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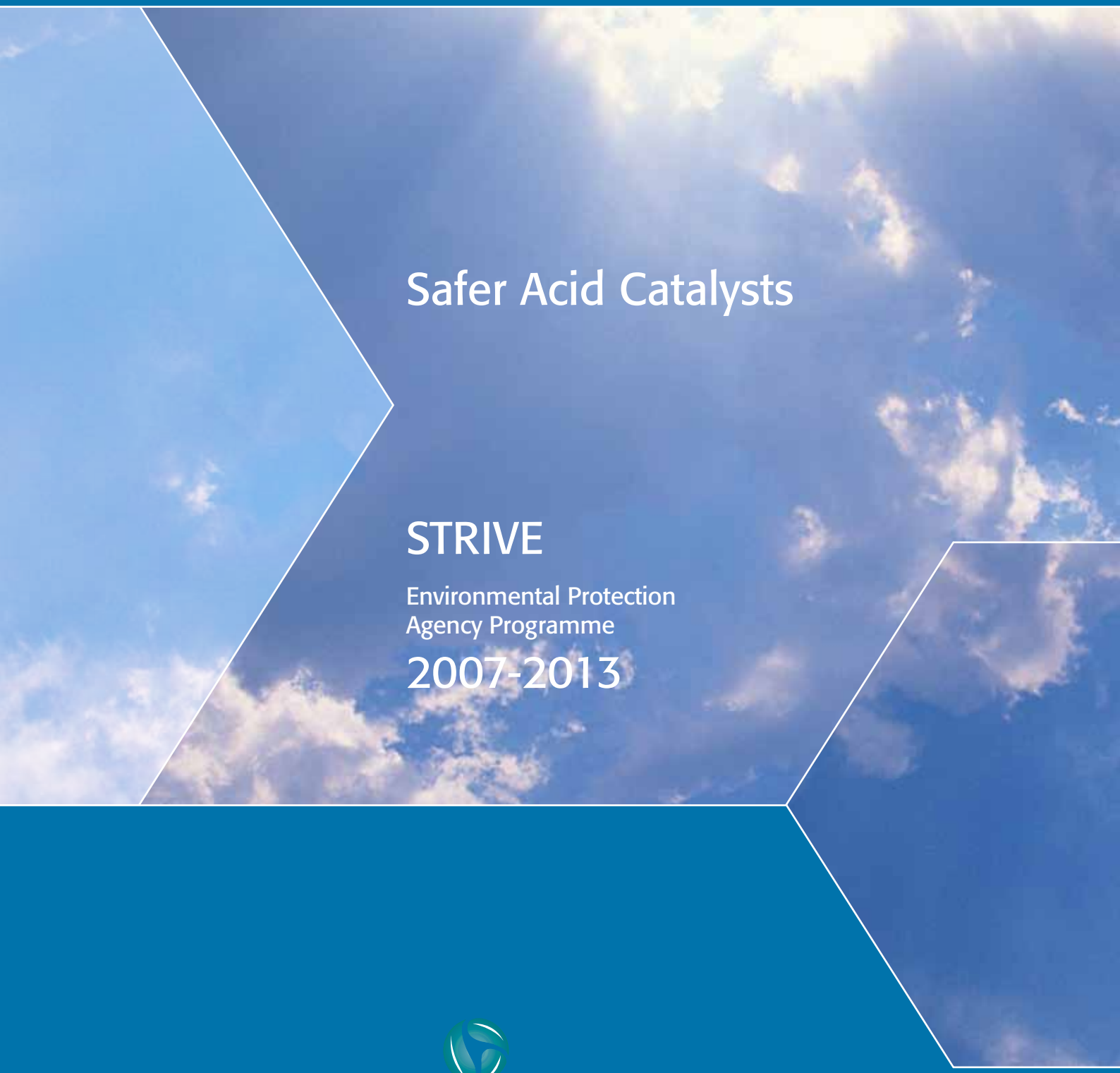

Safer Acid Catalysts

STRIVE

Environmental Protection Agency Programme

2007-2013

SSTI
Strategy for Science, Technology and Innovation

Comhshaol, Pobal agus Rialtas Áitiúil
Environment, Community and Local Government

Environmental Protection Agency

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EPA STRIVE Programme 2007–2013

Safer Acid Catalysts

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Synthesis Report

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Prepared for the Environmental Protection Agency

by

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DISCLAIMER

The EPA STRIVE Programme addresses the need for research in Ireland to inform policymakers and other stakeholders on a range of questions in relation to environmental protection. These reports are intended as contributions to the necessary debate on the protection of the environment.

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Executive Summary

European Union REACH (Registration, Evaluation, Authorisation, and Restriction of Chemical Substances) chemical control laws were implemented in 2007 to protect humans and the environment by ensuring information was available on the hazards of chemicals so they can be assessed and managed. This is now a global trend: for instance, amendments to TSCA (Toxic Substances Control Act) in the US in 2010 shifted the burden of demonstrating the safety of chemicals from the US Environmental Protection Agency to manufacturers. China's Ministry of Environmental Protection (formed in 2008) strengthened safety initiatives and recently greatly expanded the toxicity data requirement before import or production of chemicals not listed on their current chemical inventory.

Current national policy includes the government's promotion and strategy of a SMART Green Economy, national priority areas (including processing technologies and materials), the EPA's *2020 Vision – Sustainable Use of Resources* and EU policy *Horizon 2020 and 2013 – COST Action CM1206* (Exchange of Ionic liquids), which demonstrate the relevance of green chemistry projects.

Part of the research strategy was to replace 'traditional synthetic methods' with 'a greener alternative'. The inherent advantage of green chemical transformations are improved resource efficiency. This is realised by: (i) reducing the quantity of chemicals required to produce the target material; (ii) reducing the number of steps to manufacture the product; and (iii) reducing the waste generated. In the first two points, one must consider the benefit of utilising less chemicals (including solvent), together with the positive effect on the environment (e.g. lower energy consumption, reduced CO_2 emissions, improved air quality, and less waste treatment) when producing these raw materials. Also, by reducing the toxicity and increasing the biodegradability of chemicals utilised, the waste stream can be more easily treated, avoiding the need for landfill or incineration. Green chemistry can thus lead to significant reductions on the impact on the environment. Cost savings due to reduced chemical consumption and cheaper chemical manufacture are a stimulus for industry uptake of green chemistry methodologies.

The design of safer chemicals is a worthwhile goal. Anastas and Warner (1998) provided a roadmap for this when they published the *12 Principles of Green Chemistry*. Fundamental to their approach was a combined interdisciplinary strategy where the toxicity and biodegradation assessment of chemicals (e.g. acid catalysts) is combined with a 'greener' or less environmentally damaging synthetic route for preparing them. To realise this, where possible environmentally benign chemicals should be utilised. This should be coupled with short syntheses (few steps) of the target acid catalysts.

Acid catalysts (e.g. hydrochloric and sulfuric acid) are corrosive chemicals which require careful handling and storage. Accidental spillage and clean-up requires special personal protection equipment. Of interest to industry are safer acid catalysts, in particular catalysts that are only acidic when activated as required. The advantage is that this type of acid catalyst is convenient to handle and store due to its counter-intuitive classification as 'non-acidic'.

The main objective of this work was to design and synthesise a range of low-antimicrobial toxicity and biodegradable acid catalysts, and to explore their use in several classes of reactions.

The project had five main aims:

1 Developing short green synthetic routes to our target acid catalysts;

2 Identifying acid catalysts with undesirable high antimicrobial toxicity;

3 Completing biodegradation studies (CO_2 Headspace Test) to evaluate target acid catalysts breakdown;

4 Determining the reactions where our catalyst is effective, including reaction scope and role as solvent;

5 Applying green chemistry metrics to reduce the environmental impact of synthetic methods.

Previous work by the team lead to the discovery of a class of non-acidic chemicals which could be activated (switched-on), when added to solvent. Limitations of this work, however, included low catalytic activity, requiring the use of large quantities of catalyst to ensure high yields. We proposed that a new class of acid catalysts (imidazolium salts) would have higher activity. Over the last decade, there has been great interest in industry regarding this class of compounds as replacement chemicals. The team has studied the biodegradation of these salts, and previously reported poor breakdown under the CO_2 Headspace Test conditions. Thus, the development of biodegradable imidazolium salts is a major and worthwhile goal.

Our hypothesis was that the modifications performed to change the catalyst's molecular structure to improve performance would also improve biodegradation and reduce toxicity. This in turn results in reducing the negative impact on the environment.

We successfully improved the activity of the acid catalysts, allowing a decrease in the quantity of catalyst from 10 mol% to 0.05 mol% (i.e. 200x less), while maintaining excellent yields. During the development phase of the project, antimicrobial toxicity data for several acid catalysts was unacceptably high. The tandem approach of toxicity screening and acid catalyst performance evaluation meant we could direct the research towards lower toxicity targets. The recommended final acid catalysts have low antimicrobial toxicity. In addition, green chemistry metrics to analyse the efficiency of the synthesis of the acid catalyst and waste generation were applied. By identifying the most environmentally damaging processes, and developing greener alternatives, we now have a cleaner synthesis of our recommended acid catalysts.

A major challenge of the project was to prepare biodegradable acid catalysts. Predicting accurately biodegradation (i.e. computer modelling) of this class of compound (imidazolium salts) is not currently possible. This is in part due to the lack of experimental data to train modelling programmes. We successfully obtained biodegradation data for our imidazolium acid catalysts: however, none of these chemicals passed the CO_2 Headspace Test. No significant breakdown of the imidazolium structure was observed, despite the wide range of modifications explored. While disappointing, this data directs future biodegradable chemical investigations towards alternative structures. In addition, this experimental data will assist in the refinement of biodegradation prediction calculations.

The impact of the work over the duration of the project has been stepwise. Our first publication reported catalyst performance only. The second combined performance and antimicrobial toxicity and was published in the leading Royal Society of Chemistry journal in the field, *Green Chemistry* (IF 6.8) in 2010. Our latest dissemination is a series of three back-to-back papers in *Green Chemistry*, reporting catalyst performance, antimicrobial toxicity, biodegradation, green chemistry metrics and catalyst recycling. These papers are the triple front cover articles for the *Green Chemistry* 2013 October issue, with the first of the series also highlighted as a 'Hot Article' by reviewers.

This justifies and validates the current research decision to our approach to jointly assess the toxicity, biodegradation, synthesis and performance of the catalysts at the development stage, which to the best of our knowledge, is unique to our Dublin City University (DCU)/Trinity College Dublin (TCD) team.

When presenting our findings at conferences in Europe and the US, the overwhelming feedback is that this type of joint assessment should be the rule rather than the exception, and this is our key recommendation.

Outputs from the project also include three book chapters, invitations to contribute to seminars (including a plenary talk at a major EU conference and environmental toxicology meetings in the US), organising an Irish Green Chemistry conference series at DCU, and the graduation of two PhD students.

1 Ionic Liquids as Catalysts

1.1 Introduction

Ionic liquids (ILs) are molten salts that are ionic (i.e. a mixture of cation and anion) in nature and that have a melting point below 100 °C (Rogers and Seddon, 2002). Salts that are liquid at room temperature are termed room temperature ILs (RTILs). ILs have received a lot of attention since the early 2000s (Wilkes, 2002) because of their unique properties – low vapour pressure, high thermal stability, recyclability, non-flammability, and control over the product distribution (Plechkova and Seddon, 2008) (Wasserscheid and Stark, 2010). Due to the need for control over fugitive emissions ILs can be used as a replacement for volatile organic compounds (VOCs), which are commonly used as solvents in organic processes. Exposure to toxic solvent vapours is avoided when using an IL solvent instead of a VOC. A large number of research articles have been published with ILs composed of different types of cations (Fig. 1.1) and anions. It would be easy to design 10^{18} possible structures of ILs by varying cations and anions, making 'designer' molecules (Seddon, 1997) (Marsh et al., 2004) (McFarlane et al., 2005) (Sheldon, 2005) (Freemantle, 1998). These designed combinations have already been found useful in different fields of chemistry, such as organic chemistry (Hallett, 2011) (Hubbard et al., 2011) (Wasserscheid and Joni, 2010) (Chowdhury et al., 2007) (Stark and Seddon, 2007), electrochemistry (Opallo and Lesniewski, 2011) (Shiddiky and Torriero, 2011) (Liu et al., 2010) (Pitner et al., 2010) (Buzzeo et al., 2004), analytical chemistry (Poole and Poole, 2011) (Ho et al., 2011) (Sun and Armstrong, 2010) (Pandey, 2006) (Koel, 2005) and biochemistry (Opallo and Lesniewski, 2011) (Dominguez de Maria and Maugeri, 2011).

There are five major classes of cations in ILs: (i) ammonium, (ii) imidazolium, (iii) pyridinium, (iv) sulfonium and (v) phosphonium (Fig. 1.1).

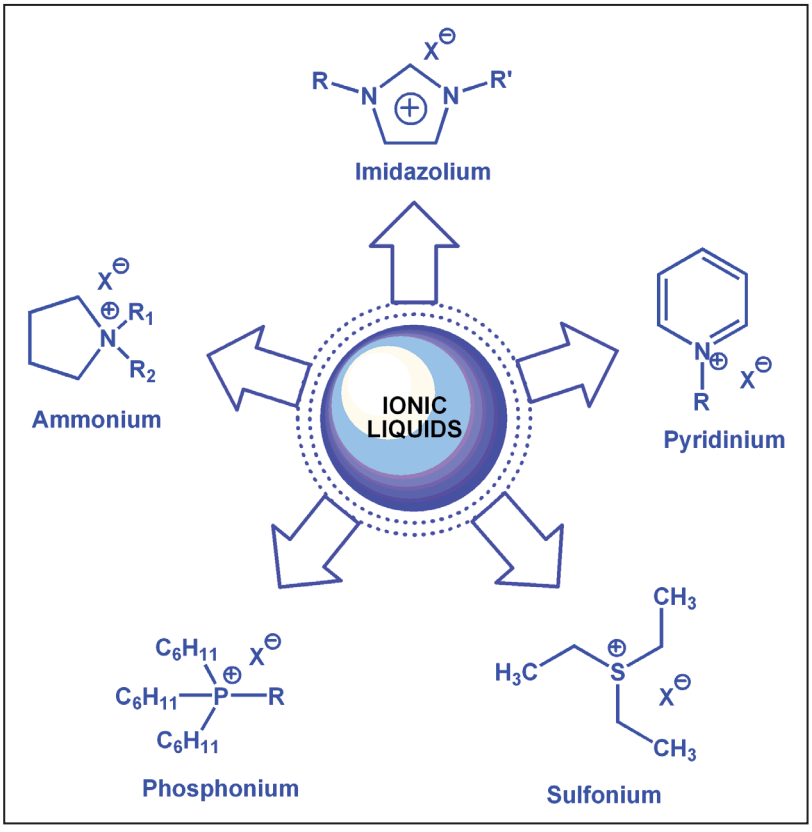


Figure 1.1. Major types of cations in ionic liquids (ILs).

Along with these, there are a large number of commonly used anions, such as halides (chloride, bromide, iodide), *bis*(trifluoromethanesulfonimide) (NTf_2^-), tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-), octyl sulfate ($OctOSO_3^-$), acetate (OAc^-) and dicynamide ($N(CN)_2^-$). A change in the anionic component can drastically affect the physical properties of an IL in terms of, for example, hydrophilicity, viscosity and melting point.

1.2 Applications of Ionic Liquids in Organic Synthesis

ILs have been widely exploited in numerous organic reactions owing to the versatility in their physical properties such as ease of product separation (Klingshrinet al., 2005) (Mizushime et al., 2001), enhancement in rate of reaction (Earle et al. 1999) (Vijayaraghavan and MacFarlane, 2004) (Rosa et al., 2001), catalyst immobilisation (Yadav et al., 2005) (Johansson et al., 2005) (Serbanovic et al., 2005) and recyclability (Picquet et al., 2003) (Forsyth et al., 2005) (Reetz et al., 2002).

Modifications in cations and/or anions have facilitated their use in organic reactions while playing a role of reagent, solvent or catalyst. This can be reflected in a huge number of publications: this section, however, discusses only the representative examples with the aim of demonstrating the versatility of ILs in organic synthesis. It will also discuss the environmental fate of ILs by addressing the importance of toxicity, eco(toxicity), biodegradation and green chemistry metrics. Exploring these parameters allows the design and synthesis of safer and greener catalyst/solvent.

1.3 Environmental Fate of Ionic Liquids

Because of their wide range of applications and versatility, ILs are used extensively in industry (Plechkova and Seddon, 2008) – triggering a waste-management issue. Further, many are completely synthetic novel compounds. Hence, it is important to study the environmental impact of such ILs before releasing them into the natural environment. With low vapour pressure (c.f. VOCs), ILs have less potential to pollute the air. Bearing an ionic nature, ILs have a

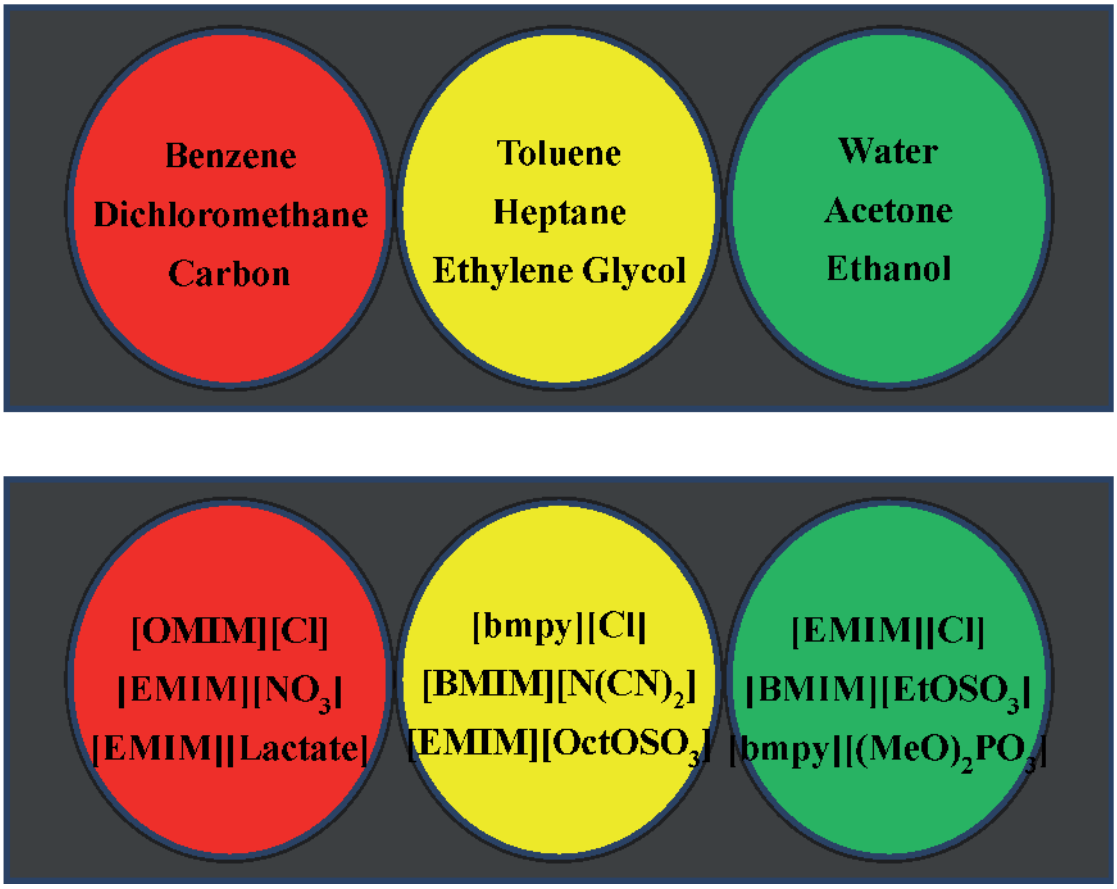


Figure 1.2. Recommendation for data representation of toxicity of ionic liquids (ILs) and commonly used organic solvents. (Wood and Stephans, 2010) (Alfonsi et al., 2008)

notably high solubility in water (McFarlane et al., 2005) (Anthony et al., 2001) (Wong et al., 2002) (except NTf_2^- & PF_6^-) which is a viable and common means by which these ILs get released in nature. Toxicity, eco-toxicity and biodegradation studies must be carried out in order to check the biocompatibility of ILs.

ILs are proposed as 'green' alternatives to VOCs (Plechkova and Seddon, 2008). In addition to the use of the 'green' label, ILs can be categorised in a 'Traffic Signal Lights' pattern as discussed at the BATIL (Biodegradation And Toxicity of Ionic Liquids) meeting in DECHEMA, Frankfurt, 2009 (Fig. 1.2) (Wood and Stephans, 2010). This allows easy comparision of the toxicity of different IL classes. As we start classifying ILs in three colours (red for high toxicity, yellow for moderate toxicity and green for low toxicity), we can find that most ILs are 'red' or 'yellow' – although this information was based solely on limited toxicity data. For an IL to be classified more accurately by a Traffic Signal Lights pattern, detailed information about the toxicity, biodegradation and ease of synthesis and so on is required. For example (Fig. 1.2), [OMIM][Cl] (Log IC_{50}: 1.6 μM in *Bacillaria paxillifer*) can be categorised as red, [BMIM][$N(CN)_2$] (EC_{50}: 1400 μM in WST-1 cell viability assay using the IPC-81 cell line) as yellow and [EMIM][Cl] (EC_{50}: 13,573 μM in *Oocystis submarina*) as green. Similar classifications can be applied to commonly used organic solvents (Fig. 1.2) (Alfonsi et al., 2008). Water is not toxic at all (hence, it is green), whereas toluene (IC_{50}: 9 mM in mRNA for specific N-methyl-D-aspartate receptors) can be considered yellow and benzene can be red, as it is known to cause cancer.

