FEATURE ARTICLE

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Enantioselective chemo- and bio-catalysis in ionic liquids

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Recent developments in the enantioselective chemo- and bio-catalysis in ionic liquids are reviewed. In many cases, the use of ionic liquids provides many advantages over reactions in conventional organic solvents in terms of activity, enantioselectivity, stability and the reusability of the solvent–catalyst systems.

Introduction

For economic, environmental and social reasons, the trend towards the application of optically pure compounds is rapidly increasing. Of the various methods used to produce single enantiomers, enantioselective catalysis using either chiral catalysts[1] or enzymes[2] is viewed as being the most attractive from the atom-economic point of view. Although a number of chemo- and bio-catalytic reactions that allow the enantioselective formation of C–H, C–C, C–O, C–N and other bonds have been discovered, some of which have gained wide acceptance because of their efficiency and selectivity, the high cost of chiral catalysts and enzymes often restricts their use in industry. Thus there is increasing demand, driven by economic considerations, to develop efficient immobilisation methods that facilitate recovery and the reuse of the expensive chemo- and bio-catalysts. Homogeneous chiral catalysts have been immobilised either by anchoring the catalyst onto a solid support (*via* covalent attachment, adsorption, ion-pair formation, encapsulation, or entrapment) or by using fluorous or aqueous biphasic systems.[3] Similarly, enzymes have been immobilised by heterogenisation, *e.g.*, by covalently attaching the enzyme to a solid support, by non-covalently adsorbing the enzyme onto a solid support, by entrapping the enzyme in a polymer gel, membrane or capsule, or by cross-linking the enzyme with a polyfunctional agent.[4] All of these approaches are of interest but often require additional catalyst- and enzyme-modifications. Moreover, the activity and/or enantioselectivity of the immobilised chemo- and bio-catalysts are usually reduced because of unsuitable chemical modifications, steric hindrance by support or mass transfer limitations, *etc*.

Dr Choong Eui Song was born in 1955 in Seoul, Korea. He received a B.S. in 1980 from Chungang University and obtained a Diploma (1985) and a Ph.D. (1988) at RWTH Aachen in Germany. Since 1989 he has worked as a Principal Research Scientist at the Korean Institute of Science and Technology (KIST). In 2001 he was appointed as Head of the National Research Laboratory for Green Chirotechnology in Korea. His research interests focus on the immobilisation of chiral catalysts, ionic liquid chemistry and the development of new pharmaceutically active compounds. He received the academic award from KIST (2000) and the Scientist of the Month Award from the Ministry of Science and Technology in Korea.

A new approach has recently been developed for catalyst separation and recycling, which involves the use of ionic liquids, *i.e.*, a salt mixture with a melting point below ambient.[5] Ionic liquids are regarded as eco-friendly alternatives to volatile organic solvents in chemical processes, due to their negligible vapor pressure and non-flammable nature. Moreover, their hydrophobicities/hydrophilicities and solvent miscibility can be tuned by selecting the appropriate cation and anion. Thus, depending on their structures, they can be designed to be immiscible with water or some organic solvent (*e.g.*, alkanes, ether, *i*-PrOH, *etc*.), which renders them more useful for facilitating catalyst recovery from the reaction mixture. Moreover, switching from an organic solvent to an ionic liquid often results in marked improvements in catalytic performance.[6] However, most of the studies in this area prior to 2000 focused on non-asymmetric catalytic reactions. Since 2000, this relatively new immobilisation method has been intensively applied to enantioselective chemo- and bio-catalysis. A broad range of enantioselective catalytic reactions have already been described, and most examples studied to date show that the use of ionic liquids can confer many advantages upon enantioselective catalytic reactions over reactions in organic solvents in terms of activity, enantioselectivity, stability and the reusability of the solvent–catalyst systems. In this article, these recent interesting results on the use of ionic liquids for the enantioselective chemo- and bio-catalysis are reviewed. Most studies in this area have involved the use of 1,3-dialkylimidazolium-type ionic liquids (Fig. 1).

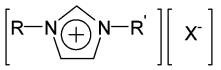

Fig. 1 1-Alkyl-3-alkylimidazolium salt (X = PF_6, SbF_6, NTf_2, BF_4, OTf, *etc*.. In this article, we have adopted the abbreviations used by many authors for dialkylimidazolium cations, *viz.*, emim for 1-ethyl-3-methylimidazolium, bmim for 1-butyl-3-methylimidazolium, *etc*.).[5]

Enantioselective chemocatalysis in ionic liquids

Asymmetric oxidation

Chiral Mn(salen) catalysed epoxidation of olefins. The catalytic asymmetric epoxidation of alkenes offers a powerful strategy for the synthesis of enantiomerically enriched epoxides. Of the several possible catalytic methods, the asymmetric epoxidation of unfunctionalised alkenes catalysed by chiral Mn(III)(salen) complexes such as homochiral [(*N*,*N*′)-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]manganese(III) chloride (Fig. 2), developed by Jacobsen and co-workers, is perhaps one of the most reliable methods.[7]

Our recently published work[8] demonstrates the usefulness of an ionic liquid in this important reaction. The epoxidations of various olefins were carried out using a chiral Mn(III)(salen) complex (Fig. 2) as a catalyst and NaOCl as the co-oxidant in a mixture of [bmim][PF_6] and CH_2Cl_2 (1 : 4 v/v). Good conversion and

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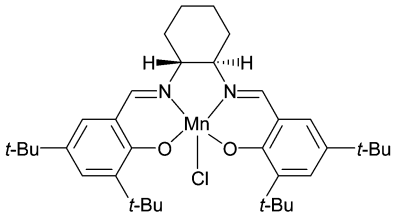
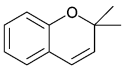
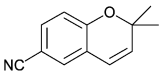
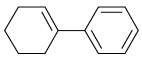


Fig. 2 (*R*,*R*)-Mn(III)(salen)Cl.

enantioselectivity were observed for all tested substrates (see Table 1). Interestingly, an enhancement in catalytic activity was obtained

Table 1 (*R*,*R*)-Mn(III)(salen)Cl catalysed asymmetric epoxidation of alkenes in [bmim][PF_6]/CH_2Cl_2

Substrate	Time/h	Yield (%)	Ee (%)	Configuration
	2	86	96	(3*R*,4*R*)
	4	72	94	(3*R*,4*R*)
	4	72	84	(1*R*,2*S*)
	3	72 (3.7 : 1)[a]	86	(1*R*,2*S*)
	4	77	84	(*S*,*S*)

[a] *cis* : *trans* selectivity.

by adding the ionic liquid to the organic solvent. The epoxidation of 2,2-dimethylchromene using 4 mol% of Mn(III)(salen) catalyst in the presence of [bmim][PF_6] was completed in 2 h, whereas the same reaction without the ionic liquid required 6 h to achieve complete conversion. This rate acceleration effect induced by the ionic liquid was shown even more dramatically when the amount of the catalyst was reduced to 0.5 mol% (Fig. 3).[9] In a mixture of

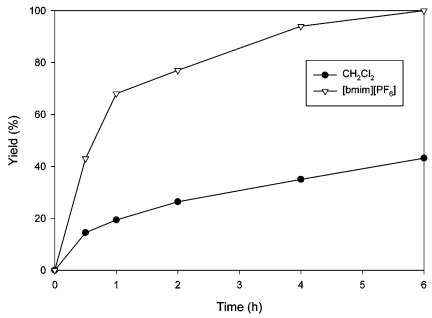
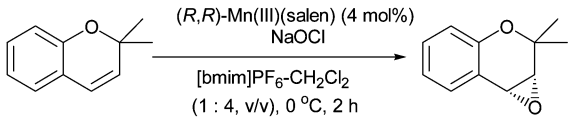


Fig. 3 Kinetic studies in the epoxidation of 2,2′-dimethylchromene using 0.5 mol% of (*R*,*R*)-Mn(III)(salen)Cl at 0 °C.

