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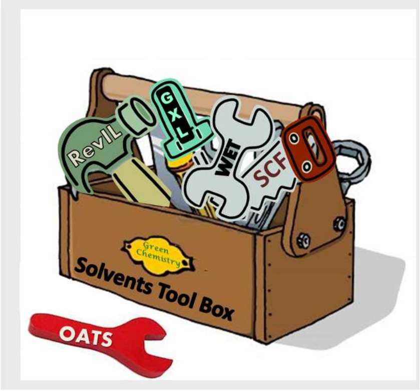

Pamela Pollet [a,c], Evan A. Davey[a], Esteban E. Urena Benavides[b], Charles A. Eckert [a,b,c], Charles L. Liotta*[a,b,c]*

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Solvents for Sustainable Chemical Processes

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Solvents for Sustainable Chemical Processes

Pamela Pollet*[a,c], Evan A. Davey[a], Esteban E. Urena Benavides[b], Charles A. Eckert[a,b,c], Charles L. Liotta*[a,b,c]

[a] School of Chemistry and Biochemistry, Georgia Institute of Technology
911 Atlantic Drive, Atlanta, GA 30332 (USA)
[b] School of Chemical and Biomolecular Engineering, Georgia Institute of Technology
311 Ferst Street, Atlanta, GA 30332 (USA)
[c] Specialty Separation Center, Georgia Institute of Technology
311 Ferst Street, Atlanta, GA 30332 (USA)

**Corresponding Authors:*
pamela.pollet@chemistry.gatech.edu ; charles.liotta@chemistry.gatech.edu

Abstract

The properties and some key applications of solvents such as (1) supercritical fluids (SCFs), (2) gas-expanded liquids (GXLs) and organic-aqueous tunable solvents (OATS), (3) water at elevated temperature (WET), and (4) switchable solvents like reversible ionic liquids (RevILs) are discussed in this review. Each system offers a unique set of properties to enable alternative strategies for varied applications. These applications range from chemical transformations, product separation, catalyst recycling, nanomaterial processing, and CO_2 capture. For each application, however, the common thrust is to enable greener and sustainable solutions for chemical processes.

1. Introduction

The Brundtland Commission of the United Nations presented the following definition of sustainable development: "development that meets the needs of the present without compromising the ability of future generations to meet their own needs."[1] How then does this definition relate to solvents for green and sustainable chemical processes? The answer is quite

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simple. What we seek are processes that are not only green, but also economically favorable to promote their implementation by industry.

Qualitatively, green or greener chemical processes are defined as processes in which there is an effective and measurable minimization of the environmental footprint. “Greenness” can be achieved in many ways; for example, by circumventing the use of hazardous or toxic materials or maintaining some quotient of renewable resource.[2] In fact, the chemical industry has developed numerous metrics to evaluate life cycle and the greenness of a particular process (carbon efficiency, mass efficiency, E-factor, etc.).[3] Integrating sustainability and greenness early on as inherent components of the chemistry and engineering design are key to the evolution of sustainable technologies—in contrast with remediation approaches that are often accompanied by modest improvements and high cost. The bottom line is that for a process to be both green and sustainable, it must address both environmental and economic consideration. The coupling of greenness and sustainability is the future of industrial processes.

Solvents are omnipresent in wet chemical processes and are also one of the major contributors to industrial waste streams. Herein, we consider “green and sustainable solvents”. A green and sustainable solvent can be defined as a solvent that addresses environmental issues, contributes to the optimization of the overall process, and is cost-effective. Specific process considerations must include reaction rates, product yields and selectivity, product separation, and recycling strategies for both the catalyst and the solvent. It is, however, unlikely that a universal green and sustainable solvent can be identified. Rather, one can envision establishing a tool-box or a portfolio of solvents that offer options and flexibility to the end user in order to meet the defined sets of requirements and constraints for a given chemical process.

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The purpose of this review is to highlight *solvent systems* that were designed to simultaneously address reaction, separation and recycling challenges. By addressing all of these factors in the early stages of process research and development – in lieu of treating each component as separate and distinct– the overall process will be inherently more sustainable.

2. **Solvents**

Qualitatively, a solvent is defined as any liquid, gas, solid, gas-expanded liquid, or supercritical fluid in which a solute is dissolved, either partially or completely. Solvents are usually categorized in two broad groups: polar and non-polar. Polar solvents are usually hydrophilic and often exhibit appreciable solubility in water, whereas non-polar solvents are lipophilic and readily dissolve in organic media. These classifications are usually further divided into additional subclasses: protic, dipolar aprotic, and non-polar organic solvents based on *quantitative* parameters such as the dielectric constant and dipole moment, and solvatochromic parameters, such as the Kamlet-Taft[4] and the $E_T(30)$ parameters.[5]

It is instructive to make a generalized comparison between the solvent systems discussed in this review and simple gases and organic liquids. As illustrated in Figure 1, a compromise usually exists between transport properties (expressed as diffusion coefficient, D_A) and solvation (expressed as Kamlet-Taft dipolarity/polarizability parameter, π^*). Gases exhibit high diffusion coefficients but are essentially “poor” solvents as indicated by their low π^*. In contrast, at the other extreme, ionic liquids are “good” solvents with poor transport properties. The “property gap” between gases and ionic liquids can be filled by solvents systems such as supercritical fluids (SCF’s), gas-expanded liquids (GXL’s), near-critical water, and common organic solvents (organic liquids). Each system illustrated in Figure 1 offers a unique set of properties, which

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include but are not limited to transport properties and solvation. This toolbox of solvent systems can provide the basis for addressing specific challenges of a given process.

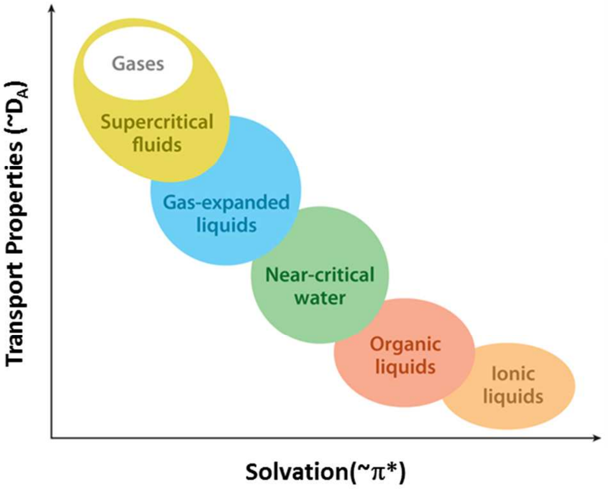

Figure 1. Compromise of transport ability and solvent power for various types of solvents.

Solvents have countless applications and often play multiple roles in chemical processes. For instance, they bring reactants together to facilitate reaction and provide a means of temperature control for both endothermic and exothermic transformations. In academic laboratories, the scale of reaction is often small enough that solvent recovery is not usually considered. In industry, however, the choice of solvent system is dependent upon its ability to facilitate a particular reaction, promote a facile separation of product, and potentially be recovered and recycled. When multiple solvents are employed in a single process (solvents are often changed for a given reaction or isolation/purification step) the associated cost and waste stream issues are compounded. A more holistic approach to solvent choice is envisioned. The vision involves using solvent systems whose properties can be modified at will to meet the requirements of particular steps in the overall process. Herein, we report the physicochemical properties and highlight key applications for: (1) supercritical fluids (SCF's), with emphasis on

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supercritical CO_2, (2) gas-expanded liquids (GXL's) and organic-aqueous tunable solvents (OATS), (3) water at elevated temperature (WET), (4) switchable solvents, specifically sulfolenes and reversible ionic liquids (RevILs). Appropriate references to previously reviewed examples will be given. Only when necessary will these previous examples be discussed.

3. Supercritical Fluids

For over 40 years, supercritical fluids have received significant attention as alternatives to traditional solvents, leading to a broad range of applications. A SCF is a fluid at conditions slightly above its critical temperature (T_c) and pressure (P_c). Figure 2 shows a generalized temperature-pressure graph which illustrates the supercritical region. As the temperature and accompanying pressure are increased the liquid becomes less dense and the vapor becomes more dense. At the critical point they converge to ultimately become identical. The compressibility is the slope of the isotherm, and it is infinite at the critical point. In fact, all of the special properties of SCF's occur in the region of very high compressibility.[6, 7] Two well-known yet very different fluids are water (T_c 373°C; P_c 22.1 MPa) and carbon dioxide (T_c 31°C; P_c 7.4 MPa). CO_2 has a readily accessible critical point; moreover it is abundant, cheap, non-flammable, non-toxic and recyclable. Not surprisingly, supercritical CO_2 ($scCO_2$) has been the most studied supercritical fluid. Another common SCF with a readily accessible critical point is ethane (T_c 32°C; P_c 4.9MPa). Unlike CO_2, however, its high flammability imposes a significant safety constraint. To a lesser extent, other SCFs have been used; these include ethylene, propylene, propane, ammonia, and dimethyl ether.[8, 9]

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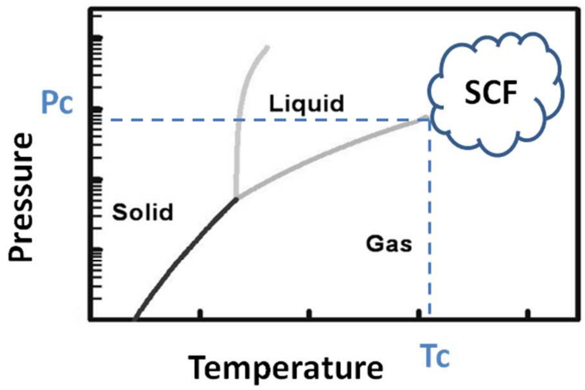

Figure 2. General phase diagram for supercritical fluids.

While SCF's are generally less dense than liquid solvents they are still sufficiently dense to provide appreciable solvation for a wide variety of solutes. Moreover, small pressure changes result in large density changes and enormous changes in the accompanying solute solubility. Figure 3 draws the contrast for typical solubility plots in a SCF and an ideal gas. Clearly, a dramatic enhancement of solubility of solutes (up to almost 6 orders of magnitude) is observed in SCF compare to an ideal gas.

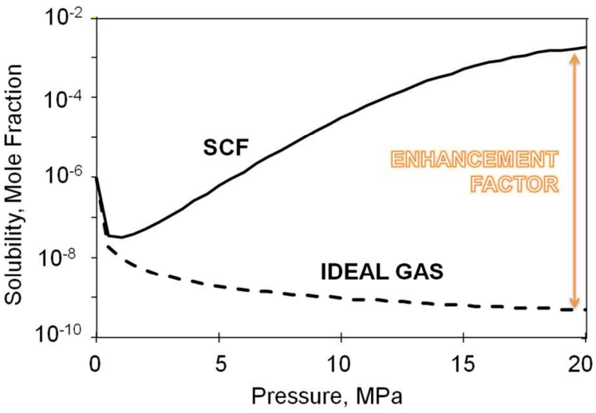

Figure 3. Solubility enhancement with SCF over ideal gas.

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Note that at low pressure the SCF is ideal, but typically at a few MPa, the solubility begins to be enhanced and at higher pressures this enhancement (relative to an ideal gas) can be many decades. A specific example is shown in Figure 4, in which the solubility of salicylic acid is plotted as a function of $scCO_2$ density. At the two reported temperatures (40 and 55^{o}C), the solubility enhancement is about two orders of magnitude over a range of densities from 6 to 18 Mol/L.[10, 11]

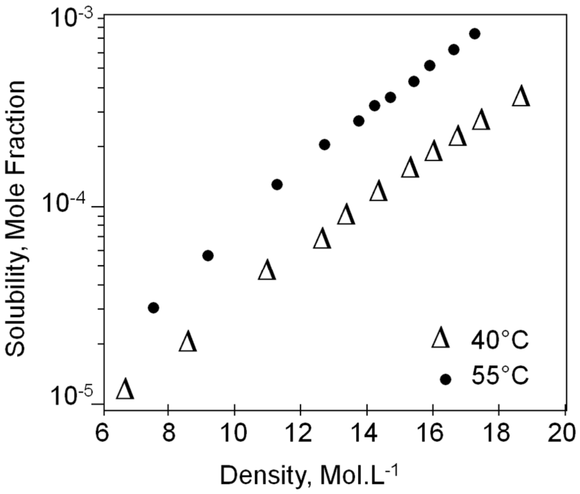

Figure 4. Solubility of salicylic acid (2-hydroxybenzoic acid) in $scCO_2$.

The solubility in a SCF can also be manipulated by adding small amounts of a co-solvent such as acetone or ethanol. A dramatic effect is shown in Figure 5, where the relative solubilities of anthracene and acridine are significantly changed upon the addition of only 1% methanol cosolvent. The increased solubility of acridine has been attributed to a specific solvent/solute interaction—specifically, the hydrogen bonding of the alcohol proton with the basic nitrogen atom in acridine.[12-14]

As a result of the ability to manipulate properties of SCFs with pressure or addition of co-solvent (i.e. tunability), a broad array of applications have been reported which include liquid-

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solid extractions, reaction media for the synthesis of specialty chemicals (e.g. pharmaceuticals), controlled precipitation of solids, and tailoring of chemical and morphological characteristics of materials.[15-32] SCFs have proven most advantageous in situations where their unique tunable properties (e.g. diffusivity, transport ability) dramatically out-perform traditional solvents. In this section we report some of such key applications with a focus on scCO$_2$.

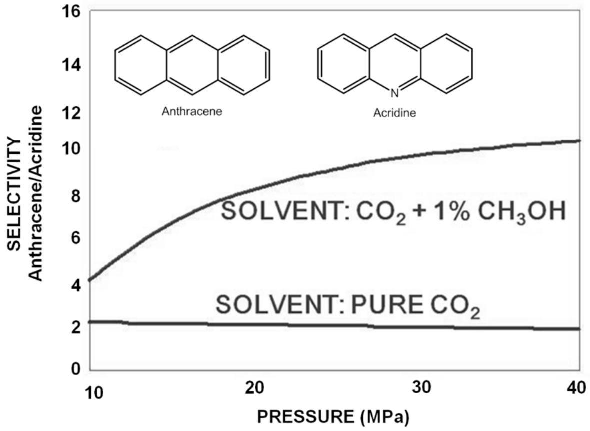

Figure 5. Cosolvent effect on selectivity of anthracene and acridine.

