HOMOGENEOUS CATALYST RECOVERY AND RECYCLE WITH CO_2

Historical Background

Catalytic synthesis can be achieved by using either homogeneous or heterogeneous organometallic complexes, or homogeneous enzymatic biocatalysts. However, each of these methods offers advantages and disadvantages that must be balanced cautiously. Homogeneously catalyzed reactions are highly efficient in terms of selectivity (i.e. regioselectivity, enantiomeric excesses) and reaction rates, due to their monomolecular nature. Unfortunately, catalyst recovery can be very difficult (due to the homogeneous nature of the solution) and product contamination by residual catalyst or metal species is a problem. In contrast, heterogeneously catalyzed reactions allow easy and efficient separation of high value products from the catalyst and metal derivatives. However, selectivity and rates are often limited by the multiphasic nature of this system and/or variations in active site distribution from the catalyst preparation.

Catalyst separation is crucial for industrial processes – to minimize the waste streams and to develop potential catalyst recycling strategies. Therefore, efforts have been made to improve the recovery of highly selective homogeneous catalysts by developing new multiphasic solvent systems. One scheme developed for this purpose is aqueous biphasic catalysis.

With aqueous biphasic catalysis, catalyst recovery can be achieved most easily by maintaining an aqueous catalyst-rich phase separate from the substrate-containing (nonpolar) organic phase. The catalyst is immobilized in an aqueous phase by modifying the catalyst ligands with one or more polar functionalities, such as sulfonate or carboxylate salts.[1] This renders the catalyst completely insoluble in the substrate- (and later product-) containing organic phase, so that decantation of the organic phase results in no loss of catalyst. The aqueous layer can be recycled many times, yielding high catalyst turnover with little metallic contamination of the product. This "heterogenized" homogeneous system can improve the lifetime of organometallic catalysts by orders of magnitude.

Aqueous biphasic catalysis has become an important industrial technique.[2-4] The traditional water/organic biphasic technique, popularized by the Ruhrchemie/Rhône-Poulenc process, is performed annually on a 600,000 metric ton scale.[5] In this process, propylene is hydroformylated to form butyraldehyde. While the solubility of propylene in water (200 ppm) is sufficient for catalysis, the technique cannot be extended to longer-chain olefins, such as 1-octene (<3 ppm solubility).[6] We overcome these limitations via the addition of a polar organic co-solvent coupled with subsequent phase splitting induced by dissolution of gaseous carbon dioxide.

Water is an attractive solvent because of its natural abundance, low cost and non-toxicity. Water is the only ambient liquid processing solvent that excels in these three areas. The recycling of aqueous organometallic catalysts represents a fundamental application of the core principles of green chemistry and sustainable technology through the reduction of waste streams and remediation and the combination of atom economical catalytic chemistry with water, a non-toxic processing solvent.

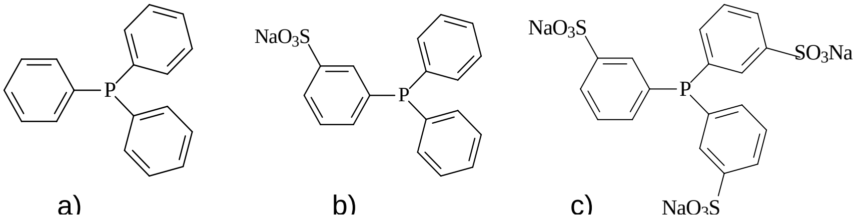


Figure 1. Catalyst ligands a) Triphenylphospine (TPP)
b) Triphenylphospine mono-sulfonated sodium salt (TPPMS)
c) Triphenylphospine tris-sulfonated sodium salt (TPPTS)

As a consequence of the immiscibilty of water with nonpolar organic compounds, opportunities exist to create uniquely water-soluble species for catalyst immobilization. Traditional organometallic ligands, such as triphenyl phosphine (PPh_3), have been modified via sodium sulfonate attachments at the *meta* position of the aromatic rings. This charged species, triphenylphosphinetrisulfonate (TPPTS, Figure 1c), has preferential solubility in the water-rich layer of any aqueous biphasic mixture.

