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Ionic Green Solvents from Renewable Resources

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Nature provides a vast new vista of opportunities for the preparation of new recyclable solvents. Natural compounds have been recently used to prepare the cationic or anionic moiety of room-temperature ionic liquids. In many cases, these new solvents, based on modifications of natural products, contain chiral centres and/or specific functional groups. This paper is an overview in an area of research that is destined for rapid development and expansion.

Introduction

In recent years, the choice of the solvent for performing a reaction has become an increasingly important task; selective reagents are used for chemical transformations, and the choice of the solvent may determine high reaction rates and high selectivity. At the same time, as a response to increasing legislative and social pressure and an increasingly "green"-conscious industrial community, researchers have started to examine more eco-friendly and sustainable chemical processes. Toxicity and recycling considerations are influencing the choice of the solvent to use for industrial reactions. Ionic liquids (ILs, Figure 1), represent a class of alternative solvents currently receiving serious consideration with the promise of both environmental and technological benefits. The development of reactions in ILs is not only important on the laboratory scale but also for industrial applications, and although very few have come to execution, several are at pilot scale.[1] The main processes that use an IL are BASF's BASIL process and the Dimerosol process,[2] whereas the biphasic hydrosilylation in ILs is set for industrial implementation in the near future.[3]

A number of room-temperature ILs based on large organic cations in combination with weakly coordinating anions such as tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-) and bis(trifluoromethanesulfonyl)imide (NTf_2^-) have been synthesized, characterized and applied in organic synthesis and catalyzed processes. All these compounds are reasonably air- and moisture-stable and are capable of dissolving a wide range of organic, organometallic

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Burkhard König (left) received his doctorate in 1991 from the University of Hamburg under the direction of Prof. A. de Meijere. He continued his scientific education as a postdoctoral fellow with Prof. M. A. Bennett, Canberra, and Prof. B. M. Trost, Stanford. In 1996, he obtained his "Habilitation" at the University of Braunschweig. Since 1999, he has been full professor of organic chemistry at the University of Regensburg. Part of his current research interest is the development of new solvents based on renewable materials.

Giovanni Imperato (right) studied chemistry at the University of Pisa and received his diploma in 2002. He continued his scientific education at the University of Regensburg, supported by a fellowship of the German Environmental foundation (DBU) and received his Ph.D. degree in 2006. In his Ph.D. work, he established a new kind of carbohydrate-based ionic liquid.

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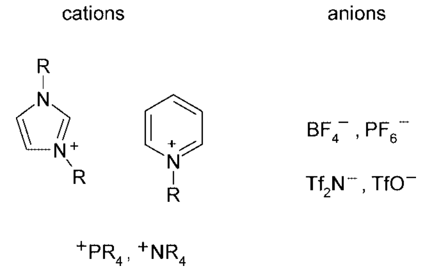


Figure 1. Cations and anions of room-temperature ILs.

and inorganic compounds.[4] Moreover, these salts are generally non-flammable, possess a negligible vapour pressure, a high thermal and chemical stability and offer the possibility of recycling. These characteristics render them promising replacements for volatile organic solvents (VOCs), which are a source of environmental problems. It is, however, noteworthy that ILs represent an extremely large class of compounds (estimated at more than 10^{18} different compounds), and not all ILs necessarily possess all these properties. Recently, it has been shown that selected families of commonly used aprotic ILs can be distilled at 200–300 °C and low pressure,[5] that a large group of ILs are combustible[6] and that some commercially available ILs may be toxic for fish[7] or other aquatic species.[8] Of course, these latter data cannot be considered an evidence that all ILs are not "environmentally-benign" solvents, but they simply show that the properties of ILs vary widely and extending the properties of a class of ILs to all low melting-salts may lead to an inappropriate and dangerous use.

Finally, it is noteworthy that commonly used ILs are generally synthetic chemicals arising from petroleum. As this resource continues to be consumed at a prodigious pace, and given the rather turbulent conditions present in some of the major oil-producing parts of the world, alternative, non-toxic and biodegradable materials, possibly based on biorenewable resources, are of considerable interest[9] and great practical benefit. Biorenewable natural compounds are ideal materials from the environmental and economic viewpoints.

ILs have been extensively reviewed in the last five years, with particular focus on their synthesis and applications.[4] Our common interest in the area of green solvents from renewable resources prompted us to focus our attention in this microreview on the more recent advances in this area. It is needless to say that a vast number of publications dealing with this topic have been recently published (including reviews and minireviews),[10] and probably many are in press—a comprehensive discussion is, therefore, far beyond the scope of this review. This microreview presents recent advances in this area, accompanied by selected older work, when necessary, to better illustrate the direction the field is moving in.

Natural Products as Sources of the Cation Side of Room-Temperature ILs

Both anions and cations can be obtained from natural sources. However, whereas relatively little has been reported regarding natural or biorenewable anions, the case is different for cations. Natural nitrogen-containing compounds (amines, amino alcohols and amino acids) have been preferentially used to obtain asymmetric cations, although recently other classes of compounds have also been employed. Two different strategies have been pursued in the derivatization approaches: 1) the simple exhaustive alkylation of nitrogen, followed by anion exchange and 2) the transformation of the natural compounds (amino alcohols or amino acids) into heterocyclic systems through a more complex sequence of synthetic steps. Generally, the first approach presents the advantage of containing the costs of derivatization, while the second one gives materials with improved properties.

