Tetrahedron 66 (2010) 1082–1090

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Benign coupling of reactions and separations with reversible ionic liquids

Ryan Hart [a], Pamela Pollet [b,c], Dominique J. Hahne [d], Ejae John [b], Veronica Llopis-Mestre [b], Vittoria Blasucci [a], Hillary Huttenhower [b], Walter Leitner [d], Charles A. Eckert [a,b,c], Charles L. Liotta [a,b,c,*]

[a] Department of Chemical & Biomolecular Engineering, Georgia Institute of Technology, Atlanta GA, 30332, USA
[b] Department of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta GA, 30332, USA
[c] Specialty Separations Center, Georgia Institute of Technology, Atlanta GA, 30332, USA
[d] Institut für Technische und Makromolekulare Chemie, RWTH-Aachen, 52074 Aachen, Germany

ARTICLE INFO

Article history:
Received 24 July 2009
Accepted 24 October 2009
Available online 10 November 2009

ABSTRACT

Reversible ionic liquids are a novel class of solvents that combine an effective medium where reactions occur with a 'built-in' separation ability for facile recovery of the products and catalysts, making the solvent available for recycle. We report the utility of these solvents in a number of reactions (Claisen–Schmidt condensation, Heck C–C coupling, and CO_2 capture) and discuss the effectiveness of the separation. We also provide insight into the challenges and limitations of using these unique solvent systems to couple reactions and separations.

Published by Elsevier Ltd.

1. Introduction

In academic research laboratories and commercial scale processing alike, reactions and separations are often times thought of as two separate unit operations. Commonly, chemists first develop an optimal set of reaction conditions for a given reaction, and then hand off the product mixture to an engineer to design the separation. The end result is that separations in industrial chemical production comprise a large fraction of the total production cost. Additionally, many multi-step synthetic procedures involve switching between polar and nonpolar solvents to create a homogeneous reaction phase, thereby increasing the number of separation steps required. To eliminate the intermediate separation steps and final product purification stage, one would ideally want a solvent that switches polarity and solubility properties as desired. To ensure viability in commercial scale processing and to reduce further the environmental impact that the chemical industry has, one would also want the ideal solvent system to be recyclable. The desire to combine a solvent that will facilitate a reaction and then offer a separation, combined with the ability to be reused for sustainable processing, led to the development of reversible ionic liquids (RevILs) as a specific class of 'switchable solvents.'[1–4]

Room temperature ionic liquids (ILs) have received much attention from the scientific community in recent years. There is almost a limitless combination of anions and cations that can be used, and some say that ILs are the answer to all solution chemistry problems a chemist or engineer could face. However, the one issue most researchers do not address when dealing with reactions in ILs is the separation step. ILs have proven to be very effective as reaction media, but isolating products or catalysts from the solvent remains difficult, except for very volatile products that can be easily stripped from the IL. This problem becomes even more severe if purification of the ILs for recovery or recycling is considered. It quickly becomes evident that when the separation step is considered in the overall processing scheme, the appeal of using ILs in organic synthesis is quickly diminished.

In recent years we have examined many techniques to couple reactions and separations, including: supercritical fluids,[5–15] near-critical fluids,[11,16–20] phase-transfer catalysts,[21–23] gas-expanded liquids,[10,11,24–27] the Organic Aqueous Tunable Solvents process (OATS),[28–30] and piperylene sulfone (a recyclable DMSO substitute).[31–33] The most recent and exciting addition to our arsenal of novel solvent systems are reversible ionic liquids. Just like conventional ILs, reversible ionic liquids can be designed for a specific application, where we can adjust the molecular architecture of the solvent system to achieve the desired solvent properties. Going beyond the synthesis and characterization of RevILs, we have examined the use of these unique solvent systems for a variety of industrially relevant applications. In addition to a discussion of the positive aspects of RevILs in reactions and separations, the challenges and limitations of these solvent systems will also be addressed.

2. Background on reversible ionic liquids

A large number of chemical processes involving reactions and separations are performed in solution. The solvent provides

---

* Corresponding author. Fax: +404 385 3210.
E-mail address: Charles.liotta@chemistry.gatech.edu (C.L. Liotta).

0040-4020/$ – see front matter Published by Elsevier Ltd.
doi:10.1016/j.tet.2009.11.014

a means of bringing reactants together to facilitate reaction. It also provides a means of temperature control for both endothermic and exothermic reactions. The difference in solute solubilities in various solvents is the basis for crystallization and extraction as unit operations in separation processes. The chemical industry has a continuous demand for better solvent alternatives for chemical processes—solvents in which reactions can occur in high yields at reasonable rates under relatively mild reaction conditions, where product isolation is facile, and where recycle of the solvent system is possible.

Tunable solvents are defined as solvents that change their physico–chemical properties continuously upon variation of external stimuli such as pressure, temperature or composition. An illustrative example is provided by the biphasic system containing room temperature ILs and supercritical carbon dioxide ($scCO_2$), where the physico–chemical properties such as gas solubility, viscosity, and melting points depend strongly on the amount of dissolved CO_2 present in the IL phase.[34] Such changes can drastically influence the chemical reactivity in these systems, as demonstrated by catalytic hydrogenation reactions in IL/$scCO_2$.[35] In contrast, *switchable solvents* change properties as a step-wise function via changes in their molecular structure upon application of external stimuli. In other words, they can be switched 'on' and 'off' by reversible chemical transformations. The Liotta–Eckert–Jessop groups reported the first example of switchable solvent, which can be switched back and forth from a molecular liquid to an ionic liquid upon reaction with CO_2.[2,3] A schematic representation is shown for the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and alcohol system (Fig. 1).

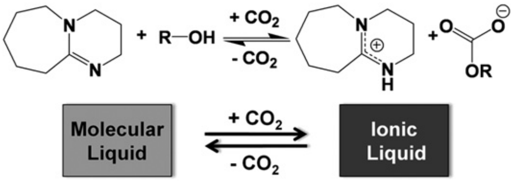

Figure 1. Reversible switch from a molecular liquid mixture of DBU and alcohol (R–OH) to the ionic liquid $[DBUH]^+[RCO_3]^-$ upon addition of CO_2. R=C_1 to C_{12}.

Traditional ionic liquids, such as $[BMIM][BF_4]$, [BMIM][BTA], or $[BMIM][RSO_4]$ (to name just a few popular ones) have been widely explored during the past decade for synthetic transformations with marked success.[36,37] To this day however, efficiently achieving both reaction and separation in traditional ionic liquids remains a major challenge. The inherent ionic nature of molten salts and their relatively high viscosity often precludes distillation of the IL itself or precipitation of the product. Commonly, the product is extracted from the IL with a nonpolar solvent such as hexane.[38] The extraction strategy is product-dependent, generates significant amounts of organic waste, and disposal or regeneration of the contaminated IL phase can be costly. Extraction of the product with $scCO_2$ has been shown to be a possible separation technique, and in many cases represents an environmentally benign alternative.[8,39–41] In all cases, separations from ILs are typically restricted to removal of very nonpolar and/or highly volatile components. With the advent of switchable systems, this situation is fundamentally changed. For the case of RevILs, the solvent can take two different forms—molecular and ionic—and each form exhibits considerably different properties. The resulting property change upon switching from one solvent form to another is so drastic that it opens up unique opportunities to address simultaneously reactions and separations. This article discusses two classes of RevILs, a two-component system and a single component system.

