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Are Ionic Liquids Suitable Media for Organocatalytic Reactions?

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Recent developments in organocatalysis have shown that these reactions can be advantageously performed in nonclassical media, such as ionic liquids or water. Among many organocatalysts, proline and its derivatives have attracted enormous attention, and these compounds have recently also been efficiently utilized in ionic liquids. Performing organocatalytic reactions in such media offer possibilities for easy catalyst recovery and reuse, on top of simplified product isolation.

Introduction

Investigation of greener alternatives to conventional organic solvents is an important part of today's drive towards sustainable chemistry.[1] Thanks to their useful and highly adjustable properties, ionic liquids belong among the most promising candidates. The usefulness of ionic liquids as replacement media in organic synthesis has been demonstrated in a great number of examples.[2] Furthermore, ionic liquids can be tailor-made for special purposes, and the resulting task-specific ionic liquids offer exciting opportunities for achieving desired properties or functions.[3] Many catalysts and reagents have been supported in the ionic liquid phase, resulting in enhanced reactivities and selectivities in numerous important transformations;[4] because of its versatility, special attention in immobilization and derivatization has been devoted to proline.[5] Among these functional solvents, acidic or protic ionic liquids have found a wide range of applications.[6] Ionic liquids incorporating a chiral cation or anion can induce interesting levels of stereoselectivity in a range of asymmetric reactions.[7] In many cases, ionic liquids with chiral centers and/or specific functional groups are prepared from renewable resources.[8]

Recent interest in catalysis with small organic molecules has led to the identification of numerous efficient transformations. These developments have been summed up in two books[9] and many reviews.[10] L-Proline and other amino-

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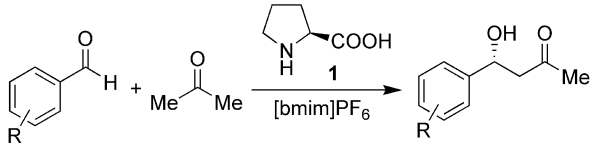
acid-derived organocatalysts or their analogues act through the formation of enamines[11] or iminium salts[12] with aldehydes or ketones. Chiral urea or thiourea derivatives, which act as hydrogen-bond catalysts[13] or chiral Brønsted acids, represent a special class of organocatalysts.[14]

The most frequently used solvents for organocatalytic reactions are DMSO, DMF, acetonitrile, chloroform, or alcohols. Water, seawater, or brine are also attractive, environmentally benign, reaction media for organocatalytic reactions.[15] Some organocatalytic reactions benefit from the presence of water, although this issue is not so clear.[16] There are also several reports of imidazolium-derived organocatalysts that have been used without solvent or in conventional media. This may seem counterintuitive at first sight, but because of the insolubility of this type of catalysts they can often be recycled.

This microreview aims to give information on possible applications of ionic liquids as reaction media for organocatalytic reactions and also to point out some unusual observations of usage of ionic liquids in such transformations.

Aldol Reactions

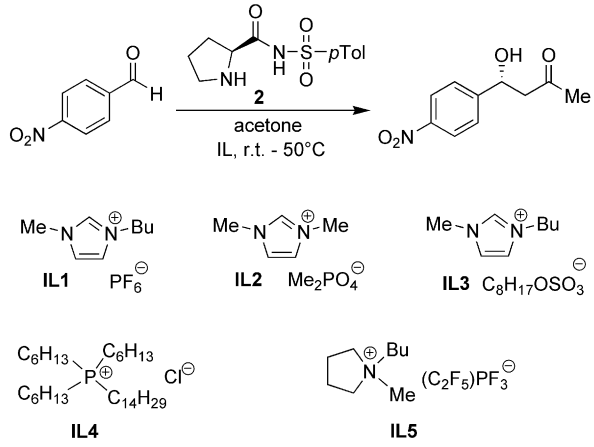
In 2000, a report by List, Lerner, and Barbas on L-proline-catalyzed aldol reactions sparked the current interest in reactions catalyzed by small organic molecules.[17] The first paper on usage of ionic liquids as solvents therefore also dealt with aldol reactions of different aromatic aldehydes with a range of ketones.[18] In the reaction depicted in Scheme 1, we found that the use of ionic liquids enabled the amount of L-proline (**1**) to be lowered from 30 mol-% to 5 mol-%, the product still being isolated in 89% yield and 74% *ee*.