One of the simplest approaches for the preparation of room-temperature ILs was recently reported by Davis and co-workers.[11] Choline chloride, a natural ammonium salt having a high melting point (302 °C), has been transformed into ILs by a 1:2 stoichiometric combination with tin(II) chloride or zinc(II) chloride. Although both of these salts, which show interesting catalytic properties, are liquids at room temperature and not moisture-sensitive, they have the disadvantage of being highly viscous. Improved results have, therefore, been obtained through the combination of choline salts with urea; the simple 1:2 mixture of choline chloride and urea affords a material having a freezing point of 12 °C (Figure 2). Moreover, this mixture exhibits rather unusual solubility and miscibility proprieties; highly ionic (metal salts) or strong hydrogen-bonding compounds (unprotected sugars and cellulose[12]) are significantly soluble in this eutectic liquid, whereas acetone, acetonitrile, ethyl acetate and toluene are completely immiscible with it. Besides urea, other hydrogen-bond donors (ethylene glycol, carboxylic acids, etc.) form eutectic solvents with quaternary ammonium cations.[13] The ability of these media to dissolve metal cations provides a promising perspective for applications in selected electrochemical processes (e.g. electroplating and electropolishing).[13]

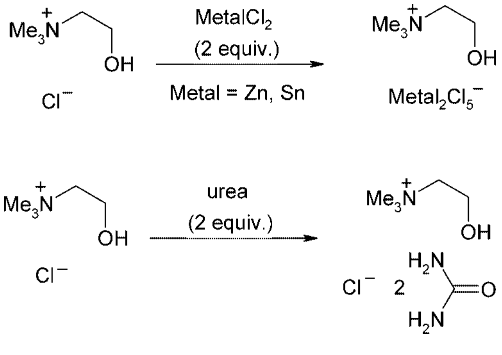
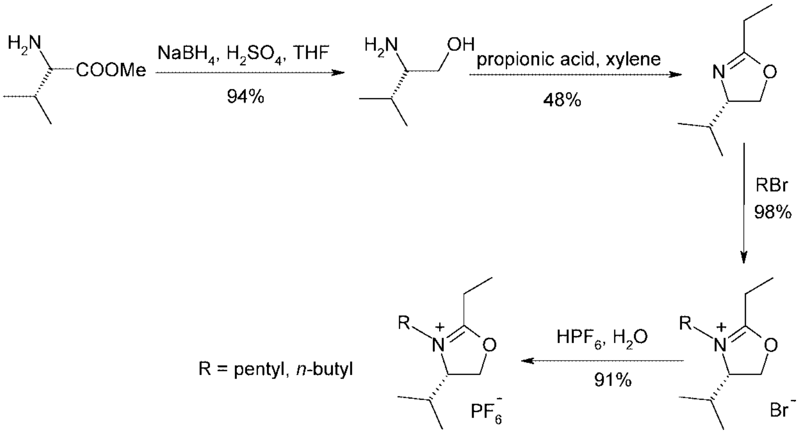


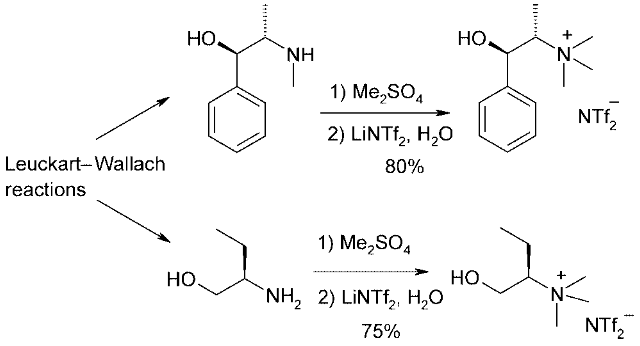
Figure 2. Choline chloride-derived room-temperature ILs.



Scheme 1. Oxazolinium ILs from (*S*)-valine.

Natural compounds, easily available and containing one or more chiral carbons, have been used by Wasserscheid and co-workers to synthesize chiral ILs.[14] Although the inherent chirality of these ILs has been only marginally explored (related to the application of solvents in asymmetric organic reactions), positive results have been obtained when these salts have been used as chiral shift reagents or chiral phases for gas chromatography. Three different groups of chiral salts were reported in this communication: those based on the oxazolinium cation, those based on hydroxy ammonium salts and those based on ephedrinium salts. The oxazolinium cations were prepared in four steps (40% overall yield), starting from (*S*)-valine (Scheme 1). Reduction of the (*S*)-valine methyl ester, following Masamune's protocol with $NaBH_4$–H_2SO_4 in THF, afforded the corresponding amino alcohol. Cyclization into oxazoline and subsequent quaternization with bromopentane or bromoethane gave the corresponding salts, which after anion metathesis with aqueous HPF_6, afforded the expected ILs. The melting points of the synthesized salts are between 63 °C and 79 °C. Although the oxazolinium ILs can be prepared on multigram scale, the relatively low overall yield and low stability under acidic conditions preclude their use as solvents.

