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Catalytic reactions in ionic liquids

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The chemical industry is under considerable pressure to replace many of the volatile organic compounds (VOCs) that are currently used as solvents in organic synthesis. The toxic and/or hazardous properties of many solvents, notably chlorinated hydrocarbons, combined with serious environmental issues, such as atmospheric emissions and contamination of aqueous effluents is making their use prohibitive. This is an important driving force in the quest for novel reaction media. Curzons and coworkers,[1] for example, recently noted that rigorous management of solvent use is likely to result in the greatest improvement towards greener processes for the manufacture of pharmaceutical intermediates. The current emphasis on novel reaction media is also motivated by the need for efficient methods for recycling homogeneous catalysts. The key to waste minimisation in chemicals manufacture is the widespread substitution of classical 'stoichiometric' syntheses by atom efficient, catalytic alternatives.[2] In the context of homogeneous catalysis, efficient recycling of the catalyst is a *conditio sine qua non* for economically and environmentally attractive processes. Motivated by one or both of the above issues much attention has been devoted to homogeneous catalysis in aqueous biphasic[3,4] and fluorous biphasic[5] systems as well as in supercritical carbon dioxide.[6] Similarly, the use of ionic liquids as novel reaction media may offer a convenient solution to both the solvent emission and the catalyst recycling problem.[7,8]

Historical development

What are ionic liquids? Quite simply, they are liquids that are composed entirely of ions. Molten sodium chloride, for example, is an ionic liquid but a solution of sodium chloride in water is an ionic solution. The term molten salts, which was previously used to describe such materials, evokes an image of high-temperature, viscous and highly corrosive media. The term ionic liquid, in contrast, implies a material that is fluid at (or close to) ambient temperature, is colourless, has a low viscosity and is easily handled, *i.e.* a material with attractive properties for a solvent. Room temperature ionic liquids are generally salts of organic cations, *e.g.* tetraalkylammonium, tetraalkylphosphonium, *N*-alkylpyridinium, 1,3-dialkylimidazolium and trialkylsulfonium cations (Fig. 1).

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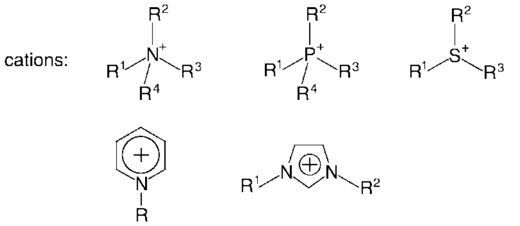
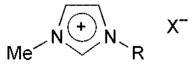


anions: BF_4^-, PF_6^-, SbF_6^-, NO_3^-, $CF_3SO_3^-$, $(CF_3SO_3)_2N^-$, $ArSO_3^-$, $CF_3CO_2^-$, $CH_3CO_2^-$, $Al_2Cl_7^-$

Fig. 1 Structures of ionic liquids.

In order to be liquid at room temperature, the cation should preferably be unsymmetrical, *e.g.* R^1 and R^2 should be different alkyl groups in the dialkylimidazolium cation. The melting point is also influenced by the nature of the anion (see Table 1).

Table 1 Melting points of some dialkylimidazolium salts



R	X	mp/°C
Me	Cl	125
Et	Cl	87
n-Bu	Cl	65
Et	NO_3	38
Et	$AlCl_4$	7
Et	BF_4	6
Et	CF_3SO_3	−9
Et	$(CF_3SO_3)_2N$	−3
Et	CF_3CO_2	−14
n-Bu	CF_3SO_3	16

Room temperature ionic liquids are not new. Ethylammonium nitrate, which is liquid at room temperature (but usually contains 200–600 ppm water) was first described in 1914.[9] In the late 1940s, *N*-alkylpyridinium chloroaluminates were studied as electrolytes for electroplating aluminium. These systems were reanimated by the groups of Hussey,[10] Osteryoung[11] and Wilkes[12] in the late 1970s. The first examples of ionic liquids based on dialkylimidazolium cations were reported in the early 1980s by Wilkes and coworkers.[12] They contained

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chloroaluminate anions ($AlCl_4^-$ or $Al_2Cl_7^-$) and proved to be useful catalysts/solvents for Friedel–Crafts acylations.[13] However, a serious obstacle for widespread use of these ionic liquids is the high reactivity of the chloroaluminate anion towards water.

The first example of the new ionic liquids, that currently are receiving so much attention as novel media for homogeneous catalysis, ethylmethylimidazolium tetrafluoroborate ($emimBF_4$)† was reported by Wilkes *et al.* in 1992.[14] The synthesis of the corresponding hexafluorophosphate followed shortly thereafter.[15] In contrast to the chloroaluminate salts the fluoroborates and hexafluorophosphates are stable towards hydrolysis. Subsequently, 1,3-dialkylimidazolium salts containing a wide variety of anions, *e.g.* $CF_3SO_3^-$, $[CF_3SO_2]_2N^-$, $CF_3CO_2^-$, $CH_3CO_2^-$, $PhSO_3^-$ and many more have been prepared.[16]

Ionic liquids can be prepared by direct quaternisation of the appropriate amine or phosphine. Different anions can subsequently be introduced by anion exchange. It is beyond the scope of this review to discuss in detail the synthesis of ionic liquids and the reader is referred to excellent reviews for many details.[17–20] It is important to note, however, that ionic liquids, owing to their non-volatile nature, cannot be purified by distillation. Consequently, they should be produced in high purity. For example, if synthesis involves exchange of chloride ions it is important that no chloride ions remain in the product as they may seriously impede catalysis by strongly coordinating to low valent transition metal complexes.

The hydrophilicity/lipophilicity of an ionic liquid can be modified by a suitable choice of anion, *e.g.* $bmimBF_4$ is completely miscible with water while the PF_6 salt is largely immiscible with water. The lipophilicity of dialkylimidazolium salts, or other ionic liquids, can also be increased by increasing the chain length of the alkyl groups.[21]

Ionic liquids containing 'fluorous ponytails' have even been described.[22] When these are added to conventional ionic liquids they facilitate emulsification with perfluorocarbons. This provides the possibility of performing (catalytic) reactions in ionic liquids/perfluorocarbon biphasic systems.