Synthesis

Despite the examples shown above, scCO$_2$ is a relatively poor solvent.[33,34-36,32] Performing a chemical transformation usually requires a reasonable solubility of the reactants in the reaction medium. This can be challenging in a SCF, especially if ionic reactants are involved in the process. In these cases, phase transfer catalysis has been successfully employed for reactions conducted in scCO$_2$ and scEthane. Reactions involving nucleophilic substitution involving anionic nucleophiles and organic substrates and base-promoted alkylation reactions have been reported (Figure 6).[18, 22, 37] For instance, benzyl chloride was reacted with solid

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potassium cyanide in the presence of the phase transfer catalyst (PTC) tetra-n-heptylammonium bromide (THAB), to form phenylacetonitrile. In the absence of the PTC, only 5% product was formed in 48 hours. In contrast, in the presence of 10 mol% catalyst, 100% yield of product was obtained in 10 hours.

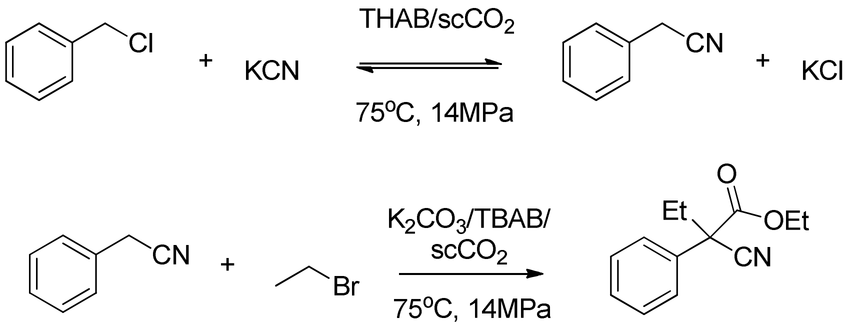

Figure 6. Example reactions in supercritical fluids: substitution of benzyl chloride with potassium cyanide to form phenylacetonitrile in $scCO_2$ (top), formation of α-phenyl-α-ethylcyanoacetate during the alkylation of phenylacetonitrile with $scCO_2$ (bottom).

Unlike the classical phase transfer catalysis mechanism, the phase transfer catalyst has limited solubility in the $scCO_2$ and resides almost exclusively on the surface of the cyanide salt. The experimental results suggest that the actual substitution process takes place on the surface of the ionic solid (Figure 7) within a region rich in both cyanide ion and catalyst. Indeed, the addition of 5 mol% acetone to the $scCO_2$, while increasing the solubility of the catalyst in the fluid phase, actually decreased the overall rate of reaction—an observation consistent with the reaction taking place on the surface of the solid.

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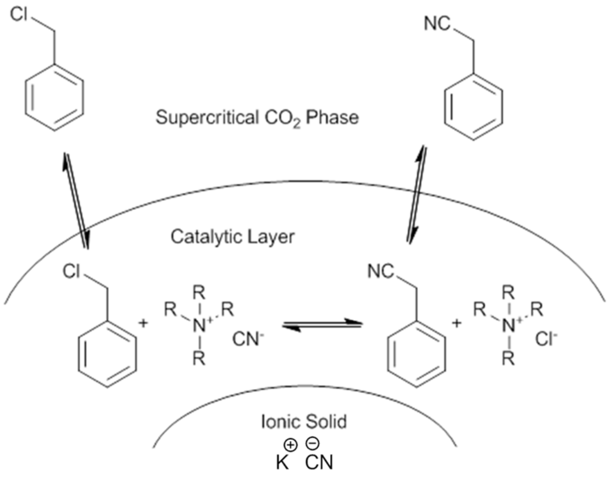

Figure 7. Mechanism of PTC reaction in $scCO_2$.[18]

In the alkylation of phenylacetonitrile with ethyl bromide catalyzed by tetra-n-butylammonium chloride (TBAC), the use of $scCO_2$ leads exclusively to ethyl α-phenyl-α-ethylcyanoacetate (Figure 6). In this particular example, the CO_2 acted as both solvent and reactant. Successful alkylation was easily achieved when supercritical ethane (scEthane) was substituted for $scCO_2$ (Figure 8).[37]

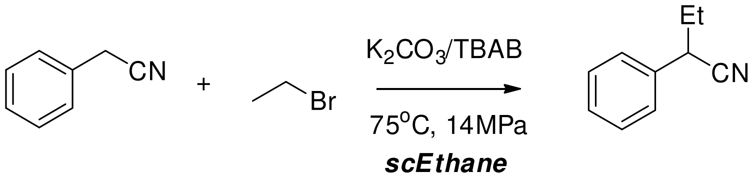

Figure 8. Carbonate promoted alkylation of phenylacetonitrile in scEthane.[18, 37]

More recently, the use of packed bed reactors (PBR) to conduct Suzuki-Miyaura coupling reactions has been reported. This process mode is an effective alternative when reactants are soluble in $scCO_2$ but the catalyst is not. Continuous flow processes are usually considered greener than corresponding batch processes since they are usually accompanied by reduced

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energy requirements and the waste generation.[38, 39] Specifically the coupling of *p*-tolylboronic acid and iodobenzene to form 4-methylbiphenyl in continuous mode was conducted in $scCO_2$. Pd(II)EnCat 40 ($Pd(OAc)_2$/polyurea)[40] and tetra-n-butylammonium methoxide (Bu_4NOMe) were used as solid supported catalyst and base, respectively (Figure 9).[25] A conversion of 81% at 100°C and 16.6 MPa was achieved when 10% methanol was added as a co-solvent. When the co-solvent ratio was decreased to 1.5%, the conversion fell to 21 %. This clearly highlights a key role of the co-solvent in improving the solubility of reaction partners in supercritical fluids of low polarity. The same reaction conducted in a 9:1 mixture of toluene and methanol produced a 74% yield. Unlike traditional solvents, however, CO_2 enables facile product recovery and solvent recycling upon depressurization. In their report, the authors identified two main challenges: catalyst leaching and blockage of the packed bed reactor (PBR). Although leaching was not directly quantified, the color of the catalyst was reported to change from brown to black—consistent with the formation of Pd(0). In addition, the catalytic activity decreased to 41 % after recycling. Furthermore, the blockage of the catalyst bed, mainly due the accumulation of reaction by-products with low CO_2 solubility (i.e. Bu_4NI, $B(OH)_2OCH_3$), was a limiting factor with respect to the overall process. Thus, developing effective catalyst immobilization will be key for the viable implementation of such processes.

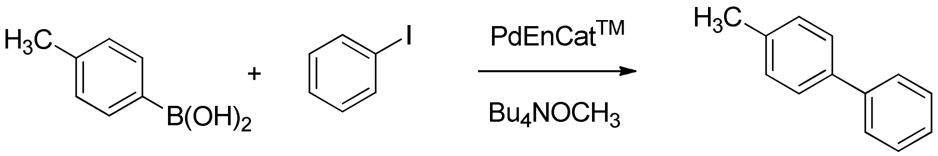

Figure 9. Reaction scheme for Suzuki-Miyaura reaction of p-methyl boronic and iodobenzene in Packed Bed Reactor (PBR).[25]

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The acid catalyzed self-condensation of propanal in $scCO_2$ to form 2-methyl-2-pentenal was also conducted in a packed bed reactor (Figure 10). The reaction proceeds via the 3-hydroxy-2-methylpentanal intermediate which subsequently losses a molecule of water to afford the 2-methyl-2-pentenal.

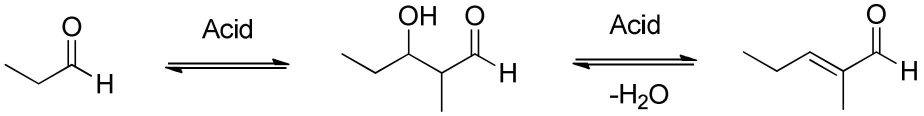

Figure 10. Acid catalyzed self-aldol condensation of propanal to the product.

The selectivity (product *vs*. intermediate) and conversion were recorded as a function of acid catalyst and solvent. Of the eight acid catalysts tested, Amberlyst 15 gave the best selectivity (99%) for the desired product 2-methyl-2-pentenal. A conversion of 43% was reported at 95°C and 10 MPa. When the reaction was carried out neat (in the absence of CO_2), the selectivity dropped to 35% at 95°C. The authors suggested that the difference of selectivity results from the low solubility of the intermediate 3-hydroxy-2-methylpentanal in $scCO_2$. It is believed that the CO_2-insoluble 3-hydroxy-2-methylpentanal essentially resides on the insoluble acid catalyst's surface driving forward the dehydration step to the final product.[28] In this example, advantage was taken of the relatively poor solvent character of CO_2 to synergistically improve reaction selectivity and post-reaction product separation. This application is not an isolated example. Similar synergetic benefits have been reported for the metathesis of 1-octene to 7-tetradecene catalyzed by Re_2O_7 supported on γ-Al_2O_3. In this case, the continuous metathesis reaction of 1-octene in $scCO_2$ to produce 7-tetradecene was conducted with a conversion of 75 % and a selectivity[41] of 95 % (Figure 11). Although comparable initial conversion (65 %) and selectivity (90 %) were obtained when *n*-hexane was used as solvent, the selectivity decreased to 0 % (in the outlet stream) after 15 min. In contrast, when $scCO_2$ was employed, the selectivity

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remained unchanged for 40 min, after which it gradually decreased to 40 % at 90 min.[27] The decrease of reactivity over time was attributed to the coating of the catalyst bed with insoluble side-products. Washing the catalytic bed with acetone and $scCO_2$ allowed for the recovery of the initial selectivity of 95%.

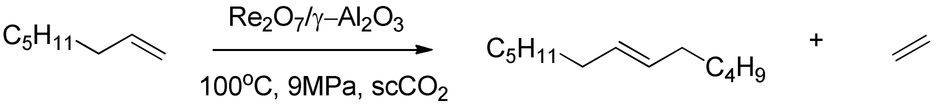

Figure 11. Methatesis reaction of 1-octene to 7-tetreadecene in $scCO_2$.

Continuous flow processes in $scCO_2$ can also be superior to traditional processes for oxidation reactions since oxygen is completely soluble in non-flammable CO_2.[15, 24,42] For example, the platinum catalyzed oxidations of 1- and 2-octanol to 1-octanal and 2-octanone, respectively, were performed in $scCO_2$ with oxygen as the oxidizing reagent (Figure 12).[19] The reaction was carried out in flow mode (packed bed reactor) at 10 MPa. The 1-octanal and 2-octanone were each obtained in 75 % yield at 150°C and 135°C, respectively. Importantly, the 1-octanal was selectively produced—no octanoic acid (over-oxidation product) was observed and no mass losses were detected.

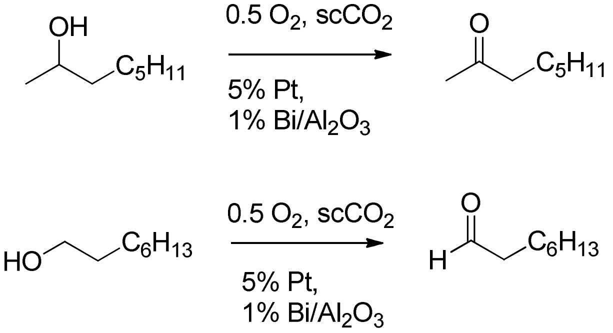

Figure 12. Oxidation of 2-octanol and 1-octanol in $scCO_2$.[19]

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Materials Processing

Producing materials in a sustainable manner is essential to the prospect of green technologies. This is particularly important in today's context in which nanotechnology-enabled products are omnipresent. In fact, the revenues generated from nanotechnology derived products are predicted to reach $1 trillion by 2015 (for Europe and United States combined).[43] Unquestionably, the impact of greener and sustainable processes for the manufacture of nanomaterials will be far–reaching from scientific, environmental and financial points of view. The unique properties of $scCO_2$, such as the high diffusivity and modest solvation of solutes, are beneficial for the processing of advanced materials. Within this framework, CO_2 enabling strategies for the controlled synthesis of nanoparticles, thin film deposition, particle formation and nano-composites processing have been reported.[16, 17, 21, 23, 26, 29, 44] Specifically, the rapid expansion of supercritical solutions (RESS) and supercritical antisolvent (SAS) precipitation methods enable the formation of micron and submicron size particles, most often for pharmaceutical applications.[16, 21, 45-49] Both RESS and SAS technologies have been widely implemented and reviewed.[16, 21, 45-49]

Since the size, density and shape of nanoparticles govern their properties and ultimately their applications, supercritical fluids have been explored as solvent for their synthesis and deposition.[50-55] Casciato et *al.* reported the $scCO_2$ mediated synthesis and deposition of silver nanoparticles (AgNPs) on silicon and glass surfaces for application in Surface-Enhanced Raman Spectroscopy (SERS).[17] The authors explored the mechanisms and parameters governing the heterogeneous deposition of AgNPs, ultimately understanding how to tune particle's size, density and surface coverage onto the support. For example, the histogram plotting fraction versus AgNPs diameter (deposited on HCl-treated silicon support) as a function of temperature

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(60-180°C) is shown in Figure 13A. The mean particle size of the nanoparticles decreases from 196, to 104, and to 27 nm as the temperature increases from 60, 120, 180 °C, respectively. Overall, their results are consistent with the deposition process being reaction rate limited (reduction of the silver precursor with hydrogen) rather than being limited by the transport of the precursor Ag(hfac)(COD) to the surface (Figure 13B). This is in part due to the high solubility of the silver precursor in $scCO_2$ and contrasts with other, traditional systems like chemical vapor deposition that are often transport-limited. From a process standpoint, the two variables (temperature and surface) can be efficiently adjusted to tune the AgNPs mean size, density and surface coverage. Finally, the SERS fabricated in this study were analyzed and tested exhibiting enhanced sensitivity, up to three orders of magnitude greater sensitivity than SERS previously reported. Hence, the $sc\text{-}CO_2$ mediated route for the synthesis and deposition of AgNP not only offer a green alternative, it also enables tunability and superior performance.

