# DESIGNING PHASE SELECTIVE SOLUBLE POLYMERS FOR APPLICATIONS IN ORGANIC CHEMISTRY

A Dissertation

by

CHUNMEI LI

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

August 2003

Major Subject: Chemistry

# DESIGNING PHASE SELECTIVE SOLUBLE POLYMERS FOR APPLICATIONS IN ORGANIC CHEMISTRY

A Dissertation

by

CHUNMEI LI

Submitted to Texas A&M University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Approved as to style and content by:

David E. Bergbreiter
(Chair of Committee)

Eric E. Simanek
(Member)

Francois P. Gabbai
(Member)

Aydin Akgerman
(Member)

Emile A. Schweikert
(Head of Department)

August 2003

Major Subject: Chemistry

# ABSTRACT

Designing Phase Selective Soluble Polymers for Applications in Organic Chemistry.

(August 2003)

Chunmei Li, B.E., Dalian University of Technology

Chair of Advisory Committee: Dr. David E. Bergbreiter

Soluble polymers as supports are gaining more attention now. Developing new polymers, new reagents and catalysts, new separation systems are thus of great interest as these sorts of materials' applications in synthesis and catalysis increase. The work described in the succeeding chapters describes my efforts to synthesize new catalysts that can be attached to polymer supports, to study their catalytic activity and to study separation efficiency. Most of the work is on polyacrylamide polymers. Both organometallic catalysts and organic catalysts have been studied. Liquid/liquid separation was the technique mainly investigated. In addition, a new separation scheme called latent biphasic system which is a new liquid/liquid separation method is described. Finally, studies with the Cremer group where the LCST behavior of polyacrylamides was studied using dark field methods are also discussed.

# ACKNOWLEDGMENTS

I would like to thank my advisor, Dr. David Bergbreiter, for his guidance in both chemistry and research ethics, for his enthusiasm towards my research, and for putting education at a higher place than publishing papers. A Ph.D. degree might not be anything impressive, but to me it is a great success, comparing how much I knew when I walked into Dr. Bergbreiter's group five years ago and how much I know now. The training in Chemistry and English, and the encouragement and influence I obtained from Dr. Bergbreiter, mean much more to my life than what can be represented by a degree certificate.

I would like to thank Dr. Yunshan Liu, who convinced me to join Dr. Bergbreiter's group and constantly gave me advice on my research throughout my graduate career; Dr. Philip L. Osburn, who gave me a tremendous amount of help in lab techniques as well as chemistry knowledge; Dr. Justine G. Franchina, for getting me familiarized with doing chemistry experiments five years ago, from how to use hot plates to how to run polymerizations. Other former and current group members, Dr. Jonathon D. Frels, Andrew M.  Kippenberger, Steven M. Furyk, Dr. Jun Li are also acknowledged for frequently discussing my research with me. I thank my collaborators Dr. Paul S. Cremer, Dr. Eric E. Simanek, Dr. Hanbin Mao, Dr. Yanjie Zhang and Sergio O. Gonzales for making my chemistry applicable to broader situations. I thank Dr.

Karine G. Poullennec and Bin Wu for helping me with my chemistry courses in my first semester here.

I thank Dr. Eric E. Simanek, Dr. Francois P. Gabbai, Dr. Aydin Akgerman for serving as my committee members.

I thank my mother, Yingshu Cui, and my father, Quande Li, for their education and guidance. I thank my brother, Haitao Li, and my sister-in-law, Liqiu Cui, who came to Texas A&M together with me, and made my life much easier. I thank my friends, Loan K. Vo, Mr. and Mrs. Pennington, Zhihong Wang and Jianqiu Fu for their emotional support and for making my graduate career more colorful.

Finally, I would like to acknowledge the National Science foundation, the Welch Foundation and the Petroleum Research Foundation for their financial support to make this research possible.

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

FIGURE Page

# CHAPTER I

# INTRODUCTION

While polymers are widely recognized as important components of the materials used in society, they also have important roles in synthesis. With the development of combinatorial chemistry, solid-phase organic syntheses that employ polymers have been extensively used to make large libraries of compounds, such as quinoline derivatives, amino ketones, amino esters, amino nitriles, amino sugars, and alditol derivatives, etc.[1,2] Attaching reagents or catalysts onto polymer supports leads to many advantages that traditional solution phase chemistry does not offer. Most importantly, polymer-supported species can be easily separated from the rest of the material by using their solubility properties. In addition to simple purification, such separations also make it possible to use an excess amount of reagents to drive reactions to completion because these unused reagents do not complicate the purification process. Moreover, the polymer-bound species once isolated can be recycled for multiple steps if the polymer is not changed in the reactions.

## History

Ion exchange resins were the earliest polymers to make a significant impact as synthetic reactive polymers.[3,4] They were first prepared in 1935 as materials for water

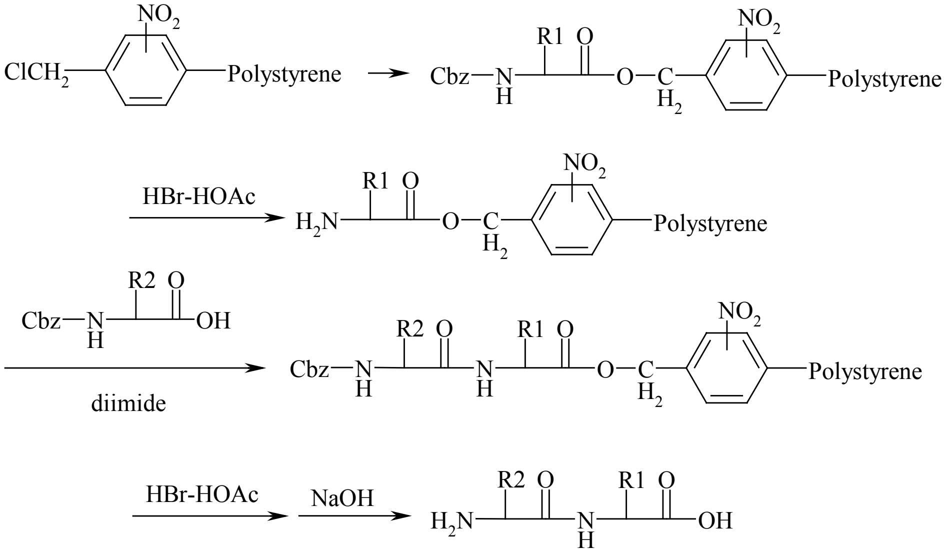
---

This dissertation follows the style and format of *Journal of the American Chemical Society.*

treatment. The initial resins used were condensation polymers formed from the reactions of formaldehyde with phenolic or aromatic amine derivatives. Later cation exchangers and anion exchangers based on crosslinked polymers of vinyl aromatic hydrocarbons appeared in both Europe and the United States. Indeed, the advent of ammonium hydroxide supported on these polymers as strong-base anion exchangers in the 1950s made complete water demineralization possible resulting in a new industry that continues today.[5,6]

In the 1960s, Merrifield reported the use of crosslinked polystyrene in peptide synthesis.[7] This concept of using polymers as supports for peptide synthesis brought synthetic chemistry into a new era. Merrifield subsequently received the Nobel Prize for this revolutionary work -- work that constitutes one of the bases for the current biotechnology revolution.

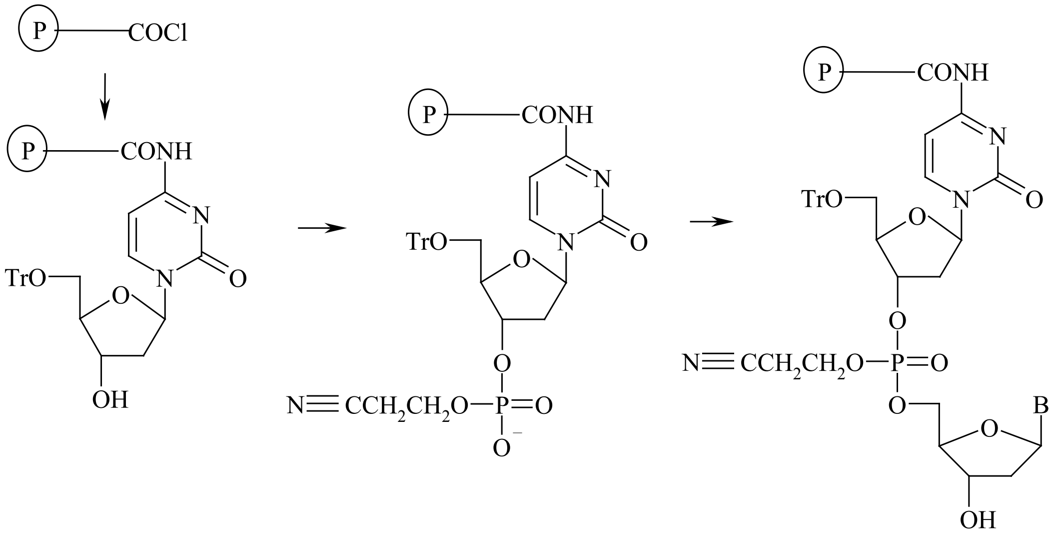
The polymer support used by Merrifield was a copolymer of styrene and divinylbenzene with varying degrees of cross linking. Functionalization of this or other polymer supports can be accomplished by methods such as polymerization or copolymerization of monomers with the desired functionality, by chemical modification of preexisting polymers to obtain the target functional groups, or by combining both methods. Merrifield’s resin was partially chloromethylated after polymerization then nitrated to provide a site for attachment of an *N*-protected amino acid to the bead. Nitration was necessary because the benzyl ether linkage without the nitro group was not stable to the acidic condition required for removal of Cbz group. Attaching the amino acid to the polymer not only immobilized the amino acid, but also isolated it from other molecules such as other amino acids bound to the same bead. Once the *N*-protecting group was removed, the polymer-bound amino acid could be coupled to a second *N*-protected amino acid by standard peptide synthesis methodology. After deprotection of the amino group of the dipeptide so formed, a third amino acid could be attached. These coupling reactions could be repeated until the desired polypeptide was built up. Then the peptide was cleaved from the polymer by a series of now standard cleavage reactions to obtain the target polypeptide.



Scheme 1. Peptide synthesis using Merrifield resin

Peptide synthesis requires a large amount of repetitive reactions, so the chemistry without polymer supports involves tedious purification steps. The overall yield is typically too low to be practical. When the synthesis is carried out on the solid support, only a simple filtration is required for purification. The overall yield does not drop much even if long peptide chains are being synthesized. This procedure can be carried out by an automated system where all the steps are carried out mechanically without tedious manual operations.[8,9,10] In an automated system, the supporting resin containing the C-terminal amino acid was left in the reaction chamber during the entire synthesis. Thus, the manipulations required for the synthesis of a polypeptide chain consisted simply of pumping the proper solvents or regents into and out of the vessel in a certain sequence at certain times. Several companies produce automatic peptide synthesizers that use this methodology.[11]

Soon after Merrifield's polystyrene resin came into being, Letsinger introduced solid phase oligonucleotide synthesis.[12] In his procedure, a polystyrene resin was again used but with an acid chloride as the reactive functional group. The first deoxyribonucleoside A, G, or C was then attached to the resin through its side chain amino-group. The free 3'-hydroxy group was phosphorylated with an activated phosphomonoester, and the resulting phosphodiester was again activated and coupled with a second nucleotide. The free 3'-hydroxyl group on the resulting nucleotide then served as a new linker, so that an additional nucleotide unit could be added to the chain by repetition of the phosphorylation, activation, and condensation steps.



Scheme 2. Synthesis of oligonucleotide using polystyrene resin

The application of polystyrene supports in peptide and nucleotide synthesis greatly facilitated the synthesis and purification of these biologically important materials. Long peptides and nucleotides are now routinely synthesized with high yield and high accuracy predominantly using solid supports.

Merrifield's concept of carrying out synthesis on polymer supports not only revolutionized the fields of peptide synthesis and oligonucleotide synthesis, but also spread quickly to other areas of organic chemistry. Many organic synthetic reactions have now been performed on solid phase. This includes the synthesis of oligosaccharides[13,14,15,16] and the synthesis of ketones and aldehydes,[17] etc.

Although crosslinked polystyrene is still the most commonly used insoluble support for synthesis, other heterogeneous polymer supports have been developed too. For example, Sheppard has used polydimethylacylamide as a support for solid phase synthesis of peptides.[18] He used polyacrylamide resins with ethylene bisacrylamide crosslinks as a support. This polymer, unlike commercially available polyacrylamide which has methylene bisacrylamide as the crosslinking agent, is completely stable under the reaction conditions required. This polymer is very polar. It swells 10-15 fold in *N, N*-dimethylformamide (DMF). It is commercially available under the name Pepsyn. Other later modifications were made on this polymer to make it even more suitable for peptide synthesis. [19,20,21]

Insoluble inorganic supports can be used too. Adams used controlled pore glass (CPG) as a solid support for nucleotide synthesis. The glass was functionalized with long-chain alkylamine groups. The coated glass displayed exceptional properties: it was rigid and nonswelling; it was chemically stable to a broad range of nucleophilic and electrophilic reagents; it was stable to heat. Most importantly, the coupling reactions were nearly quantitative because the amino functionality was very reactive in the initial condensation with 3'-succinoyl nucleosides, and the phosphoramidite reagents had good accessibility to the 5'-hydroxyl groups on the growing DNA chain. The experiments aiming at making long nucleotide sequences were very successful. Repetitive cycle yields were above 98% in all the cases when different nucleotide sequences were synthesized.[22]

Cotton also has some attractive properties as a common polymer for support of reagents and catalysts. It can be cut into pieces whose exact size is appropriate to the scale of the synthesis. The pieces can be transferred between steps of the synthesis simply by using tweezers. Cotton can be dipped into the respective solutions and dried by squeezing it between two pieces of filter paper or by centrifugation. The cotton pieces can be easily processed without filtration. It has been used for synthesis,[23] including synthesis of libraries.[24]

For example, Schwabacher has used cotton threads as linear supports to prepare peptides and to evaluate binding of a small library of peptides to streptavidin.[25] In his procedure, the support was wrapped around cylinders of different diameters for each reaction step. This meant that various positions on the linear support were correlated with specific synthetic protocols. Thus, the product thread had libraries of peptides organized in a one dimensional sequence up and down the thread. Since the reactions took place on many sections of the linear support simultaneously with each reagent handled only once per step, the synthesis was fully parallel. Evaluation of the combinatorial library was carried out by treatment of the thread library with fluorophores. Localization of fluorescence at a particular region along the thread indicated binding to the library member in that position. The fluorescence properties of each region were monitored sequentially by pulling the thread through a fluorometer at a constant speed, resulting in a time trace of fluorescence signals. Using this approach, full library analysis and fully parallel synthesis could be realized simultaneously.

Graft copolymers of styrene and ethylene glycol (PS-PEG) were also made. For example, the first TentaGel was synthesized in 1981 by grafting ethylene oxide from a polystyrene backbone using a benzyl ether linkage.[26] This first generation of PS-PEG resin was mainly used in solid-phase peptide synthesis and oligonucleotide synthesis. As the resin showed excellent pressure resistance, it was used, at that time, in newly developed flow through peptide synthesizers. To improve its acid stability, the second generation of TentaGel was designed with ethylene functionality as the linker between PEG and polystyrene instead of the methylene group, as shown in Figure 1.[27] The PS-PEG beads displayed relatively uniform swelling in a variety of solvents with medium to high polarity, ranging from toluene to water. Substrates on this support exhibited excellent reaction kinetics in peptide synthesis.[28]

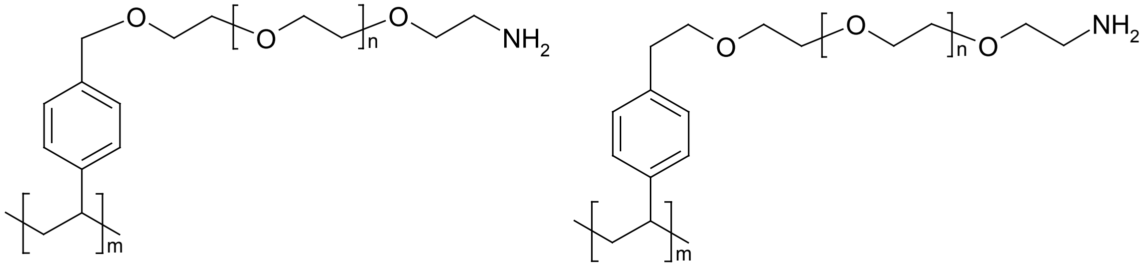
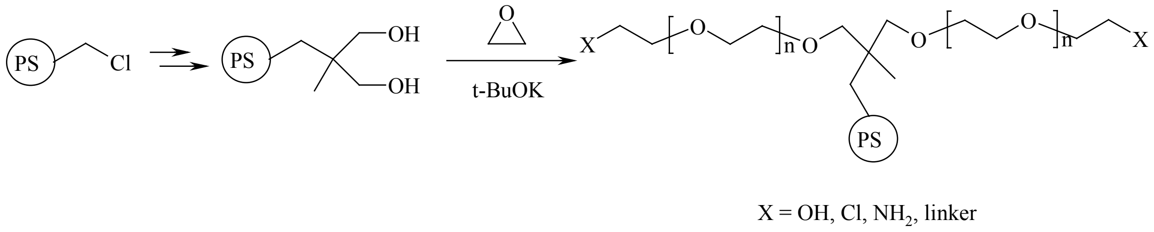


Figure 1. TentaGel (original formulation and current formulation)

Gooding's approach to improve the acid stability of the first generation TentaGel was to replace the benzyl ether linkage with an aliphatic linkage.[29] The functional group loading was increased by bifurcation prior to ethylene oxide grafting, as shown in Scheme 3.



Scheme 3. Preparation of ArgoGel

The polymer was known as "ArgoGel(AG)". AG-OH and AG-$NH_2$ displayed excellent chemical stability to the strongly acidic conditions often employed in TFA cleavage. This new PS-PEG graft copolymer had twice the loading capacity relative to conventional monofunctional PS-PEG graft copolymers, while the equivalent PEG molecular weights remained the same. The resins also displayed good swelling in solvents ranging from toluene to water. ArgoGel became commercially available in 1996, and has been used in many syntheses including the preparation of substituted imidazoles,[30] *N*-alkyl sulfonamides,[31,32] acylamines,[33,34] 4-arylazetidin-2-ones,[35] aminothiazoles,[36] and benzofurans.[37]

## Soluble polymer supports

All the polymers and supports mentioned above are insoluble. However, soluble polymers are gaining increasing attention as supports throughout all stages of a synthesis and purification process since they can combine the advantages of homogeneous reactions, solution phase characterization and simple separations. Since chemistry occurs in the solution phase, the reaction conditions that work in classical organic chemistry can be applied in a synthesis with the polymer support. Purification can occur in a variety of ways but is generally facilitated through application of macromolecular properties of the support. Routine characterization methods, such as UV-vis[38], IR, $^1$H NMR[39], $^{13}$C NMR spectroscopies[40], titration, derivatization and relaxation time effects[41] can all be used to characterize the polymer-bound species. Some new approaches for separation, recovery and recycling of homogeneous catalysts are reviewed recently in *Science*.[42]

## Separating soluble polymers from solution

### *Solid/liquid separation*

There are a variety of ways to separate soluble polymers from solution, and they basically fall into two categories: solid/liquid separation and liquid/liquid separation. Solvent precipitation is among the earliest solid/liquid separation methods used for recovery and reuse of soluble polymer-bound catalysts. In this scheme (Figure 2), a polymer-bound catalyst is first prepared and characterized. It is then added to a solution of the substrate. After the product has formed, the solution of polymer-bound catalyst and product is added to an excess of a solvent that is a poor solvent for the polymer but a good solvent for the product. This leads to precipitation of the polymer and the catalyst that bound to the polymer. Solid/liquid separation via centrifugation or filtration then yields the solid polymer-bound catalyst that can be redissolved in fresh solvent with fresh substrate and reused.

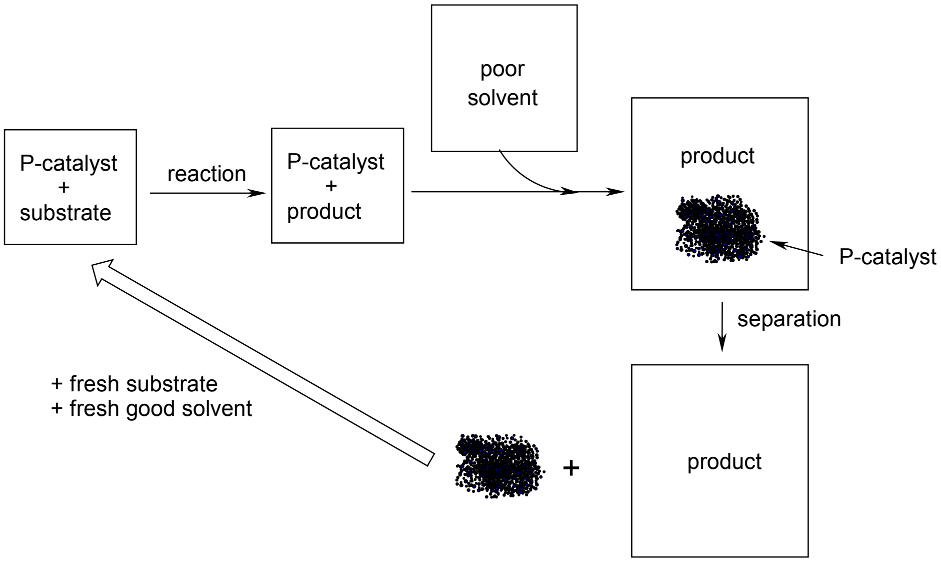


Figure 2. Using solvent precipitation to recycle polymer-bound catalysts

Polymer precipitation can also be used in bioseparations. These procedures often involve several precipitation steps. First, a ligand specific for a target protein is conjugated to a soluble polymer. This synthetic step itself might employ a solvent precipitation as a purification step. Then, this polymer-ligand adduct is redissolved in an appropriate solvent and added to a solution of the protein target. If affinity precipitation occurs, complex formation leads to precipitation of the protein/polymer-ligand complex. The desired protein can then be isolated from this insoluble precipitate by various methods. In some cases, a solvent can be used that will wash the protein off this protein/polymer-ligand complex without concomitant dissolution of the polymer-ligand species. In other cases, the solid is redissolved in another solvent under conditions where the protein can dissociate from the complex. Selective precipitation of the polymer from this solution then produces a solution containing only protein. Various ligands such as triazine dyes, sugars, protease inhibitors, antibodies and nucleotides have all been successfully used for such affinity separations. [43]

Some polymers have solubility that depends on temperature. In many cases, a polymer is soluble at high temperatures but insoluble when cooled down. These types of polymers are said to have normal temperature dependent solubility. Polymers with this property can be easily separated from solution. They can be dissolved at high temperatures, and when they are done serving their function, the solution can be cooled down so that the polymers and species bound to them precipitate. Filtration or centrifugation then separates the polymers from the rest of the material, as shown in Figure 3.

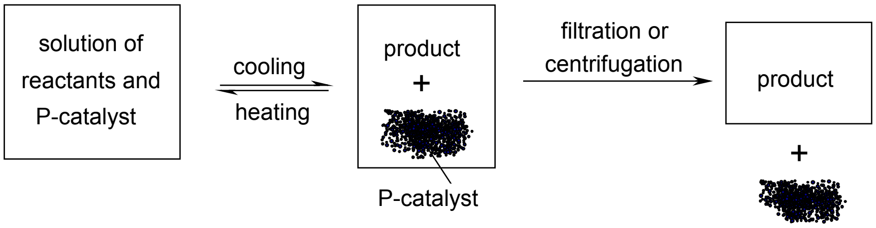
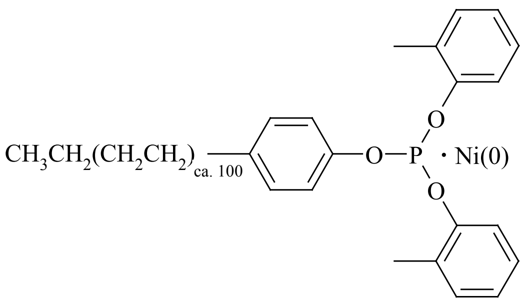


Figure 3. Separating polymers with normal temperature dependent solubility

Polyethylene is a typical example of a polymer with strong normal temperature-dependent solubility. It does not dissolve in any regular organic solvent at room temperature. However, it has very good solubility when heated. For example, it forms a solution in toluene at elevated temperature with a concentration of 1 g of polymer/10 mL of solvent.

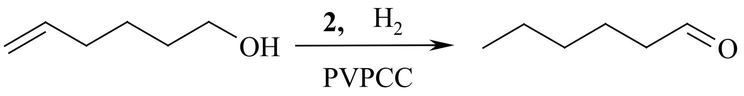
Bergbreiter's group was the first to take advantage of the temperature-dependent solubility of polyethylene to design recoverable but soluble polymer supports for catalysts. Using the separation scheme shown in Figure 3, polyethylene was successfully used as a recoverable support for ligands or catalysts for reactions such as hydrogenation,[41] hydroformylation,[44] allylic substitution,[45] etc. In all cases, reactions were carried out in homogeneous conditions at elevated temperatures, and separations were done by filtration or centrifugation at room temperature. The solubility property of these catalysts was a direct consequence of the solubility characteristics of the polyethylene portion of this polymer. The solid precipitated cleanly. Products or starting material that are not attached to the polyethylene oligomer did not contaminate the recovered catalyst.

Polyethylene-bound triarylphosphite is an example of the pioneering work in this area. Here the polyethylene was used to support Ni(0) to form a catalyst (**1**) for butadiene cyclooligomerization.[46] The reactions were carried out in toluene at 100 $^{o}$C. This polymer-bound catalyst exhibited the same selectivity and reactivity as its low molecular weight analogue. Furthermore, when the ligand to metal ratio was changed, the influence on the product selectivity of this varying ligand:nickel ratio was the same as similar experiments done with a low molecular weight catalyst and ligand. After reactions, the mixture was cooled down to room temperature, and the polymer-bound catalyst precipitated from solution. After filtration in inert atmosphere, the catalyst could be isolated and reused for multiple cycles.



**1**

Polymer supports make traditional chemistry easier to carry out. Sometimes they even make impossible things possible. For example, phosphine-ligated metal species usually cannot coexist with a strong oxidizing agent. An oxidizing agent oxidizes the phosphine species and leads to dissociation of the attached metal. However, a simultaneous oxidation/reduction reaction using these two types of reagents was carried out using polymers as supports.[47] The reaction was shown in equation 1.

 (1)

**2** = $[CH_3(CH_2CH_2)nCH_2PPh_2]_3RhCl$

The Rh catalyst for this hydrogenation was attached to nonpolar polyethylene, to form catalyst **2**. The oxidizing reagent was a polar ion exchange polymer -- insoluble poly(vinylpyridinium chlorochromate) (PVPCC). The different polarity of polyethylene and PVPCC made mixing of these polymers and hence the reagents on the polymers energetically unfavorable. Thus, the otherwise incompatible Cr(VI) and Rh(I) species could be used simultaneously. After the reaction, the products and the two polymeric reagents could be easily separated using their different solubility properties. Filtration at high temperature first isolated the insoluble oxidant from the rest of the material. Then the solution was cooled down to room temperature. The polyethylene-supported Rh(I) catalyst precipitated from solution, ready to be filtered and recycled.

There are also examples where soluble polymers have inverse temperature-dependent solubility. These polymers are soluble at low temperature but insoluble when heated. Polymers with this type of solubility property can be used as supports for recoverable catalysts if the process is reversible. A catalytic reaction can be done at low temperature homogeneously. After the reaction, the solution can be heated to precipitate the polymer-bound catalysts. Filtration or centrifugation then separates the polymer from the substrates and products, as shown in Figure 4.

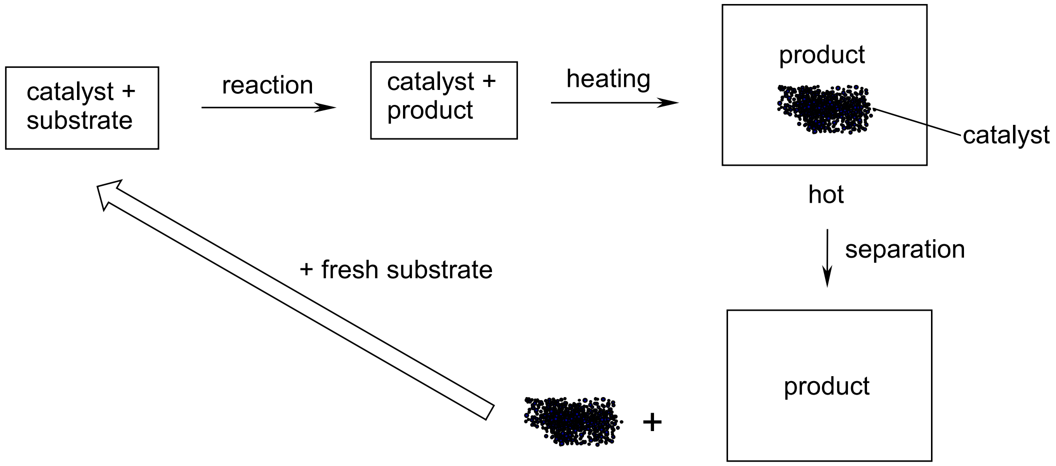
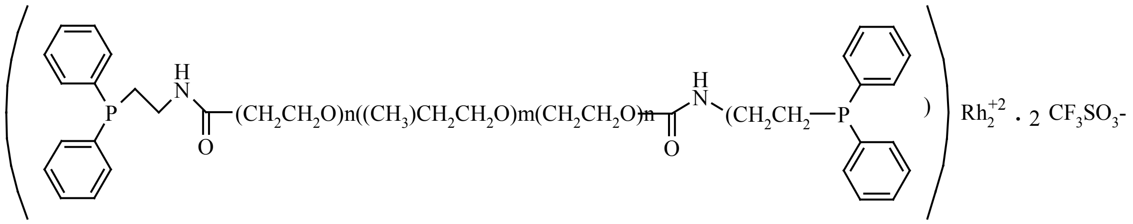


Figure 4. Separation of polymers with inverse temperature-dependent solubility

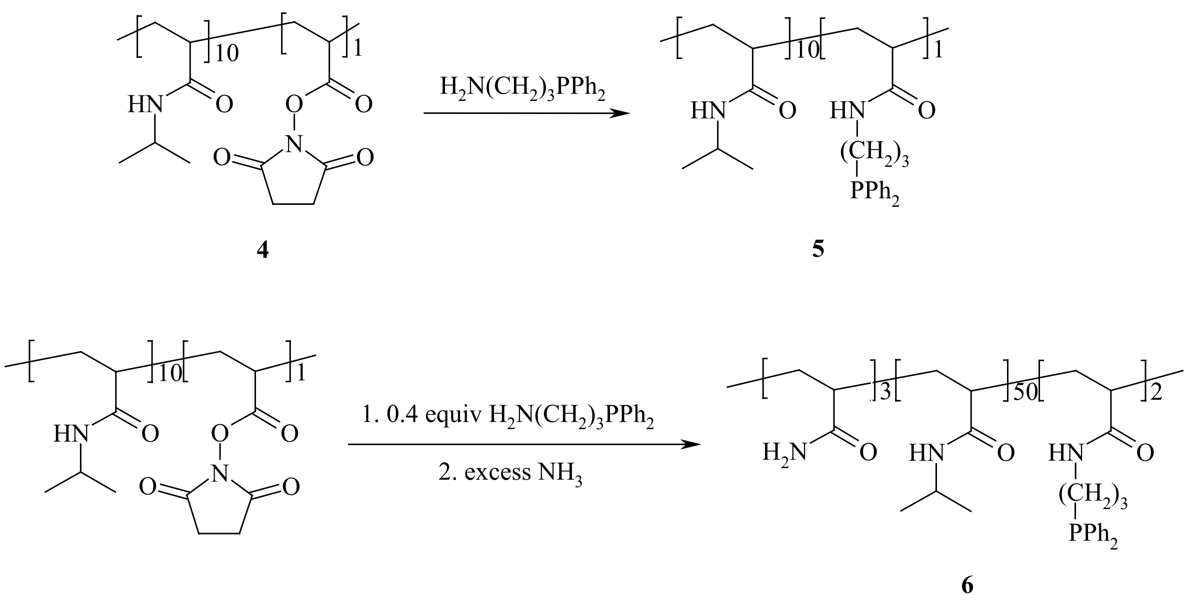
The temperature at which such phase separation occurs is called the lower critical solution temperature (LCST).[48] Most of the common examples seen occur in aqueous solutions between 0 and 100 $^{o}$C. Examples in other solvents were reported, too.[49] However, in other solvents the precipitation or phase separation of a polymer often occurs above the boiling point of the solvent, requiring a pressurized apparatus.

Precipitation on heating was first used to prepare "smart" polymers for catalysts and substrates.[50,51,52,53] Smart materials respond to changes in their environment in predictable and pronounced ways. This effect was first shown using commercially available triblock copolymers of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) as a support for phosphine ligands. The cationic Rh(I) catalyst supported on this ligand had an activity controllable by the "smart" ligand with changing temperature.[50] The block copolymer used had an inverse temperature dependent solubility in water. The exact LCST varied with the proportion of PEO/PPO in the starting oligomer. A typical oligomer having a molecular weight of 2500 and 20 mol% ethylene oxide was soluble at 0 °C in water but insoluble above room temperature. When the cationic Rh(I) catalyst **3** was prepared, it proved to be competent in catalysis of a hydrogenation reaction of allyl alcohol in water at 25 °C. When heated up to 50 °C, the reaction stopped due to the precipitation of the catalyst **3.** This process was fully reversible. This behavior is potentially useful for regulating exothermic reactions. However, this catalyst was not recycled. The polymeric catalyst turned into an oily phase when heated and it was not practical to recover this oily phase.



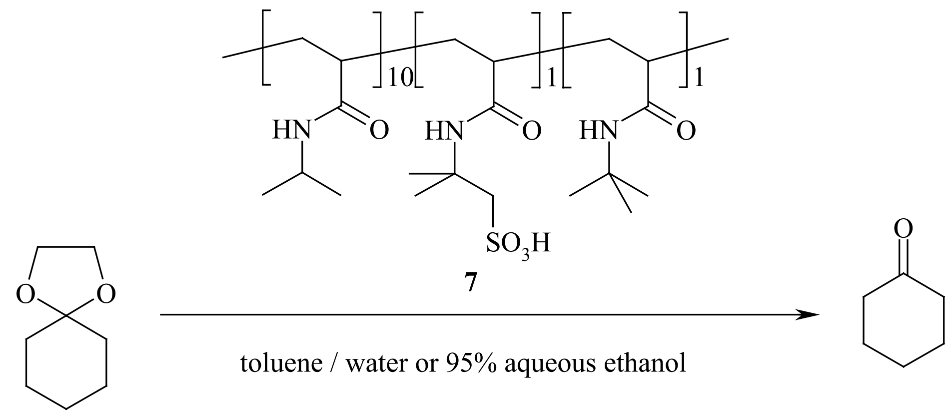
**3**

Poly(*N*-isopropylacrylamide) (PNIPAM) separates as solid from aqueous solutions on heating,[54] and the precipitation temperature can be tuned by comonomers. For example, PNIPAM was used as a support for a phosphine ligand so that the ligand could be recovered from the aqueous solution by heating.[55] However, due to the hydrophobicity of the aminopropyldiphenylphosphine, the copolymer **5** obtained from reacting aminopropyldiphenylphosphine with PNIPAM-supported active ester NASI was insoluble in water. In order to obtain a PNIPAM-supported phosphine ligand soluble in water, a substoichiometric amount of this aminated phosphine ligand was used to consume a portion of the active ester groups in **4**. The remaining active ester was converted to a more hydrophilic amide group. The polymer **6** so obtained was hydrophilic enough that it did dissolve in water or mixed aqueous/organic media at room temperature. However, it was still hydrophobic enough to precipitate when heated. The polymer precipitate could be isolated using filtration and was reusable. This phosphine ligand was used to support Pd(0) for nucleophilic allylic substitution reactions and sp-sp$^2$ coupling reactions of aryl iodides with terminal alkynes. The activities observed were comparable to activities seen for their low molecular weight complexes with alkyldiphenylphosphine ligated Pd(0).



Scheme 4. Changing the hydrophilic/hydrophobic balance for tuning the LCST of PNIPAM support

Using a mixture of amines with different hydrophilicity is a general approach to tune the LCST of a polymer. Another example is the polymer **7**.[50] The copolymer of *N*-isopropylacrylamide and the acrylamide containing the sulfonic acid was too hydrophilic to precipitate below 100 °C, so *N-tert*-butylacrylamide was introduced as the third monomer to increase the hydrophobicity of the copolymer. The LCST of the terpolymer **7** obtained was 33 – 35 °C, which was a very convenient temperature range to work with. The acid catalyst was active in acetal hydrolysis, such as hydrolysis of the dioxospirodecane shown in equation 2. Catalytic activity could be turned on or off by cooling or heating, since the solubility of the catalyst responded to the temperature change. The catalyst could be precipitated from solution by heating. It was reusable after filtration. The separation was shown to be complete by dye-labeling.



7

toluene / water or 95% aqueous ethanol

(2)

Wong and others immobilized enzymes on polyacrylamide.[56,57,58] The supported enzymes were nearly as active as their soluble forms, and could be recovered for reuse after gentle heating and precipitation. PNIPAM was also used in industry to generate recoverable and reusable “smart” catalysts for biotechnology and chiral chemistry applications.[59]

Oligosaccharides have also been synthesized on the polyacrylamide through enzymatic glycosylation by Wong and Bergbreiter.[56] The products were isolated with polymer conjugates by thermal precipitation. Then the desired trisaccharide was cleaved from the polymer. Compared to other solution-phase and solid-phase oligosaccharide syntheses, this method greatly simplified product purification since size exclusion chromatography was not required to isolate the product from the reaction mixture.

Precipitation of polymers from water solutions can also be induced by pH change. For example, methyl methacrylate-methyacrylic acid copolymers precipitate from aqueous solutions on acidification to pH 5, whereas methyl methacrylate-dimethylaminethylmethacrylate copolymers are soluble in acidic conditions but precipitate from slightly alkaline media.[60] After such a polymer precipitates, it can be isolated by filtration or centrifugation. By adding a fresh solution with the appropriate pH, a catalyst bound to this polymer can be redissolved and reused, as shown in Figure 5.

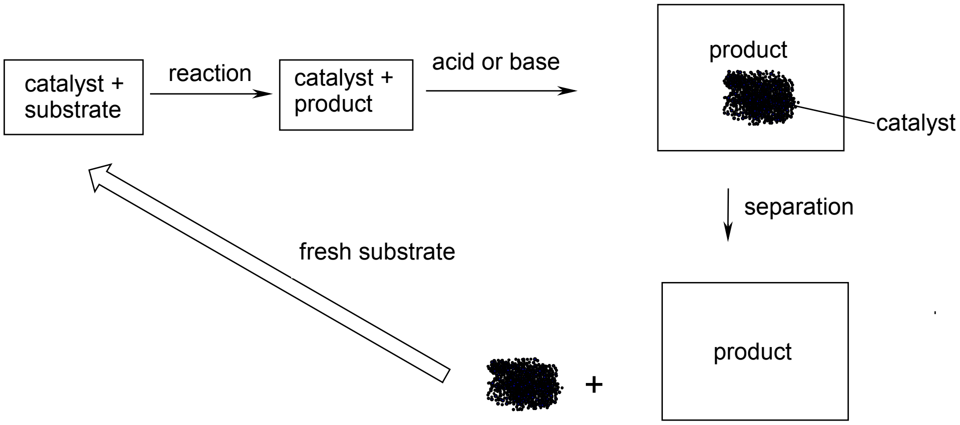


Figure 5. Separation of soluble polymers by pH change

A wide range of smart polymers has been used for the development of reversibly soluble biocatalysts whose solubility is controlled by pH[61,62]. For example, hydroxypropylmethylcellulose acetate succinate is a pH-responsive, reversibly soluble polymer. It was used to immobilize β-glucosidase for repeated hydrolysis of the water-insoluble compound phlorizidin. About 75% of the initial activity of the supported catalyst was retained after five cycles.[63]

pH-responsive polymers have also been used in drug delivery. For example, a dry pH-responsive polymer, poly[(*N*, *N*-dimethylamino)ethyl methacrylate-co-ethylacrylamide] was mechanically mixed and compressed with glucose oxidase, bovine serum albumin and insulin to produce an insulin-loaded matrix. When this matrix was exposed to glucose, it oxidized glucose to form gluconic acid. This decreased the pH, which resulted in protonation and swelling of the polymer which released insulin. The

Separation of soluble polymers by pH change insulin release stopped within 10 min of glucose removal and could be a restimulated by glucose addition.[64]

### *Liquid/liquid separation*

Liquid/liquid separation is a way of separating a soluble polymer when the polymer has selective solubility in one phase of a biphasic mixure. Such a process can actually be even simpler than filtration. Indeed, extraction is involved in the work up of most organic reactions.

Membrane filtration is a useful liquid/liquid separation technique used to separate a solution of a polymer from a solution of a product. In this method, pressure gradients speed the separation of polymer from the rest of the material using a membrane whose permeability effects separation of species based on their difference in size.[65] It was used in some of the earliest work using soluble polymer-bound catalysts, although the efficiency of recovery may not always be high enough for practical use in a continuous reactor. It was also well adapted to separation of dendrimer-bound catalysts because of the globular structure of these hyperbranched polymers. With membrane systems, catalysts can be used in continuous reactions, shown in Figure 6, while other separations offer using catalyst in batch-type processes. When a polymer-bound catalyst is used in a continuous-flow membrane reactor (CFMR) with membrane filtration, depletion of the polymer through the membrane has to be considered. For practical applications, the overall retention of the polymer must be very high to keep a high activity in a CFMR for long reaction times. If a polymer has retention of 0.95, only 25% of the polymer remains in the reactor after the reactor has been flushed with 30 times its volume of a solvent. To obtain a catalyst system that remains in the reactor over a prolonged period of time, retention of at least 0.999 is required.[66]

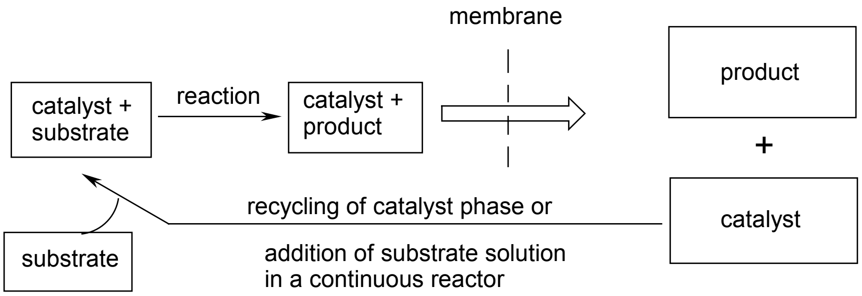
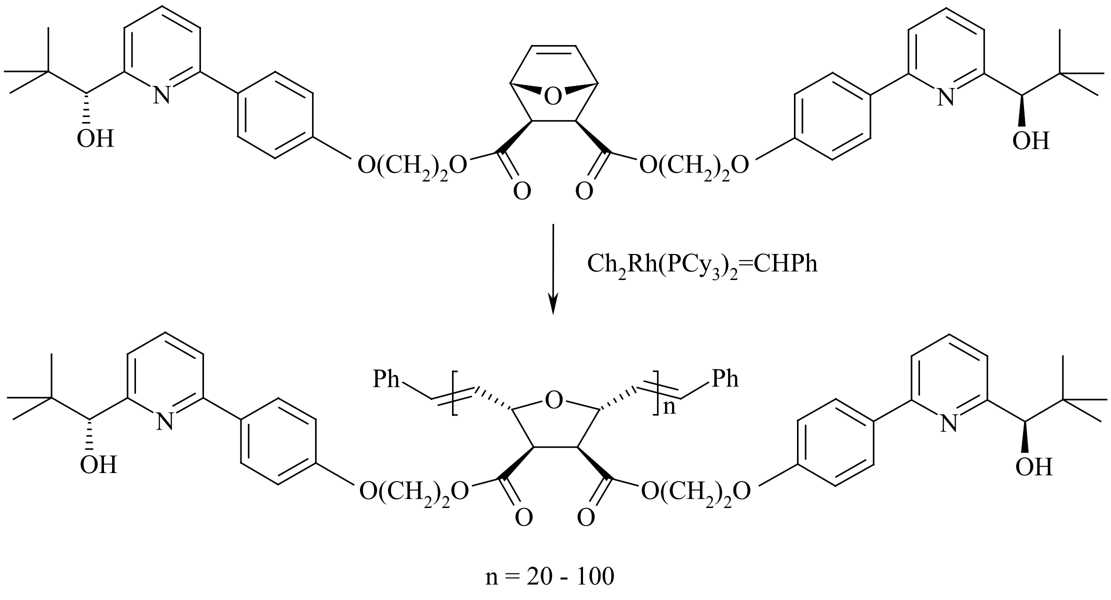


Figure 6. Separating soluble polymers using membrane filtration

Polymer **8** derived from a metathesis polymerization (Scheme 5) is an example of a new type of polymer that was used to support a catalyst and was recovered using ultrafiltration. The size of this polymer is such that it could be separated from the products by ultrafiltration.[67]

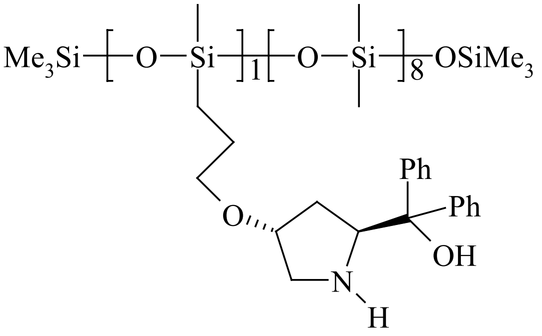


**8**

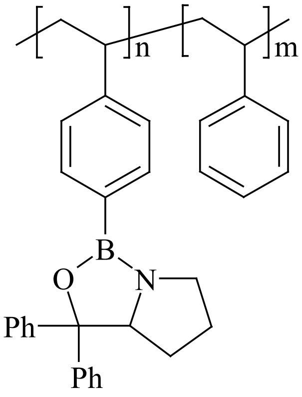
Scheme 5. Synthesis of polymer **8** recoverable by ultrafiltration

Ultrafiltration was also used to recover catalytically active Rh(I) complexes that were ionically tethered to soluble polyelectrolytes.[68] The soluble polymer used in this example is a poly(diallyldimethyl ammonium salt). The anions are mixtures of $(C_6F_5)_4B^-$ and $[HRh(CO)(NaTPPTS)_3]$. Rh(I) was electrostatically bound to the polymer to form a catalyst for hydroformylation of hexene. The activities of the resulting catalysts were comparable to those of a low molecular weight catalyst. In workup, a 50000 molecular weight cutoff poly(ether sulfone) membrane was used. A 10-fold amount of solvent with respect to the cell volume was pumped through the cell to separate the catalyst from the hydroformylation products. Retention of 99.8% of the Rh(I) per cell volume was obtained, and the authors noted that the loss of Rh(I) was probably caused by oxidation of phosphine ligand due to the excess solvent used and the handling. This would not be a problem in a continuous reactor.

