# Novel Solvents for Sustainable Production of Specialty Chemicals

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tunable, switchable, near-critical water, gas-expanded liquids

## Abstract

We discuss novel solvents that improve the sustainability of various chemical reactions and processes. These alternative solvents include organic-aqueous tunable solvents; near-critical water; switchable piperylene sulfone, a volatile dimethylsulfoxide substitute; and reversible ionic liquids. These solvents are advantageous to a wide variety of reactions because they reduce waste and energy demand by coupling homogeneous reactions with heterogeneous separations, acting as in situ acid or base catalysts, and providing simple and efficient postreaction separations.

## INTRODUCTION

Sustainability has become an essential concept in chemical manufacturing as well as in research and development in academia, industry, and governmental laboratories. Our society is focusing on conserving resources, minimizing energy usage, and reducing the anthropological impact on the planet. Sustainability embodies both the economics of the process and the environmental impact, with concomitant social responsibility. This review will explore the use of novel solvent systems in the development of sustainable reactions and separations.

The solvents discussed here provide simple and efficient vehicles for conducting both reactions and separations. This benefit is achieved by simply exposing the solvent system to an external physical or chemical stimulus, which results in a dramatic change in the system's properties. We emphasize applications that combine chemical reactions and separations in which these novel solvent systems provide a distinct advantage over common solvent systems. This review will discuss and compare the properties and uses of supercritical fluids, gas-expanded liquids (GXLs), near-critical water (NCW), reversible ionic liquids (RevILs), and a new volatile dimethyl sulfoxide (DMSO) substitute.

**Figure 1** qualitatively relates the solvent power (in terms of the Kamlet-Taft polarizability/ dipolarity, $\pi^*$) and transport ability (in terms of the diffusion coefficient, $D_A$) for the relevant solvents. Liquids are strong solvents but have low diffusion coefficients [approximately $10^5$ smaller than gases (1, 2)]. Gases have excellent transport properties but are weak solvents. Supercritical fluids such as $CO_2$ (sc$CO_2$) are much stronger solvents than gaseous $CO_2$ and have much higher diffusion coefficients than liquids. Therefore, sc$CO_2$ is used for many extraction processes on the industrial scale, as discussed by Brunner (3). For example, Korea-based UMAX Co. utilizes sc$CO_2$ to produce 8,000 liter $day^{-1}$ of sesame oil. GXLs, mixtures of organics and dissolved gases, are stronger solvents than supercritical fluids and have better diffusion coefficients than liquids. For example, GXLs efficiently remove polyhydroxystyrene-based films and postplasma-etch residue in small-scale integrated circuits (4). For any given process, the choice of solvent system depends on the physical and chemical properties of the reactants and products, the processing requirements, and the environmental considerations.

It is important to develop reaction processes in a holistic manner. Holistically, having a high-yield reaction is not enough; separation of the desired product from the reaction system is also of
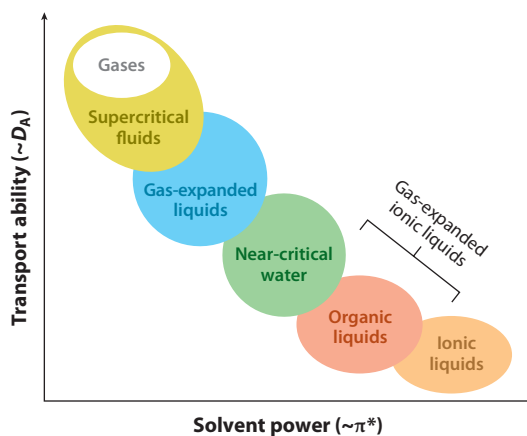


**Figure 1**

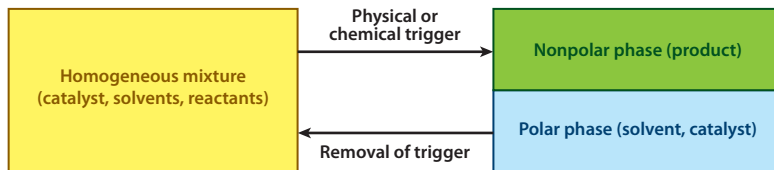Solvent power and transport ability of various solvents.

**Figure 2**

General schematic of a process using tunable and smart solvents.

paramount importance. Homogeneous reactions are usually superior to heterogeneous reactions in terms of reaction rates and selectivity, especially for catalytic processes involving enzymes. However, the difficulty of separating and recycling the catalyst seriously limits applications of homogeneous catalysis. The alternative solvent systems discussed here are sustainable because they combine homogeneous reactions with heterogeneous separations, as shown in **Figure 2**. We describe two types of sustainable solvent systems for sustainable production of specialty chemicals: (*a*) tunable solvents and (*b*) smart switchable solvents.

## TUNABLE SOLVENTS

Tunable solvents are those with physical properties that are gradually adjustable and can be controlled precisely. These include supercritical fluids, GXLs, and NCW. Because extensive reviews of supercritical fluids have appeared (5–16), these systems are referred to only in passing.

### Organic-Aqueous and Organic-Polyethylene Glycol Tunable Solvents

These tunable solvents are homogeneous mixtures of aprotic organics [examples are acetonitrile (ACN) and tetrahydrofuran (THF)] and polar protic solvents [water or polyethylene glycol (PEG)] that undergo a phase split to form biphasic liquid-liquid mixtures upon the addition of an antisolvent gas (17). The phase splitting—from monophasic to biphasic—results from the difference in the antisolvent gas solubility between the aprotic organic solvent and the polar protic solvent. $CO_2$ is completely miscible with most organics but has only slight solubility in aqueous media, and thus is an effective antisolvent in promoting phase splitting. The resulting biphasic system consists of a GXL and a polar liquid phase. The physical properties of GXLs are readily tuned by pressure. Ford et al. (18) reported the $\pi^*$ of $CO_2$-expanded ACN as a function of $CO_2$ mole fraction (**Figure 3**). The $\pi^*$ value decreases gradually from 0.75 for pure ACN to approximately 0.6 (similar to methanol) at $x_{CO_2} = 0.4$ to near zero (similar to cyclohexane) at $x_{CO_2} = 0.9$. GXLs are used as homogeneous reaction media for improved mass transfer and solubility of gaseous reactants, but these applications are not reviewed here.

Organic-aqueous tunable solvents (OATS) provide an efficient method for catalyst recovery and recycling by separating hydrophilic catalysts from organophilic substrates. In OATS, the reaction is carried out homogeneously before gas is added to yield a biphasic system. The heterogeneous phases consist of an organic-rich phase, which is normally the product phase, and an aqueous-rich phase in which the hydrophilic catalyst is retained. OATS offer improved rates, yields, and selectivities (characteristics of homogeneous systems) as well as simple catalyst separation and recycling (characteristics of heterogeneous separations). The applicability of OATS to reactions and separations depends on phase equilibria; one needs a phase split with a large liquid-liquid region and an asymmetric composition distribution for efficient product separation (19). Lazzaroni
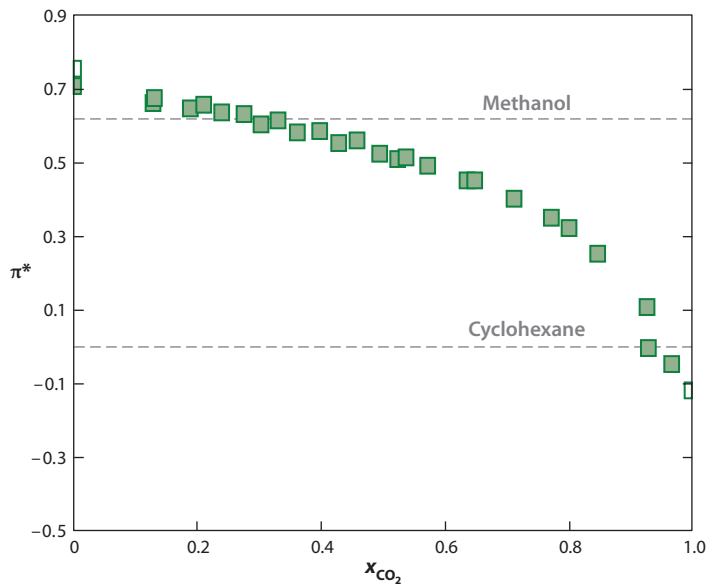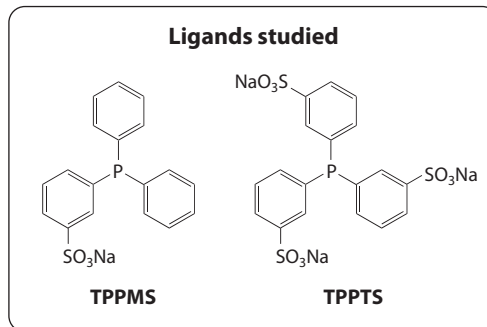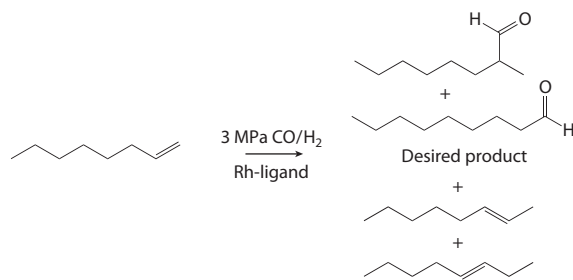
**Figure 3**

