

Applications of Ionic Liquids in Synthesis and Catalysis

by Paul J. Dyson and Tilmann J. Geldbach

The “modern ionic liquids” described in the first article in this issue by Keith Johnson have certainly captured the imagination of chemists across the globe, and without at doubt, nowhere more than in synthesis and catalysis.¹ The reasons for such phenomenal interest in this area are due to several factors, notably:

1. synthetic chemists are limited by the available molecular solvents in which they can conduct chemistry;
2. increasingly the solvents chemists like to use are banned by international protocols determined to reduce pollution, of which volatile organic compounds represent a significant part; and
3. the prospect of discovering new chemistry or the ability to design a solvent that facilitates/ allows a specific reaction to occur.

The reasons stated above are all important and many papers in the literature respond directly to such challenges. However, there are a large number of papers that justify their existence merely to the fact that ionic liquids are perceived as “green”—since they do not evaporate under ambient conditions—and apart from this aspect, little novelty or insights are reported. In the remainder of this article we have selected examples from the literature that demonstrate the potential of ionic liquids in synthetic applications. These not only offer new opportunities on how to perform known reactions, but can even be tailored to meet specific synthetic needs.

Ionic Liquids as Solvents

How do chemists use ionic liquids in place of organic solvents? It may seem like the answer to this question is very simple, perhaps entirely obvious, *i.e.* “just dissolve your compounds in the ionic liquid and get on with it,” but the reality is somewhat more complicated. Synthetic chemists have geared up virtually everything of what they do to being conducted in volatile solvents. After all, the solvent is not

part of the product, just something added prior to the reaction and then later removed; thus elimination should be as facile as possible. How then can non-volatile ionic liquids be used—presumably the rotary evaporator can be thrown away?² While removal of the solvent by evaporation is no longer an option the reverse, distillation of the product may become possible instead, if it is sufficiently volatile. Other, well-established techniques for the isolation of a product include extraction with supercritical CO₂ or simple phase separation, provided that the product is immiscible in the ionic liquid. Such approaches are not new: biphasic (or multiphasic) processes where a catalyst immobilized in an aqueous phase together with water-soluble substrates leads to the formation of a second phase comprised of the reaction product, have been used industrially for many years.³ However, water is somewhat limited as a solvent; hence the attractiveness of ionic liquids and some specific strategies and examples are outlined below.

Stoichiometric Organic Synthesis

Many organic reactions have been studied in ionic liquids, mostly with the expectation that the ionic solvent will accelerate product formation or alter the selectivity of the reaction and many notable and impressive examples have been reported.⁴ In this respect the Diels-Alder reaction is a particularly interesting case as higher reaction rates and selectivities are obtained in polar solvents compared to non-polar solvents,⁵ and *endo:exo* product selectivities are often higher in aqueous solution.⁶ These effects have been attributed to enhanced hydrogen bonding between the solvent and the transition state, as well as to enforced hydrophobic interactions, essentially creating a hydrophobic pocket, which facilitates alignment of the substrates.⁷ The first example of a Diels-Alder reaction involving an ionic liquid, *viz.* [EtNH₃][NO₃], was published by Jaeger and Tucker in 1989⁸ with results comparable with those obtained in water. The cycloaddition

of cyclopentadiene to methyl acrylate in chloroaluminate ionic liquids takes place with very high rates and selectivities (*endo:exo* ratio = 15), unfortunately the ionic liquids cannot be reused.⁹ Chloroaluminate ionic liquids have also been shown to promote selectivities toward different products depending on the mol fraction of aluminum(III)chloride employed.¹⁰ However, despite the considerable potential for Diels-Alder reactions due to the variety of cation-anion combinations that are available, it does not appear that the benefits of using ionic liquids are at present significant enough to warrant their frequent or large scale use.

