 23 and 40°C, respectively. The residual 1-butyl bromide was removed under vacuum at 80°C (94%). A similar experiment on the same scale, but using conventional heating (oil bath, 50°C, 6 h), did not afford any product. An experiment on a relatively large scale (55 mmol of 1-bromobutane and 50 mmol of MIM) afforded 98% yield.

2.1.2. *General MW procedure for the synthesis of α-tosyloxyketones*

A mixture of arylmethylketone (1 mmol) and [hydroxy(tosyloxy)iodo] benzene (1.2 mmoles) was placed in an alumina bath inside the MW oven and irradiated for 30 seconds at 50% power level. After completion of the reaction, determined by TLC examination, the crude products were washed with hexane to afford α-tosyloxyarylmethylketones that were used in subsequent reactions.

2.1.3. *Synthesis of 2-aroylbenzo[b]furans (Scheme 4)*

Salicylaldehyde (0.122 mg, 1 mmol), potassium fluoride (KF)-alumina (0.620 g, 0.2 mmol of KF), and α -tosyloxyketone (1 mmol) were mixed in a glass tube and then placed in an alumina bath inside the MW oven and irradiated (intermittently with 1.5 min intervals; 130°C). On completion of the reaction, followed by TLC examination (hexane:ethyl acetate, 9:1), the product was extracted into methylene chloride, the solvent was removed, and the residue was crystallized from ethanol to afford high yield of 2-aroylbenzo[b]furans.

2.1.4. *Synthesis of 2,4-disubstituted thiazoles (Scheme 4)*

α-Tosyloxyketone (1 mmol), appropriate thioamide (1 mmol), and montmorillonite K 10 clay (125 mg) were mixed thoroughly using a pestle and mortar. The reaction mixture was placed into a glass tube and exposed to MW irradiation in an alumina bath for 2–5 min (intermittently with 1.5 minute intervals; 130°C). The product was extracted into methylene chloride and purified by crystallization from ethanol-hexane to afford corresponding thiazoles.

2.1.5. *Synthesis of 3-aryl-5,6-dihydroimidazo[2,1-b] thiazole (Scheme 4)*

α-Tosyloxyketone (1 mmol), ethylenethiourea (1 mmol) and montmorillonite K 10 clay (100 mg) were mixed thoroughly in a pestle and mortar. The contents were transferred into a glass tube followed by intermittent MW irradiation in an alumina bath for 3 minutes. The ensuing thiazole salt was neutralized by the addition of a dilute aqueous sodium hydroxide. The product was extracted into methylene chloride and purified by crystallization from benzene-hexane to afford corresponding 3-aryl-5,6-dihydroimidazo[2,1-b] thiazole (Scheme 4).

2.1.6. *Reactions in Aqueous Media-synthesis of N-aryl Azacycloalkanes*

In a representative reaction, 1.0 mmol aniline derivatives, 1.1 mmol dihalides, and 1.1 mmol potassium carbonate in 2 mL of distilled water were placed in a 10 mL crimp-sealed thick-wall reaction tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in the MW cavity (CEM Discover Focused Microwave Synthesis System with a build-in infrared temperature sensor), operated at 120 ± 5°C, power 80–100 Watt and pressure 65–70 psi, for 20 minutes. After completion of the reaction, the organic portion was extracted into ethyl acetate. Removal of the solvent under reduced pressure and flash column chromatography furnished the desired product.

2.1.7. *Nucleophilic Substitution Reactions in Aqueous Media-synthesis of Azides*

The representative experimental procedure is as follows: 1,4-dibromobutane (1 mmol, 0.215 g) and sodium azide (2.5 mmol, 0.163 g) in water (2 mL) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 120 $\pm$ 5^{o}C (temperature monitored by a built-in infrared sensor), power 70–100 Watt and pressure 60–100 psi, for 30 minutes. After completion of the reaction, diethyl ether was added to extract the alkyl azide. GC/MS analysis indicated the disappearance of alkyl halides. FT-IR spectrum of crude product was obtained using a FT-IR spectrometer and the formation of alkyl azide was confirmed by the characteristic IR adsorption around 2100 cm^{-1}. Removal of the solvent under reduced pressure (rotary evaporator) afforded the product, 1,4-diazido-butane (0.125 g) in 89% yield.

2.1.8. *Synthesis of 2-amino-2-chromenes in Water*

A mixture of benzaldehyde (2 mmol), malononitrile (2 mmol), α-naphthol (2 mmol), and MgO (50 mg) in water (15 mL) was refluxed for 1 h. After completion of the reaction, as indicated by TLC, the mixture was extracted with ethyl acetate (3 × 5 mL). The organic phase was dried, filtered, and excess ethyl acetate was distilled off (filtration of both organic and aqueous phases led to recovery of solid magnesium oxide). The residue was recrystallized from methanol to afford the pure product in 86% yield.

3. Conclusions

The eco-friendly advantages of these reactions may be found in instances where catalytic amounts of reagents or supported agents are used since they provide reduction or elimination of solvents or utilize water as reaction media, thus preventing pollution ‘at source’. Although not delineated completely, the reaction rate enhancements achieved in these methods may be ascribable to non-thermal effects. The rationalization of microwave effects and mechanistic considerations possibly involving the intermediacy of polar transition states have been discussed.[34,36] The use of synthesis processes that employ MW/ultrasonic irradiation to shorten the reaction time and eliminate or minimize side product formation is already finding acceptance in pharmaceutical industry (combinatorial chemistry) and polymer syntheses and may pave the way towards the greener and more sustainable approach to chemical syntheses.[39]

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THE GREENEST REAGENT IN ORGANIC SYNTHESIS: LIGHT

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Abstract: A photon substitutes a chemical reagent in a large number of useful chemical syntheses. Some examples are presented and the advantages/ limitation of photochemical reactions are discussed.

Keywords: Photochemistry, Green Chemistry, Organic Synthesis

1. Introduction

Synthesizing organic molecules under mild conditions and with the minimal environmental impact is one of the main targets of green chemistry. 'Traditional' synthetic methods often involve rather harsh conditions. As an example, many methods for carbon-carbon bond formation involve an enolate as the key intermediate and thus are carried out under strongly basic conditions and/or require the introduction of activating groups, which leads to a poor atom economy.

As a matter of fact, 'green' chemistry is a pervasive concept in present day chemistry, and particularly in synthesis, or at least is a commonly used word. Perhaps too much. There is a tendency to apply the label 'green' to any method that appears to be, at least in the Authors' opinion, innovative with respect to the state-of-art science. Thus 'green' takes the place of previously used adjectives such as 'new' or 'novel' that had become meaningless due to excessive use (actually, some important chemistry journals have decided to ban such adjectives from the title of the manuscripts they publish).

P. Tundo and V. Esposito (eds.), *Green Chemical Reactions.*

Certainly, for most synthetic chemists the concern about the green aspects is nowadays present in their search for new synthetic methods. Green aspects are then put in evidence in the corresponding publications.[1,2] Most often, however, this is applied to any method discovered that allows making a compound to react in a way that is either impossible by 'conventional' chemistry, or possible only under severe conditions. This is something that is 'new' and can be added to the choice of methods a synthetic chemist has available. Typically, a catalyst is used that makes the reaction occur under 'milder' conditions.

Although it is obvious that it is useful for synthetic chemistry to have available a new reaction, the label 'green' should be applied with some caution.

For example, being able to carry out the reaction at a lower temperature is not necessarily a big step forward in the sense of green chemistry when this implies using an expensive catalyst, the preparation of which is quite time – and reagent – consuming, or which requires strictly controlled reaction conditions, such as using a thoroughly dried solvent, avoiding contact with air and so on. The correct application of the principles of green chemistry demands that all the aspects of the process are taken into account.

Thus, the overall balance must evaluate everything that comes before the step considered (including the production of reagents and of the energy that are to be used in that step) and what comes after it (e. g. side-products to be disposed off, heat to be dispersed). It may turn out that using milder conditions and carrying out the reaction at a lower temperature is less advantageous when considered all the aspects indicated above, than when limiting the consideration to single step, e.g. because it requires more steps for the preparation of the reagents, or it consumes more energy, so that the seemingly green method is not such when correctly considered.

This does not mean that the proposed method is no important step forward in science and clearly it is only learning more about the behavior of chemical compounds that new alternatives become available and can be ultimately developed into actually green paths. What should be stressed is that a method can be considered green only when it really satisfies all of the required characteristics.

2. Photochemistry as a Green Synthetic Method

The above caution should certainly apply to photochemical reactions. For the reasons introduced below, one may think that photochemistry is *per se* a green method, but it is not necessarily so. Photochemically reactions are induced by light absorption, which promotes one of the reagents to its excited state – that is thus induced to react – leaving no residue behind.

Thus no chemical is added and no side-product deriving from it is formed, nor is heating applied. In a sense, thus, the photon is indeed the ideal green reagent. Added to the fact that photochemical reactions involve electronically excited states, the energy of which is comparable to that of chemical bonds, and quite often cause a deep-seated transformation of the reagents structure that have hardly an equivalent among thermal reactions, these characteristics give indeed to photochemistry a special role in green synthesis, or at least a great potential, since these advantages have been scarcely exploited as yet, even in 'pure' research by the academia, let alone being applied in the industry.[3]

The present discussion will be explicitly limited to applications where the photochemical methods appears synthetically significant and the question of the assessment of the 'greenness' of the overall process, from production of light to final isolation of the products will be explicitly taken into consideration.

The discussion will be articulated in the following way. First, a short overview about the synthetic potential of photochemistry proper, that is the chemistry of excited states (eq. 1), will be given.

$$A + h\nu \rightarrow A^* \rightarrow B \qquad (1)$$

Second, a different perspective will be taken by considering photochemistry as a way for arriving under mild conditions at high energy (though ground state) intermediates such as radicals or cations (eq. 2), through the examples of the activation of aliphatic C-H bonds and that of aromatic C-X bonds.

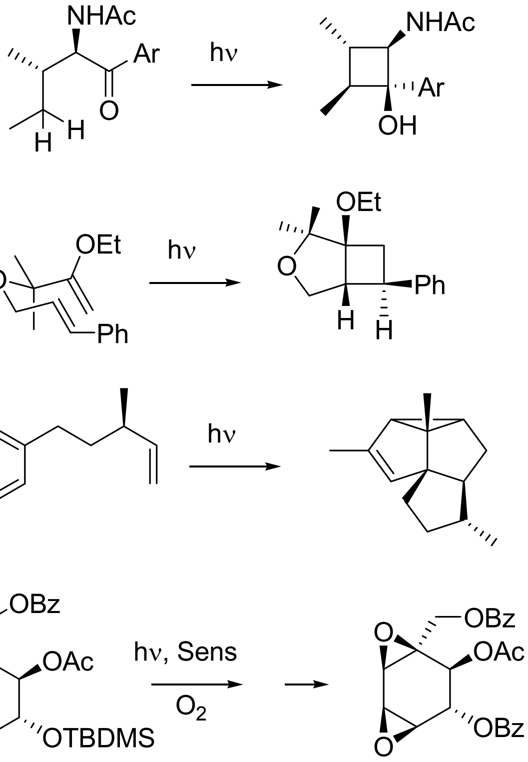
$$\text{A-X} + h\nu \rightarrow \text{A-X}^* \rightarrow \text{A}^{\bullet}, \text{A}^{+}, \ldots \rightarrow \text{Products} \qquad (2)$$

Finally, it will be discussed how the green characteristics of photoinduced reaction can be assessed.

3. Some Synthetically Useful Photochemical Reactions

Synthetically useful photochemical reactions are discussed in various books and reviews; in some of these also the practical aspects are considered.[4–6]

To have a rough idea of the potential of the method, please have a look to the syntheses below that are among those considered typical in a recent book (Scheme 1).[7] These are a cyclization to hydroxycyclobutane via H-abstraction,[8] a 2 + 2 alkene cycloaddition,[9] a '*meta*' benzene-olefin cycloaddition,[10] and a dye sensitized addition of singlet oxygen.[11] Please consider whether there are facile thermal alternatives to these straightforward photochemical reactions.



Scheme 1

4. Activation of the Aliphatic C-H Bond

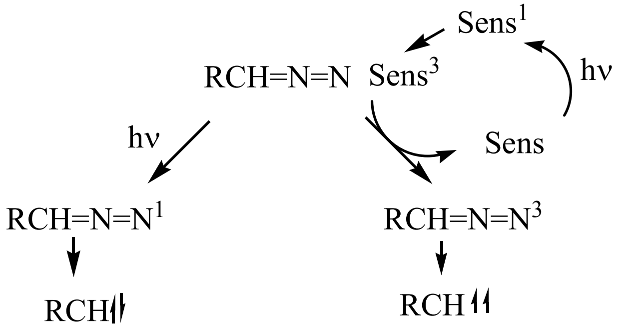
In the two following sections a different aspect of photoinduced reactions will be considered, where the important bond forming step does not occur directly at the level of the excited state, but rather via a high energy, but ground state, intermediate produced photochemically (see eq. 2). Of course the best known (and largely applied) cases are here radical chain processes where the initiator is photochemically activated, such as chlorination, sulfochlorination and the like.

$$Cl_2 + h\nu \rightarrow 2\ Cl^{\bullet}\ \text{(initiation)}$$

$$Cl^{\bullet} + RH \rightarrow R^{\bullet} + HCl\ \text{(propagation)}$$

$$R^{\bullet} + Cl_2 \rightarrow RCl + Cl^{\bullet}\ \text{(propagation)}$$

These will not discussed here, where it will rather referred to reactions in which the photon is a reagent and must be used stoichiometrically. Typical cases where this principle applies are the unimolecular fragmentation of an excited state *not* followed by a chain process. Such fragmentation may lead either to a pair of radicals (homolytic cleavage) or of ions (heterolytic cleavage), or, when starting from a diazo derivative, to a carbene (and correspondingly a nitrene from an azide). The photochemical production of carbenes (Scheme 2) is familiar to many organic chemists.[12]

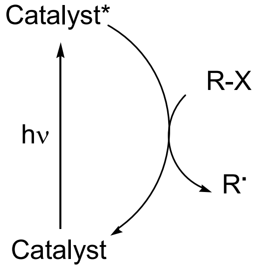


Scheme 2

This method of preparing carbenes has the advantage with respect to thermal or redox induced generation that it occurs under mild conditions, no reagent is added and often one can chose the multiplicity of the carbene generated, singlet or triplet, by the method of irradiation, viz. direct excitation of the precursor (a diazo derivative) in the first case or indirectly via a sensitizer that absorb the light, intersystem crosses to the triplet state and generates the triplet of the diazo compound via energy transfer in the second one.