The two-component systems presented here are composed of an equimolar mixture of *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butylguanidine (TMBG) or DBU and an alcohol such as methanol. Although not discussed in this article, it should be noted that Weiss and coworkers have investigated other two-component systems involving guanidines or amidines with amines.[42–44] Just like the DBU/alcohol system, the TMBG/alcohol system reacts with CO_2 (under atmospheric conditions) to form the corresponding ionic liquid, *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butyl-guanidinium alkylcarbonate (Fig. 2). The reaction of alcohols with CO_2 in the presence of amidines or guanidines to form ionic liquids is an equilibrium reaction governed by many factors such as structure, temperature, and pressure. Studies to understand the effect of each parameter are currently ongoing.

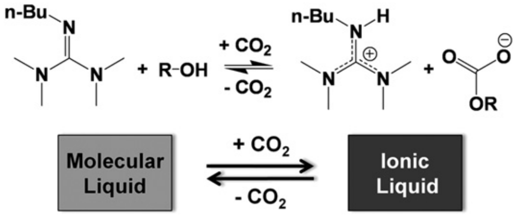

Figure 2. Reversible switch from a molecular liquid mixture of TMBG and alcohol (R–OH) to the ionic liquid $[TMBGH]+[RCO_3]^-$ upon addition of CO_2. R=C_1 to C_{12}.

The major distinction between the one-component and the two-component systems is that the one-component system does not require the presence of an equimolar amount of alcohol, simplifying the reaction system and subsequent processing schemes. Reaction of CO_2 with the amine precursors, trialkoxy- or trialkylsilylpropylamines, forms the corresponding ionic liquids (Fig. 3). It should be emphasized that the reaction of amines with CO_2 to form carbamic acids and/or carbamates has long been known and used for CO_2 separation.[45–47] In addition, the formation of carbamates decreases the nucleophilicity of the nitrogen, making the reversible carbamate formation a successful protecting strategy for the amine group.[13,25,48]

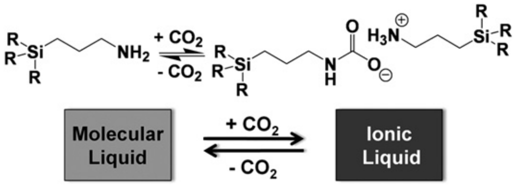

Figure 3. One-component system: reversible switch from a molecular liquid (trialkoxy- or trialkyl- silylpropylamine) to its corresponding ionic liquid upon addition of CO_2. R=OC_1, OC_2, C_2 or C_3.

The synthesis and characterization of both classes of reversible ionic liquids is reported herein, with an emphasis on the stepwise property change upon switching from the neutral to the ionic state and back. We discuss the use of RevILs for integration of reaction and separation in the Claisen–Schmidt condensation reaction, Heck reaction, and CO_2 capture. Additionally, we also discuss some limitations and challenges that have been observed.

3. Two-components RevILs

3.1. Physical properties and synthesis

The two-component reversible ionic liquids are prepared by bubbling CO_2 through equimolar solutions of TMBG or DBU and various alcohols (from methanol to dodecanol) (Figs. 1 and 2). The reversible formation of the ionic products was characterized by ^{1}H and ^{13}C NMR, elemental analysis, FTIR, melting points, differential scanning calorimetry (DSC), and conductivity measurements.[3] Reversal of the ionic liquid back to the molecular liquid can be achieved by bubbling N_2 (or other inert gases) through the ionic liquid or in the case of TMBG based systems, by heating at temperatures above 60 °C.

Conductivity measurements clearly demonstrate the reversibility and repeatability of the formation of the ionic versus molecular species for three consecutive cycles (Fig. 4). At the beginning of the experiment, the equimolar mixture of TMBG/methanol in chloroform does not conduct electricity (0 μS/cm). As CO_2 is bubbled into the solution, conductivity increases sharply to 250 μS/cm. This is consistent with the formation of the ionic species *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butyl-guanidinium methylcarbonate. Upon heating the solution the conductivity decreases to ∼0 μS/cm, confirming the complete and repeatable reversal of the ionic liquid to the molecular liquid.

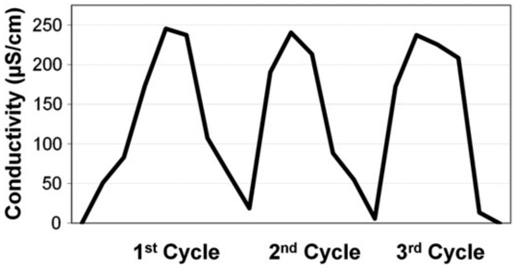

Figure 4. Conductivity of TMBG/methanol in chloroform solvent as a function of CO_2 addition and elimination.

The relative polarity of the molecular liquid precursor and the corresponding ionic liquid was determined via UV–vis absorption measurement of the Nile Red dye (a common solvatochromic probe).[3] Equimolar mixtures of DBU/alcohol or TMBG/alcohol become significantly more polar when exposed to CO_2, as shown by the shift of the λ_{max} to longer wavelengths (Fig. 5). For example, the TMBG/methanol mixture exhibits a λ_{max} of 538.0 nm while the λ_{max} of the corresponding ionic liquid (*N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butylguanidinium methylcarbonate) is 554.0 nm, corresponding to a shift of 16.0 nm. Such a shift in λ_{max} represents a polarity switch akin to going from chloroform to acetic acid. The Nile Red experiments suggest that the polarity of both molecular and ionic forms depend on the length of the alkyl chain on the alcohol. However, the reported λ_{max} values fall well within the range found for non-switchable ionic liquids.[49] The many possible combinations of base and alcohol give a wide selection of solvent switches. Using shorter alcohols gives a greater difference between the polarities of the ionic and neutral forms of the solvent. Furthermore, switchable solvents based on TMBG have a larger switch in polarity compared to those based upon DBU; the ionic forms of the two systems are nearly comparable while the neutral form of TMBG is significantly less polar than that of DBU.

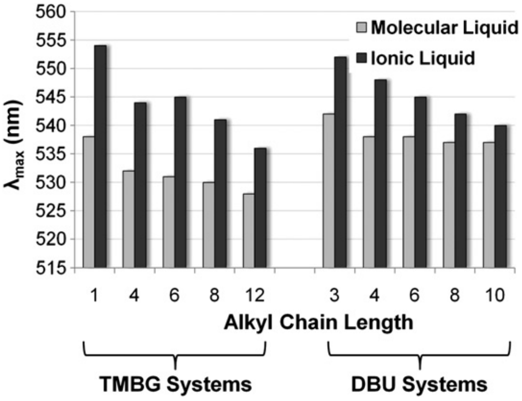

Figure 5. The polarity of the neutral and ionic forms of the DBU/alcohol and TMBG/alcohol solvents as a function of the alcohol chain length.

