ACCOUNTS
of chemical research

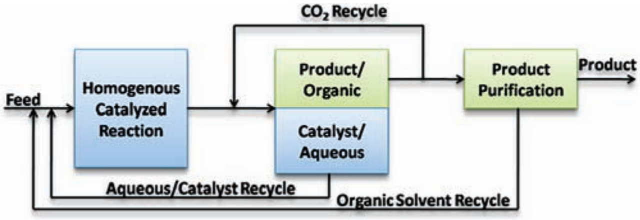
# Organic Aqueous Tunable Solvents (OATS): A Vehicle for Coupling Reactions and Separations

PAMELA POLLET,[†,§] RYAN J. HART,[‡] CHARLES A. ECKERT,[†,‡,§]
AND CHARLES. L. LIOTTA[*,†,‡,§]

[†]*Department of Chemistry & Biochemistry, Georgia Institute of Technology, Atlanta, Georgia 30332,* [‡]*Department of Chemical & Biomolecular Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332,* [§]*Specialty Separations Center, Georgia Institute of Technology, Atlanta, Georgia 30332*

RECEIVED ON MARCH 2, 2010

## CONSPECTUS



In laboratory-based chemical synthesis, the choice of the solvent and the means of product purification are rarely determined by cost or environmental impact considerations. When a reaction is scaled up for industrial applications, however, these choices are critical: the separation of product from the solvent, starting materials, and byproduct usually constitutes 60−80% of the overall cost of a process. In response, researchers have developed solvents and solvent-handling methods to optimize both the reaction and the subsequent separation steps on the manufacturing scale. These include "switchable" solvents, which are designed so that their physical properties can be changed abruptly, as well as "tunable" solvents, wherein the solvent's properties change continuously through the application of an external stimulus. In this Account, we describe the organic aqueous tunable solvent (OATS) system, examining two instructive and successful areas of application of OATS as well as its clear potential for further refinement.

OATS systems address the limitations of biphasic processes by optimizing reactions and separations simultaneously. The reaction is performed *homogeneously* in a miscible aqueous−organic solvent mixture, such as water−tetrahydrofuran (THF). The efficient product separation is conducted *heterogeneously* by the simple addition of modest pressures of $CO_2$ (50−60 bar) to the system. Under these conditions, the water−THF phase splits into two relatively immiscible phases: the organic THF phase contains the hydrophobic product, and the aqueous phase contains the hydrophilic catalyst. We take advantage of the unique properties of OATS to develop environmentally benign and cost-competitive processes relevant in industrial applications. Specifically, we describe the use of OATS for optimizing the reaction, separation, design, and recycling of (i) Rh-catalyzed hydroformylation of olefins such as 1-octene and (ii) enzyme-catalyzed hydrolysis of 2-phenylacetate.

We discuss the advantages of these OATS systems over more traditional processes. We also consider future directions that can be taken with these proven systems as well as related innovations that have recently been reported, including the use of poly(ethylene glycol) (PEG) as a tunable adjunct in the solvent and the substitution of propane for $CO_2$ as the external stimulus. OATS systems in fact represent the ultimate goal for a sustainable process, because in an idealized setup there is only reactant coming in and product going out; in principle, there is no waste stream.

## 1. Introduction and Background

Chemical processes inevitably involve a reaction followed by a separation and/or purification of the desired product. From an economic standpoint, most of the capital and operating costs are in the separation step; they are generally 60−80% of the overall cost. From an environmental standpoint, each of these steps (reaction, separation, and purification) contributes to the environmental footprint of the process. Innovations have integrated and continue to integrate economic and environmental considerations (sustainability) into

10.1021/ar100036j

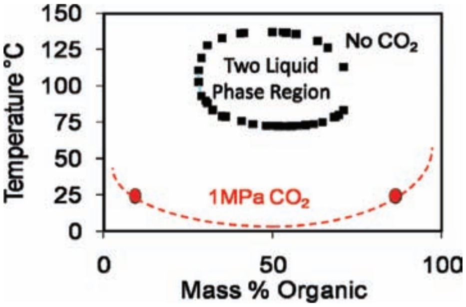


**FIGURE 1.** Liquid−liquid phase boundary for THF/water. The effect of 1.0 MPa of $CO_2$.

chemical processes. However, organic solvents remain the basis of most chemical operations, driving many of our solution chemistry and separation issues. The development of solvents that facilitate reaction and subsequent product separation synergistically is therefore paramount to achieving both economically competitive and environmentally conscious alternatives.

Tunable and "switchable" solvents were specifically invented to address and optimize both reaction and separation. For instance, switchable solvents are solvents that facilitate reaction and subsequent product recovery via their "built-in" ability to change their physical properties abruptly.[1] In contrast, tunable solvents are defined as solvents that change properties continuously upon application of an external stimulus. Supercritrical fluids (SCF),[2] near-critical liquids,[2d,3] and gas-expanded liquids (GXLs)[2d,4] are examples of tunable solvents. More specifically, GXLs are generally miscible mixtures of an organic solvent with a gas, most often $CO_2$, at moderate pressure (3−8 MPa). Operationally, GXLs are formed by the dissolution of $CO_2$ into organic liquids. $CO_2$ is a poor solvent, whereas typical organics such as acetone and THF are good solvents; thus a wide range of solvent properties are easily accessible.[4f,5] $CO_2$ is an ideal antisolvent because it is environmentally benign, easily removed, and recyclable.

At moderate pressures (less than 8 MPa), 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 fluid processing). In contrast, $CO_2$ is virtually insoluble in water. Therefore, addition of $CO_2$ to a miscible organic/water mixture can result in a phase separation. This ability of "switching" from a single phase (aqueous/organic mixture) to a multiphasic system upon addition of modest pressure of $CO_2$ is central to organic aqueous tunable solvent (OATS).

