Catalysts **2013**, *3*, 709-725; doi:10.3390/catal3030709

OPEN ACCESS

catalysts

ISSN 2073-4344

www.mdpi.com/journal/catalysts

Review

Ionic Liquid Immobilized Organocatalysts for Asymmetric Reactions in Aqueous Media

Yupu Qiao and Allan D. Headley *

Department of Chemistry, Texas A&M University-Commerce, Commerce, TX 75429-3011, USA; E-Mail: yupu.qiao@tamuc.edu

* Author to whom correspondence should be addressed; E-Mail: allan.headley@tamuc.edu; Tel.: +1-903-468-8106; Fax: +1-903-468-6020.

Received: 1 July 2013; in revised form: 6 August 2013 / Accepted: 23 August 2013 / Published: 11 September 2013

Abstract: Ionic liquids are organic salts with melting points typically below ambient or reaction temperature. The unique combination of physical properties of ionic liquids, such as lack of measurable vapor pressure, high thermal and chemical stability, make them ideal to be used as reusable homogenous support for catalysts. In addition, the solubility of ionic liquids in various reaction media can be controlled and easily fine-tuned by modification of the structures of their cations and anions. As a result, ionic liquid immobilized organocatalysts are very effective in aqueous media and can be separated easily from organic solvents, as well as aqueous phases by simply adjusting the polarity of the media. Ionic liquid immobilized organocatalysts are not only very versatile compounds that are effective catalysts for a wide spectrum of reactions, but are also environmentally friendly and recyclable organocatalysts. Herein, we provide a summary of the past decade in the area of asymmetric catalysis in aqueous media for a wide variety of reactions in which ionic liquid and related ammonium salt immobilized organocatalysts are used.

Keywords: ionic liquids; organocatalysis; water; asymmetric reaction

---

1. Introduction and Background

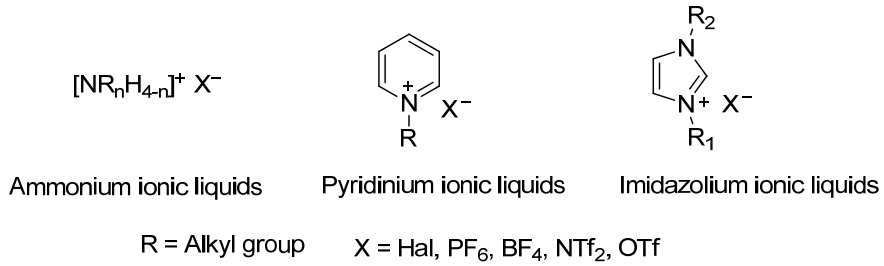
Recently, organocatalysis has emerged as the third pillar of asymmetric catalysis together with transition-metal and biocatalysis [1–8]. Compared with transition-metal catalysts, the cost and toxicity of organocatalysts are low, thus making organocatalysts beneficial for the production of

pharmaceutical intermediates. Moreover, organocatalysts are tolerant of water and air, and are usually easy to use. These properties have propelled the explosive development of various organocatalysts for a wide variety of fundamental transformations [9,10]. Nevertheless, a major challenge faced in the use of organocatalysts is low efficiency as a result of high catalyst loading; usually 10–20 mol% is required in order to complete transformations in reasonable timescales. More important, for organocatalyzed processes typically carried out in organic solvents, it is difficult to separate the catalyst for recycling. In order to address these limitations, the design and synthesis of efficient, easily recoverable and reusable catalysts are active research areas.

Over the past decades, research in the field of ionic liquid (IL) chemistry has grown phenomenally with the promise of green chemistry, environmental and technological benefits [11–16], examples of the main types of ionic liquids are shown in Figure 1. In 1914, Paul Walden reported the first synthesis of room-temperature ionic liquid ethylammonium nitrate [17]. It took over 60 years for the field of ionic liquid to bloom to where it is today. Interest in ionic liquids started with the discovery of a new class of ionic liquids based on alkyl-substituted imidazolium and pyridinium cations, with halide or tetrahalogenoaluminate anions. Since then, there have been numerous applications of ionic liquids, especially as the electrolytes for batteries [18,19]. Ionic liquids are most simply defined as organic salts with melting points below some arbitrary temperature, such as 100 °C, and are thermally stable over a wide temperature range. In particular, some ionic liquids can maintain their liquid state at temperatures as high as 200 °C [20,21]. As a result, ionic liquids have been employed in a wide variety of reactions as environmentally benign solvents, suitable for a range of organic reactions [11,12,22–26]. Besides, ionic liquids are non-flammable, lack measurable vapor pressure, and have high thermal and chemical stabilities; hence they are perfect solvents for polar compounds [27–30]. Another attractive property of ILs is their enormous diversity. By modifying the structures of their cations or anions, the properties of ionic liquids can be fine-tuned readily so that they can easily be separated from an organic phase, as well as aqueous media.

One of the recent prominent achievements in this field is the use of ionic liquids as homogeneous immobilization of organocatalysts in organic synthesis [31,32]. When ionic liquid immobilized catalysts are used to induce organic reactions, such reactions are usually carried out in polar solvents, which can form a homogeneous system. After the reaction is complete, a less polar solvent, such as diethyl ether, is added and the IL immobilized catalyst can be easily separated from the organic phase due to solubility differences. As a result, the IL immobilized catalyst is regenerated and can be used for further reactions.

Figure 1. The three main types of ionic liquids (IL).



Water is known to be the cheapest, environmentally benign, safe and most abundant compound on the earth's surface; and it has attracted a great deal of attention from a green chemistry perspective [33–43]. In addition, water also holds some unique physical and chemical properties, such as high surface tension, hydrogen bonding capability, high dielectric constant and high cohesive energy density [44–46]. In nature, both type I and type II aldolases catalyze the direct aldol reaction in an aqueous environment [47]. From the mechanism of enzyme catalysis, type I aldolases utilizes a lysine residue to form an iminium ion with a carbonyl group of the substrate, followed by enamine formation to realize the stereocontrol. Type II aldolases are metal ion dependent enzymes in which Zn^{2+} ions are used as essential cofactors to achieve stereocontrol. As a result, a mimic of class I aldolase catalysis in aqueous environment will give new inspiration to organic chemists. Water, however, is not typically recognized as a suitable solvent for organic reactions, because it has the potential to deteriorate catalytic activity and stereocontrol since it has the ability to disrupt hydrogen bonds and other polar interactions among catalysts and substrate molecules [45]. Hence, unique opportunities and challenges exist for the design and development of novel catalytic systems for asymmetric reactions in aqueous environments. Meanwhile, from a green chemistry and sustainable development perspective, it would be advantageous if high enantiocontrol is achieved by using recyclable organocatalysts in water. In this review, we present recent exciting progress in ionic liquid and related ammonium salt immobilized organocatalysis in aqueous media.

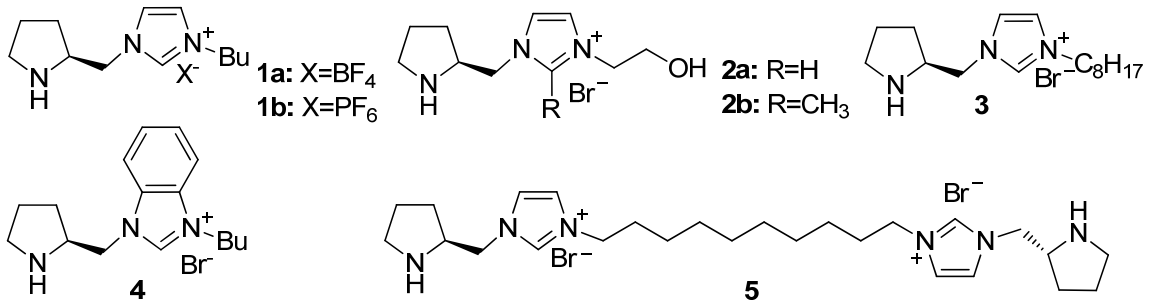
2. Ionic Liquids Immobilized Asymmetric Organocatalysis in Aqueous Media