Kamlet-Taft dipolarity and polarizability ($\pi^*$) of acetonitrile/$CO_2$ mixtures as a function of $CO_2$ mole fraction, $x$ (18); the dotted lines represent $\pi^*$ values of methanol and cyclohexane for comparison.

et al. (20) showed that as $CO_2$ pressure increases, the phase separation between the two phases improves; less water is present in the organic-rich phase, and less organic is in the aqueous phase. Similarly, propane can phase split homogeneous mixtures of THF/$H_2O$ (62 vol% THF) at lower pressures (when compared with $CO_2$) (17); the amount of water in propane-expanded THF is 3 wt% at 0.8 MPa compared with 9 wt% in $CO_2$-expanded THF at 4 MPa. Propane eliminates the in situ carbonic acid formation from the reaction of $CO_2$ with water and so may be more suitable when using acid-sensitive catalysts such as enzymes.

Hydroformylation reactions of hydrophobic 1-octene and *p*-methylstyrene in THF/$H_2O$ and ACN/$H_2O$, respectively, were chosen as model reactions in OATS. These ran under synthesis gas pressure (mole ratio of 1:1 CO:$H_2$) to produce branched and linear aldehydes in the presence of a rhodium catalyst with substituted triphenylphosphine (TPP) ligands. Because hydroformylation reactions are carried out under pressure (17, 21–23), additional $CO_2$ pressure for OATS does not require equipment modifications (17). Industrial hydroformylations are run in biphasic aqueous-organic systems (24) in which the reaction occurs in the aqueous phase in the presence of the water-soluble sulfonated Rh/TPP catalyst, and the products are extracted into the organic phase. As a consequence, this approach is practical only for (slightly) water-soluble alkenes (mainly C3 and C4) (25, 26). For example, the solubility of propene in water is 200 ppm, whereas the solubility of 1-octene in water is 2.7 ppm (27, 28).

Thus, OATS permit the homogeneous hydroformylation of virtually water-insoluble alkenes such as 1-octene in THF-$H_2O$ mixtures to form 1-nonanal (the desired product), 2-nonanal, and isomers, as shown in **Scheme 1** (22). Rh catalysts with two different water-soluble phosphine ligands were used: monosulfonated triphenylphosphine (TPPMS) and trisulfonated triphenylphosphine (TPPTS). **Figure 4** shows the advantage of homogeneous reaction; conversion to products increases from less than 10% (biphasic) to 80% (monophasic) with TPPTS as the ligand, and the selectivity toward the desired aldehyde product increases to more than 75%.

**Ligands studied**

TPPMS

TPPTS

**Scheme 1**

Hydroformylation of 1-octene to 1-nonanal and other products.

The concentration ratios of the product and/or ligand were used to evaluate separation efficiency in OATS. **Figure 5** shows the ligand distribution between the phases as a function of $CO_2$ pressure (29); higher $CO_2$ pressure improves the distribution, but TPPTS also shows more efficient retention in the aqueous phase compared with TPPMS, as the larger number of sulfonate groups makes it more hydrophilic. In either case, more than 99.9% of both ligands partition into the aqueous phase with moderate $CO_2$ pressure (3 MPa). 1-Nonanal shows a similar trend, with removal efficiency of 99% at 3 MPa of $CO_2$. We demonstrate the recycling of the catalyst for three consecutive reactions with consistent catalytic activity and a turnover frequency (TOF) of 51 ± 3 h$^{-1}$. Less than 1 ppm of Rh leached into the organic layer as measured by atomic absorption spectroscopy, comparable with leaching from a Zeolite-Y supported Rh/TPP catalyst (30).

Blasucci et al. (17) reported the hydroformylation of *p*-methylstyrene to produce 2-(*p*-tolyl)propanal (branched product) and 3-(*p*-tolyl)propanal in ACN/H$_2$O OATS. The desired branched aldehyde is a model for the intermediate [2-(4-isobutylphenyl)propanal] in ibuprofen synthesis (31, 32). With experimental conditions similar to the 1-octene hydroformylation above, the TOF was 92 h$^{-1}$ at 40°C and 406 h$^{-1}$ at 80°C; the yield of the branched product was 95% at 40°C and 80% at 80°C. The yield reduction of the branched product with temperature is
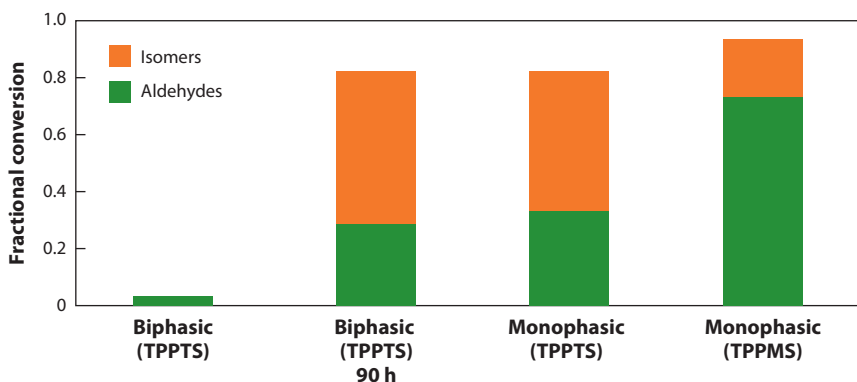


**Figure 4**

Aldehyde yield for monophasic and biphasic hydroformylation of 1-octene with Rh/ligand at 120°C and 3 MPa of synthesis gas (22). Abbreviations: TPPTS, trisulfonated triphenylphosphine; TPPMS, monosulfonated triphenylphosphine.
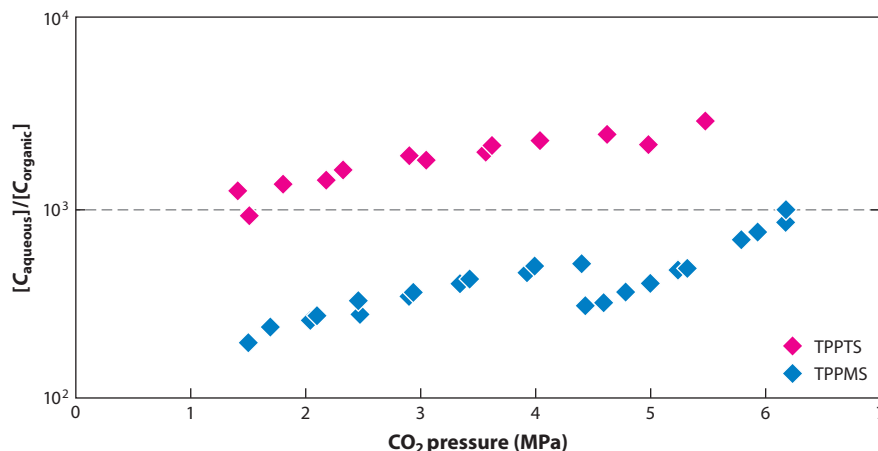
**Figure 5**

