CARBON DIOXIDE AS A BENIGN SOLVENT FOR HOMOGENEOUS CATALYST RECOVERY AND RECYCLE

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A little learning is a dangerous thing;

Drink deep, or taste not the Pierian spring:

There shallow drafts intoxicate the brain,

And drinking largely sobers us again.

Alexander Pope

If we knew what it was we were doing, it would not be called research, would it?

Albert Einstein

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SUMMARY

We have successfully investigated the use of CO_2 as a miscibility switch to create an environment in which we can run a homogeneously catalyzed reaction while maintaining a heterogeneous separation. We explored the use of this technique with fluorous biphasic systems, a fluorous solid support, and aqueous biphasic systems.

In the case of the fluorous systems, CO_2 was added to induce solubility of the fluorous catalyst. When the reaction was completed, CO_2 was vented and the system returned to a biphasic state, making the separation easy.

For the aqueous biphasic systems, the organic phase is chosen such that it is fully miscible with water at ambient conditions. Examples include acetonitrile, THF, and dioxane. The addition of CO_2 reduces the polarity of the solvent and causes a phase split. The recovery of the water-soluble catalyst is once again heterogeneous.

The application to aqueous biphasic systems is the most exciting studied. Aqueous biphasic systems are used industrially in the hydroformylation of propylene. With our technique, these systems can be extended to more hydrophobic substrates. We have shown a rate increase of 65 fold and 99% product recovery at modest pressures for the hydroformylation of 1-octene.

These aqueous biphasic systems also show much promise in the arena of enzyme catalyzed reactions. We can create an environment in which the enzyme kinetics will no longer be mass transfer limited.

CHAPTER I

INTRODUCTION

One major concern for industry and researchers alike is that of homogeneous catalyst recovery. With a push for greener processing and a need for greater product purity, any metal loss to waste streams must be avoided. The concern with homogeneous catalysts is that they are difficult to recover, but heterogeneous catalysts (which are easier to recover) tend to have lower, variable activities and selectivities. It is also far easier to modify a homogeneous catalyst for a given process by changing the ligands.

For these reasons, many researchers are currently investigating methods involving tradeoffs between activity and recovery. We investigate the use of CO_2 to manipulate phase behavior to allow for a truly homogeneous reaction while maintaining a heterogeneous separation.

We've improved upon the fluorous biphasic system in Chapter III. We can add CO_2 to a system of 2 immiscible liquids, a fluorocarbon and an organic solvent, to make the system monophasic. Since the catalyst used is tagged to impart selective fluorous solubility, making the system monophasic brings the catalyst into contact with the reactants. Once the CO_2 pressure is removed and the phases split, the catalyst returns to its sequestered state in the fluorous phase.

The properties that made fluorous solvents so attractive are proving to be its downfall. Fluorous solvents are highly inert and nonflammable. Once you are done with them, they're extremely difficult to dispose of. If any of the fluorous solvent makes it into the environment, the fact that they are so inert can lead to bioaccumulation. In Chapter IV, we replace the fluorocarbon solvent with a solid fluorinated phase to selectively trap fluorinated catalysts.

Chapter V gives a brief introduction of **O**rganic **A**queous **T**unable **S**olvents. This chapter includes partitioning data and a pH of study of dissolved CO_2.

In Chapter VI, we show how OATS systems can be used to improve upon current work in aqueous biphasic systems. We chose the hydroformylation of 1-octene to show the applicability of these systems for a much broader class of substrates than the current aqueous biphasic system.

Chapter VII has recommendations on future directions in the same vein as the experiments presented here. The OATS systems presented in Chapters V and VI are the most promising by far. Industrially relevant reactions are outlined for these systems.

CHAPTER II

BACKGROUND

Various approaches have been taken in order to work towards homogeneous activities with heterogeneous catalysts or facile separation of homogeneous separations. This background sections breaks these approaches into three main categories (overcoming mass transfer, heterogenization or supported catalysis, and biphasic operation) even though some approaches can fit more than one heading. Examples and caveats are given for each heading. This is merely meant to give the reader an idea of the wide array of techniques that are currently being explored.

Overcoming Mass Transfer Limitations

One of the biggest drawbacks to heterogeneous (or otherwise biphasic) catalysis is the mass transfer limitations inherent to the system. This section deals with approaches that have started on the heterogeneous side and worked towards homogenous activities by overcoming some of the mass transfer limitations.

Phase Transfer Catalysis (PTC)

Phase transfer catalysis is used to overcome mass transfer limitations on a reaction involving immiscible reactants, normally an organic substrate and an anionic reactant. A phase transfer catalyst is typically a cation with bulky organic groups designed to pull the anion reactant into the organic phase, which usually has low polarity and would be unable to support salts on its own (Kalck 1998). The PTC must also allow enough charge separation between the anion and itself so that the anion is free to react.

While PTC processes are very industrially significant, they generally involve the formation of an unwanted salt as a by-product, which poses environmentally unfriendly disposal issues.

Catalyst recovery can also be fairly expensive and involve several extraction phases (Hanson 1998). The last traces of the catalyst are often the hardest to remove, but the removal is crucial to pharmaceutical processing and products that may be sensitive to the catalyst. Xie et. al. (Xie, Brown et al. 2002) have shown that the partition coefficient of the PTC can be greatly affected with variations in CO_2 pressure. Since PTCs are salts, the addition of CO_2 will force them into the aqueous phase. This approach can greatly decrease the number and volume of aqueous washes needed in order to obtain decent product purity.

In an interesting and recent twist on PTC, β-cyclodextrin cups are used in aqueous biphasic systems to shuttle hydrophilic reactants into an aqueous phase where the reaction takes place. Monflier has shown that the use of these cups can enhance the rate by a factor of 2 to 10(Monflier, Fremy et al. 1995). The β-cyclodextrin cups were used in a ratio of 14:1 to the metal center. This is almost three times the amount of ligand present and represents a large cost for the process. The technique is quite effective at sequestering the metal from the product in the organic phase, but the loss of cyclodextrin to the product stream will be costly in the long run.

“Promoter” Ligands

In many liquid-liquid biphasic systems, the catalyst is preferentially soluble in one liquid phase and the products and reactants in the other. The reaction rate, therefore, is vastly affected by any change in the solubility of the reactant in the catalyst phase. One group decided the best way to overcome this was with the use of what they call promoter ligands (Chaudhari, Bhanage et al. 1995), or ligands that are soluble in the organic (reactant) phase instead of the aqueous (catalyst) phase. Triphenyl phophine was added to aqueous biphasic system catalyzed by a rhodium triphenylphosphine tris-sulfonated salt complex. Chaudhari et. al. witnessed a rate enhancement of 10 to 50 fold depending on the amount of promoter ligand added. It seems that the promoter ligands should work by bringing the catalyst into the organic phase, but the authors claim there was no measurable metal leaching.

In a similar approach, Hanson’s group is investigating the use of the amphiphilic ligands. These ligands are designed to be surface active by including long alkane chains on water-soluble ligands. Hanson’s group found increased reaction rates for 1-octene, but rates dropped off again for longer chain alkanes (Hanson 1998). Although catalyst leaching is not discussed, the modifications to the ligand that make them surface active will also increase their solubility in the organic phase. This increased solubility could lead to loss of metal.

Supported Catalysts

Supported catalysts are homogeneous catalysts that have been modified to become heterogeneous. The metal centers are bound to a recoverable support in some fashion instead of only associating with free ligands.

Catalyst Tethering

One approach to supporting catalysts is to fix the catalyst on a solid support, or catalyst tethering. The most common catalyst supports are organic polymers, silica, and aluminum oxide. Catalyst tethering typically becomes a balancing act between preventing the leaching of metal centers off of the support and maintaining sufficient activity and selectivity for industrial applications (Monteil 1994). In order to maintain activity the catalyst is typically only bound to the surface by one ligand. The problem arises during the catalytic cycle when one ligand must be released so that the metal center can complex with the reactant(s) (Katritzky 1990). If the ligand released is the ligand tethering the catalyst, the metal center dissolves in solution and the process is faced with a separation of a homogeneous catalyst. In order to ensure this doesn't happen, attempts have been made to attach the metal center to more than one ligand on the surface, this unfortunately makes the metal less accessible to larger reactants and therefore unusable in some processes (Katritzky 1990).

Supported Aqueous Phase Catalysis

In this newer method of making homogeneous catalysts heterogeneous first reported by Arhancet et. al. (Arhancet, Davis et al. 1989), a silica surface must be carefully wetted so that only a thin layer of water is adsorbed on the hydrophilic surface. The water at the surface is then impregnated with a water soluble catalyst. Too much water (>67 wt.%) is reported to cause catalyst instability since water is lost to the reaction solvent.

SAP improves upon the reaction rates in biphasic systems due to the greatly increased surface area. However, there are many more mass transfer steps to overcome and understand (Jauregui-Haza, Pardillo-Fontdevila et al. 2003). For any gas-liquid reaction, the gas and reactant will both have to diffuse into the second liquid phase.

For water sensitive reactions, ethylene glycol can also be used as the immobilized liquid phase. Calcium phosphate has also successfully been used as the hydrophobic support (Dessoudeix, Jauregui-Haza et al. 2002).

Dendrimers

Dendrimers are a highly symmetric class of macromolecules with potentially interesting applications in catalysis. Due to their highly branched, repetitive nature, one molecule can have many sites for metal bonding. If the interior sites are used for catalysis, the dendrimer can act as a size selective sieve for the reaction (Niu 2001). Since they are macromolecules, they can be recovered easily by membrane separation or precipitated out of solution easily and recovered by filtration.

Dendrimer "branches" have also been grafted onto solid supports for easier recovery (Bourque, Maltais et al. 1999). In this case, the ends of the branch are acting as catalyst ligands. This approach is just a more expensive version of conventionally tethered catalysts. Dendrimers are also costly to produce since it becomes more difficult to purify at higher generations. There appears to still be a great risk for metal leaching.

Polymer Bound

Another option is to reversibly bind the active metal center to a high molecular weight polymer that can be filtered out after reaction completion. Ahmed et. al. explored the use of a catalyst such as this for olefin metathesis (Ahmed, Barrett et al. 1999). The metal center will dissociate from the polymer to begin its catalytic cycle and the metal can be trapped again after the reaction is complete. The group was able to reduce the ruthenium in the final product to 55 ppm through filtration, evaporation, and chromatography. The reaction rate, however, could only be maintained for the first two runs. The reaction rate in the third run fell off dramatically. Styrene had to be added to the reaction mixture to keep the catalyst from decomposing in the absence of substrate.

Bergbreiter on the other hand, uses polymeric ligands with thermal dependent solubilities (Bergbreiter 1987; Osburn and Bergbreiter 2001). Polyethylene oligomers are soluble at elevated temperatures and can be filtered out of solution at room temperature. Poly(alkene oxide) block copolymers and poly(N-alkylacrylamides) exhibit inverse temperature-dependent solubility. These ligands are soluble in aqueous solutions at or below room temperature. They will come out of solution at higher temperatures.

Bergbrieter has successfully shown that his thermomorphic ligands can isolate metals and that his catalytic conversions show no decreases over three cycles (Bergbreiter, Osburn et al. 2001).

Biphasic Systems

Biphasic operation involves minimal thermal stress and the least costly recycle (Cornils and Herrmann 1996). Many biphasic systems consist of two immiscible liquids. The catalyst will preferentially soluble in one liquid phase and the reactant in the other. This type of system is quite efficient for catalyst recovery and recycle. The reaction rate, however, tends to suffer from mass transfer limitations.

Aqueous Biphasic

The most famous of all aqueous biphasic systems is that of the Ruhrchemie/Rhône-Poulenc (RCH/RP) process. The RCH/RP process is the industrial hydroformylation of propylene under biphasic conditions. The catalyst remains in an aqueous phase, while the reactant is in an immiscible organic phase. This is approach is quite elegant, but is really only applicable for lower molecular weight olefins. As the chain length increases, the solubility of the olefin decreases as does the reaction rate. For this reason, many of the approaches above have been tried to increase the reaction rate of long chain olefins. This approach has also been used industrially for various other reactions (Cornils 1998).

Fluorous Biphasic

Fluorocarbons have many properties that make them attractive for synthesis; they are inert, apolar, and thermally stable (de Wolf, van Koten et al. 1999). At room temperature, they are typically immiscible with organics. The fluorous biphasic system will utilize a ‘fluorinated’ catalyst that is preferentially soluble in the fluorous phase.

Upon heating, many fluorous solvents will become miscible with the organic phase allowing the reaction to run homogeneously (Horvath and Rabai 1994). Cooling the reaction mixture will cause a phase split allowing for an easy separation of the products from the catalyst.

Fluorinated solvents are also very expensive and environmentally persistent due to their chemical inertness. Many of these thermomorphic systems will have measurable miscibilities meaning small amounts of fluorous solvents can be lost during each separation. The fluorinated catalyst can also be lost with any lost fluorocarbon.

You can see that the different approaches taken are almost as numerous as the number of researchers. The end goal in all cases is to somehow obtain both homogeneous and heterogeneous catalyst benefits. There are always tradeoffs between the benefits gained and the downside to the approach. A decision on how to proceed is done by weighing the drawbacks inherent in the approach to what will be gained.

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CHAPTER III

USE OF SUPERCRITICAL CARBON DIOXIDE TO IMPROVE FLUOROUS BIPHASIC CHEMISTRY

Introduction

The use of supercritical CO_2 (*sc*CO_2) in fluorous biphasic systems can allow us to achieve miscibility of solvents without the need to heat the system. By applying CO_2 pressure to a fluorous-organic biphasic system, the two phases will become miscible, thus allowing the reactants to come in contact with the catalyst. With the removal of CO_2 pressure, the system will return to its original biphasic state allowing for a simple separation (Figure 3-1).

A fluorous biphasic system typically consists of an organic phase containing the reactants and a fluorous phase containing the catalyst. Fluorous biphasic chemistry is of particular interest to the academic community since the catalyst phase can be made miscible with the reactant phase at higher temperatures (Horvath and Rabai 1994). This temperature dependent miscibility will allow the reaction to proceed with all the benefits of a homogeneous catalyzed reaction, while retaining the easy catalyst recovery indicative of a biphasic system.

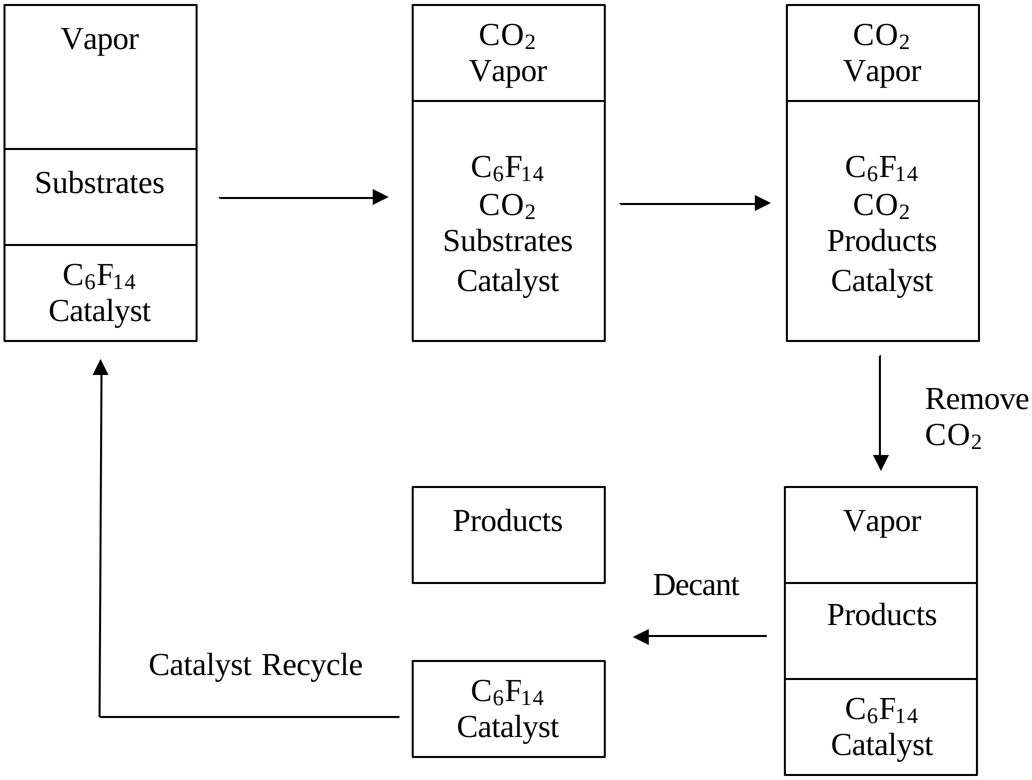

Figure 3-1 Fluorous biphasic made monophasic reaction scheme

To render the catalyst preferentially soluble in the fluorous phase, one must “tag” the catalyst with fluorous moieties (Horvath 1998). Horvath considered the most effective fluorous tags to be perfluoroalkyl chains (linear or branched) with high carbon numbers. However, it has been our experience that high molecular weight perfluoropolyethers impart better solubility in fluorous solvents.