[bmim][PF_6] and CH_2Cl_2 (1 : 4 v/v), the above reaction was completed in 6 h, whereas without the ionic liquid only *ca.* 40% conversion was observed in the same time. Moreover, the use of an ionic liquid solvent allows for easier catalyst recycling, without the need for catalyst modification. By washing the organic phase with water, concentrating the organic phase, and then extracting the product with hexane, the ionic catalyst solution can be recovered. However, the enantioselectivity and activity of the recovered catalyst decreased upon reuse. After five cycles, the yield and enantioselectivity dropped from 83 to 53% and from 96 to 88% ee, respectively (Scheme 1). This deterioration may be due to degradation of the salen catalyst under oxidation conditions. Nevertheless, to the best of our knowledge, Jacobsen's catalyst



86% yield, 96% ee (1st run)
73% yield, 90% ee (2nd run)
73% yield, 90% ee (3rd run)
60% yield, 89% ee (4th run)
53% yield, 88% ee (5th run)

Scheme 1

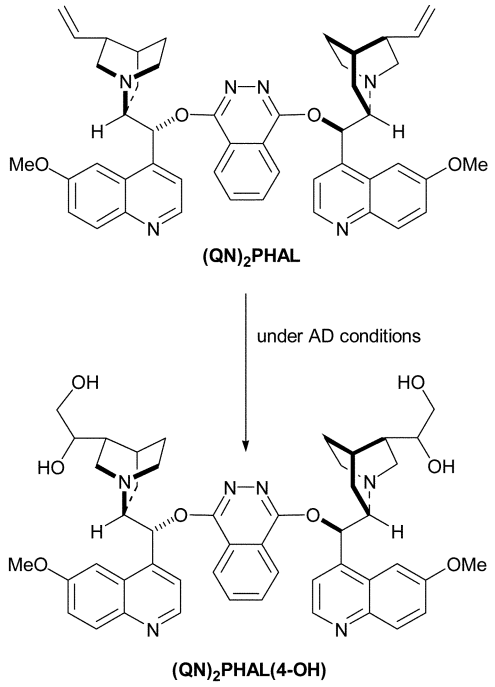
immobilised in an ionic liquid constitutes one of the most efficient and recyclable catalytic systems[3] available for the asymmetric epoxidation of alkenes.

After we had published the results of this previous study, Gaillon and Bedioui reported upon the electroassisted biomimetic activation of molecular oxygen by a chiral Mn(salen) complex in [bmim][PF_6].[10] In this study, evidence was provided of the formation of the highly reactive [Mn(V)=O]$^+$ manganese-oxo intermediate, which is capable of transferring its oxygen to an olefin. This method has potential in electrocatalytic asymmetric epoxidations using molecular oxygen in ionic liquid media. However, no preparative scale experimental data has been reported.

Os-Catalysed asymmetric dihydroxylation of olefins. The Sharpless Os-catalysed asymmetric dihydroxylation (AD) of olefins provides one of the most elegant methods of synthesising chiral vicinal diols.[11] Although the AD reaction offers a number of processes that could be applied to the synthesis of chiral drugs, natural products and fine chemicals, the high cost and the toxicity of osmium, and the possible contamination of the product with osmium catalyst have restricted industrial use of the AD reaction. In order to explore the possibility that the catalytic components can be used repetitively, several attempts have been made to immobilise this catalytic system.[12–15] Early approaches to immobilising OsO_4 on solid-supported alkaloid ligands suffered from several disadvantages, such as, the need for the complicated synthesis of the supported ligand system and reduced catalytic efficiency.[12] Moreover, effective osmium recovery has failed in all cases. Recently, alternative methods of immobilising the osmium catalyst; by microencapsulation of OsO_4 in a polymer matrix,[13] by using an ion-exchange technique[14] or by osmylation of macroporous resins bearing residual vinyl groups such as Amberlite XAD-4,[15] have been reported. Although recycling experiments using this type of immobilised osmium catalyst have been successfully performed for several reuses, higher loading (1–5 mol%) of immobilised osmium catalyst was generally required than that needed in homogeneous AD reactions. In homogeneous cases, 0.2 mol% of osmium is enough to complete most reactions.

Recently, we found that combination of the ionic liquids [bmim][PF_6] or [bmim][SbF_6] with a highly polar bis-cinchona alkaloid [$(QN)_2$PHAL(4-OH)] generated *in situ* from $(QN)_2$PHAL [1,4-bis(9-*O*-quininyl)phthalazine][16] during the AD reaction (Scheme 2) provides a simple and highly practical approach to the immobilisation of both catalytic components (osmium and the alkaloid ligand).[17]

Initially, to investigate the effect of an ionic liquid on the AD reaction, and upon the recyclability of the catalytic components, AD reactions were carried out with the well-known ligand, 1,4-bis(9-*O*-dihydroquininyl)phthalazine [$(DHQ)_2$PHAL] (Fig. 4), using standard Upjohn conditions[18] (using *N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant) in the presence of [bmim][PF_6] at 20 °C. The results obtained were comparable to those obtained without an ionic liquid. For example, the AD reaction of *trans*-stilbene afforded the corresponding diol in 94% yield with an ee of 97%. The diol product was extracted from the residue with pre-cooled



Scheme 2

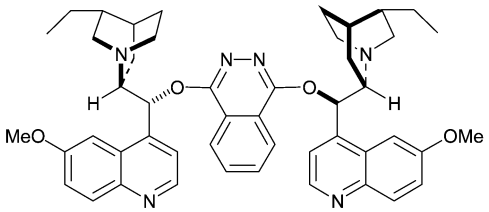


Fig. 4 $(DHQ)_2PHAL$.

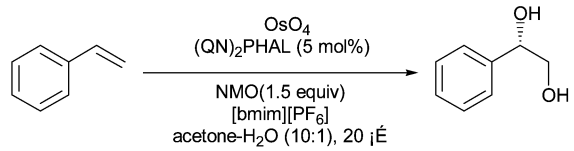
(0 °C) diethyl ether after all the volatiles had been removed under reduced pressure. However, further reuse of the remaining ionic liquid phase resulted in a dramatic yield reduction (45% after 24 h), presumably due to severe leaching of both osmium and $(DHQ)_2PHAL$ during ether extraction. Leaching of the catalytic components during the extraction can be ascribed to the partial solubility of $(DHQ)_2PHAL$ in ether.

Since the complex formation between OsO_4 and an alkaloid ligand is expected to be reversible, lowering the concentration of the chiral ligand in the ionic liquid phase might result in more OsO_4 leaching from the ionic liquid phase. Therefore, we presumed that the use of an alkaloid ligand that can be strongly immobilised in an ionic liquid, could minimise Os leaching during product extraction. To prove this, we used 1,4-bis(9-*O*-quininyl)phthalazine [$(QN)_2PHAL$] as a ligand, which would be converted to the alkaloid [$(QN)_2PHAL(4\text{-}OH)$] bearing highly polar residues (four hydroxy groups) under dihydroxylation conditions (Scheme 2). Such polar residues will increase the preferential solubility of chiral ligands to the ionic liquids. The use of $(QN)_2PHAL$ instead of $(DHQ)_2PHAL$ afforded the same yields and ee's (Table 2) and, as expected, dramatically increased the recyclability of both catalytic components. The recovered ionic liquid phase, containing both osmium and the ligand [$(QN)_2PHAL(4\text{-}OH)$], could be recycled several times, even in recycling experiments using 0.1 mol% of OsO_4 (Scheme 3). In the case of recycling experiments using 0.1 mol% of OsO_4, the total turnover number (TON) was found to be *ca.* 2370. To the best of our knowledge, this is the highest total TON value ever reported under Upjohn conditions. Thus, this AD procedure incorporating ionic liquids minimises catalyst consumption and reduces osmium contamination both in the product and in the process waste. Moreover, the $(QN)_2PHAL$ ligand is much cheaper than conventional AD ligands, such as $(DHQ)_2PHAL$.[16] Further optimisation of product extraction procedure (*e.g.* extraction with supercritical CO_2) can make this AD process more environmentally friendly and economical.

