PHASE SELECTIVELY SOLUBLE POLYMER SUPPORTS TO FACILITATE HOMOGENEOUS CATALYSIS

A Dissertation

by

DENISSE ORTIZ-ACOSTA

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

December 2007

Major Subject: Chemistry

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Approved by:

Chair of Committee,	David E. Bergbreiter
Committee Members,	Daniel A. Singleton
	Eric Simanek
	Daniel Shantz
Head of Department,	David H. Russell

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ABSTRACT

Phase Selectively Soluble Polymer Supports to Facilitate Homogeneous Catalysis.

(December 2007)

Denisse Ortiz-Acosta, B.S., University of Puerto Rico at Rio Piedras

Chair of Advisory Committee: Dr. David E. Bergbreiter

Soluble polymers that have phase selective solubility are useful in synthesis because they simplify purification and separation. Such selectively soluble polymers simplify catalyst, reagent, and product recovery and enable the use of Green chemistry principles in homogeneous catalysis. However, while homopolymers have been reported that have excellent thermal and phase-dependent solubility, less is known about copolymers. Also, less is known about the phase selective solubility of polar aprotic *N*,*N*-dialkyl polyacrylamides. This work describes a library synthesis of dye-labeled poly(*N*-*n*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers and study of the effects of polymer composition in phase selective solubility of these copolymers. To study the relative importance of *n*-octadecyl versus *n*-butyl groups, copolymers with different ratios of *n*-octadecylacrylamide and *n*-butylacrylamide but with similar degrees of polymerization and polydispersity were prepared by a split-pool synthesis using a highly soluble poly(*N*-acryloxy-2-dodecylsuccinimide) as the precursor. Polymer sequestrants were used to remove excess amines and the byproduct *N*-hydroxyl-2-dodecylsuccinimide without fractionation of the polyacrylamides. Results demonstrated

that poly(*N*-*n*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers' phase selective solubility is equally dependant of the polar *n*-butyl and nonpolar *n*-octadecyl groups on the copolymers.

Dye-labeled poly(*N*,*N*-dialkylacrylamide)s prepared by the polymerization of *N*,*N*-dialkylacrylamides monomers with methyl, ethyl, propyl, butyl, hexyl, and dodecyl *N*-alkyl groups in a variety of thermomorphic or latent biphasic polar/nonpolar solvent mixtures were also prepared. Studies showed that poly(*N*,*N*-dialkylacrylamide)s have phase selective solubility that is highly dependent of the size of the *N*-alkyl group.

Soluble polymers are known to be useful supports for catalysts. This thesis also describes approaches to immobilization of a variety of catalysts on polyisobutylene (PIB). The most effective of these catalysts were analogs of pyridyl *N*-oxides that have been used as organocatalysts for the catalytic allylation of a variety of aromatic aldehydes. PIB-supported *N*-oxide promoted the allylation of aldehydes in up to 99% isolated yield. The products were isolated in the polar phase of a thermomorphic system and the catalyst was recycled through five cycles.

DEDICATION

To my mother, my grandmother, and my grandfather for always being there unconditionally. To Ricardo, my husband and the love of my life.

ACKNOWLEDGMENTS

I would like to start thanking Dr. Elba Reyes for her advice when I was a freshman and for her support and for strongly believing in me. I sincerely thank Dr. Ingrid Montes for being such a great teacher and friend, for listening to me, and for all her support. I would also like to thank Dr. Néstor M. Carballeira for giving me the opportunity to work in his research lab, for teaching me the great value of chemistry, for his guidance, his patience, and for caring about me. I also thank Dr. Mayra Pagán, my mentor, for teaching me laboratory techniques.

I would like to give my deepest thanks to Professor David E. Bergbreiter for giving me the opportunity to work in his research lab, for being a great mentor, for his guidance, his help, and his support. I will always remember him for his love of chemistry and teaching, which is always well appreciated.