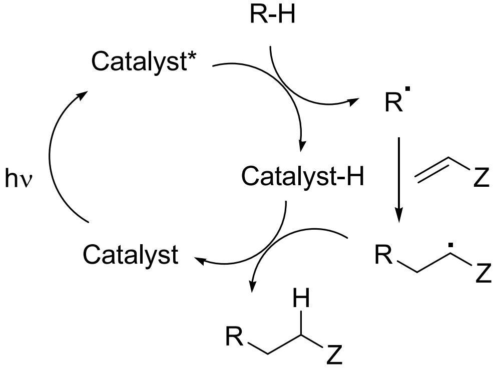
Applying the same idea to the activation of an aliphatic C-H bond would be a major goal, but is not as simple as one may hope. Direct irradiation of the precursor can not be contemplated because simple aliphatic derivatives do not absorb at convenient wavelengths (i.e. those at which efficiently emitting lamps are available), but only in the extreme UV. At any rate, even when the way to reach the excited state is found, more than one chemical (fragmentation) path is usually available, making the process less clean that it may be desired. However, the use of photocatalysts may help, particularly for reactions via aliphatic carbon-centered radicals.

We mean by photocatalyst a compound that has no effect in the ground state, but in the excited state is able to initiate the desired process, in a typical case by cleaving a σ C-X (usually C-H) bond (Scheme 3).



Scheme 3

The thus formed alkyl radical undergoes some chemical transformation, typically addition to an electrophilic alkene, but in the following course of the reaction the hydrogen is transferred back from the reduced catalyst to the intermediate radical. In this way the catalyst is regenerated and a new cycle is initiated by the absorption of a photon (Scheme 4).

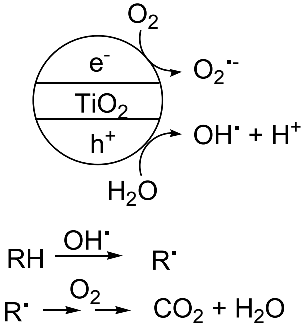


Scheme 4

As it appears from the scheme, this process is stoichiometric in light, well different from the above mentioned chain processes. The use of the term photocatalyst in this meaning is not common, since this term is rather referred to the oxidation and mineralization of organic pollutants caused by irradiation in the presence of semiconductor (e.g. TiO_2, ZnS, CdS) powders. However, the mechanism in Scheme 4 seems strictly analogous to the usual concept of catalysis, with the additional requirement of *photo* activation and thus joining the two words and defining the process as photocatalytic seems to us natural, as illustrated in a recent review.[13]

The role of catalyst can be plaid by a variety of compounds, which abstract effectively hydrogen from C-H bonds, such as aromatic ketones as well as inorganic compounds such as polyoxoanions or the above mentioned semiconductor oxides or sulfides. With the ketones, back hydrogen transfer is sometimes too slow and thus the photocatalyst is not fully regenerated, requiring addition in a relatively high amount (in some cases up to equimolecular, thus making difficult to apply the concept of catalyst). However, polyoxoanions are not consumed and are effective in a low amount, typically 1/50th of the reagent.[13]

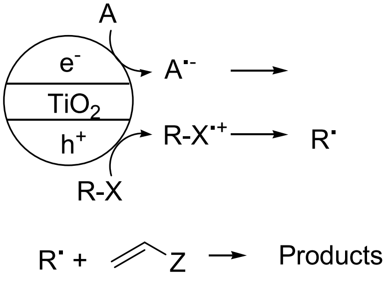
This holds also for semiconductor solids, where absorption of light causes the promotion of electron to the conduction band and thus the generation of a microelectrode, since on the surface of the solid are present both excess conduction electrons and holes in the valence band. Obviously these recombine in a short time, but molecules adsorbed on the surface may intercept the momentary charge separation and undergo both reduction and oxidation. In the case of oxygen equilibrated aqueous solutions, water is oxidized to hydroxide radical and oxygen is reduced to superoxide anion. The OH radical attacks many, perhaps most organic molecules initiating a process that may lead to complete mineralization to carbon dioxide and water (Scheme 5).[14]



Scheme 5

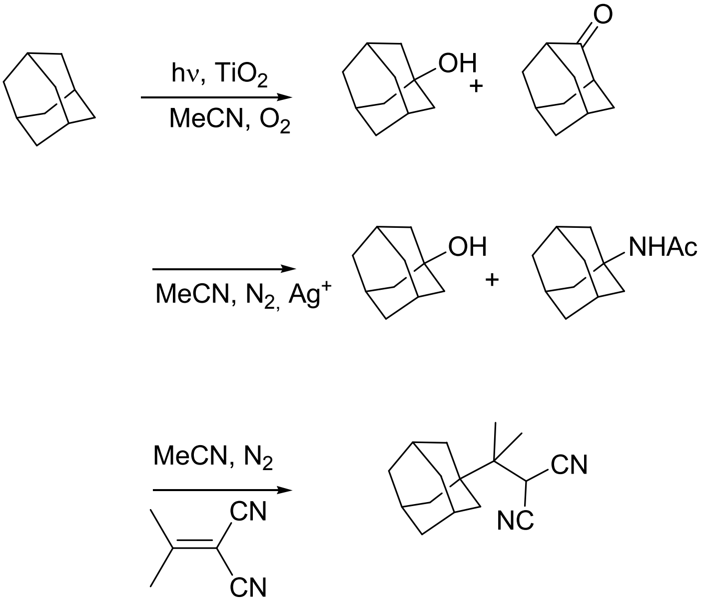
Hence the application for the recover of polluted water of industrial of agricultural origin by mineralization of the organic contaminants, as one of the most promising ‘advanced oxidation’ processes. In organic solvents and in the absence of oxygen, however, organic molecules may be preferentially absorbed and be either oxidized or reduced and one (or both) or the resulting radical ions can cleave offering a different entry to neutral radicals (Scheme 6).

The same path can be followed also by some organic photocatalysts that in the excited state are either strong oxidants or strong reductans.



Scheme 6

Below, some examples of radical alkylation processes are reported that give an idea of the scope of the method. These include the activation of an alkane, adamantane, finally leading to various trapping products (with formation of C-O, C-N, C-C bonds according to the reagents and conditions used), as well as benzylation reactions (Scheme 7).[15]



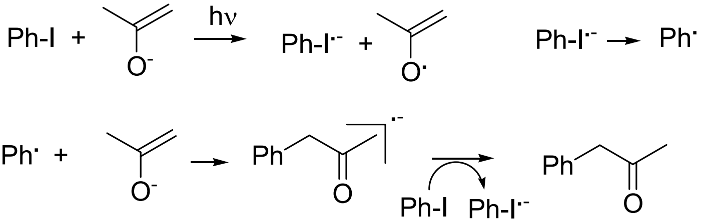
Scheme 7

Results by using TiO_2, decatungstate or benzophenone as the photocatalysts are similar. Notice that the generation of alkyl radicals through the attack of an aggressive reagent such as the excited photocatalyst mimics the pyrolysis, e.g. that of alkanes that initiates the combustion process. As seen above, in the presence of oxygen photocatalysis achieves the ‘cold combustion’ of a hydrocarbon to finally give carbon dioxide and water.

From the synthetic point of view, what is interesting is trapping by electrophilic alkenes leading to formation of a carbon-carbon bond. The synthetic advantage of generating radicals by cleavage of a strong C-H bond under mild conditions can be easily guessed. Even when compared with reactions where the radical is generated by cleavage of a more usual precursor, such as a bromide or iodide, the mild conditions of the photochemical alternative make give an advantage in terms of selectivity.[13]

5. Activation of an Aromatic C-X Bond

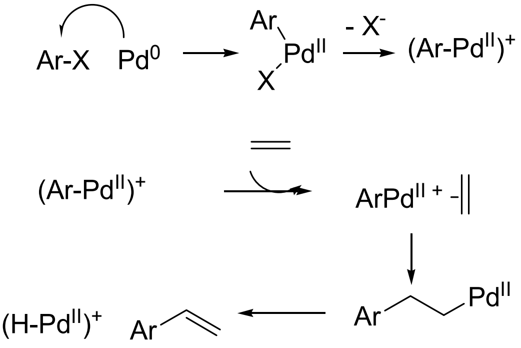
As it is well known, nucleophilic substitution of a C-X bond, one of the key synthetic reactions with aliphatic compounds is severely limited with aromatic derivatives, where it occurs thermally only with electron-withdrawing substituted compounds and/or under severe conditions. Alternatives include time honored reactions involving the phenyl radical generated by decomposition of diazonium salts after a reductive step, such as the Meerwein and the Gomberg-Bachmann reactions, as well as the (often photoinitiated) $S_{RN}1$ reaction, where a (usually weak, e.g. carbon-iodine) bond is cleaved after monoelectronic reduction to give an aryl radical as the active inter-mediate that adds to an enolate, cyanide or other nucleophiles (and thus again with an aryl radical as the key intermediate, Scheme 8).[16]



Scheme 8

However, the real breakthrough in this area is due to the development of catalysis by transition metals, with the Heck, Suzuki, Sonogashira reactions and other related coupling process.[17]

This is an interesting point for understanding the role of photochemical vs. thermal activation. Thus, in ground state metal catalysis donation from the aryl halide to the metal and back donation from the metal to the antibonding orbital weakens the aryl-halide bond and may lead to oxidative addition onto the metal centre. In this complex, the aryl group has a cation character, or at least the aryl-metal moiety has a cationic character (Scheme 9).[18]



Scheme 9

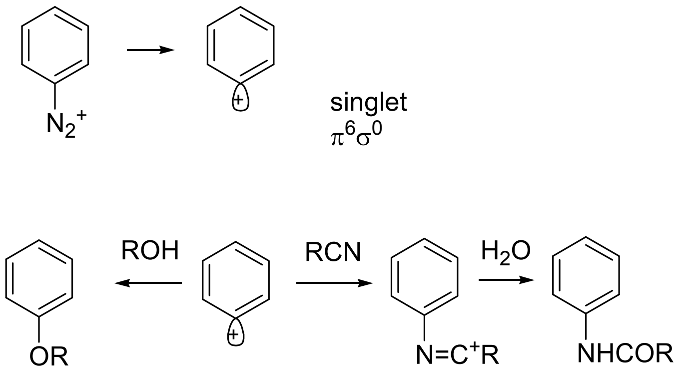
On the other hand, absorption of a photon promotes an electron from a bonding to an antibonding orbital. This activation may lead to aryl-halide bond fragmentation generating *directly* a carbocation (phenyl cation).

$$\text{Ar-X} + h\nu \rightarrow \text{Ar}-\text{X}^* \rightarrow \text{Ar}^+ + \text{X}^-$$

The phenyl cation is a quite aggressive intermediate, since heterolytic cleavage of a $\sigma_{C\text{-}X}$ bond leaves an empty σ orbital, while the upper-lying π orbitals are filled. Taking away electron from a more stabilized orbital is obviously more expensive and the phenyl cation is more reactive than the corresponding anion, where the σ orbital is filled. One may expect that the reactivity is so high that any selectivity is precluded and the reaction can have no sensible application.

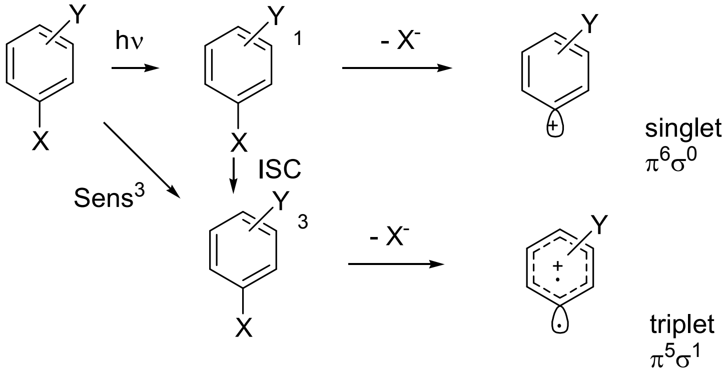
However, this unusual intermediate exists in two spin states, singlet and triplet, quite similarly to the case of carbenes (and for the same reasons, two orbitals of similar energy have only two electrons to share). In the singlet state, the σ_{C-X} orbital remains empty so that this has actually the characteristics of a localized carbocation and reacts with any nucleophile, and indeed in this case there is no selectivity. Typically, when generated in the singlet state the phenyl cation reacts with any nucleophile present, first of all the solvent, giving ethers in alcohols and amides in nitriles (Scheme 10).

Thermal decomposition of an organic molecule, a closed shell species and thus a singlet, leads to a singlet phenylium ion. This is what happens when an aryldiazonium salt is decomposed. This reaction, however, only in a few cases is useful due to the lack of selectivity and also because it is difficult avoiding competition by the electron transfer path, leading to the phenyl radical rather than the cation (see above).



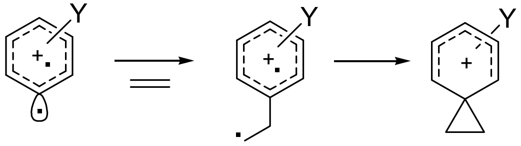
Scheme 10

However, in photochemistry both excited states, singlet and triplet, of the precursor can be reached, e.g. by direct irradiation and by spontaneous intersystem crossing (ISC) or by sensitization. The multiplicity of the state that undergoes the cleavage determines that of the cation. In the case of electron-donating substituted aryl halides fragmentation occurs in most cases from the triplet and forms the triplet cation (Scheme 11).[19]



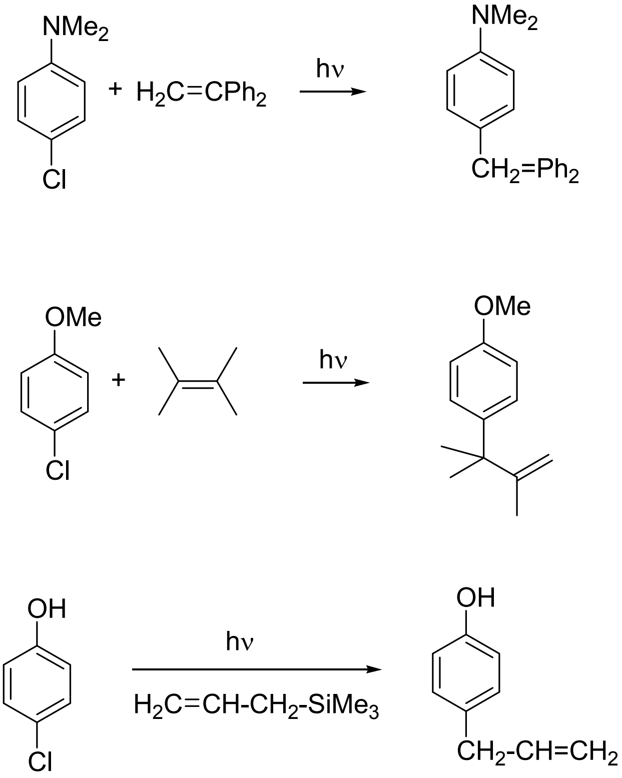
Scheme 11

This differs from the singlet counterpart for the demotion of one of the π electrons to the σ space (π^5 σ^1 configuration). Thus, two (orthogonal) singly occupied orbitals give to this intermediate the character of a diradicalic rather than of a localized cation. In other terms singlet and triplet phenyl cations resemble the respective spin states of carbenes. As a result, in this multiplicity the triplet phenyl cation reacts efficiently with π nucleophiles, with which it forms a single bond generating a diradicalic adduct that then further evolves to more stablilized species. For example addition to an alkene gives a distonic diradical cation that then intersystem crosses to the singlet surface a form a closed shell cation, a phenonium ion (Scheme 12).[18]

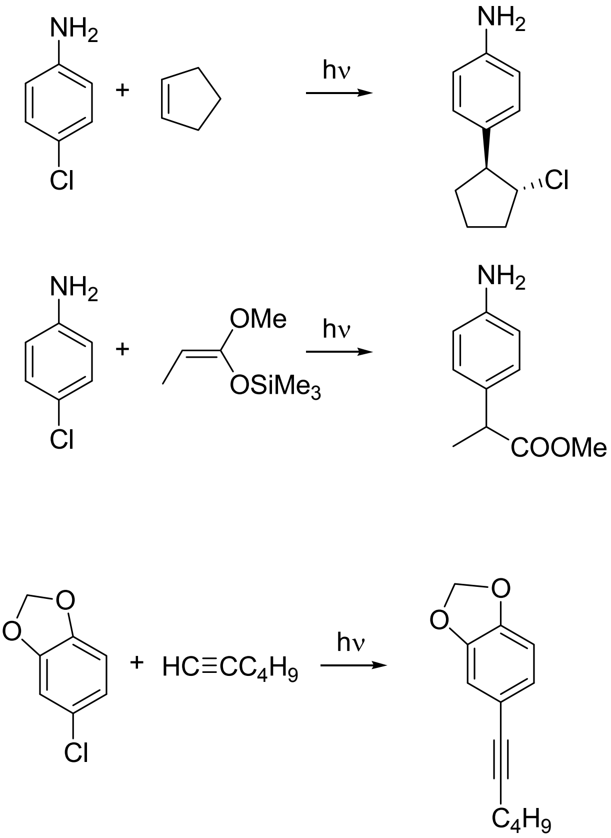


Scheme 12

On the contrary, the triplet reacts much less easily with n nucleophiles such as alcohols or water, because much of the positive charge is on the ring, not on the formally divalent position. Therefore, the triplet is a useful intermediate for arylation reactions via formation of a carbon-carbon bond.