Partitioning of hydrophilic monosulfonated triphenylphosphine (TPPMS) and trisulfonated
triphenylphosphine (TPPTS) in the aqueous phase as a function of $CO_2$ pressure in tetrahydrofuran
(THF)/$H_2O$ (70:30 v:v) at 25°C (29). Abbreviation: C, concentration.

attributed to β-hydride elimination (23), in which the intermediate complex of the catalyst with
the branched product is converted back into the starting material at higher temperatures. The
styrene conversion rates in OATS show at least an order of magnitude improvement over both
a heterogeneous system using solid supports (21) and an IL-modified silica sol-gel (33). Also,
the branched product selectivity improves by more than 30% in OATS compared with hetero-
geneously catalyzed reactions. At 2.5 MPa of $CO_2$, more than 99% of the branched aldehyde
product partitions into the ACN-rich phase.

OATS can overcome the challenges of enzymatic reactions of hydrophobic substrates in aque-
ous media (34). For example, Hill et al. (35) reported the kinetic resolution of *rac*-1-phenylethyl
acetate to (*R*)-1-phenylethanol using *Candida antarctica* lipase B (CAL B) (**Scheme 2**) in OATS
systems. The substrate saturation and pseudo-first-order rate constants are shown in **Table 1**.
Carbonic acid formation during separations necessitates the use of a buffer to maintain the solu-
tion at near-neutral pH to protect the enzymes. The highest substrate saturation and rate constant
were in a sodium phosphate monobasic monohydrate (hereafter referred to as phosphate)-buffered
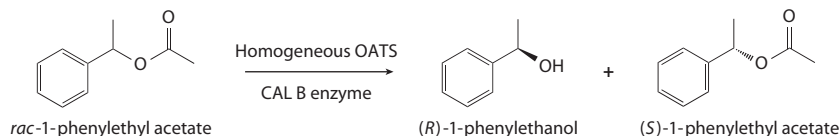


**Scheme 2**

Kinetic resolution of *rac*-1-phenylethyl acetate to (*R*)-1-phenylethanol using CAL B.
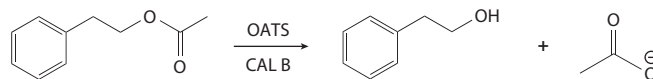


**Scheme 3**

Hydrolysis of 2-phenylethyl acetate to 2-phenylethanol.

**Table 1  Reaction parameters for *Candida antarctica* lipase B (CAL B) kinetic resolution of *rac*-1-phenylethyl acetate to (*R*)-1-phenylethanol at room temperature in 30 vol% organic organic-aqueous tunable solvent (OATS) (35)**

| Organic solvent (30 vol%) | Substrate saturation (mM) | Pseudo-first-order rate constant ($s^{-1}$) | Product enantiomeric excess (ee) |
|---|---|---|---|
| Acetone | $18.1 \pm 0.9$ | $0.003 \pm 0.001$ | >99% |
| Acetonitrile | $9.1 \pm 0.5$ | $0.009 \pm 0.001$ | >99% |
| (1,4)-Dioxane | $17.7 \pm 0.8$ | $0.014 \pm 0.001$ | >99% |

1,4-dioxane-$H_2O$ OATS system. Broering et al. (34) reported the CAL B–catalyzed hydrolysis of 2-phenylethyl acetate (2PEA) to 2-phenylethanol (2PE) in a phosphate-buffered 1,4-dioxane-$H_2O$ system (**Scheme 3**). The reaction rates with 8 mM and near-saturation 2PEA concentrations are shown in **Figure 6**. In contrast, the corresponding reaction rate in water is negligible owing to the limited solubility of 2PEA. As the fraction of dioxane increases, the reaction rate decreases, for example from 0.2 mM $min^{-1}$ at 10 vol% dioxane to 0.05 mM $min^{-1}$ at 30 vol% dioxane, possibly owing to enzyme deactivation. However, the solubility of 2PEA improves dramatically in the presence of dioxane, which compensates for the deactivation of the enzyme and causes the near-saturated 2PEA reaction rate to improve from 0.15 mM $min^{-1}$ at 10% dioxane to 0.22 mM $min^{-1}$ at 40% dioxane. We demonstrated recycling of the enzyme in six consecutive reaction cycles with an average conversion of 61% over two hours and with product removal of 80% after each cycle; the enzyme maintained a catalytic activity of approximately 85% after five recycles. The use of nonacid-forming tunable mixtures, such as propane/OATS, could eliminate the need for buffer solutions and minimize enzyme deactivation.

In some cases, the reactants interfere with the phase splitting and impose limitations on the use of OATS. Tunable solvents consisting of PEG 400 and organics are alternative systems that could circumvent this problem. PEG is miscible with most organics and can complex with cations and activate anions in reactions containing salts; it is a medium for the reaction process as well as a participant in the reaction (36). Blasucci et al. (17) reported the C-O coupling reaction of 1-bromo-3,5-dimethylbenzene and *o*-cresol with potassium hydroxide to produce *o*-tolyl-3,5-xylyl ether (**Scheme 4**) as well as the reaction of 1-bromo-3,5-di-*tert*-butylbenzene and potassium hydroxide to yield 3,5-di-*tert*-butylphenol (**Scheme 5**) in PEG (60 wt%)-dioxane
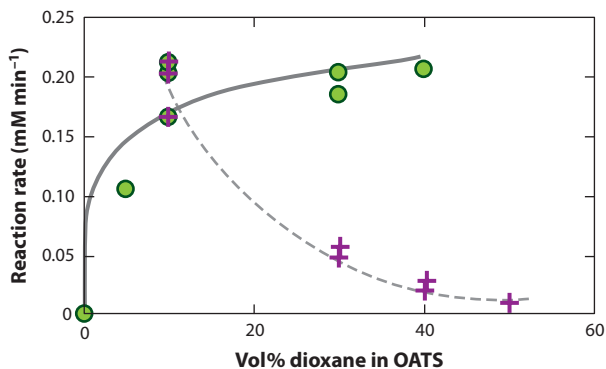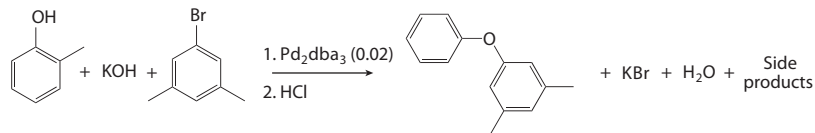


**Figure 6**

Monophasic ester hydrolysis reaction rates for 8 mM (*purple crosses*) and near-saturated (*green circles*) 2-phenylethyl acetate (2PEA) solutions as a function of 1,4-dioxane fraction in dioxane/$H_2O$ at room temperature (34). Abbreviation: OATS: organic-aqueous tunable solvents.

**Scheme 4**

Reaction of 1-bromo-3,5-dimethylbenzene and *o*-cresol with potassium hydroxide to produce
*o*-tolyl-3,5-xylyl ether. Abbreviation: dba, dibenzylideneacetone.
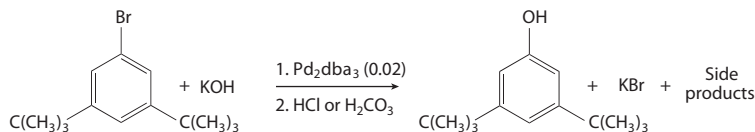


**Scheme 5**

Reaction of 1-bromo-3,5-di-*tert*-butylbenzene with potassium hydroxide to produce 3,5-di-*tert*-butylphenol.
Abbreviation: dba, dibenzylideneacetone.

