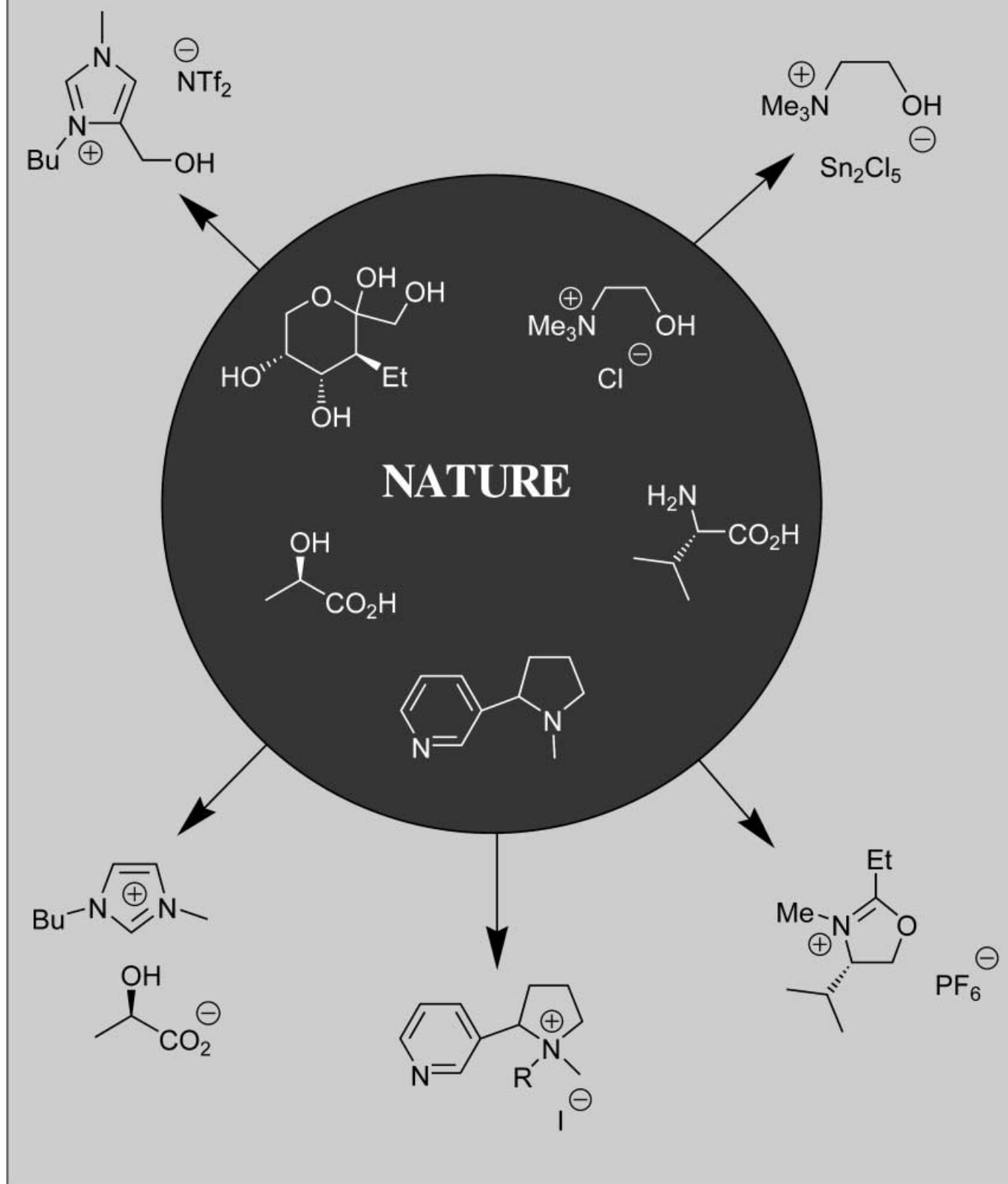


## NEW IONIC LIQUIDS



# Greener Solvents: Room Temperature Ionic Liquids from Biorenewable Sources

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**Abstract:** Room temperature ionic liquids (RTILs) have attracted a great deal of interest as environmentally benign (green) solvents for organic synthesis. More recently, RTILs that are chiral, less expensive, or functionalized (protic or Lewis basic) have been developed. In many cases, these new solvents are based on the modification of natural products. This paper is an overview of these new biorenewable RTILs.