This temperature-dependent approach, however, is not without drawbacks. In order to access this desired miscibility at a reasonable temperature, the fluorocarbon solvent will likely have a measurable mutual miscibility with the organic phase. This mutual miscibility can lead to the loss of the fluorous solvent, as well as the leaching of catalytic species. For instance, in the hydroformylation of 1-decene (Horvath and Mozelski 1998), a consistent 0.5% loss of rhodium is seen over nine runs. In some systems of interest, up to 14% loss of a toxic catalyst is measured (Barthel-Rosa and Gladysz 1999). If the product is thermally labile or the temperature must be kept low to prevent side reactions, this approach would not be suitable.

One example of the phase split with *sc*CO_2 is shown in Figure 3-2. The system consists of a fluorous tagged cobalt catalyst sequestered in FC-75. As seen in the picture furthest to left, the catalytic phase is fully immiscible with that of toluene. With the addition of 33 bars of CO_2, the phases become fully miscible; when the CO_2 pressure is removed, the system returns to its original biphasic state. The ease of this biphasic separation helps reduce the energy consumption of industrial processes. Decantation is a mechanical process; therefore, the energy costs are lower than for other types of separation such as distillation and evaporation (Ulrich, 1984).

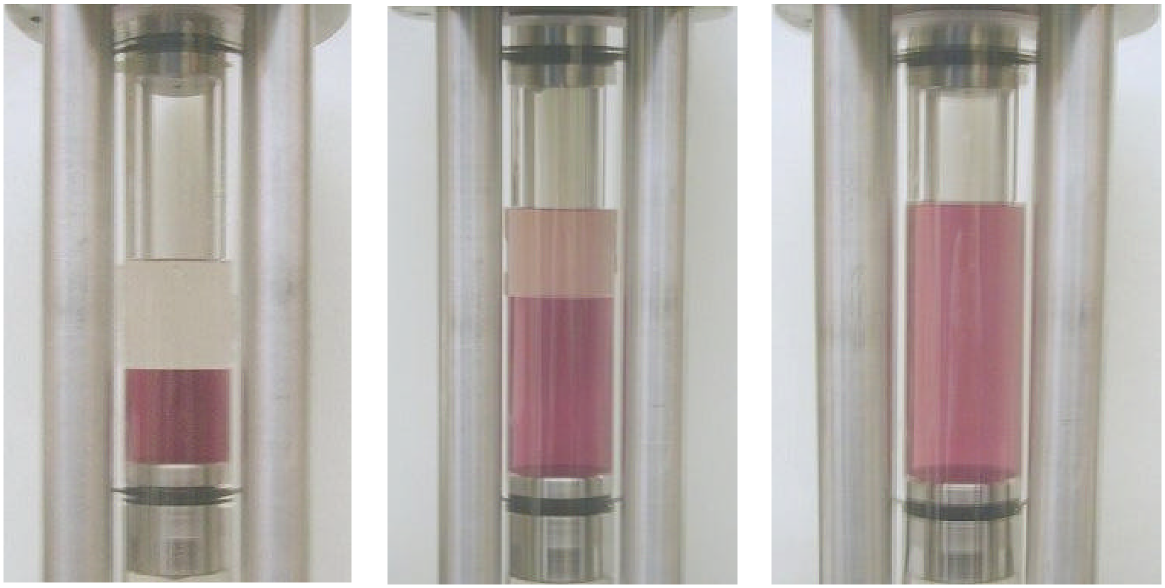

Figure 3-2 Phase miscibility with CO_2 pressure

In addition, the use of *sc*CO_2 will increase the gas solubilities in our reaction system. This enhanced solubility will decrease the mass-transfer limitations in gas-liquid reactions, thereby improving upon reaction rates seen in systems involving gas-liquid reactions. Using these fluorous biphasic systems may also eliminate the need for any organic solvent. The ideal system for this work would consist of a high molecular weight fluorinated solvent, and the organic phase would simply be the neat reactant.

Experimental Materials

All organic chemicals used in the experiments were HPLC grade, obtained from Sigma-Aldrich Chemical Co. and not further purified. SFC Grade carbon dioxide (99.99%) was obtained from Matheson Gas Products. The CO_2 was further purified to remove trace water using a Matheson (Model 450B) gas purifier and filter cartridge (Type 451). UHP grade hydrogen and was obtained from AirGas and used as received. FC-40 (95% perfluorotributylamine) and FC-75 (90% perfluoro-1-butyltetrahydrofuran) were obtained from 3M. Perfluorohexane (99%) was obtained from Sigma-Aldrich.

Apparatus and Procedure

Phase Behavior Apparatus.

A schematic of the phase behavior apparatus is shown in Figure 3-3. The viewable high-pressure cell used was a 60 ml Jerguson gauge mounted on a rotor arm to facilitate mixing. Graphite seals were used in all experiments. All degassed organic and fluorous liquids were added from evacuated 100 mL Whitey pressure vessels using a gas-tight SGE luer-lock syringe and 316 stainless steel HiP valves. The CO_2 was supplied by a high-pressure syringe pump (Isco, Inc., Model 500D) through stainless-steel tubing (3.18 mm OD and 1.52 mm ID) to HiP valves at one end of the boiler gauge. An HiP hand syringe pump was used to increase or decrease the volume in the system through the same valve. The air bath was constructed from ½” thick sheets of 20” x 24” polycarbonate. The air bath temperature was monitored using an Omega K-type thermocouple accurate to ±0.1 °C and controlled using an Omega CN76000 PID controller. Pressure was measured using a Druck DPI 260 gauge with PDCR 910 transducer having a range of 0-20 MPa and calibrated to an accuracy of ±0.01 MPa.

Reactor Apparatus.

Figure 3-4 is a schematic of the reaction apparatus. The reactor was a stainless-steel batch reactor (Parr Instrument Company, Model 4561) with a maximum working pressure of 208 bar and a maximum working temperature of 350°C. Stirring was provided by a magnetic drive (Parr Instrument Company, Model A1120HC) equipped with an impeller. The seal between the stirrer and the reactor was made with a teflon gasket, and the seal between the reactor body and the reactor head was made with a flat Teflon gasket held in a confined recess in the reactor head. The internal volume of the reactor was determined to be approximately 305 mL by filling the reactor with a known mass of pure CO_2 and measuring the pressure at several temperatures.

A PID temperature controller and tachometer (Parr Instrument Company, Model 4842) were used to control the temperature of the reactor to ± 1°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 housed in an aluminum shell. A digital pressure transducer (Heise, Model 901B) was used to monitor constantly

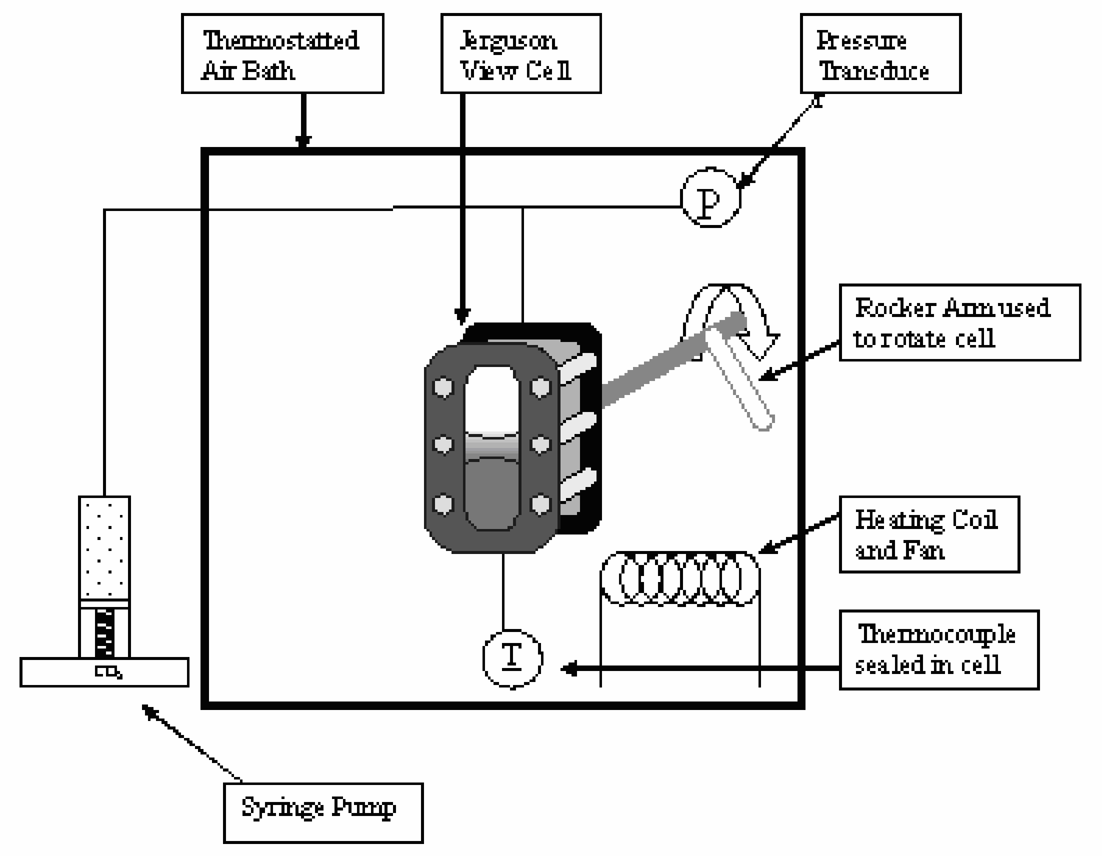

Figure 3-3 Schematic of the apparatus used in all phase behavior measurements.

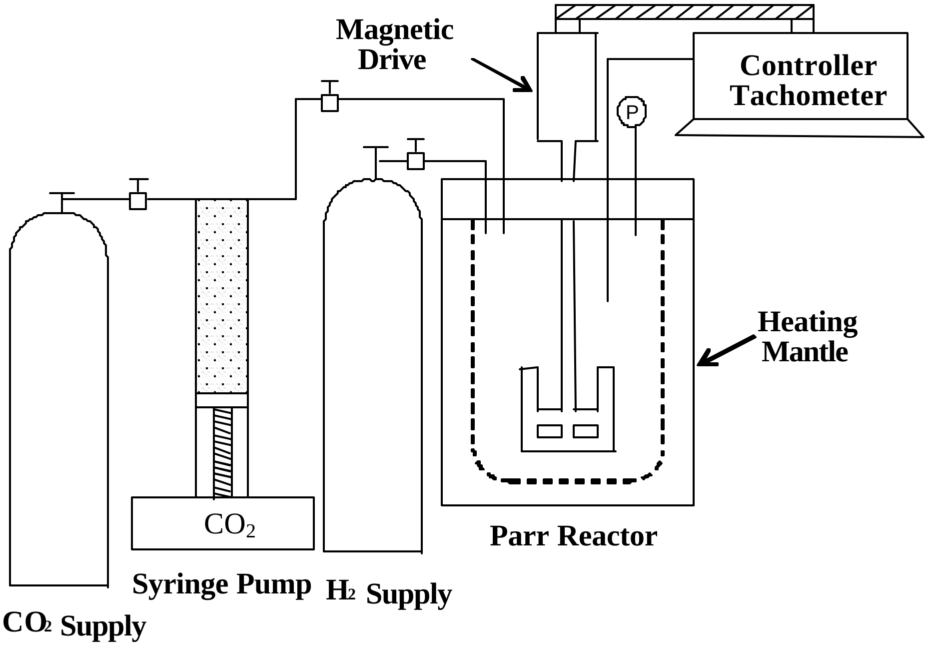

Figure 3-4 Schematic of the reactor.

the reactor pressure, and a safety rupture disk, made of Inconel, was used to ensure the pressure in the reactor remained below the reactor pressure rating.

The Parr reactor was modified by replacing all of the standard valves and fittings with low volume HiP valves and fittings to decrease the reactor dead volume. The CO_2 was supplied by a high pressure syringe pump (Isco, Inc., Model 500D) through stainless steel tubing (3.18 mm OD and 1.52 mm ID) to one inlet port on the reactor head. H_2 gas was added to the reactor through stainless steel tubing (3.18 mm OD and 1.52 mm ID) to a second inlet port. All liquids were added to the vessel immediately prior to sealing.

Fluorous G4-PAMAM Dendrimer Synthesis.

This synthesis follows that described in the literature (Chechik, 2000, JACS). 0.0001 moles of G4-PAMAM dendrimer were dissolved in 20 ml of water in a 125 ml Erlenmeyer flask. 0.001 moles of K_2PdCl_4 (10:1 Pd:dendrimer) were then added to the mixture. 0.1 M HCl was added and the solution pH monitored until a value of approximately 2 was achieved. Under these conditions, the terminal amine groups of the PAMAM dendrimer are protonated, and the Pd^{2+} ions are solvated through specific interactions with the *interior* amine groups only due to protonation of the 64 terminal amines. Addition of 0.006 moles aqueous $NaBH_4$ (5 molar excess) reduced the Pd^{2+} to Pd^0 nanoparticles in the center of the dendrimer. 0.1 M aqueous KOH was next added to neutralize the acid and bring the solution pH to approximately 7. According to Crooks (Chechik, 2000, JACS), the size of the nanoparticles encapsulated within the dendrimer is easily controlled by the molar ratio of the metal salt to the dendrimer. A 10:1 loading creates Pd^0 particles that are an average of 10 molecules (approximately 4.5 nm) in diameter. 0.096 moles of Poly(hexafluoropropylene oxide-co-difluoromethylene oxide) carboxylic acid were dissolved in the aqueous solution to complex with the 64 terminal amines (plus 50% excess), creating fluorous quaternary ammonium salts. The mixture was allowed to stir for 30 minutes.

The (brown) contents of the flask were then transferred to a 125 ml separatory funnel. Next, approximately 5 ml of FC-40 were added to the funnel, which was shaken vigorously for 5 minutes. The phases were allowed to separate for 1 hour and the characteristic brown palladium color was observed only in the FC-40 phase. Additional FC-40 was added to the recovered fluorous phase to obtain a catalytic solution of the desired concentration.

Hydrogenation Procedure.

5 mL of allyl alcohol was added to the Parr reactor. 0.73 mL of a 200mM solution of the G4-PAMAM dendrimer catalyst was then added. FC-40 was added to bring the total volume in the Parr to 40 mL. Hydrogen gas was added in 100% excess (roughly 14 – 15 bar). In the case of the homogeneous reaction, CO_2 was then added to bring the total pressure up to 83 bar. The stir rate in the reactor was kept at 750 rpm during the addition of CO_2 to insure the complete dissolution of gaseous CO_2 into the reaction mixture. To maintain consistency, the biphasic reaction was also stirred at 750 rpm for a comparable time at the beginning of the reaction. In both cases, the stir rate was then reduced to 250 rpm and allowed to proceed for the specified time period.

Experimental Results

As discussed elsewhere (West, Hallett et al. 2004), miscibility of organic and fluorous phases is mostly dependent on the solubility of CO_2 in the organic phase. As CO_2 dissolves in both phases and they both become CO_2 rich, the two phases will merge. In order to estimate the solubility of allyl alcohol with FC-40, we looked at data that was readily available. Following the trends in Table 1, it appears that allyl alcohol should behave most like ethanol. Using the phase data of West and Hallett (West, Hallett et al. 2004) (Table 2) with that prediction, the miscibility pressure of the allyl alcohol / FC-40 system was estimated to be at least 60 bar.

Table 3-1 Solvent Properties of Selected Solvents

	Allyl Alcohol	Methanol	Ethanol	Acetone
T_c <K>	545.1	512.5	514	508.2
P_c <bar>	56.2	80.84	61.4	47.01
ν	68.5	40.6	58.6	73.8
δ <cm^3/mol>	25.7	29.44	26.14	19.73
ε	21.6	32.7	24.6	21.4

To ensure our reaction was actually monophasic at our desired conditions, initial experiments were done in a windowed Parr reactor. The reactor was loaded with 5 mL allyl alcohol and 35 mL of FC-40. 14 bar of hydrogen pressure was added, and CO_2 was added to bring the pressure to 60 bar. The system was allowed to reach equilibrium and the contents of the reactor were inspected to determine if the system had become fully miscible. More CO_2 was slowly added to the system and the contents were inspected periodically until we were satisfied the two phases were fully miscible. The final pressure of the Parr reactor at 83 bar was recorded and set as the experimental standard for the reaction runs.

Figure 3-5 shows the reaction scheme for the hydgrogenation of allyl alcohol to propanol and a schematic of the dendrimer core where the Pd nanoparticles reside. Reaction rates of the hydrogenation were measured via 20-minute batch experiments and are reported in turnover number (TON), or moles product formed per moles of catalyst and turnover frequency (TOF), or moles product produced per moles of catalyst per hour. Reaction runs were completed at 25°C to compare monophasic and biphasic reaction results. Reactions without catalyst were also run in order to determine the effect of the dendrimer catalyst. The results are shown in Table 3 below.