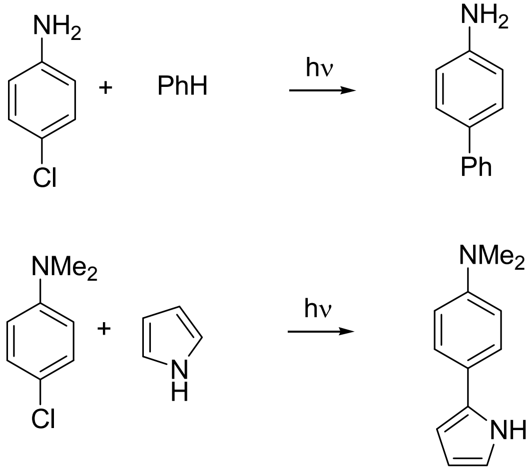
Scheme 13a



Scheme 13b

As a matter of fact the photochemically generation of the *triplet* phenyl cation is synthetically equivalent to activation by metal catalysis that likewise produces a sort of phenyl cation complexes to the metal by oxidative addition of the aryl halide and elimination of the halide anion (see above).[18] In fact, a photochemical parallel has been found for most type of metal catalyzed arylations, via reactions that occur from the same or similar reagents.

The formation of arylalkanes, alkenes and alkynes as well of more functionalized derivatives and some bi(hetero)aryls is exemplified in some schemes below, in order to illustrate the contribution of this reaction to 'green' synthesis' (Scheme 13a–c).[20–22]



Scheme 13

6. Is a Synthesis Through a Photochemical Process Really ‘green’?

As mentioned in the introductory section, the idea behind this presentation is not merely to illustrate the synthetic potential of photochemistry by showing the variety of accessible paths, but also to discuss explicitly the ‘green’ characteristics of photochemical reactions. The photon substitutes a chemical reagent and thus addition of a activating chemical, e.g. an acid, a base, an oxidant all of which have to be produced, to the mixture as well as formation of side-products arising from such reagent, e.g. salts from neutralization of acid and bases, reduced oxidant (that add to the waste to be eliminated at the end of the process).

However, light has to be produced and this consumes energy, just as in the case of the reagents mentioned, energy that ultimately arises from petroleum. An important step forward, to which increasing attention is being devoted, is using solar light.[23]

An attempt has been done to assess the environmental harmfulness of a few photochemical processes compared to thermal reactions that are closely analogue. The result of this comparison is that the strong point of photochemical processes is their directness. Quite often a product can be obtained starting from a less functionalized derivative in the photochemical alternative and thus is advantageous from the point of view of atom economy (a lower number of steps is required for obtaining the same chemical transformation, and/or a lower number of protecting/activating groups that need to be introduced and to be eliminated at the end).[24]

The weak point is that in order that a photochemical process takes place, a photon must be absorbed, and this generally implies using a low concentration of the substrate, otherwise all of the light is absorbed in the first thin layer of the solution close to the surface of the vessel (causing an inefficient conversion, particularly if the photoproduct absorb light of the same wavelength and sometimes causing successive photoreactions and polymerizations).

Although there are technical expedients that partially diminish the troubles, this remains a major limitation, because even if the solvent can be recovered, this at any rate implies considerable expenses and investment for recovering and recycling. Along with the requirement of a proper design for photochemical reactor that is different from those for thermal reactions, this factor discourages industrial application of photochemistry and, as a conesquence, also the academic activity in this field. However, some of the characteristics of photochemical reactions make them more versatile and give a basic advantage under the 'green' aspect.

7. Conclusions

It is clear from the above that there is a long way before photochemistry acquires an important role in industrial chemistry. However, there are in fact some peculiar characteristics in these reactions that makes them indeed 'green', or at least suitable candidates for green procedures. Therefore, it may be expected that as far as concern about the environmental aspects of chemical synthesis grows, application of photochemistry will take a more important role.

Aknowledgment

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HYDROGEN PEROXIDE IN GREEN OXIDATION REACTIONS: RECENT CATALYTIC PROCESSES

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Abstract: Hydrogen peroxide constitutes a potentially green and environmentally-friendly oxidant because it releases only water as by-product. Thus, much efforts have been put into the research for ideal conditions for its use in oxidation reactions. This chapter focuses on the recent applications of hydrogen peroxide in epoxidation reactions catalyzed by transition metal catalysts, illustrating both homogeneous and heterogeneous catalysis. An overview of the recent findings in asymmetric catalytic epoxidations is also given.

Keywords: Oxidation, green chemistry, heterogeneous, catalysis, hydrogen peroxide

1. Introduction

Oxidation reactions are among the most numerous and useful of the Industrial processes and, at the same time, the most hazardous and polluting ones. They often occur with high E-factor, defined by Sheldon as the mass of waste, corresponding to all compounds used which are not incorporated in the product, per mass unit of product.[1] Indeed, oxidation reactions often deliver considerable amounts of toxic waste, e.g., metal salts in oxidations carried out with stoichiometric Cr(VI) or Mn(VII) derivatives, or nitrogen oxides from reactions with HNO_3. In a green chemistry context, it is of paramount importance to develop alternative oxidation methods making use of cleaner oxidants, which minimize the waste, producing only benign waste. Processes occurring under simple and mild conditions should be privileged, also for energy saving issues, and this implies the use of catalysis.[2]

P. Tundo and V. Esposito (eds.), *Green Chemical Reactions.*

Highly efficient catalysts are then needed, ideally economic and comercially, or easily available, ones. Their possible recovery and re-use is also an important goal and therefore heterogeneous catalysts or heterogeneized homogeneous catalysts have to be taken into account.

2. Hydrogen Peroxide: an Environmentally Friendly Terminal Oxidant

Nowadays, a chemical process for the production of a desired product has to be evaluated considering its conversion, chemical yield and selectivity, but also its atom efficiency, according to the atom economy principle established by Trost in 1991.[3]

In other words, the best chemical process for the formation of a product is in principle the one that limits as much as possible the weight amount of co-products formed according to the stoichiometry of the process. Applying this concept to the field of oxidation reactions implies that oxidants with a higher active oxygen percentage content, i.e., the mass amount of oxygen transferred to the substrate with respect to the total mass of the oxidant, should be privileged.

TABLE 1. Common oxidants ordered by active oxygen content.

Oxidant	**Active oxygen content (wt.%)**	**Waste product**
O_2	100.0	Nothing or H_2O
O_2/reductor	50.0	H_2O
H_2O_2	47.0	H_2O
N_2O	36.4	N_2
O_3	33.3	O_2
$KMnO_4$	30.4	Mn(II) salts
HNO_3	25.0	NOx
CrO_3	24.0	Cr(III) salts
NaOCl	21.6	NaCl
CH_3COOH	21.1	CH_3COOH
*t*BuOOH	17.8	*t*BuOH
$C_5H_{11}NO_2$ (NMO)	13.7	$C_5H_{11}NO$ (NMM)
$KHSO_5$	10.5	$KHSO_4$
mClC_6H_4COOOH	9.3	*m*ClC_6H_4COOH
$Me_3SiOOSiMe_3$	9.0	$Me_3SiOOSiMe_3$
$NaIO_4$	7.5	$NaIO_3$
PHIO	7.3	PhI

A number of common oxidants are reported in Table 1, ordered according to their active oxygen content. It is evident that O_2 is the ideal oxidant to be used. However, very few reactions have been found so far where both oxygen atoms can be transferred to the substrate.[4] More often, oxidations by O_2 occur with transfer of one oxygen atom to the substrate and formation of 1 equivalent of H_2O, then O_2 acts as an oxidant with 50% of active oxygen content. Immediately after, with a 47% oxygen content, comes H_2O_2, which also releases 1 equivalent of H_2O. The nature of the waste released is of course a relevant factor in choosing the appropriate oxidant and water is the best possible waste from the point of view of hazards and toxicity. Therefore O_2 and H_2O_2 stem as the oxidants of choice. However, O_2 is more difficult to be activated, requiring often harsh conditions of temperature and/or pressure. Moreover, oxidations with O_2 often occur with poor selectivity. For these reasons, H_2O_2 is a more practical oxidant and its use for organic transformations has been investigated intensively in the past and in recent years. We will report here some selected catalytic oxidations, focusing mainly on epoxidations, with the use of H_2O_2 as a terminal oxidant in order to elucidate some useful strategies and the most recent highlights.

2.1. INDUSTRIAL PRODUCTION OF HYDROGEN PEROXIDE

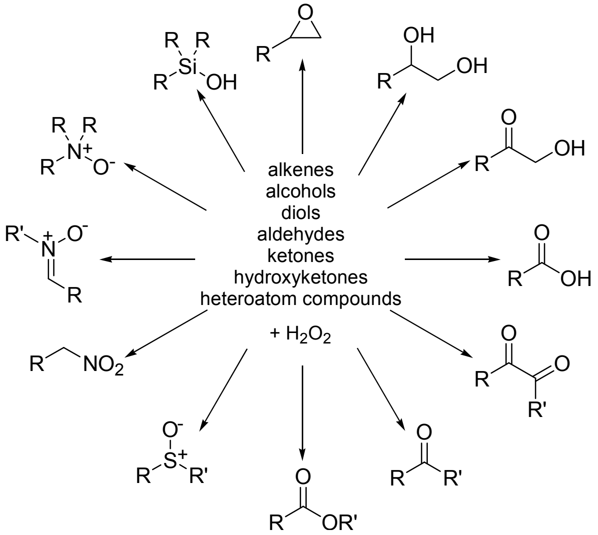
Hydrogen peroxide is produced annually in 2.2×10^6 tons worldwide, almost exclusively (>95%) by means of the alkylanthraquinone autoxidation (AO) process:[5] it is relatively cheap (ca. 0.6 €/Kg), and is used mainly as a bleaching agent in the paper and textile industries and as a component or a reagent for detergents. It is commercialized as aqueous solutions at different concentrations or as solid complexes with inorganic salts (e.g., sodium percarbonate, $2Na_2CO_3 \cdot 3H_2O_2$) or organic compounds (e.g., urea hydrogen peroxide, UHP, $NH_2CONH_2 \cdot H_2O_2$).

2.2. DECOMPOSITION OF HYDROGEN PEROXIDE

Hydrogen peroxide is susceptible of decomposition to H_2O and O_2 (catalase reaction), which is quite exothermic ($\Delta H^o = -100.4$ KJ/mol), for which reason is considered to be an hazardous reagent. However, only the use of highly concentrated aqueous solutions of H_2O_2 (>70%) poses serious hazard problems. Use of less concentrated solutions and of solid UHP is safe, providing that simple precautions (avoid concentrating or distilling with H_2O_2 still present, avoid contamination with undesired metals and derivatives and with undesired organic compounds) are followed.

2.3. ACTIVATION OF HYDROGEN PEROXIDE

Conversely, H_2O_2 reacts sluggishly with organic compounds and requires to be activated. Under appropriate conditions, it is able to perform a multitude of oxidative transformations (Scheme 1).



Scheme 1. Selected oxidative transformations performed by H_2O_2

Activation of H_2O_2 may be achieved under several different conditions: nucleophilic activation, electrophilic activation, radical activation, activation by means of organic compounds which give different and more active peroxidic species, activation by use of transition metal derivatives. Emphasis will be given to this last modality, which occurs via formation of metal-oxo or metal-peroxo complexes, which are the actual catalytic species responsible for the oxidation of organic substrates.

3. Early Transition Metal Catalysts

3.1. HOMOGENEOUS CATALYSTS

High valent early transition metal derivatives are known to catalyze the epoxidation of alkenes by peroxides (e.g., *t*-butylhydroperoxide) through the formation of active metal-peroxy species, which deliver the metal linked oxygen, acting as an electrophile, to the alkene. More substituted alkenes are then more reactive than monosubstituted ones. Hydrogen peroxide may also give the epoxidation by this same mechanism. The formed epoxides are usually stable, apart from those destabilized by electronic (e.g., styrene oxide) or steric (e.g., cyclohexene oxide) factors, which tend easily to undergo nucleophilic ring-opening to the corresponding diols. However, complexes of these metals are rarely used with aqueous hydrogen peroxide, since they are unstable to H_2O_2 and/or H_2O. An exception which has been evidenced early is that of polyheteroacids.

Venturello and co-workers reported that in the presence of aqueous H_2O_2 a phosphotungstate of the Keggin type gives phosphotungstate anions possessing four W atoms, each one displaying 2 peroxo moieties.

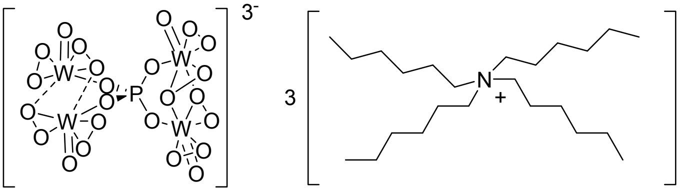
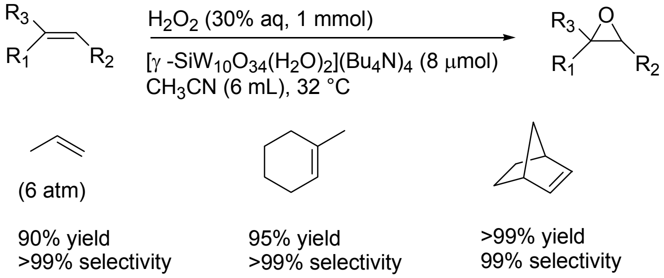


Figure 1. Phosphotungstate-based oxidation catalyst.