Table 2 Asymmetric dihydroxylation of olefins using $(QN)_2PHAL$ ligand in the presence of the ionic liquid [bmim][X][a]

Olefin	X	Yield (%)	Ee (%)	Absolute configuration
trans-Stilbene	SbF_6	92	94	*S*,*S*
trans-Stilbene	PF_6	95	97	*S*,*S*
Styrene	PF_6	89	72	*S*
β-Methyl-*trans*-styrene	PF_6	92	90	*S*,*S*
Methyl *trans*-cinnamate	PF_6	96	94	2*R*,3*S*
Methyl *p*-methoxy-*trans*-cinnamate	PF_6	93	96	2*R*,3*S*
α-Methylstyrene	PF_6	98	63	*S*

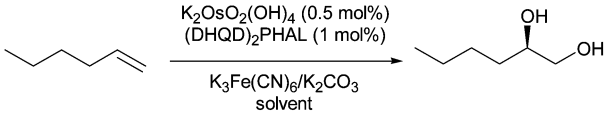
[a] Olefins were added for 12–24 h.



Using 1 mol% of OsO_4:
92%, 98% ee (1st run); 88%, 96% ee (2nd run); 91%, 94% ee (3rd run)
70%, 94% ee (4th run); 50%, 94% ee (5th run)
Using 0.1 mol% of OsO_4:
90%, 98% ee (1st run); 89%, 92% ee (2nd run); 58%, 89% ee (3rd run)

Scheme 3

Recently, Afonso *et al.*[19] reported that AD reactions using $K_3Fe(CN)_6$ as the co-oxidant can also be carried out in [bmim][PF_6], and that after reaction the ionic solution containing both osmium and ligand can be recovered and reused several times (Scheme 4). However, when we examined the same reaction using $K_3Fe(CN)_6$ as the co-oxidant, we found that the presence of ionic liquids always resulted in a negative effect on enantioselectivity. The ee's of diol products declined with an increase in the ionic liquid concentration.



In [bmim][PF_6]/H_2O:
78%, 88% ee (1st run); 70%, 83% ee (9th run)
In [bmim][PF_6]/*t*-BuOH/H_2O:
78%, 88% ee (1st run); 70%, 83% ee (9th run)

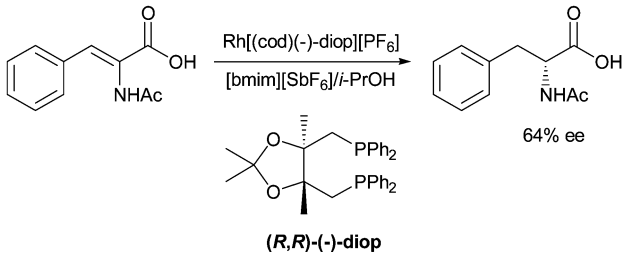
Scheme 4

Asymmetric reduction

Asymmetric hydrogenation. The transition metal-catalysed asymmetric hydrogenation of olefins is one of the first and most important asymmetric catalytic reactions. High activity and enantioselectivity have been achieved using Rh, Ir and Ru complexes of chiral phosphine, phosphite or their hybrid ligands. However, these metals and ligands are usually very expensive and air-sensitive, which limits their industrial applications. Therefore, their recycling is a prerequisite for large-scale applications. Over the last few years, several research groups have attempted to immobilise homogeneous chiral hydrogenation catalysts using ionic liquids.[20–23,25,26] The results obtained so far seem to be highly promising. Expensive chiral Ru and Rh complexes can be

recovered by simple phase separation and then recycled, without the need for any catalyst modification. Moreover, in some cases, it was observed that in ionic liquids the air-sensitive catalysts showed increased stability.

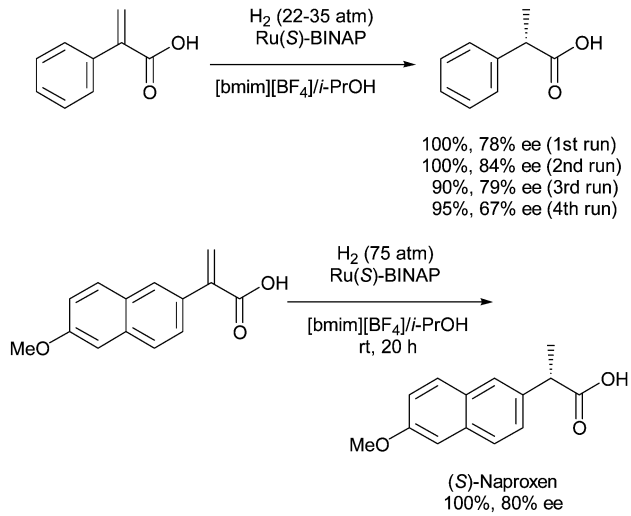
The first asymmetric hydrogenation reactions in an ionic liquid were studied by the group of Chauvin in 1995.[20] In a biphasic [bmim][SbF_6]/*i*-PrOH mixture, α-acetamidocinnamic acid was hydrogenated in the presence of [Rh(COD)((−)-DIOP)]PF_6 catalyst (COD = cycloocta-1,5-diene) to (*S*)-phenylalanine with 64% ee (Scheme 5). Moreover, the product, contained in isopropyl



Scheme 5

alcohol, was separated quantitatively by simple phase separation and the recovered ionic liquid phase containing the catalyst proved reusable.

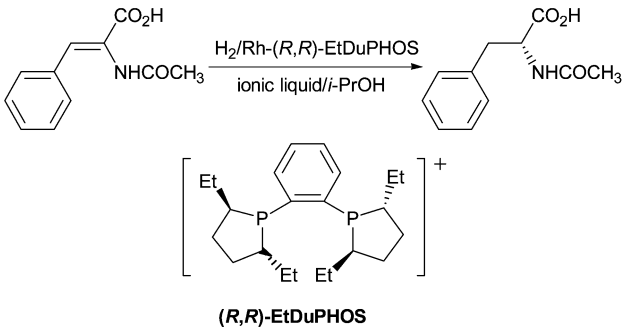
Similarly, Dupont and coworkers[21] studied the asymmetric hydrogenation of 2-phenylacrylic acid in a biphasic [bmim][BF_4]/*i*-PrOH system using Ru(COD)Cl_2/BINAP/NEt_3 as catalyst. The ee's obtained in these asymmetric hydrogenations were similar to those obtained in homogeneous organic media. It was also found in these cases that the catalytic ionic solution was reusable several times over with ee's ranging from 67 to 84% (Scheme 6). This



Scheme 6

catalyst system was also used for the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid to give an anti-inflammatory drug, Naproxen, in 80% ee (Scheme 6).