For example, in the phase diagram for THF/water (Figure 1), the upper loop shows the two-phase region where THF and water are only partly miscible.[6] To achieve phase separation in this binary system, the temperature must be raised above the lower critical solution temperature of 72 °C. Yet, the region inside this loop does not offer an efficient separation since the mutual miscibilities between water and THF are significant, leading to considerable contamination of each phase. However, by application of only 1 MPa of $CO_2$ pressure on the water/THF system, the critical temperature is lowered dramatically and the split becomes quite significant.[7] This unique ability offers powerful opportunities to develop strategies to separate and recycle homogeneous catalysts efficiently.[2d,4e,8] Similarly in other systems such as acetonitrile/water, the addition of $CO_2$ can raise an upper critical solution temperature to achieve similar goals.[2d,9]

The separation and recycling of homogeneous catalysts has enormous implications for sustainable technology. Homogeneous catalysts are generally more active and more selective than heterogeneous catalysts. Furthermore, they eliminate all mass transport limitations. Homogeneous catalysts are especially useful for chiral syntheses because they almost always result in superior enantiomeric excesses compared with heterogeneous catalysis. However, they are often expensive or toxic. But most importantly, the separation of the catalyst from the products is nontrivial. This is often cost- and solvent-intensive because of their inherently homogeneous nature. Strategies such as catalyst tethering have been explored with various degrees of success to improve the catalyst separation from the products.[10]

Organic aqueous tunable solvents (OATS) differentiate themselves by taking a phase equilibrium approach: the reaction is carried out homogeneously in a single phase, and then a phase separation is triggered upon application of a stimulus (such as $CO_2$ pressure) to form a heterogeneous system. The newly formed multiphasic system allows for easy and efficient product recovery (in the GXL phase) and catalyst recycling (in the aqueous phase). In addition, OATS systems allow for enhanced separation as the antisolvent ($CO_2$) renders the organic phase a weaker solvent.[9] Figure 2 illustrates the advantages of OATS for enhanced separation. On the left is the homogeneous, miscible solvent mixture water/THF and a hydrophilic catalyst analogue (a dye) at atmospheric pressure. At 30 bar of $CO_2$ pressure, the phase split has taken place (on the right), with the upper phase being the $CO_2$−THF-expanded phase and the lower phase the water-rich phase. The hydrophilic catalyst analog partitions predominantly in the aqueous phase; in fact, it could not be detected in the organic phase. The resulting distribution coefficient is therefore greater than $10^6$.

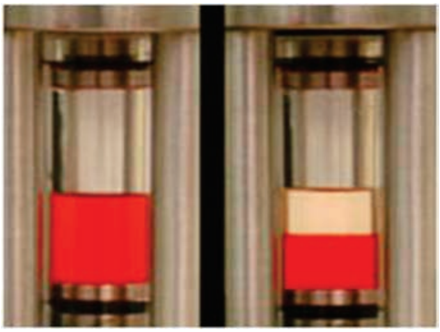


**FIGURE 2.** Water−THF mixture with dilute water-solute dye (red): left side, ambient pressure; right side, 3.0 MPa of $CO_2$ pressure.

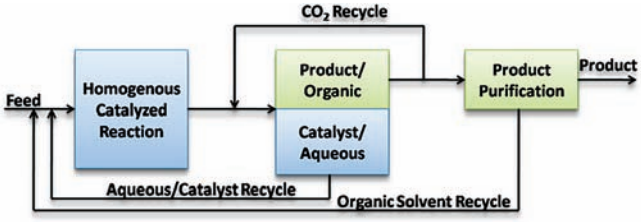


**FIGURE 3.** Schematic for an OATS-mediated process.

A general processing scheme (Figure 3) highlights the three key features of OATS processes: (1) the reaction is performed homogeneously (maximizing reaction performance), (2) the product separation and isolation is conducted heterogeneously (optimizing product recovery), and (3) the organic solvent, aqueous phase (containing the catalyst or additives) and $CO_2$ can all be recycled (minimizing the waste stream of the process). The diagram is ideal for a sustainable process; there is only reactant coming in and only product coming out. All other streams are recycled, and in principle, there is no waste stream.

OATS offer unique advantages for coupling reaction and separation. We report herein (1) the Rh-catalyzed hydroformylation of olefins like 1-octene and (2) the enzyme-catalyzed hydrolysis of 2-phenylacetate reaction, coupled with separation and catalyst recycling schemes in OATS.

## 2. Description of Application: Hydroformylation of Olefins

The hydroformylation of propylene to form butyraldehyde has been widely explored (Figure 4).[11] In fact, the water/organic biphasic technique, popularized by the Ruhrchemie/Rhône-Poulenc process, produces 900 000 t annually.[12] In this process, the aqueous phase contains the hydrophilic catalyst, while the organic phase is essentially propene, butyraldehyde, or both. The heterogeneous nature of this process allows for the hydrophilic catalyst to be easily separated and recycled. It is important to note that the reaction is taking place in the aqueous phase, making the solubility of the alkene in the aqueous phase a critical factor for the viability of the process. While the solubility of propylene in water (200 ppm)[13] is sufficient for catalysis, the biphasic approach cannot be extended to longer-chain olefins, such as 1-octene (<3 ppm solubility).[14]

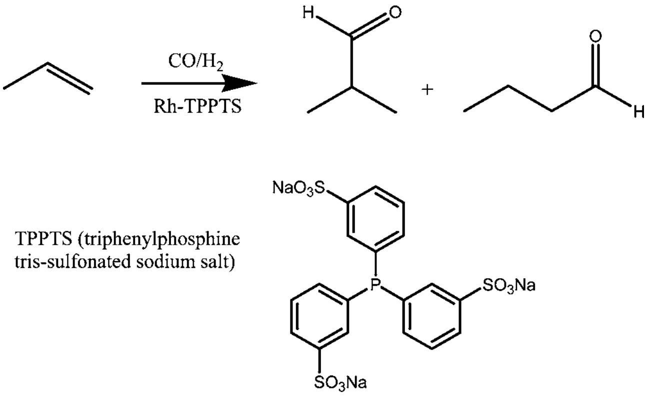


**FIGURE 4.** Hydroformylation of propene to butanal (linear product) and 2-methylpropanal (branched product).

Hallett et al. demonstrated the benefits of OATS to couple the homogeneously catalyzed hydroformylation of 1-octene with a heterogeneous separation (Figure 5).[4e] The 1-octene solubility limit is increased more than 10 000-fold by the addition of tetrahydrofuran (THF) as cosolvent in a 70% (v/v) THF/water mixture, securing a homogeneous reaction. The partitioning of the catalyst in the $CO_2$-induced biphasic system represents a key variable in the industrial process, because easy catalyst recovery is the biggest advantage of a biphasic system. Hence, the solubility of the two hydrophilic ligands (TPPTS and TPPMS, Figure 5) in THF was investigated as a function of $CO_2$ pressure.

In the absence of $CO_2$, both TPPTS and TPPMS were completely soluble in the mixed solvent (70% (v/v) THF/water). Upon the application of $CO_2$ pressure, however, both ligands partitioned favorably into the aqueous phase (Figure 6). TPPTS partition coefficients were slightly superior to those of TTPMS. (The partition coefficients were defined as the ratio of the ligand concentration in the aqueous phase to the ligand concentration in the organic phase; they were determined via UV measurements.) For example, the partition coefficient of TPPTS in a 70:30 (v/v) THF/$H_2O$ mixture varied from 1400 to 4100 as the $CO_2$ pressure was increased from 20 to 50 bar (Figure 2). The partition coefficients for TPPMS were slightly lower, varying from 1000 to 2600 from 17 to 44 bar. Regardless of $CO_2$ pressure, the hydrophobic, nonsulfonated TPP was insoluble in the aqueous phase. Operationally, the results demonstrate that the reaction can be run homogeneously in the absence of $CO_2$. However, upon modest $CO_2$ pressure, both TPPMS and TPPTS would be retained dominantly in the aqueous phase, ensuring >99.9% recovery.