2.1. Imidazolium Immobilized Organocatalysts

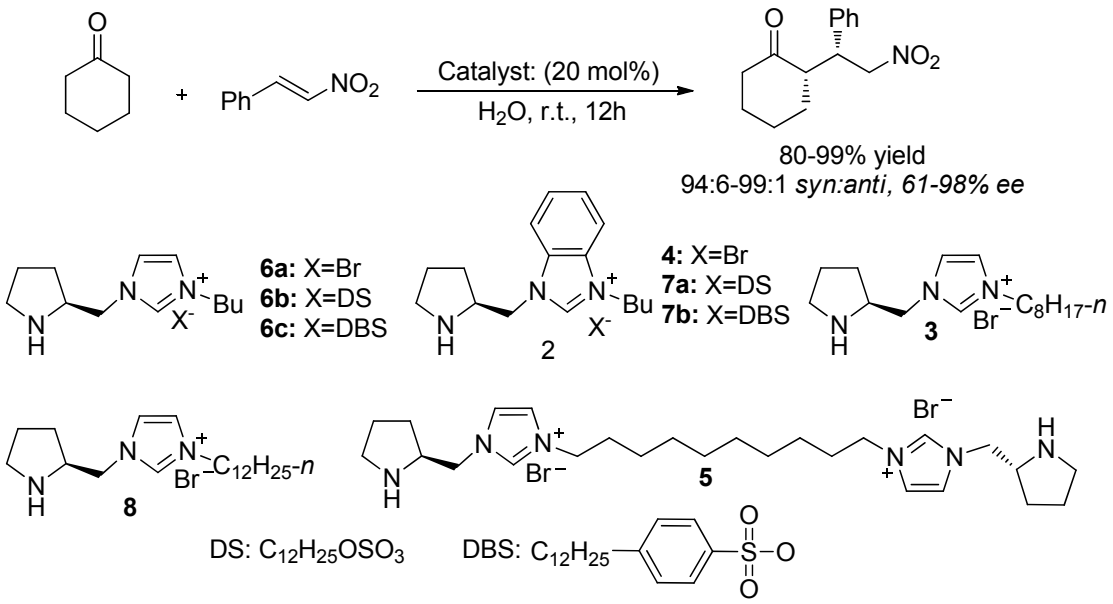
In 2006, Luo and Cheng group reported the design and synthesis of a series of the pyrrolidine-type ILs **1a**–**5** from the "chiral pool" using L-proline as a starting material [48]. The direct aldol reactions of acylic and cylic ketones with aromatic aldehydes were examined using IL **1a** (Figure 2), high yields (up to 99%) with poor diastereoselectivities and modest enantioselectivities were obtained using this catalyst, with acetic acid and water as additives [49]. Due to the lack of directing hydrogen bonds and electrostatic interactions between the participating aldehyde and the enamine intermediate, the selectivities were very poor. The hydrogen bonding with proline is believed to stabilize the transition state [50–52]. The recyclability of IL immobilized catalyst **1a** was also examined by using cyclopentenone as donor for the aldol reaction; the catalyst could be easily recovered and reused up to six times with only a slight decrease in activity. Nevertheless, the *syn*/*anti* selectivity was observed to decrease from 4.8:1 to 2.1:1 and the enantioselectivity of the major diastereomer was found to be lower (5–11% *ee*) than the minor diastereomer (26–37% *ee*). Shown in Scheme 1 are other immobilized pyrrolidine catalysts.

In 2007, the same group reported the surfactant-type IL immobilized organocatalyzed asymmetric Michael reactions of nitrostyrene in pure water [53]. These catalysts **3**–**8** can be easily synthesized by exchange of the anion with a surfactant sulfonate anion by anion metathesis or neutralization. Catalyst **7b** was found to be the optimal catalyst, affording the desired product in 93% yield, 97:3 *syn/anti* and 97% *ee*. Under aqueous conditions, catalyst **3**, **6c** and **8** with long alkyl chains on the imidazolium cations gave poor yields owing to the polymerization of nitrostyrene (Scheme 1).

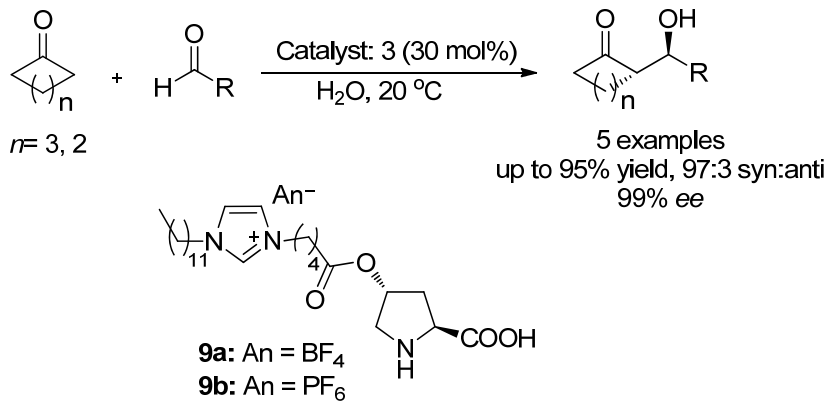
Figure 2. Ionic liquid (IL) immobilized pyrroline-type catalysts.



Scheme 1. Surfactant-type IL immobilized organocatalysts for asymmetric Michael reaction.



Scheme 2. Asymmetric aldol reaction catalyzed by IL immobilized proline catalyst **9**.

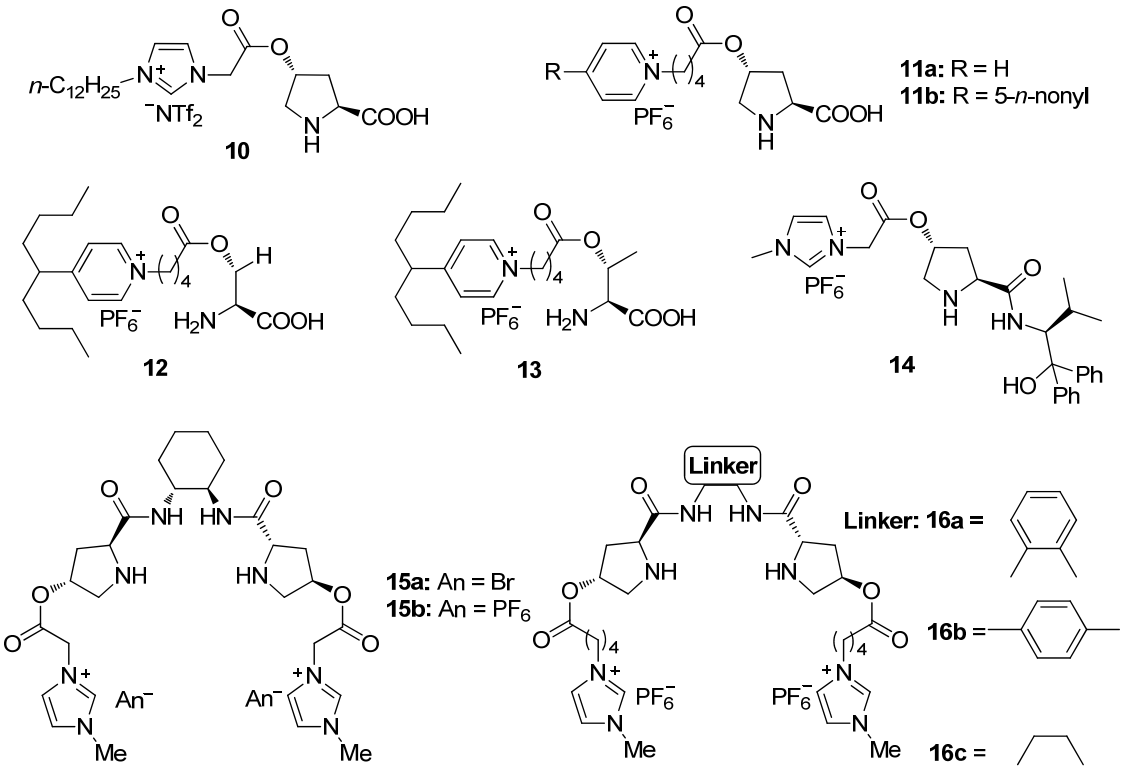


In 2008, Zlotin *et al.* [54] designed and synthesized a new type of IL immobilized proline catalysts, **9a** and **9b**, which contain a long-chain hydrocarbon group (Scheme 2). Owing to the amphiphilic character of the two catalysts, excellent diastereoselectivities (*anti*/*syn* ratio up to 97:3) and enantioselectivities (up to 99% *ee*) of the aldol reaction between cyclic ketones and aromatic aldehydes in water were obtained. Furthermore, replacement of the long-chain hydrocarbon group with a shorter chain resulted in the catalyst being inactive in an aqueous environment, highlighting the importance of

the long-chain hydrocarbon group in the catalyst to the catalytic system. Moreover, the catalyst can be recycled at least five times in water without significant loss of activities and selectivities.