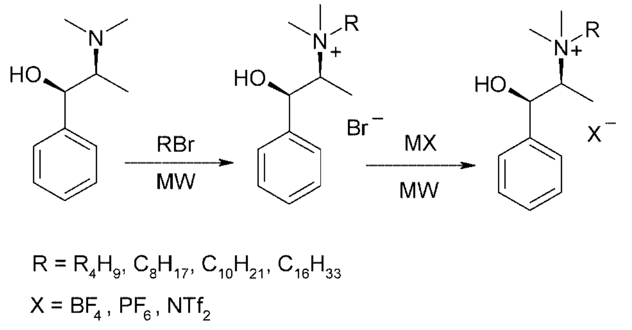
ILs based on hydroxy ammonium and ephedrinium salts were prepared on a kilogram scale in a similar manner. The enantiopure amino alcohols, (*R*)-2-aminobutan-1-ol and (–)-ephedrine, were methylated by dimethyl sulfate in dichloromethane, the solvent was removed under reduced pressure and the residues were dissolved in water. The corresponding NTf_2^- salts have been obtained by anion metathesis, with an aqueous solution of *N*-lithiotrifluoromethanesulfonimide ($LiNTf_2$) (Scheme 2). The ephedrinium salt has a melting point of 54 °C and is insoluble in water; the salt obtained from (*R*)-2-aminobutan-1-ol is liquid down to –18 °C. Although no data have been reported on the use of these ILs as solvents for organic reactions, NMR investigations (^{19}F NMR spectroscopy) showed evidence of diastereomeric interactions between the enantiopure chiral IL derived from ephedrine and a racemic mixture of the sodium salt of the Mosher acid. The ability to discriminate between enantiomers has also been demonstrated with the same class of chiral ILs as a stationary phase in gas chromatography.[15] Several chiral ILs have been used with success to separate the enantiomers of a range of chiral compounds, including alcohols and sulfoxides, showing that ILs are actually more effective stationary phases than biological molecules.[15]



Scheme 2. Ammonium ILs from (–)-ephedrine and (*R*)-2-aminobutan-1-ol.

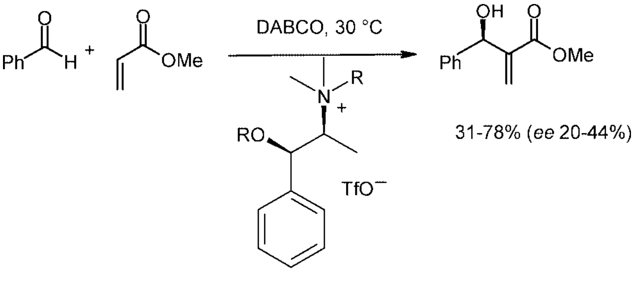
More recently, other ephedrinium salts were prepared by Vo-Thanh and co-workers[16] under solvent-free conditions and microwave activation. The synthesis of these ILs involves two steps (Scheme 3). First, (1*R*,2*S*)-*N*-alkylmethylephedrinium bromide salts were produced by the direct alkylation of (1*R*,2*S*)-*N*-methylephedrine (previously prepared by the reductive amination of ephedrine by the Eschweiler–Clarck procedure). Four different alkyl chain lengths were tested. Subsequently, to lower the melting points, the anion exchange of the (1*R*,2*S*)-*N*-alkylmethylephedrinium bromide salts with alkaline or ammonium salts of large anions (BF_4^-, PF_6^- and NTf_2^-) was performed, yielding ten ILs, characterized by melting points lower than room temperature.

It is noteworthy that these latter ILs have been used as solvents and the sole source of chirality in the Baylis–Hillman reaction of benzaldehyde and methyl acrylate, in the



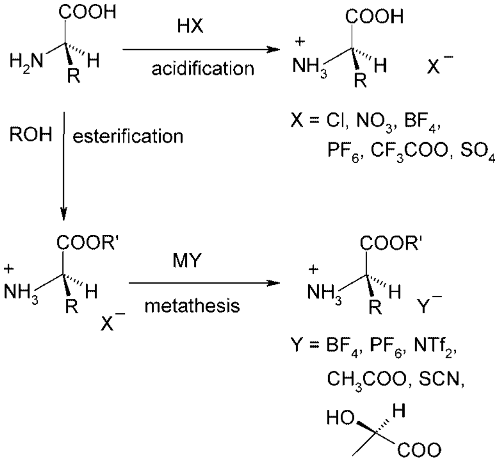
Scheme 3. Solvent-free, microwave-assisted preparation of (1*R*,2*S*)-*N*-alkylmethylephedrinium salts.

presence of an equiv. of DABCO, representing one of the first examples of significant asymmetric induction by chiral ILs[16] (Scheme 4).



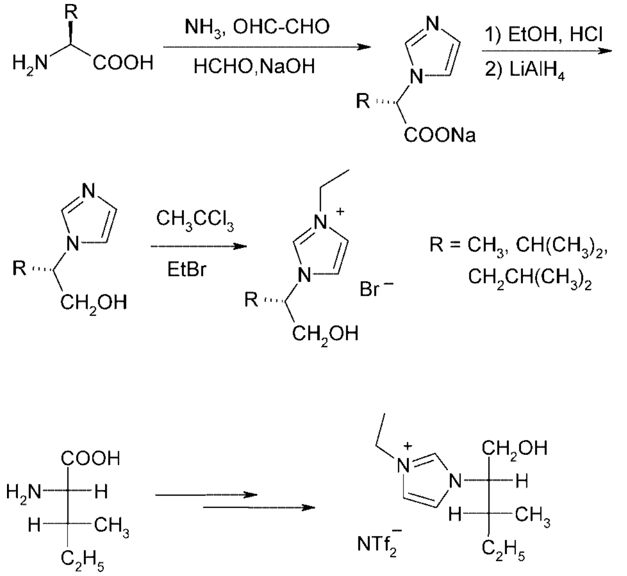
Scheme 4. A Baylis–Hilman reaction in a chiral IL.