1.3.1 Biodegradation of Ionic Liquids

Many ILs are well known for being stable to heating and in a variety of reaction conditions. Although this is an important property in their applications, it can raise issues regarding degradation and bioaccumulation when released in nature. Accumulated data on the anti-microbial toxicity of novel ILs can be used as a preliminary guideline before performing biodegradation tests. The biological test system has its limitations, such as when reported toxicity data is only available for certain individual organisms, whereas biodegradation assays usually have a large sample group of organisms. Also, breakdown products/intermediates of ILs can be toxic, which can be resistant to further degradation, which leads to the issue of bioaccummulation. Hence, it is important to perform biodegradation studies of ILs (Coleman and Gathergood, 2010). Boethling et al. (2007) in their review article 'Designing small molecules for biodegradability' gave useful and general 'Rule of thumb' guidelines for the design and synthesis of environmental friendly chemicals. According to their observations, compounds containing unsubstituted alkyl chains, benzene rings, oxygen functionalities such as esters, aldehydes, and carboxylic acids (potential sites for enzymatic hydrolysis) greatly increase biodegradation. Whereas compounds containing halogens, branched chains, heterocycles, functional groups such as nitro, nitroso and arylamines motifs, adversely affect the biodegradation. The Organisation of Economic and Cooperation and Development (OECD) has approved several biodegradation study methods (OECD, 2003) (see Table 1.1).

Table 1.1. Biodegradation methods in use.

Test No.	Name	Analytical method
OECD 301 A	Dissolved organic carbon (DOC) Die-Away	DOC
OECD 301 B	CO_2 evolution	CO_2 evolution
OECD 301 C	MITI (Ministry of International Trade and Industry, Japan)	Oxygen consumption
OECD 301 D	Closed bottle test	Dissolved oxygen
OECD 301 E	Modified OECD screening	DOC
OECD 301 F	Manometric respirometry	Oxygen consumption
ISO 14593	CO_2 headspace test	CO_2 evolution
OECD 309	OECD 309	^{14}C labelling
ASTM 5988	ASTM 5988	CO_2 production / Biochemical oxygen demand

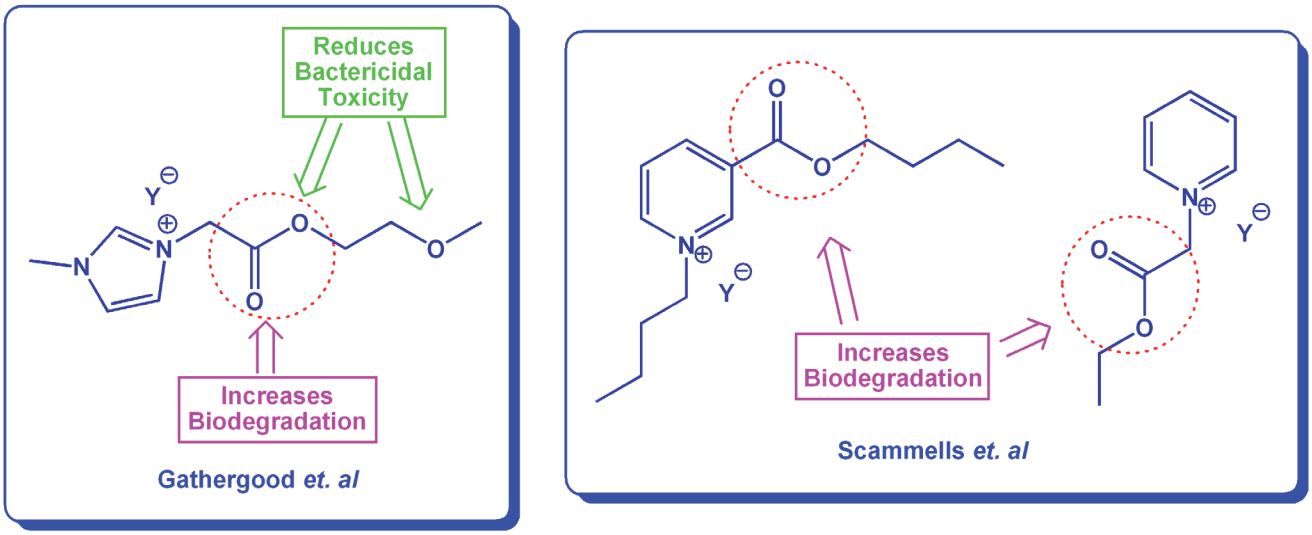


Figure 1.3. Guidelines for designing 'green' ionic liquids (ILs).

1.3.2 Guidelines for Designing 'Green' Ionic Liquid Catalysts/Solvents

From the literature (Boethling et al., 2007) (Boethling, 1996) the following observations were made and are summarised in Fig. 1.3 (Morrissey, 2009) (Gathergood, 2002) (Garcia, 2004) (Harjani, 2009):

- In general, linear alkyl chains can increase biodegradation in comparison to branched hydrocarbon chains;
- Oxygen-containing functionalities, such as ester and hydroxyl groups in the side-chain of imidazolium cation, not only reduces microbial toxicity but also increases rate of biodegradation. This is, however, not effective in phosphonium-based ILs;
- Ether substitution reduces bactericidal toxicity;
- Ester substitutions at 1 and 3 position of pyridinium cation can improve biodegradation.

1.4 Conclusion

This section has demonstrated that ILs have great potential and versatility in organic synthesis, with the dual ability to act as a solvent and as a catalyst. ILs were found to be possible replacements over traditional VOSs. Such IL solvents were found to be useful in transition metal catalysed reactions. They not only enabled catalyst immobilisation, but also increased the recyclability of expensive transition metal catalysts. Ease of product separation and their stability against a variety of reagents have proven their important characteristics.

It has been shown that modification in the cationic part of the ILs, according to the requirements of the aforementioned reactions, enabled them to act as organocatalysts or ligands for transition metal catalysts. These IL catalysts have shown comparative catalytic activity against known organocatalysts, but such materials had a distinct advantage in that the ILs could be recycled, with no discernible loss of activity. In order to increase recyclability, IL catalysts/ligands were grafted onto a solid/polymer support. These modifications helped to separate IL catalysts from the reaction mixture.

We have also illustrated the efforts attempted by the scientific community to evaluate the 'greenness' of ILs, by using toxicity and biodegradation methods. The majority of ILs are non-natural molecules, so it is important to check their biocompatibility. Toxicity studies can serve as a 'first post' primary evaluation of biodegradation. A variety of test systems, including fungi, bacteria, algae, enzymes, rat cell line, human cell line and fish and so on were implemented to check the toxicity of ILs. Most of these test systems have shown that toxicity of the ILs comes from the cationic component. Important observations from such test systems also concluded that (a) toxicity depends on the alkyl chain length and (b) incorporation of oxygen functionalities (ether, ester, and hydroxyl, etc.) reduces the toxicity.

A number of OECD tests (2003) were found to be useful in the estimation of biodegradation. These tests mainly involve calculation of CO_2 evolution and oxygen consumed and showed that most of the 1,3-dialkyl imidazolium ILs are non-biodegradable, in most of the test systems. Although the alkyl side-chain can undergo degradation, the imidazole core can still persist during biodegradation studies. Introduction of oxygen functionality such as ether/ester, either in the side-chain of the imidazolium cation or at the C_1 or C_3 position of the pyridinium cation, were found to increase the rate of biodegradation.

Target ILs were designed and selected based on the literature discussed in this section. According to guidelines, ILs with ester and amide functionality in the side-chains or heterocyclic core were designed. ILs that pass biodegradation tests, have low microbial toxicity and that can be synthesised by short routes was a major goal of this project.

2 Synthesis of Ionic Liquids – Four Generations

2.1 Rationale

As noted above, in order to design 'green' ILs, factors such as toxicity, eco-toxicity and biodegradation have to be considered (Coleman and Gathergood, 2010) (Ranke et al., 2007) (Ranke and Jastorff, 2000). There are some commonly used cations – such as imidazolium, pyridinium, phosphonium, and sulfonium – used in the design of ILs (Fig. 1.1). Among these classes of ILs, the imidazolium class was studied in most detail due to its unique properties, such as easy preparation, low viscosity and low melting points (Wasserscheid and Welton, 2003).

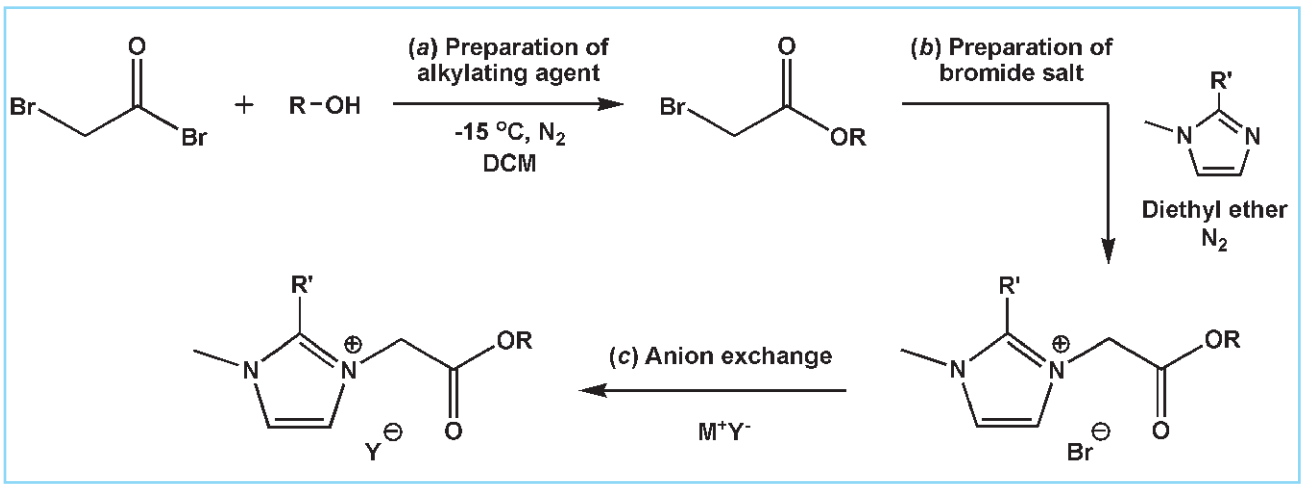
The Gathergood group has previously described how the incorporation of oxygen functionalities into the side-chain of imidazolium-based ILs, such as esters (Gathergood and Scammells, 2002) (Gathergood et al., 2004) (Garcia et al., 2005) (Gathergood et al., 2006) and ethers (Morrissey et al., 2009) helps to improve biodegradability and reduce antimicrobial toxicity. ILs with long hydrocarbon side-chains have been reported to be toxic to bacteria and fungi, due to their lipophilicity (Carson et al., 2009) (Docherty and Kulpa, 2005) (Bernot et al., 2005) (Bernot et al., 2005) (Swatloski et al., 2004) (Pretti et al., 2006) (Pham et al., 2008). According to these guidelines above, ILs with ester and amide functionality in the side-chains, were selected as a target for this project.

The main objective of this work was to design and synthesise a range of antimicrobially non-toxic and biodegradable ILs and to explore their use in several classes of reactions in organic synthesis, as both catalyst and/or solvent.

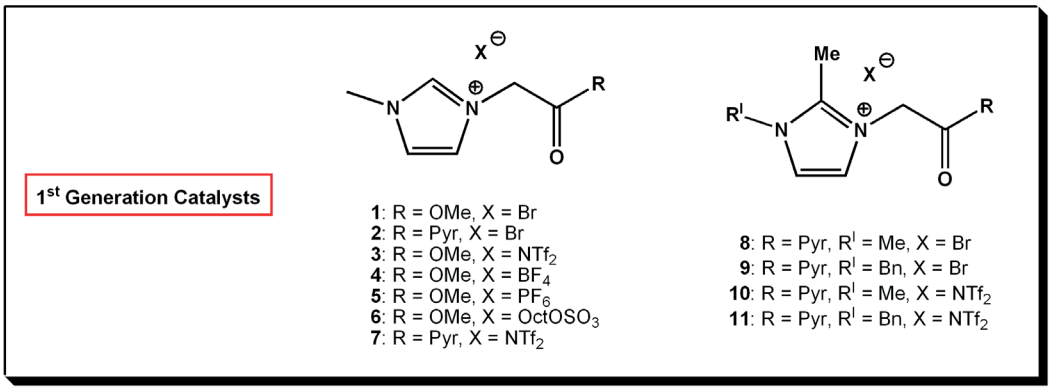
2.2 Synthesis of Ionic Liquids – First Generation

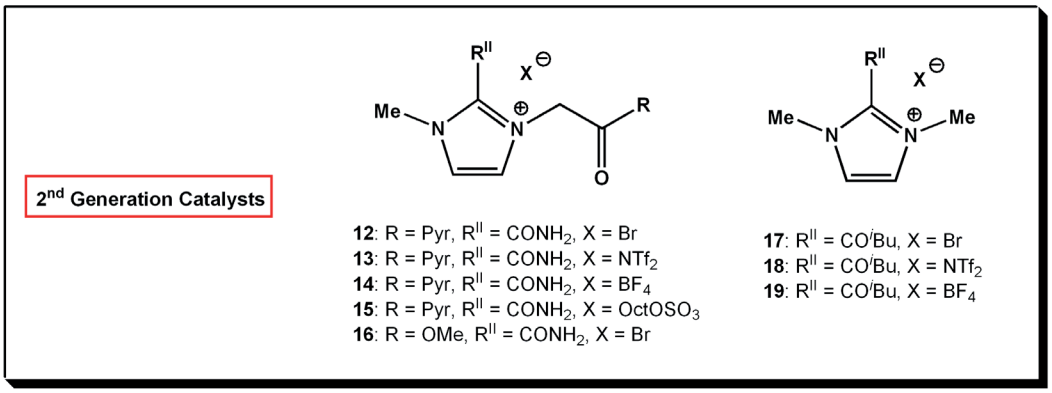
The ILs have been designed to be used as catalysts in acetalisation reactions and as a solvent in carbonyl-ene reactions. Several amide side-chain ILs have been synthesised along with ester side-chains, due to the unknown stability of the latter in the above reactions. The preparation of ILs has been carried out in three simple steps (see Scheme 2.1).

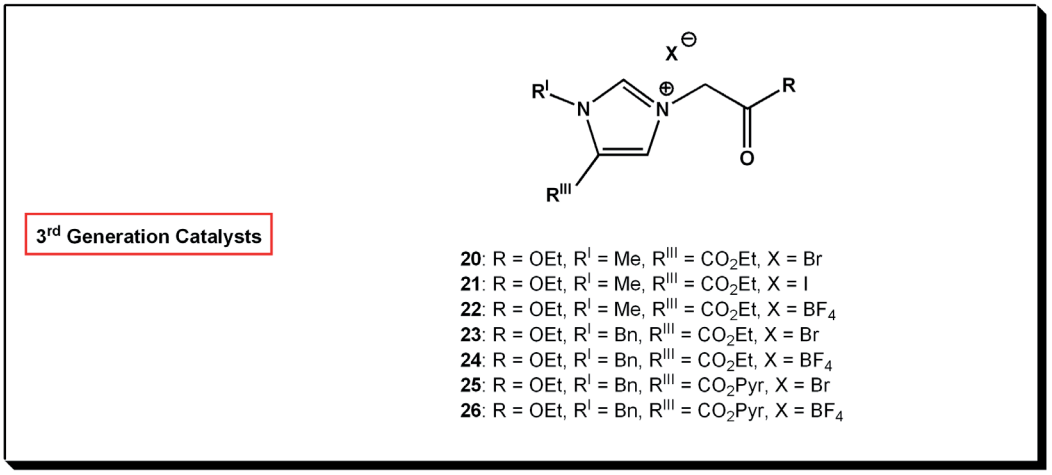
In general, higher yields were achieved in the preparation of α-bromoesters (84–89%) than α-bromoamides (47–55%) for step (a) Scheme 2.1. Subsequent alkylation of 1-methylimidazole or 1,2-dimethylimidazole, step (b) with α-bromoesters/amides led to the bromide salts (**1** and **8**) respectively (94 and 71%). In the last step (c) in the synthesis, anion metathesis was performed (49–99% yield) on the synthesised bromide salts. A series of anion-exchange reactions were performed on the bromide salts (**1, 2, 8** and **9**) to obtain *bis*(trifluorom ethanesulfonimide) (NTf_2^-), tetrafluoroborate (BF_4^-),

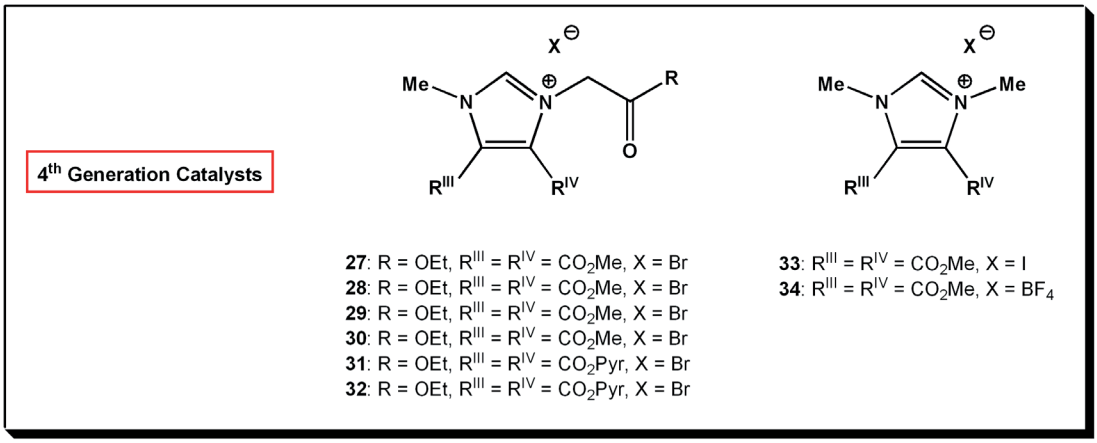


Scheme 2.1. Synthesis of ester side-chain ionic liquids (ILs) – first generation









Pyr =

Figure 2.1. Target ionic liquids (ILs).

hexafluorophosphate (PF_6^-), dicyanamide ($N(CN)_2^-$) and octyl sulfate ($OctOSO_3^-$) anion analogues. *Bis*(trifluoromethanesulfonimide) and octyl sulfate anion exchange was carried out in water with the product isolated easily by stirring imidazolium bromide salts with $LiNTf_2$ and Na $OctOSO_3$, respectively.

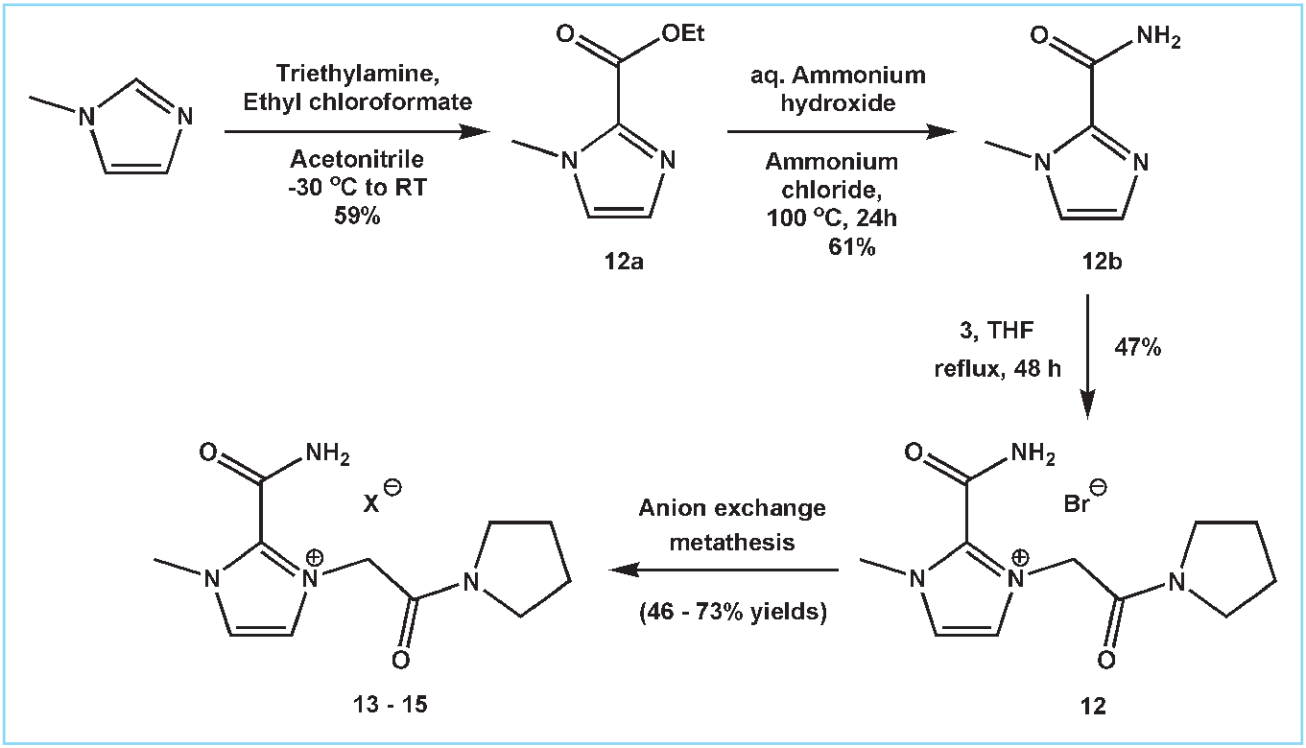
2.3 Synthesis of Ionic Liquids – Second Generation

Biodegradation studies of pyridinium-based ILs have shown that esters at either the 1 or 3-position have a beneficial effect on degradation of the heterocyclic core, independent of the anion (Harjani et al., 2009). Such incorporation of ester substitution onto the imidazole ring could help to increase biodegradability of imidazolium cation. The 2-position was selected initially (Scheme 2.2). Also, substitution at the 2-position of 1-methylimidazole, with electron-withdrawing groups, had the potential to increase catalytic activity in acetalisation reactions (Myles et al., 2010).