An oxazaborolidine catalyst, **9,** was used for asymmetric reduction of alkyl aryl ketones to the corresponding alcohols. High enantioselectivities and chemical yields were obtained. After a reaction, the soluble inorganic polymer-supported catalyst ligands were separated from the products and recovered by nanofiltration. Retention of 98.5% was observed. Polystyrene-supported oxazaborolidine **10** was also used successfully to catalyze the enantioselective reduction of ketones in a CFMR with 99.94% retention.[69]

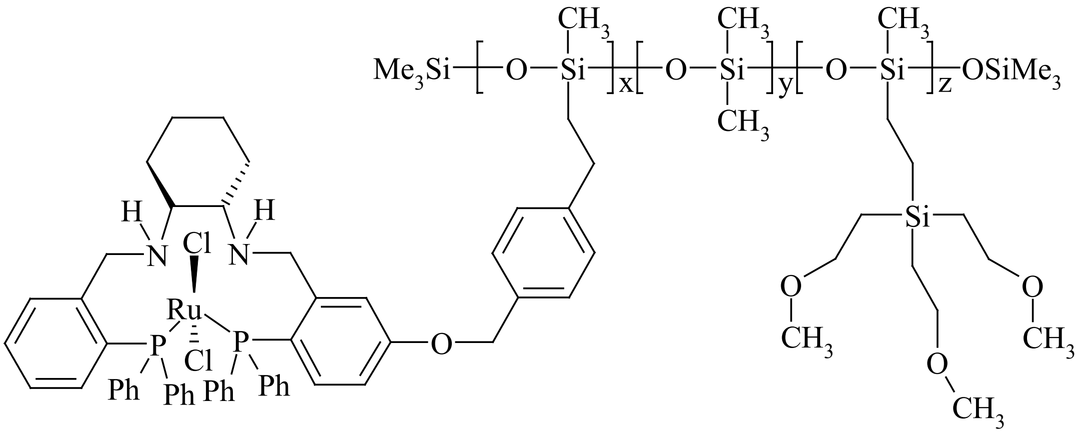


**9**



**10**

Siloxane polymer **11** was used in a membrane reactor for transfer hydrogenation of acetophenone using 2-propanol as the hydrogen source in a CFMR.[70] Retention of the catalyst was 99.5%. This catalyst was shown be less active than a carbonyl reductase enzyme for the same reaction. The major reason was that the enzyme was better retained by the membrane and more stable.



**11**

Water-soluble polymers have been widely used as supports in aqueous biphasic catalysis. In this scheme, an organic phase and an aqueous phase are used. These phases are not miscible with each other, so the reaction is carried out heterogeneously. The polymers stay in the aqueous phase throughout the reaction, and catalysis can happen in the organic phase, the aqueous phase or at the interface. After reaction, a liquid/liquid separation separates the polymer from the organic phase, and the aqueous solution can be reused (Figure 7).

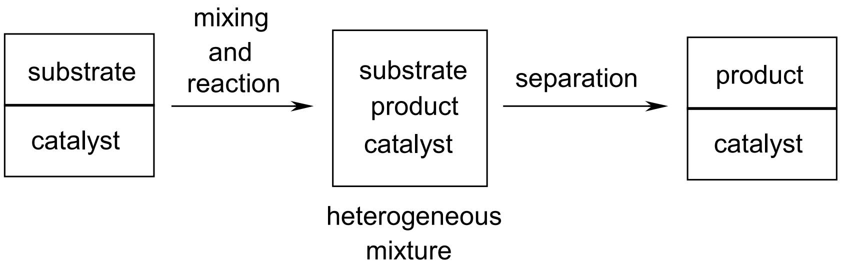
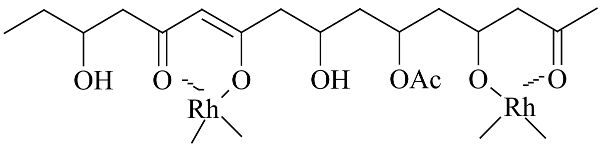


Figure 7. Separating soluble polymers after aqueous biphasic catalysis

Alper and Chen prepared catalyst **12** and used it in hydroformylation of 1-octene.[71] The activity and selectivity were good and the same activity and selectivity were observed when the catalyst was reused 3 times using the separation method shown in Figure 7. No catalysis occurred in the organic phase, suggesting that the soluble polymer-bound Rh(I) catalyst resided exclusively in the aqueous phase.



**12**

An alternative to normal biphasic catalysis is thermoregulated phase-transfer catalysis.[72,73] In this chemistry, a biphasic mixture is again used and the solubility of the catalyst is changed by changing temperature. Polymer supports are used that have inverse temperature-dependent solubility in water, and the catalysts prepared are at least partially soluble in the organic phase at high temperature and only soluble in the aqueous phase at low temperature. So that the catalyst transfers into the organic phase to catalyze a reaction at a higher temperature, and returns to the aqueous phase to be separated from the products at a lower temperature, as shown in Figure 8. Such catalysts are used much like ordinary aqueous biphasic catalysts, except that catalysis occurs homogeneously.

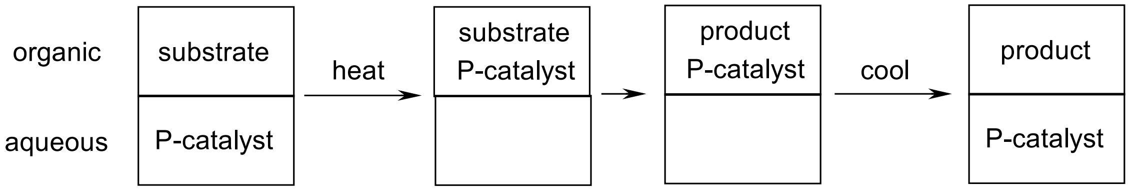
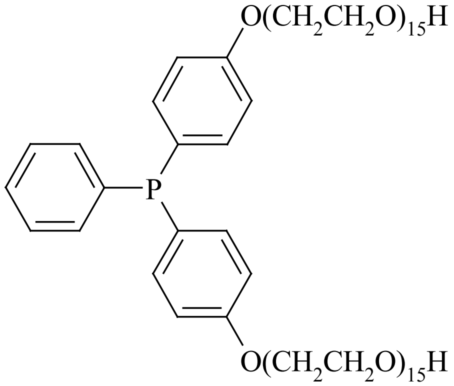


Figure 8. Using polymer-bound catalysts in thermoregulated phase-transfer catalysis

Poly(alkene oxide) is typically used as the supports for catalysts in this system. For example, polymer **13** was used to ligate a Rh(I) catalyst for hydrogenation of allyl alcohol.[72] The catalyst had a LCST of 52 °C. The hydrogen uptake rate was monitored at different temperatures, and an anti Arrhenius kinetic behavior was observed. At 70 °C, the reaction rate decreased by a factor of 7 in comparison to the reaction rate at 30 °C, due to the inverse temperature dependent solubility of the polymer-bound catalyst.



**13**

Fluorous phase catalysis is another approach used to carry out biphasic chemistry.[74,75] In this case, the system is biphasic throughout the process like aqueous biphasic catalysis. A fluorinated polymer can be used in such systems. Such fluorinated polymers are only soluble in the fluorous phase so separation can be carried out by a simple liquid/liquid separation as shown in Figure 9.[76]

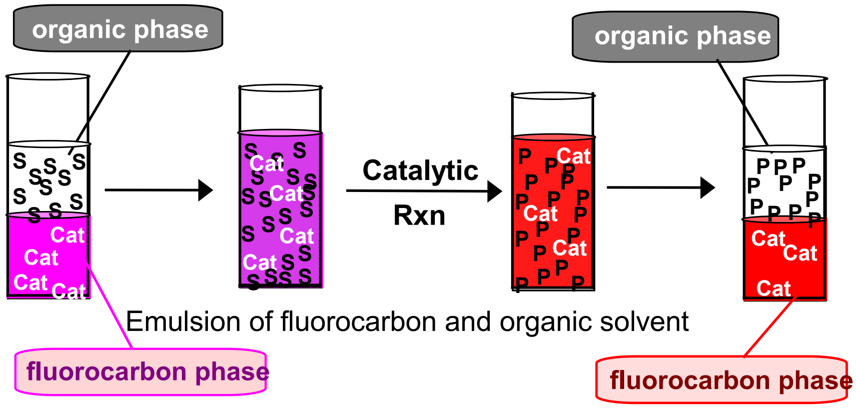
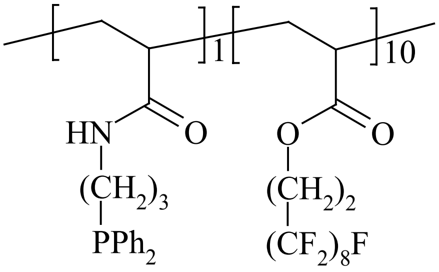


Figure 9. Separating soluble polymers in fluorous biphasic system

The polymeric phosphine **14** is an example of a fluorous polymer that had been successfully used as a ligand for Rh(I) in hydrogenations in fluorous biphasic system.[77] The fluorocarbon chains served as a phase handle to keep the polymer in the fluorous phase. After the reaction, the mixture was allowed to stand to separate the fluorous phase from the organic phase. The organic phase was removed and the fluorous phase containing the catalyst could be reused by adding fresh substrate solution in inert atmosphere. The catalyst was recycled 15 times, and the catalytic activity still remained the same. A similar polymer with a 1:20 ratio of the two monomers was used in supercritical carbon dioxide ($scCO_2$), as a ligand for Rh(I) complex in hydrogenation of 1-octene.[78] The long perfluoroalkyl groups gave the polymer good solubility in $scCO_2$.



**14**

Gladysz recently used a fluorous catalyst in a single phase system.[79] The fluorous phosphine $P((CH_2)_2(CF_2)_7CF_3)_3$ exhibited ca. 600-fold solubility increase in *n*-octane between -20 (0.104 mM) and 80 °C (63.4 mM) and 1500-fold solubility increases between -20 and 100 °C (151 mM). It catalyzed conjugate additions of alcohols to methyl propiolate under homogeneous conditions in *n*-octane at 65 °C and can be recovered by simple cooling and precipitation and used again. This avoided the use of fluorous solvents during the reaction or workup, which are expensive and can leach in small amounts.

Both aqueous and fluorous biphasic catalysis take advantage of the profound phase preference polymers have for one phase over the other in a biphasic system. However, both systems typically involve heterogeneous reactions. Figure 10 illustrates how thermomorphic and inverted thermomorphic system can be used for soluble polymer-bound catalyst separations that include a homogeneous reaction and a biphasic separation.[80,81]

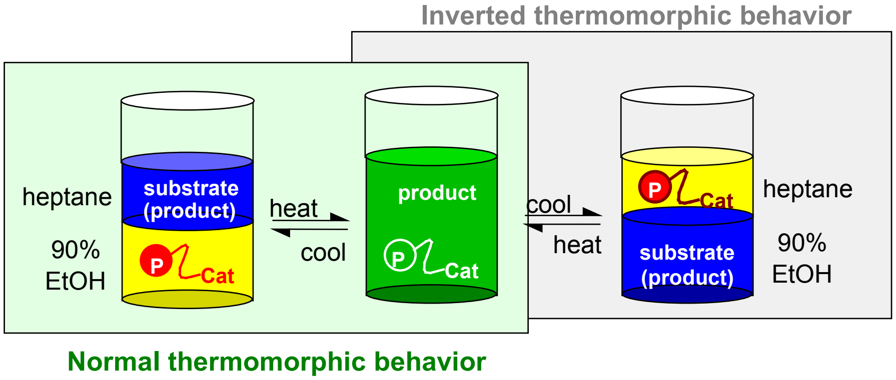


Figure 10. Normal thermomorphic behavior and inverted thermomorphic behavior

In this scheme, a solvent mixture is used that is biphasic at rest. When heated, the mixture becomes miscible. The process is completely reversible. When a soluble polymer with strong phase selectivity at rest but good solubility hot is used, catalysts or ligands bound to this polymer can be used homogeneously at elevated temperature. After reaction, when the mixture is cooled down, the phase containing the polymer-bound species separates from the phase containing products. The solution of polymer-bound catalyst can then be separated and reused.

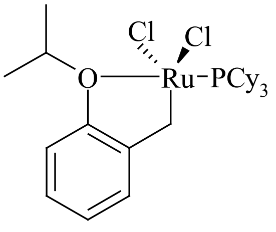
The solvent combinations usually used vary. Examples include heptane/90% aq. ethanol, heptane/DMF, heptane/DMA, and toluene/75% aq. ethanol. In the last case, the system does not become completely miscible when heated. When the polymers used are selectively soluble in the polar phase, the system is named thermomorphic or normal thermomorphic; when the polymers are selectively soluble in the nonpolar phase, it is named inverted thermomorphic. Polar polymers that have been used in a normal thermomorphic separation include poly(ethylene oxide), poly(*N*-isopropylacrylamide), and dendrimers. Poly(*N*-octadecylacrylamide) (PNODAM) has been used in inverted thermomorphic system. Designing more polymers for this system will be one topic in this dissertation.

The use of water, perfluorinated solvents, ionic liquids and supercritical carbon dioxide in biphasic systems is reviewed recently by Keim.[82]

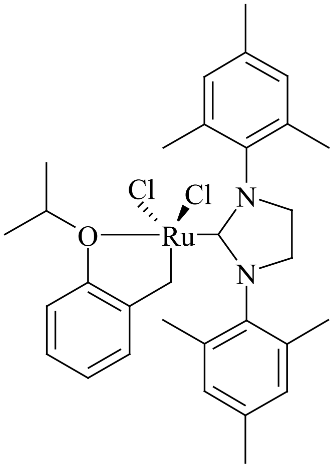
### *Separation of dendrimer supports*

Dendrimers as soluble supports have recently attracted a lot of attention. Since their structures are well-defined, the structures of catalysts supported on these dendrimers can be precisely controlled. The loading and location of catalysts on the supports can be regulated, which can be very important for the catalytic performance in some cases.

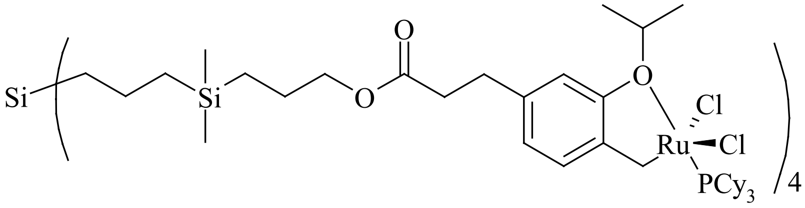
A variety of methods can be used to separate dendrimer-supported catalysts from solution. Precipitation, biphasic catalysis, thermomorphic processes, and immobilization on insoluble supports are techniques discussed above that have all been used. Also, as noted above, the globular shape of the high generations of dendrimers makes them particularly suitable for membrane filtration.



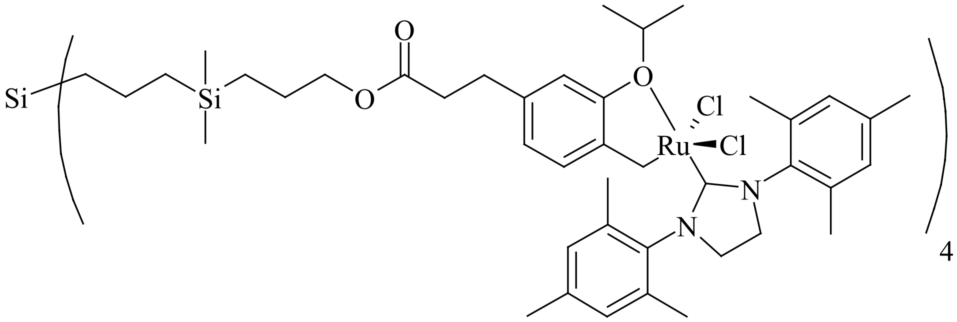
**15**



**16**



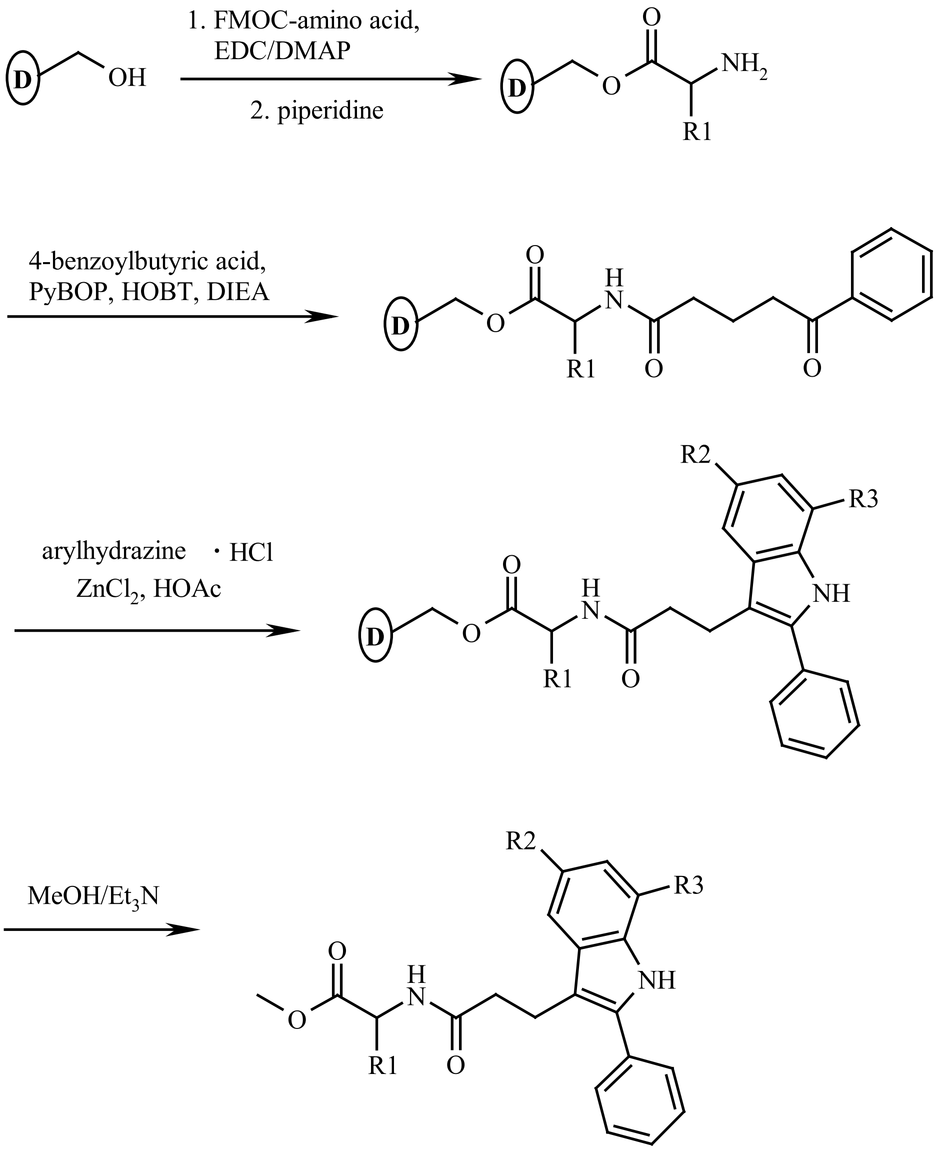
**17**



**18**

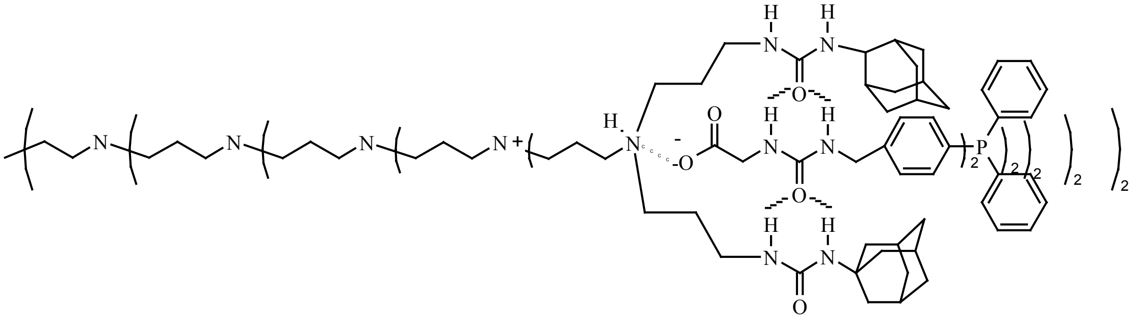
Hoveyda utilized the physical properties of dendrimers to enhance the separation of dendritic catalysts from products on a silica column.[83] The low molecular weight catalysts **15** and **16** were made for catalyzing the ring closing metathesis of dienes into hetero- and carbocyclic trisubstituted alkenes. The catalysts were recovered using column chromatography. The catalyst fractions had Rf values similar to those of the metathesis products, which made the separation inconvenient. The author reasoned that immobilization of the catalysts on dendrimers would facilitate the separation, since the macromolecular complexes should have different polarities from the other monomers. These dendritic catalysts **17** and **18** were applied to RCM reactions with good catalytic activities. As predicted, they were readily and completely separated from the products by column chromatography.

Combinatorial chemistry on heterogeneous solid-phase has been transferred onto homogeneous dendrimer-support for the synthesis of six different indoles (Scheme 6).[84] The synthesis involved attaching an amino acid to the dendrimer support by esterification, followed by a condensation with ketoacids and a subsequent reaction with an arylhydrazine hydrochloride. The indole could then be cleaved from the support by methanolysis. All intermediates were purified by size exclusion chromatography. Yields of the six dendrimer-supported indoles were all above 90%, and no impurities were observed.



Scheme 6. Dendrimer-supported indole synthesis

In most systems reported so far the substrates or catalysts were covalently linked to the dendritic support. An alternative approach is the noncovalent anchoring of catalysts to the soluble support using well-defined binding sites. For example, phosphine ligands have been noncovalently anchored in the periphery of poly(propylene imine) dendrimers to obtain ligand **19**[85] using a specific binding motif that is complementary to that of the dendrimer support. The binding was based on a combination of ionic interactions and the formation of multiple hydrogen bonds. The ligand obtained was used successfully as a ligand for Pd catalysts to catalyze allylic amination reactions in both batch processes and CFMRs. The activity and selectivity of the dendrimer-bound catalysts were similar to those of the corresponding low molecular weight catalysts, because every active site on the dendrimer acted as an independent catalyst. The authors envisioned that due to the reversible nature of this type of anchoring, controlled de- and refunctionalization of the support could be achieved using this noncovalent linking. Changing the catalyst loading during catalysis also became a possibility. Furthermore, using a noncovalent approach, multicomponent assemblies could be built for tandem reactions and combinatorial techniques.



**19**

# CHAPTER II

# POLYMER-SUPPORTED CATALYSTS FOR SOLVENTS PRECIPITATION[*]

## Introduction

Solvent precipitation is still the most routinely used technique for separating polymers from solution. Linear polystyrene and PEG are the most commonly used soluble polymers in literature for synthesis and catalysis. Both of these polymers are typically recovered and separated from products or solutions by solvent precipitation followed by filtration or centrifugation. These polymers as well as PNIPAM were investigated here as solvent precipitable supports for catalysts. While varying degrees of success were obtained using these catalysts, solvent precipitation was nonetheless generally useful in separating and recovering a soluble polymer.

## Results and discussion

### *Linear Polystyrene*

Linear polystyrene was one of the first soluble polymers used in synthesis and catalysis and it is suitable for solvent precipitation. It is soluble in tetrahydrofuran (THF), dichloromethane, chloroform, benzene, ethyl acetate. It is insoluble in water, methanol, ethanol, or heptane. A typical way of purifying linear polystyrene or polystyrene-supported species is to dissolve the polymer in dichloromethane, and to then add this

---

[*] Reproduced in part with permission from *Organic Letters.* Copyright 2001 American Chemical Society.

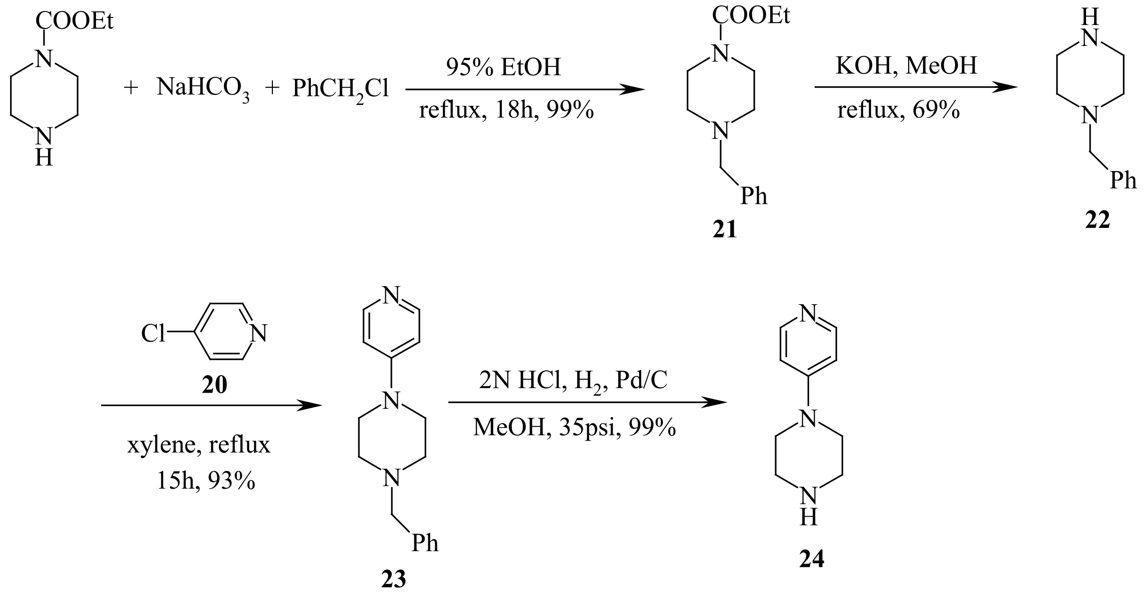
solution to an excess amount of methanol. The polymer precipitates and can be recovered by filtration or centrifugation.

Linear polystyrene has been used for the synthesis of polypeptides.[86,87,88] It is also a good soluble support for catalysts. For example, in Bayer's work, linear polystyrene was partially chloromethylated, and the resulting benzylic chloride was then substituted by diphenylphosphine. Similar chemistry is used to functionalize crosslinked polystyrene resin.[65,89] The soluble polystyrene-bound phosphine so formed was used as ligand to prepare catalytically active Rh and Pd complexes. Both homogeneous hydrogenation and hydroformylation reactions were carried out using these polymer-bound catalysts. The catalysts were recovered by ultrafiltration or solvent precipitation. Attaching catalysts to polystyrene allows easy recovery and reuse of the catalyst. The chemistry of linear polystyrene as a support mirrors that of crosslinked polystyrene. However the soluble polymer has an advantage over catalysts on the solid support since the synthesis, characterization and catalysis can now be carried out in solution phase.

The application of polystyrenes as supports for catalysts was studied in this dissertation as well. Both polystyrene and poly(4-*tert*-butylstyrene) were studied. The latter polymer could be separated by methods other than solvent precipitation. Such separations are described in another chapter of this dissertation.

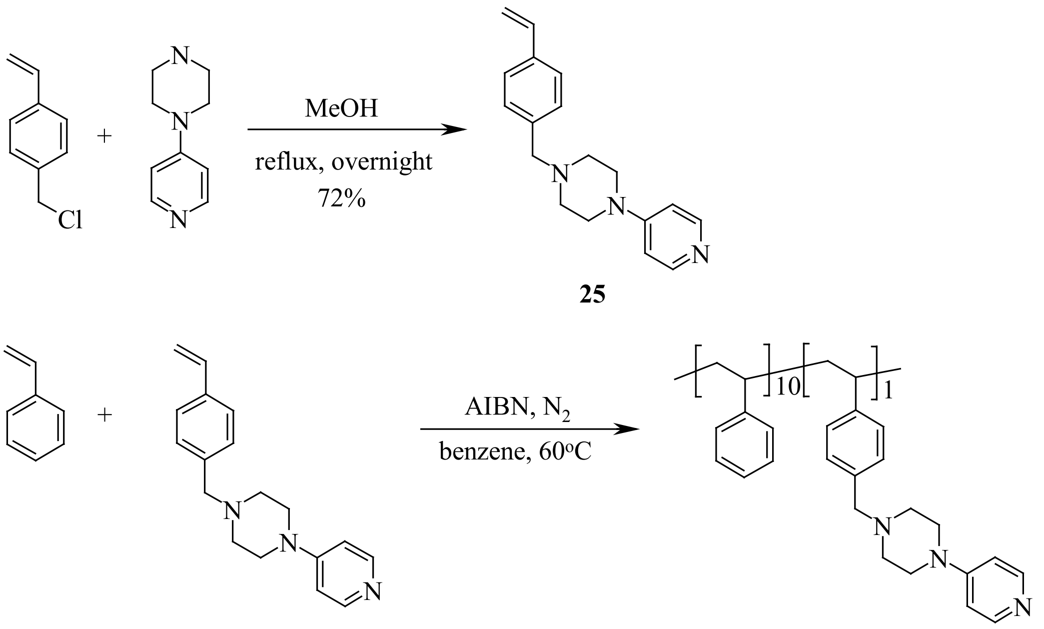
The nucleophilic catalyst **26** is an example of a linear soluble polystyrene-supported catalyst. Catalyst **26** is an analog of the well-known low molecular weight catalyst 4-dimethylaminopyridine (DMAP). DMAP is a catalyst first used by Steglich and Hofle for acylation of 1-methylcyclohexanol.[90] It is an active and versatile catalyst for a wide variety of tasks such as acylation, Baylis-Hillman reaction, benzoylation, carbamoylation, esterification, formylation, lactonization, phosphorylation, silylation and tritylation.[91,92,93,94,95] Besides having high catalytic activity, it is also easy to synthesize. The synthesis of one of dialkylaminopyridine catalysts - *N*-(4-pyridyl)piperazine is described below. This compound was used both as a precursor in synthesis of **26** and as a common precursor for different polymer-supported catalysts described elsewhere in this dissertation. These substituted pyridine catalysts are stable during reactions. This is very important for making recyclable catalysts. Some polymer-supported catalysts I have studied, although easily separated from the rest of the material after reactions, are not stable during reactions and recovery. Such polymer-bound catalysts cannot retain the same catalytic activity when reused, even if they are quantitatively isolable. DMAP, unlike many transition metal catalysts complexed by phosphine ligands, is stable to air, heat and water. This has been recognized by many others too. Thus, the synthesis and application of recoverable alkylaminopyridine catalysts using both insoluble polymer supports[96,97,98,99,100,101,102,103,104] and soluble polymer supports[105,106,107] has been widely studied.

The synthesis of *N*-(4-pyridyl)piperazine is shown in Scheme 7. Piperazine was chosen so that two heteroatoms were available, one for coupling to the pyridine and the other for coupling to 4-vinylbenzylchloride, respectively. The synthesis began with commercially available ethyl 1-carboxylpiperazine. The amine was protected using benzyl chloride. Then the carbamate protecting group was cleaved using KOH. The free amine **22** so released was coupled to 4-chloropyridine **20** using DCC. The necessary 4-chloropyridine was obtained by treating commercially available 4-chloropyridine hydrochloride with triethylamine. The *N*-benzyl protecting group was finally removed using hydrogenolysis to yield compound **24**.



Scheme 7. Synthesis of *N*-(4-pyridyl)piperazine

The piperazine derivative of pyridine **24** was used as a common precursor for a variety of polymeric catalysts including a linear polystyrene-bound acylation catalyst **26**, which was made by copolymerization of styrene and a catalyst-substituted styrene derivative **25**. To make compound **25**, *N*-(4-pyridyl)piperazine was allowed to react with 2 equivalent of 4-vinylbenzylchloride. The excess 4-vinylbenzylchloride in this reaction was separated from the product by column chromatography. The monomer **25** so obtained was then copolymerized with styrene using the standard reaction conditions for making homopolystyrene to give the desired polystyrene-supported DAAP catalyst **26**.[108] The mole fraction of catalyst substituted monomer in the copolymer was predetermined by adjusting the mole fraction of styrene and substituted styrene **25** in the feed. The ratio of the comonomers in the polymer was readily quantified using simple $^1$H NMR spectroscopy, by integrating the peak at 8.2 ppm due to two of the pyridine protons and the peaks at 7.2-6.2 ppm due to the rest of the aromatic protons.

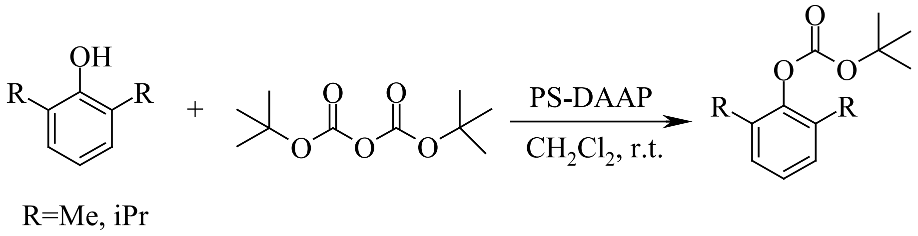


**25**

PS-DAAP
**26**

Scheme 8. Synthesis of PS-DAAP

Catalyst **26** was used to catalyze reactions between hindered phenols and Boc anhydride (equation 3). This reaction has previously been described as a useful way to protect phenols as their Boc derivatives under mild conditions.[109] The reaction using catalyst **26** was run at room temperature in dichloromethane. After the reaction, the dichloromethane solution was poured into an excess amount of methanol, and the polymer-supported catalyst precipitated from solution. After filtration, the supernatant was worked up to isolate the product. The polymer-bound catalyst isolated in the filtration step could be redissolved in dichloromethane solution containing the substrate and reused in subsequent catalytic cycles. The isolated yield of reactions catalyzed by PS-DAAP **26** and DMAP is listed in Table 1. The activity of catalyst **26** was comparable to that of DMAP. Since there was no significant decrease of activity when the polymer-bound catalyst was reused, the total turnover number was much higher than that of unsupported DMAP. The initial rates of phenol acylations using Boc anhydride were also compared to those for similar reactions catalyzed by DMAP. These studies will be discussed later in this chapter.



(3)

*Synthesis on poly(ethylene glycol) support*

PEG is another very commonly used soluble polymer support.[65] It has been used as a support for hydrogenation catalysts,[51,110] for chinchona alkaloid ligands in the Sharpless AD reaction,[111,112,113,114,115] for phase transfer catalysts,[116,117,118,119] for epoxidation catalysts,[120,121] and for carbon-carbon bond forming catalysts.[39,81,122,123,124,125] Besides serving as a support for catalysts, PEG is also widely used for applications including serving as a soluble support for the synthesis of oligopeptides[126,127] and oligonucleotides,[128] oligosaccharides.[129,130,131,132] PEG has utility in drug delivery[133] and as a water-soluble agent for inducing membrane fusion.[134]

Table 1. Catalytic activities for Boc-protection of phenols

| R | Catalyst[a] | Time (min) | Yield (%)[b] |
|---|---|---|---|
| Me | DMAP | 5 | 92 |
| Me | PS-DAAP **26** | 5 | 92(1st cycle)<br>97(2nd cycle)<br>94(3rd cycle) |
| i-Pr | DMAP | 30 | 95 |
| i-Pr | PS-DAAP **26** | 45 | 91(1st cycle)<br>93(2nd cycle)<br>89(3rd cycle) |

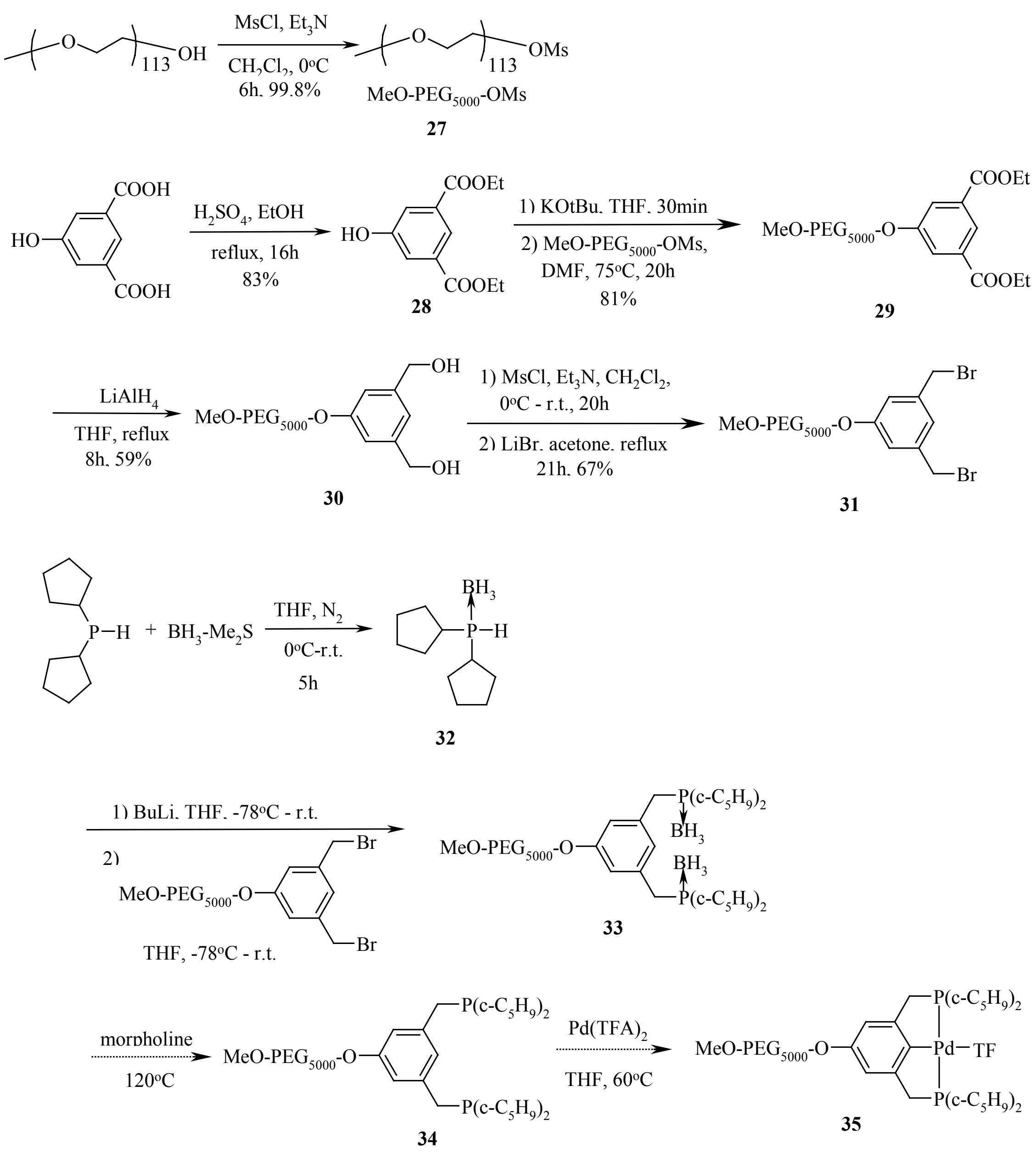
[a]In all these reactions, 5 mol% of catalysts were used relative to the phenol substrates, with 1.02 equivalent of Boc anhydride relative to the phenol substrates. [b]The yield is the isolated yield, and the products were characterized by $^1$H NMR spectroscopy.

PEG-bound catalysts and ligands are usually recovered from solutions by solvent precipitation. PEG derivatives are soluble in DMF, dichloromethane, toluene, acetonitrile, water, and methanol. PEG derivatives are insoluble in diethyl ether, *tert*-butyl methyl ether, isopropanol and cold ethanol.

Characterization of PEG-immobilized organic molecules is similar to characterization of low molecular weight compounds since the polymer does not interfere with spectroscopic or chemical methods of analysis. PEG does have an interfering peak due to the large amount of $CH_2$ protons at 3.6 ppm. However the $^{13}$C satellite peaks of the PEG backbone peak at 0.2 ppm upfield and 0.2 ppm downfield from the peak at 3.6 ppm can be used as an internal integration standard, allowing for easy monitoring of chemical reactions by $^1$H NMR spectroscopy. In the case of MeO-PEG, the single methoxy group (3.4 ppm) can also be used as an integration standard.

Our group has used poly(alkene oxide) copolymers whose end group chemistry is like that of PEG to make smart ligands.[27] Recently SCS catalysts were successfully attached to PEG to make recyclable Heck catalysts.[81] Inspired by these results, I attempted to make a PEG-supported PCP-Pd catalyst for carbon-carbon bond forming reactions. This catalyst was expected to be more active than the SCS catalysts our group had already studied. This PCP catalyst too should have good stability both under the reaction conditions and during workup. This type of catalyst was first reported by Milstein to be highly active and highly stable for C-C coupling reactions.[135] Dr. Sulikowski's group and our group had previously made some PCP catalysts and used them in catalysis.[136,137] The attempt to make a PEG-supported PCP catalyst was however, not successful. Nonetheless, I have included a description of this work here since this work serves as an illustration of the advantages and disadvantages of syntheses carried out on polymer supports.

The synthesis of a PEG-supported PCP-Pd(II) catalyst I attempted is shown in Scheme 9. Most of these steps were successfully carried out and the separation/recovery of the products was facilitated by the PEG support. However the last two steps in dotted arrows were not successfully accomplished because of problems with phosphine oxidation.