3.2. Claisen–Schmidt condensation reaction of butanone and benzaldehyde

The Claisen–Schmidt condensation of butanone and benzaldehyde yields three products: the internal enone (3-methyl-4-phenylbut-3-en-2-one), the terminal enone (1-phenyl-pent-1-en-3-one) and water (Fig. 6).[20,50] Under basic conditions, the terminal enone product is the predominant product formed.[51]

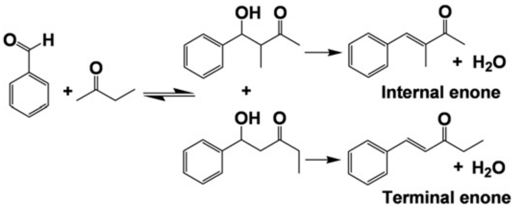

Figure 6. Claisen–Schmidt condensation of 2-butanone and benzaldehyde.

The reaction of butanone and benzaldehyde was carried out in TMBG, which played the dual role of base catalyst and solvent.[52,53] The isolation of the enone products was performed by adding octane and methanol to the reaction mixture, followed by the addition of CO_2, which triggered the formation of the ionic liquid. Under these conditions an octane phase separated from the newly developed ionic liquid phase. The enone products were predominantly in the octane phase and were easily separated by decantation. After 24 h at room temperature or 3 h at 80 °C, yields of 48% and 44% in enone products were obtained, respectively (Table 1). The formation of the terminal and internal enone products was also studied as a function of time at 80 °C. As the reaction time increased, the yields first increased from 13% at 1 h to 44% at 3 h and then began to decrease after 4 h (Table 1). The decrease was attributed to competing condensation processes between the enone products and the benzaldehyde, resulting in lower overall yields of the desired products. As a consequence, short reaction times to partial conversions were necessary in order to develop a process in which isolated yields were maximized and solvent recycle was possible (Fig. 7).

Table 1
Reaction conditions and yields for the condensation of butanone and benzaldehyde in the presence of TMBG

Temperature (°C)	Time (h)	Yield (%)
Room Temp	24	48
80	1	13
80	2	24
80	3	44

The first attempt to recycle TMBG upon reversal of the ionic liquid failed. Water, a product from the condensation reaction, reacted with TMBG and CO_2 to form the *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butylguanidium carbonate. The formation of the carbonate salt resulted in a dramatic increase in the viscosity of the ionic liquid. This, coupled with the severe conditions for the reversal of the

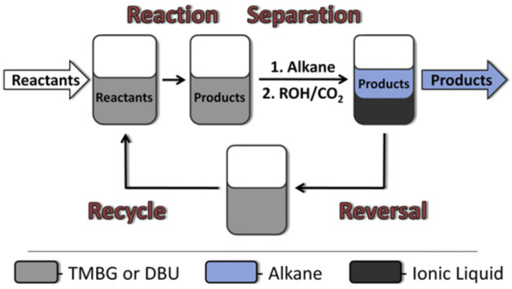

Figure 7. Process that couples reaction and separation for the Claisen–Schmidt condensation of butanone and benzaldehyde.

carbonate salt, precluded recycling. However, the reversal of the ionic liquid and recycle of TMBG were successful when the reaction mixture was dried over magnesium sulfate (and filtered) prior to reaction with CO_2. By introducing the drying step into the process, the TMBG was successfully recycled three times. The isolated yields in enone products were 34, 32 and 34% for each cycle with a consistent product distribution of 95% terminal enone product. Again, it should be emphasized that partial conversion was necessary in order to avoid the higher condensation products, thus providing recycle for the Claisen–Schmidt condensation in RevILs.

3.3. Heck reaction—reaction of bromobenzene and styrene

Palladium catalyzed C–C coupling reactions between an aryl halide and a substituted alkene, also known as Heck reactions, are useful chemical transformations in many synthetic processes. Heck reactions inherently cause the formation of HX (X=halide; Fig. 8), which needs to be neutralized by a base to recover the catalyst. Therefore, stoichiometric amounts of salt are formed as a by-product.

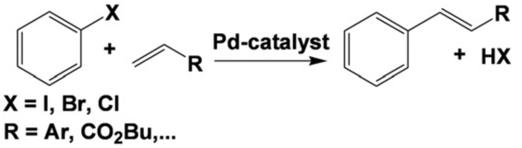

Figure 8. General reaction scheme for Heck-type coupling reactions.

In attempts to facilitate product isolation and recycle of the catalyst, ionic liquids have been widely explored to immobilize Pd complex catalysts for C–C bond formation.[37,54] In some cases, beneficial effects of the ionic environment on the efficiency and selectivity of the catalyst have been observed. It was also demonstrated that the organic products can be extracted and catalyst solutions can be reused. Some extractions have included the use of $scCO_2$ as an extraction medium.[55,56] In most cases, however, the accumulation of stoichiometric amounts of salts in the IL was not addressed. The presence of salts makes any continuous processing problematic and will ultimately limit batch-wise recycling. [For a notable exception using a triphasic system of H_2O/IL/organic, see Perosa, et al.[57]] The unique properties of RevILs open new opportunities to make Heck processes more efficient as well as more environmentally-friendly by combining an efficient reaction with the ability to selectively separate the desired products, salt by-product, and catalyst.

Heck reactions were investigated in the two-component reversible ionic liquid mixture of DBU/hexanol. The overall process was designed to couple the reaction, which was carried out under ionic conditions, and a two-stage separation: first isolating the nonpolar product from the ionic liquid, and second by precipitating the salt by-product from the nonpolar solvent mixture. In principle, the reversible 'switch' from ionic to molecular solvent should enable the separation of product and by-product sequentially, leading to a recycling of the solvent system and the catalyst (Fig. 9).

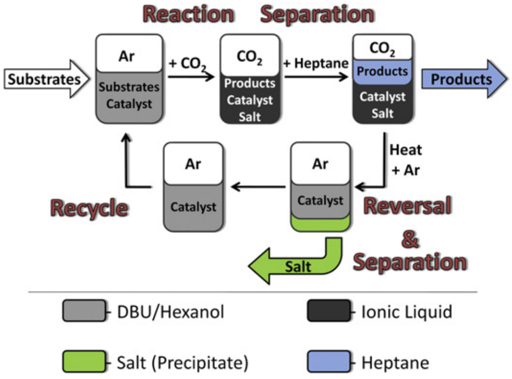

Figure 9. General reaction/separation scheme for the Heck reaction in the reversible ionic liquid solvent system.

As a benchmark reaction, the palladium catalyzed Heck reaction of bromobenzene and styrene was investigated (Fig. 10). *E*-stilbene was produced as the major product. Other isomers (1,1-diphenylethylene and *Z*-Stilbene) were obtained in yields of less than 5%.