More recently, these workers performed a more detailed study of the asymmetric hydrogenation of α-acetamidocinnamic acid with chiral Rh(I)-EtDuPHOS complex immobilised in [bmim][BF_4] and [bmim][PF_6] (Scheme 7).[22] The authors described the remarkable effects of the molecular hydrogen concentration in the ionic catalyst layer, rather than the effects of hydrogen pressure in the gas phase, on the conversion and enantioselectivity of these reactions. As shown in Table 3, enantioselectivity and conversion increase when the solubility of molecular hydrogen increases in the liquid phase. The much higher enantioselectivity and conversion in the case of



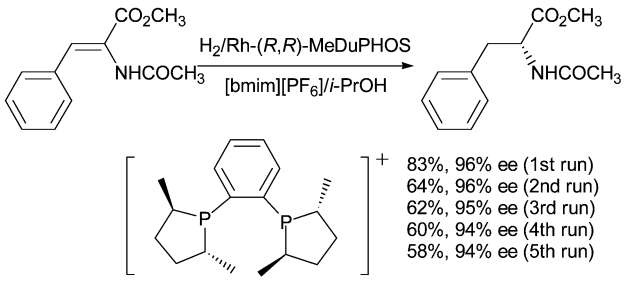
Scheme 7

Table 3 The asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid: the effect of hydrogen concentration in the liquid phase on the conversion and the enantioselectivity

Solvent	*P*/atm	H_2 solubility/mol L^{-1}	Conversion (%)	Ee (%)
[bmim][PF_6]	5	4.4×10^{-3}	7	66
[bmim][PF_6]	50	4.4×10^{-2}	26	81
[bmim][PF_6]	100	8.9×10^{-1}	41	90
[bmim][BF_4]	50	1.5×10^{-1}	73	93
i-PrOH	50	129.3	99	94

[bmim][BF_4] *versus* [bmim][PF_6] can be explained by the higher solubility of hydrogen in [bmim][BF_4]. The solubility of hydrogen in [bmim][BF_4] was found to be almost four times higher than in [bmim][PF_6].

Recently, Guernik *et al*. reported upon the catalyst stabilisation effect of an ionic liquid in the asymmetric hydrogenation of olefins.[23] Rh-MeDuPHOS complex immobilised in [bmim][PF_6] was found to catalyse the asymmetric hydrogenation of enamides (methyl α-acetamidoacrylate and methyl α-acetamidocinnamate) with enantioselectivities similar to those obtained using the same catalyst dissolved in organic solvent (*i*-PrOH). Interestingly, the ionic liquid stabilised this highly air-sensitive catalyst, enabling all experiments including catalyst recycling to be carried out in a normal atmosphere without any significant loss of enantioselectivity (*e.g.*, methyl α-acetamidocinnamate as the substrate, 96% ee for the first run and 94% ee for the fifth run, Scheme 8). On the other

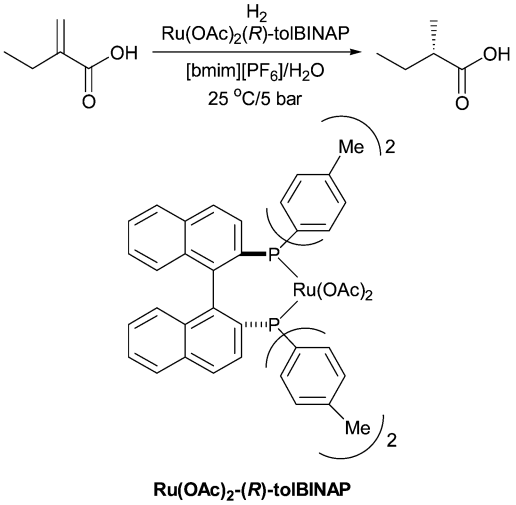


Scheme 8

hand, in the absence of ionic liquid, when a catalyst prepared in an inert atmosphere was exposed to air for a few minutes it almost totally lost its catalytic activity. This stabilising effect of the ionic liquid is considered to be due to the entrapment of the air-sensitive complex in the ionic liquid, *i.e.*, ionic liquids can protect the air-sensitive complex from attack by atmospheric oxygen.

In biphasic ionic liquid/*i*-PrOH solvent systems, a gradual decrease in yield and ee's of the hydrogenated products is often

observed upon reusing a catalyst. This loss of efficiency results from a leaching of the catalyst from the ionic liquid phase to the product/*i*-PrOH solution, due to the slight mutual solubility of the two phases. This problem seems to be solved to some extent by using supercritical CO_2 for product extraction.[24,25] Jessop and coworkers[25] undertook the asymmetric hydrogenation of tiglic acid using Ru-tolBINAP catalyst precursors in wet [bmim][PF_6] (Scheme 9). The product was then extracted from the ionic liquid



Ru(OAc)$_2$-(*R*)-tolBINAP

Scheme 9

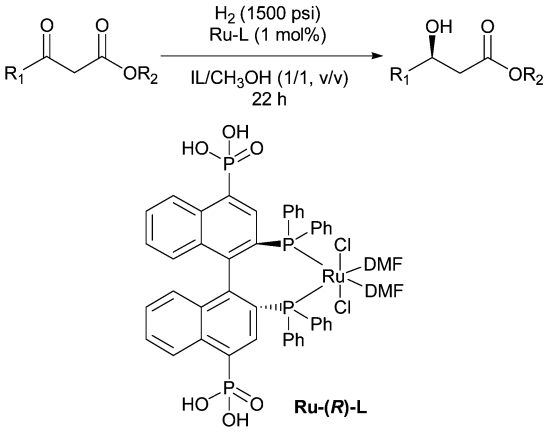
catalytic solution using supercritical CO_2. An extremely pure product was obtained from the CO_2 effluent, which was not contaminated by ionic liquid or catalyst. Conversion of up to 99% and ee's of 90% were obtained. The recovered ionic liquid catalytic solution could be reused up to four times with no apparent reduction in conversion or enantioselectivity (Table 4).

Table 4 The asymmetric hydrogenation of tiglic acid in [bmim][PF_6]/H_2O followed by extraction with scCO_2

Run	Catalyst solution	Ee (%)	Conversion (%)
1	Fresh	85	99
2	Recycled from run 1	90	98
3	Recycled from run 2	88	97
4	Recycled from run 3	87	98
5	Recycled from run 4	91	97

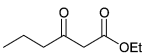
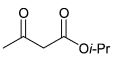
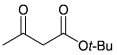
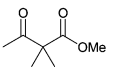
To increase the preferential solubility of BINAP-Ru type catalysts in ionic liquids and, thus, to reduce the possibility of these catalysts leaching into the organic layer during product extraction, Ngo *et al.*[26] recently designed polar phosphonic acid-derived Ru-BINAP systems and used these polar catalysts to catalyze asymmetric hydrogenation of β-keto esters in ionic liquids (Scheme 10). Higher ee values were obtained than those obtained from homogeneous reactions in MeOH (Table 5). The ionic liquid-immobilized catalysts were recycled by simple extraction and used four times without any significant loss of activity or enantioselectivity. However, subsequent uses of recycled catalyst led to a significant drop in activity and selectivity (Scheme 11).