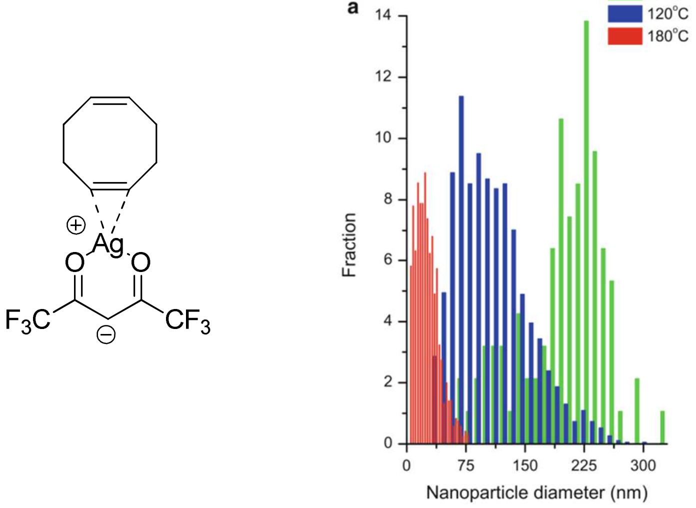

Figure 13. Structure of the precursor 1,1,1,5,5,5-hexafluoroacetylacetonate cyclooctadiene Ag(hfac)(COD) and particle size distribution of silver nanoparticles deposited from $scCO_2$ onto a HCl treated silicon surface. *Reprinted with kind permission from Springer Science and Business Media* (M. Casciato, G. Levitin, D. Hess and M. Grover, *J. Nanopart. Res.*, 2012, 14, 1-15).[17]

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Undoubtedly, technologies based on $scCO_2$ offer a range of opportunities. Some inherent advantages are the facile recyclability, low toxicity, high transport properties, non-flammability and tunability of solvent properties. These have all been exploited in different fields of science and technology which include, but are not limited to, the synthesis of specialty chemicals, fabrication of selective membranes, assembly of thin film electronic devices and nanoparticle synthesis and deposition. [16, 21, 23, 29, 56-59] In some cases, supercritical fluids require pressures than may not be desirable, even with CO_2 which has a relatively low critical pressure. For this reason, Gas eXpanded Liquids (GXLs) have emerged as a lower pressure alternative.

4. Gas-Expanded Liquids

Gas-expanded liquids (GXLs) are miscible mixtures of an organic solvent with a gas—most often CO_2—at moderate pressures (3-8 MPa).[60-62] Gaseous CO_2 has infinite solubility in many organic solvents including alcohols, ketones, ethers, and esters (at much lower pressures than those required for supercritical fluids). Operationally, GXLs are formed by the dissolution of CO_2 into organic liquids leading to volume expansion as shown in Figure 14.

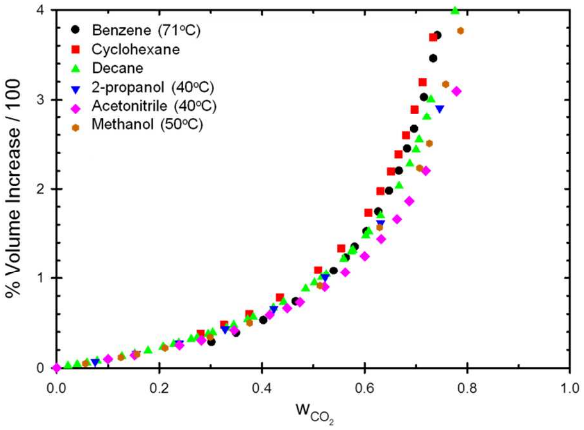

Figure 14. Volume expansion with CO_2 for benzene, cyclohexane, decane, 2-propanol, acetonitrile and methanol.

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In contrast to $scCO_2$, typical organics such as acetone and THF are relatively good solvents with dielectric constants substantially greater than CO_2. With the addition of CO_2 to these solvents, the dielectric constant of the resulting media can be tuned to any value between that of the pure organic solvent and that of pure CO_2. Thus a wide range of solvent properties are easily accessible with GXLs. These changes of solvent properties can be quantitatively measured with the Kamlet-Taft solvatochromic parameters (i.e. π^*, α, β, etc.), and dielectric constant. For example, Figure 15 shows the polarity changes (expressed as π^*) of methanol, acetone and acetonitrile as a function of CO_2 mol fraction (X_{CO2}) at 40 °C.[63-65] The polarity of all solvents decreases non-linearly as the CO_2 concentration is increased; the effect on π^* is smaller at lower X_{CO2} but π^* decreases rapidly at X_{CO2} approaches unity. This is especially true for $X_{CO2} > 0.6$.

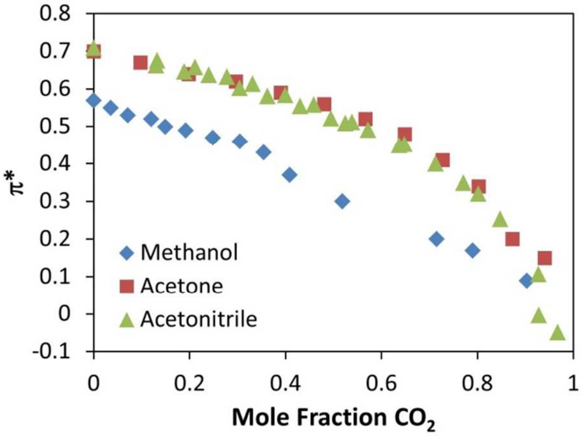

Figure 15. Experimental π^* values for gas-expanded methanol (using 4-nitoanisole),[65] acetone (N,N-dimethyl-4-nitoaniline) [65] and acetonitrile (using 4-nitro-anisole)[63, 64, 66] as a function of CO_2 mol fraction at 40 °C.

The Kamlet-Taft parameters α and β (i.e. ability to donate or accept hydrogen bonds, respectively) are also affected with the addition of CO_2 to organic solvents but to a much lesser

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extent compared π*. For example, the α values for the binary mixture of acetone and CO_2 remain relatively constant up to $X_{CO2} < 0.8$. Above this value a sharp increase is observed.[64, 65, 66] Interestingly, the α value for methanol remains constant up to $X_{CO2} = 0.9$. Wyatt *et al.* suggested a possible reason for this behavior. It was postulated that, even at the high concentrations of CO_2, the solvatochromic molecular probe is preferentially solvated by the methanol.[65] The basicity β of acetonitrile increases from 0.4 (pure acetonitrile) to 0.5 at $X_{CO2} = 0.9$ and then decreases sharply towards the value of pure $CO_{2.}$ In the case of acetone no change is observed.[64, 65] In contrast, a steady reduction in the value of β is observed as CO_2 is added to methanol; the β values ranged from 0.65 for pure methanol to 0.30 when X_{CO2} is 0.8.[65]

As a consequence of solvent tunable polarity with the addition of CO_2, by just adjusting CO_2 pressure it is possible to control the solubility of solutes. Figure 16 illustrates the solubility of phenanthrene in acetone at 25°C as a function of CO_2 pressure. The point designated in red is pure CO_2—a liquid just below its critical point. The mol fraction of phenanthrene in acetone is reduced from 0.17 in pure acetone to 0.0044 at 50.6 bar (5.06 MPa).[67-69] Thus, by simply adjusting CO2 pressure, the polarity of a solvent system can be tuned for a wide variety of processes. The broad impact of GXL technology is primarily due to this ability of using CO_2 pressure to control solvent polarity.

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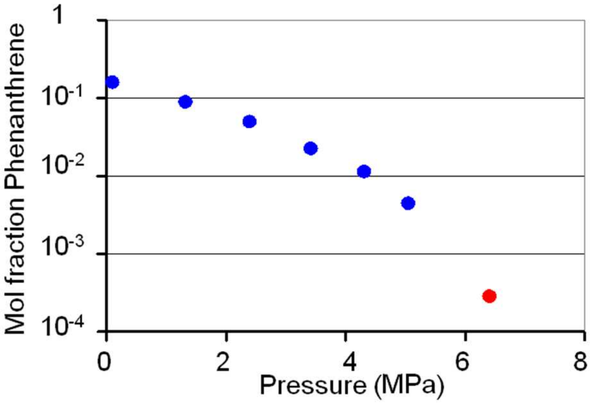

Figure 16. Solubility of phenantrene in gas expanded acetone as a function of CO_2 pressure.

Beyond the tuning of the physical properties of alcohols, the addition of CO2 to alcohols is accompanied by the formation of alkylcarbonic acids; the acid-base properties of the alcohol solvent are changed (Figure 17). These acids have been successfully used as in-situ, reversible acid catalysts for the several synthetic transformations; these include the formation of ketals,[70] the preparation of diazonium salts,[71, 72] and hydration of pinenes.[73, 74]

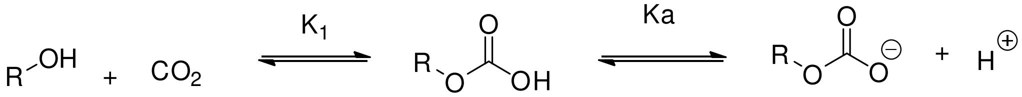

Figure 17. *In situ* formation of alkyl carbonic acids in CO_2 expanded alcohols.[75,76]

The equilibrium constants (K_1 and K_a) for the system shown in Figure 17 are dependent on the structure of the particular alcohol. Given the complexity in measuring each constant separately, an effective equilibrium constant, $K_{eff} = K_1K_a$ has been reported. The pK_{eff} has been measured for methanol, ethanol and benzyl alcohol as 8.97, 10.1 and 12.4 respectively.[75]

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In situ acid catalysis using methylcarbonic acid has been demonstrated for the formation of ketals in gas expanded methanol as shown in Figure 18. In the case of the acid-catalyzed formation of the dimethylketal of cyclohexanone, a rate enhancement of 135% was observed in CO_2 expanded methanol at 0.35 MPa and 50 °C compare to methanol alone (Figure 19). At higher pressures the rate enhancement decreased. This was probably due to the lower polarity of the solvent since there is a greater quantity of CO_2 in the methanol. The enhancement of reaction rate was less significant at lower temperatures. When the reaction was run at lower temperatures, the maximum enhancement factor occurred at higher pressures. Thus, at 40 °C, the reaction rate increased 100% at 2MPa; while at 25 °C a maximum enhancement of 85 % was observed at 1.5 MPa.[77]

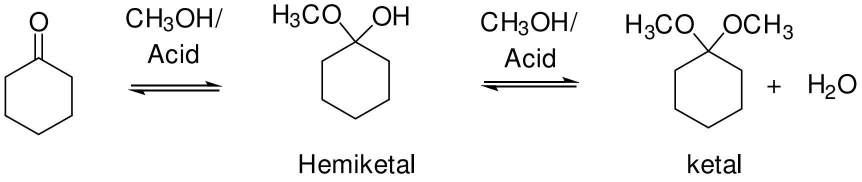

Figure 18. Ketal formation in gas-expanded alcohol.

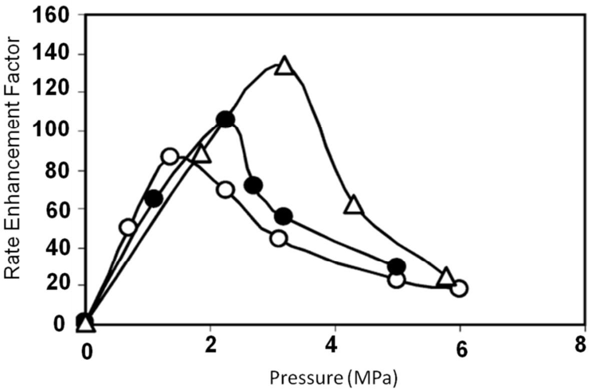

Figure 19. Enhancement of rate constant for cyclohexanone ketal formation in gas expanded methanol. Symbols key: (○) 25 °C, (●) 40 °C and (△) 50 °C. Reprinted with permission from (X. Xie, C. L. Liotta and C. A. Eckert, Ind. Eng. Chem. Res., 2004, 43, 2605-2609). Copyright (2004) American Chemical Society.[77]

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Xie et al. reported the hydrogenation of nitriles to form the corresponding primary amines in CO_2-expanded THF and ethanol (Figure 20). Mechanistically, the hydrogenation of nitriles proceeds stepwise via an imine intermediate to yield the primary amine product. However, the intermediate imine species is quite reactive and can react with the amine product, which ultimately produces the corresponding secondary amine. However, the authors report that the hydrogenation of phenylacetonitrile in CO_2-expanded ethanol produces a 97% yield of benzylamine. In the absence of CO_2, only a 0.01% yield was obtained (the undesired secondary amine was the major product obtained with 87% yield). In addition, the production of secondary amine (dibenzylamine) was effectively suppressed from 99% in the absence of CO_2 to 0.15% in the presence of CO_2 (3 MPa). The dramatic increase of selectivity toward the primary amine results from its *in-situ* reaction with CO_2 to form the corresponding ammonium ethylcarbonate and ammonium carbamate species. The formation and precipitation of these species serve as *in-situ, reversible* protection of the primary amine, preventing further and unwanted side reactions.[78] Thus, CO_2 expanded liquids can provide substantial advantages in reversibly protecting amine functionalities from taking part in undesired reactions.[78]

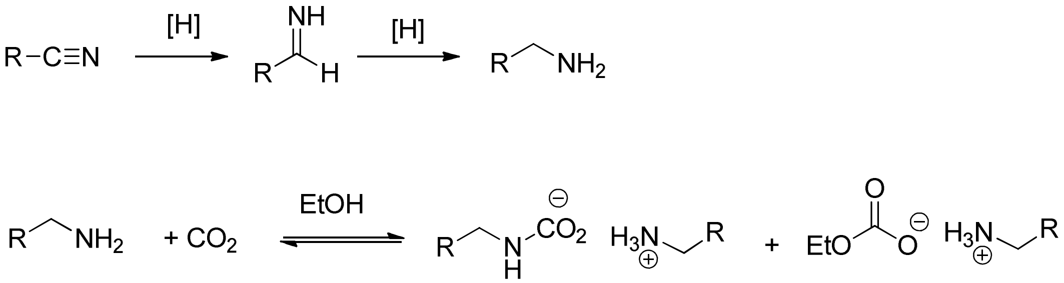

Figure 20. Hydrogenation of nitriles to form primary amines and the *in situ* protection of the synthesized amine with CO_2.