Although amino acids and their derivatives are the most abundant natural source of quaternary nitrogen cations, they have rarely been directly used to prepare the cations of ILs. Recently, however, a simple procedure for the preparation of two other families of ILs, starting from natural α-amino acids and α-amino acid esters, has been reported.[17] More than one hundred ILs were synthesized by a one-step acidification of the amino acids in water, followed by evaporation of the water in air and under vacuum (Scheme 5). Due to strong hydrogen bonds involving the carboxylic acid functionality, most of the salts derived from α-amino acids have high melting points, whereas the corresponding ester-derived salts are viscous oils at room temperature. In all cases, the chiral centres present in the original α-amino acids have been successfully retained in the final ILs, and all ILs show thermal stability up to 200 °C. Within this class of ILs, a family of novel salts with amino acids as cations and environmentally benign materials as anions (e.g. nitrate and saccharide) have been synthesized and characterized.[18] The ILs obtained have the same characteristics (thermal stabilities, phase behaviour and viscosities) as conventional imidazolium ILs and the same chiralities as natural amino acids. Their application in the cycloaddition of cyclopentadiene to methyl acrylate has given stereoselectivities similar to those obtained in [bmim][BF$_4$]. Unfortunately, despite the chiral nature of the solvent, the enantiomeric excesses of the *endo* and *exo* products are found to be less than 3%.[18]



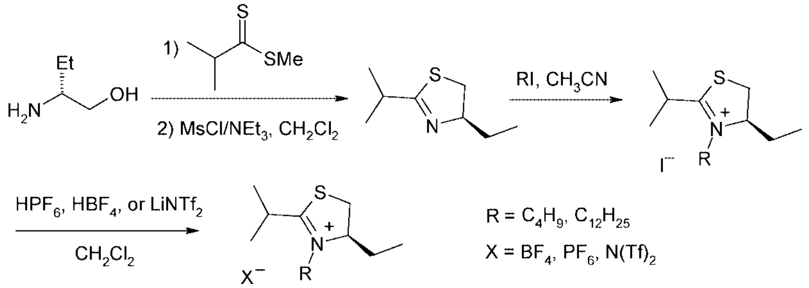
Scheme 5. Strategy for the synthesis of amino acid-based ILs.

Natural amino acids have also been used to obtain imidazolium-based ILs. In 2003, Bao and co-workers[19] described the synthesis of chiral imidazolium ILs, starting from L-alanine, L-leucine or L-valine. The synthetic procedure (four steps) gave the expected products in 30–33% overall yield. The imidazolium ring was formed by condensation of the amino acid with the proper aldehyde under basic conditions (Scheme 6), and the subsequent esterification of the acid functionality gave the expected imidazoylalkanoic ester. Reduction of the ester function, followed by nitrogen alkylation, gave the expected chiral imidazolium-based ILs bearing a hydroxy group on the alkyl chain. The presence of the hydroxy group increases the miscibility of these ILs with water and polar solvents (e.g. MeOH and acetone) and makes them immiscible with weakly polar solvents; their melting points range from 5 °C to 16 °C.



Scheme 6. An imidazolium IL from an amino acid.

The same approach has been used by Armstrong and co-workers[20] to synthesize imidazolium ILs bearing two chiral centres, starting from L-isoleucine (Scheme 6), whereas chi-



Scheme 7. Thiazolinium IL from an amino alcohol.

ral imidazolium salts were prepared in five steps by Guillemin and co-workers, starting from *N*-Boc-(*S*)-valine.[21] More recently, (*S*)-histidine has been used as a chiral precursor for a novel family of chiral amino acid and peptidic ILs.[22]

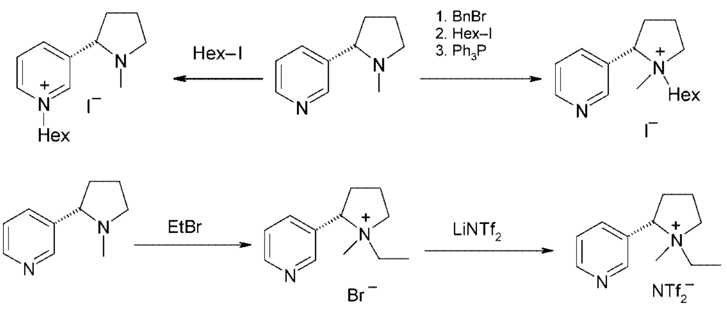
On the other hand, thiazolinium-based chiral ILs have been prepared with amino alcohols as the chiral material. Gaumond and co-workers have synthesized[23] these new ILs in four steps starting from (*R*)-2-aminobutan-1-ol or L-phenylalaninol, in fairly good overall yield (60–68%). The synthesis, summarized in Scheme 7, starts with the reaction of the amino alcohol with a dithioester, followed by cyclization of the formed thioamide, nitrogen alkylation and metathesis of the anion. The melting points of these ILs depend on the length of the *N*-alkyl chain and on the nature of the counter anions and range from 137 °C to below 0 °C. At variance with the chiral oxazolinium-based ILs, the thiazolinium ILs are stable under basic and even acidic conditions.

Finally, chiral amino alcohols have been recently used to design a series of imidazolium-based ILs bearing a chiral substituent at C-2.[24] These ILs were assembled by incorporating chiral side chains on the C-2 positions of the imidazolium cation rings through condensation reactions involving 1-methyl-2-imidazolecarboxaldehyde and an amino alcohol, followed by reduction. These salts overcome the shortcomings of their traditional counterparts that show deprotonation side-reactions at their C-2 positions. (Figure 3)

Another natural product that potentially could give three different types of ILs is nicotine. Nicotine can be alkylated on the pyridine ring, on the pyrrolidine ring or on both rings. Initial efforts have focused on the two monocations, as shown in Scheme 8. The preparation of the pyridinium salts simply requires the use of an alkylating agent with a better leaving group than pyridine, such as an alkyl iodide, and the synthesis of the pyrrolidinium salts takes advantage of the ability to selectively alkylate the pyrrolidine moiety, as reported by Shibagaki et al.[25] However, (–)-*N*-ethylnicotinium NTf_2^- was prepared simply by the alkylation of nicotine with ethyl bromide, followed by anion metathesis with $LiNTf_2$. The viscosity of all these salts is higher than that of the corresponding, simple, imidazolium salts.