Scheme 1. L-Proline-catalyzed aldol reactions between aromatic aldehydes and acetone in an IL.

With 4-(trifluoromethyl)benzaldehyde, the reaction medium containing the catalyst was reused three times with only a slight decrease in the enantioselectivity of the reaction (from 73 to 63% *ee*). This reaction also proceeded better in ionic liquid than in DMSO both with other aliphatic and with alicyclic ketones. Similar results were also described by Loh et al.,[19] although they used 30 mol-% of L-proline. The reaction between benzaldehyde and acetone in [bmim]PF_6 was run four times with one batch of L-proline. Yields and enantiomeric excesses of the aldol product remained almost unchained throughout the cycles (58–52%, 71–67% *ee*). Cordova[20] described auto-aldol reactions of aliphatic aldehydes in a DMSO/[bmim]PF_6 1:1.5 mixture as the solvent. In the presence of 5 mol-% of L-proline, the resulting aldol products were isolated in very good yields, with *dr* values of 4:1 and 99% *ee*. Liebscher et al.[21] used a guanidine-derived ionic liquid for the same reaction; under the best conditions (–25 °C, 20 mol-% of L-proline) the highest yield was 82% with 78% *ee*.

Prolinamides are also efficient catalysts for aldol reactions between aldehydes and ketones. Guo and coworkers[22] utilized an amide derived from (1*S*,2*S*)-2-amino-1,2-diphenylethan-1-ol for this reaction in ionic liquids. In [bmim]BF_4, both aromatic and aliphatic aldehydes afforded aldol products in good yields and with high enantioselectivities (91–99% *ee*). The catalytic system was recycled twice without loss of its efficiency. The aldol reaction of acetone with 4-nitrobenzaldehyde was also catalyzed well by the simpler Berkessel's catalyst – *N*-tolylsulfonyl-L-prolineamide (**2**).[23] Several ionic liquids were tested, and the best results were achieved in ionic liquids **IL1**, **IL3**, and **IL5** (up to 90% yields and 68% *ee*). Interestingly, no reaction was observed in **IL2** and **IL4** (Scheme 2).



Scheme 2. Aldol reactions between 4-nitrobenzaldehyde and acetone in various ILs catalyzed by *N*-toluenesulfonyl-L-proline amide.

Even though simple organocatalysts can be efficiently used in ionic liquids, catalyst recyclability is often limited because of its leaching. Attachment of an imidazolium moiety onto the organocatalyst was suggested as a possible improvement. Several pyrrolidine-derived catalysts were synthesized and tested as efficient and recoverable organocatalysts for direct asymmetric aldol reactions between aromatic aldehydes and aliphatic ketones. Lombardo et al.[24] described very good results in the aldol reaction between acetone and 4-nitrobenzaldehyde in the presence of L-proline derivative **3**, grafted with an imidazolium moiety (Figure 1). Reactions were carried out in [bmim]NTf_2 in the presence of 5 mol-% of the catalyst, and products were isolated in yields of up to 75% and 85% *ee* with TONs of 15. A similar catalyst had been used earlier for aldol reactions in conventional solvents such as acetone and dimethylsulfoxide.[25] In the same reaction, Gruttadauria et al.[26] used dimethylimidazolium-functionalized silica **4**, which served as a matrix for L-proline (Figure 1). Reactions were performed in excess acetone, but yields were lower than those obtained with simple L-proline in DMSO or [bmim]PF_6. On the other hand, this catalyst system was regenerated and repeatedly gave good yields of aldol products with high enantio-