Catalyzed Reactions

It was known for many years that ionic liquids could dissolve transition metal complexes and support organic chemistry. Chauvin and Osteryoung independently combined these ideas with Chauvin showing that nickel complexes dissolved in acidic chloroaluminate ionic liquids catalyze the dimerization of alkenes¹¹ while Osteryoung used Ziegler-Natta catalysts in a similar solvent to polymerize ethylene.¹² But it was Zaworotko's water-stable ionic liquids that contain tetrafluoroborate, hexafluorophosphate, nitrate, sulfate and acetate anions that really moved things forward. Using these ionic liquids Chauvin and Dupont demonstrated their potential in hydrogenation catalysis¹³ and showed that reaction rates and selectivities could be enhanced.

It is impossible to describe all the catalyzed reactions that have been reported in ionic liquids, although just about every important reaction has been performed with varying degrees of success.¹⁴ What has become apparent is that frequently used and well-established homogeneous catalysts need to be modified in order to work effectively in ionic liquids. For example, it was shown that activation of a pre-catalyst can be thermodynamically hindered in an ionic liquid, affording no catalysis at all if reaction conditions are not adapted properly.¹⁵ In addition to catalyst activation, sufficient

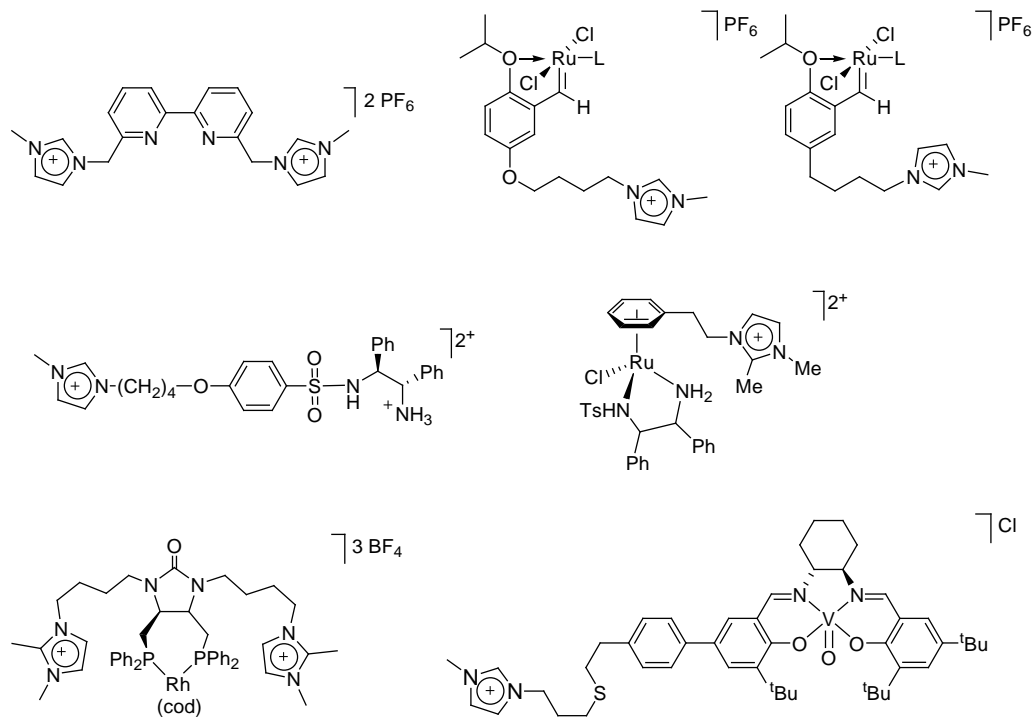


Fig. 1. Imidazolium tagged ligands/catalysts that enhance immobilization in ionic liquids and improve catalyst recycling/reuse.

retention of the catalyst in the ionic liquid is important in order to provide good recycling. The most versatile approach used to anchor homogeneous catalysts in ionic liquid phases is to attach charged groups to the ligands bound to the metal catalyst centre; some recent examples of ligands/catalysts modified in this manner are shown in Fig. 1. Imidazolium groups have been widely used for this purpose, since

the majority of catalyzed reactions reported to date have been carried out in imidazolium-based ionic liquids.