Although all of the examples discussed above are related to the use of natural products bearing at least one nitrogen atom, more recently, other classes of natural compounds have been used to obtain solvents. Feder-Kubis and co-workers[26] have proposed the synthesis of an IL based on (1*R*,2*S*,5*R*)-(–)-menthol by a Menschutkin quaternization of the corresponding chloro methyl derivative, as shown in Scheme 9. Since these chloride salts generally exhibit rather high melting points (the sole exception being the trimethyl derivative, which has a m.p. of 31–33 °C), the initially formed salts were converted into the corresponding NTf_2^- derivatives by anion metathesis, yielding viscous liquids.

The same (–)-chloromethyl menthyl ether and its enantiomer were used by Armstrong and co-workers[27] for the synthesis of chiral imidazolium salts. These salts have been



Scheme 8. Nicotine-based ILs.

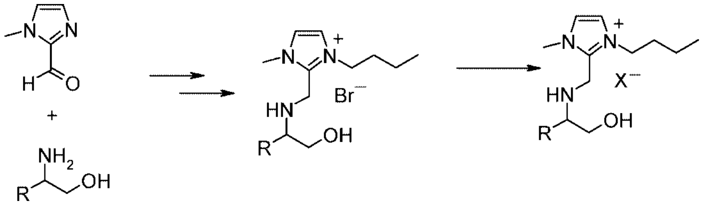
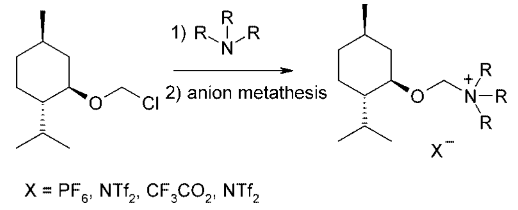


Figure 3. Imidazolium ILs from chiral amino alcohols.



Scheme 9. Synthesis of menthol salts.

used as solvents, in the presence of a base, in the enantioselective photooxidation of dibenzobicyclo[2.2.2]octatrienedicarboxylic acid.

Analogously, imidazolium salts bearing a chiral group at the N-1 position (Figure 4) have been obtained by the reaction of methylimidazole with the triflates of (*S*)-ethyl lactate, ditosyl tartrate and (1*S*,2*S*,5*S*)-myrtanol tosylate,[28] whereas imidazolium and pyridinium salts with a chiral side chain derived from (3*R*)-citronellol were prepared from the corresponding citronellyl bromide and alkylimidazole or pyridine.[29]

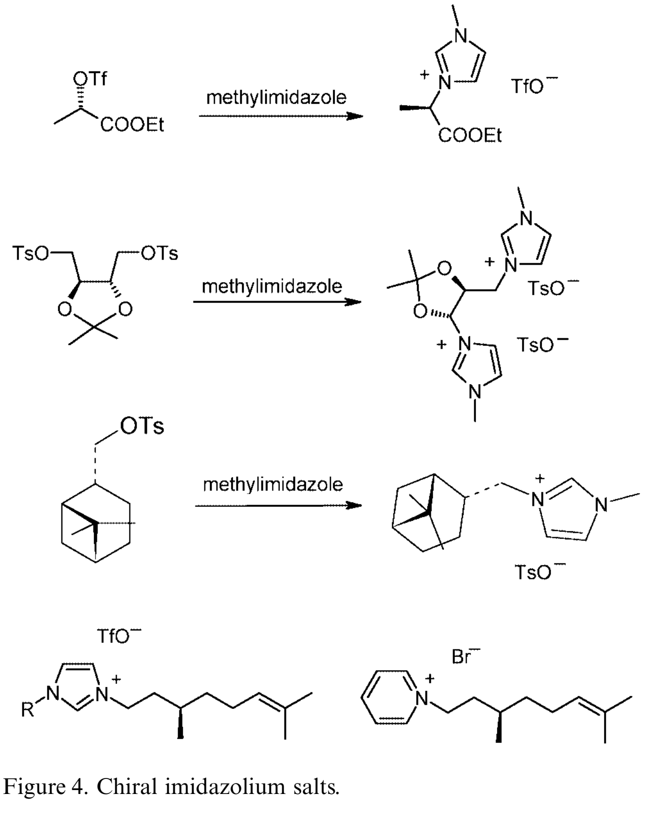


Figure 4. Chiral imidazolium salts.