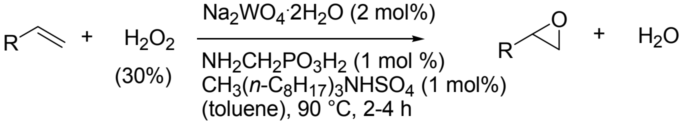
This species, completely characterized also by X-ray diffraction studies as its tetrahexylammonium salt (Figure 1),[6] was responsible for the epoxidation of a series of structurally diversified olefins with typical selectivities of ca. 95% and chemical yields in the range 85–95%.[7] These catalysts have found industrial applications in the epoxidation of alkenes and in the oxidative cleavage of alkenes to carboxylic acids. The favourable characteristics of these catalysts are thermal stability, ease of synthesis, stability to oxidation, solubility in both water and organic solvents, effectiveness as phase transfer catalysts.

More recently Mizuno has found a related silicadecatungstate catalyst which displayed exceptional efficiency in the epoxidation of alkenes with 30% aqueous H_2O_2 (Scheme 2), either in terms of catalyst activity, selectivity, and efficiency in use of H_2O_2.[8] Moreover, the catalyst could be recovered and recycled up to 5 times with no loss of activity.



Scheme 2. Mizuno's epoxidation of alkenes promoted by silicadecatungstate and acqueous H_2O_2

Excellent yields in the epoxidation of alkenes, including terminal ones, have also been obtained by Noyori and co-workers by using $Na_2WO_4 \cdot 2H_2O$ as the catalyst precursor under solvent-free (or in toluene) and halide free conditions (Scheme 3).[9] The efficiency of the reaction is dependent on the use of aminomethylphosphonic acid and trioctylmethyl ammonium hydrogensulfate as additives in 1 mol% amount, which are the best performing conditions.

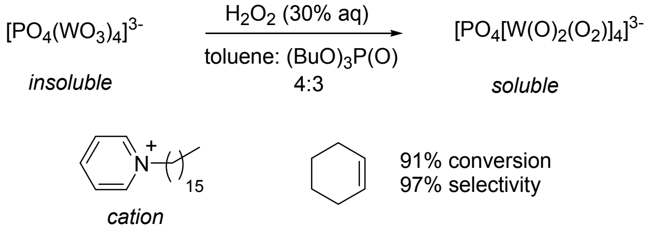


Scheme 3. Noyory's epoxidation of alkenes promoted by tungstate anions and acqueous H_2O_2

3.2. HETEROGENEOUS CATALYSTS

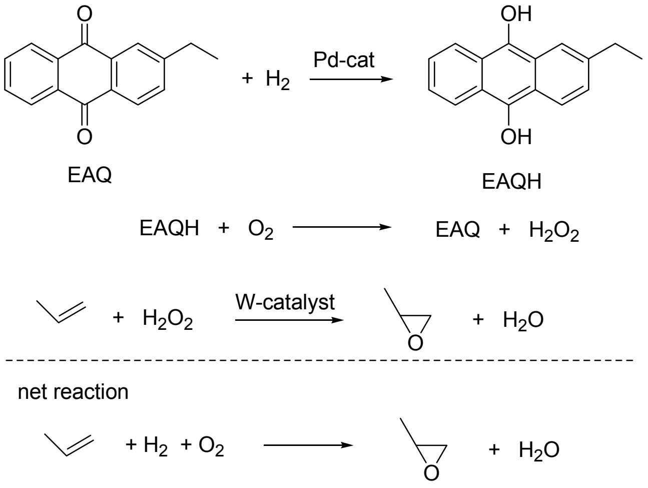
Early transition metals have been used for epoxidation reactions also in heterogeneous catalysis. Most notably, the titanium silicalite TS-1, a zeolite containing Ti synthesized by chemists at EniChem,[10] has found applications with aqueous H_2O_2 in the epoxidation of lower olefins,[11] in the oxidation of alcohols, of alkanes, in the oxidation of phenol to resorcin and hydroquinone and in the ammoximation of cyclohexanone to cyclohexanone oxime, which is the first step in the synthesis of caprolactam employed for the production of nylon 6. The key for the success of these oxidations is a hydrophobic environment inside the cavity of the zeolite which is believed to preserve the Ti atoms from deactivation. Other favourable features of TS-1 are high surface area and adsorbing power and high activity and selectivity. A limitation to the use of TS-1 rests in the diameter of its pores, which is ca. 5.5 Å and allows only small molecules to enter to be oxidized by the intermediate Ti-peroxy active species. An important application of TS-1 is the synthesis of propylene oxide, which is one of the top 50 chemicals more produced worldwide (4×10^6 tons/year). Its classical industrial production with the chlorohydrin process using Cl_2 and NaOH typically produces considerable amount of chemical waste: 2.01 tons of NaCl (a co-product) and 0.102 tons of dichloropropane (a side-product) per ton of propylene oxide. Oxidation of propene with H_2O_2 catalyzed by TS-1 encompasses the problems of waste formation.[12]

Recently, another interesting process has been reported for the epoxidation of a broad series of alkenes, including propene and alkenes which afford sensitive epoxides. This represents a smart extension of the use of a Venturello type catalyst in a pseudo-heterogeneous catalytic fashion, in such a way to have the advantages of both heterogeneous and homogeneous catalysis.[13] The method makes use of a phosphotungstate whose counterions are pyridinium substituted at nitrogen with linear C_{16} chains and of a peculiar 4:3 toluene-tributylphosphate solvent mixture. In this solvent the pre-catalyst is insoluble, but upon reaction with H_2O_2 it gives the catalytically active W-peroxo complex which is soluble (Scheme 4).



Scheme 4. Preparation of a pseudo-heterogeneous phosphotungstate catalyst

Then, the catalytic action is performed under homogeneous conditions and, at the end of the reaction, H_2O_2 being completely consumed, the pre-catalyst precipitates and can be easily filtered off and recovered. Both conversions and selectivities of this method are very good. Finally, as in the case of TS-1, this epoxidation system was combined with the 2-ethylanthraquinone (EAQ)/2-ethylanthrahydroquinone (EAHQ) process for hydrogen peroxide formation, and good conversion and selectivity were obtained for propylene oxide in three consecutive cycles. The catalyst was recovered and reused in between every cycle (Scheme 5).[13]



Scheme 5. Epoxidation of alkenes through O_2 activation

In an effort to overcome the limitations in dimension of substrate imposed by TS-1, ordered mesoporous materials having uniform pore diameters which can be regulated in the range 1.5–10 nm have been considered, with particular attention devoted to MCM-41.[14] In order to obtain redox active catalysts from these materials a redox active metal has to be introduced. Two strategies have been employed for introducing Ti and obtaining a redox active Ti-MCM-41 catalyst: the first consists simply in inducing an isomorphous substitution of Si with Ti by adding a Ti source during the synthesis of the material;[15] the second one considers a successive anchoring of Ti to the free OH groups at the surface of MCM-41.[16] The redox molecular sieves obtained in this way have a high surface area and large and adjustable pore dimensions and indeed they could effect epoxidation of bulky alkenes and terpenes. However, they did not find any practical application, due to high cost of the catalysts and their low activity and stability.

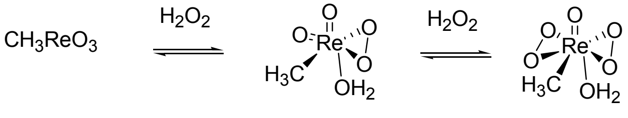
4. Rhenium Catalyzed Epoxidations

The use of rhenium-based systems for the epoxidation of alkenes has increased considerably during the last 10 years.[17,18,19,20,21]

4.1. METHYLTRIOXORHENIUM (MTO): AN EFFICIENT EPOXIDATION CATALYST

The first major breakthrough came in 1991 when Herrmann introduced methyltrioxorhenium (MTO) as a powerful catalyst for alkene epoxidation, using hydrogen peroxide as the terminal oxidant.[22] This organometallic rhenium compound, now commercially available, was first detected by Beattie and Jones in 1979, produced in tiny amounts from the reaction of $(CH_3)_4ReO$ with air.[23] The high solubility of MTO in virtually any solvent from pentane to water makes this compound particularly attractive for catalytic applications.

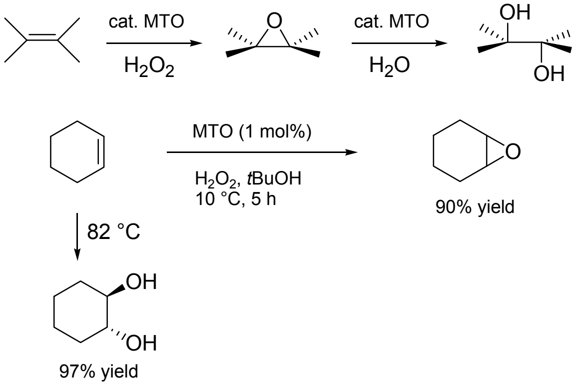
MTO activates hydrogen peroxide by forming a mono-peroxo complex which undergoes further reaction to yield a bis-peroxorhenium complex. Both complexes are active as oxygen transfer species (Scheme 6).



Scheme 6. Hydrogen peroxide activation by methyltrioxorhenium

The formation of these species, both of which probably coordinate a water molecule, is evident from the appearance of an intense yellow color of the solution. The bis-peroxorhenium complex is the most stable species. The protons of the coordinated water molecule are highly acidic, with consequences for the epoxidation reactions.

In the original report on alkene epoxidation using MTO, Herrmann and coworkers employed as the terminal oxidant a solution of hydrogen peroxide in *tert*-butanol, prepared by mixing *tert*-butanol and aqueous hydrogen peroxide followed by the addition of anhydrous $MgSO_4$. After filtration, this essentially water-free solution of hydrogen peroxide was used in epoxidation reactions. Epoxidation of various alkenes using 0.1–1 mol% of MTO and the H_2O_2/*t*BuOH solution generally resulted in high conversion into the corresponding epoxides, but a significant amount of trans 1,2-diol was often formed via ring opening of the epoxide (Scheme 7).[22]



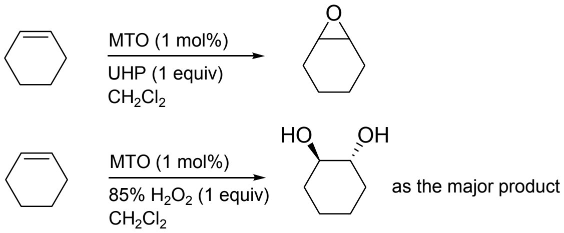
Scheme 7. Epoxidation of alkenes using MTO catalyst

4.2. UREA HYDROGEN PEROXIDE AS STOICHIOMETRIC OXIDANT

In the attempt to overcome this problem, Adam introduced the urea/ hydrogen peroxide (UHP) adduct as the terminal oxidant for the MTO catalyzed epoxidation of alkenes.[24] This resulted in substantially better selectivity for several olefins, although substrates leading to highly sensitive epoxides still suffered from deleterious ring opening reactions (Scheme 8).

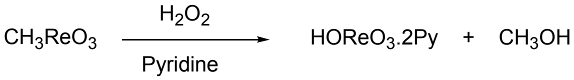
4.3. EFFECT OF LIGANDS

A major progress in the use of MTO as an epoxidation catalyst was made in 1996, when Sharpless and coworkers reported the use of sub-stoichiometric amounts of pyridine as co-catalyst in the system.[25] Use of dichloromethane instead of *tert*-butanol and introduction of 12 mol% of pyridine allowed the



Scheme 8. Epoxidation of alkenes using MTO catalyst in the presence of Pyridine

synthesis of even very sensitive epoxides using aqueous hydrogen peroxide as the terminal oxidant. However, MTO decomposition to catalytically inert perrhenate and methanol is favoured by a basic medium, such as the presence of pyridine in combination with hydrogen peroxide (Scheme 9).



$$CH_3ReO_3 \xrightarrow[\text{Pyridine}]{H_2O_2} HOReO_3.2Py + CH_3OH$$

Scheme 9. Decomposition of MTO catalyst under basic conditions

Thus, the addition of pyridine led to certain improvement in terms of rate and selectivity for epoxide formation, at the expense of catalyst lifetime. This turned out to be a minor problem for highly reactive substrates such as tetra-, tri- and *cis*-di-substituted alkenes, but not for less electron rich substrates such as terminal alkenes. Using the pyridine (12 mol%) conditions did not fully convert either 1-decene or styrene even after prolonged reaction times.

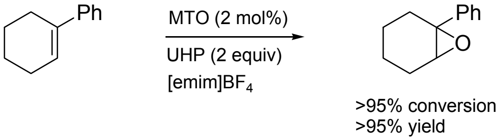
An improvement in epoxidation of terminal alkenes came upon changing pyridine with the less-basic 3-cyanopyridine.[26] This additive allowed also the epoxidation of *trans*-disubstituted alkenes, which showed reluctant to oxidation using the parent pyridine system.[27] In this reactions the amount of catalyst was reduced to 0.2–0.3 mol% with only 1–2 mol% of 3-cyanopyridine added. Herrmann and co-workers proposed an improvement to the Sharpless system by employing pyrazole as an additive.[28] Pyrazole is a less basic heterocycle compared to pyridine ($pK_a = 2.5$ *vs* $pK_a = 5.4$) and it is perhaps the most effective for the majority of alkenes, although for certain labile compounds pyridine would be the preferred additive.

4.4. THE SEARCH FOR GREENER SOLVENTS: MTO IN IONIC LIQUIDS

The high solubility of the MTO catalyst in practivally any solvent broadens the spectrum of reaction media to be considered for performing epoxidations. The most commonly used solvent, however, is still dichloromethane.

From an environmental point of view this is not certainly the best choice in large scale epoxidations.

The use of non-volatile ionic liquids as environmentally benign solvents has received significant attention recently. Abu-Omar and coworkers developed an efficient MTO-catalyzed epoxidation protocol using 1-ethyl-3-methylimidazolium tetrafuoroborate, [emim]BF_4, as the solvent and ureahydrogen peroxide (UHP) as the terminal oxidant.[29,30] Employing these essentially water-free conditions, high conversions and good epoxide-selectivity were obtained for the epoxidation of variously substituted alkenes, even with those affording very acid sensitive epoxides such as 1-phenyl cyclohexene (Scheme 10).

