Combining Homogeneous Catalysis with Heterogeneous Separation using Tunable Solvent Systems †

Vittoria M. Blasucci,^{‡,||} Zainul A. Husain,^{‡,||} Ali Z. Fadhel,^{‡,||} Megan E. Donaldson,^{‡,||} Eduardo Vyhmeister,^{‡,||} Pamela Pollet,^{\$,||} Charles L. Liotta,^{*,‡,\$,||} and Charles A. Eckert^{*,‡,\$,||}

Georgia Institute of Technology, School of Chemical & Biomolecular Engineering, 311 Ferst Drive, Atlanta, Georgia 30332-0100, Georgia Institute of Technology, School of Chemistry & Biochemistry, 901 Atlantic Drive, Atlanta, Georgia 30332-0400, and Georgia Institute of Technology, Specialty Separations Center, Atlanta, Georgia 30332-0100

Received: July 30, 2009; Revised Manuscript Received: September 14, 2009

Tunable solvent systems couple homogeneous catalytic reactions to heterogeneous separations, thereby combining multiple unit operations into a single step and subsequently reducing waste generation and improving process economics. In addition, tunable solvents can require less energy than traditional separations, such as distillation. We extend the impact of such solvents by reporting on the application of two previously described carbon dioxide tunable solvent systems: polyethylene glycol (PEG)/organic tunable solvents (POTS) and organic/aqueous tunable solvents (OATS). In particular, we studied: (1) 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*-butylbenol in PEG400/1,4-dioxane/water and (2) the rhodium-catalyzed hydroformylation of p-methylstyrene in water/ acetonitrile to form 2-(p-tolyl) propanal. In addition, we introduce 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.

1. Introduction

We exploit tunable solvent systems to couple the benefits of both homogeneous and heterogeneous catalysis. Separation is more facile in heterogeneous catalysis, but reactivity and product selectivity suffer and mass transfer limitations may dominate.¹ In the investigated tunable systems, gas, either CO₂ or propane, is added to the homogeneous reaction phase to induce a postreaction phase-split between the polar protic component (water or polyethylene glycol (PEG)) and the relatively nonpolar aprotic component (acetonitrile, dioxane, or tetrahydrofuran), as shown in Figure 1. Operationally, this phase split is easily reversed upon gas depressurization, thereby allowing a solvent switch between homogeneous and heterogeneous and vice versa. Whereas tunable solvents include both supercritical and nearcritical fluids, here we focus on those whose properties, such as solvent power and diffusivity, can be gradually adjusted through the use of a pressurized gas, most commonly carbon dioxide (CO₂).² Several such tunable solvent systems have been published.³⁻⁹ Here we expand the use of these systems with new applications for the pharmaceutical and fine chemical industries, and we characterize a novel propane-based tunable solvent.

In designing tunable solvent systems, the applicability of the system to real processes depends strongly on phase equilibria. There is generally a limited region in pressure-temperature- composition space where two liquid phases exist. That region

[§] Georgia Institute of Technology, School of Chemistry & Biochemistry.



Figure 1. Tunable solvent system schematic where L1 is the polar liquid and L2 is the less-polar liquid.

is most useful if it occurs under readily attainable conditions and if it is large. Furthermore, one seeks an area of relatively wide disparity in the compositions of the two liquid phases so that solvent waste is minimized and the solute distribution is as skewed as possible to yield efficient separation. Fluids are selected where specific interactions (hydrogen bonds, Lewis acid/base interactions, etc.) give preferential distributions. Finally, we need to choose fluids that do not interfere with the chemistry of the reaction. Then, such systems may be applied to couple homogeneous reaction to heterogeneous separation for enhanced reaction rates and minimal environmental impact.

We report (1) the palladium-catalyzed 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 PEG 400/1,4-dioxane/water, (2) the rhodium-catalyzed hydroformylation of *p*-methylstyrene in water/acetonitrile to form 2-(*p*-tolyl) propanal, and (3) the phase behavior of a propane-induced tetrahydrofuran (THF)/water tunable solvent system. Although here we describe the first application of PEGbased tunable solvents and propane tunable solvents, organic/ aqueous tunable solvent (OATS) systems, using CO₂ as a switch, have been used for enzyme recycle in biocatalytic reactions^{3,4} and for catalyst recycle in the hydroformylation of 1-octene.⁹

 $^{^{\}dagger}$ Part of the special issue "Green Chemistry in Energy Production Symposium".

^{*} Corresponding author.

[‡] Georgia Institute of Technology, School of Chemical & Biomolecular Engineering.