In 2009, Zlotin *et al.* [55] reported the introduction of proline, serine, or threonine units to new chiral ionic liquids, which were investigated as recyclable organocatalysts for aldol reactions of various ketone donors with aromatic aldehydes. The authors found that catalyst **10** and **13** (Figure 3) could effectively catalyze the aldol reaction in the presence of water with high distereo- (up to 98:2) and enantioselectivity (up to >99% *ee*). The authors further discovered that catalyst **11b** (Figure 3), in which 4-hydroxyproline was successfully tethered to the 4-(5-*n*-nonyl)-pyridinium hexafluorophosphate ionic-liquid moieties, could be reused eight times without significant loss of its catalytic activity and enantioselectivity.

Figure 3. Different types of ionic liquid immobilized organocatalysts.



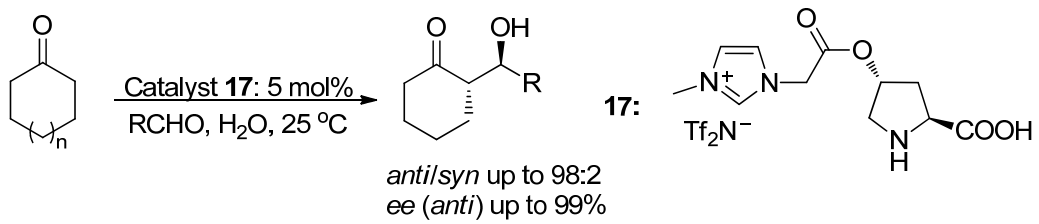
Later, the same research group described that IL immobilized prolinamide **14** (Figure 3) was shown to be highly effective when used for enantioselective aldol reactions of unmodified ketones with aldehydes [56]. Compared to catalysts that have a free carboxylic group, this catalyst demonstrated even higher yields, better regio-, diastereo- and enantioselectivities in an aqueous environment. Another advantage is that the catalyst can be readily recovered and reused four times and displayed the same selectivity and slightly lowered activity.

In 2011, the group of Zlotin reported a C_2-symmetric immobilized organocatalyst **15** (Figure 3) containing a (1*R*,2*R*)-bis[(*S*)-prolinamido]cyclohexane unit bearing two imidazolium$^+$/PF_6^- ion pairs for carrying out asymmetric aldol reactions [57]. High diastereo- (*dr anti*/*syn* up to 99:1) and enantioselectivities (up to 99% *ee*) were observed for a broad range of substrates of linear or cyclic ketones to aromatic aldehydes in aqueous media. Remarkably, the catalyst could be reused up to 10 reaction cycles without reactivation.

Later, the same research group designed and synthesized a series of ionic liquid immobilized C_2-symmetric amides of (*S*)-proline bearing achiral diamine units **16** (Figure 3) to carry out asymmetric aldol reactions in water [58]. High enantioselectivities and yields were observed for a large variety of cyclic and acyclic ketones as donors and aromatic (heteroaromatic) aldehydes as acceptors. Compared to the previous catalysts, these catalysts demonstrated the same activity and enantioselectivity, but were more readily available and less expensive. Moreover, the authors found that catalyst **16b** (Figure 3) showed excellent recoverability, and the catalyst could be reused 15 times with a gradual reduction in yield, while still retaining its high *dr* and *ee* values which were similar to those obtained for the reaction performed in the presence of freshly prepared catalyst.

In 2008, Lombardo *et al.* [59] utilized the ionic tag concept and attached the imidazolium ionic liquid moiety into *trans*-4-hydroxy-L-proline to prepare the IL immobilized organocatalyst **17** (Scheme 3), which was applied to the enantioselective aldol reactions with high enantioselectivity and diastereoselectivity under aqueous biphasic conditions.

Scheme 3. Aldol reaction catalyzed by an imidazolium-tagged *trans*-4-hydroxy-L-proline **17**.



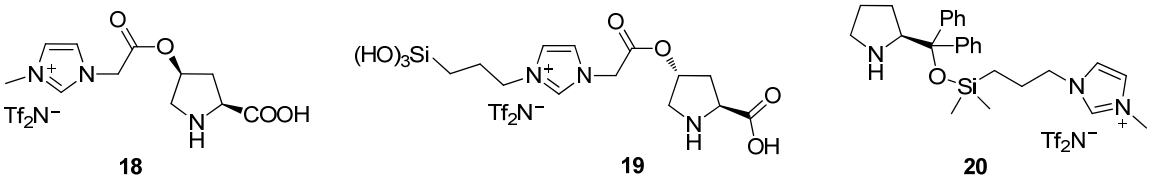
Later, using the same strategy, the authors synthesized ionic-tagged *cis*-4-hydroxy-L-proline **18** (Figure 4). They found that catalyst loading could be reduced to 0.1 mol% in the case of electron-poor aromatic aldehydes with *ee* up to 99%. Under the same reaction conditions, many substrates afforded "enzymatic-like" levels of *ee*s [60]. The recyclability of the catalyst was examined and shown that the product could be readily isolated by extraction using diethyl ether after the excess ketone was removed by vacuum. The catalyst could be recycled four times and showed identical catalytic properties in all reaction cycles in terms of catalytic activity and selectivity.

Lombardo *et al.* [61] prepared a novel water-soluble organocatalyst **19** (Figure 4) and used it as a catalyst for the aldol reactions of cyclic ketones and aromatic aldehydes. It was found that the three hydrophilic portions that are a part of the catalyst made it soluble in water, and the highly hydrophobic anion allowed the catalyst to be transported into the organic phase of the biphasic ketone–water system where the aldol reaction took place. As a result, high enantioselectivities and *anti*-diastereoselectivities (up to ≤99%) were obtained.

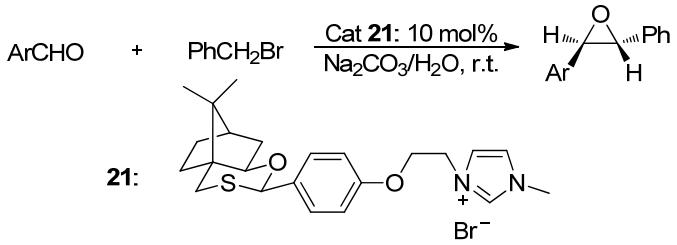
In 2009, Lombardo *et al.* [62] reported an ion-tagged diphenylprolinol silyl ether **20** (Figure 4) catalyzed Michael addition of aliphatic aldehydes to nitroalkenes. The authors observed that catalyst loading can be decreased to 0.25–5 mol% in the presence of only a slight excess of aldehyde (1.2–2 equiv.) to achieve a high 99.5% *ee*. Both CH_2Cl_2 and water could be used as the solvent for the reaction, and CH_2Cl_2 was a much better solvent compared to water for the reactions of propanal with aromatic nitroalkenes. However, water was a better reaction medium when less reactive aliphatic nitroalkenes or longer chain aldehydes were used. This phenomenon can be ascribed to poor solubility in water when

the molecular weight of aldehyde increases. When sterically hindered nitroalkenes or aldehydes were used, an acid as additive was necessary to ensure high conversions.

Figure 4. Different kinds of ionic liquid immobilized organocatalysts.



