Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3081–3093

TETRAHEDRON: *ASYMMETRY*

TETRAHEDRON: ASYMMETRY REPORT NUMBER 61

Ionic liquids and chirality: opportunities and challenges

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Received 26 June 2003; accepted 24 July 2003

Abstract—This review deals with recent advances in the investigation of ionic liquids (ILs) in the field of chirality, i.e. asymmetric synthesis and new chiral solvents.

Contents

1. Introduction

One of the main fields of interest for further studies in chemistry is the avoidance of toxic and environmentally unfriendly organic solvents. In this context, much attention has been devoted recently to the quest for novel reaction media. Ionic liquids (ILs), ion containing liquids, which combine good and tuneable solubility properties with a negligible vapor pressure and excellent thermal stabilities have rapidly found a place of choice as valuable substitutes for many volatile solvents.[1] The common classes of ILs comprise: alkylammonium salts, alkyl pyridinium salts and *N*,*N*′-dialkyl imidazolium salts (Scheme 1).

Numerous organic,[2] organometallic[2,3] and biocatalyzed[3c,4] reactions have been performed with success in these new media. Owing to their unique properties, it soon became apparent that ILs are more

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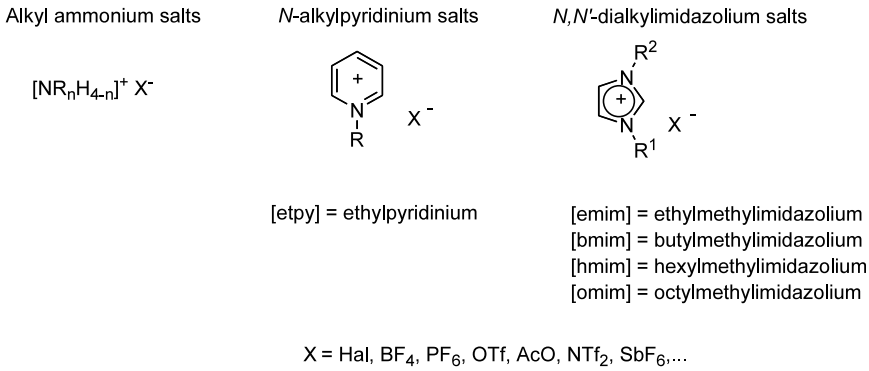
doi:10.1016/S0957-4166(03)00596-2



Scheme 1. Main classes of ionic liquids.

than simple neoteric solvents. With respect to reactions carried out in conventional solvents, reactions in ILs have different thermodynamic and kinetic behaviors, which often lead to improved process performance. Better selectivity and/or conversion have been demonstrated. Furthermore, ionic liquids allow an enhanced stability of organometallic reagents and biocatalysts, an easy product recovery as well as possible recycling of homogeneous catalysts.

From these additional benefits, it is reasonable to expect that ionic liquids could also play a significant role in asymmetric synthesis, one of the prime concerns for industry and academia. Their polar and non-coordinating properties hold considerable potential for enantioselective reactions since profound effects on reactivities and selectivities can be expected. Surprisingly, it is only very recently that attention has really been focused on the application of ILs as reaction media for enantioselective processes. The first example in asymmetric synthesis was proposed by Chauvin in 1995;[12] however, most of the related studies were published after 2000. Three different strategies may be envisioned to achieve an asymmetric reaction in ILs: (i) the chirality can arise from a chiral substrate or a chiral reagent and the ionic liquid is used to replace with benefit the environmentally unfriendly organic solvent; (ii) the chirality can arise from a catalyst (transition-metal catalyst or biocatalyst) and the ionic liquid is used to stabilize and/or to allow the recovery of the chiral catalyst; (iii) the chiral discrimination is promoted by the ionic liquid itself (e.g. a chiral ionic liquid) which acts as a chiral promoter (Fig. 1).

Even though asymmetric synthesis in ILs is still at a preliminary stage, all these possibilities have been the subject of recent research and the results are often promising when not exciting. The aim of this review is to highlight the opportunities that ionic liquids could offer to chiral discrimination including asymmetric synthesis and resolutions of racemates and to disclose the concept needed for development in this emerging field.

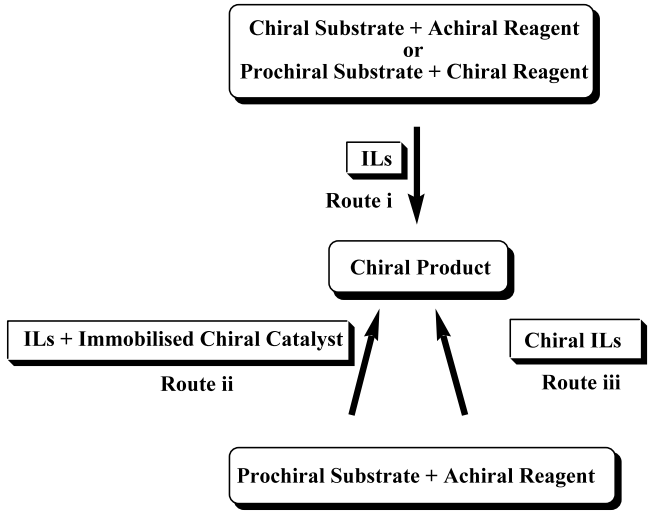


Figure 1. Possible routes for asymmetric syntheses in ILs.

2. Asymmetric synthesis and catalysis in ILs

2.1. Asymmetric synthesis in ILs

In this first series of examples, the asymmetry is carried by either a reagent or a chiral organic catalyst, which is not necessarily immobilized into the ILs. Results which were observed in IL favorably compare with those obtained in conventional solvents, both in terms of reactivity and stereoselectivity.

2.1.1. Asymmetric aldol reactions. The asymmetric aldol reaction is a very powerful methodology for the synthesis of useful building blocks in total synthesis. In recent years, the metal free proline-catalyzed aldol reaction has received considerable attention. This reaction was found to be solvent dependent and DMSO allowed the best results. To avoid the use of this solvent, two groups have tested ionic liquids as solvents.

Loh et al.[5] first examined the reaction between benzaldehyde and propanone in different ionic liquids:

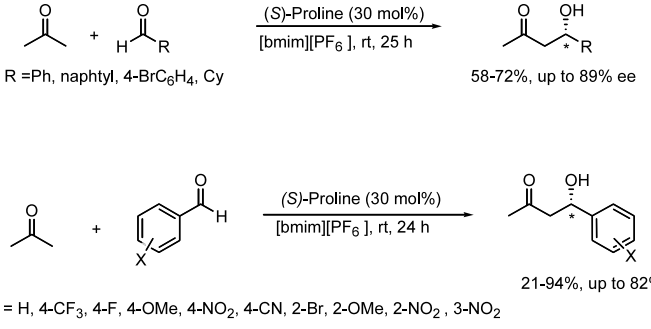
[hmim][BF_4], [omim][Cl], [omim][BF_4] and [bmim][PF_6]. All of them gave the desired aldol product but only [bmim][PF_6] was suitable to avoid the formation of the competing elimination product. Whatever the IL used, the enantiomeric excesses were comparable or higher than those obtained in DMSO, the reference solvent. Extending the reaction in [bmim][PF_6] to various aldehydes (aromatic and aliphatic derivatives) afforded the aldol products in good yields with moderate to excellent ee values (69–89%) (Scheme 2). L-proline, immobilized in the IL, was reused four times without significant decrease in yield and enantiomeric excess.

The same year, Toma's group studied the reaction of propanone with various benzaldehyde derivatives bearing electron-withdrawing or electron-donating groups in [bmim][PF_6].[6] Good yields (up to 94%) with reasonable enantioselectivities (up to 82%) were obtained (Scheme 2). The chiral catalyst being immobilized in [bmim][PF_6], the system was reused two or three times, with only a slight decrease in yield and enantioselectivity except for *p*-cyano and *o*-nitro derivatives (70–46% ee and 82–54% ee, respectively). The influence of catalyst amount was studied with the *p*-CF_3-benzaldehyde derivative. Lowering the amount of catalyst from 30 to 1% slightly decreased the yield (92–74%) but not the enantioselectivity. Other ketones were tested with *p*-CF_3-benzaldehyde. Cyclobutanone, cyclopentanone and cyclohexanone yielded the corresponding aldol products but only cyclohexanone gave good de (>20/1 in favor of the *anti* diastereomer) and ee (93%).