^{II} Georgia Institute of Technology, Specialty Separations Center.

For the latter case, the reaction rate was augmented by two orders of magnitude from the biphasic reaction consistently over three recycles, and a 99.9% product separation and catalyst recovery were obtained.

PEG offers many advantages as a tunable solvent component. PEG can increase rates of reactions involving salts because of its ability to complex cations and activate anions for reaction.¹⁰ PEG is attractive because of its low cost, thermal stability, negligible vapor pressure, biodegradability, and nontoxicity.¹¹ PEG can surpass water as the tunable solvent's polar phase by expanding the list of soluble organic cosolvents. We investigate a polyethylene glycol/organic tunable solvent (POTS) system, with CO₂ as a miscibility switch, for the catalytic production of phenols or aromatic ethers. Current technologies for their production suffer from harsh reaction conditions (400 °C and 30 MPa), poor atom economy, and/or hazardous intermediates.¹² Recently, Buchwald et al. used a biphasic organic/water solvent system for the mild palladium-catalyzed route to these molecules via carbon–oxygen coupling of aryl halides to hydroxide salts.¹³ The presence of the reactants disrupted the system's phase behavior and did not allow for a homogeneous reaction phase as in OATS. However, the C-O coupling reactions benefit from a homogeneous system and catalyst recycle, as provided by POTS. Carbon dioxide serves a dual purpose for phenol production by not only acting as the separation switch but also generating in situ carbonic acid, utilizing the equilibrium with water, for postreaction workup. Postreaction neutralization is required because the pK_a of most phenols is lower than the reaction media pH. At 0.95 MPa of CO₂, the pH of the aqueous phase of the water/dioxane system was reduced to <3.4Furthermore, our group has published on the use of this equilibrium in acid catalysis.¹⁴ Any residual carbonic acid is easily reversed upon venting CO₂. The results for both reaction conversion and catalyst/product partitioning follow.

We applied OATS to the hydroformylation of p-methylstyrene, which is an intermediate step in ibuprofen manufacturing.¹⁵ For the industrial scale hydroformylation process, OATS can be implemented with minimal or no modification to existing facilities because the separation of products from the catalysts can be achieved with pressures similar to those used during the reaction. We report conversion and branched product yields as well as partitioning of both the reactant and desired product between the two liquid phases as a function of CO₂ pressure. Because of the benefits of using CO₂ (such as nonflammability and nontoxicity) as an OATS antisolvent, only a few reports have been made on other small gas molecules that could serve the same purpose.^{16–18} However, we have found that using propane as an antisolvent may provide several advantages over CO₂. These include drastically lowering phase split/operating pressures, elimination of carbonic acid formation from the equilibrium between CO2 and water for pH sensitive reactions, avoiding the use of buffers and subsequent solids handling, and decreased product (organic-rich) phase contamination. These advantages may or may not substantiate introducing the use of a flammable gas. The phase diagram for THF/water/propane is presented herein.

2. Experimental Methods

Materials. The following materials were degassed by bubbling either nitrogen or argon through the liquids for 0.5 h: PEG 400 (Sigma-Aldrich), 1,4-dioxane (Fischer Scientific, 99.9%), HPLC grade water (Sigma-Aldrich), and 1-bromo-3,5-dimethylbenzene (Alfa Aesar, 98%). Carbon dioxide was supercritical fluid chromatography grade (SFC grade, Air Gas, 99.999%) and

further purified via a Matheson gas purifier and filter cartridge (model 450B, type 451 filter). The following materials were used as received from the suppliers: tris(dibenzylideneacetone)dipalladium (Pd₂dba₃, Strem, 21% Pd), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (P1, Sigma-Aldrich, 97%), o-tolyl-3,5-xylyl ether (TCI America, >97%), 1-bromo-3,5-di-tertbutylbenzene (Alfa Aesar, 99%), HPLC grade tetrahydrofuran (THF, Sigma-Aldrich, 99.9%), instrument grade propane (Airgas, 99.5%), synthesis gas (syngas, 1:1 molar ratio of H₂:CO), o-cresol (Sigma-Aldrich, >99%), and 2,4-di-tert-butylphenol (Alfa Aesar, 97%). The following solvents were degassed by the freeze-pump-thaw method: HPLC grade water (Sigma-Aldrich), HPLC grade acetonitrile (Sigma-Aldrich, >99.9%), and p-methylstyrene (Alfa Aesar, >98%). Also, the following materials were used as received and stored in a nitrogen-filled glovebox: triphenylphosphine-3-sulfonic acid sodium salt (TPPMS, TCI America, > 90%) and rhodium(I) dicarbonyl acetylacetonate (Rh(acac), Sigma-Aldrich, 98%). Potassium hydroxide (KOH, EMD Chemicals) pellets were ground to fine particles.