Once an organometallic complex has been immobilized in the aqueous phase, the issue becomes one of mass transfer. On a small scale inter-phase contact is achieved by vigorous mixing to effect high surface area for substrate diffusion into the catalyst-containing aqueous phase. In the ideal limit, the organic portion of the reaction system would contain only neat reactant, with the aqueous catalyst having negligible solubility in the organic phase to prevent loss to the environment and the organic product(s) possessing limited solubility in the aqueous phase to promote easy product isolation. However, highly insoluble substrates will often limit reaction yield because inter-phase substrate diffusion is slow, even in reactors with high stirring rates.[7] To mitigate this limitation, several approaches have been investigated. The three most successful are the addition of organic co-solvents, the use of surface-active organometallic catalyst ligands, and the replacement of the aqueous phase with a fluorinated solvent.

The most common approach to overcome transport limitations involves the addition of cosolvents,[8] but the cosolvent often hinders the separation process.[9] Cornils's work[9] showed that the catalyst partitioned into the organic phase without the aqueous ligands in the form of $Rh_2(\mu\text{-}S^tBu)_2(CO)_4$. This unacceptable catalyst leaching and product poisoning is not experienced in the traditional Ruhrchemie/Rhone-Poulenc process.[10]

Another method involves using surface active ligands rather than the traditional TPPTS (triphenylphosphine trisulfonate sodium salt).[11] These surface active ligands do show increased yields for the hydroformylation of 1-octene; however the yields drop off again as the size of the substrate is increased. This reference does not include any discussion of catalyst leaching. However, the surface active ligands will also have a measurable solubility in the organic phase, again hindering the separation of the catalyst from the desired products.

One approach to overcoming the low solubility of substrates and apply the aqueous biphasic concept to water-sensitive reactions involves fluorous biphasic catalysis.[12] Here organometallic catalysts are sequestered in the fluorous phase of an organic/fluorous biphasic mixture. Rapid growth in the fluorous field has resulted in the publication of several hundred research papers in the past five years. Unfortunately, the catalyst partitioning in fluorous biphasic systems is not as favorable as in aqueous biphasic systems. Also, fluorinated compounds are environmentally persistent, making them an undesirable reaction solvent.[13] Further, multiple ponytails are often required to impart preferential solubility to most organometallic complexes,[14] while only one is required for most aqueous biphasic systems.

In our alternative approach, we show that reactions can be run homogeneously water/co-solvent mixtures, even those involving polar compounds such as acetonitrile,[15] and after reaction CO_2 can be used to induce immiscibility. CO_2 is a cheap, safe, non-toxic, non-flammable additive used to replace a nonpolar organic extraction solvent, and removal of the co-solvent becomes trivial. This alternative enables the use of hydrophilic co-solvents to improve reaction rates and provides an avenue for thermally labile components to be used under homogeneous conditions in these solvent systems. The addition of gaseous CO_2 to organic solvents to form gas-expanded liquids (GXLs) has recently been proven an effective means of improving mass transfer and gas solubilities in organic reactions.[16-18] GXLs possess physical properties intermediate between liquids and supercritical fluids, with some of the advantages inherent in each. GXLs represent an exciting new area of homogeneous catalysis.

We have developed **O**rganic-**A**queous **T**unable **S**olvents (**OATS**),[16,19] where cheap, benign, and easily-separable CO_2 is used as an antisolvent to separate a miscible mixture into an aqueous phase and a gas-expanded organic phase. Although little CO_2 dissolves in water, it is quite miscible with most organics, and radically lowers the solvent power of the organic phase for ions and other polar compounds.[15] This permits ready dissolution of hydrophobic substrates in the organic-aqueous mixture for reaction, and facile separation of hydrophobic products and unreacted substrate with the gas-expanded liquid after CO_2 addition. The use of a hydrophilic catalyst permits facile recycle with the aqueous phase. We control the quality of the phase split and the partition values by adjusting the CO_2 pressure. Finally, after decantation of the gas-expanded organic phase, depressurization permits CO_2 recycle and simplified product purification. (see Figure 2) Note that CO_2 will be present only during the separation stage of the OATS process. Therefore, any effects of CO_2 on system phase behavior, system pH or substrate/catalyst solubility will not affect the reaction chemistry. Additionally, the pressures required for separation (20-50 bar) are usually *lower* than those employed in the reaction (50-200 bar).