Catalysis in ionic liquids: general considerations

Room temperature ionic liquids exhibit many properties which make them potentially attractive media for homogeneous catalysis:

- They have essentially no vapour pressure, *i.e.* they do not evaporate and are easy to contain.
- They generally have reasonable thermal stability. While tetraalkylammonium salts have limited thermal stability, owing to decomposition *via* the Hoffmann elimination, $emimBF_4$ is reportedly stable up to 300 °C and emim(CF_3SO_2)$_2$N up to 400 °C.[16a] In other words many ionic liquids have liquid ranges of more than 300 °C, compared to the 100 °C liquid range of water.
- They are able to dissolve a wide range of organic, inorganic and organometallic compounds.
- The solubility of gases, *e.g.* H_2, CO and O_2, is generally good which makes them attractive solvents for catalytic hydrogenations, carbonylations, hydroformylations, and aerobic oxidations.
- They are immiscible with some organic solvents, *e.g.* alkanes, and, hence, can be used in two-phase systems. Similarly, lipophilic ionic liquids can be used in aqueous biphasic systems.
- Polarity and hydrophilicity/lipophilicity can be readily adjusted by a suitable choice of cation/anion (see earlier) and ionic liquids have been referred to as 'designer solvents'.[7]
- They are often composed of weakly coordinating anions, *e.g.* BF_4^- and PF_6^- and, hence, have the potential to be highly polar yet non-coordinating solvents. They can be expected, therefore, to have a strong rate-enhancing effect on reactions involving cationic intermediates.
- Ionic liquids containing chloroaluminate ions are strong Lewis, Franklin and Brønsted acids. Protons present in $emimAlCl_4$ have been shown to be superacidic with Hammett acidities up to −18.[23] Such highly acidic ionic liquids are, nonetheless, easily handled and offer potential as non-volatile replacements for hazardous acids such as HF in several acid-catalysed reactions.

Faced with these numerous potential benefits one may wonder if ionic liquids have any problems associated with their use. Atmospheric emissions may not be an issue but, when used on an industrial scale, small amounts of ionic liquids will inevitably find their way into the environment *via* the proverbial 'mechanical losses'. So, what is known about their potential environmental impact? A cursory examination of the literature reveals a dearth of information regarding the biodegradability and toxicity of ionic liquids. A prerequisite for industrial use is, therefore, the generation of appropriate data to enable the assessment of the potential environmental impact of ionic liquids.

Another question which arises in any discussion of ionic liquids as reaction media pertains to the isolation of soluble reaction products. Volatile products can be separated by distillation. Non-volatile products, on the other hand, can be separated by solvent extraction. Although this seems paradoxical—using an ionic liquid to avoid atmospheric emissions and subsequently using a volatile organic solvent to extract the product—it could have environmental benefits. For example, substituting an environmentally unacceptable solvent by an ionic liquid as the reaction medium, followed by extraction with a more benign organic solvent would constitute an environmental benefit. In this context it is worth noting the use of supercritical carbon dioxide to extract products from ionic liquids, which is currently the focus of attention.[24] Quite remarkably, $scCO_2$ is highly soluble (up to 60 mol%) in $bmimPF_6$ while the latter is insoluble in $scCO_2$. Naphthalene, for example, was recovered quantitatively from $bmimPF_6$ by $scCO_2$ extraction, without any contamination of the extract by the ionic liquid.

One can envisage various scenarios for catalysis in and/or by ionic liquids:

- Monophasic systems in which the catalyst and substrate are dissolved in the ionic liquid.
- Monophasic systems in which the ionic liquid acts as both the solvent and the catalyst, *e.g.* dialkylimidazolium chloroaluminates as Friedel–Crafts catalysts (see later).
- Biphasic systems in which the catalyst resides in the ionic liquid and the substrate/product in the second phase or *vice versa.*
- Mono- or biphasic systems in which the anion of the ionic liquid acts as a ligand for the homogeneous catalyst, *e.g.* a sulfonated phosphine ligand (see later).
- Triphasic systems comprising, for example, an ionic liquid, water and an organic phase in which the catalyst resides in the ionic liquid, the substrate and product in the organic phase and salts formed in the reaction are extracted into the aqueous phase, *e.g.* in Heck reactions (see later).

The first example of homogeneous transition metal catalysis in an ionic liquid is the platinum catalysed hydroformylation of ethene in tetraethylammonium trichlorostannate, described by Parshall in 1972.[25] This ionic liquid (referred to as a molten salt back in those days) has a melting point of 78 °C. These results were largely ignored for two decades. The potential of ionic liquids as novel media for homogeneous catalysis became more widely appreciated largely due to the pioneering studies and extensive promotion of the groups of Seddon[17] and Chauvin and Olivier-Bourbigou[18] and, more recently, the groups of Welton[19] and Keim and Wasserscheid.[20] In the last five years their use as novel media for, *inter alia*, catalytic hydrogenations, hydroformylations, isomerisations, olefin dimerisations, oligomerisations and polymerisations and Heck couplings, has been rapidly expanding. The salient features of these studies will be reviewed in the ensuing discussion, with emphasis on their potential as clean synthetic methodologies.

Hydrogenation

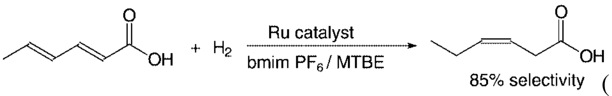
The first example of catalytic hydrogenation in an ionic liquid was reported by Chauvin *et al.* in 1995.[26] A solution of the cationic [Rh nbd$(Ph_3P)_2$]PF_6 complex [nbd = norbornadiene (bicyclo[2.2.1]hepta-2,5-diene)] in bmimPF_6 or bmimSbF_6 was shown to be an effective catalyst for the biphasic hydrogenation of pent-1-ene. Reaction rates were up to five times higher than in acetone as solvent which was attributed to the formation of an unsolvated cationic rhodium(III) dihydride complex with two free coordination sites in the nonsolvating ionic liquid. In contrast, poor results were obtained with bmimBF_4 which was ascribed to the presence of trace amounts of strongly coordinating chloride ions in their sample of this ionic liquid. The catalyst solution in the ionic liquid could be reused with rhodium losses below the detection limit of 0.02%.

Similarly, advantage was taken of the biphasic system to perform the selective hydrogenation of cyclohexadiene. The solubility of cyclohexadiene in bmimSbF_6 is about five times that of cyclohexene and, hence, the latter was obtained in 98% selectivity at 96% conversion.

Dupont and coworkers[27] performed the biphasic hydrogenation of cyclohexene with $Rh(cod)_2BF_4$ (cod = cycloocta-1,5-diene) in ionic liquids. They observed roughly equal rates (turnover frequencies of *ca.* 50 h^{-1}) in bmimBF_4 and bmimPF_6 (presumably their bmimBF_4 was chloride-free).