Reaction of 1-Bromo-3,5-dimethylbenzene and o-Cresol with Potassium Hydroxide to Produce o-Tolyl-3,5-xylyl Ether in POTS. Solid components including potassium hydroxide (1 equiv, 220 mg, 1 M concentration), o-cresol (1 equiv, 420 mg, 1 M concentration), Pd₂dba₃ (0.02 equiv, 77 mg), and P1 ligand (0.08 equiv, 136 mg) were added to glass carousel reaction tubes (radleys carousel 12 plus reaction station) equipped with magnetic stir bars and degassed. The metal-toligand molar ratio was maintained at 1:2 for all experiments. PEG 400 (4.0 mL/100 wt %, 2.8 mL/72 wt %, or 2.3 mL/60 wt %), 1,4-dioxane (0.0 mL/0 wt %, 1.2 mL/28 wt % or 1.0 mL/ 24 wt %), and water (0.0 mL/0 wt %, 0.0 mL/0 wt %, or 0.7 mL/16 wt %) were then introduced via an airtight degassed syringe to keep the total solvent volume at 4 mL. The carousel was then temperature-controlled at 80 °C. The tops of the tubes were water-cooled. After 1 h at 80 °C, 1-bromo-3,5-dimethylbenzene (1 equiv, 0.5 mL, 1 M concentration) was added to begin the overnight reaction. Postreaction, the glass tubes were cooled to room temperature, and the mixture was neutralized by one of the following techniques: the addition of 8 mL of 1 M hydrochloric acid or bubbling CO₂ for 0.5 h. The products were then extracted into 8 mL of diethyl ether and analyzed using gas chromatography-mass spectroscopy (GCMS) (Agilent GC-HP 6890 with a GCMS-HP 5973 detector and HP-5MS column). All reactions were run in triplicate.

Separation of o-Tolyl-3,5-xylyl Ether using POTS. Partitioning experiments were run in a 60 mL high-pressure Jerguson cell. The cell temperature was monitored in situ with a thermocouple (Omega type K) calibrated against a platinum RTD (Omega PRP-4) with DP251 Precision RTD benchtop thermometer (DP251 Omega), providing an accuracy of ± 0.2 K. Pressure in the cell was measured using a Druck pressure transducer (PDCR 910) and read-out box (DPI 260) calibrated against a hydraulic piston pressure gauge (Ruska, GE Infrastructure Sensing) with an uncertainty of ± 0.1 bar. The cell was manually shaken by a rotating shaft. The cell was first evacuated. 1,4-Dioxane (4 mL/60 wt %), PEG 400 (9 mL/26 wt %), water (2 mL/14 wt %), and o-tolyl-3,5-xylyl ether (1.2 mL, 0.5 M concentration) were premixed and added to the cell via an airtight syringe. CO₂ was added to the cell by an ISCO syringe pump to the desired separation pressure. After equilibrium was ascertained, three 0.5 mL samples were taken from each liquid phase using a sample loop. The samples were rinsed and diluted in methanol and then analyzed by GCMS (as





described above). The average value for the three samples is reported. The direct sampling method compares well with the synthetic method described by Lazzaroni et al.^{19,20}

Separation of PdP1₂ Using POTS. The partitioning of the catalyst, PdP1₂, between the PEG-rich and dioxane-rich phases was determined using the experimental procedure and Jerguson apparatus, as previously outlined. P1 (110 mg, 20 mM concentration) and Pd₂dba₃ (66 mg, 5 mM concentration) were mixed and heated to 80 °C for 30 min in the ternary solvent system prior to injection into the cell. Sample concentrations were determined by ICP-MS and ICP-OES analyses (Columbia Analytical Services: lower detection limits 2 and 20 ppm, respectively).

Reaction of 1-Bromo-3,5-di-*tert*-butylbenzene with Potassium Hydroxide to Produce 3,5-Di-*tert*-butylphenol in POTS. Solid components including potassium hydroxide (3 equiv, 660 mg, 3 M concentration), Pd₂dba₃ (0.02 equiv, 77 mg), P1 ligand (0.08 equiv, 136 mg), and 1-bromo-3,5-di-*tert*-butylbenzene (1 equiv, 1.04 g, 1 M concentration) were added to glass carousel reaction tubes (as previously described) and degassed. PEG 400 (4 mL/100 wt %, 2.8 mL/72 wt %, or 2.3 mL/60 wt %), 1,4dioxane (0.0 mL/0 wt %, 1 mL/28 wt %, or 1.2 mL/24 wt %), and water (0.0 mL/0 wt %, 0.0 mL/0 wt %, or 0.7 mL/16 wt %) were then introduced via an airtight degassed syringe to keep the total solvent volume at 4 mL. The carousel was then temperature controlled at 80 °C for the overnight reaction. Workup of the products was performed according to the procedure outlined for *o*-tolyl-3,5-xylyl ether production.