(24 wt%)-$H_2O$ (16 wt%) tunable solvent. At 80°C, the conversion of 1-bromo-3,5-
dimethylbenzene is 80 ± 10% efficient, and the yield of *o*-cresol is 71 ± 2%. The conversion
of 1-bromo-3,5-di-*tert*-butylbenzene is 80 ± 7% efficient, and the selectivity for 3,5-di-*tert*-
butylphenol is 68 ± 2%. The presence of water improved the conversion and product selectivity
(**Schemes 4** and **5**) compared with neat PEG and a PEG-dioxane mixture. As with OATS, $CO_2$
was the immiscibility trigger, and the *o*-tolyl-3,5-xylyl ether partitioning is shown in **Figure 7**.

In PEG/dioxane with 1% water, the product recovery is only 50%, and the ether product
partitions equally between the PEG-rich phase and water-rich phase. Both phases dissolve large
amounts of $CO_2$, and their properties are similar. However, the addition of 14 wt% water increases
the separation efficiency from 50% to approximately 75% at 4.7 MPa of $CO_2$. Water increases
the polarity of the PEG-rich phase and hydrogen bonds to PEG, which could disrupt the inter-
action between PEG and the solute molecule and yield a more efficient product removal. Similar
trends occurred for 3,5-di-*tert*-butylphenol and the Pd catalyst. Normally for these reactions a
postreaction neutralization is required because the p$K_a$ of the phenols is lower than that of the
reaction medium. For example, the p$K_a$ of phenol is 10. The conventional neutralization scheme
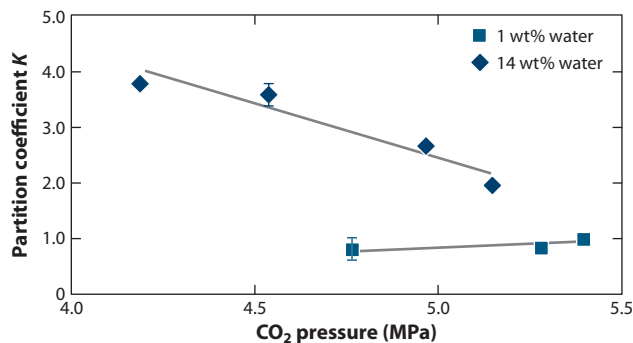


**Figure 7**

Partitioning of *o*-tolyl-3,5-xylyl ether in the polyethylene glycol (PEG)-rich phase as a function of $CO_2$
pressure and water content at room temperature (17).

Annu. Rev. Chem. Biomol. Eng. 2011.2:189-210. Downloaded from www.annualreviews.org
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using mineral acids creates waste and often deactivates the catalyst. The PEG/organic/$H_2O$ tunable system approach utilizes the in situ carbonic acid formed by the reaction of $CO_2$ with water to replace the mineral acid. Thus, this solvent system alleviates additional waste production and provides an efficient route to recycling the system by maintaining the integrity of the catalyst from cycle to cycle.

## Near-Critical Fluids

NCW is hot liquid water (critical point: 374°C, 22.1 MPa) at temperatures of 200–350°C. The specific gravity is 0.7–0.8, and the dielectric constant decreases to 20 at 275°C (37) owing to diminished hydrogen bonding (38, 39). Thus, NCW has physical properties similar to those of ambient acetone (40). This results in a marked improvement in the solubility of nonpolar organics even as NCW remains an effective medium for dissolving ionic compounds. We conduct reactions between hydrophobic organic molecules and hydrophilic ionic reactants under homogeneous conditions in the near-critical temperature range and then cool to isolate the organic. Additionally, the dissociation constant of water, $K_W$, increases gradually from $10^{-14}$ at 25°C to approximately $10^{-11}$ at 275°C (41). This increase in $K_W$ offers opportunities for both acid and base catalysis, avoiding the need for added acids and bases and the subsequent waste-intensive neutralization steps.

The solubilities of many hydrophobic organics in NCW have been reported (42–54). For example, the solubility of benzene increases from 500 ppm at ambient conditions to complete miscibility at 305°C (50). The phase behavior of the toluene-water system is shown in **Figure 8** (42–45, 48, 55). This dramatic increase in solubility permits homogeneous reactions in NCW followed by facile separation merely by cooling. Comprehensive reviews of the use of NCW for reactions are available (40, 56–64). Here, we discuss examples that take advantage of the tunable properties of NCW to couple reaction and separation.
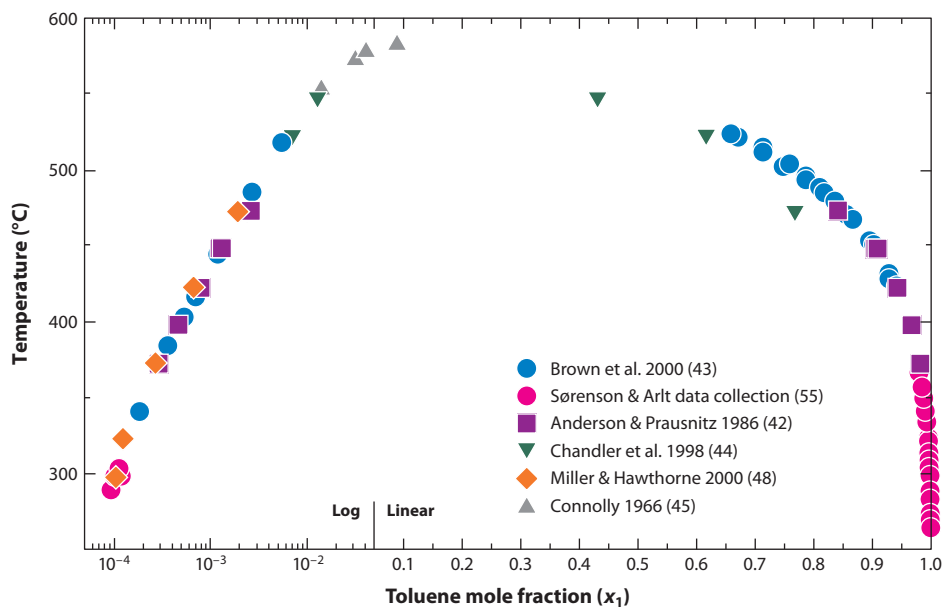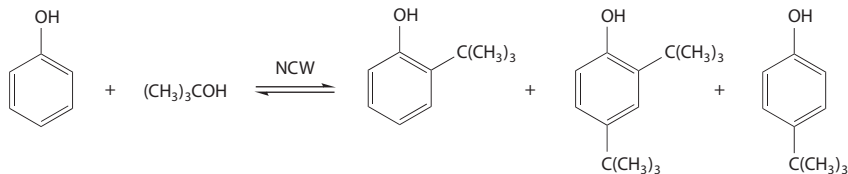


**Figure 8**

Liquid-liquid phase behavior of toluene and water at saturation pressure (42–45, 48, 55).
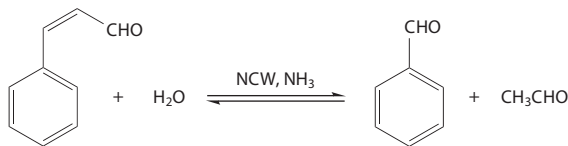
**Scheme 6**

Alkylation of phenol with *tert*-butanol to produce 2-*tert*-butylphenol, 2,4-di-*tert*-butylphenol, and 4-*tert*-butylphenol.