Asymmetric transfer hydrogenation. Tetralkyl- and tetraaryl-phosphonium molten salts have also been used as media for catalyst immobilisation in rhodium-catalysed transfer hydrogenation reactions.[27] For example, the reduction of acetophenone by $Rh_2(OAc)_4$/(−)-DIOP immobilised in ethyl-tri-*n*-octylphosphonium tosylate salt (mp = 68–72 °C) in the presence of KOH/*i*-PrOH at 120 °C afforded 1-phenethylethanol (92% ee) in 50% yield (Scheme 12). This tosylate salt is a liquid at the reaction

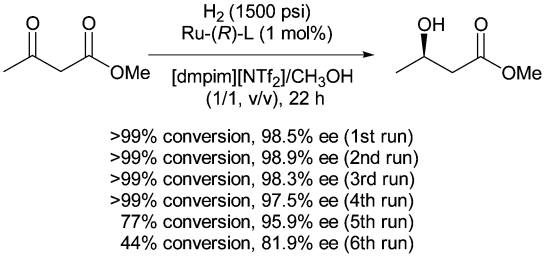


Scheme 10 Asymmetric hydrogenation of β-ketoesters in ionic liquids

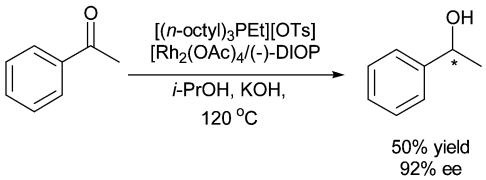
Table 5 Ee values for asymmetric hydrogenation of β-ketoesters using Ru-(*R*)-L as a catalyst in ionic liquids

Substrate	MeOH	[dmpim][NTf_2][a]	[bmim][BF_4]	[bmim][PF_6]
	98.3	99.0	98.9	99.3
	98.6	99.3	99.1	99.1
	94.2	98.1	98.9	98.9
	96.7	97.5	98.5	97.5
	91.7	95.1	96.3	94.9

[a] dmpim is the 1,2-dimethyl-3-propylimidazolium cation.



Scheme 11 Recycling and reuse of Ru-(*R*)-L catalyst for hydrogenation of methyl acetoacetate in [dmpim][NTf_2].



Scheme 12

temperature and a solid at room temperature. Therefore, when the mixture is cooled to room temperature after the reaction, a mixture of phosphonium salt and catalyst remain as a solid. Thus, the product phase was simply separated by decantation (*i.e.*, by "pouring off" the organic products). UV analysis showed no leaching of the rhodium catalyst in the product phase. However, no data on recycling experiments have been reported.

Asymmetric carbon–carbon and carbon–heteroatom bond formation

Asymmetric ring opening of epoxides with azide. Asymmetric ring opening reactions (ARO) of epoxides by trimethylsilyl azide ($TMSN_3$) catalysed by the chiral Cr(salen) complex (Fig. 5)

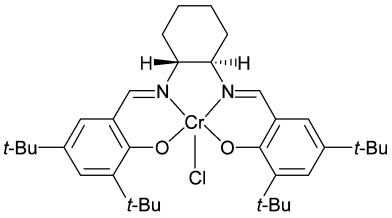
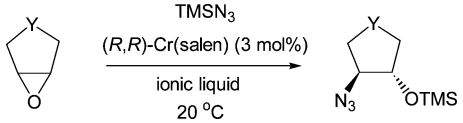


Fig. 5 (*R*,*R*)-Cr(salen) complex.

has been recognised as an attractive approach to the synthesis of optically pure β-amino alcohols.[28] In particular, the chiral Cr(salen) catalyst exhibits indefinite stability under catalytic conditions, which allows its repeated recycling. Jacobsen and coworkers reported that this reaction can be run without solvents and that the catalyst can be recycled a number of times without loss of activity or enantioselectivity.[29] However, this catalyst recycling procedure involves the potentially hazardous distillation of neat liquid azides, which can not be applied to large scale applications.

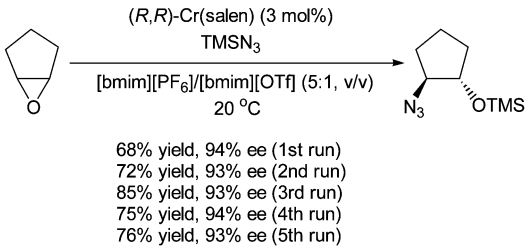
We recently developed a highly practical recycling procedure for the chiral Cr(salen) complex using [bmim] salts.[30] Our procedure consists of running a reaction of meso-epoxides with $TMSN_3$ in the presence of catalytic amounts of (*R*,*R*)-Cr(salen) complex (Fig. 5) dissolved in the [bmim] salts. As shown in Table 6, the yield and

Table 6 Chiral Cr(salen) catalysed asymmetric ring opening of meso-epoxides in ionic liquids



Substrate	Ionic liquid	Time/h	Yield (%)	Ee (%)
CH_2	[bmim][PF_6]	28	76	94
CH_2	[bmim][SbF_6]	28	75	87
CH_2	[bmim][BF_4]	28	5	3
CH_2	[bmim][OTf]	28	Trace	—
$(CH_2)_2$	[bmim][PF_6]	18	86	85
O	[bmim][PF_6]	18	74	97

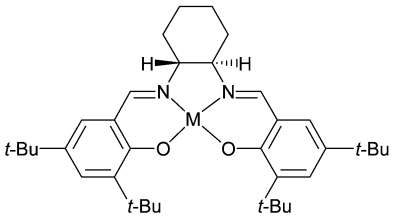
enantioselectivity of this reaction are strongly dependent upon the nature of the counteranion. While the reaction performed in hydrophobic [PF_6] and [SbF_6] salts produced high yields and degrees of enantioselectivity (similar to those obtained in organic solvents), the reaction failed to proceed in hydrophilic [BF_4] and [OTf] salts. Although, when hydrophobic ionic liquids were used, excellent results were achieved, the catalyst existed as a suspended form in these ionic liquids, when hexane was added to the reaction mixture after reaction to extract the product. On the other hand, although the reaction hardly proceeded in hydrophilic ionic liquids, the catalyst dissolved in these ionic liquids, to form a clear red–brown solution, which facilitates its separation from the hexane phase. Thus, the best recyclable catalytic system was obtained by immobilising the catalyst in a 5/1 v/v mixture of hydrophobic [bmim][PF_6] and hydrophilic [bmim][OTf]. The recovered ionic liquid phase containing the catalyst was reused several times without any loss of activity and enantioselectivity even after being used five times (Scheme 13). Moreover, this recycling procedure is free of hazardous procedures, such as the distillation of azide product, and moreover, provides the additional advantage of being able to use a catalyst without any modification of the structure.



68% yield, 94% ee (1st run)
72% yield, 93% ee (2nd run)
85% yield, 93% ee (3rd run)
75% yield, 94% ee (4th run)
76% yield, 93% ee (5th run)

Scheme 13

Jacobsen's chiral Co(III)(salen) complex catalysed hydrolytic kinetic resolution of racemic epoxides. The hydrolytic kinetic resolution (HKR) of racemic epoxides using Jacobsen's chiral (salen)Co(III)(OAc) complex (see Fig. 6) as a catalyst is one

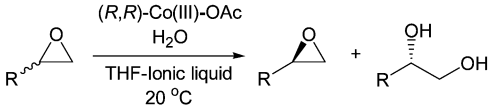


M = Co: (*R*,*R*)-Co(II)(salen)
M = Co(OAc): (*R*,*R*)-Co(III)(salen)-OAc

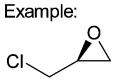
Fig. 6 (*R*,*R*)-Co(salen) complexes.

of the most practical approaches to the preparation of enantiopure terminal epoxides.[28,31] The chiral catalyst is readily accessible, and displays high enantioselectivity. However, this catalyst provides relatively low turnover numbers. To facilitate catalyst separation and reuse, some attempts to anchor Jacobsen's catalyst onto insoluble supports have been made.[32] Although these heterogeneous analogues of Co(III)(salen)·OAc produced almost the same enantioselectivities as those of the homogeneous version, complicated synthetic manipulations were required for their preparations. Moreover, during the reaction, these solid-bound catalysts,[32] as well as the homogeneous ones,[31*a*] are reduced to the Co(II)(salen) complex (Fig. 6), which is known to be inactive for HKR, and thus, they need to be re-oxidised to the Co(III) complex with acetic acid under air before being used in the next run.