**Keywords:** environmentally benign · green chemistry · ionic liquids · solvolysis

## Introduction

As the demands for more ideal synthetic practices continue to increase, greater and greater attention is focused on the development of new and improved synthetic methods. One major topic of interest is alternatives to conventional organic solvents, since these materials are widely used and exhibit a number of hazardous properties (including volatility, flammability, and toxicity). A number of new solvents have been reported over the past several years, including water, supercritical fluids, fluorinated solvents, and room temperature ionic liquids.<sup>[1]</sup>

This last category, room temperature ionic liquids (RTILs), has garnered the greatest attention in recent years. RTILs are most simply defined as salts that are liquid at or below room temperature. There are a wide variety of materials that fall into this category, but they are generally exemplified by the combination of a large organic cation (most commonly imidazolium) with a weakly coordinating anion (Figure 1). RTILs exhibit many properties similar to conventional organic solvents, particularly with respect to their ability to dissolve a wide range of organic, organometallic, and even some inorganic compounds. At the same time, by modifying

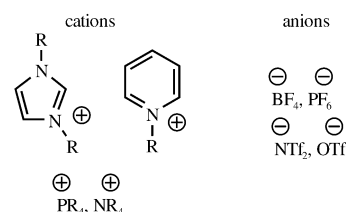


Figure 1. Room temperature ionic liquids.

the cation and the anion, they can be tuned to be immiscible with either low polarity organic solvents (hexanes, toluene, ether, super critical CO<sub>2</sub>) or high polarity solvents (water, methanol).<sup>[2]</sup> This enables conventional extraction methods to be employed in product separation. Further, since the RTILs are not volatile, products can often be separated by distillation. As a result, the recovered solvent can be recycled. Combined with the observation that many transition metal catalysts are effectively retained in RTILs, a tremendous explosion in the use of RTILs as recyclable solvent/catalysts for transition metal catalyzed reactions has occurred within the last few years.<sup>[3]</sup>

By remaining focused on imidazole-derived RTILs, however, the opportunity to fully explore the versatility afforded by RTILs is being largely ignored. Indeed, one major omission is “functionalized” RTILs. Thus, while the basic imidazolium RTIL is well suited as a substitute for “inert” conventional solvents (THF, acetonitrile, methylene chloride), until recently there were no protic and nucleophilic RTILs. Nucleophilic conventional solvents (pyridine, HMPA) are of particular importance in synthesis as catalytic solvents for acylation reactions, but are also highly toxic and hazardous compounds. As a result, a non-volatile and recyclable alternative would be of great potential practical benefit.

A second potential concern with imidazole-derived RTILs is the expense and source of these solvents.<sup>[4]</sup> The most typical anions are either of limited stability (tetrafluoroborate, hexafluorophosphate) or quite expensive and require environmentally unfriendly syntheses (triflimide, triflate). The cation component is also expensive and further is heavily dependent upon petroleum feed stocks. Given the rather turbulent conditions present in some of the major oil-producing parts of the world, alternative feed stocks could be of great practical benefit.

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To address functionality, expense, and source issues with RTILs requires a fundamental shift in where we look for RTILs. Fortunately, by remembering that any compound that can be made into an anion or cation has the potential to be a RTIL considerably expands the range of possible choices. New variations based upon this realization are appearing and one of the major sources of inspiration is nature.<sup>[5]</sup>

In theory, both the anion and cation components of a RTIL could be obtained from natural sources. On the anion side, very little has been reported so far. 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 does indicate that phosphate-based RTILs are readily achievable with a wide variety of quaternary ammonium salts (Figure 2).<sup>[6]</sup> Similarly, alkyl sulfates, though not themselves natural materials, have been reported by Wasserscheid as low cost and more readily synthesized new anions for imidazolium RTILs.<sup>[7]</sup>

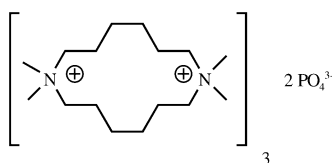
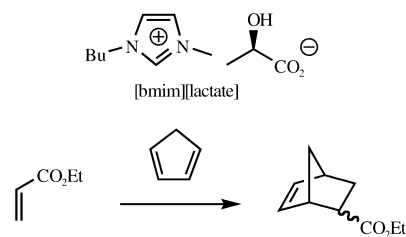


Figure 2. Phosphate based RTILs.

