DOI: 10.1002/anie.200703305

Ionic Liquids

"Nonsolvent" Applications of Ionic Liquids in Biotransformations and Organocatalysis

*Pablo Domínguez de María**

biocatalysis · biotransformations · enzyme catalysis · ionic liquids · organocatalysis

The application of room-temperature ionic liquids (RTILs) as (co)solvents and/or reagents is well documented. However, RTILS also have "nonsolvent" applications in biotransformations and organocatalysis. Examples are the anchoring of substrates to RTILs; ionic-liquid-coated enzymes (ILCE) and enzyme–IL colyophilization; the construction of biocatalytic ternary reaction systems; the combination of enzymes, RTILs, membranes, and (bio)electrochemistry; and ionic-liquid-supported organocatalysts. These strategies provide more robust, more efficient, and more enantioselective bio- and organocatalysts with many practical applications. As shown herein, RTILs offer a wide range of promising alternatives to conventional chemistry.

1. Background

During the last three years alone, more than 4000 publications on room-temperature ionic liquids (RTILs) appeared.[1] An overview of this field is also provided by a number of important articles, including a short history on the development of RTILs,[2] as well as several comprehensive reviews on different aspects of RTILs, such as their use as general (co)solvents for reactions and catalysis,[3] their use as chiral solvents[4] and reagents in synthesis (reactivity),[5] and their chemical properties.[6] Although RTILs are usually regarded as "green solvents", it is not yet absolutely clear whether all of these chemicals fall into this category, as many toxicological studies are still pending or debatable.[1,7] This aspect has also contributed to stimulate the synthesis of RTILs from biorenewable raw materials.[8]

The increasing interest in RTILs is derived from their special properties. In essence, RTILs are simply a composition of ions and remain liquid because the anions and cations do not pack well; thus, crystallization or solidification is prevented. Consequently, RTILs have low melting points and are liquids at a wide range of temperatures, a property which enables their use as solvents for many different chemical reactions.[3] Furthermore, they are nonflammable and have a negligible vapor pressure. Therefore, they do not evaporate and are easy to contain. This property facilitates the workup of products that can be distilled readily from the RTIL reaction medium. However, it can also be a drawback, as a simple distillation is sometimes not feasible in practice. In such cases, the separation of products from the RTIL is more problematic.

Another advantage of RTILs is their enormous diversity. They can be fine-tuned by changing the anion or cation to produce derivatives with different polarities and/or properties. The variability of the polarity of the RTIL enables the dissolution of many substrates, as well as certain gases, and leads to the concept of tailor-made solvents for a certain synthesis, that is, to the well-known and already widely used task-specific ionic liquids.[3c,f]

2. RTILs in Biotransformations

The use of enzymes and whole cells for catalysis in the chemical industry is of great interest, as environmentally friendly alternative syntheses are able, in many cases, to compete economically with well-established chemical processes.[9] Tailor-made enzymes and cells can be produced efficiently and cost effectively on a large scale for selected applications as "designer bugs".[9,10] The combination of these recombinant tailor-made biocatalysts with the appropriate solvents and/or type of reactor is key to the successful construction of a bioprocess.[9b] As many enzymes can catalyze reactions in organic solvents, there is much interest in the use of RTILs as (co)solvents to create novel reaction media for such biocatalytic processes.

[*] Dr. P. Domínguez de María
AkzoNobel BV
Chemicals Process and Product Technology Department (CPT)
Velperweg 76, P.O. Box 9300, 6800 SB Arnhem (The Netherlands)
Fax: (+31) 26-366-5871
E-mail: pablo.dominguez@akzonobel.com

The first combination of enzymes and ionic liquids was developed as early as in 1984[11] with the investigation of the enzymatic activity and stability of alkaline phosphatase in aqueous mixtures of $[EtNH_3][NO_3]$. In 2000, several reports on biotransformations in ionic liquids appeared within a few months: Erbeldinger et al. reported the first biotransformation in an ionic liquid with the synthesis of Z-aspartame in the presence of the protease thermolysin in $[BMIM][PF_6]$ (containing 5 vol% water; BMIM = 1-butyl-3-methylimidazolium).[12a] Lye and co-workers described the first whole-cell biotransformation in an ionic liquid,[12b] and Sheldon and co-workers disclosed the first biotransformation with a free enzyme in a water-free ionic-liquid system.[12c] Also in 2000, a patent on enzymatic reactions in ionic liquids was filed by Kragl et al.,[13] who used RTILs at a concentration of 25 vol% or higher as reaction media for enzymatic reactions. Since then, the use of ionic liquids as (co)solvents in biotransformations in combination with many enzymes, substrates, and processes has become an important topic of research. Examples include the use of lipases,[12c,14] proteases,[12,15] glycosidases,[16] epoxide hydrolases,[17] oxidoreductases,[18] hydroxynitrile lyases,[19] peroxidases,[20] and even whole cells.[12b,21] As the polarity of RTILs can also be modulated, they can be used as (co)solvents that are miscible with either water or organic solvents, or even in ternary systems (see Section 2.3). With the enzymes mentioned, RTILs were used as the only solvent, as a cosolvent, or in a biphasic medium. Some experiments even led to interesting combinations of RTILs with supercritical CO_2 and efficient methods of water removal (i.e., pervaporation), to enhance conversion in esterifications.[22] Several specific and extensive reviews deal with applications of RTILs in biotransformations.[3e,g,h,k,l,23]

It is not the aim of this Minireview to review this field again, but to pinpoint other applications of RTILs in biotransformations. Such applications are based on the improvement of enzyme stability or the enhancement of enantioselectivity and/or activity in organic solvents with RTILs as additives, as well as the combination of RTILs with different aspects of biochemical engineering, such as substrate anchoring, membranes, and electro(bio)chemistry.

Pablo Domínguez de María was born in Gran Canaria (Spain) in 1974. He studied pharmacy and chemistry in Madrid and completed his PhD in 2002 in the Faculty of Pharmacy at Complutense University in Madrid. After two years at Degussa AG (Germany) as a postdoctoral research scientist, he moved to AkzoNobel BV in Arnhem (The Netherlands) in 2005. His main scientific interests are industrially useful biocatalytic processes and new trends in white biotechnology and organocatalysis. In 2005, he was awarded the Young Scientist Prize by the Iberoamerican Academy of Pharmacy.

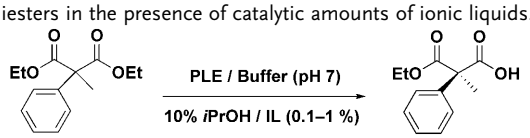
2.1. RTILs as Simple Additives in Biotransformations

During the last few decades, considerable effort has been devoted to the evaluation of possibilities for enzyme-based catalysis in non-aqueous media. In such environments, enzymes display lower activities than those observed under natural conditions. In an attempt to improve enzyme activity, strategies ranging from the biological modification of the protein to the tailoring of the reaction medium to a particular reaction have been applied with varying success. Among these methods, the addition of cosolvents and the concomitant use of excipients and salts during lyophilization processes are of particular interest with respect to RTILs,[24] as in some cases the addition of RTILs may have an analogous effect to that described for salt additives. Indeed, hydrophilic RTILs dissociate into the individual cations and anions when fully dissolved in water and thus act as an ion source to the system, rather than as an ionic-network structure.