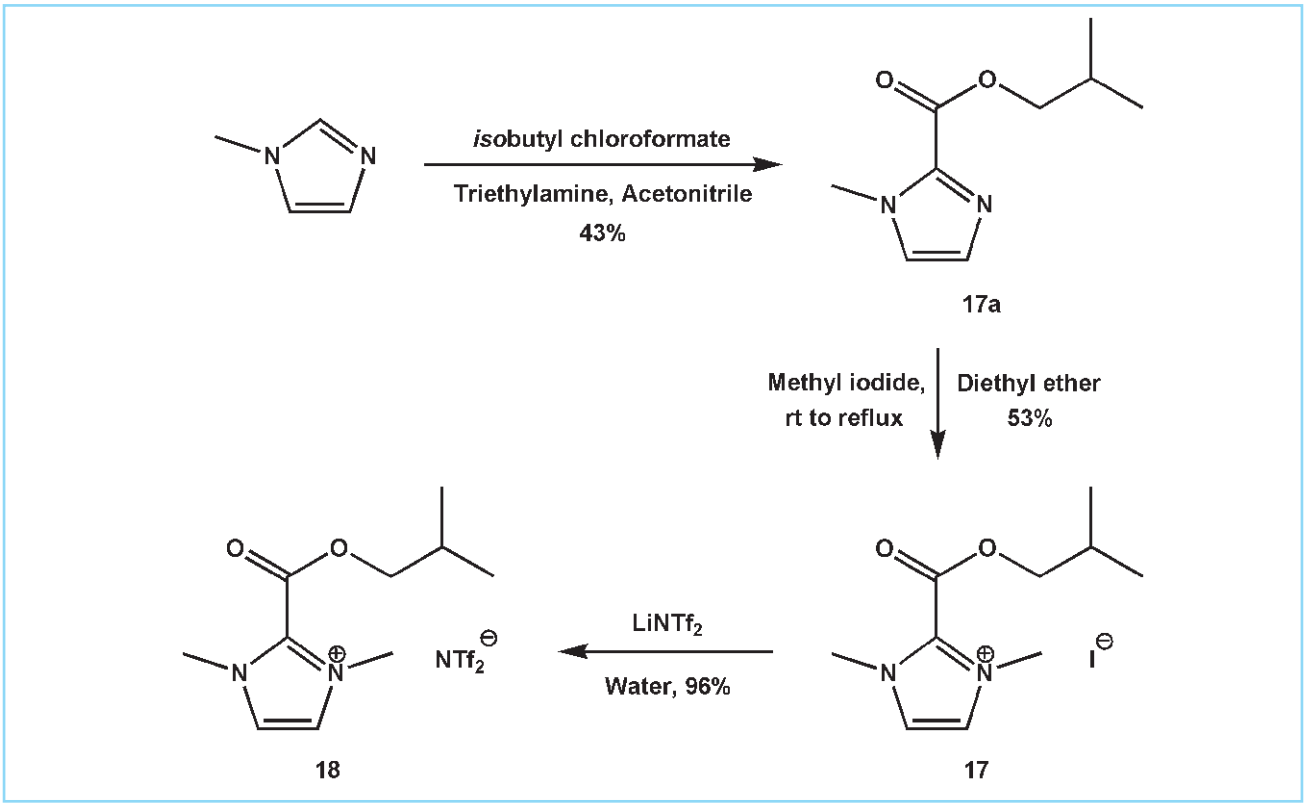
The commercially available lithium salt of 1-methylimidazole-2-carboxylic acid was subjected to esterification under reflux conditions with methanol. However, decarboxylation was observed because of the favourability of carbene formation. Considerable effort to avoid decarboxylation proved fruitless. Next the more stable primary amide (**12b**) was prepared by heating the 2-ethyl ester (**12a**) to 100 °C with an aqueous ammonium hydroxide and ammonium chloride (5 mol%) as a catalyst under atmospheric pressure. The product (**12b**) precipitated from the reaction mixture as needle-shaped crystals when cooled to the room temperature (Krzysztof and William Lown, 1987) (Davey, 1987).

N-alkylation of the imidazole **12b** by methyl bromoacetate gave the required product (**16**) as a pink powder in 17% yield (Fig. 2.1). However, alkylation with α-bromoamides was more efficient, giving the pyrrolidine amide side-chain product (**12**) as a white powder in 47% yield. Anion exchange gave products **13**–**15** (Scheme 2.2).

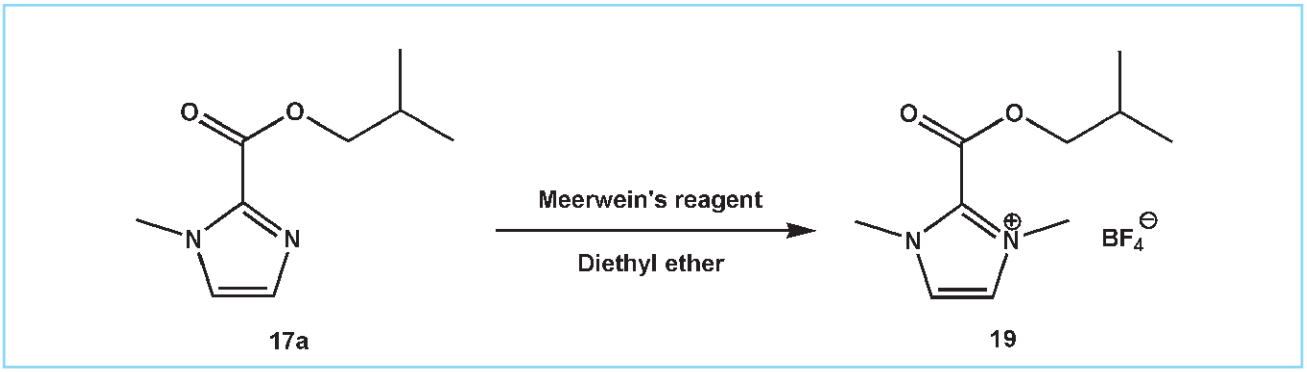
The reaction scope and stabilities of these amide ILs would later be compared with similar ester ILs. With this objective in mind, the hindered *iso*butyl ester was synthesised. However, because of its steric bulk, the *iso*butyl ester rendered the imidazole difficult to alkylate using methyl bromoacetate, and no alkylation was observed even after reflux in toluene. To overcome this difficulty, the less hindered alkylating agent methyl iodide was selected with the product **17** isolated as a white solid in 53% yield (Scheme 2.3). Anion exchange was carried out using aqueous lithium *bis*(trifluoromethanesulfonimide) to give the NTf_2^- salt as a pale yellow solid (**18**) in 96% yield.



Scheme 2.2. Synthesis of 2-position amide substituted ionic liquid (IL) – second generation.



Scheme 2.3. Synthesis of 2-position ester substituted iodide and NTf_2^- salts.

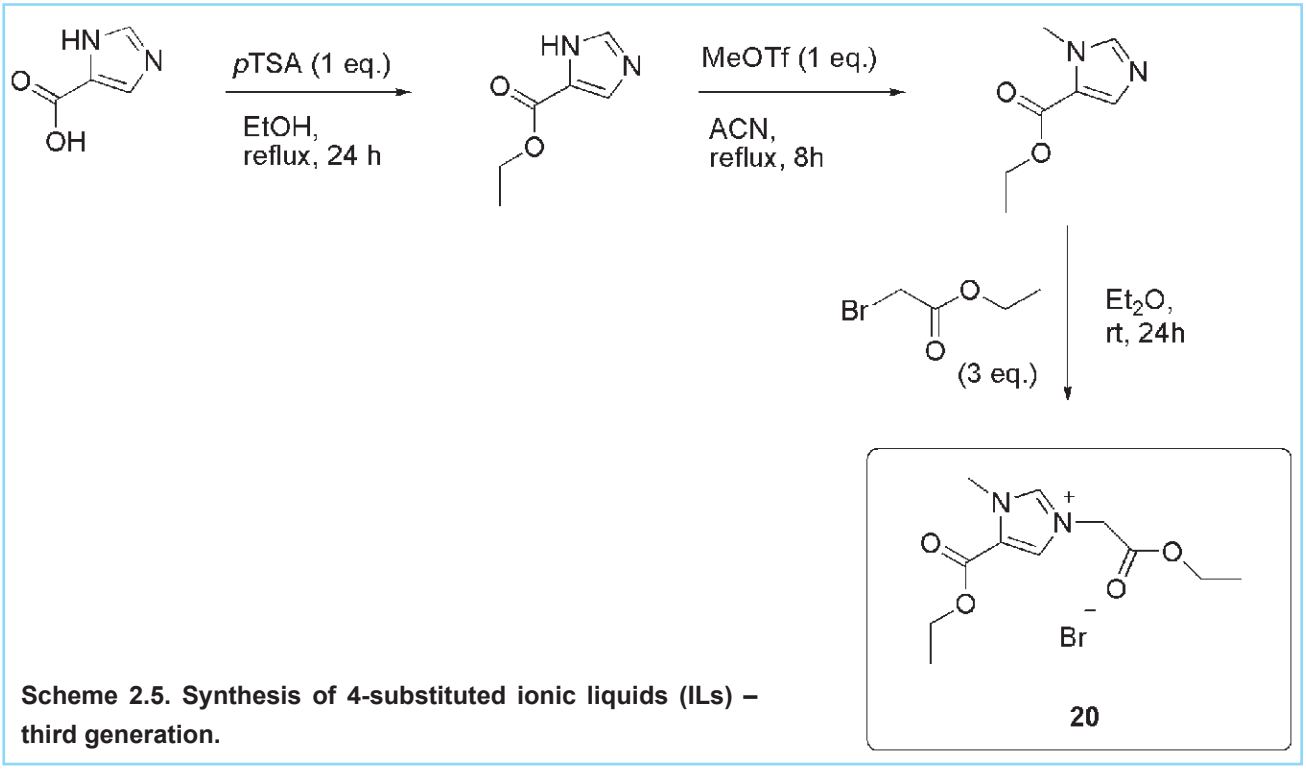


Scheme 2.4. Synthesis of BF_4 ionic liquid (IL) 19 by excluding an extra step.

Instead of exchanging the iodide to the tetrafluoroborate salt, imidazole **17a** was directly reacted with Meerwein's salt, that is trimethyloxonium tetrafluoroborate to give tetrafluoroborate salt **19** in excellent yield (97%) (Egashira et al., 2006) (Scheme 2.4).

2.4 Synthesis of Ionic Liquids – Third Generation

Imidazolium catalyst **20** with an electron withdrawing group (EWG) at the 4 position are classed as 'third generation', and were synthesised from 4-imidazoledicarboxylic acid (Scheme 2.5).



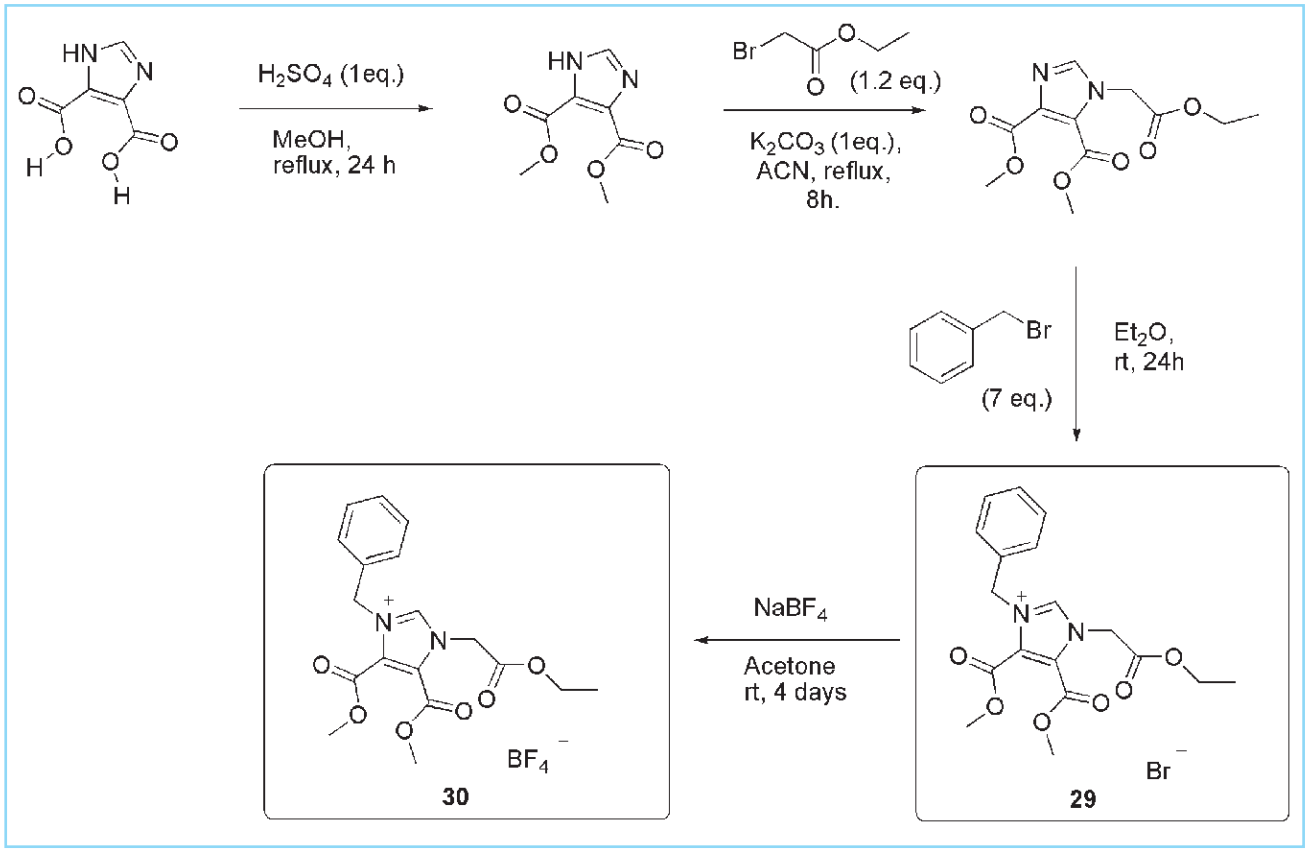
Scheme 2.5. Synthesis of 4-substituted ionic liquids (ILs) – third generation.

The successful synthesis of catalyst **20** has therefore been carried out and optimum procedures for the synthesis of these new class of molecules in good yields has been developed whilst overcoming the various initial problems encountered with the synthesis and purification of these compounds. The testing of these third-generation catalysts in the acetalisation of benzlaldehyde is discussed in the next section and the activity of these molecules is compared to our previous un-substituted generations of imidazolium salts.

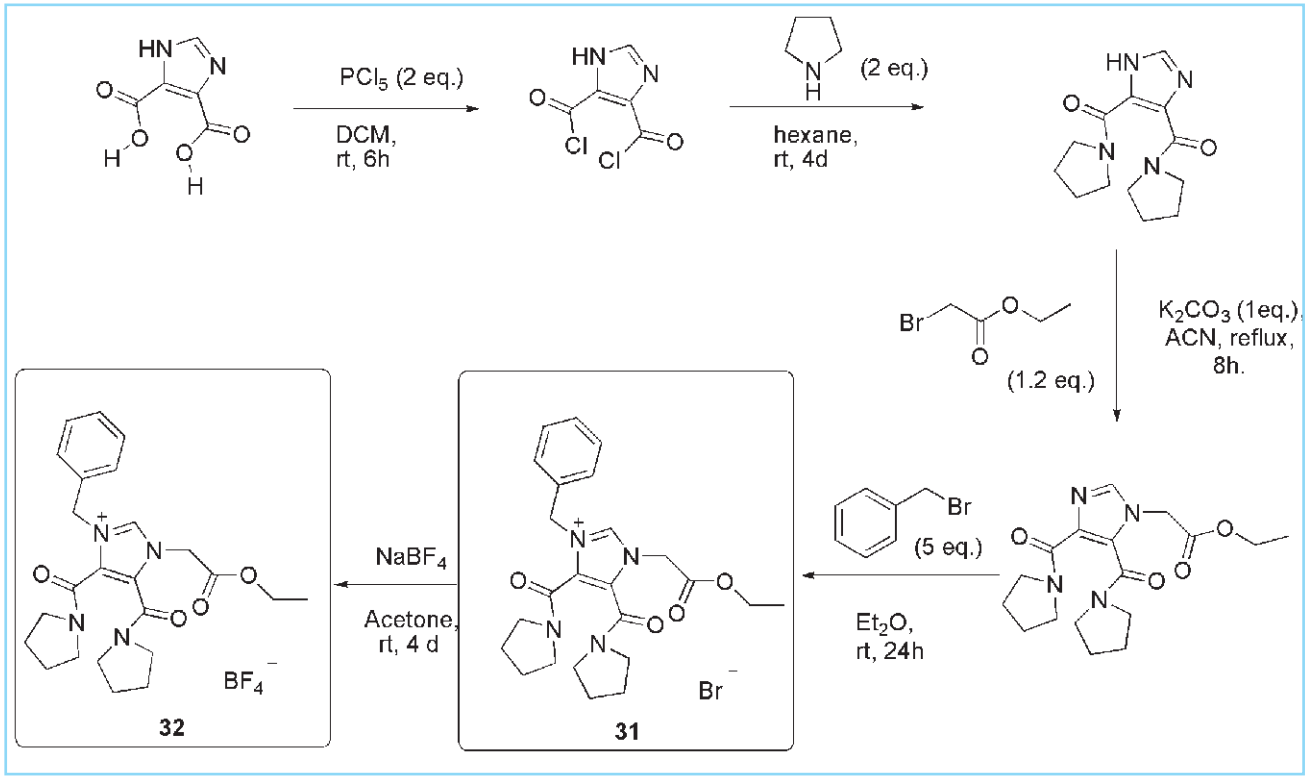
2.5 Synthesis of Ionic Liquids – Fourth Generation

The aim of this section was the synthesis of new imidazolium catalyst candidates possessing various electron-withdrawing groups. The initial synthesis (Scheme 2.6) involved three steps followed by a counter-ion exchange to synthesise two catalyst candidates. The synthesis involved the esterification of 4,5-imidazoledicarboxylic acid: this ester material was extremely susceptible to hydrolysis and so care had to be taken during work-up and purification. This step was followed by the alkylation of the methyl ester using ethyl bromoacetate. This alkylation step proved problematic – many different solvent systems and bases were used before finding these optimum conditions. Once this reaction was optimised a second alkyaltion was carried out using benzyl bromide forming the quaternary salt. Various other alkylating agents proved unsuccessful. The bromide catalyst salt **29** was then purified by column chromatography and a counter-ion exchange was carried out using sodium tetrafluoroborate in acetone, giving catalyst **30**.

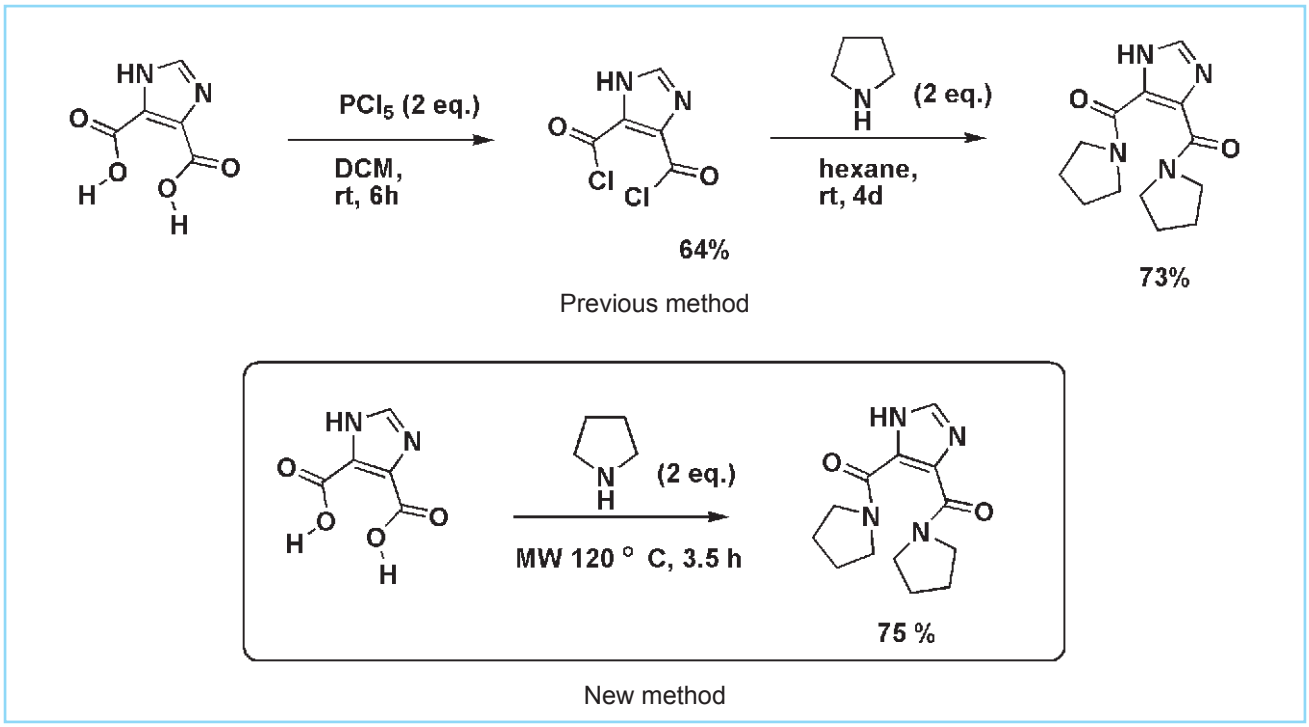
The amide-substituted catalyst candidates were also synthesised following the procedure in Scheme 2.7. The acyl chloride was obtained from 4,5-imidazole dicarboxylic acid and phosphorous pentachloride in dichloromethane (DCM). Coupling of the acyl chloride with pyrrolidine in hexane gave the diamide. Once the amide-derived molecule was obtained, the alkylation steps and counterion exchange were carried out as with the ester-derived molecule, leading to the synthesis of catalysts **31** and **32**.