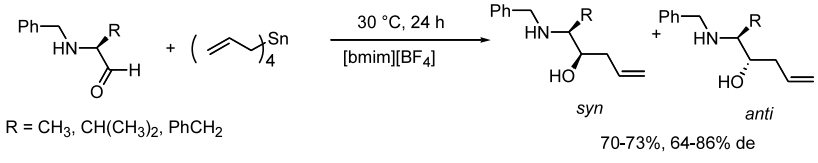
Synthesis of halogenated materials catalyzed by proline or antibody in ILs was recently described by Kitazume et al.[7] The use of proline in [emim][OTf] allowed enantioselective aldol reactions between aromatic aldehydes and chloracetone in high selectivity (up to 99/1 dr and 88% ee). The obtained chloroaldols were transformed into the corresponding epoxides in the same solvent. The same group also showed that fluoromethylated imines reacted with hydroxyacetone in the presence of antibody aldolase 38C2-ionic liquid system, giving a fluoromethylated carbinol.

2.1.2. Asymmetric allylation reactions. McCluskey et al. reported the allylation of *N*-protected aminoaldehydes using tetra-allylstannane in [bmim][BF_4].[8] Reactions were conducted at 30°C for 24 h and afforded the corresponding homoallylic alcohol derivatives after extraction with diethylether (Scheme 3). Whatever the substrate, yields were slightly lower (10% less) in ionic liquid than in methanol, however diastereoselectivity was the same in both media (up to 86% de).

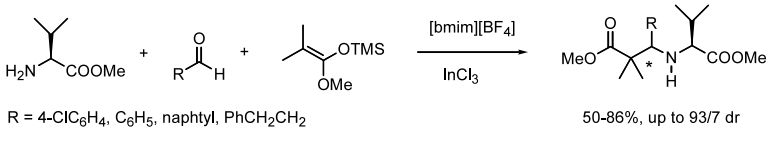
2.1.3. Asymmetric Mannich type reaction. In 2003, Loh et al studied the indium catalyzed asymmetric three component Mannich type reaction using aldehyde, amine and silyl enol ether in ionic liquids.[9] The chiral auxiliary used was the L-valine methyl ester. Different ionic liquids were tested in the $InCl_3$ mediated reaction of *p*-chlorobenzaldehyde: [bmim][BF_4], [hmim][BF_4], [omim][BF_4] and [omim][Cl] (Scheme 4). Reactions pro-



Scheme 2. Proline-catalyzed aldol reaction in [bmim][PF_6].



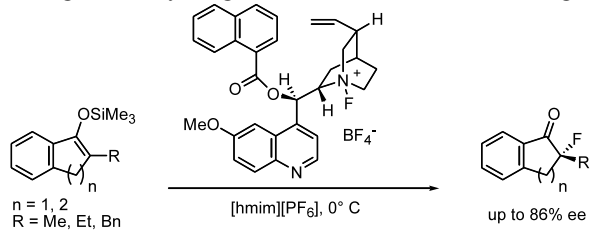
Scheme 3. Allylation of *N*-protected aminoaldehydes in [bmim][BF_4].



Scheme 4. $InCl_3$-catalyzed asymmetric Mannich type reaction in [bmim][BF_4].

ceeded with good diastereoselectivity (up to 93/7) in all [BF_4] ionic liquids but no reaction occurred in [omim][Cl]. The authors showed that shorter chain length on the ionic liquid cation afforded better yields in Mannich type product and lowered the amount of aldol side product. Extending the reaction to various aromatic and aliphatic aldehydes, even enolizable ones, afforded the Mannich type product with moderate to good yields and high diastereoselectivities. All attempts to recycle the ionic liquid/$InCl_3$ system failed. With $In(OTf)_3$ in [hmim][BF_4], the heterogenized catalyst was reused three times. However an important decrease in yield was observed in the third cycle.

2.1.4. Asymmetric fluorination reactions. Some of us have demonstrated that enantioselective electrophilic fluorination performed by *N*-fluorocinchonium salts in ionic liquids presents substantial advantages over the use of classical solvents (Scheme 5). ILs proved to be superior to acetonitrile in terms of enantioselectivity and experimental conditions.[10] ILs can selectively dissolve the cinchona alkaloids in preference to Et_2O, allowing the recycling of the IL and the chiral agent.

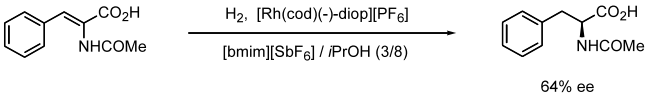


Scheme 5. Enantioselective electrophilic fluorination of silyl enol ether in ILs.

2.2. Asymmetric catalysis in ILs

The major difficulties associated with asymmetric homogeneous catalysis are the separation of the organic products and the recovery of the expensive chiral catalyst. Aiming to achieve this goal, many strategies have been investigated. A possible solution is to use catalysts that are immobilized on a solid support. However, a partial loss of activity and/or selectivity is often observed. Another solution is to use a two-phase system, in which the preferred phase differs for the catalyst and the organic product. In that case, structural modifications of the catalyst are often needed. Recently, an alternative solution for catalyst separation and recycling involving the use of ionic liquids appeared in the literature.[11] In these solvents, catalyst having polar or ionic behavior can be immobilized and thus easily separated from the organic product. Moreover, enhanced stability of the transition-metal catalyst, as well as excellent reactivity and enantioselectivity were reported in these promising new media.

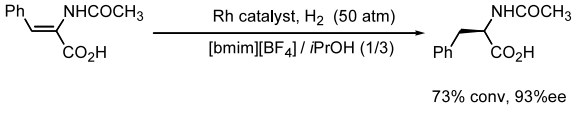
2.2.1. Asymmetric hydrogenation. In 1995, Chauvin et al. proposed the first enantioselective metal-catalyzed



Scheme 6. Rhodium-catalyzed asymmetric hydrogenation of α-acetamidocinnamic acid in [bmim][SbF_6]/*iso*-propanol system.

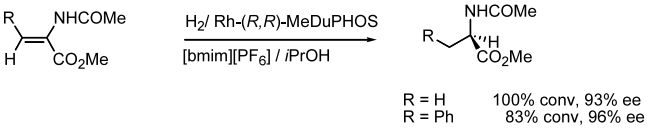
reaction in ionic liquids.[12] They reported the enantioselective hydrogenation of α-acetamidocinnamic acid in the biphasic system [bmim][SbF_6]/*i*PrOH (3/8) catalyzed by [Rh(cod){(−)-diop}][PF_6]. The reaction afforded (*S*)-*N*-acetylphenylalanine in 64% ee (Scheme 6). The product was easily and quantitatively separated and the ionic liquid recovered.

It was further demonstrated by Dupont et al. that asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid with the chiral rhodium catalyst [(−)-1,2-bis ((2*R*,5*R*) - 2,5 - diethylphospholano)benzene(cyclooctadiene) rhodium(I) trifluoromethylsulfonate] proceeded in two other ionic liquids, [bmim][PF_6] and [bmim][BF_4] (Scheme 7).[13] The authors showed that the molecular hydrogen concentration in the ionic phase rather than the pressure in the gas phase had a dramatic effect on the conversion and the enantioselectivity of the reaction. Molecular hydrogen being four times less soluble in the hydrophobic [bmim][PF_6] than in the hydrophilic [BF_4] IL, the best result was obtained in [bmim][BF_4] (73% conv., 93% ee). After extraction of the product, the IL containing the chiral catalyst solution could be reused for further hydrogenation (4), with similar enantioselectivity. However, after the fourth cycle, conversion dropped from 73% to 35% presumably because of catalyst leaching from the ionic liquid to the extraction solvent.



Scheme 7. Rhodium-catalyzed asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid in [bmim][BF_4]/*iso*-propanol system.