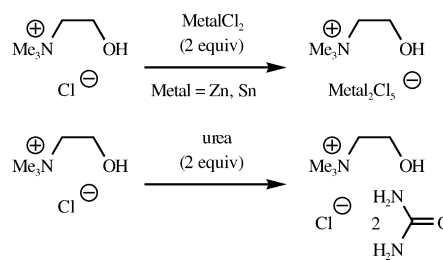
In examining the more traditionally organic anions found in nature, the most common ones are carboxylate salts, such as acetate, mandelate, lactate, and tartrate. The latter three of these are particularly interesting since they are chiral compounds, and tartrate in particular is readily available in both antipodes. As a result, these anions would provide a simple entry into the area of chiral solvents with potential applications in resolution chemistry, chromatography, and even synthesis.<sup>[8]</sup> Unfortunately, salts of these anions typically exhibit higher melting points than the corresponding tetrafluoroborate, hexafluorophosphate, or triflimide salts.<sup>[9]</sup> As a result, only a single report using one of these chiral anions has appeared. This communication from Earle and co-workers was one of the early studies of the rate acceleration of Diels–Alder reactions in RTILs.<sup>[10]</sup> A series of *N*-butyl-*N*-methylimidazolium RTILs were examined as solvents for simple Diels–Alder reactions between cyclopentadiene and acrylonitrile or ethyl acrylate (Table 1). The lactate salt provided slightly lower *endo/exo* selectivity than either a triflate or tetrafluoroborate salt and provided a reaction rate that was in between these two salts. Unfortunately, no enantioselectivity was observed in this cycloaddition in the lactate salt.

While little has been reported regarding natural or bio-renewable anions, the case is different for cations. One of the simplest RTILs was reported by Davies and co-workers (Scheme 1). It is directly derived from a naturally occurring ammonium salt, namely choline chloride. Choline chloride itself is a high melting solid (302 °C), but room temperature ionic liquids have been prepared in two fashions. The first

Table 1. Diels–Alder reactions in Earle’s lactate RTIL.



Solvent	<i>t</i> [h]	Yield [%]	<i>endo/exo</i> Ratio
[bmim][OTf]	18	96	6.0:1
[bmim][lactate]	24	99	3.7:1
[bmim][lactate]	2	87 (99)	4.4:1
[bmim][PF6]	1	36	8.0:1

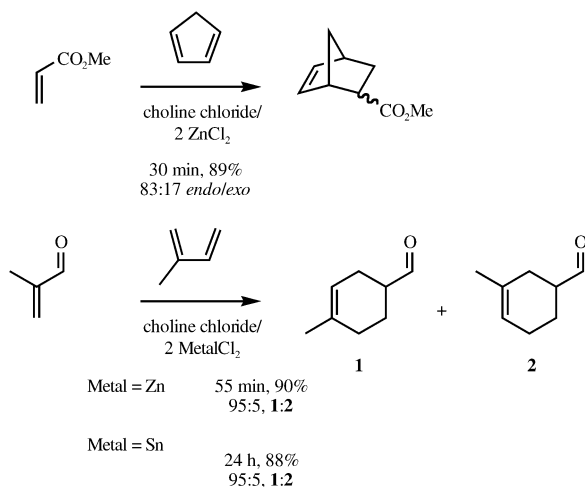


Scheme 1. Choline chloride derived RTILs.

method was the 1:2 stoichiometric combination of choline chloride with tin(II) chloride or zinc chloride.<sup>[11]</sup> The freezing points of each of these salts were both around ambient temperature (23–25 °C for the zinc salt and 43–45 °C for the tin salt). Interestingly, a 1:1:1 combination of choline chloride, tin(II) chloride, and zinc chloride formed a liquid with a freezing point slightly lower than that of the simple zinc salt (21–23 °C). All of these materials do suffer from the disadvantage that they are highly viscous. On the other hand, they are easy to prepare and quite tolerant of moisture—unlike the corresponding aluminum chloride and ferric chloride salts.<sup>[12]</sup>