As seen in Figure 3-6, the monophasic system shows a 70% increase in turnover number and turnover frequency over the biphasic system. This increase in reaction rate seems to indicate that the monophasic system allows better mass transfer between the gas and liquid phases, as expected. However, we expected to see a greater increase than was observed due to the enhanced gas solubility of our monophasic system. One possible explanation for these results lies in the experimental method used, specifically, the use of stirring. One method of overcoming gas-liquid mass transfer limitations is to increase the stir rate. During the initial 7.5 minutes of the experimental runs, both systems were vigorously stirred. This high rate of stirring in the biphasic system helped to decrease the mass transfer limitations inherent to the system.

It does appear that our system had double the TOF. Chechik and Crooks (Chechik and Crooks 2000) found that the same catalyst had a TOF of 400. However, the reaction system the authors used was slightly different than the one used in this work.

Table 3-2 Miscibility pressures measured at 25 °C for three fluorous solvents: perfluorohexane, FC-75 and FC-40. (Dashed line = not measured)

Miscibilty Pressure (MPa) at 25°C

Solvent	$\mathbf{C_6F_{14}}$	**FC-75**	**FC-40**
Ethyl Acetate	1.65	1.78	2.57
THF	1.92	1.92	2.58
Chloroform	1.93	--	--
Acetone	2.15	2.37	3.04
Cyclohexane	2.64	2.69	3.40
Propionic Acid	2.74	--	--
Acetic Acid	2.76	--	--
Toluene	3.23	3.35	3.42
Decane	3.61		4.45
Acetonitrile	4.00	4.02	--
DMF	4.41	--	--
Nitromethane	4.42	--	--
Ethanol	4.44	--	--
Methanol	4.59	4.74	--
Decalin	5.39	5.77	--

Because of the variation between the two systems, a direct comparison between the two is difficult at best.

Summary

These findings prove that CO_2 can be used to improve fluorous biphasic chemistry. Using CO_2 pressure as a miscibility switch can extend the fluorous-biphasic concept to fluorous solvents possessing better processing properties while retaining facile catalyst recovery. These improved properties include reduced vapor pressuresand lower miscibilities with organic solvents. These physical properties are of particular importance since any miscibility with organic solvents will lead to loss of the fluorous solvent and potentially the fluorinated catalyst. The higher the vapor pressure of the fluorous solvent, the greater the potential for loss to the atmosphere. These losses should be avoided since fluorocarbons can act as greenhouse gasses. However, the boiling point of the fluorous solvent used in this work, FC-40, is around 14°C, making it undesirable for scaled up processes. The principle of the experiments remains the same for solvents with more attractive physical properties. Solvents with lower vapor pressures will simply require more CO_2 in order to experience the same phase behavior.

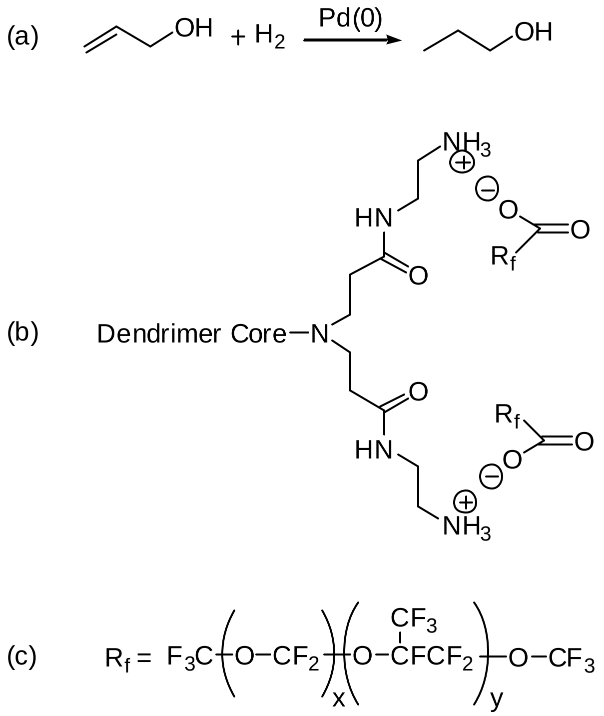

Figure 3-5 (a, b, & c) a) Reaction of allyl alcohol to n-propanol b) Depiction of dendrimer "branch" c) fluorous carboxylates.

Table 3-3 Reaction results for the hydrogenation of allyl alcohol to propanol at room temperature for 20min

Rxn Time (min)	Substrate:Catalyst	Solvent	% conv	ToN	ToF	P_{H2}	P_{Total}	System Type
20	No Catalyst	FC-40	3.6			210	1230	Monophasic
20	5000	FC-40	12	606	1818	210	1225	Monophasic
20	5000	FC-40	13	633	1898	210	1250	Monophasic
20	5000	FC-40	9.9	496	1487	215	1220	Monophasic
20	5000	FC-40	5	231	694	210	210	Biphasic
20	5000	FC-40	9	453	1358	210	210	Biphasic
20	5000	FC-40	5.3	265	795	210	210	Biphasic
20	5000	FC-40	7.5	375	1136	220	220	Biphasic
20	5000	FC-40	6.82	341	1022	210	210	Biphasic
20	5000	FC-40	7.5	374	1122	210	210	Biphasic

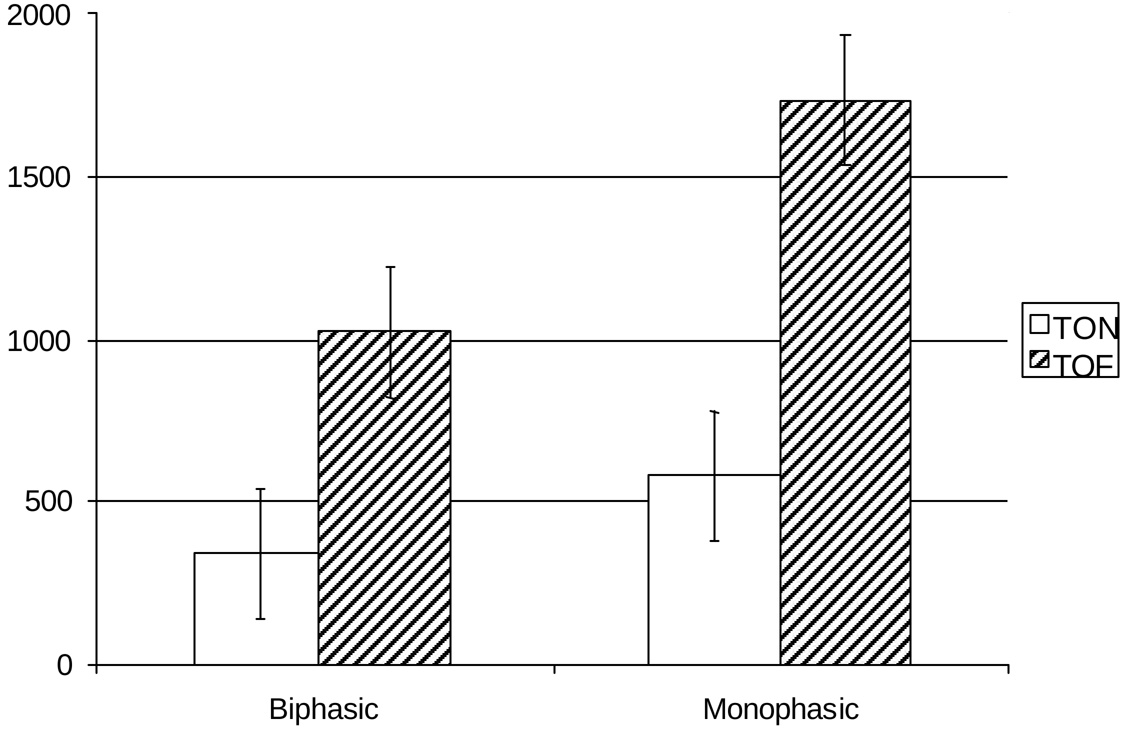

Figure 3-6 Comparison of catalyst efficiency in biphasic and monophasic systems.

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CHAPTER IV

USE OF MODIFIED SILICA AS A HOMOGENEOUS CATALYST SUPPORT

Introduction

Although the use of a fluorous phase for catalyst recycle (as discussed in Chapter III) can lead to a number of processing benefits, the disadvantages of this system must also be considered. Due to the strong nature of the carbon-fluorine bond, fluorocarbons are highly inert. This makes them unreactive but also environmentally persistent. This persistence can lead to the potential for bioaccumulation (Kannan, Franson et al. 2001). In addition, the high cost of fluorous solvents makes it desirable to eliminate the fluorocarbon phase.

The use of a modified silica support can allow us to maintain the processing benefits of the fluorous biphasic system without the downside of the costly solvents. By grafting high molecular weight fluorous tails onto a silica surface, we create a solid support that will behave in the same manner as the fluorous phase. The catalyst should easily partition on and off the surface allowing for a homogeneous reaction while preserving the heterogeneous separation.

Fluorinated catalysts are actually low melting solids, which can be exploited for catalyst recovery and recycle as was seen in a study done by Wende et. al.(Wende, Meier et al. 2001). After the reaction is completed, the mixture is cooled (<0°C) causing the catalyst to precipitate. The solid is then recovered and recycled with minimal loss in activity. While this is an excellent method, the cost of cooling and heating process streams and the difficulty in recovering such a small amount of solid would not make this process industrially viable. More complex catalysts can also be harmed during the crystallization process.

Zhang et. al. have proven the use of the fluorinated silica in chromatography (Zhang, Curran et al. 2002). The fluorinated silica is modified with perfluoroheptane groups (Curran, Hadida et al. 1997). While this level of fluorination is sufficient for chromatagraphic purposes, we decided to use high (~550 Da) molecular weight perfluoropolyethers to modify the surface. We felt this level of fluorination would act as a better surface to adsorb catalysts onto.

Instead of using temperature to vary miscibility of the catalyst, we have decided to use CO_2 pressure, since it is well known that fluorous molecules will dissolve in CO_2 (Carroll and Holmes 1998). CO_2 also offers processing benefits when used as a reaction solvent because it is easily removed by simple venting. We speculated that the previously mentioned fluorous catalysts should stick preferentially to the surface of the modified silica. This fact can be used to bring the catalyst off the silica surface into the reaction medium using CO_2 pressure allowing the catalyst to act homogeneously. The removal of CO_2 should allow the catalyst to redeposit on the silica surface allowing for a simple separation by filtration. Figure 4-1 shows how the model system should work.

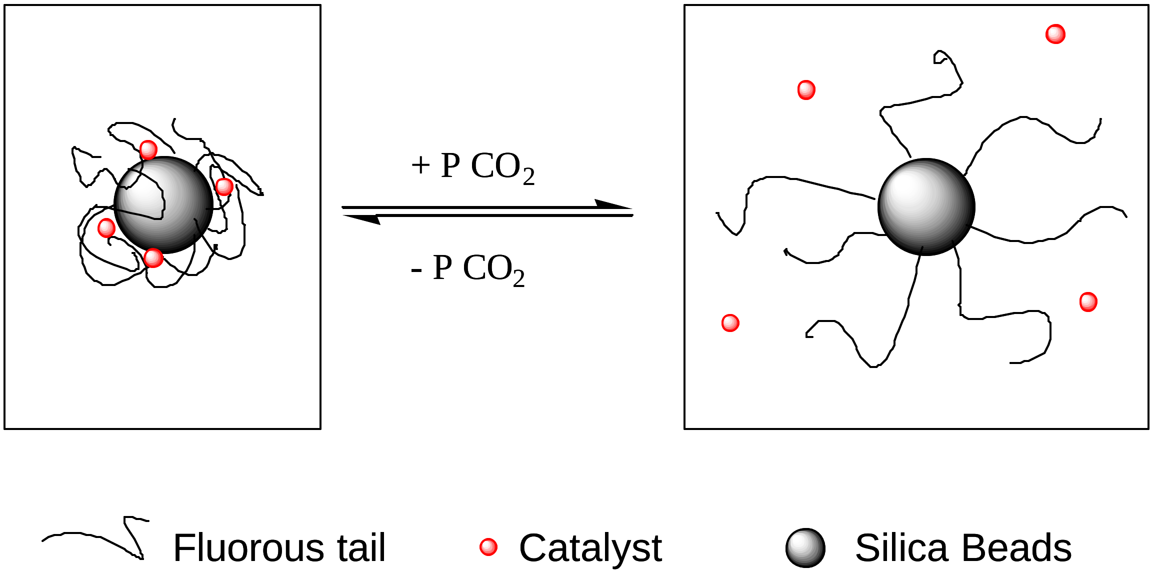


Figure 4-1 Depiction of catalyst shuttling

Experimental Materials

All organic chemicals used in the experiments were HPLC grade, obtained from Sigma-Aldrich Chemical Co. and not further purified. SFC Grade carbon dioxide (99.99%) was obtained from Matheson Gas Products. The CO_2 was further purified to remove trace water using a Matheson (Model 450B) gas purifier and filter cartridge (Type 451). UHP grade hydrogen and was obtained from AirGas and used as received. FC-40 (95% perfluorotributylamine) and FC-75 (90% perfluoro-1-butyltetrahydrofuran) were obtained from 3M. Perfluorohexane (99%) was obtained from Sigma-Aldrich. Low molecular weight (~550 Da) fluorous alcohols were used as purchased from Sigma-Aldrich. High molecular weight (~1750 Da) fluorous were used as purchased from DuPont under the trade name Krytox.

Apparatus and Procedure

Silica gel was modified in a two step process. A fluorinated alcohol $R_fCH_2CH_2OH$ (R_f = poly(hexafluoropropylene oxide) was reacted with $SiCl_4$ (alcohol:$SiCl_4$ = 2:1) for a week in stirred THF under nitrogen atmosphere. The HCl offgas was trapped in triethylamine/water. The $SiCl_2(OR_f)_2$ thus obtained was then reacted under nitrogen with normal silica gel for 5 days to produce the fluorous silica gel, which was washed repeatedly with water, perfluorohexane, toluene and methanol to remove impurities.

UV measurements were taken using a specially designed cell and a Hewlett Packard UV Model #8453. The UV response was calibrated at ambient conditions using solutions containing known concentrations of the solute of interest. The cell was loaded with the fluorinated silica, the compound of interest, and an organic solvent. For air sensitive compounds, this loading was completed under a nitrogen atmosphere.

The cobalt catalyst, $Co(O_2CR_f)_2$ (where R_f is a perfluoropolyether tail), was prepared from $Co(ClO_4)_2$ and poly(hexafluoropropylene oxide-co-difluoromethylene oxide) monocarboxylic acid (MW=550) in an analogous manner to the method of Vincent et al. (Vincent, Rabion et al. 1997) for the preparation of $Co(O_2C_2H_4C_8F_{17})_2$. Elemental analysis Obsd.: C 21.3%, H 0.2%, Co 4.8%, F 56.6%, O 17.1%. Calcd. for an approximate formula of $C_{20}H_2CoF_{36}O_{12}$: C 20.4%, H 0.2%, Co 5.0%, F 58.1%, O 16.3%. Because the complex contains polymeric groups, some variation in the formula and analysis is expected.

Hydrogenations were performed using a fluorinated version of Wilkinson's catalyst. 10 mg of catalyst was added to a glass vial along with 50 mg of the fluorinated silica, a microstir bar, and degassed styrene (100:1 substrate to catalyst ratio). The glass vial was placed inside a pressure vessel in order to keep the vial upright. The pressure vessel was allowed to come to thermal equilibrium in a temperature bath maintained at 40°C. The pressure vessel was flushed with hydrogen. 30 bar of hydrogen and 60 bar of CO_2 were then added. The reaction was allowed to run overnight. The pressure was released slowly and the vessel was opened in a glove box. The liquid was removed using a syringe so as to disturb the catalyst as little as possible. The silica was washed three times with clean cyclohexane in order to remove as much product as possible. Styrene and cyclohexane were then added to the silica with deposited catalyst and the reaction cycle was repeated.

Experimental Results

In order to measure the partitioning of the catalyst, 1,4-Bis(perfluorooctyl)benzene was chosen as an analogue for our catalyst (Fig 4-2). The analogue was chosen for initial experiments since it is cheaper and less air-sensitive than the fluorinated version of Wilkinson's catalyst. This molecule is readily assayed as it is UV active and should behave the same way as our catalyst in that it will partition on off the fluorous silica. By measuring the UV response as a function of pressure, we will be able to determine how much of the molecule is partitioning into the reaction medium and whether or not any of our catalyst analogue remains in solution after the removal of CO_2 pressure.

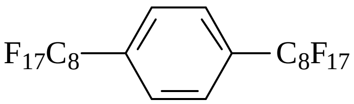


Figure 4-2 1,4-Bis(perfluorooctyl)benzene

We examined the behavior of the analogue in both acetonitrile and methanol. Figure 4-3 shows the concentration of the analogue in an acetonitrile solution versus CO_2 pressure. The line indicates the maximum concentration in solution based on the amount of compound added to the cell and the expansion of the solution. Unsurprisingly, the behavior shows a maximum. As CO_2 is added to the system, the analogue partitions off of the silica surface into solution. Dissolved CO_2, however, will also increase the overall volume of solution present. Eventually, the compound will stop partitioning off of the surface leaving only the volume expansion to change the measured concentration. At this point, the measured concentration will fall since the amount of compound in solution is constant, but the volume is still increasing.