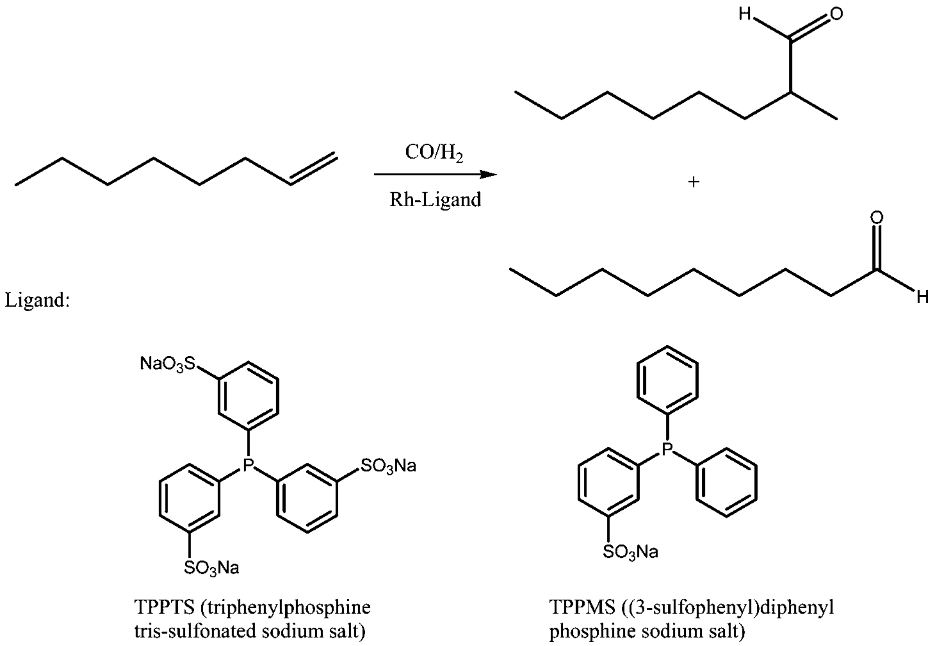


**FIGURE 5.** Hydroformylation of 1-octene to form 1-nonanal (linear product) and 2-methyloctanal (branched product).

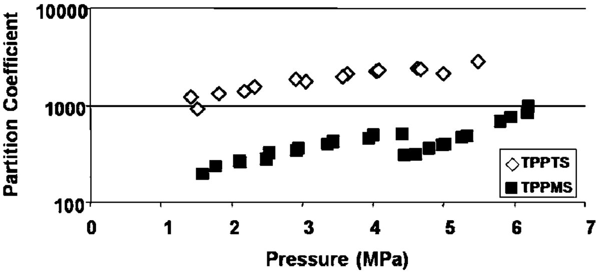


**FIGURE 6.** Partition coefficient of TPPTS and TPPMS ligands in 70/30 (v/v) mixture THF/water at 25 °C as a function of $CO_2$ pressure.

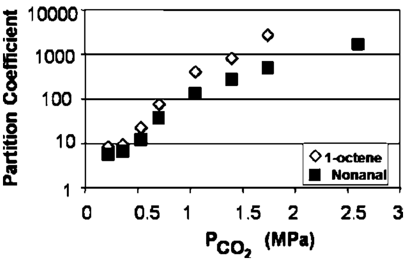


**FIGURE 7.** Partitioning of 1-octene and nonan-1-al between GX-THF and water at 25 °C as a function of $CO_2$ pressure.

The partitioning of 1-octene (the starting material) and nonan-1-al (the linear aldehyde product) between the water-rich and organic-rich phases was also reported as a function of added carbon dioxide in the $CO_2$/THF/water ternary system at 25 °C (Figure 7).[4e] The concentration of 1-octene in the THF-rich phase increased by more than 2 orders of magnitude at only 17 bar of $CO_2$. The nonanal partitioning was also high; at 26 bar of $CO_2$, the nonan-1-al was 2500 times more soluble in the GXL phase than in the aqueous phase. Further, the 7 bar of $CO_2$ pressure required for 99% recovery of 1-nonanal is much lower than the syngas pressure required for the reaction (31 bar).

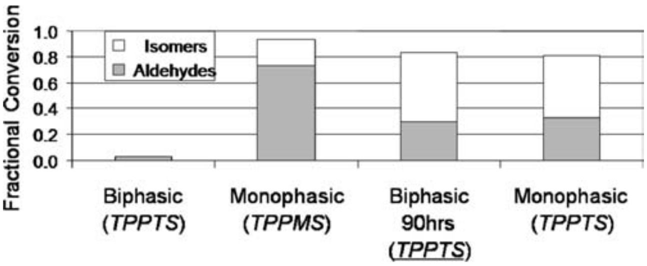


**FIGURE 8.** Product distributions for monophasic and biphasic hydroformylation using Rh/ligand at 120 °C. Each reaction was performed for 1 h with a substrate/Rh ratio of 500:1 and ligand/metal ratio of 10:1. The monophasic systems contained a 70:30 (v/v) mixture of THF/water, while biphasic systems contained no THF.

The product yields and reaction selectivity toward the linear or branched aldehyde products was investigated for the Rh-catalyzed-hydroformylation of 1-octene as a function of catalysts, specifically Rh-TPP (triphenylphosphine), Rh-TPPTS (triphenylphosphine tris-sulfonated sodium salt), and Rh-TPPMS (3-sulfophenyl)diphenyl phosphine sodium salt).[4e] The linear-to-branched ratio was found to vary slightly from ligand to ligand. The most remarkable difference in the effect of the ligands was observed in the product distribution (Figure 8). At 120 °C, the turnover frequency (TOF, based on yield of aldehydes) of a classic biphasic system was roughly 4 $h^{-1}$ whereas for the OATS monophasic system it was 350 $h^{-1}$. The TPPTS ligand yielded approximately equal amounts of aldehydes and olefin isomers: 38% each of aldehydes and isomers at 120 °C, 24% aldehydes and 28% isomers at 80 °C, and 1%

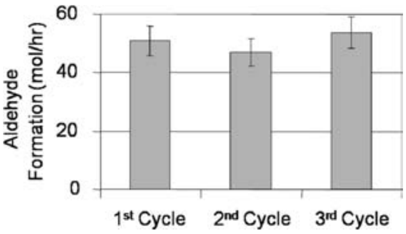


**FIGURE 9.** Aldehyde production (TOF) for successive hydroformaylation with recycled Rh/TPPMS catalyst at 120 °C. Each reaction was performed for 1 h with a substrate/Rh ratio of 546:1 and a ligand/metal ratio of 10.6:1. The yield on each cycle exceeded 80%.

each of aldehydes and isomers at 40 °C (the remainder in each case was unreacted 1-octene). Meanwhile, the TPPMS yielded 72% aldehydes and 20% olefin isomers at 120 °C, 85% aldehydes and only 4% isomers at 80 °C, and 21% aldehydes and 1% isomers at 40 °C. Neither sulfonated ligand system performed as well as the unmodified TPP (91% aldehydes, no isomers at 120 °C). The authors hypothesized that the difference in aldehyde/isomer ratio was caused by the electronic effects resulting from adding the sulfonate groups in the meta-position on the phenyl rings.