Recently, we observed that ionic liquids caused an interesting effect in this catalytic reaction.[33] In the chiral Co(III)(salen)-catalysed HKR of racemic epoxides using catalytic amounts of (*R*,*R*)-Co(III)(salen)·OAc in a mixture (4/1, v/v) of THF and an ionic liquid, [bmim][X] (X = PF_6, NTf_2), at 20 °C, the yields and enantiomeric excesses were quite comparable to those[31*a*] obtained without ionic liquids (Scheme 14).



Example:

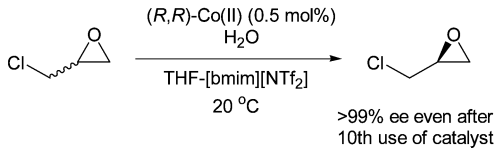


Using 0.5 mol% of (*R*,*R*)-Co(III)-OAc
>99% ee (24 h)
Using 0.025 mol% of (*R*,*R*)-Co(III)-OAc
>99% ee (60 h)

Scheme 14

Interestingly, it was found by UV and XPS analysis of the recovered ionic liquid phase that the oxidation state of the Co(salen) complex dissolved in the recovered ionic liquid phase was not +II, but +III. As mentioned above, when organic solvents are used as the reaction media, the Co(III)(salen)·OAc is reduced to the Co(II)(salen)complex during the HKR reactions. More inter-

estingly, it was also found that catalytically inactive Co(II)(salen) complex can be directly used as a catalyst precursor instead of Co(III)(salen)·OAc catalyst in the presence of the ionic liquid. The Co(II)(salen) complex is oxidised, in the absence of acetic acid, to the catalytically active Co(III) complex during the HKR reactions, which may not be possible in conventional organic solvents. Thus, all HKRs of racemic epichlorohydrin using catalytic amounts of (*R*,*R*)-Co(II)(salen) complex in [bmim][PF_6] or [bmim][NTf_2] proceeded smoothly, even when only 0.025 mol% of (*R*,*R*)-Co(II)(salen) was used. For example, enantiomerically pure epichlorohydrin was obtained after 70 h using 0.025 mol% of Co(II)(salen) complex. Here again, the catalytically active Co(III) oxidation state is stabilised against reduction to the Co(II) complex, which enables the reuse of the recovered catalyst for subsequent runs without additional re-oxidation. This catalytic system involving the ionic liquid [bmim][NTf_2] was reusable up to ten times without any loss of activity and enantioselectivity (>99% ee) (Scheme 15). However, it is not clear yet why, in the presence of an

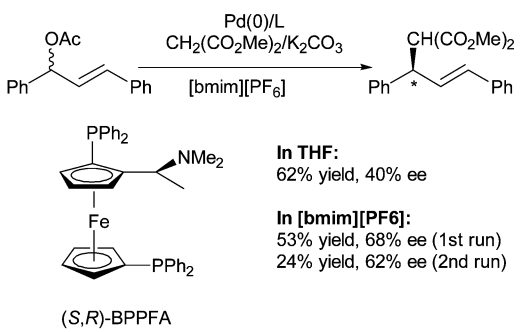


Scheme 15

ionic liquid, the Co(II) complex is oxidised without the use of acetic acid during the reaction to the catalytically active Co(III) complex and why this oxidation state is maintained.

Pd-Catalysed asymmetric allylic substitution. Pd-Catalysed asymmetric allylic substitution reactions are a useful synthetic method for asymmetric C–C and C–X bond formation. A number of homogeneous chiral ligands have been developed for this type of reaction.[34] However, most catalytic systems developed to date have relatively low turnover numbers and frequencies, and, moreover, are expensive. Thus, this catalytic enantioselective transformation has been studied in its heterogeneous form in an effort to provide the possibility of reuse of the catalytic components.[3] However, all attempts until now have required catalyst modification.

Recently, Toma *et al*.[35] performed the enantioselective Pd-catalysed allylic substitution in the presence of ionic liquids and observed an significant increase in enantioselectivity *versus* that achieved in organic solvent. For example, chiral Pd-ferrocenylphosphine complexes such as the BPPFA-Pd complex catalysed the allylic substitution of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxypro-1-ene in [bmim][PF_6] to give the product with 68% ee, which was higher than that (40% ee) observed in THF (Scheme 16).[35a] On recycling,

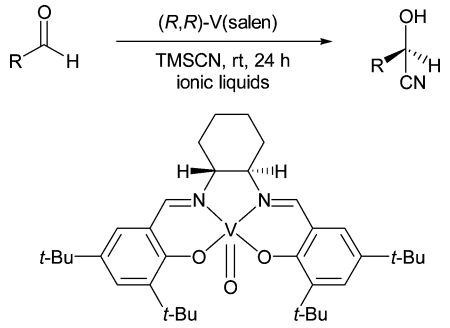


Scheme 16

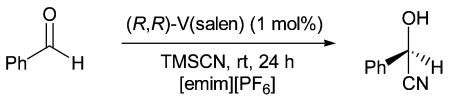
however, this system gave reduced yields and ee values. Decrease in activity and selectivity was explained as being due to the leaching of catalyst during product extraction with toluene from the ionic liquid.

Enantioselective cyanosilylation of aldehydes catalysed by chiral vanadium(salen) complex. Optically pure cyanohydrins are versatile synthetic intermediates in the synthesis of a wide range of homochiral products such as, α-hydroxy acids and β-hydroxy amines. Many catalytic enantioselective hydrocyanations and silylcyanations of aldehydes and ketones have been reported.[36] Recently, Corma and coworkers[37] undertook the enantioselective cyanosilylation of aldehydes using chiral vanadium(salen) complex as catalyst in various ionic liquids, and found that yield and enantioselectivity are strongly dependent upon the nature of the counteranion (Table 7). While the reaction performed in hydrophobic [PF_6] salts gave similar yields and degrees of enantioselectivity to those obtained in CH_2Cl_2, the system gave much lower yields and ee's in hydrophilic [BF_4] and [Cl] salts. The products were easily separated from the reaction mixture by hexane extraction. The remaining [bmim][PF_6] ionic liquid phase containing the catalyst was found to be reusable for at least four further cycles without loosing activity and selectivity (Scheme 17).

Table 7 Enantioselective cyanosilylation of aldehydes catalysed by chiral vanadyl salen complex



Aldehyde	Solvent	Conversion (%)	Ee (%)
Benzaldehyde	CH_2Cl_2	90	90
Benzaldehyde	[emim][PF_6]	85	89
Benzaldehyde	[bmim][PF_6]	83	85
Benzaldehyde	[bmim][Cl]	40	35
Benzaldehyde	[bmim][BF_4]	63	5
trans-Cinnamaldehyde	[emim][PF_6]	76	98
ortho-Fluorobenzaldehyde	[emim][PF_6]	81	86
Hexanal	[emim][PF_6]	97	83



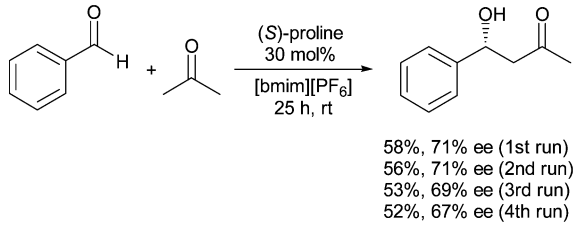
85%, 89% ee (1st run); 79%, 88% ee (2nd run);
89%, 90% ee (3rd run); 80%, 88% ee (4th run);
83%, 89% ee (5th run)

Scheme 17

Proline-catalysed direct asymmetric aldol reaction. The asymmetric aldol reaction is one of the most efficient processes for the synthesis of optically active β-hydroxy carbonyl compounds. Of these, the direct asymmetric aldol reaction between an aldehyde and an unmodified ketone is the most attractive from the point of view of atom economy. The direct catalytic aldol reaction does not require a preconversion of ketone or ester moiety into a more reactive species such as a silyl ether or a ketene silyl acetal.