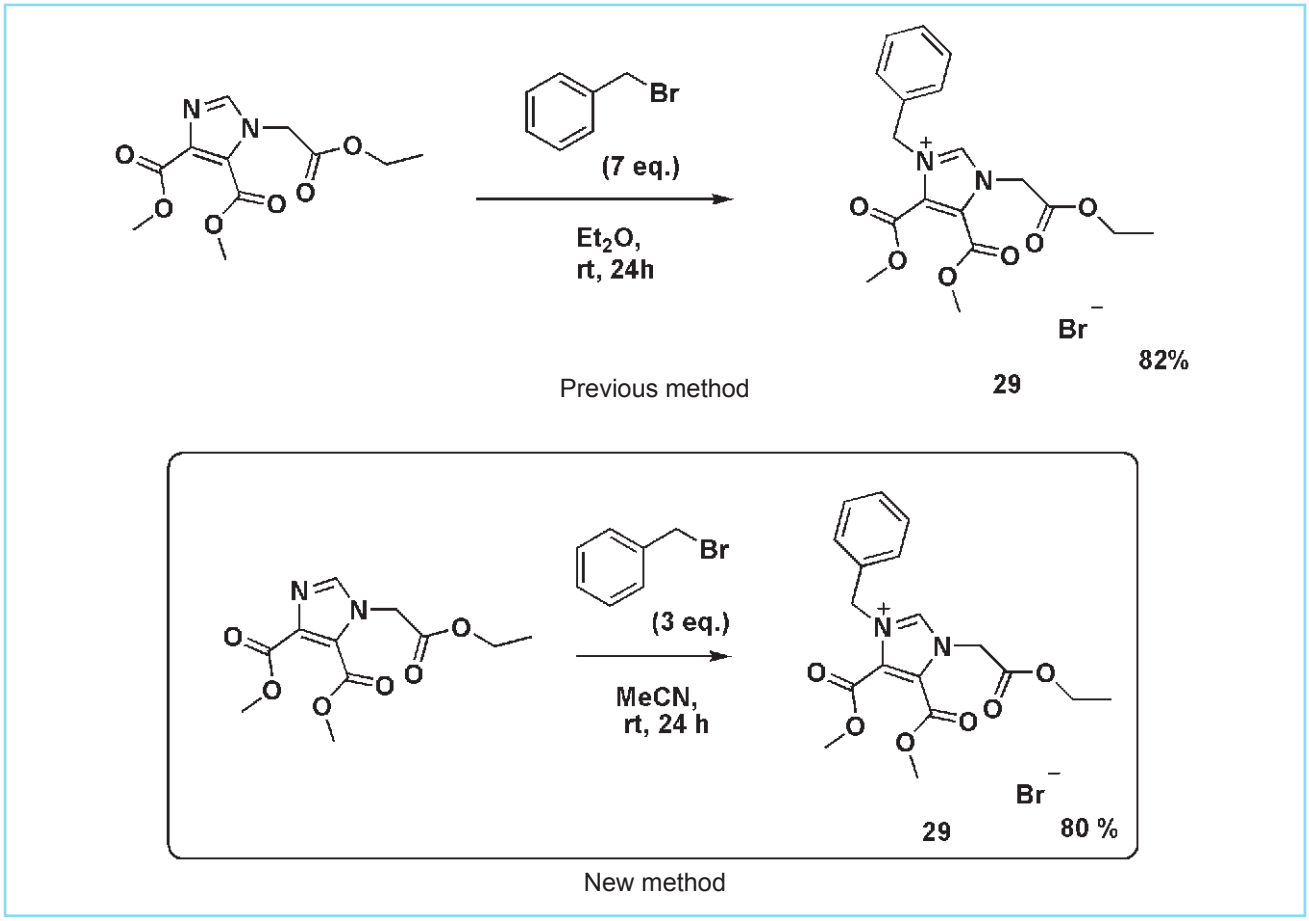
Scheme 2.6. Synthesis of 4,5-diester substituted ionic liquids (ILs) – fourth generation.



Scheme 2.7. Synthesis of 4,5-diamide substituted ionic liquids (ILs).



Scheme 2.8. Improved synthesis of diamide imidazole.



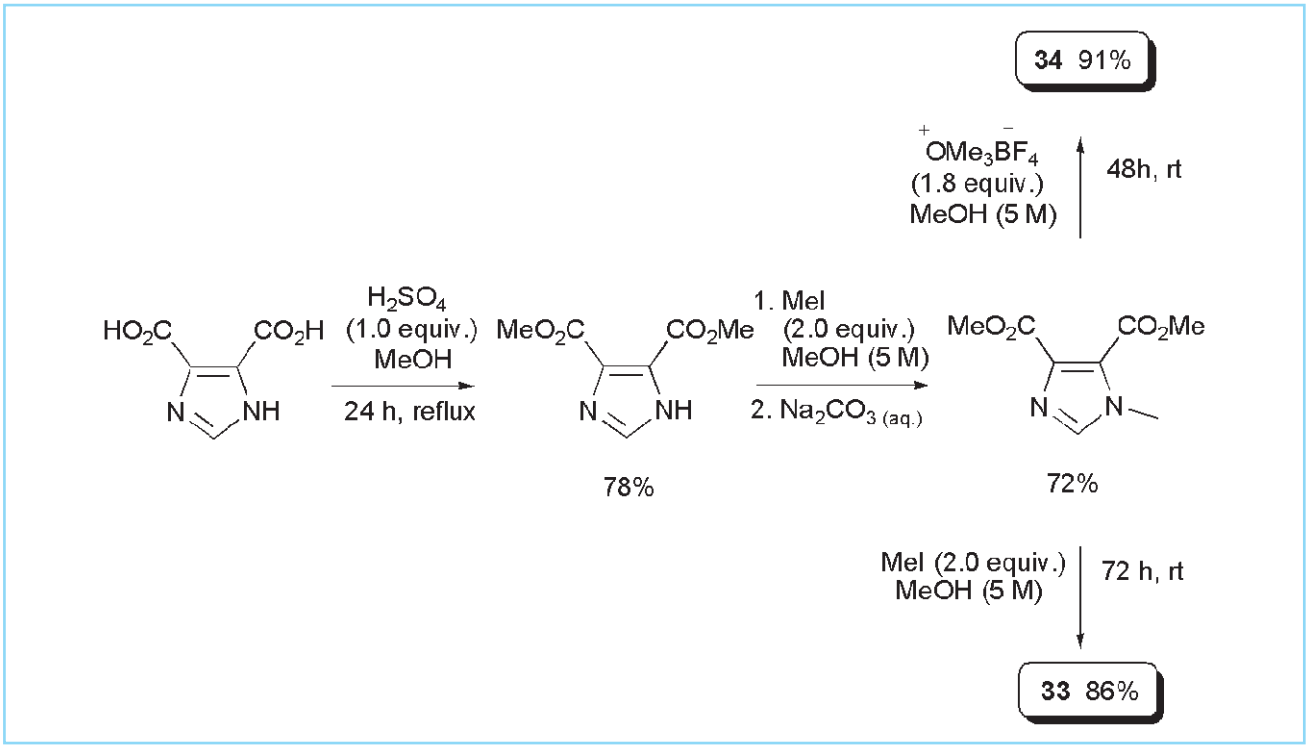
Scheme 2.9. Improved synthesis of 4,5 diester 29.

2.6 Optimisation in Catalyst Synthesis

Part of our research strategy was to replace 'traditional synthetic methods' with 'a greener alternative' – where appropriate and possible – within the time frame of the project. This included reducing or eliminating hazardous chemicals from a reaction step, solvent telescoping, reducing the number of steps, reducing quantities of reagents and catalysts. Example of avoiding the use of toxic solvents (DCM and hexane), and corrosive reagents PCl_5 and replacing them with a 'solventless' alternative is given in Scheme 2.8. In addition, a four-day reaction was replaced with a 3.5 h microwave promoted alternative.

Scheme 2.9 demonstrates how a reduction in the amount of benzylbromide for 7 eq. to 3 eq. is possible by changing the solvent. Less than half the orginal quantity of reagents is now required.

In Scheme 2.10 methanol is used as the solvent for all three steps (telescoping), leading to more energy-efficient chemical processing as the rigours of drying/ removal of incompatible solvents are allieviated.



Scheme 2.10. Synthesis of 33 and 34 from the inexpensive diacid.

3 Applications of Ionic Liquids in Acetalisation Reactions

3.1 Rationale

Connon and Procuranti (2007, 2008) reported an application of pyridinium salts as effective catalysts of acetalisation reactions. An ester group at either the 3 or both the 3 and 5 positions of the pyridinium ring has shown excellent catalytic activity with very low catalyst loading in the acetalisation of benzaldehyde with methanol. Interestingly, the catalyst is not acidic in nature, but can act as a Brønsted acid in the presence of protic media. The most active catalyst pyridinium, 3,5-*bis*(ethoxycarbonyl)-1-(phenylmethyl) bromide showed excellent catalytic activity (5 mol% loading) in the protection of a variety of aldehydes with methanol and was also found to be useful in diol and dithiol protections as shown in Scheme 3.1 (Procuranti and Connon, 2007) (Procuranti and Connon, 2008) (Procuranti et al., 2009). Its catalytic activity was predicted to occur through nucleophilic attack of the alcohol to the pyridinium to generate Brønsted acidic species. On the basis of these studies, imidazolium IL catalysts for acetalisation reactions have been designed.

3.2 Imidazolium Ionic Liquid/Catalyst (First Generation) for Acetalisation Reactions

A range of ester and amide side-chain imidazolium ILs was prepared. The catalytic activity of all these imidazolium salts was evaluated by their performance in the acetalisation of benzaldehyde in methanol (Scheme 3.1). In the absence of catalyst, acetalisation was not found to occur after 24 hours. Each of the bromide salts showed poor catalytic activity, independent of ester or amide side-chain (9% to 13% conversions) and 1,2-dimethylimidazolium and 1-benzylimidazolium cations did not demonstrate any significant effect. When the anion, *bis*(trifluoromethane sulfonimide) was used, conversions using amide side-chain ILs were increased marginally (up to max. 29%), whereas ester side-chain ILs (**3**) with the NTf_2 anion gave 51% conversion.

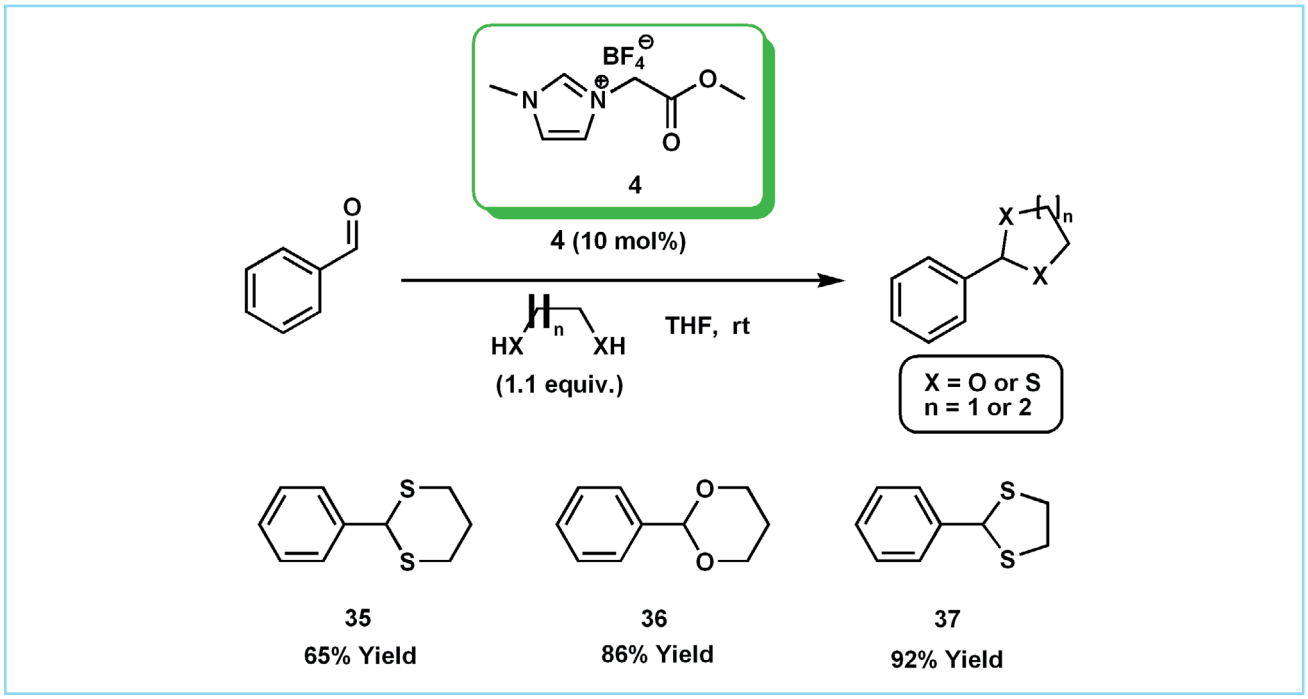
At 5 mol% loading the BF_4^- salt of the methyl ester side-chain imidazolium cation (**4**) gave the highest conversion, 85%, to the required product.

Hexafluorophosphate (PF_6^-) and octyl sulfate ($OctOSO_3^-$) derivatives performed poorly in this reaction with 33% (**5**) and 12% (**6**) yields obtained respectively. Hence, anion exchange from Br^- to BF_4^- greatly influenced the acetalisation of benzaldehyde with methanol.

One of the important characteristics of this IL catalyst was its lack of acidity which eliminates handling hazards. It was proposed that the catalyst was able to generate an active Brønsted acidic species, but only in the presence of a protic medium. In the presence of methanol, methanol probably attacks the 2-position of the imidazole, as it is the most electron deficient, to generate the Brønsted acid HBF_4.

The most active first-generation imidazolium catalyst **4** was further studied in the acetalisation of a variety of aldehydes with methanol at room temperature. These reactions showed good to excellent conversions with 5–10% catalyst loading. The saturated aldehyde 3-phenylpropanal reacted with deuterated methanol in the presence of 1 mol% catalyst and gave quantitative conversion in only 1 minute. The diol and dithiol protection of benzaldehyde also showed very good results.

The BF_4^- catalyst **4** promoted protection of benzaldehyde with 1,2-ethanedithiol and gave 92% conversion (**37**), whereas 1,3-propanedithiol and 1,3-propanediol gave **35** (65% conversion) and **36** (86% conversion) respectively (Scheme 3.1). Recyclability evaluation of the most active BF_4 anion catalyst **4** was performed using the 1,3-dithiolane protection of benzaldehyde. After 24 h of reaction, a co-solvent was added in order to precipitate the catalyst from the reaction mixture and the dissolved product could then be decanted in order to isolate the catalyst. Catalyst **4** was recycled and reused 15 times without any significant decrease in activity (Fig. 3.1).



Scheme 3.1. Diol/dithiol protection of benzaldehyde.

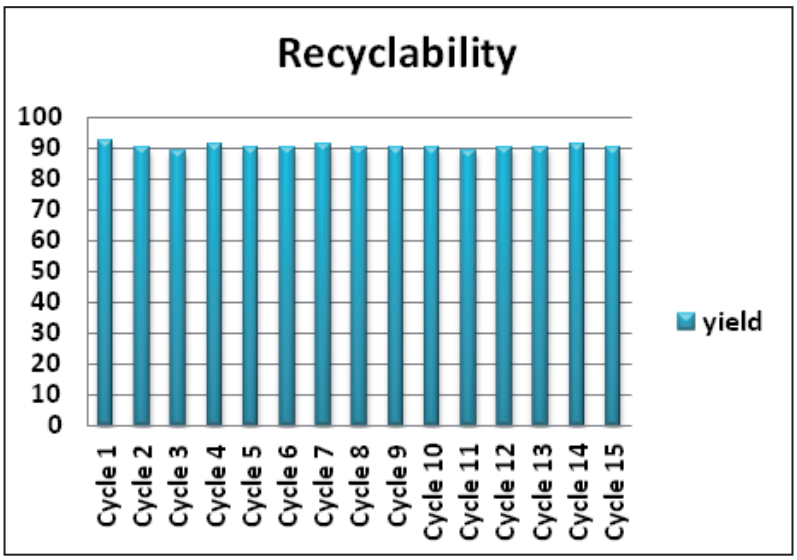


Fig. 3.1. Recyclability of ionic liquid (IL) catalyst 4.

3.3 Imidazolium Ionic Liquid/Catalyst (Second Generation) for Acetalisation Reactions

Biodegradation studies of pyridinium-based ILs have shown that ester substitution at either the 1 or 3 position has a beneficial effect on the degradation of the heterocyclic core, regardless of the anion (Harjani et al., 2009). Moreover, previously published biodegradation studies have shown that only the side-chain of the imidazolium ILs undergo degradation, whereas the imidazole core was found to persist in most OECD tests (Stolte et al., 2008). Hence, in an effort to increase the biodegradation, ester substitution of the imidazole ring was designed. In addition, incorporation of electron withdrawing groups via ester substitution of the imidazole ring was expected to increase catalytic activity of the ILs in the acetalisation reaction. A series of ester and amide substituted derivatives at the C-2, C-4

and both the C-4 and C-5 positions of the imidazolium ILs were designed, prepared and tested using the acetalisation of benzaldehyde with methanol (Myles et al., 2013) (Gore et al., 2013).

Table 3.1. Acetalisation of benzaldehyde using modified second-generation imidazolium ionic liquid (IL) as a catalyst.

Entry	Ionic liquid (IL) catalyst	Loading (mol %)	Conversion (%)
1	**14***	10	94
2	**19**	10	99
3	**12**	1	83
4	**14**	1	86
5	**15**	1	80
6	**17**	1	86
7	**19**	1	91
8	**18**	1	85
9	**19**	0.1	72

*Note: All compound numbers are bold in tables throughout document.

Ester and amide substitution at the C-2 position of imidazolium ILs (Schemes 2.3–2.5) has been found to greatly increase the catalytic activity. At the starting point of the catalyst screening process, BF_4^- salts of both ester- and amide-substituted ILs were selected as catalysts in the acetalisation of benzaldehyde. Catalyst **14** with amide substitution at the C-2 position showed 94% conversion, whereas ester-substituted IL **19** gave quantitative conversion (Table 3.1). Furthermore, all C-2 substituted IL catalysts were tested at 1 mol% loading for the acetalisation of benzaldehyde and when the amount of the catalyst **19** was decreased to 0.1 mol%, conversion decreased to 72% (Entry 9, Table 3.1). This can be supported by the proposed mode of action (Section 3.2). C-2 substituted ILs are more sterically hindered which may account for this drop in yield. Almost all C-4 and C-5 di-subtituted imidazolium IL catalysts have shown quantitative conversions with 1 mol% catalyst loading.

While it was clear that the first- and second-generation Il/catalyst represented a considerable step forward in terms of catalytic actvity, we were aware that the designs were not optimal. One particular cause for concern was the location of the electron-withdrawing group: while installing this at C-2 allows the maximum amount of both inductive and mesomeric forms of electron withdrawal to be exerted by the amide/ester moiety at the proposed site of nucleophilic attack by methanol, it also introduces a degree of counterproductive steric crowding (i.e. **14** and **19**), which would be expected to limit catalyst performance.

3.4 Imidazolium Ionic Liquid/Catalyst (Third Generation) for Acetalisation Reactions

It therefore seemed prudent to design a library of catalysts characterised by the location of the electron-withdrawing group at a further remove from C-2. The C-4 substituted analogues **21**–**26** were therefore duly prepared and evaluated under identical conditions (Table 3.2). This strategy was successful – when utilised at 1 mol% loading, catalysts **21**–**24** and **26** promoted the reaction in essentially quantitative yield (Entries 1–4 and 6). Imidazolium ion **25** (which incorporates an iodide counteranion) is also an excellent catalyst (the product is formed in 95% yield) yet is perceptibly less active than the other members of the library (Entry 5). Since the ranking of **21**–**24** and **26** on the basis of activity could not be determined at 1 mol% loading, these materials were then re-evaluated at 0.1 mol% levels under otherwise identical conditions. Product yields remained high (Entries 7–12), but none of the catalysts was capable of promoting the reaction to >90% yield inside 24 h. The nature of the anion-activating substituent (*i.e.* ester *vs.* amide) and *N*-alkyl moiety appears to have little impact on efficacy in these systems.

Table 3.2. Aprotic C-4 substituted imidazolium ions: catalyst evaluation.

Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**23**	1	>98
2	**24**	1	>98
3	**21**	1	>98
4	**22**	1	>98
5	**25**	1	95
6	**26**	1	>98
7	**23**	0.1	81
8	**24**	0.1	88
9	**21**	0.1	78
11	**22**	0.1	86
12	**26**	0.1	85

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

3.5 Imidazolium Ionic Liquid/Catalyst (Fourth Generation) in Acetalisation Reactions

Given the dramatic effect of the introduction of one electron-withdrawing group (especially when not located at C-2) on catalyst activity, the final step in the optimisation study involved the design of catalysts characterised by the presence of two such groups at C-4 and C-5 (Table 3.3). As expected, catalysts **27**–**34** all proved highly active at 1 mol% levels (Entries 1–8), with only the iodide **33** failing to promote the reaction to completion (Entry 7). At 0.1 mol% loading, product yields were attenuated: however, using catalysts incorporating the tetrafluoroborate counteranion (*i.e.* Entries **10**, **12**, **14** and **15**), yields remained over 90%.

Table 3.3. Aprotic C-4/C-5 disubstituted imidazolium ions: catalyst evaluation.

Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**29**	1	>98
2	**30**	1	>98
3	**27**	1	>98
4	**28**	1	>98
5	**31**	1	>98
6	**32**	1	>98
7	**33**	1	98
8	**34**	1	>98
9	**29**	0.1	89
10	**30**	0.1	94
11	**27**	0.1	86
12	**28**	0.1	92
13	**31**	0.1	82
14	**32**	0.1	91
15	**34**	0.1	92

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

In addition to the catalyst activity exhibited by the optimum structure identified by this study (*i.e.* **30**), the performance of the simple structures **33** and **34** was also particularly gratifying: these materials are readily prepared from the inexpensive 4,5-imidazole carboxylic acid in a relatively atom-economic fashion (see Scheme 2.11) and are capable of acting as synthetically useful catalysts at loadings 5–50 times lower than those previously necessary using the optimal first-generation material **4**. Their activity is such that one is no longer dependent on the nature of the anion to ensure high product yields – the iodide **33** can promote the formation of benzaldehyde dimethyl acetal in >90% yield at just 1 mol% loading. The general catalyst order of activity (*i.e.* C-2 substituted < C-4 substituted < C-4/C-5 disubstituted) and the diminished influence of the anion relative to the case with **4** is in line with what one would expect from the mechanistic hypothesis outlined in Scheme 5.1, which provides further evidence supporting this most unusual proposed mode of action.