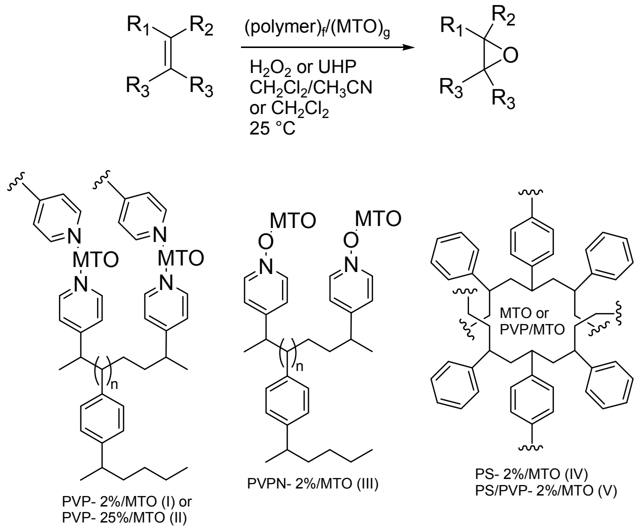


Scheme 10. Epoxidation of alkenes using MTO catalyst in the presence of ureahydrogen peroxide in ionic liquids

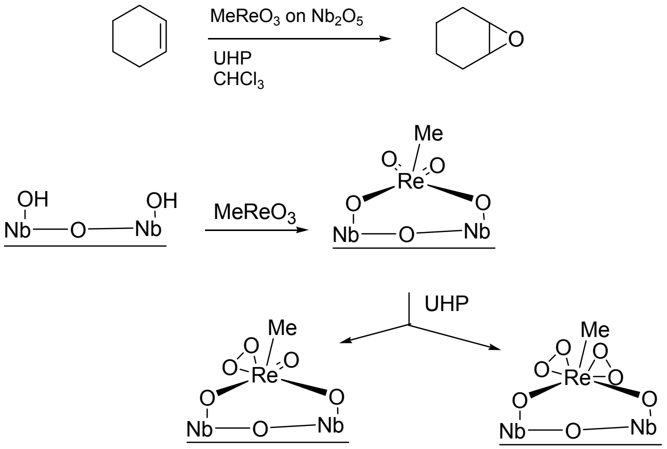
4.5. HETEROGENEIZED MTO

The immobilization of catalysts or catalyst precursors on solid supports is a common technique for simplifying reaction procedures and/or increasing the stability of the catalyst. The homogeneous MTO catalyst can be transformed into a heterogeneous system in a number of different ways. In a recent approach by Saladino and coworkers, poly(4-vinylpyridine) and poly(4-vinylpyridine) *N*-oxides were used as the catalyst carrier.[31] The MTO-catalyst obtained from 25% cross-linked poly(4-vinylpyridine) with divinylbenzene proved to catalyze efficiently the formation of even hydrolytically sensitive epoxides in the presence of aqueous hydrogen peroxide (Scheme 11). The catalyst could be recycled up to 5 times without any significant loss of activity.

Recently, Bouh and Espenson reported that MTO supported on niobia catalyzed the epoxidation of various fatty oils using UHP as the terminal oxidant (Scheme 12).[32] Oleic acid, linoleic acid and linolenic acid were all epoxidized in high yields (80–100%) within less than 2 h. Moreover, the catalyst could be recycled and reused without any loss of activity.



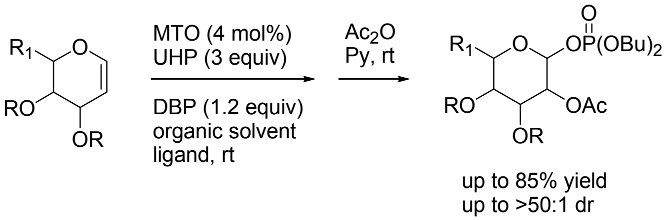
Scheme 11. MTO catalyst immobilized on solid supports



Scheme 12. Epoxidation catalysis performed by niobia-supported MTO

4.6. DOMINO MTO-CATALYZED EPOXIDATION-NUCLEOPHILIC RING OPENING OF GLYCALS

Epoxidation of glycals affords labile and unstable epoxides, but in the presence of suitable nucleophiles interesting sugar derivatives could be obtained.[33] The MTO-catalyzed domino epoxidation-methanolysis of glycals afforded the corresponding methyl glycosides in high yields and good diastereoselectivities. Heterogeneized MTO was also used successfully for this reaction.[34] In the presence of dibutylphosphate (DBP) as nucleophile, valuable glycosylphosphates were formed (Scheme 13). In this reaction the effect of added ligands was remarkable. Indeed, introduction of sub-stoichiometric amounts of pyridine or imidazole resulted in acceleration of the reaction and improvement of epoxidation selectivities.[35]

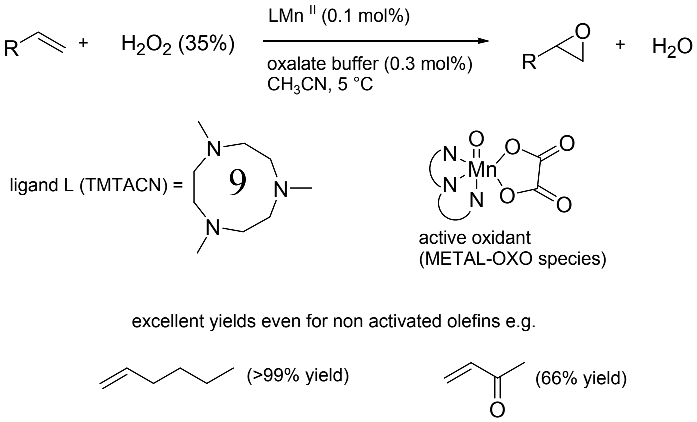


Scheme 13. MTO-catalyzed epoxidation-methanolysis of glycals

5. Manganese Catalyzed Epoxidations

Another metal which is known to activate peroxide in nature is manganese.

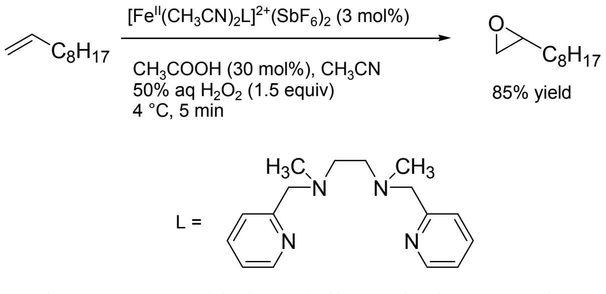
Indeed, the interest in using manganese complex as catalysts for the epoxidation of alkenes comes from biologically relevant oxidations with manganese porphyrins. In contrast to the other systems based on peroxometal species, manganese based catalysts probably involve an oxomanganese (V) complex as the active oxidant. Apart from porphyrin and salen catalysts, manganese complexes of *N*-alkylated 1,4,7-triazacyclononane (e.g., TMTACN), have been found to catalyze the epoxidation of alkenes efficiently in the presence of acid additives (tipically oxalic acid) and hydrogen peroxide (Scheme 14).[36] Reactions performed without any acid required a huge excess of hydrogen peroxide for efficient epoxidation. This method is environmentally friendly since the solvent is acetonitrile and not a chlorinated hydrocarbon.



Scheme 14. Epoxidation of alkenes by manganese complexes

6. Iron Catalyzed Epoxidations

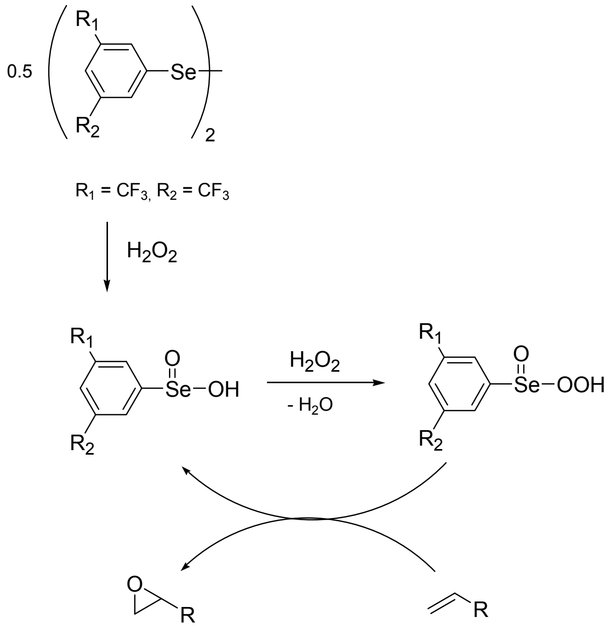
Iron is known to decompose hydrogen peroxide very efficiently (catalase activity). Consequently, the reports on efficient epoxidation with hydrogen peroxide are limited. Recently, a family of biomimetic non-heme iron complexes containing a tetradentate amine core was identified. Jacobsen described a high yielding conversion of olefins to epoxides, using 3 mol% of the iron catalyst, up to 30 mol% acetic acid and only 1.5 equiv of 50% hydrogen peroxide (Scheme 15).[37] For a variety of substituted as well as terminal alkenes, complete conversion of the alkene was obtained leading to 77–85% isolated yields. Acetic acid was essential to obtain high epoxide yields.



Scheme 15. Epoxidation of alkenes by iron complexes

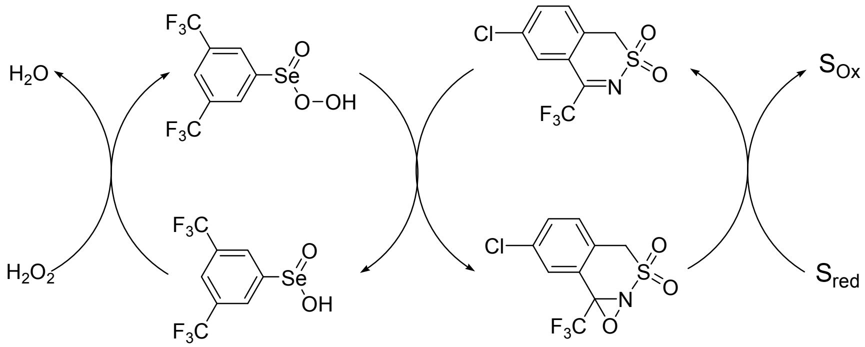
7. Selenium Catalyzed Epoxidations

Another class of catalysts that are able to activate hydrogen peroxide is based on organic derivatives of borderline elements, such as arsenic and selenium. Arylseleninic acids are well known to react, without any additional catalyst, with hydrogen peroxide to form the corresponding peracids.[38] Arends, Sheldon and coworkers recently investigated a range of substituted benzeneseleninic acids in epoxidations with hydrogen peroxide using 2,2,2-trifluoroethanol (excellent solvent for eletrophilic oxidations requiring polar, non coordinating solvents) as the solvent.[39] They found that with 3,5-bis(trifluoromethyl)benzeneseleninic acid as the catalyst, even sensitive epoxides could be formed in nearly quantitative yields. Reaction times varied from 0.5 h for substituted olefins to 4 h for terminal non-activated olefins. The starting compound is bis(3,5-bis(trifluoromethyl)phenyl)-diselenide, which forms in situ the seleninic acid (Scheme 16).



Scheme 16. Epoxidation of alkenes promoted by arylselenic acids and H_2O_2

Recently, 3,5-bis(trifluoromethyl)benzeneseleninic acid has been used in a tandem catalytic epoxidation.[40] The concept of tandem catalysis has been applied to oxidation reactions by Bäckvall and co-workers for the direct dihydroxylation of olefins using a couple catalytic system and hydrogen peroxide as the terminal oxidant.[41] In this context, the seleninic acid was used in combination with a trifluoromethyl oxaziridine catalyst (Scheme 17), using urea hydrogen peroxide as the terminal oxidant.[40] This system showed



Scheme 17. Tandem-catalysis by seleninic acid and trifluoromethyl oxaziridine

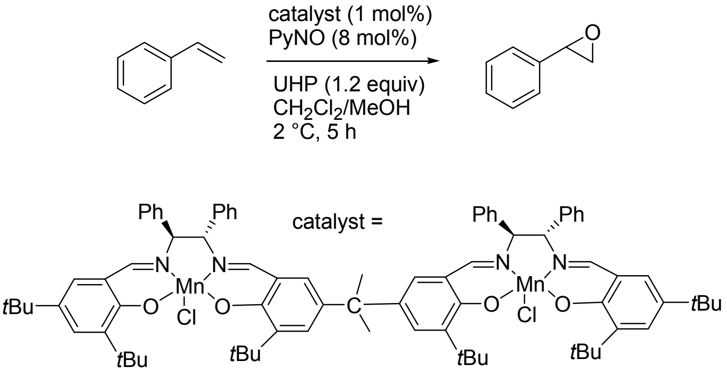
broad scope, being extremely efficient in epoxidation of internal, terminal, and even electron poor alkenes. Moreover, it was successful in Bayer-Villiger oxidation and in the oxidation of unactivated C-H bonds.

8. Asymmetric Epoxidations

Asymmetric epoxidation of alkenes is an extremely important and challenging target, since there is still no reliable and general method for converting simple alkenes into epoxides with good enantioselectivity. In particular, the asymmetric epoxidation of terminal nonactivated olefins remains an area to be developed. In terms of environmental impact, the challenge is to develop catalysts able to perform asymmetric epoxidations with a wider scope using H_2O_2 as oxidant.[42]

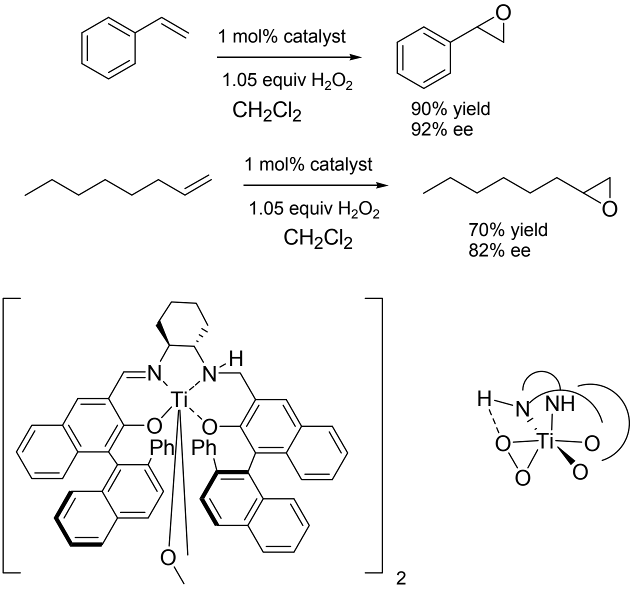
Some efforts were made in order to obtain good enantioselectivities in the epoxidation of simple olefins using methyltrioxorhenium (MTO), urea hydrogen peroxide (UHP) and six different chiral non racemic 2-substituted pyridine ligands, some of which are novel.[43] UHP was chosen as the hydrogen peroxide source in order to avoid unfavourable competition from water for vacant sites on the metal. However, poor enantioselectivity was reached (3–12% ee).

Complete conversions and good enantiomeric excesses (64–100%) were achieved in the asymmetric epoxidation of chromenes and indene using UHP as oxidant and a novel dimeric homochiral Mn(III) Schiff base as catalyst. The reactions were carried out in the presence of carboxylate salts and nitrogen and oxygen coordinating co-catalysts. However, the epoxidation of styrene unfortunately proceeded with incomplete conversion and only 23% ee. Modification of the catalyst and use of pyridine *N*-oxide as cocatalyst allowed improvement of the ee to 61% (Scheme 18).[44]



Scheme 18. Asymmetric oxidation of styrene promoted by manganese catalyst

Recent independent studies form Katsuki[45,46] and Beller[47] groups have changed the state of the art in the area of metal-catalyzed asymmetric epoxidations. They established, respectively, that Ti- and Ru- based com-plexes can be used for asymmetric epoxidation with H_2O_2.