The same group showed that $RuCl_2(Ph_3P)_3$ in bmimBF_4 is an effective catalyst for the biphasic hydrogenation of olefins, with turnover frequencies up to 540 h^{-1}.[28] Similarly, $(bmim)_3$-$Co(CN)_5$ dissolved in bmimBF_4 catalysed the hydrogenation of butadiene to but-1-ene, in 100% selectivity at complete conversion.[28]

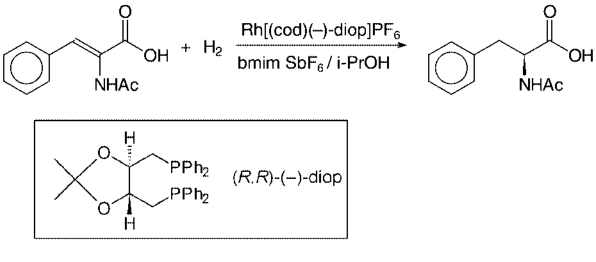
More recently, the ruthenium-catalysed hydrogenation of sorbic acid to *cis*-hex-3-enoic acid (Reaction 1) was achieved in a biphasic bmimPF_6–methyl *tert*-butyl ether system.[29]



(1)

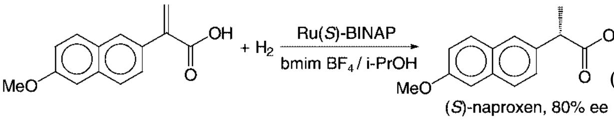
The ruthenium cluster, $[H_4Ru(\eta^6\text{-}C_6H_6)_4]$ $[BF_4]_2$ in bmimBF_4 was shown to be an effective catalyst for the hydrogenation of arenes, to the corresponding cycloalkanes, at 90 °C and 60 bar.[30] The cycloalkane product formed a separate phase which was decanted and the ionic liquid phase, containing the catalyst, could be repeatedly recycled.

Enantioselective hydrogenation in ionic liquids is of particular interest as it could provide a means for facile recycling of metal complexes of expensive chiral ligands. In their original study Chauvin *et al.*[26] reported that [Rh(cod)(−)-(diop)]PF_6 catalysed the enantioselective hydrogenation of α-acetamidocinnamic acid to (*S*)-phenylalanine, in 64% ee, in a biphasic bmimSbF_6–isopropyl alcohol (Reaction 2). The observed enantioselectivity is what one would expect with diop which is not a particularly good ligand for this reaction. The product, contained in the isopropyl alcohol, could be separated quantitatively and the recovered ionic liquid, containing the catalyst, reused.



(2)

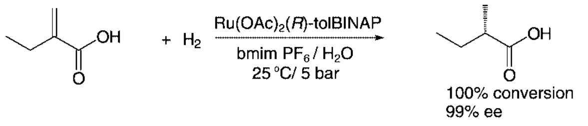
Similarly, Dupont and coworkers[31] extended their studies of ruthenium-catalysed hydrogenations in ionic liquids to enantioselective reactions. The chiral $[RuCl_2(S)\text{-BINAP}]_2NEt_3$ complex was shown to catalyse the asymmetric hydrogenation of 2-phenylacrylic acid and 2-(6-methoxy-2-naphthyl)acrylic acid in bmimBF_4–isopropyl alcohol. The latter afforded the antiinflammatory drug, (*S*)-naproxen, in 80% ee (Reaction 3). The product could be quantitatively separated and the recovered ionic liquid catalyst solution recycled several times without any significant change in activity or selectivity.



(3)

An interesting recent development is the use of a biphasic ionic liquid–supercritical CO_2 for catalytic hydrogenation[32,33] and other processes (see later). Tumas and coworkers[32] showed that the catalytic hydrogenation of olefins could be conducted in a biphasic bmimPF_6–scCO_2 system. The ionic liquid phase containing the catalyst was separated by decantation and reused in up to four consecutive batches.

Jessop and coworkers[33] extended this concept to the asymmetric hydrogenation of tiglic acid (Reaction 4) and the precursor of the antiinflammatory drug ibuprofen (Reaction 5) using $Ru(OAc)_2$(tolBINAP) as the catalyst.



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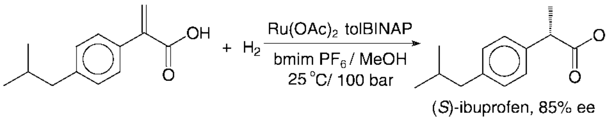


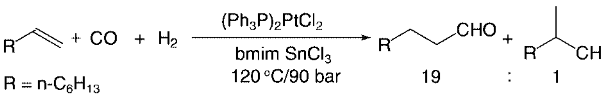
(5)

They found that Reaction 4 was more selective in a bmimPF_6–water biphasic mixture while Reaction 5 gave poor enantioselectivities in the wet ionic liquid. In this case the best result (85% ee) was obtained using methanol as cosolvent at 100 bar H_2 pressure. In both cases the product was separated by scCO_2 extraction when the reaction was complete. The different solvent effects observed with the two substrates was assumed to be due to the solubility of H_2 in the reaction mixture. The hydrogen concentration dependence of asymmetric catalytic hydrogenation with ruthenium BINAP complexes is known to be dependent on the substrate.[34] Class I substrates such as the ibuprofen precursor give higher enantioselectivities at high H_2 concentration while class II substrates, exemplified by tiglic acid, give higher enantioselectivities at low H_2 concentrations.

Hydroformylation

Hydroformylation of propene in an aqueous biphasic system, using a water-soluble rhodium complex of the sodium salt of trisulfonated triphenylphosphine (tppts) forms the basis of the Ruhr Chemie Rhone Poulenc process for the manufacture of butanal.[35] Unfortunately this process is limited to C_2 to C_5 olefins owing to the very low solubility of higher olefins in water. Hence, one can envisage that the use of an appropriate ionic liquid could provide the basis for biphasic hydroformylation of higher olefins.

As noted earlier, Parshall showed, in 1972, that platinum-catalysed hydroformylations could be performed in tetraethylammonium trichlorostannate melts.[25] More recently, Waffenschmidt and Wasserscheid[36] studied the platinum-catalysed hydroformylation of oct-1-ene in bmimSnCl$_3$ (Reaction 6)



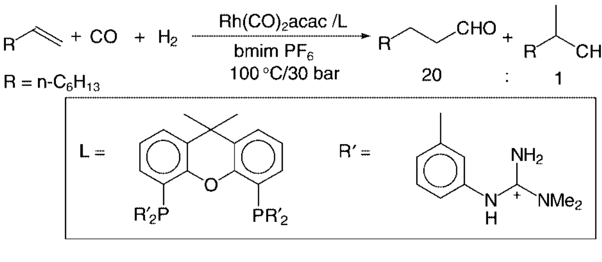
(6)

which is liquid at room temperature. Despite the limited solubility of oct-1-ene in the ionic liquid, high activities (TOF = 126 h^{-1}) were observed together with a remarkably high regioselectivity (n/iso = 19). The product was recovered by phase separation and no leaching of platinum was observed.