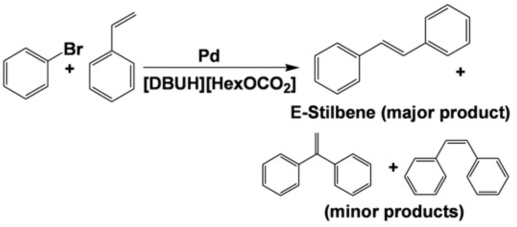

Figure 10. Heck reaction of bromobenzene and styrene in the reversible ionic liquid $[DBUH]^+[HexOCO_2]^-$.

Several forms of palladium were compared in the reaction process. Palladium acetate and palladium chloride in the presence and absence of triphenylphosphine ligand were compared. In addition, the preformed palladium chloride–triphenylphosphine complex was also investigated (Table 2). The following general procedure was employed. The required amount of palladium catalyst was introduced into the reaction vessel in a toluene solution. The solvent was then removed under reduced pressure, and the preformed reversible ionic liquid was added. The starting materials, bromobenzene (1 equiv) and the styrene (1.2 equiv), were introduced into the reaction vessel and the vessel pressurized with CO_2. The reaction mixture was kept at temperature for three days. After cooling and depressurization, the reaction products were extracted with heptane and analyzed via GC with tridecane as internal standard.

Table 2
Effect of catalyst type and concentration on the Heck reaction of bromobenzene and styrene at 115 °C and 30 bar CO_2

Entry	Catalyst	Concentration (mol %)	Ligand	Yield (% *E*-stilbene)
1	$Pd(OAc)_2$	0.5	—	0
2[a]	$Pd(OAc)_2$	0.5	TPP	2
3	$PdCl_2$	0.5	—	26
4[a]	$PdCl_2$	0.5	TPP	31
5	$PdCl_2(TPP)_2$	0.5	—	87
7	$PdCl_2(TPP)_2$	1	—	83
8	$PdCl_2(TPP)_2$	2	—	97

[a] - Catalyst precusor and ligand were dissolved in acetonitrile and combined in the reaction vessel. After stirring for 20 min the solvent was removed under reduced pressure.

The isolated complex $PdCl_2(TPP)_2$ (TPP=triphenylphosphine, PPh_3) was found to give the best performance, with up to a 97% yield of *E*-stilbene using a catalyst loading of 2 mol % (Table 2). The effect of temperature and CO_2 pressure on the yields of product was also investigated (Table 3). Carrying out the coupling under 30 bar of CO_2 at 115 °C was found to afford the higher yield in *E*-stilbene. No additional base was required in these experiments since free DBU, in equilibrium with the ionic species, was found to act as a scavenger for HBr.

Table 3
Effect of CO_2 pressure and temperature on the Heck reaction of bromobenzene and styrene

Entry	Temperature (°C)	Pressure (bar)	Yield (%)
1	100	30	9
2	115	30	87
3[a]	115	0	22
4	115	50	39
5	140	30	65

[a] - 2 mol % $PdCl_2(TPP)2$.

Extraction of the product(s) from the reaction mixture was carried out under a CO_2 atmosphere to ensure that $[DBUH]^+[HexOCO_2]^-$ remained in the ionic form. However, GC analysis indicated that some free DBU and hexanol were also extracted into the heptane phase. After phase separation, the ionic phase was heated and purged with argon to revert back to the DBU/hexanol molecular liquid. A colorless precipitate separated from the solution; it was filtered off and identified as the HBr salt of DBU by NMR spectroscopy. The supernatant solution remained yellow, suggesting the presence of dissolved palladium catalyst.

The application of RevILs to the Heck reaction offers a new and potentially effective solution for the problem of salt accumulation. The reaction was carried out in the ionic liquid form of the solvent, from which the nonpolar product could be isolated by extraction. Reversing the solvent to its molecular liquid state caused the salt by-product to precipitate. After separation of the salt, the solvent (containing the catalyst) was switched back to its ionic form and was used for another Heck reaction showing significant activity[†]. We are currently developing an optimized recycle procedure for the Heck reaction using RevILs.

4. One-component RevILs

4.1. Synthesis and properties

Just as in the two-component systems, the one-component reversible ionic liquids are prepared by bubbling CO_2 through a primary amine molecular liquid precursor to cause the conversion to the ionic liquid. Here we discuss four one-component RevIL solvent systems (Fig. 11). The reversible formation of the ionic products was characterized by ^1H and ^{13}C NMR, elemental analysis, FTIR, and DSC.[4,58] Reversibility back to the molecular liquid with these systems is easily achieved by heating or stripping with an inert gas. From a processing standpoint, the one-component system is superior to the two-component system due to the elimination of the need for stoichiometric alcohol. With the two-component system, the DSC results indicated that some of the alcohol is lost with the release of CO_2 (especially the lower MW alcohols). However, for the one-component system the loss of CO_2 occurs at a temperature substantially different (>100 °C) from the evaporation of the molecular liquid. The one-component system also affords ease of processing and ionic liquid preparation, as the consideration of reactant stoichiometry can be ignored (when compared to the two-component systems).

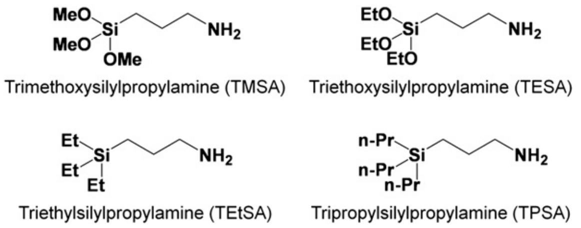

Figure 11. The one-component reversible ionic liquid precursor molecules.

Because the presence of water can result in the cleavage of the Si–O bond in the trialkoxysilylpropylamines, we developed ionic liquids based on trialkylsilylpropylamines. Stability tests of the one-component RevILs revealed that while under wet conditions the trialkoxy- RevILs did in fact degrade quickly, the trialkyl- RevILs showed no loss of structural integrity over the period of several months.[58] This is an important consideration for the application of the one-component RevIL solvents to applications where water is either present, required or produced.

The Nile Red experiments show for the one-component systems that the conversion from the molecular solvent form to the ionic form results in a drastic change in polarity (Fig. 12).[58] The magnitude in change of polarity for all four RevILs is about 10 nm, which is less than for some of the two-component solvents where the polarity change was found to be a function of the base and alcohol used. Just like the two-component systems, however, the polarity of both the molecular liquid form and ionic liquid form decrease as the alkyl chain length on the Si- group is increased.

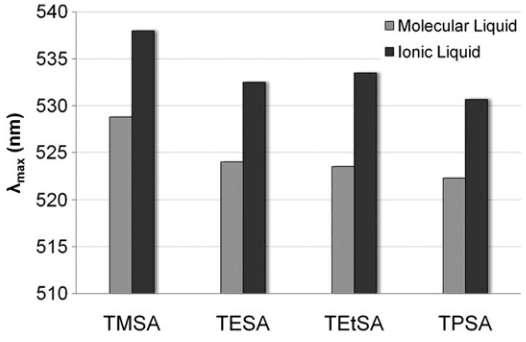

Figure 12. The polarity of the neutral and ionic forms of the one-component reversible ionic liquid solvents.