The effects of salts on proteins in aqueous media can usually be correlated well by using the so-called Hofmeister series of ions.[25,26] Normally, the effects of ions on protein stability are attributed to the ability of the ion to modify the water structure and thus influence the hydration environment of the protein. Strongly hydrated ions, which increase the strength of the water-network structure, are called kosmotropes (from the Greek, "structure makers"), whereas those weakly hydrated ions that decrease the structure of water are called chaotropes ("structure breakers"). Other ions with intermediate properties are defined as borderline. On the basis of the Hofmeister series, Zhao and co-workers investigated the influence of RTILs as independent ions on enzymatic behavior.[27] They showed that when hydrophilic RTILs are used for enzymatic synthesis, a mixture of strong kosmotropic anions with chaotropic (or borderline) cations improves the catalytic performance of, for example, proteases. However, the mechanisms of enzyme catalysis and the role of the RTIL ions in these processes are still not fully understood. If one takes into account the enormous diversity of enzymes, substrates, and reactor systems that are commonly employed in biotransformations, as well as the number of (by-)products formed and interactions that occur, the systematization of the results is a highly attractive, but very challenging, task. This topic is currently under intense discussion.[23e,27,28]

Some RTILs were used successfully as additives (0.1–1%) in the desymmetrization of prochiral malonate diesters under the catalysis of pig liver esterase (PLE; Table 1).[29] The appropriate combination of a cosolvent (isopropanol, 10%) with a catalytic amount of certain RTILs (0.1–1%) led to a significant increase in the rate of the enzymatic reaction and in the enantioselectivity of PLE for the substrate. The results illustrate how the addition of small amounts of some ions can produce changes in enzyme activity and/or enantioselectivity. As RTILs can be adjusted precisely for desired applications, their application in these low concentrations (<1%) in biocatalysis is promising. PLE is a powerful biocatalyst that was cloned recently by Bornscheuer et al. and overexpressed efficiently in a bacterial host.[30a] This study opens up the possibility of applications of PLE in research fields in which

Table 1: PLE-catalyzed desymmetrization of 2,2-disubstituted malonic acid diesters in the presence of catalytic amounts of ionic liquids.[29,30b]



RTIL (0.1–1 %)	*t* [min]	Conversion [%]	*ee* [%]
only buffer	95	>90	78 (*R*)
isopropanol (10%) in buffer	200	>90	95 (*R*)
[quaternary ammonium][$CH_3SO_4^-$]	55	>90	97 (*R*)
[quaternary ammonium][Cl^-]	65	>90	97 (*R*)
[quaternary ammonium][$CH_3PO_4^-$]	95	>90	95 (*R*)
[imidazolium][Cl^-]	105	>90	92 (*R*)

coated enzyme could be reused several times.[32] Similar promising results were reported by Itoh et al., who used the same enzyme (the lipase from *Pseudomonas cepacia*) with [BDIM][cetyl-PEG-10-sulfate] as the coating agent (BDIM = 1-butyl-2,3-dimethylimidazolium, PEG = poly(ethyleneglycol)).[31c] In this case, after the ionic liquid had been mixed with the enzyme solution, a lyophilization was conducted. More recently, the same research group extended this strategy to other lipases (e.g. the lipase from *Candida rugosa*) and to other molecules and reactions.[31b] Selected examples of this concept are depicted in Table 2. Interestingly, in some cases, the use of an ILCE does not lead to improvements in enantioselectivity, but to the acceleration of the enzymatic reaction.[31b] This effect could be very useful for commercial applications. Some examples are shown in Scheme 1.

In an attempt to explain these unprecedented effects, Itoh et al. focused on MALDI-TOF mass spectrometric analysis of the ILCE derivatives.[31b] From these experiments, it became clear that the ionic-liquid coating agent binds to the enzyme and thus supplies the enzyme with a (more or less) flexible microenvironment for the reaction. Moreover, the substrate must also play a role, as, depending on the substrate, remarkable changes or no effects at all were observed. The ILCE strategy was applied recently to protect lipase B from *Candida antarctica* in reactions at high temperatures (95 °C), either in hexane or under solvent-free conditions. These coated derivatives were more stable that the free enzyme under these harsh reaction conditions;[33] therefore, better enzymatic activity was observed, as well as an improved

its use was previously not permitted because of its animal origin (e.g., in pharmaceuticals).[30b]

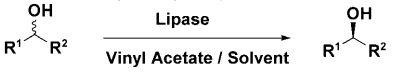
Analogous acceleration effects and/or improvements in enantioselectivity have been observed for other hydrolases. The enzymes were treated in RTILs prior to their use in hydrolysis, transesterification, or esterification reactions in aqueous or organic media.[31] The results of these investigations are discussed extensively in the following section, as they are related to the strategy of coating enzymes with ionic liquids.

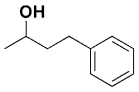
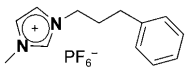
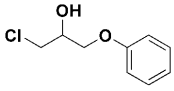
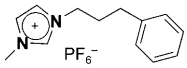
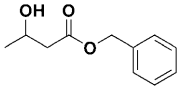
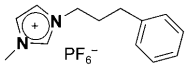
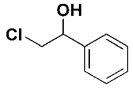
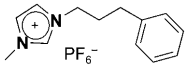
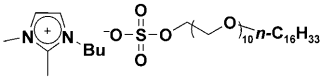
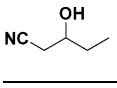
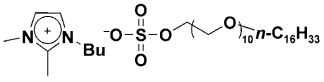
2.2. RTILs for Coating Enzymes: The ILCE Concept

In parallel to the strategy described in Section 2.1—the use of RTILS as additives—another interesting research field has emerged: Ionic liquids with melting points ranging from 50 to 100 °C are used to coat (and protect) enzymes with the formation of biocatalysts termed ionic-liquid-coated enzymes (ILCEs).[32] In the simpler form of this process, the ionic liquids are heated and melted; at a later stage, enzymes are aggregated and dispersed gently through this melted liquid. The mixture is subsequently cooled and cut into small pieces, which are the actual ILCE biocatalysts. These enzymatic derivatives display better catalytic activities, stabilities, and/or enantioselectivities.

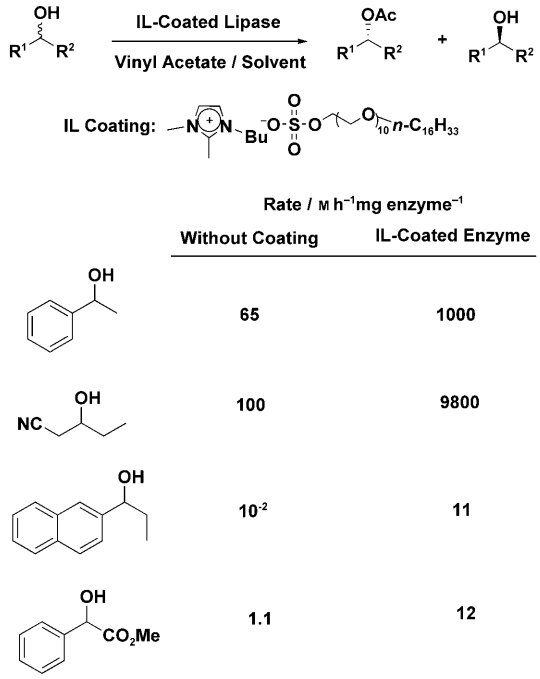
Lee and Kim reported the coating of a lipase from *Pseudomonas cepacia* with [PPMIM][PF_6] ([PPMIM] = 1-(3′-phenylpropyl)-3-methylimidazolium).[32] This ionic liquid melts at 53 °C and is therefore extremely useful for such coating purposes. The coated enzyme catalyzed the transesterification of vinyl acetate with different racemic secondary alcohols in toluene with markedly higher enantioselectivities than those observed for the free enzyme. Furthermore, the

Table 2: Kinetic resolution of chiral alcohols. Selected examples of changes in enzymatic enantioselectivity (*E*) upon the addition of the free (native) enzyme or the IL-coated enzyme.[a]



Substrate	IL coating agent	*E*	Ref.
		native: 265 coated: 532	[32a]
		native: 293 coated: 574	[32a]
		native: 107 coated: 156	[32a]
		native: 198 coated: 176	[32a]
		native: 17 coated: 96	[31c]
		native: 39 coated: 40	[31b]

[a] For further information and more examples, see references [31, 32].