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Organic Aqueous Tunable Solvents (OATS)

When reactions are being conducted between a hydrophilic catalyst and a hydrophobic substrate to form a hydrophobic product, it is quite common to employ mixed solvents in order to provide a homogeneous reaction system. Thus, THF-water, acetonitrile-water, and dioxane-water are quite common mixed solvent vehicles for these homogenous reaction processes. Ideally, it would be advantageous to develop a process in which the reaction is performed under homogeneous conditions followed by an induced phase split separating the aqueous and organic solvent components. The hydrophilic catalyst would then be located in the aqueous phase and the hydrophobic product in the organic phase. The overall process would enable a facile separation/isolation of product and a means of recycling the catalyst. Organic Aqueous Tunable Solvents (OATS) potentially provide a vehicle to accomplish this strategy.

While gaseous CO_2 has infinite solubility in many organic solvents, it is virtually insoluble in water. As a consequence, the addition of CO_2 to an organic/water homogeneous mixture can result in a phase splitting into an aqueous phase and an organic phase. In fact, this ability of “switching” from a single liquid phase (aqueous/organic mixture) to a two liquid phase system upon addition of modest pressure of CO_2 (< 6MPa) is central to the concept of OATS. Consider, for example, Figure 21. From a phase equilibrium point of view, the two phase regions for water/THF mixtures is found between 75-140 ^{0}C.[79] Thus, to achieve phase separation (in the absence of CO_2) the temperature must be raised above the lower critical solution temperature of 72°C. In contrast, in the presence of only 1 MPa of CO_2, the lower critical solution temperature decreases to less than 25^{o}C and a phase split is achieved. The extent of the phase separation is a function of the CO_2 pressure applied as shown in the ternary diagram for THF/Water/CO_2 system at 25^{o}C (Figure 22). Each tie line connects the composition of an

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organic rich phase in equilibrium with an aqueous rich phase at a given pressure. Increasing the pressure from 1.03 MPa to 5.17 MPa reduces the amount of water in the organic phase from 30 mol % to 2 mol % while the fraction of THF in the aqueous phase decreases from 11 mol % to 2 mol %.[80]

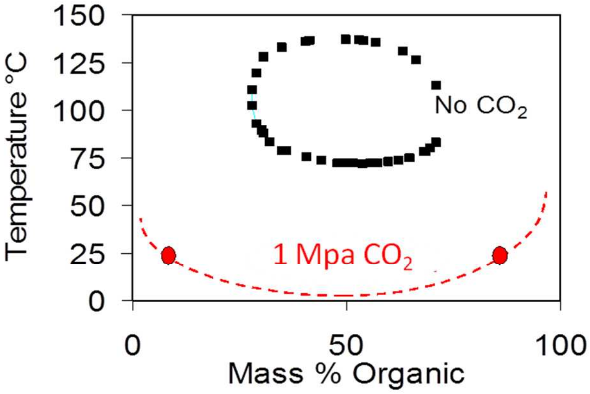

Figure 21. Liquid-liquid phase boundaries for THF/Water with and without CO_2.

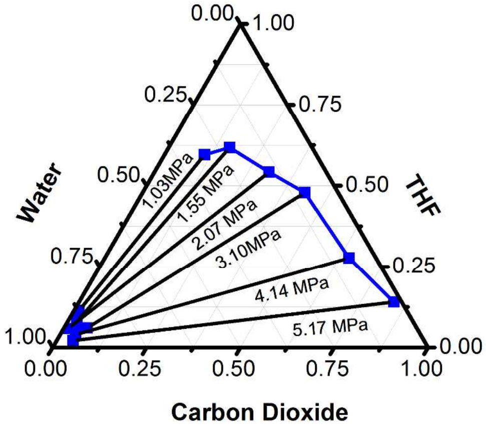

Figure 22. Ternary diagram of the system THF/Water/CO_2 at 25 °C, showing the liquid-liquid equilibrium at various CO_2 pressures.

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Figure 23 visually compares a water/THF solvent system in the absence and in the presence of CO_2. A hydrophilic organic red dye was used as a visual mock catalyst. In the absence of CO_2 the system was homogeneous (left photo). After the addition of 2MPa of CO_2 phase splitting occured (right photo). The CO_2-organic rich phase (THF and CO_2) is on the top and the aqueous phase containing the hydrophilic dye is on the bottom. The partition coefficient of the dye was greater than 10^6 (which correspond to the limit of detection of the spectrophotometer). This unique ability to manipulate phase behavior upon addition of CO_2 at moderate pressures offers opportunities to develop strategies to conduct reactions homogeneously and to separate/isolate products and catalysts heterogeneously. In addition, catalyst recycle protocols are now possible.

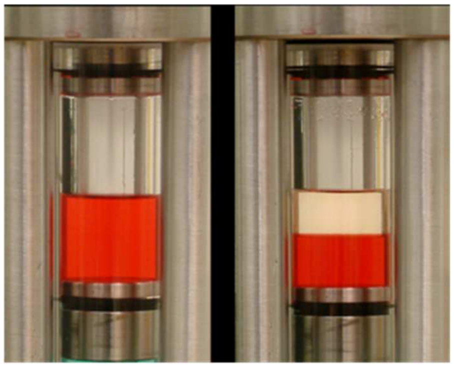

Figure 23. Water-THF-CO_2 Equilibria. Left: No CO_2, a single phase. Right: 2 MPa of CO_2, two liquid phases with dye partitioning $>10^6$.

The general processing schematic in Figure 24 highlights the three key features of OATS processes: (1) the reaction is performed homogeneously (reaction efficiency), (2) the product separation/isolation is conducted heterogeneously (optimizing product recovery) and (3) the organic solvent, catalyst-bearing aqueous phase and CO_2 can all be recycled. This schematic also demonstrates the relationship between OATS and the principle of a green/sustainability process.

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Only one feed stream is entering and only one product stream is exiting. All other streams are recycled, maximizing efficiency and minimizing waste stream.

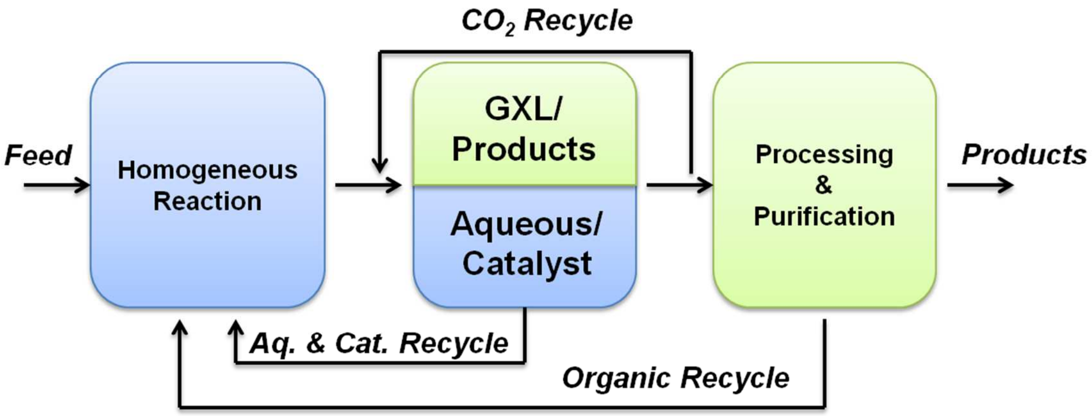

Figure 24. Schematic of a OATS-mediated process.

Industrially, the hydroformylation of propylene to form butyraldehyde is performed via a water/organic biphasic process resulting in ~600,000 metric tons annually. In this process, the aqueous phase contains the hydrophilic catalyst while the organic phase is essentially the propene reactant and/or butyraldehyde products. The heterogeneous nature of this process allows for the hydrophilic catalyst to be easily separated and recycled. It is important to understand that the reaction is still taking place in the aqueous phase; some solubility of the alkene in the aqueous phase is therefore essential to the viability of the process. While the solubility of propylene in water (~200 ppm) is indeed sufficient from an industrial standpoint, the negligible water solubility of longer-chain olefins prohibits such biphasic processes. This is exactly where the OATS technology could provide a competitive and sustainable alternative.

Hydroformylation reactions of 1-octene (Figure 25) and p-methylstyrene (an analog for an ibuprofen precursor) were successfully conducted using OATS technology.[64, 81-83]

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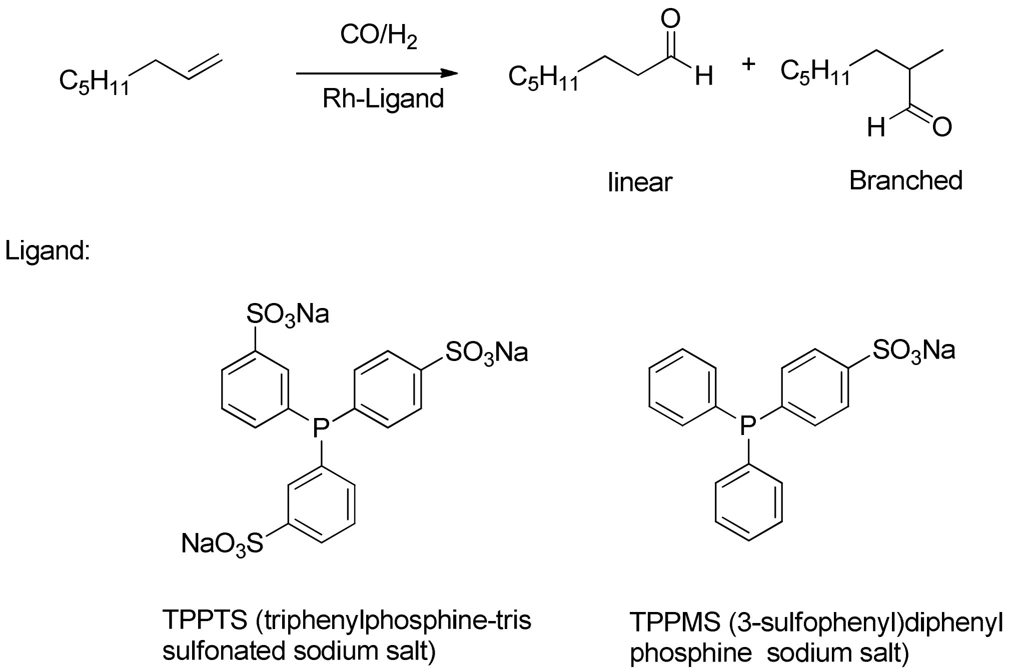

Figure 25. Hydroformylation of 1-octene to form 1-nonanal (linear product) and 2-methyloctanal (branched product).

The solubility of the 1-octene in water is less than 3ppm. However, it is increased more than 10,000-fold by the addition of tetrahydrofuran (THF) as cosolvent. A 70/30 (vol/vol) THF-water mixture produces a viable homogeneous system for conducting the hydroformylation of 1-octene. Specifically, the reaction of 1-octene with syngas in the presence of a rhodium catalyst produced the two isomeric aldehyde products, 1-nonanal (linear product) and 2-methyloctanal (branched product).[64] Three ligands with very different hydrophilic character were employed: triphenylphosphine (TPP), triphenylphosphine monosulfonate sodium salt (TPPMS) and triphenylphosphine trisulfonate sodium salt (TPPTS). The partition behavior of the ligands, 1-octene and the aldehyde products as a function of CO_2 pressure were reported. Overall, TPPMS ligand emerged as the optimum choice. The reaction performed efficiently. The aldehyde products were obtained in 85% yield at 80°C with only 4% isomerization of the 1-octene to

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internal alkenes.[84] And in contrast with the TPP based catalyst, the hydrophilic TPPMS catalyst was easily separated, recovered and recycled three times upon phase splitting with the addition of CO_2. The TOFs were consistent from cycle to cycle, ranging from 51 to 47 to 54 h^{-1}, indicative of the retention of catalytic activity. Importantly, no rhodium leaching was detected in the organic phase (using atomic absorption spectroscopy with a detection limit of < 1 ppm).[64]

Enzyme-catalyzed processes have also been successfully conducted with OATS technology. The hydrolysis of α-phenylethyl acetate to α-phenylethyl alcohol was catalyzed by *Candida antarctica* lipase B (CALB) in a dioxane/water system at 25 °C (Figure 26).[85] The reaction was highly selective, yielding exclusively *(R)*-1-phenylethanol. Again, the addition of 5.0 MPa of CO_2 to the reaction mixture allowed for the facile separation of products in the organic-rich phase and the subsequent recovery of the CALB catalyst.

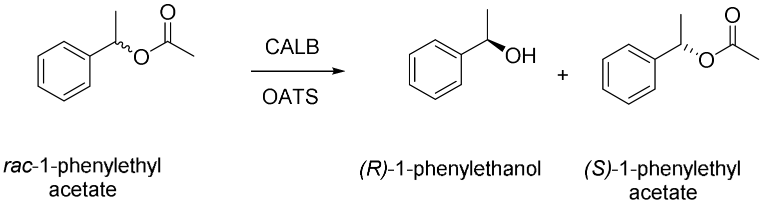

Figure 26. Selective CALB catalyzed enantiomeric hydrolysis of a racemic mixture of 1-phenylethyl acetate in an OATS.