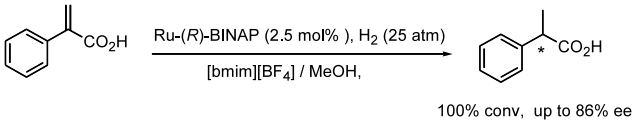
Another type of chiral rhodium complex [Rh-MeDuPHOS] was immobilized in [bmim][PF_6] and used in asymmetric hydrogenation of related enamides.[14] The reaction was performed in the biphasic [bmim][PF_6]/*i*PrOH system (Scheme 8). The α-amino acid derivatives were obtained with high yields and enantioselectivities (93–96%) comparable to those obtained in *i*PrOH (97–99%). Compared to organic



Scheme 8. Rhodium–DuPHOS-catalyzed asymmetric hydrogenation of enamides in [bmim][PF_6]/*iso*-propanol system.

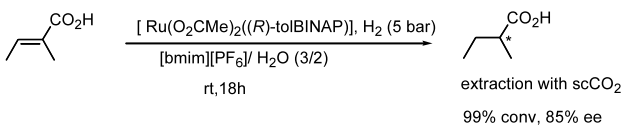
solvent, ionic liquid provides superior stability to the air sensitive rhodium complex. Thus, recycling of the catalyst was possible and good enantioselectivities were still observed after five cycles. However, the activity decreased as early as the first cycle from 83 to 66%, as an example, for methyl α-acetamido-cinnamate.

In 1997, Dupont et al. studied the asymmetric hydrogenation of 2-arylacrylic acids by [BINAP–Ru–$(OAc)_2$] complex in [bmim][BF_4]/alcohol medium (Scheme 9).[15] A homogeneous phase was formed with methanol, whereas a biphasic system was obtained with *i*PrOH. With both systems, conversions ($\geq$95%) and enantioselectivities (86% ee) were similar or higher than those obtained in pure alcohol. Asymmetric induction did not seem to depend on hydrogen pressure or catalyst amount. ILs were also found to be very useful to improve the troublesome recovery of the product and the recycling of the catalyst. Practically, with the [bmim][BF_4]/*i*PrOH system, the hydrogenated products were recovered in the *i*PrOH phase after simple decantation. The Ru–BINAP catalyst, immobilized in the ionic liquid, was reused several times without significant loss of activity and enantioselectivity. This catalytic system was applied successfully to the synthesis of (*S*)-naproxen.



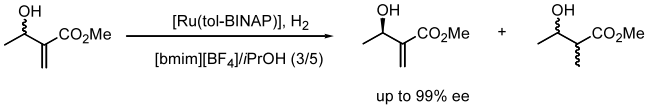
Scheme 9. [Ru–(BINAP)]-catalyzed asymmetric hydrogenation of arylacrylic acids in [bmim][BF_4]/methanol system.

Jessop et al. reported the hydrogenation of tiglic acid catalyzed by the [Ru $(O_2CMe)_2$((*R*)-tolBINAP)] complex in [bmim][PF_6]/H_2O system. Excellent conversion (99%) and good enantioselectivity (85%) were obtained (Scheme 10).[16] The enantioselectivity was shown to be hydrogen pressure dependent in wet [bmim][PF_6]. At low pressure, the amount of water had no effect on the enantioselectivity but at higher pressure adding water enhanced the enantiomeric excess. To avoid totally the use of organic solvents, the authors used supercritical carbon dioxide ($scCO_2$) to recover the organic product (2-methylbutanoic acid) from the reaction mixture. The ruthenium catalyst being insoluble in $scCO_2$, only water was contaminating the product. The catalyst, immobilized in the ionic liquid phase, was efficiently reused five cycles with retained activity and *even* enhanced enantioselectivity (up to 91% ee).



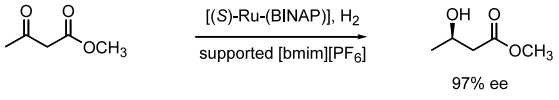
Scheme 10. Ruthenium complex-catalyzed asymmetric hydrogenation of tiglic acid in [bmim][PF_6]/H_2O system.

Dupont et al. also investigated the influence of hydrogen pressure on the kinetic resolution of (±)-methyl-3-hydroxy-2-methylenebutanoate catalyzed by [$RuCl_2$-(*S*)-tolBINAP]$_2$·NEt_3 complex immobilized in [bmim]-[BF_4] (Scheme 11).[13] Here again, the enantiomeric differentiation is a function of hydrogen pressure. With a low H_2 pressure of 4 atmospheres, the starting material was recovered with 29% yield and an excellent enantioselectivity of 99%. These results are comparable with those obtained in organic solvents (MeOH).



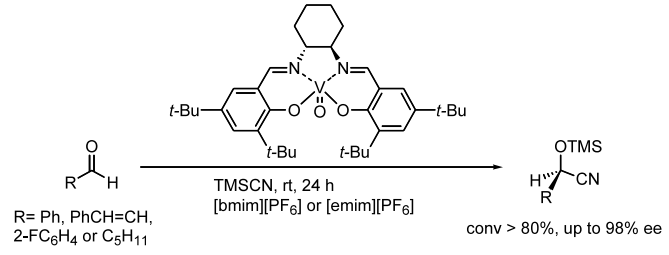
Scheme 11. Kinetic resolution of methyl-3-hydroxy-2-methylenebutanoate by ruthenium-catalyzed asymmetric hydrogenation in [bmim][BF_4].

In 2003, Vankelecom et al. proposed a new recyclable heterogeneous system using a supported ionic liquid for the asymmetric hydrogenation of methylacetoacetate catalyzed by a [Ru-(BINAP)] catalyst.[17] The heterogeneous system is a polymeric phase obtained by simple mixing of the ionic liquid, the transition metal catalyst and poly-(diallyldimethylammonium chloride). Using this supported IL, the leaching of the catalyst with solvents that form a biphasic system is avoided. The only exception is water, which dissolves the polymer. The supported ionic liquid phase dissolved in *i*PrOH gave higher activity and identical enantioselectivity than the biphasic IL/*i*PrOH system (Scheme 12) but the performances obtained in *i*PrOH could not be reached. However, the supported ionic liquid phase can be reused several times with retained activity and enantioselectivity.

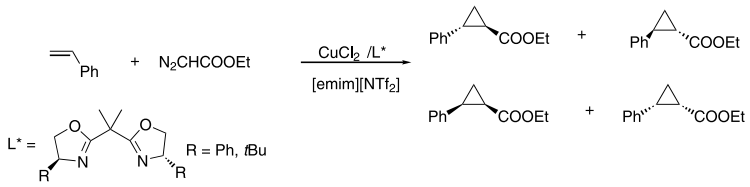


Scheme 12. [Ru–(BINAP)]/asymmetric hydrogenation of methylacetoacetate using a supported [Bmim][PF_6].

2.2.2. Asymmetric synthesis of cyanohydrins. Baleizão et al. used ionic liquids to replace the volatile CH_2Cl_2 in the asymmetric synthesis of silylated cyanohydrins



Scheme 13. Enantioselective synthesis of cyanohydrins catalyzed by a chiral vanadyl salen complex in imidazolium [PF_6] ionic liquids.

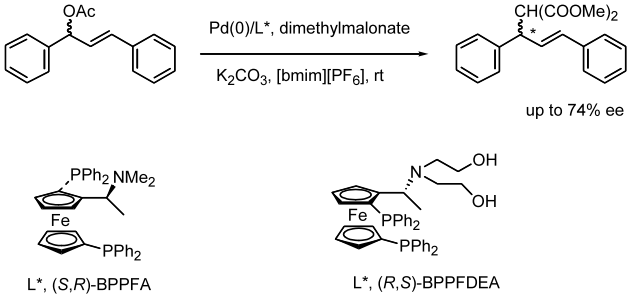


Scheme 14. Palladium-catalyzed enantioselective cyclopropanation of styrene with ethyldiazoacetate.

using TMSCN and a chiral vanadyl–(salen) complex.[18] The role of the counter anion is dramatic. When [bmim][Cl] or [bmim][BF_4] were used, low yield and enantioselectivity were obtained. However, excellent conversions (>80%) and enantioselectivities similar to those obtained in CH_2Cl_2 were obtained in [emim][PF_6] and [bmim][PF_6] (Scheme 13). Moreover, the mass balance of the recovered products is excellent. Remarkably, the recovered ionic liquid phase containing the expensive vanadium catalyst can be reused four times without significant loss of activity.