I would like to express my gratitude to the members of Bergbreiter's group, especially Patrick, Film, Tian, and Shawn for their friendship and long discussions, both chemical and casual. I give special thanks to Film for giving us shelter during the last month at College Station. I would also like to thank Nydea Avilés-Ramos, with whom I worked during a summer, for letting me teach her about chemistry and for being such a good friend.

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CHAPTER I

INTRODUCTION

Homogeneous catalysis has gained more importance over the last decades. Homogeneous catalysts offer excellent activity and selectivity, and they often allow the use of mild reaction conditions. However, the metals used in the catalytic reactions most popular in organic synthesis like palladium, rhodium, and platinum are generally very expensive. The organic ligands that tailor a catalysts' selectivity or activity may be equally costly. In addition to metal and ligand costs, metal and ligand contamination in a product may be undesirable on environmental or toxicological grounds. Also, while organocatalysts avoid the toxicity of metals, the synthesis of complex non-metal, organocatalysts can be very expensive too. As a result, there has been a broad effort for over 40 years to develop procedures that enable the recovery and recycling of homogeneous catalysts including both organometallic and organic catalysts.

One of the earliest strategies developed to address the problem of catalyst recovery and separation from products was to attach the catalyst to a polymer support. The idea behind this work stemmed from earlier work where insoluble supports were used first in peptide synthesis and later in organic synthesis.[1, 2] The use of polymer supports in synthesis was first introduced by the Nobel Laureate, Robert Bruce Merrifield. Merrifield's goal was to develop a more efficient synthesis procedure to

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

prepare peptides.[3] Merrifield's idea was that if a growing chain is attached to a solid support at all stages of the synthesis, the product will be insoluble in the reaction solution and will therefore be easier to purify because it can be separated from excess reagents and byproducts by a simple filtration and washing. Merrifield described the solid phase synthesis strategy as having both the advantages of simplification and acceleration of multistep synthesis. As he noted, it avoids large losses of product encountered during the isolation and purification of the product, and as a result lead to higher yields of products. It also has specific advantages in peptide synthesis as it increases solvation and decreases aggregation of the intermediates during the reaction.

Merrifield showed beginning in the 1960s that insoluble, cross-linked polymers facilitated the purification and separations steps that occur in peptide synthesis. Since those early papers describing insoluble polymer supports by Merrifield, solid phase synthesis has become a significant area in organic chemistry. The success of Merrifield's approach now is no longer limited to the synthesis of biological molecules. Indeed, the use of solid phase polymer supports has evolved to a point where they are not only used for peptide synthesis, but they are also used in routine synthesis of more common organic molecules in areas like combinatorial chemistry or drug discovery.

The insoluble polymer support most commonly used for synthesis is divinylbenzene- crosslinked polystyrene. This type of support is also known as Merrifield resin. As noted above, a vast area of research has been developed around the use of insoluble polymeric materials as supports for products, reagents and sequestrants. The main advantage of solid phase polymer supports in each of these areas is the

support's insolubility. In the case of product synthesis, the advantage is the ease of product separation and recycling. In a typical solid phase synthesis, only a simple filtration is needed to isolate the polymer-bound product. Then, the product can be cleaved from the resin, and the resin can be washed for further purification. Generally, pure products are obtained when using this type of systems.

Ley and coworkers' research is an example of the impact solid phase supports have had in synthesis. Their work often involves using new immobilized reagents and scavengers to facilitate the clean synthesis of drugs and other complex natural products in multistep sequences.[4] This strategy avoids using conventional purification techniques, such as extraction, crystallization, distillation, and chromatography. Figure 1 shows the concept behind the use of insoluble polymer supported reagents and scavengers. First, the reaction is performed in the presence of the solid phase reagent with excess of a reactant. Then, the excess of reactants and byproduct can be scavenged by the subsequent treatment with the appropriate sequestrating resin.