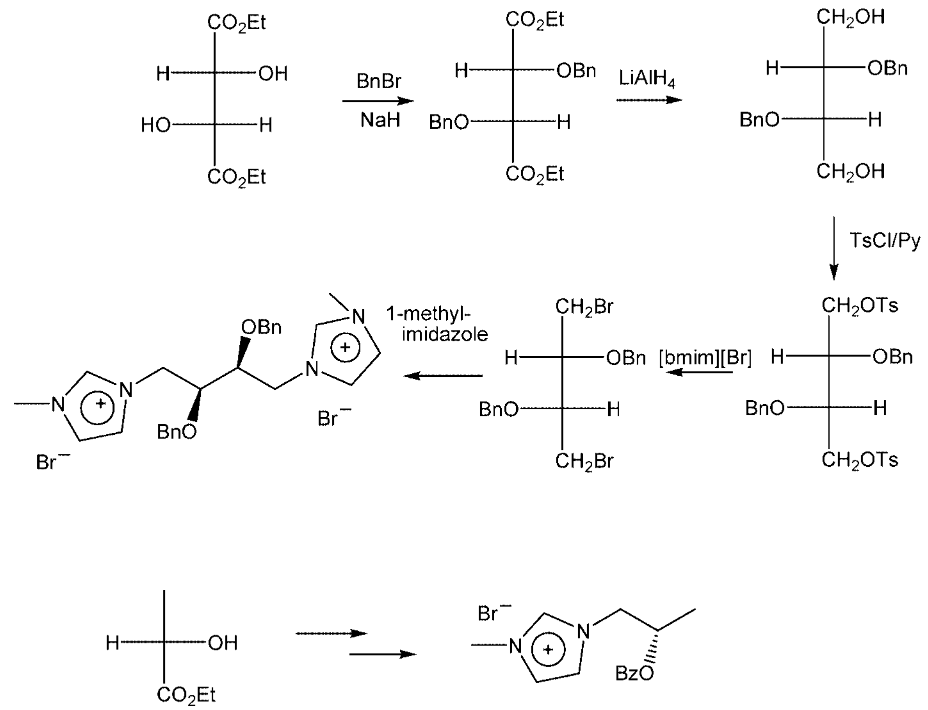
A similar approach has been followed[30] by Bao and coworkers to synthesize two kinds of novel chiral ILs based on imidazolium, starting from commercially available and inexpensive L-(+)-diethyl tartrate and L-(–)-ethyl lactate (Scheme 10). Briefly, the enantiopure esters have been *O*-benzylated with sodium hydride and benzyl bromide. Reduction with $LiAlH_4$ gave the corresponding alcohols, from which tosyl derivatives were prepared under standard conditions. Transformation into the corresponding bromides was performed with 1-methyl-3-butylimidazolium bromides; under these conditions, the reaction went to completion in only 1 h with rather high yields, and the reagent-solvent could be recycled. Finally, the target molecules were obtained by a quaternization reaction with 1-methylimidazole in acetone. These ILs, obtained in good overall yields (44–60 %), were used as reaction media and chiral reagents for enantioselective Michael additions. However, the enantiomeric excesses were moderate.

A series of chiral pinene-based ILs bearing different anions (Scheme 11) has been recently designed by Malhotra and co-workers,[31] who tested their potential in asymmetric synthesis. In particular, as a model reaction, the copper-catalyzed addition of diethylzinc to enones was investigated, showing that the chiral reaction medium has a significant influence on chiral induction.[32] Contemporaneously, the group of Armstrong has synthesized new ILs derived from (–)-*N*-benzyl-*N*-methylephedrine, D-(+)-carnitinenitrile chloride and (–)-*N*-butylscopolaminium bromide.[20]

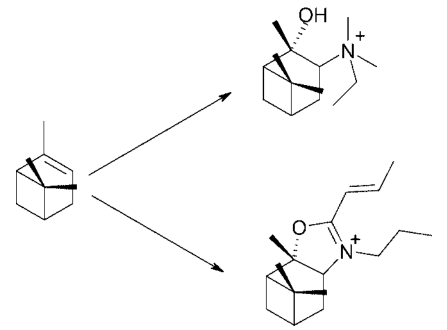
Finally, Scheme 12 illustrates several new chiral ILs derived from carbohydrates. Ammonium and sulfonium triflates have been synthesized, starting from selectively protected 1-deoxy sugars, after transformation of the primary hydroxy group into the corresponding triflate.[33]

All these examples show how simple natural compounds can be included in the structure of ILs. However, it is worth noting that natural compounds that do not appear to be capable of being transformed into cations can also be used as a source of new room-temperature ILs. Imidazolium ILs have been synthesized by Handy[34] and co-workers starting from fructose. Although fructose has no quaternizable elements, it can readily be converted into (hydroxymethyl)-imidazole by a modification of the method reported by Trotter and Darby (Scheme 13).

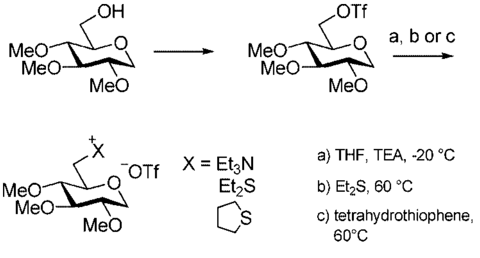
After two sequential alkylations and an anion metathesis step, hydroxymethylene imidazole is obtained. The new IL can be prepared on multi-gram scale in 65–72 % overall yield. The proprieties of these new protic ILs were investigated. All the examined salts were completely miscible with



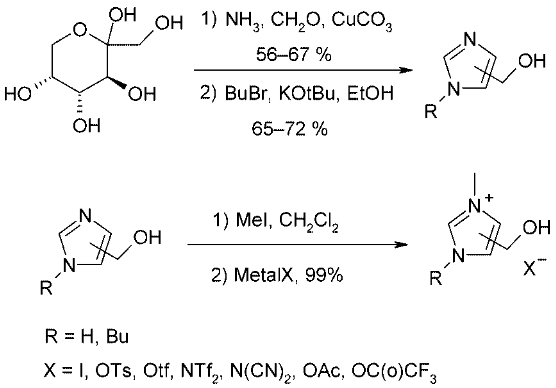
Scheme 10. Synthesis of chiral imidazolium salts from hydroxy esters.



Scheme 11. ILs from α-pinene.



Scheme 12. ILs from sugars.