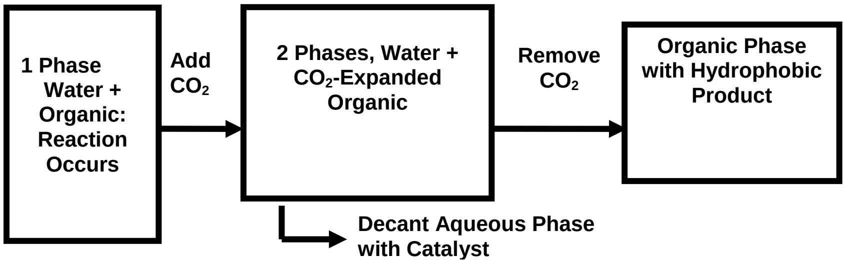
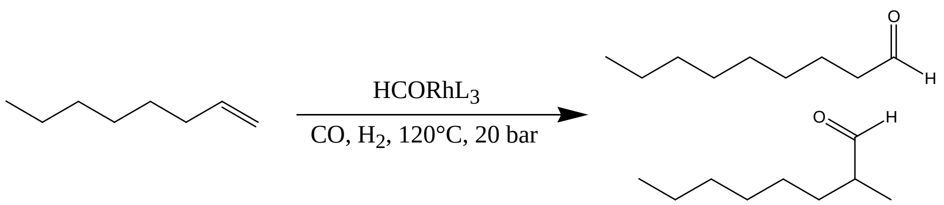


Figure 2. Diagram of OATS Process.

The OATS concept was tested on the catalytic hydroformylation of 1-octene, a very hydrophobic substrate. (Scheme 1).



Scheme 1. Hydroformylation of 1-octene.

This reaction was selected as a “proof of principle” for this technology because it has previously been shown to be inactive for traditional aqueous biphasic systems.[20] The catalyst used was a Rh/TPPTS complex, the water soluble catalyst used industrially in the Rhône Poulenc/Ruhrchemie process.[21]

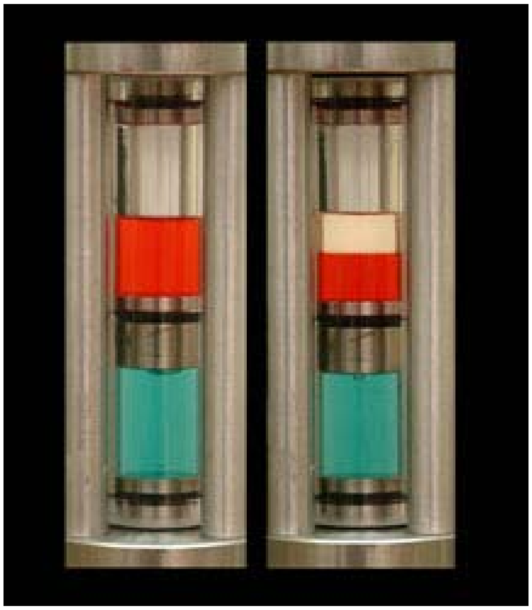
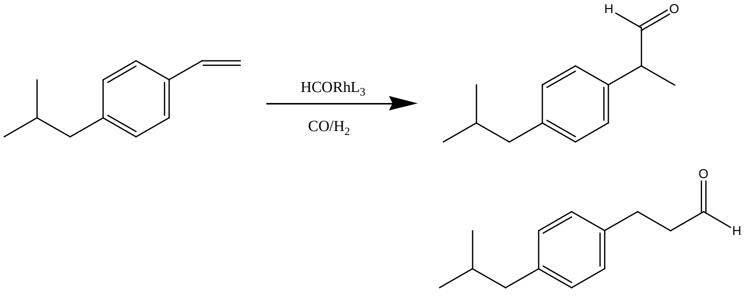


Figure 3. Left side: Miscible Solution of THF/Water at 1 bar. Right side: phase separation at 30 bar CO_2. The partition coefficient of the water-soluble dye (red) is greater than 10^6!

In this example, we started with a single homogeneous phase of tetrahydrofuran and water, which has the advantage of dissolving both hydrophobic and hydrophilic species. After the reaction occurs in this single homogeneous phase, addition of just one percent CO_2, which requires less than 10 bar pressure, causes the split of into one phase rich in water and another rich in tetrahydrofuran. Again the aqueous phase, with catalyst, is readily decanted and subsequent depressurization returns the organic phase with the product free of catalyst. Since CO_2 and water form two distinct phases, we would expect the partitioning of solute to depend on the nature of the solute, with polar and hydrogen-bonding molecules and salts to favor the water phase, and non-polar molecules to favor the carbon dioxide phase. What we were not expecting was the magnitude of partitioning that we found. To show the enormous change in distribution coefficient possible with this method, we show Figure 3, where a THF/Water mixture at 1 bar contains a colored hydrophilic catalyst surrogate. At only 30 bar, the separation observed is better than a factor of 10^6!