2.2.3. Asymmetric cyclopropanation. In 2001, Mayoral et al. reported the immobilization of (bis)-oxazoline-copper catalysts in ionic liquids and their use in enantioselective cyclopropanation of styrene with ethyldiazoacetate.[19] Different ionic liquids (imidazolium and ammonium salts) were tested and the results obtained in these media were compared with those obtained in CH_2Cl_2. The best results, comparable to those obtained with the expensive $Cu(OTf)_2$ in CH_2Cl_2, were obtained with the low cost $CuCl_2$ in [emim][NTf_2]. Thus, both the nature of the copper salt and the choice of the IL are crucial because of the rapid anion exchange between the two salts. The catalyst dissolved in the IL was recycled twice without loss of activity or selectivity (Scheme 14).

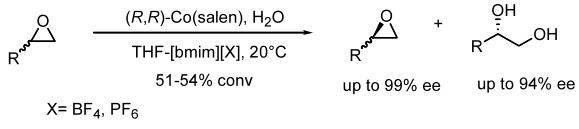
2.2.4. Asymmetric allylic substitution. Catalyst recycling is also of major concern in asymmetric allylic substitution of *C*-nucleophiles catalyzed by palladium(0). To overcome this problem, Toma et al. described enantioselective allylic substitution reactions of dimethylmalonate and (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene catalyzed by (*S*,*R*)-BPPFA and (*R*,*S*)-BPPFDEA in [bmim][PF_6] (Scheme 15).[20] A significant increase in enantioselectivity was observed in this IL compared to THF for both catalysts, however with a superiority for (*R*,*S*)-BPPFDEA. The ionic liquid containing the catalyst could be recycled after washing with water and drying over sodium sulfate. Enantioselectivity was preserved after the second run, however a decrease in product yield was always observed with (*R*,*S*)-BPPFDEA.



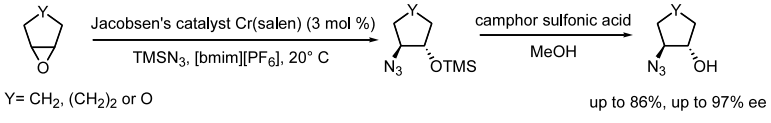
Scheme 15. Asymmetric allylic substitution of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene in [bmim][PF_6].

2.2.5. Asymmetric ring-opening of epoxides. The asymmetric ring-opening of *meso* epoxides by $TMSN_3$ catalyzed by Jacobsen's Cr–(salen) complex was studied in four different ionic liquids [bmim][X].[21] Both activity and enantioselectivity depend on the nature of the anion [X^-]. Hydrophobic ionic liquids such as [bmim][PF_6] or [bmim][SbF_6] gave the products in good yields (up to 86%) and enantiomeric excesses (up to 97%) (Scheme 16). In the hydrophilic ionic liquid [bmim][BF_4], the product was obtained in 5% yield and 3% ee. No reaction occurred in [bmim][OTf]. However, the catalyst was more efficiently immobilized in the hydrophilic ILs. To circumvent this difficulty, a homogeneous mixture of hydrophobic and hydrophilic ionic liquids [bmim][PF_6]/[bmim][OTf] (5/1) was found to be the best choice to allow good conversion, enantioselectivity and recycling of the catalyst (at least five times with retained activity and selectivity).

The same group recently described the chiral Co^{III}–(salen)-catalyzed hydrolytic kinetic resolution (HKR) of

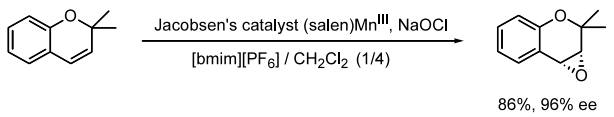


Scheme 17. Co-(Salen)-catalyzed hydrolytic kinetic resolution of racemic epoxides in [bmim][X].



Scheme 16. Cr–(Salen)-catalyzed enantioselective ring-opening of *meso* epoxides in [bmim][PF_6].

racemic epoxides in ionic liquids.[22] Enantiomerically pure epoxides were obtained by reactions performed in [bmim][PF_6] or [bmim][NTf_2] (Scheme 17). The recovered ionic liquid phase containing Co^{III}–(salen) complex was reused up to ten times without any loss of activity and stereoselectivity.

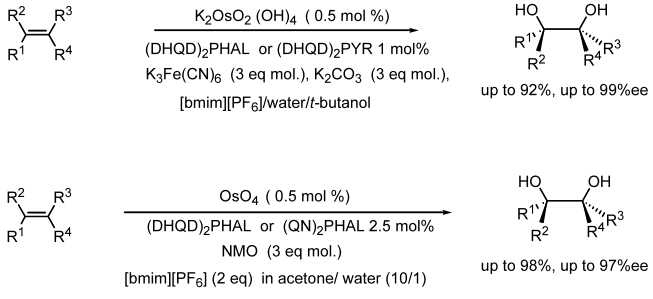


Scheme 18. Mn^{III}(Salen)-catalyzed epoxidation of alkenes.

2.2.6. Asymmetric epoxidation of alkenes. The asymmetric epoxidation of alkenes with Jacobsen's Mn^{III}–(salen) catalyst was examined in ionic liquids by Song's group.[23] The chiral catalyst was immobilized in [bmim][PF_6]. The reaction occurred at 0°C using NaOCl as oxidizing agent. Since [bmim][PF_6] was solid at this temperature, the reaction was performed in a homogeneous medium formed with [bmim][PF_6]/CH_2Cl_2 (1/4). Performances of the reaction in terms of conversion and enantioselectivity (up to 96%) were comparable to those obtained in pure CH_2Cl_2 (Scheme 18). Moreover, an enhanced reactivity of the catalyst was noticed in the ionic liquid medium. Both catalyst and ionic liquid could be recovered and reused five times. However, enantioselectivity and activity decreased slightly after each cycle presumably because of a minor degradation of the catalyst.

2.2.7. Asymmetric dihydroxylation of alkenes. The osmium-catalyzed asymmetric dihydroxylation of alkenes is a powerful methodology for the synthesis of chiral vicinal diols. However, the high cost of the catalyst and the high toxicity of osmium have precluded the industrial application of this reaction. Recycling of the catalyst using ionic liquids was recently envisioned by two groups.

Afonso studied the hydroxylation of alkenes using $K_2OsO_2(OH)_4$/$K_3Fe(CN)_6$ in two ionic liquid containing systems: biphasic [bmim][PF_6]/water and monophasic [bmim][PF_6]/water/*t*-butanol.[24] The results obtained were compared to those obtained in the homogeneous *t*-butanol/water medium. Two ligands were chosen for this study, [1,4-bis (9-*O*-dihydroquinidinyl) phthalazine ($(DHQD)_2PHAL$) and 1,4-bis (9-*O*-dihydroquinidinyl) biphenyl-pyrimidine ($(DHQD)_2PYR$)] (Scheme 19). For each substrate, there is always one system (catalyst, ligand, ionic liquid) that gives comparable or higher yields and enantiomeric excesses than the water/*t*-butanol system. More interesting is the fact that the use of ionic liquids provided an easy procedure for the recycling of osmium/ligand catalyst. Even after ten cycles, yields and enantioselectivities were retained indicating an enhanced stability of the catalyst in the IL. Moreover, determination of the osmium content by inductively coupled plasma spectroscopy analysis (ICP) in the organic phase showed that the contamination was very low (<3%).



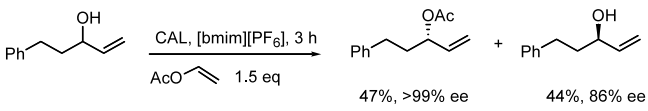
Scheme 19. Asymmetric dihydroxylation of alkenes in the presence of [bmim][PF_6] as co-solvent.

Song et al. studied the OsO_4 dihydroxylation of *trans*-stilbene and methyl *trans*-cinnamate using a bis cinchona alkaloid, $(QN)_2PHAL$, as ligand under Upjohn conditions (*N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant).[25] The reaction was performed in a water/acetone mixture in the presence of 2 equiv. of [bmim][PF_6] (Scheme 19). The results obtained in the presence of the ionic liquid were comparable to those obtained without ionic liquid (yield up to 98% and ee up to 97%), however, the rate of the reaction was much faster in the presence of the ionic liquid. Furthermore, over-oxidation of the diol which is a common side-reaction in dihydroxylation, was not observed in the presence of [bmim][PF_6]. Using $(DHQ)_2PHAL$ instead of $(QN)_2PHAL$ afforded same yields and ees but allowed the recycling of the expensive chiral catalyst. The ionic liquid/osmium ligand system could be reused several times with a maintained enantioselectivity but a gradual decrease of the catalytic activity (90–58% after three runs). Nevertheless, the highest turnover number ever reported was obtained after 3 runs (TON = 2370).