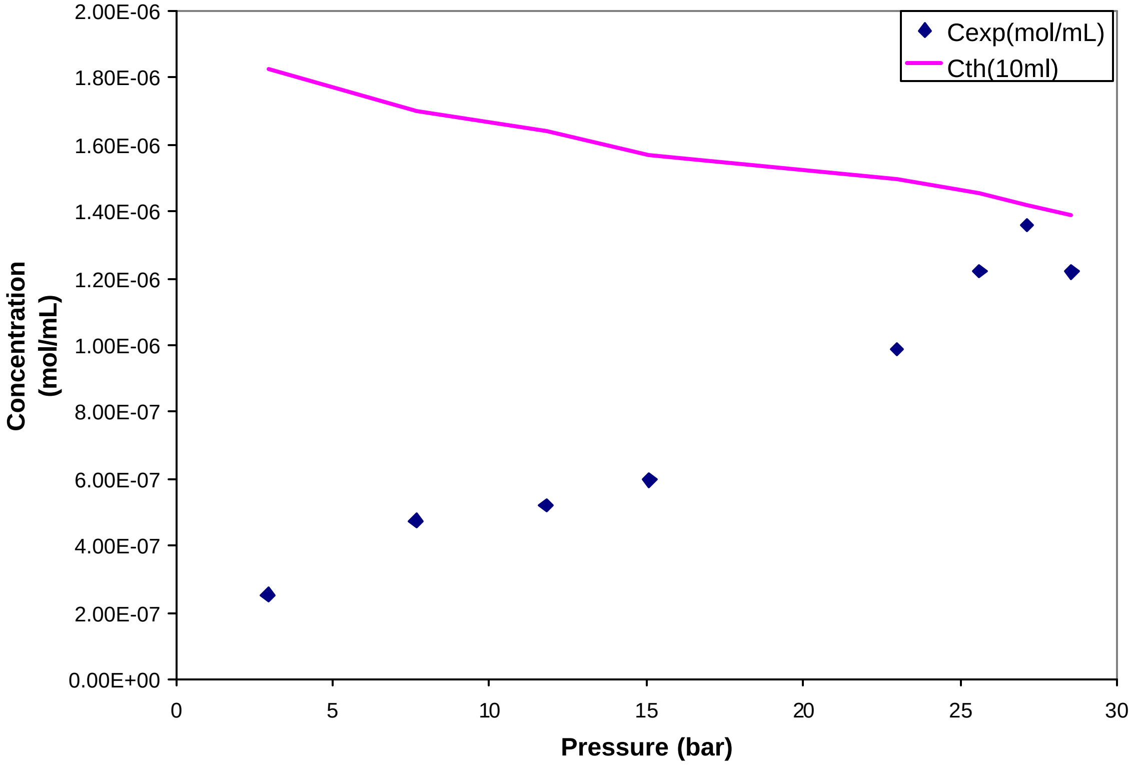


Figure 4-3 Concentration in acetonitrile of bis(perfluoro-octyl)benzene as a function of CO_2 pressure at room temperature

Table 4-1 summarizes the rest of the partitioning experiments. All experiments were done at room temperature. The partitioning is reported as fraction of compound in solution. This is also based on the maximum theoretical value discussed above and shown as a line in the previous figure. Methanol and acetonitrile were used as model organic solvents since they are both transparent in the UV and did not interfere with our measurements.

From the table and the figures, we can see that the more fluorous nature that the compound has the greater ability we have to selectively bring it into solution with CO_2 pressure. Conversely, the less fluorous the compound the more likely that it is to come off the silica surface in the absence of CO_2. The concentration of the compound in solution approaches the theoretical maximum at roughly 26 bar. These partitioning results are very promising for selectively bringing catalysts into solution for reaction and returning it to the surface after the reaction is complete.

Table 4-1 Summary of partitioning data at 25°C

		Fraction in solution			Volume (mL)	
Compound	**Solvent**	**w/o CO_2**	**w/ CO_2**	**P (bar)**	**As loaded**	**Gas Expanded**
Co(O-PFPE)	C_6H_{12}	1.00%	99.00%	68.3	30	60
Bis(perfluorooctyl)benzene	CH_3OH	11.67%	97.87%	31.7	30	50
Bis(perfluorooctyl)benzene	CH_3CN	10.94%	97.83%	31.1	30	37
Fl-Wilkinson's	C_6H_{12}	2.39%	97.61%	28.6	6	12
Fl-Wilkinson's	CH_3OH	1.22%	98.55%	28.6	6	7.2
Fl-BiNOL	C_6H_{12}	0.29%	99.56%	39.7	6	9.9

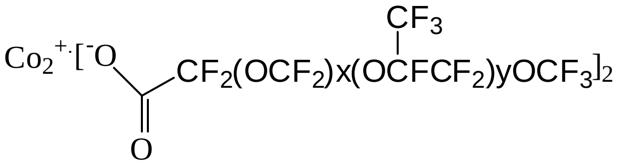


Figure 4-4 Cobalt catalyt (Co(O-PFPE))

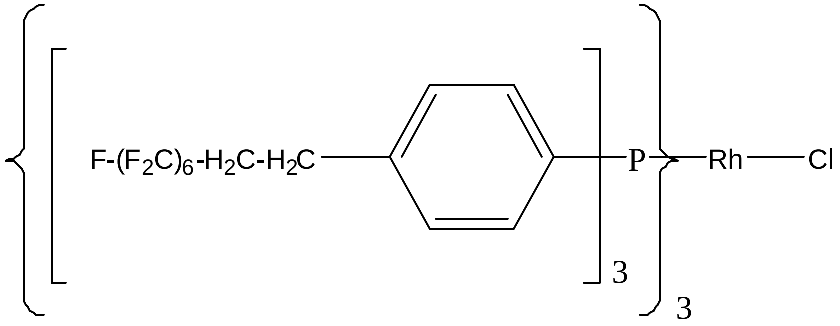
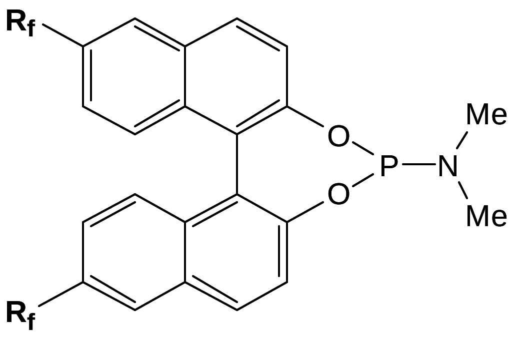


Figure 4-5 Fluorous Wilkinson’s catalyst



$R_f = [C_6F_{13}(CH_2)_2]_3$-Si-

Figure 4-6 Fluorous monophos

The hydrogenation of styrene to ethylbenzene (Fig. 4-7) was examined to ensure that there is no loss of catalyst activity occurs upon recycle. The silica changed from white to light brown/orange in color upon depressurization and the reaction medium was clear indicating the catalyst had deposited on the silica. GC results for the first five runs show complete (>99%) hydrogenation.

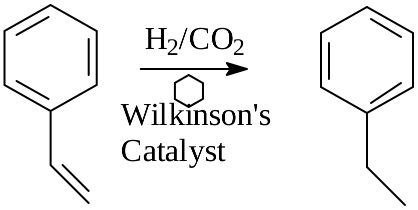


Figure 4-7 Hydrogenation of styrene

Another series of hydrogenations were run limiting the reaction to one hour (instead of overnight). The conversions were, in order of run, 47, 61, 72, 58, and 46%. These results show that nothing drastic is happening to the catalyst during the recycle process.

We were unable to test for colloidal rhodium which can also catalyze hydrogenations. We thought the best test to answer the question of what is actually catalyzing the reaction would be an asymmetric reaction (Figure 4-8). The partitioning results for fluorous-BINOL indicate we should have no problems recycling the catalyst. The fluorous monophos used in the reaction is structurely similar, but easier to synthesize.

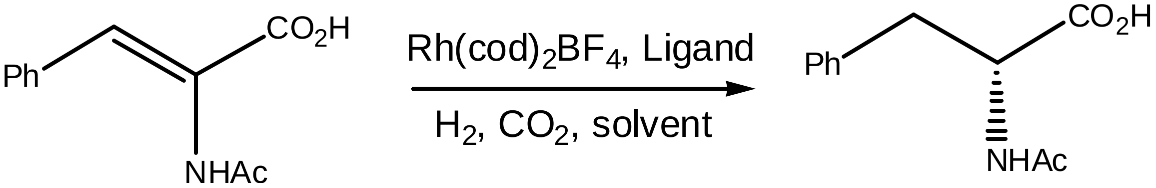


Figure 4-8 Asymmetric hydrogenation

The fluorous monophos is capable of 83% ee with 100% conversion in CO_2 expanded solvents. However, in the presence of silica the enantiomeric excess drops to under 15% with complete conversion. Tests indicate that the silica does not racemize the product in the presence of CO_2. This leaves the possibility that the silica adversely affects the chiral catalyst.

One group has found that SFC CO_2 actually makes “inaccessible” silanol groups accessible and reactive (McCool and Tripp 2005). It is possible and even probable that these newly reactive silanol groups are responsible for the deactivation of our catalyst.

Summary

We have shown that we can selectively draw a catalyst into solution using CO_2 pressure and return it to the silica surface after the reaction is complete making highly fluorinated silica a viable option for catalyst recovery and recycle. The fluorous silica is also much cheaper and cleaner than its fluorous solvent counterparts. Since it is a solid it will also be much easier to recover from solution than a solvent that has a measurable solubility in organic solvents.

This technique is probably best applied to achiral reactions where the catalyst may not be as sensitive to the deactivation route we have seen here. It may also be possible to use a high molecular weight fluorous polymer instead of the fluorous silica.

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CHAPTER V

PARTITIONING IN ORGANIC AQUEOUS TUNABLE SOLVENTS (OR OATS)

Introduction

This work focuses on using pressure, in particular CO_2 pressure, to effect separations by tuning solvent properties. Another term used to describe solvent systems that are controlled using CO_2 pressure is Gas eXpanded Liquid or GXL. GXL's are of particular interest since the solvent power can be tuned between that of an organic solvent and that of a gas. With such a wide range of available solvent power, it is easy to change the solvent to fit the situation.

Before these systems can be applied, however, we must understand how the addition of CO_2 affects the phase behavior and other solvent properties. This chapter will investigate both experimentally and through modeling how CO_2 affects solvent systems that are of particular interest to this thesis.

Organic Aqueous Tunable Solvents (OATS) are one subset of GXLs. They are of particular interest since they are mixed solvent with both organic and aqueous traits that can be easily split with the addition of CO_2. At ambient conditions, when there is just one liquid phase, the mixed solvent can dissolve both salts and organic substrates. CO_2 preferentially dissolves in the organic portion of the mixed solvent to facilitate the phase split. When the solvent is split into two liquid phases, the salts remain in the aqueous phase and the organic substrate in the now gas-expanded organic solvent.

With the move to greener processing, the use of water as opposed to organic solvents is seen as a desired benefit in catalyst recycling processes (Wei, Keh et al. 2004). From a green processing standpoint, the catalyst should be water soluble and the substrate should have little solubility in the water phase for the easiest product isolation and catalyst recycle. This biphasic operation is not ideal for efficient catalysis since the substrate reactivity will be hindered by its low solubility in the aqueous phase. The OATS system can satisfy both of these requirements which is what makes it so powerful. In the absence of CO_2 pressure, it is the ideal system for homogeneous catalysis. With CO_2 pressure, efficient product recovery and facile catalyst recycle are possible.

The implications of this type of system are far reaching in pairing a homogeneous reaction with a heterogeneous separation. These systems can easily be applied to reactions that are catalyzed by water soluble catalysts, both organo-metallic and enzymatic.

Experimental Materials

All organic chemicals used in the experiments were HPLC grade, obtained from Sigma-Aldrich Chemical Company. SFC Grade carbon dioxide (99.99%) was obtained from Air Gas. The CO_2 was further purified to remove trace water using a Matheson (Model 450B) gas purifier and filter cartridge (Type 451).

Apparatus and Procedure

Partitioning experiments of 1-octene and nonanal were performed in a windowed Parr reactor. The reactor was fitted with two diptubes attached to two sampling loops available from Valco and two 6-way valves so that samples could be taken from both phases at various pressures. Figure 5-1 shows an example of a sample loop connected to a Parr reactor. The sample loop is then flushed out and collected for analysis. The samples were analyzed using a GC/MS which was calibrated with the compounds of interest.

Measurement of the partition coefficients of 1-octene were performed at 25 ºC. Tetrahydrofuran (35 mL), water (15 mL), and 1-octene (1 mL) were loaded into the windowed Parr vessel, which was then sealed. CO_2 was then added from a syringe pump (ISCO, Inc., Model 500D). The vessel was then heated and stirred to equilibrium and the pressure recorded. The stirring was discontinued and the system was allowed to come to equilibrium prior to sampling. The sample loop was flushed with approximately three times its volume with the phase being sampled, then the valve position was switched and the sample loop was emptied and flushed with at least six times its volume of tetrahydrofuran. This procedure was performed on samples from each liquid phase. The concentrations of 1-octene in each phase was determined using an Agilent 6890 GC-FID, and the response was calibrated using standards of known concentration.

Sampling GXLs using the sample loops was verified by sampling 1-octene in gas expanded acetonitrile. Using the volume expansion data of Kordikowski (Kordikowski, Schenk et al. 1995), we were able to estimate the expanded volume of our system and verify the calculated concentration with GC results.

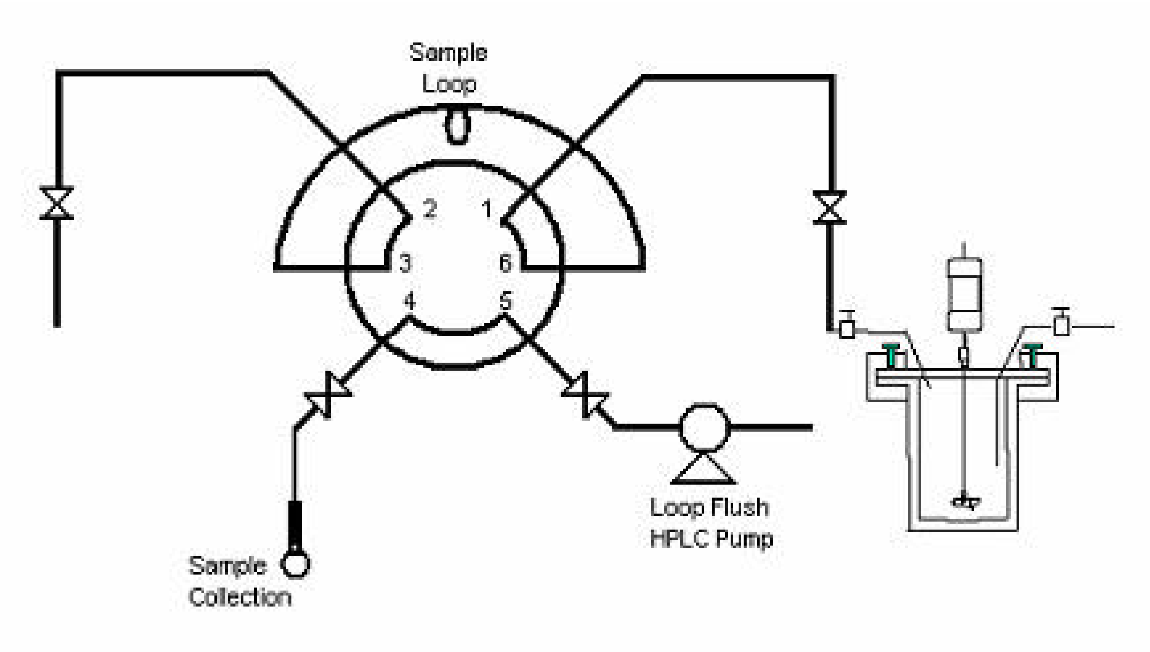

Figure 5-1 Sample loop for collection of samples

Other high pressure partitioning experiments were completed in an Agilent UV using a specially designed high pressure cell. The UV was calibrated at amibent conditions using various dilutions of the compound of interest following A= εcl. Where A is the measured absorbance from the UV, ε the absorbtivity specific to the solvent and solute, c is the known concentration and l is the path length. Once ε is known, measurements taken at high pressure can be used to calculate the concentration present.

Experimental Results

The first system of particular interest is the reaction system for the hydroformylation of 1-octene in THF / water. We looked at the effect of added CO_2 pressure to a system very much like that of our reaction system. Using the same composition of THF / water, we did a pressure dependent study of the partition coefficients of 1-octene and nonanal (recactant and product respectively). The only omission was that of the organo-metallic catalyst. The salt groups on the catalyst should only make the separation easier by making the aqueous phase less organophilic during the separation.