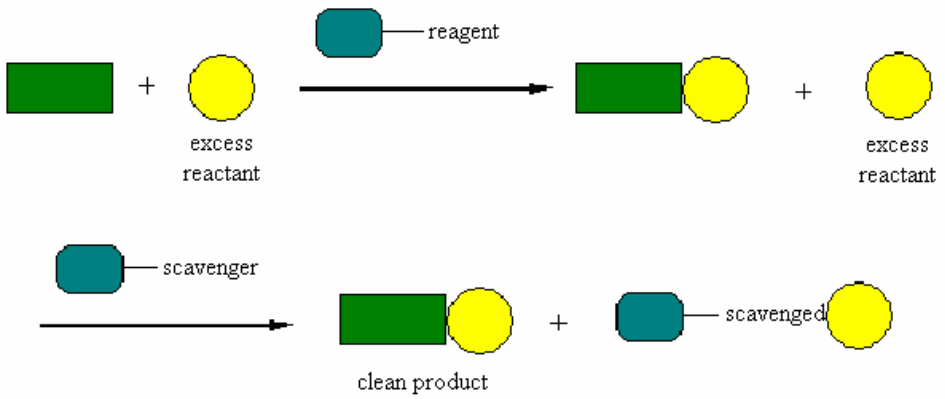
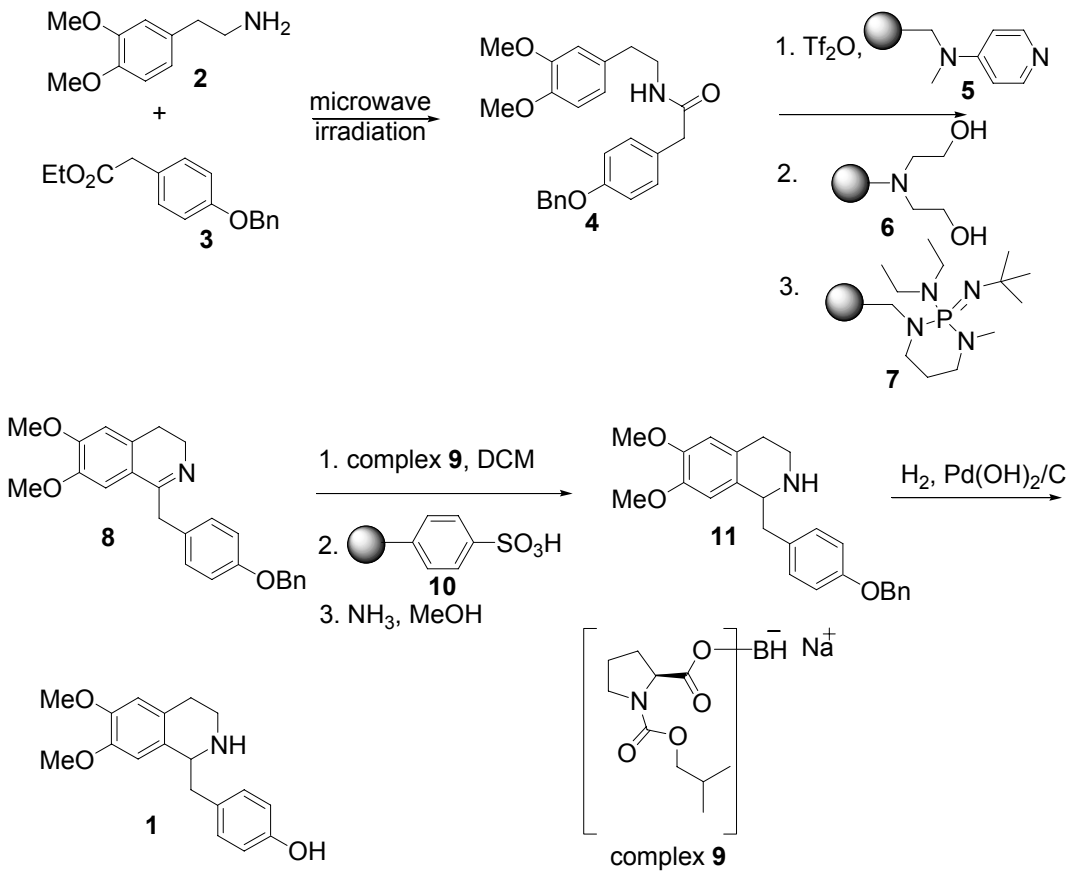


Figure 1. The use of solid supported reagents and scavengers in organic synthesis.