Scheme 9. Proposed synthesis of PEG-supported PCP-Pd(II) catalyst

The synthesis started from commercially available PEG. Commercial PEG can be obtained as a diol or a monoether derivative depending on whether it is produced by anionic polymerization of ethylene oxide by methoxide anion or hydroxide. The polymer we used here was a mono methoxy-terminated PEG. The terminal hydroxyl group was activated with methanesulfonylchloride to form mesylate **27**. Then 5-hydroxyisophthalic acid that had been esterified to form the diester **28** was treated with potassium *tert*-butoxide. The phenolate so formed was then allowed to react with the mesylate-terminated PEG. The PEG-bound diester **29** was then reduced to diol **30** using lithium aluminum hydride. The diol so formed was converted to the mesylate using methanesulfonyl chloride and to the dibromide **31** using lithium bromide.

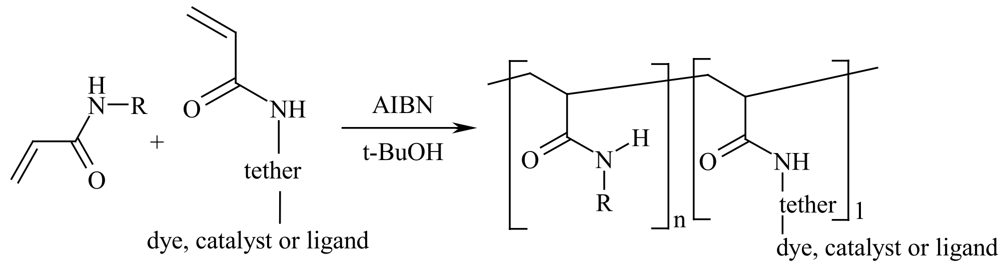
Phosphine ligands were introduced onto **31** using a phosphine-borane complex. Dicyclopentylphosphine (DCP) is an extremely air sensitive, pyrophoric material. To prevent it from being oxidized during the multiple step synthesis, DCP was converted to a stable phosphine-borane adduct **32**.[137] Phosphine-borane adducts are readily available using borane-dimethyl sulfide or borane tetrahydrofuran complexes as the source of $BH_3$. Deboronation can be accomplished using various reagents, including $Et_2NH$[138], morpholine[137], 1,4-diazabicyclo[2.2.2]octane (DABCO) and $HBF_4$[139]. $BH_3$ serves as a protecting group of phosphines during purification procedures or during chemical manipulations. It also serves as an activating group. Secondary phosphine-boranes are easily deprotonated to give the corresponding anions, which can be treated with a variety of electrophiles to afford new functionalized complexes.[140] The phosphine-borane complex **32** of interest here was generated by treating DCP with borane-dimethylsulfide in THF under nitrogen. The resulting compound was air stable and could be readily recrystallized from THF/hexanes to afford a highly pure crystalline solid. It was then deprotonated with n-butyllithium and the resulting phosphide was treated with the bromide **31** to give the air-stable PEG-supported phosphine-borane compound **33**.

Except for the esterification and the phosphine-borane complex formation steps which did not involve PEG, all of the rest of the steps involved a workup that was simplified by the presence of a PEG group. In most of the cases the reaction mixture was poured into an excess amount of diethyl ether, and the polymer-bound product precipitated. Filtration then isolated the product. One of the useful properties of PEG is that it is easily crystallized due to its helical structures. This crystallization reduces the chance of inclusions during precipitation procedures. Thus, the intermediates in the above synthesis were further purified by dissolving the PEG support in hot isopropanol. Cooling the solution allowed the polymer to crystallize. Filtration then isolated purer PEG derivatives.

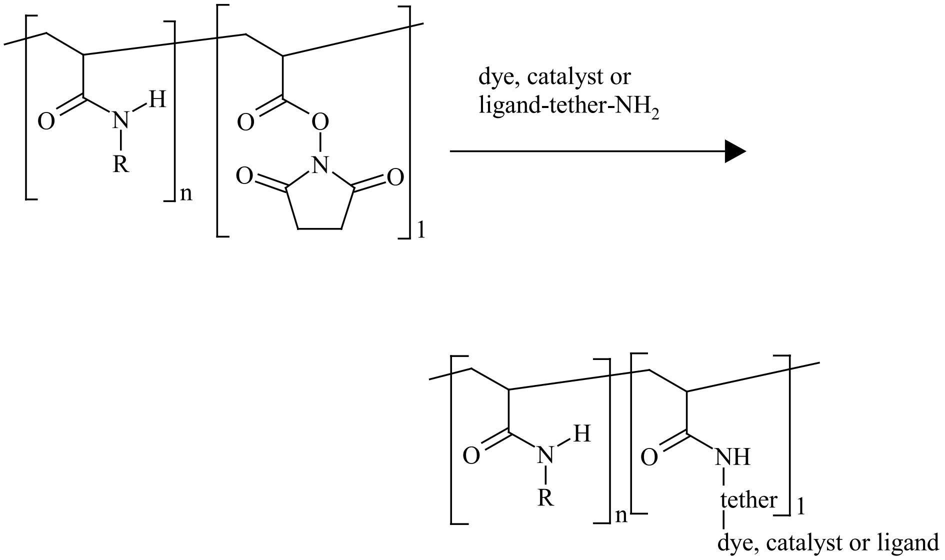
The next step shown in Scheme 9 is formation of the free phosphine ligand **34** from the phosphine-borane by deprotection with morpholine at 120 $^{o}$C. The morpholine-borane complex was to then be sublimed. Pd(TFA)$_2$ was to then be used for palladation. These two steps carried out in one pot under an inert atmosphere should have produced the PCP-Pd complex **35**. However, presumably due to adventitious oxygen, a mixture of phosphine, phosphine oxide, palladated phosphine and other species formed. The same reaction carried out with a low molecular weight analog also generated a mixture, but the PCP-Pd complex could be separated cleanly from the rest of the material using column chromatography. The PEG-supported mixture after palladation, however, cannot be separated this way. This shows a disadvantage of using a polymer support - a reaction has to go to completion and only generate the desired products. While a low molecular weight product can be separated from low molecular weight impurities, a polymer-bound product cannot be easily separated from impurities supported on the polymer.

### *PNIPAM-supported catalysts*

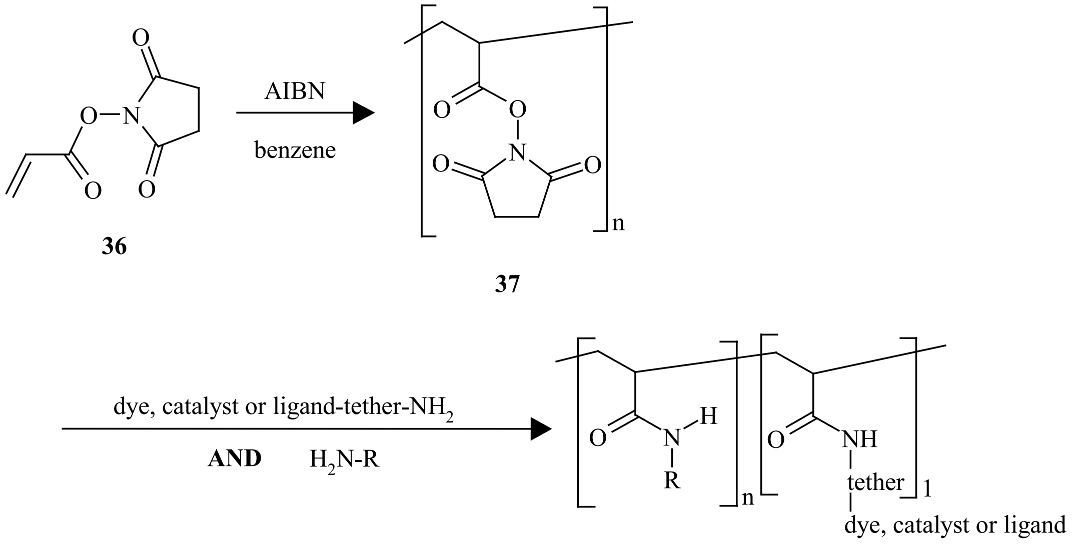
Although linear polystyrene and PEG are still the most commonly used soluble polymer supports, other soluble polymers are receiving increasing attention. For example, our group has used polyalkylacrylamides as soluble polymer supports in synthesis and catalysis, with most of this effort focusing on PNIPAM. PNIPAM has the advantage that it can be easily functionalized by copolymerization, and the functional group loading can be controlled by adjusting the feed ratio of the comonomers in the polymerization. PNIPAM can also be separated from solution by heat-induced precipitation. Liquid/liquid separation and recovery procedures using thermomorphic separation techniques discussed in other chapters work too. Finally, there are many different ways to attach reagents or catalysts to polyalkylacrylamide supports. Some commonly used methods in our group are shown in equation 4-6.


H
N—R
+
O
NH
tether
dye, catalyst or ligand
AIBN
t-BuOH
O
N
H
R
n
O
NH
tether
1
dye, catalyst or ligand

(4)

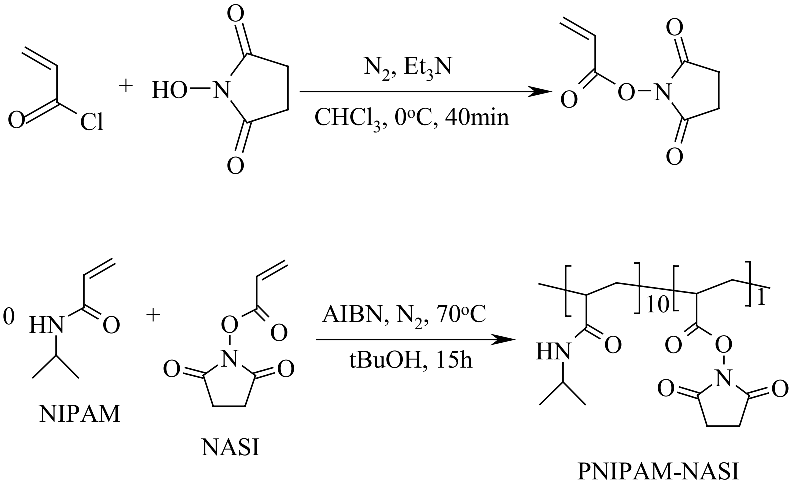

O
N
H
R
n
O
O
N
O
O
1
dye, catalyst or
ligand-tether-NH2
O
N
H
R
n
O
NH
tether
1
dye, catalyst or ligand

(5)


O
O—N
O
O
36
AIBN
benzene
O
O
N
O
O
n
37
dye, catalyst or ligand-tether-NH2
AND H2N-R
O
N
H
R
n
O
NH
tether
1
dye, catalyst or ligand

(6)

A copolymerization of the alkylacrylamide and a functional group substituted acrylamide can give the desired polymer directly (equation 4). Alternatively, an intermediate copolymer polyacrylamide-co-poly(*N*-acryloxysuccinimide) can be used (equation 5). *N*-Acryloxysuccinimide (NASI) contains an active ester which readily undergoes substitution reactions with primary amines. This is the most commonly used method in our group for functionalization of PNIPAM. The synthesis of the common intermediate PNIPAM-NASI is shown in Scheme 10. NASI was made from the reaction of acryloyl chloride with *N*-hydroxysuccinimide. This monomer was then copolymerized with *N*-isopropylacrylamide using 2,2'-azobis(2-methylpropionitrile) (AIBN) as the initiator. The ratio of the two repeating units on the copolymer backbone usually equals the ratio of the monomers in the feed for the polymerization. This ratio can be measured in the case of PNIPAM-NASI by comparing the integral of the isopropyl protons and the integral of the succinimide protons. The polymer obtained was a PNIPAM-NASI copolymer and not just an admixture of PNIPAM and PNASI, since the homopolymer of NASI was not soluble in the $CDCl_3$ used for NMR spectroscopy while the product of the synthesis in Scheme 10 was soluble in $CDCl_3$.

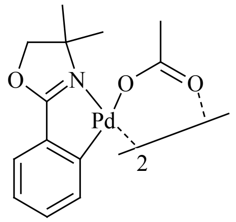


Scheme 10. Synthesis of PNIPAM-NASI

Another route to make a functionalized poly(alkylacrylamide) starts from an active intermediate polymer PNASI **37** (equation 6), made from polymerizing NASI **36** in benzene using AIBN as an initiator. A primary amine or a mixture of primary amines can then be used to substitute the active ester to obtain the desired multifunctional polymers. Whitesides had previously used a similar approach with sequential amidation of the polymeric active ester groups by various amines as synthetic route to polymeric inhibitors useful in biology.[141]

*PNIPAM-oxazoline-Pd(II) catalyst*

A PNIPAM-supported Pd(II) complex was made according to the second route (equation 5) and studied as a catalyst for C-C bond forming reactions. The low molecular weight analog **38** was made by Boubekeur back in 1989.[142] At that time he was interested in C-H activation via a palladium complex. Meilstein later used several structurally similar compounds in catalysis of Heck reactions,[143] and the catalysts were shown to be highly active and highly stable. These catalysts also avoided the need for a phosphine group – a problem in the synthesis of **35** above. Thus, we were interested in studying routes to attach compound **38** to PNIPAM to obtain a polymer-supported Pd(II) catalyst.

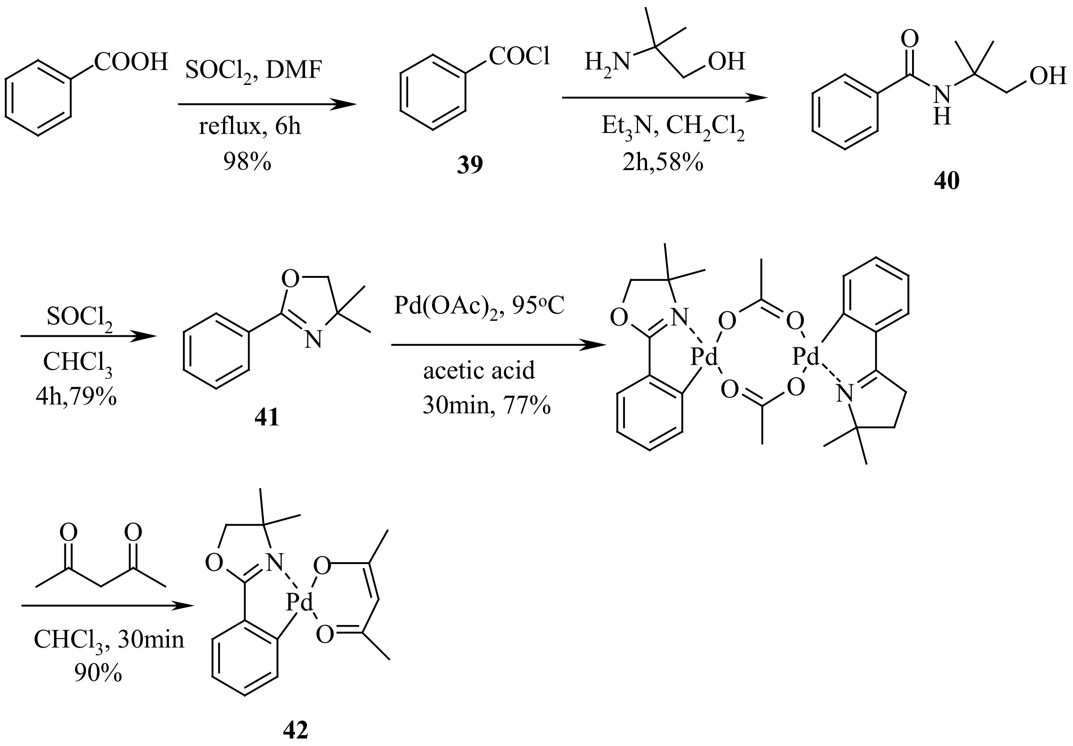


**38**

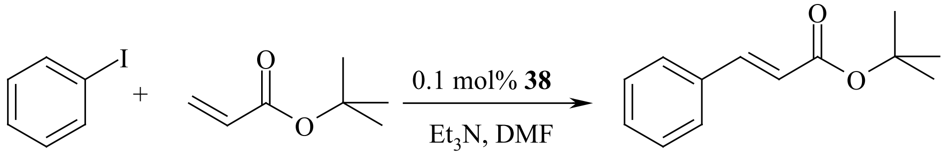
The low molecular weight catalyst **38** was synthesized first, as shown in Scheme 11. Benzoic acid was converted to the acid chloride **39** by treating with thionyl chloride. The acid chloride was then coupled with 2-amino-2-methyl propanol to give the amide derivative **40**. Oxazoline formation was achieved using thionyl chloride. Treating the oxazoline **41** with $Pd(OAc)_2$ then gave the palladium dimer **38** as a dark yellow compound. The dimer could be broken up into monomers by treating it with acac ligand, to give the light yellow palladium(II) species **42**, shown in Scheme 11.

This catalyst **38** was relatively stable in comparison to phosphine-based palladium catalyst such as $Pd(PPh_3)_4$. It could be left in air or in solution without noticeable decomposition. Heating this compound in refluxing 90% aqueous ethanol did not cause decomposition either. However, when it was refluxed in ethanol in the presence of KOH or hydrazine, Pd black formed.

The first reaction run with this catalyst was the Heck reaction of iodobenzene with methyl acrylate in DMF at 140 °C in the presence of triethylamine (equation 7). The amount of catalyst used was 1 mol% relative to iodobenzene, and the reaction was complete in 18 hours shown by GC analysis. Upon completion of the reaction, more substrates were added to the reaction mixture and catalysis resumed with about the same rate. This suggested that this catalyst should be reusable once it is supported on polymer.



Scheme 11. Synthesis of compound **38** and its monomeric derivative **42**

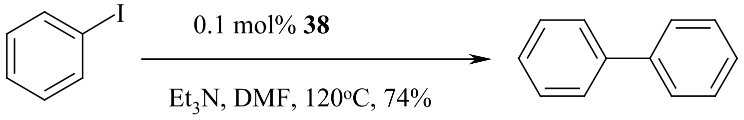


(7)

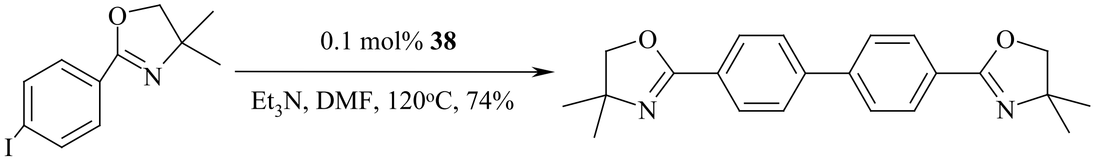
To see how active this catalyst was, another Heck reaction was tried using iodobenzene and unactivated 1-nonene in DMF at 140 °C in the presence of triethylamine, using a catalyst loading of 0.1 mol% relative to iodobenzene. After heating the reaction solution overnight, TLC showed that the starting iodobenzene disappeared, so the DMF solution was poured into water and extracted with dichloromethane. The $^{1}$H NMR spectroscopy of the material obtained did not look clean and it was different from those of other Heck products seen before. However, it reminded us of the biphenyl product from Suzuki reactions. After comparing the spectrum with that of biphenyl, we found out that the reaction actually going on was a homocoupling reaction of iodobenzene, a process called the Ullman reaction that normally uses Cu as a reductant.[144]

Another reaction was run without the interference of the alkene using 0.1 mol% of the catalyst **38**, as shown in equation 8. No effort was made to remove oxygen or water from the solution. The solution was heated overnight, then poured into water and the biphenyl product precipitated. After filtration, a pure product was obtained with 74% yield. Another substrate **43** was also successfully homocoupled using catalyst **38**, shown in equation 9. This catalyst, although active, was not reusable for homocoupling of aryl iodides. When more aryliodide was added after completion of a reaction, no further catalysis occurred.

The use of Pd(II) catalysts for iodobenzene homocoupling reactions has literature precedence.[145] In the reported example, the reaction was run at 110 °C using 0.5 mol% of a Pd(II) catalyst under nitrogen, with 85% yield. The DMF used was degassed and the reaction was run under anhydrous conditions.



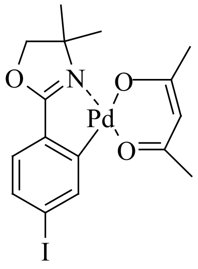
(8)



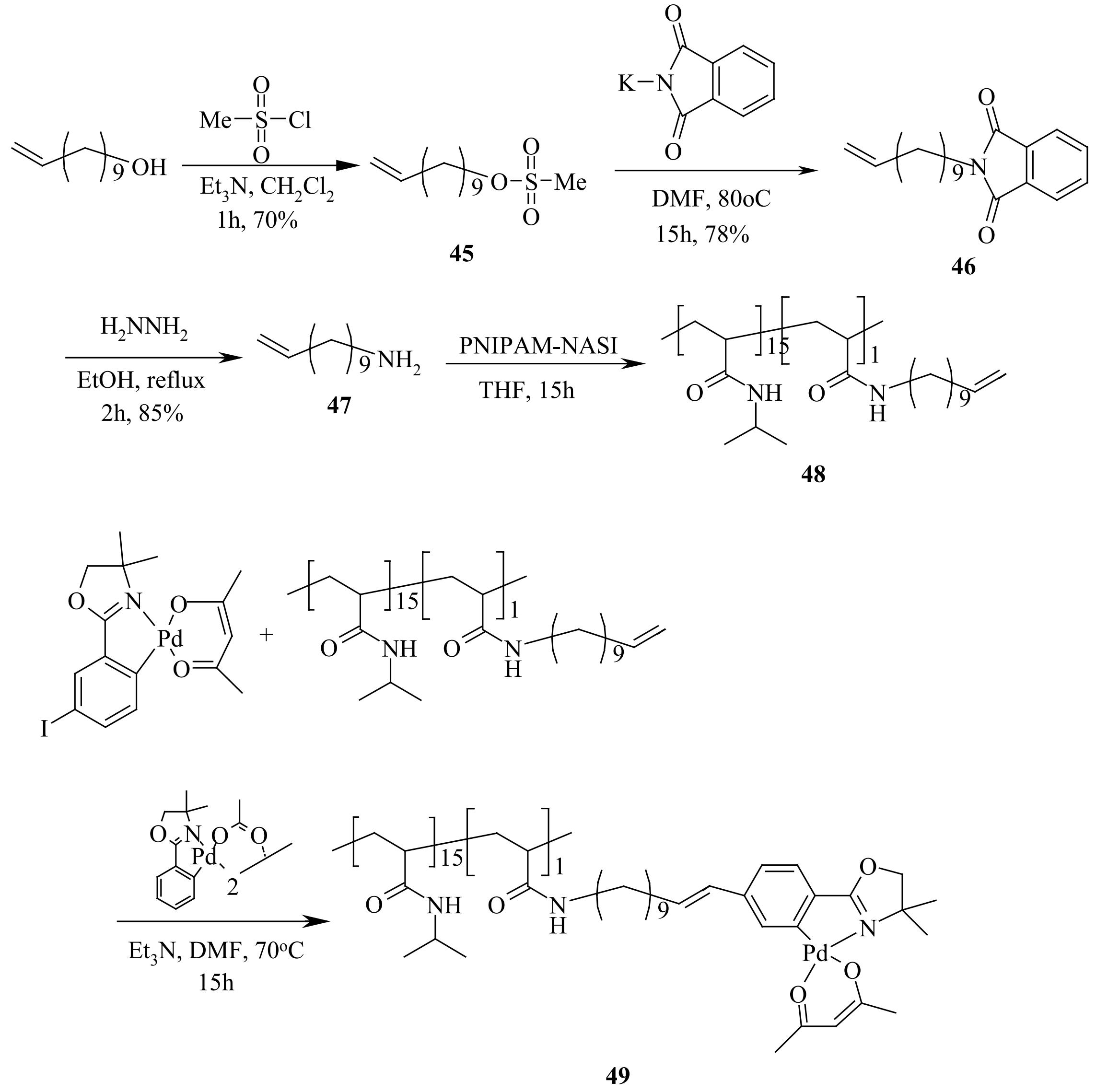
**43**

(9)

To attach this oxazoline-Pd(II) catalyst **38** to PNIPAM support for Heck reactions, a similar complex **44** was made with an iodo group on the aromatic ring. The idea was to attach **44** to a PNIPAM-supported vinyl group by a Heck reaction. The synthesis of compound **44** was similar to that of **42**. PNIPAM with a pendant vinyl group was prepared using ω-undecylalcohol and PNIPAM-NASI. A long alkyl chain was chosen to keep the active catalyst far enough from the polymer backbone so that it can be seen clearly from $^1$H NMR spectroscopy. The hydroxyl group of ω-undecylalcohol was converted to a mesylate using methane sulfonyl chloride. The mesylate **45** was transformed into an imide using potassium phthalimide. The imide bond on **46** was cleaved using hydrazine to release the free amine **47**, which was then allowed to react with PNIPAM-NASI to give the polymer-supported alkene **48**. Coupling of the aryl iodide and the polymer-bound alkene was then carried out using a Heck reaction to give the polymer-supported Pd(II) catalyst **49**. Compound **38** was used as a catalyst for this reaction, but it might not be necessary since both the aryl iodide **44** and the product **49** were Heck catalysts.



**44**



Scheme 12. Synthesis of the PNIPAM-supported Pd(II) catalyst

Heck reactions of arylhalides and *tert*-butylacrylate using the polymer-bound catalyst were carried out and the results are shown in Table 2.

Table 2. Results of Heck reactions using PNIPAM-bound Pd(II) catalyst **49**.

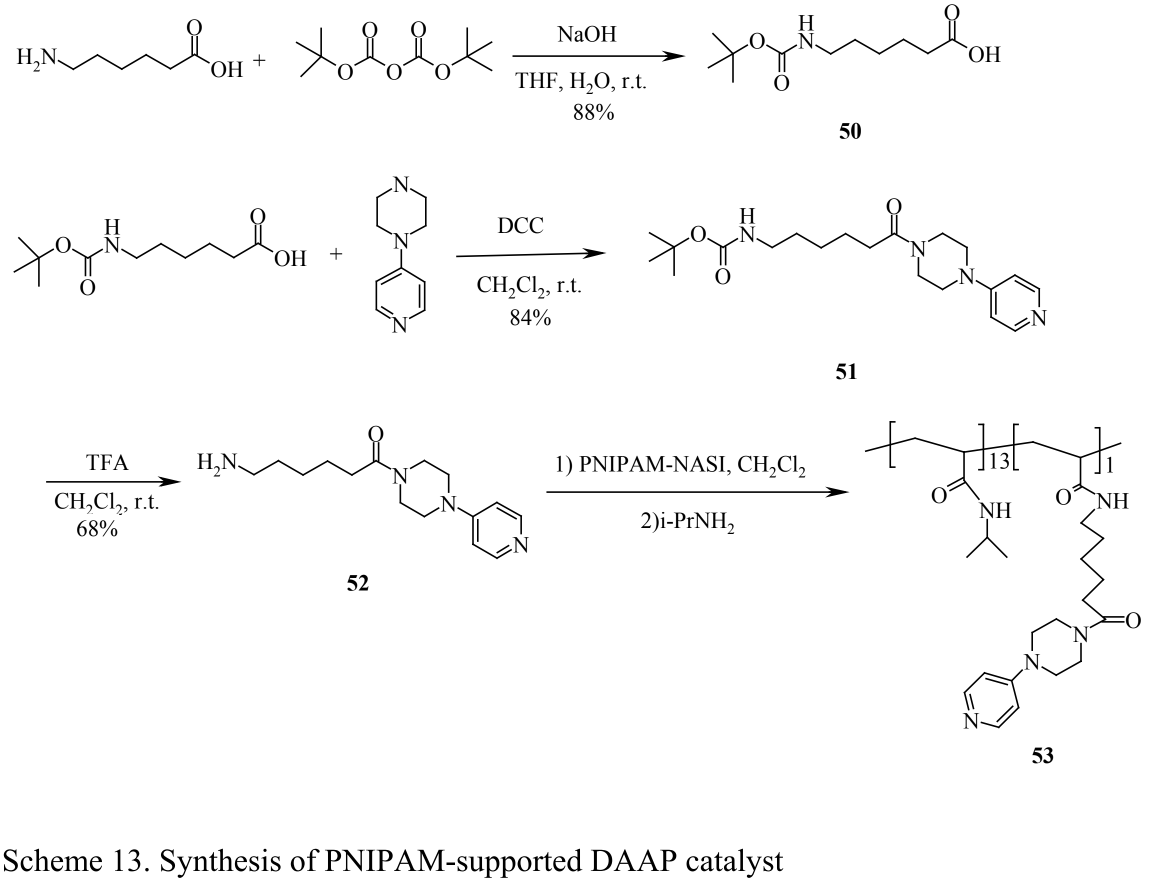
| Cycle number | Substrate | Catalyst loading (mol%)[a] | Temperature ($^{o}$C) | Time (h) | Conversion (%)[b] |
|---|---|---|---|---|---|
| 1 | PhI | 1 | 70 | 18 | 89.1 |
| 2 | PhI | 1 | 70 | 18 | 99.7 |
| 3 | PhI | 1 | 70 | 17 | 98.8 |
| 4 | PhBr | 1 | 70 | 16 | 0 |
| 5 | 1-iodonaphthalene | 1 | 70 | 16 | >99[c] |
| 6 | PhI | 1 | 70 | 24 | 92.8 |
| 7 | PhI | 2 | 70 | 24 | 96.5 |
| 8 | PhBr | 1 | 140 | 17 | 0[d] |

[a]The catalyst loading was determined relative to the aryl halide substrates. [b]The conversion was based on GC analysis of the products. [c]The yield was an isolated yield. The product was characterized by $^{1}$H NMR spectroscopy. [d] Pd(0) was presumed to have formed based on the appearance of black precipitate.

These reactions were carried out in air without any effort to remove oxygen. After each cycle, the reaction mixture was poured from the DMF solution into an excess amount of ether, to precipitate the polymer-bound catalyst. Filtration isolated the catalyst which was reused for the next cycle. The results showed that this catalyst worked fine for reactions of aryl iodides. However, when bromobenzene was used, the reaction did not proceed and the metal dissociated from the oxazoline ligand to form Pd black. The narrow range of substrates severely limits this catalyst’s utility.

*PNIPAM-DAAP for acylation of tertiary alcohol and phenol*

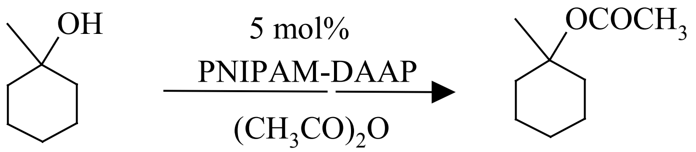
To attach the DMAP analog **24** to PNIPAM, a linker was needed between compound **24** and PNIPAM-NASI. This linker was chosen to be 6-aminohexanoic acid. It is long enough so that the DAAP functionality can be seen clearly from $^1H$ NMR spectroscopy after being attached to the polymer support. The free amine of this ω-amino acid was protected first using Boc anhydride (Scheme 13). The carboxylic acid **50** was then coupled to *N*-(4-pyridyl)piperazine using DCC. The protecting group on **51** was removed using TFA to give the free amine-terminated DAAP catalyst **52**, which was then attached to PNIPAM support following the general scheme shown in equation 5.



Scheme 13. Synthesis of PNIPAM-supported DAAP catalyst

The catalyst loading was determined by both $^1$H NMR spectroscopy and titration to be ca. 8 mol%. Titration of the 4-dialkylaminopyridine groups of **53** shows that the basic groups in this polymer have a p$K_a$ of 9.7. This p$K_a$ was estimated using the software program BEST[146] because polymer **53** is insoluble in water at pH values above 10. The same software and titrimetric analysis yielded a p$K_a$ of 9.9 for DMAP. The similarity of the pKa of DMAP and **53** provides further evidence of the similarity of the DAAP groups in **53** to their low molecular weight analogue DMAP. This experiment also shows that protonation/deprotonation and solution/precipitation is another way to recover this soluble polymeric catalyst. This process was shown to be effective, quantitative and reversible by repeatedly adding HCl and NaOH to an aqueous solution of dye-labeled PNIPAM-supported DAAP catalyst **55**, introduced later in this chapter. In this experiment, the solubility was monitored both visually and by UV-visible spectroscopy.

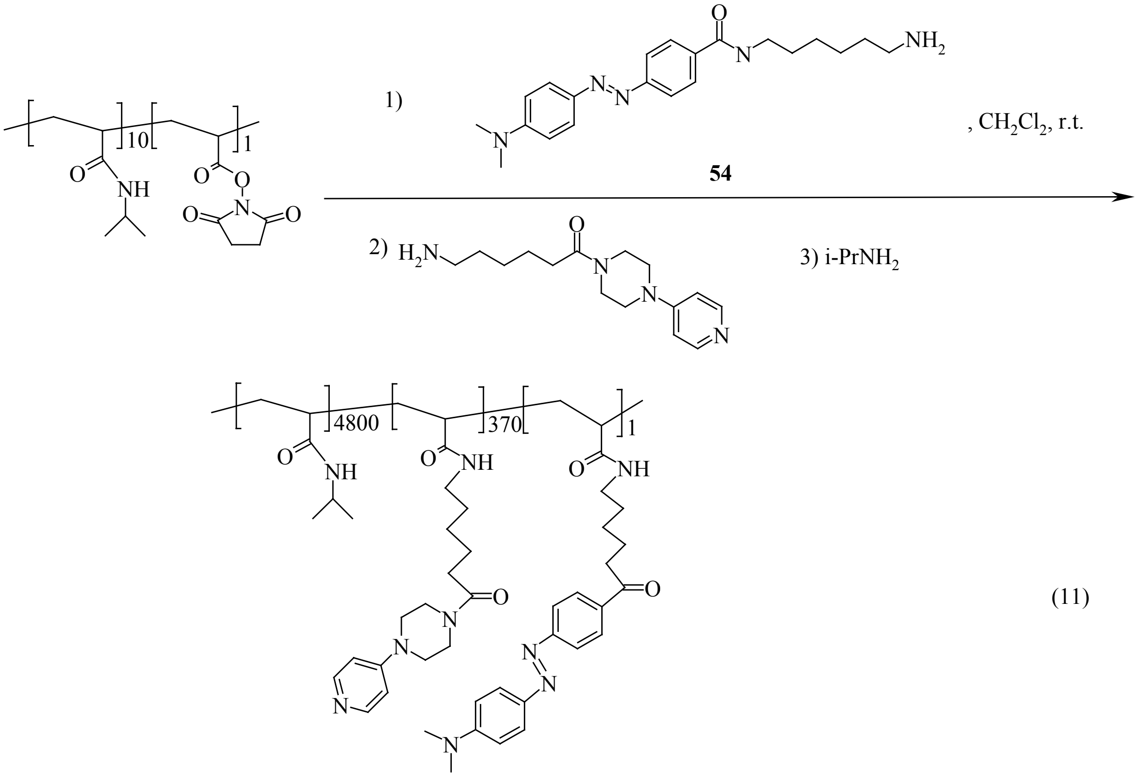
To evaluate its catalytic activity, the polymer-bound catalyst **53** was used in acylation chemistry typical for DMAP.[92] 1-Methylcyclohexanol reacted readily with acetic anhydride in the presence of 5 mol% **53** using triethylamine as the penultimate base in dichloromethane. (equation 10) The reaction was followed by GC using ethyl benzene as the internal standard. After the reaction was complete, the polymer-bound catalyst could be recovered by pouring the dichloromethane solution into hexanes, and the polymer precipitated which could be filtered and used again. The hexanes solution could be subjected to aqueous workup to obtain the ester product. However, there was a slight decrease in rate with increasing cycle numbers. This loss in activity could be due to some unknown catalyst degradation. Alternatively, we know that a small amount of polymer was physically lost after each cycle in handling. To find out the cause for the activity decrease, a quantitative assay for recovered catalyst was required. This was conveniently accomplished using a terfunctional polymer as described below.



(10)

### *Using a dye label to probe the activity and separation efficiency of PNIPAM-DAAP catalyst*

Analysis of the efficacy of catalyst separation and recovery is often unnecessarily complicated because of the lack of readily identifiable labels on the catalysts or species involved in such separations. However, a polymer has the potential to bind not only a catalyst but also a visible dye probe that could be used as a simple ‘phase indicator’ or marker for a polymer-bound catalyst’s location or concentration. The dye-labeled PNIPAM described below does precisely this, providing a simple way to monitor separability, concentration and recovery for soluble polymer-bound catalysts. These dye labels have been subsequently used to simplify analysis of separation both with PNIPAM and the polymers described in the rest of this dissertation. Incorporating methyl red into the polymer support was accomplished using the same methods used to attach catalysts to PNIPAM. An example of the synthesis of the methyl red labeled PNIPAM polymer is shown in equation 11.



PNIPAM-DAAP-MR **55**

(11)

In this synthesis of **55**, an amine-terminated methyl red derivative and an amine-terminated catalyst were used in successive steps to derivatize the active ester NASI groups. Then any unreacted NASI groups were converted to the *N*-isopropyl amide groups by adding an excess of isopropylamine. The terpolymer **55** so formed thus has three elements - the phase selectivity determinant, the catalyst, and the phase selectivity indicator.

The loading of the 4-dialkylaminopyridine catalyst on this polymer was ca. 8 mol% determined by $^1$H NMR spectroscopy. The methyl-red loading was ca. 0.02 mol% as determined by UV-visible spectroscopy ($\lambda_{max}$ = 430 nm in dichloromethane) assuming that the polymer-bound catalyst **55** and the low molecular weight amine-terminated methyl red **54** have the same extinction coefficient in dichloromethane. The UV spectra of **54** and **55** are given in Figure 11. Since the absorption is correlated with the dye concentration, the catalyst concentration could be calculated by the UV absorption of the polymer solution.

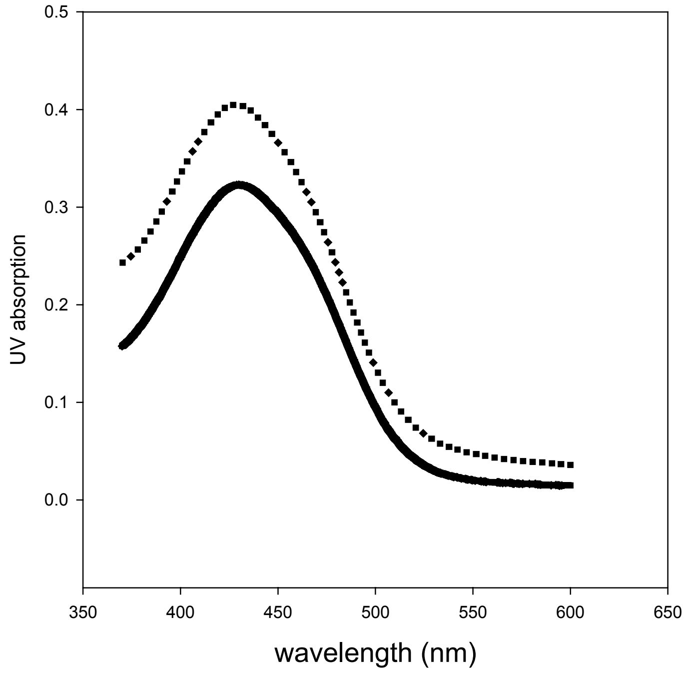


Figure 11. UV-visible spectra of (—) **54** and (---) **55**. The $\lambda_{max}$ of **54** was 432 nm and the $\lambda_{max}$ of **55** was 423 nm

The activity of the catalyst **55** was quantitatively assayed using acylation of 1-methylcyclohexanol in dichloromethane. Gas chromatography was used to monitor the reaction. The amount of catalyst used was 5 mol% relative to the alcohol. In order to avoid nonlinear behavior at higher conversion, only initial rates were measured and compared to those for a similar reaction catalyzed by DMAP. A plot of the $\ln([ROH]/[ROH]_0)$ versus time in Figure 12 was linear, indicating that the reaction was first order in alcohol. The rate constant for 4-dimethylaminopyridine was calculated to be 0.1783 $h^{-1}$. A similar kinetics analysis using catalyst **55** yielded a rate constant of 0.1200 $h^{-1}$.

Separation of the polymer-bound catalyst **55** was shown to be quantitative using UV-visible analysis. When the 1-methylcyclohexanol reaction mixture was poured into hexanes, the polyacrylamide catalyst **55** precipitated. UV-visible analysis of the supernatant after filtration gave no detectable absorption for the azo dye constituent in **55** (an absorption of dye that was as small as A = 0.02 could have been detected). After filtration and isolation of the polymer, **55** could be redissolved in dichloromethane and used again. It was used through four cycles with no loss in activity. Complete retention of activity of the catalysts in these subsequent cycles was determined by comparison of the initial rates of each reaction with one another (Figure. 13). An advantage of the catalyst **55** in these comparisons was that the small physical losses expected for filtration and handling of these catalysts (ca. 2% per cycle) do not obfuscate the analysis of catalyst recyclability since the amount of catalyst in each cycle can be easily and accurately quantified by UV-visible spectroscopy.

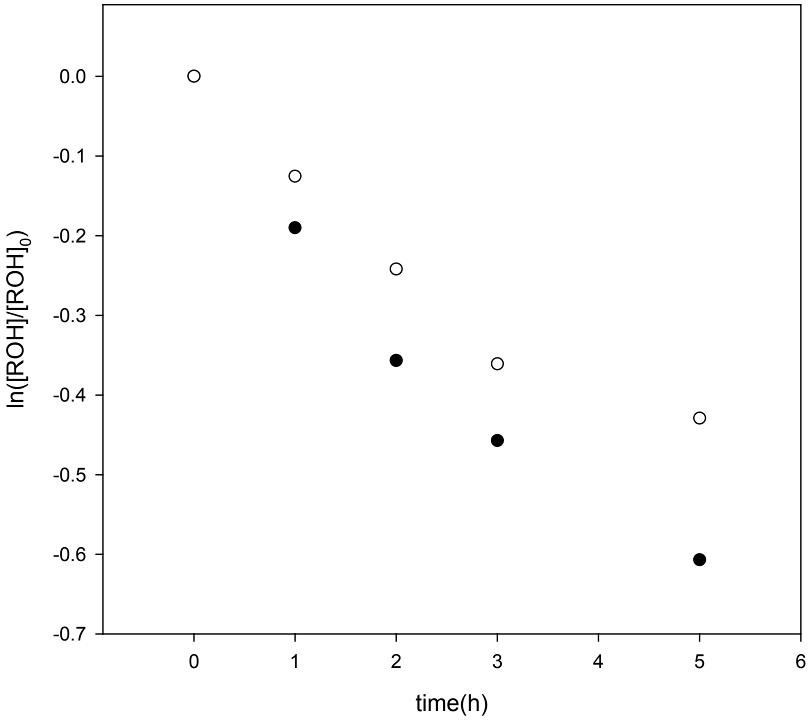


Figure 12. Catalytic activity of (●) DMAP and (○) PNIPAM-MR **55** in acylation of 1-methylcyclohexanol carried out at room temperature in dichloromethane at 30 $^{o}$C in dichloromethane

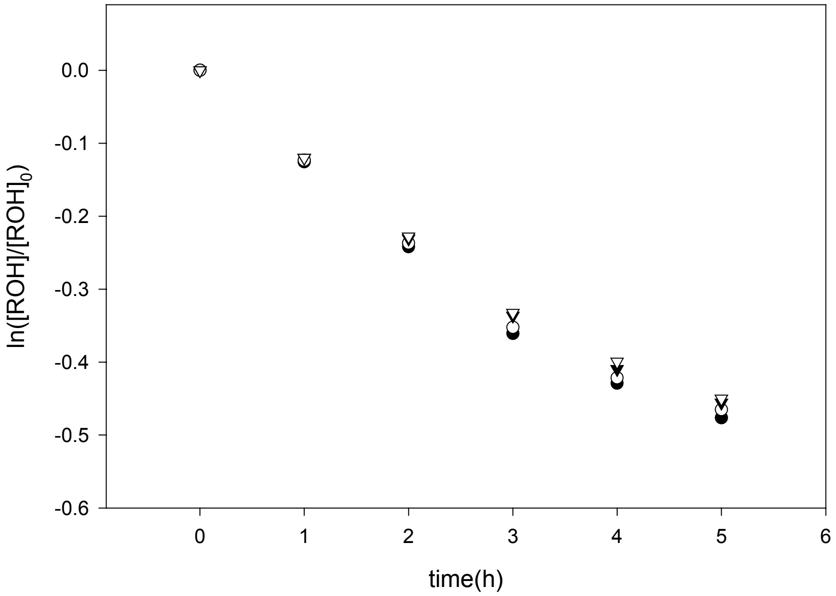


Figure 13. Initial rates of acylation of 1-methylcyclohexanol catalyzed by PNIPAM-DAAP-MR **55** in (♦) the first cycle, (◊) the second cycle, (▼) the third cycle and (□) the fourth cycle carried out at 30 °C in dichloromethane.