Overall, catalysis with the TPPMS ligand (at 80 °C) compares favorably with that for the TPP system (at 120 °C) in terms of conversion to aldehydes (85% versus 91%, respectively) and isomers (4% versus 1%). In contrast with the TPP-based catalyst, the hydrophobic TPPMS catalyst is easily separated, recovered, and recycled using OATS. Indeed, the TPPMS was recycled successfully three times with the organic phase being removed and refreshed after each run. The TOFs were consistent from cycle to cycle, varying from 51 to 47 to 54 $h^{-1}$ (Figure 9). The consistency in the reaction rate upon recycle corroborates minimal loss of activity of the catalyst. In addition, no rhodium losses/leaching in the organic phase were detected using atomic absorption spectroscopy (AAS) (detection limit <1 ppm).

Blasucci et al. reported the Rh−TPPMS-catalyzed hydroformylation of *p*-methylstyrene in OATS (Figure 10).[15] *p*-Methylstyrene cannot isomerize like 1-octene and was chosen as a model compound because it is an analog to an ibuprofen precursor, *p*-(2-methylpropyl)styrene.[16] Thus, the study focused on optimizing the aldehyde product yield along with the branched (desired) to linear selectivity.

The conversion and branched product selectivity after 1 h of reaction time are shown in Figure 11. The selectivity toward the branched aldehyde is altered moderately by the increase in temperature (>95% at 40 °C, 80−85% at 80 °C). This decrease in branched product yield with increasing temperature was attributed to the competing hydride elimination reaction.[15,16] At 80 °C, complete conversion of the starting material occurs in less than an hour. The turnover frequency (TOF, moles reacted per moles catalyst per hour) of the homogeneous TPPMS catalyst is 92, 406, and 402 at 40, 80, and 120 °C, respectively, an order of magnitude higher than with the comparable heterogeneous catalyst.[17]

The partitioning of *p*-methylstyrene and 2-(*p*-tolyl)propanal between the aqueous- and acetonitrile-rich liquid phases at ambient temperature was measured as a function of $CO_2$ pressure (Figure 12). The recovery of 99.5% of the product and reactants was achieved upon the addition of 3 MPa of $CO_2$ pressure. Interestingly, an exponential increase in the partition coefficient of both the *p*-methylstyrene and 2-(*p*-tolyl)-propanal occurred with increasing $CO_2$ pressure. This was explained by the decreased organic content in the water phase and decreased water content in the organic phase.[9] At higher pressures of $CO_2$, one would expect the partition coefficient's exponential increase to plateau (as seen the octane system, Figure 7) due to the partitioning of the product reaching its maximum and the dilution of the gas-expanded organic phase.

The hydroformylation reaction of 1-octene and *p*-methylstyrene was successfully conducted homogeneously in OATS. In contrast with more traditional approaches, the separation was carried out heterogeneously by applying modest pressure of $CO_2$. The resulting GXL-product rich phase could be easily separated, while the aqueous-catalyst phase was recycled.

## 3. Description of Application: Enzymatic Catalysis

Enzymes are an important class of hydrophilic catalysts and are frequently used with hydrophobic substrates. Eckert et al. reported the alcohol dehydrogenase (ADH)-catalyzed reduction of hydrophobic ketones in OATS (Figure 13),[2d] where the organic−aqueous miscible solvent was dimethyl ether (DME) and water. This particular OATS system allowed for the enhanced solubility of the hydrophobic substrate 4-*tert*-butylcyclohexanone by a factor of 5 with only 10% DME. In addition, the addition of DME stabilized the NADH cofactor, increasing its half-life by a factor of 2. However, there was about a 10-fold reduction in enzyme activity for the reaction in DME−water mixtures for three substrates (acetone, 2-hexanone, and cyclohexanone). After reaction, the DME-rich phase (containing the product) was separated from the aqueous phase (containing the enzyme) for recycle of the catalyst.

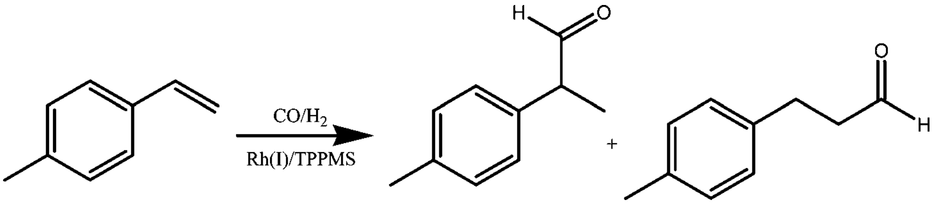


**FIGURE 10.** Hydroformylation of *p*-methylstyrene to the 2-(*p*-tolyl)propanal (branched product) and the 3-(*p*-tolyl)propanal (linear product).

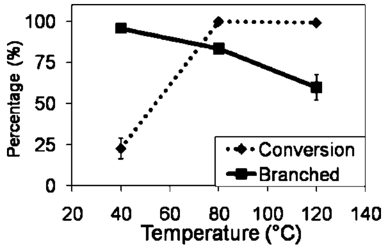


**FIGURE 11.** Conversion and 2-(*p*-tolyl)propanal selectivity of *p*-methylstyrene hydroformylation after 1 h. Error bars represent root mean-square deviations.

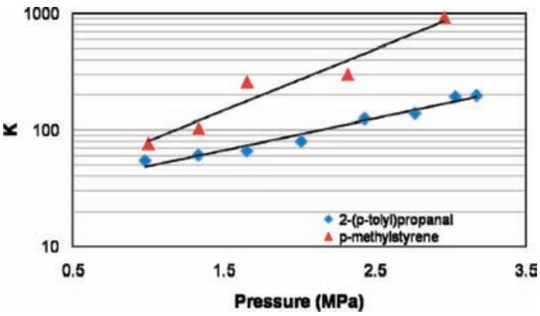


**FIGURE 12.** Partition coefficient versus pressure for 2-(*p*-tolyl)propanal and *p*-methylstyrene between acetonitrile- and water-rich liquid phases at room temperature.