Nanoparticle Processing

Preparation of nanosize particles for surface deposition is traditionally performed using wet chemical methods such as precipitation[86] or reverse micelle methods[87-91]. The principle is relatively simple: the nanoparticles are synthesized and stabilized in solution (dispersed) by capping agents, usually molecules like dodecanethiol. Post-synthesis, the separation and/or deposition of the nanoparticles from solution is achieved by adding an anti-solvent. The role of

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the anti-solvent is to alter the solubility of the capped nanoparticles, effectively lowering the dispersibility of the ligand-coated nanoparticles in solution and causing their precipitation. This process must be well controlled to obtain ordered and uniform deposition onto the chosen surface. In practice, the deposition (or dewetting) step can be challenging with liquid solvents, owing essentially to capillary forces and high surface tension at the liquid/vapor interface. In contrast, CO_2 pressure is an effective, recyclable, and inexpensive means to tune the composition and physico-chemical properties (density, viscosity, diffusivity, solvent strength, and surface tension) of organic solvents. Precisely, GXLs will offer marked benefits compare to traditional methods to: (1) minimize wetting and surface tensions effects, (2) allow for a precise control over the deposition step simply by controlling pressure, (3) improve commercial viability—in contrast with SCF mediated processes, no fluorinated (CO_2-philic) ligands are necessary, moderate pressure and higher particles concentration are possible, (4) minimize waste-streams. The effectiveness of GXLs-mediated process to improve the deposition of dodecanethiol-stabilized silver nanoparticle (AgNP) in hexane on carbon grid was effectively demonstrated by Mc Leod (Figure 27).[92] The dodecane thiol-stabilized AgNP were prepared by literature reported methods[86, 93] (arrested precipitation) and then re-dispersed into chloroform or hexane for subsequent deposition. TEM images (A, B in Figure 27) of the deposited AgNP obtained from evaporation of hexane in air show local disorder, agglomeration of the nanoparticles and percolating networks. In contrast, the AgNP particles deposited via the CO_2-expanded hexane method are closely packed with no major defects (C,D in Figure 27). Expanding the organic solvent with CO_2 enables the controlled deposition of nanoparticles leading to evenly dispersed nanoparticles over a wide surface area, free of unwanted features such as local high concentration and random interconnected particle network. Since the deposition of nanoparticles

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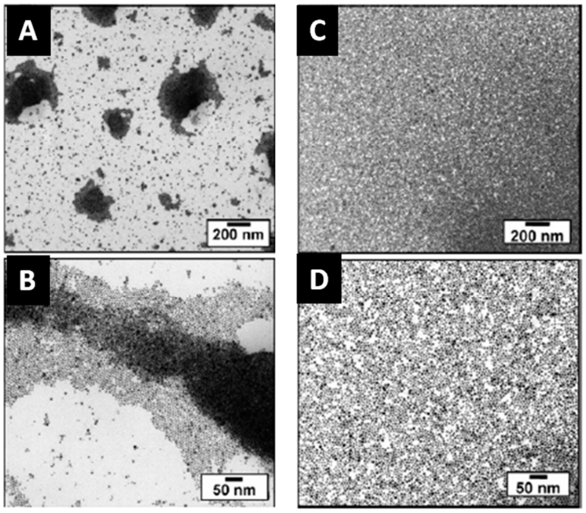
from a CO_2 expanded liquids is size-dependent; experimental protocoles have been developed to selectively fractionate a polydispersed suspension into several fractions with narrower size distributions at scales ranging from 1mL to 20 mL of nanoparticle suspensions.[94-99]



A & B. Dodecanethiol coated AgNP deposited <u>from hexane evaporation</u>.
C & D. Dodecanethiol coated AgNP deposited <u>from CO_2-expanded hexane</u> (25°C from 100 to 800 psi).

Figure 27. TEM images of AgNP obtained from traditional hexane evaporation and GXL deposition techniques. Reprinted (adapted) with permission from M. C. McLeod, C. L. Kitchens and C. B. Roberts, Langmuir, 2005, 21, 2414-2418. Copyright (YEAR) American Chemical Society.

<u>Water at Elevated Temperature</u>

Water at elevated temperatures represents an environmentally benign solvent system for conducting a wide variety of synthetic transformations and subsequent separations. The physiochemical properties of water at elevated temperature are considerably different from water at ambient temperature. Over the range of temperatures from ambient to 275°C (1) the density decreases from 1g/cc temperatures to 0.75g/cc, (2) the dielectric constant decreases from 78 to approximately 20 (Figure 28) , and (3) the auto-ionization constant, K_W, increases from 10^{-14} to 10^{-11} (Figure 29).[100] Thus, as the temperature increases, the physiochemical properties of water

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begin to resemble organic solvents in that the solubility of organic molecules increases. For instance, at saturation pressure, a gradual change of dielectric constant is observed from 78 at ambient temperature to approximately 50 at 125°C, 40 at 175°C and 20 at near critical conditions (300°C). Each of these temperatures reflects the dielectric constant of DMSO (47), acetonitrile (37.5), and acetone (21), respectively. In principle, water at elevated temperature, in place of typical organic solvents, may provide a potentially green vehicle for conducting chemical processes.

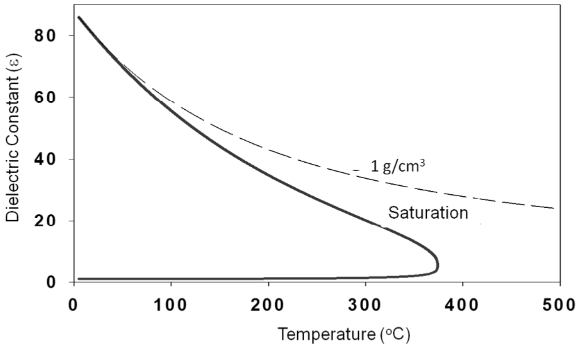

Figure 28. Dielectric constant of water as a function of temperature from 0-500°C. Correlation from Uematsu and Franck[101].

Reaction can be conducted under homogeneous conditions at elevated temperatures, where the dielectric constant of the medium resembles typical organic solvents. The subsequent product separation/isolation can be achieved by simply cooling the reaction mixture to ambient temperatures initiating a phase separation of the organic product from the water. It should be pointed out that the reduced dielectric constant of water at elevated temperatures, while increasing the solubility of non-polar organics, reduces the solubility of inorganic salts.

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Therefore, for applications as a reaction medium, a careful balance must be struck for the desired solubility of ionic and nonionic species.[102-104]

As the temperature of water increases the concentrations of hydronium and hydroxide ions increase; K_w increases from 10^{-14} at 25°C to nearly 10^{-11} at approximately 250°C (Figure 29). Thus, acid-base catalysis processes are also enhanced. This is another major motivation for using water at elevated temperature as a reaction solvent.[105] Interestingly, at the relatively moderate temperature of 125°C for example, a significant change in the auto-dissociation constant is already in place ($K_w \approx 10^{-12}$). Thus, by simply heating the water solvent, there is a major increase in the concentration of hydronium and hydroxide ions available. Upon cooling to room temperature the hydronium and hydroxide ion concentrations revert back to "ordinary" water. No neutralization is necessary at the end of the reaction and no accompanying salt waste disposal issues need to be addressed.

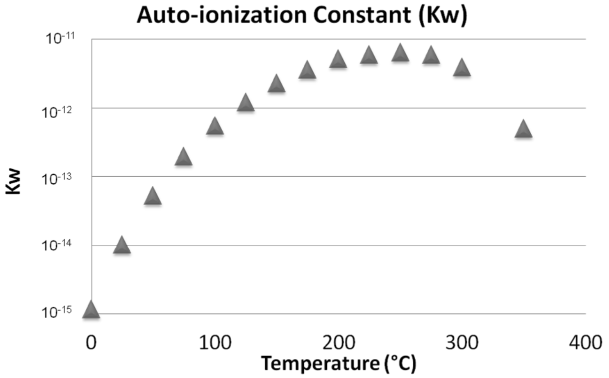

Figure 29. Dissociation constant of water as a function of temperature from 0-350°C.

A wide range of chemical transformations in water at elevated temperature have been reported in the literature.[106-109,110] While the most common type of reactions studied are hydrolyses,[74, 111-115] bond-formation reactions such as Friedel-Craft alkylations[116, 117], and

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acylations[118], skeletal rearrangements[119, 120], and condensation reactions[121] have also been reported (Table 1). It must be emphasized that, unlike "ordinary" Friedel-Craft alkylations and acylations, alkyl halides, acyl halides, and corrosive Lewis acids are not necessary; alcohols are used in place of alkyl halides and carboxylic acids are used in place of acyl halides. Nevertheless, it should be noted that many of the reactions produce water and, as a consequence, the yields of these reactions conducted in water are equilibrium governed.[122] For instance, in the case of the Friedel & Craft acylation of resorcinol at 290°C, the equilibrium yields is ~ 1% in water and ~ 50% in neat acetic acid. Table 1 provides an overview of some chemical reactions that can be conducted in water at temperatures from 200 to 300°C.

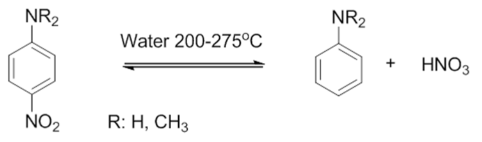
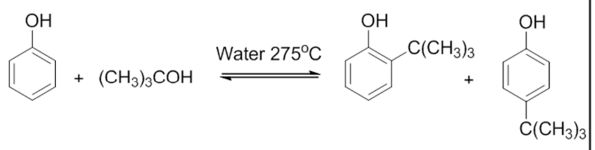
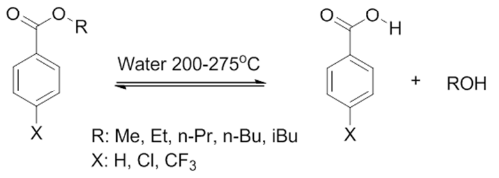
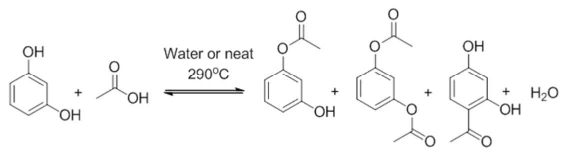
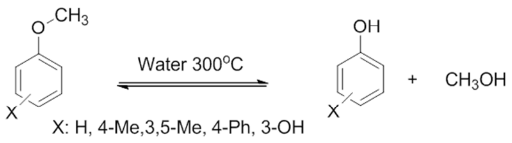
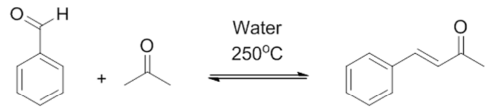
Hydrolysis of 4-nitroanilines [110]	Friedel & Craft ***alkylations*** [111,112]
	
Hydrolysis of esters[107]	Friedel & Craft ***acylations***[113]
	
Hydrolysis of substituted anisole[107]	***Condensation*** of benzaldehyde with acetone[116]
	

Table 1. Reactions (hydrolyses, acylations, alkylations and condensations) conducted in water at elevated temperature.

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Hydrolysis in Water at Elevated Temperature

The combination of increased dissociation constant of liquid water and relatively high temperature has resulted in successful strategies for acid and base catalyzed transformations.[123-125] To illustrate this, recent efforts to use water at elevated temperature applied for biomass processing such as the algae hydrothermal treatment[126, 127] and other renewable feedstock have been reported.[127-134] In this context, chemical reactions, both catalyzed and uncatalyzed, in water near or above its critical point is conducive to convert biomass into hydrogen, methane and/or liquid fuels. Water at elevated temperature can also provide a means of efficient, fast, and selective removal of protecting groups such as esters, ethers, amides, carbamates by tuning the temperature of the reaction. Successful examples are reported in the literature[135, 136, 109] at temperatures ranging from 100 to 300^{o}C. In these examples, the key parameter is reaction temperature.

C-C Bond Formation in Water at Elevated Temperature

Water has also been employed for chemical transformations at relatively moderate temperature (100-200^{o}C). In this context, the motivation did not rely as heavily on the changes in properties of water at elevated temperature but rather on its potential as an alternative to organic solvents. This could be most advantageous when one or several of the reaction partners are hydrophilic. Specific examples include carbon-carbon bond forming reactions such as coupling reactions which call for complex set of reagents to be present in order to obtain high yields (>80%).[137-139] Significant success has been reported when water was used as the sole solvent at temperatures between 100 and 200^{o}C for the coupling of phenylboronic acids and various haloaromatics (Figure 30). In some cases, the addition of a co-solvent such as an alcohol and/or

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the use of microwave (MW) radiation for fast heating was explored. Leadbeater and Marco reported coupling yields up to 98% in water at 150°C with conventional and with MW heating.[140, 141] The catalyst used was palladium acetate; no ligands were necessary. The procedure did include sodium carbonate as the base as well as a phase transfer catalyst (tetra-n-butylammonium bromide).

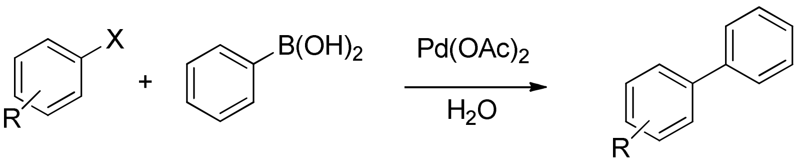

Figure 30. Suzuki Coupling reaction of substituted halobenzene and phenylboronic.

The ability to perform acid and base-catalyzed processes without the addition of acids or bases enables a simplification of the traditional procedures. Additionally, the tunability of near-critical water allows for a unique control of reaction rates and selectivities that are not available through traditional processing techniques. The potential major advantage of water at elevated temperature is providing a vehicle for conducting a homogeneous reaction at elevated temperatures and allowing for a facile product separation by returning to room temperature accompanied by a phase split. Other advantages include replacing environmentally undesirable catalysts, eliminating unwanted byproducts, improved selectivity, and elimination of mass transfer limitations commonly present in heterogeneous systems.

5. Switchable Solvents

Switchable solvents are a unique class of solvent systems that were developed to synergistically optimize reaction and product separation. A switchable solvent has properties that can be altered in response to a change in temperature and/or pressure. The two classes of

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switchable solvents that will be discussed are: (1) sulfolenes such as piperylene sulfone (PS)—a volatile and recyclable DMSO substitute and (2) one and two-component ionic liquids- solvent systems that can be reversibly switched between a molecular liquid~~s~~ and an ionic liquid.

Sulfolenes - "Volatile" and recyclable DMSO Substitutes

Dimethylsulfoxide (DMSO) is a dipolar, aprotic solvent which can dissolve both organic solutes and partially or completely dissolve many inorganic salts. In principle, DMSO would be an ideal solvent for conducting many chemical transformations. Unfortunately, while reactions usually proceed in excellent yields, isolation of the products is difficult at best. Since DMSO has a high boiling point (189^{o}C at 51.7torr) separation of products by distillation is inefficient. As a consequence, product separation is often achieved by phase separating the product with the addition of water. This, of course, would make the recycling of the DMSO solvent difficult as well as expensive. Recycling is usually not even considered. The bottom line is that a "greener" polar, aprotic substitute for DMSO which has favorable properties for conducting reactions and which can be recycled is desperately needed.[42, 142-144]

Sulfolenes derivatives are known to undergo *reversible* cheletropic reactions to their corresponding diene and sulfur dioxide. The cheletropic reaction of conjugated dienes with SO_2 to produce sulfolenes is an example of a concerted pericyclic process.[145] Sulfolenes derived from reaction of 1,3-butadiene, 1,3-pentadiene (piperylene), and 2-methyl-1,3-butadiene (isoprene) were reported in 1946 (Table 2).[145]

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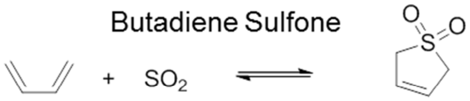
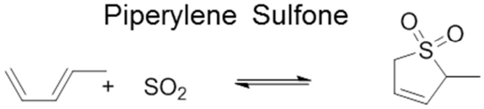
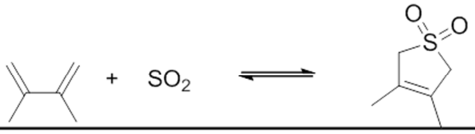
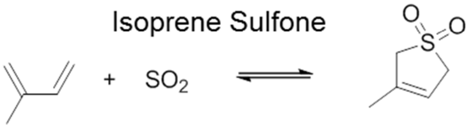
Cheletropic Reaction of dienes and SO_2 to Sulfolenes	Melting Point of Sulfolene (°C)
Butadiene Sulfone 	64-65
Piperylene Sulfone 	-12
2,3-Dimethylbutadiene Sulfone 	134-136
Isoprene Sulfone 	63-64

Table 2.Sulfolenes and corresponding melting points.