The ruthenium- and cobalt-catalysed hydroformylation of internal and terminal olefins in molten tetra-*n*-butylphosphonium bromide was reported by Knifton in 1987.[37] More recently, the rhodium-catalysed hydroformylation of hex-1-ene was conducted in molten phosphonium tosylates, *e.g.* $Bu_3PEt^+TsO^-$ and $Ph_3PEt^+TsO^-$ having melting points of 81–83 °C and 94–95 °C, respectively, at 120 °C and 40 bar.[38] Advantage was taken of the higher melting points of these 'ionic liquids' to decant the product from the solid catalyst medium at room temperature.

Chauvin and coworkers[26] investigated the rhodium-catalysed biphasic hydroformylation of pen-1-tene in bmimPF$_6$. High activities (TOF = 333 h^{-1} compared with 297 h^{-1} in toluene) were observed with the neutral Rh(CO)$_2$(acac)–Ph$_3$P as the catalyst precursor but some leaching of the catalyst into the organic phase occurred. This could be avoided by using Rh(CO)$_2$acac with tppts or tppms (monosulfonated triphenylphosphine) as the catalyst precursor, albeit at the expense of rate (TOF = 59 h^{-1} with tppms). Higher activities (TOF = 810 h^{-1}) and high regioselectivity (n/iso = 16) were observed in the biphasic hydroformylation of oct-1-ene in bmimPF$_6$ using cationic cobaltocenium diphosphine ligands but some catalyst leaching ($<0.5\%$) was observed.[39]

Better results were obtained with cationic guanidine-modified diphosphine ligands containing a xanthene backbone.[40] Xanthene-based diphosphine ligands with large bite angles (P–metal–P ~ 110°) are known to give high selectivities ($\geqslant 98\%$) towards the linear aldehyde.[41] Biphasic hydroformylation of oct-1-ene, using rhodium complexes of these ligands in bmimPF$_6$ (Reaction 7), afforded high regioselectivities (*ca.* 20)



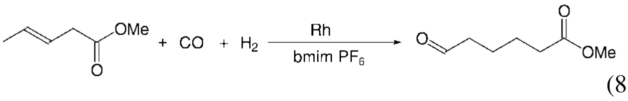
(7)

and the catalyst could be recycled ten times (resulting in an overall turnover number of 3500) without detectable ($<0.07\%$) leaching of Rh to the organic phase.

The group of Olivier-Bourbignou[42] has recently explored the use of a wide range of ionic liquids, based on imidazolium and pyrrolidinium cations and weakly coordinating anions, for the biphasic hydroformylation of hex-1-ene catalysed by rhodium complexes of modified phosphine and phosphite ligands. The latter are, in contrast, unstable in aqueous biphasic media. The rate and regioselectivity could be optimized by choosing a suitable combination of cation, anion and phosphine or phosphite ligand. Rhodium leaching was minimised by modification of the ligands with cationic (guanidinium or pyridinium) or anionic (sulfonate) groups.

Another interesting recent development is the rhodium-catalysd biphasic hydroformylation of oct-1-ene in bmimPF$_6$–scCO$_2$ in a continuous flow process.[43] Because of the low solubility of Rh–tppms and Rh–tppts complexes in the ionic liquid, $[pmim]^+Ph_2PC_6H_4SO_3^-$ (pmim = 1-propyl-3-methylimidazolium) was synthesised and used together with Rh$_2$(OAc)$_4$ as the catalyst precursor. Aldehydes were produced at a constant rate for 72 h albeit with moderate regioselectivity (n/iso = 3.8). Analysis of recovered products revealed that <1 ppm Rh is leached into the organic phase.

The monophasic hydroformylation of methylpent-3-enoate in bmimPF$_6$ has been reported.[44] The linear aldehyde product (Reaction 8) is a precursor of adipic acid in an alternative

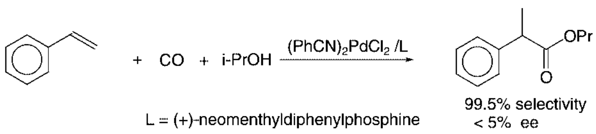


(8)

butadiene-based route. The product was removed by distillation (0.2 mbar/110 °C) and the ionic liquid recycled ten times without significant loss in activity.

Alkoxycarbonylation

Much less attention has been focused on carbonylation reactions in ionic liquids. The biphasic palladium-catalysed alkoxycarbonylation of styrene (Reaction 9) in bmimBF$_4$–cyclohexane has been reported.[45] Very high regioselectivities ($\geqslant 99.5\%$ iso) were obtained, using PdCl$_2$(PhCN)$_2$ in combination with (+)-neomenthyldiphenylphosphine and toluene-*p*-sulfonic acid, under mild conditions (70 °C and 10 bar).



(9)

More recently, the palladium-catalysed alkoxycarbonylation and amidocarbonylation of aryl bromides and iodides in bmimBF$_4$ and bmimPF$_6$ has been described.[46] Enhanced reactivities were observed compared to conventional media and the ionic liquid–catalyst could be recycled.

Olefin dimerisation and oligomerisation

The nickel-catalysed dimerisation of lower olefins in ionic liquids containing chloroaluminate anions is probably the most investigated reaction in ionic liquids.[18,26,47–49] As early as 1990 the group of Chauvin at the Institut Francais du Petrole (IFP) reported the nickel-catalysed dimerisation of propene in bmimAlCl$_4$.[47] The catalyst precursor consisted of L$_2$NiCl$_2$ (L = Ph$_3$P or pyridine) in combination with EtAlCl$_2$ (bmimCl–AlCl$_3$–EtAlCl$_2$ = 1 : 1.2 : 0.25). The active catalyst is a cationic nickel(II) complex, $[LNiCH_2CH_3]^+AlCl_4^-$, formed by reaction of L$_2$NiCl$_2$ with EtAlCl$_2$. Since ionic liquids promote the dissociation of ionic metal complexes it was envisaged that they would have a beneficial effect on this reaction.[18]

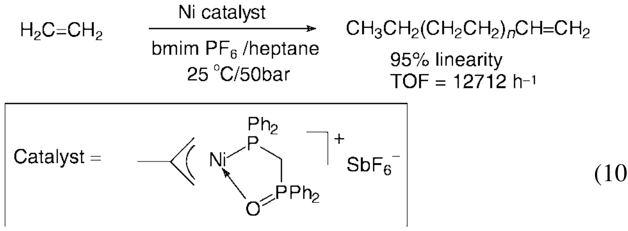
This proved to be the case: at 5 °C and atmospheric pressure productivities (>250 kg dimers per g Ni) much higher than those observed in organic solvents were achieved.[18,47,48] The mixture of dimers obtained, containing 2,3-dimethylbutene as the major component (83%), has commercial importance as the precursor of octane boosters for reformulated gasoline. It has been produced since the mid-seventies by the IFP 'Dimersol' process (25 units worldwide with a production of 3.4×10^6 tons per annum) in a single-phase solvent-free medium.