Other approaches have been used to facilitate catalyst reuse and in the context of continuous flow processes supported ionic liquid phase (SILP) catalysis has been quite extensively studied.¹⁶ The general concept involves the immobilization of imidazolium and other ionic fragments onto solid supports using

appropriate functional groups attached to the cation and a charged catalyst then resides within the ionic matrix. The concept is illustrated in Fig. 2 for the racemic epoxidation of olefins using a peroxotungstenate catalyst, $[\{W(=O)(O_2)_2(H_2O)_2(\mu-O)\}]^{2-}$, supported on ionic liquid modified silica.¹⁷ The solid support was reacted with 1-octyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium, affording a SiO_2

(continued on next page)

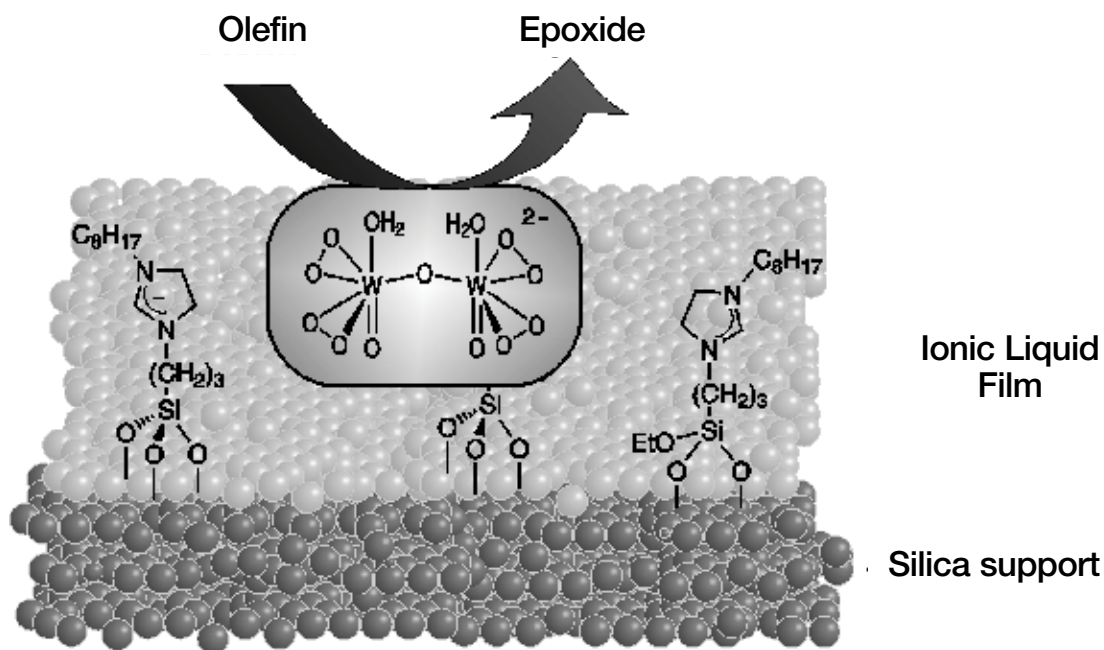


Fig. 2. A tungstenate catalyst immobilized on ionic liquid modified silica.

surface on which the ionic liquid is covalently bound. This heterogeneous catalyst was successfully used to epoxidise olefins using H_2O_2 as oxidant and reaction rates were comparable to those observed under homogeneous conditions.