4.2. CO_2 Capture application

One of the most daunting tasks facing the chemical industry today is the need to develop an energy-efficient process to capture CO_2 from existing point source emitters. For the application of flue gas treatment from coal-fired power plants, alkanolamines have received much interest as a reactant to remove selectively the CO_2 from dilute feed streams. Because the product from the reaction of alkanolamines with CO_2 is a solid, an additional solvent (commonly water) is needed for continuous processing. The regeneration of reactant is achieved through thermal processing, but much energy is

---

[†] Heck Reaction Recycle: The DBU/hexanol solution containing the Pd-species was treated with CO_2 to switch back to the ionic form, and recharged with additional preformed ionic liquid to compensate for losses from handling. Fresh substrates were added, the mixture was pressurized with 30 bar CO_2 and stirred at 115 °C for three days. After reaction, the mixture was treated as before for sequential product/salt separation and catalyst recycle. With 87% yield of *E*-Stilbene in the first run and 55% in the second, the recovered catalyst solution displayed lower activity than fresh catalyst.

wasted through heating of the solvent. The one-component RevILs overcome this energy waste by combining the reactant with the solvent to eliminate the need of an added solvent. Here we are using the reaction-induced switch of the RevILs to give separation.

As previously reported, the RevILs behave as dual-capture solvents for CO_2 capture: (1) the highly selective and efficient separation through the chemical reaction of CO_2 with the molecular liquid to form the ionic liquid and (2) the high capacities offered by the physical absorption of the CO_2 into the ionic liquid (Fig. 13).[58] The capacity from reaction was calculated using a stoichiometric ratio for CO_2:amine of 1:2. Due to the relative bulkiness of the silylated amines, the capacities for reaction are all fairly low and relatively similar. But a significant enhancement in capacity is observed when the physical absorption is combined with the capacity through reaction. The physical absorption capacities indicate that the bulkier side groups attached to the molecule result in higher capacity. We believe that this is due to the decreased packing efficiency of the molecules leaving more space for the CO_2 in the ionic liquid matrix.

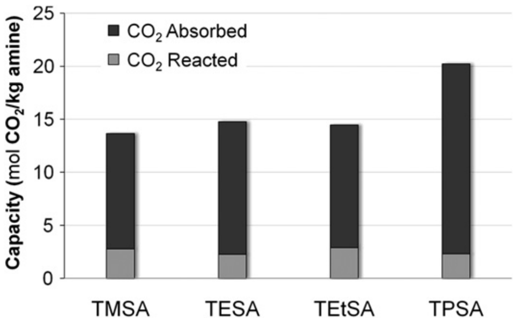

Figure 13. CO_2 capacities (reported here as mol of CO_2 per kg amine) for both capture through reaction (calculated) and physical absorption (measured at 35 °C and 62 bar), showing the combined effect.

The one-component RevILs, just as the two-component RevILs and conventional ILs, have an almost unlimited possibility of structural variability that would give rise to unique solvents. The drastic change in properties observed as they are switched from molecular form to ionic indicates potential to be used as solvents for synthesis to combine reaction and separation. All one-component candidates show promise as CO_2 capture agents that use reaction to give separation, and we are continuing to investigate how the branching on the side chain can result in more favorable properties for such applications.

5. Reversible ionic liquids: challenges and limitations

Realistically, reversible ionic liquids are not the solution to all reaction-separation problems. In this section, their limitations and challenges are discussed for three reactions and one processing issue: 1) the cyanosilylation of cyclohexanone, 2) the Michael addition of 2-cyclohexenone, 3) the Michael addition of aniline to 1,3-diphenyl-propenone and 4) viscosity of ionic liquid form.

5.1. Cyanosilylation of cyclohexanone

The cyanosilylation of cyclohexanone with trimethylsilyl cyanide (TMSCN) was carried out in TMBG at room temperature (Fig. 14). The isolation of the product was performed by adding heptane and methanol to the reaction mixture. The addition of CO_2 triggered the formation of the ionic liquid, which resulted in a two-phase system, the ionic liquid and the heptane phases. The product 1-trimethylsilyloxy-1-cyclohexanecarbonitrile partitioned predominantly into the heptane phase, thus facilitating its separation from the reaction mixture.

Figure 14. Cyanosilylation of cyclohexanone in TMBG.

The variation of reaction time (1.5 to 16 h) as well as of the molar ratio of TMBG to cyclohexanone (0.02/1 to 1/1) had little or no effect on the reaction yields, which were essentially quantitative. However, the analysis of the ionic liquid phase (via NMR) indicates the formation of the ionic by-product *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butyl-*N*″-trimethylsilylguanidinium cyanide (Fig. 15).[59] The formation of this ionic by-product is detrimental as it is irreversible and its presence drastically increases the viscosity of the ionic liquid phase, precluding the quantitative reversal of the ionic liquid for recycle. The formation of the silyl salt was minimized, but not eliminated, by adding heptane at the reaction stage as opposed to the separation stage. The product yields were not affected; they remained quantitative (96 to 98%). Under these conditions, the recycling of TMBG upon reversal of the ionic liquid phase was investigated at two molar ratios of TMBG to cyclohexanone to TMSCN, 0.4/1/1.2 and 1/1/2, respectively (Table 4). In the first cycle, the 1-trimethylsilyloxy-1-cyclohexanecarbonitrile product was isolated with 86 and 96% yields (Table 4, entries 1–1 & 2–1, respectively). The ionic liquid phase was then reversed upon heating at 50 °C for 4 h. The resulting TMBG was reused for a second cycle, yielding the desired product in 54 and 56% (Table 4, entry 1–2 & 2–2, respectively). The loss of yields upon recycle has been attributed to the contamination of the guanidine precursor with the by-product (*N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butyl-*N*″-trimethylsilylguanidinium cyanide).

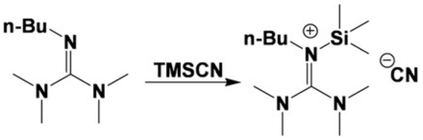

Figure 15. Formation of the by-product *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butyl-N″-trimethylsilyl guanidinium cyanide.

Table 4
Cyanosilylation of cyclohexanone coupled with the recycling of the ionic liquid phase

Entry	Mole Ratio TMBG/Cyclohexanone/TMSCN	Time (h)	Yield (%)
1–1	0.4/1/1.2	17	96
1–2	0.4/1/1.2	16	54
2–1	1/1/1.2	16	86
2–2	1/1/1.2	16	56

5.2. Michael addition of dimethylmalonate to 2-cyclohexenone

The base-catalyzed Michael addition of dimethyl malonate to 2-cyclohexenone was carried out in TMBG at 80 °C. In all experiments, the ratio of TMBG to malonate to 2-cyclohexenone was 1/1/1. Upon addition of methanol, hexane and CO_2, the formation of the ionic liquid yielded two phases, the ionic liquid and the hexane phase. The analysis by GC–MS of the hexane phase showed the complete disappearance of the starting materials. The ^1H NMR analysis showed that the product existed in the ionic form and was present exclusively in the ionic liquid phase. The reason for this is simply that in a basic medium like TMBG the α-carbon of the β-diester product is deprotonated resulting exclusively in the ionic product (Fig. 16). An acidic work-up with 10% aqueous HCl was performed yielding the neutral form of the product, which now partitioned predominantly into the hexane phase. The neutral product was subsequently isolated in 86 to 100% yields. Although TMBG can be recovered and eventually recycled, the necessity of an acidic work-up complicates the overall process providing little advantage for coupling the reaction and separation.