Scheme 13. Synthesis of ILs based on fructose as the starting material.

acetonitrile, acetone, dichloromethane and ethyl acetate and immiscible with hydrocarbon solvents. Furthermore, these new protic ILs have been utilized in two different applications—as solvents in the Heck reaction and as supports for homogeneous supported-phase synthesis.

The possibility of using carbohydrate/urea/salt mixtures (Figure 5) as new organic media for organic reactions has been reported by König and co-workers.[35] The examined mixtures show melting points in the range of 65–85 °C and their polarities, evaluated with solvatochromic dyes, are comparable to DMF and DMSO. These new solvents were investigated in some typical organic reactions: Diels–Alder cycloadditions, Stille reactions, Suzuki coupling, Wilkinson hydrogenations and aldol reactions. The results show that they are suitable media for different organic reactions, and their water solubility facilitates workup procedures. The use of Lewis acids (e.g. to enhance the *endo*/*exo* selectivity of Diels–Alder reactions) is possible in these melts with good results. Control of the reaction stereochemistry by the chiral melt, unfortunately, has not been observed.

Finally, the possibility of using natural polyalcohols to increase the liquid range of ILs has been investigated by Chiappe and co-workers.[36] The eutectic mixtures of butylpyridinium bromide ([bupy][Br]/sorbitol, 3:1 and 2:1) are

Figure 5. Sorbitol/urea/NH_4Cl (70:20:10) melt at 80 °C.

viscous liquids at room temperature, which show improved properties in L-proline-catalyzed aldol condensations; they are able to reduce the formation of elimination by-products.

Natural Products as Sources of the Anion Side of Room-Temperature ILs

Very little has so far been reported on the exploration of anions prepared from natural or renewable materials. In part, this is doubtless due to the fact that the most ubiquitous naturally occurring anion, chloride, typically forms high-melting salts. Other simple anions, such as sulfate and phosphate, have likewise been largely avoided, although a report by Engel and co-workers shows that phosphate-based room-temperature ILs are readily achievable with a wide variety of quaternary ammonium salts.[37] In examining the more traditionally organic anions found in nature, the most common ones are the carboxylate salts acetate, lactate and tartrate. The latter is particularly interesting, since both antipodes are available in nature. As a result, these anions would provide a simple entry into the area of chiral solvents with potential applications in resolution chemistry and even synthesis. Unfortunately, salts of these anions typically exhibit higher melting points than the corresponding BF_4^-, PF_6^- or NTf_2^- salts.

In 1998, Seddon and co-workers reported[38] the use of [bmim][lactate] (Figure 6) as the solvent in the Diels–Alder reaction between cyclopentadiene and acrylonitrile or ethyl acrylate. The lactate salt provided a slightly lower *endo*/*exo* selectivity than the corresponding triflate or BF_4^- salts, whereas the reaction rate was between those of reactions performed in the other two salts. Unfortunately, no enantioselectivity was observed for this cycloaddition process when performed in the chiral lactate salt. This latter result has probably discouraged the use of lactate ILs in other applications.

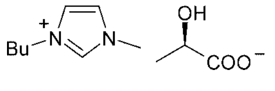
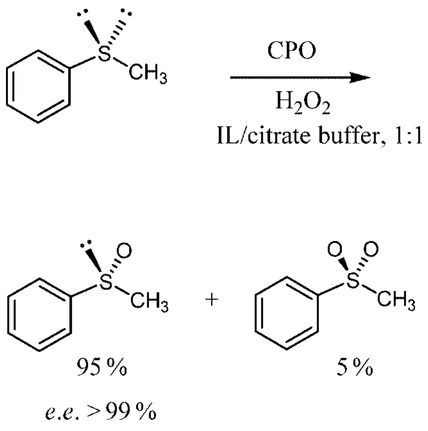


Figure 6. Composition of [bmim][lactate].

While there are situations in which ILs with fluoride will remain indispensable, identifying other (preferably innocuous) ions for formulating ILs is desirable, especially for large-volume applications.[39] Recently, Chiappe and co-workers have synthesized[40] some cholinium-based ILs having as counteranions the simple, naturally occurring species acetate, phosphate or citrate (Figure 7).



IL = $[N_{1112OH}]$[Citr]

Figure 7. Use of cholinium-based ILs as the cosolvent in chloroperoxidase-(CPO-)catalyzed reactions.

These ILs have been used as co-solvents for chloroperoxidase-(CPO-)catalyzed reactions. As compared to the behaviour observed in conventional organic solvents, CPO in cholinium citrate ($[N_{1112OH}]$[Citr]) presents enhanced activity, stability and selectivity.[40]

In 2004, Davis and co-workers reported[41a] the use of saccharin and acesulfame as the anions of new ILs. As alkali-metal salts, the anions arising from both compounds are in widespread use in foodstuffs as non-nutritive sweeteners. When incorporated into ILs, these anions exhibit properties that partly resemble those of certain fluorous anions with a m.p. below 100 °C. Both of these sweetener anions are *N*-acyl-*N*-sulfonyl imides (Figure 8) and show a similarity to the TSAC anion, introduced by Matsumoto et al.[41b] as a substitute for NTf_2^- in ILs chemistry. However, the saccharinate (Sac) and acesulfamate (Ace) are, unlike TSAC and NTf_2^-, non-fluorinated anions, and both have a well-established toxicological profile.[42]