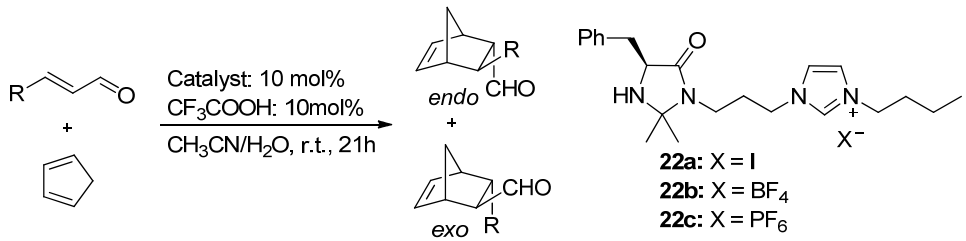
Scheme 4. Ionic liquid immobilized organocatalyst **21** catalyzed epoxidation reaction.



In 2009, Huang *et al.* [63] reported a new ionic liquid immobilized organocatalyst **21** (Scheme 4) as an organocatalyst for the epoxidation reaction of aromatic aldehydes and benzyl bromide in water with reasonable yields (41–67%), excellent diastereoselectivities (*dr* = 95:5–100:0), and moderate enantioselectivities ranging from 42% to 72% *ee* were obtained. Moreover, the organocatalyst **21** (Scheme 4) could be easily reused five times without a remarkable decrease in yields or enantioselectivities. Especially noteworthy is the fact that this was the first asymmetric epoxidation via ylide route in pure water.

In 2012, Loh and co-workers [64] described the use of ionic liquid-immobilized imidazolidinone **22** (Scheme 5) as an organocatalyst to catalyze enantioselective Diels–Alder reaction. They discovered that when the reactions were carried out in CH_3CN-H_2O, comparatively high yields were achieved, and a slightly higher *ee* for both the *exo* and *endo* isomers was obtained. In addition, to address the poor solubility of α, β-unsaturated aldehydes in CH_3CN-H_2O, a more polar solvent system of CH_3NO_2-H_2O instead of CH_3CN-H_2O was employed, leading to good to excellent yields of the desired products while maintaining their excellent enantioselectivities. Furthermore, due to the ionic liquid unit that is contained in the catalyst, catalyst **22** can be readily recovered and recycled up to five times while still retaining its high catalytic activity which is in accordance with the goals of green chemistry.

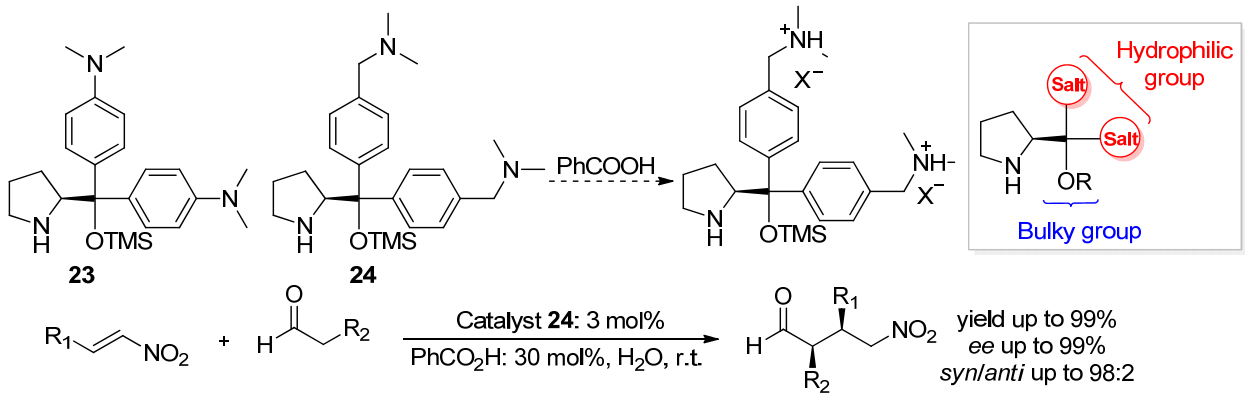
Scheme 5. Enantioselective Diels–Alder reaction catalyzed by ionic liquid-immobilized imidazolidinone **22**.



2.2. Ammonium Salt Immobilized Organocatalysts

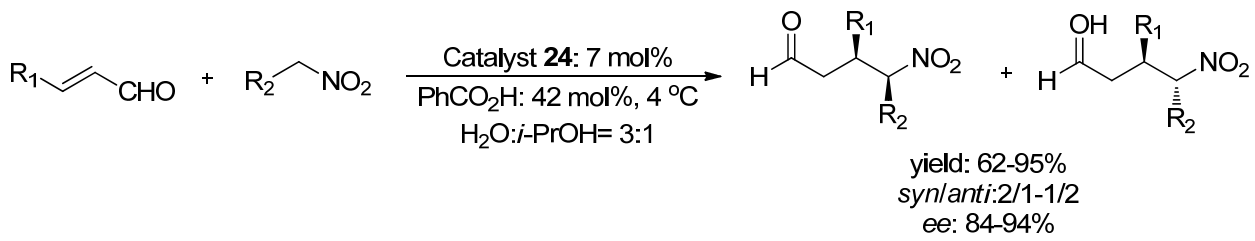
In 2009, Bukuo Ni and co-workers [65] designed and synthesized a series of interesting, novel diarylprolinol silyl ether salt catalysts, which were used as efficient, water-soluble, and recyclable organocatalysts to induce Michael addition of aldehydes and nitroalkenes. The authors found that catalyst **24** (Scheme 6) in combination with benzoic acid as additive can form ammonium salts, which not only enhanced the aqueous solubility of the catalyst but also provided easily recyclable catalysts by capitalizing on their solubility characteristics. In addition, the loading of catalyst and aldehydes could be reduced to 3 mol% and two equivalents, respectively, without any deleterious effect on the yields and enantioselectivities. Moreover, after the reaction was completed, the product could be easily extracted by the mixture of Et_2O-hexane, and the aqueous phase was used directly in the next cycle by adding another batch of reagents and benzoic acid. The catalyst can be recycled easily and retained its activity and selectivity over six reaction cycles. This new approach represents a rare successful example that combines the high efficiency and selectivity of homogeneous catalysis with the ease of separation and recyclability of heterogeneous catalysis.

Scheme 6. Organocatalytic asymmetric Michael reaction using novel water-soluble organocatalyst.

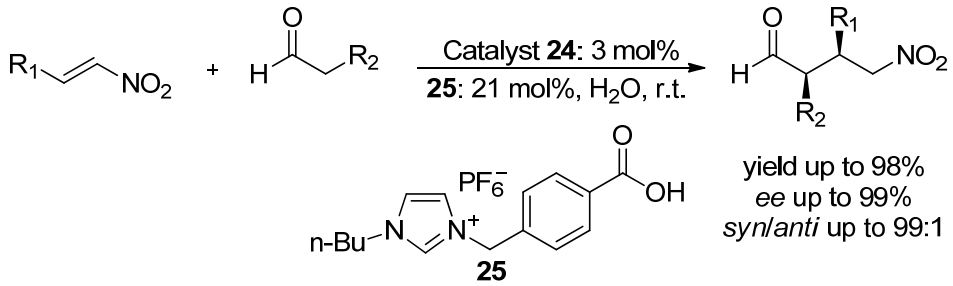


In 2010, the same research group reported that diarylprolinol silyl ether **24** was shown to be highly effective when used in combination with benzoic acid as additive for the catalytic asymmetric conjugate addition of nitroalkanes to α,β-unsaturated aldehydes in aqueous media [66]. A major advantage of the catalytic system is the low donor nitroalkane loading of two equivalents. Furthermore, the advantages associated with this catalyst were the ease for recyclability and reusability with relatively little loss in activity (Scheme 7).

Scheme 7. Reaction of nitroalkanes to α,β-unsaturated aldehydes catalyzed by **24**.