Separation of 2,4-Di-*tert***-butylphenol using POTS.** The partitioning of a structural isomer of 3,5-di-*tert*-butylphenol, 2,4-di-*tert*-butylphenol (650 mg, 0.5 M concentration), between the PEG-rich and dioxane-rich phases was determined using the experimental procedure and apparatus, as previously outlined for the separation of *o*-tolyl-3,5-xylyl ether using POTS.

p-Methylstyrene Hydroformylation in OATS. p-Methylstyrene hydroformylations were carried out in a 300 mL stainless steel Parr autoclave (Parr Instrument Company, model 4561). The reaction pressure was monitored with a digital pressure transducer (Heise, model 901B) providing an accuracy of ± 0.7 bar. A proportional integral derivative (PID) temperature controller and tachometer (Parr Instrument Company, model 4842) were used to control the temperature of the reactor to ± 2 °C and the stirring speed to ± 5 rpm. The temperature inside the reactor was monitored with a type J thermocouple, and heat was provided by a high-temperature heating mantle. The reactor was evacuated and flushed with 3.5 bar of syngas. The degassed p-methylstyrene and catalyst solution (70/30 v/v of acetonitrile/ water) were added using gastight syringes. The total volume of the reaction mixture was 50 mL with a p-methylstyrene concentration of 0.15 M. The concentration equivalence of Rh(acac) and TPPMS is 0.0025 and 0.017, respectively. The reactor was heated to the desired reaction temperature, stirred at 300 rpm, and subsequently pressurized with 30 bar of syngas. After a 1 h reaction period, a liquid phase sample was withdrawn and captured in acetone. The samples were analyzed using an Agilent GC-FID (model 6890) with an Agilent column (model HP-5MS). External standards of known concentrations were used to calibrate the FID response.

Separation of *p*-Methylstyrene and 2-(*p*-Tolyl) Propanal in OATS. The partitioning of *p*-methylstyrene (2.0 mL, 0.15 M concentration) and 2-(*p*-tolyl) propanal (2.3 mL, 0.15 M concentration) between the acetonitrile- and water-rich liquid phases (loaded with 98 mL of 70/30 v/v acetonitrile/water solution) was determined at room temperature using the Parr autoclave described above. CO_2 was added to the cell until the desired pressure was reached using an ISCO syringe pump. After equilibrium, three 0.1 mL samples of the acetonitrile-rich phase and three 0.5 mL samples of the water-rich phase were taken using a six-way sample loop and analyzed using the Agilent GC-FID described above.

Propane OATS Phase Equilibria. Phase equilibria for the water/propane/THF ternary system were determined by direct sampling using the fixed volume Jerguson apparatus, as described above. The Jerguson cell was loaded using an airtight syringe with a 55 wt % water and 45 wt % THF mixture (12 and 10 g, respectively). Propane was added to the cell using an ISCO syringe pump. Three 0.5 mL samples were removed from each liquid phase via a six-way sample loop and bubbled into and rinsed with methanol using an HPLC pump. These samples were analyzed for water content via Karl Fischer titration (Mitsubishi Kasei Corporation CA-20 moisturemeter). The organic content was measured via GCMS (as described above) and quantified against a calibration curve. We determined the propane content by measuring the volume displaced while expanding three 0.5 mL liquid phase samples into the headspace of an inverted buret filled with water. The mass of propane was calculated from the displaced volume via the ideal gas equation at standard temperature and pressure after allowing the temperature to reach equilibrium.