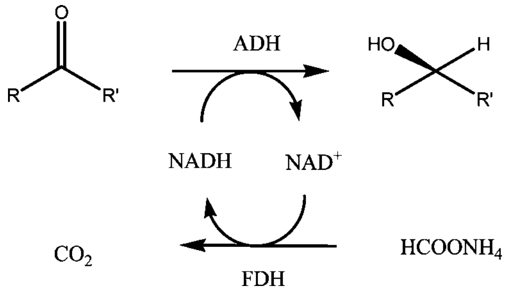


**FIGURE 13.** ADH-catalyzed reduction of ketones with NADH regeneration.

Biocatalytic reactions and separations with soluble *Candida antarctica* lipase B (CALB) were also conducted in OATS. CALB is an attractive choice for use in OATS as a versatile enzyme for esterifications of hydrophobic acids and alcohols as well as for ester hydrolyses in a range of solvents and in supercritical $CO_2$.[18] Broering et al. reported the hydrolysis of 2-phenethyl acetate (PEA) to 2-phenylethanol (2PE) (Figure 14).[19] The hydrolysis of PEA in buffered dioxane (40%) OATS yielded an average of 50% conversion per cycle, and a volumetric productivity (expressed by the space–time yield) of 27.4 g $L^{-1}$ $d^{-1}$. This is almost 5 times more than that observed in pure dioxane.

Upon optimization, the OATS system offered an 80% recovery of reaction products in the organic phase, displaying less than 10% apparent biocatalyst activity loss after six recycles. Specifically, a 40% dioxane/60% water mixture was chosen because this mixture provided increased substrate solubility and the highest observable reaction rate. After 2 h of reaction, $CO_2$ pressure was added to induce a phase split. The two resulting phases were the GXL-dioxane phase and the aqueous-rich phase. The organic layer was decanted under pressure, and after the removal of $CO_2$, the next cycle began upon the addition of the buffer solution containing PEA in dioxane. The cycle time, from the beginning of one reaction to the next, averaged three hours. Two trials of six consecutive reactions and separations were conducted. The results are shown in Figure 15.

The CALB-catalyzed reaction was first-order with respect to PEA concentration, with an apparent rate constant of 0.0067 $min^{-1}$. This observation indicates that the enzyme kinetics were not substrate-saturated at these concentrations. The conversion decreased by 10–15% by the sixth reaction, suggesting some deactivation of CALB. However, since some of enzyme was removed due to sampling; the total enzyme concentration in the reactor was diluted as new solution was added to begin new cycles. This dilution effect could account for 11% of the 15% loss of conversion by the sixth reaction. In addition, the pH of the reaction mixture decreased from 8 to 5.5 over six cycles (Figure 15). This was most likely owing to residual $CO_2$ and accumulation of acetate in the aqueous phase. CALB reaction rates would decrease by up to 20% when the pH was reduced from 8 to 5; thus, the pH drift could also explain the conversion loss.

Biocatalytic OATS reaction–separation schemes fulfill an identified need to develop new techniques to meet current challenges in biochemical synthesis.[20] By integrating reaction and separation, simpler and simultaneously more efficient processes with a reduced physical footprint could be designed. Biocatalysis in OATS is feasible and can be an effective option for designing biocatalytic processes, especially

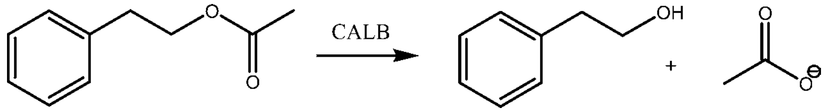


**FIGURE 14.** CALB-catalyzed hydrolysis of 2-phenethyl acetate (PEA) to 2-phenylethanol (2PE).

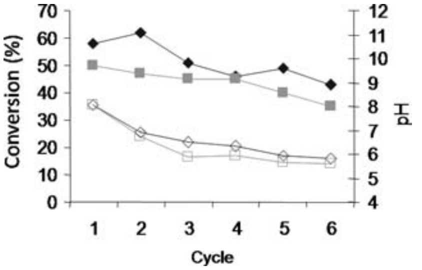


**FIGURE 15.** Conversion (◆, ■) and initial pH (◇, □) of recycled OATS reactions for trial A (◆) and trial B (■).

when hydrophobic substrates are involved. The major limitations of this technique for enzyme catalyst are loss of activity due to the polarity of the organic solvent and the effect of low pH on denaturation of enzymes. The first is controlled by careful choice of enzyme; the second can be ameliorated by buffering or by using a gas other than $CO_2$, such as ethylene.

## 4. Potential Future Applications

The impact of OATS was extended with the recent applications of poly(ethylene glycol) (PEG)/organic tunable solvents (POTS) for the palladium-catalyzed carbon−oxygen coupling of 1-bromo-3,5-dimethylbenzene and *o*-cresol to potassium hydroxide to produce *o*-tolyl-3,5-xylyl ether and 1-bromo-3,5-di-*tert*-butylbenzene to potassium hydroxide to produce 3,5-di-*tert*-butylphenol in PEG400/1,4-dioxane/water.[15] The ether product was four times more concentrated in the organic-rich phase, and the catalyst was nearly 30 times more concentrated in the PEG-rich phase. In the synthesis of 3,5-di-*tert*-butylphenol, the (alcohol) product affinity for the PEG-rich phase made the separation less efficient than for the ether product. The rhodium-catalyzed hydroformylation of *p*-methylstyrene in water/acetonitrile to form 2-(*p*-tolyl)propanal was also reported.[15]