Thermal treatment of a sulfolene reverses the reaction (retrocheletropic reaction) with the reformation of the conjugated diene and sulfur dioxide. The melting points of sulfolenes vary greatly with structure as shown in Table 2. Unlike most sulfolenes, piperylene sulfone (PS) is a liquid at room temperature and can be used as a reaction solvent without noticeable decomposition at temperatures ranging from room temperature to 80°C. Butadiene sulfone (BS) is liquid above 65°C, commercially available, and can be an alternative solvent for reactions conducted at somewhat higher temperatures (80-120°C).

Experimentally, piperylene sulfone is synthesized from *trans*-1,3-pentadiene (*trans*-piperylene) and sulfur dioxide in the presence of a radical inhibitor as shown in Figure 31.[145,146] The synthesis can also be carried out using the commercially available and inexpensive 1,3-pentadiene, which is a mixture of trans- and cis- isomers. It is believed that only the trans-isomer reacts with SO_2 to produce the sulfolene. Recently, Marus *et al.* reported an efficient scalable

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synthesis of PS that included a separation process using liquid CO_2.[147, 148]

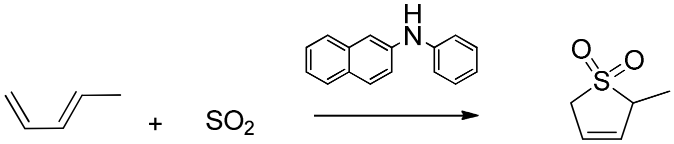

Figure 31. Synthesis of piperylene sulfone.

Table 3 summarizes a comparison of some physical properties and solvatochromic parameters[4, 5, 36, 149] between PS and DMSO.[150] For the most part, there is a striking similarity between the two solvents. The dipole moments and dielectric constants of the two solvents are quite close. In addition, the solvatochromic parameters are also comparable although PS has a lower β value (0.46) compared to DMSO (0.76) suggesting a lower hydrogen bond donor ability.

	DMSO	**Piperylene Sulfone**
Boiling point (°C)	189 (34/3Torr)	85 (7Torr)
Melting point (°C)	16-19	-12
Dipole moment (D)	4.27	5.32
α β π^* E_T30 (KJ/mol)	0 0.76 1.00 189	0 0.46 0.87 189
ε	46.7	42.5

Table 3: Physical properties of DMSO and Piperylene Sulfone

Unlike DMSO, however, PS can undergo a concerted retro-cheletropic process—a

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property which can potentially (1) facilitate product isolation and (2) enable solvent regeneration and recycling. Indeed, at temperatures greater than 100ºC piperylene sulfone *cleanly and efficiently* decomposes back to gaseous *trans*-1,3-pentadiene (b.p. 42ºC) and sulfur dioxide (b.p. -10ºC) (Figure 32). The products of this decomposition can be collected and subsequently be allowed to react in order to reform the piperylene sulfone solvent.

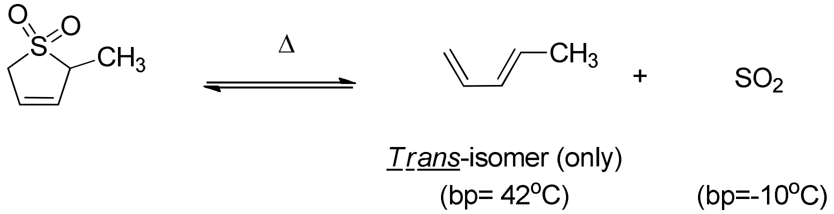

Figure 32. Reversible decomposition of piperylene sulfone into trans-piperylene and sulfur dioxide.

Differential scanning calorimetry coupled with thermogravimetric analysis was performed on piperylene sulfone. Heating at 5 °C/min for 20 minutes and then holding at 120°C for 30 minutes triggered the decomposition, leaving virtually no residual mass. It is important to recognize that the solvent decomposition must be quantitative (i.e. yielding no residue) to successfully achieve facile product recovery and efficient solvent recycling.

Piperylene sulfone is one of a number of possible unsaturated cyclic sulfone (sulfolenes) that can be employed as solvents. Others sulfolenes such as butadiene sulfone and isoprene sulfone are also of interest as media for conducting reactions (Table 2). Figure 33 graphically illustrates the half-life associated with each of these sulfones (piperylene sulfone, butadiene sulfone, and isoprene sulfone) as a function of temperature. The data indicate that the rate of reversal is structure dependent. Drake *et. al*. found that piperylene sulfone exhibited reversal at lower temperatures with an half-life of approximately 60 min at 100°C.[151] In contrast, a comparable half-life for the thermal reversal of butadiene sulfone and isoprene sulfone took

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place at 125°C; clearly, these two sulfolenes are substantially more thermally stable than piperylene sulfone.

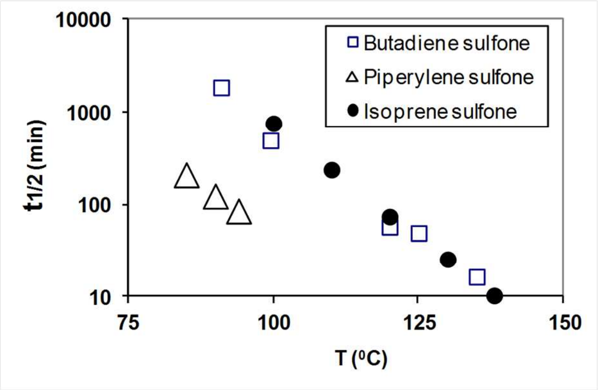

Figure 33. Decomposition half-life of ■ = butadiene sulfone, • = isoprene sulfone, and Δ = piperylene sulfone.[145]

Reactions in Piperylene Sulfone

In order to establish the scope of piperylene sulfone as a substitute for DMSO, a series of nucleophilic substitution reactions were conducted in the two solvents. Vinci *et al.* reported the rates of reaction of benzyl chloride with a variety of anionic nucleophiles in both piperylene sulfone and DMSO at 40ºC.[150] The reactions are heterogeneous since most of the anionic nucleophilic salts are only partially soluble in the solvents. The results are shown in Table 4. Although the reactions proceed at a slower rate in PS compared to DMSO, the yields are comparable. Surprisingly, no reaction was observed between benzyl chloride and potassium cyanide in anhydrous PS. Only in the presence of trace amounts of water (0.1 wt %) did the reaction proceed. As a result of this observation, reaction rates were screened in the presence of trace quantities of water. In PS and DMSO alike, it was speculated that the addition of water increased the mass transfer and possibly the solubility of the salts in the organic phase, thus increasing the overall reaction rates.

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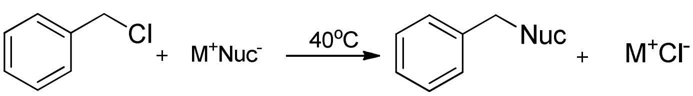

2nd Order Rate Constant k x10^{1} (mL mol^{-1} sec^{-1})				
Nucleophile	DMSO	DMSO (3% H_2O)	Piperylene Sulfone	Piperylene Sulfone (1% H_2O)[a]
KTA[b]	> 1800	> 1800	> 1800	> 1800
NaPDTC[c]	> 1800	> 1800	> 1800	> 1800
KSCN	1.4 (± 0.1)	1.7 (± 0.1)	2.1 (± 0.1)	2.3 (± 0.2)
KOAc	3.4 (± 0.1)	11.0 (± 0.1)	0.013 (± 0.004)	0.19 (± 0.01)
KCN	5.8 (± 0.8)	17 (± 5)	no rxn	0.15 (± 0.01)
CsN_3	69 (± 1)	16.7 (± 0.9)	2.4 (± 0.9)	5.8 (± 0.9)
CsOAc	22.7 (± 0.6)	16.4 (± 0.2)	0.35 (± 0.04)	0.35 (± 0.06)

[a] only rate constants for PS (1wt%water) are presented. [b]Potassium thioacetate. [c] Sodium pyrrolidinedithiocarbamate.

Table 4. Second order rate constants for nucleophilic displacement reactions in DMSO, DMSO with 3% water, PS, and PS with 1% water at 40°C.

The solvent decomposition, product isolation, and solvent regeneration and recycling sequence were also reported for the reaction of benzyl chloride and potassium thiocyanate (Figure 34). Specifically, after the reaction of benzyl chloride with potassium thiocyanate in piperylene sulfone at 40°C was complete, the product reaction mixture was heated to 110ºC. This

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initiated the decomposition of the solvent to gaseous *trans*-piperylene and sulfur dioxide leaving behind the solvent-free product residue**.** The pure benzyl thiocyanate was isolated from the residues in 96% yield. The gases were collected in a second vessel containing liquid sulfur dioxide at -30ºC. Piperylene sulfone was quantitatively reformed at room temperature and isolated in 87 % yield. Since the reaction was conducted on a very small scale, it is conjectured that, on a much larger scale, the piperylene sulfone recovery will be close to quantitative.

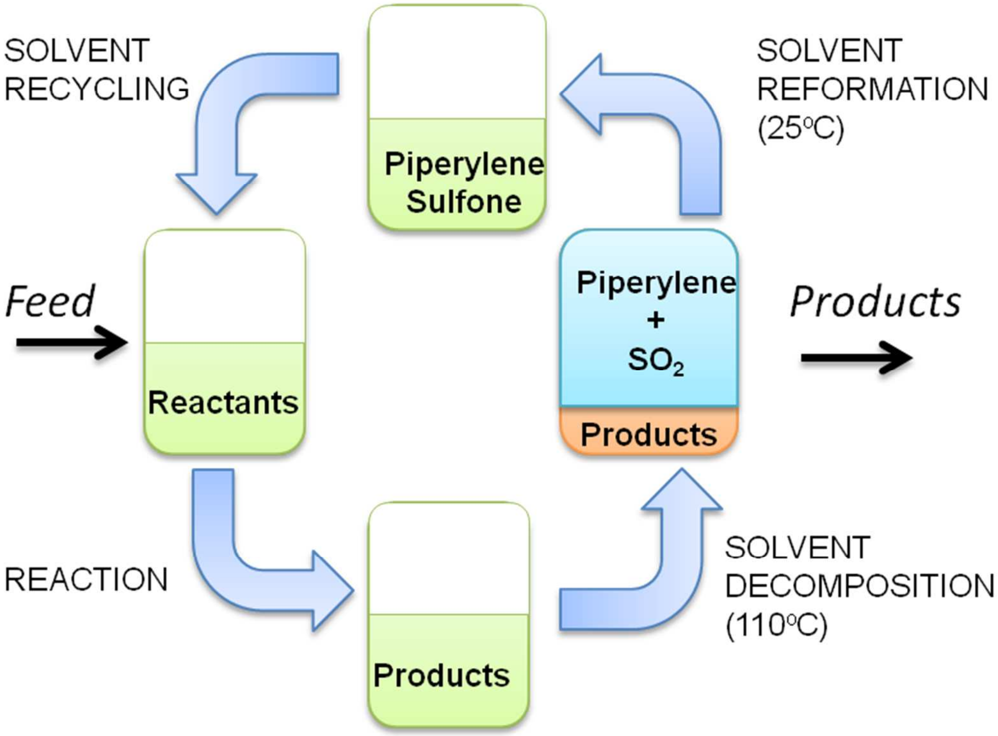

Figure 34. Recycling and reformation process of piperylene sulfone.

Piperylene sulfone was investigated by Jiang *et al*. as a recyclable green replacement for DMSO in room temperature copper-catalyzed aerobic oxidation of alcohols.[152] Very high turnover frequency (over 31 h^{-1}) for the room temperature aerobic oxidation of alcohols in piperylene sulfone was observed. The immiscibility between piperylene sulfone and *n*-pentane

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facilitated product isolation as well as recovery and reuse of the catalytic system. Various copper salts were examined as the pre-catalyst in the presence of DMAP (4-dimethylaminopyridine) and acetamido-TEMPO for the oxidation of 4-methoxybenzyl alcohol to 4-methoxy benzaldehyde (Figure 35). Copper (I) bromide was shown to be optimal, yielding the highest turnover frequency (33.3 h^{-1}). Furthermore, using ^{1}H NMR analysis, the authors could not detect any over-oxidized product (4-methoxybenzoic acid).

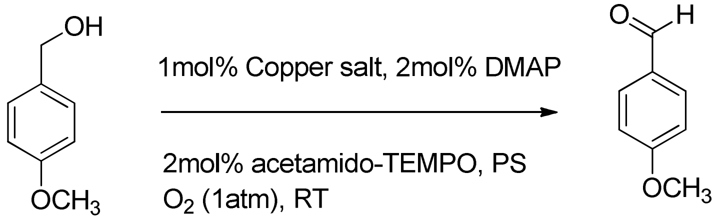

Figure 35. Oxidation of 4-methoxybenzyl alcohol in piperylene sulfone.