As seen from Figure 5-2, the partition coefficient can be greatly enhanced with small amounts of CO_2 pressure. In fact, at roughly 7 bar 99% of the product and reactant can be recovered. This recovery pressure is much lower than the pressure of the reaction allowing for easier industrial incorporation. Of course, engineers will always prefer to predict the behavior of a system of interest rather than measure it. Lazzaroni et. al. used this data and verified that this system is best fit by using the HVOS-UNIQUAC model (Lazzaroni, Bush et al. 2004).

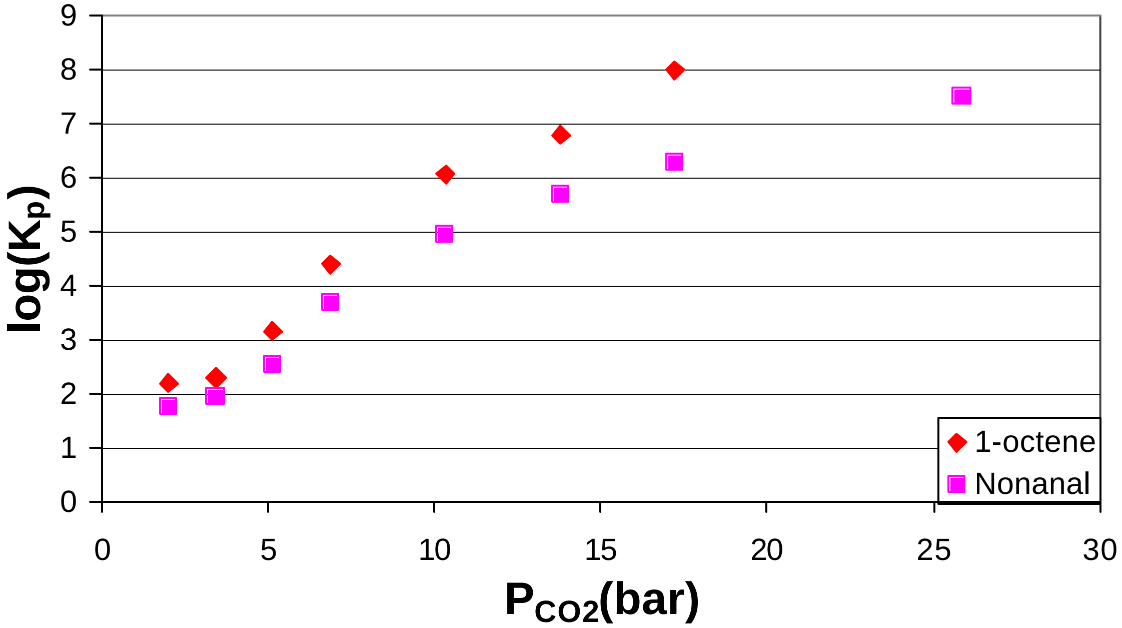

Figure 5-2 Partition coefficients of 1-octene and nonanal at various CO_2 pressures

Another application of these OATS systems that is of particular interest to this group is the use of these systems for enzymatic reactions, since enzymes can be far more active and selective than their organo-metallic counterparts. The only drawback for these systems is that enzymes are typically most active in water where as the substrates of interest exhibit little to no solubility in water, creating a scenario where the reaction of interest is highly mass transfer limited or worse, takes place at the interface. This scenario seems to be an excellent fit for the use of easily separable mixed solvents, such as OATS.

To test the viability of our OATS concept for enzyme catalyzed reactions, we tested the partitioning of sec-phenyl ethanol in a 50/50 (by volume) mixture of acetonitrile and water (Figure 5-3). The reaction of sec-phenyl ethanol is of interest since it's an example of an enantioselective reduction of a ketone. Enantioselective reductions of ketones are very important to the pharmaceutical industry. Biocatalysis of this type of reaction is well used in this area (Lorraine, King et al. 1996; Crocq, Masson et al. 1997; Zaks and Dodds 1997).

These partitioning experiments were in done in parallel to a series of experiments designed to test the activity of the desired enzyme in various compositions of solvents. LL-CR was tested in acetonitrile-water and dioxane-water mixtures (Broering, Jones et al. 2004). Early tests with THF show irreparable harm to the enzyme. These three solvents were chosen because we know we can split mixtures of them with water with the addition of CO_2 pressure. Figure 5-4 shows an example of these tests. For this enzymatic reaction, the activity only decreases with the addition of organic solvent. However, the overall reaction rate should go up with the increased solubility of the

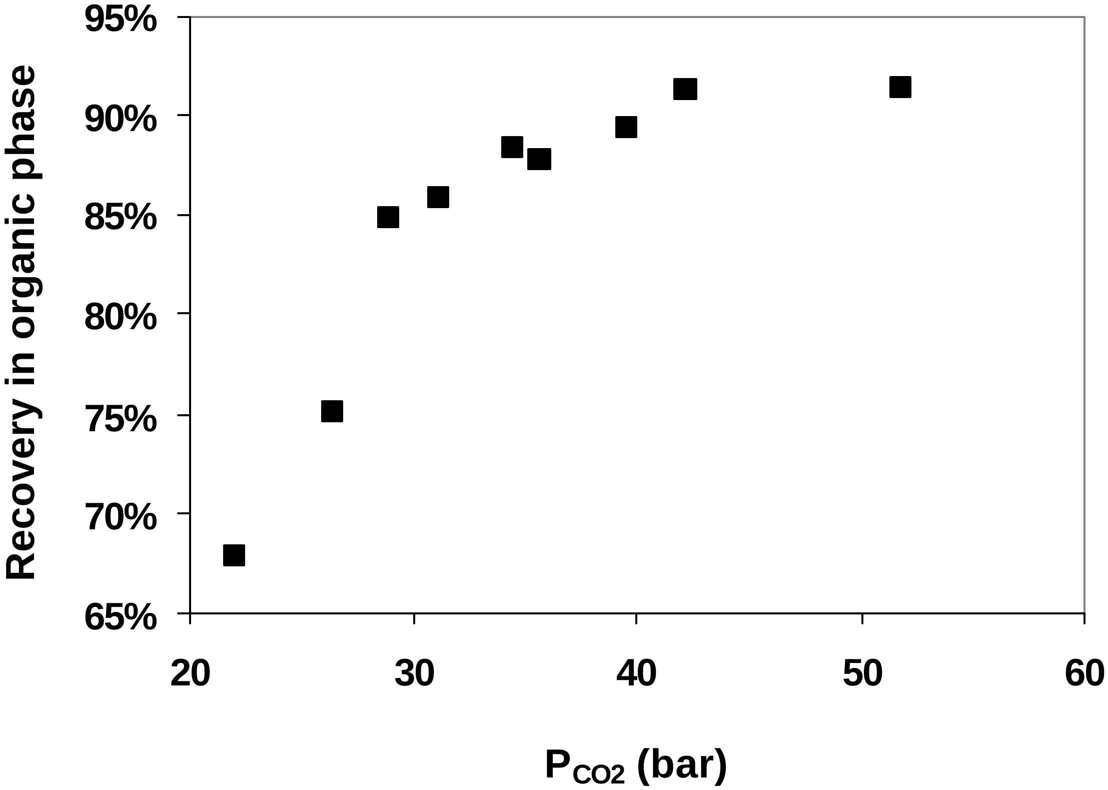

Figure 5-3 Recovery of sec-phenylethanol in an OATS system

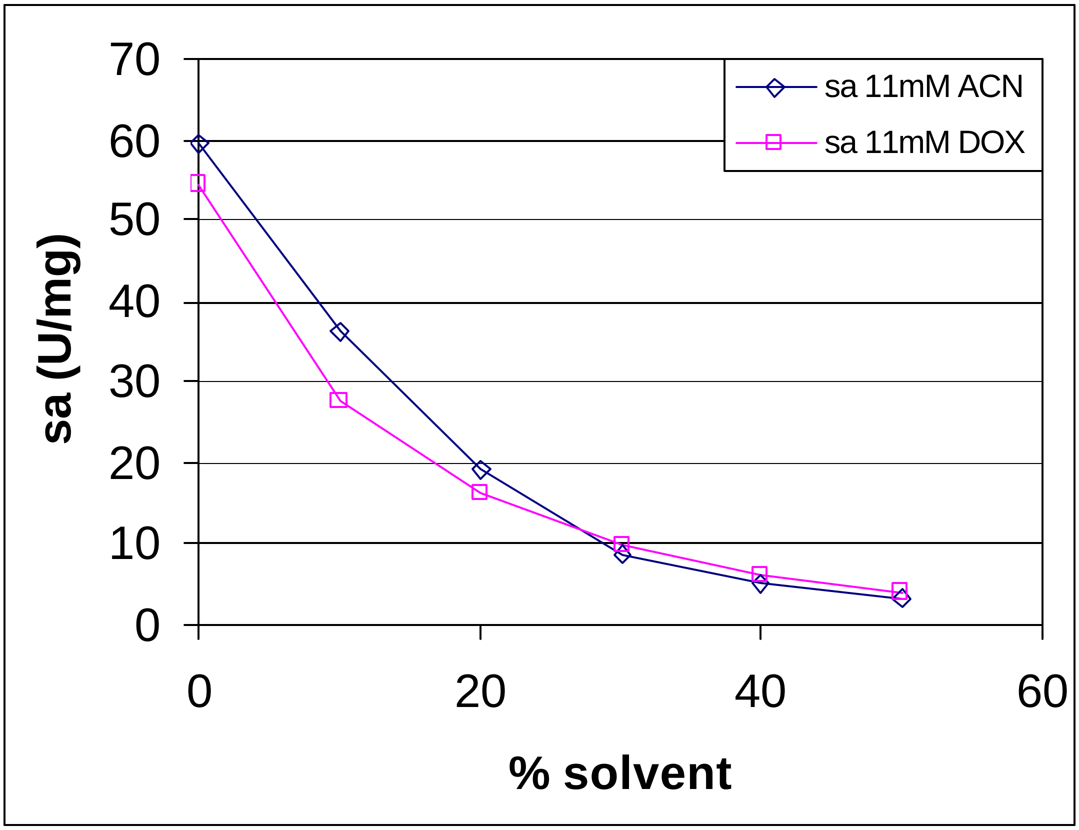

Figure 5-4 Specific activity of LL-CR for acetophenone at 11 mM in acetonitrile-water and dioxane-water systems

substrate. This scenario is an example of competing effects on the actual rate of the reaction. The reaction will most definitely be mass-transfer limited due to the substrate insolubility at lower organic solvent concentrations. But, the enzyme activity decreases with increasing organic composition. The real question is – does the increase in solubility make up for the loss of enyzme activity?

Another hurdle for the use of OATS is the fact that enzymes can usually only withstand small swings in pH. The use of dissolved CO_2 as an anti-solvent will drastically lower the pH of the aqueous phase. Even a small amount of dissolved carbon dioxide will lower the pH of an aqueous phase.

CO_2 predominately undergoes the following reactions to form carbonic acid when dissolved at neutral pH.

$$(CO_2)_{aq} + H_2O \xleftrightarrow{I} (H_2CO_3)_{aq} \xleftrightarrow{II} (HCO_3^-)_{aq} + (H^+)_{aq}$$

The first step, the formation of carbonic acid (I), is the rate determining step while the second, dissociation of the acidic ion (II), is quite quick (Nguyen and Ha 1984). In order to understand the effect of dissolved CO_2 during the separation process, we used bromocresol green, an indicator dye usable between pH 3.8 and 5.4 to construct a calibration curve in the UV using solutions of known pH measured with a pH probe. Then, we used the same indicator dye in a specially designed high pressure cell (Dillow, Hafner et al. 1997). By following the spectra, we were able to determine the pH under pressure (Figure 5-5).

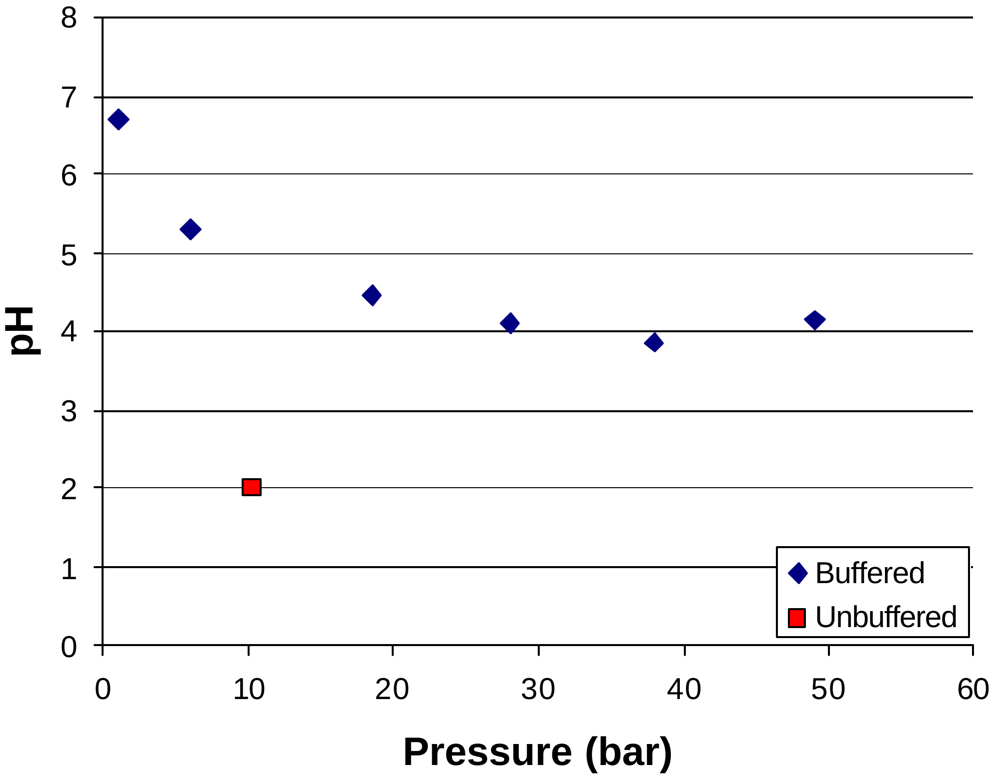

Figure 5-5 pH study in 20% acetonitrile / 80% water with NH_4CO_3 as buffer

In an attempt to counteract the negative effects of the use of CO_2, we studied the use of various concentrations of NH_4HCO_3 in pure water. Since we knew the basic behavior (Figure 5-5) and that the enzyme-containing phase will be mostly water during the separation, this was sufficient as a first experiment to determine the necessary concentration. We used the apparatus and calibration curve mentioned above and measured the end point where the separation would take place. If we could maintain the pH there, we felt that we'd be ready to move onto the reaction. The results are shown in Figure 5-6.

As seen in Figure 5-6, CO_2 will drastically affect the pH of water without buffer. We can also tell 0.1 mol/L is sufficient and the change is quite small moving from 0.1 to 1 mol/L. The small concentration needed to maintain pH is good news for us since the added salts can enhance the phase split of water and acetonitrile (or dioxane). If we needed large quantities of buffer, it would be difficult to create an OATS system that would be monophasic at ambient conditions.

Summary

The partitioning results indicate that the use of OATS systems to recover products and catalysts is highly promising. The hydroformylation reaction is of particular interest for industrial implentation since that process already uses high pressure. High pressure tends to be an anathema for industrial processes since the cost for the equipment and safety measures can be exorbitant. Plants running a gas-liquid reaction at high pressures will already have many of these measures in place making it a more attractive alternative.

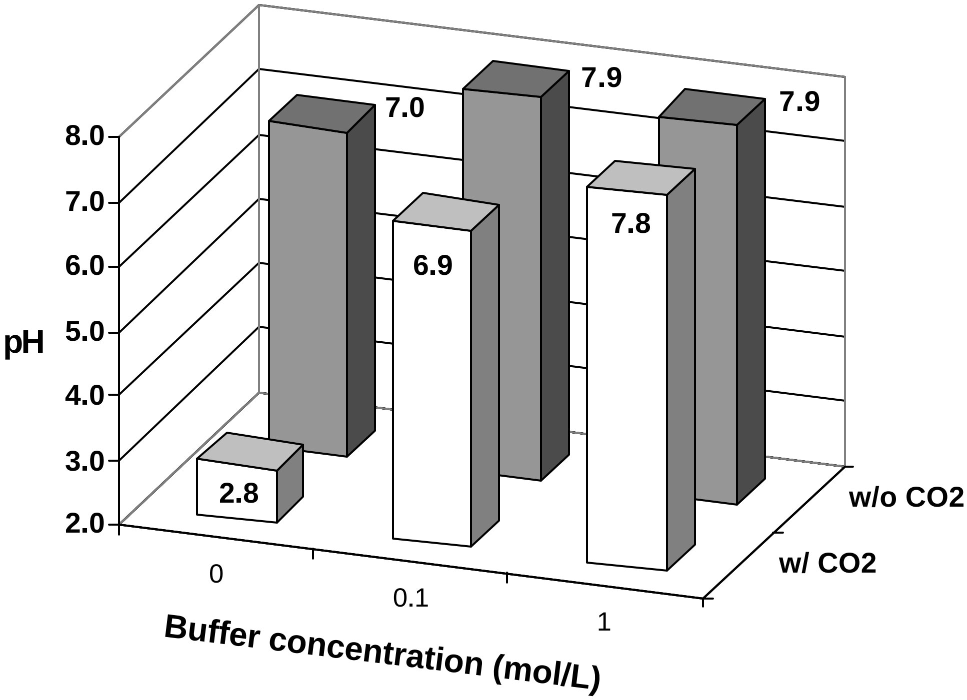

Figure 5-6 Buffering capacity of NH_4CO_3 in water

For the enzyme reactions, another thing to note is that some of the ethers used in the OATS systems can actually have a detrimental effect on the activity and lifetime of the enzymes in question, such as THF. It's a fine balance determining the ratio of organic solvent to water that will allow decent functionality of the enzyme, maintain buffering, and still allow for a quality separation of the desired product from the aqueous phase. Enzymes will typically have the best activity in solutions containing the minimum amount of organic solvent. By examining the phase data of Lazzaroni (Lazzaroni 2005), we determined that for each organic-water pair there exists a minimum of organic solvent that must be present for a phase split to occur. This sets the lower bound for the system composition. More research and experiments will have to be done to find a situation where the increased solubility of the substrate will compensate for the lowered enzyme activity.