The methodology was subsequently extended to the dimerisation of butenes. The isooctene product constitutes the feedstock for the manufacture of isononanols (plasticizers) by hydroformylation. A productivity of > 100 kg dimers per g Ni was obtained at 10 °C.

Conducting these dimerisations as biphasic reactions in ionic liquids affords several benefits:[18] a better selectivity to dimers (owing to their low solubility in the ionic liquid), a better use of the catalyst components and, hence, reduced disposal costs, substantially reduced reactor size, no corrosion and broader scope (to less reactive, higher olefins).

The nickel-catalysed biphasic dimerisation of olefins in ionic liquids is being offered for licensing by IFP under the acronym ‘Difasol process’ and is likely to be the first large scale application of biphasic catalysis in ionic liquids.

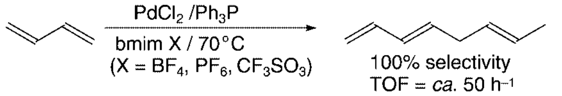
Wasserscheid and Keim[20,50] have developed alternative, alkylaluminium-free nickel catalysts for the linear dimerisation of but-1-ene. A turnover frequency of 1240 h^{-1} and a dimer selectivity of 98% (64% linearity) was observed at 25 °C. More recently, the same group reported[51] the use of cationic nickel complexes for the biphasic oligomerisation of ethene to higher α-olefins in $bmimPF_6$ (Reaction 10). The products separated as a clear and colourless layer and the catalyst-containing ionic liquid could be recycled with leaching below the detection limit (0.1%).



(10)

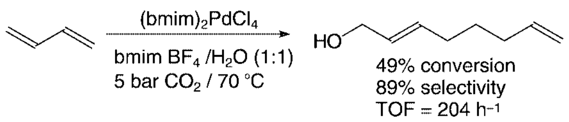
The palladium-catalysed dimerisation of butadiene to octa-1,3,6-triene and octa-1,3,7-triene is industrially important as the products have a wide range of applications, *e.g.* as comonomers and in the synthesis of plasticizers, adhesives and fragrances. Since these octatrienes rapidly polymerise in the presence of air, separation of the product from the homogeneous catalyst, *e.g.* by distillation, presents a serious problem. This would seem, therefore, to be an attractive target for biphasic catalysis in an ionic liquid.

Dupont and coworkers[52] have reported that $PdCl_2$–Ph_3P (1:4) catalyses the biphasic dimerisation of butadiene (Reaction 11) in bmimX (X = BF_4, PF_6 or CF_3SO_3) at 70 °C, affording octa-1,3,6-triene in 100% selectivity.



(11)

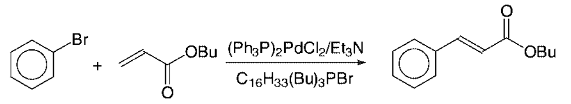
The same group reported[53] that when the reaction is performed with $(bmim)_2PdCl_4$ in $bmimBF_4$–H_2O (roughly 1 : 1 v/v) selective telomerisation resulted to afford octa-2,7-dien-1-ol (Reaction 12). As is also observed in other mono- and biphasic telomerisations of butadiene, the presence of carbon dioxide was essential for high activity. Using 5 bar CO_2 a turnover frequency of 204 h^{-1} and a selectivity of 89% (11% octa-1,3,6-triene) at 49% conversion was observed at 70 °C. Interestingly, the reaction is monophasic under the reaction conditions but cooling the mixture to 5 °C produces two phases and the ionic liquid phase can be separated and recycled. This methodology is a potentially attractive alternative to the aqueous biphasic telomerisation of butadiene developed by Kuraray.[3,4]



(12)

Heck reactions

The Heck and related C–C coupling reactions are of major importance in organic synthesis and are finding wide application in the manufacture of fine chemicals.[54] The first example of a Heck coupling in an ionic liquid was reported by Kaufmann *et al.* in 1996.[55] Butyl *trans*-cinnamate was produced in high yield by reaction of bromobenzene with butyl acrylate in molten tetraalkylammonium and tetraalkylphosphonium bromide salts (Reaction 13). No formation of palladium metal was observed and the product was isolated by distillation from the ionic liquid.

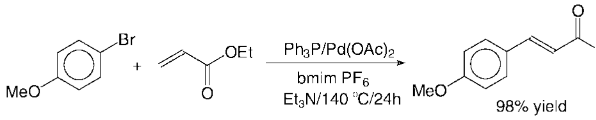


(13)

Herrmann and Böhm[56] subsequently showed that molten Bu_4NBr (mp 103 °C) is a particularly suitable reaction medium for Heck reactions, affording superior results compared with commonly used organic solvents such as DMF. For example, in the reaction of bromobenzene with styrene, using diiodobis(1,3-dimethylimidazolin-2-ylidine)palladium(II) as the catalyst, the yield of stilbene was increased from 20% in DMF to 99% in Bu_4NBr under otherwise identical conditions. The product was separated by distillation and the catalyst containing ionic liquid recycled up to 13 times without significant loss of activity.

Seddon and coworkers[57] performed Heck couplings in $bmimPF_6$ or *n*-hexylpyridinium PF_6 using $PdCl_2$ or $Pd(OAc)_2$–Ar_3P as the catalyst and Et_3N or $NaHCO_3$ as the base.

For example, $Pd(OAc)_2$–Ph_3P-catalysed coupling of 4-bromoanisole with ethyl acrylate (Reaction 14) in $bmimPF_6$ at 140 °C, afforded ethyl 4-methoxycinnamate in 98% yield.



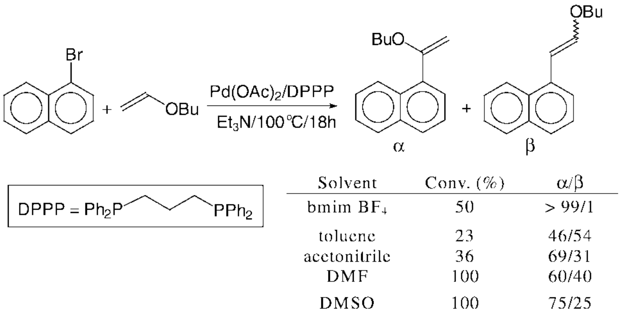
(14)

The high solubility of the catalyst in the ionic liquid allows for product isolation by extraction into a hydrocarbon, *e.g.* hexane or toluene. Furthermore, if water is added a triphasic system is obtained in which the salt formed in the reaction, Et_3NHBr, is extracted into the aqueous phase.