Ionic liquids have further proven to be excellent solvents to both immobilize and stabilize nanoparticle catalysts. Nanoparticles were first identified in ionic liquids as species formed during Heck reactions using Pd(II) compounds as catalyst precursors.¹⁸ Dupont *et al.* reported the controlled preparation of transition metal nanoparticles in ionic liquids by reduction of the metal complex with molecular hydrogen in the absence of stabilizers, and demonstrated their application in hydrogenation and C-C coupling reactions.¹⁹ It is believed that both electrostatic and coordination effects of imidazolium cations contribute to nanoparticle stabilization by ionic liquids.²⁰ However, particularly more forcing reaction conditions may nevertheless require the presence of additional stabilizers to avoid aggregation of nanoparticles in the ionic liquid. For example, PVP (poly(*N*-vinyl-2-pyrrolidone)) has been used for nanoparticles synthesis in ionic liquids,²¹ in addition, thiol-functionalized ionic liquids²² and ionic liquids-like copolymers²³ have been developed to stabilize

ionic liquid soluble nanoparticles. It has also been demonstrated that nanoparticles stabilized by an ionic liquid polymer can be efficiently transferred between phases via anion exchange,²⁴ which could have important applications in catalysis with respect to product separation.

Ionic Liquids by Design

The application of ionic liquids in catalysis is not without problems, one being that yields and selectivities can vary according to the batch of ionic liquid used. Impurities such as halides, and to lesser extent organic compounds of low volatility, have been implicated in reproducibility problems.²⁵ Halide contamination originates from the salt metathesis reaction frequently used to prepare ionic liquids, although many alternative "halide-free" routes are now available.²⁶ In addition to the synthesis of highly pure ionic liquids, the prospect of designing ionic liquids that exhibit specific properties to enhance catalytic activity opens up new dimensions and possibilities in catalysis and the design of so-called task specific ionic liquids (*i.e.*, ionic liquids containing functional groups) is helping to push the boundaries of ionic liquid catalysis.²⁷ A selection of functionalized ionic liquid cations is shown in Fig. 3, many of which have been developed for applications in catalysis.

As an example, nitrile functionalized ionic liquids were developed with a view to improve catalyst retention in reactions employing simple palladium salts as catalyst precursors, as it was envisaged that the nitrile group could weakly coordinate to the metal center thereby anchoring it in the ionic liquid phase. Such ionic liquids have been utilized in Suzuki and Stille coupling reactions and they exhibit excellent recycling properties relative to other ionic liquids.²⁸ The superior activity observed in the nitrile system was not only the result of better catalyst retention in the coordinating ionic liquid, but also due to improved catalyst stability. In the Stille coupling reaction between iodobenzene and tributylphenyltin, well-defined palladium nanoparticles were identified in which the nitrile-functionalized ionic liquid appears to act as a stabilizer preventing agglomeration and ultimately catalyst deactivation.

Functionalized ionic liquids may also act as supports for the synthesis of certain molecules thereby facilitating purification and isolation. A hydroxy-functionalized imidazolium ionic liquid was utilized for the synthesis of a pentapeptide (Fig. 4).²⁹ Advantages in using a functionalized ionic liquid relative to other supports lies in their lower cost (as compared to perfluorated