The second method for creating a RTIL using choline chloride was its combination with various ureas (Scheme 1).<sup>[13]</sup> Of the various combinations studied, the simple 2:1 mixture of urea and choline chloride afforded a material with a freezing point of 12 °C, which is well below that of either component. This material is inherently less viscous than the zinc chloride-based RTILs, but is still quite viscous (1100 cP). It also exhibits good conductivity and moisture stability. More importantly, however, it exhibits rather unusual solubility and miscibility properties. Highly ionic or strongly hydrogen-bonding compounds are freely soluble in this choline chloride/urea RTIL. Even water-insoluble AgCl is soluble up to 0.66 M in the choline chloride/urea RTIL. At the same time, solvents or compounds that are not ionic or strongly hydrogen-bonding are not soluble, which means that a wide range of conventional organic solvents (acetone, acetonitrile, ethyl acetate, toluene) are immiscible with this RTIL. These solubility/miscibility properties are dramatically different from other RTILs and could result in a number of highly valuable applications.

Davies and co-workers have subsequently studied the application of the choline salts as Lewis acidic solvents for Diels–Alder reactions (Scheme 2).<sup>[14]</sup> Several interesting and useful observations were made during the course of these



Scheme 2. Diels–Alder reactions in choline chloride RTILs.

efforts. First was the ease with which the product could be separated from the reaction mixture. Both the dienes and the Diels–Alder adducts are insoluble in the choline chloride/zinc chloride RTIL. As a result, the product and any excess diene can be decanted at the end of the reaction. In their small-scale reactions, a second extraction with some hexanes was performed to insure complete separation. The remaining RTIL layer could then be recycled at least five times without any loss in activity.

The other main observation dealt with the viscosity of the reaction medium. The simple choline chloride/zinc chloride RTIL is highly viscous and, due to the heterogeneous nature of the Diels–Alder reaction in this solvent, the reaction had to be stirred using a mechanical stirrer. The addition of water in an amount equimolar to the amount of zinc chloride used to form the RTIL greatly reduced this viscosity and allowed for efficient normal magnetic stirring. At the same time, the presence of this water did not significantly effect the rate of the Diels–Alder reaction.

Wasserscheid and co-workers have also examined some simple ammonium RTILs, but in their case they have examined chiral materials (Figure 3). Thus, they have reported the synthesis of three families of new chiral RTILs.<sup>[15]</sup> The first two of these, RTILs **3** and **4**, are based on valine or ephedrine as their ultimate source. Unfortunately, neither of these materials was a liquid at room temperature and RTIL **3**

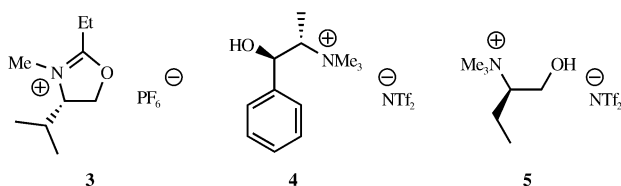
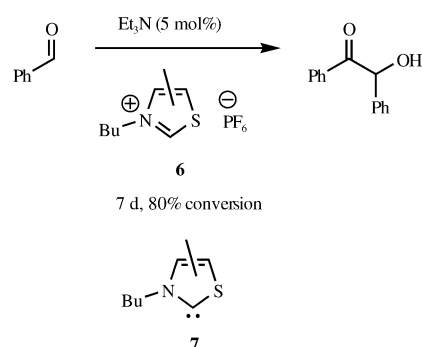


Figure 3. Wasserscheid's chiral RTILs.

exhibited only modest stability under aqueous acidic conditions (hydrolysis to the amino alcohol being the main decomposition pathway). On the other hand, RTIL **5** is a liquid even at  $-18^{\circ}\text{C}$ . It can be readily prepared in three steps on kilogram scale starting from (*R*)-2-aminobutan-1-ol. There are a number of potential applications for this material, including as a resolution agent, as an asymmetric solvent, and even as a mobile or stationary phase for chromatography. Presently, the only reported study is the observation that the trifluoromethyl signal of the sodium salt of racemic Mandel's ester in  $^{19}\text{F}$  NMR spectroscopy can be resolved using mixtures of RTIL **5** and deuteromethylene chloride.