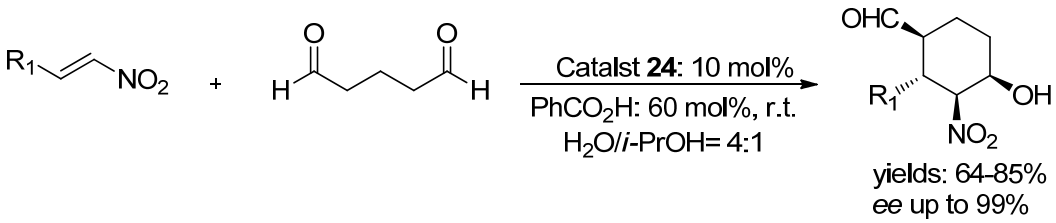
Scheme 8. Michael addition of aldehydes to nitroolefins catalyzed by **24** and **25**.



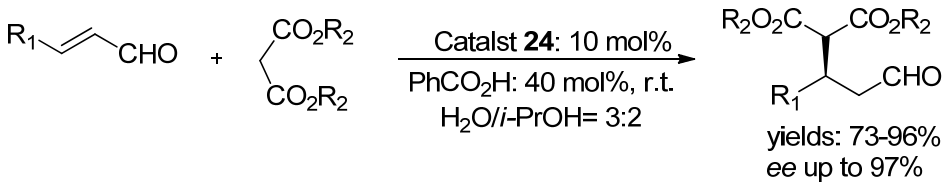
In 2011, the research group of Headley [67] reported a novel strategy for the asymmetric Michael addition of aldehydes to nitroolefins, using ionic liquid-supported benzoic acid **25** (Scheme 8) instead of benzoic acid in combination with organocatalyst **24** gave the desired Michael adducts with excellent diastereo- and enantioselectivities in water. Compared to earlier publications, the notable features of this organocatalytic system are that the catalytic system could be reused directly without adding new acid and the catalyst could be recycled more than 12 times without significant loss of enantioselectivity.

The domino reaction is an efficient and elegant strategy that constructs complex molecules from simple precursors in a single process [68–72]. These reactions avoid time-consuming and costly protection/deprotection processes as well as the purification of intermediates, and represent a flourishing area in organic chemistry. In 2011, Headley and co-workers [73] described the use of the same catalytic system for the domino Michael/Henry reaction of pentane-1,5-dial with various nitroolefins in an aqueous media affording the desired products in good yields (65–85%) and excellent enantioselectivities (99%) (Scheme 9). More importantly, the catalyst could be recycled up to four times resulting in good yield and up to seven times with good enantioselectivity.

Scheme 9. Reaction of pentane-1,5-dial with nitroolefines catalyzed by **24**.



Scheme 10. Michael reaction of malonate to α,β-unsaturated aldehydes.

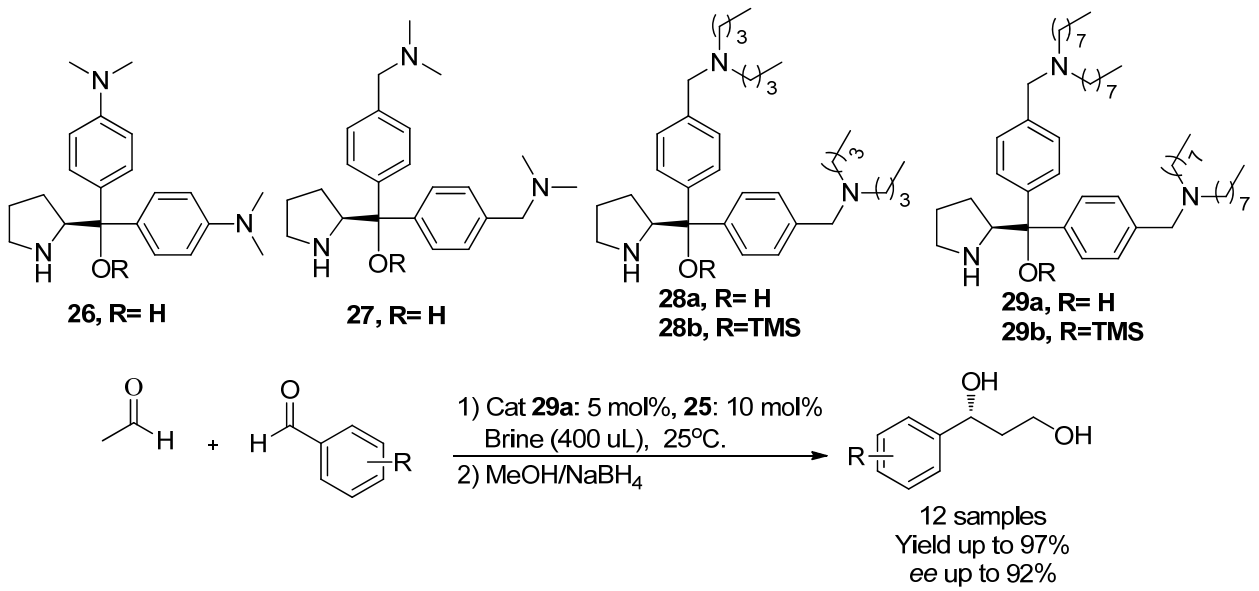


In 2012, Headley [74] found that pyrrolidine-based organocatalyst such as **24** was very effective for the Michael reaction of malonate to α, β-unsaturated aldehydes in the presence of a mixed solvent system *i.e.*, H_2O/*i*-PrOH (Scheme 10). Different catalysts and different equivalents of acid were evaluated for this reaction. The best result was achieved by the addition of 40 mol% benzoic acid to 10 mol% of the catalyst, good to excellent yields (73%–96%) and high to excellent enantioselectivities (up to 97%)

were obtained. The recyclability of the catalyst **24** was also tested and the catalyst could be recycled up to four times with gradual reductions in yields and enantioselectivity observed after the second cycle.

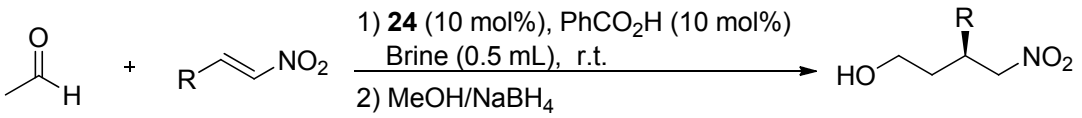
The direct crossed-aldol reaction is considered to be one of the key transformations for carbon-carbon bond formation [47,75–78]. However, acetaldehyde, which is considered the simplest of the enolizable carbonyls, is known to be very reactive due to the fact that various undesired side products of poly-aldolization, dehydration, Tishchenko-type processes and oligomerization are formed [79]. In 2013, Headley *et al.* [80] developed a new type of diarylprolinol-based catalysts and studied the efficiency of these catalysts on the asymmetric direct crossed-aldol reaction of acetaldehyde in aqueous media (Scheme 11). The best result in terms of yields and enantioselectivities was observed with catalyst **29a** in combination with a newly developed ionic liquid immobilized benzoic acid **25** as co-catalyst. In particular, the catalyst loading could be reduced to 5 mol%, high yields (up to 97%) and high enantioselectivities (up to 92% *ee*) were also achieved for a wide variety of aromatic aldehydes.

Scheme 11. Organocatalytic direct crossed-aldol reactions of acetaldehyde.



The Michael reaction of acetaldehyde with nitroolefins in aqueous media was also investigated by the same group using the same catalytic system [81]. Catalyst **24** (Scheme 12) in combination with benzoic acid as co-catalyst was found to be highly effective, relatively good yields (30–61%) and high enantioselectivities (80–97% *ee*) were observed for a broad variety of nitrostryenes, including the electron-deficient and electron-rich nitrostyrenes, heteroatom containing aryl-substituted nitroalkene and alkyl-substituted nitroalkenes.