Scheme 1. Selected examples of the improvement of enzymatic rates when enzymes are coated with RTILs.[31b]

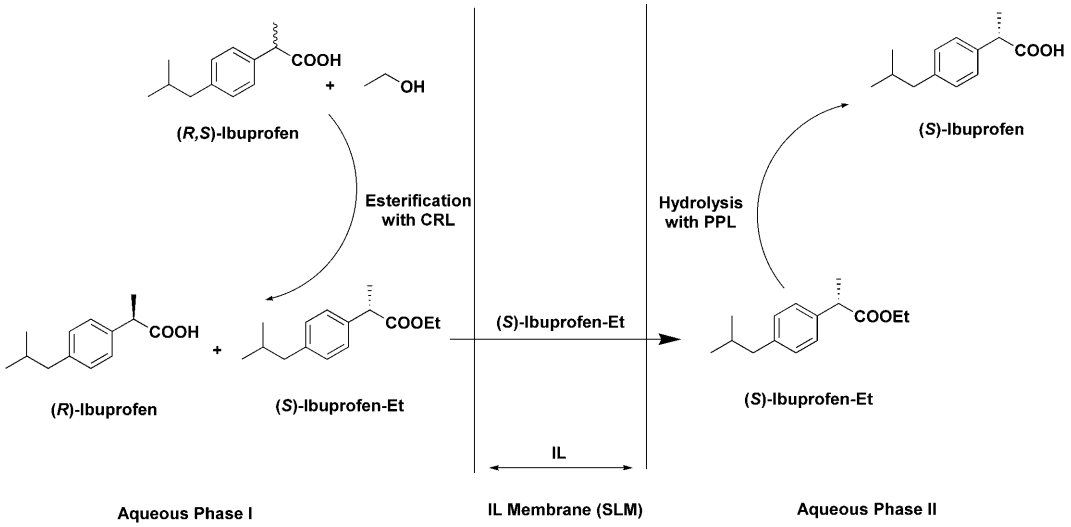
reusability of the biocatalyst. This stabilization was also observed when lipases were co-immobilized with ionic liquids in sol–gel derivatives,[34] and the strategy was used successfully with laccases as biocatalysts.[35]

The use of RTILs as stabilizing agents in biotransformations formed the starting point for studies on the colyophilization of enzymes with a combination of RTILs and poly(ethylene glycol) (PEG). In this way, better, more robust biocatalysts are generally produced.[36] This use of PEG as an additive in biotransformations is interesting, as PEG is well known for its enzyme-stabilizing properties, for example, the stabilization of PLE,[30c] in organic media.[24] However, much more research is needed to gain a full understanding of the causes of this stabilization, and for the development of innovative applications.

2.3. Combination of RTILs with Membranes and Biotransformations

For practical applications, such as hydrolytic reactions, enzymes dispersed in and/or coated with RTILs according to the strategies described in Section 2.2 were adsorbed subsequently onto ceramic membranes. However, the results have only been moderately successful so far, presumably because of transfer limitations of substrates/products of this specific system, as a result of the polarity of the RTILs employed.[37] The idea is interesting from a practical point of view; therefore, there will probably be more examples in this field in future with different types of RTILs.

Another approach is based on two other analogous concepts: supported-ionic-liquid phases (SILPs) and supported-ionic-liquid membranes (SLMs).[38] In these systems, RTILs act as a separative phase of two additional phases. The RTIL phase can separate two aqueous phases, two non-aqueous phases, or an aqueous phase from a non-aqueous phase. In some cases, these RTILs are confined between two membranes. This strategy, which was used for the combination of two enzymes, namely two lipases, and three different phases, is very interesting from a biocatalytic viewpoint. The resulting compartmentalization of the reaction media avoids the formation of by-products and/or facilitates the recovery of the products in the workup. For example, the process was used successfully for kinetic resolutions with hydrolases to furnish (*S*)-ibuprofen (Scheme 2).[39] In aqueous phase I, the lipase from *Candida rugosa* catalyzes the enantioselective esterification of racemic (*R*,*S*)-ibuprofen, a reaction that has been reported widely in the literature.[40] The ester diffuses selectively over the IL membrane system and is further



Scheme 2. Supported-ionic-liquid membrane for the enzyme-catalyzed resolution of (*R*,*S*)-ibuprofen. Aqueous phase I is composed of 65% (v/v) ethanol in a buffer (pH 6.3) and the substrate (10 mM). Aqueous phase II is composed entirely of the buffer (pH 6.3).[39]

hydrolyzed in aqueous phase II by porcine pancreas lipase (PPL; Scheme 2). This strategy is extremely useful, as membranes and RTILs can be tuned for many practical applications.

Another attractive field of research is the combination of enzymes and RTILs with electrochemistry, as RTILs show a relatively wide potential window of electrochemical stability and ionic conductivity. Interesting examples with horseradish peroxidase (HRP) have been described.[20c,41] For example, the ILCE concept (see Section 2.2) has been combined successfully with the co-immobilization of RTILs and HRP in sol–gel materials.[41b,c] As stated previously, analogous co-immobilization methods have also been employed for other enzymes, such as lipases.[34] Furthermore, an ionic liquid supported on a nafion membrane was used to entrap HRP effectively.[41a]

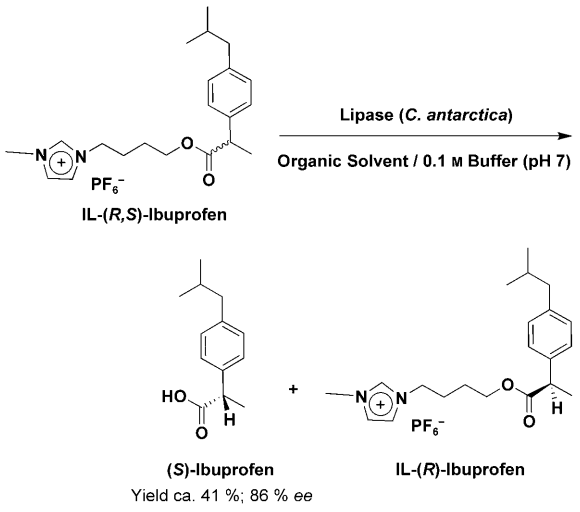
2.4. Substrate–RTIL Anchoring in Biotransformations

The anchoring of supporting molecules to RTILs is known in organic synthesis as ionic-liquid-phase organic synthesis (IoLiPOS; see also Section 3).[42] The anchoring of RTILs to substrates may be an attractive alternative for synthetic purposes, as it may facilitate the workup and purification of products, as well as the recovery of nontransformed substrates. Recently, the kinetic resolution of (*R*,*S*)-ibuprofen catalyzed by the lipase from *Candida antarctica* was carried out by first anchoring this substrate to the ionic liquid [BMIM][PF_6] to form IL ibuprofen esters. Even under nonoptimized conditions, high yields and enantioselectivities were observed (Scheme 3).[43]

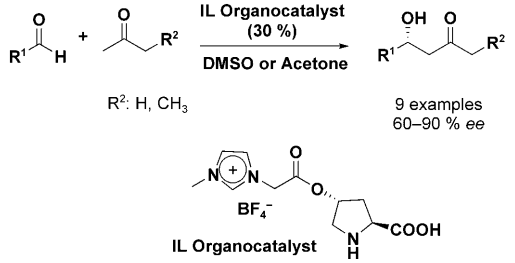
3. RTILs in Organocatalysis

Asymmetric organocatalysis enables many chemical transformations to be carried out, usually under mild reaction conditions. A broad range of practical applications have already been developed. For example, the use of proline and derivatives as (organo)catalysts for aldol condensations results in a very elegant and effective route to a plethora of important chiral building blocks.[44] The use of RTILs as (co)solvents for organocatalytic reactions is also well known, and some interesting reactions have been developed (although the solubility of organocatalysts and/or substrates in RTILs is not always satisfactory). Such reactions include useful organocatalytic aldol condensations, Mannich reactions, and α aminoxylation reactions.[3a,45] The versatility of RTILs and the huge number of synthetic alternatives offered by organocatalysis should lead to the development of new innovative strategies in the near future.