We are now using the OATS technology for the catalytic hydroformylation of hydrophobic olefins. It is important to note that the dependence of the linear to branched (L:B) ratio on syngas pressure is different for different substrates. Aliphatic olefins, such as propylene or 1-octene, are desired for the potential formation of straight-chain aldehydes for use as chemical feedstocks or fragrance compounds (butyraldehyde or pelargonaldehyde) and thus a high L:B is desired. Aromatic olefins, such as 4-isobutylstyrene or (5-methxoy-1-naphthyl)ethylene, are often used to make pharmaceuticals or pharmaceutical precursors (ibuprofen or naproxen). For these substrates a low L:B ratio is desired. While several different substrates of each type will be tested for substrate specificity, 1-octene and 4-isobutylstyrene will serve as model reactants of each type for detailed optimization.



Scheme 2. Hydroformylation of *p*-isobutylstyrene.

We also measure distribution coefficients for the catalysts in we have two experimental apparatus. For solutes that absorb in the UV-Visible spectrum, we use *in situ* spectroscopy, similar to one we have used for fluid-polymer partitioning.[22] We use a high-pressure optical cell with two parallel paths as shown in Figure 4. Liquid and solute are added to the cell, and then the cell is pressurized with CO_2. The concentrations in each phase are then calculated from the UV-Vis absorption peak. For cases where the partition coefficients are very large, are able to measure only the concentration in the more dilute phase, and then calculate the concentration in the other phase from mass balance.

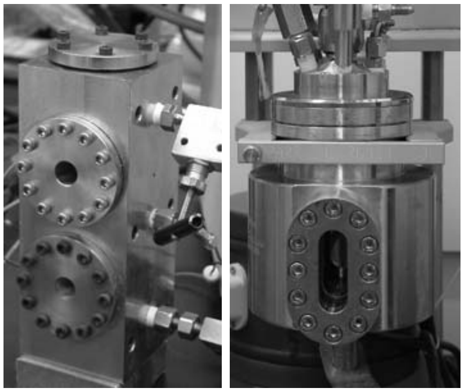


Figure 4. Parallel path high-pressure optical cell (left). Windowed Parr autoclave (right).

For substrate and product partitioning, we use a 300 mL windowed-Parr high-pressure vessel shown in Figure 4. We have sample dip tubes at various depths. Through the window, we can be sure which phase we are sampling from. The samples will then be analyzed by gas chromatography.

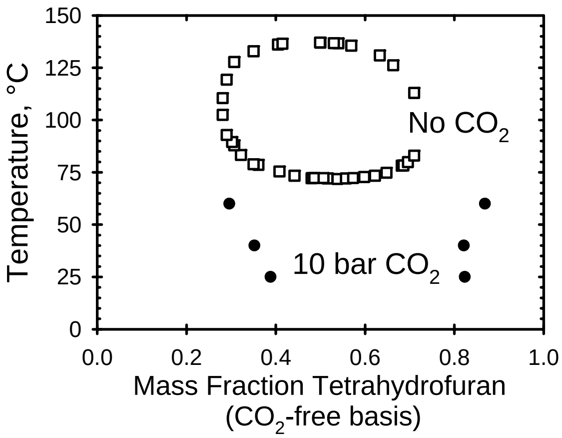


Figure 5. Liquid-liquid phase boundaries for THF/Water. Squares are the data of Matous et al,[23]; circles have been measured by us.[15]

One solvent system we use is THF-water. THF is an inexpensive, relatively benign and nonreactive solvent which is completely miscible with water at ambient temperature; it has in fact a lower critical solution temperature (LCST) at about 70°C. However, very modest CO_2 uptake will cause liquid-liquid phase separation. The onset occurs with only about 2% CO_2 in the liquid and just 10 bar will reduce the LCST to around 0°C. (see Figure 5)

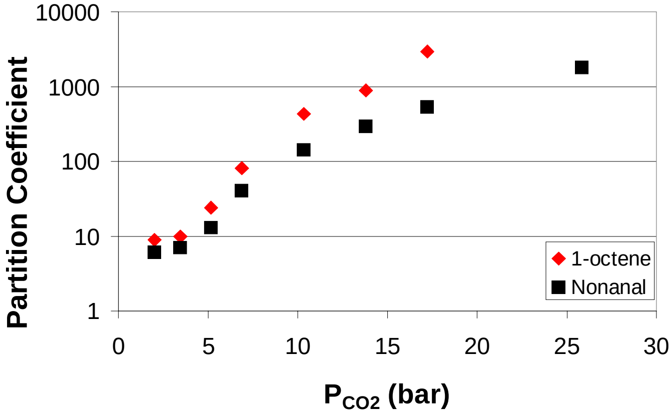


Figure 6. Partitioning of 1-octene[15] and nonan-1-al between GX-THF and water vs. CO_2 pressure.