3. Asymmetric biocatalysis in ILs

Enantioselective enzyme-catalyzed reactions carried out in ionic liquids are the subject of intense research.[26–28] In organic solvents, enzymes often suffer from reduced activity, selectivity, or stability. Furthermore, hydroxylic solvents such as methanol, diethylene glycol, or 1,2-propanediol are not suitable for acylation because of competition with the substrate. Other solvents such as *N*-methylformamide denature lipases. Ionic liquids were successfully exploited as alternative media for enzyme-catalyzed reactions leading to markedly enhanced enantioselectivity and reactivity. Moreover, the thermal deactivation of enzymes was prevented in ionic liquids, which acted as stabilizing agents.

Itoh et al. described the lipase-catalyzed kinetic resolution of 5-phenyl-1-penten-3-ol by transesterification in ionic liquids in the absence of added water (Scheme 20).[29] The results were dependent on the counter anion of the imidazolium. ILs containing $[PF_6]^-$ and $[BF_4]^-$

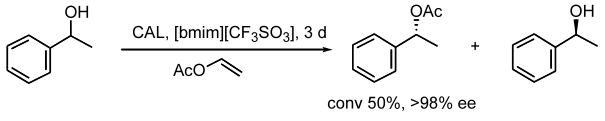


Scheme 20. Lipase-catalyzed kinetic resolution of 5-phenyl-1-penten-3-ol by trans-esterification in ILs.

anions were preferred to those with $[OTf]^-$, $[SbF_6]^-$ and $[TFA]^-$ to reach high rate of reaction and high enantioselectivity. Recycling of the *Candida antartica* lipase (CAL) in the ionic liquid was demonstrated, though the reaction rate considerably dropped. It is worth noting that lipases do not dissolve in ionic liquids, but remain in suspension.

The acylation reaction was also mediated under reduced pressure at 40°C using methyl esters as acyl donors and *C. antartica* lipase.[30] Acylated products were obtained in optically pure form in three consecutive runs without drop in the reaction rate contrary to previous results from the authors, thus demonstrating the stability of the lipase under these reaction conditions.

The kinetic resolution of 1-phenylethanol in ionic liquids was first reported by Kragl et al. (Scheme 21).[31,32] In this case $[bmim][CF_3SO_3]$ and $[bmim][(CF_3SO_2)_2N]$ displayed higher performances. The best enzyme (CAL) was reused three times with less than 10% loss of activity per cycle while the enantioselectivity was not influenced. It is worth noting that virtually no reaction occurred in $[bmim][BF_4]$ and $[bmim][PF_6]$. In 2003, Lozano et al. demonstrated that free and immobilized CAL B dispersed in an ionic liquid such as $[bmim][(CF_3SO_2)_2N]$ or $[emim][(CF_3SO_2)_2N]$ could be used in combination with supercritical carbon dioxide for the continuous kinetic resolution of *rac*-phenylethanol under extreme denaturative conditions (120–150°C and 10 Mpa). Excellent activity, stability and enantioselectivity levels were reached in this continuous operation demonstrating the high potential of ionic liquids in biocatalysis.[33]

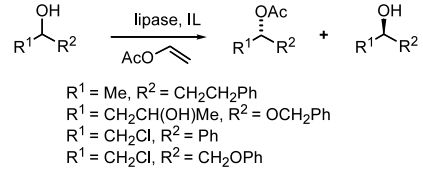


Scheme 21. Kinetic resolution of 1-phenylethanol in ILs.

Kazlauskas et al. described the lipase-catalyzed enantioselective acylation of 1-phenylethanol leading to high enantioselectivities in ionic liquids treated beforehand with aqueous sodium carbonate.[34] The authors suspected silver ions, which are used in the metathesis to prepare $[BF_4]^-$ and $[PF_6]^-$ based ionic liquids or acidic impurities, to slow down or inhibit the enzymatic reaction. The deactivation by silver ions in some ionic liquids could be explained by the disruption of disulfide links formed between two cysteine residues. The purification of the ionic liquid with aqueous sodium carbonate allowed reliable lipase-catalyzed kinetic resolution.

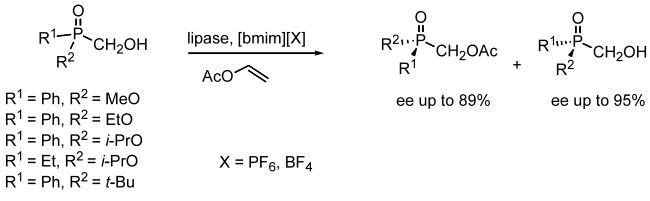
Although conventional organic solvents are avoided in the above-mentioned reactions, they are nevertheless added in work-up procedures. To avoid totally organic solvents, two groups, Iborra et al.[35] and Reetz and Leitner[36] have independently described the lipase-catalyzed kinetic resolution of 1-phenylethanol in $[bmim][(CF_3SO_2)_2N]$ using supercritical carbon dioxide as the mobile phase in a batch wise process or in a continuous flow operation. The lipase B from *C. antartica* was stable under the reaction conditions and showed efficient recycling.

Other substrates were submitted to lipase-catalyzed transesterification as reported by Kim et al. (Scheme 22).[37] *C. antartica* lipase B (CAL B) and *Pseudomonas cepacia* lipase (PCL) were chosen and evaluated in $[emim][BF_4]$ and $[bmim][PF_6]$. The enantioselectivities of lipases were markedly enhanced in ionic liquids compared to THF or toluene, and consistently higher in hydrophobic $[bmim][PF_6]$ than in hydrophilic $[emim][BF_4]$. Ionic liquid-coated *P. cepacia* lipase was also examined in the transesterification carried out in toluene. Performances of the immobilized enzyme (activity, enantioselectivity and recycling) were better than those of the native lipase.[38]



Scheme 22. Lipase-catalyzed kinetic resolution of various alcohols.

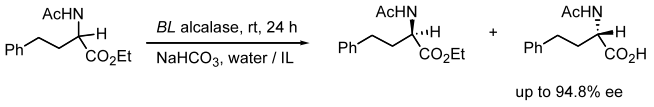
Kielbasinski et al. examined the lipase-catalyzed acetylation of racemic hydroxymethylphosphinates and hydroxymethylphosphine oxides in $[bmim][BF_4]$ and $[bmim][PF_6]$ (Scheme 23).[39] The acetates were produced in up to 89% ee and the recovered alcohols in up to 95% ee. Lipase AK and *Pseudomonas fluorescens* lipase were evaluated and proved to be up to six times more enantioselective in $[bmim][PF_6]$ than in common organic solvents.



Scheme 23. Lipase-catalyzed acetylation of racemic hydroxymethylphosphinates and hydroxymethylphosphine oxides.

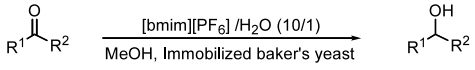
Enzymatic resolution of homophenylalanine ester in $[emim][BF_4]$ and $[EtPy][BF_4]$ mediated by *Bacillus licheniforms* alcalase was reported by Malhotra et al. (Scheme 24).[40] It was demonstrated that the use of mixed solvents such as water/ionic liquid led to lower enantioselectivity than water alone. The authors assumed that high concentration of ionic liquid in water denatures the enzyme and thus decreases the enantioselectivity. Various *N*-acetyl amino acid esters were submitted to the kinetic resolution in a solvent mixture [EtPy][TFA]/water (15/85) and results were comparable to those obtained in acetonitrile.[41]

The baker's yeast reduction of several ketones was studied by Howarth et al. (Scheme 25).[42] Its use is in



Scheme 24. Enzymatic resolution of homophenylalanine ester.

general limited to aqueous solvent systems and some apolar solvents such as liquefied petroleum gas, alkanes, benzene or carbon tetrachloride. In this study, moisture stable ionic liquids, which are very polar solvents, were used for the reduction of various ketones and β-ketoesters. Since inactivation of the yeast can be avoided by adding a small amount of water to make a surrounded protective layer, the reaction was performed in an ionic liquid/water mixture. The enantioselectivities obtained in this new medium were comparable to those observed in a classical media.