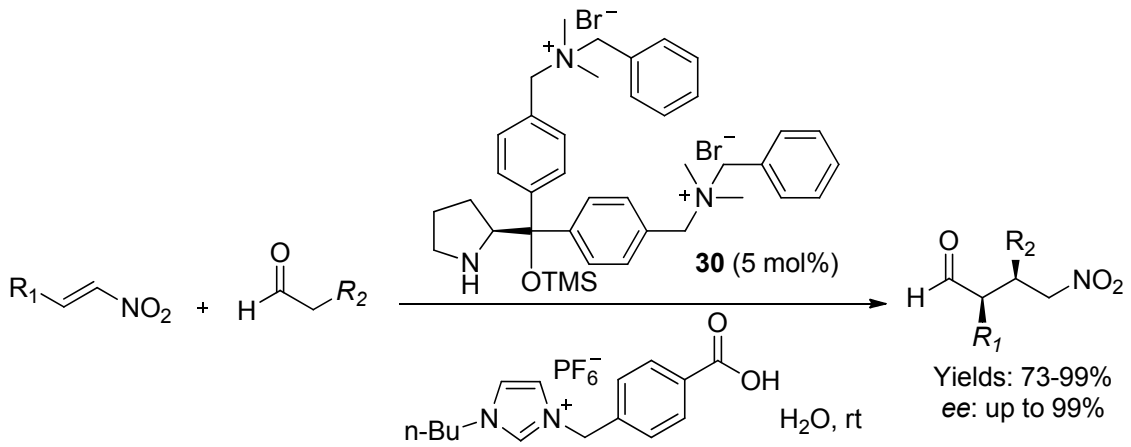
Scheme 12 Asymmetric Michael reaction involving acetaldehyde and various nitroalkenes.



In 2013, an interesting ionic liquid immobilization technique was exploited by the Headley group in the synthesis of pyrrolidine-based organocatalyst **30** (Scheme 13). They discovered that catalyst **30** in

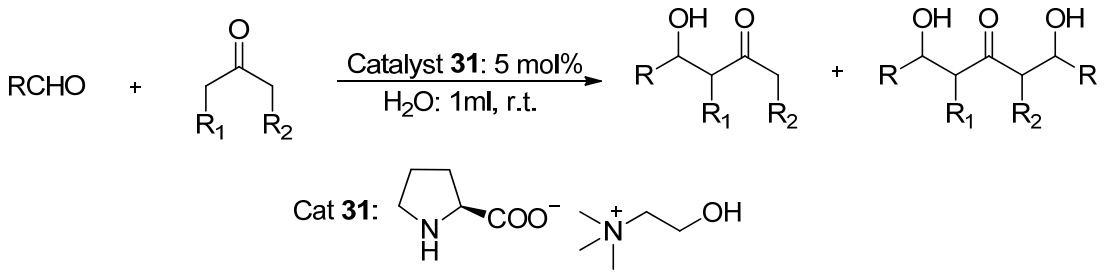
the presence of a newly developed ionic liquid-supported benzoic acid as co-catalyst was shown to be highly effective in the asymmetric Michael reaction in water [82]. For the reactions studied, excellent diastereo- and enantioselectivities were obtained with only 5 mol% of catalyst loading. Another advantage of the system was that after extraction of the product, the catalyst remained in the aqueous layer and could be reused in subsequent reactions for ten times without significant loss of enantioselectivity.

Scheme 13. Organocatalytic asymmetric Michael reaction using aldehydes and nitroalkenes.



A novel idea of using biorenewable nontoxic raw materials through a simple and green route to synthesize IL [Choline][Pro] **31** (Scheme 14) was led by Hu and co-workers [83]. They found that this catalyst could be used to catalyze direct aldol reactions between ketones and aromatic aldehydes efficiently in water in a very short time with good yields. In addition, the authors observed that the reaction mixtures separated into an aqueous phase and an organic phase after the reaction was completed, and the catalyst was dissolved in aqueous phase, which means that the IL could be easily recycled. It was important to note that the aqueous phase could be recycled three times without obvious decrease in yields.

Scheme 14. Direct aldol reaction of aromatic aldehydes and ketones.

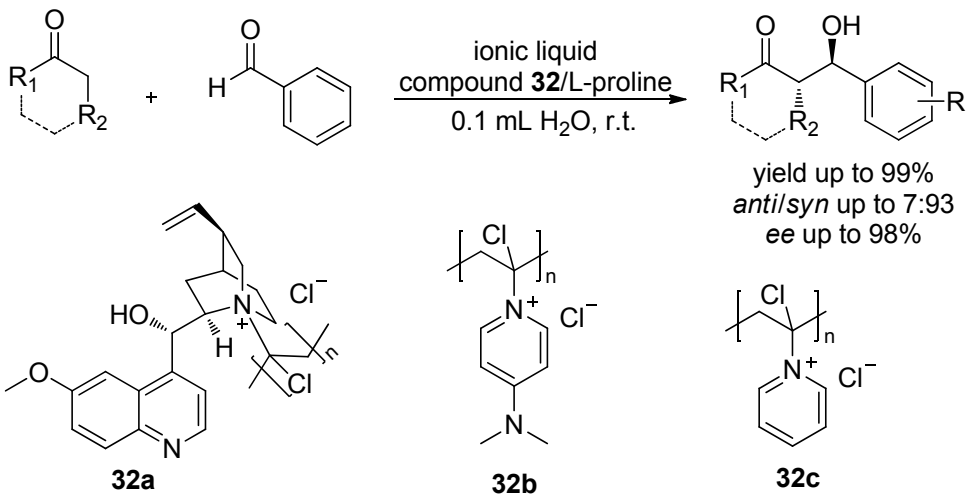


2.3. Other Heterocyclic Immobilized Organocatalysts

In 2012, the Cui group [84] developed a series of polyvinylidene chloride (PVDC)-immobilized ionic liquids (Scheme 15) which were derived from 4-dimethylaminopyridine. The authors observed that these catalysts were used together with L-proline as efficient asymmetric organocatalysts for asymmetric aldol reactions between cyclohexanone and aromatic aldehydes in the presence of water. High yields of up to 99%, as well as diastereoselectivities of up to 6:94, and excellent

enantioselectivities of up to 98% were obtained. Another advantage of the catalytic system is the ease in recyclability and reusability; the results showed that the yield remained the same and only a slight reduction in selectivity after seven recycles.

Scheme 15. Asymmetric aldol reactions catalyzed by compound **32**/L-proline.



3. Conclusions and Outlook

This short review focuses on the application and recyclability of recently developed ionic liquid and related ammonium salt immobilized organocatalysts in asymmetric reactions. The main advantages of these types of catalysts are that they are environmentally benign and eco-friendly, and they can be easily recovered and reused many times without loss of activity and selectivity. In addition, these catalysts also present a new approach to meet the environmental challenges faced by industry. Large amounts of conventional catalysts are presently being used to ensure high yields in the synthesis of specific compounds, including pharmaceutical compounds. Since ionic liquid and related ammonium salt immobilized catalysts are typically recyclable, large amounts are typically not required. Moreover, water as the solvent in organic transformations provides an important avenue to expand the study of green chemistry and the field of sustainable catalysis in this media. Although this field is still in its infancy, the future is very promising. The development of organic reactions in aqueous media should benefit academia and industry. In nature, virtually all biological processes take place in an aqueous environment, and as a result, gaining a deeper understanding of reactions in aqueous medium will also contribute to our understanding of the detailed mechanisms in the chemistry of life. There is a bright future for further design of more efficient and practical, novel, ionic liquid immobilized organocatalysts that are functional under mild catalytic conditions.

Acknowledgments

We are grateful to the National Science Foundation for financial support of this research (CHE-1213287).