It was also noted that palladium complexes of imidazolylidene carbenes, formed by reaction of the base with the imidazolium cation, may be implicated in these reactions.[57]

This was later confirmed by Xiao and coworkers[58] who observed a significantly enhanced rate of the Heck coupling in bmimBr compared to the same reaction in $bmimBF_4$. This difference could be explained by the formation of the corresponding palladium–carbene complexes (which were isolated and characterised) in the former but not in the latter. The isolated carbene complexes were shown to be active catalysts when redissolved in bmimBr. Presumably, the formation of the carbene in bmimBr can be attributed to the stronger basicity of bromide compared to tetrafluoroborate.

The Heck arylation of electron-rich enol ethers generally leads to a mixture of regio isomers owing to competition between cationic and neutral pathways, leading to α- and β-arylation, respectively (Reaction 15). The ionic pathway is favoured with aryl triflates but these are less available and much more expensive than the corresponding chlorides and bromides. The ionic pathway would also be expected to be favoured by conducting the reaction in an ionic liquid and this proved to be the case. Thus, Xiao and coworkers[59] achieved > 99% selectivity to the α-arylation product in the Heck coupling of 1-bromonaphthalene to butyl vinyl ether in $bmimBF_4$ (Reaction 15). In contrast, the same reaction in toluene, acetonitrile, DMF or DMSO afforded mixtures of the α- and β-regio isomers. A range of 4-substituted bromobenzenes were similarly shown to give α-/β-regioselectivities of > 99%.



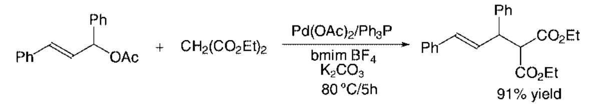
Solvent	Conv. (%)	α/β
bmim BF$_4$	50	> 99/1
toluene	23	46/54
acetonitrile	36	69/31
DMF	100	60/40
DMSO	100	75/25

(15)

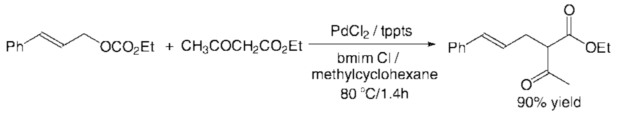
Similarly, palladium-catalysed Stille[60a] and Negishi[60b] couplings and nickel-catalysed coupling of aryl halides[61] in bmimBF$_4$ and bmimPF$_6$, respectively, have also been described.

Palladium-catalysed allylic substitution

Palladium-catalysed allylic substitution by carbon nucleophiles constitutes another synthetically useful method for the generation of C–C bonds. These reactions have also been performed in ionic liquids, both in a mono- and biphasic system, using Pd(OAc)$_2$–Ph$_3$P (with K_2CO_3 as base) in bmimBF$_4$ (Reaction 16)[62] and PdCl$_2$–tppts in bmimCl–methylcyclohexane (Reaction 17),[63] respectively. In the latter case distinct advantages compared to the corresponding aqueous biphasic system were noted: an order of magnitude higher activity and improved selectivity owing to suppression of the competing reaction with water as a nucleophile and a much decreased phosphonium salt formation (by reaction of tppts with the Pd–allyl complex).



(16)



(17)

Reaction (16) has also been performed using chiral ferrocenylphosphine complexes of palladium, in bmimPF$_6$.[64] The product was obtained in moderate enantioselectivity (62–74% ee), which was higher than that observed in conventional solvents.

Catalytic oxidations

Considering the commercial importance of catalytic oxidations, and the fact that ionic liquids are expected to be relatively inert towards autoxidation with O_2, surprisingly little attention has been devoted to performing such reactions in ionic liquids. The Ni(acac)$_2$-catalysed aerobic oxidation of aromatic aldehydes, to the corresponding carboxylic acids, in bmimPF$_6$ has been described.[65] However, rather high (3 mol%) catalyst loadings were used and this can hardly be considered a challenging oxidation.

The methyltrioxorhenium (MTO)-catalysed epoxidation of olefins with the urea–H_2O_2 adduct (UHP) in emimBF$_4$ has been reported.[66] Both the UHP and the MTO are soluble in emimBF$_4$ and the medium remains homogeneous throughout the reaction. It should be noted, however, that the substrates were generally highly reactive olefins and when the more challenging dec-1-ene was used, a long reaction time (72 h) was needed for moderate conversion (46%) using 2 equivalents of oxidant. When 30% aq. H_2O_2 was used as the oxidant this led to ring opening of sensitive epoxides.

Asymmetric Jacobsen-Katsuki epoxidation, with NaOCl catalysed by a chiral Mn Schiff's base complex has been conducted in bmimPF$_6$.[67] However, dichloromethane was required as a cosolvent, as the ionic liquid solidifies at the reaction temperature (0 °C), which nullifies one of the primary incentives for using an ionic liquid. The ionic liquid, containing the catalyst, could be recovered and recycled 4 times albeit with a significant loss in yield.

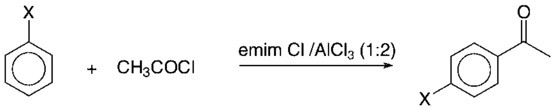
A more recent, and very exciting development, is the electroassisted biomimetic activation of molecular oxygen by a chiral Mn Schiff's base complex in bmimPF$_6$ described by Gaillon and Bedioui.[68] Evidence was provided for the formation of the highly reactive oxomanganese(V) intermediate that could transfer its oxygen to an olefin. This would appear to offer potential for clean, electrocatalytic oxidations with molecular oxygen in ionic liquid media.

Lewis and Brønsted acid catalysis in ionic liquids

Ionic liquids containing chloroaluminate ($AlCl_4^-$, $Al_2Cl_7^-$) anions are strong Lewis acids and if protons are present they are superacidic (see earlier). Coupled with the fact that they are relatively easy to handle this makes these materials attractive non-volatile alternatives for standard Lewis acid catalysts, such as $AlCl_3$, and hazardous Brønsted acids such as HF. The ionic liquid can function as both a catalyst and a solvent for acid catalysed processes. Since Lewis and Brønsted acid-mediated processes generally involve cationic intermediates, *e.g.* carbenium and acylium ions, one would also expect to see substantial rate enhancements in ionic liquids. Indeed, some of the first reactions to be studied in ionic liquids were Friedel–Crafts alkylations and acylations. Wilkes and coworkers[69] showed that ionic liquids derived from the reaction of emimCl with $AlCl_3$ exhibit a wide range of Lewis acidity depending on the molar ratio of reactants. A 1 : 1 mixture affords the tetrachloroaluminate, emimAlCl$_4$, which is referred to as being neutral and is not active as a Friedel–Crafts catalyst. In contrast, the 2 : 1 adduct, emimAl$_2$Cl$_7$ is strongly acidic and was shown to be very active in Friedel–Crafts alkylations and acylations.[69] For example, a mixture of benzene, acetyl chloride and emimAl$_2$Cl$_7$ in the molar ratio 1.1 : 1.0 : 0.5 (*i.e.* less than a stoichiometric amount of the ionic liquid) afforded complete conversion to acetophenone in less than 5 minutes at room temperature. Spectral evidence suggested the formation of the free acylium cation, CH_3CO^+, in the ionic liquid medium.