Traditionally, Friedel-Crafts reactions use aluminum chloride ($AlCl_3$), which is corrosive, water-sensitive, difficult to handle, and used in greater than stoichiometric quantities, leading to substantial waste generation. Chandler et al. (65) reported the Lewis acid–free Friedel-Crafts alkylation of phenol with *tert*-butyl alcohol in water at 275°C (**Scheme 6**). The yield of 2-*tert*-butylphenol reached 17 mol% after 30 h and then decreased to an equilibrium concentration of 10%; the yield of 4-*tert*-butylphenol increased linearly to 20% after 50 h of reaction time. The 2-*tert*-butylphenol and 4-*tert*-butylphenol yields in NCW were similar to acid-catalyzed reactions reported in the literature that use a fivefold excess of $HClO_4$ (66).

The reaction of *p*-cresol with *tert*-butyl alcohol to produce 2-*tert*-butyl-4-methylphenol proceeds faster than that of phenol with *tert*-butyl alcohol in NCW; at equilibrium at 275°C, the 2-*tert*-butyl-4-methylohenol concentration is 20%. Rate constants for the alkylation of both phenol and *p*-cresol with *tert*-butanol increase by approximately an order of magnitude as the temperature increases from 250°C to 300°C (67).

Brown et al. (68) reported the Lewis acid–free acylation of phenol and resorcinol with acetic acid in NCW as well as in near-critical acetic acid in the temperature range of 250–300°C. In NCW at 250°C, the conversion was negligible owing to the back reaction of the 2,4-dihydroxyacetophenone; the equilibrium lies far to the left because of the high concentration of water. The authors demonstrated the reversal of 2,4-dihydroxyacetophenone to resorcinol and acetic acid in NCW at 250°C. Acylations are irreversible in traditional Friedel-Crafts reactions owing to complexation of the Lewis acid catalyst with the carbonyl oxygen of the product. To overcome the back reaction, the acylations of phenol and resorcinol were carried out in pure acetic acid at 290°C. Resorcinol was converted to 2,4-dihydroxyacetophenone with an equilibrium yield of more than 50 mol%, and phenol was converted to 2-hydroxyacetophenone, 4-hydroxyacetophenone, and phenyl acetate with a combined equilibrium yield of 8 mol%, with 2-methylchromone and 4-methylcoumarine as by-products. The absence of water in the initial near-critical acetic acid system enhances the equilibrium concentration of the desired product. Thus, NCW for Friedel-Crafts acylations could eliminate the use of mineral or Lewis acids and eliminate the subsequent neutralization steps that generate large quantities of waste salt for each pound of products (69).

NCW can also be used for base-catalyzed aldol condensation reactions. Lu et al. (70) reported the use of NCW and $NH_3$-enriched NCW for the hydrolysis of cinnamaldehyde (the forward reaction) and condensation of benzaldehyde with acetaldehyde (the reverse reaction) (**Scheme 7**). By adding 52.8 mg liter$^{-1}$ of $NH_3$ in NCW, the rate constant for cinnamaldehyde hydrolysis increased from 0.0019 ± 0.0004 min$^{-1}$ to 0.0104 ± 0.0008 min$^{-1}$, and the yield of benzaldehyde increased from 30% to 50%. In addition, the condensation reaction of benzaldehyde with acetaldehyde was carried out with a fivefold excess of acetaldehyde to provide favorable equilibrium for the production of cinnamaldehyde. The kinetic analysis of this reaction has similar results as the hydrolysis of cinnamaldehyde, where the reaction rate increases from

**Scheme 7**

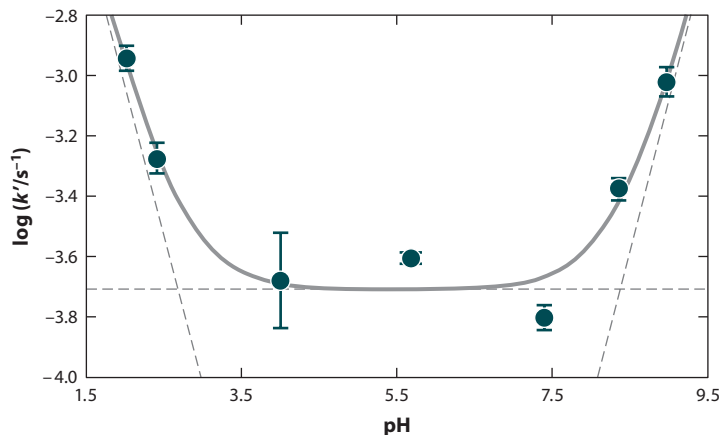Cinnamaldehyde hydrolysis and benzaldehyde condensation.



**Figure 9**

Pseudo-first-order rate constant ($k'$) for bisphenol A cleavage to form *p*-isopropenylphenol as a function of system pH at 250°C (72). Reprinted with permission from the American Chemical Society.

0.0042 $\pm$ 0.0004 liter mol$^{-1}$ min$^{-1}$ to 0.0213 $\pm$ 0.0043 liter mol$^{-1}$ min$^{-1}$ as the amount of NH$_3$ increases.[1]

Hunter & Savage (71, 72) reported the cleavage of bisphenol A to form *p*-isopropenylphenol and phenol at different pH values; the pH was adjusted by adding H$_2$SO$_4$, HCl, or NaOH. The pseudo-first-order rate constant ($k'$) was determined at different solution pH values. Log ($k'$) reached a maximum of −2.94 at pH = 2.0 and a similar value of −3.02 at pH = 9.0. In the pH range of 3.5–7.5, the rate constant was roughly constant, approximately −3.7 (**Figure 9**). In NCW, the cleavage of bisphenol A exhibits specific acid catalysis at low pH and specific base catalysis at high pH. The second-order rate constant for specific acid catalysis ($k_A$) is 0.094 $\pm$ 0.053 liter mol$^{-1}$ s$^{-1}$, the second-order rate constant for specific base catalysis ($k_B$) is 0.19 $\pm$ 0.12 liter mol$^{-1}$ s$^{-1}$, and the pseudo-first-order rate constant resulting from general acid or general base catalysis due to water at these conditions ($k_W$) is 2.0 $\times$ 10$^{-4}$ $\pm$ 6.8 $\times$ 10$^{-5}$ s$^{-1}$. The value of $k_W$ shows that neat NCW performs both general acid and general base catalysis.

## SWITCHABLE OR SMART SOLVENT SYSTEMS

Switchable or smart solvents undergo a step change in physical properties upon application of a stimulus. The two discussed here are chemically reversible systems based on (*a*) retro-cheletropic reactions and (*b*) amine-CO$_2$ reactions.

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[1]In the kinetic analysis, it was assumed that the gas phase ammonia concentration could be calculated with the ideal gas law; at higher pressures this introduces some error.

**Table 2   Comparison of physical properties and solvent parameters for dimethyl sulfoxide (DMSO) and piperylene sulfone at 25°C**

| Physical properties | DMSO | Piperylene sulfone |
|---|---|---|
| Boiling point (°C) | 189 | 85 (7 torr) |
| Melting point (°C) | 16–19 | −12 |
| Dipole moment, $\mu$ (D) | 4.27 | 5.32 |
| $\alpha$ | 0 | 0 |
| $\beta$ | 0.76 | 0.46 |
| $\pi^*$ | 1.00 | 0.87 |
| $E_T(30)$ (kJ mol$^{-1}$)[a] | 189.0 | 189.0 |
| Dielectric constant ($\varepsilon$) | 46.7 | 42.6 |

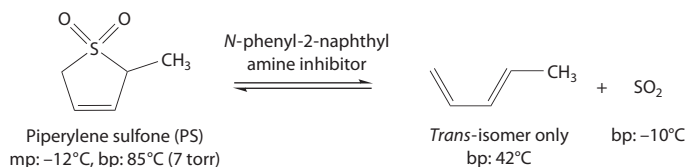[a]$E_T(30)$ is the energy required for Reichardt's dye to change from the ground state to the excited state and is a function of the polarity of the solvent.