3.5.1 Substrate Scope

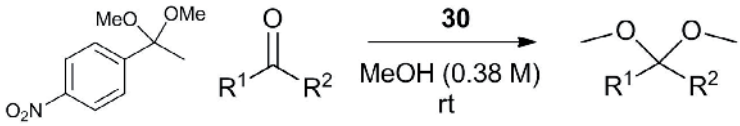
With an active and easily prepared catalyst in hand, research focus then turned to the question of substrate scope (Table 3.4). Catalyst **30** could catalyse the smooth acetalisation of activated- (Entries 1–3), hindered- (Entry 4), deactivated- (Entry 5), heterocyclic- (Entry 6) and α,β-unsaturated aldehydes (Entry 7) with higher (excellent) isolated product yields *at 10–50 times lower catalyst loading* (in shorter reaction times) than those required for the synthesis of these acetals using catalyst **4**. We also found that **30** could promote the ketalisation of *p*-nitrobenzaldehyde in good yield – a reaction which was completely beyond the scope of catalyst **4**.

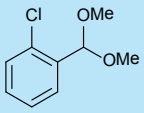
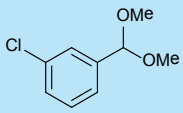
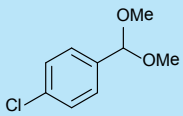
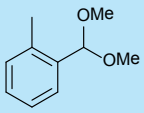
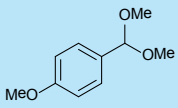
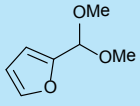
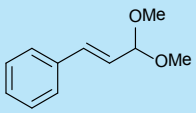
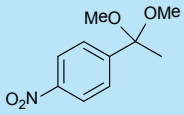
The synthetically useful dithiolane (a product usually formed under elevated temperatures) and dioxane derivatives **37** and **36** could also be formed from benzaldehyde in good to excellent yields at room temperature catalysed by **30** at low loading (Scheme 3.2).

3.5.2 Catalyst Recycling

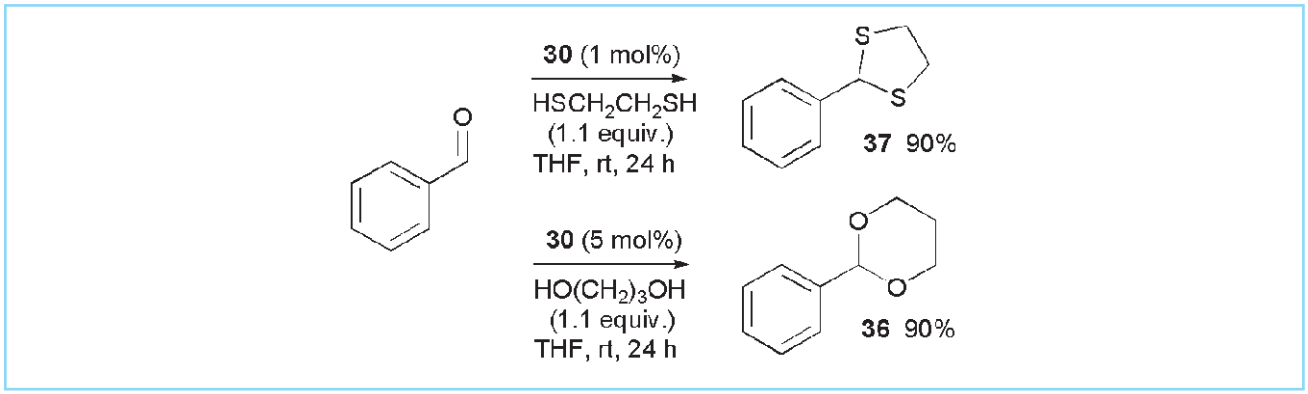
While at this juncture the superior activity and potential utility of **30** (relative to **4**) was beyond doubt, we were also interested in evaluating the recyclability of **30**. We carried out the protection of benzaldehyde as its dithiolane derivative **37** (Table 3.5). After 24 h, co-solvent was added to precipitate the catalyst and the solution containing the product was decanted and dried *in vacuo* to give **37** in an excellent yield. The solid catalyst was dried *in vacuo* to remove the condensation water and reused in five subsequent iterative cycles *without any loss of catalytic activity being observed*. The study was terminated at this point as the catalyst appeared to be beginning to show physical signs of decomposition. While **30** could not be recycled as many times as **4** (which was recycled in our previous study 14 times), **30** was employed at considerably lower loading in this study (1 mol% vs 10 mol%), and as such can be considered more recyclable than **4** due to its significantly superior turn over number (TON) over the accumulated cycles.

Table 3.4. Catalytic acetalisation/ketalisation: evaluation of substrate scope.



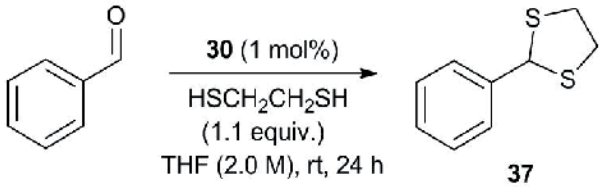
Entry	Product	Loading (mol%)	Time (h)	Yield (%)[a]
1		0.1	24	95
2		0.1	24	96
3		0.1	24	98
4		1	24	90
5		1	24	92
6		1	24	92
7		1	24	90
8		10	48	63[b]

[a]Isolated yield after chromatography. [b]Reaction at 35 °C



Scheme 3.2. Dithiolane/dioxane formation: stoichiometric nucleophiles.

Table 3.5. Catalyst recycling.



Entry	Cycle	Yield (%)[a]
1	1	94
2	2	94
3	3	94
4	4	95
5	5	94

[a]Determined by ^{1}H NMR spectroscopy using an internal standard.

4 Applications of Imidazolium Ionic Liquids (First and Second Generation) in Asymmetric Carbonyl-Ene Reaction of Trifluoropyruvate

4.1 Rationale

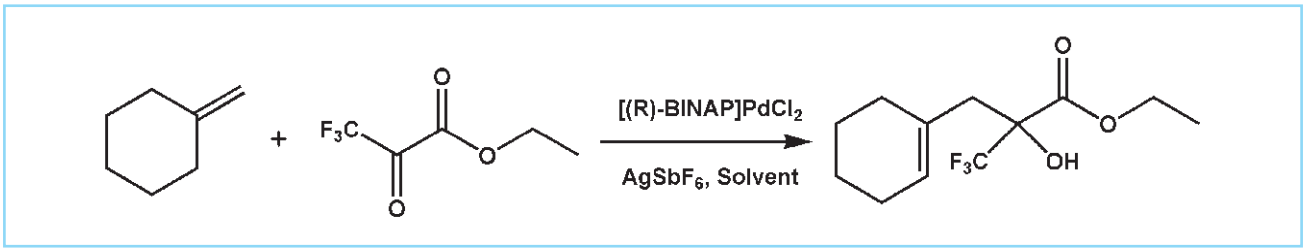
The current research effort was directed by the development of environmentally friendly ILs, which can also offer performance advantages over established methods. In previous studies, these ILs have shown their performance in reactions such as Diels-Alder (Bouquillon et al., 2007), hydrogenation (Bouquillon et al., 2007) (Morrissey et al., 2009) and acetalisation (Myles et al., 2010). Scheme 4.1 presents the 'Enantioselective Carbonyl-Ene Reactions of trifluropyruvate catalysed by chiral Palladium(II)-BINAP catalyst in low toxicity Ionic Liquids'. The performance of these ILs is investigated with comparison to conventional ILs and common organic solvents, as well as the recyclability of the catalyst/IL media.

4.2 Scope of Ionic Liquids as a Solvent

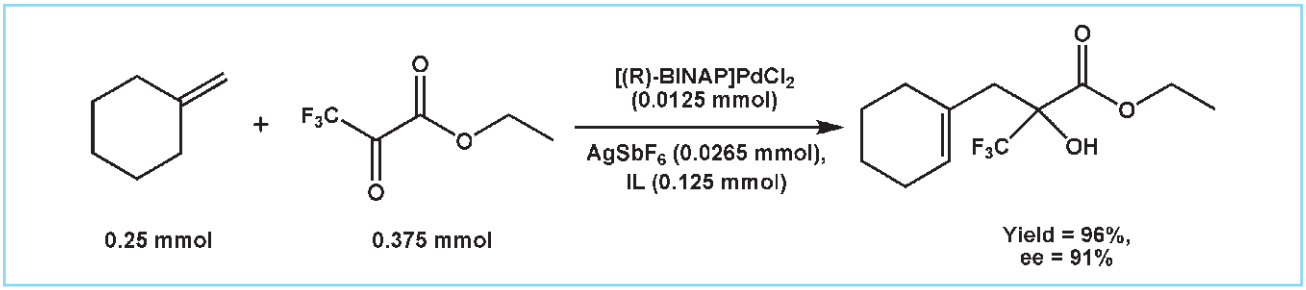
Dichloromethane is the commonly used solvent for the carbonyl-ene reaction. The difficulty of recycling the expensive palladium catalyst from the traditional organic solvents is one limitation of this reaction. Along with some traditional organic solvents a number of ester- and amide- side-chained ILs have been used as a solvent in this reaction (Table 4.1).

4.3 Optimisation of Reaction Conditions

Optimal reaction conditions (Scheme 4.2) were investigated by varying a number of parameters such as amount of either substrates, amount of catalyst and IL, temperature and time required for the reaction.

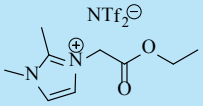
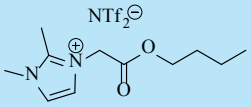
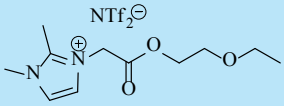
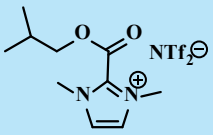
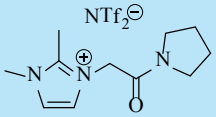
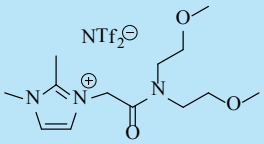
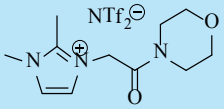
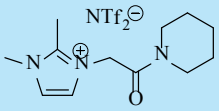
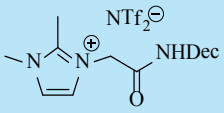


Scheme 4.1. Carbonyl-ene reaction with ethyl trifluoropyruvate.



Scheme 4.2. Carbonyl-ene reaction in low antimicrobial toxicity ionic liquid (IL).

Table 4.1. Solvent screen.

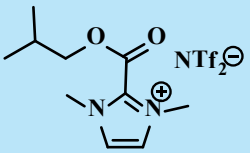
Entry	Solvent	Isolated yield (%)	ee (%)
1	Dichloromethane	93	90
2	Diethyl ether	68	98
3	Tetrahydrofuran	0	-
4	Toluene	84	96
5		76	85
6		78	90
7		77	89
8		96	91
9		89	92
10		85	89
11		90	91
12		89	91
13		82	92

Ee: enantiomeric excess

4.4 Recyclability

C-2-ester substituted IL has shown good recyclability up to six recycles maintaining high yield and enantiomeric excess (Table 4.2). Due to the possible catalyst immobilisation, the expensive palladium catalyst was recycled and reused along with IL.

Table 4.2. Recycling study.

Cycle	ester IL	Yield (%)	ee (%)
1		96	91
2		92	91
3		90	92
4		92	93
5		92	93
6		90	92
7		92	91
8		77	84

Ee: enantiomeric excess

4.5 Substrate Scope

The IL and catalyst reaction media was found to be effective with a variety of cyclic/acyclic alkenes (Fig. 4.1). A good to excellent enantiomeric excess was observed with the good yields.

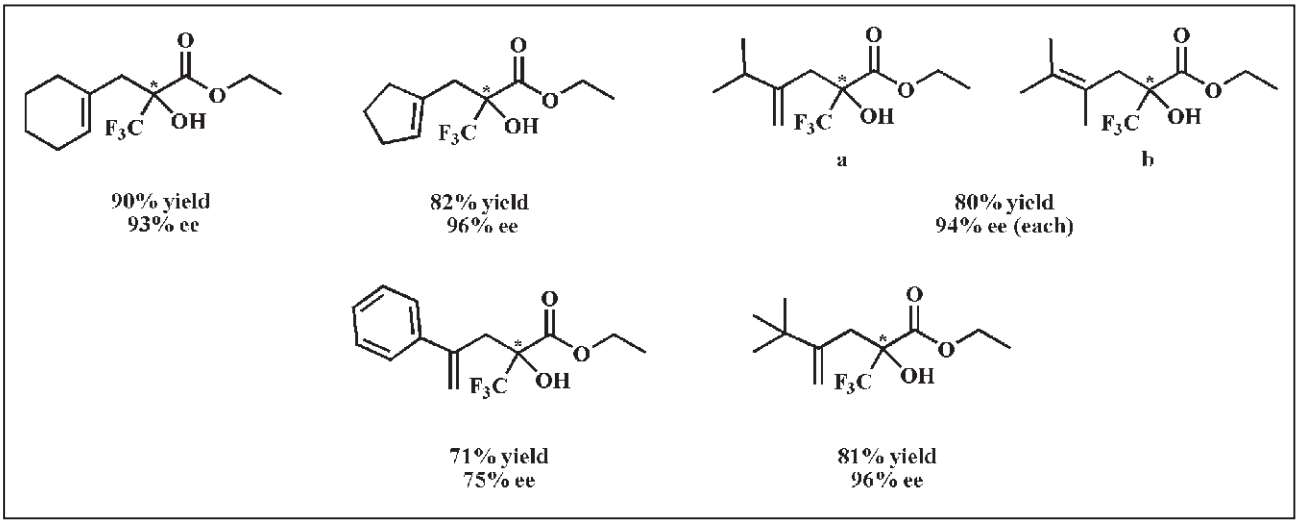


Figure 4.1. Substrate scope.

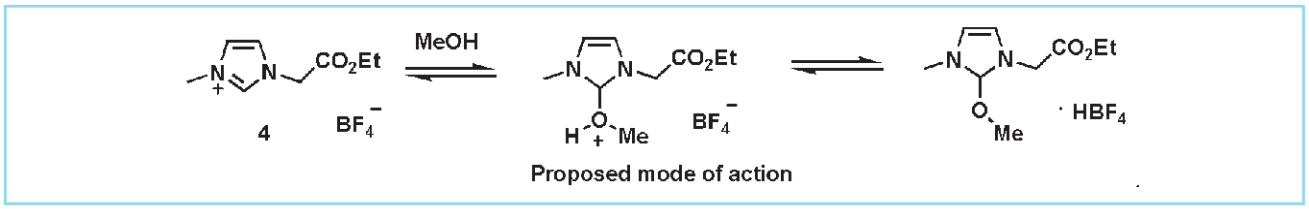
5 Catalysis Studies – Acid Catalysis beyond Acetalisation

5.1 Hydrolysis

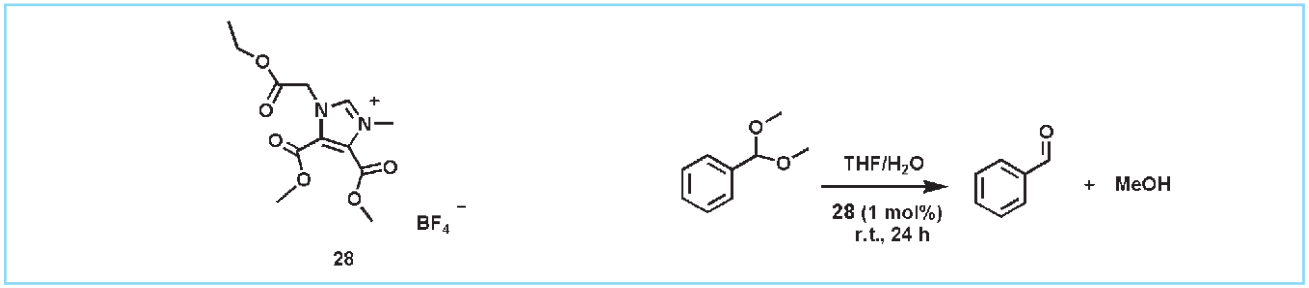
Based on the mode of action of the catalyst (Scheme 5.1), the reverse reaction of the acetalisation, that is, the hydrolysis of the acetal to furnish the aldehyde is feasible. Using the benzaldehyde dimethyl acetal, this proved to be the case for substrate **28**, giving the benzaldehyde in yield >98% (Scheme 5.2). Based on this premise the deprotection of dithianes should also occur. However, this reaction is known to be difficult, generally requiring harsh reagents such as mercury salts or metal-based compounds such as copper(II) nitrate. These reagents are also generally used in either high loadings or quantitatively. Owing to the previously observed affinity of **29** for thiols we wanted to determine if it could be employed as a mild deprotecting agent for dithianes. An initial reaction was carried out using **38** (Scheme 5.3), furnishing the benzaldehyde in 46% yield.

5.1.1 Optimisation

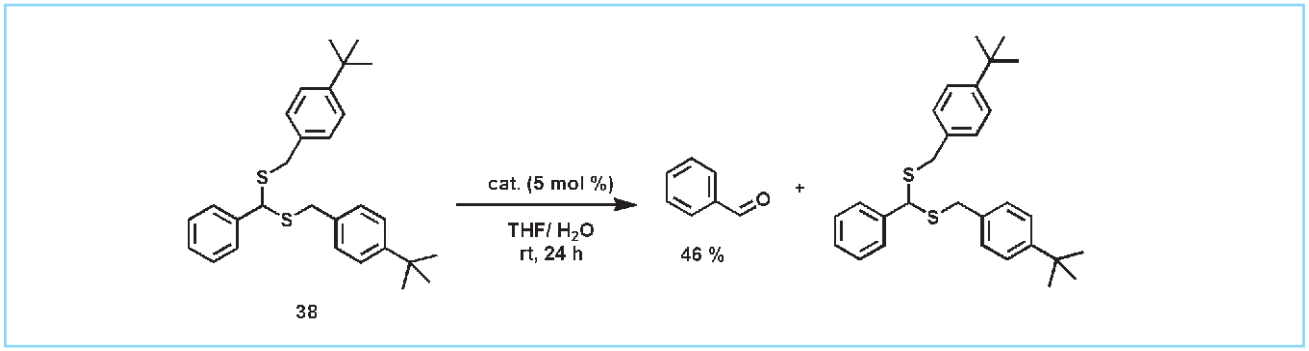
This promising result led to the optimisation of the hydrolysis of the dithiane **38** using catalyst **28,** eventually giving benzaldehyde in 92% yield with 10 mol% catalyst in two 5 mol% additions over 48h (Scheme 5.4).



Scheme 5.1. Catalyst mode of action.



Scheme 5.2. Hydrolysis of methyl acetal.



Scheme 5.3. Dithiane deprotection using catalyst 28.

The hydrolysis of the more synthetically useful dithane and ditholane was then carried out under these optimised conditions with **35** hydrolysing to benzaldehyde with a 71% yield after 48h and 20 mol% catalyst. Further optimisation was then carried out of the reaction to yield conversions of catalytically useful yields for the 5 and 6 membered dithianes. After multiple experiments the solvent system was changed to one of dioxane:water (10:1) (Scheme 5.5), leading to yields of 76% (5 membered) and 86% (6 membered).

A second method of deprotection involved the use of a 'sacrificial' aldehyde which reacted with the generated dithiane, hence preventing the reformation of the dithiane with the desired aldehyde product. Various aliphatic aldehydes were added to the reaction, both with solvent and as solvent (as outlined in the Table 5.1). It was found that the most effective aldehyde additive was propanal: the use of this aldehyde as a solvent gave a yield of 81%.

Table 5.1. Effect of aldehyde additive.

Solvent	Yield (%)
Propanal	81
Butanal	80
Pentanal	79
Propanal (10 eq)/dioxane	77

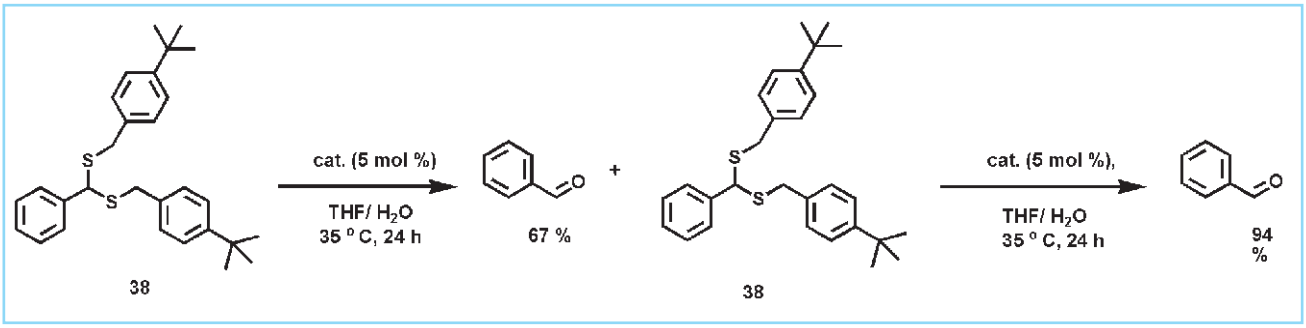
5.1.2 Substrate Scope

Two effective methods of dithiane hydrolysis were therefore developed. The substrate scope with respect to aldehyde-derived dithaines was then investigated with various dithianes formed and deprotected using the imidazole catalyst. Table 5.2 lists the aldehyde products and their respective yields.

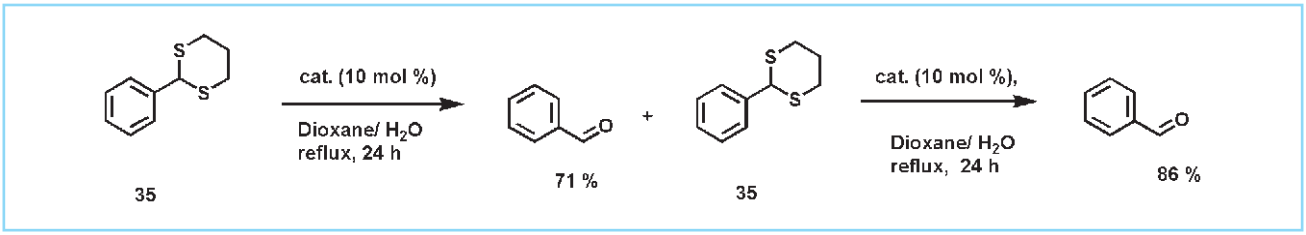
Table 5.2. Substrate scope.