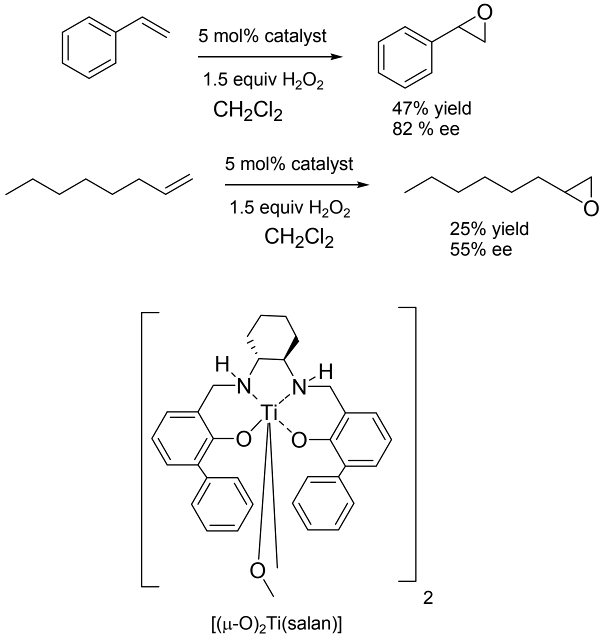


[(μ-O)$_2$Ti(salalen)]

Scheme 19. Proposed structure of a peroxotitanium catalysis intermediate

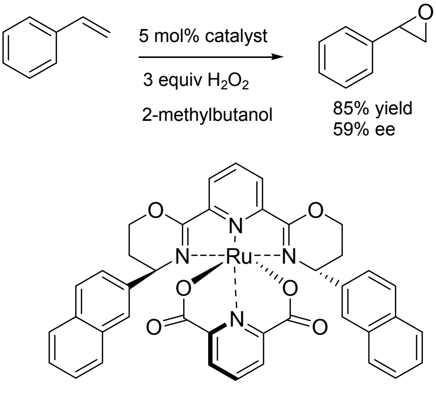
For the titanium catalyzed epoxidation, only 1 mol% of catalyst and 1.05 equiv. of H_2O_2 are required to obtain high yields and selectivities. Not only activated olefins gave excellent results, but also for simple styrene a 93% ee can be achieved by using this chiral titanium complex.[45] It was speculated that this peroxotitanium species is activated by an intramolecular hydrogen bond with the amine proton (Scheme 19).

Katsuki and co-workers later designed another similar catalyst, which was less robust (5 mol% required) and less selective than the previous one, but its ease of synthesis and tunability offer a major advantage (Scheme 20).[46]



Scheme 20. Asymmetric oxidation of styrene promoted by titanium catalyst

Finally, Beller and coworkers introduced a new approach towards the optimisation of activity and selectivity in Ru-catalyzed asymmetric epoxidations. Their catalysts contained pyridine dicarboxylate (pydic) as the second ligand. Although excellent results (e.g., 85% yield and 59% ee for styrene) were obtained using 5 mol% of catalyst, the authors reported that a similar level of efficiency could be achieved with only 0.5 mol% of catalyst (Scheme 21).[48]



Scheme 21. Pyridine-dicarboxilate-based ruthenium catalyst

9. Conclusions

Hydrogen peroxide has proved to be an ideal reagent for green oxidation processes, being highly efficient and selective upon activation by transition metal derivatives. In this review, its properties have been exemplified highlighting the recently developed processes for epoxidation of alkenes, either in the field of homogeneous and heterogeneous catalysis. Recent findings in enantioselective epoxidation of simple unfunctionalized alkenes have also been addressed. Research in these fields continues to be very active and additional innovative applications are expected. Major progresses in application of catalyzed hydrogen peroxide oxidations of organic compounds in industrial processes will be surely achieved, based on the newly discovered reactions and pushed by alternative and less expensive processes currently under study for the industrial production of H_2O_2.

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DIMETHYL CARBONATE: GREEN SOLVENT AND AMBIDENT REAGENT

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Abstract: DMC is a versatile compound which represents an attractive eco-friendly alternative to both methyl halides (or dimethyl sulfate) and phosgene for methylation and carbonylation processes, respectively. DMC, produced nowadays by a clean process, possesses properties of no toxicity and biodegradability which makes it a true green reagent to be used in syntheses that prevent pollution at the source. The reactivity of DMC is tunable: at $T \leq 90°C$, methoxycarbonylations take place, while at higher reaction temperatures, methylation reactions are observed with a variety of nucleophiles. Besides, DMC-mediated methylations are catalytic reactions which use safe solids (alkaline carbonates) avoiding the formation of undesirable inorganic salts as by-products. The high selectivity in methylation reactions is due to the ambident electrophilic character of DMC which reacts on its hard centre (the carbonyl group) with harder nucleophiles and on its soft one (the methyl group) with softer nucleophiles, according to the Hard-Soft Acid and Base (HSAB) theory.

Keywords: Dimethylcarbonate, Hard-Soft Reactivity, Green Chemistry

P. Tundo and V. Esposito (eds.), *Green Chemical Reactions.*

1. Introduction

Green chemistry was introduced with the aim to overcome health and environmental problems at the source by developing cleaner chemical processes for chemical industry through the design of innovative and environmentally benign chemical reactions. However this approach started to take hold only in the last two decades as a consequence of a combination of factors, including economic, regulatory, scientific, and even social factors. Each of these incentives has combined to make the 1990s the period during which green chemistry was introduced and has found implementtation and commercialization on a wide industrial scale.

Green organic syntheses[1] must include, if not all, at least some of the following requirements: avoid waste,[2] be atom efficient,[3] avoid the use and production of toxic and dangerous chemicals, produce compounds that perform better or as well as the existing ones, and are biodegradable, avoid auxiliary substances (e.g. solvents) or use eco-compatible solvents (water or dense CO_2), reduce energy requirements, use renewable materials, and use catalysts rather than stoichiometric reagents.[4]

In particular it is important to find a replacement for toxic and dangerous reagents produced by eco-unfriendly processes and that are responsible for producing expensive-to-dispose-of inorganic salts. Methyl halides (CH_3X, X = I, Br, Cl), dimethylsulfate (DMS), and phosgene ($COCl_2$) are a representative examples of undesirable reagents used for methylation and carboxymethylation reactions. All these reagents are toxic and corrosive chemicals. Moreover the reaction requires a stoichiometric amount of a base as catalyst and produces a stoichiometric amount of inorganic salts that need to be disposed of.

Dimethylcarbonate (DMC) is an environmentally benign substitute for dimethyl sulphate and methyl halides since it is a well-known non-toxic reagent as compared to other carboxylating or alkylating agents (phosgene and methyl halides, respectively). Besides DMC does not produce inorganic salts. In fact, the leaving group, methyl carbonate, decomposes giving as by products only methanol and CO_2.

2. Properties of DMC

DMC is classified as a flammable liquid, smells like methanol and does not have irritating or mutagenic effects either by contact or inhalation. Therefore, it can be handled safely without the special precautions required for the poisonous and mutagenic methyl halides and DMS, and extremely toxic phosgene.

DMC has been produced for long time from phosgene and methanol. In this synthesis HCl was an unwanted side product (Scheme 1).

$$2CH_3OH + COCl_2 \longrightarrow CH_3OCOOCH_3 + 2HCl$$

Scheme 1. Synthesis of DMC by phosgene

However since the middle eighties DMC is no longer produced from phosgene, but by oxidative carbonylation of methanol with oxygen through a process developed by Enichem (Italy)[5,6]:

$$2CH_3OH + 1/_2O_2 + CO \xrightarrow{\text{Cu salt}} CH_3OCOOCH_3 + H_2O$$

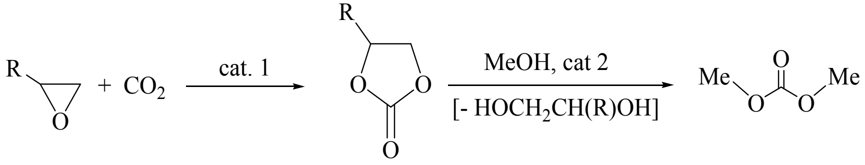
Scheme 2. Enichem synthesis of DMC[5a]

The most relevant features of this process are:

- low-cost and widely available raw materials with low toxicity;
- high production rates;
- non-toxic and easy disposable by-products (carbon dioxide and water)
- high quality product.

The new technology does not produce any by-products that are difficult to dispose of. The DMC obtained has also low toxicity and ecotoxicity (biodegradability >90% at 28 days OECD 301C; acute toxicity for fish; no effect at 1000 mg/l OECD 203).

Another industrial procedure developed and recently industrialized in China is the cleavage of cyclic carbonates (Scheme 3). Importantly, this synthesis doesn't use any chlorine.[7]



Scheme 3. Insertion of CO_2 to epoxides and cleavage of cyclic carbonates. Step 1. Catalyst: MgO, CaO. Step 2. Catalyst: zeolites exchanged with alkali and/or earth metal ions. R = H and CH_3

3. Reactivity of Dimethylcarbonates According to the Hard-Soft Acid Base Theory

DMC is a well-known non-toxic reagent showing three main green chemistry features[8] as compared to other carboxylating or alkylating agents (phosgene and methyl halides, respectively):[9]

1. DMC does not produce inorganic salts in either acylation[10] (eq. 1) or alkylation[11] (eq. 2) reactions:

$$\mathrm{Nu^- + CH_3OCOOCH_3 \rightleftharpoons NuCOOCH_3 + CH_3O^-} \quad (1)$$

$$\mathrm{Nu^- + CH_3OCOOCH_3 \longrightarrow NuCH_3 + CH_3OCOO^-} \quad (2)$$

$$\mathrm{CH_3OCOO^- \longrightarrow CH_3O^- + CO_2} \quad (3)$$

   In fact, since the leaving group, methyl carbonate, decomposes (reaction 3), the base is restored and can be used in truly catalytic amounts. This feature allows utilization of continuous-flow (c-f) procedures (i.e. gas-liquid phase-transfer catalysis, GL PTC,[12] and continuously stirred tank reactor, CSTR[13]).

2. Since reaction 1 is an equilibrium and reaction 2 is not, the product of the process can be controlled, temperature being the key factor. In fact, because methylation reactions involve higher Gibbs activation energies, low temperatures allow carboxymethylation, whereas high temperatures give methylation derivatives.[14] Moreover, also operating at 200–250°C, decomposition and polymerization products or tars are not formed and usually clear reaction mixtures are obtained.

3. DMC has a very selective behaviour reacting with different nuclephiles (such as amines, CH_2 acidic compounds phenols etc.) acting as alkylating or carboxymethylating agent. This different reactivity of DMC with different nucleophiles may be rationalized by the Hard-Soft Acid and Base (HSAB) theory. Ralph Pearson introduced the Hard-Soft Acid-Basic (HSAB) theory in early 1963[15,16] as an attempt to unify inorganic and organic reactions. The principles of the HSAB theory were further developed by Mèndez,[17] and by Klopman.[18,19] According to the proposed theory hard nucleophiles preferably react with hard electrophiles and viceversa.[20] DMC, as electrophile, has three reactive centers that can interact with nucleophiles: the carbonyl, and two methyl groups (Figure 1). Such centers can be classified according to the HSBA principle: the

carbonyl group is the harder electrophile, as a result of its polarized positive charge and sp2 hybridization; the two methyl groups represent softer electrophiles, thanks to their sp3 orbital and their saturated carbon atom.

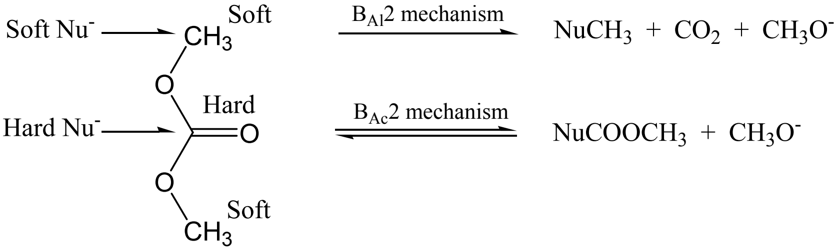


Figure 1. Hard and soft centres in the molecule of DMC.

Many ambident nucleophiles are known, but few ambident electrophiles have been studied. Many investigations verified the compliance of reactivity of ambident nucleophiles and electrophiles with the HSAB theory. Among the ambident electrophiles we can mention esters and particularly propiolactones,[21a-d] α,β-unsaturated carbonyls,[22] 3-chloro-1,2-benzoisothiazol,[23] and tricholocarbonates.[24] Actually, also alkyl halides are included among the ambident electrophiles, as they react with nucleophiles, yielding either products of substitution reactions (soft-soft reaction) or alkenes (hard-hard interaction).[25] By this regard, the reaction of 2-bromoethylarenes with different phenoxide anions is relevant: it yields different mixtures of ethers and alkenes, according to the nucleophilic nature of the anion species which can modulate the reaction outcome.[26] Here the reactivity of some soft/hard mono and bidentate nucleophiles with DMC is compared: nucleophiles at nitrogen, oxygen, and sulphur are considered. According to their nature, nucleophiles can discriminate between the carbon atoms of DMC. Some reactions have been already observed, while others are here reported for the first time.

3.1. REACTIVITY OF DIMETHYLCARBONATE WITH DIFFERENT NUCLEOPHILES

3.1.1. *Nucleophiles containing an acidic CH_2 moiety*

The reaction of CH_2 acidic compounds (such as arylacetonitriles, aryl acetates, aryloxyacetic esters, sulfones, sulfoxides, and lactones)[27] with DMC is highly selective, as it yields the sole monomethyl derivative. Regardless of the high temperature and the great excess of alkylating agent (DMC is also the solvent of the reactions), at complete conversion of the substrate selectivity for the monomethylated product is often >99%. Table 1 reports the selectivity in the monomethylation of some CH_2 acidic compounds.

TABLE 1. Monomethylation of several CH_2 acidic compounds (from ref. 27a).