selectivities over 13 cycles. In continuation of the theme of covalently modified silica, these authors also used a tripeptide catalyst (H-Pro-Pro-Asp-NH_2) instead of proline. This modification, however, resulted in less stable catalysts with diminishing conversions over consecutive runs.[27] Other amino acids, such as siloxyserine,[28] arginine, and lysine[29] have also recently been tested with good results as organocatalysts for direct aldol reactions in ionic liquids. Imidazolium-tagged organocatalysts can be used even in media other than ionic liquids, because of their insolubility in organic solvents or water. The catalysts **5** and **6** were easily recycled and reused in aldol reactions several times with only slight decreases in activity.[30]

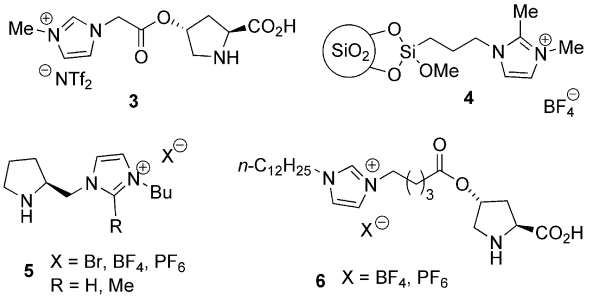
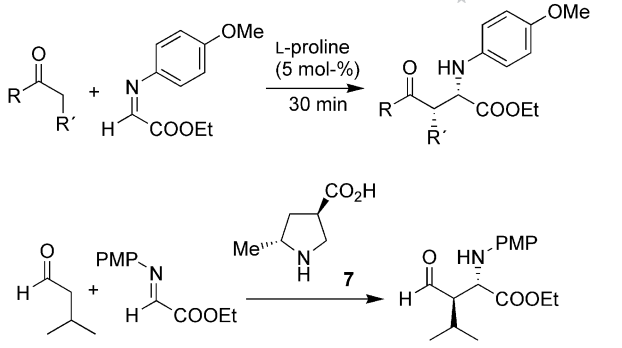


Figure 1. L-Proline derivatives immobilized on imidazolium and an ionic liquid immobilized on silica gel.

From the results presented above it can be concluded that the organocatalyzed aldol reaction has been thoroughly studied and that replacement of conventional solvents with ionic liquids results in better yields. Unmodified organocatalysts in ionic liquids can be used for three cycles with only slight decreases in activity. In some cases improvements have been achieved by attachment of an ionic moiety onto an organocatalyst.

Mannich Reaction

The Mannich reaction is a useful transformation affording many interesting aminocarbonyl compounds.[31] It is therefore often used as a benchmark organocatalytic reaction, but only a few papers have described this reaction in ionic liquids. Barbas et al.[32] found that Mannich reactions, in the presence of 5 mol-% of L-proline, were 4–50 times faster in [bmim]BF_4 than in organic solvents. It is of interest to note that both the diastereoselectivities and the enantioselectivities of the reactions were excellent (*dr* 19:1, 99% *ee*; Scheme 3). The catalyst in ionic liquid was used over four consecutive reaction cycles with only a slight decrease in yields and with constant enantioselectivity. The authors also noted a poor performance of hydroxyacetone in Mannich reactions in ionic liquids. In development of the anti-Mannich reaction, Tanaka and Barbas found that catalyst **7** was less active in ionic liquid than in other media.[33] In [bmim]BF_4 the product was isolated in 35% yield and 77% *ee*, in comparison with 85% and 99% *ee* in DMSO (Scheme 3).

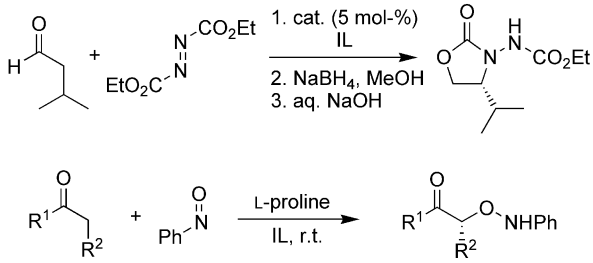


Scheme 3. Mannich reactions in ILs.