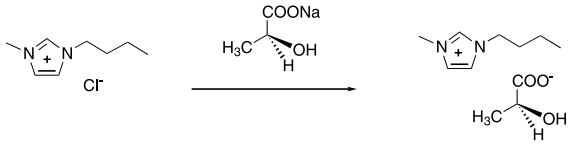


Scheme 25. Baker's yeast reduction of ketones in [bmim]-$[PF_6]/H_2O$.

4. Chiral ionic liquids: synthesis and applications

Asymmetric induction is mainly achieved by the use of chiral substrates or reagents, chiral catalysts or enzymes. Chiral solvents were also evaluated[43] even if they have been mainly used for the NMR determination of the optical purity of compounds.[44,45] The first use of a chiral solvent in asymmetric synthesis was reported in 1975 by Seebach.[46] Using a chiral aminoether as solvent, low enantioselectivities were obtained in the electrochemical reduction of ketones. A few reports then appeared in the literature[47] but the difficult syntheses of chiral solvents and their high cost often precluded their use. Recently, few examples of chiral ionic liquids (CILs) have been reported in the literature. Due to their ease of synthesis and to their peculiar properties, these new chiral solvents should play a central role in enantioselective organic chemistry and hopefully expand the scope of chiral solvents. For example, one can expect a significant transfer of chirality in these solvents due to their high degree of organization. It has been reported that most of ILs possess a polymeric behavior and are highly ordered H-bonded liquids (three-dimensional networks of anions and cations linked together by hydrogen bonds).[48] In addition, it was recently shown that hydrogen bonding is involved in controlling the *endo*-selectivity of Diels–Alder reactions.[49] These findings suggest that CILs could be highly more efficient than classical chiral solvents for asymmetric induction.

From a synthetic point of view, chirality in these new solvents can arise from the anion or the cation. Seddon et al. have reported the sole example of a chiral ionic liquid in which the chirality is settled on the anion.[50] The [bmim][lactate] was prepared by anion exchange between [bmim][Cl] and commercially available sodium

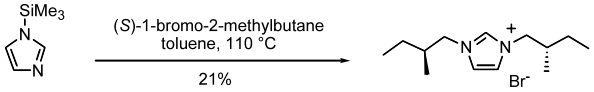


Scheme 26. Synthesis of lactate imidazolium IL.

(*S*)-2-hydroxypropionate (Scheme 26). This ionic liquid was used in asymmetric Diels–Alder reactions between ethyl acrylate and cyclopentadiene. The Diels–Alder adducts were simply isolated by decanting off the upper organic layer. A good *endo*:*exo* selectivity of 4.4/1 was obtained but no enantioselectivity was observed.

In the next examples, chirality in ILs is brought by the cation and results either from a stereogenic center, a chiral axis or a chiral plane.

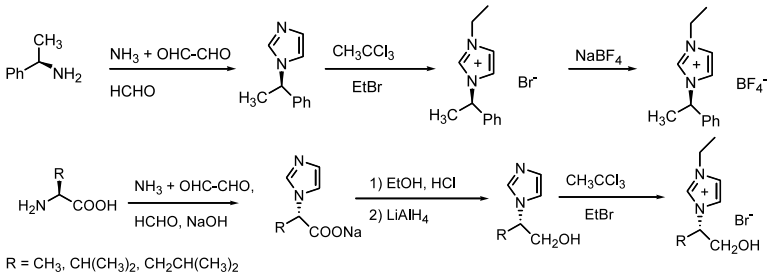
In 1997, Howarth et al. reported the first example of a chiral ionic liquid and its evaluation as Lewis acid in asymmetric Diels–Alder reactions between crotonaldehyde or methacrolein and cyclopentadiene.[51] Although this chiral IL, an imidazolium based salt, was not used as a solvent, we think it of interest to cite this work. 3-Bis-((*S*)-2-methyl-butyl)-1*H*-imidazol-1-ium bromide was synthesized in 21% yield by bis-alkylation of trimethylsilylimidazole with the expensive chiral (*S*)-1-bromo-2-methylbutane (Scheme 27). Attempts at carrying out enantioselective Diels–Alder reactions using this IL as a chiral Lewis acid (0.2 equiv.) failed to produce an enantiomeric excess superior to 5%.



Scheme 27. Synthesis of chiral imidazolium salts.

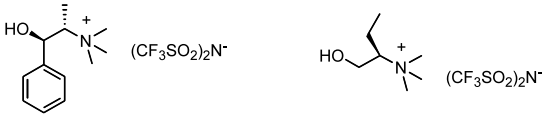
A more reliable approach to prepare enantiomerically pure chiral ILs is to use precursors derived from the chiral pool. Different groups including ours have recently used this strategy. The chirality being already present on the starting material, no asymmetric synthesis was required thus allowing rapid syntheses of large amounts of chiral ionic liquids.

Bao et al. reported the synthesis, in four steps, of new chiral imidazolium salts derived either from chiral amines or from natural amino acids (α-phenylethylamine, (*S*)-alanine, (*S*)-leucine and (*S*)-valine) and aldehydes (Scheme 28).[52] The chiral imidazolium salts were obtained in 30–33% overall yield. The IL derived from the chiral amine has a high melting point (90°C), which lowers its interest in chiral transformations. The other ILs that derived from chiral amino alcohols have melting points in the range 5–16°C, which makes them potential solvents for asymmetric reactions. The properties of these chiral ILs are similar to those of usual imidazolium ILs in terms of thermal and chemical stability, miscibility with water and common organic substrates. Their potential in asymmetric induction is still to be evaluated.



Scheme 28. Synthesis of imidazolium salts derived from chiral amine or aminoacids.

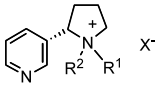
Wasserscheid et al. prepared in kg scale two new families of chiral ionic liquids[53,54] based on ammonium and oxazolinium cations starting from different natural precursors. Chiral hydroxyammonium salts were prepared in good yields (75–80%) from enantiopure aminoalcohols [(−) ephedrine and (*R*)-2-aminobutan-1-ol] (Scheme 29). These chiral ammonium ILs having a [$(CF_3SO_2)_2N$] counter-anion display melting points ranging from −18 to 54°C. Diastereomeric interactions between enantiopure (−)-*N*,*N*-dimethylephedrinium bis(trifluoromethansulfon)imidate and a racemic substrate (Mosher's acid sodium salt) have been demonstrated by ^{19}F NMR which makes this chiral ionic liquid interesting candidate for enantioselective reactions.



Scheme 29. Chiral ammonium salts derived from the chiral pool.

Oxazolinium salts were obtained as depicted in Scheme 30 from (*S*)-valine in 40% overall yield. The [PF_6] chiral ILs have melting points ranging from 63 to 79°C. These rather high melting points, the low yield synthesis and the low stability of the oxazolinium cation in acidic media (ring-opening of the oxazoline) have precluded their use as solvents in asymmetric reactions.

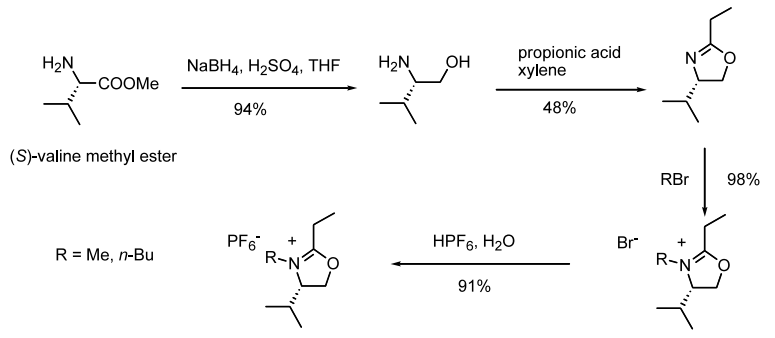
Another amine also derived from the chiral pool (nicotine) was used for the synthesis of ionic liquids. In 2001, Kitazume patented optically active ionic liquids derived from natural (*S*)-nicotine. (−)-*N*-Ethylnicotinium-bis(trifluoromethanesulfonyl)amide was prepared by alkylation with an alkyl bromide followed by anion metathesis with $(CF_3SO_2)_2NLi$ (Scheme 31).[55] This chiral IL was examined as solvent in the kinetic resolution of 1-(4-methoxyphenyl)-ethanol mediated by the *P. cepacia* lipase. The reaction was carried out at room temperature without any co-solvent. Low enantioselectivities were obtained in this new media.