Recently it was found that L-proline catalyses the direct asymmetric aldol reaction.[38] However, a very low turnover number (*ca*. 3) and a strong solvent influence on the resulting enantiopurity of products limits the use of this reaction in large-scale processes. In an attempt to recover and reuse the proline catalyst, it was immobilised on a silica surface,[39] however, a significant reduction in enantioselectivity was observed.

Recently, two research groups[40] reported independently that this reaction can be carried out successfully in ionic liquids with comparable or better ee's than those obtained in organic solvents. For example, the benzaldehyde aldol product with acetone was obtained with 71% ee[40*a*] (76% ee in ref. 40*b*) in [bmim][PF_6]. However, a lower ee (60%) was obtained in DMSO.[38] After reaction, the immobilised proline in the ionic liquid phase was simply recovered and reused in subsequent reactions without a significant loss of activity or enantioselectivity (Scheme 18).



Scheme 18

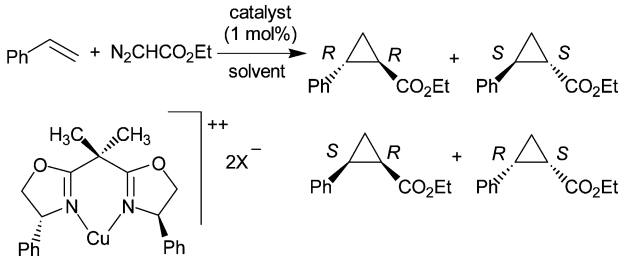
Enantioselective cyclopropanation. Asymmetric catalytic cycloaddition of electrophilic metal carbenes to prochiral olefins is a facile methodology for highly enantioselective cyclopropane synthesis. Among the reported chiral catalysts, the chiral bis(oxazoline)Cu complexes are the most extensively used catalysts. Chiral bis(oxazoline)-copper complexes have also been successfully used in other catalytic asymmetric C–C bond forming reactions such as Diels–Alder reactions, Ene reactions and Mukayama aldol reactions.[41] However, this versatile catalytic system suffers from one major drawback, that is, the TON is too low (10–100). Their separation and recycling is therefore a prerequisite for successful large-scale applications. Although many attempts[42] have been made to develop efficient immobilisation methods for this type of catalyst, the results obtained have been far from satisfactory.

Recently, the chiral bis(oxazoline)-Cu-catalysed enantioselective cyclopropanation of styrene with ethyl diazoacetate was studied in ionic liquids with a view toward catalyst recycling.[43] The interesting effect of ionic liquids was demonstrated by the result obtained with bis(oxazoline)-$CuCl_2$ complex in [emim][NTf_2]. Both yield and enantioselectivity were much higher than those obtained with $CuCl_2$ in CH_2Cl_2, and were similar to those obtained with $Cu(OTf)_2$ complex (Table 8). This result seems to indicate that the active species is the $Cu(NTf_2)$ complex of bis(oxazoline). The NTf_2 anion seems to behave more like triflate than chloride. Therefore, this method provides a clear advantage in that inexpensive $CuCl_2$ can be used instead of the expensive and moisture-sensitive $Cu(OTf_2)$. Moreover, the complex dissolved in [emim][NTf_2] was successfully recycled twice without loss of activity or enantioselectivity.

Enantioselective biocatalysis in ionic liquids

Another exciting recent development in the use of ionic liquids is the application of enantioselective biocatalysis in these solvents.[44] Although only a small range of enzymes (mainly lipases) have been investigated to date, the results reported so far suggest that the use of ionic liquids as solvents in enzymatic reactions can also provide many advantages. In lipase-catalysed reactions, in particular, the enantioselectivity and operational stability are often better than in traditional media.

Table 8 The asymmetric cyclopropanation of styrene with ethyl diazoacetate catalysed by bis(oxazoline)-copper complexes



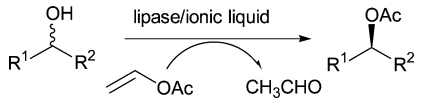
CuX_2	Solvent	Run	Yield (%)	Ee *trans* (%)	Ee *cis* (%)
$Cu(OTf)_2$	CH_2Cl_2	1	33	60	51
$CuCl_2$	CH_2Cl_2	1	19	17	13
$CuCl_2$	[emim][NTf_2]	1	34	55	47
		2	32	53	45
		3	33	53	44

Improved enantioselectivity

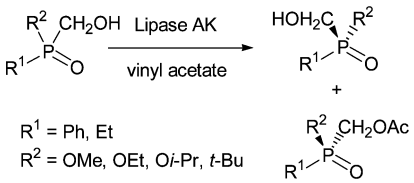
The first example of enantioselective biocatalysis in ionic liquids was reported by Kragl and coworkers.[45] This paper reports the screening of nine different lipases against ten different ionic liquids for the kinetic resolution of *rac*-1-phenylethanol by transesterification with vinyl acetate. Good activities and, in some cases, improved enantioselectivities were observed compared with the same reaction in methyl *tert*-butyl ether (MTBE), although quite different reactivity patterns were observed in different ionic liquids. Soon after the publication of this paper, Kim and coworkers[46] reported that the use of ionic liquids in the lipase-mediated kinetic resolution of racemic alcohols can markedly enhance enantioselectivity. All tested transesterification reactions of vinyl acetate with four different alcohol substrates in [bmim][BF_4] and [bmim][PF_6] employing lipases such as *Candida antarctica* lipase B (CaLB, immobilised) and *Pseudomonas cepacia* (PCL, native) proceeded much more enantioselectively (up to 25 times) than in THF or toluene. In general, higher enantioselectivities of lipases were obtained in hydrophobic PF_6 salt than in hydrophilic BF_4 salt (Table 9).

Of several papers describing the use of ionic liquids in the lipase-catalysed kinetic resolution of racemic alcohols,[47] Kielbasinski *et al*. first demonstrated that ionic liquids are also a promising medium for the kinetic resolution of racemic heteroatom substrates (Scheme 19).[47*d*] The resolutions of racemic phosphorous-substituted primary alcohols catalysed by lipase AK or lipase from *Pseudomonas fluorescens* were up to six times more enantioselective in [bmim][PF_6] than in diisopropyl ether. On the other hand, the analogous reactions performed in hydrophilic BF_4 salt were practically non-stereoselective. Recently, Zhao and Malhotra[48] showed that the ionic liquid, *N*-ethyl pyridinium trifluoroacetate ([epy][OTf]) may be a good substitute for organic solvents in the protease (*Bacillus licheniforms* alcalase)-catalysed kinetic resolution of *N*-acetyl amino acid esters (Scheme 20). Using ionic liquid ([epy][OTf]-water (15 : 85)) instead of acetonitrile–water (15 : 85), the reaction proceeded more enantioselectively. In particular, the production of two L-amino acids (L-serine and L-4-chlorophenylalanine) was not achievable in acetonitrile–water using alcalase, while the same resolution reactions were successfully achieved using ionic liquid [epy][OTf]. In all cases, a highly enantiomeric amino acid (86–97% ee) was obtained.