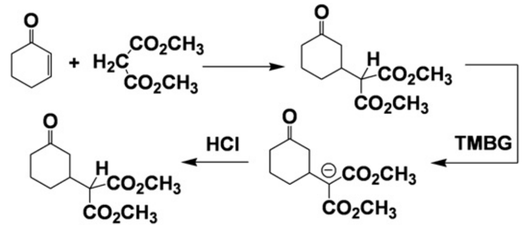

Figure 16. Base-catalyzed Michael addition of dimethylmalonate and 2-cyclohexenone.

5.3. Michael addition of aniline to 1,3-diphenyl-propenone

The Michael addition of aniline to 1,3-diphenyl-propenone (chalcone) was carried out by first dissolving the reaction partners in a methanol:heptane mixture (1:4) followed by the addition of TMBG (in equimolar ratio relative to methanol) (Fig. 17). The reaction was run at 80 °C for 18 h. The isolation of the 1,3-diphenyl-3-phenylamino-propan-1-one product was performed by bubbling CO_2 throughout the mixture (forming the ionic liquid) resulting in a two-phase ionic liquid and heptane system. The 1,3-diphenyl-3-phenylamino-propan-1-one partitioned predominantly into the heptane phase, from which it was isolated in 86% yield. After reversal of the ionic liquid at 60 °C for 4 h, the TMBG was recycled. In the second cycle, the isolated yield decreased to 45%. We conjecture that the accumulation of organic materials in the ionic liquid phase changes the product partitioning in recycle attempts when compared to the first cycle.

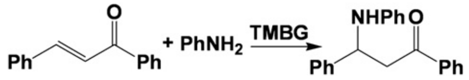

Figure 17. TMBG-catalyzed addition of aniline to 1,3-diphenyl-propenone.

5.4. Viscosity of reversible ionic liquids

Another important processing factor examined for the RevILs is viscosity (Fig. 18),[58] where the viscosity change in going from molecular form to ionic form is about three orders of magnitude. And although the data suggest there is potential for altering the structure of the RevIL to decrease the viscosity of both molecular and ionic solvent forms, the magnitude in change is still significant enough to pose complications in continuous flow processing of the RevILs and must be considered when designing a process.

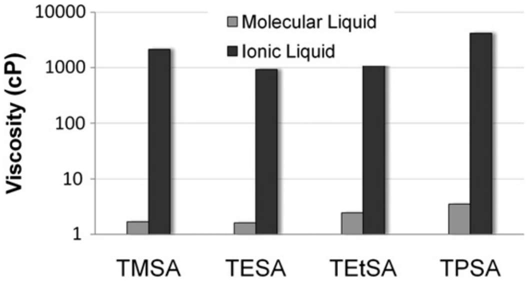

Figure 18. The viscosity of the neutral and ionic forms of the one-component reversible ionic liquid solvents.

6. Conclusions

While conventional room temperature ionic liquids are often cited as environmentally-friendly alternative solvents, current research continues to indicate that they will face severe limitations in applicability due to separation difficulties. In this paper, we present two reactions (Claisen–Schmidt condensation and Heck coupling) that were successfully carried out in RevILs with the added capabilities of easy separation of the product and recycling of the solvent system. In addition, we emphasized the limitations and challenges of RevILs for the cyanosilylation of cyclohexanone and two examples of Michael additions. The ability to couple reaction and separation in a common solvent system allows for the development of sustainable processing in the chemical industry, that is, simpler, more efficient, and more environmentally-benign than solvents commonly used today. By treating a typical reaction/separation process inter-dependently rather than independently, we are changing the approach that research laboratories and commercial plants take in the design of processes. With proper care and technique, we show that reversible ionic liquids are capable of being recycled, completely eliminating the need to purify or dispose of waste. Additionally, they facilitate catalyst recovery, yielding efficient separations of expensive catalysts for reuse. We continue to investigate other possible systems where switchable solvent systems have much promise in our attempt to push the envelope of sustainable solvent systems.

7. Experimental

7.1. General

GC–MS analyses to quantify the concentrations of reactants and products were conducted on an HP 6890 GC–MS. Standard calibration curves of all starting materials and products were prepared. If the reaction was recycled, the desired products were isolated, characterized by NMR and compared to literature values.

7.2. Claisen–Schmidt condensation of butanone and benzaldehyde

The butanone (1.7 mL, 0.019 mol) and the benzaldehyde (2.03 mL, 0.019 mol) were added to TMBG (4.1 g, 0.024 mol). The reaction was then stirred at room temperature or at 80 °C for the desired amount of time. After cooling, $MgSO_4$ was added to the reaction mixture and stirred for ∼30 min before being filtered. Methanol (1 mL) and heptane (1 mL) were then added and CO_2 was bubbled through the mixture for ∼1 h. The heptane phase was analyzed by GC–MS. The products isolated from the hexane phase and from the ionic liquid phase were analyzed by ^1H NMR. *1-phenyl-pent-1-en-3-one*[60]: ^1H NMR: ($CDCl_3$): 1.16 (3H, t), 2.7 (2H, q), 6.7 (1H, d), 7.37–7.4 (3H, m), 7.5–7.6 (3H, m). *4-phenyl-3-methyl-3-buten-2-one*: ^1H (DMSO-d_6): 1.87 (d, 3H), 2.37 (s, 3H), 7.3–7.45 (m, 4H), 7.59 (s, 1H).

7.3. General procedure for the Heck Reaction

Styrene was distilled under reduced pressure, filtered through neutral alumina oxide and stored under argon at −20 °C. DBU was dried over CaH_2, distilled under reduced pressure and stored under argon. Acetonitrile was dried by molecular sieves and kept under argon.