Aldehyde	Yield (%)
2-chlorobenzladehyde	78
3-chlorobenzaldehdye	84
4-chlorobenzaldehyde	86
o-tolualdehyde	65
3-methoxybenzaldehyde	76
4-methoxybenzaldehyde	74
2-thiophenaldehyde	78
Hydrocinnamaldehyde	85

Ketone-derived dithianes was also attempted using the method with dioxane and water as solvent. However, low yields were observed for the ketones with the highest yield obtained for acetophenone dithiane being 32%. Higher yields were obtained under microwave conditions, with 58% obtained for acetophenone and yields of 62% for activated *p*-NO_2 acetophenone and 53% for aliphantic cyclohexanone.



Scheme 5.4. Optimised deprotection of dithiane.



Scheme 5.5. Optimised deprotection of cyclic dithiane.

5.2 Conclusion

The deprotection of a dithane derived from aldehydes has been demonstrated with high efficiency using an imidazolium catalyst. Ketone-derived dithanes, considerably more challenging substrates, were also deprotected in 50–60% yield, after considerable optimisation and refinement of the reaction conditions. These ‘green’ deprotection methods are of immense interest to chemists in academia and industry.

6 Antimicrobial Toxicity Assessment of Ionic Liquids/ Catalysts

6.1 Rationale

ILs have been studied extensively in organic chemistry due to their unique properties such as low vapour pressure, high thermal stability, recyclability, non-flammability, and control over the product distribution (Rogers and Seddon, 2002). They have shown tremendous potential as reagents, non-volatile solvents and catalysts (Plechkova and Seddon, 2008) (Wasserscheid and Stark, 2010). As a result, ILs have already generated – and are continually generating – great interest from the chemical industry. Further, many of these ILs are totally synthetic novel compounds. Hence, it is important to check their toxicity and eco-toxicological properties: biodegradation and bioaccumulation of these materials must be studied. Although toxicity testing can be useful as the primary step towards the study of biodegradation, computer modelling can also be useful for predicting the biodegradation (Hallett, 2011) (Hubbard et al., 2011) (Wasserscheid and Joni, 2010, pp. 41–63) (Chowdhury et al., 2007) (Stark and Seddon, 2007, pp. 836–920) (Myles et al., 2010) (Gujar and White, 2009). Working with our collaborator in the Czech Republic (CZ), a panel of 12 fungi and 8 bacteria was selected. ILs which have low antimicrobial toxicity in the CZ screen (test only validated to maximum concentration of 2 mM) were then prioritised for addition antimicrobial toxicity screening at high concentrations at Dublin City University (DCU). The strains screened in DCU are more commonly found in the environment.

6.2 Procedure

6.2.1 Antifungal Toxicity Screening

In vitro antifungal activities (Clinical Laboratory Standard Institute, 2008a and 2008b) of the compounds were evaluated on a panel of four ATCC strains (*Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon asahii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Charles University, CZ. Three ATCC strains were used as the quality control strains. All the isolates were maintained on Sabouraud dextrose agar before testing.

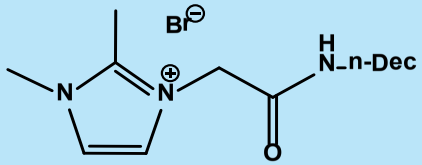
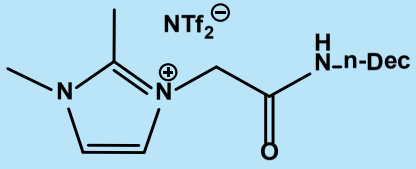
6.2.2 Antibacterial Toxicity Screening

In vitro antibacterial activity (Clinical Laboratory Standard Institute, 2006) of the compounds were evaluated on a panel of three ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus aureus* MRSA HK5996/08, *Staphylococcus epidermidis* HK6966/08, *Enterococcus* sp. HK14365/08, *Klebsiella pneumoniae* HK11750/08, *Klebsiella pneumoniae* ESBL HK14368/08) from the collection of bacterial strains deposited at the Department of Biological and Medical Sciences, Charles University, CZ. The above-mentioned ATCC strains also served as the quality control strains. All the isolates were maintained on Mueller-Hinton agar before testing.

6.2.3 Study of Toxicological Effect of 1,3 and 1,2,3-substituted Imidazolium Cations – First Generation

The bromide salts of ILs containing ester and amide side-chains were non-toxic up to 2000 μM with the exception of compound **39**. ILs with ester-side-chain (i.e. methyl, butyl and ethoxyethyl) were found to not inhibit the growth of all fungi and bacteria up to 2000 μM concentration after 48 hours. A similar response was observed in ILs with amide side-chains of cyclic amines **2, 8, 9,** pyrrolidine, piperidine and morpholine. IL **39** demonstrated inhibition of growth in the tested fungi and bacterial strains at different concentrations (Tables 6.1 and 6.2). This is due to the long alkyl side-chain of the cationic component. This observation is in agreement with literature observations. (Opallo and Lesniewski, 2011) (Shiddiky and Torriero, 2011) (Liu et al., 2010) (Pitner et al., 2010, p. 191–201) (Buzzeo et al., 2004). In most of the strains, antifungal and antibacterial toxicity of

Table 6.1. MIC_{80} values of ILs 39 and 40 in antifungal screening (Concentration in μM).

	Time / Strain	*Candida albicans* ATCC 44859	*Candida albicans* ATCC 90028	*Candida parapsilosis* ATCC 22019	*Candida krusei* ATCC 6258	*Candida krusei* E28	*Candida tropicalis* 156	*Candida glabrata* 20/I	*Candida lusitaniae* 2446/I	*Trichosporon beigelii* 1188	*Aspergillus fumigates* 231*	*Absidia corymbifera* 272*	*Trichophyton mentagrophytes* 445*
 **39**	24h	125	125	62.5	7.81	3.9	3.9	31.25	250	250	250	250	250 [a]
	48h	250	125	62.5	7.81	3.9	3.9	62.5	250	250	250	250	250 [b]
 **40**	24h	250	250	62.5	31.25	15.62	15.62	62.5	250	250	250	>1000	250 [a]
	48h	250	250	125	31.25	31.25	31.25	125	250	500	500	>1000	250 [b]

* MIC_{50} values were determined, [a] MIC_{50} after 72h, [b] MIC_{50} after 120h

39 observed after 24h was retained after 48h, whereas in some cases toxicity was decreased after 48h. This is probably caused by the parent IL being broken down into metabolites with a lower toxicity profile toward the test microrganism.

6.3 Study of Toxicological Effect of Anions

In order to check the effect of anions in the test system, a variety of commonly used anions incorporated with cations discussed above were selected. All the anions of methyl ester-side-chain ILs, that is NTf_2^- (**3**), BF_4^- (**4**), PF_6^- (**5**) and $OctOSO_3^-$ (**6**) and ILs with butyl and ethoxyethyl ester side-chain with NTf_2 anions were found to be non-toxic up to 2000 μM concentration in the test system.

Similar results were obtained with amide side-chain ILs **7**, **10**, **11** (pyrrolidine amides) and morpholine amides. Piperidine amide side-chain salts of NTf_2^-, BF_4^-, $OctOSO_3^-$ and $N(CN)_2^-$ anions were also non-toxic up to 2000 μM concentration. Again, only the decyl amide side-chain IL (**40**) resulted in toxicity (<2000 μM) against all fungi (except *Absidia corymbifera* [272]) and bacteria (except *Pseudomonas aeruginosa* (ATCC [9027]). It was significant that the toxicity of the decyl amide side-chain IL decreased, when incorporated with the NTf_2 anion, if compared with its bromide salt. Overall, significant toxicity effects of different anions incorporated with imidazolium ILs were not found in the current test system.

6.4 Study of Toxicological Effect of Modifications at C-2-position of Imidazolium Core – Second Generation

Ester and amide substitution at the C-2-position of the imidazole core was designed to facilitate biodegradation of the derivatised ILs. Hence, toxicity assessment, especially antimicrobial toxicity studies, were an important step towards designing safer modified imidazolium ILs.

All the ILs (**12**–**19**), with different anions, were subjected to the test system. No significant toxicity was observed up to 2000 μM concentration. ILs with isobutyl ester (**17**, **18** and **19**) and primary amide functionalities (**12**–**16**) at 2-position did not show any anti-fungal or anti-bacterial toxicity in screen. Although a variety of anions were incorporated with the imidazolium-core-modified ILs, no significant anion effect was observed.

6.5 Study of Toxicological effect of Modifications at C-4-position of Imidazolium Core – Third Generation

Antimicrobial activity was not observed for **20**–**25** (Fig. 2.1) at the highest concentration screened (2.0 mM). Functional groups around the C-1 CH_2CO_2Et imidazolium motif tolerated by the fungi and bacteria strains screened include: (i) -CH_2 ester (-$CH_2CO_2CH_2CH_3$), at C-4, and alkyl (methyl) at C-3; bromide (**20**), iodide (**21**) and BF_4 (**22**); (ii) -CH_2 ester (-$CH_2CO_2CH_2CH_3$), at C-4, and benzyl at C-3, bromide (**23**), and BF_4 (**24**); (iii) CH_2amide (-$CH_2CONC_4H_8$) at C-4, amide (-$CONH_2$) at C-2, and benzyl at C-3; bromide (**25**).

We were pleased that substitution with an ester or amide in the C-4 position of the imidazoilium ILs, for a range of C-1 and C-3 substituted examples, did not increase antimicrobial toxicity.

6.6 Study of Toxicological Effect of Modifications at C-4/5-position of Imidazolium Core – Fourth Generation

In tandem with our search for more active catalysts 4,5 disubstituted imidazolium structures were proposed. Given the dramatic effect of the introduction of one electron withdrawing group (especially when not located at C-2) on catalyst activity, the final step in our optimisation study involved the design of catalysts characterised by the presence of two such groups at C-4 and C-5 (Fig. 2.1).

ILs based on the C-1 CH_2CO_2Et imidazolium motif (**27**–**31, 33 and 34**) were selected for direct comparison to earlier catalysts activity/toxicity/biodegradation. This series of compounds contained the first examples where hydrophobicity (reduced solubility in media for antimicrobial screening) was apparent. The solubility limit for **27** and **28** was 0.5 mM, and 1.0 mM for **31**. ILs **29** and **30** were soluble at the maximum concentration limit for the test 2.0 mM.

Table 6.2. MIC_{95} values of ILs 39 and 40 in antibacterial screening (concentration in μM).

	Strain	*Staphylococcus aureus* ATCC 6538	*Staphylococcus aureus* HK 5996/08	*Staphylococcus epidermidis* HK 6966/08	*Enterococcus sp.* HK 14365/08	*Escherichia coli* ATCC 8739	*Klebsiella pneumonia* HK 11750/08	*Klebsiella pneumonia ESBL* HK 14368/08	*Pseudomonas aeruginosa* ATCC 9027
	24h	62.5	125	31.25	125	250	500	1000	1000
	48h	125	125	62.5	125	500	1000	1000	1000
	24h	62.5	125	250	62.5	250	250	250	1000
	48h	62.5	125	250	125	250	250	250	>1000

Antifungal activity was not observed for **27**–**31** at the highest concentration screened (0.5, 1.0 or 2.0 mM) (Table 6.3). Functional groups around the C-1 CH_2CO_2Et imidazolium motif tolerated by the fungi and bacteria strains screened include: (i) -CH_2ester (-$CH_2CO_2CH_3$), at C-4 and C-5, and alkyl (methyl) at C-3; bromide (**27**) and BF_4 (**28**); (ii) -CH_2ester (-$CH_2CO_2CH_3$), at C-4 and C-5, and benzyl at C-3; bromide (**29**), and BF_4 (**30**); and (iii) CH_2amide (-$CH_2CONC_4H_8$) at C-4 and C-5, and benzyl at C-3; bromide (**31**).

Antimicrobial activity was observed for the first time for this class of compounds, however only to some Gram positive strains. ILs **27**–**31** did not show toxicity to the Gram negative strains (*E. coli*, *Klebsiella pneumoniae*, *Klebsiella pneumoniae-ESBL*, *Pseudomonas aeruginosa*). The Gram positive strain most sensitive to C-4, C-5 disustituted imidazolium ILs was *S. epidermidis* (MIC values 0.25 mM, **27**; 1.0 mM **29** and 2.0 **28**). IL **28** was also active against *S. aureus* H 5996/08 (MIC 2.0 mM), and **29** against *S. aureus* CCM 4516/08 (MIC 1.0 mM). ILs **28** and **31** were non-toxic to all bacteria screened unto the solubility limits, 0.5 mM and 1.0 mM, respectively.

A decision was made at this stage of the project to simplify the design of the catalyst. This was based on reducing the lipophilicity, thus improving water solubility, with the aim of designing low antimicrobial toxicity ILs/catalysts. A green chemistry metrics study (*vida supra*) was running concurrently with the catalyst peformance study, and the requirement for a short, efficient synthesis of the catalysts was now a priority. As such, ILs/catalysts **33** and **34** were prepared. IL **33** shows antifungal activity (MIC_{80}) against several strains at the concentration 0.5 mM.

Table 6.3. Antifungal activity of C-4/C-5 disubstituted (MIC [μM]).

Strain	Time (h)	MIC_{80} Values of ionic liquids (ILs) (Concentration in μM)						
		27	**28**	**29**	**30**	**31**	**33**	**34**
Candida albicans	24	>500	>500	>2000	>2000	>1000	**500**	>500
ATCC 44859	48	>500	>500	>2000	>2000	>1000	**500**	>500
Candida albicans	24	>500	>500	>2000	>2000	>1000	**500**	>500
ATCC 90028	48	>500	>500	>2000	>2000	>1000	**500**	>500
Candida parapsilosis	24	>500	>500	>2000	>2000	>1000	**500**	>500
ATCC 22019	48	>500	>500	>2000	>2000	>1000	**500**	>500
Candida krusei	24	>500	>500	>2000	>2000	>1000	**1000**	>500
ATCC 6258	48	>500	>500	>2000	>2000	>1000	**1000**	>500
Candida krusei	24	>500	>500	>2000	>2000	>1000	**1000**	>500
E28	48	>500	>500	>2000	>2000	>1000	**1000**	>500
Candida tropicalis	24	>500	>500	>2000	>2000	>1000	**1000**	>500
156	48	>500	>500	>2000	>2000	>1000	**1000**	>500
Candida glabrata	24	>500	>500	>2000	>2000	>1000	**1000**	>500
20/I	48	>500	>500	>2000	>2000	>1000	**1000**	>500
Candida lusitaniae	24	>500	>500	>2000	>2000	>1000	**1000**	>500
2446/I	48	>500	>500	>2000	>2000	>1000	**1000**	>500
Trichosporon beigelii	24	>500	>500	>2000	>2000	>1000	**500**	>500
1188	48	>500	>500	>2000	>2000	>1000	**500**	>500
Aspergillus fumigatus	24	>500	>500	>2000	>2000	>1000	**500**	>500
231*	48	>500	>500	>2000	>2000	>1000	**500**	>500
Absidia corymbifera	24	>500	>500	>2000	>2000	>1000	**2000**	>500
272*	48	>500	>500	>2000	>2000	>1000	>2000	>500
Trichophyton	72	>500	>500	>2000	>2000	>1000	**500**	>500
mentagrophytes 445*	120	>500	>500	>2000	>2000	>1000	**500**	>500

*MIC_{50}

Table 6.4. Antibacterial activity of C-4/C-5 disubstituted (MIC [μM]).

Strain	Time (h)	MIC_{95} Values of ionic liquids (ILs) (Concentration in μM)						
		27	**28**	**29**	**30**	**31**	**33**	**34**
Staphylococcus aureus ATCC 6538	24	>500	>500	>2000	**2000**	>1000	**500**	>500
	48	>500	>500	>2000	**2000**	>1000	**500**	>500
Staphylococcus aureus HK 5996/08	24	>500	>500	**2000**	>2000	>1000	**500**	>500
	48	>500	>500	**2000**	>2000	>1000	**500**	>500
Staphylococcus epidermidis HK 6966/08	24	**250**	>500	**2000**	**1000**	>1000	**500**	>500
	48	**250**	>500	**2000**	**1000**	>1000	**500**	>500
Enterococcus sp. HK 14365/08	24	>500	>500	>2000	>2000	>1000	**1000**	>500
	48	>500	>500	>2000	>2000	>1000	**2000**	>500
Escherichia coli, ATCC 8739	24	>500	>500	>2000	>2000	>1000	**1000**	>500
	48	>500	>500	>2000	>2000	>1000	**2000**	>500
Klebsiella pneumonia HK 11750/08	24	>500	>500	>2000	>2000	>1000	**2000**	>500
	48	>500	>500	>2000	>2000	>1000	**2000**	>500
Klebsiella pneumonia, ESBL HK 14368/08	24	>500	>500	>2000	>2000	>1000	**2000**	>500
	48	>500	>500	>2000	>2000	>1000	**2000**	>500
Pseudomonas aeruginosa ATCC 9027	24	>500	>500	>2000	>2000	>1000	>2000	>500
	48	>500	>500	>2000	>2000	>1000	>2000	>500

Antibacterial activity (MIC_{95}) of **33** was observed at 0.5 mM concentration against *Staphylococcus* strains. IL **34** did not show any antifungal and antibacterial activity upto 0.5 mM, which was the maximum concentration limit due to the poor solubility of IL in the test (Table 6.4).

6.7 Antibacterial Toxicity Studies in Dublin City University

Further studies of some representative ILs were carried out in DCU on a panel of bacteria, including *E. coli, Bacillus subtilis, Pseudomonas fluorescens, Pseudomonas Putida* (CP1) and *Pseudomonas Putida* (KT2440). Minimum inhibitory concentrations (MICs) for compounds were determined by serial two-fold dilutions in Mueller-hinton or nutrient broth using the microtiter broth dilution technique described by Amsterdam. All assays were done in triplicate.

The selection of compounds for this test system was based on the issue of solubility of some of the ILs. Only water-soluble ILs were used in this test. Due to their poor solubility, the NTf_2^- salts were excluded from the test. Bromide salts of 1-methylimidazolium IL with methyl ester side-chain (**1**) and 1,2-dimethylimidazolium IL with pyrrolidine amide side-chain (**8**) were non-toxic up to 200 mM concentration. Octyl sulfate anion of methyl ester side-chain IL (**6**) was found to be toxic to *E. coli*, *Pseudomonas fluorescens* and *Pseudomonas Putida* (CP1) at 200 mM concentration.

IL **2** containing a 1-methylimidazolium core with pyrrolidine amide side-chain only showed inhibition to *E. coli* above 100 mM concentration. Another pyrrolidine amide side-chain 1-benzylimidazolium bromide salt (**9**) was found to be toxic to *E. coli, Bacillus subtilis, Pseudomonas fluorescens and Pseudomonas Putida* (CP1) above 50 mM concentration. C-2 amide substituted ILs with bromide (**12**) and tetrafluoroborate anion (**14**) were non-toxic up to 200 mM concentration (Table 6.5), whereas the corresponding octyl sulfate anion (**15**) resulted in inhibition within the test system. The inhibition found in **6** and **15** was probably due to the presence of a long alkyl hydrocarbon chain in octyl sulfate anion. The iodide salt of a C-2 isobutyl ester substituted 1,3-dimethylimidazolium cation (**17**) demonstrated inhibition to *Escherichia coli, Bacillus subtilis, Pseudomonas fluorescens* and *Pseudomonas Putida* (CP1) above 100 mM concentration.

Table 6.5. MIC_{50} values of ionic liquids (ILs) performed in Dublin City University (DCU) in antibacterial screening.

	Compounds (concentration in mM)								
Strains	**1**	**2**	**8**	**9**	**6**	**12**	**14**	**15**	**17**
E. coli	>200	100	>200	50	200	>200	>200	100	100
Bacillus subtilis	>200	>200	>200	50	>200	>200	>200	50	100
Pseudomonas fluorescens	>200	>200	>200	50	200	>200	>200	50	100
Pseudomonas Putida (CP1)	>200	>200	>200	50	200	>200	>200	100	200
Pseudomonas Putida (KT2440)	>200	>200	>200	>200	>200	>200	>200	100	>200

6.8 Conclusion

Antimicrobial screening of the novel ILs has given useful information about their respective toxicological properties. The amide (pyrrolidine, piperidine and morpholine) and ester (methyl, butyl and ethoxyethyl) side-chain ILs were non-toxic to a panel of 12 fungal and 8 bacterial strains up to 2000 μM concentration. Only ILs with decyl amide side-chains showed high toxicity in the above test system. No significant anion effect was observed up to the 2000 μM concentration range. Toxicological effects of some ILs were further tested at high concentration against a panel of five environmentally significant microbial strains. This study has shown that most of the ILs were non-toxic up to very high (i.e. 200 mM) concentrations. Although this is only a preliminary test screening, further toxicological analysis will be needed to evaluate the toxicity of the novel ILs comprehensively.

7 Biodegradation of Ionic Liquids

7.1 Biodegradation Method – CO_2 Headspace Test

To evaluate the biodegradability of the test ILs, the 'CO_2 Headspace' test (ISO 14593) was applied. There are several biodegradation study methods: however, the CO_2 Headspace test was chosen as this is particularly suited for charged, volatile and water soluble compounds (Merretting-Bruns, 2000) (Alexander, 1995) (Evans and Moore, 1995).

7.2 Biodegradation Study of Ionic Liquids/Catalysts (First Generation)

In order to evaluate the biocompatibility of the novel ester and amide side-chain ILs, the CO_2 Headspace was used to investigate a biodegradation study of their bromide salts. Along with the bromide salts, biodegradation of the most active first-generation catalyst (for acetalisation reaction) with BF_4 anion was also studied.

ILs (**1**, **2**, **4, 8** and **9**) did not pass the CO_2 Headspace test (>60% required to pass). Low to negligible biodegradation was observed, with amide ILs **2**, **8** and **9** resistant to breakdown. The presence of the amide and benzyl group in **9** did not facilitate breakdown under the conditions of the test. This agrees with our previous results and studies from other groups, where amides (Alexander, 1995) (Evans and Moore, 1995) and benzyl (Gathergood et al., 2004) (Stolte et al., 2008) substituents did not lead to enhanced biodegradation. Reference experiments performed concurrently with the biodegradation tests confirm that ILs (**1**, **2**, **4, 8** and **9**) were non-toxic to the inoculum, albeit with poor biodegradation. Imidazolium ILs containing a methyl ester (**1** and **4**) gave low biodegradation values of 10 and 14% respectively after 28 days (Table 7.1). No significant effect is observed between the bromide and BF_4 counterion. As both these anions do not contribute to the carbon dioxide evolved on breakdown, the propensity for the cation to biodegrade is determined. Hydrolysis of the methyl ester, and the conversion of a single carbon in **1** and **4** to CO_2, can account for the degree of biodegradation observed. As is apparent due the increased stability of the amide vs methyl ester, ILs **2**, **8** and **9** are postulated to remain intact during the biodegradation test. All of the biodegradation data in Table 7.1 for the amide and ester ILs (**1**, **2**, **4, 8** and **9**) suggest that the imidazolium core is not cleaved during the CO_2 Headspace test.