3. Results and Discussion

Reaction of 1-Bromo-3,5-dimethylbenzene and o-Cresol with Potassium Hydroxide to Produce o-Tolyl-3,5-xylyl Ether in POTS. We previously reported the POTS phase behavior for PEG 400/1,4-dioxane/CO2.3 The room-temperature phase diagram showed good separation between the two liquid phases at moderate pressures (i.e., 6 MPa). Less than 1 wt % PEG 400 was found in the dioxane-rich phase under these conditions. Therefore, the reaction between 1-bromo-3,5-dimethylbenzene and o-cresol with potassium hydroxide to produce o-tolyl-3,5-xylyl ether, shown in Scheme 1, was run in three sets of solvent systems including PEG 400/1,4-dioxane/water (60, 24, 16 wt %, respectively), PEG 400/1,4-dioxane (72, 28 wt %, respectively), and PEG 400. Dilute acid was used during the workup procedure to quantify phenol produced as a side product. The results of these experiments are shown in Table 1. In terms of both conversion and selectivity, the ternary solvent

 TABLE 1: Conversion and Selectivity to o-Tolyl-3,5-xylyl

 Ether in Three Different Solvent Environments

solvent system	conversion (%)	selectivity (%)
PEG 400	60 ± 6	64 ± 2
PEG 400/1,4-dioxane	64 ± 10	62 ± 1
PEG 400/1,4-dioxane/water	81 ± 9	66 ± 6

system is the most efficient. Side products detected were m-xylene, 3,5-dimethlyphenol, 3,3'-5,5'-tetra-methlbiphenyl, and 1,1'-oxybis[3,5-dimethyl]benzene.

The partitioning of the reaction product, o-tolyl-3,5-xylyl ether, between the dioxane- and PEG-rich phases was determined at ambient temperature as a function of pressure and concentration of water. The partition coefficient, K, is defined as the concentration of the solute in the organic phase divided by the concentration of the solute in the polar phase. The partition coefficient can be used as a guide for determining the efficiency of the separation process. Figure 2 displays these results for pressures ranging from 4.2 to 5.4 MPa. The addition of water to the solvent system increases the partitioning of the ether into the organic-rich phase. This could be due to any or all of the following effects: (1) an increased polarity of the polar phase, (2) hydrogen bonding between PEG and water disrupting the interaction between PEG and the solute molecule, and (3) 2 mL increased volume of the PEG phase from water (dilution effect). The partition coefficient of o-tolyl-3,5-xylyl ether, in the case of the ternary solvent system, is highest at lower CO_2 pressures. We attribute this to a dilution effect, where adding more CO₂ preferentially expands the volume of the organic phase, thereby decreasing the concentration of ether in this phase. The trend reverses with minimal water present because the volumes of both the PEG and dioxane phase expand by similar amounts. On the other hand, when water is present in cosolvent amounts, the PEG-rich phase expands very little when compared with the dioxane-rich phase because of the limited solubility of CO_2 in water. Optimal results were obtained near the phase split pressure, 4.2 MPa, and in a three component solvent system, (PEG 400 (60 wt %)/1,4-dioxane (26 wt %)/ water (14 wt %)), where o-tolyl-3,5-xylyl ether is four times more concentrated in the organic-rich phase than in the PEGrich phase. Therefore, both our reaction and separation are most efficient in this ternary solvent system.

The separation of the catalyst, $PdP1_2$ (where P1 is 2-di-*tert*butylphosphino-2',4',6'-triisopropylbiphenyl), from the organicrich phase was also determined at room temperature as a function of CO₂ pressures ranging from 4.5 to 4.8 MPa. The ternary solvent system of PEG 400 (60 wt %)/1,4-dioxane (26 wt %)/water (14 wt %) was used to provide optimal partitioning.



Figure 2. Partition coefficient versus CO_2 pressure for *o*-tolyl-3,5xylyl ether between 1,4-dioxane-rich and PEG-rich liquid phases at various concentrations of water and room temperature. (Error bars represent root-mean-square deviations.)



Figure 3. Partition coefficient versus CO₂ pressure for the catalyst, PdP1₂, between 1,4-dioxane-rich and PEG-rich liquid phases at room temperature. (Error bars represent root-mean-square deviations.)

Figure 3 illustrates that the partition coefficient for the catalyst versus pressure follows a similar trend as o-tolyl-3,5-xylyl ether. Increasing CO₂ pressure improves catalyst retention in the PEG-rich phase but decreases product separation into the organic-rich phase, thereby necessitating an optimization. This result can also be explained by a dilution effect where as pressure is increased, the dioxane phase is preferentially volume expanded over the PEG phase. Figure 3 also shows that at 4.8 MPa, *K* equals 0.038, which corresponds to the catalyst being 27 times more concentrated in the PEG-rich phase than in the product phase (1/*K*). This limited solubility of the catalyst in the gas-expanded dioxane phase could be further decreased by structurally modifying the nonpolar, bulky side groups of the ligand, P1.