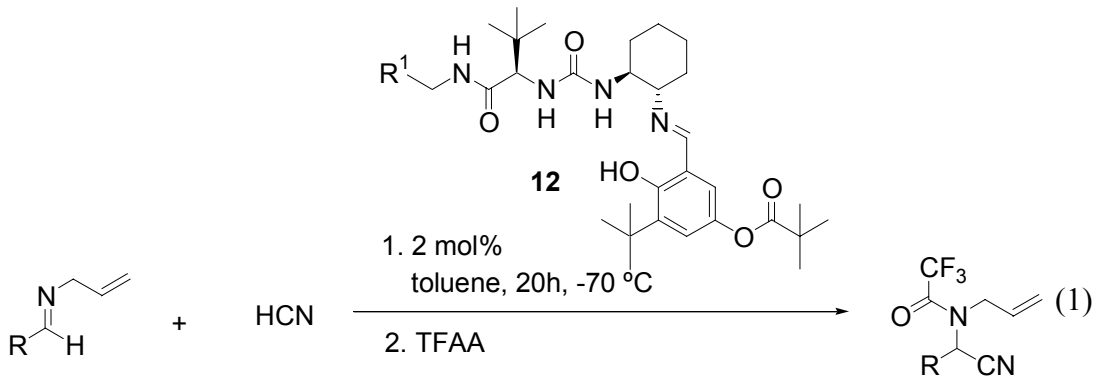
Recently, Ley described the enantioselective synthesis of (-)-norarmepavine **1**, a tetrahydrobenzylisoquinoline alkaloid isolated from the plant *Nelumbo lutea* in 1963.[5] The synthesis of (-)-norarmepavine **1** illustrates Ley's approach to synthesis with polymer supports. The synthesis starts with the coupling of amine **2** with ethyl-4-benzyloxyphenylacetate **3** to afford the amide **4** (Scheme 1). Then, the Bischler-Napieralski cyclization was carried out in the presence of the polymer supported 4-dimethylaminopyridine **5** and excess of triflic anhydride in dichloromethane at 0 ºC to afford the cyclic product **8**. The excess of triflic acid was quenched with polystyrene supported *N*-(2-hydroxyethyl)aminomethyl **6**. The free base was generated after the treatment of the product with the supported 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphazene **7**. Then, the imine was reduced with complex **9**. The product was trapped on a sulfonic acid resin **10** and released after washing the resin with methanolic ammonia. Finally, (-)-norarmepavine **1** was obtained after the cleavage of the benzyl group using a hydrogenation procedure.[4]

Scheme 1. Enantioselective synthesis of (-)-norarmepavine **1.**



The strategy of using resin supports to facilitate synthesis can also be applied to facilitate catalyst recovery and recycling. Jacobsen recently reported the immobilization of a urea derivative **12**, an efficient organocatalyst used for the asymmetric Strecker reaction, on a polystyrene resin.[6] A typical reaction consists of the treatment of the imine with HCN, or TMSCN, in the presence of 2 mol% of the insoluble polymer supported urea catalyst **12** (eq. 1). The reactions were carried out in toluene at -70 ºC to -78 ºC for 20 h. After completion of the reaction, the resin supported catalyst **12** was

removed by filtration and clean products were isolated as trifluoroacetamides in 96-97% yields and 92-93% e.e. Only a slight reduction on enantioselectivity was observed (96% to 93%) for the resin catalyst **12** compared with the low molecular weight catalyst. The resin was reused in up to 10 cycles with similar activity and enantioselectivity. Since the Jacobsen thiourea has demonstrated high efficiency in the hydrocyanation reaction, the solid supported organocatalyst is already been used commercially by Rhodia ChiRex for the synthesis of highly enantiomerically enriched α-amino acids.[7]