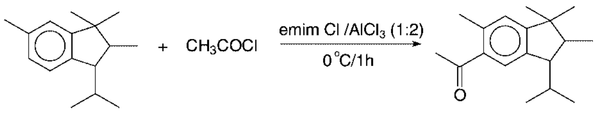
The Friedel–Crafts alkylation of benzene with long chain α-olefins is used industrially for the manufacture of more than two million tons of linear alkylbenzenes worldwide. The products are the precursors of the corresponding alkylbenzene sulfonates which are widely used as surfactants. Traditionally the reaction is performed using liquid HF or $AlCl_3$ as the catalyst. The production of linear alkylbenzenes using chloroaluminate ionic liquids has been described.[17a] The potential to retrofit existing installations with the ionic liquid catalyst offers enormous benefits with regard to reduced catalyst consumption, ease of product separation and elimination of caustic quenching associated with catalyst leaching. Chloroaluminate ionic liquids modified with HCl were recently shown[70] to give higher rates and more favourable product distributions in Friedel–Crafts alkylations, which was attributed to the superacidities of these media. In this context it is also worth mentioning the work of Hölderich *et al.*[71] who showed that ionic liquids immobilised on inorganic supports (SiO_2, Al_2O_3, TiO_2, ZrO_2) are effective catalysts for Friedel–Crafts alkylation of aromatics. Activities were higher than those observed with a conventional zeolite catalyst and no leaching of the ionic liquid from the surface was observed. Reactions were performed in batch, continuous liquid-phase and continuous gas-phase operation. For example, alkylation of benzene with dodecene afforded the mono-alkylated product in 98% selectivity at 99% conversion at 80 °C.

Seddon and coworkers[72] studied the Friedel–Crafts acylation of toluene, chlorobenzene and anisole with acetyl chloride in emimAl_2Cl_7 and obtained excellent regioselectivities to the *para* isomer (Reaction 18). Similarly, the fragrance chemical, traseolide, was obtained in 99% yield as a single isomer (Reaction 19). It should be noted, however, that the question of product recovery from the reaction medium still needs to be addressed in these systems. As in conventional $AlCl_3$-promoted acylations the ketone product forms a strong complex with the chloroaluminate ionic liquid.



R	Temp/°C	Time/h	Yield(%)
MeO	−10	0.25	99
Me	20	1	98
Cl	20	24	97

(18)



traseolide
99% yield

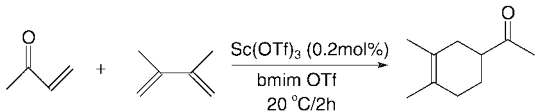
(19)

Lanthanide triflates, in particular $Sc(OTf)_3$, have been widely studied as water-tolerant Lewis acids in a variety of transformations, including Friedel–Crafts alkylations and acylations.[73] Song and coworkers[74] have recently shown that $Sc(OTf)_3$ catalyses the Friedel–Crafts alkylation of aromatics with olefins in hydrophobic ionic liquids, *e.g.* bmimPF_6 and bmimSbF_6. In contrast, no reaction was observed in common organic solvents, water or hydrophilic ionic liquids such as bmimBF_4 or bmimOTf. For example, reaction of benzene with cyclohexene (Reaction 20) afforded cyclohexylbenzene in 92% yield at >99% cyclohexene conversion in bmimSbF_6 at 20 °C for 12 h. The product formed a separate layer and, after phase separation, the ionic liquid phase, containing the catalyst, was recycled to afford 92% yield of cyclohexylbenzene at >99% conversion. Although high catalyst loadings (20 mol%) were used the ease of separation and recycling of the catalyst offers potential environmental and economic benefits.

> 99% conversion
1st run 90% yield
2nd run 92% yield

(20)

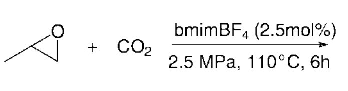
The same group has recently reported[75] that $Sc(OTf)_3$ catalyses Diels–Alder reactions in bmimX (X = BF_4, SbF_6 or OTf), in this case at much lower catalyst loadings (0.2 m%). In contrast to the Friedel–Crafts alkylation (see above) the product did not form a separate phase and was recovered by extraction with ether. It was shown, however, that the ionic liquid containing the catalyst could be recycled eleven times without loss of activity (Reaction 21). Furthermore, improved *endo*/*exo* selectivities were observed with cyclic dienes.



1st run 94% yield
11th run 90% yield

(21)

Another reaction catalysed by Lewis acids is the cycloaddition of carbon dioxide to epoxides, affording cyclic carbonates. It was recently reported that this reaction is catalysed by bmimBF_4.[76] When propene oxide was allowed to react with CO_2 (2.5 MPa) at 110 °C for 6 h in the presence of bmimBF_4 (2.5 mol%), propene carbonate was obtained in 100% yield (Reaction 22).



(22)

100% yield

The propene carbonate was distilled from the reaction mixture and the ionic liquid catalyst recycled four times with only a minor loss in activity.

Protons in acidic ionic liquids have acidities greater than those of H_2SO_4 or liquid HF.[8,17,18] They are, for example, able to protonate benzene to the cyclohexadienyl cation. The acidic ionic liquid, bmimAl_2Cl_7, catalyses the alkylation of ethene with isobutane[18] whereas neither HF nor H_2SO_4 is effective for this reaction. The major product is 2,3-dimethylbutane (75–86%) which has a higher octane number than the products of alkylation of higher olefins. The product forms a separate upper phase and the ionic liquid is readily recycled.

Olefin oligomerisation and polymerisation is also promoted by these strongly acidic ionic liquids, *e.g.* high molecular weight polyisobutene is readily obtained from isobutene.[17] The catalytic activity and degree of polymerisation is determined by the chain length of the alkyl group in the 1-alkyl-3-methylimidazolium or *N*-alkylpyridinium cation which provides a convenient mechanism for controlling the product distribution. Polyisobutene is a commercially important lubricant and the ionic liquid process has several advantages compared with the conventional process which employs a supported or dissolved $AlCl_3$ catalyst. The polymer forms a separate phase and is readily separated and reused which obviates the need for an aqueous wash and, hence, reduces waste and costs. Moreover, the process can be easily retrofitted into existing production facilities.