Recently, we also have found that ionic liquids are an excellent medium for Mannich reactions in the presence of modified Berkessel's catalyst.[34] In addition, three-component Mannich reactions, catalyzed by L-proline in amide ionic liquids, between isovaleraldehyde, acetone, and aromatic amines have been described. Yields of products and enantioselectivities were good to excellent (72–96%, 28–99% *ee*).[35]

α-Amination and Aminoxylation of Carbonyl Compounds

Expansion of the proline enamine activation concept to direct derivatization of carbonyl compounds with heteroatoms marked an important step forward in the development of organocatalytic methods. Addition of proline-formed enamines to diazadicarboxylates leads to α-amination of aldehydes (Scheme 4).[36] Ionic liquids also proved to be useful for this reaction.[37] Several catalysts have been tested, and again simple L-proline was found to be the best (65 min, 85%, 84% *ee*). L-Thiazolidine-4-carboxylic acid (**8**; Scheme 5, below) was even more enantioselective, but the reaction was considerably slower (8 h, 17%, 92% *ee*). Several ionic liquids were tested, but the best results were achieved in the simplest and cheapest: [bmim]BF_4 and [bmim]PF_6.



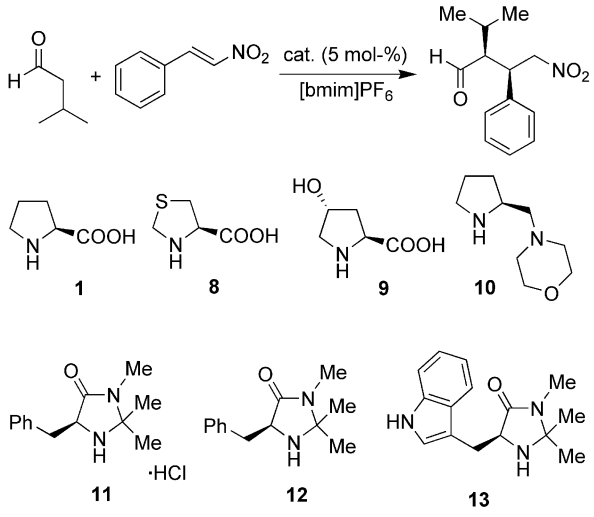
Scheme 4. Organocatalyzed α-amination and aminoxylation of carbonyl compounds in ILs.

The related proline-catalyzed additions to N=O bonds lead to valuable optically active α-hydroxyaldehydes and ketones. Huang and co-workers[38] described enantioselective aminoxylation of carbonyl compounds in ionic liquids (Scheme 4). They found that both aldehydes and ketones underwent this reaction and that yields of products were

higher in ILs ([bmim]BF_4, [bmim]PF_6) than in conventional solvents. Enantioselectivities were also excellent (95–99% *ee*). The same reaction with similar results has also been reported independently.[39] Ionic liquid containing L-proline was recycled four times without any decrease in yield and enantioselectivity.

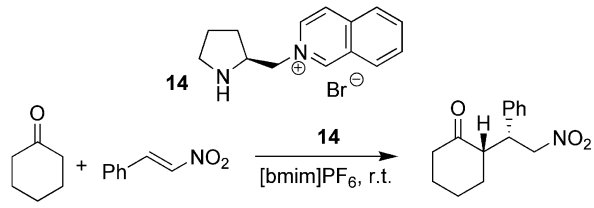
Michael Additions

Asymmetric 1,4-conjugate additions catalyzed by small organic molecules have also been a very active area of research in recent years.[40] Study of Michael additions in ionic liquids started with our work on Michael additions of aliphatic aldehydes and ketones to β-nitrostyrene (Scheme 5).[41] Of several ionic liquids tested, [bmim]laurate was the best (*dr* 25:1, 58% *ee*). The addition of isovaleraldehyde to β-nitrostyrene in [bmim]BF_4 afforded the product in 95% yield, but only with 43% *ee*. We evaluated several organocatalysts, and the most efficient were amino acids **1**, **8**, and **9** (at higher temperature). MacMillan's catalysts **11**–**13** were not active in this reaction.