(1)

While there are advantages to using insoluble resins, there are disadvantages in the use of insoluble polymer supports too. Most of these disadvantages stem from the heterogeneous conditions of the reaction mixture. Some problems are also associated with solid phase polymer resins. For example, the characterization of crosslinked polymer supported catalysts is more difficult than the low molecular weight catalyst using solution-phase NMR spectroscopy. The characterization of insoluble resins must rely on the use of sophisticated techniques, such as multidimensional NMR spectroscopy

and high resolution magic angle spinning. Also, non-linear kinetic behavior is often observed. This is due to the difficulty of diffusion of the solution phase organic materials into the solid phase. Another problem encountered with the diffusion limitations of resins is the unequal distribution, or access, of a species like a catalyst in the resin to the components of a chemical reaction mixture. In addition to the problems described above, species on an insoluble resins can suffer decomposition or deactivation either by heating or for some other reasons. If a catalyst or other resin bound species were bound to the resin by weak bond (e.g. through a phosphine ligand) ligand dissociation can result in leaching of the resin-bound species into the solution phase. These difficulties lead to decreases in rate, yield, and chemo-, regio-, and enantioselectivity of the processes.

As a result of all these difficulties, a number of groups have described efforts to use soluble polymer supported reagents or catalysts as an alternative to the traditional insoluble polymers used in solid phase synthesis. The use of soluble polymer supports is thought to be advantageous as it reinstates the homogeneous reaction conditions. Soluble polymers however can still facilitate product, catalyst, sequestrant, or reagent recovery and recycling by using the macromolecular properties of the soluble polymer. Soluble polymer supports have the advantage of being characterizable by liquid phase techniques such as NMR, UV-vis, IR, and fluorescence spectroscopy. Additionally, soluble polymer supports can be designed so that the bound species have activity and selectivity similar to their low molecular weight analogs. Both Bergbreiter's group and others have studied new strategies to enable new catalyst, reagents, or sequestrant recovery and

recycling with soluble polymers. This dissertation describes examples of this chemistry and approaches to using such strategies for catalyst recovery and recycling.

Strategies for soluble polymer support separation

The separation of soluble polymer supports involved in all chemistry described above is not experimentally difficult and the concept is a sound strategy as evidenced by the utility of polymeric reagents and sequestrants in high throughput chemistry. However, an important aspect of these strategies that use polymer supports is that the polymer needs to be isolated from the products only at the end of the reaction. In a solid phase synthesis, the polymer supported catalyst, reagent or sequestrant is insoluble at all times- this insolubility is only needed at the end of the reaction when a simple filtration is used to isolate the polymer from the products or polymer-bound product from reagents. In contrast, soluble polymer supports can be designed so that they are phase separated from the products only at the end of the reaction. The separation of polymer bound species from the product still relies on the macromolecular properties of the polymer support. Thus, soluble polymer supports differ in that they can be used in the same phase as the substrate or reagent during the reaction with the separation step occurring only after the reaction is complete. The separation techniques for soluble polymer supports are grouped into two categories: solid-liquid separation and liquid-liquid separation.

In solid-liquid separation, an environmental change is needed to induce precipitation of the polymer from the homogeneous reaction mixture. The most

frequently used solid-liquid type of separation is based on solvent precipitation (Figure 2). In a solvent precipitation procedure, first the polymer supported species is dissolved in a solvent containing substrates or reagents. Then, at the end of the reaction the solution containing the polymer support is added to a different solvent that induces polymer precipitation. While the polymer is insoluble under these conditions, the product and other species present remain dissolved in the solvent mixture. The precipitated soluble polymer support can be isolated by filtration and, in many cases, the polymer can be recycled.