Another interesting RTIL that, while not a natural product itself, is closely related to a natural product is thiazolium RTIL **6** (Scheme 3).<sup>[16]</sup> Prepared in two steps from 4-methyl or 5-methylthiazole, this RTIL is structurally related to thiamine.



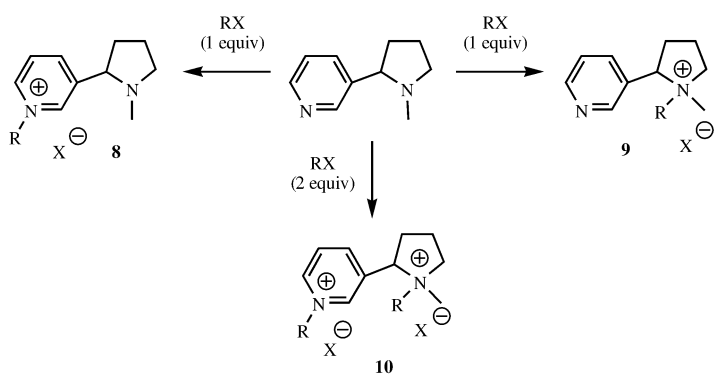
Scheme 3. Thiamine RTILs and the benzoin condensation.

Thiamine and related salts have been used for a number of years as catalysts for the Benzoin condensation.<sup>[17]</sup> Davies and co-workers reported that a 1:1 mixture of thiazolium RTIL **6** and toluene could be used as the solvent/catalyst for the benzoin condensation of benzaldehyde. The addition of 5 mol% triethylamine was all that was required to initiate this reaction. While rather sluggish (80% conversion after 7 d), separation of the toluene layer and the addition of fresh benzaldehyde resulted in further reaction; this indicates that the solvent and catalytic species responsible for the condensation (carbene **7**) could both be recycled in a simple manner.

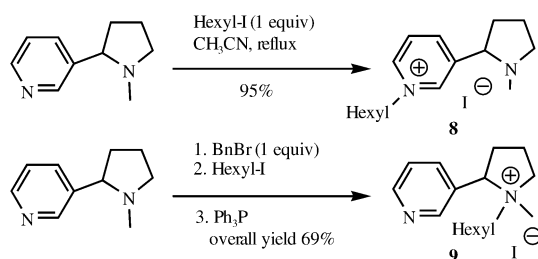
Remaining in the area of catalytic, nucleophilic solvents, Handy and co-workers have investigated the use of RTILs based on nicotine. In theory, there are three types of RTILs available from nicotine: two different monocations (**8** and **9**) and one dication **10** (Scheme 4). Initial efforts have focused on the two monocations.

The preparation of the monocation **8** simply requires the use of a better leaving group (such as an alkyl iodide) in a polar aprotic solvent (Scheme 5).<sup>[18]</sup> The preparation of **9** is not quite as simple, but takes advantage of the ability to selectively alkylate the pyridine moiety as reported by Shibagaki.<sup>[19]</sup> The final iodide salts **8** and **9** were highly viscous liquids at room temperature. Both the triflimide and dicyanimide salts were prepared via metathesis and are qualitatively less viscous, but still difficult transfer via syringe.

Both of these RTILs were used in standard acylation reactions. Initially, RTIL **8** was not expected to be an overly



Scheme 4. Three classes of nicotine-derived RTILs.



Scheme 5. Monocation RTIL preparations.

effective catalyst, due to the absence of the nucleophilic pyridine. It was therefore surprising to discover that it did effectively mediate the acylation of 2-phenylethanol with acetic anhydride (Table 2). This reaction was considerably faster than the background reaction of 2-phenylethanol with acetic anhydride in the absence of any solvent (entry 1 versus 2). Further, the same reaction solvent was also capable of catalyzing the acylation of a more hindered secondary alcohol, 1-phenylethanol (entry 5). At room temperature, however, no reaction was observed with a tertiary alcohol.