## Sulfones

It is challenging to react, for example, a relatively polar reactant, such as a hydrophilic anionic nucleophile, with a relatively nonpolar reactant, such as a hydrophobic organic electrophile. In such cases dipolar, aprotic solvents such as DMSO or dimethylformamide are commonly employed, as they can partially or completely dissolve the reactants to facilitate the reaction. However, the isolation of the product is very difficult because dipolar, aprotic solvents are high boiling and thus difficult to remove and separate from the product. The common procedures for isolating products from these expensive solvents preclude facile recycling. The cyclic $\beta$,$\gamma$-unsaturated sulfones (also known as sulfolenes) discussed here have been proposed as alternative solvents for facilitating chemical processes and permitting solvent recycling.

Sulfolenes have solvent properties similar to those of dipolar, aprotic solvents such as DMSO. **Table 2** lists for comparison the solvatochromic properties and the dielectric constants of a typical sulfolene, piperylene sulfone (PS), and DMSO. Sulfolenes are formed by a reversible addition of two gas molecules, a diene and sulfur dioxide. Because they revert back to the original gases at moderate temperatures, sulfolenes provide an efficient and simple method of solvent separation and recycling as well as product isolation and purification. Sulfolenes have a variety of properties depending on their structure. For example, PS (melting point −12°C), butadiene sulfone (BS; melting point 65°C), and 2,3-dimethylbutadiene sulfone (melting point 135°C) decompose at successively higher temperatures, so at least the first two sulfolenes can be used for different applications depending on the required reaction/process temperatures.

PS is formed by reaction of SO$_2$ with *trans*-1,3-pentadiene (*trans*-piperylene) in the presence of a radical inhibitor (such as *N*-phenyl-2-naphtylamine), as shown in **Scheme 8**. The inhibitor prevents the polymerization of the piperylene.



Piperylene sulfone (PS)
mp: −12°C, bp: 85°C (7 torr)

*N*-phenyl-2-naphthyl amine inhibitor

*Trans*-isomer only
bp: 42°C

+ SO$_2$

bp: −10°C

**Scheme 8**

Switchable solvent PS formed by the reaction of *trans*-piperylene and sulfur dioxide.
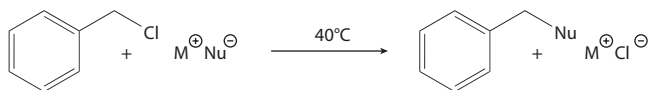
**Scheme 9**

Nucleophilic displacement reactions.

**Table 3  Second-order rate constant $k \times 10$ (ml mol$^{-1}$ s$^{-1}$) for nucleophilic displacement reactions in piperylene sulfone and dimethyl sulfoxide (DMSO)**

| Nucleophile | DMSO | DMSO (3% H$_2$O) | Piperylene sulfone | Piperylene sulfone (1% H$_2$O) |
|---|---|---|---|---|
| KTA | >1,800 | >1,800 | >1,800 | >1,800 |
| NaPDTC | >1,800 | >1,800 | >1,800 | >1,800 |
| 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 ± 5.0 | No reaction | 0.15 ± 0.01 |

Abbreviations: KTA: potassium thioacetate; NaPDTC: sodium pyrrolidinedithiocarbamate; KOAc: potassium acetate.

Vinci et al. (73) reported the rates of the substitution reaction of benzyl chloride with various anionic nucleophiles (**Scheme 9**) in both PS and DMSO at 40°C (**Table 3**). In general, the rate constants are slightly greater in PS than in DMSO. The product yields were quantitative in both solvents.[2] After the reaction was complete, product isolation involved simply the heating of the reaction medium to 110°C to decompose the PS to gaseous *trans*-piperylene and SO$_2$. The solvent-free benzyl thiocyanate residue was isolated with 96% yield. The gases were collected, and PS was reformed with 87% yield.[3] The reformation and reuse of the PS are achieved by condensing the gases in liquid sulfur dioxide at −30°C.

In addition to substitution reactions, oxidations also take place readily in PS. Jiang et al. (74) reported the room-temperature aerobic oxidation of alcohols in PS with copper(I) bromide (1 mol%), 4-dimethylaminopyridine (2 mol%), and acetamido-TEMPO (2,2,6,6-tetramethyl-1-piperidine-1-oxyl, 2 mol%). The oxidation of 4-methoxybenzylalcohol to 4-methoxy benzaldehyde proceeded to completion with a TOF of 33 h$^{-1}$ and without overoxidation. Aerobic oxidation of benzyl alcohol to benzaldehyde (**Scheme 10**) also had a 98% yield after 3 h. Product removal from PS and catalyst reuse were achieved by using *n*-pentane to extract the product; the catalytic components and PS are insoluble in *n*-pentane. For the next cycle fresh benzyl alcohol was added, and multiple recycles of the catalyst were demonstrated.

Donaldson et al. (75) used PS and BS as solvents for the reaction of β-pinene with water to form α-terpineol, where the sulfolenes acted as a switchable in situ Bronsted acid catalyst. The unreacted SO$_2$ forms the in situ acid catalyst sulfurous acid in the presence of water. This sulfurous acid is eliminated from the reaction mixture by elevating the temperature to 100°C, at which it dissociates into sulfur dioxide and water. Generally, acid-catalyzed reactions use mineral acids that require neutralization and generate salt wastes. At 45°C in PS/H$_2$O (10 vol% H$_2$O), the conversion of β-pinene to α-terpineol increased linearly over 3.5 h to 90% with a

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[2]The addition of small amounts of water to the reaction mixture improves the rate in both PS and DMSO for the reaction of benzyl chloride with KOAc, KCN, and KSCN. This improvement could result from the improved solubility of the reacting salts.

[3]The small scale of the laboratory experiment results in some losses in the solvent recycling process; greater solvent recovery yields are expected on a larger scale.
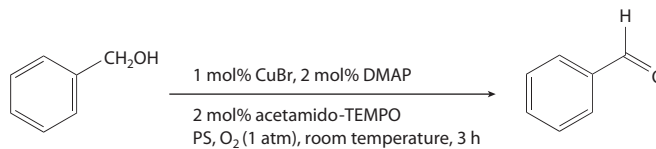
**Scheme 10**

Oxidation of benzylalcohol to benzaldehyde. Abbreviation: DMAP, 4-dimethylaminopyridine.

pseudo-first-order rate constant of $2.1 \pm 0.2 \times 10^{-4}$ s$^{-1}$. The selectivity of $\alpha$-terpineol reached 60% after 30 min and remained constant. In BS/H$_2$O (20 vol% H$_2$O), the conversion of $\beta$-pinene was more than 95% after 6 h at 55°C with a pseudo-first-order rate constant of $5.7 \pm 1.5 \times 10^{-5}$ s$^{-1}$ and 50% selectivity to $\alpha$-terpineol. The solvent and acid catalyst were recycled for five consecutive reactions with consistent catalytic activity. After each reaction, the products were extracted with $n$-hexane, which left the acid catalyst intact. It is postulated that the slower reaction in BS than in PS is due to the smaller concentration of free SO$_2$, owing to the greater stability of BS at the reaction temperature.

The application of PS is limited to reactions at temperatures below its decomposition temperature. An alternative for higher reaction temperatures is BS, which melts at 64°C and undergoes rapid decomposition at approximately 160°C.

## Reversible Ionic Liquids

RevILs are formed by the reversible reaction of compounds with basic nitrogen functionalities (molecular liquids) with CO$_2$ at ambient pressure to form a liquid salt (IL). The process results in a step change in properties such as polarity or viscosity. RevILs exhibit negligible vapor pressures: Their physical properties are tuned by modifying the structure of the molecular liquid precursor. Historically, conventional ILs have been used for many reactions, but in many cases product isolation and purification have presented challenges. RevILs offer a solution to circumvent these challenges.