Gruttadauria et al. described a ternary combination of silica gel, an anchored monolayer of an ionic liquid, and proline for aldol condensations under heterogeneous organocatalytic conditions. Under these conditions, the catalyst could be reused for several cycles without significant loss of activity or enantioselectivity.[46] Another interesting strategy is attachment of the organocatalyst to the RTIL to form an IL-supported organocatalyst. This approach is connected with the concept of task-specific ionic liquids (TSILs),[3c,f] which are also known as "functional ionic liquids" (FILs). In this case, attractive properties of RTILs can be combined with asymmetric organocatalysis to provide powerful systems for synthetic applications. For example, Miao and Chan described the use of IL esters of (2*S*,4*R*)-4-hydroxyproline to catalyze direct asymmetric aldol condensations. These reactions were comparable in terms of yields and enantioselectivities to those carried out without the implementation of the IL anchoring system (Scheme 4), but had the advantage that the IL organocatalyst could be recovered readily and reused.[47]



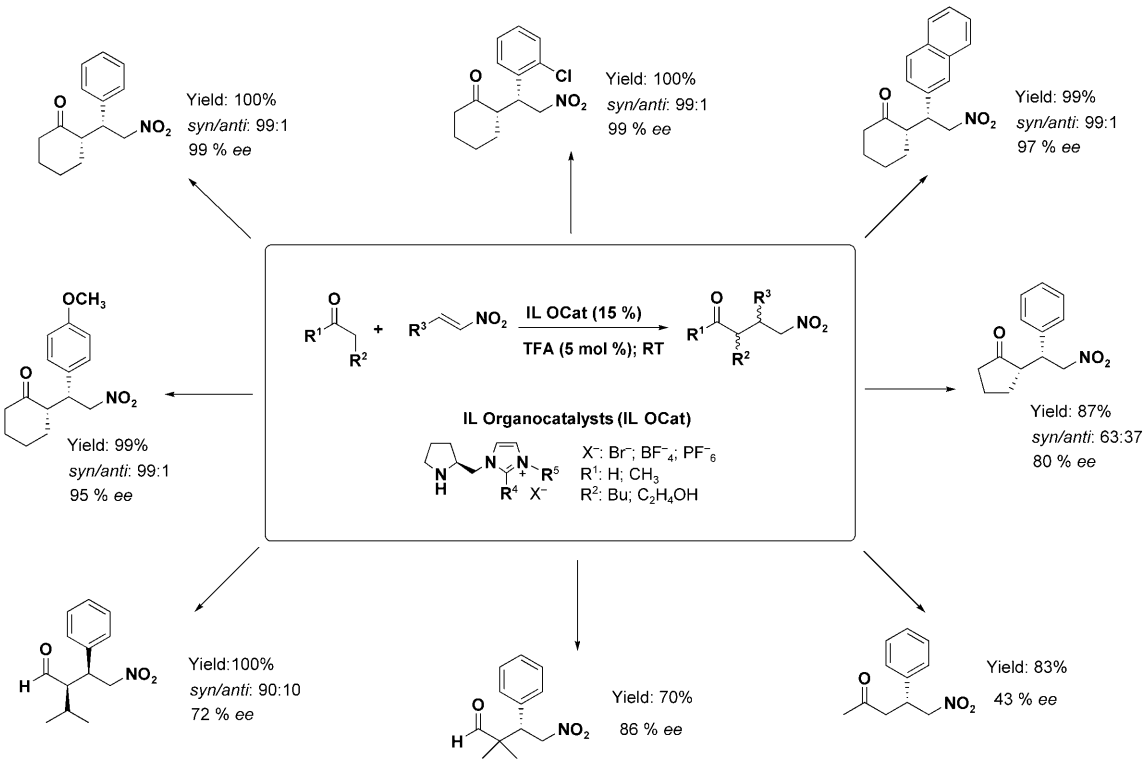
Scheme 3. Reaction with RTIL-anchored substrates: Lipase-catalyzed chiral resolution of an IL derivative of (*R*,*S*)-ibuprofen to yield the enantiomerically pure drug.[43]



Scheme 4. Combination of an FIL with a proline derivative, as reported by Miao and Chan. DMSO = dimethyl sulfoxide.[47]

The organocatalytic asymmetric Michael addition of ketones and different nitroalkenes on the basis of an analogous concept has also been described in detail.[48] In this particular case, fine-tuning of the ionic liquid by careful selection of the cation and anion led to higher enantioselectivity. The effects of such changes need to be investigated in more detail. Selected examples are depicted in Scheme 5.

In a variant of these asymmetric organocatalytic Michael addition reactions, IL organocatalysts have been used with large aliphatic anions (such as sodium dodecyl sulfate (SDS)) as the counterion for the organocatalyst. This interesting strategy enables organocatalysis under aqueous conditions, whereby the IL organocatalyst plays a double role: as the

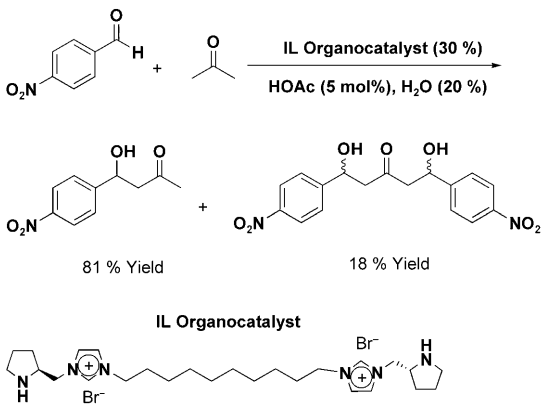


Scheme 5. Selected recent examples of the asymmetric Michael addition of ketones to nitroalkenes in the presence of an IL organocatalyst. More examples and further synthetic details can be found in reference [48]. TFA = trifluoroacetic acid.

catalyst and as a dissolving agent for substrates and products in water.[49]

The combination of RTILs with organocatalysis also led to interesting results for aldol condensations. For example, significant amounts of the bisaldol product were formed when *p*-nitrobenzaldehyde was treated with acetone in the presence of certain IL organocatalysts in a mixture of water and acetic acid (Scheme 6).[50]

The careful tuning of synthetic conditions and the selection of the right IL organocatalyst enabled efficient Claisen–Schmidt reactions to be conducted under solvent-free conditions.[51] The reaction affords in high yields a huge number of useful α,β-unsaturated ketones, which are valuable



Scheme 6. Bisaldol condensation between *p*-nitrobenzaldehyde and acetone in the presence of a tailor-made IL organocatalyst. More examples and further information can be found in reference [50].

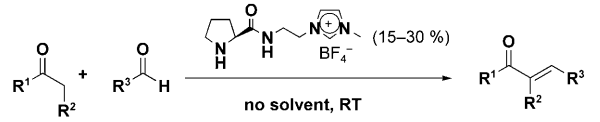
synthetic building blocks. Once again, the proper combination of organocatalyst and RTIL enables the recovery and reuse of the IL organocatalyst. Selected examples are depicted in Table 3.