The required amount of catalyst was introduced as a toluene solution into a 10 ml windowed autoclave. The solvent was removed under reduced pressure. DBU (2.00 mL, 13.2 mmol) and hexanol (1.68 mL, 13.2 mmol) were combined in a Schlenk flask under nitrogen atmosphere. CO_2 was sparged trough the solution until the exothermic reaction cooled down. The produced ionic liquid was added to the catalyst, followed by bromobenzene (0.21 mL, 2.0 mmol) and styrene (0.27 mL, 2.4 mmol). The reaction was pressurized with the required CO_2 pressure and stirred for three days at the respective reaction temperature. After cooling down and depressurizing, the reaction mixture was transferred to a Schlenk flask, which was kept under CO_2 at atmospheric pressure. The reaction mixture was extracted with heptane. The heptane phase was evaporated under reduced pressure and analyzed by HP 5890 Series II GC, using tridecane as an internal standard. The reversible ionic liquid was sparged with argon and heated to convert to the molecular phase, precipitating the salt. The supernatant solvent was removed, converted to the ionic liquid and fresh ionic liquid was added. The ionic liquid, containing the catalyst was charged with fresh substrates in the autoclave and treated as mentioned before. The precipitate was washed with pentane and dried under reduced pressure to be analyzed by NMR. *DBU·HBr salt*: ^{1}H ($CDCl_3$): d=1.54–1.77 (6H, m), 1.88–2.00 (2H, m), 2.81 (2H, br s), 3.30–3.47 (6H, m), 4.82 (1H, br s). ^{13}C ($CDCl_3$) d=20.3, 24.5, 27.4, 29.3, 33.5, 39.4, 48.8, 54.3, 165.3.

7.4. Cyanosilylation of cyclohexanone

Trimethylsilyl cyanide (0.8 mL, 0.006 mol) was added to TMBG (0.003–0.006 mol) at room temperature with stirring. Cyclohexanone (0.5 mL, 0.005 mol) was then added slowly at room temperature. After reaction completion, methanol (1 equivalent relative to TMBG) and heptane (0.8 mL) were added. CO_2 was bubbled through the mixture for 1 h to form the ionic liquid. The heptane phase was analyzed by GC–MS and the ionic liquid phase and the isolated product by ^{1}H & ^{13}C NMR. *1-trimethylsilyloxy-1-cyclohexane-carbonitrile.* ^{1}H (DMSO-d_6): 0.2 (s, 9H), 1.48–1.7 (m, 8H), 1.9 (m, 2H). ^{13}C (DMSO-d_6): 1.4, 22.4, 23.8, 38.6, 70.5, 121. *TMBG/TMS-CN salt*: ^{1}H (DMSO-d_6): 0.1 (s, 9H), 0.82 (t, 3H), 0.98 (m, 2H), 1.25 (m, 2H), 2.8 (s, 12H). ^{13}C (DMSO-d_6): 1.1, 13.9, 18.8, 19.7, 31.7, 39.1, 123.4, 161.3.

7.5. Michael addition of dimethyl malonate to 2-cyclohexenone

Cyclohexenone (0.17 mL, 1.75 mmol) was added to TMBG (0.3 g, 1.75 mmol). Dimethyl malonate (0.2 mL, 1.75 mmol) was then added at room temperature. The reaction was heated to 80 °C for 16 h. After cooling, methanol was added (0.07 mL, 1.75 mmol) and CO_2 was bubbled through the mixture for approximately 1 h. The heptane phase was analyzed by GC–MS and the ionic liquid phase by ^{1}H NMR. When HCl work up was performed, the reaction mixture was treated with aqueous HCl (10%) for ∼1 h. Ether was then added and the biphasic mixture was stirred for ∼1 h. The ether phase was then analyzed by GC–MS. After removal of the ether, the isolated product was characterized by ^{1}H NMR. *3[bis(methoxy-carbonyl)methyl]cyclohexanone*. ^{1}H ($CDCl_3$): 1.4–1.55 (m, 1H), 1.65–1.8 (m, 2H), 1.9–2.0 (m, 1H), 2–2.15 (m, 1H), 2.3–2.55 (m, 5H), 3.3 (d, 1H), 3.75 (s, 6H).

7.6. Michael addition of aniline to 1,3-diphenyl-propenone

Aniline (0.05 mL, 0.5 mmol) and 1,3-diphenyl-propenone (0.11 g, 0.5 mmol) are added to the mixture methanol (0.5 mL) and heptane (2 mL). TMBG was then added (1.8 g, 0.01 mol) and the reaction mixture heated at 80 °C for 16 h. After cooling, methanol (0.5 mL) and heptane (0.5 mL) were added and CO_2 was bubbled through the mixture for ∼1 h. The heptane phase was analyzed by GC–MS. The ionic liquid phase and the isolated product characterized were analyzed by ^{1}H NMR. *3-(N-phenylamino)-1,3-diphenyl-1-acetone.* ^{1}H ($CDCl_3$): 3.46 (d, 1H), 3.49 (d, 1H), 5.02 (m, 1H), 6.57 (d, 2H), 6.67 (m, 1H), 7.05 (m, 2H), 7.25 (d, 1H), 7.3–7.34 (m, 2H), 7.78–7.59 (m, 5H), 7.92 (d, 2H).

Acknowledgements

This project was funded by the US Department of Energy grant NT0005287 and by the National Science Foundation grant 07,22,905. We would like to thank Dr. Leslie Gelbaum, the NMR Center Manager at Georgia Tech, for his assistance with the analysis and interpretation of the NMR spectra.