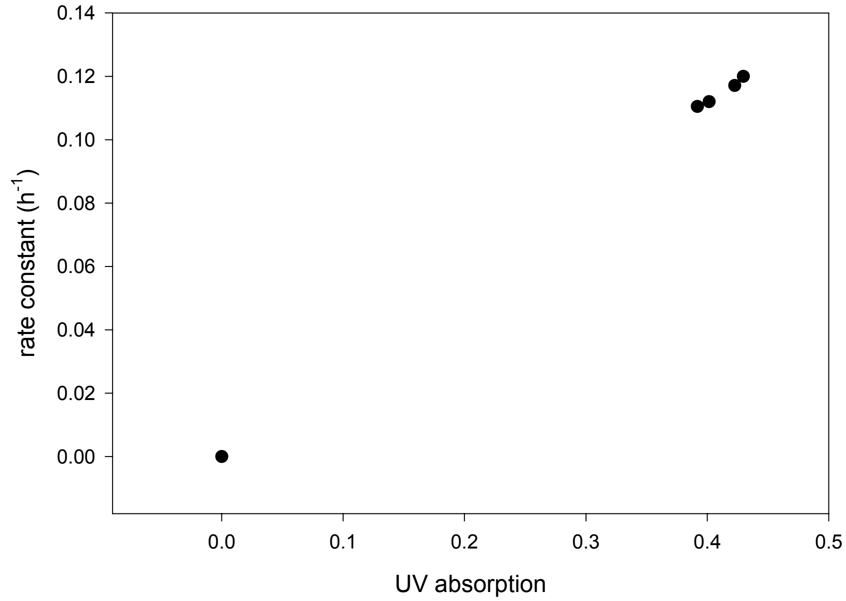
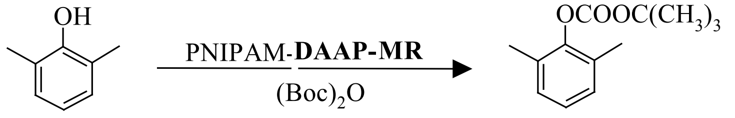


Figure 14. Correlation of rate constant with UV absorption of the reaction solution when **55** was used to catalyze acylation of cyclohexanol in dichloromethane at 30 °C

Catalyst **55** was also used to catalyze the reactions between hindered phenols and Boc anhydride using 5 mol% of the catalyst (equation 12). Catalyst **55** could be recovered from these reaction mixtures after the reactions using precipitation by pouring the dichloromethane reaction solution into excess hexanes. After filtration, the polymer-bound catalyst could be isolated, redissolved in dichloromethane, and reused. The reactions were monitored by IR, and the results are compared with results for a similar DMAP catalyzed reaction in Table 3.



(12)

Table 3. Catalytic activities for Boc-protection of 2,6-disubstituted phenols

| R[a] | Catalyst | Catalyst loading[b] | Time(min) | Yield (%)[c] |
|---|---|---|---|---|
| Me | DMAP | 5 mol% | 5 | 92 |
| Me | **55** | 5 mol% | 30 | 95(1st cycle)<br>91(2nd cycle)<br>94(3rd cycle) |
| i-Pr | DMAP | 5 mol% | 30 | 95 |
| i-Pr | **55** | 5 mol% | 60 | 90(1st cycle)<br>89(2nd cycle)<br>90(3rd cycle) |

[a] Phenols with substituents on 2,6- position were used as the substrates. [b] The amount of catalyst used was determined relative to the amount of the phenol substrates. A nearly stoichoimetric amount of Boc anhydride was used relative to the phenol substrates. [c] Isolated yield was used and the products were characterized by $^1$H NMR spectroscopy.

DMAP also efficiently catalyzed the acylation of 2,6-di-*tert*-butylphenol. However, the polymer-bound catalyst **55** showed no activity for this substrate. To identify whether the problem was the steric hindrance or the lipophilicity of the phenol substrate, a control reaction with 3,5-di-*tert*-butylphenol was carried out with catalyst **55**. Good catalytic activity was seen. Apparently, 2,6-di-*tert*-butylphenol did not undergo acylation due to the steric effect of the two *tert*-butyl groups.

To compare the initial rates for polystyrene-supported DAAP **26**, PNIPAM-supported DAAP **55** and 4-dimethylaminopyridine, a lower catalyst concentration (0.25% catalyst to phenol) was used and 2,6-diisopropylphenol was chosen as the substrate. The reactions were monitored by GC and the rates were plotted in Figure 15.

The rate constants for DMAP, PS-DAAP **26** and PNIPAM-DAAP-MR **55** were calculated to be 0.24 h$^{-1}$, 0.13 h$^{-1}$ and 0.17 h$^{-1}$, respectively.

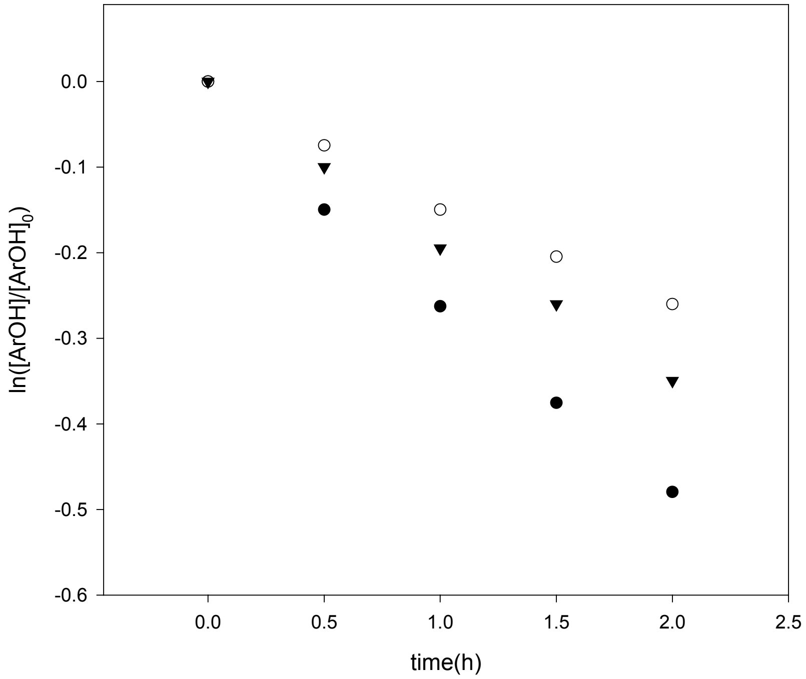


Figure 15. Acylation of 2,6-diisopropylphenol using various nucleophilic catalysts. (●) DMAP, (○) PS-DAAP **26,** and (▼) PNIPAM-DAAP-MR **55**

# CHAPTER III

# USING SOLUBLE SUPPORTS IN THERMOMORPHIC SYSTEMS[†]

## Introduction

Thermomorphic systems are very convenient and efficient for separation of polymer-bound catalysts after reactions. Depending on whether the catalysts prefer the polar phase or the nonpolar phase, thermomorphic systems are further divided into normal thermomorphic systems and inverse thermomorphic systems. In a normal thermomorphic system, a polymer-bound catalyst stays in the polar phase of a biphasic mixture at room temperature. When this mixture is heated up to a certain temperature, the two phases become miscible and homogeneous catalysis proceeds at this condition. After the reaction, the solution is cooled to room temperature and the catalyst phase separates from the product phase. No precipitation or filtration is involved. After developing this method our group has applied it successfully in catalysis using soluble polymer supports. Examples included the PNIPAM-bound Rh(I) catalyst for hydrogenations of alkenes in heptane/90% aq. ethanol at 70 $^{o}$C, the PNIPAM-bound Pd(0) catalyst for allylic substitutions of cinnamyl acetate with secondary amines in heptane/90% aq. ethanol at 70 $^{o}$C,[80] the PEG-supported Pd(II) catalyst for Heck

---

[†] Reproduced in part with permission from *Journal of the American Chemical Society* Copyright 2003 American Chemical Society.

reactions in heptane/90% aq. DMA at 95 °C and the PNIPAM-supported Pd(0) catalyst for Heck reactions in heptane/90% aq. ethanol at 75 °C.[81]

Inverted thermomorphic systems were subsequently developed where the polymer resided in the nonpolar phase and the product was isolated from the polar phase. Poly(*N*-octadecylacrylamide) (PNODAM) was the first polymer support designed for inverted thermomorphic systems.[40] The octadecyl group renders this polymer readily soluble in the nonpolar heptane but insoluble in polar solvents such as water, ethanol, and *N, N*-dimethylformamide (DMF). This polymer has been used as a support for an SCS-Pd(II) catalyst and a metal sequestrant in thermomorphic systems.

Using PNIPAM and PNODAM as supports for catalysts in thermomorphic systems is further described in this chapter. The focus of this chapter, however, is on exploring the effect of minor changes in polymer structure on phase selective solubility in thermomorphic liquid/liquid mixtures. Poly(*N*-alkylacrylamide)s with different substituents on the nitrogen atoms were studied. Understanding the change of polymers' solubility property with their structures is a guidance for us in designing new polymer supports for liquid/liquid separation systems.

## Results and Discussion

### *Phase Selective Solubility Study*

Phase selective solubility can readily be engineered into a polymer. Small changes in the size of the *N*-alkyl group of a poly(*N*-alkylacrylamide) lead to significant changes in phase selective solubility in situations where a polymer can dissolve either in a polar or nonpolar phase of a thermomorphic mixture of heptane/90% EtOH-$H_2O$. Our past work showed that poly(*N*-isopropylacrylamide) **56** and poly(*N*-octadecylacrylamide) **57** labeled with *p*-methyl red have very different solubilities.[40, 80] As shown in Figure 16, samples of these two polymers labeled with the protonated form of *p*-methyl red exhibited opposite phase selective solubility.

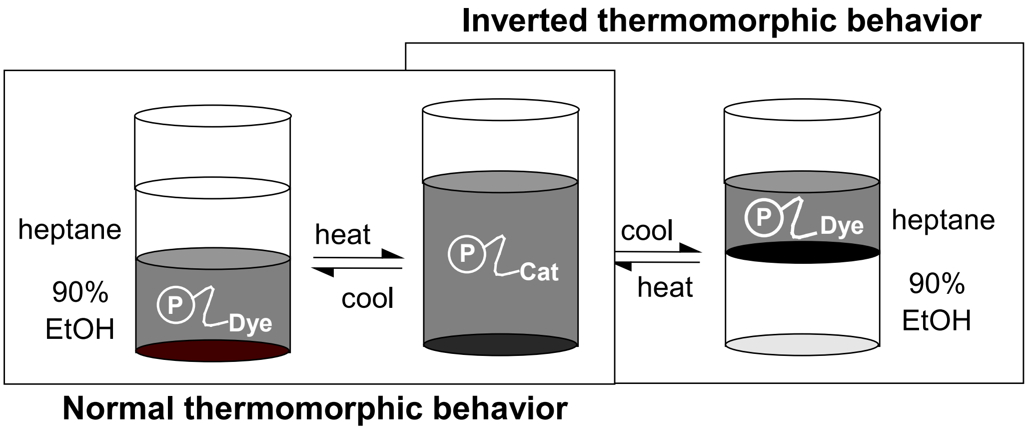
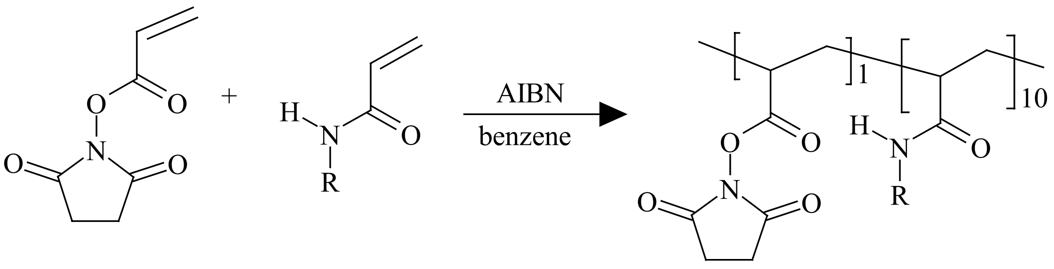


Figure 16. Normal and inverse thermomorphic separations of a poly(*N*-alkylacrylamide)-bound azo dye (a surrogate for a catalyst, reagent or substrate) in a thermomorphic heptane/90% EtOH-$H_2O$ mixture

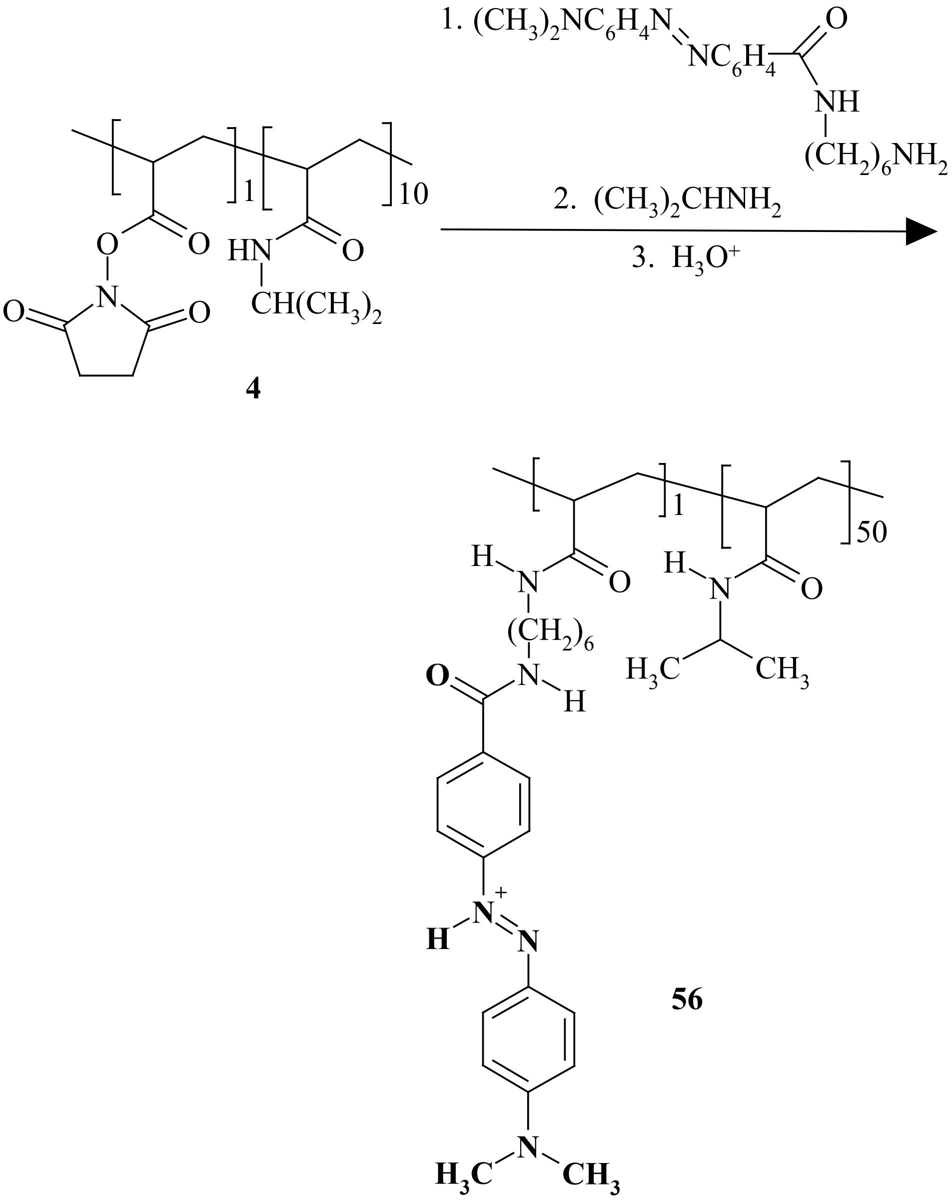
when placed in a mixture of a nonpolar solvent (heptane) and a polar solvent (90% ethanol-water). These polymers were prepared by a conventional radical copolymerization of the respective *N*-isopropylacrylamide or *N*-octadecylacrylamide monomer with NASI (equation 13). The product copolymer's (**4** or **58**) active ester group was then allowed to react first with a primary amine-derivative of p-methyl red and then with isopropylamine or octadecylamine (to consume any unreacted NASI ester) to form the dye-labeled poly(*N*-isopropylacrylamide) (PNIPAM) **56** (equation 14) or poly(*N*-octadecylacrylamide) (PNODAM) **57** (equation 15). The product polymers were labeled with a 1-2 mol % loading of methyl red as the azo dye label and were red in acidic solution or yellow in neutral solution. The unprotonated form of the azo dye-labeled **56** had a $\lambda_{max}$ at 437 nm in EtOH. The same neutral dye supported on **57** dissolved in heptane had a $\lambda_{max}$ at 419 nm. The protonated form of the azo dye-labeled **56** had a $\lambda_{max}$ at 513 nm in a 90% EtOH-$H_2O$ solution. The same protonated dye supported on **57** dissolved in heptane had a $\lambda_{max}$ at 515 nm. A typical molecular weight ($M_v$) of the PNIPAM polymer **56** (THF, 30 °C)[147] was 6 x $10^5$ Da. Both polymers **56** and **57** were readily soluble in a 70 °C miscible mixture consisting of equal volumes of heptane and 90:10 (v/v) ethanol:water, but **56** and **57** had significantly different solubilities at room temperature. Cooling either a hot heptane/EtOH-$H_2O$ homogeneous solution of **56** or **57** produced a biphasic mixture with a less dense nonpolar phase containing mostly heptane (ca. 3% ethanol was in the heptane phase after cooling-mediated phase separation) and a more dense polar phase consisting mostly of ethanol and water (ca. 7% heptane is in the polar phase after cooling-mediated phase separation). In the case of the polar polymer **56**, >99.9% of the polymer was in polar phase. This estimate is based on the absorbance difference of the nonpolar and polar phases (the absorbance was <0.002 for the nonpolar phase and >2.00 for the polar phase). These estimates assumed that **56** or **57** would have similar extinction coefficients in the polar or nonpolar phase. The extent of phase separation was also readily assayed visually for either the protonated or nonprotonated dye-labeled polymers. In contrast, cooling a hot heptane/EtOH-$H_2O$ solution containing **57** produced a biphasic mixture where >99.9% of the nonpolar PNODAM-bound dye was in the nonpolar phase. This differential phase selective solubility of a polar and nonpolar polymer-bound dye mirrors the phase selective solubility behavior of similar polymer-bound catalysts and led us to explore in greater detail both the extent of phase selective solubility of such polymers and the effect of polymer structure on such phase selective solubility.



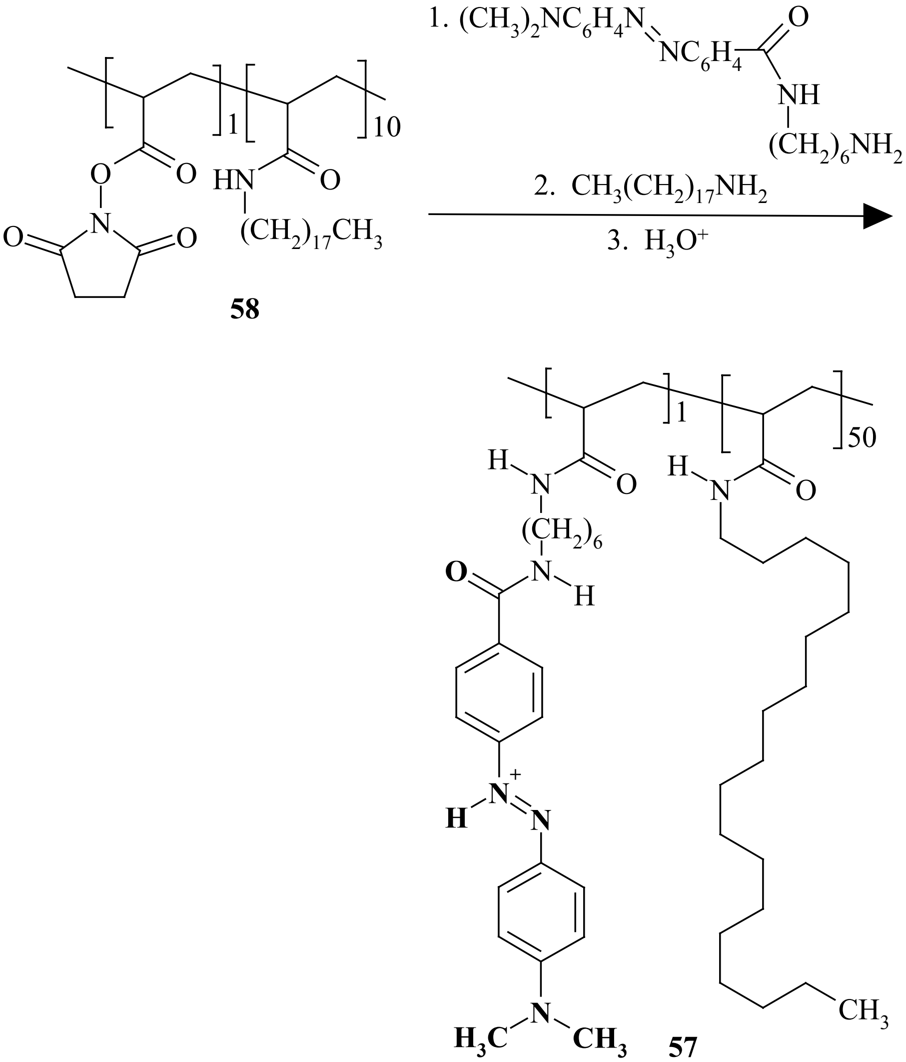
(13)

**4**: R = $-CH(CH_3)_2$
**58**: R = $-(CH_2)_{17}CH_3$

To further test the extent of phase selective solubility, Ms. Jackie Besinaiz prepared analogs of **56** and **57** that contain dansyl groups using the reactions shown in equations 16 and 17. The resultant polymers **59** and **60** behaved exactly the same as the methyl red-labeled polymers **56** and **57**. However, assays of the concentration of these fluorophore-labeled polymers were more sensitive. This allowed us to both use a lower loading of probe on the polymer and to estimate that phase selective solubilities of **56** or **57** are as high as $>10^5$:1 in polar or $>10^4$:1 nonpolar solvents, respectively.



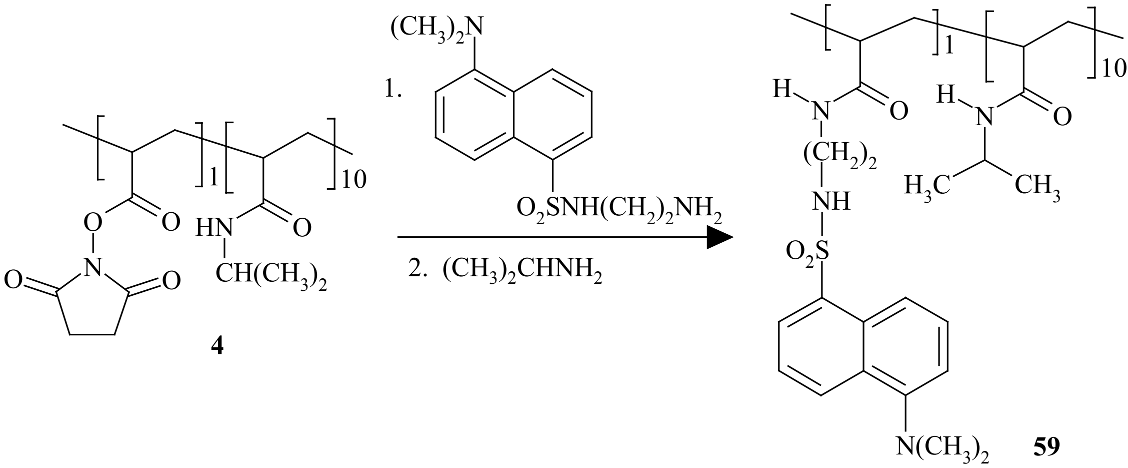
(14)


1. (CH3)2NC6H4N=NC6H4C(O)NH(CH2)6NH2
2. CH3(CH2)17NH2
3. H3O+
1
10
1
50
(CH2)17CH3
(CH2)6
H3C
CH3
CH3

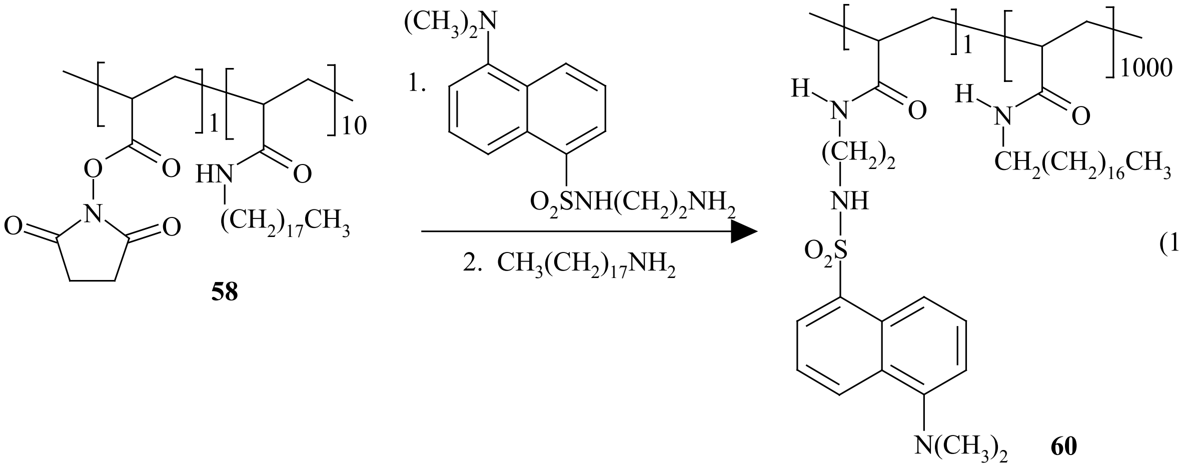
**58**

**57**

(15)



(16)



(17)

Table 4 lists the phase selective solubility of the both dye and fluorophore-labeled polymers in several solvent mixtures. The solvent mixtures in this list are all thermomorphic (they are biphasic at one temperature and completely monophasic at another temperature). Immiscible mixtures of polar and nonpolar solvents (e.g. water and heptane) or other solvents with varying temperature dependent miscibility (e.g. toluene and 85% EtOH-$H_2O$) are not listed here. Generally, such solvents have comparable (>99.9%) phase selective solubilities for the polar and nonpolar polymer-bound dyes **56** and **57** in the polar and nonpolar phases of these biphasic mixtures. Phase selective solubility of polymers in solvents like those listed in Table 4 were studied in more detail in this work because similar polymer-supported species and similar solvent mixtures are useful in homogeneous catalytic reactions and catalyst recovery. High selective solubility of a dye-labeled polymer can be presumed to be predictive of high levels of separation of a similar ligand- or catalyst-containing polymer in synthetic chemistry since the dye or fluorophore in these polymers is a surrogate for a catalyst, reagent or substrate.

The high phase selective solubility of these polymers has important consequences for catalysis. Whitesides previously noted[148] that biphasic systems using enzymes as macromolecular catalysts in aqueous biphasic reactors often cannot be readily recovered without resort to countercurrent operation with multiple partitions of the product mixture because enzyme phase selectivities (distribution coefficients) are typically between 0.1 to 10 in ternary aqueous biphasic systems. He correlated the recovery of enzymes with their distribution coefficients in biphasic systems (equations 18 and 19).

$$K = C_1/C_2 \tag{18}$$

$$A_1/A_0 = (1 + V_2(KV_1)^{-1})^{-1} \tag{19}$$

Table 4. Spectroscopic Estimates of Solubility for *p*-Methyl Red- and Dansyl-Labeled Poly(*N*-alkylacrylamide)s ((PNIPAM) and Poly(*N*-Octadecylacrylamide) (PNODAM)) and p-Methyl Red-Labeled Poly(ethylene glycol) in Various Thermomorphic or Biphasic Solvent Mixtures.

| Polymer Probe | Solvent Mixture | Nonpolar Phase Solubility[a] |
|---|---|---|
| Methyl Red-PNIPAM | heptane-EtOH (aq)[b] | < 0.1 % |
| Methyl Red-PNIPAM | heptane-DMF[c] | < 0.1 % |
| Dansyl-PNIPAM | heptane-EtOH (aq)[b] | < 0.01 % |
| Methyl Red-PNODAM | heptane-EtOH (aq)[b] | > 99.9 % |
| Methyl Red-$PEG_{5000}$ | heptane-EtOH (aq)[b] | < 0.1 % |
| Methyl Red-PNODAM | heptane-DMF[c] | > 99.9 % |
| Dansyl-PNODAM | heptane-EtOH (aq)[b] | > 99.99 % |
| Dansyl-PNIPAM | heptane-DMF[c] | < 0.001 % |
| Dansyl-PNODAM | heptane-DMF[c] | > 99.99 % |
| Methyl Red-PNIPAM | $Et_3N$-water[d] | > 99.9 % ($Et_3N$ phase) |
| Dansyl-PNIPAM | $Et_3N$-water[d] | > 99.9 % ($Et_3N$ phase) |

[a] The relative amounts of polymer-bound dye or fluorophore were measured in each phase after a miscible hot homogeneous mixture of solvents and polymer were cooled to

room temperature to form a biphasic mixture. Relative solubilities (e.g. >99.9 % or <0.001 %) were estimates based on the minimum detectable amount of probe after a series of serial dilutions. [b]This solvent mixture consisted of a 1:1 (vol:vol) mixture of heptane and EtOH-$H_2O$ (90 % EtOH by volume). [c]This solvent mixture consisted of a 1:1 (vol:vol) mixture of heptane and dimethylformamide. [d]This solvent mixture consisted of a 1:1 (vol:vol) mixture of triethylamine and $H_2O$ and differed from the other solvent mixtures in that it was miscible cold (0 °C) and biphasic hot (25 °C).

$C_1$ and $C_2$ represent the solute concentration in the upper phase and the lower phase, respectively; $V_1$ and $V_2$ represent the corresponding volume; $A_0$ is the initial quantity of solute; and $A_1$ is the solute quantity after separation. In a system where $V_1 = V_2$, the amount of enzyme recovered after a single cycle is typically between 9% (when K = 0.1) and 91 % (when K = 10). (Table 5) However, the phase selective solubility of up to >100,000:1 seen for the linear poly(*N*-alkylacrylamide) supports and the use of roughly equal volumes of the polar and nonpolar phases means that a separation can easily effect >99.999% polymer (and presumably catalyst) recovery.

Table 5. Correlation of the loss of solute with the distribution coefficients[a]

| K | Loss of solute (%) |
|---|---|
| 0.1 | 90.9 |
| 1 | 50.0 |
| 10 | 9.1 |
| 100 | 1.0 |
| 10000 | 0.01 |
| 100000 | 0.001 |

[a]The loss of solute is calculated from equation 19, assuming an equal volume of the two immiscible solvents were used.

Most of the examples in Table 4 above are for the two polymers that have been used in catalysis and synthesis – PNIPAM and PNODAM. PEG derivatives too have been widely used as supports in polymer supported chemistry and in thermomorphic systems. Phase selective solubility of one example – commercially available $PEG_{5000}$ was briefly examined. This polar polymer has phase selective solubility like that of the polar PNIPAM derivative. However, unlike the poly(*N*-alkylacrylamide)s, it would not be as simple to tinker with the polymer microstructure to design a heptane-soluble support. Moreover, our work showed that high selective phase solubility was only obtained for this polymer after continuously extracting an aqueous solution of this polymer with heptane either before methyl red labeling or as a methyl red labeled derivative. We believe this extraction removes lower molecular weight PEG derivatives that are not as phase selective soluble.

A caveat for Table 4 is that the poly(*N*-alkylacrylamide)s listed here only contain *N*-isopropyl and *N*-octadecyl substituents. These substitutents of these poly(*N*-alkylacrylamide)s are significantly different. We also wished to ascertain how sensitive phase selective solubility is to the size (hydrophobicity) of the pendant *N*-alkyl groups of these poly(*N*-alkylacrylamides). It was already known that the *N*-alkyl substituent's hydrophobicity affects poly(*N*-alkylacrylamide)s' temperature dependent solubility.[149,150] Such effects are useful in synthesis and varying the nature of an *N*-alkyl substituent can produce quite subtle changes.[50,53,56,151]

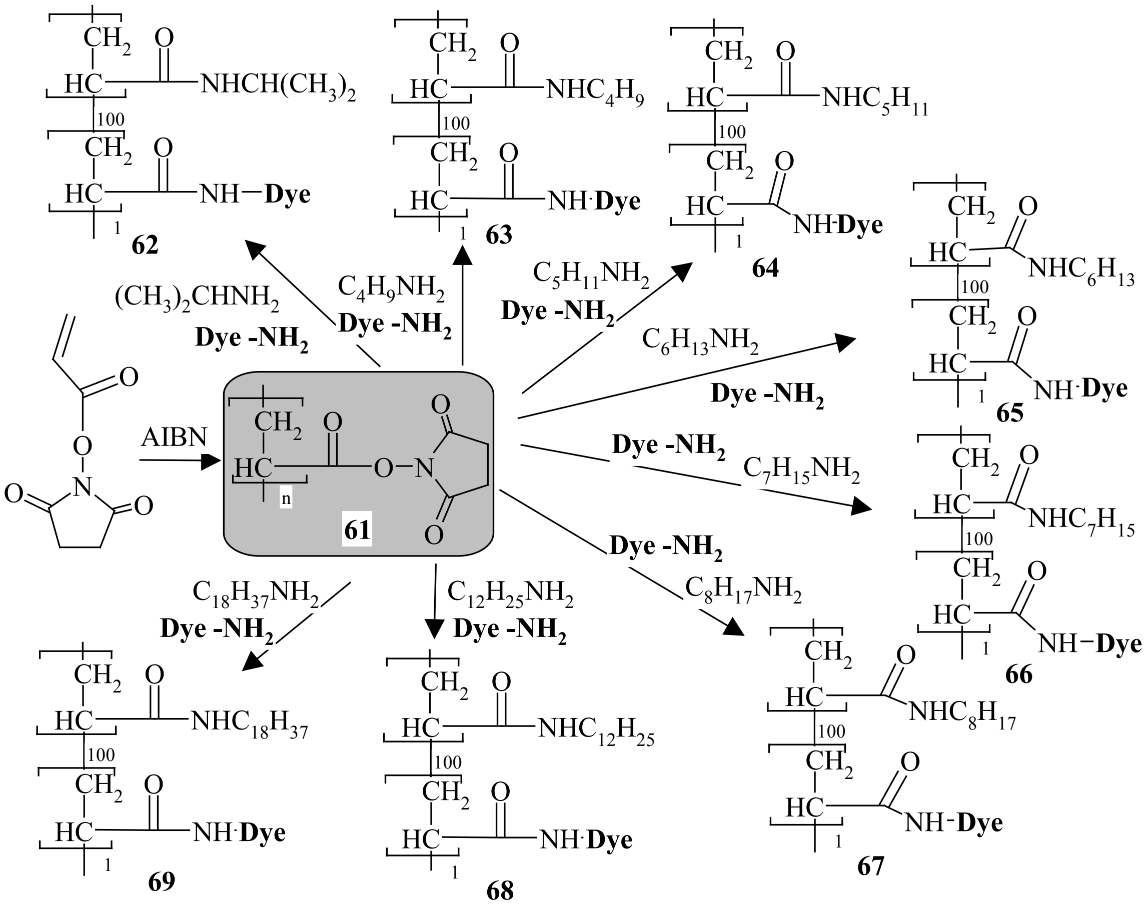
It was expected that phase selective solubility of polymers too would be affected by the hydrophobicity of the *N*-alkyl substituent. However, it was not clear if small changes in polymer substituent structure would lead to dramatic changes in polymer solubility. The difference between PNIPAM and PNODAM shows that there is a spectrum of phase selective solubility that is dependent on the size of the *N*-alkyl substituents. However, these *N*-alkyl substituents are so different that they are likely to be at the extremes of the polar-phase soluble or nonpolar-phase soluble regions of this phase selective solubility behavior spectrum. Predicting the effects intermediate sized *N*-alkyl groups have on solubility is less certain. A comparison of solubility parameters calculated using substituent effects for two poly(*N*-alkylacrylamide)s that differ by only one or two methylene groups in their *N*-alkyl substituents suggests that changing alkyl group size by a few carbons would lead to less than 1% change in the solubility parameter $\delta$.[152] However, the solubility of poly(*N*-alkylacrylamide)s like PNIPAM and

PNODAM is affected by polar effects and hydrogen bonding so the relative solubility of poly(*N*-alkylacrylamide)s with similar alkyl substituents is best tested experimentally.

There are some experimental problems associated with directly comparing the phase selective solubility of a series of poly(*N*-alkylacrylamide)s prepared by polymerization reactions like equation 13. Specifically, a comparison between different poly(*N*-alkylacrylamide)s is complicated because conventional radical polymerization leads to polymers that do not necessarily have the same polydispersity and degree of polymerization. Indeed, it is difficult to prepare samples of the same polymer in batch to batch reactions such that the degree of polymerization and polydispersity are identical. While it is possible that the degree of polymerization and the polydispersity are not important factors in phase selective solubility, it is better to avoid this ambiguity. Therefore, the synthesis of polymeric active esters was used that was developed originally by Ringsdorf[153] as a route to a library of poly(*N*-alkylacrylamide) polymers that can be compared without the ambiguities of variable polydispersity and degree of polymerization.

Ms. Reagan Hughes, who worked in our lab as an undergraduate student, used a pool-split synthesis route to prepare libraries of poly(*N*-alkylacrylamide)s. This chemistry employs a common polymer precursor and no fractionation steps. Thus, this chemistry leads to a library of polymer samples, all of which have the same degree of polymerization and polydispersity but which vary in the structure of their pendant *N*-alkyl groups. By combining this synthesis with a labeling procedure using the azo dye described above, we have been able to study the effect of *N*-alkyl group structure on the spectrum of phase selective solubility for poly(*N*-alkylacrylamide)s. The results allow us to directly assay and compare the effects of polymer structure on polymer phase selective solubility.

Before using this chemistry to make a library to test phase selective solubility, we carried out several control experiments. First, to verify that the procedure in Scheme 14 produces polymer products that behave the same as the products prepared using equation 13-15, dye-labeled PNIPAM and PNODAM polymers **62** and **69** were prepared separately via the reactive polyacrylate **61** and compared these polymers to **56** and **57**. In this synthesis, a homopolymer of NASI was prepared using AIBN initiation. The product active ester homopolymer was then allowed to react with a 50% molar excess of a 100:1 (mole:mole) mixture containing either isopropylamine or octadecylamine and an amine-containing derivative of methyl red. In this first synthesis, the product PNIPAM and PNODAM polymers **62** and **69** were separated from excess amines and isolated by solvent precipitation. The phase selective solubility of these methyl red-labeled PNIPAM and PNODAM polymers was identical to that seen for **56** or **57** prepared via the more conventional route (equation 14 and 15).



Scheme 14. Pool split synthesis of a library of poly(*N*-alkylacrylamide)s that vary only in the size of their *N*-alkyl substituent

Next a purification procedure was developed for removal of the excess amines in the syntheses of Scheme 14. Excess amine is required in Scheme 14 to ensure no reactive ester remains in the product polymer. It was previously shown that unreacted NASI esters could hydrolyze readily to form acrylic acid groups[50] – an event that would produce a terpolymer whose phase selective solubility might be quite different than that of the desired poly(*N*-alkylacrylamide) due to the presence of carboxylic acid groups.

Excess amine avoids this problem, ensuring complete consumption of all the NASI groups. However, the resulting presence of unreacted low molecular weight dye complicates the analysis of the phase selective solubility of the products. Thus, a purification step was required that would remove low molecular weight amines without any fractionation of the product poly(*N*-alkylacrylamide)s. Such a separation can be accomplished by solvent precipitation (vide supra). However, solvent precipitation is a potential fractionation step and we wanted to maintain in our library synthesis the same polydispersity and degree of polymerization for all samples. Therefore, excess low molecular weight amines from our product poly(*N*-alkylacrylamide) library members were removed using a sulfonated ion exchange resin that was previously shown to be a useful amine sequestration agent in parallel synthesis of amines from carbamates.[154] In a control experiment, it was shown that polymers like **62** and **69** do not react with this sequestration agent – a sulfonated ion exchange resin (Amberlyst 15). This was expected since earlier work had shown that this resin readily reacts chemioselectively with simple amines and/or BOC-protected amines but that it does not react with amides. The lack of reactivity of poly(*N*-alkylacrylamides) with the sulfonated crosslinked polystyrene was confirmed by the observation (UV visible analysis) of no change in the solution concentration of the chromophore due to **62** on treatment of a THF solution of **62** with this polymeric sulfonic acid.

Once procedures were in hand to remove the excess amine and dye used in synthesis of poly(*N*-alkylacrylamide)s prepared via the polymeric active ester **61**, Ms. Hughes prepared a small library of poly(*N*-alkylacrylamide)s **62** and **69** containing *N*-

isopropyl, *N*-*n*-butyl, *N*-*n*-pentyl, *N*-*n*-hexyl, *N*-*n*-heptyl, *N*-*n*-octyl, *N*-*n*-dodecyl, and *N*-*n*-octadecyl groups. A common precursor polymer **61** was prepared and portions of this polymer were added to DMF solutions containing a 1.5-fold excess of a 100:1 mixture of a primary amine and a primary amine derivative of methyl red. The reaction mixtures were heated to 50 °C to ensure solubility of all the reaction components. After 24 h, the reaction mixture was cooled and a sulfonic acid containing ion exchange resin (Amberlyst 15) was added. Shaking the resulting mixture for 24 h removed any excess low molecular weight amine or unbound dye. At this point, a qualitative measure of the similarity of the samples of polymers **62** and **69** was the visual similarity of color for the 8 different solutions, all of which had the same concentration of chromophore. The remaining solvent was then removed at reduced pressure to yield samples of **62** and **69** that were used directly in phase selective solubility studies.

Once a collection of methyl red labeled poly(*N*-alkyl acrylamides) **62** and **69** with different sized *N*-alkyl side chains was in hand, the phase selective solubility of these polymers was tested using visible spectroscopy. In each test, an individual poly(*N*-alkylacrylamide) was added to a mixture of a 1:1 (vol:vol) mixture of heptane and 90% aqueous ethanol (EtOH:$H_2O$ = 90:10 (v/v)). Heating to 70 °C produced a single miscible solution from this solvent mixture and also dissolved the polymer. At this point, the mixtures were cooled to room temperature at which time two phases, a nonpolar heptane phase and a polar aqueous ethanol phase formed. In general, phase separation occurred readily. If phase separation were slow, centrifugation was used to facilitate complete phase separation. Each phase was then sampled and analyzed by UV-visible spectroscopy.

The results of these studies were that methyl red labeled poly(*N*-alkylacrylamide) polymers with eight, twelve, and eighteen carbon chains had phase selective solubility in heptane. No (<0.5%) methyl red labeled polymer could be detected in the polar phase in these three cases. Poly(*N*-alkylacrylamide)s with three, four, or five carbon chains had phase selective solubility in the polar ethanol phase. No (<0.5%) methyl red labeled polymer could be detected in the nonpolar heptane phase in these two cases. Intermediate phase selective solubility was seen for poly(*N*-alkylacrylamide)s containing six or seven carbons in the pendant *N*-alkyl amido groups. Poly(*N*-hexylacrylamide) was 85% soluble in the heptane phase (average of two experiments). Poly(*N*-heptylacrylamide) had 91% phase selective solubility in the heptane phase (average of two experiments). These results are summarized graphically in Figure 17. These experiments all involved analysis of the methyl red-containing polymers under conditions where the methyl red is not protonated. This work was also replicated by another undergraduate student, Mr. Alvaro Resines.