The recyclability of the optimized catalytic system (Copper Bromide, CuBr, acetamido-TEMPO, and DMAP) for aerobic oxidation of benzyl alcohol in piperylene sulfone was also reported. The schematic of the overall process is shown in Figure 36. The product, benzaldehyde, was extracted with *n*-pentane in 98 % yield. The recovery and reuse of the catalytic/solvent system was easily accomplished because piperylene sulfone and the catalytic components (CuBr, acetamido-TEMPO, and DMAP) were insoluble in *n*-pentane. After the extraction of benzaldehyde from the reaction mixture with *n*-pentane, another reaction cycle was started by simply adding fresh benzyl alcohol. The catalytic systems proved to be readily recyclable for two additional runs with only a slight drop in activity, 88% and 82 % yield respectively. Thus, the PS phase containing the catalysts can be recycled as long as the catalyst activity remains high (Recycle Stream (1)). Once the catalyst system is no longer functioning effectively the piperylene sulfone can be decomposed into piperylene and SO_2. The PS then can be reformed

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and recycled (Recycle stream (2)) and the catalyst residue disposed. This contrasts with a DMSO-mediated process where both DMSO and the catalyst system would have to be disposed.

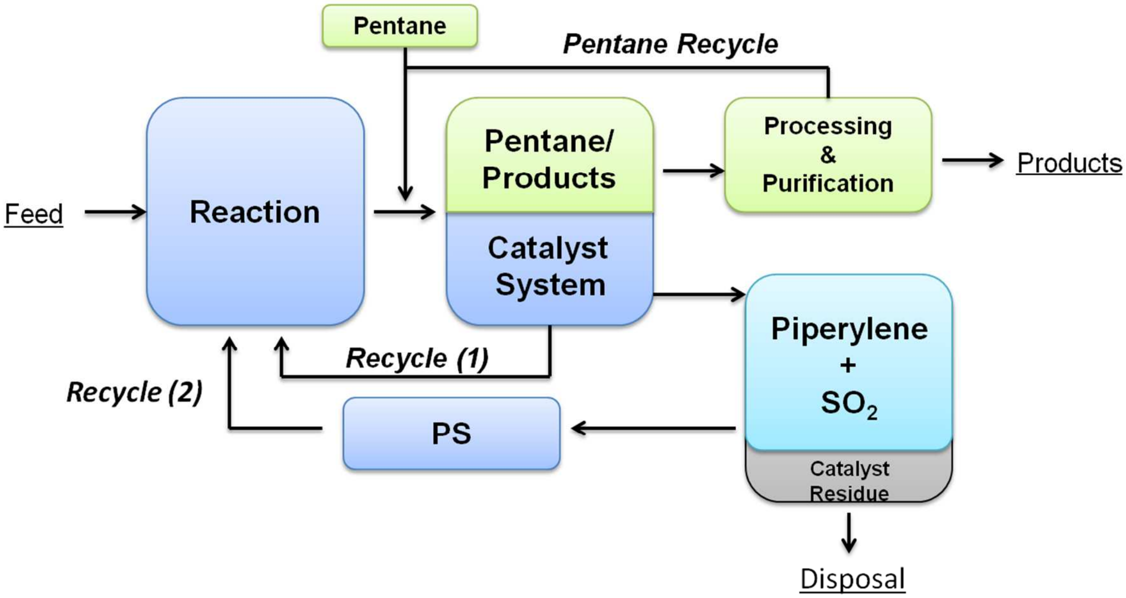


Figure 36. Process schematic for the PS-mediated oxidations of alcohols.

Subsequently, the three-component recyclable catalytic system was then applied to various primary alcohols (aromatic, heteroaromatic, allylic) with high yields (Table 5).

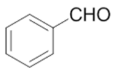
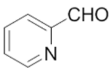
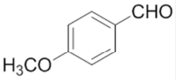
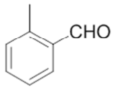
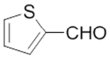
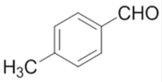
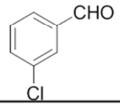
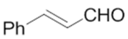
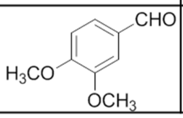
Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
	98		84		96
	88		91		90
	92		94		89

Table 5. Aldehydes prepared from their corresponding alcohols in PS with 1mol% CuBr, 2mol% DMAP, 2mol% acetamido-TEMPO, 1atm O_2, room temperature, 3hrs.

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Acid catalysts are omnipresent in the chemical industry. In fact, 100 million metric tons of products are produced each year via acid catalyzed reactions.[153] Piperylene sulfone and butadiene sulfone were investigated as switchable solvents that can simultaneously act as both a solvent *and* a Bronsted acid catalyst.[154] As was the case for piperylene sulfone, butadiene sulfone can also be employed as solvent but at temperatures greater than its melting point (65°C). It can also be thermally decomposed at reasonable temperatures (~160°C) to produce two gaseous products (butadiene and sulfur dioxide) for facile isolation of the products of reaction (Figure 37, top). The butadiene and the sulfur dioxide can be subsequently trapped in liquid sulfur dioxide (-30°C) to reform butadiene sulfone.

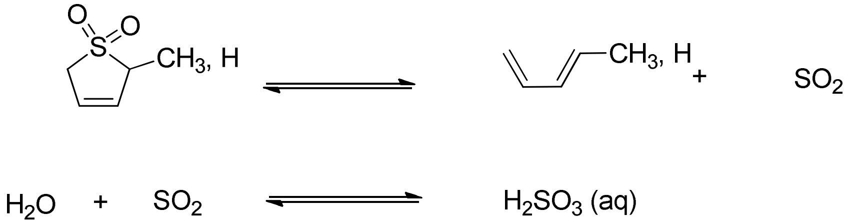

Figure 37. Formation of sulfurous acid through equilibrium reaction between SO_2 and water for butadiene sulfone (H) or piperylene sulfone (CH_3).

At temperatures slightly above ambient conditions (30 -60°C), both sulfolenes are in equilibrium with small quantities of sulfur dioxide. In the presence of water, small quantities of the in-situ sulfurous acid are produced (Figure 37). Advantage was taken of this in the *in situ* acid-catalyzed hydrolysis of *β*-pinene to α-terpineol (Figure 38). The reaction was optimized as a function of the following key variables: 1) the quantity of SO_2 in equilibrium with the diene, 2) the concentration of water, 3) the temperature, and 4) the time.

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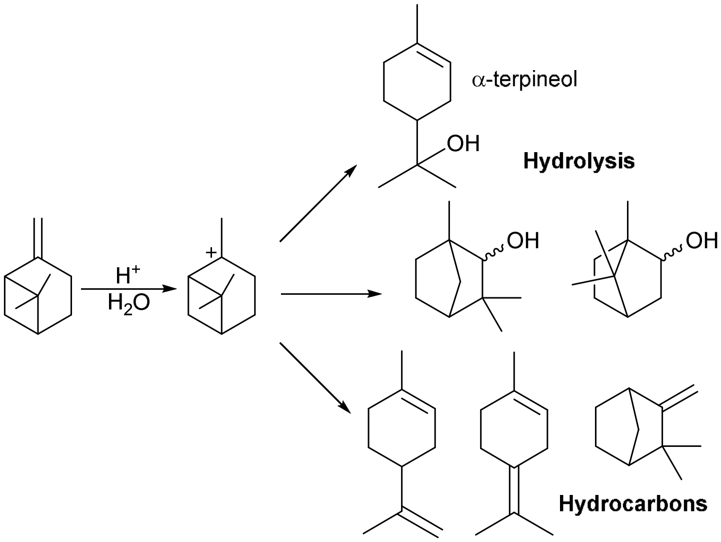

Figure 38. Acid catalyzed hydrolysis of β-pinene.

The sulfolene/water systems were optimized for both conversion and selectively towards terpineol (Table 6). In comparison with traditional hydrolysis conditions,[155, 156] sulfolene/water solvent systems offer improved terpineol selectivity and comparable conversions while not requiring added acid.

System	Acid	Conditions	Conversion (%)	Selectivity (%)
Conventional	Sulfuric	0.073 N acid, Acetone/water (95/5), 75°C, 1h	88	42
Solid	Heteropoly	0.003M acid, acetic acid/water, 25°C, 2h	92	42
Reversible	Sulfurous	BS/water (85/15), 65°C, 2h	81	57
Reversible	Sulfurous	BS/water (80/20), 65°C, 2h	91	48

Table 6. Conversion and Selectivity of β-pinene hydrolysis in various systems.

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Reversible Ionic Liquids

Over the last decade there has been a plethora of publications dealing with the use of ionic liquids as solvent media for reactions and separations. Classically, ionic liquids (ILs) are salts with melting points near or below ambient temperature. Some advantageous properties include negligible vapor pressure, non flammability, a wide liquid temperature range, excellent solvent properties, high thermal conductivity, and immiscibility with many organic solvents.[157-167] Their properties can be tailored by tuning the structure. This includes the structure of the cationic portion of the salt, the anionic portion, and the subsequent pairing of specific cations with specific anions. As a consequence, there has been a phenomenal growth in the syntheses and applications of classical ionic liquids over the last decade. This growth has been attributed to their unique properties and the assumptions that they are green. Classical ionic liquids like BMIM-PF_6 or BMIM-BF_4 (Figure 39), for example, have been widely explored as media for synthetic transformations. However, while reactions usually proceed in reasonably good to high yields, the separation of products from these media is often problematic. The inherent ionic nature of molten salts and their relatively high viscosity often precludes distillation of the product from the ionic liquid or the use of precipitation of the product from the ionic liquid.

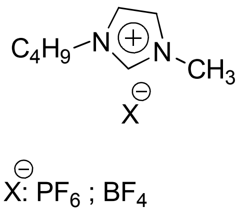

Figure 39. Structure of BMIM-PF_6 & BMIM-BF_4

In contrast to the classical ionic liquids, the ionic liquid formed from the reaction of low boiling dimethylamine with gaseous carbon dioxide (*N,N*-dimethylammonium *N',N'*-

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dimethylcarbamate (DIMCARB)) can actually be "distilled." What is actually happening is that, under the influence of heat, the liquid ionic salt is reverting back to dimethylamine and carbon dioxide and then, upon collection, reforming the liquid ionic salt at ambient temperatures.[168-173]

When employing classical ionic liquids as reaction solvents it is common practice to extract the products using a non-polar solvent as hexane. This strategy is, however, product-dependent. It also generates significant amount of organic waste and often results in a contaminated IL phase which could result in costly disposal issues. Furthermore, if recycling of classical ionic liquid is possible, it generally requires extensive washing with water or organic solvents creating large amounts of additional waste.

Like classical ILs, reversible ionic liquids (RevILs) can be designed for a specific application, where the molecular architecture of the ionic solvent system can be adjusted to achieve the desired solvent properties. In contrast with classical ILs, however, RevILs can be switched back and forth from a molecular liquid (non-ionic liquid like an organic amine) to an ionic liquid upon the reversible reaction with CO_2 (Figure 40). Hence, reversible ionic liquids can, in principle, present a solution to the issues of product separation and solvent purification encountered by classical ionic liquids. Indeed, RevILs have been utilized for a range of industrially relevant processes including CO_2 capture,[174, 175] chemical transformations like Claisen-Schmidt reactions and Heck couplings, [176] polymerization,[177] and crude oil recovery.[178-180] Furthermore, the RevILs offers the opportunity to recycle the solvent for the same or different reactions, which is important in the cases that the molecular liquids must be synthesized and/or may be derived from non-renewable resources.

Two-Component Reversible Ionic Liquids

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The Liotta-Eckert-Jessop groups reported the first examples of two-component reversible ionic liquids based upon 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and *N*,*N*,*N*',*N*'-tetramethyl-*N*''-butylguanidine (TMBG) and an alcohol (Figure 40).[176, 177, 181] Experimentally, these RevILs are prepared by bubbling CO_2 through equimolar solutions of TMBG or DBU and various primary alcohols (from methanol to dodecanol). Reversal of the ionic liquid back to the molecular liquid can be easily achieved by bubbling N_2 (or other inert gases) through the ionic liquid and/or by mild heating (60°C). The ionic products were each characterized by ^{1}H and ^{13}C NMR, elemental analysis, FT-IR, melting points, differential scanning calorimetry (DSC), and conductivity measurements.[182]

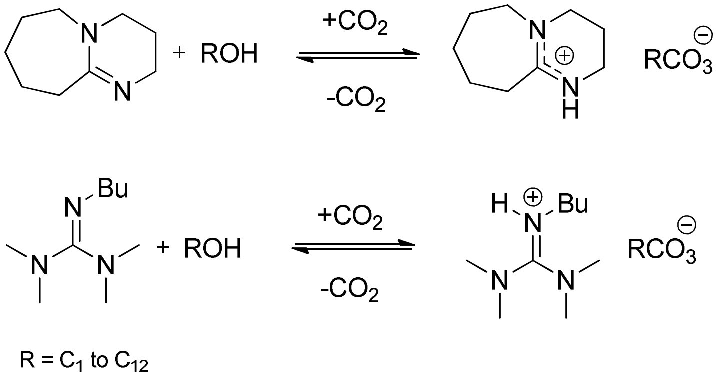

Figure 40. Two-component RevILs. The molecular liquids are composed of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (top) or *N*,*N*,*N*',*N*'-tetramethyl-*N*''-butylguanidine (TMBG) (bottom) and alcohol (ROH). Under CO_2 pressure, a reversible switch forms ionic liquids $[DBUH]^+[RCO_3]^-$ and $[TMBGH]^+[RCO_3]^-$, respectively.

The relative polarities of the molecular liquid and the corresponding ionic liquids were determined via UV-Vis absorption measurements of the Nile Red dye (a common solvatochromic probe). 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. For example, the DBU:1-hexanol mixture exhibits a λ_{max} at 536.0 nm while the

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λ_{max} of the corresponding ionic liquid is 543.0 nm. This corresponds to a shift of 7.0 nm (Table 7). Such a shift in λ_{max} represents a polarity switch similar to that in proceed from chloroform to traditional ionic liquid like [bmim][PF_6]. The Nile Red experiments indicate that the polarity of both neutral liquids and ionic salts depend on the length of the alkyl chain on the alcohol. The many possible combinations of nitrogen bases and alcohols provide a wide range of solvent switches. The use of 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 (up to 16 nm) 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.

Solvent	**$E_T(30)$, kcal/mol**	**λ_{max}(Nile Red) nm**
$CHCl_3$	39.1	537.6
CH_2Cl_2	40.7	535.2
Mixture[a] + N_2	44	536
DMF	43.2	541.2
Propanoic acid	50.5	542.4
Mixture[a] + CO_2	53	543
[bmim]PF_6[b]	52.3	547.5

Table 7. Solvent Parameters for common molecular and ionic liquids. [a]Mixture = 1:1 molar ratio of DBU:1-hexanol. [b][bmim] = 1-Butyl-3-methylimidazolium.