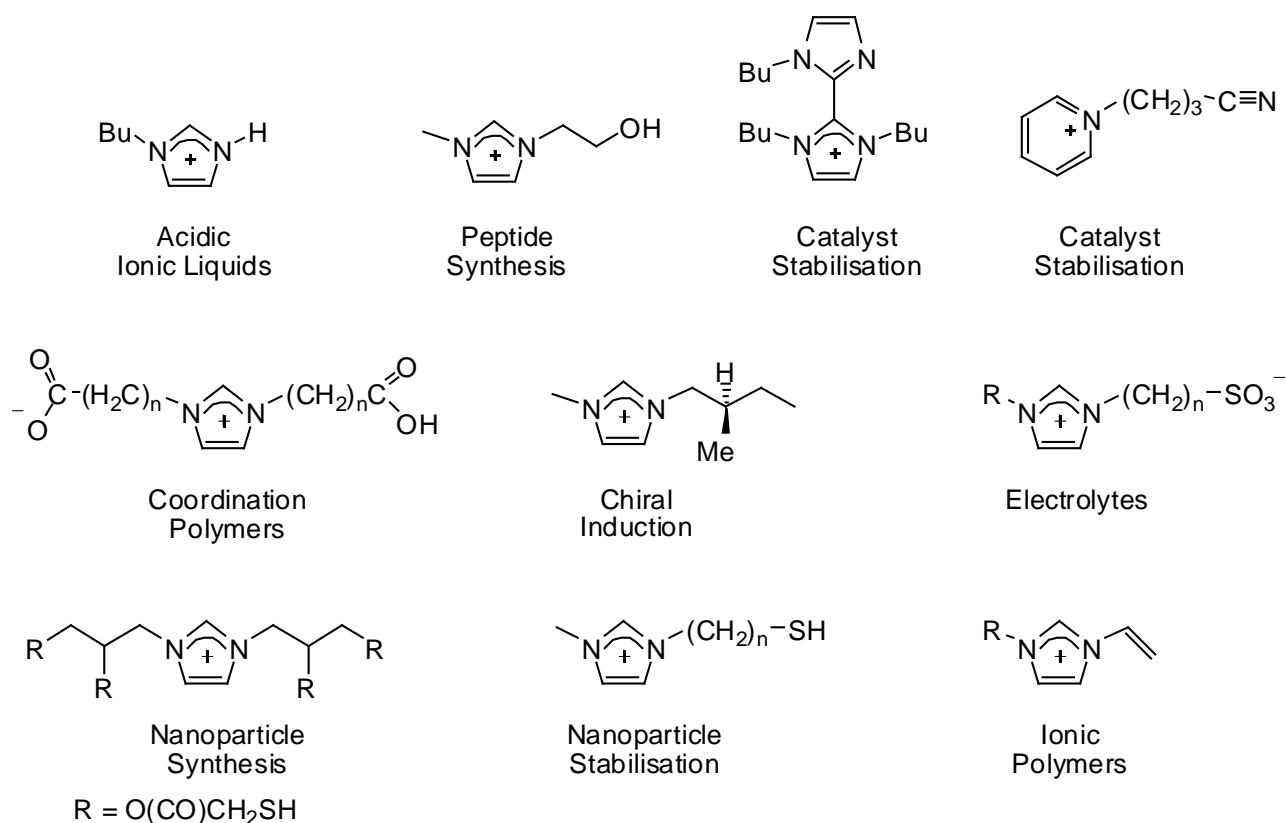


Fig. 3. Examples for functionalized ionic liquid cations.

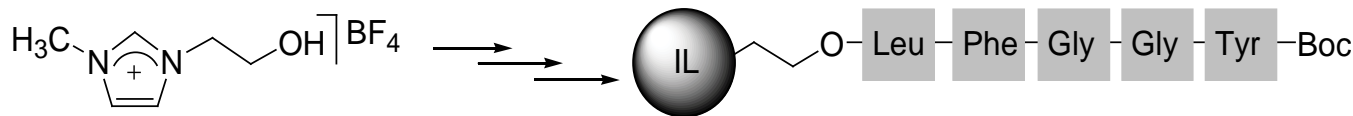


Fig. 4. Peptide synthesis using ionic liquid supports.

or polymeric supports), their high loading capacity and facile analysis of the intermediates by spectroscopic methods.

One potential problem with functionalized ionic liquids is that their viscosities tend to be higher than their non-functionalized analogues, despite maintaining very low melting points. It has recently been found, however, that the viscosity of these ionic liquids can be reduced by using asymmetric functionalized anions in combination with the functionalized cation.³⁰ In this way it becomes possible not only to control the chemical properties of an ionic liquid for a specific task, but also to adapt the physical properties, and in this way, true designer solvents are obtained. Currently, the design and realization of ionic liquids is done mostly within synthetic laboratories using qualitative ideas, but increasingly useful theoretical approaches³¹ may soon allow chemists to design their ionic liquids on a computer before attempting to prepare them in the laboratory.