Poly(ethylene glycol), poly(*N*-isopropylacrylamide), poly(octadecylacrylate), poly(*N*-octadecylacrylamide), and linear polystyrene are examples of polymers that can be isolated by solvent precipitation. Poly(ethylene glycol) and poly(*N*-isopropylacrylamide) are soluble in solvents such as water and dichloromethane, and insoluble in solvents such as hexane and diethyl ether. Poly(octadecylacrylate), poly(*N*-octadecylacrylamide), and polystyrene are soluble in toluene, hexane, dichloromethane, and other non-polar solvents, but insoluble in methanol. However, solvent precipitation is limited to solid polymers that have a well-defined solubility. Although this separation scheme is simple, the large amounts of solvent needed to induce precipitation can be a problem both, environmentally and economically. This requirement for the use of excessive amounts of solvent limits the widespread adoption of this approach.

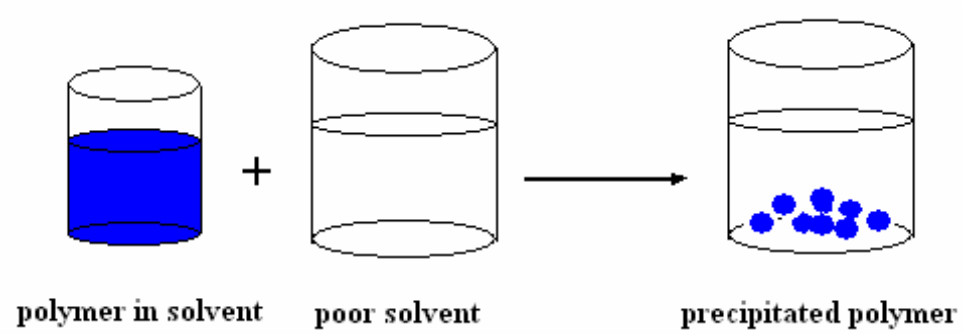


Figure 2. Polymer separation by solvent precipitation.

An alternative approach to solid/liquid separation of a polymer bound species from solution can be based on the temperature dependent solubility of polymers (Figure 3). Such separations can either employ a polymer with normal temperature dependent solubility or with inverse temperature dependent solubility. Polyethylene is an example of a polymer that has a noticeable normal temperature-dependent solubility. Polyethylene with a d.p. of >100 is insoluble in all solvents at room temperature. However, at a concentration of 0.1 g/mL, polyethylene with M_n of ca. 2400 Da becomes soluble at 100 ºC in a nonpolar solvent like toluene. However, while polyethylene is soluble in hot toluene, when the solution of polyethylene in toluene is allowed to cool to room temperature, the polymer can be recovered quantitatively by filtration or centrifugation. Many catalysts have been attached to polyethylene oligomers and such catalysts have been used in a variety of organic reactions.[8-17] These experiments have demonstrated that polyethylene supported catalysts have equivalent activity to their low molecular weight octadecyl or nonadecyl analogs.[18]