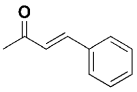
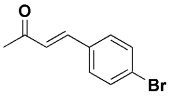
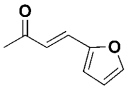
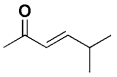
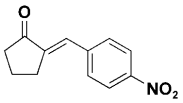
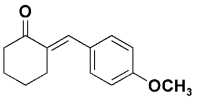
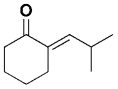
This IL-organocatalyst concept has also been employed in Baylis–Hillman and Morita–Baylis–Hillman reactions with quinuclidine derivatives conveniently anchored to RTILs as organocatalysts (Scheme 7). The reactions proceeded efficiently under solvent-free conditions, and the organocatalyst could be recovered and reused. In this case, the RTIL acts as a cocatalyst by providing the right protic environment for good conversion.[52]

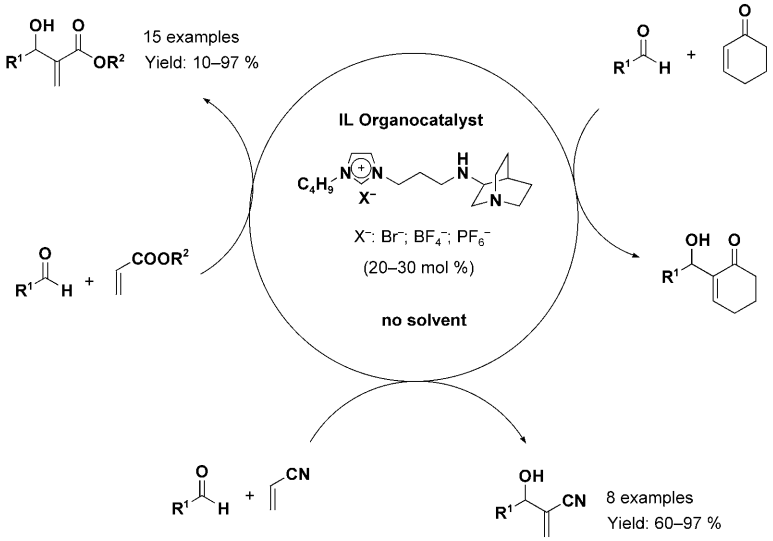
4. Outlook

RTILs are useful not only—as often described in the literature—as (co)solvents for bio- and organocatalysis. RTILs can be used in combination with enzymatic and organocatalytic systems in a range of further applications. The use of RTILs can lead to a better understanding of many chemical and enzymatic processes. However, it is impossible to know whether, in the future, RTILs will be a "good solution" or remain a "good solution waiting for a problem". An increase in fundamental research in this field can be expected in the coming years, and the increased use of RTILs will probably lead to a decrease in their price. Of course, from an industrial point of view, the most cost-effective and most competitive variant of a certain application will always become established.

Table 3: Examples of the IL organocatalytic Claisen–Schmidt reaction under solvent-free conditions.[51]



Product	*t* [h]	Yield [%]
	36	81
	36	88
	36	78
	24	86
	16	96
	24	87
	16	92



Scheme 7. Baylis–Hillman and Morita–Baylis–Hillman reactions catalyzed by IL organocatalysts (derivatives of quinuclidine) under solvent-free conditions.[52]

Addendum

Since the submission of this Minireview, several interesting publications have appeared: Lourenço and Afonso reported a further example of substrate anchoring and biocatalysis (see Section 2.4),[53] and Aprile et al. described novel organocatalysts immobilized on silica for aldol condensations (see Section 3).[54] Fukaya et al. described novel bioionic liquids (see Section 1).[55]

I thank Gerrald Bargeman, Boris Kuzmanovic, Ab van der Meer, and Robert W. van Gemert for many fruitful and inspiring scientific discussions.

Received: July 23, 2007
Addendum: October 9, 2007
Published online: July 24, 2008

[1] D. R. MacFarlane, K. R. Seddon, *Aust. J. Chem.* **2007**, *60*, 3–5.
[2] J. S. Wilkes, *Green Chem.* **2002**, *4*, 73–80.
[3] a) V. I. Parvulescu, C. Hardacre, *Chem. Rev.* **2007**, *107*, 2615–2665; b) J. Durand, E. Teuma, M. Gómez, *C. R. Chim.* **2007**, *10*, 152–177; c) Z. Conrad Zhang, *Adv. Catal.* **2006**, *49*, 153–237; d) S. Lee, *Chem. Commun.* **2006**, 1049–1063; e) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267–278; f) N. Jain, A. Kumar, S. Chauban, S. M. S. Chauban, *Tetrahedron* **2005**, *61*, 1015–1060; g) J. H. Davis, Jr., *Chem. Lett.* **2004**, *33*, 1072–1077; h) C. E. Song, *Chem. Commun.* **2004**, 1033–1043; i) S. V. Dzyuba, R. A. Bartsch, *Angew. Chem.* **2003**, *115*, 158–160; *Angew. Chem. Int. Ed.* **2003**, *42*, 148–150; j) P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, **2003**; k) J. Dupont, R. F. de Souza, P. A. Z. Suarez, *Chem. Rev.* **2002**, *102*, 3667–3692; l) H. Zhao, S. V. Malhotra, *Aldrichimica Acta* **2002**, *35*, 75–83; m) R. A. Sheldon, *Chem. Commun.* **2001**, 2399–2407; n) C. M. Gordon, *Appl. Catal. A* **2001**, *222*, 101–117; o) J. F. Brennecke, E. J. Maginn, *AIChE J.* **2001**, *47*, 2384–2389; p) P. Wasserscheid, W. Keim, *Angew. Chem.* **2000**, *112*, 3926–3945; *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789; q) M. J. Earle, K. R. Seddon, *Pure Appl. Chem.* **2000**, *72*, 1391–1398; r) T. Welton, *Chem. Rev.* **1999**, *99*, 2071–2084.
[4] C. Baudequin, D. Brégeon, J. Levillain, F. Guillen, J. C. Plaquevent, A. C. Gaumont, *Tetrahedron: Asymmetry* **2005**, *16*, 3921–3945.
[5] S. Chowdhury, R. S. Mohan, J. L. Scott, *Tetrahedron* **2007**, *63*, 2363–2389.
[6] For recent studies and reviews, see: a) P. A. Hunt, I. R. Gould, B. Kirchner, *Aust. J. Chem.* **2007**, *60*, 9–14; b) E. I. Izgorodina, M. Forsyth, D. R. MacFarlane, *Aust. J. Chem.* **2007**, *60*, 15–20; c) J. S. Wilkes, *J. Mol. Catal. A* **2004**, *214*, 11–17; d) J. Dupont, *J. Braz. Chem. Soc.* **2004**, *15*, 341–350; e) J. L. Anderson, J. Ding, T. Welton, D. W. Armstrong, *J. Am. Chem. Soc.* **2002**, *124*, 14247–14254; f) J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker, R. D. Rogers, *Green Chem.* **2001**, *3*, 156–164.
[7] a) A. S. Wells, V. T. Coombe, *Org. Process Res. Dev.* **2006**, *10*, 794–798; b) P. J. Scammells, J. L. Scott, R. D. Singer, *Aust. J. Chem.* **2005**, *58*, 155–169; c) F. Stock, J. Hoffmann, J. Ranke, R. Störmann, B. Ondruschka, B. Jastorff, *Green Chem.* **2004**, *6*, 286–290; d) B. Jarstoff, R. Störmann, J. Ranke, K. Möllter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nüchter, B. Ondruschka, J. Filser, *Green Chem.* **2003**, *5*, 136–142.
[8] a) Y. Fukaya, Y. Iizuka, K. Sekikawa, H. Ohno, *Green Chem.* **2007**, *9*, 1155–1157; b) J. Ranke, S. Stolte, R. Störmann, J.

Arning, B. Jastorff, *Chem. Rev.* **2007**, *107*, 2183 – 2206; c) S. T. Handy, *Chem. Eur. J.* **2003**, *9*, 2938 – 2944.