Scheme 5. Michael addition of cyclohexanone to (*E*)-β-nitrostyrene.

Michael addition of cyclohexanone to β-nitrostyrene was also described by Xu et al.,[42] who used the functionalized ionic liquid **14** as catalyst and performed the reaction in several solvents (Scheme 6). The results are given in Table 1. In the ionic liquid the reaction proceeded with high yield (94%) and selectivity (*dr* 94:6, 99% *ee*) in the presence of only 5–10 mol-% of the catalyst, whereas in classical solvents catalyst loading had to be increased up to 20 mol-%. The reaction medium was recycled four times without any deleterious effect on yields and selectivity. The same reaction was also studied by Rasalkar et al., who employed simple L-proline as catalyst.[43] They observed high *syn* selectivity and enantioselectivities up to 75% *ee*. The catalytic system was used three times, with the yield remaining constant but the enantiomeric excess of the product decreasing.



Scheme 6. Organocatalyzed Michael addition of cyclohexanone to (*E*)-β-nitrostyrene.

Table 1. Results of Michael addition of cyclohexanone to (*E*)-β-nitrostyrene in various solvents.

Solvent	% Yield	*dr*	% *ee*
MeOH	94	92:8	0
CH_2Cl_2	94	92:8	59
THF	27	93:7	27
DMSO	37	91:9	24
–	91	90:10	63
[bmim]BF_4	94	94:6	99

Xu et al.[44] also used the immobilized L-proline derivative **15** (Figure 2) for the Michael addition of cyclohexanone to (*E*)-β-nitrostyrene. The reaction was performed in various solvents ([bmim]PF_6, DMSO, DMF, or *i*PrOH), but no significant differences were observed between them. The catalytic system in the ionic liquid was recycled three times with constant yields and selectivity, but the reaction times had to be prolonged from 24 to 100 h. Tsogoeva et al.[45] investigated the Michael addition of 2-nitropropane to cyclohex-2-enone catalyzed by several tripeptide organocatalysts, such as **16** (Figure 2). Interestingly, the addition in [bmim]PF_6 was slower than that in organic solvents such as $CHCl_3$, DMF, or DMSO.

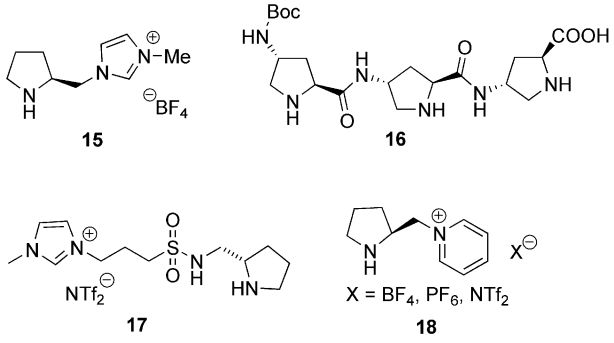


Figure 2. Organocatalysts for Michael additions.

Headley and co-workers described the pyrrolidine-based chiral ionic liquids **17** and **18** (Figure 2), which were used as recyclable and efficient organocatalysts for asymmetric Michael additions of carbonyl compounds to nitrostyrenes. The reactions proceeded with good yields and with high diastereoselectivities and enantioselectivities.[46]

We were interested in whether the Michael addition of 3-methylbutanal to (*E*)-β-nitrostyrene can also be catalyzed by *N*-tolylsulfonyl-L-prolineamide (**2**), and so we decided to test this reaction in several ionic liquids as reaction media.[47]

We were surprised by three interesting observations: a) no reaction was observed in ionic liquid **IL6** (Figure 3), with a substituted 2-position, b) addition of water (10 equiv.) was necessary to produce good yields in reasonable times, and c) the structure of the major diastereoisomer depended on the structure of the ionic liquid. All the ionic liquids used should, at least in principle, be neutral. We found, however, that the pH values of their 10% aqueous solutions range from 1.58 to 8.32. The acido-basic properties of the resulting solutions had a dramatic effect on the studied reaction. The results are summarized in Table 2.