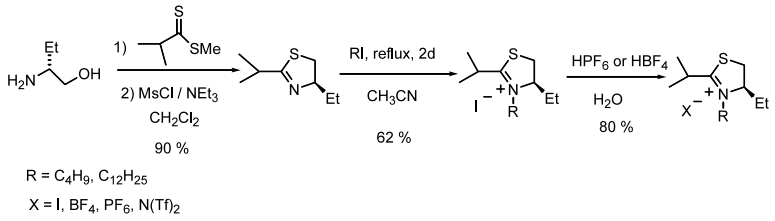
Scheme 31. Nicotine based chiral ILs.

In 2003, our group proposed a novel class of chiral ionic liquids based on thiazolinium salts. These new chiral ILs were prepared in multi-gram scale by alkylation of chiral thiazolines derived from the chiral pool followed by anion exchange.[56] The thiazoline precursors were synthesized according to previous report from reaction between dithioester and the low cost (*R*)-2 aminobutan-1-ol (Scheme 32). Melting points are depending on the length of the *N*-alkyl chain and on the nature of the counter anion (from 137°C to temperature below 0°C). Thiazolinium based ILs show good thermal stability. Moreover, they are stable under basic and even under acidic conditions unlike oxazolinium salts. Their use in asymmetric synthesis is currently under progress.

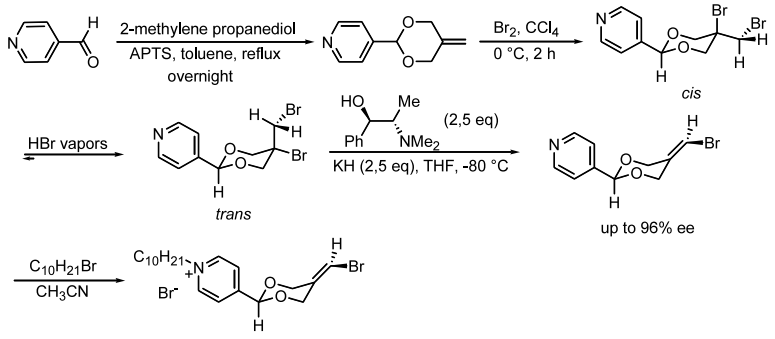
The same year, our group also proposed for the first time the design and synthesis of pyridinium ionic liquid



Scheme 30. Chiral oxazolinium ILs derived from natural amino acids.



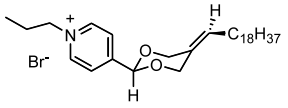
Scheme 32. Chiral thiazolinium based ILs derived from natural amino alcohol.



Scheme 33. First series of axially chiral ILs.

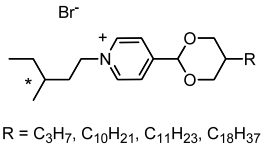
crystals with axial chirality.[57] These new pyridinium salts with a 1,3-dioxan ring in their central core were synthesized by enantioselective dehydrohalogenation using chiral alkoxides. It is important to note than these chiral ILs are not obtained from the chiral pool but are synthesized via an enantioselective reaction. The dibrominated cyclic acetals are obtained from the ethylenic precursor, which was prepared by acetalization. The stereospecific bromination gave exclusively the *cis* dibrominated acetal, which was isomerized into its *trans* isomer by treatment with hydrobromic acid vapors. Finally, an excess of chiral alkoxide derived from *N*-*N*′-dimethylnorephedrine, yielded the brominated compound bearing a chiral axis in excellent enantioselectivity and yield (Scheme 33). The development of a large series of chiral ILs is easy from the obtained chiron.

The chiral ILs are obtained directly either by quaternization or by a two-step sequence (cross-coupling and quaternization) for the compound indicated in Scheme 34. The main potential advantages of these chiral ILs in asymmetric synthesis are their low melting points (below −20°C in certain cases), and a high liquid crystal organization.



Scheme 34. Axially chiral IL with liquid crystal properties.

In parallel to this work, Haramoto et al. proposed a chiral IL with the same 1,3-dioxan ring but with the chirality settled on the alkylpyridinium chain.[58] Four ionic liquid were synthesized in four steps with yield ranging from 28 to 48% (Scheme 35).



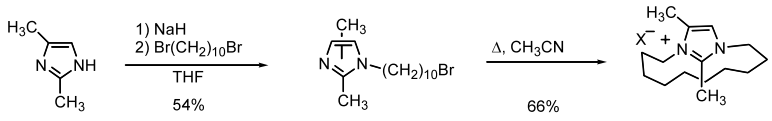
Scheme 35. Chiral IL in 1,3-dioxan series with central chirality.

The melting points are not known and no liquid crystal properties were observed. The authors explained that the presence of the alkyl chain on the nitrogen atom of the pyridinic moiety is a disadvantage for the presence of a liquid crystal transition.

Finally, one example using planar chirality was proposed in the literature. Saigo et al. designed the first example of chiral imidazolium salts with cyclophane-type planar chirality. The salt was easily prepared in two steps: *N*-alkylation followed by cyclization. The yield was however quite low (36%) mainly because of the formation of undesired oligomeric salts (Scheme 36).[59] In this structure, the C(4) methyl group is essential to induce the planar chirality and to lower the melting point. The C(2) methyl group is placed to avoid the racemization of the planar-chiral cyclophane. With the bis-(pentafluoroethanesulfonyl)-imide counter ion, a melting point of −20°C was obtained. Diastereomeric interactions between the imidazolium cation and silver(I)-(+)-10-camphorsulfonate were observed by ^{1}H NMR, thus demonstrating the chiral recognition ability of this new IL. However, before being used as a chiral solvent, this new racemic IL salt should be resolved.

5. Outlook

In this review are compiled in an exhaustive manner different attempts to perform asymmetric reactions out



Scheme 36. Synthesis of a chiral imidazolium salt with cyclophane planar chirality.

in ionic liquids. It is now well established that numerous 'classical' asymmetric reactions can be realized in ILs with high efficiency, both in terms of yield and stereoselectivity. This is demonstrated by various studies in the fields of organic, catalytic and biocatalytic asymmetric synthesis. In some examples, the use of IL instead of a classical solvent gives better results. A fascinating aspect of this chemistry is the emergence of a new paradigm in organic synthesis, including asymmetric synthesis, i.e. the concept of 'tailor-made' solvent, which could be in the future specifically designed for a given reaction. Worthy of interest is the possibility to immobilize chiral catalytic systems, thus allowing to recycle both the solvent and the catalyst for further reactions. ILs open up new perspectives in enzymatic chemistry and biocatalysis. In particular, highly polar anhydrous ionic liquids should serve for biotransformations of polar substrates such as amino acids, nucleotides and carbohydrates with enhanced activity, enantioselectivity and stability. Obviously, the ionic liquid has to be fine-tuned to the substrate and the enzyme or the whole-cell biocatalyst. Due to the large choice of ionic liquids it is likely to find one with satisfactory properties. Finally, some chiral ILs belonging to different classes of chiral compounds have been synthesized. Very few applications of these new chiral solvents have been described, and their real potential in asymmetric synthesis remains to be proven. Clearly, future studies in this field will focus on this possibility of a renewal in the chemistry of chiral solvents.