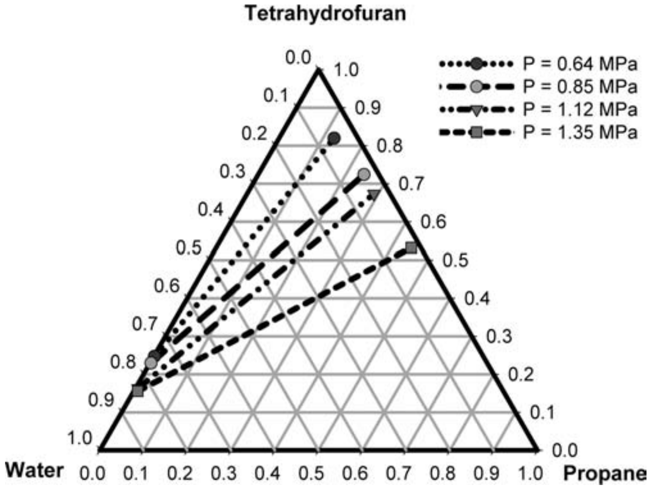


**FIGURE 16.** Ternary phase behavior diagram of the water/propane/THF system at 313 K with composition in wt %.

**TABLE 1.** Ternary Phase Behavior of Carbon Dioxide/Tetrahydrofuran/Water System at 313 K in Weight Percent

| | water-rich phase (L1) | | | tetrahydrofuran-rich phase (L2) | | |
|---|---|---|---|---|---|---|
| *P* (MPa) | $\chi_{CO_2}$ | $\chi_{THF}$ | $\chi_{H_2O}$ | $\chi_{CO_2}$ | $\chi_{THF}$ | $\chi_{H_2O}$ |
| 0.99 | 0.013 | 0.117 | 25.1 | 0.045 | 0.511 | 0.444 |
| 2.42 | 0.028 | 0.072 | 21.7 | 0.23 | 0.545 | 0.225 |
| 3.86 | 0.015 | 0.047 | 20.2 | 0.421 | 0.464 | 0.115 |
| 4.49 | 0.005 | 0.038 | 20.7 | 0.557 | 0.381 | 0.062 |
| 5.21 | 0.03 | 0.033 | 19.9 | 0.625 | 0.324 | 0.051 |

**TABLE 2.** Ternary Phase Behavior of Propane + Tetrahydrofuran + Water System at 313 K in Weight Percent

| | water-rich phase (L1) | | | tetrahydrofuran-rich phase (L2) | | |
|---|---|---|---|---|---|---|
| P (MPa) | $\chi$Propane | $\chi$THF | $\chi H_2O$ | $\chi$Propane | $\chi$THF | $\chi H_2O$ |
| 0.64 | 0.001 | 0.247 | 0.752 | 0.126 | 0.819 | 0.055 |
| 0.85 | 0.002 | 0.229 | 0.769 | 0.242 | 0.724 | 0.034 |
| 1.12 | 0.006 | 0.163 | 0.831 | 0.29 | 0.673 | 0.037 |
| 1.35 | 0.009 | 0.155 | 0.836 | 0.446 | 0.532 | 0.022 |

In addition, the authors report a novel tunable solvent system based on a modified OATS where propane replaces carbon dioxide. This represents the first use of propane in a tunable solvent system. The phase behavior of propane/water/THF was measured (Figure 16).[15] This system has the potential to improve phase purity, to use lower operating pressures, and to eliminate acid formation when compared with $CO_2$-based OATS (Tables 1 and 2). This could be a powerful alternative for enzyme-catalyzed process, eliminating the need for buffering (required when $CO_2$ is employed). These are just some examples where careful design of tunable solvent systems can benefit reaction and separation simultaneously.

## 5. Conclusions

Organic aqueous tunable solvents (OATS) are most effective when (1) they provide comparable or enhanced catalyst activity (in the homogeneous form), (2) the catalyst is efficiently retained in the aqueous phase (after the induced phase split), and (3) the product partitioning to the organic-rich phase is enhanced. Metal-catalyzed hydroformylation reactions were conducted successfully in OATS with a reaction rate up to 85 times higher than traditional systems. In addition, the separation of the catalyst was trivial: upon modest $CO_2$ pressure, a phase a split occurred to form a GXL phase (product phase) and an aqueous phase (containing the hydrophilic catalyst). The product phase was separated by simple decantation allowing for the aqueous catalyst phase to be recycled. This approach proved also beneficial for enzyme-catalyzed reactions such as the hydrolysis of 2-phenethyl acetate (PEA) to 2-phenylethanol (2PE). Ultimately, OATS allowed for 80% recovery of reaction products in the organic phase and for the aqueous catalyst phase to be recycled 6 times with less than 10% apparent biocatalyst activity loss. The recent development of PEG tunable systems and the use of propane in place of $CO_2$ demonstrate the future potential of these versatile systems. OATS offers unique features to facilitate synergistically reaction and subsequent product separation to develop economically competitive and environmentally beneficial processes.

## BIOGRAPHICAL INFORMATION

**Pamela Pollet** is the senior Research Scientist in the Eckert−Liotta Research Group and the Associate Director of the Specialty Separations Center at Georgia Institute of Technology. She studies "smart" molecules, molecules that change properties upon application of stimuli, for sustainable processes. She received her Ph.D. in chemistry from the University of Rouen.

**Ryan J. Hart** is a Graduate Research Assistant in the Eckert−Liotta Research Group at Georgia Institute of Technology where he is working on his Ph.D. dissertation to study the design and development of sustainable processes that are relevant to industry applications.

**Charles A. Eckert** and **Charles L. Liotta** have been research partners for 21 years; they occupy a common laboratory space and codirect students in both Chemical Engineering and Chemistry. Their research focus is on the development of novel solvents systems for sustainable reaction processes. For the industrial implementation of their findings they jointly received the 2004 Presidential Green Chemistry Challenge Award. Dr. Liotta is a Regent's Professor and Chair of the School of Chemistry and Biochemistry. He is the recipient of the Malcolm Pruitt Award given by the Council of Chemical Research. Dr. Eckert is the J. Erskine Love, Jr., Institute Professor and Director of the Specialty Separations Center. He has won multiple national awards from both ACS and AIChE, and he a member of the National Academy of Engineering.

## REFERENCES

1 (a) Vinci, D.; Donaldson, M.; Hallett, J. P.; John, E. A.; Pollet, P.; Thomas, C. A.; Grilly, J. D.; Jessop, P. G.; Liotta, C. L.; Eckert, C. A. Piperylene sulfone: A labile and recyclable DMSO substitute. *Chem. Commun.* **2007**, (14), 1427–1429. (b) Jiang, N.; Vinci, D.; Liotta, C. L.; Eckert, C. A.; Ragauskas, A. J. Piperylene sulfone: A recyclable dimethyl sulfoxide substitute for copper-catalyzed aerobic alcohol oxidation. *Ind. Eng. Chem. Res.* **2008**, *47* (3), 627–631. (c) Donaldson, M. E.; Mestre, V. L.; Vinci, D.; Liotta, C. L.; Eckert, C. A. Switchable solvents for in-situ acid-catalyzed hydrolysis of beta-pinene. *Ind. Eng. Chem. Res.* **2009**, *48* (5), 2542–2547.