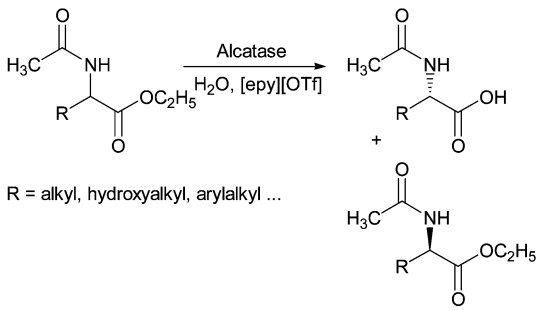
Table 9 The enantioselectivities for the lipase-catalysed transesterification in organic solvents and ionic liquids



R^1	R^2	Lipase	Solvent	*E*
CH_3	$PhCH_2CH_2$	CaLB	THF	141
			Toluene	207
			[emim][BF_4]	648
			[bmim][PF_6]	> 967
CH_3	$PhCH_2OCOCH_2$	CaLB	THF	26
			Toluene	187
			[emim][BF_4]	651
			[bmim][PF_6]	155
CH_2Cl	Ph	PCL	THF	56
			Toluene	158
			[emim][BF_4]	183
			[bmim][PF_6]	> 450
CH_2Cl	$PhOCH_2$	PCL	THF	150
			Toluene	85
			[emim][BF_4]	172
			[bmim][PF_6]	> 1000



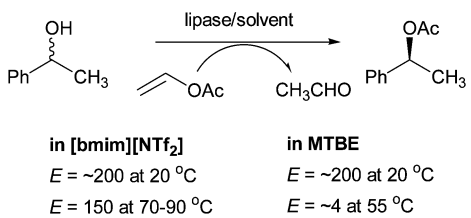
Scheme 19 The enantioselective acylation of phosphate-substituted primary alcohols.



Scheme 20 Enantioselective hydrolysis of *N*-acetyl amino acid esters.

Enhanced thermal stability of enzymes

In addition to improved enantioselectivity in ionic liquids, enhanced enzyme thermal stability has also often been observed in these solvents.[49] Kragl and coworkers[49a] found that the enantioselectivity of the lipase is much less influenced by temperature when the reaction is performed in [bmim][NTf_2] (Scheme 21). The lipase



Scheme 21

(from *Pseudomonas sp*.) mediated kinetic resolution of *rac*-1-phenylethanol by transesterification with vinyl acetate in [bmim][NTf_2] remained highly enantioselective, even when the temperature was raised from 25 to 90 °C. The *E*-value decreased from ~ 200 to ~ 150 at the boiling point of vinyl acetate (71 °C) and then remained constant. By contrast, the enantioselectivity in MTBE medium dropped dramatically (from $E = \sim 200$ to $E = \sim 4$) at the boiling point of MTBE (55 °C), which means that this solvent does not guarantee selective kinetic resolution at temperatures > 50 °C. Sheldon *et al.*[49b] also reported upon the enhanced thermal stability of CaLB in ionic liquids. Incubation of free enzyme (SP 525) or of Novozym 435 in [bmim][PF_6] at 80 °C resulted in a significant increase in activity and showed a maximum activity of 120% after 20 h and of 350% after 40 h, respectively, compared to the activity of the corresponding untreated enzyme. This activity was maintained after a long incubation period and thus, the activity of SP 525 was retained up to an incubation time of 100 h. Novozym 435 also exhibited 210% of the initial activity even after 5 days. By contrast, incubation in *t*-BuOH showed a linear deactivation with time. Very recently, Persson and Bornscheuer[49c] also reported upon the stabilising effect of ionic liquids on enzyme. The stability of the esterase from *B. stearothermophilus* at 40 °C was found to be considerably higher in ionic liquids [bmim][PF_6] and [bmim][BF_4] than in *n*-hexane or MTBE. A half-life of > 240 h was obtained in [bmim][PF_6], which was > 30- and > 3-fold higher than in *n*-hexane and MTBE.

The reason for the improvement of catalytic performances of enzymes in ionic liquids may be related to their ionic nature. Ionic liquids are likely to interact with the enzyme's charged groups, either at the active site or at its periphery (microenvironment), thus inducing changes in enzyme structure.

Enzyme recycling

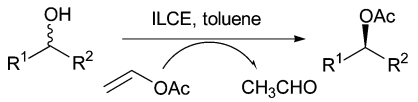
Several groups have reported upon the repeated use of lipase after the work-up procedure. In all cases, the products and the unconverted substrates were extracted either using immiscible organic solvents with ionic liquids (ether or hexane) or supercritical CO_2.[50] However, as a consequence of the work-up conditions employed, a reduction in enzyme activity occurred after each cycle. The accumulation of enzyme-inhibiting acetaldehyde oligomers produced from vinyl acetate in the ionic liquid phase may also provide a reason for the observed loss of activity.[47c] Recently, lipase (PCL) was successfully recycled several times without activity loss by entrapping this enzyme in the relatively high-melting ionic liquid [ppmim][PF_6] ([ppmim] = 1-(3′-phenylpropyl)-3-methylimidazolium),[51] which is solid at room temperature and becomes liquid at above 53 °C. In this case the enzyme was coated by simply mixing it with [ppmim][PF_6] at above 53 °C and allowing the mixture to cool. This ionic liquid-coated enzyme (ILCE) showed enhanced enantioselectivity compared to native enzyme (Table 10).

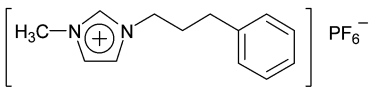
Finally, it should also be mentioned that a range of ketones can be enantioselectively reduced using an immobilised yeast in a [bmim][PF_6]–water (10 : 1) biphasic system (Scheme 22).[52] The performance of this system was found to be comparable with that of a conventional aqueous–organic medium. Until now, this is the only example whereby a biocatalyst other than hydrolases has been used successfully for enantioselective biocatalysis in ionic liquids. Moreover, this example shows that whole-cell biocatalysts, and therefore other microorganisms as well, can be active in the presence of ionic liquids.

Concluding remarks

The results discussed here demonstrate the considerable potential of ionic liquids as alternative reaction media for enantioselective chemo- and bio-catalysis. The use of ionic liquid solvents allows chiral catalysts (or enzymes) to be recycled more easily. Moreover, in many cases, the ionic liquids were observed to have a positive influence on the catalytic properties, as the reactions can be

Table 10 ILCE-Catalysed kinetic resolution of racemic alcohols[a]

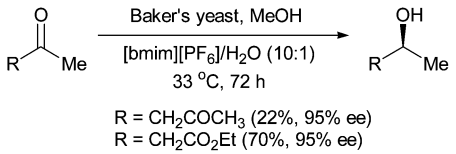




[ppmim][PF_6]

R^1	R^2	Enzyme	*E*
Me	CH_2CH_2Ph	Native	265
		ILCE	532
$ClCH_2$	CH_2OPh	Native	293
		ILCE	574

[a] ILCE: ionic liquid-coated enzyme.



Scheme 22

accelerated in suitable ionic solutions with improved enantioselectivities. Increased stability of chiral catalyst or of enzyme was also observed in the ionic liquids. However, more detailed studies are necessary to establish the reasons behind these observed advantages. Nevertheless, I believe that the use of ionic liquids can open up new perspectives for enantioselective chemo- and biocatalysis, and many more studies will be done in the near future.

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