7.3 Biodegradation Study of Ionic Liquids/Catalysts (Second Generation)

Biodegradation studies of pyridinium-based ILs have shown that ester substitution at either the 1 or 3-position has a beneficial effect on degradation of the heterocyclic core, independent of the anion (Stolte et al., 2008). Biodegradation studies in the literature have also shown that only the side-chain of the imidazolium ILs undergo degradation, whereas the imidazole core was found to persist in most of the OECD tests such as DOC Die-Away test and Closed bottle test (Harjano et al., 2009). Hence, in an effort to increase the biodegradation ester, substitution

Table 7.1. Biodegradation of ester and amide side-chain imidazolium ionic liquids (1, 2, 4, 8, 9).

Entry	Ionic liquid	Time (% biodegradation)				Confidence limits (95% CL)
		6 Days	14 Days	21 Days	28 Days	
1	**1**	14	14	11	10	(9–10)[1]
2	**4**	12	12	13	14	(13–15)[1]
3	**2**	1	3	4	3	(2–4)[1]
4	**8**	0	1	0	3	(0–5)[1]
5	**9**	0	0	0	0	(0±1.2)[2]

[1] SDS reference 28 days 85% (95% CL = 80–91%), Confidence limits (CL) were calculated from 5 replicates. [2] SDS reference 28 days 94% (95% CL = 90–98%). CL were calculated from 4 replicates.

Table 7.2. Biodegradation of second-generation imidazolium ionic liquids (ILs).

Entry	Ionic liquid	Time (% biodegradation)				Confidence limits (95% CL)
		6 Days	14 Days	21 Days	28 Days	
1	**12**	2	7	8	12	(11–13)[1]
2	**14**	7	12	11	14	(11–17)[2]
3	**16**	9	13	10	17	(9–24)[1]
4	**17**	24	31	32	30	(26–34)[3]
5	**19**	26	31	30	35	(34–36)[1]

[1] SDS reference 28 days 80% (95% CL = 76–84%), [2] SDS reference 28 days 90% (95% CL = 85–95%), [3] SDS reference 28 days 85% (95% CL = 80–91%), Confidence limits (CL) were calculated from 5 replicates.

onto the imidazole ring was designed. Based on the results from the antimicrobial toxicity studies, the C-2 substituted ILs were thought to be suitable substrates for biodegradation studies. Bromide and tetrafluoroborate anions of ester (**17** and **19**) and amide (**12**, **14** and **16**) substituted C-2 imidazolium cations were selected.

Table 7.2 gives the biodegradation data for **12**, **14**, **16**, **17** and **19**. Unfortunately, none of the ILs passed the CO_2 Headspace test. Introduction of an isobutyl ester (**17** and **19**) or a primary amide (**12**, **14** and **16**) at C-2 did not lead to a significant breakdown of the IL. Amides (**12**, **14** and **16**) gave the lowest values (12, 14 and 17% respectively, after 28 days). C-2 esters (**17** and **19**) gave moderate levels of biodegradation (30 and 35%, respectively, after 28 days). These values are similar to other CO_2 Headspace data for *n*-alkyl ester substituted imidazolium bromide ILs, (propyl ester 24%, pentyl ester 41%) (Wilkes, 2002). While the C-2 amide example **16** also contains a methyl ester subunit, the increase in biodegradation of 17% (c.f. 12% for **12**) is slight. The CO_2 Headspace biodegradation data in Table 7.2 show that the introduction of an ester or amide at the C-2 position of the imidazolium ring does not necessarily promote cleavage of the ring, leading to further breakdown products and CO_2 formation, avoiding persistence of the IL in the environment.

7.4 Biodegradation Study of Ionic Liquids/Catalysts (Third Generation)

We were pleased that substitution with an ester or amide in the C-4 position of the imidazoilium ILs, for a range of C-1 and C-3 substituted examples, did not increase antimicrobial toxicity. Based on antimicrobial toxicity alone all C-2 substitued ILs (**12–19)** are suitable for biodegradation studies. No IL was removed from the biodegradation study based on undesirable high antimicrobial toxicity. A representative subset was screened for biodegradation (**20**, **22** and **25**) (Table 7.3). Neither the C-4 ester- nor amide-substituted imidazolium rings underwent breakdown. No toxicity to the innoculum used for the biodegradation assay was found.

Table 7.3. Biodegradation of third-generation imidazolium ionic liquids (ILs).

Entry	Ionic liquid	Time (% biodegradation)				Confidence limits (95% CL)
		6 Days	14 Days	21 Days	28 Days	
1	**20**	6	5	8	10	(8–11)[1]
2	**22**	2	4	3	5	(4–7)[2]
3	**25**	0	0	0	2	(0–3)[1]

[1]SDS reference 28 days 80% (95% CL = 76–84%), [2]SDS reference 28 days 90% (95% CL = 85–95%). Confidence limits (CL) were calculated from 5 replicates.

7.5 Biodegradation Study of Ionic Liquids/Catalysts (Fourth Generation)

Biodegradation data of ILs **28**–**31** are shown in Table 7.4. Results have shown similarity between C-2 substituted and C-4/C-5 disubstituted imidazolium ILs. Again, neither ester nor amide substitution at C-4 and C-5 on imidazole ring of the ILs lead to passing the CO_2 HeadSpace test. As expected, amide-substituted IL **31** has shown negligible biodegradation, that is 2% after 28 days. Further, ester substitution at C-4/C-5 position did not facilitate breakdown. IL **28** has shown the highest biodegradation (31% after 28 days) amongst all C-4/C-5 disubstituted ILs. In the case of methyl ester substitution at C-4 and C-5 position ILs with halide anion, that is **29** and **33** have shown higher biodegradation 24 and 12%, respectively after 28 days, than BF_4 anion derivatives **30** and **33** 6 and 3% biodegradation, respectively.

7.6 Conclusion

Biodegradation studies of some ester and amide side-chain ILs, along with substituted imidazolium salts, were carried out using the CO_2 Headspace test (ISO 14593). All imidazolium ILs prepared failed to pass the minimum 60% biodegradation threshold value, in order to be classified as 'readily biodegradable'. Ester functionalised ILs displayed higher biodegradation levels than amide-functionalised ILs after 28 days. The first-generation imidazolium IL catalysts showed 10% to 14% biodegradation for methyl ester side-chain ILs, where no significant biodegradation was observed in amide side-chain ILs after 28 days (Table 7.1). The second-generation ILs with the modifications on the imidazole core did not help to break down the imidazolium ring to give complete biodegradation. C-2 substituted imidazolium ILs from Table 7.2 with isobutyl ester gave moderate (30% to 35%) biodegradation in comparison with C-2 amide substituted ILs. No significant improvement was observed after the ester/amide substitution at C-2 position of imidazolium ring.

Table 7.4. Biodegradation study fourth-generation-C-4/C-5 disubstituted.

Entry	Ionic liquid	Time (% biodegradation)				Confidence limits (95% CL)
		6 Days	14 Days	21 Days	28 Days	
1	**28**	15	21	30	31	(30–31)[1]
2	**29**	12	18	22	24	(21–26)[1]
3	**30**	1	2	3	6	(3–8)[1]
4	**31**	0	0	1	2	(0–4)[1]
5	**32**	3	9	12	12	(10.9–13.1)[2]
6	**33**	0	4	5	3	(2.5–3.5)[2]

[1]SDS reference 28 days 90% (95% CL = 85–95%). Confidence limits (CL) were calculated from 5 replicates. CL were calculated from 5 replicates. [2]SDS reference 28 days 94% (95% CL = 90–98%). CL were calculated from 4 replicates.

8 Green Chemistry Metrics

8.1 Introduction

The green chemistry metrics (Constable et al., 2008, pp. 228–47) assisted improvements in the synthetic process, by reducing the amount of solvents in the work-up and purification procedure and by reducing the number of steps to make required compounds.

8.2 Cleaner Synthesis

Detailed analysis of the metrics (Constable et al., 2008, pp. 228–47), such as the (a) Sheldon E-factor, (b) GSK Reaction Mass Efficiency, (c) Andraos Reaction Mass Efficiency, (d) Atom Economy and (e) 1/Stoichiometric Factor (excess reagents) is provided in the full technical report. These metrics assisted improvements in the synthetic process by reducing the amount of solvents used in the work-up and purification procedure and by reducing the number of steps needed to make the required compounds. For example, the synthesis of tetrafluoroborate ILs typically involves preparation of the corresponding halide salts, followed by anion-exchange metathesis. A modified approach was used in an effort to reduce the number of steps and amount of reagents and solvents in the synthesis, in which alkyl imidazoles were directly reacted to Meerwein's salt (i.e. trimethyloxonium tetrafluoroborate) to give tetrafluoroborate ILs in excellent yield. The green chemistry metrics assessment was important for assisting in the design and implementation of 'greener' synthetic methods.

9 Conclusions

In terms of the environment, green chemistry can bring significant reductions in environmental impacts from chemical processes. For industry, cost savings stemming from reduced chemical consumption and cheaper chemical manufacture are a stimulus for industry uptake of green chemistry methodologies. Green chemistry was prioritised under the EPA STRIVE research programme, where the development of safer, less toxic and biodegradable chemicals was highlighted as an important goal.

The inherent advantages of green chemical transformations are improved resource efficiency. This is realised by reducing: (i) the quantity of chemicals required to produce the target material, (ii) the number of steps to manufacture the product and (iii) the waste generated. In the first two points, one must consider the benefit of utilising less chemicals (including solvent), together with the positive effect on the environment (e.g. lower energy consumption, reduced CO_2 emissions, improved air quality, and less waste treatment) when producing these raw materials. Also, by reducing the toxicity and increasing the biodegradability of chemicals utilised, the waste stream can be treated more easily, preventing the need for landfill or incineration. Green chemistry can thus lead to significant reductions in the impact on the environment. Cost savings due to reduced chemical consumption and cheaper chemical manufacture are a stimulus for industry uptake of green chemistry methodologies.

Current national policy, including the Irish government's promotion and strategy of a SMART green economy, national priority areas (including processing technologies and materials), the EPA 2020 *Vision – Sustainable Use of Resources* and the EU policies, Horizon 2020 and 2013 COST Action CM1206 (Exchange of Ionic liquids) (EU, 2013) (European Cooperation in Science and Technology, 2013) demonstrate the relevance of green chemistry projects to European industry and the protection of the environment.

Importantly, chemical control laws in the EU (such as REACH initiated in 2007) were implemented to protect humans and the environment by ensuring information was available on the hazards of chemicals so that they can be assessed and managed. In 2010, amendments to TSCA (Toxic Substances control Act) in the US shifted the burden of demonstrating the safety of chemicals from the EPA to manufacturers. In 2008, China formed a new Ministry of Environmental Protection, which has strengthened safety initiatives and recently greatly expanded the toxicity data requirement before import or production of chemicals not listed on their current chemical inventory.

This justifies and validates the approach used in the current research to jointly assess the toxicity, biodegradation, synthesis and performance of the catalysts at the development stage, which, to the best of our knowledge, is unique to the DCU/TCD team.

The research project focused on the IL class of compounds. This was because of their almost unique ability to act as both solvent and/or a catalyst. Thus, as we develop 'rules of thumb' to design safer, low toxicity and biodegradable ILs we are assisting in the design of a wide range of useful chemicals. Indeed, owing to their unique properties, such as low vapour pressure, high thermal stability, recyclability, non-flammability, and control over the product distribution, ILs have been stated as a viable substitute for many solvents (although this should be proven on a case-by-case basis). Due to the wide range of applications and versatility, ILs are continually being assessed in industry, triggering an issue with their waste management. Hence, it is important to study the environmental impact of such ILs in case of release into the natural environment. One advantage is their very low vapour pressure, which greatly reduces air pollution from this solvent via fugitive emissions.

During this project four generations of ILs, based on modified imidazolium cations, were prepared. Where toxic solvents or reagents were required in the proof of concept that the chemical can be made, 'greener' replacements were found in many cases. This also includes shortening reaction pathways to targets, thus generating less waste. Green chemistry metrics, including analysis of solvent use, water use, solvent

telescoping, atom economy,[1] to name just a few, were also performed and priority areas that should be addressed to lead to the greatest improvement in reducing environmental impact identified.

A short and effective synthesis of a series of first generation ester side-chain ILs has been achieved. Considering the issue of stability of ester side-chain ILs, some amide side-chain salts were also prepared.

First-generation ester and amide IL catalysts were screened in acetalisation reactions. The results showed that aprotic ILs can catalyse reactions in the presence of protic media such as methanol, dithiol and so on. The most active catalyst was recycled 15 times without loss of catalytic activity.

Successful synthesis of a number of second-generation C-2-position ester-substituted ILs (**17**–**19**) and C-2-position amide-substituted ILs (**12**–**16**) was accomplished. Highly efficient synthesis of IL **19** was carried out using Meerwein's reagent, eliminating the need for anion exchange, with 100% yield. The introduction of electron-withdrawing groups at the C-2 position of the imidazole core dramatically enhanced and improved the catalytic activity of IL catalysts. All second-generation imidazolium ILs (**12**–**19**) gave similar conversions (up to 91%) when compared with the best first-generation catalyst **4,** even at 1 mol% catalyst loading.

The third-generation imidazolium core modified ILs (**20**–**26**) were then designed with electron-withdrawing groups (ester/amide) at the C-4 position. Since the ranking of **21**–**24** and **26** on the basis of activity in the acetalisation reaction could not be determined at 1 mol% loading due to their higher activity (cf. first and second generation), these materials were then re-evaluated at the lower 0.1 mol% levels under otherwise identical conditions. While product yields remained high (78–88%), none of the catalysts was capable of promoting the reaction to >90% yield inside 24 h.

The fourth-generation 4,5-substituted imidazolium core modified ILs (**27**–**34**) were prepared. As expected, catalysts **27**–**34** all proved highly active at 1 mol% levels, with only the iodide **33** failing to promote the reaction to completion within 24h. At 0.1 mol% loading, product yields were attenuated: however, using catalysts incorporating the tetrafluoroborate counteranion (**28**, **30**, **32**, and **34**), yields remained over 90%.

The optimum fourth-generation catalyst systems are prepared in a straightforward manner from an inexpensive starting material and are characterised by a marked reduction in the relative contribution of the anion to catalysis, which gives the practitioner the flexibility to choose the anion based on environmental/toxicological/solubility/chemoselectivity considerations as required.

In addition, it removes the obligation to use the hydrolytically suspect tetrafluoroborate anion associated with the first-generation catalyst series. The optimum catalyst in this study could promote, even at ambient temperature, acetalisation and thioacetalisation reactions of a range of aldehydes at catalyst loadings of 0.1–1 mol% and could catalyse both the reverse hydrolytic process and a ketalisation reaction which were beyond the scope of the earlier generations of this project. After the reaction the catalyst can be recovered by simply adding co-solvent and decanting the product. The recycled catalyst can be reused in five iterative recycles (at 1 mol% loading) without any discernible loss of catalytic activity.

Part of the research strategy was to replace 'traditional synthetic methods' with 'a greener alternative'. This includes reducing or eliminating hazardous chemicals from a reaction step. Examples include avoiding the use of toxic solvents (DCM and hexane), and corrosive reagents (e.g. PCl_5) and utilising 'solventless' alternative reactions conditions. Of note, the deprotection of a dithanes derived from aldehydes has also been demonstrated with high efficiency using our IL catalyst. These 'green' deprotection methods are of immense interest to chemists in academia and industry, because they can replace existing methods using mercury compounds.

ILs were screened as a solvent in a carbonyl-ene reaction and performed well compared to molecular solvents, such as dichloromethane, diethyl

1 Atom economy: The atom economy of a chemical reaction is a measure of the amount of starting materials that become useful products. Inefficient, wasteful processes have low atom economies. Efficient processes have high atom economies, and are important for sustainable development, as they use fewer natural resources and create less waste.

ether and toluene. Industry is engaged in a major endeavour to identify replacements for these three solvents in order to fulfill REACH requirements. Novel 2-position modified IL (**18**) gave excellent yield (96%) with 91% enantioselectivity in the reaction of methylenecyclohexane and ethyl trifluoropyruvate. The expensive (*R*)-BINAP palladium catalyst was immobilised in the IL, and recycled at least six times without loss of yield and catalytic activity.

The environmental impact of the novel ILs was tested via antimicrobial toxicity and biodegradation studies. Antimicrobial testing was performed on all synthesised ILs against 12 strains of fungi and 8 strains of bacteria. Almost all of the ester and amide side-chain ILs were found to be non-toxic up to 2 mM concentration in the test system (or solubility limit). However, the decyl amide side-chain derivatives, which have high antimicrobial toxicity, were identified. These were subsequently give a low priority in our catalyst screening study.

Some representative examples from these ILs were tested against common bacterial strains at higher concentrations (up to 200 mM). This study has shown that certain ILs can be tolerated by bacteria, even at these very high concentrations.

Biodegradation studies of some selected ester and amide side-chain ILs, along with substituted imidazolium salts, was also carried out by using the CO2 Headspace test (ISO 14593). All imidazolium ILs prepared failed to pass the minimum 60% biodegradation threshold value in order to be classified as 'readily biodegradable'. Ester-functionalised ILs displayed higher biodegradation levels than amide-functionalised ILs after 28 days. Iso-butyl ester IL/catalyst gave moderate (30% to 35%) biodegradation in comparison with C-2 amide-substituted ILs. There is no evidence to suggest the heterocyclic ring is cleaved under the biodegradation test conditions. No toxicity to the inoculum used for the biodegradation assay was found.

In order to evaluate the 'greenness' of the synthesis of IL catalysts, as noted above, Gathergood and Connon also applied some important green chemistry metrics (Section 4), such as the (a) Sheldon E-factor, (b) GSK Reaction Mass Efficiency, (c) Andraos Reaction Mass Efficiency, (d) Atom Economy and (e) 1/Stoichiometric Factor (excess reagents). These metrics assisted improvements in the synthetic process, by reducing the amount of solvents used in the work-up and purification procedure and reducing the number of steps to make the required compounds.

9.1 Future Work

The following investigations are suggested for further study:

- Incorporation of ester groups onto pyridinium rings leads to biodegradable ILs: however, this was not the case with imidazolium rings. Other nitrogen-, phosphorus- and sulphur-based examples, should be assessed to investigate the scope of this phenonomen;
- Toxicity and performance in application (whether as a solvent, catalyst or in synthesis) should be undertaken concurrently with the steps above;
- Low antimicrobial toxicity fourth-generation 'very active' catalysts screened in other acid catalysed reactions;
- Comprehensive toxicity study of lead fourth-generation IL/catalysts;
- Tandem and/or multicomponent casacade reactions investigated;
- One catalyst used in several steps.

9.2 Recommendations

The inherent advantage of green chemical transformations are improved resource efficiency. This is realised by: (i) reducing the quantity of chemicals required to produce the target material; (ii) reducing the number of steps to manufacture the product; and (iii) reducing the waste generated. In the first two points, one must consider the benefit of utilising less chemicals (including solvent), together with the positive effect on the environment (e.g. lower energy consumption, reduced CO_2 emissions, improved air quality, and less waste treatment) when producing these raw materials. Also, by reducing the toxicity and increasing the biodegradability of chemicals utilised, the waste stream can be more easily treated, avoiding the need for landfill or incineration. Green chemistry can thus lead to significant reductions on the impact on the environment. Cost savings due to reduced chemical consumption and cheaper chemical manufacture are a stimulus for industry uptake of green chemistry methodologies.

The following recommendations for green chemistry initiatives are:

- Tandem catalyst performance and toxicity assessment has led to the development of a low antimicrobial toxicity and very active fourth-generation catalyst. This approach was successful and is advised for future studies;
- Modifications which were expected to improve biodegradation and catalyst performance only promoted the latter;
- Introduction of an ester or amide group into the imidazolium ring does not give a readily biodegradable compound;
- Boethling's 'rules of thumb' (Boethling et al., 2007) (Boethling, 1996) for designing biodegradable molecules should be modified to account for poor biodegradation of first fourth-generation ILs;
- Two fourth-generation catalysts are recommended for further study. These are an iodide (**33**) and BF_4 (**34**) IL. Based on consideration all metrics assessed the iodide is preferred. Although the BF_4 gives a slightly superior performance in the catalysis study, the synthesis and use of the iodide creates less waste;
- A low antimicrobial toxicity fourth-generation IL/ catalyst can be used to replace mercury reagents in the deprotection reaction of dithianes, a commonly used transformation in synthetic organic chemistry;
- N-decyl amide imidazolium ILs should not be used as solvents and/or catalysts due to their high antimicrobial toxicity. These examples were subsequently dropped from our catalyst performance assessment;
- Several ILs were effective replacements for dichloromethane in palladium catalysed asymmetric carbonyl-ene reactions, with efficient recycling demonstrated;
- The use of green chemistry metric assessment successfully highlighted parameters which can be targeted for further improvements in the reduction of waste for fourth-generation IL preparation.