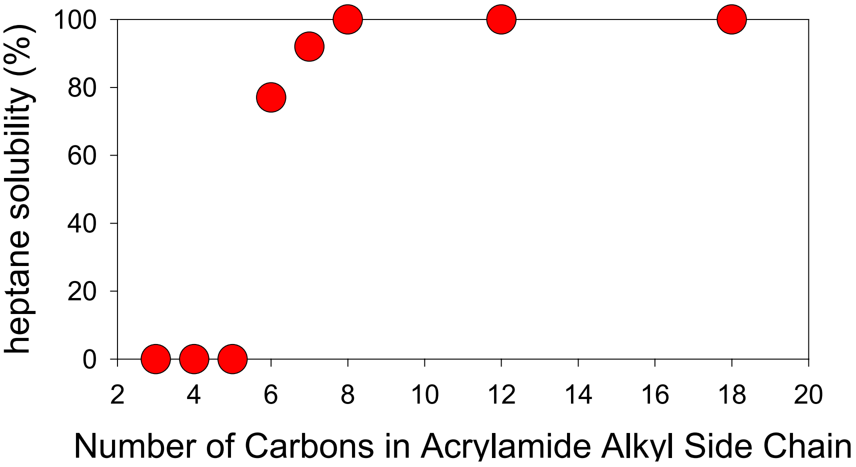


Figure 17. Heptane solubility versus the number of carbons in the *N*-alkyl group of p-methyl red-labeled poly(*N*-alkylacrylamides) prepared according to the method shown in Scheme 14 as measured by UV-visible spectroscopy of the polar and nonpolar phases of a mixture of heptane/90% ethanol-water (1:1 vol:vol) at 25 °C. In all cases, the phase selective solubility was measured after the mixture had been heated to 70 °C (miscibility) and then allowed to cool to a resting biphasic state

While the solubility differences seen for polymers **62** and **69** mirrored those seen for polymers made via equations 14 and 15, the degree of polymerization of the reactive polyester **61** used in Scheme 14 is not as large as is the case for polymer prepared by equation 14 or 15. The lower degree of polymerization of **61** was measured indirectly by analyzing the $M_n$ and $M_w$ of the PNIPAM derivative of **61** by GPC using 0.01 M LiBr in DMF as the eluent on a TOSOH BIOSEP column. This analysis showed that this PNIPAM derivative has a $M_n$ and $M_w$ of $1.8 \times 10^5$ and $3.4 \times 10^5$, respectively. This suggests that phase selective solubility can be seen for PNIPAM and PNODAM polymers with varying degrees of polymerization.

Phase selective solubility of polymers can also be achieved in thermomorphic systems that employ two polar solvents. An example of such a system would be triethylamine and water.[155] This system is also interesting because this thermomorphic solvent mixture has an LCST for its miscibility - an equal volume of these two solvents is miscible at 0 °C and immiscible at 25 °C. In this case, a PNIPAM-bound methyl red dye and the PNIPAM-bound dansyl derivative **59** were found to reside exclusively in the triethylamine phase after a homogeneous 0 °C 1:1 (vol:vol) mixture of triethylamine and water was warmed to room temperature and phase separated. This separation was completely reversible.

### *PNIPAM-DAAP-MR catalyzed acylation in a thermomorphic system*

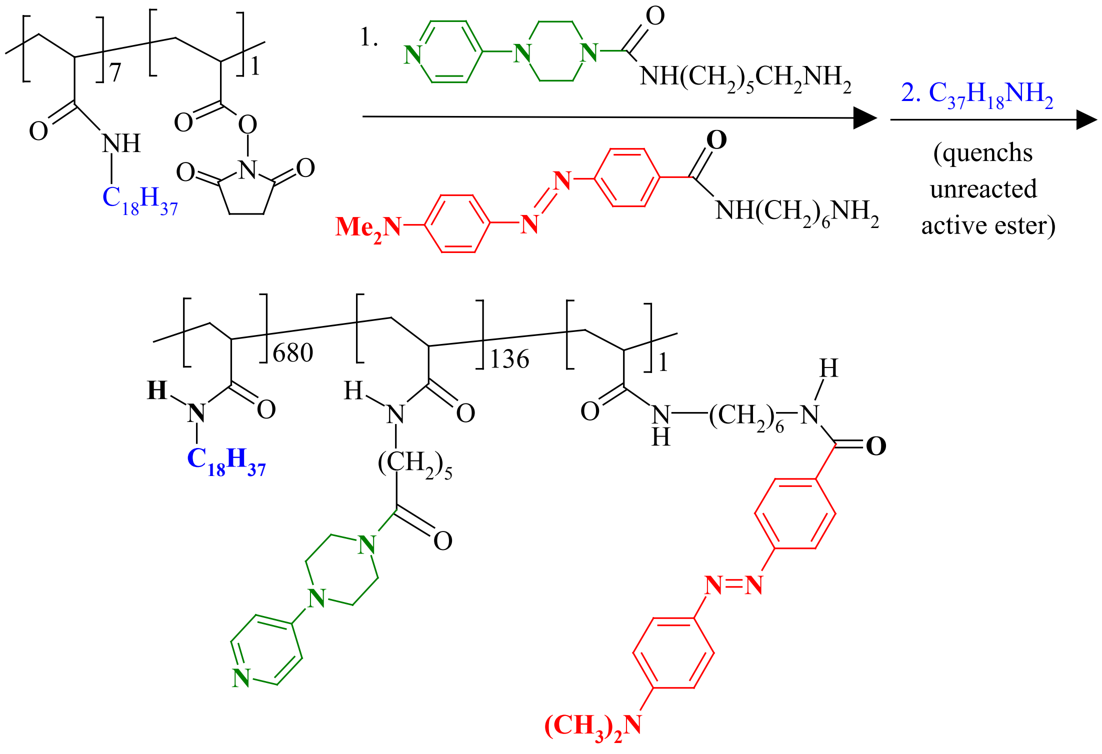
PNIPAM and PNODAM were shown to be good polymer supports to use in thermomorphic systems, so that more catalysts on these polymer supports were studied. The PNIPAM-DAAP-MR **55** previously recovered by solvent precipitation was also used in the thermomorphic system using heptane/DMF as the solvent. When the catalyst **55** (5 mol%) was dissolved in a liquid/liquid biphasic mixture of DMF and heptane at 25 °C, this polar PNIPAM-bound catalyst dissolved selectively in the polar DMF-rich phase. However, **55** was also soluble in the homogeneous solvent mixture that resulted from heating this solvent mixture to 70 °C. When cooling this thermomorphic mixture back to 25 °C, this catalyst stayed in the DMF-rich phase. The polymer was present in a resting biphasic mixture of heptane and DMF exclusively (>99.5%) in the DMF-rich phase as measured by UV-visible analysis of the DMF and the heptane phases. This makes it possible to use **55** in a homogeneous reaction and to separate it with a liquid/liquid separation after the reaction.

For example, when a substrate phenol and $(Boc)_2O$ reagent was added to the DMF-heptane mixture containing **55** and the biphasic mixture was heated, a monophasic solution formed and **55** catalyzed the acylation of 2,6-dialkylphenols by $(Boc)_2O$. After 1 h, the mixture was cooled. The phases separated and the heptane-rich phase (the nonpolar phase) containing the relatively nonpolar Boc-derivative of 2,6-diisopropylphenol was separated from the catalyst-containing DMF-rich phase. Addition of fresh heptane and substrates with a second heating and cooling cycle allowed us to repeat the process. This process was successfully used five times using 2,6-diisopropylphenol and a DMF-heptane thermomorphic system. Similar chemistry using a 90% ethanol-water/heptane thermomorphic system produced >90% yields of phenyl carbonate in the fifth cycle using $(Boc)_2O$ with both phenol and 2,6-dimethylphenol.

### *PNODAM-supported DAAP catalyst*

In inverted thermomorphic systems, the catalyst was recycled from the top nonpolar heptane phase. From an industrial point of view, there is an advantage to drain the product out from the bottom of the reactor. The following example illustrates the application of a PNODAM-supported catalyst in an inverted thermomorphic system.

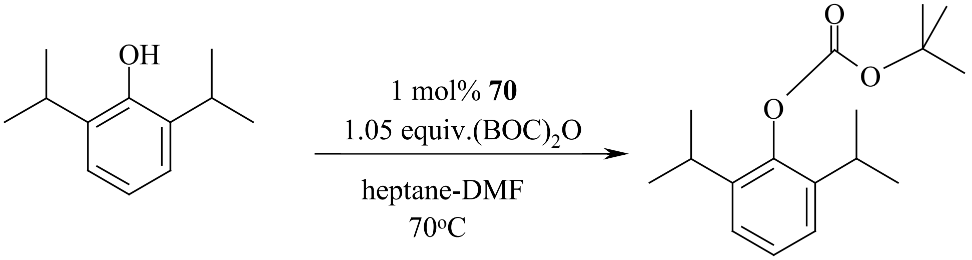
The DMAP analog **24** made earlier was attached to PNODAM, and a dye molecule was again used as a label to monitor its phase selectivity, as shown in Scheme 15. The copolymer **58** was treated with the amine-terminated methyl red **54** used earlier, to generate a labeled polymer. Then the amine-terminated catalyst was added to the above solution. Any leftover active esters were substituted by an excess of octadecylamine, to generate the terfunctional polymer **70**, with the phase selectivity determinant, the catalyst and the phase selectivity indicator all on the same polymer.



**70**

Scheme 15. Synthesis of PNODAM-DAAP-MR

The polymer-bound catalyst made in this manner was subjected to UV analysis to study its phase preference in the thermomorphic solvent mixtures. The result showed that it had >99.5% preference for the heptane phase in both heptane/aq. ethanol and heptane/DMF mixtures. Its catalytic activity was tested in the Boc protection of phenols in a 1:1 mixture of heptane and DMF, as shown in equation 20. The polymer-bound catalyst **70** was dissolved in heptane. Boc anhydride and 2,6-diisopropylphenol were dissolved in DMF. The two solutions were then mixed with each other to form a biphasic mixture, with a colored top heptane phase and a colorless bottom DMF phase. The mixture was then heated to 70 $^{o}$C with stirring, and the biphasic mixture turned into a homogeneous solution. After 30 min, the solution was cooled down to room temperature and stirring was stopped. Then the solution separated clearly into two phases, again a colored top heptane phase and a colorless bottom DMF phase. The DMF phase was poured into water and extracted with dichloromethane to obtain the product without contamination from the catalyst. The heptane phase was mixed with fresh substrates for the next catalytic cycle. The isolated yield for the first several cycles was as follows: 44%, 57%, 76%, 90%, 98%, 99%, 99%. As can be seen, the yield started very low, but went up with increasing cycle numbers, and eventually reached quantitative. Similar phenomenon was observed earlier with normal thermomorphic systems as well. This was due to the product's solubility in the catalyst phase, so the numbers listed only represented the product partitioned into the desired product phase. However, as the cycle number increased, the catalyst phase eventually became saturated with product. It was at this point that quantitative yield was obtained from the product phase.



(20)

# CHAPTER IV

# APPLICATION OF POLYMER-BOUND CATALYSTS IN LATENT BIPHASIC SYSTEMS[‡]

## Introduction

The thermomorphic systems discussed in the previous chapter are very convenient systems for catalyst separations after homogeneous reactions. However, there is a drawback with them in that reactions have to be carried out at higher temperatures to achieve homogeneity for the reaction mixture. We have been looking for ways to modify these thermomorphic systems so that reactions can be carried out at room temperature homogeneously while keeping the possibility of liquid/liquid separation. Here we describe another alternative, a latent biphasic system. In such a system, a solvent mixture at the cusp of immiscibility is prepared. Such a system can be used to carry out a reaction under homogeneous conditions. Then, after the reaction is complete, this mixture is perturbed by the addition of some perturbing agent to produce a biphasic mixture. Similar procedures were described as being useful for separating nonpolar/polar solvent mixtures using water in a Union Carbide's patent.[156,157] Chan's group has used dendrimers in this way.[158] Carbon dioxide was also recently used as a phase switcher to separate an ionic liquid from methanol.[159] This chapter describes the

---

[‡] Reproduced in part with permission from *Journal of the American Chemical Society* and *Organic Letters*. Copyright 2003 American Chemical Society.

generality of using linear polymers as supports in similar latent biphasic systems. Dye-labeled polymers are used as surrogates for catalysts on polymers to test separation efficiency and catalysts on polymers are used to demonstrate feasibility of this scheme in known homogeneous catalytic reactions.

## Results and discussion

### *Latent Biphasic Catalysis*

Mixtures of solvents have a spectrum of phase behavior. For example, ethanol/water or ethanol/heptane are miscible in all proportions. However, mixtures containing all three of these solvents vary in miscibility depending on the proportions of solvents used, the temperature, and the presence or absence of solutes. As an illustrative example, a 10.0:9.5:0.5 (vol:vol:vol) mixture of heptane, EtOH and $H_2O$ is monophasic at 25 °C, but a perturbed 10.0:9.0:1.0 mixture of these solvents is biphasic at 25 °C (Figure 18). The temperature dependence of the latter sort of mixture was used in thermomorphic reactions, as described in the previous chapter. Here we show how addition of small amounts of another solvent or salt to the former sort of monophasic mixture that is at the cusp of miscibility (a latent biphasic system) can be used as a new way to effect a separation of a catalyst from the reaction mixture after a homogeneous reaction.

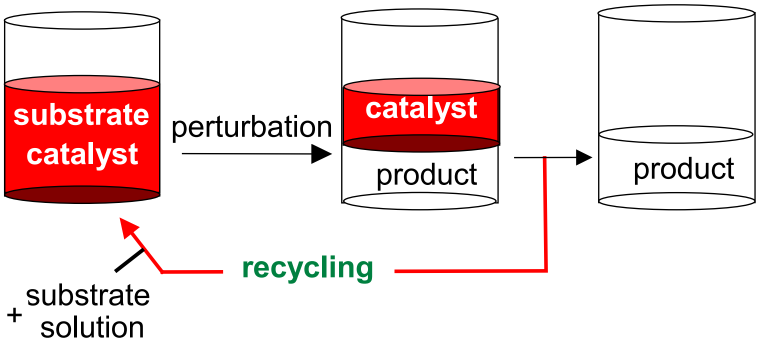


Figure 18. Latent biphasic process with a reaction occurring under monophasic conditions and separation occurring under liquid/liquid biphasic conditions after some perturbation

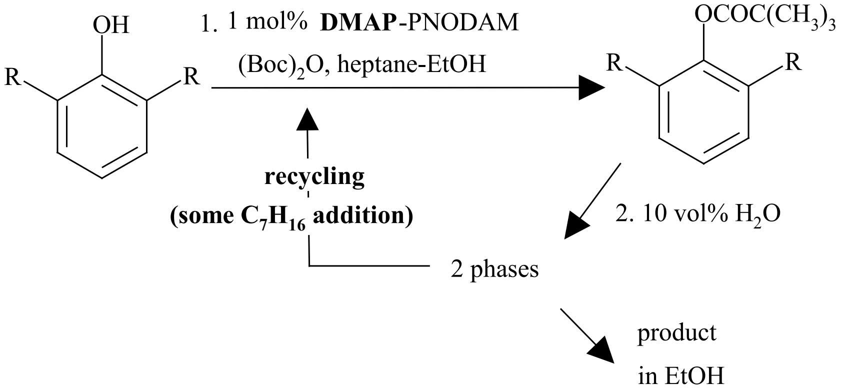
While solvent mixtures can be designed to change from a monophasic system to a biphasic system by addition of a small volume of another solvent or by the addition of a small amount of some other phase perturbing agent, that fact alone is not sufficient to effect a practical separation after a homogeneous reaction. Any practical separation scheme for a catalytic reaction requires that a catalyst selectively partition itself into one of the two phases formed after perturbation of the original monophasic system. If a catalyst were used, it should also be possible to recycle the catalyst-containing phase through multiple reaction cycles. According to equation 19 introduced in the last chapter, a phase selective solubility of at least 200:1 for the catalyst is necessary if effective separable, recyclable catalysts are to be developed. Similar considerations have been discussed previously in connection with enzymatic catalyst separations in aqueous biphasic systems and are implicitly taken into account in any extraction.[160] As shown below, such selectivity and recyclability is possible with linear polymer supports.

To test the efficacy of soluble linear polymers for separations in this latent biphasic strategy for catalyst recovery, a variety of soluble polymers containing dye labels were prepared. The dye-labeled PNODAM **57** was shown to be soluble in heptane or toluene but insoluble in an EtOH/$H_2O$ phase that contains >10% $H_2O$. A visually homogeneous solution of this lipophilic polymer-bound dye in a mixture of 10 mL each of toluene and 95% EtOH/$H_2O$ becomes biphasic on addition of 0.5 mL of $H_2O$. UV-visible analysis showed that >99.9% of the polymer-bound dye stayed in the nonpolar toluene-rich phase. Separation of this phase and addition of fresh aqueous EtOH reformed the initial monophasic mixture. Repetition of this cycle 5 times with no detectable loss of **57** in the EtOH-rich phase showed that this approach is viable as a way to recover and reuse polymeric catalysts. However, these immiscible phases have similar density that makes phase separation slow. If a 1.00:0.96:0.04 mixture (vol:vol:vol) of heptane, EtOH and $H_2O$ were used to form a 20 mL monophasic solution, addition of just 10 drops of $H_2O$ was sufficient to induce phase separation. This latter system's phases had less similar densities, making the separation cleaner, simpler, and faster. UV-visible analysis showed that >99.9% of the polymer-bound dye stayed in the nonpolar heptane-rich phase and the polymer **57** was as recyclable in this heptane/EtOH-$H_2O$ system as it was in the toluene system above.

PNIPAM also showed good separation efficiency in this heptane/EtOH-$H_2O$ latent biphasic system. When 0.5 mL of water was added to 8 mL of a 1:1 heptane-ethanol homogeneous solution of the dansyl-labeled **59**, two phases formed. More than 99.99% of the polymer stayed in the aqueous ethanol phase based on fluorescence analysis of both the heptane-rich and EtOH-rich phases for the dansyl fluorophore. PNIPAM labeled with the *p*-methyl red azo dye described above (i.e. polymer **56**) was similarly phase selectively soluble in the polar EtOH-rich phase of these heptane/EtOH-$H_2O$ mixtures after phase separation, though the extent of phase selective solubility could only be estimated at >99.9%. These results and the PNODAM result above suggest that separation and recovery of a catalyst bound to these polyacrylamides in either a nonpolar or a polar phase of a nonpolar/polar mixture should be feasible.

The most effective way to recover catalysts in a latent biphasic reaction would be to recover them in the nonpolar phase of a nonpolar/polar mixture, since the ethanol phase contains added water and cannot be reused. The isolated yields in the first cycles from the polar phase were usually higher than those obtained from the nonpolar phase. This phase preference also avoids the problem of normal thermomorphic systems, that the products in a reaction must have at least partial solubility in the nonpolar phase in order to be isolated in a reasonable fashion. Polar products are more difficult to separate from the polar polymer. For example, salt by-products generated in the Heck reaction would accumulate in the polar phase. It was therefore desirable to recover catalysts in the nonpolar phase of a nonpolar/polar mixture. This is illustrated by the examples of catalysis and sequestration described below.

The generality of this latent biphasic approach in homogeneous catalyst recovery was shown using the polymer-bound trifunctional base catalyst **70** as a DMAP analog in acylation of 2,6-dialkylphenols by $(Boc)_2O$ in either a 1:1 heptane-aqueous EtOH system (equation 21). Yields in this chemistry gradually increased from cycle to cycle as the heptane-rich phase became saturated in the product carbonate. Yields through 6 cycles for R = -H were 59%, 80%, 95%, 99%, 99%, and 99% and for R = $-CH_3$ were 35%, 66%, 89%, 99%, 99%, and 99% when a heptane/ethanol system was used. In both cases, the initially monophasic reaction mixture was perturbed to be biphasic by the addition of 10 vol% $H_2O$. The heptane phase so formed was then recycled by addition of fresh EtOH, substrate and $(Boc)_2O$. Heptane was added as needed to replace heptane lost in the EtOH-rich phase. In both series, the polymeric catalyst used was labeled with a methyl red label. The absence of detectable dye-labeled polymer in any of the cycles in the polar EtOH-rich phase indicated quantitative separation of the catalyst into the nonpolar heptane-rich phase.

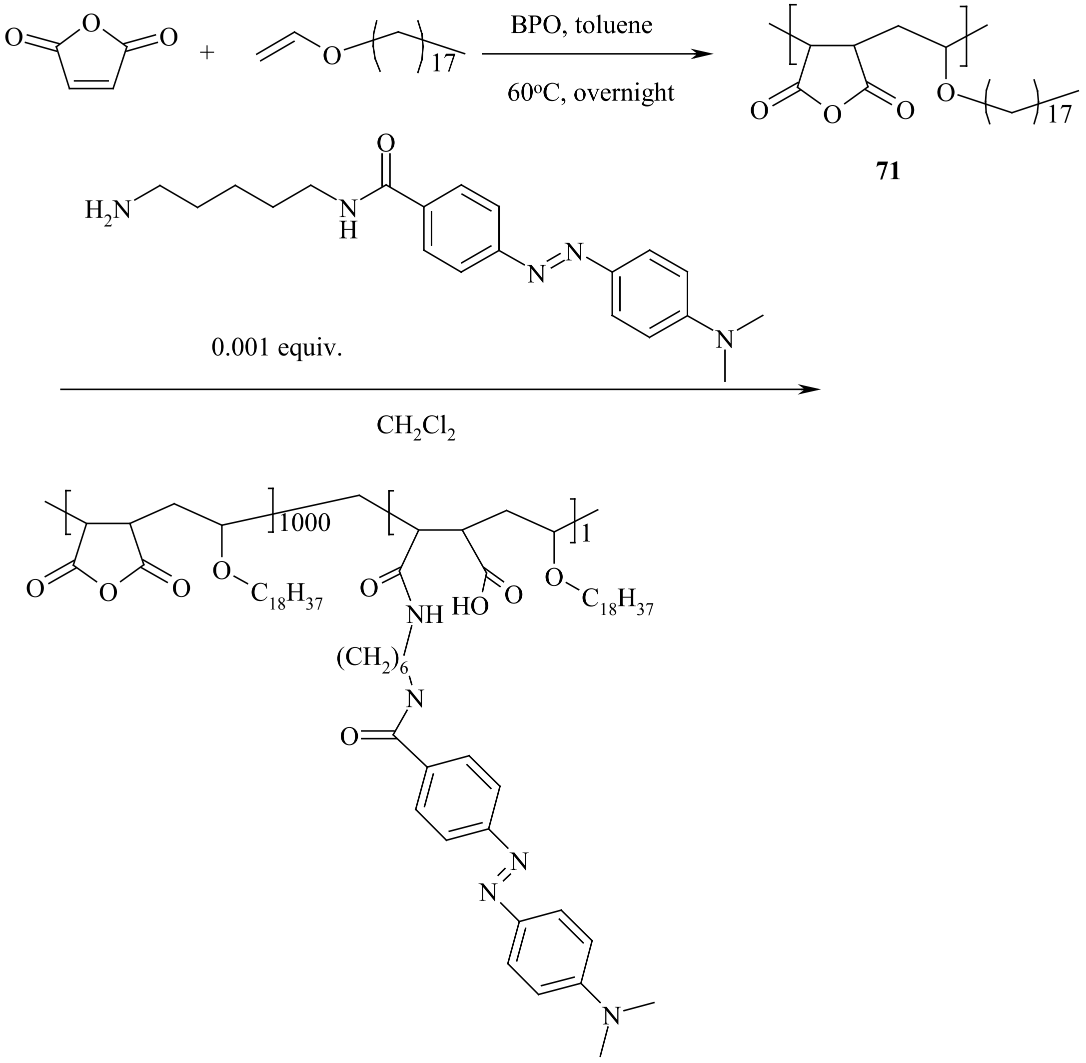


(21)

*Designing new polymers for the heptane/EtOH-$H_2O$ latent biphasic system*

To make this latent biphasic system suitable for wider applications, different types of polymers need to be designed. With the success of using the octadecyl group to change the phase selectivity of PNIPAM, we went ahead and modified the Gantrez polymer using the same approach used for PNIPAM. Gantrez is an alternating copolymer of maleic anhydride and methyl vinyl ether. To use this type of polymers in the heptane/EtOH-$H_2O$ latent biphasic system, a polymer was needed that had a strong phase preference for heptane over ethanol. The $–OCH_3$ group of Gantrez is not lipophilic enough to give the polymer strong heptane preference, so an octadecyl group was incorporated into the polymer instead of the methyl group. The synthesis of the polymer is shown in Scheme 16. A 1:1 mixture of maleic anhydride and octadecyl vinyl ether was polymerized using radical polymerization to give the alternating copolymer **71.** The polymer so formed has an anhydride loading of 2.5 mmol/g. The free amine-terminated azo dye **54** was allowed to react with the anhydride functionality so that the phase preference of this polymer **72** in multiphase systems can be easily observed or measured.

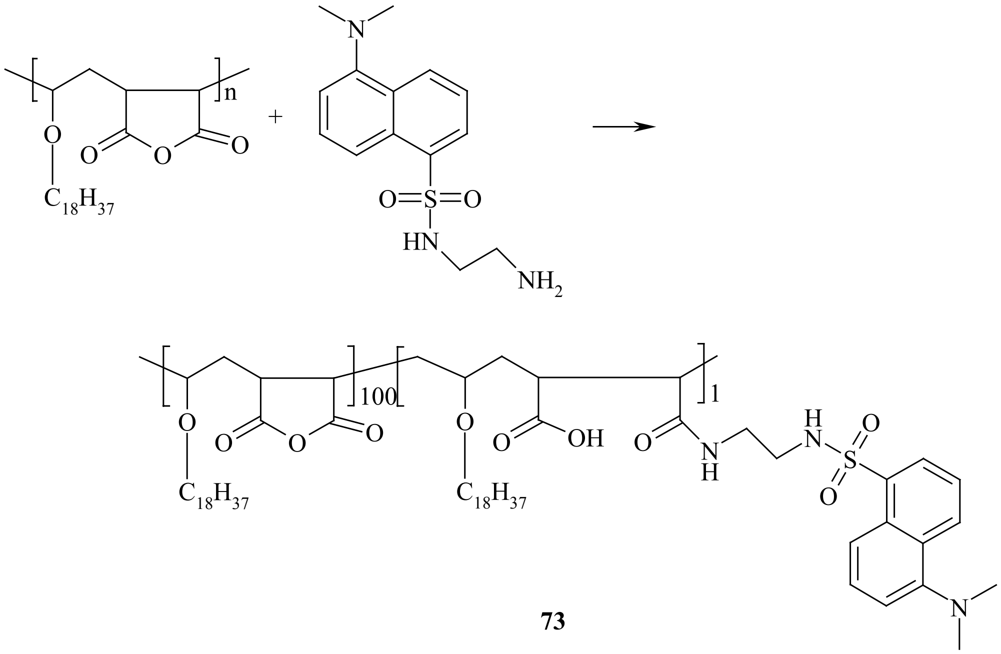
As expected, the polymer **72** stayed only in the heptane phase in the heptane/EtOH-$H_2O$ latent biphasic system after adding water to separate the two phases. Separation usually required less than 3 hours at room temperature, and there was no significant hydrolysis of the anhydride functionality under this condition. UV-visible analysis of the aqueous ethanol phase showed no absorption due to the azo dye, which meant that there was less than 0.5% polymer in the ethanol phase. Ms. Jackie Besinaiz also studied the phase selectivity of this polymer using fluorescence labeling. The synthesis of a labeled polymer **73** is shown in Scheme 16. The fluorescence measurement indicated that the polymer had greater than 99.99% selectivity for the heptane phase over the 90% aq. ethanol phase, and it had greater than 99.9% selectivity for the heptane phase over the DMF phase. So this polymer is a suitable polymer support to use in the heptane/EtOH-$H_2O$ latent biphasic system.



**71**

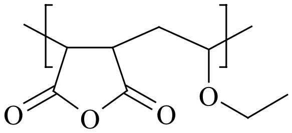
**72**

Scheme 16. Synthesis of dye-labeled amine-sequestrant Poly(maleic anhydride-*c*-octadecyl vinyl ether) (PMAOVE)



**73**

Scheme 17. Synthesis of dansyl-labeled PMAOVE

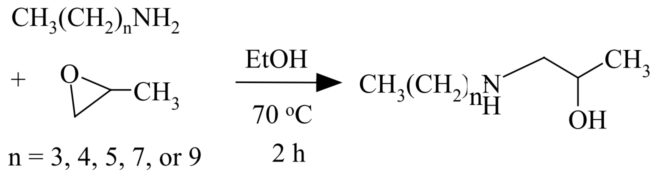


**74**

To see how much the long carbon chain can affect the solubility, a copolymer of maleic anhydride and ethyl vinyl ether was also made (poly(maleic anhydride-*c*-ethyl vinyl ether) **74**) to be compared to the octadecyl polymer **71**. Polymer **74** was soluble in hot toluene but not at room temperature, while polymer **71** was soluble in toluene at room temperature. Polymer **74** was purified by dissolving into acetone and precipitating from ether, while polymer **71** was dissolved in ether and precipitated from acetone.

These results are consistent with those noted earlier, the presence of alkyl groups of different lengths can profoundly change the solubility of a polymer.

Polymer **71** and **72** were used as selective primary amine sequestrants in the heptane/EtOH-$H_2O$ latent biphasic system. These heptane-soluble sequestrants were used to remove excess amine used in a propylene oxide alkylation of amines to form ethanolamines (equation 22). In this reaction, excess 1° amine was used to minimize over alkylation. Addition of **71** or **72** then consumed the excess 1° amine and perturbation of the resulting heptane-EtOH solution separated the product 2° amine from the scavenger resin and the sequestered 1° amine. A series of reactions used 2 equiv of butyl-, amyl-, hexyl-, octyl- or decylamine as the substrates using ethanol as the solvent. After heating to 70 °C for 2 h, the mixture was cooled to room temperature, and a heptane solution of 3 equiv. of **71** or **72** was added to form a homogeneous heptane-EtOH mixture. The excess amine was consumed within 1 min. after addition of **71** or **72**. Addition of $H_2O$ (the added water was 10% of the total volume) then produced two phases. Any 1° amine was at that point bound to the polymer and sequestered in the heptane phase. The polar phase containing the hydroxylamine products was then separated. A limitation of this chemistry was that the products derived from the more hydrophobic amine substrates have some heptane solubility. In those cases, high yields of product can only be obtained if the heptane solution is extracted with aqueous EtOH (the polymer exclusively remains in the heptane phase even after the extractions).

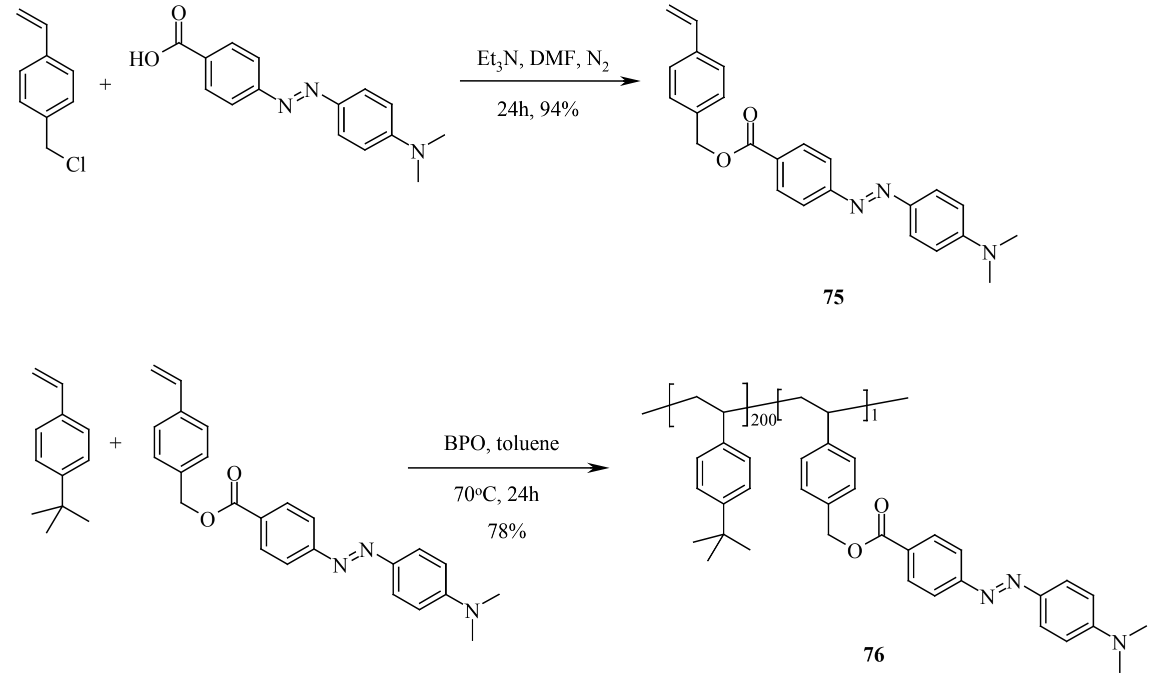


(22)

PMAOVE has also been modified to form a more stable polymer to support a Ag catalyst for formation of oxazolines in the heptane/EtOH-$H_2O$ latent biphasic system.[161] The catalyst was reused for 5 cycles with good catalytic activity. There was silver leaching in each cycle, but the amount of silver leached only accounts for <0.1% of the total silver concentration.

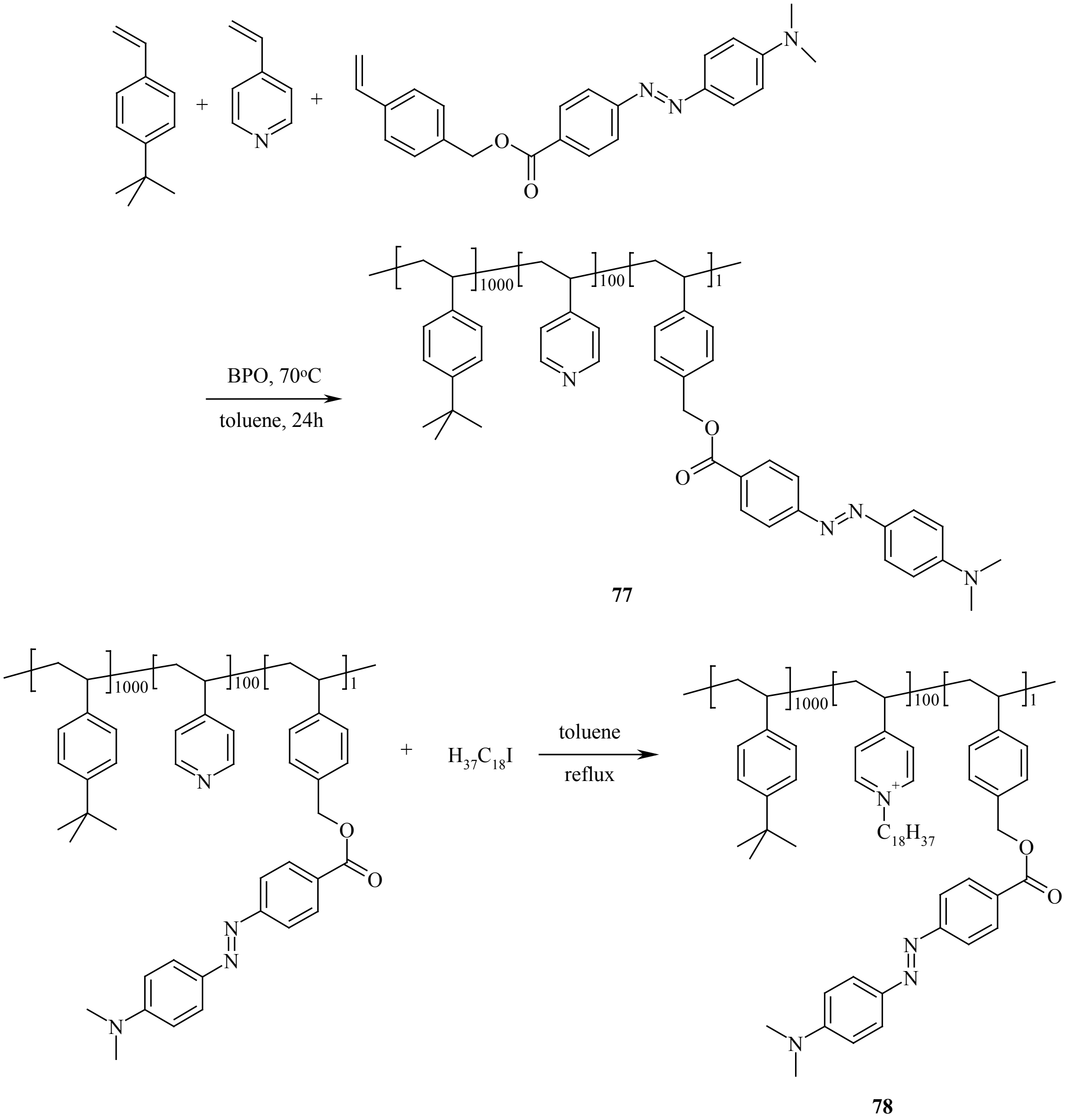
It should be a general approach to use a lipophilic group to offer a polymer heptane solubility. Besides octadecyl, other alkyl groups were also applied. For example, we have used *tert*-butyl group to tune the solubility of polystyrene support to make this polymer suitable for the heptane/EtOH-$H_2O$ latent biphasic system. Linear polystyrene is among the most commonly used soluble polymer supports for catalysts and reagents. This polymer is most commonly recovered by solvent precipitation. However, while solvent precipitation is a general way to recover soluble polymers, the excess solvents used make this a less convenient procedure in some cases. Poly(4-*tert*-butylstyrene) (PTBS) is an alternative to this polymer that uses commercially available monomers prepared by conventional radical polymerization with the same underlying chemistry as unsubstituted polystyrene, and it can be recovered by the same sort of solvent precipitation chemistry. It differs from polystyrene because it has good heptane solubility – an attribute that makes it useful in liquid/liquid biphasic separations.

When this polymer was prepared as a copolymer using a dye-labeled polystyrene **75** as a comonomer, the product copolymer **76** could be simply isolated by solvent precipitation using methanol as a polar solvent. (Scheme 18) The copolymer obtained was characterized by GPC using polystyrene standards. It has a number average molecular weight of 23,000 Dalton and a weight average molecular weight of 48,000 Dalton. It was readily soluble in heptane as expected. Moreover, this dye-labeled PTBS was phase selectively soluble in heptane when another polar phase was present. Specifically, when **76** was first dissolved in heptane and then mixed with an equal volume of either DMF or 90% aqueous ethanol, a biphasic mixture formed with the less dense heptane phase usually containing all of the dye-labeled polymer. Heating either of these biphasic solutions to 70 $^{o}$C produced a monophasic mixture. Cooling these thermomorphic mixtures of polymer and solvents back to room temperature reformed the biphasic solution. UV-visible spectroscopic analysis of the nonpolar and polar phases of the product biphasic mixture showed no detectable (<0.5%) dye in the aqueous ethanol phase. The copolymer **76** was also readily separable in the heptane/EtOH-$H_2O$ latent biphasic system. When **76** was dissolved in a miscible mixture of 1:1 heptane and ethanol and this miscible mixture was perturbed by the addition of 10% vol% water, a biphasic mixture was produced with the dye-labeled polymer exclusively in the less polar heptane-rich phase (>99.5%).



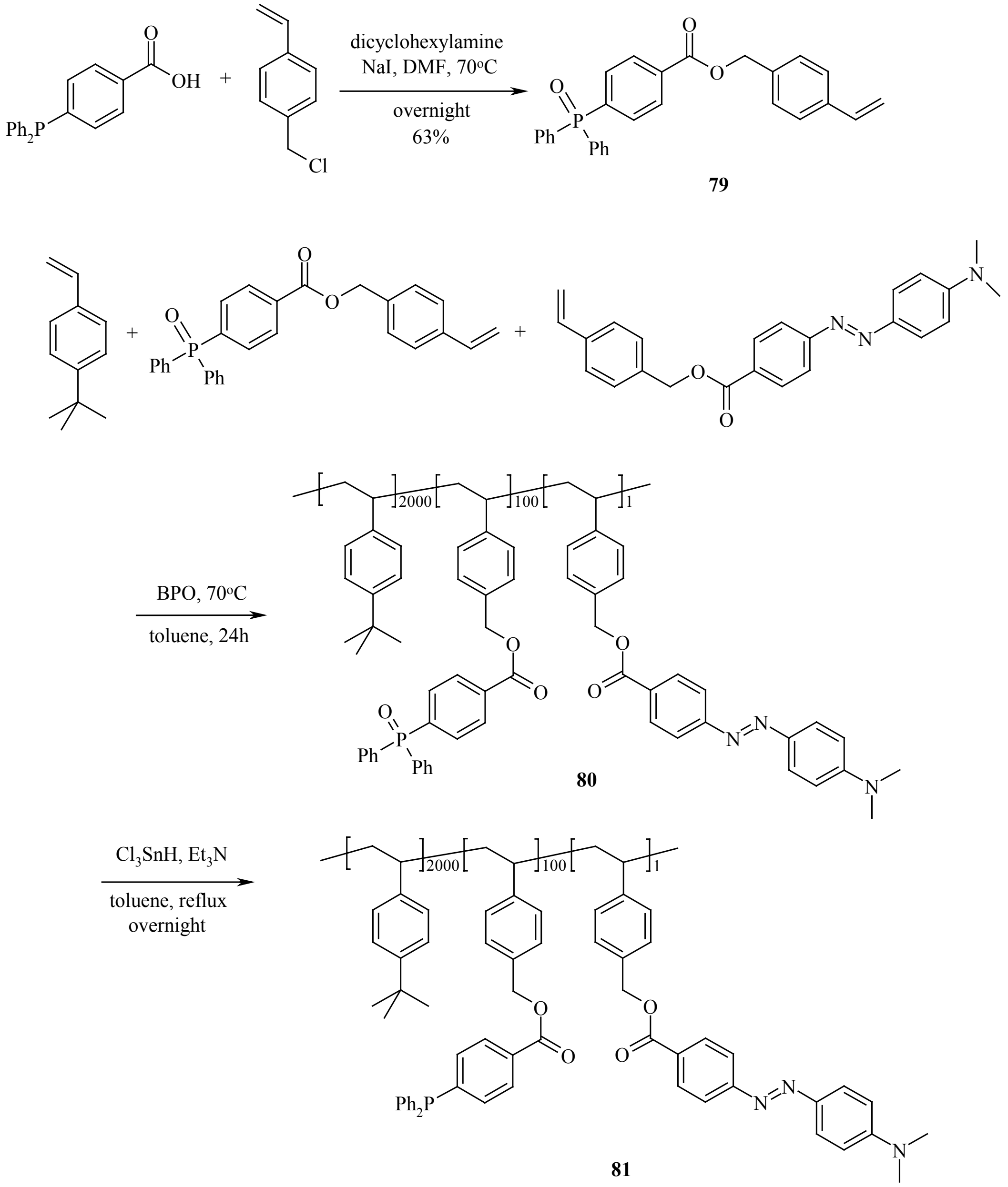
Scheme 18. Synthesis of dye-labeled poly(4-*tert*-butylstyrene)

To see to what extent we can depend on the *tert*-butyl group to determine the phase selectivity, other copolymers with polar comonomers were made (Scheme 19). A copolymer of 4-*tert*-butyl styrene and vinyl pyridine **77** showed good phase selectivity for the heptane phase in both these thermomorphic systems. But when the pyridine was converted to the pyridinium salt **78**, different solubility was observed. In the heptane/90% aqueous ethanol system, around 65% of polymer **78** stayed in the heptane phase after phase separation. In the heptane/DMF system, the polymer **78** stayed only in the DMF phase. In order to better control the phase selectivity, a longer alkyl group might be needed instead of the *tert*-butyl group in some circumstances, and this will be addressed by some on-going work in our group.



Scheme 19. Synthesis of PTBS-supported pyridine and pyridinium salt

A catalyst-containing copolymer can be prepared by copolymerization of 4-*tert*-butylstyrene with a styrene derivative of a catalyst. For example, a triarylphosphine compound was attached to the PTBS support, as shown in Scheme 20, to form a catalyst for the Michael addition of 2-nitropropanol to methylacrylate, shown in equation 23.