2 (a) Dillow, A. K.; Brown, J. S.; Liotta, C. L.; Eckert, C. A. Supercritical fluid tuning of reactions rates: The cis-trans isomerization of 4−4′-disubstituted azobenzenes. *J. Phys. Chem. A* **1998**, *102* (39), 7609–7617. (b) Brown, J. S.; Lesutis, H. P.; Lamb, D. R.; Bush, D.; Chandler, K.; West, B. L.; Liotta, C. L.; Eckert, C. A.; Schiraldi, D.; Hurley, J. S. Supercritical fluid separation for selective quaternary ammonium salt promoted esterification of terephthalic acid. *Ind. Eng. Chem. Res.* **1999**, *38* (10), 3622–3627. (c) Thompson, R. L.; Glaser, R.; Bush, D.; Liotta, C. L.; Eckert, C. A. Rate variations of a hetero-Diels-Alder reaction in supercritical fluid $CO_2$. *Ind. Eng. Chem. Res.* **1999**, *38* (11), 4220–4225. (d) Eckert, C. A.; Liotta, C. L.; Bush, D.; Brown, J. S.; Hallett, J. P. Sustainable reactions in tunable solvents. *J. Phys. Chem. B* **2004**, *108* (47), 18108–18118. (e) Koch, D.; Leitner, W. Rhodium-catalyzed hydroformylation in supercritical carbon dioxide. *J. Am. Chem. Soc.* **1998**, *120* (51), 13398–13404. (f) Furstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. Olefin metathesis in supercritical carbon dioxide. *J. Am. Chem. Soc.* **2001**, *123* (37), 9000–9006. (g) Solinas, M.; Jiang, J. Y.; Stelzer, O.; Leitner, W. A cartridge system for organometallic catalysis: Sequential catalysis and separation using supercritical carbon dioxide to switch phases. *Angew Chem Int Edit* **2005**, *44* (15), 2291–2295. (h) Maayan, G.; Ganchegui, B.; Leitner, W.; Neumann, R. Selective aerobic oxidation in supercritical carbon dioxide catalyzed by the $H_5PV_2Mo_{10}O_{40}$ polyoxometalate. *Chem. Commun.* **2006**, (21), 2230–2232.

3 (a) Patrick, H. R.; Griffith, K.; Liotta, C. L.; Eckert, C. A.; Glaser, R. Near-critical water: A benign medium for catalytic reactions. *Ind. Eng. Chem. Res.* **2001**, *40* (26), 6063–6067. (b) Chandler, K.; Deng, F. H.; Dillow, A. K.; Liotta, C. L.; Eckert, C. A. Alkylation reactions in near-critical water in the absence of acid catalysts. *Ind. Eng. Chem. Res.* **1997**, *36* (12), 5175–5179. (c) Chandler, K.; Liotta, C. L.; Eckert, C. A.; Schiraldi, D. Tuning alkylation reactions with temperature in near-critical water. *AIChE J.* **1998**, *44* (9), 2080–2087. (d) Lesutis, H. P.; Glaser, R.; Liotta, C. L.; Eckert, C. A. Acid/base-catalyzed ester hydrolysis in near-critical water. *Chem. Commun.* **1999**, (20), 2063–2064. (e) Nolen, S. A.; Liotta, C. L.; Eckert, C. A.; Glaser, R. The catalytic opportunities of near-critical water: a benign medium for conventionally acid and base catalyzed condensations for organic synthesis. *Green Chem.* **2003**, *5* (5), 663–669.

4 (a) Xie, X. F.; Liotta, C. L.; Eckert, C. A. $CO_2$-protected amine formation from nitrile and imine hydrogenation in gas-expanded liquids. *Ind. Eng. Chem. Res.* **2004**, *43* (24), 7907–7911. (b) Jessop, P. G.; Stanley, R. R.; Brown, R. A.; Eckert, C. A.; Liotta, C. L.; Ngo, T. T.; Pollet, P. Neoteric solvents for asymmetric hydrogenation: Supercritical fluids, ionic liquids, and expanded ionic liquids. *Green Chem.* **2003**, *5* (2), 123–128. (c) Chamblee, T. S.; Weikel, R. R.; Nolen, S. A.; Liotta, C. L.; Eckert, C. A. Reversible in situ acid formation for beta-pinene hydrolysis using $CO_2$ expanded liquid and hot water. *Green Chem.* **2004**, *6* (8), 382–386. (d) Weikel, R. R.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. Self-neutralizing in situ acid catalysis for single-pot synthesis of iodobenzene and methyl yellow in $CO_2$-expanded methanol. *Ind. Eng. Chem. Res.* **2007**, *46* (16), 5252–5257. (e) Hallett, J. P.; Ford, J. W.; Jones, R. S.; Pollet, P.; Thomas, C. A.; Liotta, C. L.; Eckert, C. A. Hydroformylation catalyst recycle with gas-expanded liquids. *Ind. Eng. Chem. Res.* **2008**, *47* (8), 2585–2589. (f) Jessop, P. G.; Subramaniam, B. Gas-expanded liquids. *Chem. Rev.* **2007**, *107* (6), 2666–2694.

5 Wyatt, V. T.; Bush, D.; Lu, J.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. Determination of solvatochromic solvent parameters for the characterization of gas-expanded liquids. *J. Supercrit. Fluids* **2005**, *36* (1), 16–22.

6 Matous, J.; Sobr, J.; Pick, J.; Novak, J. P. Phase equilibria in system tetrahydrofuran(1)-water(2). *Collect. Czech. Chem. Commun.* **1972**, *37* (8), 2653–2663.

7 (a) Fornari, R. E.; Alessi, P.; Kikic, I. High-pressure fluid phase-equilibria - experimental methods and systems investigated (1978−1987). *Fluid Phase Equilib.* **1990**, *57* (1−2), 1–33. (b) Dohrn, R.; Brunner, G. High-pressure fluid-phase equilibria - experimental methods and systems investigated (1988−1993). *Fluid Phase Equilib.* **1995**, *106* (1−2), 213–282. (c) Christov, M.; Dohrn, R. High-pressure fluid phase equilibria - experimental methods and systems investigated (1994−1999). *Fluid Phase Equilib.* **2002**, *202* (1), 153–218.

8 (a) Hill, E. M.; Broering, J. M.; Hallett, J. P.; Bommarius, A. S.; Liotta, C. L.; Eckert, C. A. Coupling chiral homogeneous biocatalytic reactions with benign heterogeneous separation. *Green Chem.* **2007**, *9* (8), 888–893. (b) Lu, J.; Lazzaroni, J.; Hallett, J. P.; Bommarius, A. S.; Liotta, C. L.; Eckert, C. A. Tunable solvents for homogeneous catalyst recycle. *Ind. Eng. Chem. Res.* **2004**, *43* (7), 1586–1590. (c) Hill, E. M.; Broering, J. M.; Hallett, J. P.; Eckert, C. A.; Liotta, C. L.; Bommarius, A. S. Biocatalysis and $CO_2$-induced separation and recycle using organic-aqueous tunable solvents (OATS). *Abstr. Pap. Am. Chem. Soc.* **2006**, 231.