Entry	**Substrate**	**T (°C)**	**Product**	**Conversion**	**Selectivity**[a]
1	$PhCH_2SO_2Me$	200	$PhCH(Me)SO_2Me$	98	100
2	$PhOCH_2COOH$	200	PhOCH(Me)COOMe	100	96
3	$PhCH_2CN$ (GL-PTC)	180	PhCH(Me)CN	98	99
4	$PhCH_2CN$ (batch)	180	PhCH(Me)CN	100	99.5

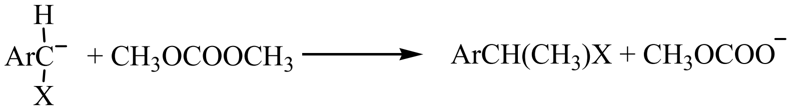
[a] Selectivity is defined as monomethylated products/(monomethylated product + dimethylated product) x 100

Scheme 4, for example, refers to monoalkylation of nitriles, esters, and sulfones. This reaction has an industrial relevance, since $ArCH(CH_3)COOH$ are well know anti-inflammatory agents.[27a]

$$ArCH_2X + CH_3OCOOCH_3 \xrightarrow[180\ °C]{K_2CO_3} ArCH(CH_3)X + CO_2 + CH_3OH$$

Scheme 4. Monoalkylation of nitriles, esters and sulfones, X = CN, $COOCH_3$, SO_2R, SO_2Ar

The reasons for the selectivity in monomethylation of these compounds are not immediately evident. Isolation of intermediates and a detailed kinetic study showed that the reaction mechanism does not imply a simple nucleophilic substitution (eq 4).[14,27a]

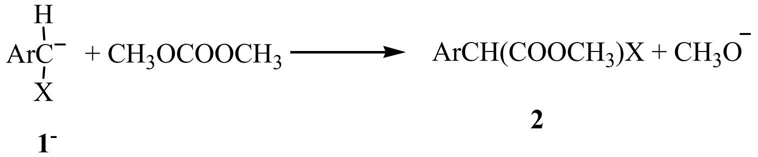


$$Ar\overset{H}{\underset{X}{C}}{}^{-} + CH_3OCOOCH_3 \longrightarrow ArCH(CH_3)X + CH_3OCOO^{-} \quad (4)$$

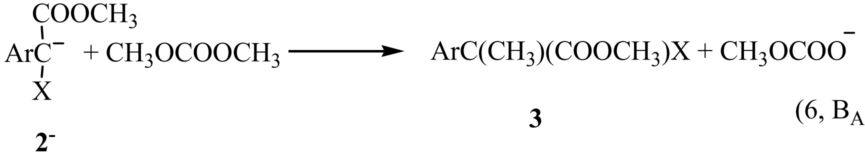
4

1⁻

In fact, monomethylation derives from an unusual reaction pathway that involves the reactivity of anion **1**⁻ and anion **2**⁻, according to two consecutive nucleophilic displacements: the first one follows a $B_{Ac}2$ mechanism, while the second occurs through a $B_{Al}2$ mechanism (eqs. 5 and 6, respectively):



$$\underset{\mathbf{1^-}}{\mathrm{Ar}\overset{\mathrm{H}}{\underset{\mathrm{X}}{\mathrm{C}^-}}} + CH_3OCOOCH_3 \longrightarrow \underset{\mathbf{2}}{ArCH(COOCH_3)X} + CH_3O^- \qquad (5, B_{Ac}2)$$



$$\underset{\mathbf{2^-}}{\mathrm{Ar}\overset{\mathrm{COOCH_3}}{\underset{\mathrm{X}}{\mathrm{C}^-}}} + CH_3OCOOCH_3 \longrightarrow \underset{\mathbf{3}}{ArC(CH_3)(COOCH_3)X} + CH_3OCOO^- \qquad (6, B_{Al}2)$$

Accordingly, **4** is produced through a series of consecutive pathways, all of them being very selective.

Scheme 5 accounts for such a behaviour: the reaction proceeds through the carboxymethylation specie **2**, which afterward reacts with the methyl of DMC.

In summary, while anion $ArCH^-X$ does not give $ArC(CH_3)_2X$, also anion $ArC^-(COOCH_3)X$ does not allow the formation of $ArC(COOCH_3)_2X$.

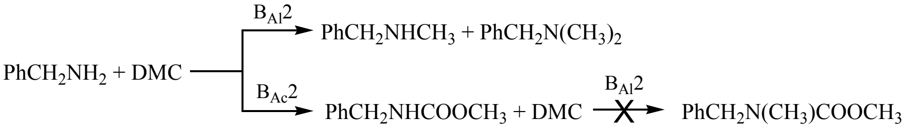
$$\begin{array}{rcl}
ArCH_2X + B & \rightleftharpoons & \underset{\mathbf{1^-}}{Ar\overset{-}{C}HX} + \overset{+}{BH} \\
\underset{\mathbf{1^-}}{Ar\overset{-}{C}HX} + CH_3OCOOCH_3 & \rightleftharpoons & \underset{\mathbf{2}}{ArCH(COOCH_3)X} + CH_3O^- \\
\overset{+}{BH} + CH_3\overset{-}{O} & \rightleftharpoons & CH_3OH \\
\underset{\mathbf{2}}{ArCH(COOCH_3)X} + B & \rightleftharpoons & \underset{\mathbf{2^-}}{Ar\overset{-}{C}(COOMe)X} + \overset{+}{BH} \\
\underset{\mathbf{2^-}}{Ar\overset{-}{C}(COOMe)X} + CH_3OCOOCH_3 & \longrightarrow & \underset{\mathbf{3}}{ArC(CH_3)(COOCH_3)X} + CO_2 + CH_3O^- \\
\underset{\mathbf{3}}{ArC(CH_3)(COOCH_3)X} + CH_3O^- & \rightleftharpoons & \underset{\mathbf{4^-}}{Ar\overset{-}{C}(CH_3)X} + CH_3OCOOCH_3 \\
\underset{\mathbf{4^-}}{Ar\overset{-}{C}(CH_3)X} + \overset{+}{BH} & \rightleftharpoons & \underset{\mathbf{4}}{ArCH(CH_3)X} + B \\
\hline
ArCH_2 + CH_3OCOOCH_3 & \longrightarrow & ArCH(CH_3)X + CO_2 + CH_3OH
\end{array}$$

Scheme 5. Reaction pathway for the monomethylation of CH_2 acidic compounds with DMC

We can assert that anions $\mathbf{1}^-$ and $\mathbf{2}^-$ give different compounds since they have different soft/hard character. Their difference in hardness provides a reason for the discrimination observed between the two electrophilic centers of DMC. The hard nucleophile $\mathbf{1}^-$ attacks only the carbonyl of DMC (eq. 5), while the anion of the product $\mathbf{2}^-$ is a softer nucleophile thus it selectively produces the methyl derivative (eq. 6). The change in hardness/softness of the anion, due to the presence of the carboxymethyl group, is enough to significantly alter the reactivity of the DMC molecule. The combination of the dual electrophilic character of DMC with its reaction products allows two consecutive steps to occur in a selective way both in the reaction sequence and yield: first the hard-hard reaction occurs and produces only a soft anion; then a soft-soft nucleophilic displacement leads to the final product. Since hard-soft and soft-hard interactions are inhibited, neither double methylation nor double carboxymethylation take place.

3.1.2. *Nitrogen nucleophiles*

In the absence of a base, aliphatic amines such as benzylamine react with DMC to give both alkylation and carboxymethylation products, without any selectivity (entry 1, Table 2 and Scheme 6); both $B_{Ac}2$ and $B_{Al}2$ mechanisms are followed, demonstrating an intermediate character of amine nitrogen towards DMC, in terms of hardness and softness.



Scheme 6. Reaction of benzylamine with DMC in the absence of a base

Strong bases, such as potassium *tert*-butylate or sodium methoxide, catalyse the reaction of carboxymethylation of aliphatic and aromatic amines at 90°C.

In fact, it is well-known that bases significantly accelerate aminolysis and transamination reactions. Bunnett[28] suggested that the direct participation of a base was the reason for the enhanced reactivity of nitrogen nucleophiles with the carbonyl. In accordance with other authors,[29] naked RNH^- is excluded from the mechanism; it looks like the role of the base is that of removing H^+ from protonated nitrogen during or after the attack, increasing in any case the negative charge on nitrogen atom. Whatever the exact mechanism may be, the presence of a base enhances the hardness of the nucleophile. So, the reactivity with harder electrophiles (the carbonyl in this case) is raised and aminolysis reactions are highly favoured. DMC represents a valid model molecule; its reactivity can explain the competition between the harder RNH^- (more or less naked) and the softer RNH_2, through the HSAB theory. The behaviour of amines in the presence and in the absence of a base reported in Table 2 confirms that since the hardness of the nucleophile is increased while operating in the presence of a base, the $B_{Ac}2$ rate is dramatically accelerated and carboxymethyl derivatives are selectively obtained. Once formed, the urethanes need the presence of a base to further react with DMC. In these conditions, their RN^-COOCH_3 anions, softer nucleophiles than RNH^-, undergo solely $B_{Al}2$ reactions. This was proved by the fact that no $RN(COOCH_3)_2$ products, deriving from a $B_{Ac}2$ reaction mechanism, were never observed.

With aliphatic amines high yields of carbamates occur quantitatively in few minutes (entries 2 and 7, Table 2). Then, if the reaction is protracted, the already formed carbamates react again with DMC to give the corresponding *N*-methyl derivative (entries 3 and 8, Table 2). Scheme 7 outlines this behaviour.

TABLE 2. Reaction of amines with DMC in the presence and absence of bases[a] (from ref. 30b).

Entry	**Amine**	**Base**	**Time**	**MNM**[b]	**DNM**[b]	**CARB**[b]	**NMC**[b]
1	Benzylamine	-	360	12	6	4	-
2	Benzylamine	$(CH_3)_3COK$	1	-	-	100	-
3	Benzylamine	$(CH_3)_3COK$	30	-	-	32	68
4	Aniline	-	360	-	-	-	-
5	Aniline	$(CH_3)_3COK$	1	-	-	100	-
6	Aniline	$(CH_3)_3COK$	180	-	-	60	40
7	1-decylamine	$(CH_3)_3COK$	1	-	-	100	-
8	1-decylamine	$(CH_3)_3COK$	60	-	-	56	44

[a] DMC reflux temperature, 90°C, molar ratio amine/DMC/base 1.0/40/1.2; MNM = mono-N-methylation; DNM = di N-methylation; CARB = Carbamate; NMC = N-methyl carbamate.

[b] values reported as percentage.

$$PhCH_2NH_2 + DMC \xrightleftharpoons{\text{base}} PhCH_2NHCOOCH_3 + CH_3OH$$

$$PhCH_2NHCOOCH_3 + DMC \xrightarrow{\text{base}} PhCH_2N(CH_3)COOCH_3 + CO_2 + CH_3OH$$

Scheme 7. Reaction of benzylamine with DMC in the presence of a base

Due to the lower nucleophilicity aromatic amines are less reactive, as in the absence of a base they do not react at the reflux temperature of DMC at 90°C (aniline, entry 4, Table 2). For example aniline was reacted in the absence of a base at 200°C in an autoclave using DMC as solvent; after 24 h the conversion was 61% without selectivity: 15% monomethylation product, 37% dimethylated product, and 9% carbamate were observed.[30] Aromatic amines in the presence of a base follow the behaviour of aliphatic ones reported in Scheme 7 even if the formation of *N*-methyl carbamate requires longer reaction time (entry 6, Table 2).

When weaker bases like potassium carbonate are used as catalysts, the reactions have to be carried out at high temperatures in an autoclave in order to achieve high conversion of the starting material. Table 3 shows results obtained with aromatic and aliphatic amines. Aliphatic amines, that are harder nucleophiles, give mainly the corresponding carbamates and methylcarbamates after 22 h, while aromatic amines react slower, and their softness is responsible for the formation of mono and dimethylated products.

TABLE 3. Reaction of amines with DMC in the presence of K_2CO_3 after 22h (from ref. 30 c).

Entry	Amine	MNM[b]	DNM[b]	CARB[b]	NMC[b]
1	Aniline	6.2	2.6	8.3	41.0
2	*p*-Chloroaniline	6.3	2.1	5.7	47.5
3	*p*-Anisidine	1.3	13.4	1.8	83.0
4	*n*-Octylamine	-	1.2	53.7	45.0
5	Phenethylamine	-	-	77.0	23.0

Conditions: T=180°C, molar ratio amine/DMC/base 1.0/40/3; MNM = mono-N-methylation; DNM = di N-methylation; CARB = Carbamate; NMC = N-methyl carbamate,[b] values reported as percentage.

In contrast, with K_2CO_3 as catalyst and under GL-PTC conditions at high temperature, monomethylation of aromatic amines occur selectively (Table 4).[5] It is well known that the role of P-T agent is to complex the alkaline metal cation thus enhancing the strength of the "naked anion".

TABLE 4. Reaction of aromatic amines with DMC under GL-PTC conditions[a] (from ref. 30d).

		Composition at the equilibrium of the reaction mixture				
Entry	**Amine**	**Amine[b]**	**MNM[b]**	**DNM[b]**	**CARB[b]**	**NMC[b]**
1	Aniline[c]	54.3	40.8	1.6	-	3.3
2	*o*-toluidine[d]	27.7	47.0	0.3	-	25.0
3	o-Chloroaniline[d]	14.6	62.7	-	-	22.7
4	p-Chloroaniline[c]	10.1	70.0	-	-	19.9

[a]Column V = 151 ml. filled with 95 g of K_2CO_3 coated with 5 wt% of PEG 6000, T = 180°C, Flow = 24 ml/h; [b]values reported as percentage; [c]molar ratio amine/DMC 1/4; [d]molar ratio amine/DMC 1/10;.

The reaction between DMC and amines to carbamates is of strong interest for the industrial field, mainly as they represent the first step of a non-phosgene route to the production of isocyanates, in fact isocyanates can be produced by thermal decomposition of carbamates, as reported in the general Scheme 8.

$$RNH_2 + DMC \overset{cat.}{\rightleftharpoons} RNHCOOCH_3 + CH_3OH$$

$$RNHCOOCH_3 \xrightarrow{\Delta} RNCO + CH_3OH$$

Scheme 8. Reactions of an amine to isocyanate.

In addition to the production of isocyanate without phosgene, carbamates themselves are relevant industrial products because they can be applied mainly in pharmaceutical and in crop protection sectors.

Strong efforts have been done by industrial companies in order to discover new processes and find suitable catalysts for the carboxymethylation of amines, in particular aromatic, with dialkylcarbonates. There are a lot of patents that report findings related to this topic, hereafter some of them are gathered.

In 1981 Bayer patented a process for the production of N,O-disubstituted carbamates (urethanes) by reacting primary aromatic amines with dialkylcarbonates in the presence of neutral or basic inorganic or organic compounds of lead, titanium, zinc or zirconium as catalysts.[31] Table 5 summarises some of the most interesting examples reported.

TABLE 5. Process for the synthesis of N,O–disubstituted urethanes (from ref. 31).

Entry	**Amine**	**Dialkyl carbonate**	**Catalyst**	**T (°C)**	**Time (h)**	**Yield of urethane (%)**
1	Aniline	DEC[a]	Ti tetra butylate	140	6	96
2	Aniline	DBC[b]	Zr tetra propylate	190	5	89
3	Aniline	DEC[a]	Pb acetate	135	6	96
4	Aniline	DEC[a]	Zn stearate	135	9	97

[a] Diethylcarbonate; [b]Dibutylcarbonate;

In the same year also DOW reported a process for preparing carbamates from an organic carbonate and an aromatic amine in the presence of catalytic quantities of compounds of Zn, Sn or Co salts of monovalent organic compounds having a pKa value of less than 2.8 and other compounds having more than one carbonyl group per molecule and oxides, sulfides and carbonates at a temperature of at least 200°C.[32-33] A wide screening of catalysts was reported in the examples, all carried out in autoclave. The best results for the carboxymethylation of aniline with DMC, in terms of carbamate selectivity, were achieved with zinc (naphthenate, pivalate, benzoate, acrylate, oxyacetate, acetate, propionate, carbonate) and tin catalysts (dibutyl tin dilaurate, dibutyltin oxide polymer, dibutyltin maleate).