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The switchable nature of the RevIL's potentially provides a vehicle for conducting a reaction and a subsequent separation by simply proceeding from a neutral liquid of one polarity to an ionic liquid of another polarity or vice versa as required. The polymerization of styrene reported by Phan *et al.* (Figure 41) is an example of this principle.[177] The polymerization was conducted with $K_2S_2O_8$ as initiator in the neutral solvent mixture consisting of DBU and 1-propanol in a ratio of 1:2.5 at 50°C. After the polymerization was complete, the solvent was switched to its ionic form by the addition of carbon dioxide. The polystyrene, which is insoluble in the ionic liquid medium, phase separated. The polymer was collected by simple filtration and the solvent was reversed to its neutral form by the application of heat and used again for another polymerization. A total of four cycles with a 97% average yield per cycle was reported.

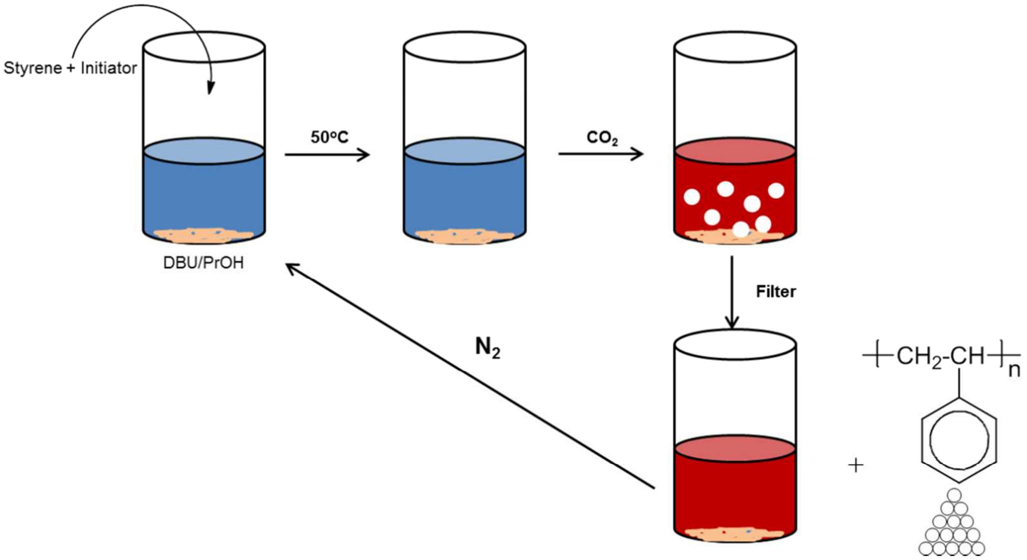

Figure 41. Polymerization of styrene in DBU/Propanol RevIL. Blue indicates molecular liquid and red indicates ionic liquid.

Hart *et al*. investigated the Claisen-Schmidt reaction between butanone and benzaldehyde in TMBG to form the terminal enone (major product), the internal enone (minor product) (Figure

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42).[183,184, 185,121, 186, 187] TMBG acted as solvent and base catalyst. After reaction completion, methanol and octane were added to the reaction mixture. Subsequent addition of carbon dioxide promoted the formation of the RevIL resulting in a liquid-liquid phase split. The enone products selectively partitioned in the octane phase and were easily separated by decantation. The ionic liquid phase was reversed to TMBG by heating and subsequently reused in another reaction. Three cycles were successfully conducted with isolated yields 34, 32, and 34% of enones (95% selectivity toward the terminal enone). Partial conversions and drying step were necessary to eliminate undesired polycondensation products and avoid formation of guanidinium carbonate ionic species, respectively.

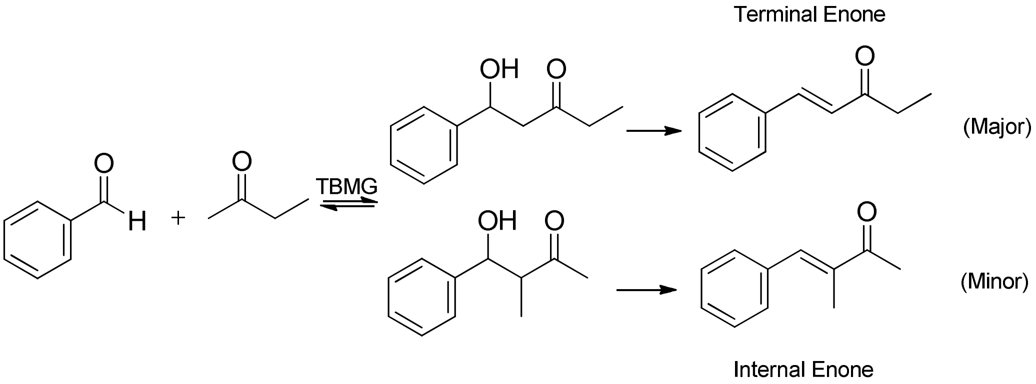

Figure 42. Claisen-Schmidt condensation of 2-butanone and benzaldehyde.

Hart *et al.* also reported Heck couplings in the RevIL from DBU/hexanol (Figure 43).[183] Heck reactions inherently result in the formation of HX (X = halide; Figure 43) which must be neutralized by a base to recover the catalyst. Therefore, stoichiometric amounts of inorganic halide salt are formed as a by-product. RevILs offered the capability to couple reaction with a two-stage separation: switching from the RevIL to the molecular liquid induced precipitation of

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unwanted inorganic salt by-products allowing for recycling of both solvent and the palladium catalyst (which remained soluble in the molecular liquid).

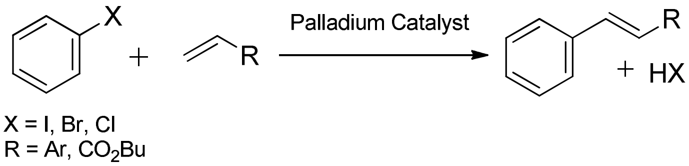

Figure 43. Palladium catalyzed Heck-type coupling reaction.

In coupling bromobenzene and styrene in the presence of 2 mol% $PdCl_2(PPh_3)_2$, *E*-stilbene was selectively synthesized in 87% yield. Furthermore, the catalyst was successfully recycled, affording 55% yield on the second cycle. An improved recycle procedure is needed in order to optimize the process and maintain high catalyst activity.

Single-Component Reversible Ionic Liquids

In 2009, Blasucci *et al.* reported the first single-component reversible ionic liquid based on trialkoxy- and trialkylsilylpropylamine structures. The application was specifically for crude oil recovery.[188] Upon reaction with CO_2, the amine forms ionic liquids composed of the corresponding carbamate anion and ammonium cation pairs (Figure 44). It is conjectured that the presence of the silicon is critical for achieving a liquid ionic material.

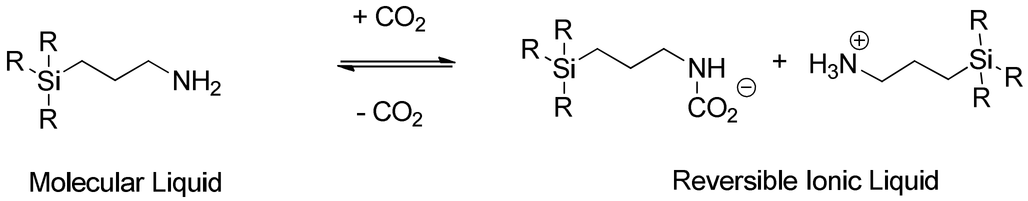

Figure 44. Silylated amines system R=alkoxy or alkyls.

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Although, oil shale feedstocks are complex and vary in composition greatly, they commonly contain hydrocarbons and contaminants such surfactants, sand, clay and ionic species. The crude oil component (i.e. non-polar hydrocarbons) was miscible with the molecular liquid, triethoxysilylamine (TESA). Upon treatment with carbon dioxide the oil phase separated from the newly formed ionic liquid, leaving impurities in a separate phase. Recyclability of the molecular liquid was tested by reversing the ionic liquid, and reconditioning the molecular liquid (removing clay, sand and insoluble ionic species), thus performing two additional cycles. Here, the one-component systems offer an advantage in term of ease of processing and ionic liquid preparation. In contrast with the two-component system, reactant stoichiometry (equimolar ratio of alcohol to guanidine or amidine) in the single component system is a non-issue.[180] Furthermore, the two-component systems which utilize low molecular weight alcohols, such as methanol, show the loss of the alcohol along with the loss of CO_2 upon reversal to the molecular liquid. Consequently, additional alcohol must be added in subsequent processes in order to maintain the correct stoichiometry. In contrast, with the one-component system, the loss of molecular liquid during the reversal step is negligible; the loss of CO_2 occurs at a temperature substantially different (<100°C) from the volatilization of the molecular liquid. [188] It should be highlighted that these systems utilized silylated amines as molecular liquid. Because of the limited hydrolytic stability of the Si-O bond hydrolytically stable trialkylsilylamines were employed. Indeed, the stability tests on the trialkylsilylamine based RevILs showed no loss of structural integrity over the period of several months under atmospheric conditions.[180]

The trialkylsilylpropylamines based RevILs have proven to be particularly attractive for energy-conscious CO_2 capture strategies.[189, 190] For these applications, the RevILs behave in a

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duel capacity: (1) the selective and efficient reaction of CO_2 with the molecular liquid to form the ionic liquid and (2) the enhanced capacities offered by the physical absorption of the CO_2 into the resulting ionic liquid. Switzer and Rohan reported a series of silylated amines for use as media in post-combustion carbon capture (Table 8).[174] The efficiency of a particular silylamine to effectively capturing CO_2 has been shown to be strongly dependent on its structure. For example, the influence of the length of the alkyl tether (between the silyl and amine groups) or the position of one or more methyl groups on the silylamine (tether or reactive amine groups) has significant effect on the CO_2 capture properties such as reaction enthalpy, viscosity, and reversal temperature. While selection of a CO_2 capture solvent is dependent on the specifications of its end application, the authors identified two silylamine solvents, 1-(aminomethyl)triethylsilane and (*trans*)-3-(triethylsilyl)prop-2-en-1-amine, as candidates for pilot-scale investigations. Overall, these systems can (1) operate neat, which provide an energy incentive (limiting the energy penalty associated with aqueous amine systems), (2) capture CO_2 efficiently via chemical reaction and physical adsorption means, (3) release CO_2 and regenerate the silylamine solvent for recycling and (4) enable a process-controlled viscosity since the viscosity is a function of the extent of conversion of the starting amine to the ionic liquid.

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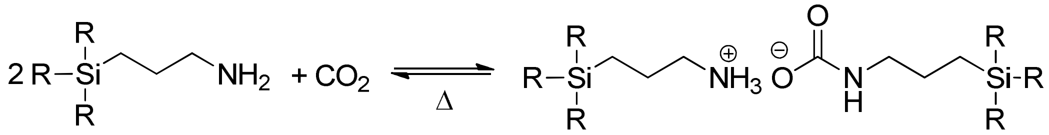

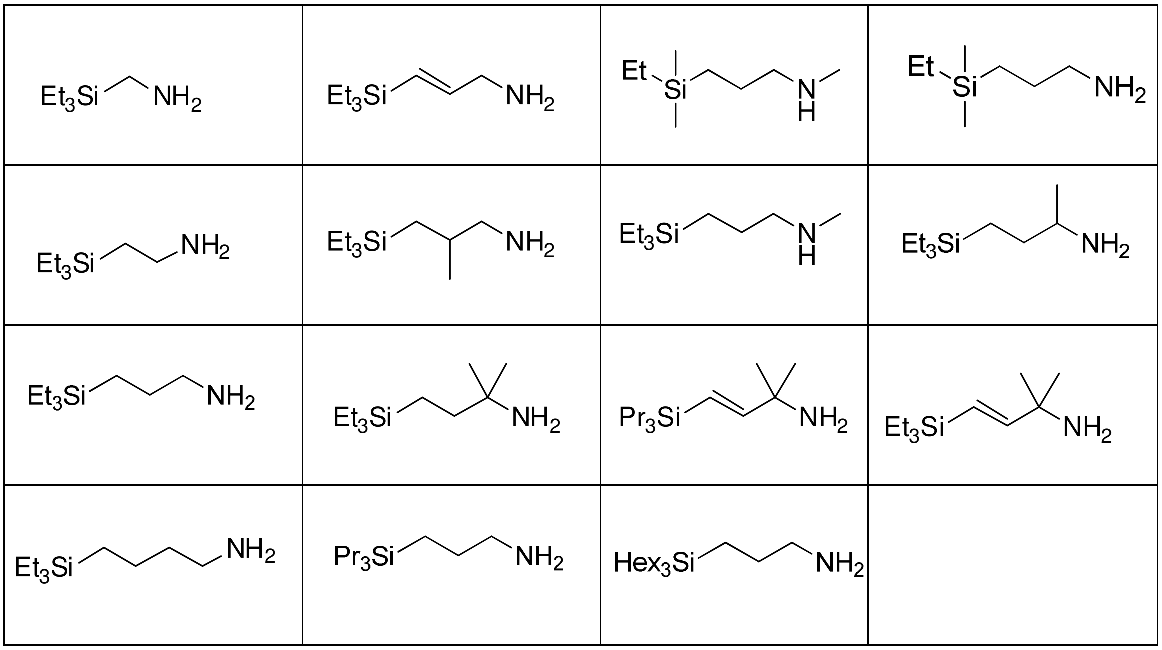

Table 8. Silylated amines tested for post-combustion CO_2 capture.

Conclusions

In this review, we have reported the physicochemical properties and some key applications for: (1) supercritical fluids, with emphasis on supercritical CO_2, (2) gas-expanded liquids and organic-aqueous tunable solvents (GXL's), (3) water at elevated temperature, (4) switchable solvents, specifically sulfolenes and reversible ionic liquids. Each system offers a unique set of properties for varied applications. These applications range from chemical transformations, product separation, catalyst recycling, nanomaterial processing, and CO_2 capture. For each application, however, the common thrust is to enable greener and sustainable solutions for chemical processes. No one traditional solvent, or for that matter any of the solvent

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systems discussed in this review, can be universally successful for all processes and separation. Innovative solutions to expand the present portfolio of sustainable and green solvents are an on-going process.

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