Jessop et al. (76) reported the first RevIL: an equimolar mixture of liquid 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and an alcohol reacts with CO$_2$ at ambient pressure to form ionic species (**Scheme 11**). Bubbling N$_2$ or argon and/or applying heat readily reverses the RevIL back to the neutral (molecular) liquid. Other examples of such systems include substituted guanidines and alcohols (77). RevILs that require the use of alcohols are known as two-component systems. Simpler systems in which neutral basic amine liquids react with CO$_2$ to form ammonium carbamate products without the need for alcohols (**Scheme 12**) are known as one-component RevILs (78, 79).
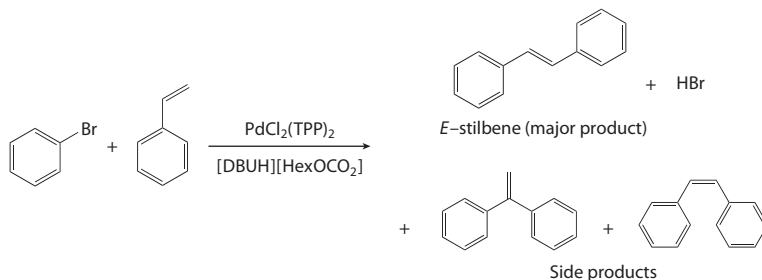


Molecular liquid          Ionic liquid

where R = C$_1$ – C$_{12}$
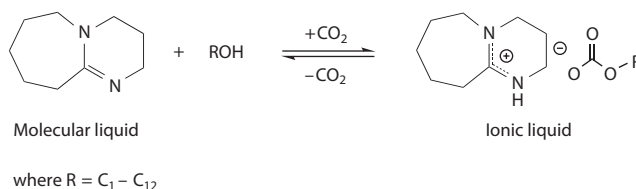
**Scheme 11**

A two-component RevIL [DBUH]$^+$[RCO$_3$]$^-$ formed by the reaction of molecular liquids 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and alcohol (ROH) with CO$_2$.
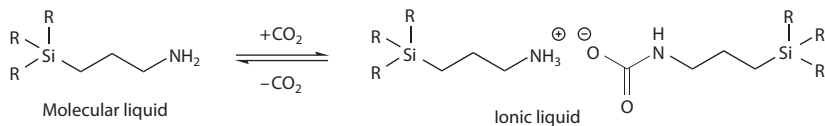
where R = OMe (OCH$_3$), OEt (OC$_2$H$_5$), Et (C$_2$H$_5$), Pr (C$_3$H$_7$), Hex (C$_6$H$_{13}$)

**Scheme 12**

One-component RevILs formed by the reaction of silylpropylamines with CO$_2$.
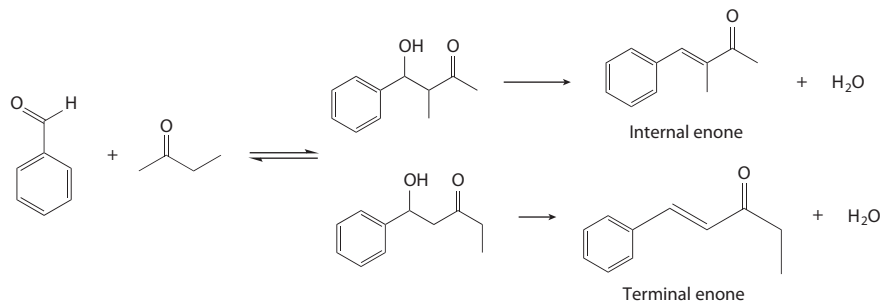


**Scheme 13**

Heck reaction of bromobenzene and styrene in the RevIL [DBUH]$^+$[HexOCO$_2$]$^-$.

Hart et al. (80) reported the palladium-catalyzed Heck reaction of bromobenzene with styrene in the DBU/hexanol/CO$_2$ RevIL to produce *E*-stilbene (>95% desired product) and isomers (1,1-diphenylethylene and *Z*-stilbene) (**Scheme 13**). Under optimum conditions (3 MPa CO$_2$, 115°C for 3 days) with a PdCl$_2$(TPP)$_2$ catalyst (TPP = triphenylphosphine, PPh$_3$) the reaction gave a 97% yield of *E*-stilbene with 2 mol% catalyst loading. After product removal by hexane extraction, the RevIL was heated and/or purged with argon to reverse back to the DBU/hexanol neutral liquids, which resulted in precipitation of the by-product DBU-HBr salt formed during the reaction process. In addition to acting as a solvent, DBU acted as a scavenger for HBr for an easy separation of the salt by-product. The solvent system and the Pd catalyst were recycled for further Heck reactions with consistent catalytic activity. Thus, the RevIL improved reaction efficiency, permitted facile separation of desired products and the salt by-product, and allowed successful catalyst recycling.

Hart et al. (80) also reported the Claisen-Schmidt condensation of butanone and benzaldehyde in 2-butyl-1,1,3,3-tetramethylguanidine (TMBG) (**Scheme 14**) to produce



**Scheme 14**

Claisen-Schmidt condensation of 2-butanone and benzaldehyde.

**Figure 10**

$CO_2$ capacities (reported here as moles of $CO_2$ per kilogram of amine) of trimethoxy (TMSA), triethoxy (TESA), triethyl (TEtSA), and tripropyl (TPSA) silylated propylamines for capture through reaction (calculated, *blue*) and physical absorption (*green*, measured at 35°C and 62 bar), showing the combined effect (78).

3-methyl-4-phenyl-but-3-en-2-one (terminal enone) and 1-phenyl-pent-1-en-3-one (internal enone). In the presence of the base TMBG, the terminal enone is the predominant product; TMBG acts as solvent as well as base catalyst. The total enone yield is 48% after 24 h at room temperature and 44% after 3 h at 80°C. The yield of enone products increased from 13% at 1 h to 44% at 3 h and then began to decrease gradually to zero after 8 h, owing to a competing condensation reaction between the enone products and the benzaldehyde. Products were isolated by adding *n*-octane and methanol to the reaction mixture and then bubbling $CO_2$ to trigger the formation of the TMBG/$CH_3OH$/$CO_2$ RevIL. Octane is immiscible with the RevIL, and the enone products partition into the octane phase. Here water is a by-product, so the recycling of TMBG requires drying with magnesium sulfate. This prevents the reaction of the water with TMBG and $CO_2$, which would result in irreversible formation of $N,N,N',N'$-tetramethyl-$N'$-butylguanidium carbonate. TMBG was recycled for three consecutive reactions with enone yields of 34%, 32%, and 34% and consistent terminal enone selectivity of 95%.

RevILs also absorb $CO_2$ from flue gas streams, where they may require less energy for $CO_2$ capture and release than the conventional alkanolamine process. The product of the alkanolamine reaction with $CO_2$ is a solid, so water is used as a solvent for continuous processing. The presence of so much water (commonly 70 vol%) increases the energy demand for the thermal regeneration of the aqueous alkanolamines. RevILs behave in a dual capacity as solvents for $CO_2$ capture: (*a*) the chemisorption of $CO_2$ by the molecular liquid to form the RevIL and (*b*) the high capacity physisorption of the $CO_2$ into the RevIL. Blasucci et al. (78, 81) reported the use of trimethoxy (TMSA), triethoxy (TESA), triethyl (TEtSA), and tripropyl (TPSA) silylated propylamines for $CO_2$ capture. The chemical capacities of these liquids are relatively low, but capacity is much improved by the physical absorption, as shown in **Figure 10**. Moreover, the physisorption is a much less exothermic process, so subsequent release of the $CO_2$ requires less energy.