Another important observation was that RTIL **8** could be recycled. Following separation of the ester product by extraction with diethyl ether, the remaining ionic liquid layer was washed with 5% aqueous sodium hydroxide to neutralize the ammonium acetate salts and restore the amine form of RTIL **8**. After drying in vacuo at 80 °C overnight, the RTIL could be used in further acylation reactions (entries 3 and 4, 7).

Table 2. Acylation reactions in nicotine-derived amine RTIL **8**.

Entry	Alcohol	Yield [%]
1		86
2		54 <sup>[a]</sup>
3		92 <sup>[b]</sup>
4		93 <sup>[c]</sup>
5		75
6		0 <sup>[a]</sup>
7		68 <sup>[b]</sup>

[a] Reaction neat after 24 h. [b] First recycling. [c] Second recycling.

As expected, the pyridine RTIL **9** was also an effective medium for acylation reactions (Table 3). It displayed similar reactivity to pyridine itself (entries 1 and 2, 5 and 6). Thus, a primary alcohol was cleanly acylated at room temperature in either solvent, while a secondary alcohol was only slowly

Table 3. Acylations in nicotine-derived pyridine RTIL **9**.

Entry	Alcohol	Yield [%]
1		86
2		89 <sup>[a]</sup>
3		86 <sup>[b]</sup>
4		85 <sup>[c]</sup>
5		< 15
6		18 <sup>[a]</sup>
7		95 <sup>[d]</sup>
8		78 <sup>[b, d]</sup>
9		99 <sup>[e]</sup>
10		0
11		0
12		42 <sup>[d]</sup>
13		56 <sup>[f]</sup>

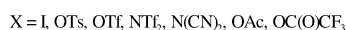
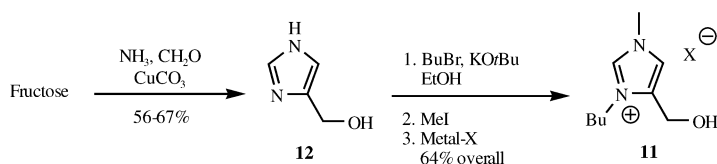
[a] Reaction in pyridine, 20 h. [b] First recycling. [c] Second recycling. [d] Reaction at 70 °C. [e] Reaction with AcCl, 2 h. [f] Reaction with AcCl, 10 h.

acylated, the reaction still not being complete after 20 hours in either solvent. The more hindered substrates could be acylated by simply heating the RTIL **9** solution to 70 °C, thereby affording excellent yields of the ester of 1-phenylethanol and more modest yields of the ester of 2-phenyl-2-propanol (entries 7 and 12). RTIL **9** is also compatible with acid chlorides, and these more active acylating agents afforded good yields of the esters of both secondary and tertiary alcohols (entries 9 and 13).

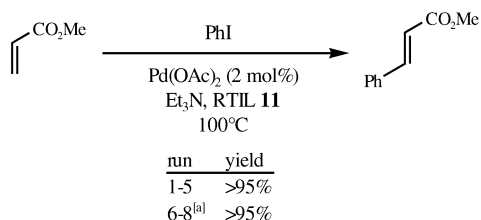
Finally, RTIL **9** could be recycled in a manner similar to that of RTIL **8** by washing with 5% aqueous sodium hydroxide. After drying in vacuo at 80 °C overnight, it could be used in further acylation reactions (entries 3 and 4, 8).

Even natural products that do not appear to be capable of being transformed into cations can be used as sources of new RTILs. An example from the Handy group is RTILs based on fructose.<sup>[20]</sup> Although fructose has no quaternizable elements, it can be readily converted into hydroxymethyleneimidazole **12** using a slight modification of the method of Trotter and Darby (Scheme 6).<sup>[21]</sup> After two sequential alkylations and an anion metathesis step, RTIL **11** is obtained.