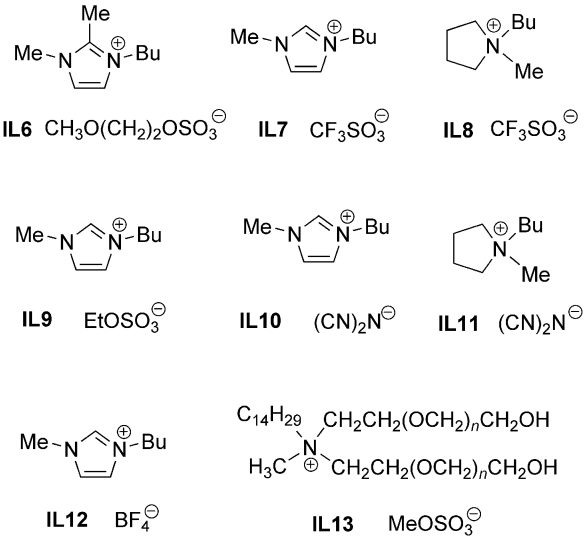
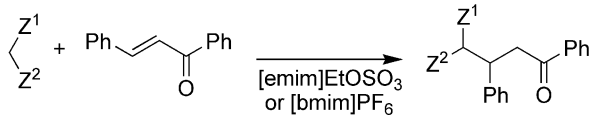


Figure 3. Structures of ionic liquids used for Michael additions of aldehydes to nitrostyrene.

Table 2. Michael addition of 3-methylbutanal to (*E*)-β-nitrostyrene catalyzed by **2**.

IL	pH of IL	% Yield	% *ee*
IL3	7.89	98	42 (+)
IL6	1.58	–	n.d.
IL7	2.58	68	18 (–)
IL8	3.09	38	30 (–)
IL9	4.33	83	42 (–)
IL10	7.09	98	28 (+)
IL11	7.09	89	20 (+)
IL12	8.32	98	70 (+)
IL13	7.01	95	28 (+)

The measured pH values of the IL solutions provided an explanation of why no reaction was observed in **IL6**. This ionic liquid is so acidic that the L-proline moiety is protonated, and no enamine of the aldehyde can be formed. The effect of pH on the stereochemical outcome of the reaction is intriguing, but we do not at present have any plausible explanation of why opposite enantiomers are formed in acidic and basic ionic liquids. The acidity of solutions is likely the result of partial anion hydrolysis or the presence of remaining acid. The fact that several aqueous solutions of ionic liquids were basic was, on the other hand, puzzling. The presence of residual amounts of *N*-methylimidazole from the preparation of ionic liquids had previously been suggested as a possible explanation, and so we set out to study the kinetics of *N*-methylimidazole-catalyzed addition of malonodinitrile to chalcone in different solvents[48] (Scheme 7).



Scheme 7.

During investigation of this reaction, we found that addition of malononitrile proceeded well even without addition of any basic catalyst (Table 3). The less reactive dimethyl malonate needed a catalyst, either L-proline or piperidine. However, L-proline likely acts only as a base, as no stereoselectivity was observed in this case. Piperidine was an even more efficient catalyst for this transformation in [emim]SO_4Et than in CH_2Cl_2, and a similar situation was also observed with the less acidic 2-nitropropane.[49]

Table 3. Michael addition of C-nucleophiles to chalcone.