Other suitable catalysts for the carboxymethylation of aromatic amines are zinc or copper carbamates. In 1997 it was patented a process[34] for the preparation of carbamates from an aromatic amine and DMC in the presence of N,N-substituted carbamate complexes of zinc and copper. Table 6 summarises results reported in some of the patent examples, high selectivity was reported with aniline, while with MDA a considerable amount of N-methyl derivatives was found.

TABLE 6. Process for the synthesis of aromatic urethanes (from ref. 34).

Entry	Amine	Catalyst	T (°C)	Time (h)	Conversion (%)	Selectivity to urethane (%)
1	Aniline	Zn diethyl-carbamate[b]	170	2	≥99	99
2	Aniline	Zn diethyl-carbamate[c]	130	11	96	98
3	MDA[a]	Zn diethyl-carbamate[c]	160	3	99	63
4	Aniline	Cu diisopropyl-carbamate[d]	170	12	98	95

[a] 4,4'-methylenedianiline; [b] amount 1.0% per mole of amine; [c] amount 1.5% per mole of amine; [d] amount 6.6% per mole of amine.

Another process for the synthesis of aromatic urethanes was obtained by reacting an organic carbonate, in particular DMC, with an aromatic diamine or polyamine in the presence of a Lewis acid catalyst[35]; the yield and selectivity is increased by a partial removal of the alcohol co-produced during the reaction. In Table 7 conditions and data found in some of the examples, carried out with Zn acetate dihydrate as catalyst, are reported. Diurethanes of MDA, 80/20 2,4/2,6 TDA and polymeric MDA (a mixture of MDA and MDA oligomers) are key intermediates as they can give by cracking the corresponding isocyanates MDI, TDI and polymeric MDI that are fundamental raw materials for the production of a wide range of polyurethanes.

TABLE 7. Process for the synthesis of aromatic urethanes (from ref. 35).

Entry	**Amine**	**$ZnAc.2H_2O$ (w% of amine)**	**T (°C)**	**Time (hours)**	**Conversion (%)**	**Selectivity to diurethanes (%)**
1	MDA[a]	4.0	140	1.5	≥99	97
2	TDA[b]	5.4	170	2.0	≥99	93
3	Polymeric MDA[e]	4.0	140	1.5	≥99	96

[a] 4,4'-methylenedianiline; [b]80/20 2,4/2,6 toluenediamine; [c] mixture of methylenedianiline and methylenedianiline oligomers.

Full processes for the preparation of aromatic isocyanates by DMC were also patented. In particular recently it was published a patent which claims an integrated process for the production of aromatic isocyanates without phosgene.[36] In the examples the various phases of the process are reported, starting form the reaction of the amine (TDA) with DMC to carbamate with zinc acetate dihydrate as catalyst, following a passivation treatment of the urethane catalytic residues and then pyrolysis of urethane in gas phase.

3.1.3. *Oxygen nucleophiles*

Alcohols give only transesterification products with DMC (Scheme 8), either under GL-PTC at 180°C or under batch conditions.[37]

$$\mathrm{ROH + DMC} \xrightleftharpoons{\mathrm{PEG,\ K_2CO_3}} \mathrm{ROCOOCH_3 + CH_3OH}$$

Scheme 9. Reaction of alcohol with DMC.

Also, operating at 200°C the reaction occurs at the carbonyl atom only. In fact, when 1-octanol was used in reactions with DMC in the presence of K_2CO_3,[38] no methyl ether was observed, but methyl octyl carbonate and dioctyl carbonate were the only products formed. Methylation of alcohols was reported to occur also operating in the presence of tertiary amines[39] (N,N'-dimethylamino-pyridine, 1,4-diazobicyclo[2,2,2]octane). In this case, however, the catalyst modifies the hard-soft character of the two centers, thus allowing the nucleophilic displacement by the alkoxide to occur.

p-Substituted phenols were used in reactions with DMC at its reflux temperature in the presence of K_2CO_3. Under such conditions the softer phenoxide anions could discriminate between the two centers of DMC and their substituent controlled the reaction outcome.

TABLE 8. Reaction of phenols with DMC in the presence of K_2CO_3[a] (from Ref. 30b).

Entry	**ArOH**	**% Conversion**	**% ArOMe**	**% ArOCOOMe**
1	p-Methoxyphenol	7.0	23	77
2	p-Cresol	36.3	39	61
3	Phenol	27.7	72	28
4	p-Chlorophenol	62.0	98	2
5	p-Cyanophenol[b]	100	100	-

[a] DMC reflux temperature, 90 °C; molar ratio phenol/DMC/K_2CO_3 1.0/40/1.2. Conversions after 53 h.

[b] 82% Conversion in the methylated derivate after 30 h.

Table 8 reports the results and clearly shows that phenoxides undergo nucleophilic substitution on either the methyl or the carbonyl group (Scheme 9). The substituent on the aromatic ring clearly influences the reactivity: softer phenoxide anions give S_N2 displacement only, while harder ones allow both $B_{Ac}2$ and $B_{Al}2$ reactions.

3.1.4. *Sulfur nucleophiles*

Aliphatic and aromatic thiols were reacted with DMC under comparable conditions: the results reported in Table 9 show that they produce only the methylated derivatives (Scheme 10): both 1-octanthiol and thiophenol (entry 2 and 3, Table 9) attack the methyl group.

$$\mathrm{ArOH + DMC \xrightarrow{K_2CO_3} ArOCH_3 + CO_2 + CH_3OH}$$

$$\mathrm{ArOH + DMC \overset{K_2CO_3}{\rightleftharpoons} ArOCOOCH_3 + CH_3OH}$$

Scheme 10. Reaction of phenols with DMC

Since the sulfur nucleophiles are very reactive, thiophenol was able to react in the absence of a base as well (entry 1), giving thioanisole. To rule completely out $RSCOOCH_3$ as a possible intermediate in the reaction, *n*-$C_8H_{17}SCOOCH_3$ was refluxed with DMC in the absence of potassium carbonate (Scheme 9): no reaction was observed after 24 h, showing that $RSCOOCH_3$ is not an intermediate in methylation reactions with thiolates.

$$\mathrm{RSH + DMC \longrightarrow RSCH_3 + CO_2 + CH_3OH}$$

$$\mathrm{RSCOOCH_3 + DMC \longrightarrow No\ reaction}$$

Scheme 11. Reaction of thiols with DMC

TABLE 9. Reactivity of thiols and alcohols with DMC in the presence and absence of K_2CO_3[a] (from ref. 40).

Entry	Thiol	Base	Time (h)	% RSMe (ROMe)	% RSCOOMe (ROCOOMe)
1	Thiophenol	-	1	27	-
2	Thiophenol	K_2CO_3	4	100	-
3	1-Octanethiol	K_2CO_3	24	34	-
4	1-Octanol	K_2CO_3	7	-	65

[a] DMC reflux temperature, 90°C; molar ratio thiol/DMC/K_2CO_3 1.0/40/1.2.

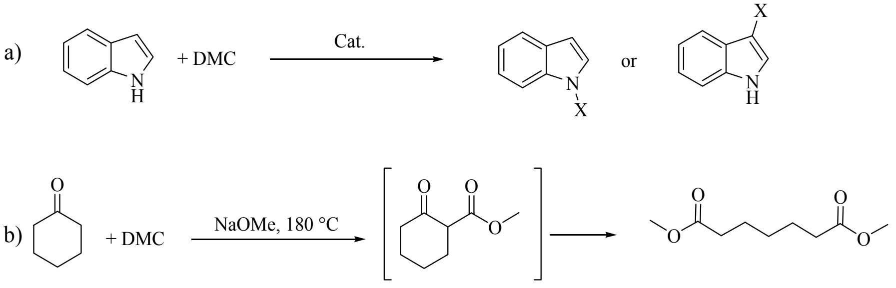
It is well established that sulfur and oxygen anions behave in an opposite way with electrophilic centres during nucleophilic substitutions.[40] The comparison of the reactivity of 1-octanthiol and 1-octanol with DMC (entries 3 and 4, Table 9) outlines the difference in chemoselectivity of RS^- and RO^- anions, due to their diverse hardness. Under all of the investigated conditions, alkoxides show a $B_{Ac}2$ reaction mechanism, differently from thiolates, which react via a $B_{Al}2$ type.

3.2. REACTIVITY OF DIMETHYLCARBONATE WITH AMBIDENT NUCLEOPHILES

Ambident nucleophiles are considered to be bidentate molecules whose nucleophilic centres have direct chemical interaction with each other, such as a ketone with its enol-carbanion tautomers.

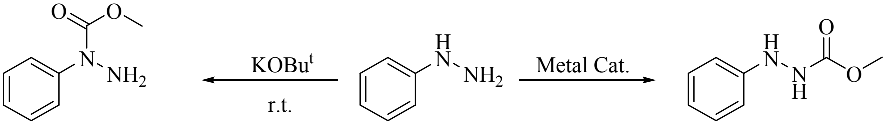
In the literature there are reactions of DMC with what would be considered ambident nucleophiles. For instance, indole is an ambident nucleophile. Using various organic chemistry procedures, reactions can either occur at the nitrogen or the conjugated arene carbon.[41] In the field of DMC chemistry, Shieh and co-workers were able to selectively methylate the nitrogen using DABCO as a catalyst in contrast to other systems that effected carboxymethylation at the same nucleophilic centre.[42] Also cyclic ketones have been successfully reacted with DMC to produce acyclic diesters via carboxymethylation at the alpha carbon.[43] In these examples, however, the ambidenticity of these systems toward DMC has not been shown (Scheme 12). Only activation of one of the two centres has occurred.

Lately some investigations have been conducted regarding the reaction of the ambident nucleophile phenylhydrazine with DMC.[44] Phenylhydrazine contains two non-equivalent nitrogen nucleophilic centres. **N-1** is relatively more acidic due to the electron withdrawing effect of the phenyl ring substituent while **N-2** possesses reactivity similar to that of an aliphatic amine.



Scheme 12. Reaction of DMC with a) Indole and b) ketones. X = CH_3 or $COOCH_3$

Both of these centres were selectively carboxymethylated (hard reaction, Scheme 13). Classical metal catalysts such as $Pb(OAc)_2$ or $Sn[O_2CCH(Et)Bu]_2$ effected **N-2** activation under refluxing conditions (Table 10, entries 4–6) whilst potassium *t*-butoxide at room temperature activated **N-1** (Table 10, entry 1). It was reasoned that the reaction with a strong base was due to the deprotonation of **N-1** creating an anion with hard nucleophilicity.[45]

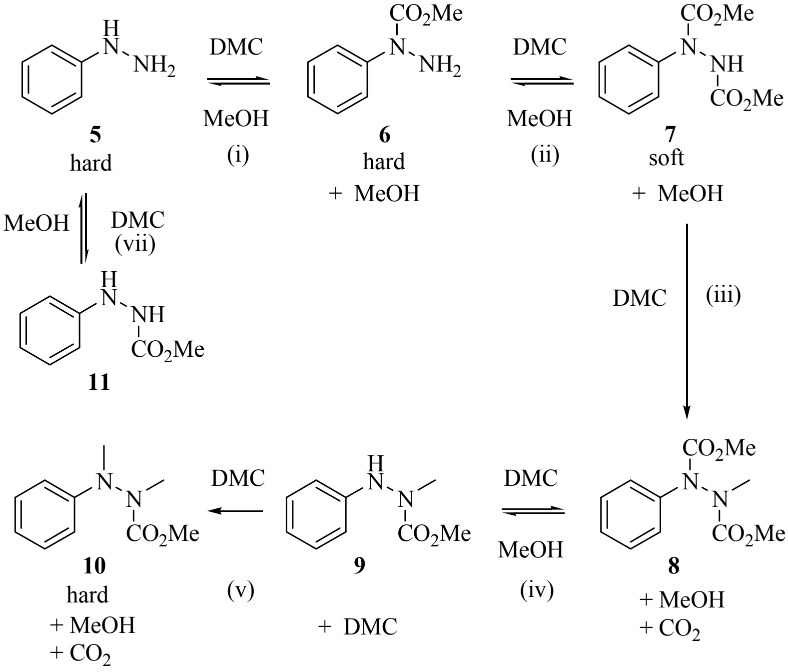


Scheme 13. Selective carboxymethylation of phenylhydrazine

Under more forcing conditions using base, cascading reactions involving carboxymethylation, methylation and methanolysis were observed (Scheme 14). The importance of the connectivity of the nitrogens to each other was shown. Firstly, a second carboxymethylation occurred at **N-2**, due to the added electron withdrawing carboxyl moiety at **N-1**, presumably lowering the pka of **N-2**. Consequentially, **N-2** underwent methylation. Possessing a carboxyl moiety, electronic stabilisation of **N-2** makes it a soft nucleophilic centre.

Methanol produced in the reaction also became a factor, as it reacted with the fully substituted hydrazine compound **9**. Methanolysis tended to occur mainly at **N-1**. This allowed for selective production of either **8** or **9** by adding or removing methanol respectively, facilitating or circumventing the methanolysis process (Table 10, entries 2 and 3).

Once **9** was produced, **N-1** was available to nucleophilically attack DMC once more. Notably, both methylation and carboxymethylation occurred thereafter, signifying that **N-1** of **9** possesses both soft and hard character. This was presumably attributable to both electron donating and withdrawing substitutents attached to the two nitrogens, once again adding to the importance of the nitrogen connectivity of this ambident nucleophile, phenyldrazine.



Scheme 14. Overall reaction of phenylhydrazine and DMC under basic conditions

TABLE 10. Reaction of phenylhydrazine with DMC (from ref. 44).

Entry	**Product**	**Base/ Catalyst**	**Equiv. Base**	**Conditions**	**Time**	**Yield (%)**
1	6	$(CH_3)_3COK$	1	Rt	25 min	85[a]
2	8	$(CH_3)_3COK$	1	Reflux, (removal of MeOH)	3 h 10 min	95[a]
3	9	NaOMe	4	Reflux 3 eq NaOMe, then 1 eq of NaOMe and MeOH reflux	5 h 40 min 3 h 30 min	79[a]
4	11	$Pb(OAc)_2$	1	Reflux	18 h	76[a]
5	11	$Pb(OAc)_2$	0.2	Reflux	20 h	70[a]
6	11	$Sn[O_2CCH(Et)Bu]_2$	0.2	Reflux	25 h 45 min	58[b]

[a] isolated product;

[b] crude product 80% of **11** and 20% of **6**;

4. Conclusions

DMC is a green solvent and reagent since it incorporates several fundamental aspects of green chemistry: it is synthesised by a green process using CO_2 as building block, it reacts selectively with a great variety of compounds as methylating or carboxymethylating reagent, it requires only catalytic amount of base and it produces no waste (high atom economy). Several industrial processes already involve DMC as reagent (or solvent) and many other are under investigation at the moment. In fact studies on DMC chemistry has demonstrated that it is possible to control the selectivity of the methylation and/or carboxymethylation reaction both on simple (amines, alcohols, thiols, etc.) and more complex nucleophiles (hydrazines, sugars, amino acids etc.). This opens new pathways for innovative green processes leading to a more eco-sustainable future.

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