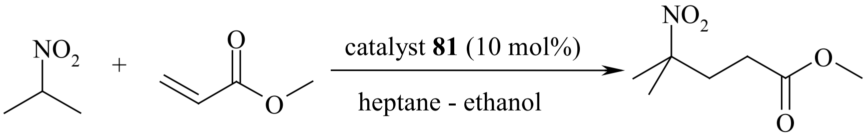
**79**

**80**

**81**

Scheme 20. Synthesis of dye-labeled PTBS-supported triarylphosphine catalyst

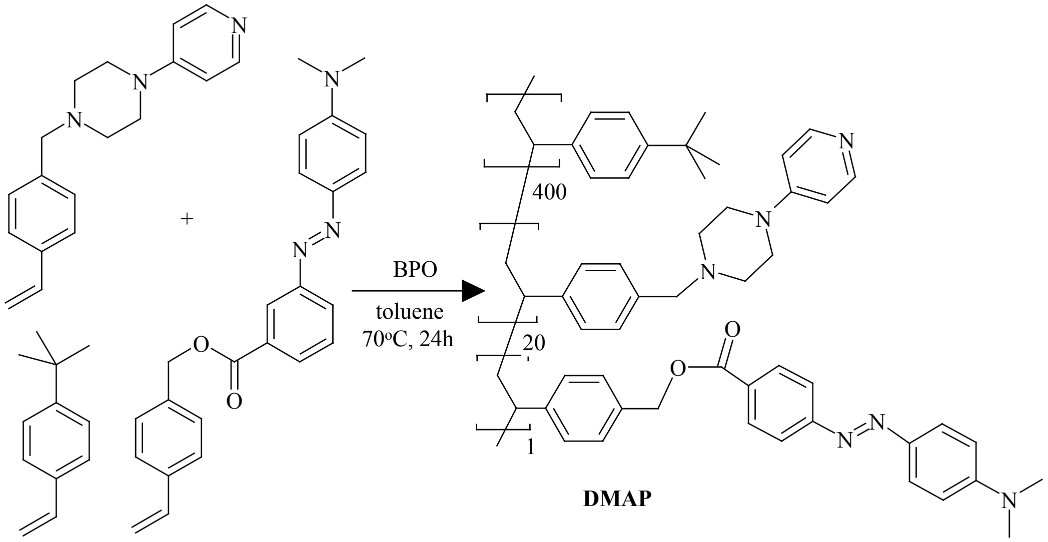
To obtain the phosphine-substituted styrene derivative, 4-vinylbenzyl chloride was coupled to 4-diphenylphosphinobenzoic acid. Instead of the phosphine, the phosphine oxide **79** was obtained. It can be reduced to the phosphine at this stage using trichlorosilane, but the workup procedure is not very simple, so it was left as the phosphine oxide until after the polymerization. Workup of the reduction product should be easier with the polymer support because only a precipitation and a filtration is required to isolate the polymer-supported phosphine. After the radical polymerization, a terpolymer of the dye-labeled PTBS supported phosphine oxide **80** was obtained. Reduction of the phosphine oxide was achieved by refluxing the polymer-bound phosphine oxide with trichlorosilane in toluene overnight under nitrogen. Then the mixture was cooled to room temperature, and added to an excess amount of methanol. The polymer **81** precipitated and $^{31}$P NMR spectroscopy indicated that the reduction was complete.



(23)

The supported catalyst was dissolved in heptane, and an equal volume of an ethanol solution of the substrates was added. The catalytic reaction was then run homogeneously at room temperature. Unlike thermomorphic systems, an elevated temperature is not required to achieve the homogeneity. After 24 hours, a small amount of water was added to induce the phase separation. The product was isolated from the ethanol phase; the non-polar substituted styrene copolymer went into the non-polar phase and was subsequently recovered by liquid/liquid phase separation. Fresh substrate solution in ethanol could then be added to the polymer solution in heptane for the next cycle of the catalytic reaction. Separation of the polymer phase from the aqueous ethanol phase was quantitative based on visual and UV-visible analysis of the dye-labeled phosphine-containing polymer concentration. The isolated yield of the addition product from the aqueous ethanol phase of the first 5 cycles was 31.5%, 56.7%, 69.0%, 72.5%, and 71.1%. As seen with thermomorphic systems and in other reactions using this latent biphasic system, the yield started low, but went up with increasing cycle numbers due to the product's solubility in heptane. As the cycle number went up, the heptane phase eventually becomes saturated with the product. This effect increases the isolated yield from the aqueous ethanol phase at higher cycle numbers. The yield in the latter cycles of this repetitive reaction was similar to that seen if the same reaction were catalyzed by triphenylphosphine.[162]

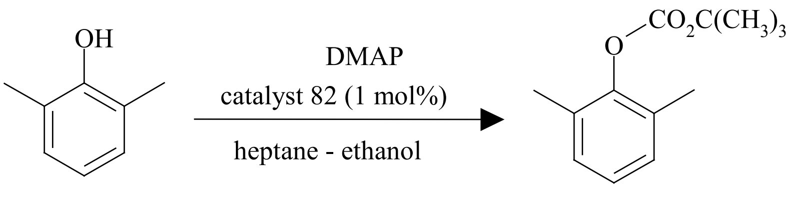
Another example of a catalyst supported on this polymer is the DAAP catalyst **82**. This catalyst was synthesized according to Scheme 21**.** In chapter II, the polystyrene-supported DAAP catalyst **26** was shown to be a good catalyst for acylation of phenols. Here we carried out similar reactions in the heptane/EtOH-$H_2O$ latent biphasic systems as well using the PTBS as a heptane soluble support for the DAAP catalyst **24**.



**82**

Scheme 21. Synthesis of dye-labeled PTBS-supported dialkylaminopyridine catalyst

The nucleophilic base catalyst **82** generated was used and recovered through 20 cycles to catalyze formation of a Boc derivative of 2,6-dimethylphenol, as shown in equation 24. Isolation and recycling of the catalyst was achieved using the same method used for the above mentioned supported phosphine catalyst. The isolated yield for the first five cycles of this reaction was 34.3%, 60.9%, 82.2%, 94.6%, 99%. Separation of the dye-labeled PTBS polymer from the aqueous ethanol phase was shown to be quantitative by both visual observation and UV-visible measurement.



(24)

This latent biphasic strategy should be a general way to carry out homogeneous reactions and separate and recover catalysts, reagents or products by biphasic separation.

However, it is important to recognize that this approach like any approach has some limitations. First, it is unlikely that any of the polymers described here would be suitable for all reactions. A specific reaction may require a different polymer – a polymer without N-H bonds for example. Second, since hundreds of different solvent mixtures might be used, it would presumably be necessary to test the phase selective solubility of a polymer with the specific solvents that are to be used. Third, the solvent mixtures used should be different in density in their biphasic state. Fourth, loss of solvent in the recovered/reused phase can occur. This problem can be minimized by using a second phase that is presaturated with this solvent. Fifth, while the polymer support for a reagent or catalyst can be designed to be selectively soluble in a particular phase, products can partition to either phase. In a repetitive process like the phenyl carbonate synthesis described above, this problem will be of minimal consequence as the recycled phase will eventually be saturated in product. In other cases, extraction of the recycled phase might be necessary to obtain a high isolated yield of a product in a single cycle. This problem is a general problem with any biphasic liquid/liquid separation strategy. Finally, it should be recognized that reactions carried out in this way involve a mixed solvent – mixed solvent conditions will not always mirror conventional chemistry carried out in a single pure solvent.

# CHAPTER V

# MEASURING LCSTS OF THERMORESPONSIVE POLY(ACRYLAMIDE)S[§]

## Introduction

Thermoprecipitation involves inducing the precipitation of polymers by temperature changes. Most polymers' solubility increases with increasing temperature, but there are polymers that have inverse temperature dependent solubilities, such as polymers mentioned in the first chapter that have LCST behavior. This behavior occurs commonly in polymers. Poly(ethylene oxide) and *N*-alkyl substituted poly(acrylamide)s are examples of polymers having LCSTs in water. These polymers are widely used as smart materials. For example, they have been used for the design of biomaterials,[163,164] as drug delivery vehicles,[165] and as chromatographic supports.[166]

The LCST behavior of polyacrylamides has received a lot of attention from researchers. There are different explanations why certain acrylamides have this behavior, but the most widely accepted explanation is based on considering the free energy of the system. From a thermodynamic point of view, the formation of hydrogen bonds between water molecules and the amide groups of the polymer contributes favorably to the enthalpy of solvation but unfavorably to the entropy of solvation. Below the critical temperature the coiled structure is favored, as the strong hydrogen bonding between the hydrophilic amide groups of the polymer and water molecules helps in the dissolution of

---

[§] Reproduced in part with permission from *Journal of the American Chemical Society*. Copyright 2003 the polymer in water. However, entropy of the system decreases due to organization of water (hydrophobic hydration). In systems where strong hydrogen bonding is possible, such interactions lower the free energy of dissolution considerably. At higher temperatures, hydrophobic interactions between hydrophobic groups increase. More importantly, the unfavorable entropy for bound water becomes dominant. The bound water is then released, leading to the transition from the coiled to the denser globule structure. The polymer chains collapse and phase separation from water is thus driven by entropy. In many cases, phase separation and precipitation is completely reversible. This differentiates the synthetic polymers from most proteins where precipitation, even if reversible, leads to irreversible loss of function.

Zhu studied the solubility behavior of a series of substituted poly(acrylamide)s.[167] He showed that poly(acrylamide) is soluble in water at all temperature up to 100 °C. It does not have an LCST in an accessible temperature range. Poly(*N,N*-dimethylacrylamide) does not precipitate either. Poly(*N*-ethylacrylamide) has an LCST of 82 °C; poly(*N*-isopropylacrylamide) has an LCST of 32 °C; the LCST of poly(*N,N*-diethylacrylamide) is also 32 °C. Poly(*N*-*tert*-butylacrylamide) does not dissolve in water, not even at low temperatures. These numbers differ from paper to paper due to changes in the measurement conditions or procedures and to the inaccuracy of the measurements.

The LCST values of aqueous polymer solutions have been determined by a wide variety of experimental techniques. These include calorimetry, viscometry, turbidimetry, light scattering, IR spectroscopy and NMR spectroscopy. Solution calorimetry provides thermodynamic parameters that lend insight into the forces responsible for the phase separation and measured transition enthalpies consistent with the loss of approximately one hydrogen bond per PNIPAM repeating unit.[168,169] Viscosity tells us about the hydrodynamic consequences of aggregation, namely a decreasing viscosity with increasing temperature, and has revealed that PNIPAM possesses a flexible coil conformation approaching the theta state as the temperature is increased towards the LCST.[170,171] UV turbidimetry can be regarded as the more automated counterpart of the classical visual observation of macroscopic phase separation. However, the precision and reproducibility of turbidimetrically measured LCST values may be affected by complications arising from variations in the aggregate size and settling of precipitates.[172] Light scattering is a technique for monitoring concentration fluctuations on a spatial scale of approximately 1000Å and has been used to detect the collapse of single PNIPAM chains at a temperature lower than that of macroscopic phase separation.[168,173] IR spectroscopy provides information on the molecular level and on possible inter- and intra-molecular interactions between functional groups, and has supported the view that the structure of water is different around a PNIPAM solute molecule as compared to water in the bulk aqueous medium.[174,175] NMR is sensitive to the local structural differences of the polymeric chains and has revealed the existence of a discontinuous transition in the relaxation times at the LCST.[176]

Most of these techniques, however, suffer from low throughput capabilities and require relatively large amounts of polymers for analysis. These factors are limitations in any study designed to probe the myriad subtle solvent and polymer structure effects that make up the molecular details of the folding mechanism. This is unfortunate, because such information obtained for the structurally more diverse synthetic polymers like polyacrylamides might be broadly applicable to the understanding of related processes such as the cold denaturation of proteins. To help remedy this situation a temperature gradient microfluidic device in combination with a dark field optical microscopy setup were designed in Dr. Cremer's group for obtaining all temperature readings in an LCST measurement simultaneously as a function of position rather than sequentially as a function of time. The process works by exploiting the fact that when a thermoresponsive polymer folds and aggregates above its LCST, the solution becomes cloudy, leading to an easy readout of the process as a function of the amount of light scattered. An especially advantageous feature of this method is the requirement of no more than 1 microliter of total solution in order to make a measurement.

## Results and Discussion

### *Using a temperature gradient device and dark field microscopy to measure polymers' LCST*

Until now LCST measurements have been made as a function of *time* using a temperature ramp. The use of a temperature gradient allows data to be collected as a function of *position* instead and makes it possible to make all the temperature measurements in a single experiment. We also thought it would be advantageous to develop a procedure that would require microscopic amounts of sample as this would allow LCST studies to be carried out with libraries of similar substrates. To explore these possibilities, we collaborated with Dr. Cremer's group and adapted the linear temperature gradient apparatus (Figure 19) recently devised in his laboratory for combinatorial temperature measurements for use in LCST studies.[177,178] Dark field optics were used to image the scattering intensity of the folded and aggregated polymers as a function of position. Under a 2 × objective, six rectangularly shaped borosilicate capillary tubes (100-µm × 1-mm × 2-cm) were placed in parallel with the temperature gradient. Temperatures along the tubes were determined by measuring the lengthwise position in a CCD camera image. As a demonstration, the tubes were filled with aqueous solutions containing 10 mg/mL of PNIPAM with varying NaCl concentrations. The phase transition temperature was determined by the midpoint of the clouding curve (Figure 20 & inset). To aid in temperature readout, two standard polymer solutions with known LCSTs were employed as internal standards to determine the slope of the temperature gradient each time an assay was performed. Using this method, the LCSTs of PNIPAM and poly(*N, N*-diethylacrylamide) (PDEAM) were found to be 30.5 $^{o}$C ± 0.16 °C and 29.3 $^{o}$C ± 0.15 °C, respectively.

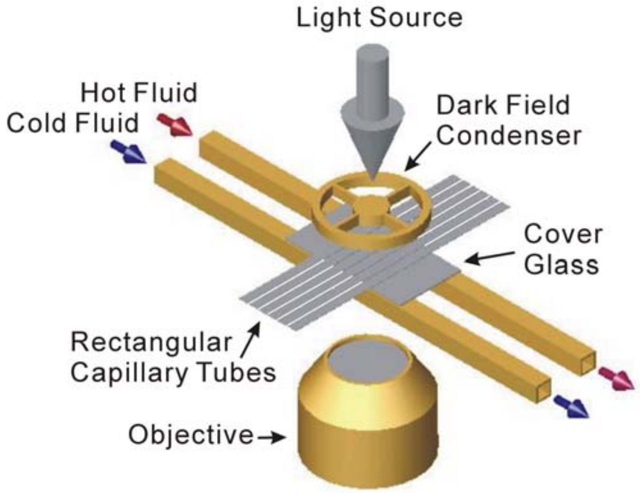


Figure 19. Schematic drawing of a temperature gradient device. Up to ten rectangular borosilicate capillary tubes were put on the temperature gradient device without noticeable temperature discrepancy across the tubes. Each CCD image fits six capillary tubes simultaneously under a 2× objective

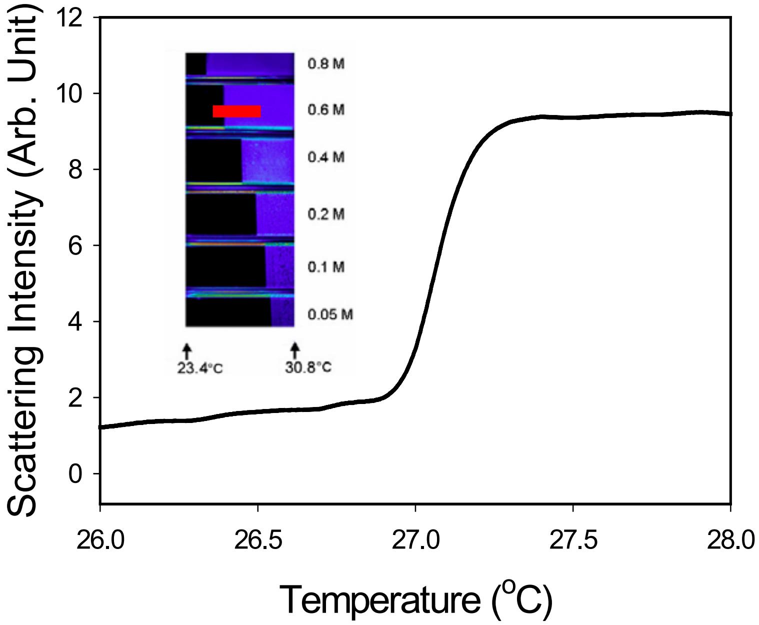


Figure 20. A typical clouding curve of PNIPAM. Mixture of 10 mg/mL PNIPAM (340 kDa) and 0.4 M NaCl was used. Temperatures at the two ends were set at 23.4 °C and 30.8 °C

Figure 20 inset. A CCD image of six samples inside square capillary tubes. PNIPAM 10mg/mL was mixed with NaCl ranging from 0.05 M to 0.8 M. The precipitant was pseudo-colored for clarity

*The LCST of the polymer mixture of PNIPAM and PDEAM*

Since the clouding curves of macromolecules in solution can be obtained with good temperature resolution over relatively short times, the time dependent evolution of the clouding process was studied simply by recording a series of time-lapse images of a given sample with a standard CCD camera. When this was done for a mixed solution of

PNIPAM and PDEAM, a series of time dependent phenomena were revealed (Figure 21). The first image was taken immediately after the mixed polymer solution was placed over the temperature gradient. As can be seen, the original clouding curve of the mixture appeared to be smooth. After 6 min, however, a higher temperature kink appeared in the curve. This further evolved into a pronounced dip after 9 min. At this point, cycling between the latter two stages occurred. However, the initial sequence of clouding behavior as well as the migration of the LCST toward a higher temperature were reproducible over many samples and within a given sample. Reversibility within the same sample was observed when the $T_{Low}$ and the $T_{High}$ sides of the tube were switched.

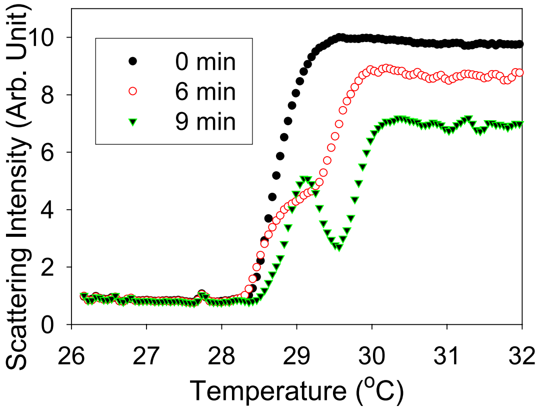


Figure 21. Kinetic studies of PNIPAM and PDEAM mixtures. PNIPAM and PDEAM were mixed as 1:1.5 molar ratio in DI water

To investigate the significance of the 0 min. conditions, experiments with mixtures of PNIPAM and PDEAM were performed. A plot of the nascent LCST temperature as a function of mole fraction of PNIPAM is shown in Figure 22.

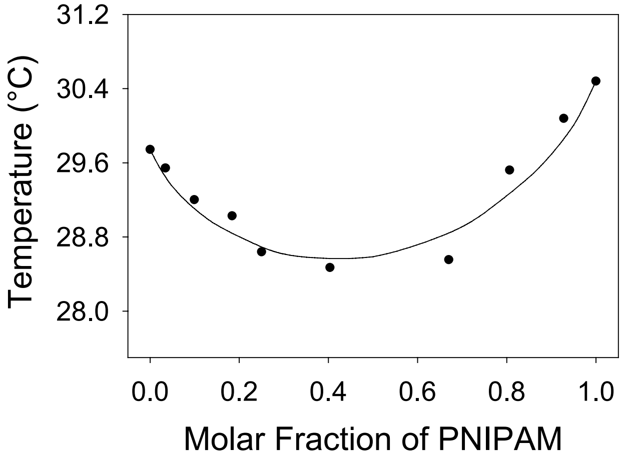


Figure 22. Plots of the initial LCST at different mole fractions of PNIPAM for PNIPAM and PDEAM mixtures. The solid line represents a fit to the data

The results bear a striking resemblance to the curve obtained for the Gibbs free energy of mixing of two substances: $G = \chi_1 G_1 + \chi_2 G_2 + nRT(\chi_1 \ln \chi_1 + \chi_2 \ln \chi_2)$. In this case $G_1$ and $G_2$ are the Gibbs free energies of pure substances 1 and 2, respectively. $\chi_1$ and $\chi_2$ are the mole fractions of substances 1 and 2, respectively. This correlation implies that the aggregation process involves the rapid (i.e. kinetically controlled) formation of aggregates of a small number of polymer chains that later segregate into pure PNIPAM and PDEAM. In other words, early aggregate formation most likely involves the mixing of PNIPAM and PDEAM. Such mixed aggregates would have higher entropy than the corresponding structures containing only one type of polymer. The difference in entropy between the pure and mixed systems should lead to a lower transition state free energy, $\Delta G^{\ddagger}$, to precipitation for the mixed complexes. Interestingly, this initial precipitate then begins to phase segregate into pure PNIPAM and PDEAM particles presumably on enthalpic grounds. To verify these assumptions, DSC studies of PNIPAM and PDEAM were performed as a function of mole fraction of PNIPAM. The results showed that the onset to the phase transition came at a lower temperature for mixed systems by amounts that exactly matched the data in Figure 22. Furthermore, the overall enthalpy for the entire precipitation process rose continuously as the amount of PNIPAM was increased. This latter result is consistent with the notion that the two polymers must ultimately segregate upon undergoing the phase transition and that PNIPAM has the higher phase transition enthalpy. The DSC studies (carried out by Dr. Hanbin Mao in Dr. Cremer's group) are provided in the experimental section.

### *Effects of salts on LCSTs of PNIPAM*

Using the methods described above, LCST measurements of PNIPAM in aqueous ionic solution were made. Both the ion type and concentration were varied and the results compared with the known Hofmeister series of salting-in and salting-out effects. Halide and alkali metal ions were used as ionic solution components. For each salt, 8 solutions with different ion concentrations were prepared. The effects of these solution components on the LCSTs of PNIPAM are plotted as a function of both the halide anion (Figure 23) as well as of the alkali cation (Figure 24). As can be seen from Figure 23, the ability of a halide to lower the LCST decreased with its size. Since fluoride has the strongest tendency to form hydrogen bonds with water molecules, less water was available to solvate the macromolecules. This essentially decreases the number of solvent molecules available to solvate the polymer and increases the concentration of polymer, thereby making it easier for molecules to aggregate or salt-out of solution. On the other hand, the low charge density of the iodide ion provided the least competition for hydration waters. In this case the unfolded state was stable to a higher temperature at each given halide anion concentration.

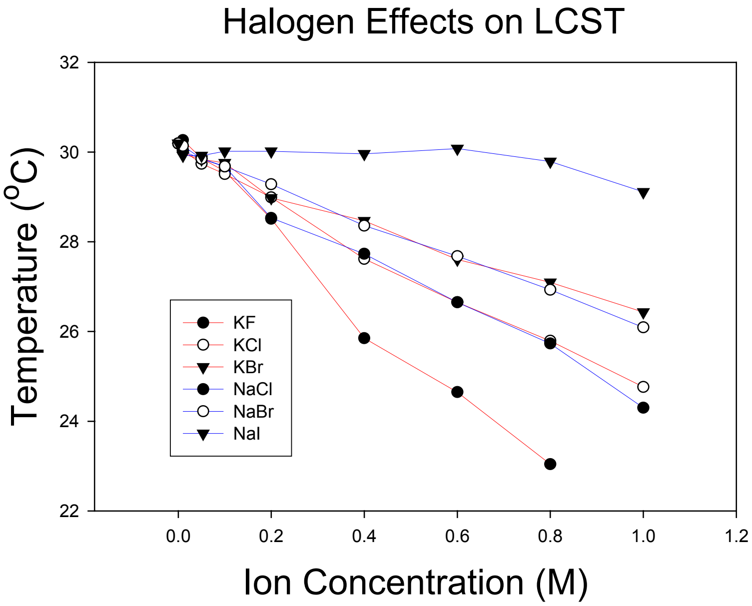


Figure 23. Effect on LCST by halogens. LCSTs of each halogen ion with eight different concentrations (0.01 M to 1.0 M) were measured. The lines were drawn as guides to the eye. The blue lines represent sodium ion solutions, while the red lines are for potassium

The situation was more complex for the alkali metal cations (Figure 24). The propensity of the cations to lower the LCST increased from lithium to sodium, then decreased from potassium to cesium (Li<Cs<Rb<K<Na). This can be explained by a combination of electrostriction[179] and charge density effects. Although higher charge density led to a stronger propensity to salt-out the polymers (as shown from Na to Cs), the attenuated propensity of $Li^+$ has been attributed to a smaller internal pressure caused

by electrostriction effects.[180] This internal pressure occurs upon addition of a salt into the aqueous solution, leading to the compression of the solvent that "squeezes out" the analyte. The series obtained here agrees well with the abilities of ions to salt out proteins and nonelectrolyte solutes.[180,181]

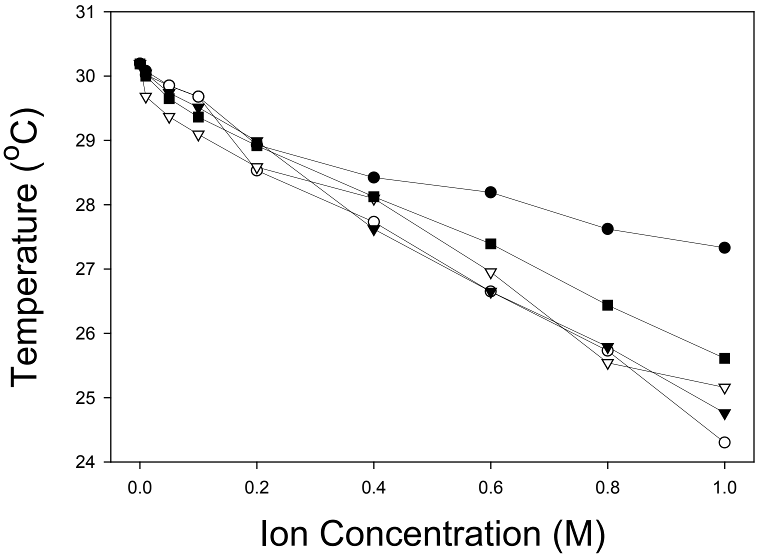


Figure 24. The effect of alkali metal ions on the LCST of PNIPAM. LCSTs of PNIPAM were measured with various alkali metal cations at eight different concentrations (0.01 M to 1.0 M) using chloride as a common anion: ●, LiCl; ■, CsCl; ∇, RbCl; ▼, KCl; and ○, NaCl

### *Effects of $D_2O$ Solutions*

Next, the effects of H-bonding with the solvent water was studied using varying mole fractions of $D_2O$ and $H_2O$. As can be seen from the data shown in Figure 25, the LCST is higher in heavy water than in light water in agreement with previous light scattering[182] and pressure perturbation calorimetry[183] measurements. Moreover, the data indicate that the temperature of the phase transition changes roughly linearly with the mole fraction of $D_2O$. The underlying reason or reasons for this increase in the LCST with $D_2O$ are not precisely known; however, the amide bonds of the PNIPAM should be relatively well exposed to water below the LCST. Since hydrogen bonding is approximately 5% stronger in $D_2O$ than in $H_2O$, it is expected that breaking these bonds to the amide moieties would be more enthalpically costly in the former case. This would explain the nearly linear change in LCST with heavy water content. On the other hand, if species such as HOD had more complex interactions with the polymer that were of great significance, one might have expected nonlinear changes instead. This is clearly not the case.

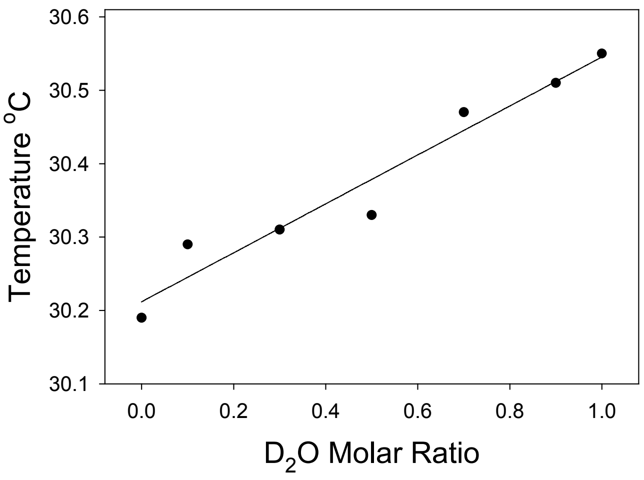
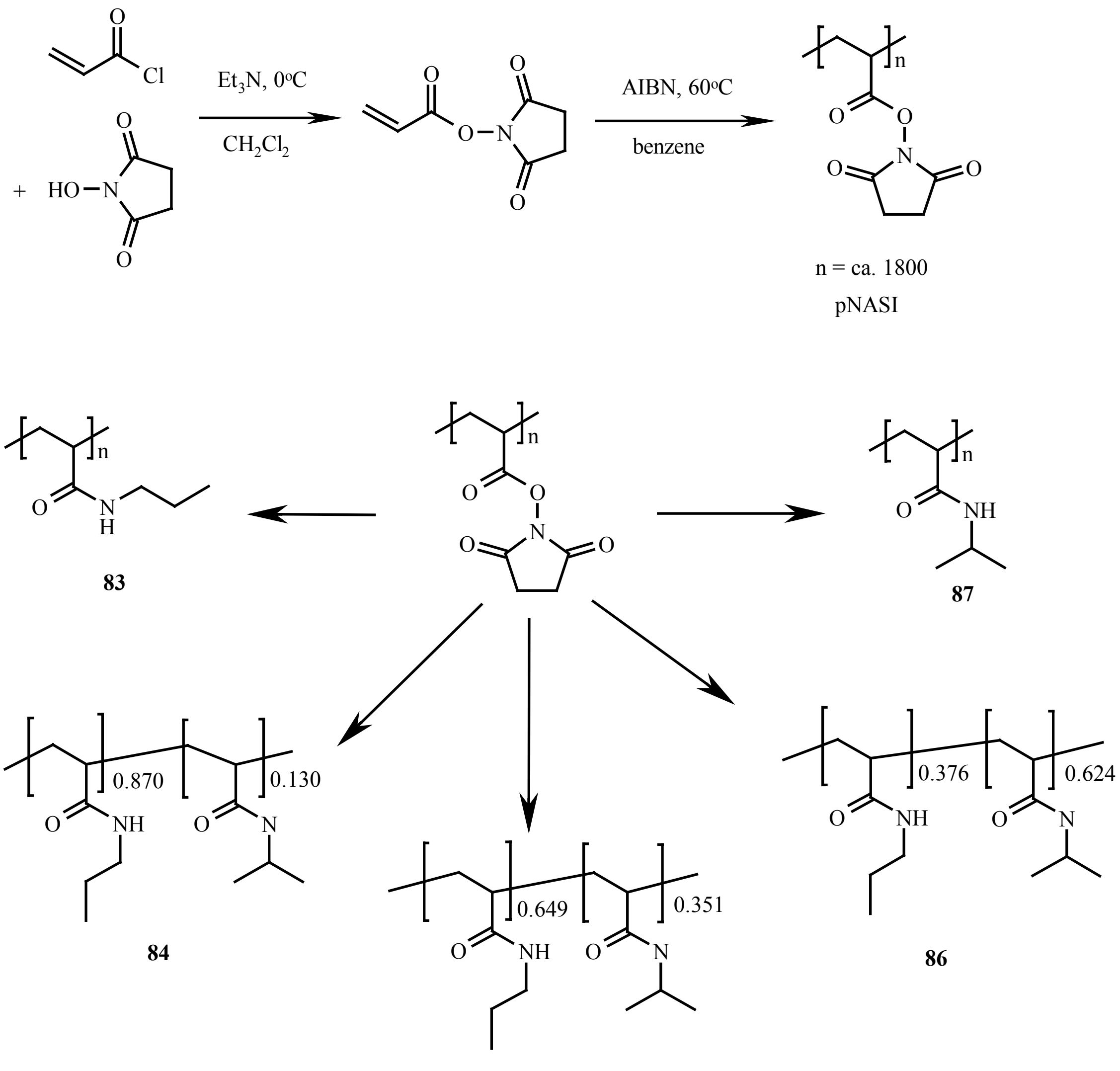


Figure 25. Effects of $D_2O$ on the LCST of PNIPAM. PNIPAM 10mg/mL was dissolved in a series of solutions with various $D_2O$ contents. The temperature gradient was from 30.2 °C to 30.6 °C

*Effects of Polymer Microstructure*

To test the utility of our apparatus for studies of the effects of polymer structure on PNIPAM-like systems, we elected to structural effects using structurally isomeric polymers by substituting varying amounts of n-propyl for isopropyl in the side chains of PNIPAM (compounds **83-87** in scheme 22). These studies were designed so that compounds **83-87** had the same degree of polymerization, polydispersity and molecular weight since they were derived from the identical polymeric intermediates (Scheme 22). LCSTs were measured for each system and the results are shown as a function of the isopropyl to n-propyl ratio in Figure 26. The difference in LCST between PNIPAM and poly(*N*-propylacrylamide) (PNPAM) was approximately 4.8 °C, and a monotonic trend can be clearly seen as the ratio of isopropyl side chains was increased. Since the two side chains are very similar the slightly lower LCST for the n-propyl group may reflect a slightly lower solvent accessible area for the linear molecule vs. the branched chain.



**83**

**87**

**84**

**86**

**85**

Scheme 22. Synthesis of copolymers of propyl and isopropyl acrylamides with different ratios of propyl and isopropyl acrylamides

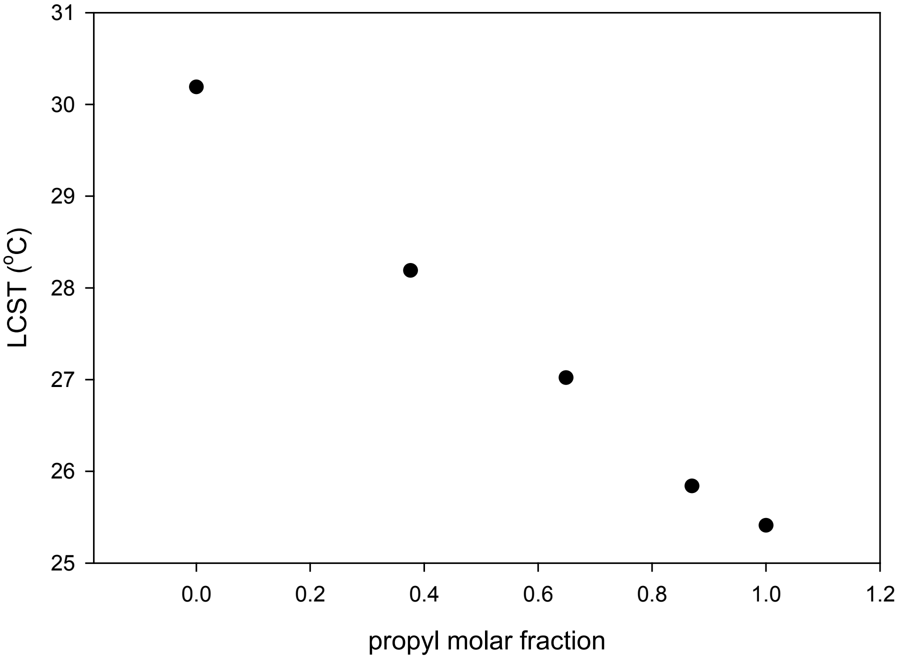


Figure 26. LCST temperatures for isomeric poly(*N*-alkylacrylamide) s containing varying ratios of isopropyl/propyl *N*-alkyl groups. The concentration of the poly(*N*-alkylacrylamide) 1-5 was 20 mg/ml in DI water

## Future direction

The precipitation process of a polymer mixture of PNIPAM and PDEAM will be studied in a more direct manner by us and Dr. Cremer's group. The specific technique used here relies on the photophysical process of direct non-radiative energy transfer between two chromophores.[184,185] The process originates in dipole-dipole interactions between a donor (D) in its excited state and an acceptor (A) in its ground state. The fluorophores must be extremely close to one another for this to happen (< 0.1 mm). In the case of small molecules in fluid solution, non-radiative energy transfer takes place when the two interacting chromophores diffuse towards each other during the lifetime of the donor. When the D and A chromophores are attached to a polymer chain, the distribution of D/A separations is related to the chain dimensions.

Factors which swell these dimensions increase the mean separation of A and D groups. Conversely, chain collapse should lead to a pronounced decrease in these distances. As a consequence the efficiency of intramolecular energy transfer should be a sensitive measure of swelling or contraction of the chain dimension, increasing sharply as the chain dimension decreases (Figure 27).

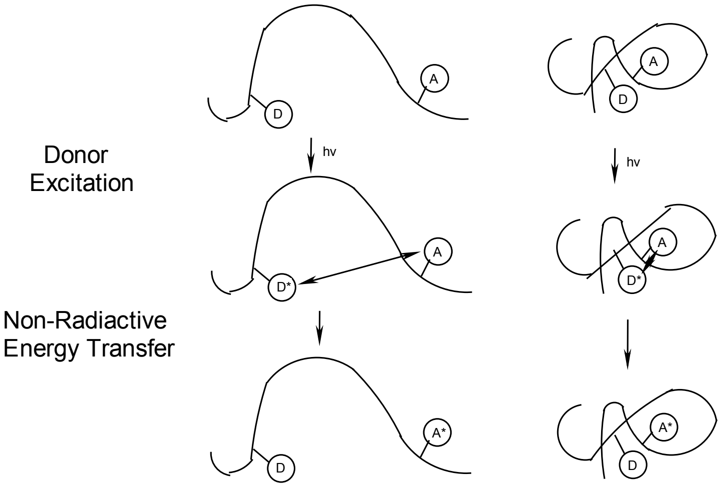


Figure 27. Influence of polymer mean dimensions on the efficiency of energy transfer between donor and acceptor labels

Winnik has used this approach previously to study the precipitation process of PNIPAM. The polymer was labeled randomly with a small amount of naphthalene (N), the energy donor, and pyrene (Py), the energy acceptor.[186] Energy transfer between naphthalene and pyrene labels was detected in aqueous solutions below their LCST. The solutions were heated to above their LCST and the extent of energy transfer between the two chromophores was measured as a function of temperature. The value was strongly temperature-dependent for solutions of the polymer in water. It increased gradually over a ca. 10 $^{o}$C temperature range to reach a constant value above the LCST. This increase in energy transfer efficiency indicated a substantial decrease of the average distance between the donor and acceptor chromophores, in agreement with a shrinking of individual polymer chains from an expended coil to a more compact globule. This fluorescence experiments provided a method to observe the conformation of individual polymer chains.

In our project, we want to test the precipitation process we proposed earlier: When the water solution of PNIPAM and PDEAM is heated, aggregation occurs first, followed by segregation. We will attach a fluorescence donor and a fluorescence acceptor to PNIPAM and PDEAM, respectively, and look into the change of fluorescence resonance energy transfer intensity during the precipitation process. If the process we proposed is right, then we should see an increase in the intensity of fluorescence resonance energy transfer, followed by a decrease in its intensity.

# CHAPTER VI

# SUMMARY

Soluble polymers are used as supports for both organometallic catalysts and organic catalysts. These catalysts can be recovered and reused using different methods, including solid/liquid separations commonly used for this purpose, and new liquid/liquid separation methods.

Solvent precipitation is a commonly used and effective way to separate soluble polymers from solution. Linear polystyrene, PEG and PNIPAM can all be separated conveniently using this method. Catalysts or reagents attached to these polymers can thus be easily separated from the rest of the material. Dye labels can be used to study their separation efficiency and other properties.

Thermomorphic systems are very convenient systems for catalysts recycling. Catalytic reactions can be run homogeneously while separations can be achieved using heterogeneous liquid/liquid separation. PNIPAM was the most commonly used support in normal thermomorphic systems. PNODAM was the first polymer designed for inverse thermomorphic systems. Changing the isopropyl group to a long alkyl chain octadecyl group made the polymer exclusively soluble in the nonpolar heptane phase in thermomorphic solvent mixtures.

The extent of the phase selective solubility of poly(*N*-alkylacrylamide)s was studied by UV-visible and fluorescence spectroscopy using poly(*N*-isopropylacrylamide) and poly(*N*-octadecylacrylamide) as representative polar and nonpolar poly(*N*-alkylacrylamide)s in a mixture of polar and nonpolar thermomorphic solvents. Phase selective solubilities of greater than 10000:1 were seen with each labeled polymer in polar and nonpolar solvents like heptane and DMF or heptane and 90% EtOH-$H_2O$. The opposite phase selective solubility of PNIPAM and PNODAM made them complementary to each other in polar/nonpolar biphasic systems.

Using a poly(*N*-acryloxysuccinimide) as a common precursor, a pool split synthesis was devised to prepare a library of poly(*N*-alkylacrylamide)s whose members varied only in the size of their *N*-alkyl substituent. The solubilities of these library members were measured in both the polar and nonpolar phases of a thermomorphic heptane/90% EtOH-$H_2O$ mixture at 25 °C. The results show that poly(*N*-pentylacrylamide) is selectively soluble (>99.5%) in the polar EtOH-rich phase at rest. Poly (*N*-alkylacrylamide)s with larger *N*-alkyl groups are predominantly ($C_6$, 85%; $C_7$, 95%) or exclusively (>$C_8$, >99.5%) in the heptane-rich phase at rest.

Latent biphasic approach is an alternative to more standard biphasic chemistry using soluble and insoluble polymers since polymers can be designed to have large distribution coefficients and phase selective solubility. While dendrimers can be used similarly, these sorts of soluble polymers are not needed to insure efficient recovery or separation of a polymer-bound catalyst or reagent. The addition of a low volume percent of a third solvent or the addition of a phase perturbing agent should also be useful in more normal biphasic reactions like fluorous biphasic chemistry where solvent or ligand/catalyst loss is a problem.

The LCST behaviors of some substituted poly(acrylamide)s were studied using a high throughput temperature gradient device. The precipitation process of mixtures of PNIPAM and PDEAM was studied and the data suggested that this precipitation involves an aggregation first, followed by a segregation. When halogens were added to aqueous solutions of PNIPAM, fluoride ion significantly lowered the LCST, and the ability of other halides to lower the LCST decreased going down the periodic column. Alkali metals also influenced the LCST of PNIPAM, and the trend followed Hofmeister series. When $D_2O$ was used instead of $H_2O$, the LCST of PNIPAM was raised by almost 0.4 °C. The LCSTs of copolymers of *N*-propylacrylamide and *N*-isopropylacrylmide were measured and the LCST changed linearly with the polymer composition.

# CHAPTER VII

# EXPERIMENTAL SECTION

**General.** AIBN was recrystallized from methanol. Benzoyl peroxide was recrystallized from $CHCl_3$/methanol. *N*-isopropylacrylamide was recrystallized from benzene/hexanes. Maleic anhydride was recrystallized from benzene. 4-*tert*-Butylstyrene was distilled before use. Other reagents and solvents were obtained from commercial sources without further purification unless otherwise specified. Gas chromatographic analyses were performed on a Shimadzu instrument equipped with a 15-m SPB (poly(5%-diphenyl-95%-dimethylsiloxane) normal phase fused silica capillary column (0.53 ID). $^1H$ spectra were recorded on Varian VXR-300 or Unity p300 spectrometers at 300 MHz. Chemical shifts were reported in ppm with $CDCl_3$ (7.27 ppm) as the internal standard. $^{13}C$ NMR spectra were recorded at 75 MHz with $CDCl_3$ (77.23 ppm) as the internal reference. Chemical shifts of $^{31}P$ NMR spectra were reported in ppm with $H_3PO_4$ (0 ppm) as the internal standard. Gel Permeation Chromatography was performed using a Ranin SD-200 HPLC system equipped with a Dynamax UV-C detector (at 254 nm). A TOSOH BIOSEP column was used. Differential scanning calorimetry (DSC) was performed using a Perkin Elmer Differential Scanning Calorimeter Pyris 1.

**4-Chloropyridine (20).** A solution of 3.75 g of 4-chloropyridine hydrochloride was prepared in 20 mL of water, and 3.5mL of triethylamine was added to this solution. After 5 min, the aqueous mixture was extracted with three 20 mL portions of diethyl ether. The combined ether extracts were dried over sodium sulfate and the solvent was removed under reduced pressure (93%). $^1$H NMR ($CDCl_3$): δ 8.2 (d, 2H), 7.3 (d, 2H).

**1-Carboxy-4-benzylpiperazine (21).** 29.2 g of ethyl 1-piperazinecarboxylate was dissolved in 60 mL of 95% ethanol. Then 23 mL of benzyl chloride and 33.6 g of sodium bicarbonate was added to the ethanol solution and the mixture was refluxed for 18 h. After cooling down to room temperature, the ethanol was removed under reduced pressure. The residue was taken into water, and potassium carbonate was added until the solution was basic. The aqueous mixture was extracted 10 times with small portions of ether. The combined ether extracts were dried over sodium sulfate, and the solvent was removed to give the product (99%). $^1$H NMR ($CDCl_3$): δ 7.3 (m, 5H), 4.1 (q, J = 7.1 Hz, 2H), 3.5 (s, 2H), 3.4 (br, 4H), 2.4 (br, 4H), 1.2 (t, J = 7.1 Hz, 3H).