The electrophilic nitration of aromatics, using a variety of nitrating agents, has also been investigated in ionic liquid solvents.[77] It was noted that nitration in ionic liquids constitutes a useful alternative to classical methods owing to easier product isolation and recovery of the ionic liquid and avoidance of problems associated with the neutralisation of large quantitities of acid.

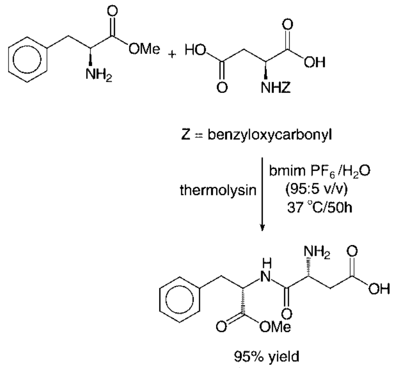
Many synthetically important rearrangement reactions are catalysed by Brønsted or Lewis acids and, hence, may benefit from using acidic ionic liquids as solvents and/or catalysts. For example, the Beckmann rearrangement of ketoximes in ionic liquids, in the presence of catalytic amounts (20 mol%) of phosphorus compounds (*e.g.* P_2O_5) was recently reported.[78]

The ionic liquid tributylhexylammonium bis(trifluoromethylsulfonyl) amide was shown[79] to be a useful solvent for the acid-catalysed cyclotrimerisation of veratryl alcohol. The methodology obviates the need for large quantities of organic solvent and strongly dehydrating acids and provides the cyclotriveratrylene (CTV) in high yield and purity. CTV is of interest as a supramolecular host compound that complexes a variety of guest molecules.

Biocatalysis in ionic liquids

Attention has recently been focused on the use of enzymes in ionic liquids. It was already noted in 1984[80] that the enzyme alkaline phosphatase is relatively stable in a 4:1 (v/v) mixture of triethylammonium nitrate and water. More recently, Lye and coworkers[81] reported a two-phase biotransformation in which $bmimPF_6$ acts as a reservoir for the substrate while the biocatalyst—whole cells of *Rhodococcus* R312—is present in the aqueous phase. Shortly thereafter two reports of enzymatic conversions in an ionic liquid medium appeared.[82,83]

Erbeldinger *et al.*[82] reported the thermolysin-catalysed synthesis of *Z*-aspartame (Reaction 23) in $bmimPF_6$ containing 5% (v/v) water. The enzyme displayed excellent stability when suspended in the ionic liquid and the activity was equal to that observed in ethyl acetate–water. A small amount of the enzyme (<3.2 mg mL^{-1}) which dissolved in the ionic liquid was completely inactive.

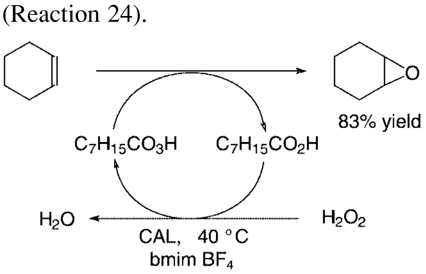


95% yield
aspartame precursor

(23)

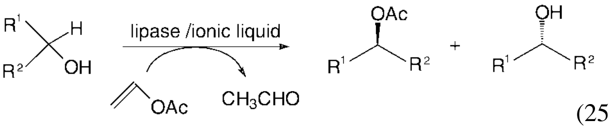
We showed[83] that *Candida antarctica* lipase is able to catalyse a variety of transformations—transesterification, ammoniolysis and perhydrolysis—in $bmimBF_4$ or $bmimPF_6$ in the absence of water. Reactions were performed with the free (NOVO SP525) or immobilized enzyme (Novozyme 435). Reaction rates were comparable with or better than those observed in conventional organic media. For example, the reaction of octanoic acid with ammonia, in $bmimBF_4$ at 40 °C, gave complete conversion to octanamide in 4 days compared to 17 days for the same conversion using ammonium carbamate in methyl isobutyl ketone.[84]

The epoxidation of cyclohexene by peroxyoctanoic acid, generated *in situ* by Novozyme 435-catalysed reaction of octanoic acid with 60% aqueous H_2O_2, proceeded smoothly in $bmimBF_4$ (Reaction 24).



(24)

Subsequently, other groups have reported on lipase-catalysed enantioselective transesterification of chiral alcohols (Reaction 25) in ionic liquids.[85–87] Kragl and coworkers[85] investigated the kinetic resolution of 1-phenylethanol with nine different lipases in ten different ionic liquids. Good activities and, in many cases, improved enantioselectivities were observed compared with the same reaction in MTBE (methyl *tert*-butyl ether). Rates and/or enantioselectivities were dependent on the anion as was also observed by Itoh and coworkers.[86] It was also shown that the product could be extracted with ether and the ionic liquid ($bmimPF_6$), containing the suspended enzyme, could be recycled.[86] Similarly, Kim and coworkers[87] observed markedly enhanced enantioselectivities in *Candida antarctica* and *Pseudomonas cepacia* lipase-catalysed transesterifications of chiral alcohols in $bmimBF_4$ and $bmimPF_6$.



(25)

Based on these initial studies the use of enzymes in ionic liquids would appear to open up a new field of nonaqueous enzymology. Ionic liquids could have added benefits for performing biotransformations with highly polar substrates, *e.g.* carbohydrates and amino acids, which are sparingly soluble in common organic solvents. We are currently investigating the scope with regard to type of enzyme, transformation and the effect of the structure of the ionic liquid.

Concluding remarks

Catalysis in ionic liquids is an exciting and burgeoning area of research (many of the references in this review are from 2000 and 2001) which holds considerable potential for industrial application. The use of ionic liquids as reaction media for catalytic transformations or, in some cases, as the catalyst itself can have a profound effect on activities and selectivities. Furthermore, precision tuning of reactions can be achieved by a suitable combination of cation and anion, *i.e.* they are truly 'designer solvents'. In the majority of cases studied the ionic liquid, containing the catalyst could be readily recycled. They provide a medium for performing clean reactions with minimum waste generation. As was remarked by Seddon[8] they could, quite literally, revolutionise the methodology of synthetic organic chemistry.

Notes and references

† We have adopted the abbreviations used by many (but not all) authors for dialkylimidazolium cations, *viz.*, emim for ethylmethylimidazolium, bmim for butylmethylimidazolium, *etc.*

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