9 Lazzaroni, M. J.; Bush, D.; Jones, R.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. High-pressure phase equilibria of some carbon dioxide-organic-water systems. *Fluid Phase Equilib.* **2004**, *224* (1), 143–154.

10 Lu, J.; Toy, P. H. Organic polymer supports for synthesis and for reagent and catalyst immobilization. *Chem. Rev.* **2009**, *109* (2), 815–838.

11 (a) Monteil, F.; Queau, R.; Kalck, P. Behavior of water-soluble dinuclear rhodium complexes in the hydroformylation reaction of oct-1-ene. *J. Organomet. Chem.* **1994**, *480* (1−2), 177–184. (b) Cornils, B. Solving the problem - heterogenized homogeneous catalysts. *Nachr. Chem., Tech. Lab.* **1994**, *42* (11), 1136–1138. (c) Kieboom, A. P. G.; Moulijn, J. A.; Sheldon, R. A.; van Leeuwen, P. W. N. M. Catalytic processes in industry. In *Catalysis: An Integrated Approach*, 2nd ed.; Averill, B. A.; Moulijn, J. A.; van Leeuwen, P. W. N. M.; van Santen, R. A., Eds., Elsevier: Amsterdam, 1999; Vol. 123, pp 29−80.

12 (a) Kohlpaintner, C. W.; Fischer, R. W.; Cornils, B. Aqueous biphasic catalysis: Ruhrchemie/Rhone-Poulenc oxo process. *Appl. Catal., A* **2001**, *221* (1−2), 219–225. (b) Cornils, B. Bulk and fine chemicals via aqueous biphasic catalysis. *J. Mol. Catal. A: Chem.* **1999**, *143* (1−3), 1–10. (c) Wiebus, E.; Cornils, B. Industrial-scale oxo synthesis with an immobilized catalyst. *Chem. Ing. Tech.* **1994**, *66* (7), 916–923. (d) Cornils, B.; Wiebus, E. Aqueous catalysts for organic-reactions. *CHEMTECH* **1995**, *25* (1), 33–38.

13 McAuliff, C. Solubility in water of paraffin cycloparaffin olefin acetylene cycloolefin and aromatic hydrocarbons. *J. Phys. Chem.* **1966**, *70* (4), 1267–1275.

14 (a) Vanleeuwen, P. W. N. M.; Roobeek, C. F. the hydroformylation of butadiene catalyzed by rhodium diphosphine complexes. *J. Mol. Catal.* **1985**, *31* (3), 345–353. (b) Herrmann, W. A.; Kohlpaintner, C. W. Water-soluble ligands, metal-complexes, and catalysts - synergism of homogeneous and heterogeneous catalysis. *Angew. Chem., Int. Ed. Engl.* **1993**, *32* (11), 1524–1544. (c) Buhling, A.; Kamer, P. C. J.; Vanleeuwen, P. W. N. M. Rhodium-catalyzed hydroformylation of higher alkenes using amphiphilic ligands. *J. Mol. Catal. A: Chem.* **1995**, *98* (2), 69–80.

15 Blasucci, V. M.; Husain, Z. A.; Fadhel, A. Z.; Donaldson, M. E.; Vyhmeister, E.; Pollet, P.; Liotta, C. L.; Eckert, C. A. Combining homogeneous catalysis with heterogeneous separation using tunable solvent systems. *J. Phys. Chem. A* **2010**, *114* (11), 3932–3938.

16 Nair, V. S.; Mathew, S. P.; Chaudhari, R. V. Kinetics of hydroformylation of styrene using homogeneous rhodium complex catalyst. *J. Mol. Catal A: Chem.* **1999**, *143*, 99–110.

17 (a) Hamza, K.; Blum, J. Highly selective hydroformylation of vinylarenes to branched aldehydes by [Rh(cod)Cl](2) entrapped in ionic liquid modified silica sol-gel. *Eur. J. Org. Chem.* **2007**, (28), 4706–4710. (b) El Ali, B.; Tijani, J.; Fettouhi, M.; El-Faer, M.; Al-Arfaj, A. Rhodium(I) and rhodium(III)-heteropolyacids supported on MCM-41 for the catalytic hydroformylation of styrene derivatives. *Appl. Catal., A* **2005**, *283* (1−2), 185–196.

18 (a) Wiktelius, D.; Johansson, M. J.; Luthman, K.; Kann, N. A biocatalytic route to P-chirogenic compounds by lipase-catalyzed desymmetrization of a prochiral phosphine-borane. *Org. Lett.* **2005**, *7* (22), 4991–4994. (b) Secundo, F.; Carrea, G.; Soregaroli, C.; Varinelli, D.; Morrone, R. Activity of different *Candida antarctica* lipase B formulations in organic solvents. *Biotechnol. Bioeng.* **2001**, *73* (2), 157–163. (c) Parker, M. C.; Brown, S. A.; Robertson, L.; Turner, N. J. Enhancement of *Candida antarctica* lipase B enantioselectivity and activity in organic solvents. *Chem. Commun.* **1998**, (20), 2247–2248. (d) Orrenius, C.; Ohrner, N.; Rotticci, D.; Mattson, A.; Hult, K.; Norin, T. *Candida antarctica* lipase-B catalyzed kinetic resolutions - substrate structure requirements for the preparation of enantiomerically enriched secondary alcanols. *Tetrahedron: Asymmetry* **1995**, *6* (5), 1217–1220. (e) Almeida, M. C.; Ruivo, R.; Maia, C.; Freire, L.; de Sampaio, T. C.; Barreiros, S. Novozym 435 activity in compressed gases. Water activity and temperature effects. *Enzyme Microb. Tech.* **1998**, *22* (6), 494–499. (f) Gandhi, N. N.; Patil, N. S.; Sawant, S. B.; Joshi, J. B.; Wangikar, P. P.; Mukesh, D. Lipase-catalyzed esterification. *Catal. Rev.* **2000**, *42* (4), 439–480. (g) Lozano, P.; de Diego, T.; Carrie, D.; Vaultier, M.; Iborra, J. L. Continuous green biocatalytic processes using ionic liquids and supercritical carbon dioxide. *Chem. Commun.* **2002**, (7), 692–693.

19 Broering, J. M.; Hill, E. M.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A.; Bommarius, A. S. Biocatalytic reaction and recycling by using $CO_2$-induced organic-aqueous tunable solvents. *Angew. Chem., Int. Ed.* **2006**, *45* (28), 4670–4673.

20 Noble, R. D.; Agrawal, R. Separations research needs for the 21st century. *Ind. Eng. Chem. Res.* **2005**, *44* (9), 2887–2892.