Camphor-based ILs (Figure 9) were described in 2005 by Y. Ishikawa[43] and co-workers. Despite the anion bulkiness and high molecular weight, the camphorsulfonate (CS) salt ([bmim][CS]) is a viscous liquid, even on a salted ice bath, while [bmim]$[CH_3SO_3]$ is solid at room temperature. By means of a specially designed ESI mass spectrometer, the authors have evaluated the cation–anion association in several sulfonate ILs, demonstrating that the bulky [CS] anion binds more loosely with the imidazolium cation than the smaller $[CH_3SO_3]$ and $[CF_3SO_3]$ anions. The significant enhancement in the *endo*/*exo* stereoselectivity found for Diels–Alder reactions between cyclopentadiene and ethyl acrylate in these new solvents was attributed to the increased

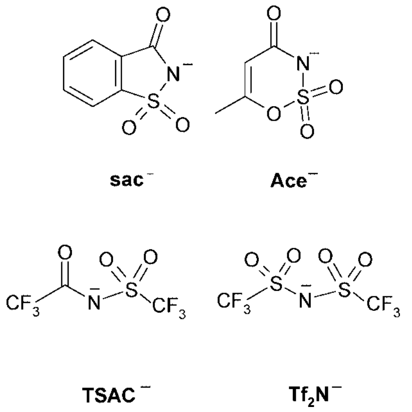
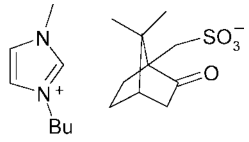


Figure 8. Structure of saccharinate (Sac), acesulfamate (Ace), and TSAC anions. The structure of the widely used bis(trifluoromethyl)imide (NTf_2^-) anion is shown for comparison.

number of free (naked) imidazolium cations, caused by the use of a CS anion. Indeed, the *endo*/*exo* selectivity of 10:3, determined in the presence of [bmim][CS], represents an excellent result for a reaction carried out without catalyst.

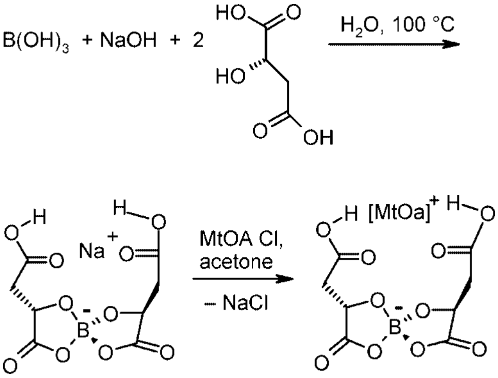


[bmim][CS]

Figure 9. Composition of [bmim][CS].

Natural amino acids have also been used to develop room-temperature ILs in which the anion is a natural compound. In the first paper, published in 2005 by Ohno and co-workers,[44] ILs were prepared starting from 1-ethyl-3-methylimidazolium hydroxide and 20 different natural amino acids; the use of imidazolium hydroxide has allowed the direct synthesis of various ILs by neutralization of the carboxylic acid functionality of the selected amino acids, without the need of a metal salt. All of the resulting amino acid ILs are transparent and nearly colourless liquids, showing a glass transition temperature ranging from –57 °C to 6 °C. However, viscosity and thermal stability require improvement. Although ammonium- and pyrrolidinium-based amino acid ILs do not show improved properties compared to the corresponding imidazolium-based salts, positive results have been obtained by introducing the tetrabutylphosphonium cation. The coupling of the *n*-tetrabutylphosphonium cation with amino acid anions has given 15 liquid salts having lower viscosities (generally, higher than 300 cP at 25 °C) and higher decomposition temperatures.[45] Furthermore, it has been recently shown[46] that tetrabutylphosphonium amino acid ILs supported on porous silica gel are able to absorb CO_2. The process is fast and reversible; the CO_2 absorption capacity at equilibrium was 50 mol-% of the ILs, but in the presence of water (1 wt.-%), the ILs can absorb equimolar amounts of CO_2. On the other hand, imidazolium ILs carrying anions of chiral- or ω-amino acids have been used as media for the enzymatic resolution of phenylalanine.[47] These ILs were capable of stabilizing the protease activity and increasing enantioselectivity at low concentrations. Higher enantiomeric excesses and yields were generally obtained in ILs based on D-amino acids; results were rationalized by invoking the kosmotropic effect of the anion.

Finally, liquids bearing chiral anions have been synthesized,[48] starting from boric acid, sodium hydroxide and chiral hydroxy acids (L-malic acid, mandelic acid and diethyl tartrate), by the exchange of the sodium ions with methyltrioctylammonium, supplied by aliquat 336 in acetone (Scheme 14).



Scheme 14. Two-step synthesis of methyltrioctylammonium dimaleatoborate.

The IL obtained, methyltrioctylammonium dimaleatoborate, has been used as the only source of chirality in the aza-Baylis–Hillman reaction between methyl vinyl ketone and *N*-(4-bromobenzylidene)-4-toluenesulfonamide with PPh_3 as the catalyst, yielding enantioselectivities up to 84% *ee*. This is the highest enantioselectivity induced to date by a solvent; the *ee*'s are comparable to those obtained with the best catalysts. Moreover, these data show that ILs bearing chiral anions can also be used to induce asymmetry. If the key to effective chirality transfer lies in a strong interaction between the solvent molecules and the intermediates or transition states, as recently suggested,[48] functional ILs offer unique possibilities to create such arrangements for a wide range of transformations.

Conclusions

In summary, nature provides a vast new vista of opportunities for the preparation of new recyclable, biodegradable, chiral and/or functionalized solvents, having improved biocompatibility. These solvents, which can often be obtained through simple derivatization procedures, have potential applications as (chiral) media in organic synthesis and enzyme-catalyzed processes, in the separation sciences (GC, HPLC), and probably, as materials in more specific applications.

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