**1-Benzylpiperazine (22).** A mixture of 63 g of 1-carboxy-4-benzylpiperazine, 28.5 g of potassium hydroxide and 170 mL of methanol was heated to reflux and the methanol was distilled off slowly during a 2 h period. Heating was continued until the temperature of the residue was 130-135 °C. The residue was then cooled to room temperature and treated with 75 mL of benzene and 100 mL of water. The aqueous mixture was extracted with two 100 mL portions of benzene. The benzene extract, after drying over magnesium sulfate and removal of solvent, was distilled to obtain a colorless oil (69%). $^1$H NMR ($CDCl_3$): δ 7.3 (m, 5H), 3.5 (s, 2H), 2.9 (t, J = 4.9 Hz, 4H), 2.4 (bt, J = 3.8 Hz, 4H), 1.9 (s, 1H). $^{13}$C NMR ($CDCl_3$) δ 138.1, 129.2, 128.2, 127.0, 63.7, 54.5, 46.1.

**1-Benzyl-4-(4-pyridyl)piperazine (23).** A solution of 8.8 g of 1-benzylpiperazine, 2.84 g of 4-chloropyridine in 20 mL of xylene that had been distilled over lithium aluminum hydride immediately before use was prepared and then allowed to reflux for 20 h. After cooling, the 1-benzylpiperazine hydrochloride precipitated and was removed by filtration. The xylene solution of the product was then evaporated to dryness and the residue was stirred in heptane. A light yellow solid precipitated from this heptane mixture yielding the product which was isolated by filtration and dried (93% yield). $^1$H NMR ($CDCl_3$): δ 8.2 (d, J = 6.5 Hz, 2H), 7.3 (m, 5H), 6.6 (d, J = 6.5 Hz, 2H), 3.5 (s, 2H), 3.3 (t, J = 5.1 Hz, 4H), 2.5 (t, J = 5.3 Hz, 4H). The 1-benzylpiperazine hydrochloride can be taken into water, treated with sodium hydroxide, and extracted with dichloromethane to regenerate 1-benzylpiperazine.

***N*-(4-Pyridyl)piperazine (24).** A solution of 1-benzyl-4-(4-pyridyl)piperazine in 55 mL of 2 N HCl and 150 mL of methanol was hydrogenated with 2.8 g. of Pd/C (10% by wt.) at room temperature at 35 psi. After the hydrogen uptake stopped, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting white solid was taken up in water, and the solution was made basic with potassium hydroxide. The precipitate that formed was collected and recrystallized from heptane (99%). $^1$H NMR ($CDCl_3$): δ 8.2 (d, J = 6.6 Hz, 2H), 6.6 (d, J = 6.6 Hz, 2H), 3.3 (t, J = 4.9 Hz, 4H), 3.0 (t, J = 5.4 Hz, 4H), 1.8 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 150.2, 108.3, 108.2, 47.0, 45.6.

**1-(4-vinylbenzyl)-4-pyridylpiperazine (25).** 4-Vinylbenzyl chloride was passed through neutral alumina. 4.32 mL of 4-vinylbenzyl chloride and 10 g of *N*-(4-pyridyl)piperazine were dissolved in 100 mL of methanol. The solution was refluxed overnight. After cooling down to room temperature, 20 mL of 6 N HCl was added, and the solution extracted three times with ether. The ether extracts were discarded and 20 g of NaOH in 20 mL of water was added to the aqueous solution dropwise. The precipitate was filtered, and chromatographed using 5% triethylamine in ethyl acetate as the eluent. Pure product was obtained in 72.1% yield. $^1$H NMR ($CDCl_3$): δ 8.2(d, 2H), 7.3(dd, 4H), 6.7(dd, 1H), 6.6(d, 2H), 5.7(d, 1H), 5.2(d, 1H), 3.5(s, 1H), 3.3(t, 4H), 2.5(t, 4H). $^{13}$C NMR ($CDCl_3$): δ155.2, 150.4, 137.6, 136.9, 136.7, 113.9, 108.5, 62.9, 52.7, 46.1.

**Polystyrene-co-poly[1-(4-vinylbenzyl)-4-pyridylpiperazine] (26)** 4.1 ml of distilled styrene and 1g of 1-(4-vinylbenzyl)-4-pyridylpiperazine **25** was dissolved in 50 ml of benzene, and the solution was purged with nitrogen for 1 h, then heated to 60 $^o$C. 25 mg of AIBN was dissolved in 5 ml of benzene, purged with nitrogen, then cannulated into the substrate solution. The solution was heated at 60 $^o$C overnight, then cooled to room temperature and poured into 300 mL of methanol. The white powder precipitated was dissolved in dichloromethane and precipitated into methanol twice. $^1$H NMR: δ 8.2(br, 2H), 7.2-6.2(br, 58H), 3.4(br, 2H), 3.3(br, 4H), 2.5(br, 4H), 2.0-1.2(br, 33H).

**Boc protection of phenols in dichloromethane.** A substituted phenol, 1.02 equiv. of $(Boc)_2O$, ethyl benzene and the catalyst (0.25 mol% for kinetic studies or 5 mol% in synthetic thermomorphic reactions) was dissolved in dichloromethane. The solution was stirred and the progress of the reaction was followed by IR or GC (ethyl benzene was used as an internal standard). Upon completion of the reaction, the solution was washed with 1N HCl, saturated $NaHCO_3$, dried over $MgSO_4$ and the solvent was removed under vacuum to afford the product.

**Synthesis of MeO-PEG-mesylate (27).** Monomethoxy-terminated PEG (20 g) and $Et_3N$ (1.7 ml) was dissolved in dichloromethane. A dichloromethane solution of methanesulfonyl chloride was added dropwise to this solution at 0 $^oC$. The reaction mixture was stirred for 6 hours, washed with HCl, $Na_2CO_3$, dried over $MgSO_4$, concentrated, then precipitated from ether to yield 99% of product **27**. $^1H$ NMR($CDCl_3$) $\delta$ 4.3 (t, 2H), 3.28-3.85 (PEG, 440H), 3.0 (s, 3H).

**Synthesis of ethyl 5-hydroxyisophthlic ester (28).** 5-Hydroxyisophthalic acid (10.0 g, 55 mmol) was dissolved in 150 mL of ethanol. To this solution was added 10 mL of concentrated $H_2SO_4$, and the solution was heated at reflux for 16 h. Ca. 50 mL of 1M solution of $NaHCO_3$ was added and the product precipitated. After filtration, a product of 10 g (83.2%) was obtained. $^1H$ NMR($CDCl_3$) $\delta$ 8.2 (s, 1H), 7.7 (s, 2H), 4.4 (q, 4H), 1.4 (t, 6H).

**Synthesis of MeO-PEG-isophthalic acid diethyl ester (29).** To a solution of diethyl 5-hydroxy isophthaliate (1.43 g, 6.00 mmol) in freshly distilled THF was added potassium *tert*-butoxide (0.674 g, 6.00 mmol). Upon addition of the base, the solution turned to a bright orange color. The solution was stirred at room temperature for 30 min. The THF was removed under reduced pressure and the salt residue was dissolved in 10 mL of DMF. This solution was added to a solution of PEG-mesylate (10.0 g, 2.0 mmol) in 50 mL of DMF. The resulting homogeneous solution was stirred at 75 $^oC$ for 20 h. After the reaction, the solution was filtered through Celite to remove insoluble materials and the filtrate was acidified to pH 4 with concentrated HCl. The solvent was then removed from the filtrate under reduced pressure. The residue was redissolved in 75 mL of MeOH. This solution was poured into 300 mL of diethyl ether, with stirring, to precipitate the product as a white solid. This solid was isolated, recrystallized from 2-propanol, and washed with further portions of cold 2-propanol before being dried under vacuum to yield 9.8 g (98%) of the product **29**: $^1$H NMR($CDCl_3$): δ 8.25 (s, 1H), 7.75 (s, 2H), 4.39 (q, 4H), 4.21 (t, 2H), 3.28-3.85 (PEG, 440H), 1.40 (t, 6H).

**Synthesis of MeO-PEG-diol (30).** A solution of **29** (9.62 g, 3.84 mmol) in dry, freshly distilled THF (150 mL) was prepared. To this solution was added lithium aluminum hydride (800 mg, 21.08 mmol) in several small portions. After the addition was complete, the reaction mixture was refluxed for 8 h. The mixture was then cooled and neutralized by the slow addition of 10 M aqueous NaOH. Neutralization was assumed to be complete upon the disappearance of all gray color from the solution and the appearance of a white, sticky precipitate. The mixture was then filtered through Celite and the solvent removed from the filtrate under reduced pressure. The resulting residue was then dissolved in 40 mL of acetone and filtered again through Celite. The filtrate was poured into 500 mL of diethyl ether to precipitate the product polymer as a white solid. The material was isolated by filtration, recrystallized from 2-propanol, and dried under vacuum to yield 9.52 g (99%) of the product **30**: $^1$H NMR ($CDCl_3$): δ 6.95 (s, 1H), 6.81 (s, 2H), 4.60 (s, 4H), 4.13 (t, 2H), 3.28-3.85 (PEG, 440 H), 2.75 (br, s, 2H).

**Synthesis of MeO-PEG-dibromide (31).** A solution of **30** (18.0 g, 7.2 mmol) in 90 mL of methylene chloride was cooled to 0 $^o$C. Triethylamine (3.0 mL, 21.6 mmol) was added and the solution was stirred at 0 °C for 10 min. Then, methane sulfonyl chloride (1.66 mL, 21.6 mmol) was added to the reaction solution dropwise, with stirring. The solution was stirred for an additional 20 min at 0 °C and then allowed to warm to room temperature. It was then stirred at room temperature for 20 h. Afterwards, the reaction solution was filtered through Celite and the filtrate was concentrated to approximately 20 mL. The filtrate was then poured into 200 mL of diethyl ether, precipitating the product dimesylate. The material was isolated by filtration and then dissolved in 90 mL of acetone. Dry lithium bromide (2.09 g, 24.0 mmol) was added and the resulting mixture was refluxed for 21 h. the reaction solution was then filtered, recrystallized from 2-propanol, and dried under vacuum, yielding 16.4 g (91%) of the PEG-dibromide **31**: $^1$H NMR ($CDCl_3$): δ 6.99 (s, 1H), 6.85(s, 2H), 4.41 (s, 4H), ), 4.17 (t, 2H), 3.28-3.85 (PEG, 440 H).

**Synthesis of dicyclopentylphosphine-borane complex (32).** Dicyclopentylphoshpine was given by Cytec Canada Inc. 5 mL of 10 M $BH_3$-$Me_2S$ (50 mmol) was added slowly into a 50 mL THF solution of dicyclopentylphosphine (8.5 g, 50 mmol) at 0 °C under nitrogen. The mixture was stirred for 2 h at this temperature and additional 3 h at 25 °C. Then the solvent THF was removed under reduced pressure. The crude product was dissolved in a mixture of 30 mL of hexanes and 5 mL of THF. After filtration, 20 mL of hexane was added to the filtrate and the mixture was subjected to recrystallization in a freezer at -5 °C overnight. The product was collected, washed with cold hexanes and dried under vacuum. 4.5 g of pure product (colorless crystals) was obtained (49%) yield. $^1$H NMR (CDCl3) δ 4.5 (two sets, 1H), 2.2 (m, 2H), 1.5-2.1 (m, 16H), 0.3 (br q, 3H). $^{31}$P NMR ($CDCl_3$) δ14.36 (br q).

**Synthesis of PEG-supported di(phosphine-borane) complex (33).** Phosphine-borane complex **32** (73 mg, 0.4 mmol) was dissolved in 5 mL of freshly distilled THF under nitrogen, then the solution was cooled using a dry ice-acetone bath. 0.18 mL of n-BuLi (0.42 mmol) hexane solution was added slowly into the above solution using a syringe. The mixture was stirred at this temperature for 2 h and then additional 1 h at room temperature. The reaction solution was again cooled using a dry ice-acetone bath and 1 g of the dibromide **31** in 10 mL of THF was added through a syringe at this temperature. After stirred at this temperature for 2 h, the reaction mixture was allowed to warm slowly to room temperature and stirred for 10 h. The solution was then added to an excess amount of ether and the product precipitated which was isolated by filtration. $^1$H NMR ($CDCl_3$): δ 6.7 (s, 3H), 4.1 (t, 2H), 3.9-3.4 (PEG, 440 H), 3.0 (d, 4H), 2.0-1.4 (br m, 44H).

***N*-Acryloxysuccinimide (36).** *N*-Hydroxysuccinimide (11.5 g) and triethylamine (15 mL) were dissolved in 150 mL of $CHCl_3$ at 0 °C. Then 10 g of acryloyl chloride was added dropwise over a 20 min period to the stirred reaction mixture under $N_2$. After being stirred for an additional 20 min at 0 °C, the solution was washed with 240 mL of ice-cold water and saturated brine, concentrated to a volume of 30 mL under reduced pressure using a rotary evaporator, dried with $MgSO_4$, and filtered. Addition of 3 mL of ethyl acetate and 20 mL of hexanes to the resulting $CHCl_3$ solution followed by stirring for 2 h with cooling to 0 °C produced a white solid precipitate that was isolated by filtration and washed with an ice cold 10 mL portion of a mixture of hexane and ethyl acetate (4:1). This washing was followed by another using a second 10-mL portion of hexane and ethyl acetate (9:1), and finally with two 10-mL hexane washings. The resulting solid was vacuum dried to yield 75% product. $^1$H NMR ($CDCl_3$): δ 6.7 (dd, 1H), 6.3 (dd, 1H), 6.3 (dd, 1H), 2.8 (s, 4H).

**10 : 1 Poly(*N*-isopropylacrylamide-c-*N*-acryloxysuccinimide) (PNIPAM-NASI) (4).** The commercial *N*-Isopropylacrylamide (NIPAM) was recrystallized before use from hexane : benzene (10:1). NIPAM (11.3g) and *N*-acryloxysuccinimide (1.69 g) were dissolved in tert-butanol (200 mL) at 70 °C under nitrogen. AIBN (50 mg) in 5 mL of tert-butanol was added at this temperature. The reaction mixture was stirred at 70 °C for 16 h and then cooled to room temperature. The solvent was removed in vacuo. The crude product copolymer was purified by repeatedly dissolving in THF (250 mL) and precipitating into hexane (700 mL). The final product was put on a high vacuum system for 24 h to yield the pure copolymer.

**Synthesis of benzoyl chloride (39).** Benzoic acid was recrystallized from aqueous ethanol. Benzoic acid (30 g) was dissolved in 150 mL of thionyl chloride. A few drops of DMF was added and the mixture was refluxed for 6 h. Thionyl chloride left was removed under reduced pressure, and the crude product was recrystallized from hexanes in 98% yield. IR (liquid film, cm$^{-1}$): 1775, 1733. $^1$H NMR ($CDCl_3$): δ8.1 (d, 2H), 7.6 (t, 1H), 7.5 (t, 2H), $^{13}$C NMR($CDCl_3$): δ168.3, 135.4, 133.2, 131.3, 129.0.

**Synthesis of *N*-(2-hydroxy-*tert*-butyl)-benzamide (40).** 2-Amino-2-methyl propanol (6.7 g, 75 mmol) and triethylamine (14.9 mL, 107 mmol) was dissolved in 150 mL of dichloromethane and cooled to 0 °C. Benzoyl chloride in 150 mL of dichloromethane was added dropwise to this solution at 0 °C. After all the benzoyl chloride was added, the solution was warmed up to room temperature and stirred for 2 h. The mixture was washed with 10 g of $Na_2CO_3$ in 100 mL water, 200 mL of 2M HCl, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was recrystallized from benzene with 58% yield. $^1$H NMR ($CDCl_3$): δ 7.7 (d, 2H), 7.4 (m, 3H), 3.7 (s, 2H), 1.4 (s, 6H).

**Synthesis of 4,4-dimethyl-2-phenyl-2-oxazoline (41).** *N*-(2-hydroxy-*tert*-butyl)-benzamide (3g) was dissolved in 80 mL of chloroform. Thionyl chloride (3.4 mL) was added dropwise to this solution over a 20-30 min period. The mixture was stirred for 4 h, then added to an excess amount of diethyl ether. The protonated product precipitated which was filtered, dissolved in water. Triethylamine was added to the water solution until the pH reached 9, then the mixture was extracted with dichloromethane, washed with water, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to obtain the product in 79% yield. $^1$H NMR ($CDCl_3$): δ7.9 (d, 2H), 7.4 (m, 3H). $^{13}$C NMR($CDCl_3$): δ162.0, 131.1, 128.2, 128.1, 128.0, 79.1, 67.5, 28.4.

**Palladation of 4,4-dimethyl-2-phenyl-2-oxazoline.** A mixture of $Pd(OAc)_2$ (1.1 g, 5 mmol) and the oxazoline **41** (5 mmol) in 5 mL of acetic acid was stirred at 95 °C for 1 h. The mixture was then cooled to room temperature. After filtration, the solid was washed with water, then dissolved in chloroform. The solution was filtered through Celite. Solvent was removed from the supernatant. The residue was recrystallized from chloroform/hexanes to obtain 77% of product **38**. $^1$H NMR ($CDCl_3$): δ 7.1 (d, 1H), 7.0

(m, 3H), 4.3-4.1 (dd, 2H), 2.2 (s, 3H), 1.4 (s, 3H), 0.8 (s, 3H). $^{13}$C NMR($CDCl_3$): δ 181.4, 172.6, 146.5,132.5, 131.4,130.0, 125.0, 123.6, 81.4, 65.1, 27.3, 24.6.

**Synthesis of monomer 42.** The dimer **38** (462 mg) and acetylacetone (0.3 mL) was stirred in 2 mL of dichloromethane for 1 h, then washed with 2 mL of 10% NaOH solution, dried over $MgSO_4$, then filtered. Solvent was removed from the supernatant under reduced pressure to obtain the dimer in 90% yield. $^1$H NMR ($CDCl_3$): δ 7.5 (d, 1H), 7.1 (m, 2H), 6.9 (t, 1H), 5.3 (s, 1H), 4.3 (s, 2H), 2.0 (s, 3H), 1.9 (s, 3H), 1.5 (s, 6H).

**General procedure of Heck reactions using 38 as a catalyst.** Iodobenzene, 1.2 equivalent of methyl acrylate, and 1.4 equivalent of triethylamine was dissolved in DMF. 1 mol% of the catalyst was added to the solution. The reaction vial was sealed and heated at 140 $^{o}$C **.** After reaction, the DMF solution was added to 10 fold amount of water, then extracted with dichloromethane 3 times. The combined dichloromethane extract was washed with water, dried over $MgSO_4$. After filtration, the solvent from the supernatant was removed under reduced pressure to obtain the product.

**General procedure of homocoupling of aryliodide using 38 as a catalyst.** Aryliodide and 1.2 equivalent of triethylamine was dissolved in DMF. 0.1 mol% of catalyst **38** was added. The reaction vial was sealed and heated at 140 $^{o}$C overnight. The DMF solution was then poured into an excess amount of water and the product precipitated which was isolated by filtration.

**Synthesis of 10-undecenyl methanesulfonate (45).** ω-Undecyl alcohol. (10 mL, 50 mmol) and triethyl amine (8.4 mL) was dissolved in dichloromethane. A dichloromethane solution of methanesulfonyl chloride (4.3 mL, 55 mmol was added dropwise at 0 $^{o}$C. After bubbling stopped, the reaction mixture was stirred for another hour then filtered. The supernatant was washed with 50 mL of 2M HCl, 50 mL of 10% NaOH, saturated NaCl, then dried over $MgSO_4$. After filtration, solvent was removed from the supernatant to obtain the product in 70% yield. $^1$H NMR ($CDCl_3$): δ 5.8 (m, 1H), 5.0 (m, 2H), 4.3 (t, 2H), 3.0 (s, 3H), 2.1 (q, 2H), 1.8 (m, 2H), 1.6 (s, 2H), 1.4 (s, 10H).

**Synthesis of 2-undec-1-enyl-isoindole-1,3-dione (46).** 10-undecenyl methanesulfonate (1g, 4.6 mmol) and potassium phthalimide (932 mg, 5.0 mmol) was suspended in DMF and the mixture was heated at 80 $^{o}$C overnight. After cooled to room temperature, the mixture was poured into an excess amount of water, and extracted with dichloromethane. The dichloromethane extract was washed with water, dried over $MgSO_4$, and filtered. Solvent was removed from the supernatant to obtain the product in 78% yield. $^1$H NMR ($CDCl_3$): δ 7.8 (m, 2H), 7.7 (m, 2H), 5.8 (m, 1H), 5.0 (m, 2H), 4.3 (t, 2H), 2.0 (q, 2H), 1.7 (m, 2H), 1.6 (s, 2H), 1.4 (s, 10H).

**Synthesis of 10-undecen-1-amine (47).** 0.09 mL of hydrazine monohydrate was added to 2-undec-1-enyl-isoindole-1,3-dione (0.3 g) in hot ethanol. The mixture was heated at reflux for 2 h, then cooled to room temperature. 1 mL of 12M HCl was added and the mixture was refluxed for another 30 min. After cooled to room temperature, the mixture was filtered. Solvent from the supernatant was removed under reduced pressure and the residue was dissolved in water. 200 mg of NaOH was added and the product precipitated. After filtration, the product was obtained in 85% yield. $^1$H NMR ($CDCl_3$): δ

5.8 (m, 1H), 5.0 (m, 2H), 2.6 (m, 2H), 2.0 (m, 2H), 1.5-1.2 (m, 14H). $^{13}$C NMR ($CDCl_3$): δ 139.0, 114.0, 42.1, 33.7, 33.6, 33.6, 29.4, 29.3, 29.0, 28.8, 26.8.

**Attaching 10-undecen-1-amine to PNIPAM-NASI.** PNIPAM-NASI (12:1, 1.5 g) was dissolved in 20 mL of THF. 170 mg of 10-undecen-1-amine in 2 mL of THF was added and the solution was stirred for 4 h. 1 mL of isopropylamine was added and the mixture was stirred for another 4 h. Then the mixture was filtered and the supernatant was added to 150 mL of hexanes. The product precipitated and was filtered. $^{1}$H NMR ($CDCl_3$): δ 5.8 (m, 1H), 5.0 (m, 2H), 4.0 (s, 15 H), 3.2-1.2 (br m, 111H), 1.0 (s, 90 H).

**Synthesis of PNIPAM-oxazoline-Pd(II) (49).** Compound **44** was synthesized in a similar way to that of **38**. 2 g of polymer **48**, 556 mg of **44**, 10 mg of **38** and 0.2 mL of triethylamine was dissolved in 20 mL of DMF. The reaction vial was sealed and heated at 70 $^{o}$C for 40 h. The mixture was then cooled to room temperature and added to 150 mL of diethyl ether. After filtration, the solid was dissolved in 20 mL of THF and added dropwise to 150 mL of hexanes. The product precipitated and was filtered. $^{1}$H NMR ($CDCl_3$): δ 7.8 (d, 1H), 7.3 (d, 1H), 7.1 (d, 2H), 5.3 (s, 1H), 4.3 (s, 2H), 4.0 (s, 15H), 2.2-1.1 (br m, 123H), 1.0 (s, 90H).

**Boc-protected 6-aminohexanoic acid (50).** A solution of 4 g of sodium hydroxide in 200 mL of 70 : 30 THF : $H_2O$ was prepared and cooled to 0 °C. Then 6.56 g of 6-aminohexanoic acid was added and 200 mL of a THF solution of 10.91 g of di-tert-butyldicarbonate was added dropwise to the basic aqueous THF solution. After the addition was complete, the reaction mixture was warmed up to room temperature and stirred for 6 h. The solvent was removed *in vacuo* and 10% HCl was added slowly until the solution was slightly acidic. The aqueous solution was extracted with four 200 mL portions of dichloromethane. The organic extract was dried over sodium sulfate, and the solvent was removed under reduced pressure (88%). $^1$H NMR ($CDCl_3$): δ 4.6 (bs, 1H), 3.1 (q, J = 6.2 Hz, 2H), 2.4 (t, J = 7.6 Hz, 2H), 1.6 (p, J = 7.5 Hz, 2H), 1.4 (m, 13H).

**Amine-terminated DAAP catalyst (52).** Boc-protected 6-aminohexanoic acid (3.39 g) was first dissolved in 20 mL of dichloromethane. Then 3.02 g of 1,3-dicyclohexylcarbodiimide in 20 mL of dichloromethane was added to the acid solution. A white precipitate started forming within 1 min. The mixture was stirred for 10 min, then 2.39 g of *N*-(4-pyridyl-)piperazine in 20 mL of dichloromethane was added and the mixture was stirred overnight at room temperature. The resulting suspension was filtered and the solid was washed with dichloromethane. The combined dichloromethane solutions were extracted with 70 mL of 15% citric acid. The aqueous phase was washed with dichloromethane and treated with sodium hydroxide solution until it was basic. The aqueous mixture was then extracted with dichloromethane, and the organic extract was washed with water, dried over magnesium sulfate, and concentrated *in vacuo* to give a Boc-protected amine **51** in 84% yield. $^1$H NMR ($CDCl_3$): δ 8.3 (d, J = 6.5 Hz, 2H), 6.6 (d, J= 6.6 Hz, 2H), 4.6 (s, 1H), 3.8 (t, J = 5.3 Hz, 2H), 3.6 (t, J = 4.6 Hz, 2H), 3.4 (t, J = 9.4 Hz, 4H), 3.1 (q, J = 6.4 Hz, 2H), 2.4 (t, J = 7.3 Hz, 2H), 1.6 (p, J= 7.4 Hz, 2H), 1.4 (m, 13H). $^{13}$C NMR ($CDCl_3$): δ 171.8, 154.8, 150.7, 150.6, 108.8, 46.3, 46.1, 45.0, 41.1, 33.3, 30.2, 28.7, 26.8, 25.0. The Boc-protected amine **51** so formed (4.15 g) was dissolved in 100 mL of dichloromethane and cooled to 0 $^o$C. Trifluoroacetic acid (TFA, 17mL) was then added and the reaction mixture was stirred at room temperature overnight. At this point, the dichloromethane solvent was removed by evaporation and 30 g of potassium carbonate in 150 mL of water was added slowly to the residue. The resulting aqueous mixture was then extracted with three 100 mL portions of dichloromethane, dried over magnesium sulfate and concentrated *in vacuo* to yield 68% of the desired product. $^1$H NMR ($CDCl_3$): δ 8.3 (d, J = 6.3 Hz, 2H), 6.7 (d, J = 6.5 Hz, 2H), 3.8 (t, J = 4.9 Hz, 2H), 3.6 (t, J = 5.6 Hz, 2H), 3.4 (t, J = 8.1 Hz, 4H), 2.7 (t, J = 6.8 Hz, 2H), 2.4 (t, J = 7.3 Hz, 2H), 1.7-1.4 (m, 6H). $^{13}$C NMR ($CDCl_3$): δ171.8, 154.8, 150.6, 108.7, 46.2, 45.0, 42.1, 41.0, 33.5, 26.9, 25.1.

**13 : 1 PNIPAM-DAAP (53)** 2.4 g of PNIPAM-NASI was dissolved in 20 mL of dichloromethane. To this solution was added 0.7 mL of triethylamine followed by 0.5 g of the amine-terminated DAAP **52** in 5 mL of dichloromethane. The mixture was stirred at room temperature overnight. Then 1 mL of isopropyl amine was added and the mixture was stirred for 4 h. The solid formed was filtered and the dichloromethane solution was concentrated to about 5 ml, then poured into 50 mL of hexanes. The white powder precipitated was filtered and dried. $^1$H NMR: δ 8.4(br, 2H), δ7.7(br, 2H), δ4.0(br, 13H), δ2.6-1.2(br), δ1.0(bs, 78H).

**Acylation of 1-methylcyclohexanol.** A solution containing 1.3 equiv. of triethylamine, ethyl benzene as an internal standard and 5 mol% catalyst **53** was dissolved in dichloromethane, and the solution was stirred at 25°C under nitrogen for 15 min. Addition of 2 equiv. of acetic anhydride was followed by addition of 1 equiv. of 1-methylcyclohexanol. The reaction progress was monitored by GC.

**Amine-terminated Methyl Red (54).** {2-[4-(Dimethylamino)phenylazo]benzoic acid} (3.866 g) and 100 mL of $CH_2Cl_2$ were added to an oven-dried flask and flushed with $N_2$. CDI (2.404 g) in 36 mL of $CH_2Cl_2$ was added via syringe and the mixture stirred vigorously under $N_2$. After stirring for 7 h, the solution was transferred by forced siphon with a cannula into a $N_2$-flushed flask containing 8.475 g of 1,6-hexanediamine in 85 mL of $CH_2Cl_2$. The mixture was stirred under a slow $N_2$ flow overnight. The resulting dark red solution was washed with water (3 × 150 mL), dried over $MgSO_4$, the solvent removed under reduced pressure and the product dried on the vacuum pump to give an orange solid (71%). $^1$H NMR ($CDCl_3$): δ 9.1 (br, 1H), 8.4 (m, 1H), 7.8-7.7 (m, 3H), 7.5 (m, 2H), 6.8 (d, 2H), 3.5 (q, 2H), 3.1 and 3.0 (2s, 6H), 2.6 (t, 2H), 1.7 (m, 4H), 1.4 (m, 6H).

**PNIPAM-DAAP-MR (55).** PNIPAM-NASI (5 g) was dissolved in 100 mL of dichloromethane, and 1.5 mL of triethylamine was added . Then 4 mg of amine-terminated methyl red **54** in 1 mL of dichloromethane was added, and the solution was stirred at room temperature for 1 h. Addition of 0.276 g of amine-terminated DAAP **52** in 10 mL of dichloromethane and overnight stirring was then followed by addition of 1 mL isopropyl amine. After 4 more hours of stirring, the solid formed was isolated by filtration and the dichloromethane solution was poured into 500 mL of hexanes. The yellow powder precipitated was filtered and dried. The polymer had UV absorption at 430 nm in dichloromethane.

***N*-Octadecylacrylamide**. Octadecylamine (26.7 g) was suspended in 500 mL of dichloromethane. Then 16.9 mL of triethylamine was added, and the mixture was cooled to 0 °C using an ice-water bath. At this point, 50 mL of a $CH_2Cl_2$ solution containing 8.9 mL of acryloyl chloride was added dropwise to the amine suspension. The reaction mixture was warmed to room temperature and stirred for 1h. The solvent was removed under reduced pressure and the residue was taken up in 250 mL of chloroform, washed with water and brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was recrystallized from acetone. The product was isolated by filtration and had mp 70-71 °C; $^1H$ NMR: $\delta$ ($CDCl_3$) 6.3 (d, 1H), 6.1 (dd, 1H), 5.6 (overlapping d and br s, 2H), 3.3 (q, 2H), 1.5 (t, 2H), 1.3 (bs, 30H), 0.9 (t, 3H); $^{13}C$ NMR $\delta$ ($CDCl_3$) 165.78, 131.18, 126.35, 39.84, 32.13, 29.90, 29.87, 29.86, 29.85, 29.79, 29.78, 29.75, 29.57, 29.51, 27.15, 22.90, 14.33; IR (thin film) 1670 $cm^{-1}$.

**Poly(*N*-octadecylacrylamide-co-NASI)(PNODAM-NASI) (58)**. Benzene (50 mL) was degassed with bubbling $N_2$ for 30 min. Then *N*-octadecylacylamide monomer (4.5 g, 13.9 mmol) and 240 mg of *N*-acryloxysuccinimide (1.39 mmol) were added. The reaction mixture was warmed to 80˚C and a solution of AIBN (12.6 mg, 0.077 mmol) in 2 mL of benzene was added. The resulting polymerization reaction mixture was stirred at 80˚C under nitrogen for 36 h. At that point, the solvent was removed at reduced pressure using a rotary evaporator and the residue was taken up in 30 mL of $CHCl_3$ and precipitated into 150 mL of cold methanol to give 4.1 g (87%) of a white powder. $^1H$ NMR $\delta$ ($CDCl_3$) 3.1 (br s, 20H), 2.8 (br s, 4H), 1.5 (br s, 27H), 1.2 (br s, 395H), 0.8 (t, 30H); IR (KBr) 1812, 17383, 1737, 1654 and 1542 $cm^{-1}$.

**Methyl Red Labeled Poly(*N*-alkylacrylamide).** The amine-terminated methyl red azo dye **54** was coupled to a sample of a copolymer of NIPAM or NODAM and NASI prepared as described above. To effect this coupling, the NASI containing copolymer was dissolved in THF. To this solution was added 0. 1-0. 2 equivalent (relative to NASI) of amine-terminated methyl red. This solution was stirred for 4 hours. Then excess amine (isopropyl or octadecylamine for PNIPAM or PNODAM, respectively) was added to consume any unreacted NASI groups and stirring was continued at room temperature overnight. Any precipitate that formed was removed by centrifugation. The product polymer was isolated by solvent precipitation with the exact procedure varying for the polar and nonpolar polymer products. In the case of the methyl red-labeled PNIPAM, the product polymer solution was added dropwise via pipette to an excess of hexanes. This formed an orange powder that was isolated by filtration. This product was characterized spectroscopically; the $^1$H NMR and IR spectrum was essentially the same as PNIPAM ($^1$H NMR $\delta$ ($CDCl_3$) 4.0 (br, s, 1H), 2.4-1.4 (br, m, 3H), 1.1 (br, 6H); IR (thin film) 1648 cm$^{-1}$). However, the presence of azo dye label was evident in UV-visible spectroscopy (EtOH); 513 nm (the protonated from of the azo dye), 437 nm (the neutral form of the azo dye). The product PNIPAM polymer's molecular weight was characterized by viscosimetry, $M_v$ = 600,000 (THF, 30 °C). In the case of the methyl red-labeled PNODAM, the solvent from the product polymer solution was first removed under reduced pressure. The resulting red polymer solid was then dissolved in $CHCl_3$ and added dropwise to an excess of methanol to form an orange powder that was isolated by filtration. As was true for PNIPAM, the $^1$H NMR and IR spectra were the same as PNODAM ($^1$H NMR δ ($CDCl_3$) 3.3(q, 2H), 1.8-1.3 (br, 5H), 1.2 (br, 30H), 0.8 (t, 3H); IR (thin film) 1651 $cm^{-1}$) but the presence of the azo dye was seen in UV-visible spectroscopy (heptane); 515 nm (the protonated form of the azo dye), 419 nm (the neutral form of the azo dye).

**Amine-terminated dansyl derivative.** A solution of 0.94 g dansyl chloride in 75 mL of THF was dropwise added to the solution of 2.4 mL of ethylenediamine in 150 mL of THF at 0 $^oC$. The solution was stirred at 0 $^oC$ for 3 h, and 10 mL of 1M KOH solution was added. The THF was evaporated, and the aqueous layer was extracted with dichloromethane. The organic layer was dried using MgSO4 and evaporated. The residue was recrystallized from benzene/hexanes (5/1, v/v) solution with a 40% yield.

**Dansyl Labeled Poly(*N*-alkylacrylamide).** The amine-terminated dansyl probe was coupled to a sample of a copolymer of NIPAM or NODAM and NASI prepared as described above. To effect this coupling, the NASI containing copolymer was dissolved in THF and 1.5 equivalent of $Et_3N$ (relative to NASI) was added. To this solution was added 0.01 equivalent of amine-terminated dansyl derivative in THF. The solution was stirred at room temperature for an hour, then 2 equiv of isopropylamine or octadecylamine were added and the mixture was stirred overnight. Any precipitate that formed during this reaction was removed by centrifugation. In the case of the PNIPAM support, the PNIPAM derivative was isolated after precipitation using excess hexanes. In the case of the PNODAM support, the PNODAM derivative was isolated after precipitation using excess methanol. The characterization results were similar to those of the corresponding dye-labeled polymers except for the polymers' fluorescence properties (vide infra).

**Poly(*N*-acryloxysuccinimide) (PNASI) (61)**. Benzene (300 mL) was first placed in a 500-mL flask that contained a reflux condenser. Bubbling of $N_2$ for 30 min was used to degas this solution. Then *N*-Acryloxysuccinimide (NASI) **36** (5 g, 29.6 mmol) was added to the flask. After it dissolved, the flask was placed in a 60 °C oil bath and allowed to heat for 30 min under nitrogen. Then a solution of azobisisobutyronitrile (AIBN) (19 mg, 0.118 mmol) in 2 mL of benzene was added and the reaction was allowed to stir at 60 °C overnight. The initially homogeneous reaction contained a significant amount of white precipitate the next day. The solvent was removed from this benzene suspension of product at reduced pressure using a rotary evaporator and the residue was dissolved in ~70 mL of dry DMF with heating. This dissolution takes some time. After the polymer had dissolved, the solution was added dropwise quickly from a pipette into 500 mL of a mixed solution containing a 40:60 (vol:vol) mixture of hexane and THF. A white powder formed which was isolated by filtration (3.7 g). The product was characterized by $^1$H NMR spectroscopy but the $^1$H NMR was of poor quality with broad peaks: $^1$H NMR δ (DMSO-$d_6$) 2.0 (s, br 2 H), 2.8 (s, br 4 H), 3.1 (s, br 1 H); $^{13}$C NMR δ (DMSO-$d_6$) (broad peaks) 171-169, 39-31, 27-24; IR (Nujol mull) 1810, 1781, 1740 cm$^{-1}$.

**Synthesis of a Library of Methyl Red-Labeled Poly(*N*-alkylacrylamide)s from a Common Poly(*N*-acryloxysuccinimide) Precursor**. Portions of PNASI were placed in separate reactors and treated as follows. Each sample of PNASI (0.59 mequiv of active ester, 100 mg) was first dissolved in DMF. Then a mixture of the primary alkylamine and a primary amine derivative of methyl red were added. Each mixture of methyl red amine and alkylamine used 0.003 g (0.00887 mmol) of the methyl red derivative and 0.887 mmol of the alkylamine. Each reaction used the same amount (ca. 0.9 mmol) of the alkylamine. Each reaction used a total volume of 20 mL of DMF. Each amidation reaction was carried out under identical conditions. The mixture of active ester polymer and amines was heated to 50 °C for 24 hours. At this point, each of the reddish solutions contained the desired methyl red-labeled poly(*N*-alkylacrylamide) copolymer, excess unreacted primary amine-terminated methyl red and excess alkylamine. While the product polymers at this point could have been isolated by a solvent precipitation as described above, such a precipitation process could fractionate the polymer, separating the polymer into fractions with differing degrees of polymerization and differing polydispersities. To avoid this, a slightly different workup was used. In this workup, the excess amine was removed from these solutions using Amberlyst 15. This treatment involved shaking each solution with 0.35 g of Amberlyst 15 for 24 h at room temperature using a wrist action shaker. The red suspensions were then filtered to remove the Amberlyst resin. The eight different polymers were then isolated from each experiment by removing the solvent under reduced pressure. Drying in vacuo led to a mixture of polymer samples that were then tested for phase selective solubility as described below. The molecular weight of the PNIPAM member of this library was determined by both viscosity and GPC ($M_n = 1.8 \times 10^5$, $M_w = 3.4 \times 10^5$, $M_v = 3.3 \times 10^5$).

**Tests of Non Reactivity of Polymer Dyes and Sulfonated Polystyrene Resin.** To test whether the Amberlyst-15 had removed all of the low molecular weight amines in each of the above experiments, one of the samples (the isopropylamine-containing derivative) was analyzed by UV-visible spectroscopy. The absorbance was noted. Then this sample was treated with an additional 300 mg of Amberlyst-15 with an additional 1 h of shaking at room temperature. At this point, the suspension was allowed to settle and the supernatant was again analyzed by UV-visible spectroscopy. At this point, the absorbance of the supernatant was unchanged. Since there was no change in intensity of the absorbance peak for the methyl red dye, this indicated that all the excess methyl red had been removed by the Amberlyst-15. This same experiment showed that Amberlyst-15 does not absorb the methyl red-labeled poly(*N*-alkylacrylamide)s since the polymer most likely to have been absorbed by the sulfonic acid-containing resin was the smallest most polar polymer, the methyl red derivative of poly(*N*-isopropylacrylamide).

**UV-visible Analysis using the Methyl Red-Labeled Polymers 3 and 4.** The procedure for analysis of phase selective solubility of the neutral form of **3** is typical of the analysis used for either **3** or **4** with the difference being the initial solvent (90% EtOH-$H_2O$ for **3** and heptane for **4**). The dye labeled polymer **3** was first dissolved in 90% aqueous ethanol so that the methyl red concentration was around $10^{-3}$ M. Then an equal volume of heptane was added and the biphasic mixture was heated to 70 $^{o}$C. At this point a homogeneous solution formed. This solution was then cooled down to room temperature and this cooling led to phase separation. This process was completely reversible. To analyze the dye content of the respective phases, the nonpolar phase and the polar phase were separated from one another. Each phase was analyzed by UV-visible spectroscopy. The $\lambda_{max}$ of these two polymers in different solvents is given in the text and in the experimental section above. The extent of phase separation was estimated by assuming the polymer bound dye would have similar extinction coefficients in either phase.

**Fluorescence Studies using the Dansyl-Labeled Polymers 5 and 6.** The dansyl-labeled polymer **5** was first dissolved in DMF or 90% aqueous ethanol so that the dansyl label concentration was $5 \times 10^{-5}$ M. Then an equal volume of heptane was added and the biphasic mixture was heated to 70 $^{o}$C to form a homogenous solution. The solution was then cooled down to room temperature to induce phase separation. The nonpolar phase and the polar phase were separated from one another, and each phase was analyzed by fluorescence spectroscopy. Experiments using **6** were identical except that the polymer was initially dissolved in heptane and then mixed with the polar solvent. All the analyses used a $\lambda_{EX}$ of 343 nm. The $\lambda_{EM}$ values depended on the individual experiment. Experiments where **5** ended up in the EtOH-rich phase had a $\lambda_{EM}$ = 513 nm. Experiments where **5** ended up in the DMF-rich phase had a $\lambda_{EM}$ = 507 nm. Experiments where **6** ended up in the heptane-rich phase from an EtOH-$H_2O$-heptane mixture had a $\lambda_{EM}$ = 496 nm. Experiments where **6** ended up in the heptane-rich phase from an DMF-heptane mixture had a $\lambda_{Em}$ = 492 nm. Experiments where **5** ended up in the $Et_3N$ phase from a miscible $Et_3N$-$H_2O$ mixture had a $\lambda_{EM}$ = 511 nm. The extent of phase separation was estimated by assuming the polymer bound fluorophore would have equivalent intensity if it were present in either phase. In the examples studied, the fluorophore was exclusively in one phase. Estimates of the amount of fluorophore that could have been detected in the other phase were based on a series of serial dilutions of the phase that had the fluorophore. A lower limit for the extent of fluorophore was estimated based on the amount of fluorophore that was detectable in the most diluted of these samples.

**Boc protection of phenols in the normal thermomorphic system using 26 as a catalyst.** A substituted phenol and $(Boc)_2O$ were dissolved in heptane, and the catalyst **26** was dissolved in DMF or 90% aqueous ethanol. The two solutions were mixed with stirring and heated to 70 $^{o}$C to form a homogeneous solution. After 1h, the solution was cooled to room temperature to separate the heptane phase from the polar phase. The heptane solution was washed with 1N HCl, saturated $NaHCO_3$, and the solvent was removed under reduced pressure to afford the product. The polar phase can be remixed with fresh substrate-containing heptane to continue catalysis.

**Dye-labeled PNODAM-supported DAAP catalyst (70).** 4g of a 4:1 PNODAM-NASI copolymer was dissolved in chloroform. 50 mg of amine-terminated methylred in chloroform was added at room temperature and the solution was stirred overnight. 500mg of the amine-terminated DAAP catalyst in chloroform was added and stirred overnight. 1g of *N*-octadecylamine was added and the mixture stirred overnight. The product was then precipitated from methanol. UV: 419nm in heptane.

**Acylation using PNODAM – supported DAAP catalyst 70.** 1 mmol of substituted phenol, 1.02 mmol of di-*tert*-butyl dicarbonyl was dissolved in 10 mL of ethanol, and 97 mg of PNODAM – supported DAAP catalyst (1 mol%) was dissolved in heptane. The two solutions were mixed and stirred for 30 min. 1.5 mL of water was added to separate the two phases. The aq. ethanol phase were concentrated and extracted with dichloromethane to obtain the product, and the heptane phase were mixed with fresh substrate solution in ethanol for the next catalytic cycle.