References

Alexander B., 1995, Biodegradation testing in the regulatory environment, 199–213 - in M. RICHARDSON, Environmental toxicology assessment, England, 1995

Alfonsi K., Colberg J., Dunn P. J., Fevig T., Jennings S., Johnson T. A., Kleine H. P., Knight C., Nagy M. A., Perry D. A., Stefaniak M., 2008, *Green Chem.*, **10**, 31–6

Anastas P., 2012, *Handbook of Green Chemistry – Green Processes – Designing Safer Chemicals*. Wiley. Series 2012

Anthony J. L., Maginn E. J., Brennecke J. F., 2001, *J. Phys. Chem. B*, **105**, 10942–9

Bernot R. J., Brueseke M. A., Evans-White M. A., Lamberti G. A., 2005, *Environ. Toxicol. Chem.*, **24**, 87–92

Bernot R. J., Kennedy E. E., Lamberti G. A., 2005, *Environ. Toxicol. Chem.*, **24**, 1759–65

Boethling R. S., 1996, *ACS Symp. Ser.*, **640**, 156–71

Boethling R. S., Sommer E., DiFiore D., 2007, *Chem. Rev.*, **107**, 2207–27

Bouquillon S., Courant T., Dean D., Gathergood N., Morrissey S., Pegot B., Scammells P. J., Singer R. D., 2007, *Aust. J. Chem.*, *60*, 843–7

Buzzeo M. C., Evans R. G., Compton R. G., 2004, *ChemPhysChem.*, **5**, 1106–20

Carson L., Chau P., Earle M., Gilea M., Gilmore B., Gorman S., McCann M., Seddon K., 2009, *Green Chem.*, **11**, 492–7

Chowdhury S. M., Ram S., Scott J. L., 2007, *Tetrahedron,* **63**(11), 2363–89

Clinical Laboratory Standard Institute, 2006, Wayne, PA, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Approved Standard - Seventh Edition. Document M07-A7.

Clinical Laboratory Standard Institute, 2008a, Wayne, PA,. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi. Approved standard. Document M38-A2.

Clinical Laboratory Standard Institute, 2008b, Wayne, PA, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. Approved standard. Document M27-A3.

Coleman D. and Gathergood N., 2010, *Chem. Soc. Rev.,* **39**, 600–37

Constable, D. J. C., Jimenez-Gonzalez, C. and Lapkin A. (2008) 'Process metrics', in *Green Chemistry Metrics: measuring and monitoring sustainable processes,* 228–47. Editors: Lapkin A. and Constable, D. J. C., Chichester, U.K.; Ames, Iowa: Wiley

Davey David D., 1987, *J. Org. Chem.*, **52**(19), 4379–81

Docherty K. M. and Kulpa, Jr. C. F., 2005, *Green Chem.*, **7**, 185–9

Dominguez de Maria P., Maugeri Z., 2011, *Cur. Opin. Chem. Biol.*, **15** (2), 220–5

Earle M. J., McCormac P. B., Seddon K. R., 1999, *Green Chem.,* **1**, 23–5

Egashira M., Yamamoto Y., Fukutake T., Yoshimoto N., Morita M., 2006, *J. Fluorine Chem.*, **127**, 1261–4

European Cooperation for Science and Technology, 2013, COST, http://www.cost.eu/domains_actions/cmst/Actions/CM1206?management

European Union, 2013, *Horizon 2020*, http://ec.europa.eu/research/horizon2020/index_en.cfm?pg=home

Evans M. and Moore K., 1995, Some observations on biodegradability testing of chemicals, 215–26, in *Environmental Toxicology Assessment*, M. Richardson, England, 1995

Forsyth S. A., Gunaratne H. Q. N., Hardacre C., McKeown A., Rooney D. W., Seddon K. R., 2005, *J. Mol. Catal. A: Chem.*, **231**, 61–6

Freemantle M., 1998, *Chem. Eng. News* **76**, (30 March), 32–7

Garcia M. T., Gathergood N., Scammells P. J., 2005, *Green Chem.*, **7**, 9–14

Gathergood N., Garcia M. T., Scammells P. J., 2004, *Green Chem.*, **6**, 166–75

Gathergood N. and Scammells P. J., 2002, *Aust. J. Chem.*, **55**, 557–60

Gathergood N., Scammells P. J., Garcia M. T, 2006, *Green Chem.*, **8**, 156–60

Gore R. G., Myles L., Spulak M., Garcia T. M., Connon S. J., Gathergood N., 2013, *Green Chem*. **15** (10), 2747–60

Gujar A. C., White M. G., 2009, *Catalysis*, **21**, 154–90

Hallett J. P., Welton T., 2011, *Chem. Rev.*, **111**, 3508–76

Harjani J. R., Farrell J., Garcia M. T., Singer R. D., Scammells P. J., 2009, *Green Chem.,* **11**(6), 821–29

Harjani J. R., Singer R. D., Garcia M. T., Scammells P. J., 2009, *Green Chem.*, **11**, 83–90

Ho T. D., Canestraro A. J., Anderson J. L., 2011, *Anal. Chim. Acta*, **695**, 18–43

Hubbard C. D., Eldik P. I. and R., 2011, *Chem. Soc. Rev.*, **40**, 272–90

Introduction to the OECD guidelines for testing of chemicals, Section 3, 2003

ISO 14593: Water quality, Evaluation of ultimate aerobic biodegradability of organic compounds in aqueous medium. Method by analysis of inorganic carbon in sealed vessels 'CO_2 headspace' test

Johansson M., Linden A. A., Baeckvall J.–E., 2005, *J. Organomet. Chem.*, **690**, 3614–19

Klingshirn M. A., R. D. Rogers R. D., Shaughnessy K. H., 2005, *J. Organomet. Chem.*, **690**, 3620–6

Koel M., 2005, *Crit. Rev. Anal. Chem.*, **35**, 177–92

Krowicki K. and William Lown J., 1987, *J. Org. Chem.,* **52** (16), 3493–501

Liu H., Liu Y., Li J., 2010, *Phys. Chem. Chem. Phys.,* **12**(8), 1685–97

Marsh K. N., Boxall J. A., Lichtenthaler R., 2004, *Fluid Phase Equilibr.*, **219**, 93–8

McFarlane J., Ridenour W. B., Luo H., Hunt R. D., Depaoli D. W., Ren R. X., 2005, *Sep. Sci. Technol.*, **40**, 1245–65

Merretting-Bruns, U. Przeglad znormalizowanych testow do badania biodegracji, Gaz, woda i technika sanitarna, 2000, 9, 6–11 (from *Korrespondenz Abwasser-Wasserwirtschaft, Abwasser, Abfall 2000*), 47, 520–6

Mizushima E., Hayashi T., Tanaka M., 2001, *Green Chem.,* **3**, 76–9

Morrissey S., Beadham I., Gathergood N., 2009, *Green Chem.*, **11**, 466–74

Morrissey S., Pegot B., Coleman D., Garcia M. T., Ferguson D., Quilty B., Gathergood N., 2009, *Green Chem.*, **11**, 475–83

Myles L., Gore R. G., Gathergood N., Connon S. J., 2013, *Green Chem.* **15** (10), 2740–6

Myles L., Gore R., Spulak M., Gathergood N., Connon S., 2010, *Green Chem.*, **12**, 1157–62

Opallo M., Lesniewski A., 2011, *J. Electroanal. Chem.*, **656**, 2–16

Pandey S., 2006, *Anal. Chim. Acta*, **556**, 38–45

Pham T. P. T., Cho C. W., Min J., Yun Y. S., 2008*, Biosci J., Bioeng.*, **105**, 425–8

Picquet M., Stutzmann S., Tkatchenko I., Tommasi I., Zimmermann J., Wasserscheid P., 2003, *Green Chem.*, **5**, 153–62

Pitner W. R., Kirsch P., Kawata K., Shinohara H., 2010, Applications of Ionic Liquids in Electrolyte Systems. *Handbook of Green Chemistry,* **6**, 191–201

Plechkova N. V. and Seddon K. R., 2008, *Chem. Soc. Rev.*, **37**, 123–50

Poole C. F., Poole S. K., 2011, *J. Sep. Science,* **34** (8), 888–900

Pretti C., Chiappe C., Pieraccini D., Gregori M., Abramo F., Monni G., Intorre L., 2006, *Green Chem.*, **8**, 238–40

Procuranti B. and Connon S. J., 2007, *Chem. Commun.* 1421–3

Procuranti B. and Connon S. J., 2008, *Org. Lett.*, **10**, 4935–8

Procuranti B., Myles L., Gathergood N., Connon S. J., 2009, *Synthesis*, **23**, 4082–6

Ranke J. and Jastorff B., 2000, *Environ. Sci. Pollut. Res.*, **7**, 105–14.

Ranke J., Stolte S., Stormann R., Arning J., Jastorff B., 2007, *Chem. Rev.*, **107,** 2183–206

REACH http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:136:0003:0280:en:PDF

Reetz M. T., Wiesenhoefer W., Francio G., Leitner W., 2002, *Chem. Commun*. 992–3

Rogers R. D. and Seddon K. R., 2002, ACS Symp. Ser. 818, ed, American Chemical Society, USA

Rosa J. N., Afonso C. A. M., Santos A. G., 2001, *Tetrahedron,* **57**, 4189–93

Seddon K. R., 1997, *J. Chem. Technol. Biotechnol.*, **68**, 351–6

Serbanovic A., Branco L. C., Nunes da Ponte M., Afonso C. A. M., 2005, *J. Organomet. Chem.*, **690**, 3600–8

Sheldon R. A., 2005, *Green Chem.*, **7**, 267–78

Shiddiky M. J. A., Torriero A. A. J., 2011, *Biosens. Bioelectron.* **26** (5), 1775–87

Stark A. and Seddon K. R., 2007, in *Kirk-Othmer Encyclopaedia of Chemical Technology*, Seidel A., JohnWiley & Sons, Inc., Hoboken, New Jersey, USA, 5, **26**, 836–920

Stolte S., Abdulkarim S., Arning J., Blomeyer-Nienstedt A., Bottin-Weber U., Matzke M., Ranke J., Jastorff B., Thoeming J., 2008, *Green Chem.*, **10**, 214–24

Sun P., Armstrong D. W., 2010, *Anal. Chim. Acta*, **661** (1), 1–16

Swatloski R. P., Holbrey J. D., Memon S. B., Caldwell G. A., Caldwell K. A., Rogers R. D., 2004, *Chem. Commun.*, 668–9

Toxic Substances Control Act (TCSA) http://environmental-legislation.blogspot.com.au/2010/09/proposed-amendments-to-toxic-substances.html

Vijayaraghavan R., MacFarlane D. R., 2004, *Aust. J. Chem.*, **57**, 129–33

Wasserscheid, P. and Joni, J. 2010. Green Organic Synthesis in Ionic Liquids. *Handbook of Green Chemistry*. **6**:39–63

Wasserscheid P. and Stark A. (Eds), 2010, *Handbook of Green Chemistry*, Volume 6: Ionic Liquids, Wiley–VCH

Wasserscheid P. and Welton T. (Eds), 2003, *Ionic Liquids in Synthesis*, Wiley-VCH

Wilkes J. S., 2002, *Green Chem.*, **4**, 73–80

Wong D. S. H., Chen J. P., Chang J. M., C. H. Chou C. H., 2002, *Fluid Phase Equilibr*, **194–7**, 1089–95

Wood N. and Stephens G., 2010; *Phys. Chem. Chem. Ph*ys., **12**, 1670–4

Yadav J. S., Reddy B. V. S., Baishya G., Reddy K. V., Narsaiah A. V., 2005, *Tetrahedron,* **61**, 9541–4

Acronyms and Annotations

ASTM	American Society for Testing and Materials
DCM	Dichloromethane
DOC	Dissolved organic carbon
Ee	Enantiomeric excess
EWG	Electron withdrawing group
ILs	Ionic liquids
MIC	Minimum inhibitory concentration
OECD	Organisation for Economic Co-operation and Development
RTIL	Room temperature ionic liquid
TON	Turnover number
VOCs	Volatile organic compounds

List of Publications

Book Chapters

Handbook of Green Chemistry – Green Processes – Designing Safer Chemicals. Wiley. Series editor: P. Anastas

Chapter Title **Design of safer chemicals – Ionic Liquids**. Ian Beadham, Monika Gurbisz and Nicholas Gathergood. **2012**, *Handbook of Green Chemistry, Chapter 6, Volume 9: Designing Safer Chemicals*, First Edition. Vol. Edited by Robert Boethling and Adelina Voutchkova, Wiley-VCH Verlag GmbH & Co. KGaA, pp. 137–58.

Chapter Title **Designing Organocatalysts – what lessons can be learned when the rebirth of an old research area coincides with the advent of green chemistry?** Ian Beadham, Monika Gurbisz and Nicholas Gathergood, **2012**, *Handbook of Green Chemistry, Chapter 7, Volume 9: Designing Safer Chemicals*, First Edition. Vol. Edited by Robert Boethling and Adelina Voutchkova., Wiley-VCH Verlag GmbH & Co. KGaA., pp. 159–226.

Rohitkumar G. Gore and Nicholas Gathergood, Chapter 9. Chapter Title **Safer and Greener Catalysts – Design of high performance, biodegradable and low toxicity ionic liquids. 2013.** *Ionic Liquids – New Aspects for the Future* (Pub. InTech) DOI: 10.5772/51879. (Ed. Jun-Ichi Kadokawa) pp. 499–535.

Papers

Gore, R. G.; Truong, T.-K.-T.; Pour, M.; Myles, L.; Connon, S. J. and Gathergood, N. **Tandem ionic liquid antimicrobial toxicity and asymmetric catalysis study: carbonyl-ene reactions with trifluoropyruvate.** *Green Chem.* (2013), **15** (10), 2727–739.

'Hot Article', *Green Chem.* (October 2013).

Myles, L.; Gore, R. G.; Gathergood, N. and Connon, S. J. **A new generation of aprotic yet Brønsted acidic imidazolium salts: low toxicity, high recyclability and greatly improved activity.** *Green Chem.* (2013), **15** (10), 2740–6.

Gore, R. G.; Myles, L.; Spulak, M.; Beadham, I.; Garcia, T. M.; Connon, S. J. and Gathergood, N**. A new generation of aprotic yet Brønsted acidic imidazolium salts: effect of ester/amide groups in the C-2, C-4 and C-5 on antimicrobial toxicity and biodegradation** *Green Chem.* (2013), **15** (10), 2747–60.

Three back-to-back papers as *Green Chem.* Cover Article, features in *Chemistry World (*October 2013).

Myles, L.; Gore, R.; Spulak, M.; Gathergood, N. and Connon, S. J. **Highly recyclable, imidazolium derived ionic liquids of low antimicrobial and antifungal toxicity: A new strategy for acid catalysis.** *Green Chem.* (2010), **12**, 1157–62.

Procuranti, B.; Myles, L.; Gathergood, N.; Connon, S. J. **Pyridinium ion catalysis of carbonyl protection reactions**. *Synthesis*, (2009), 23, 4082–6.

Conferences (Organised)

2012 July Dublin. Society of Chemical Industry Conference, Dublin City University. **Green chemistry in Ireland 2**. Chair of organising committee, http://www.soci.org/News/Ireland-green-chem-2012

2011 4 August, Limerick Society of Chemical Industry Conference, University of Limerick.**The future of the Pharmachem industry in Ireland**. Organising committee member.

2010 15 April Dublin. Society of Chemical Industry Conference, Dublin City University. **Green chemistry in Ireland**. Chair of organising committee, http://www.soci.org/News/Ireland-green-chem-2010.aspx

2009 19–23 November New Orleans, US, Society for Environmental Toxicology and Chemistry (SETAC) Conference, Green Chemistry Session Organiser and Chair.

An Ghníomhaireacht um Chaomhnú Comhshaoil

Is í an Gníomhaireacht um Chaomhnú Comhshaoil (EPA) comhlachta reachtúil a chosnaíonn an comhshaol do mhuintir na tíre go léir. Rialaímid agus déanaimid maoirsiú ar ghníomhaíochtaí a d'fhéadfadh truailliú a chruthú murach sin. Cinntímid go bhfuil eolas cruinn ann ar threochtaí comhshaoil ionas go nglactar aon chéim is gá. Is iad na príomh-nithe a bhfuilimid gníomhach leo ná comhshaol na hÉireann a chosaint agus cinntiú go bhfuil forbairt inbhuanaithe.

Is comhlacht poiblí neamhspleách í an Ghníomhaireacht um Chaomhnú Comhshaoil (EPA) a bunaíodh i mí Iúil 1993 faoin Acht fán nGníomhaireacht um Chaomhnú Comhshaoil 1992. Ó thaobh an Rialtais, is í an Roinn Comhshaoil, Pobal agus Rialtais Áitiúil.

ÁR bhFREAGRACHTAÍ

CEADÚNÚ

Bíonn ceadúnais á n-eisiúint againn i gcomhair na nithe seo a leanas chun a chinntiú nach mbíonn astuithe uathu ag cur sláinte an phobail ná an comhshaol i mbaol:

- áiseanna dramhaíola (m.sh., líonadh talún, loisceoirí, stáisiúin aistrithe dramhaíola);
- gníomhaíochtaí tionsclaíocha ar scála mór (m.sh., déantúsaíocht cógaisíochta, déantúsaíocht stroighne, stáisiúin chumhachta);
- diantalmhaíocht;
- úsáid faoi shrian agus scaoileadh smachtaithe Orgánach Géinathraithe (GMO);
- mór-áiseanna stórais peitreail;
- scardadh dramhuisce;
- dumpáil mara.

FEIDHMIÚ COMHSHAOIL NÁISIÚNTA

- Stiúradh os cionn 2,000 iniúchadh agus cigireacht de áiseanna a fuair ceadúnas ón nGníomhaireacht gach bliain
- Maoirsiú freagrachtaí cosanta comhshaoil údarás áitiúla thar sé earnáil - aer, fuaim, dramhaíl, dramhuisce agus caighdeán uisce
- Obair le húdaráis áitiúla agus leis na Gardaí chun stop a chur le gníomhaíocht mhídhleathach dramhaíola trí comhordú a dhéanamh ar líonra forfheidhmithe náisiúnta, díriú isteach ar chiontóirí, stiúradh fiosrúcháin agus maoirsiú leigheas na bhfadhbanna.
- An dlí a chur orthu siúd a bhriseann dlí comhshaoil agus a dhéanann dochar don chomhshaol mar thoradh ar a ngníomhaíochtaí.

MONATÓIREACHT, ANAILÍS AGUS TUAIRISCIÚ AR AN GCOMHSHAOL

- Monatóireacht ar chaighdeán aeir agus caighdeáin aibhneacha, locha, uiscí taoide agus uiscí talaimh; leibhéil agus sruth aibhneacha a thomhas.
- Tuairisciú neamhspleách chun cabhrú le rialtais náisiúnta agus áitiúla cinntí a dhéanamh.

RIALÚ ASTUITHE GÁIS CEAPTHA TEASA NA HÉIREANN

- Cainníochtú astuithe gáis ceaptha teasa na hÉireann i gcomhthéacs ár dtiomantas Kyoto.
- Cur i bhfeidhm na Treorach um Thrádáil Astuithe, a bhfuil baint aige le hos cionn 100 cuideachta atá ina mór-ghineadóirí dé-ocsaíd charbóin in Éirinn.

TAIGHDE AGUS FORBAIRT COMHSHAOIL

- Taighde ar shaincheisteanna comhshaoil a chomhordú (cosúil le caighdéan aeir agus uisce, athrú aeráide, bithéagsúlacht, teicneolaíochtaí comhshaoil).

MEASÚNÚ STRAITÉISEACH COMHSHAOIL

- Ag déanamh measúnú ar thionchar phleananna agus chláracha ar chomhshaol na hÉireann (cosúil le pleananna bainistíochta dramhaíola agus forbartha).

PLEANÁIL, OIDEACHAS AGUS TREOIR CHOMHSHAOIL

- Treoir a thabhairt don phobal agus do thionscal ar cheisteanna comhshaoil éagsúla (m.sh., iarratais ar cheadúnais, seachaint dramhaíola agus rialacháin chomhshaoil).
- Eolas níos fearr ar an gcomhshaol a scaipeadh (trí cláracha teilifíse comhshaoil agus pacáistí acmhainne do bhunscoileanna agus do mheánscoileanna).

BAINISTÍOCHT DRAMHAÍOLA FHORGHNÍOMHACH

- Cur chun cinn seachaint agus laghdú dramhaíola trí chomhordú An Chláir Náisiúnta um Chosc Dramhaíola, lena n-áirítear cur i bhfeidhm na dTionscnamh Freagrachta Táirgeoirí.
- Cur i bhfeidhm Rialachán ar nós na treoracha maidir le Trealamh Leictreach agus Leictreonach Caite agus le Srianadh Substaintí Guaiseacha agus substaintí a dhéanann ídiú ar an gcrios ózóin.
- Plean Náisiúnta Bainistíochta um Dramhaíl Ghuaiseach a fhorbairt chun dramhaíl ghuaiseach a sheachaint agus a bhainistiú.

STRUCHTÚR NA GNÍOMHAIREACHTA

Bunaíodh an Ghníomhaireacht i 1993 chun comhshaol na hÉireann a chosaint. Tá an eagraíocht á bhainistiú ag Bord lánaimseartha, ar a bhfuil Príomhstiúrthóir agus ceithre Stiúrthóir.

Tá obair na Gníomhaireachta ar siúl trí ceithre Oifig:

- An Oifig Aeráide, Ceadúnaithe agus Úsáide Acmhainní
- An Oifig um Fhorfheidhmiúchán Comhshaoil
- An Oifig um Measúnacht Comhshaoil
- An Oifig Cumarsáide agus Seirbhísí Corparáide

Tá Coiste Comhairleach ag an nGníomhaireacht le cabhrú léi. Tá dáréag ball air agus tagann siad le chéile cúpla uair in aghaidh na bliana le plé a dhéanamh ar cheisteanna ar ábhar imní iad agus le comhairle a thabhairt don Bhord.

Science, Technology, Research and Innovation for the Environment (STRIVE) 2007-2013

The Science, Technology, Research and Innovation for the Environment (STRIVE) programme covers the period 2007 to 2013.

The programme comprises three key measures: Sustainable Development, Cleaner Production and Environmental Technologies, and A Healthy Environment; together with two supporting measures: EPA Environmental Research Centre (ERC) and Capacity & Capability Building. The seven principal thematic areas for the programme are Climate Change; Waste, Resource Management and Chemicals; Water Quality and the Aquatic Environment; Air Quality, Atmospheric Deposition and Noise; Impacts on Biodiversity; Soils and Land-use; and Socio-economic Considerations. In addition, other emerging issues will be addressed as the need arises.

The funding for the programme (approximately €100 million) comes from the Environmental Research Sub-Programme of the National Development Plan (NDP), the Inter-Departmental Committee for the Strategy for Science, Technology and Innovation (IDC-SSTI); and EPA core funding and co-funding by economic sectors.

The EPA has a statutory role to co-ordinate environmental research in Ireland and is organising and administering the STRIVE programme on behalf of the Department of the Environment, Heritage and Local Government.

Environmental Protection Agency
An Ghníomhaireacht um Chaomhnú Comhshaoil

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