The dilute partitioning of 1-octene and nonan-1-al between the water rich and organic rich phase was measured as a function of added carbon dioxide in the carbon dioxide + tetrahydrofuran + water ternary system. At low pressures the concentration of 1-octene is 10 times greater in the tetrahydrofuran-rich than in the water-rich phase and increases to 3000 times greater at a pressure of 17 bar. The nonanal partitioning was similar, with the partitioning varying from 8:1 at low pressure up to 2500:1 at 26 bar. (see

Figure 6) The addition of small amounts of carbon dioxide was reported to cause a large change in water content in the two equilibrium phases, which greatly affects partitioning. These data establish that the recovery of the hydrophobic products and unused reactants from the reaction mixture will be greatly simplified by the CO_2 addition. The CO_2 pressure required for 99% recovery of nonanal (7 bar) was much lower than the syngas pressure during the reaction (31 bar). These modest pressure requirements demonstrate the feasibility of this technique for industrial separations.

The OATS technology represents an important step toward advanced energy efficient, renewable and pollution prevention technologies for reaction systems and processes. This technology provides an opportunity to combine all the advantages of homogeneous catalysis (catalytic efficiency and reduction of waste byproducts) with heterogeneous separations (easy recovery of catalysts and reduced catalyst waste).

Pollution prevention comes from the following sources:

- Reduced emissions of volatile organic compounds (VOCs) through a reduction in organic solvent usage
- Reduction in overall process waste by enabling usage of more highly active catalysts, eliminating some reaction steps
- Reduction of heavy metal waste through improved recovery of organometallic catalysts
- Reduction in byproduct waste through more selective catalysis
- 100% atom and 100% carbon efficiency in hydroformylation reactions

Reductions in energy usage proceed from the following sources:

- Reduced energy associated with solvent separation
- Reduced energy associated with byproduct separation
- Reduced energy associated with catalyst separation

In a typical industrial chemical process, separation costs consume 50-80% of the total operating costs. The use of CO_2 at moderate pressures to effect more efficient separations presents a major opportunity to improve energy efficiency. The development of efficient recycling techniques for homogeneous catalysts provides an opportunity to use more active and selective homogeneous catalysts in place of traditional heterogeneous catalysts. The proliferation of recyclable, highly active catalysts would reduce the waste associated with separation of byproduct mixtures and provide an opportunity to produce safer and more effective products. Additionally, the OATS technology reduces the amount of organic solvent needed for these separation processes, leading lower to VOC emissions. Since more than thirty million tons of VOCs are released annually, even a 10% reduction in these levels would have a significant impact on air quality. The reduction of waste associated with improved separations, along with increased catalyst recovery and 100% atom and carbon efficiency provide solid examples of the potential advantages of employing OATS to hydroformylations as a means of advancing pollution prevention and benign manufacturing in the chemical industry. The reduction in waste coupled with savings associated with reduced separations costs provides the potential for this technology to be both an economical and environmentally benign alternative to traditional chemical processing.

Aqueous biphasic catalysis represents a proven industrial technique for ensuring easy recovery of valuable organometallic catalysts. Organic-Aqueous Tunable Solvents (OATS) offers a means of applying the concepts of aqueous biphasic chemistry while overcoming the drawbacks associated with poor organic substrate solubility in water. We use OATS to improve the hydroformylation of hydrophobic substrate using aqueous catalysts. Homogeneous catalysts represent highly active and selective industrial catalysts, but poor recovery techniques have hampered widespread implementation. Through the application of OATS, the recovery of highly active homogeneous catalysts is greatly simplified. The lessons learned from theses studies will be applied to future investigations dealing with other reaction types – oxidations, telomerizations and carbonylations – and to asymmetric catalytic processes, including hydroformylations, hydrogenations and oxidations.

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