References and notes

1. Heldebrant, D. J.; Jessop, P. G.; Thomas, C. A.; Eckert, C. A.; Liotta, C. L. *J. Org. Chem.* **2005**, *70*, 5335–5338.
2. Jessop, P. G.; Heldebrant, D. J.; Li, X. W.; Eckert, C. A.; Liotta, C. L. *Nature* **2005**, *436*, 1102.
3. Phan, L.; Chiu, D.; Heldebrant, D. J.; Huttenhower, H.; John, E.; Li, X. W.; Pollet, P.; Wang, R. Y.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *Ind. Eng. Chem. Res.* **2008**, *47*, 539–545.
4. Blasucci, V.; Dilek, C.; Huttenhower, H.; John, E.; Llopis-Mestre, V.; Pollet, P.; Eckert, C. A.; Liotta, C. L. *Chem. Commun.* **2009**, 116–118.
5. Dillow, A. K.; Brown, J. S.; Liotta, C. L.; Eckert, C. A. *J. Phys. Chem. A* **1998**, *102*, 7609–7617.
6. Brown, J. S.; Lesutis, H. P.; Lamb, D. R.; Bush, D.; Chandler, K.; West, B. L.; Liotta, C. L.; Eckert, C. A.; Schiraldi, D.; Hurley, J. S. *Ind. Eng. Chem. Res.* **1999**, *38*, 3622–3627.
7. Thompson, R. L.; Glaser, R.; Bush, D.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **1999**, *38*, 4220–4225.
8. Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254–1255.
9. Nolen, S. A.; Lu, J.; Brown, J. S.; Pollet, P.; Eason, B. C.; Griffith, K. N.; Glaser, R.; Bush, D.; Lamb, D. R.; Liotta, C. L.; Eckert, C. A.; Thiele, G. F.; Bartels, K. A. *Ind. Eng. Chem. Res.* **2002**, *41*, 316–323.
10. Jessop, P.G.; Stanley, R.R.; Brown, R.A.; Eckert, C.A.; Liotta, C.L.; Ngo, T.T.; Pollet, P. Neoteric solvents for asymmetric hydrogenation: supercritical fluids, ionic liquids, and expanded ionic liquids, 2003.
11. Eckert, C. A.; Liotta, C. L.; Bush, D.; Brown, J. S.; Hallett, J. P. *J. Phys. Chem. B* **2004**, *108*, 18108–18118.
12. Koch, D.; Leitner, W. *J. Am. Chem. Soc.* **1998**, *120*, 13398–13404.
13. Furstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000–9006.
14. Solinas, M.; Jiang, J. Y.; Stelzer, O.; Leitner, W. *Angew. Chem., Int. Ed.* **2005**, *44*, 2291–2295.
15. Maayan, G.; Ganchegui, B.; Leitner, W.; Neumann, R. *Chem. Commun.* **2006**, 2230–2232.
16. Chandler, K.; Deng, F. H.; Dillow, A. K.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **1997**, *36*, 5175–5179.
17. Chandler, K.; Liotta, C. L.; Eckert, C. A.; Schiraldi, D. *Aiche J.* **1998**, *44*, 2080–2087.
18. Lesutis, H. P.; Glaser, R.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **1999**, 2063–2064.
19. Patrick, H. R.; Griffith, K.; Liotta, C. L.; Eckert, C. A.; Glaser, R. *Ind. Eng. Chem. Res.* **2001**, *40*, 6063–6067.
20. Nolen, S.; L.L., C.; Eckert, C. A.; Glaser, R. *Green. Chem.* **2003**, *5*, 663–669.
21. Chandler, K.; Culp, C. W.; Lamb, D. R.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **1998**, *37*, 3252–3259.
22. Wheeler, C.; Lamb, D. R.; Jayachandran, J. P.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **2002**, *41*, 1763–1767.
23. Jayachandran, J. P.; Wheeler, C.; Eason, B. C.; Liotta, C. L.; Eckert, C. A. *J. Supercrit. Fluids* **2003**, *27*, 179–186.
24. Chamblee, T. S.; Weikel, R. R.; Nolen, S. A.; Liotta, C. L.; Eckert, C. A. *Green Chem.* **2004**, *6*, 382–386.
25. Xie, X. F.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **2004**, *43*, 7907–7911.
26. Weikel, R. R.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **2007**, *46*, 5252–5257.
27. Hallett, J. P.; Ford, J. W.; Jones, R. S.; Pollet, P.; Thomas, C. A.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **2008**, *47*, 2585–2589.
28. Lu, J.; Lazzaroni, J.; Hallett, J. P.; Bommarius, A. S.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **2004**, *43*, 1586–1590.
29. Broering, J. M.; Hill, E. M.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A.; Bommarius, A. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4670–4673.
30. Hill, E. M.; Broering, J. M.; Hallett, J. P.; Bommarius, A. S.; Liotta, C. L.; Eckert, C. A. *Green Chem.* **2007**, *9*, 888–893.
31. Vinci, D.; Donaldson, M.; Hallett, J. P.; John, E. A.; Pollet, P.; Thomas, C. A.; Grilly, J. D.; Jessop, P. G.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **2007**, 1427–1429.
32. Jiang, N.; Vinci, D.; Liotta, C. L.; Eckert, C. A.; Ragauskas, A. J. *Ind. Eng. Chem. Res.* **2008**, *47*, 627–631.

33. Donaldson, M. E.; Mestre, V. L.; Vinci, D.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **2009**, *48*, 2542–2547.
34. *Topics in Organometallic Chemistry*; Langanke, J., Leitner, W., Eds.; Springer: Berlin/Heidelberg, 2008; Vol. 23, pp 91–108.
35. Solinas, M.; Pfaltz, A.; Cozzi, P. G.; Leitner, W. *J. Am. Chem. Soc.* **2004**, *126*, 16142–16147.
36. *Ionic Liquids III: Fundamentals, Progress, Challenges, and Opportunities*; American Chemical Society: Washington, DC, 2005.
37. *Ionic Liquids in Synthesis* 2nd, completely rev. and enl. ed.; Wiley–VCH: Weinheim, 2008.
38. Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083.
39. Blanchard, L. A.; Hancu, D.; Beckman, E. J.; Brennecke, J. F. *Nature* **1999**, *399*, 28–29.
40. Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746–756.
41. Cole-Hamilton, D. J. *Science* **2003**, *299*, 1702–1706.
42. Yamada, T.; Lukac, P. J.; George, M.; Weiss, R. G. *Chem. Mater.* **2007**, *19*, 967–969.
43. Yamada, T.; Lukac, P. J.; Yu, T.; Weiss, R. G. *Chem. Mater.* **2007**, *19*, 4761–4768.
44. Yu, T.; Yamada, T.; Gaviola, G. C.; Weiss, R. G. *Chem. Mater.* **2008**, *20*, 5337–5344.
45. Dibenedetto, A.; Aresta, M.; Fragale, C.; Narracci, M. *Green Chem.* **2002**, *4*, 439–443.
46. Aresta, M.; Ballivet-Tkatchenko, D.; Dell'Amico, D. B.; Bonnet, M. C.; Boschi, D.; Calderazzo, F.; Faure, R. E.; Labella, L.; Marchetti, F. *Chem. Commun.* **2000**, 1099–1100.
47. Hirst, L. L.; Pinkel, I. I. *Indu. Eng. Chem.* **1936**, *28*, 1313–1315.
48. Wittmann, K.; Wisniewski, W.; Mynott, R.; Leitner, W.; Kranemann, C. L.; Rische, T.; Eilbracht, P.; Kluwer, S.; Ernsting, J. M.; Elsevier, C. L. *Chem.—Eur. J.* **2001**, *7*, 4584–4589.
49. Carmichael, A. J.; Seddon, K. R. *J. Phys. Org. Chem.* **2000**, *13*, 591–595.
50. Sundberg, R. J.; Francis, A. C. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 3rd ed.; Plenum: New York, NY, 1990.
51. M. Stiles, D. W.; Hudson, G. *JACS* **1959**, *81*, 628–632.
52. Costa, M.; Chiusoli, G. P.; Taffurelli, D.; Dalmonego, G. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1541–1546.
53. Toshio Isobe, K. F.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7770–7773.
54. Mo, J.; Xiao, J. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4152–4157.
55. Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997–1000.
56. Yoon, B.; Yen, C. H.; Mekki, S.; Wherland, S.; Wai, C. M. *Ind. Eng. Chem. Res.* **2006**, *45*, 4433–4435.
57. Perosa, A.; Tundo, P.; Selva, M.; Canton, P. *Chem. Commun.* **2006**, 4480–4482.
58. Blasucci, V.; Hart, R.; Llopis-Mestre, V.; Hahne, D.J.; Burlager, M.; Huttenhower, H.; B.J.R., T.; Liotta, C.L.; Eckert, C.A. *Fuel*, in press.
59. Wang, L.; Jiang, X. H. J.; Liu, X.; Feng, X. *Tetrahedron Lett.* **2006**, *47*, 1581–1584.
60. Phillip Peac, D. J. C.; Jennefer, A. K.; Inderjit, M.; Ian, H.; Lynne, C.; Tim, W.; Martin, W. *Tetrahedron* **2006**, *62*, 1864–1876.