## Reversible Ionic Liquids for Extraction Processes

The abrupt change in the properties of smart solvent systems such as RevILs may also be used for extractions. Jessop et al. (82) reported the extraction of soybean oil from soybeans using *tert*-butyl amidine, as shown in **Figure 11**; this solvent switches from nonpolar to polar as well as from
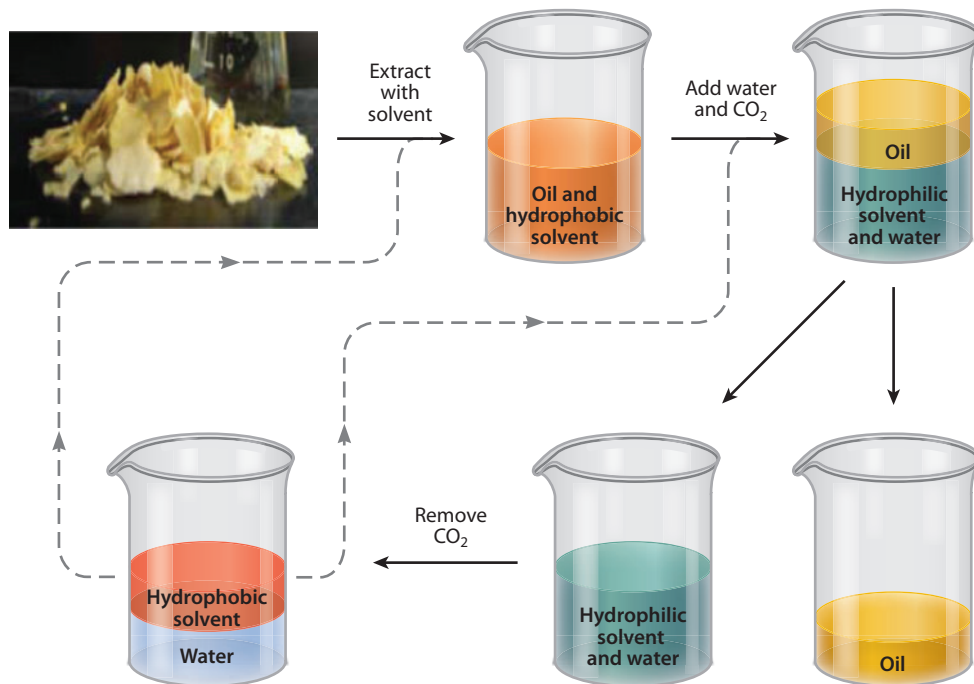
**Figure 11**

The use of switchable amidine solvent to extract oil from soybeans by chemical manipulation of the solvent properties (82). Reprinted with permission from the Royal Society of Chemistry.

hydrophobic to hydrophilic. In the hydrophobic and nonpolar form (prior to reaction with $CO_2$), *tert*-butyl amidine is used to extract oil from soybean flakes with an extraction efficiency similar to that of hexane (8.8 wt% oil). The amidine is then recovered from the oil into water by reaction with carbonated water to form a water-soluble bicarbonate salt; in this process the amidine becomes hydrophilic and is recovered from the soybean oil with 96% efficiency. Finally, the amidine is separated from the aqueous solution by bubbling air through it to strip the $CO_2$ and revert the ionic species into its initial nonpolar hydrophobic form. This solvent provides an alternative to hexane in oil extraction processes, eliminating the need for distillation of the hexane from the oil and reducing energy requirements and volatile organic emissions. However, amidine losses into the oil may need to be reduced for economic gains and practical application of this system.

Similarly, Desset et al. (83) reported the use of an amidine-containing TPP ligand and rhodium as a switchable catalyst for the hydroformylation of 1-octene. The reversible reaction of the catalyst with $CO_2$ was used to transfer the catalyst from an aqueous phase to a toluene phase. In the neutral form, the amidine-based catalyst is soluble in toluene and is used for homogeneous hydroformylation of 1-octene with a TOF of approximately 10,000 h$^{-1}$. Once the reaction is complete, water is added, followed by treatment with $CO_2$; the catalyst partitions into the immiscible aqueous phase. Rh recovery in the aqueous phase was satisfactory with leaching of approximately 1 ppm into the organic phase (0.5% of catalyst loading), comparable with the example discussed earlier using the OATS system. The reversal reaction is achieved by heating to 60°C and bubbling $N_2$ for 1.5 hours; the catalyst transfers to the toluene phase and is used for subsequent reactions. Three recycles of the catalyst were demonstrated with minor loss of activity.

**Table 4  Summary of suitable applications, advantages, and challenges of the various solvents discussed in this review**

| Solvent | Good applications | Advantages | Challenges |
|---|---|---|---|
| GXL | In situ acid catalysis<br>Nanoparticle size fractionation<br>Antisolvent crystallization<br>Extractions<br>Microscale surface treatment | Improved transport over liquids<br>Stronger solvent than SCF—tunable properties<br>Moderate T&P (compared with scCO$_2$, NCW) | Special equipment<br>Cost of compression<br>CO$_2$ reactivity |
| OATS | Hydrophobic substrates—with high boiling temperatures—and water-soluble catalysts<br>Postreaction acidic neutralization<br>Intermediate steps in synthesis | Moderate T&P<br>Nonthermal separations (ideal for enzymes)<br>Diverse and flexible (mixtures and gases)—versatile | Special equipment<br>Cost of compression<br>Acidity effect on catalyst<br>Acidity effect on equipment<br>CO$_2$ reactivity<br>Further processing required<br>Phase behavior may limit applications |
| scCO$_2$ | Extraction (selective)<br>Polymer reactions<br>Polymer treatment<br>Waste treatment | Benign, cheap, and safe<br>Simple separation<br>Well-known properties | Highest P, special equipment<br>Cost of compression<br>Acidity and reactivity<br>Weakest solvent |
| NCW | Hydrolysis<br>Acid/base catalysis of hydrophobic substrates<br>Hydrophobic substrates with water-soluble catalysts (thermal stability required) | Simplest separation (cooling)<br>Significant solubility improvement of hydrophobics<br>Elimination of postreaction neutralization | Highest T (high energy demand)<br>Reaction with reactor walls<br>Lack of product stabilization with acid/base<br>Hydrolysis of substrates |
| RevILs | Base catalysis<br>Hydrophobic substrates and ionic catalysts<br>Selective gas separation<br>Microemulsions | Simple separation<br>Drastic change in polarity<br>Designer solvent—versatile | Expensive—leaching<br>Side reactions<br>Synthesis |
| Sulfones | Separation and recovery of thermally labile compounds<br>Separation and recovery of involatile compounds<br>Acid/base catalysis | Built-in separation<br>Strong solvent | Requires handling SO$_2$—safety concerns<br>Low T for regeneration<br>Corrosion and acidity |

Abbreviations: GXL, gas-expanded liquid; SCF, supercritical fluid; T&P, temperature and pressure; scCO$_2$, supercritical CO$_2$; NCW, near-critical water; OATS, organic-aqueous tunable solvents; RevILs, reversible ionic liquids.

## CONCLUSIONS

Tunable solvents and smart switchable solvents can improve specific families of chemical reactions and processes. These solvents change properties upon application of physical or chemical stimuli and, as a consequence, provide facile separation techniques. Each of these different solvents has advantages and limitations, summarized in **Table 4**, and the applications depend on the specifics of each reaction or process. For example, enzymatic reactions benefit from OATS, in which reactions of hydrophobic substrates are carried out homogeneously and postreaction separations are efficient and do not cause significant enzyme deactivation. Obviously, NCW is not a suitable medium for such systems because enzymes are highly temperature sensitive. NCW is a suitable system for acid alkylation reactions, however; the $K_W$ of water at elevated temperatures catalyzes the alkylation of hydrophobic substrates—which have sufficient solubility in water at these temperatures—and

eliminates the need for added acids. Therefore, NCW has the potential to be an environmentally benign alternative to conventional alkylation solvents.

Smart, switchable solvents change properties abruptly and are reversible. For example, cyclic unsaturated β,γ-sulfones have similar solvent strength as dipolar and aprotic organics such as DMSO and offer a built-in solvent separation because they decompose into gases. They can also be used for in situ acid catalysis. The easy removal of sulfolenes is the main advantage in using them in reaction processes and selective extractions. Another type of switchable solvent discussed in this review is RevILs, which change polarity and are used for separating products from catalysts as well as selectively capturing $CO_2$ from flue gas streams. RevILs are easy to form at atmospheric temperature and pressure, and their unique properties continue to find new applications.

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# Contents

Errata

An online log of corrections to *Annual Review of Chemical and Biomolecular Engineering*
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