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CHAPTER VI

USE OF NOVEL SOLVENTS FOR RECOVERY AND RECYCLE OF A HYDROFORMYLATION CATALYST

Introduction

Aqueous biphasic catalysis is one technique used industrially to sequester a catalyst for easy recycle. The water soluble catalyst is sequestered in an aqueous phase, while the reactant is in an organic phase (Herrmann 1993; Horváth and Joo 1995; Cornils and Herrmann 1998). This approach works well for lower molecular weight olefins such as ethylene and propylene (Cornils and Herrmann 1998; Cornils 1999). Even for these short chain olefins, intense mixing is needed to overcome the mass transfer limitations presented by the small solubility of the reactant in the aqueous phase. Since the reaction actually takes place in the aqueous phase, as the length of the olefin is increased the reaction rate will decrease dramatically due to the decrease in solubility. Olefins with eight or more carbons have virtually no solubility in water making it difficult to apply this approach to longer chain olefins (Herrmann 1993) and other hydrophobic substrates such as drug precursors.

Gas-expanded liquids (GXLs) are a new and benign class of liquid solvents which may offer many advantages for separations, reactions, and advanced materials. GXLs are intermediate in properties between normal liquids and supercritical fluids, both in solvating power and in transport properties, and these properties are highly tunable by simple pressure variations. GXLs are formed by the dissolution of a gas, usually CO_2, in organic liquids. GXLs have been used for a variety of applications, including gas-antisolvent (GAS) crystallization (Winters, Knutson et al. 1996; Bertucco, Lora et al. 1998), particle production (Bertucco 1999), and as a reaction solvent (Musie, Wei et al. 2001; West, Culp et al. 2001; Wei, Musie et al. 2002; Ablan, Hallett et al. 2003; Chamblee, Weikel et al. 2004; West, Hallett et al. 2004).

For this work, we have used **O**rganic-**A**queous **T**unable **S**olvents (**OATS**) (Eckert, Liotta et al. 2004; Lu, Lazzaroni et al. 2004) which are mixed solvents that are fully miscible at ambient conditions but can be easily separated with the addition of CO_2. Little CO_2 will dissolve in water but will dissolve readily in organic phases. Adding CO_2 to a system like ours will drastically lower the solvent power of the organic phase for ions and other polar compounds causing a phase split (Lazzaroni, Bush et al. 2004). The composition of these systems can easily be adjusted to dissolve both a hydrophobic substrate and a hydrophilic catalyst. The solubility of 1-octene in water, for example, is only 2.7 ppm (McAuliffe 1966) (by mass), but is soluble in our system containing a water-soluble catalyst. This makes the reaction homogeneous while maintaining the ability to have a heterogeneous separation as in aqueous biphasic chemistry. Once the reaction has been run, CO_2 pressure can be used to split the water from the organic phase. Since the catalyst is water soluble, it will remain in the water phase and the separation becomes a biphasic separation (Figure 6-1). The aqueous phase containing the catalyst can now be easily recycled, and the CO_2 is easily vented from the organic phase containing the products.

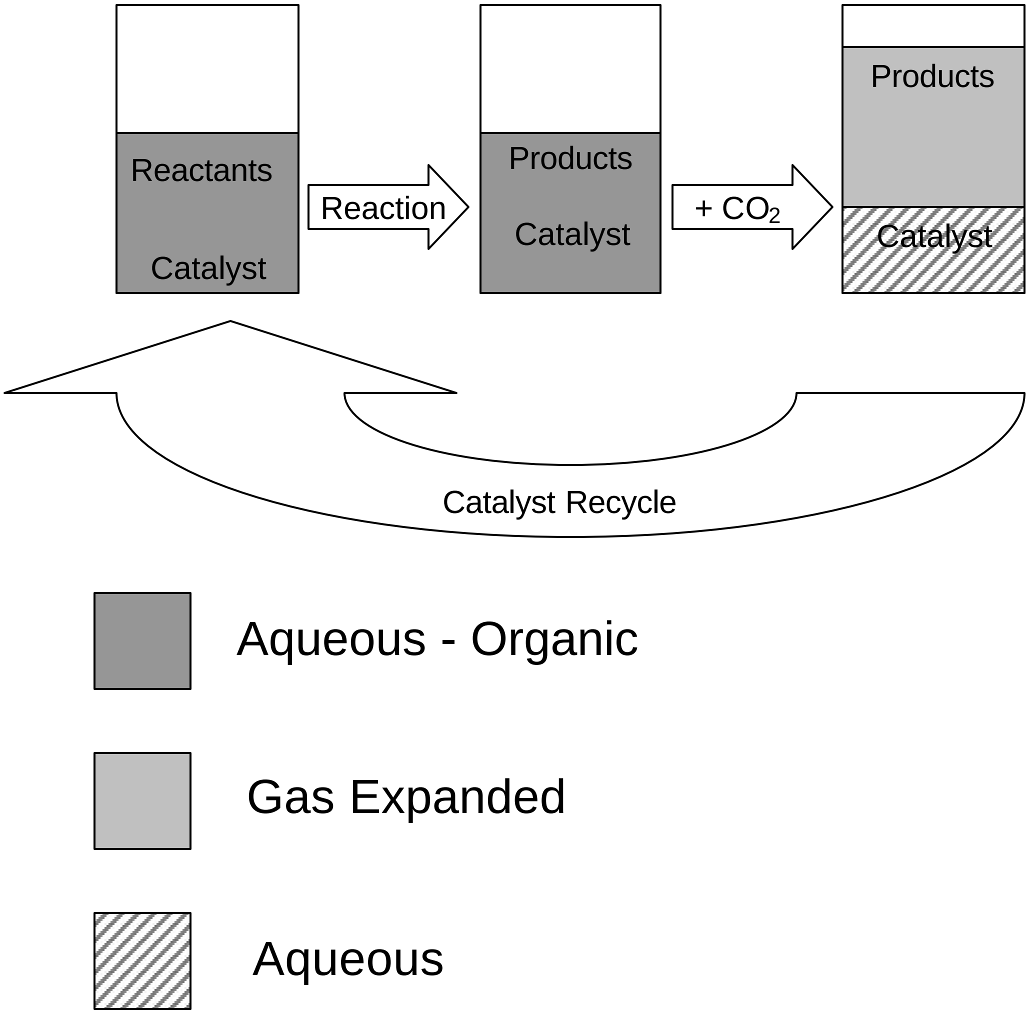

Figure 6-1 OATS reaction scheme

Other researchers have tried various methods to increase the reaction rates of higher order olefins in aqueous biphasic systems. One of these approaches is the addition of co-solvents (Monteil 1994). The addition of co-solvents greatly increases the reaction rates, but the co-solvent will invariably hinder the separation process (Cornils 1995). The work of Monteil et. al. shows that 20% of the rhodium does indeed partition into the organic phase in the form of $Rh_2(\mu\text{-}S^tBu)_2(CO)_4$ (Monteil 1994). This catalyst leaching is unacceptable due to the expensive nature of the metals as well as product poisoning and is not experienced in the traditional Ruhrchemie/Rhone-Poulenc process (Kohlpaintner, Fischer et al. 2001).

Another method involves using use surface active ligands rather than the traditional TPPTS (triphenylphosphine trisulfonate sodium salt) ligands (Hanson 1998). 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 (Hanson 1998). Hanson's work does not include any discussion of catalyst leaching, but 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.

Experimental Materials

All organic chemicals used in the experiments were HPLC grade, obtained from Sigma-Aldrich Chemical Company. The HPLC water and THF were degassed using the freeze-pump-thaw method on a schlenk line apparatus. SFC Grade carbon dioxide (99.99%) was obtained from Air Gas. The CO_2 was further purified to remove trace water using a Matheson (Model 450B) gas purifier and filter cartridge (Type 451). UHP grade syngas (50 / 50 CO / H_2) and was obtained from AirGas and used as received.

Apparatus and Procedure

The reactions were carried in a 300 mL stainless steel autoclave reactor (Parr Instrument Company, Model 4561) with a maximum working pressure of 208 bar and a maximum working temperature of 350°C (Figure 6-2). Stirring was provided by a magnetic drive (Parr Instrument Company, Model A1120HC) equipped with a four-blade 85° pitched-blade impeller. The seal between the stirrer and the reactor was made with a teflon gasket, and the seal between the reactor body and the reactor head was made with a flat Teflon gasket held in a confined recess in the reactor head. The internal volume of the reactor was determined to be approximately 305 mL by filling the reactor with a known mass of pure CO_2 and measuring the pressure at several temperatures.

A PID temperature controller and tachometer (Parr Instrument Company, Model 4842) were used to control the temperature of the reactor to ± 1°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 housed in an aluminum shell. A digital pressure transducer (Heise, Model 901B) was used to monitor constantly the reactor pressure, and a safety rupture disk, made of Inconel, was used to ensure the pressure in the reactor remained below the reactor pressure rating.

The Parr reactor was modified by replacing all of the standard valves and fittings with low volume HiP valves and fittings to decrease the reactor dead volume. Syngas was added to the reactor through stainless steel tubing (3.18 mm OD and 1.52 mm ID) to

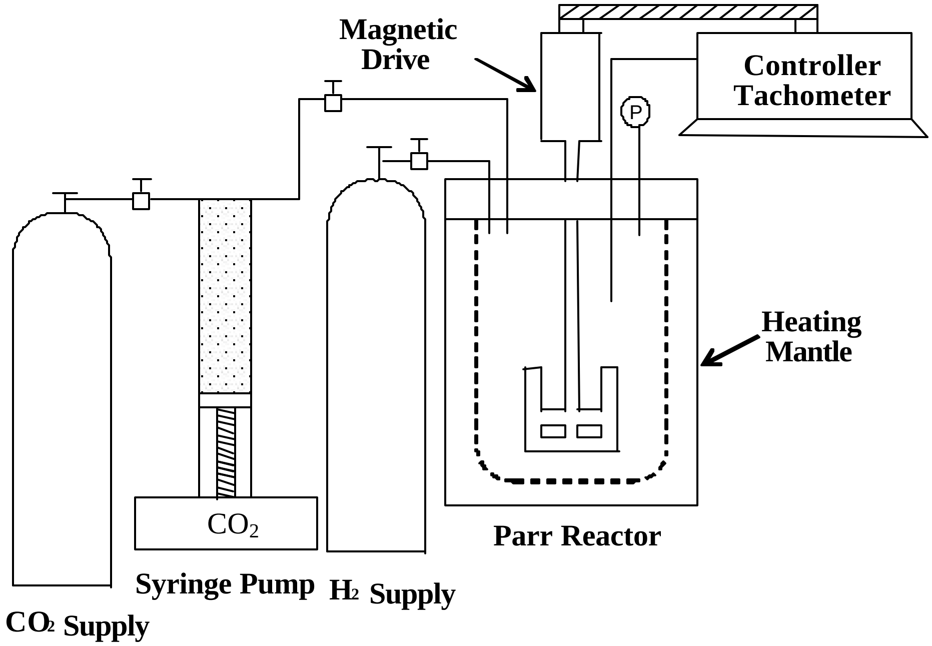

Figure 6-2 Parr reactor set-up

a second inlet port. Prior to any reactions, the reactor was evacuated using a Fisher Scientific Maxima C plus vacuum pump for a minimum of 20 minutes. The reactor was then flushed three times with approximately 3.5 bar syngas (STP). Catalyst precursor and ligand solutions were added using Hamilton SampleLock gas-tight syringes with luer locks. Degassed water and degassed THF were also added by the same method to make 15 mL water and 35 mL of THF total. The reactor was then heated to the desired reaction temperature. The catalyst was formed in-situ under mild syn-gas pressure during the time it took to pre-heat the reactor. 1 mL of 1-octene was then added to the reactor with a syringe and the reactor was pressurized to approximately 31 bar with syngas to start the reaction. The reaction was then allowed to proceed for the desired time, typically 1 hour. To stop the reaction, the reactor was quenched with an ice bath until the temperature was below that of room temperature. The reactor was then depressurized through stainless steel tubing submerged in THF to catch any volatiles. The reactor contents were added to the THF and analyzed using an Agilent GC-FID (model 6890). External standards of know concentrations of 1-octene and nonanal were used to calibrate the GC.

Catalyst Synthesis

For a limited number of experiments, the catalyst was synthesized prior to the reaction using a method set forth by Ahmad (Ahmed 1972).

> A solution of rhodium trichloride 3-hydrate (0.26 g, 1.0 mmol) in ethanol (20 mL) is added to vigorously stirred, boiling solution of triphenylphosphine (2.64 g, 10 mmol) in ethanol (100 mL). After a delay of 15 s, aqueous formaldehyde (10 mL, 40% w/v solution) and a solution of potassium hydroxide (0.8 g) in hot ethanol (20 mL) are added rapidly and successively to the vigorously stirred, boiling reaction mixture. The mixture is heated under reflux for 10 min and then allowed

> to cool to room temperature. The bright yellow, crystalline product is filtered; washed with ethanol, water, ethanol, and n-hexane; and dried *in vacuo*.

Some adaptations were made since the desired phosphine ligands were water-soluble and air sensitive. All solvents used in the synthesis were degassed prior to use using freeze-pump-thaw methods on a schlenk line apparatus. The synthesis and purification were also done on the schlenk line. The reaction itself was done in a mixture of water and ethanol to ensure the solubility of the phosphines and finished catalyst precursor.

Recycle Experiments

In order to determine the ability of our system to recover catalysts with no detriment to the activity, we performed a series of experiments designed to reuse the catalyst after the phase separation. The reactions were carried out as above in a windowed version of the Parr vessel. The reactor was also fitted with a diptube in order to draw out the organic phase under pressure. Once the diptube was installed, the reactor was filled with a known volume of water and pressurized. The amount of water drawn off was recorded and the volume remaining in the reactor was calculated. The CO_2 for phase separation was supplied by a high pressure syringe pump (Isco, Inc., Model 500D) through stainless steel tubing (3.18 mm OD and 1.52 mm ID) to one inlet port on the reactor head. The syringe pump was also used to maintain the reactor at constant pressure during the withdrawal of the organic phase.

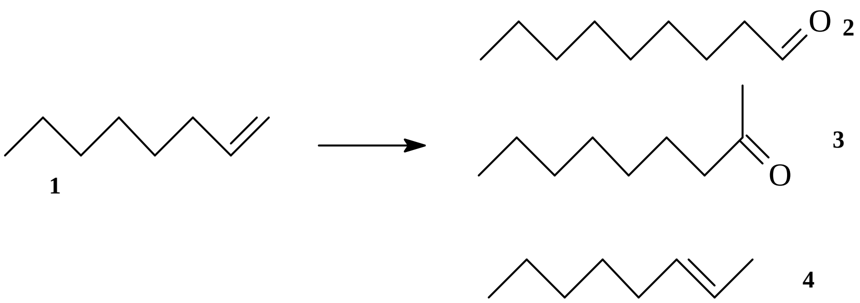

Figure 6-3 Reaction scheme for the hydroformylation of 1-octene

Experimental Results

The hydroformylation of 1-octene (Figure 6-3) was carried out at 40°C, 80°C, and 120°C with TPPTS (triphenylphosphine tris-sulfonated sodium salt) and TPPMS (triphenylphosphine mono-sulfonated sodium salt) used as the catalyst ligands (Figure 6-3c and a respectively). The reaction was baselined with TPP (triphenylphosphine) (Figure 6-3a) in the mixed solvent reaction system. Reaction results are summarized in Table 6-1. The linear to branched ratio stayed approximately constant across our temperature range at 2.1 ± 0.3. This is lower than other ligands being used for hydroformylation reactions. One caveat is the fact that most ligands are tested using propylene. Since propylene cannot undergo isomerization, one path to the branched product is eliminated.