Reaction of 1-Bromo-3,5-di-tert-butylbenzene and Potassium Hydroxide to Produce 3,5-Di-tert-butylphenol in POTS. The reaction between 1-bromo-3,5-di-tert-butylbenzene and potassium hydroxide to produce 3,5-di-tert-butylphenol is shown in Scheme 2. This reaction was chosen for the CO₂-philic character of the phenol, increasing its partitioning potential into the gas-expanded product phase. Three sets of solvent reaction environments were investigated including: PEG 400, PEG 400 (72 wt %)/1,4-dioxane (28 wt %), or PEG 400 (60 wt %)/1,4dioxane (24 wt %)/water (16 wt %). Conversion and selectivity to phenol (using aqueous HCl workup) after an overnight reaction are shown in Table 2. Side products that were formed were 3,5-di-tert-butylbenzene and 3,3'-5,5'-tetra-tert-butylphenylether. Higher conversions were achieved in the systems without water as a cosolvent; however, as conversion increased, selectivity suffered. The use of CO_2 as a postreaction neutralization medium was examined in the ternary solvent system of PEG 400/1,4-dioxane/water. This workup method proved to be efficient because the overnight reaction showed 76% conversion and 71% selectivity to phenol, values matching those obtained when using a dilute acid workup. Therefore, the cost and waste associated with traditional neutralizations is eliminated.

The partitioning of 2,4-di-*tert*-butylphenol, a regioisomer of 3,5-di-*tert*-butylbenzene, between the dioxane-rich and PEG-rich phases was determined at room temperature as a function of pressure ranging from 4.2 to 4.7 MPa in the ternary solvent mixture (PEG 400 (60 wt %)/1,4-dioxane (26 wt %)/water (14 wt %) (See Figure 4). The same trend is seen as that with *o*-tolyl-3,5-xylyl ether partitioning, where an increased CO₂ pressure decreases the partition coefficient. However, the partition coefficient reached a maximum of unity slightly above the phase split pressure at 4.2 MPa.

p-Methylstyrene Hydroformylation and Separation in OATS. We have previously reported the ternary acetonitrile/ aqueous/CO₂ phase behavior, which showed 12 mol % water in the organic-rich phase at 40 °C and 3.1 MPa. Under these



TABLE 2: Conversion and Selectivity to3,5-Di-*tert*-butylphenol in Three Different SolventEnvironments

solvent system	conversion (%)	selectivity (%)
PEG 400	100 ± 0	60 ± 6
PEG 400/1,4-dioxane	100 ± 0	44 ± 4
PEG 400/1 4-dioxane/water	80 ± 7	68 ± 2

conditions, the water-rich phase contains only 7 mol % acetonitrile. A two-liquid-phase region exists over a large pressure range, 3.3 MPa span.7 We now report this OATS system for the hydroformylation of *p*-methylstyrene, as shown in Scheme 3. Styrene reacts with CO and H₂ in the presence of rhodium(I) dicarbonyl acetylacetonate (Rh(acac)) and triphenylphosphine-3-sulfonic acid sodium salt (TPPMS) to produce linear and branched aldehydes. The branched aldehyde, 2-(ptolyl) propanal, is the desired product because it is used to produce ibuprofen through oxidation.¹⁵ The conversion and branched product selectivity after 1 h of reaction time are shown in Figure 5; the selectivity is >95% at 40 °C. Complete conversion of the starting material occurs in <1 h at 80 °C. The turnover frequency (TOF, moles reacted per moles catalyst per hour) of the homogeneous catalyst is 92, 406, and 402 at 40, 80, and 120 °C, respectively. These data show an order of magnitude increase in the rate of reaction when compared with heterogeneously catalyzed hydroformylations reported in literature.^{21,22} The decrease in branched product yield with increasing temperature is due to the competing β -hydride elimination reaction, which returns the branched product back to *p*-methylstyrene.¹⁵



Figure 4. Partition coefficient versus CO₂ pressure for 2,4-di-*tert*butylphenol between 1,4-dioxane- and PEG-rich liquid phases at room temperature. (Error bars represent root-mean-square deviations.)





Figure 6 shows the partitioning of p-methylstyrene and 2-(ptolyl) propanal between the aqueous- and acetonitrile-rich liquid phases at ambient temperature as a function of CO₂ pressure between 1.0 and 3.5 MPa. The separation of the products and reactants from the aqueous phase, which contains the catalyst, is important for simplified downstream processing. We are able to achieve 99.5% recovery of both the product and reactants at 3 MPa into the gas-expanded organic phase. For both molecules, an exponential increase in the partition coefficient is seen with increasing CO₂ pressure because of the decreased organic content in the water phase and decreased water content in the organic phase.⁷ Although both *p*-methylstyrene and 2-(*p*-tolyl) propanal distribute primarily into the acetonitrile-rich phase, *p*-methylstyrene has a larger partitioning value because of its decreased polarity when compared with the branched aldehyde product. This facile CO₂-induced separation may offer a green alternative to more traditional waste-generating and energyintensive methods such as liquid-liquid extraction or distillation.