[9] See, for example: a) A. M. Thayer, *Chem. Eng. News* **2006**, *84*, 15 – 31; b) A. Liese, K. Seelbach, C. Wandrey, *Industrial Biotransformations*, Wiley-VCH, Weinheim, **2006**; c) H. E. Schoemaker, D. Mink, M. G. Wubbolts, *Science* **2003**, *299*, 1694 – 1697.

[10] For selected reviews and examples, see: a) E. Gabor, K. Liebeton, F. Niehaus, J. Eck, P. Lorentz, *Biotechnol. J.* **2007**, *2*, 201 – 206; b) H. Gröger, F. Chamouleau, N. Orologas, C. Rollmann, K. H. Drauz, W. Hummel, A. Weckbecker, O. May, *Angew. Chem.* **2006**, *118*, 5806 – 5809; *Angew. Chem. Int. Ed.* **2006**, *45*, 5677 – 5681; c) P. Lorenz, J. Eck, *Nat. Rev. Microbiol.* **2005**, *3*, 510 – 516; d) M. T. Reetz, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5716 – 5722.

[11] D. K. Magnuson, J. W. Bodley, D. F. Evans, *J. Solution Chem.* **1984**, *13*, 583 – 587.

[12] a) M. Erbeldinger, A. J. Mesiano, A. J. Russel, *Biotechnol. Prog.* **2000**, *16*, 1129 – 1131; b) S. G. Cull, J. D. Holbrey, V. Vargas-Mora, K. R. Seddon, G. J. Lye, *Biotechnol. Bioeng.* **2000**, *69*, 227 – 233; c) R. Madeira Lau, F. van Rantwijk, K. R. Seddon, R. A. Sheldon, *Org. Lett.* **2000**, *2*, 26, 4189 – 4191.

[13] U. Kragl, N. Kaftzik, S. Schofer, P. Wasserscheid, US2004/0096932A1, **2004**.

[14] For selected recent examples (since 2006) and classic studies on the use of lipases and RTILs, see: a) J. T. Gorke, K. Okrasa, A. Louwagie, R. J. Kazlauskas, F. Srienc, *J. Biotechnol.* **2007**, *132*, 306 – 313; b) S. Ha, M. N. Lan, S. H. Lee, S. M. Hwang, Y. M. Koo, *Enzyme Microb. Technol.* **2007**, *41*, 480 – 483; c) T. Raab, R. Bel-Rhlid, G. Williamson, C. E. Hansen, D. Chaillot, *J. Mol. Catal. B* **2007**, *44*, 60 – 65; d) S. Shah, M. Gupta, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 921 – 924; e) B. K. Liu, N. Wang, Z. C. Chen, Q. Wu, X. F. Lin, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3769 – 3771; f) Z. Guo, X. Xu, *Green Chem.* **2006**, *8*, 54 – 62; g) Y. Tsukada, K. Iwamoto, H. Furutani, Y. Matsushita, Y. Abe, K. Matsumoto, K. Mondo, S. Hayase, M. Kawatsura, T. Itoh, *Tetrahedron Lett.* **2006**, *47*, 1801 – 1804; h) C. Pilissão, M. G. Nascimento, *Tetrahedron: Asymmetry* **2006**, *17*, 428 – 433; i) M. H. Katsoura, A. C. Polydera, L. Tsironis, A. D. Tselepis, H. Stamatis, *J. Biotechnol.* **2006**, *123*, 491 – 503; j) F. Ganske, U. T. Bornscheuer, *Org. Lett.* **2005**, *7*, 3097 – 3098; k) S. Park, R. J. Kazlauskas, *J. Org. Chem.* **2001**, *66*, 8395 – 8401; l) K. W. Kim, B. Song, M. Y. Choi, M. J. Kim, *Org. Lett.* **2001**, *3*, 1507 – 1509.

[15] a) H. Zhao, L. Jackson, Z. Song, O. Olubajo, *Tetrahedron: Asymmetry* **2006**, *17*, 2491 – 2498; b) H. Zhao, L. Jackson, Z. Song, O. Olubajo, *Tetrahedron: Asymmetry* **2006**, *17*, 1549 – 1553; c) W. Lou, M. Zong, H. Wu, *Biotechnol. Appl. Biochem.* **2005**, *41*, 151 – 156; d) Y. Y. Liu, W. Y. Lou, M. H. Zong, R. Xu, X. Hong, H. Wu, *Biocatal. Biotransform.* **2005**, *23*, 89 – 95; e) W. Y. Lou, M. H. Zong, H. Wu, *Biocatal. Biotransform.* **2004**, *22*, 171 – 176.

[16] a) M. Lang, T. Kamrat, B. Nidetzky, *Biotechnol. Bioeng.* **2006**, *95*, 1093 – 1100; b) N. Kaftzik, P. Wasserscheid, U. Kragl, *Org. Process Res. Dev.* **2002**, *6*, 553 – 557.

[17] C. Chiappe, E. Leandri, S. Lucchesi, D. Pieraccini, B. D. Hammock, C. Morisseau, *J. Mol. Catal. B* **2004**, *27*, 243 – 248.

[18] a) S. Lutz-Wahl, E. M. Trost, B. Wagner, A. Manns, L. Fischer, *J. Biotechnol.* **2006**, *124*, 163 – 171; b) M. Eckstein, M. Villela Filho, A. Liese, U. Kragl, *Chem. Commun.* **2004**, 1084 – 1085.

[19] R. P. Gaisberger, M. H. Fechter, H. Griengl, *Tetrahedron: Asymmetry* **2004**, *15*, 2959 – 2963.

[20] a) D. Das, A. Dasgupta, P. K. Das, *Tetrahedron Lett.* **2007**, *48*, 5635 – 5639; b) A. Kumar, N. Jain, S. M. S. Chauban, *Synlett* **2007**, 411 – 414; c) S. Sgalla, G. Fabrizi, S. Cacchi, A. Macone, A. Bonamore, A. Boffi, *J. Mol. Catal. B* **2007**, *44*, 144 – 148; d) H. Chen, Y. Wang, Y. Liu, Y. Wang, L. Qi, S. Dong, *Electrochem. Commun.* **2007**, *9*, 469 – 474; e) M. F. Machado, J. M. Saraiva, *Biotechnol. Lett.* **2005**, *27*, 1233 – 1239; f) K. Okrasa, E. Guibe-Jampel, M. Therisod, *Tetrahedron: Asymmetry* **2003**, *14*, 2487 – 2490.

[21] a) H. Pfruender, R. Jones, D. Weuster-Botz, *J. Biotechnol.* **2006**, *124*, 182 – 190; b) W. Y. Lou, M. H. Zong, T. J. Smith, *Green Chem.* **2006**, *8*, 147 – 155; c) A. Lenourry, J. M. Gardiner, G. Stephens, *Biotechnol. Lett.* **2005**, *27*, 161 – 165; d) H. Pfründer, M. Amidjojo, U. Kragl, D. Weuster-Botz, *Angew. Chem.* **2004**, *116*, 4629 – 4631; *Angew. Chem. Int. Ed.* **2004**, *43*, 4529 – 4531; e) J. Howarth, P. James, J. Dai, *Tetrahedron Lett.* **2001**, *42*, 7517 – 7519.

[22] a) P. Lozano, T. de Diego, T. Sauer, M. Vaultier, S. Gmouh, J. L. Iborra, *J. Supercrit. Fluids* **2007**, *40*, 93 – 100; b) R. Irimescu, K. Kato, *Tetrahedron Lett.* **2004**, *45*, 523 – 525; c) L. Gubicza, N. Nemestóthy, T. Fráter, K. Bélafi-Bakó, *Green Chem.* **2003**, *5*, 236 – 239; d) P. Lozano, T. de Diego, D. Carrié, M. Vaultier, J. L. Iborra, *Chem. Commun.* **2002**, 692 – 693; e) M. T. Reetz, W. Wiesenhöfer, G. Franció, W. Leitner, *Chem. Commun.* **2002**, 992 – 993; f) K. Bélafi-Bakó, N. Dörmö, O. Ulbert, L. Gubicza, *Desalination* **2002**, *149*, 267 – 268.