**Poly(maleic anhydride-c-octadecyl vinyl ether) (PMAOVE) (71).** Maleic anhydride was recrystallized from benzene before use. In 30 mL toluene, maleic anhydride (3.3 g, 33.7 mmol) and octadecyl vinyl ether (10 g, 33.7 mmol) were combined. The reaction was evacuated and backfilled with nitrogen five times. The reaction was heated to 60 °C and benzoyl peroxide (10 mg, 0.041 mmol) was added as a solution in 2 mL of toluene. The reaction was heated for 20 h. It was then diluted with 40 mL ether and poured into 900 mL acetone to provide a white powder. The precipitate was filtered and dried (10.5g, 79%). $^1$H NMR ($CDCl_3$, $\delta$): 0.83 (t, 3 H), 1.1-1.6 (br m, 36H), 2.8-3.7 (br s, 4.5H), 3.8-4.5 (br s, 1.5 H). IR (KBr, $cm^{-1}$): IR (KBr, $cm^{-1}$): 1859, 1781, 1724, 1465.

Molecular weight of benzyl imide: Mn = 730,000; Mw = 1,950,000IR(cm-1): 1861.0, 1781.8, 1219.0.

**Dye-labeled polyMAn-alt-polyOVE (72)** 2.25g of polyMAn-alt-polyOVE was dissolved in dichloromethane. A dichloromethane solution containing 2.5 mg of the amine-terminated azo dye was added to this solution and the solution was stirred for 1h. The product was precipitated from acetone. UV: 430 nm in heptane.

**Preparation of PMAOVE-dansyl (73).** One gram of the PMAOVE was dissolved in 5 mL of ether and 7.4 mg of dansyl dissolved in 5 mL of ether was then added. This was allowed to react for 1 hour. The polymer was then precipitated out by adding the solution dropwise to acetone.

**PolyMAn-alt-polyEVE (74)** Maleic anhydride(MAn) was recrystallized from benzene, ethyl vinyl ether was distilled before use and benzoyl peroxide(BPO) was recrystallized from MeOH. 2.9g of MAn, 2.9g of ethyl vinyl ether and 10 mg of BPO was mixed with distilled toluene. The mixture was freeze-pump-thawed 3 times and heated at 60oC for 20h. The product was filtered, dissolved in acetone, and precipitated from ether. IR(cm-1): 1860.7, 1779.5, 1228.6.

**Poly(4-*tert*-butylstyrene)-co-poly(4-vinylbenzyl chloride) (10:1).** A mixture of 18.3 mL of 4-*tert*-butylstyrene, 1.4 mL of 4-vinylbenzyl chloride and 240 mg of benzoyl peroxide were dissolved in 100 mL of toluene under nitrogen, and the solution was heated at 70 $^{o}$C for 24 h. After cooling to room temperature, the solution was added dropwise to 500 mL of methanol to precipitate the product polymer. The product polymer was characterized by $^{1}$H NMR spectroscopy ($CDCl_3$) δ 7.2-6.1 (br, m, 44H), 4.6-4.4 (br, s, 2H), 2.0-1.4 (br, m, 33H), 1.2 (br, s, 90H).

**Dye-substituted styrene derivative (75).** A mixture of 1.4 mL of 4-vinylbenzyl chloride and 1.346 g of methyl red were dissolved in 5 mL of distilled DMF in the presence of 1.05 mL of triethylamine. The solution was stirred for 24 h, and then poured into 50 mL of water. The solid precipitate that formed was isolated by filtration and the product so isolated was purified by column chromatography using 4:1 (vol:vol) hexane:ethyl acetate as the eluent. The product was isolated in 94% yield. $^{1}$H NMR ($CDCl_3$): δ 8.2 (d, 8.8 Hz, 2H), 7.9 (dd, J = 8.8, 9.3 Hz, 4H), 7.4 (s, 4H), 6.8 (d, 9.3 Hz, 2H), 6.7 (dd, J = 11.0, 17.6 Hz, 1H), 5.8 (d, 17.6 Hz, 1H), 5.4 (s, 2H), 5.3 (d, 11.0 Hz, 1H), 3.1 (s, 6H). $^{13}$C NMR: δ 166.4, 156.3, 153.1, 143.9, 137.8, 136.6, 135.7, 130.9, 130.2, 128.7, 126.6, 125.7, 122.2, 114.6, 111.7, 66.8, 40.5. MS (ESI): 386 $(M + H)^+$, calcd 386.454, found 386.185.

**Dye-labeled poly(4-*tert*-butylstyrene) (76).** A mixture of 1 mL of 4-*tert*-butylstyrene, 10 mg of dye-substituted styrene and 12 mg of benzoyl peroxide were dissolved in 10 mL of toluene under nitrogen. The solution was heated at 70 °C for 24 h, cooled to room temperature, and the product polymer solution was added dropwise to 50 mL of methanol to precipitate the polymer. $^1$H NMR: δ 7.2-6.1 (br, m, 4H), 2.0-1.4 (br, m, 3H), 1.2 (bs, 9H). UV: 427 nm in heptane.

**Dye-labeled poly(4-*tert*-butylstyrene)-co-poly(4-vinylpyridine) (10:1) (77).** A mixture of 5 mL of 4-*tert*-butylstyrene, 0.3 mL of 4-vinylpyridine, 100 mg of methyl red substituted styrene and 60 mg of benzoyl peroxide were dissolved in 30 mL of toluene under nitrogen. The mixture was heated at 70 °C for 24 h. After cooling to room temperature, the solution was added dropwise to 200 mL of methanol to precipitate the product. $^1$H NMR: δ 8.3-8.0 (br, m, 4H), 7.2-6.0 (br, m, 40H), 2.0-1.4 (br, m, 33H), 1.2 (bs, 90H). UV: 427 nm in heptane.

**Dye-labeled poly(4-*tert*-butylstyrene)-co-poly(octadecyl 4-vinylpyridinium iodide) (78).** A mixture of 400 mg of (4-*tert*-butylstyrene)-co-poly(4-vinylpyridine) and 270 mg of octadecyl iodide were heated to reflux in toluene overnight. The reaction was monitored by observing the changes in the chemical shifts of the pyridine protons from 8.3-8.0 ppm to 9.0-8.6 ppm. The solvent toluene was removed under reduced pressure, and the residue was dissolved in heptane. An equal volume of DMF was added. After stirring rigorously, the mixture was allowed to separate into two phases. Most of the dye labeled polymer went into the DMF phase. DMF was removed from this phase under reduced pressure, and the residue was used for UV measurement without further purification. UV: 427 nm in DMF.

**Phosphine oxide substituted styrene derivative (79).** A mixture of 4.9 g of 4-diphenylphosphino benzoic acid and 6 mL of dicyclohexylamine were dissolved in 20 mL of DMF and heated to 70 °C for 20 min. At that point, 2.25 mL of 4-vinylbenzyl chloride was added followed by a small amount of NaI. The mixture so formed was heated overnight. After filtration to remove the solid that formed, the DMF solution of the product was poured into water and extracted with dichloromethane. A crude product was obtained after removal of the $CH_2Cl_2$ under reduced pressure. This crude product was passed through silica gel, using 1:1 hexanes:ethyl acetate as the eluent. Removal of the solvent yielded the product in 63% yield. $^1$H NMR: δ 8.2 (d, 5.9 Hz, 2H), 7.8-7.4 (m, 16H), 6.7 (dd, J= 10.7, 17.5 Hz, 1H), 5.8 (d, 17.5 Hz, 1H), 5.4 (s, 2H), 5.2 (d, 10.7 Hz, 1H). $^{13}$C NMR: δ 165.8, 136.5, 136.3, 133.4, 132.5, 132.4, 132.3, 132.2, 131.6, 129.8, 129.7, 128.9, 128.8, 126.7, 114.7, 67.1. $^{31}$P NMR ($CDCl_3$): δ 29.0. MS (ESI): 439 (M + H)$^+$, calcd 439.434, found 439.143.

**Dye-labeled poly(4-*tert*-butylstyrene) supported phosphine oxide (80).** A mixture of 5 mL of 4-*tert*-butylstyrene, 600 mg of the phoshpine oxide substituted styrene, 5.3 mg of dye substituted styrene and 63 mg of benzoyl peroxide were dissolved in 50 mL of toluene under nitrogen, then heated at 70 °C for 24 h. The solution was then cooled to room temperature, and added dropwise into 300 mL of methanol. After filtration, the solid was dried under vacuum. $^1$H NMR: δ 8.1-7.4 (m, 10H), 7.1-6.0 (m, 88H), 4.8 (bs, 2H), 2.2-1.4 (m, 63H), 1.2 (bs, 180H). $^{31}$P NMR ($CDCl_3$): δ 29.1. UV: 430 nm in heptane.

**Dye-labeled poly(4-*tert*-butylstyrene) supported phosphine catalyst (81).** A toluene solution (10 mL) containing 1 g of the polymer-supported phosphine oxide was prepared under nitrogen. Then 0.14 mL of trichlorosilane and 0.21 mL of triethylamine were added and the solution was heated at reflux overnight. The product solution was then cooled down to room temperature and poured into 100 mL of methanol. After filtration, the solid was dried under vacuum. $^1$H NMR: δ 8.1-7.4 (m, 10H), 7.2-6.0 (m, 88H), 5.0 (bs, 2H), 2.4-1.5 (m, 63H), 1.2 (bs, 180H). $^{13}$C NMR: δ 165.8, 138.3, 137.9, 137.5, 136.4, 135.2, 132.5, 132.4, 132.3, 132.2, 129.7, 128.9, 128.8, 126.7, 114.7, 67.2. $^{31}$P NMR ($CDCl_3$): δ -4.7. UV: 430 nm in heptane.

**Michael addition in a latent biphasic system.** A heptane solution of 365 mg of the polymer-supported catalyst **81** was first prepared using 10 mL of heptane. Separately, 0.18 mL of 2-nitropropane and 0.09 mL of methyl acrylate were dissolved in 10 mL of ethanol. The two solutions were then mixed and stirred for 24 h. At that point, 1.5 mL of water was then added to the homogeneous mixture to induce phase separation. The aqueous ethanol phase was concentrated under vacuum to isolate the product, and the heptane phase was mixed with fresh substrates for the next cycle.

**Dye-labeled poly(4-*tert*-butylstyrene)-supported DAAP catalyst (82).** A mixture of 6.6 mL of 4-*tert*-butylstyrene, 1 g of 1-(4-vinylbenzyl)-4-pyridylpiperazine, 50 mg of dye substituted styrene and 87 mg of benzoyl peroxide was dissolved in 50 mL of toluene under nitrogen. The mixture was heated at 70 °C for 24 h. After cooling to room temperature, the product solution was added dropwise to 300 mL of methanol to precipitate the product polymer that was characterized by NMR and UV spectroscopy. $^1$H NMR: δ 8.2 (bs, 2H), 7.2-6.1 (br, m, 86H), 3.2 (bs, 4H), 2.5 (bs, 4H), 2.0-1.4 (br, m, 63H), 1.2 (bs, 180H). UV: 425 nm in heptane.

**Acylation of phenols in a latent biphasic system.** The polymer-supported catalyst **5** (88 mg) was dissolved in 4 mL of heptane. Separately, 305 mg of 2,6-dimethylphenol and 557 mg of $Boc_2O$ were dissolved in 4 mL of ethanol. The two solutions were then mixed and stirred for 1 h. 0.6 mL of water was then added to the homogeneous mixture to induce the phase separation. The aqueous ethanol phase was concentrated under vacuum to isolate the product and the heptane phase was mixed with fresh substrates for the next cycle.

**Synthesis of poly(*N*-isopropylacrylamide) (PNIPAM) from poly(*N*-acryloxysuccinimide) (pNASI).** 1.69 g of pNASI were dissolved in DMF. 0.85 mL of isopropylamine was added to the solution. The mixture was stirred for 12 h, filtered, and added dropwise to an excess amount of ether. The precipitate was filtered, redissolved in THF and precipitated from hexanes. $^1$H NMR: δ4.0 (br, s, 1H), 2.4 – 1.4 (br, m, 3H), 1.1 (br, 6H). IR (cm$^{-1}$): 1648. $M_w = 340{,}000$, $M_n = 180{,}000$. Polydispersity 1.89.

**Synthesis of *N*, *N*-diethylacrylamide.** A solution of acryloyl chloride (4.67 mL, 0.0574 mol) in $CH_2Cl_2$ (3 mL) was added dropwise to distilled diethylamine (20.8 mL, 0.20 mol) previously dissolved in $CH_2Cl_2$ (45 mL) at 0°C under $N_2$ atmosphere. The reaction mixture was stirred for 4h, filtered, and washed with HCl, concentrated on a rotavapor, then vacuum dried. Distillation yielded the colorless oil in 75% yield. $^1$H NMR: δ6.6 (dd, 1H), 6.4 (dd, 1H), 5.6 (dd, 1H), 3.4 (q, 4H), 1.2 (q, 6H).

**Polymerization of *N*, *N*-diethylacrylamide.** *N*, *N*-Diethylacrylamide (1.27 g, 10 mmol) was added to an oven-dried, 3-neck, 50 mL flask and then condensed with 1.5 mL methanol under $N_2$. The flask was evacuated first and flushed with $N_2$ three times. Then it was placed in an oil bath and heated to 60 °C. A solution of AIBN (8 mg, 0.05 mmol) in methanol was placed in a separate vial, evacuated first and flushed with $N_2$ three times. Once the reaction was stabilized at 60 °C for an hour, the $N_2$ purged AIBN solution was added and stirred at 60 °C for 6 hours. The reaction mixture was then cooled down and 5 mL of acetone was added, then the polymer was precipitated from 50 mL of hexane. IR (cm$^{-1}$): 1631. $M_w$ = 230,000, $M_n$ = 110,000. Polydispersity 2.09.

**Measurements of lower critical solution temperature (LCST).** A temperature gradient device was fabricated using two square brass tubes (O. D. 1/8 inch, K & S Engineering, Chicago, IL) placed parallel to each other with a 3 mm gap. After applying a small amount of vacuum grease to the surface of each brass tube to ensure uniform thermal contact, a piece of borosilicate cover glass (VWR Scientific, Inc., Media, PA), working as a sample stage, was placed over these two tubes. Rectangularly shaped borosilicate capillary tubes with a high aspect ratio (100 μm × 1 mm × 2 cm) were placed parallel to the direction of the thermal gradient. The capillary tubes were sealed with vacuum grease at both ends to prevent leakage of the polymer solution inside. The temperature gradient was regulated via two water circulators (Fisher Scientific, Pittsburgh, PA) by pumping hot and cold antifreeze fluid, respectively, through the two brass tubes. The temperature gradient device was placed under a dark field condenser of an inverted microscopy (Nikon, Eclipse TE 2000-U) and dark field images of capillary tubes containing various polymer solutions at different temperatures were recorded using a CCD camera. Each CCD image can fit 6 capillary tubes under a 2× objective. Two capillary tubes containing 10 mg/ml PNIPAM in DI water (LCST 30.5°C) and 10 mg/ml PNIPAM in 0.7 M KCl solution (LCST 26.3 °C), respectively, served as internal standards.

**Differential scanning calorimetry (DSC) measurements.** PNIPAM and poly-(*N,N*-diethylacrylamide) (PDEAM) polymers were dissolved separately in DI water to a concentration of 10 mg/ml. DSC was performed immediately after mixing of these two polymer solutions to a desired molar ratio. The DSC scanning range was set from 20.00 °C to 45.00 °C and the scan rate was 5.00 °C/min. The DSC data were analyzed using Thermal Analysis Instrument Control and Data Analysis: Pyris Thermal Analysis System Version 3.70. The initial onset point of the heat flow curve was used as the nascent LCST of the polymer mixture, which is plotted in Figure 28. The solid line represents a fit to the data. The enthalpy change versus molar fraction of PNIPAM in PNIPAM/PDEAM mixtures is plotted in Figure 29.

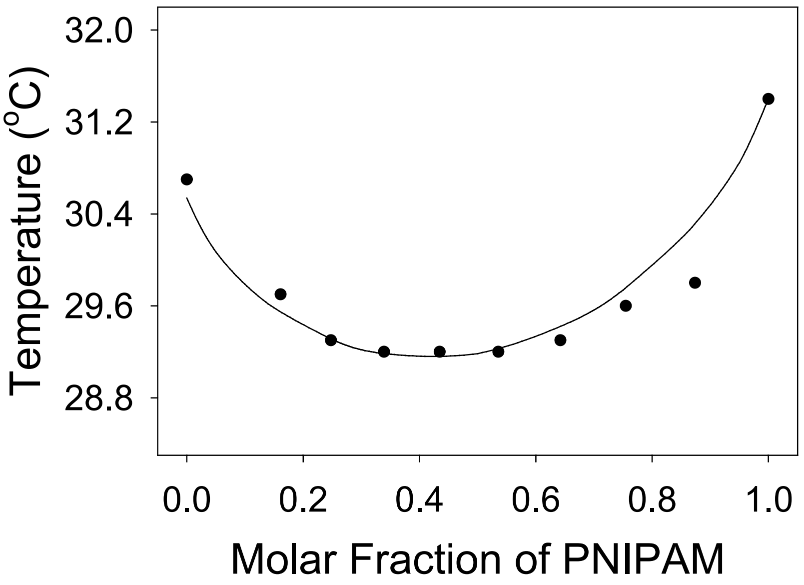


Figure. 28 Onset temperature for phase transition measurements made by differential scanning calorimetry

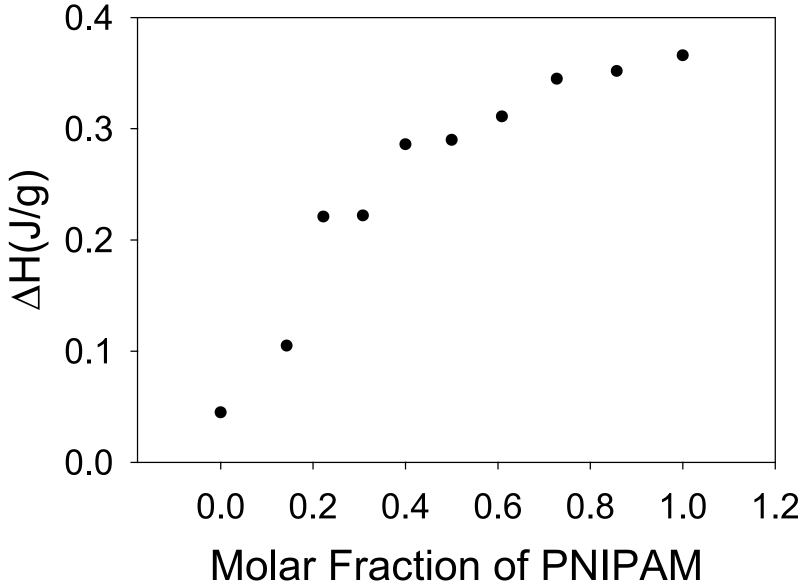


Figure 29 The enthalpy change vs. molar fraction of PNIPAM in PNIPAM/PDEAM mixtures.

**Synthesis of homo- and co-polymers of acrylamides 83-87 from poly(*N*-acryloxysuccinimide) (pNASI).** 0.1 g of pNASI were dissolved in 1 mL of DMF. A mixture of propylamine and isopropylamine (3 mmol total) in 1 mL DMF (feeding ratio: 1:0 for **83**, 2:1 for **84**, 2:3 for **85**, 1:4 for **86** and 0:1 for **87**) were added to the pNASI solution and the mixture was stirred for 12 h. After filtration, the filtrate was added dropwise to a 20 mL of diethylether. The precipitate was filtered, redissolved in 1 mL of THF and precipitated from 10 mL of hexanes.

**Fabrication of temperature gradient device**. Briefly, two 1/8th inch wide hollow square brass tubes (K&S Engineering, Chicago, IL) were laid in parallel and separated by 3 mm stints made of glass slides. The two brass tubes were then fixed into position using clamps and put under a darkfield condenser in an inverted microscope

(Nikon, Eclipse TE 2000-U). To establish the temperature gradient, hot and cold antifreeze solutions were circulated through individual brass tubes separately using standard waterbath circulators (Fisher Scientific, Pittsburgh, PA). A coverglass was laid on top of two brass tubes by applying vacuum grease and the linear tempearture gradient was confirmed by taking temperature measurements at various points perpendicular to the copper tubes.

**LCST measurement of thermoresponsive polymers.** To measure the LCSTs of thermoresponsive polymers, rectangularly shaped borosilicate capillary tubes (Vitrocom, Mountain Lakes, NJ) with a high aspect ratio (100 μm × 1 mm × 2cm) were used as sample containers. Polymer solutions were introduced into the tubes through capillary action and they were subsequently sealed with vacuum grease before being laid parallel to the temperature gradient. Polymer clouding was imaged using a CCD camera through a darkfield condenser. Two standard polymer solutions, PNIPAM 10mg/mL (LCST 30.2 °C) and PNIPAM 10mg/mL mixed with 0.7 M KCl (LCST 26.0 °C) were used as internal temperature standards to determine the temperature gradient for every experiment. Clouding curves of polymers were plotted from linescans of scattering intensity drawn along the temperature gradient where pixel positions were converted to temperatures according to the gradient obtained in the reference samples. The LCST was defined as the midpoint of in the clouding curve.

# REFERENCE

[1] Kobayashi, S. *Chem. Soc. Rev.***1999,** *28,* 1.

[2] Kobayashi, S. *Curr. Opin. Chem.. Biol.* **2000,** *4,* 338.

[3] Adams, B. A.; Holmes, E. L. *J. Soc. Chem. Ind.* **1935,** *54,* 1.

[4] Helfferich, F. *Ion Exchange*; McGraw Hill: New York, 1962.

[5] Wheaton, R. M.; Bauman, W. C. *Ind. Eng. Chem.* **1951,** *43,* 1088.

[6] McBurney, C. H. *US Patents* **1952**, 2,591,573 and 2,591,574.

[7] Merrifield, R. B. *J. Am. Chem. Soc.* **1963,** *85,* 2149.

[8] Merrifield, R. B. *Science* **1965,** *150,* 178.

[9] Merrifield, R. B.; Steward, J. M. *Nature* **1965,** *207,* 522.

[10] Sheppard, R. C. *Chem. Br.* **1988,** *24,* 557.

[11] Sheppard, R. C. *Chem. Br.* **1983,** *19,* 402.

[12] Letsinger, R. L.; Kornet, M. J.; Mahadevan, V.; Jerina, D. M. *J. Am. Chem. Soc.* **1964,** *86,* 5163.

[13] Frechet, J. M. , Schuerch, C. *J. Am. Chem. Soc.* **1971,** *93,* 492.

[14] Guthrie, R. D.; Jenkins, A. D.; Stehlicek, J *J. Chem. Soc., Ser. C* **1971,** 2690.

[15] Excoffier, G.; Gagnaire, D.; Utille, J. P.; Vgnon, M. *Tetrahedron Lett.* **1972,** *50,* 5065.

[16] Zehavi, U., Patchornik, A. *J. Am. Chem. Soc.* **1973,** *95,* 5673.

[17] Weinshenker, N. M.; Shen, C. M. *Tetrahedron Lett.* **1972,** *32,* 3285.

[18] Atherton, E.; Clive, D. L. J.; Sheppard, R. C. *J. Am. Chem. Soc.* **1975,** *97,* 6584.

[19] Atherton, E.; Brown, E.; Sheppard, R. C.; Rosevear, A. *J. Chem. Soc. Chem. Commun.* **1981,** 1151.

[20] Goddard, P.; McMurry, J. S.; Sheppard, R. C.; Emson, P. *J. Chem. Soc. Chem. Commun.* **1988,** *15,* 1025.

[21] Sparrow, J. T.; Knieb-Cordonier, N. G.; Obeyseskere, N. U.; McMurray, J. S. *Pep. Res.* **1996,** *9,* 297.

[22] Adams, S. P.; Kavka, K. S.; Wykes, E. J.; Holder, S. B.; Galluppi, G. R. *J. Am. Chem. Soc.* **1983,** *105,* 661.

[23] Rinnova, M.; Jezek, J.; Malon, P.; Lebl, M. *Pept. Res.* **1993,** *6,* 88.

[24] Eichler, J.; Houghten, R. A. *Biochemistry* **1993,** *32,* 11035.

[25] Schwabacher, A. W.; Shen, Y.; Johnson, C. W. *J. Am. Chem. Soc.* **1999,** *121,* 8669.

[26] Lehr, B.; Egelhaaf, H. –J.; Fritz, H.; Rapp, W.; Bayer, E.; Oelkrug, D. *Macromolecules* **1996,** *29,* 7931.

[27] Hudson, D. *J. Combinatorial Chem.* **1999,** *1,* 333.

[28] Bayer, E.; Rapp, W. *Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications*; Plenum Press: New York, 1992; 325.

[29] Gooding, O. W.; Baudart, S.; Deegan, T. L.; Heisler, K.; Labadie, J. W,; Newcomb, W. S.; Porco, J. A., Jr.; van Eikeren, P. *J. Comb. Chem.* **1999,** *1,* 113.

[30] Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998,** *63,* 2800.

[31] Porco, J. A., Jr.; Deegan, T. L.; Devonport, W.; Gooding, O. W.; Labadie, J. W.; MacDonald, A. A.; Newcomb, W. S.; van Eikeren, P. *Drugs Future* **1998,** *23,* 71.

[32] Dankwardt, S. M.; Smith, D. B.; Porco, J. A., Jr.; Nguyen, C. H. *Synlett* **1997,** 854.

[33] Swayze, E. E. *Tetrahedron Lett.* **1997,** *38,* 8465.

[34] Swayze, E. E. *Tetrahedron Lett.* **1997,** *38,* 8643.

[35] Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997,** *62,* 7820.

[36] Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998,** *63,* 196.

[37] Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997,** *62,* 5678.

[38] Bergbreiter, D. E.; Osburn, P. L.; Li, C. *Organic Lett.* **2002,** *4,* 737.

[39] Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. *J. Am. Chem. Soc.* **1999,** *121*, 9531.

[40] Bergbreiter, D. E. ; Osburn, P. L.; Frels, J. D. *J. Am. Chem. Soc.* **2001***, 123,* 11105**.**

[41] Bergbreiter, D. E.; Chandran, R. *J. Am. Chem. Soc.* **1987,** *109,* 174.

[42] Cole-Hamilton, D. J. *Science* **2003,** *299,* 1702.

[43] Gupta, M. N.; Mattiasson, B. *Highly Selective Separations in Biotechnology*; Blackie Academic & Professional: Glasgow, UK, 1994**,** 7.

[44] Karakhanov, E. A.; Runova, E. A.; Berezkin, G. V.; Neimerovets, E. B. *Macromol. Symp.* **1994,** *80,* 231.

[45] Bergbreiter, D. E.; Weatherford, D. A. *J. Org. Chem.* **1989,** *54,* 2726.

[46] Bergbreiter, D. E.; Chandran, R. *J. Org. Chem.* **1986,** *51,* 4754.

[47] Bergbreiter, D. E.; Chandran, R. *J. Am. Chem. Soc.* **1985,** *107,* 4792.

[48] Taylor, L. D.; Cerankowski, L. D. *J. Polym. Sci., Polym. Chem. Ed.* **1975,** *13,* 2551.

[49] Bovey, R. A.; Winslow, F. H., Eds. *Macromolecules-An Introduction to Polymer Science*; Academic Press: New York, 1979, 295.

[50] Bergbreiter, D. E.; Case, B.; Liu, Y.-S.; Caraway, J. W. *Macromolecules* **1998,** *31,* 6053.

[51] Bergbreiter, D. E.; Zhang, L.; Mariagnanam, V. M. *J. Am. Chem. Soc.* **1993,** *115,* 9295.

[52] Bergbreiter, D. E.; Mariagnanam, V. M.; Zhang, L. *Adv. Mater.* **1995,** *7,* 69.

[53] Bergbreiter, D. E.; Caraway, J. W. *J. Am. Chem. Soc.***1996,** *118,* 6092.

[54] Galaev, I. Y.; Mattiasson, B. *Enzyme Microb. Technol.* **1993,** *15*, 354.

[55] Bergbreiter, D. E.; Liu, Y.-S. *Tetrahedron Lett.* **1997,** *38,* 7843.

[56] Huang, X.; Witte, K. L.; Bergbretier, D. E.; Wong, C.-H. *Adv. Synth. Catal.* **2001,** *343,* 675.

[57] Hoshino, K.; Taniguchi, M.; Kawaberi, H.; Takeda, Y.; Morohashi, S.; Sasakura, T. *J. Ferment. Bioeng.* **1997,** *83,* 246.

[58] Arica, M. Y.; Oktem, H. A.; Oktem, Z.; Tuncel, S. A. *Polymer International* **1999,** *48,* 879.

[59] For detail about applications of PNIPAM in industry, see http://www.polium.com/

[60] Galaev, I. Y.; Gupta, M. N.; Mattiasson, B. *Chemtech* **1996,** *26,* 19.

[61] Cong, L.; Kaul, R.; Dissing, U.; Mattiasson, B. *J. Biotechnol.* **1995,** *42,* 75.

[62] Chen, J. P.; Chang, K. C. *J. Chem. Technol. Biotechnol.* **1994,** *60,* 133.

[63] Hoshino, K.; Taniguchi, M.; Ueoka, H.; Ohkuwa, M.; Chida, C.; Morohashi, S.; Sasakura, T. *J. Ferment. Bioeng.* **1997,** *82,* 253.

[64] Yuk, S. H.; Cho, S. H.; Lee, S. H. *Macromolecules* **1997,** *30,* 6856.

[65] Bayer, E.; Schurig, V. *Angewandte Chem. , Int. Ed. Engl.* **1975,** *14,* 493.

[66] van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev.* **2002,** *102,* 3717.

[67] Bolm, C.; Dinter, C. L.; Seger, A.; Hocker, H.; Brozio, J. *J. Org. Chem.* **1999,** *64,* 5730.

[68] Schwab, E.; Mecking, S. *Organometallics* **2001,** *20,* 5504.

[69] Giffels, G.; Beliczey, J.; Felder, M.; Kragl, U. *Tetrahedron: Asymmetry* ***1998,*** *9,* 691.

[70] Laue, S.; Greiner, L.; Woltinger, J.; Liese, A. *Adv. Synth. Catal.* **2001,** *343,* 711.

[71] Chen, J.; Alper, H. *J. Am. Chem. Soc.* **1997,** *119,* 893.

[72] Zheng, X.; Jiang, J.; Liu, X.; Jin, Z. *Catal. Today* **1998,** *44,* 175.

[73] Chen, R.; Liu, X.; Jin, Z. *J. Organomet. Chem.* **1998,** *571,* 201.

[74] Horvath, I. T. *Acc. Chem. Res.* **1998,** *31,* 641.

[75] De Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rec.* **1999,** *28,* 37.

[76] Bergbreiter, D. E.; Franchina, J. G. *Chem. Commun.* **1997,** *16,* 1531.

[77] Bergbreiter, D. E.; Franchina, J. G.; Case, B. L.; *Org. Lett.* **2000,** *2,* 393.

[78] Kani, I.; Omary, M. A.; Rawashdeh-Omary, M. A.; Lopez-Castillo, Z. K.; Flores, R.; Akgerman, A.; Fackler, J. P., Jr. *Tetrahedron* **2002,** *58,* 3923.

[79] Wende, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2003,** *125,* 5861.

[80] Bergbreiter, D. E.; Liu, Y.-S.; Osburn, P. L. *J. Am. Chem. Soc.* **1998,** *120,* 4250.

[81] Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000,** *122,* 9058.

[82] Keim W. *Green Chemistry* **2003,** *5,* 105.

[83] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000,** *122,* 8168.

[84] Kim, R. M.; Manna, M.; Hutchins, S. M. ; Griffin, P. R.; Yates, N. A.; Bernick, A. M.; Champman, K. T. *Proc. Natl. Acad. Sci. U.S.A.* **1996,** *93,* 10012.

[85] De Groot, D.; de Waal, B. F. M.; Reek, J. N. H.; Schenning, A. P. H. J.; Kamer, P. C. J.; Meijer, E. W.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2001,** *123,* 8453.

[86] Shemyakin, M. M.; Ovchinnikov, Y. A.; Kivyushkin, a. A.; Kozhevnikoya, I. V. *Tetrahedron Lett.* **1965,** *6,* 2323.

[87] Maher, J. J.; Furey, M. E.; Greenberg, L. J. *Tetrahedron Lett.* **1971,** *12,* 27.

[88] Narita, M.; hirta, M.; Kusano, K.; Itsuno, S.-I.; Ue, M.; Okawara, M. *Pept. Chem.* **1980,** *17,* 107.

[89] Evans, G. O.; Pittman, C. U., Jr.; McMillan, R.; Beach, R. T.; Jones, R. *J. Organomet. Chem.* **1974,** *67,* 295.

[90] Steglich, W.; Hoefle, G. *Angew. Chem., Int. Ed. Engl.* **1969,** *8,* 981.

[91] Hoefle, G.; Steglish, W.; Vorbrueggen, H. *Angew. Chem. Int. Ed. Engl.* **1978,** *17,* 569.

[92] Scriven, E. F. V. *Chem. Soc. Rev.* **1983,** *12,*129.

[93] Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979,** 99.

[94] Kellner, H. A.; Schneiderwind, R. G. K.; Eckert, H.; Ugi, I. K. *Angew. Chem., Int. Ed. Engl.* **1981,** *20,* 577.

[95] Kirichenko, A. I.; Litvinenko, L. M.; Dotsenko, I. N.; Kotenko, N. G.; Nikkel'sen, E.; Berestetskaya, V. D. *Dokl. Akad. Nauk. SSSR, Ser. Khim.* **1979,** *244,* 1125; *Chem. Abstr.* **1979,** *90,* 601.

[96] Guendouz, F.; Jacquier, R.; Verducci, J. *Tetrahedron* **1988,** *44,* 7095.

[97] Tomoi, M.; Akada, Y.; Kakiuchi, H. *Makromol. Chem., Rapid Comm.* **1982,** *3,* 537.

[98] Shinkai, S.; Tsuji, H.; Hara, Y.; Manabe, O. *Bull. Chem. Soc. Japan* **1981,** *54,* 631.

[99] Storck, W.; Manecke, G. *J. Mol. Catal.* **1985,** *30,* 145.

[100] Koning, C. E.; Eshuis, J. J. W.; Viersen, F. J.; Challa, G. *Reactive Polymers* **1986,** *4,* 293.

[101] Tomoi, M.; Goto, M.; Kakiushi, H. *J. Polym. Sci. Part A, Polym. Chem.* **1987,** *25,* 77.

[102] Deratani, A.; Darling, G. D.; Frechet, J. M. J. *Polymer* **1987,** *28,* 825.

[103] Deratani, A.; Darling, G. D.; Horak, D.; Frechet, J. M. J. *Macromolecules* **1987,** *20,* 767.

[104] Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978,** *34,* 2069.

[105] Hierl, M. A.; Gamson, E. P.; Klotz, I. M. *J. Am. Chem. Soc.* **1979,** *101,* 6020.

[106] Delaney, E. J.; Wood, L. E.; Klotz, I. M. *J. Am. Chem. Soc.* **1982,** *104,* 799.

[107] Menger, F. M.; McCann, D. J. *J. Org. Chem.* **1985,** *50,* 3928.

[108] Inoue, K.; Nishikawa, Y.; Tanigaki, T. *J. Am. Chem. Soc.* **1991,** *113,* 7609.

[109] Hansen M. M., Riggs, J. R. *Tetrahedron Letters* **1998**, 39, 2705.

[110] Fan, Q.-H.; Deng, G.-J.; Lin, C.-C.; Chan, A. S. C. *Tetrahedron Asymmetry* **2001,** *12,* 1241.

[111] Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996,** *118,* 7632.

[112] Han, H.; Janda, K. D. *Tetrahedron Lett.* **1997,** *38,* 1527.

[113] Han, H.; Janda, K. D. *Angew. Chem., Int. Ed. Engl.* **1997,** *36,* 1731.

[114] Bolm, C.; Gerlach, A. *Angew. Chem., Int. Ed. Engl.* **1997,** *36,* 741.

[115] Kuang, Y.-Q.; Zhang, S.-Y.; Wei, L.-L. *Tetrahedron Lett.* **2001,** *42,* 5925.

[116] Kimura, Y.; Regen, S. L. *J. Org. Chem..* **1982,** *47,* 2493.

[117] Grinberg, S.; Shaubi, E. *Tetrahedron* **1991,** *47,* 2895.

[118] Grinberg, S.; Kas'yanov, V.; Srinivas, B. *React. Funct. Polym.* **1997,** *34,* 53.

[119] Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Org. Lett.* **2000,** *2,* 1737.

[120] Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000,** *122,* 6929.

[121] Flood, R. W.; Geller, T. P.; Petty, S. A.; Roberts, S. M.; Skidmore, J.; Volk, M. *Org. Lett.* **2001,** *3,* 683.

[122] Glos, M.; Reiser, O. *Org. Lett.* **2000,** *2,* 2045.

[123] Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. *J. Org. Chem.* **2001,** *66,* 3160.

[124] Yao, Q. *Angew. Chem., Int. Ed. Engl.* **2000,** *39,* 3896.

[125] Benaglia, M.; Celentano, G.; Cozzi, F. *Adv. Synth. Catal.* **2001,** *343,* 171.

[126] Bayer, E.; Mutter, M. *Nature* **1972,** *237,* 512.

[127] Pillai, V. N. R.; Mutter, M.; Bayer, E.; Gatfield, I. *J. Org. Chem.* **1980,** *45,* 5364.

[128] Bonora, G. M.; Scremin, C. L.; Colonna, F. P.; Garbesi, A. *Nucleic Acids Res.* **1990,** *18,* 3155.

[129] Chiu, S.-H. L.; Anderson, L. *Carbohydr. Res.* **1976,** *50,* 227.

[130] Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1991,** *113,* 5095.

[131] Verduyn, R.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas.* **1993,** *112,* 464.

[132] Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1995,** *117,* 2116.

[133] Bueckmann, A. F.; Morr, M.; Johansson, G. *Makromol. Chem.* **1981,** *182,* 1379.

[134] Ohno, H.; Sakai, T.; Tsuchida, E.; Honda, K.; Sasakawa, S. *Biochem. Biophs. Res. Commun.* **1981,** *102,* 426.

[135] Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119,* 11687.

[136] Kiewel, K.; Liu, Y.; Bergbreiter, D. E.; Sulikowski, G. A. *Tetrahedron Lett.* **1999,** *40,* 8945.

[137] Liu, Y.-S. The use of soluble polymer-supports in catalysis and synthesis, Ph.D. Dissertation, Texas A&M University, College Station, TX, December 1998.

[138] Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117,* 9075.

[139] McKinstry L.; Livinghouse T. *Tetrahedron* **1995**, *51,* 7655.

[140] Carboni B.; Monnier L. *Tetrahedron* **1999**, *55,* 1197.

[141] Mammen, M.; Dahmann, G.; Whitesides, G. M. *J. Med. Chem.* **1995,** *38,* 4179.

[142] Balavoine, G.; Clinet, J. C.; Zerbib, P.; Boubekeur, K. *J. Organomet. Chem.* **1990,** *389,* 259.

[143] Ohff, M.; Ohff, A.; Milstein, D. *Chem. Comm.* **1999**, *4,* 357.

[144] Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chemical Reviews* **2002**, *102*, 1359.

[145] Luo, F.-T.; Jeevanandam, A.; Basu, M. K. *Tetrahedron Lett.* **1998,** *39,* 7939.

[146] Martell, A. E.; Motekaitis, R. J. *The Determination and Use of Stability Constants,* 2nd ed.; VCH Publishers: New York, 1992, 171.

[147] Winnik, F. M. *Macromolecules* **1990,** *23,* 233.

[148] Pollak, A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976,** *98,* 289.

[149] Taylor, L. D.; Cerankowski, L. D. *J. Polym. Sci., Polym. Chem. Ed.* **1975,** *13,* 2551.

[150] Schild, H. G. *Prog. Polym. Sci.* **1972,** *17,* 163.

[151] Mao, H.; Li, C.; Zhang, Y.; Bergbreiter, D. E.; Cremer, P. S. *J. Am. Chem. Soc.* **2003,** *125,* 2850.

[152] Stevens, M. P. *Polymer Chemistry, An Introduction*; Oxford University Press: New York, 1999, 38.

[153] Batz, H. G.; Franzmann, G.; Ringsdorf, H. *Angew. Chem., Int. Ed. Engl.* **1972,** *11,* 1103.

[154] Liu, Y.-S.; Zhao, C.; Berbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998,** *63,* 3471.

[155] We are grateful to our colleague, Professor Paul Cremer, who brought these thermomorphic systems that have an LCST to our attention.

[156] Argyropoulos, J. N.; Kanel, J. S.; Tulchinsky, M. L.; Miller, D. J.; Morrison, D. L.; Foley, P.; Bryant, D. R. Metal-ligand complex catalyzed hydroformylation processes, separation of products from catalyst residues, and derivatization of products. *US Patent* 6307108, **2001**.

[157] Abatjoglou, A. G.; Peterson, R. R.; Bryant, D. R. *Chem. Ind.* **1996,** *68,* 133.

[158] Deng, G. –J.; Fan, Q. –H.; Chen, X. –M.; Liu, D. S.; Chan, A. S. C. *Chem. Commun.* **2002**, *15,* 1570.

[159] Scurto, A. M.; Aki, S. N. V. K.; Brennecke, J. F. *J. Am. Chem. Soc.* **2002,** *124,* 10276.

[160] Pollak, A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 289.

[161] Bergbreiter, D. E.; Osburn, P. L.; Smith, T.; Li, C.; Frels, J. D. *J. Am. Chem. Soc.* **2003,** *125,* 6254.

[162] White, D. A.; Baizer, M. M. *Tetrahedron Letter* **1973**, *37*, 3597.

[163] Hubbell, J. A. *Curr. Op. Biotech.* **1999,** *10,* 123.

[164] Sakiyama-Elbert, S. E.; Hubbell, J. A. *Annu. Rev. Mater. Res.* **2001,** *31,* 183.

[165] Langer, R. *Nature* **1998,** *392,* 5.

[166] Kanazawa, H.; Matsushima, Y.; Okano, T. *Adv. Chromatogr.* **2001,** *41,* 311.

[167] Liu., H. Y.; Zhu, X. X. *Polymer Preprints* **2000,** *41,* 998.

[168] Fujishige, S.; Kubota, K.; Ando, I. *J. Phys. Chem.* **1989,** *93,* 3311.

[169] Schild, H. G.; Tirrell, D. A. *J. Phys. Chem.* **1990,** *94,* 4352.

[170] Heskins, M.; Guillet, J. E. *J. Macromol. Sci. Chem.* **1968,** *A2(8)*, 1441.

[171] Kubota, K.; Fujishige, S.; Ando, I. *Polymer J.* **1990,** *22,* 15.

[172] Cole, C.; Schreiner, S. M.; Priest, J. H.; Monji, N.; Hoffman, A. S. *Am. Chem.. Soc. Symp. Ser.* **1987,** *350,* 245.

[173] Kubota, K.; Fujishige, S.; Ando, I. *J. Phys. Chem.* **1990,** *94,* 5154.

[174] Snyder, W. D.; Klotz, I. M. *J. Am. Chem. Soc.* **1975,** *97,* 4999.

[175] Scarpa, J. S.; Mueller, D. D.; Klotz, I. M. *J. Am. Chem. Soc.* **1967,** *89,* 6024.

[176] Gundlach, D. P.; Burdett, K. A. *J. Appl. Polym. Sci.* **1994,** *51,* 731.

[177] Mao, H.; Holden, M. A.; You, M.; Cremer, P. S. *Anal. Chem.* **2002**, *74*, 5071.

[178] Mao, H.; Yang, T.; Cremer, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4432.

[179] McDevit, W. F.; Long, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 1773.

[180] Janado, M.; Yano, Y.; Doi, Y.; Sakamoto, H. *J. Sol. Chem.* **1983**, *12*, 741.

[181] von Hippel, P. H.; Schleich, T. *Accounts Chem. Res.* **1969**, *2*, 257.

[182] Wang, X. H.; Wu, C. *Macromolecules* **1999,** *32*, 4299.

[183] Kujawa, P.; Winnik, F. W. *Macromolecules* **2001**, *34*, 4130.

[184] Forster, T. *Discuss. Faraday Soc.* **1959,** *27,* 7.

[185] Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*; Plenum: New York, 1983, Chapter10.

[186] Winnik, F. M. *Polymer* **1990,** *31,* 2125.

# VITA

Chunmei Li obtained her Bachelor of engineering degree in Chemical Engineering from Dalian University of Technology, P. R. China in 1998 and came to the Chemistry Department of Texas A&M. She joined Prof. Bergbreiter's group in November, 1998. She received a Ph.D. degree in August, 2003. Her permanent address is: 6#59, Wenming St., Hailun, Heilongjiang Province, 152300, P. R. China.