The overall conversion rate of 1-octene for the three ligands in the monophasic system is close to constant. The biggest difference between the three ligands is the product distribution or rate of isomerization. These results caused us to hypothesize that the cause may be the increased basicity of the phosphine from the sulfonate groups on the phenyl rings. The negative charge on the sulfonic acid group can pertube the “charge” on

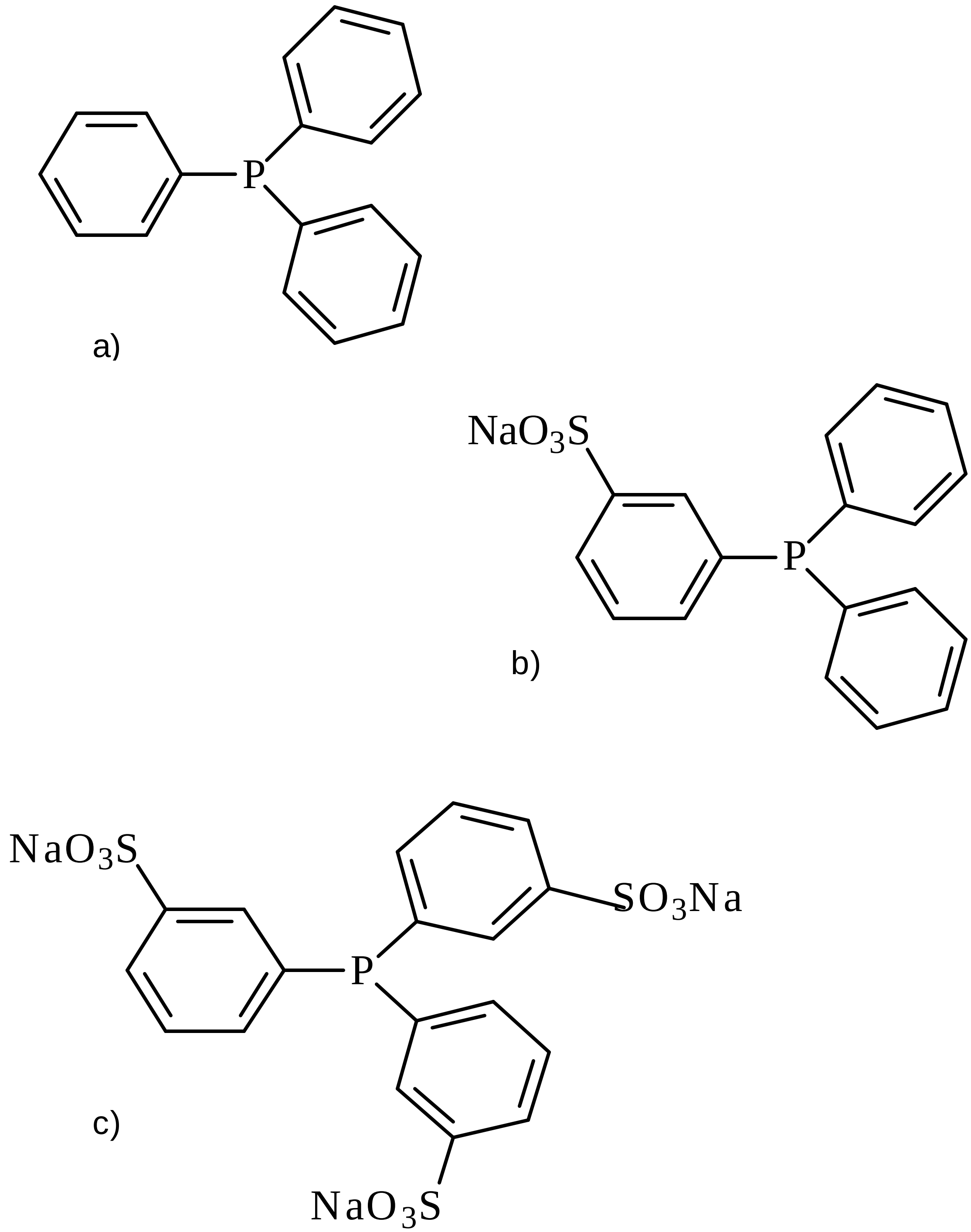

Figure 6-4 Catalyst ligands a) Triphenylphospine (TPP) b) Triphenylphospine mono-sulfonated sodium salt (TPPMS) c) Triphenylphospine tris-sulfonated sodium salt (TPPTS)

Table 6-1 Overview of reaction results.

Ligand	T (°C)	Percent Conversion to Aldehydes	Linear to Branched	Percent Isomerization (octenes)	TOF
TPPMS (synth)	120	76 ± 8	2.3 ± 0.2	19 ± 8	370 ± 50
TPPMS	120	72 ± 4	2.3 ± 0.2	20 ± 5	350 ± 20
	80	85 ± 0	2.4 ± 0.0	4 ± 0	390 ± 10
	40	21 ± 4	1.7 ± 0.2	1 ± 1	95 ± 25
TPPTS	120	38	2.86	38	115
	80	24	2.47	28	108
	40	1	1.54	1	7
TPP	120	91	2.67	0	457

the phosphine via a field effect. When comparing the basicity of TPP, TPPTS, and TPPMS to the yield of isomers, a strong trend was observed (Figure 6-5). This plot is a Bronsted-like plot and shows how the pKa of the ligand can correlate with the nucleophilicty of the phosphine. Looking at the proposed reaction mechanism of Bianchini (Bianchini 2000), it becomes apparent that there are multiple steps in which the phosphine catalyst must dissociate for the reaction to take place.

The increased basicity of the sulfonated phosphines creates a stronger bond between the metal center and the phosphine. These stronger bonds create a scenario where the phosphines could be competing for coordination sites with the carbon monoxide. When the olefin coordinates with the metal center in the absence of a CO ligand, it can undergo a shift of the double bond forming undesirable isomers. Some of these isomers can also undergo hydroformylation creating undesirable aldehydes as well. These side reactions need to be limited as much as possible since the side products can not be recycled to form the desired products.

For this reason, recycle experiments were carried out using TPPMS as the ligand of choice since the salt group on the TPPMS should be enough to impart selective partitioning into the water phase while reducing the side reactions as much as possible. The similarity of the linear-to-branched ratios and overall catalytic activity leads us to believe the electronic effects of the sulfonate groups only affect the reaction by allowing isomerizations to occur and do not affect the selectivity toward the desired aldehydes. For comparison, we examined the biphasic system consisting of 50 mL water and 1mL 1-octene with TPPTS as the ligand. No isomerization was observed after the standard

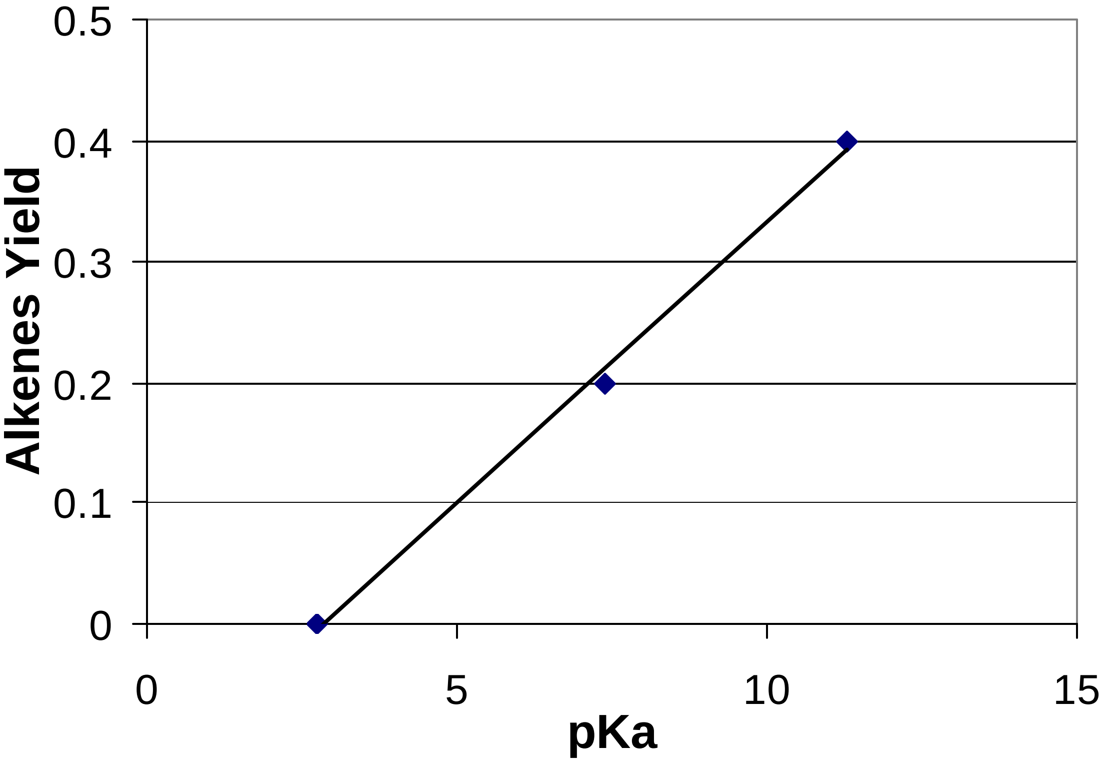

Figure 6-5 Trend of alkene yield with pKa of phospine.

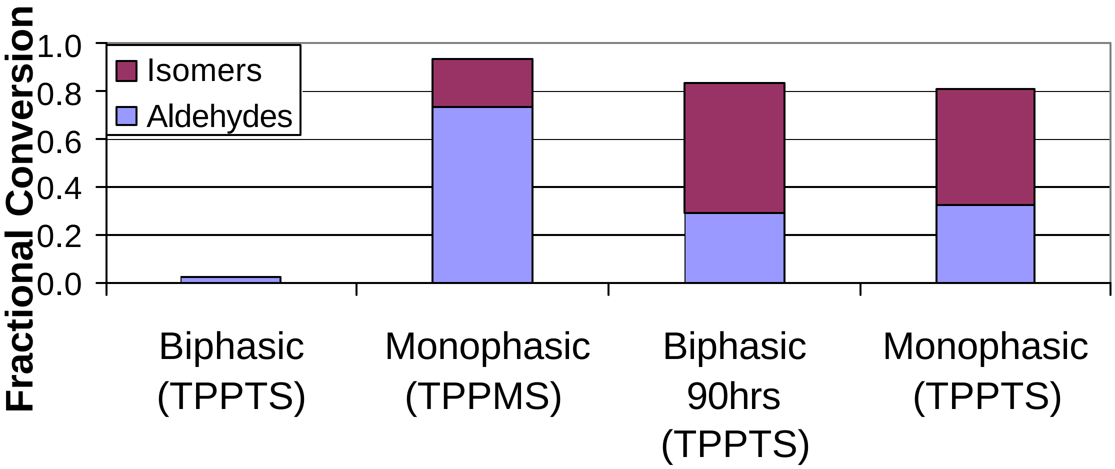

Figure 6-6 Comparison of reaction systems at 120°C and 1 hour unless noted otherwise

reaction time of one hour but the reaction rate was significantly lower. By extending the reaction time of the biphasic system to 90 hours, we found that the two reaction rates, aldehyde formation and isomerization, took place at the same relative rates as in the monophasic system (Figure 6-6). These results were further evidence that the phenomenon is most likely caused by the ligands in question.

The monophasic, or mixed solvent, system shows marked improvement over the more common biphasic system. The turnover frequency (based on yield of aldehydes) of the biphasic system was roughly 5 hr-1 where the TOF for our monophasic system was 325 hr-1. This is an increase of 65 fold. By changing to the TPPMS ligand we were also able to minimize the isomerization of the substrate (Figure 6-5).

Finally, to demonstrate the recyclability of our homogeneous catalyst, the reaction was run three times with the organic phase being removed and refreshed after each run. The organic phase was tested with a GC-FID and calculations were based on the phase behavior of Lazzaroni et. al. The results show that the aldehyde production is approximately constant for each run (Figure 6-7). This constant reaction rate indicates that the recycle process does result in any loss of activity of our catalyst.

Summary

We have shown we can tailor an OATS system to improve the reaction rate of 1-octene by a factor of 65 while retaining constant reaction rate over three runs. The constant rate over three runs implies that most, if not all, of the active rhodium species was retained during separation. Full catalyst retention is also supported by the ligand partitioning data. We were also able to tailor the water soluble catalyst for the selective formation of nonanal from 1-octene using TPPMS as our ligand.

There appears to be a strong trend when comparing the pKa of the phosphine ligands used in this work to the rate of isomerization of 1-octene. For this reason, the water soluble catalyst with the lowest pKa was chosen for the work. The ligand in question was TPPMS (triphenyl phosphine mono-sulfanted salt). The ligand with two salt groups (TPPDS) is not commercially available but may be a good trade-off between water solubility and isomerization rate. Another option may be to use both TPPTS and TPPMS as ligands. Other options include changing the water-soluble group or attempting to use alkyl spacers to further insulate the aromatic ring from the sulfonate moiety.

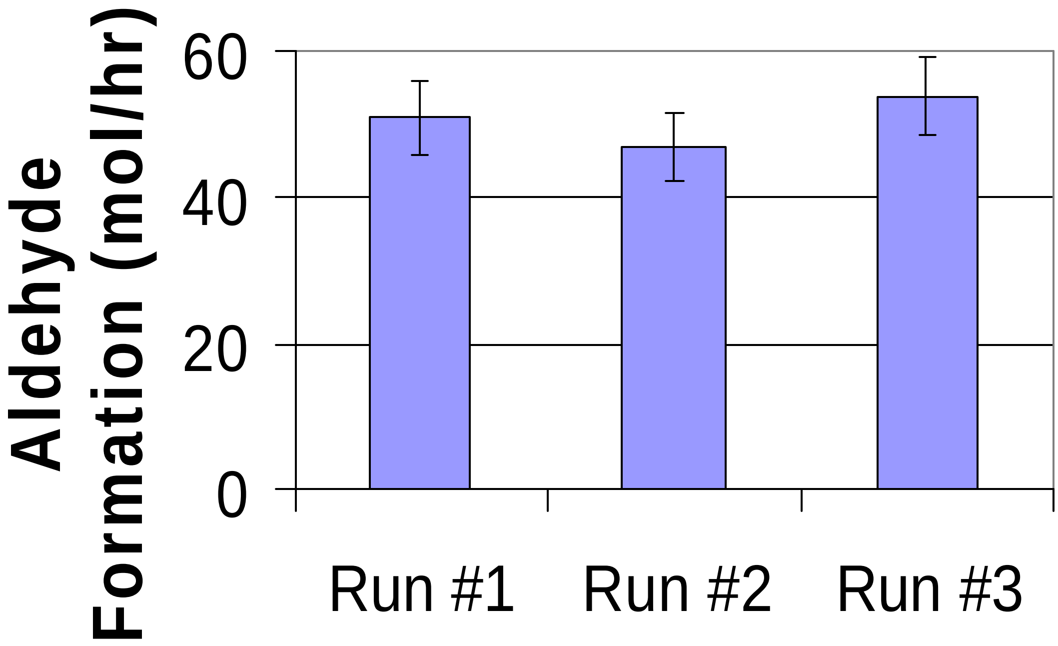

Figure 6-7 Reaction results for recycle experiment

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CHAPTER VII

CONCLUSIONS AND RECOMMENDATIONS

Several approaches to recovering homogeneous catalysts have been presented here. Some of these are more promising than others. The fluorous biphasic systems discussed succeed in recycling catalysts and are sufficient for lab scale syntheses. However, the cost in dollars and to the environment is too great for this approach to scale up to the industrial level. The fluorous silica was the logical next step after learning of the environmental concerns associated with the fluorous solvents. The silica concept raises its own concerns with deactivation of complex catalysts. Many more experiments are required to fully understand some of the results we have seen.

The most promising approach presented here is that of the OATS systems. The partitioning is the best out of all of systems presented here (Fig 7-1). The PEG partitioning number is an estimate. We expect the PEG to be more miscible. We have increased the turn over frequency by a factor of 65. The ability to recycle the catalyst with no loss to activity is also noted. The ease of product recovery under pressure has also been presented.