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Dalko, P.I.; Moisan, L. In the Golden Age of Organocatalysis. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.
2. List, B. The ying and yang of asymmetric aminocatalysis. *Chem. Commun*. **2006**, 819–824.
3. Dondoni, A.; Massi, A. Asymmetric Organocatalysis: From Infancy to Adolescence. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660.
4. MacMillan, D.W.C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304–308.
5. Bertelsen, S.; Jørgensen, K.A. Organocatalysis—After the gold rush. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.
6. Jacobsen, E.N.; MacMillan, D.W.C. Organocatalysis. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618–20619.
7. Hernandez, J.G.; Juaristi, E. Recent efforts directed to the development of more sustainable asymmetric organocatalysis. *Chem. Commun.* **2012**, *48*, 5396–5409.
8. *Asymmetric Organocatalysis*; American Chemical Society: Washington, DC, USA, 2004; pp. 487–631.
9. *Organic Catalysis*; Wiley-VCH: Weinheim, Germany, 2004; pp. 1007–1249.
10. *Organocatalysis*; American Chemical Society: Washington, DC, USA, 2007; pp. 5413–5883.
11. Welton, T. Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis. *Chem. Rev.* **1999**, *99*, 2071–2084.
12. Sheldon, R. Catalytic reactions in ionic liquids. *Chem. Commun.* **2001**, 2399–2407.
13. Dupont, J.; de Souza, R.F.; Suarez, P.A.Z. Ionic Liquid (Molten Salt) Phase Organometallic Catalysis. *Chem. Rev.* **2002**, *102*, 3667–3692.
14. Weingaertner, H. Understanding Ionic Liquids at the Molecular Level: Facts, Problems, and Controversies. *Angew. Chem. Int. Ed.* **2008**, *47*, 654–670.
15. Lee, J.W.; Shin, J.Y.; Chun, Y.S.; Jang, H.B.; Song, C.E.; Lee, S.-G. Toward Understanding the Origin of Positive Effects of Ionic Liquids on Catalysis: Formation of More Reactive Catalysts and Stabilization of Reactive Intermediates and Transition States in Ionic Liquids. *Acc. Chem. Res.* **2010**, *43*, 985–994.
16. Dupont, J. From Molten Salts to Ionic Liquids: A "Nano" Journey. *Acc. Chem. Res.* **2011**, *44*, 1223–1231.
17. Walden, P. Molecular weights and electrical conductivity of several fused salts. *Bull. Acad. Imper. Sci. (St. Petersburg.)* **1914**, 405–422.
18. Chum, H.L.; Koch, V.R.; Miller, L.L.; Osteryoung, R.A. An electrochemical scrutiny of organometallic iron complexes and hexamethylbenzene in a room temperature molten salt. *J. Am. Chem. Soc.* **1975**, *97*, 3264–3265.
19. Wilkes, J.S.; Levisky, J.A.; Wilson, R.A.; Hussey, C.L. Dialkylimidazolium Chloroaluminate Melts: A New Class of Room-Temperature Ionic Liquids for Electrochemistry, Spectroscopy, and Synthesis. *Inorg. Chem.* **1982**, *21*, 1263–1264.

20. Diaw, M.; Chagnes, A.; Carre, B.; Willmann, P.; Lemordant, D. Mixed ionic liquid as electrolyte for lithium batteries. *J. Power Sour.* **2005**, *146*, 682–684.
21. Chiappe, C.; Pieraccini, D. Ionic liquids: Solvent properties and organic reactivity. *J. Phys. Org. Chem.* **2005**, *18*, 275–297.
22. Song, C.E. Enantioselective chemo- and bio-catalysis in ionic liquids. *Chem. Commun.* **2004**, 1033–1043.
23. Lee, S. Functionalized imidazolium salts for task-specific ionic liquids and their applications. *Chem. Commun.* **2006**, 1049–1063.
24. Pârvulescu, V.I.; Hardacre, C. Catalysis in Ionic Liquids. *Chem. Rev.* **2007**, *107*, 2615–2665.
25. Martins, M.A.P.; Frizzo, C.P.; Moreira, D.N.; Zanatta, N.; Bonacorso, H.G. Ionic Liquids in Heterocyclic Synthesis. *Chem. Rev.* **2008**, *108*, 2015–2050.
26. Hallett, J.P.; Welton, T. Room-Temperature Ionic Liquids: Solvents for Synthesis and Catalysis. 2. *Chem. Rev.* **2011**, *111*, 3508–3576.
27. Hunt, P.A.; Gould, I.R.; Kirchner, B. The Structure of Imidazolium-Based Ionic Liquids: Insights from Ion-Pair Interactions. *Aust. J. Chem.* **2007**, *60*, 9–14.
28. Wilkes, J.S. Properties of ionic liquid solvents for catalysis. *J. Mol. Catal. A* **2004**, *214*, 11–17.
29. Anderson, J.L.; Ding, J.; Welton, T.; Armstrong, D.W. Characterizing ionic liquids on the basis of multiple solvation interactions. *J. Am. Chem. Soc.* **2002**, *124*, 14247–14254.
30. Huddleston, J.G.; Visser, A.E.; Reichert, W.M.; Willauer, H.D.; Broker, G.A.; Rogers, R.D. Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation. *Green Chem.* **2001**, *3*, 156–164.
31. Miao, W.; Chan, T.H. Ionic-Liquid-Supported Synthesis: A Novel Liquid-Phase Strategy for Organic Synthesis. *Acc. Chem. Res.* **2006**, *39*, 897–908.
32. Handy, S.T.; Okello, M. Homogeneous Supported Synthesis Using Ionic Liquid Supports: Tunable Separation Properties. *J. Org. Chem.* **2005**, *70*, 2874–2877.
33. Breslow, R. Hydrophobic effects on simple organic reactions in water. *Acc. Chem. Res*. **1991**, *24*, 159–164.
34. Lindstrom, U.M. Stereoselective Organic Reactions in Water. *Chem. Rev.* **2002**, *102*, 2751–2772.
35. Li, C.-J. Organic reactions in aqueous media with a focus on C-C bond formations: A decade update. *Chem. Rev*. **2005**, *105*, 3095–3165.
36. Li, C.-J.; Chen, L. Organic chemistry in water. *Chem. Soc. Rev.* **2006**, *35*, 68–82.
37. Brogan, A.P.; Dickerson, T.J.; Janda, K.D. Enamine-Based Aldol Organocatalysis in Water: Are They Really "All Wet"? *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102.
38. Hayashi, Y. In Water or in the Presence of Water. *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104.
39. Paradowska, J.; Stodulski, M.; Mlynarski, J. Catalysts Based on Amino Acids for Asymmetric Reactions in Water. *Angew. Chem. Int. Ed.* **2009**, *48*, 4288–4297.
40. Gruttadauria, M.; Giacalone, F.; Noto, R. Water in stereoselective organocatalytic reactions. *Adv. Synth. Catal.* **2009**, *351*, 33–57.
41. Raj, M.; Singh, V.K. Organocatalytic reactions in water. *Chem. Commun*. **2009**, 6687–6703.
42. Mase, N.; Barbas, C.F., III. In water, on water, and by water: Mimicking nature's aldolases with organocatalysis and water. *Org. Biomol. Chem*. **2010**, *8*, 4043–4050.

43. Butler, R.N.; Coyne, A.G. Water: Nature's Reaction Enforcer—Comparative Effects for Organic Synthesis "In-Water" and "On-Water". *Chem. Rev.* **2010**, *110*, 6302–6337.
44. Pirrunga, M.C.; Sarma, K.D. Aqueous medium effects on multi-component reactions. *Tetrahedron* **2005**, *61*, 11456–11472.
45. Klijn, J.E.; Engberts, J.B.F.N. Organic chemistry: Fast reactions "on water". *Nature* **2005**, *435*, 746–747.
46. Pirrung, M.C. Acceleration of organic reactions through aqueous solvent effects. *Chem. Eur. J.* **2006**, *12*, 1312–1317.
47. Machajewski, T.D.; Wong, C.-H. The Catalytic Asymmetric Aldol Reaction. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1375.
48. Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. Functionalized Chiral Ionic Liquids as Highly Efficient Asymmetric Organocatalysts for Michael Addition to Nitroolefins. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097.
49. Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. Functionalized ionic liquids catalyzed direct aldol reactions. *Tetrahedron* **2007**, *63*, 1923–1930.
50. Bahmanyar, S.; Houk, K.N. The origin of stereoselectivity in proline-catalyzed intramolecular Aldol Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912.
51. Hoang, L.; Bahmanyar, S.; Houk, K.N.; List, B. Kinetic and Stereochemical Evidence for the Involvement of Only One Proline Molecule in the Transition States of Proline-Catalyzed Intra- and Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 16–17.
52. Bahmanyar, S.; Houk, K.N.; Martin, H.J.; List, B. Quantum Mechanical Predictions of the Stereoselectivities of Proline-Catalyzed Asymmetric Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479.
53. Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. Surfactant-type asymmetric organocatalyst: Organocatalytic asymmetric Michael addition to nitrostyrenes in water. *Chem. Commun.* **2006**, 3687–3689.
54. Siyutkin, D.E.; Kucherenko, A.S.; Struchkova, M.I.; Zlotin, S.G. A novel (*S*)-proline-modified task-specific chiral ionic liquid-an amphiphilic recoverable catalyst for direct asymmetric aldol reactions in water. *Tetrahedron Lett.* **2008**, *49*, 1212–1216.
55. Siyutkin, D.E.; Kucherenko, A.S.; Zlotin, S.G. Hydroxy-α-amino acids modified by ionic liquid moieties: recoverable organocatalysts for asymmetric aldol reactions in the presence of water. *Tetrahedron* **2009**, *65*, 1366–1372.
56. Siyutkin, D.E.; Kucherenko, A.S.; Zlotin, S.G. A new (*S*)-prolinamide modified by an ionic liquid moiety—A high performance recoverable catalyst for asymmetric aldol reactions in aqueous media. *Tetrahedron* **2010**, *66*, 513–518.
57. Kochetkov, S.V.; Kucherenko, A.S.; Zlotin, S.G. (1*R*,2*R*)-Bis[(*S*)-prolinamido]cyclohexane Modified with Ionic Groups: The First C_2-Symmetric Immobilized Organocatalyst for Asymmetric Aldol Reactions in Aqueous Media. *Eur. J. Org. Chem.* **2011**, 6128–6133.
58. Kochetkov, S.V.; Kucherenko, A.S.; Kryshtal, G.V.; Zhdankina, G.M.; Zlotin, S.G. Simple Ionic Liquid Supported C_2-Symmetric Bisprolinamides as Recoverable Organocatalysts for the Asymmetric Aldol Reaction in the Presence of Water. *Eur. J. Org. Chem.* **2012**, 7129–7134.