These protic RTILs have been utilized in two different applications. The first is simply as a biorenewable alternative to conventional imidazole-derived RTILs for transition metal catalyzed reactions (Scheme 7). Thus, the Heck reaction was performed using RTIL **11** in combination with a simple homogeneous catalyst, palladium acetate.<sup>[22]</sup> Using these



Scheme 6. Fructose-derived ionic liquid synthesis.

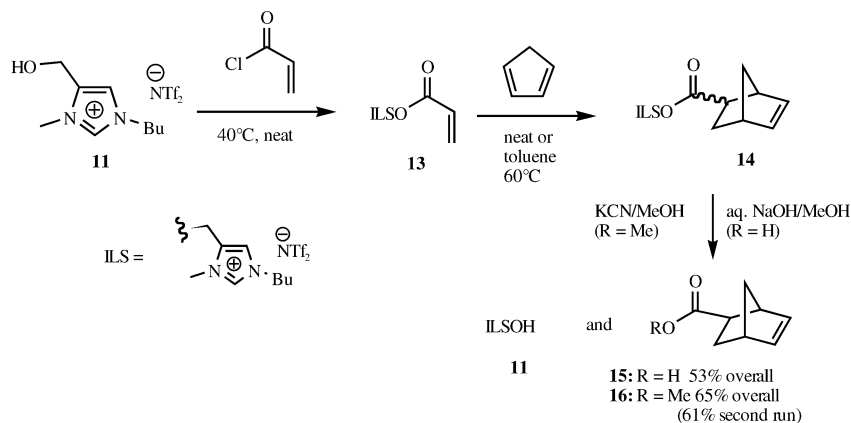


Scheme 7. Heck reactions in fructose-derived RTIL. [a] Recycling after washing RTIL/catalyst layer with water.

conditions, results quite comparable to those reported by Seddon and co-workers in [bmim] salts were obtained. The yields were uniformly >95%, with no side reactions being observed. Additionally, the solvent and catalyst could be recycled at least five times without any need for purification other than extraction of the cinnamate product with cyclohexane. By the fifth recycling, the medium had become relatively viscous (doubtless due to the build-up of triethylammonium iodide). Washing with water and drying in vacuo at 80 °C for five hours was sufficient to return the ionic liquid to its original state. This restored solvent/catalyst, could then be reused at least another three times.

The second application of RTIL **11** by Handy and co-workers has been as a support for homogeneous supported-phase synthesis. This type of alternative to heterogeneous, polystyrene-based supported combinatorial synthesis has been greatly popularized by Janda using polyethyleneglycol-based soluble polymers.<sup>[23]</sup> In the case of RTIL **11**, it serves as a low molecular weight support that still allows for facile product/by-product separation using either extraction or distillation.

In an initial application, RTIL **11** was acylated with acryloyl chloride (Scheme 8).<sup>[24]</sup> The acrylate product **13** was isolated



Scheme 8. Supported synthesis using fructose-derived RTIL.

by washing with saturated sodium bicarbonate to remove acidic by-products. After drying in vacuo, Diels–Alder reactions with acrylate **12** were performed, either neat or in the presence of a conventional solvent such as toluene. The Diels–Alder product **14** was isolated by simply evaporating the volatile components. Finally, the Diels–Alder adduct itself was obtained free of the support by either basic hydrolysis of the ester linkage or by potassium cyanide mediated transesterification with methanol. In either case, the organic product **15/16** was separated by extraction with cyclohexane and isolated in 53 to 65% overall yield from RTIL support **11**. Following extraction, RTIL **11** could be used in another acylation/Diels–Alder/hydrolysis reaction cycle, thereby demonstrating the ability of these materials to serve as recyclable supports. This recycling worked well when the potassium cyanide mediated transesterification was employed, but was more difficult in the case of basic hydrolysis. The RTIL support **11** that was recovered following basic hydrolysis was dark brown and not pure as determined by NMR. The impurities were likely the result of imidazolium carbene generation and reaction of this species with the other compounds present in the reaction medium.<sup>[25]</sup>

In summary, nature provides a vast new vista of opportunities for the preparation of new, recyclable, chiral, and/or functional RTIL solvents. The materials highlighted in this review are only the beginning of what promises to be an exciting new area of creative exploration as chemists design the next generation of “ideal” solvents.

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