[23] a) S. Cantone, U. Hanefeld, A. Basso, *Green Chem.* **2007**, *9*, 954 – 971; b) F. van Rantwijk, R. A. Sheldon, *Chem. Rev.* **2007**, *107*, 2757 – 2785; c) Z. Yang, W. Pan, *Enzyme Microb. Technol.* **2005**, *37*, 19 – 25; d) P. Lozano, T. de Diego, S. Gmouh, M. Vaultier, J. L. Iborra, *Biotechnol. Prog.* **2004**, *20*, 661 – 669; e) S. Park, R. J. Kazlauskas, *Curr. Opin. Biotechnol.* **2003**, *14*, 432 – 437; f) F. van Rantwijk, R. Madeira Lau, R. A. Sheldon, *Trends Biotechnol.* **2003**, *21*, 131 – 138; g) R. A. Sheldon, R. Madeira Lau, M. J. Sorgedrager, F. van Rantwijk, K. R. Seddon, *Green Chem.* **2002**, *4*, 147 – 151; h) U. Kragl, M. Eckstein, N. Kaftzik, *Curr. Opin. Biotechnol.* **2002**, *13*, 565 – 571.

[24] a) J. C. Wu, S. S. Lee, M. M. B. Mahmood, Y. Chow, M. M. R. Talukder, W. J. Choi, *J. Mol. Catal. B* **2007**, *45*, 108 – 112; b) E. P. Hudson, R. K. Eppler, D. S. Clark, *Curr. Opin. Biotechnol.* **2005**, *16*, 637 – 643; c) M. N. Gupta, I. Roy, *Eur. J. Biochem.* **2004**, *271*, 2575 – 2583; d) F. Secundo, G. Carrea, *Chem. Eur. J.* **2003**, *9*, 3194 – 3199; e) M. Persson, E. Wehtje, P. Adlercreutz, *ChemBioChem* **2002**, *3*, 566 – 571; f) M. Y. Lee, J. S. Dordick, *Curr. Opin. Biotechnol.* **2002**, *13*, 376 – 384.

[25] a) W. Kunz, J. Henle, B. W. Ninham, *Curr. Opin. Colloid Interface Sci.* **2004**, *9*, 19 – 37; b) F. Hofmeister, *Arch. Exp. Pathol. Pharmakol.* **1888**, *24*, 247 – 260.

[26] a) K. D. Collins, *Methods* **2004**, *34*, 300 – 311; b) R. L. Baldwin, *Biophys. J.* **1996**, *71*, 2056 – 2063.

[27] a) H. Zhao, S. Campbell, J. Solomon, Z. Y. Song, O. Olubajo, *Chin. J. Chem.* **2006**, *24*, 580 – 584; b) H. Zhao, O. Olubajo, Z. Song, A. L. Sims, T. E. Person, R. A. Lawal, L. A. Holley, *Bioorg. Chem.* **2006**, *34*, 15 – 25; c) H. Zhao, S. M. Campbell, L. Jackson, Z. Song, O. Olubajo, *Tetrahedron: Asymmetry* **2006**, *17*, 377 – 383; d) H. Zhao, *J. Chem. Technol. Biotechnol.* **2006**, *81*, 877 – 891; e) H. Zhao, *J. Mol. Catal. B* **2005**, *37*, 16 – 25.

[28] For examples of the influence of RTILs on enzyme stability, see: a) D. Sate, M. Janssen, G. Stephens, R. A. Sheldon, K. R. Seddon, J. R. Lu, *Green Chem.* **2007**, *9*, 859 – 867; b) S. Shah, M. N. Gupta, *Biochim. Biophys. Acta* **2007**, *1770*, 94 – 98; c) A. Ruiz Toral, A. P. de Los Ríos, F. J. Hernández, M. H. A. Janssen, R. Schoevaart, F. van Rantwijk, R. A. Sheldon, *Enzyme Microb. Technol.* **2007**, *40*, 1095 – 1099; d) O. Ulbert, K. Belafi-Bako, K. Tonova, L. Gubicza, *Biocatal. Biotransform.* **2005**, *23*, 177 – 183; e) P. Lozano, T. De Diego, S. Gmouh, M. Vaultier, J. L. Iborra, *Biocatal. Biotransform.* **2005**, *23*, 169 – 176; f) T. De Diego, P. Lozano, S. Gmouh, M. Vaultier, J. L. Iborra, *Biomacromolecules* **2005**, *6*, 1457 – 1464; g) R. Madeira Lau, M. J. Sorgedrager, G. Carrea, F. Van Rantwijk, F. Secundo, R. A. Sheldon, *Green Chem.* **2004**, *6*, 483 – 487; h) T. De Diego, P. Lozano, S. Gmouh, M. Vaultier, J. L. Iborra, *Biotechnol. Bioeng.* **2004**, *88*, 916 – 924;

i) S. N. Baker, M. McCleskey, S. Pandey, G. A. Baker, *Chem. Commun.* **2004**, 940 – 941; j) J. L. Klaar, A. M. Jesionowski, J. A. Berberich, R. Moulton, A. J. Russell, *J. Am. Chem. Soc.* **2003**, *125*, 4125 – 4131.

[29] a) S. Wallert, J. I. Grayson, K. H. Drauz, H. Gröger, C. Bolm, P. Domínguez de María, F. Chamouleau, WO 2006/005409A1., **2006**; b) S. Wallert, K. H. Drauz, J. I. Grayson, H. Gröger, P. Domínguez de María, C. Bolm, *Green Chem.* **2005**, *7*, 602 – 605.

[30] a) D. Böttcher, E. Brüsehaber, K. Doderer, U. T. Bornscheuer, *Appl. Microbiol. Biotechnol.* **2007**, *73*, 1282 – 1289; b) for a recent review on synthetic applications of PLE, see: P. Domínguez de María, C. A. García-Burgos, G. Bargeman, R. W. van Gemert, *Synthesis* **2007**, 1439 – 1452.

[31] a) D. T. Dang, S. H. Ha, S. M. Lee, W. J. Chang, Y. M. Koo, *J. Mol. Catal. B* **2007**, *45*, 118 – 121; b) T. Itoh, Y. Matsushita, Y. Abe, S. Han, S. Wada, S. Hayase, M. Kawatsura, S. Takai, M. Morimoto, Y. Hirose, *Chem. Eur. J.* **2006**, *12*, 9228 – 9237; c) T. Itoh, S. Han, Y. Matsushita, S. Hayase, *Green Chem.* **2004**, *6*, 437 – 439.

[32] a) J. K. Lee, M. J. Kim, *J. Org. Chem.* **2002**, *67*, 6845 – 6847; b) M. J. Kim, J. K. Lee, WO 03/057871A1, **2003**.

[33] a) P. Lozano, R. Piamtongkam, K. Kohns, T. De Diego, M. Vaultier, J. L. Iborra, *Green Chem.* **2007**, *9*, 780 – 784; b) P. Lozano, T. De Diego, T. Sauer, M. Vaultier, S. Gmouh, J. L. Iborra, *J. Supercrit. Fluids* **2007**, *40*, 93 – 100.

[34] S. H. Lee, T. T. Doan, S. H. Ha, Y. M. Koo, *J. Mol. Catal. B* **2007**, *45*, 57 – 61.

[35] M. B. Turner, S. K. Spear, J. D. Holbrey, R. D. Rogers, *Biomacromolecules* **2004**, *5*, 1379 – 1384.