59. Lombardo, M.; Pasi, F.; Easwar, S.; Trombini, C. Direct Asymmetric Aldol Reaction Catalyzed by an Imidazolium-Tagged *trans*-4-Hydroxy-L-proline under Aqueous Biphasic Conditions. *Synlett* **2008**, 2471–2474.
60. Lombardo, M.; Easwar, S.; Pasi, F.; Trombini, C. The Ion Tag Strategy as a Route to Highly Efficient Organocatalysts for the Direct Asymmetric Aldol Reaction. *Adv. Synth. Catal.* **2009**, *351*, 276–282.
61. Lombardo, M.; Easwar, S.; Marco, A.D.; Pasia, F.; Trombini, C. A modular approach to catalyst hydrophobicity for an asymmetric aldol reaction in a biphasic aqueous environment. *Org. Biomol. Chem.* **2008**, *6*, 4224–4229.
62. Lombardo, M.; Chiarucci, M.; Quintavalla, A.; Trombini, C. Highly Efficient Ion-Tagged Catalyst for the Enantioselective Michael Addition of Aldehydes to Nitroalkenes. *Adv. Synth. Catal.* **2009**, *351*, 2801–2806.
63. Li, J.; Hua, F.; Xie, X.-K.; Liu, F.; Huang, Z.-Z. Synthesis of new functionalized chiral ionic liquid and its organocatalytic asymmetric epoxidation in water. *Catal. Commun.* **2009**, *11*, 276–279.
64. Shen, Z.-L.; Cheong, H.-L.; Lai, Y.-C.; Loo, W.-Y.; Loh, T.-P. Application of recyclable ionic liquid-supported imidazolidinone catalyst in enantioselective Diels–Alder reactions. *Green Chem.* **2012**, *14*, 2626–2630.
65. Zheng, Z.; Perkins, B.; Ni, B. Diarylprolinol Silyl Ether Salts as New, Efficient, Water-Soluble, and Recyclable Organocatalysts for the Asymmetric Michael Addition on Water. *J. Am. Chem. Soc.* **2010**, *132*, 50–51.
66. Ghosh, S.K.; Zheng, Z.; Ni, B. Highly Active Water-Soluble and Recyclable Organocatalyst for the Asymmetric 1,4-Conjugate Addition of Nitroalkanes to α,β-Unsaturated Aldehydes. *Adv. Synth. Catal.* **2010**, *352*, 2378–2382.
67. Sarkar, D.; Bhattarai, R.; Headley, A.D.; Ni, B. A Novel Recyclable Organocatalytic System for the Highly Asymmetric Michael Addition of Aldehydes to Nitroolefins in Water. *Synthesis* **2011**, 1993–1997.
68. Tietze, L.F.; Brasche, G.; Gericke, K.M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.
69. Walji, A.M.; MacMillan, D.W.C. Strategies to Bypass the Taxol Problem. Enantioselective Cascade Catalysis, a New Approach for the Efficient Construction of Molecular Complexity. *Synlett* **2007**, *10*, 1477–1489.
70. Enders, D.; Grondal, C.; Hüttl, M.R.M. Asymmetric Organocatalytic Domino Reactions. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.
71. Guillena, G.; Ramon, D.J.; Yus, M. Organocatalytic enantioselective multicomponent reactions (OEMCRs). *Tetrahedron* **2007**, *18*, 693–700.
72. Yu, X.; Wang, W. Organocatalysis: Asymmetric cascade reactions catalysed by chiral secondary amines. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046.
73. Chintala, P.; Ghosh, S.K.; Long, E.; Headley, A.D.; Ni, B. The Application of a Recyclable Organocatalytic System to the Asymmetric Domino Michael/Henry Reaction in Aqueous Media. *Adv. Synth.Catal.* **2011**, *353*, 2905–2909.

74. Ghosh, S.K.; Dhungana, K.; Headley, A.D.; Ni, B. Highly Enantioselective and Recyclable Organocatalytic Michael Addition of Malalonates to α,β-Unsaturated Aldehydes in Aqueous Media. *Org. Biomol. Chem.* **2012**, *10*, 8322–8325.
75. Denmark, S.E.; Stavenger, R.A. Asymmetric Catalysis of Aldol Reactions with Chiral Lewis Bases (Trichlorosilyl Enolates). *Acc. Chem. Res.* **2000**, *33*, 432–440.
76. Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, Germany, 2004; Volumes 1–2.
77. Saito, S.; Yamamoto, H. Design of Acid−Base Catalysis for the Asymmetric Direct Aldol Reaction. *Acc. Chem. Res.* **2004**, *37*, 570–579.
78. Trost, B.M.; Brindle, C.S. The direct catalytic asymmetric aldol reaction. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632.
79. Alcaide, B.; Almendros, P. Organocatalytic Reactions with Acetaldehyde. *Angew. Chem. Int. Ed.* **2008**, *47*, 4632–4634.
80. Qiao, Y.; Chen, Q.; Lin, S.; Ni, B.; Headley, A.D. Organocatalytic Direct Asymmetric Crossed-Aldol Reactions of Acetaldehyde in Aqueous Media. *J. Org. Chem.* **2013**, *78*, 2693–2697.
81. Qiao, Y.; He, J.; Ni, B.; Headley, A.D. Asymmetric Michael Reaction of Acetaldehyde with Nitroolefins Catalyzed by Highly Water-Compatible Organocatalysts in Aqueous Media. *Adv. Synth. Catal.* **2012**, *354*, 2849–2853.
82. Ghosh, S.K.; Qiao, Y.; Ni, B.; Headley, A.D. Asymmetric Michael reactions catalyzed by a highly efficient and recyclable quaternary ammonium ionic liquid-supported organocatalyst in aqueous media. *Org. Biomol. Chem.* **2013**, *11*, 1801–1804.
83. Hu, S.; Jiang, T.; Zhang, Z.; Zhu, A.; Han, B.; Song, J.; Xie, Y.; Li, W. Functional ionic liquid from biorenewable materials: Synthesis and application as a catalyst in direct aldol reactions. *Tetrahedron Lett.* **2007**, *48*, 5613–5617.
84. Zhang, X.; Zhao, W.; Qu, C.; Yang, L.; Cui, Y. Efficient asymmetric aldol reaction catalyzed by polyvinylidene chloride-supported ionic liquid/L-proline catalyst system. *Tetrahedron* **2012**, *23*, 468–473.