Outlook

Ionic liquids provide chemists with the opportunity of studying reactions in a fascinating new environment. While the fundamental properties of ionic liquids are being unraveled chemists are developing new methods to handle and study them. In terms of their application as solvents in biphasic catalysis many notable achievements have already been made, with an ionic liquid process already in industrial use³² and another may be implemented soon,³³ but what is particularly fascinating is that not only is the catalyst modified to improve its performance in the ionic liquids, but the ionic liquid can also be modified and fine-tuned to enhance the performance of a chemical reaction. ■

Acknowledgments

The long term support of the Swiss National Science Foundation is greatly appreciated; Novartis and Degussa are also thanked for additional support.

References

- For reviews, see: (a) K. R. Seddon, *J. Chem. Technol. Biotechnol.*, **68**, 351 (1997); (b) C. M. Gordon, *App. Catal. A*, **222**, 101 (2001); (c) H. Olivier-Bourbigou, L. Magna, *J. Mol. Catal. A*, **182-183**, 419 (2002); (d) J. Dupont, R. F. de Souza, P. A. Z. Suarez, *Chem. Rev.*, **102**, 3667 (2002); (e) T. Welton, *Coord. Chem. Rev.*, **248**, 2459 (2004).
- Some ionic liquids can indeed be distilled, see e.g. M. J. Earle, J. M. S. S. Esperança, M. A. Gilea, J. N. Canongia Lopez, L. P. N. Rebelo, J. W. Magee, K. R. Seddon, and J. A. Widegren, *Nature*, **439**, 831 (2006).
- B. Cornils, *J. Mol. Catal. A*, **143**, 1 (1999).
- C. Chiappe and D. Pieraccini, *J. Phys. Org. Chem.*, **18**, 275 (2005).
- C. Cativiela, J. I. Garcia, J. A. Mayoral, A. J. Royo, L. Salvatella, X. Assfeld, and M. F. Ruiz-Lopez, *J. Phys. Org. Chem.*, **5**, 230 (1992).
- W. Blokzijl, M. Blandammer, and J. Engberts, *J. Am. Chem. Soc.*, **113**, 4241 (1991).
- R. Breslow, *Acc. Chem. Res.*, **24**, 159 (1991).
- D. A. Jaeger and C. E. Tucker, *Tet. Lett.*, **30**, 1785 (1989).
- C. Lee, *Tet. Lett.*, **40**, 2461 (1999).
- A. Kumar and S. S. Pawar, *J. Org. Chem.*, **69**, 1419 (2004).
- Y. Chauvin, B. Gilbert, and I. Guibard, *Chem. Commun.*, **23**, 1715 (1990).
- R. T. Carlin and R. A. Osteryoung, *J. Mol. Catal.*, **63**, 125 (1990).
- (a) Y. Chauvin, L. Mussmann, and H. Olivier, *Angew. Chem. Int. Ed. Engl.*, **34**, 2698 (1995); (b) P. A. Z. Suarez, J. E. L. Dullius, S. Einloft, R. F. de Souza, and J. Dupont, *Polyhedron*, **15**, 1217 (1996).
- T. J. Geldbach and P. J. Dyson, *Metal-Catalysed Reactions in Ionic Liquids*, Springer (2005).
- C. Dagueuet and P. J. Dyson, *Organometallics*, **23**, 6080 (2004).
- (a) C. P. Mehnert, *Chem. Eur. J.*, **11**, 50 (2005); (b) A. Riisager, R. Fehrmann, M. Haumann, and P. Wasserscheid, *Eur. J. Chem.*, **12**, 695 (2006).
- K. Yamaguchi, C. Yoshida, S. Uchida, and N. Mizuno, *J. Am. Chem. Soc.*, **127**, 530 (2005).
- R. R. Deshmukh, R. Rajagopal, and K. V. Srinivasan, *Chem. Commun.*, **17**, 1544 (2001).