Propane OATS Phase Behavior. Unlike CO_2 , propane does not react with water; therefore, no in situ acid is formed. Reactions sensitive to pH such as enzymatic and base-catalyzed reactions are made possible by the elimination of carbonic acid from a CO_2 tunable solvent system. Buffers used in traditional/ CO_2 -induced OATS systems can create processing problems because the addition of gas pressure may cause the buffer to salt out, rendering the buffer ineffective and introducing process



Figure 5. Conversion and 2-(*p*-tolyl)propanal selectivity of *p*-methylstyrene hydroformylation after 1 h. (Error bars represent root-mean-square deviations.)



Figure 6. Partition coefficient versus pressure for 2-(*p*-tolyl) propanal and *p*-methylstyrene between acetonitrile- and water-rich liquid phases at room temperature.



Water 0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 Propane

Figure 7. Ternary phase behavior of the water + propane + tetrahydrofuran system at T = 303 K with compositions in wt %.

Tetrahydrofuran



Figure 8. Ternary phase behavior of the water + propane +

tetrahydrofuran system at T = 313 K with compositions in wt %.

difficulty associated with solids handling. The propane-OATS system does not require a buffer to control pH.

We report the mass composition of each liquid phase for water/propane/THF over a representative range of pressures encompassing the three-phase region. The vapor phase was assumed to be mostly propane and was therefore not measured. The cloud points for this system at 303 and 313 K are 0.24 and 0.28 MPa, respectively. These cloud point pressures are the lowest reported in the literature for any tunable solvent system. A low-phase split pressure enables reduced energy consumption and lower operating costs.

Figure 7 shows the mass composition of each liquid phase in the water/propane/THF system at 303 K and pressures ranging from 0.43 to 0.92 MPa. Figure 8 shows the same ternary system at 313 K and pressures ranging from 0.64 to 1.35 MPa. Tables 3 and 4 correspond to Figures 7 and 8, respectively. The phase equilibria at 303 and 313 K show the same trend. At both temperatures studied, the THF-rich phase has only 3 wt % water at pressures greater than 0.8 MPa. The water concentrations in the organic-rich product phase are a measure of the quality of separation because the catalyst can be designed to be hydrophilic and the product is usually hydrophobic. In contrast, the 298 K water/CO₂/THF system described by Lazzaroni et al. has an organic phase water content of 9 wt % at pressures >4.0 MPa.⁵

TABLE 3: Ternary Phase Behavior of the Water (x1) + Propane (x2) + Tetrahydrofuran (x3) System at 303 K with Compositions in Weight Percent

	water-rich phase (L1)			tetrahydrofuran-rich phase (L2)		
P (MPa)	x1	x2	x3	x1	x2	x3
0.43	0.706	0.008	0.286	0.061	0.083	0.856
0.56	0.711	0.006	0.283	0.040	0.175	0.785
0.80	0.776	0.016	0.208	0.031	0.310	0.659
0.92	0.820	0.024	0.156	0.028	0.452	0.520

TABLE 4: Ternary Phase Behavior of the Water (x1) + Propane (x2) + Tetrahydrofuran (x3) System at 313 K with Compositions in Weight Percent

	water-rich phase (L1)			tetrahydrofuran-rich phase (L2)		
P (MPa)	x1	x2	x3	x1	x2	x3
0.64	0.752	0.001	0.247	0.055	0.126	0.819
1.12	0.769	0.002	0.229	0.034	0.242	0.724
1.35	0.836	0.009	0.155	0.022	0.446	0.532

Overall propane reduces the cloud point pressure for OATS by a factor of four and increases organic phase purity by a factor of three.