References

1. (a) Freemantle, M. *C&E News*, August 24, **1998**, p. 32; May 15, **2000**, p. 37; January 1, **1999**, p. 9; (b) Carmichael, H. *Chem. Brit*., January **2000**, p. 36; (c) Holbrey, J. D.; Seddon, K. R. *Clean Prod. Processes* **1999**, *1*, 223.
2. For reviews, see: (a) Welton, T. *Chem. Rev*. **1999**, *99*, 2071–2083; (b) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev*. **2002**, *102*, 3667–3692; (c) Olivier-Bourbigou, H.; Magna, L.; *J. Mol. Cat. A: Chem*. **2002**, *3484*, 1–19.
3. For other reviews, see: (a) Sheldon, R. *Chem. Commun*. **2001**, 2399–2407; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 3772–3789; (c) Gordon, C. M. *Appl. Catal. A : Gen*. **2001**, *222*, 101–117; (d) Dyson, P. J. *Transition Met. Chem*. **2002**, *27*, 353–358.
4. Sheldon, R. A.; Lau, R. M.; Sorgedrager, M. J.; van Rantwijk, F.; Seddon, K. R. *Green Chem*. **2002**, *4*, 147–151.
5. Loh, T. P.; Feng, L. C.; Yang, H. Y.; Yang, J. Y. *Tetrahedron Lett*. **2002**, *43*, 8741–8743.
6. Kotrusz, P.; Kmentová, I.; Gotov, B.; Toma, S.; Solcániová, E. *Chem. Commun*. **2002**, 2510–2511.
7. Kitazume, T.; Jiang, Z.; Kasai, K.; Mihara, Y.; Suzuki, M. *J. Fluorine Chem*. **2003**, *121*, 205–212.
8. McCluskey, A.; Garner, J.; Young, D. J.; Caballero, S. *Tetrahedron Lett*. **2000**, *41*, 8147–8151.
9. Chen, S. L.; Ji, S. J.; Loh, T. P. *Tetrahedron Lett*. **2003**, *44*, 2405–2408.
10. Baudequin, C.; Plaquevent, J.-C.; Audouard, C.; Cahard, D. *Green Chem*. **2002**, *4*, 584–586.
11. Tzschuche, C. C.; Market, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed. Engl*. **2002**, *41*, 3964–4000.
12. Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2698–2700.
13. Berger, A.; de Souza, R. F.; Delgado, M. R.; Dupont, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1825–1828.
14. Guernik, S.; Wolfson, A.; Herskowitz, M.; Greenspoon, N.; Geresh, S. *Chem. Commun*. **2001**, 2314–2315.
15. Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *8*, 177–179.
16. (a) Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc*. **2001**, *123*, 1254–1255; (b) Jessop, P. G.; Stanley, R. R.; Brown, R. A.; Eckert, C. A.; Liotta, C. L.; Ngo, T. T.; Pollet, P. *Green Chem*. **2003**, *5*, 3–8.
17. Wolfson, A.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron Lett*. **2003**, *44*, 1195–1198.
18. Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Green Chem*. **2002**, *4*, 272–274.
19. Fraile, J. M.; Garciã, J. I.; Herrerias, C. I.; Mayoral, J. A.; Carrié, D.; Vaultier, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1891–1894.
20. Toma, S.; Gotov, B.; Kmentová, I.; Solcániová, E. *Green Chem*. **2000**, *2*, 149–151.
21. Song, C. E.; Oh, C. R.; Roh, E. J.; Choo, D. J. *Chem. Commun*. **2000**, 1743–1744.
22. Oh, C. R.; Choo, D. J.; Shim, W. H.; Lee, D. H.; Roh, E. J.; Lee, S.-g.; Song, C. E. *Chem. Commun*. **2003**, 1100–1101.
23. Song, C. E.; Roh, E. J. *Chem. Commun*. **2000**, 837–838.
24. Branco, L. C.; Afonso, C. A. M. *Chem. Commun*. **2002**, 3036–3037.
25. Song, C. E.; Jung, D-u.; Roh, E. J.; Lee, S.-g.; Chi, D. Y. *Chem. Commun*. **2002**, 3038–3039.
26. Sheldon, R. A.; Lau, R. M.; Sorgedrager, M. J.; van Rantwijk, F.; Seddon, K. R. *Green Chem*. **2002**, *4*, 147–151.
27. Kragl, U.; Eckstein, M.; Kaftzik, N. *Curr. Opin. Biotechnol*. **2002**, *13*, 565–571.
28. van Rantwijk, F.; Lau, R. M.; Sheldon, R. A. *Trends Biotechnol*. **2003**, *21*, 131–138.
29. Itoh, T.; Akasaki, E.; Kudo, K.; Shirakami, S. *Chem. Lett*. **2001**, 262–263.
30. Itoh, T.; Akasaki, E.; Nishimura, Y. *Chem. Lett*. **2002**, 154–155.
31. Eckstein, M.; Wasserscheid, P.; Kragl, U. *Biotechnol. Lett*. **2002**, *24*, 763–767.

32. Schöfer, S. H.; Kaftzik, N.; Wasserscheid, P.; Kragl, U. *Chem. Commun.* **2001**, 425–426.
33. Lozano, P.; de Diego, T.; Carrié, D.; Vaultier, M.; Iborra, J. L. *Biotechnol. Prog.* **2003**, *19*, 380–382.
34. Park, S.; Kazlauskas, R. J. *J. Org. Chem.* **2001**, *66*, 8395–8401.
35. Lozano, P.; de Diego, T.; Carrié, D.; Vaultier, M.; Iborra, J. L. *Chem. Commun.* **2002**, 692–693.
36. Reetz, M. T.; Wiesenhöfer, W.; Franciò, G.; Leitner, W. *Chem. Commun.* **2002**, 992–993.
37. Kim, K-W.; Song, B.; Choi, M-Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 1507–1509.
38. Lee, J. K.; Kim, M.-J. *J. Org. Chem.* **2002**, *67*, 6845–6847.
39. Kielbasinski, P.; Albrycht, M.; Luczak, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2002**, *13*, 735–738.
40. Zhao, H.; Luo, R. G.; Malhotra, S. V. *Biotechnol. Progress* **2003**, *19*, 1016–1018.
41. Zhao, H.; Malhotra, S. V. *Biotechnol. Lett.* **2002**, *24*, 1257–1259.
42. Howarth, J.; James, P.; Dai, J. *Tetrahedron Lett.* **2001**, *42*, 7517–7519.
43. March, J. *Advanced Organic Chemistry*; McGraw-Hill: New York, 1977; pp. 106–108.
44. For a review of NMR chiral solvating agent, see: Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263–331.
45. For NMR databases in chiral solvents, see: Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2002**, *4*, 411–414 and references cited therein.
46. Seebach, D.; Oei, H. A. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634–636.
47. Ulbert, O.; Szarka, Á.; Halasi, S.; Somogyi, B.; Bélafi-Bakó, K.; Gubicza, L. *Biotechnol. Techn.* **1999**, *13*, 299–302.
48. (a) Dupont, J.; Suarez, P. A. Z.; de Souza, R. F.; Burrow, R. A.; Kintzinger, J. P. *Chem. Eur. J.* **2000**, *6*, 2377–2381; (b) Hagiwara, R.; Ito, Y. *J. Fluorine Chem.* **2000**, *105*, 221–227; (c) Schröder, U.; Wadhawan, J. D.; Compton, R. G.; Marken, F.; Suarez, P. A. Z.; Consorti, C. S.; de Souza, R. F.; Dupont, J. *New J. Chem.* **2000**, *24*, 1009–1015.
49. Aggarwal, A.; Lancaster, N. L.; Sethi, A. R.; Welton, T. *Green Chem.* **2002**, *4*, 517–520.
50. Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23–25.
51. Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097–3100.
52. Bao, W.; Wang, Z.; Li, Y. *J. Org. Chem.* **2003**, *68*, 591–593.
53. Wasserscheid, P.; Bösmann, A.; Bolm, C. *Chem. Commun.* **2002**, 200–201.
54. Bösmann, A.; Wasserscheid, P.; Bolm, C.; Keim, W. DE10003708 2001.
55. Kitazume, T. US 0031875 2001.
56. Levillain, J.; Dubant, G.; Abrunhosa, I.; Gulea, M.; Gaumont, A. C., submitted.
57. Baudoux, J.; Judeinstein, P.; Cahard, D.; Plaquevent, J. C., to be submitted
58. Haramoto, Y.; Miyashita, T.; Nanasawa, M.; Aoki, Y.; Nohira, H. *Liq. Cryst.* **2002**, *29*, 87–90.
59. Ishida, Y.; Miyauchi, H.; Saigo, K. *Chem. Commun.* **2002**, 2240–2241.