Donor	Solvent	Catalyst	% Yield
Dimethyl malonate	[emim]OSO_3Et	L-proline	0
Dimethyl malonate	[emim]OSO_3Et	piperidine	59
Dimethyl malonate	CH_2Cl_2	L-proline	0
Dimethyl malonate	CH_2Cl_2	piperidine	0
2-Nitropropane	[bmim]PF_6	L-proline	31
2-Nitropropane	[bmim]PF_6	piperidine	90
2-Nitropropane	[emim]OSO_3Et	L-proline	25
2-Nitropropane	[emim]OSO_3Et	piperidine	95
2-Nitropropane	CH_2Cl_2	L-proline	0
2-Nitropropane	CH_2Cl_2	piperidine	0

The reaction medium has a profound effect on this transformation. Our study revealed that several ionic liquids contain, from their preparation, some quantities of unreacted *N*-methylimidazole, which can act as a basic catalyst (Table 4). We also showed that *N*-methylimidazole and piperidine are stronger bases in ionic liquids than in classical solvents. This is in agreement with results presented recently by D'Anna and co-workers.[50]

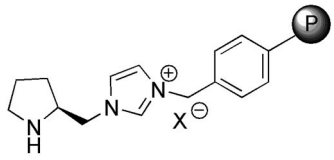
Table 4. Solvent effect on the reaction rate of the *N*-methylimidazole-catalyzed (5 mol-%) Michael addition of malonodinitrile to chalcone.

Solvent	K ($\times 10^{-4}$) [s^{-1}]	$t_{1/2}$ [s]
CH_2Cl_2	no reaction	–
CH_3CN	0.30	23105
THF	1.26	5501
[emim]SO_4Et	1.80	3851
[bmim]PF_6	1.70	4077
[bmim]PF_6[a]	18.9	366
[bmmim]PF_6	5.50	1260
[bmim]$N(CN)_2$	3.69	1879
[empyr]SO_4Et	0.61	11438
[empyr]SO_4Et[b]	0.26	27182

[a] 1 mol-% of piperidine was used as a catalyst. [b] 5 mol-% of pyridine was used as a catalyst.

Sulfur nucleophiles add well to various Michael acceptors, and several organocatalyzed reactions have been described.[51] We also attempted Michael additions of thiophenols to chalcone in several ionic liquids and found, to our surprise, that the additions proceeded very well, but without any stereoselectivity.[52]

Polymer-immobilized pyrrolidine-based chiral ionic liquids **19** (Figure 4) were found to be highly efficient catalysts for Michael additions of carbonyl compounds to nitrostyrenes under solvent-free conditions. The corresponding adducts were achieved in high yields (up to 97%) and diastereoselectivities (*syn*/*anti* up to 99:1), with excellent enantioselectivities (up to 99% *ee* for *syn* diastereoisomer).[53]



19 X = Cl, BF_4, PF_6

Figure 4. Polymer-anchored organocatalysts **19**.

The presented data suggest that the use of ionic liquids can have a positive influence on organocatalyzed Michael additions. However special features of the ionic liquids must be carefully considered.

Conclusions

In this short overview, we have shown that ionic liquids can be used as reaction media for organocatalyzed reactions, especially for reactions proceeding through enamine intermediates. The advantage of such experiments is that often smaller amounts of the catalyst can be used than in common organic solvents and that the reaction media can be recycled for several times. On the other hand, several reactions that run even worse in ionic liquids have also been described. There is also some danger with reactions that proceed through iminium ion intermediates, in which amine impurity in ionic liquid can act as a strong base and no stereoselectivity of the reaction under study can be observed. It is therefore advisable to measure the pH of an aqueous solution of the ionic liquid (if it is soluble in water) and to check the reaction in ionic liquid without the addition of organocatalyst. The non-innocent nature of ionic liquids in metal-catalyzed, especially Pd-catalyzed, reactions has already been demonstrated. Ease of carbene formation from imidazolium ionic liquids must be kept in mind; in organocatalysis, too, there is a growing number of *N*-heterocyclic carbene-catalyzed reactions.[54]

At present it is probably premature to answer the question posed in the title of this microreview. More studies will have to be performed to give unambiguous answers, but we believe that organocatalysis and ionic liquids can be a very useful combination.

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