[36] a) K. Nakashima, J. Okada, T. Maruyama, N. Kamiya, M. Goto, *Sci. Technol. Adv. Mater.* **2006**, *7*, 692 – 698; b) K. Nakashima, T. Maruyama, N. Kamiya, M. Goto, *Chem. Commun.* **2005**, 4297 – 4299; c) T. Maruyama, H. Yamamura, T. Kotani, N. Kamiya, M. Goto, *Org. Biomol. Chem.* **2004**, *2*, 1239 – 1244; d) T. Maruyama, S. Nagasawa, M. Goto, *Biotechnol. Lett.* **2002**, *24*, 1341 – 1345.

[37] M. Mori, R. Gómez García, M. P. Belleville, D. Paolucci-Jeanjean, J. Sánchez, P. Lozano, M. Vaultier, G. Ríos, *Catal. Today* **2005**, *104*, 313 – 317.

[38] See, for example: a) C. P. Mehnert, *Chem. Eur. J.* **2005**, *11*, 50 – 56; b) M. H. Valkenberg, C. de Castro, W. F. Hoelderich, *Green Chem.* **2002**, *4*, 88 – 93; c) L. C. Branco, J. G. Crespo, C. A. M. Afonso, *Angew. Chem.* **2002**, *114*, 2895 – 2897; *Angew. Chem. Int. Ed.* **2002**, *41*, 2771 – 2773.

[39] a) E. Miyako, T. Maruyama, N. Kamiya, M. Goto, *Chem. Commun.* **2003**, 2926 – 2927; b) E. Miyako, T. Maruyama, N. Kamiya, M. Goto, *Biotechnol. Lett.* **2003**, *25*, 805 – 808; c) E. Miyako, T. Maruyama, N. Kamiya, M. Goto, *J. Biosci. Bioeng.* **2003**, *96*, 370 – 374.

[40] a) P. Domínguez de María, A. R. Alcántara, J. D. Carballeira, R. M. de La Casa, C. A. García-Burgos, M. J. Hernáiz, J. M. Sánchez-Montero, J. V. Sinisterra, *Curr. Org. Chem.* **2006**, *10*, 1053 – 1066; b) P. Domínguez de María, J. M. Sánchez-Montero, J. V. Sinisterra, A. R. Alcántara, *Biotechnol. Adv.* **2006**, *24*, 180 – 196.

[41] a) Y. Liu, L. Shi, M. Wang, Z. Li, H. Liu, J. Li, *Green Chem.* **2005**, *7*, 655 – 658; b) Y. Liu, M. Wang, J. Li, Z. Li, P. He, H. Liu, J. Li, *Chem. Commun.* **2005**, 1778 – 1780; c) F. Zhao, X. Wu, M. Wang, Y. Liu, L. Gao, S. Dong, *Anal. Chem.* **2004**, *76*, 4960 – 4967.

[42] See, for example: a) S. T. Handy, M. Okello, *J. Org. Chem.* **2005**, *70*, 2874 – 2877; b) H. Hakkou, J. J. Eynde, J. Hamelin, J. P. Bazureau, *Synthesis* **2004**, 1793 – 1798; c) W. Miao, T. H. Chan, *Org. Lett.* **2003**, *5*, 5003 – 5005.

[43] P. U. Naik, S. J. Nara, J. R. Harjani, M. M. Salunkhe, *J. Mol. Catal. B* **2007**, *44*, 93 – 98.

[44] For reviews, books, and important studies on organocatalysis, see: a) G. Guillena, D. J. Ramon, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693 – 700; b) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365; c) M. J. Gaunt, C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8 – 27; d) D. Enders, M. R. Huettl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861 – 863; e) G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, *17*, 1465 – 1492; f) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042 – 8046; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876 – 7880; g) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719 – 724; h) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; i) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248 – 5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138 – 5175; j) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401 – 3430; k) B. List, *Tetrahedron* **2002**, *58*, 5573 – 5590; l) H. Gröger, *Chem. Eur. J.* **2001**, *7*, 5246 – 5251; m) H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 545 – 548; *Angew. Chem. Int. Ed.* **2001**, *40*, 529 – 532; n) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260 – 5267; o) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395 – 2396.

[45] See, for example: a) M. Meciarova, S. Toma, A. Berkessel, B. Koch, *Lett. Org. Chem.* **2006**, *3*, 437 – 441; b) K. Huang, Z. Z. Huang, X. L. Li, *J. Org. Chem.* **2006**, *71*, 8320 – 8323; c) H. M. Guo, H. Y. Niu, M. X. Xue, Q. X. Guo, L. F. Cun, A. Q. Mi, Y. Jiang, J. J. Wang, *Green Chem.* **2006**, *8*, 682 – 684; d) H. M. Guo, L. F. Cun, L. Z. Gong, A. Q. Mi, Y. Z. Jiang, *Chem. Commun.* **2005**, 1450 – 1452; e) M. Rasalkar, M. K. Potdar, S. Mohile, M. M. Salunkhe, *J. Mol. Catal. A* **2005**, *235*, 267 – 270; f) P. Kotrusz, S. Alemayehu, S. Toma, H. G. Schmalz, A. Adler, *Eur. J. Org. Chem.* **2005**, 4904 – 4911; g) A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 3949 – 3952; h) R. Dere, R. Pal, P. Patil, M. Salunkhe, *Tetrahedron Lett.* **2003**, *44*, 5351 – 5353; i) N. S. Chowdari, D. B. Ramachary, C. F. Barbas III, *Synlett* **2003**, 1906 – 1909; j) T. Kitazume, Z. Jiang, K. Kasai, Y. Mihara, M. Suzuki, *J. Fluorine Chem.* **2003**, *121*, 205 – 212; k) P. Kotrusz, I. Kmentova, B. Gotov, S. Toma, E. Solcaniova, *Chem. Commun.* **2002**, 2510 – 2511; l) T. Loh, L. C. Feng, H. Y. Yang, J. Y. Yang, *Tetrahedron Lett.* **2002**, *43*, 8741 – 8743.

[46] M. Gruttadauria, S. Riela, C. Aprile, P. Lo Meo, F. D'Anna, R. Noto, *Adv. Synth. Catal.* **2006**, *348*, 82 – 92.

[47] W. Miao, T. H. Chan, *Adv. Synth. Catal.* **2006**, *348*, 1711 – 1718.

[48] a) B. Ni, Q. Zhang, A. D. Headley, *Green Chem.* **2007**, *9*, 737 – 739; b) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J. P. Cheng, *Angew. Chem.* **2006**, *118*, 3165 – 3169; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093 – 3097.

[49] a) S. Luo, X. Mi, S. Liu, H. Xu, J. P. Cheng, *Chem. Commun.* **2006**, 3687 – 3689; b) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281 – 8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103 – 8104.

[50] S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J. P. Cheng, *Tetrahedron* **2007**, *63*, 1923 – 1930.

[51] S. D. Yang, L. Y. Wu, Z. Y. Yan, Z. L. Pan, Y. M. Liang, *J. Mol. Catal. A* **2007**, *268*, 107 – 111.

[52] a) X. Mi, S. Luo, H. Xu, L. Zhang, J. P. Chen, *Tetrahedron* **2006**, *62*, 2537 – 2544; b) X. Mi, S. Luo, J. P. Cheng, *J. Org. Chem.* **2005**, *70*, 2338 – 2341.

[53] N. M. T. Lourenço, C. A. M. Afonso, *Angew. Chem.* **2007**, *119*, 8326 – 8329; *Angew. Chem. Int. Ed.* **2007**, *46*, 8178 – 8181.

[54] C. Aprile, F. Giacalone, M. Gruttadauria, A. Mossuto Marculescu, R. Noto, J. D. Revell, H. Wennemers, *Green Chem.* **2007**, *9*, 1328 – 1334.

[55] Y. Fukaya, Y. Iizuka, K. Sekikawa, H. Ohno *Green Chem.* **2007**, *9*, 1155 – 1157.