- (a) J. Dupont, G. S. Fonseca, A. P. Umpierre, P. F. P. Fichtner, and S. R. Teixeira, *J. Am. Chem. Soc.*, **124**, 4228 (2002); (b) C. W. Scheeren, G. Machado, J. Dupont, P. F. P. Fichtner, and S. R. Teixeira, *Inorg. Chem.*, **42**, 4738 (2003).
- L. Starkey Ott, M. L. Cline, M. Deetlefs, K. R. Seddon, and R. G. Finke, *J. Am. Chem. Soc.*, **127**, 5758 (2005).
- X.-D. Mu, D. J. Evans, and Y. Kou, *Catal. Lett.*, **97**, 151 (2004).
- H. Itoh, K. Naka, and Y. Chujo, *J. Am. Chem. Soc.*, **126**, 3026 (2004); (b) K.-S. Kim, D. Demberelnyamba, and H. Lee, *Langmuir*, **20**, 556 (2004).
- N. Yan, C. Zhao, C. Luo, P. J. Dyson, H. Liu, and Y. Kou, *J. Am. Chem. Soc.*, **128**, 8714 (2006).
- D. Zhao, Z. Fei, W.-H. Ang, and P. J. Dyson, *Small*, **2**, 879 (2006).
- P. J. Dyson, *Transit. Met. Chem.*, **27**, 353 (2002).
- (a) P. Bonhôte, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram, and M. Grätzel, *Inorg. Chem.*, **35**, 1168 (1996); (b) R. F. de Souza, V. Rech, and J. Dupont, *Adv. Synth. Catal.*, **344**, 153 (2002); (c) M. Picquet, I. Tkatchenko, I. Tommasi, P. Wasserscheid, and J. Zimmermann, *Adv. Synth. Catal.*, **345**, 959 (2003).
- (a) J. H. Davis, Jr., *Chem. Lett.*, **33**, 1072 (2004); (b) Z. Fei, T. J. Geldbach, D. Zhao, and P. J. Dyson, *Chem. Eur. J.*, **12**, 2122 (2006); (c) H. Xue, R. Verma, and J. M. Shreeve, *J. Fluorine Chem.*, **127**, 159 (2006).
- (a) D. Zhao, Z. Fei, T. J. Geldbach, R. Scopelliti, and P. J. Dyson, *J. Am. Chem. Soc.*, **126**, 15876 (2004); (b) C. Chiappe, D. Pieraccini, D. Zhao, Z. Fei, and P. J. Dyson, *Adv. Synth. Catal.*, **348**, 68 (2006).
- W. Miao and T.-H. Chan, *J. Org. Chem.*, **70**, 3251 (2005).
- D. Zhao, Z. Fei, C. A. Ohlin, G. Laurenczy, and P. J. Dyson, *Chem. Commun.*, **21**, 2500 (2004).
- For example see: (a) C. G. Hanke, S. L. Price, and R. M. Linden-Bell, *Mol. Phys.*, **99**, 801 (2001); (b) C. Hardacre, S. E. J. McMath, M. Nieuwenhuyzen, D. T. Bowron, and A. K. Soper, *J. Phys.: Condens. Matter.*, **15**, S159 (2003); (c) I. Krossing, J. M. Slattery, C. Dagueuet, P. J. Dyson, A. Oleinikova, and H. Weingärtner, *J. Am. Chem. Soc.*, **128**, 13427 (2006).
- "News of the Week" in *Chem. Eng. News*, **81**, 9, (March 31, 2003).
- T. J. Geldbach, D. Zhao, N. C. Castillo, G. Laurenczy, B. Weyershausen, and P. J. Dyson, *J. Am. Chem. Soc.*, **128**, 9773 (2006).

About the Authors

PAUL DYSON is the Director of the Laboratory of Organometallic and Medicinal Chemistry (since 2002) at the Swiss Federal Institute of Technology in Lausanne (EPFL) where he has worked since 2002, previously residing in the UK. He may be reached at Paul.Dyson@epfl.ch.

TILMANN GELDBACH currently works for Chemspeed Technologies (Basel, Switzerland), previously working with Paul Dyson in the field of ionic liquids. Together they co-authored a book entitled, *Metal Catalysed Reactions in Ionic liquids* published by Springer in 2005 as part of the book series *Catalysis by Metal Complexes*. He may be reached at tilmann.geldbach@chemspeed.com.