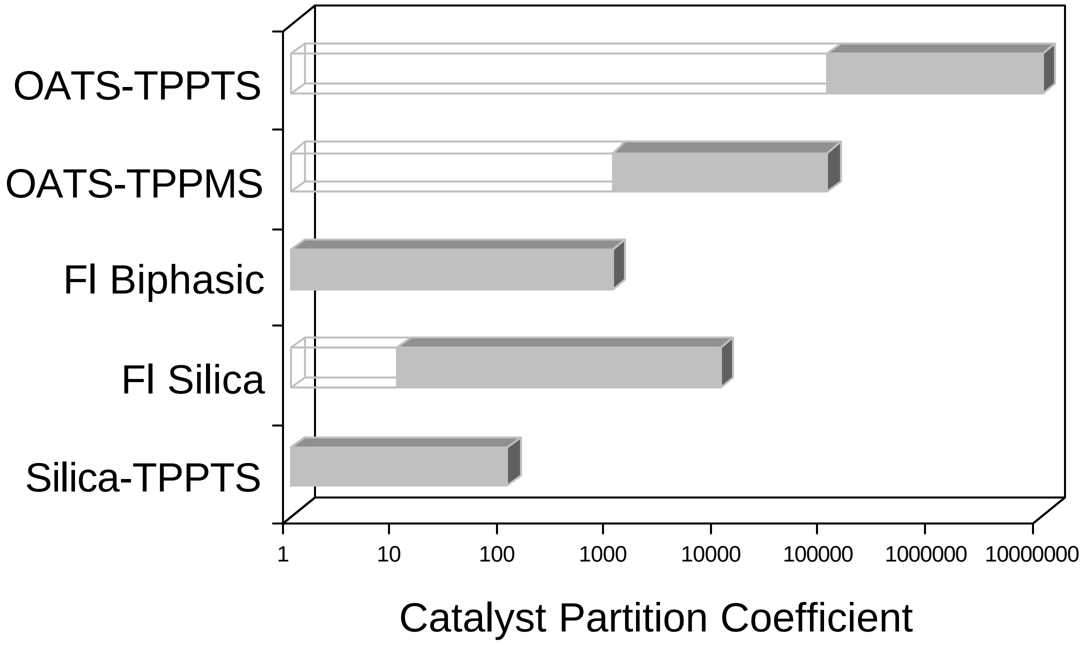

Figure 7-1 Comparison of partitioning coefficients for methods presented in this thesis

Fluorous Silica

The problem with the fluorinated silica approach is the deactivation of sensitive catalysts. Since these specially prepared catalysts are expensive and time-consuming to synthesize, we must eliminate this deactivation. If we can modify the silica under CO_2 pressure all of the silanol sites should be accessible for modification (McCool and Tripp 2005). The experiments presented here in Chapter 4 could then be retried to determine if this is the cause.

Another option currently under investigation by this group is the replacement of the silica with fluoropolymers which should not experience the acidic effects seen with the fluorinated silica.

OATS

One of the biggest hindrances in the OATS project was the need to determine why our system experienced more isomerization than we could find reported elsewhere. We discovered that the issue is actually the water soluble moieties on the triphenylphosphine. The sulfonate groups affect the basicity of the phosphine via a field effect. The increased basicity of the phosphine created stronger bonds with the metal center disallowing the dissociation of the ligand necessary for the catalytic cycle.

To improve the hydroformylation of linear alkenes, we should look at the possibility of using other 'tags' to impart water solubility (Fig 7-2). It would be beneficial to measure the pKa of any ligands before trying any hydroformylations. Fig 7-3 shows the relationship between conversion to isomers and pKa. The partitioning

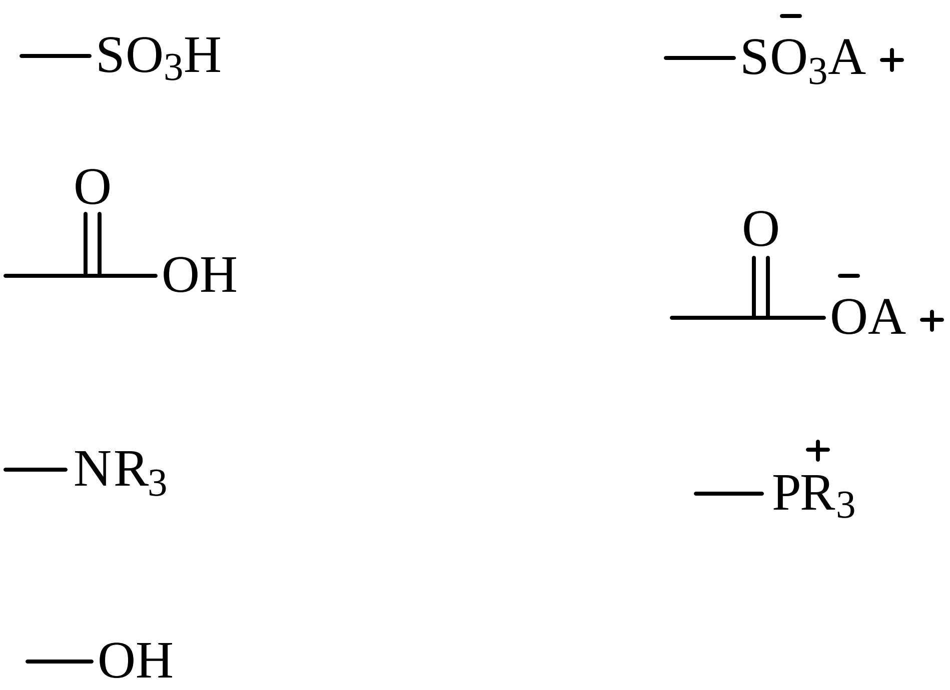

Figure 7-2 Groups that may be attached to ligands to impart water-solubility

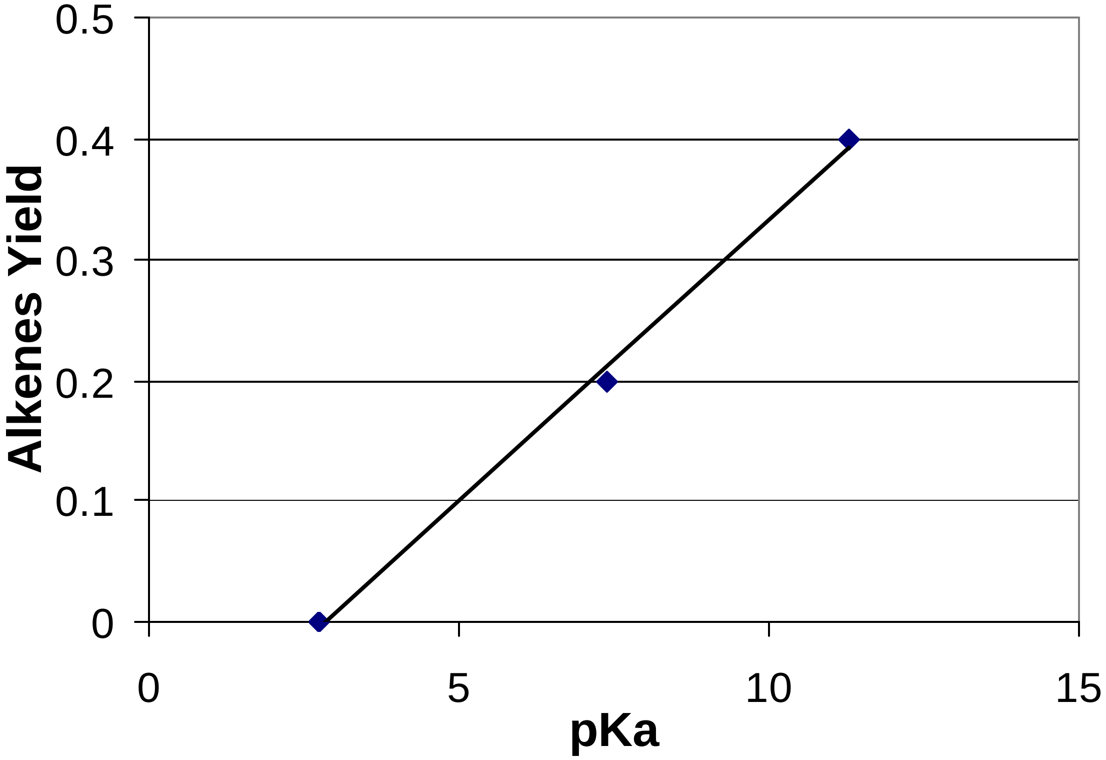

Figure 7-3 Trend of alkene yield with pKa of phospine.

should also be measured before performing any reactions to ensure that the catalyst will be able to be recycled.

Another interesting experiment would be to see if buffering the reaction mixture has any effect on the rate of isomerization. Perhaps a more basic environment would help negate the ligand binding effects. Klein et. al. have shown that at pH close to neutral selectivity to linear aldehydes is greatly increased (Klein, Jackstell et al. 2005). It would also be beneficial to rule out possible solvent effects by performing the hydroformylations in acetonitrile-water and dioxane-water mixtures.

The most important step forward, however, will be to apply this approach to more meaningful reactions. Focus should be placed on industries willing to pay the capital cost required for high pressure separations. One such arena is the pharmaceutical industry. Pharmaceutical companies are most interested in asymmetric reactions. There are many researchers investigating asymmetric hydroformylations and hydrogenations as routes to drugs and drug precursors (Nanno, Sakai et al. 1995; Horiuchi, Ohta et al. 1997; Nozaki, Nanno et al. 1997).

BINAPHOS (Figure 7-4) is one of the most promising ligands for asymmetric hydroformylations. It has also been used in the formation of (R)-2-methyl-4-aminobutanaol (Cobley, Gardner et al. 2004) which in turn is used in the formation of a potent NK_1 antagonist (Ikeura, Doi et al. 1998). More recently, it has been used on heterocyclic olefins to produce other types of biologically active molecules (Horiuchi, Ohta et al. 1997)

For water solubility, the ligand will have to be modified. The easiest method would be by direct sulfonation. Herrmann et. al. (Herrmann, Albanese et al. 1995) have proposed a method by which the degree of sulfonation can be controlled. They have used the used the method to synthesize BINAS-8 (NAPHOS with 8 sulfonate groups) as opposed to the mixture of NAPHOS with 4 to 8 sulfonate groups. They have also been able to selectively make TPPDS which would be interesting to test in our system in its own right.

Looking at the proposed catalytic cycle of Nozaki (Nozaki, Matsuo et al. 2003), the BINAPHOS ligand should not dissociate so we should not have the same problems we did with the hydroformylation of 1-octene. Even if the sulfonated version of BINAPHOS creates stronger bonds to the rhodium center, the only affect will be that of better catalyst recovery. A comparison of BINAPHOS to the sulfonated version will also help determine the validity of our hypothesis regarding the hydroformylation of 1-octene. If there is no difference between the two chiral ligands, it will more proof that our theory is right.

Organic **P**EG **T**unable **S**ystems

Our group has recently begun looking into the use of PEG systems similar to the OATS systems presented in this thesis. PEG behaves much like water in its ability to readily dissolve salts and other polar compounds. PEG is also fully miscible with the same types of organic solvents that water is at ambient conditions. For these reasons, PEG seems like a good alternative to water in our OATS systems for reactions that may be sensitive to water. Asymmetric hydrogenations are typically very sensitive to water in the system (Herrmann 1993). Water will drastically reduce the enantiomeric excess for several such reactions. It only makes sense that the asymmetric hydrogenations can be examined in these systems instead.

A sulfonated form of BINAP (Figure 7-5) has been prepared (Wan and Davis 1993) and used by Wan (Wan and Davis 1994) in a supported aqueous phase. No metal leaching was observed, but e.e.'s were limited by the fact the ruthenium complex was in water. When methanol was used as the solvent, e.e.'s of up to 96.1% were observed. In our PEG systems, we should be able to obtain execellent e.e.'s and still maintain nearly quantitative catalyst partitioning.

Wan and Davis used the catalyst in a route to naproxen (Figure 7-6). The 2-(6'-methoxy-2'-naphtyl)acrylic acid used for the reaction is not commercially available. A similar precursor (atropic acid) is available but costs roughly 50 times as much as the naproxen. A more industrially relevant reaction may be that of the production (S)-Metolachlor (Fig. 7-7). Roughly 10,000 tons a year are produced making it the largest scale asymmetric hydrogenation (Cornils and Herrmann 1998).

Several groups are also using the same ligand in the hydrogenation of ketones to form chiral alcohols (Guo, Lough et al. 2004; Hu and Lin 2005) which are widely used in the fine chemicals industry.

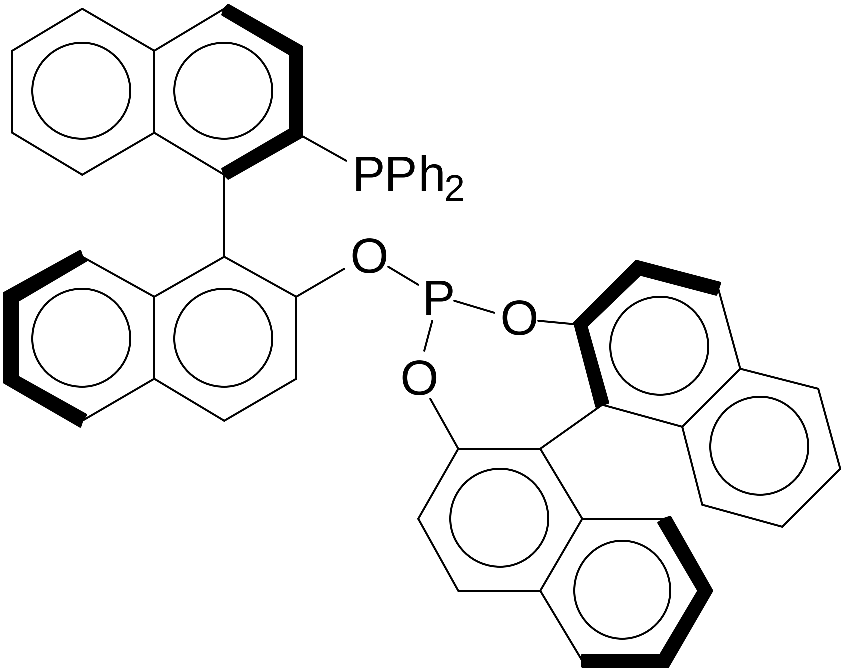

Figure 7-4 BINAPHOS Ligand

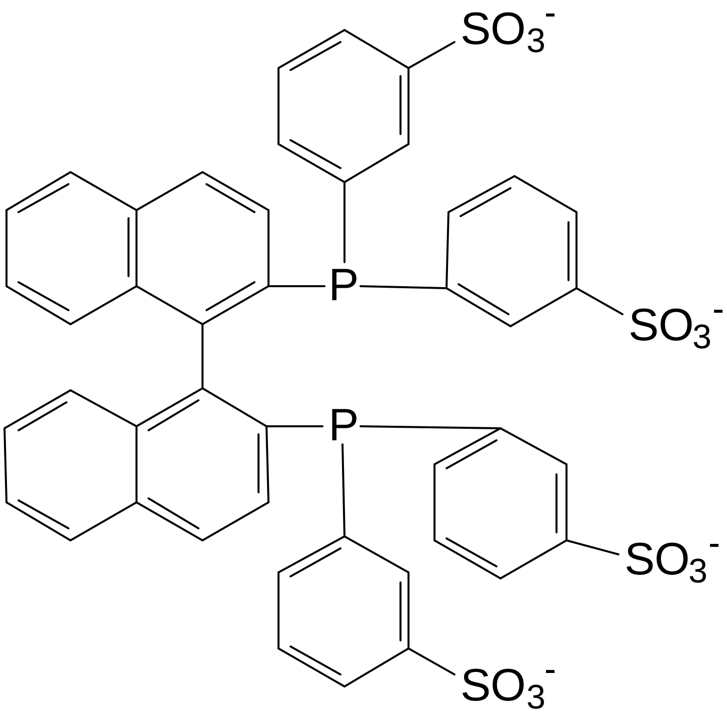

Figure 7-5 Sulfonated BINAP

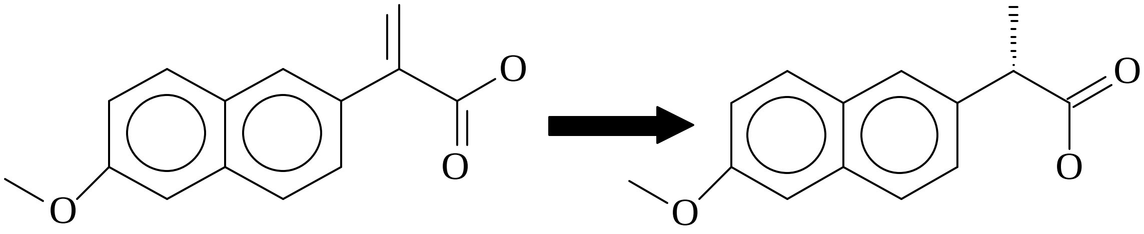

Figure 7-6 Asymmetric hydrogenation of 2-(6’-methoxy-2’-naphtyl)acrylic acid to form Naproxen

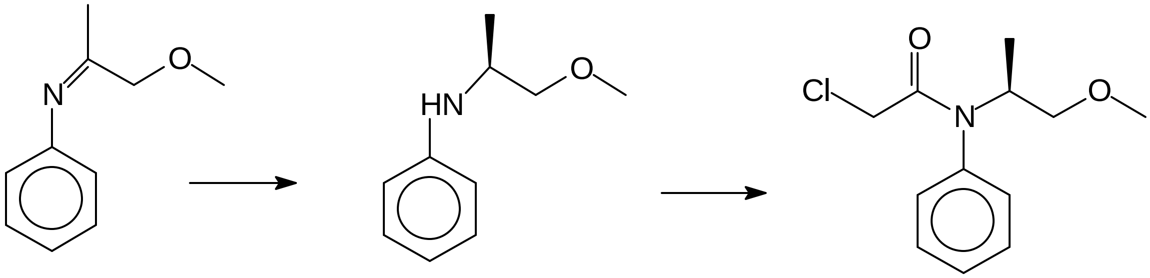

Figure 7-7 Two step production of (S)-Metolachlor

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