4. Summary

Tunable solvent systems offer facile solutions toward the goal of coupling homogeneous catalytic reaction with heterogeneous separation. We have demonstrated two novel applications of tunable solvent systems with this goal in mind. When producing o-tolyl-3,5-xylyl ether in the ternary system of PEG/dioxane/ water, we show conversion of 80%, and upon separation, the product is up to four times more concentrated in the organicrich phase and the catalyst is up to nearly 30 times more concentrated in the PEG-rich phase. The similar trend of the product and the catalyst partition coefficient with CO₂ pressure requires an overall process optimization to determine the most effective operating conditions. The reaction to 3,5-dimethylphenol reached up to 100% conversion but was not as favorably partitioned into the organic phase as the ether product. This is the first report of the application of PEG-based tunable solvents. The hydroformylation of *p*-methylstyrene in OATS showed elevated TOF (up to 400) and selectivity (up to 95%) at mild temperatures. Facile product/reactant recovery was obtained at pressures as low as 3 MPa, which is similar to the pressure required for the reaction. The phase behavior of propane/water/ THF was characterized. This system improves phase purity, lowers operating pressures, and eliminates acid formation when compared with CO₂-based OATS. Overall, these examples illustrate the diverse application of tunable solvent systems once carefully designed to benefit reaction and separation simultaneously. This work shows promise for ongoing experiments, which consist of validating solvent and catalyst reuse by optimizing process recycle.

Acknowledgment. OATS work was funded by the NSF project no. CTS-0553690. Special thanks to two undergraduates from the Georgia Institute of Technology, Andy Wu and Sarah Lencenski, for their assistance with OATS experiments.

References and Notes

(1) Dijkstra, H. P.; Van Klink, G. P. M.; Van Koten, G. Acc. Chem. Res. 2002, 35, 798–810.

(2) Li, H.; Maroncelli, M. J. Phys. Chem. B 2006, 110, 21189-21197.

(3) Hill, E. M. B.; James, M.; Hallett, J.; Bommarius, A.; Liotta, C.; Eckert, C. *Green Chem.* **2007**, *9*, 888–893.

(4) Broering, J. M. H.; Hill, E.; Hallett, J.; Liotta, C.; Eckert, C.; Bommarius, A. Angew. Chem. 2006, 45, 4670–4673.

(5) Donaldson, M.; Draucker, L.; Blasucci, V.; Liotta, C.; Eckert, C. Fluid Phase Equilib. 2009, 277, 81–86.

(6) Draucker, L.; Hallett, J.; Bush, D.; Eckert, C. Fluid Phase Equilib. 2006, 241, 20–24.

(7) Lazzaroni, M. J.; Bush, D.; Jones, R.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. *Fluid Phase Equilib.* **2004**, 224, 143–154.

(8) Mellein, B. R.; Brennecke, J. F. J. Phys. Chem. B 2007, 111, 9001–9009.

(9) Hallett, J. P.; Ford, J. W.; Jones, R. S.; Pollet, P.; Thomas, C. A.;

Liotta, C. L.; Eckert, C. A. *J. Ind. Eng. Chem. Res.* **2008**, *47*, 2585–2589. (10) Code of Federal Regulations, Title 21, Volume 3, CITE 21CFR172.820; FDA, 2001.

(11) Weissermel, K.; Arpe, H. J. *Industrial Organic Chemistry*, 3rd ed.; VCH Publishers: New York, 1997.

(12) Anderson, A.; Ikawa, T.; Tundel, R.; Buchwald, S. J. Am. Chem. Soc. 2006, 128, 10694–10695.

(13) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman and Hall: New York, 1994.

(14) Weikel, R.; Hallett, J.; Liotta, C.; Eckert, C. Top. Catal. 2006, 37, 75–80.

(15) Nair, V. S.; Mathew, S. P.; Chaudhari, R. V. J. Mol. Catal A: Chem. **1999**, *143*, 99–110.

(16) Elgin, J. C.; Weinstock, J. J. J. Chem. Eng. Data 1959, 4, 3–12.
(17) Adrian, T.; Wendland, M.; Hasse, H.; Maurer, G. J. Supercrit. Fluids 1998, 12, 185–221.

(18) Freitag, J.; Sanz Diez, M. T.; Tuma, D.; Ulanova, T. V.; Maurer, G. J. Supercrit. Fluids 2004, 32, 1–13.

(19) Hill, E. M. Benign Tunable Solvents for Improved Processing of Pharmaceutically Relevant Products and Catalysts. Ph.D. Dissertation, Georgia Institute of Technology, August 2007.

(20) Lazzaroni, M. J. Optimizing Solvent Selection for Separation and Reaction. Ph.D. Dissertation, Georgia Institute of Technology, July 2004.

(21) Hamza, K.; Blum, J. Eur. J. Org. Chem. 2007, 28, 4706-4710.

(22) El, A. B.; Tijani, J.; Fettouhi, M.; El-Faer, M.; Al-Arfaj, A. Appl. Catal., A 2005, 283, 185–196.

JP907325Y