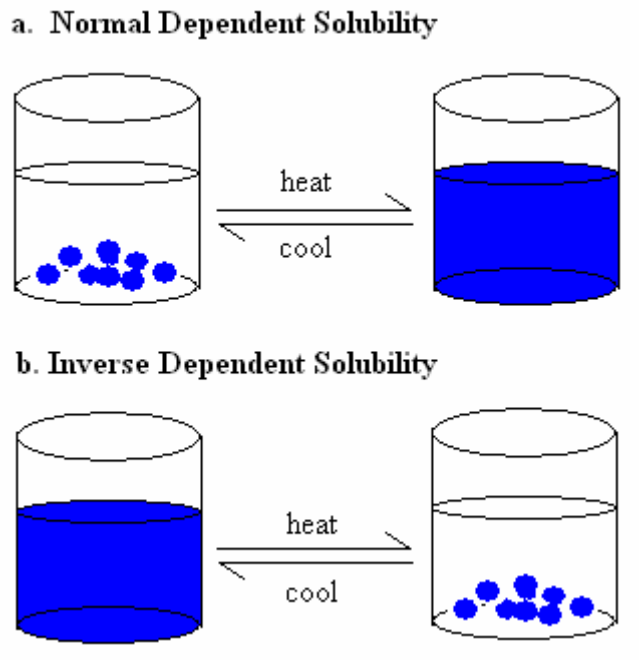


Figure 3. Separation by thermal precipitation.

Polymers that exhibit inverse temperature dependent solubility are also useful in organic reactions and can be easily isolated from a reaction mixture (Figure 3b). Such polymers are soluble at low temperature but are insoluble at high temperatures because they have what is known as a lower critical solution temperature. Poly(ethylene oxide-co-propylene oxide-co- ethylene oxide) (Pluronic copolymer) and poly(*N*-isopropylacrylamide) are two common polymers studied that exhibit inverse temperature dependent solubility. The phase separation upon heating was first shown to be useful in catalysis by using Pluronic copolymer supported phosphine ligated Rh(I) catalyst for hydrogenation catalysis.[19, 20] PNIPAM bound catalysts have also been used for catalytic reactions such as allylic substitution[21] and alkyne-aryl iodide coupling.[22] PNIPAM has an LCST of 31 ºC. After the catalytic reaction is completed with a PNIPAM supported

catalyst, the reaction mixture is heated to over 31 ºC and the PNIPAM-supported catalyst precipitates out of solution. The PNIPAM-supported catalyst can be easily isolated by centrifugation. Advantages to this procedure are that the LCST of a polymer can be tuned by altering the polymer structure.[23, 24] In some cases, the LCST may depend on the identity and concentration of other components (e.g. salts) in the reaction solution.[25]

pH-dependent solubility is another characteristic of polymers that can be used for solid-liquid phase separation. Polymers like poly(acrylic acid), polyethylene imine, and Gantrez derivatives (poly(maleic anhydride-co-methyl vinyl ether) derivatives) have pH-dependent solubility. Recently, our group reported the use of a Gantrez derivative as a pH-sensitive polymer support for hydrogenation catalysis.[26] The reaction of the anhydride groups on Gantrez polymer with a phosphine-containing amine followed by quenching of the remaining anhydrides with aqueous acid formed a polymer that contained carboxylic acid groups and varying amounts of phosphine groups that were used to ligate Rh(I) catalyst to form a polymer-bound hydrogenation catalyst. This polymer-bound catalyst is soluble in water on its basic form at pH >7.5. The polymer support could be isolated upon acidification and redissolved in fresh substrate solution at a pH= 7.5. The polymer supported Rh(I) catalysts was reused in a total of three cycles with no significant loss in activity.

Although precipitation is a simple and fast procedure for separation of a polymer bound species from solution, other separation schemes have been developed for polymer supported catalyst recovery and recycling. Liquid-liquid separations are the second widely used way to separate polymer supported species from a solution that contains

products, byproducts, reagents, or catalysts. Two approaches are used- membrane filtration and the use of biphasic systems of liquids with different densities.

Membrane filtration is a common technique used in liquid-liquid separations. Membrane filtration uses a semi-permeable membrane to separate macromolecular species from smaller molecules. The kind of membrane that will be used to separate large macromolecules from small molecules largely depends on the size and geometry of the species to be separated. Also, the permeability of the membrane depends on the pore size distribution of the membrane, the hydrophobicity or hydrophilicity of the system, and on solvent polarity. The membrane needs to be chosen so that it is stable under operational conditions, and inert towards the macromolecules, substrates, intermediates, and products present in solution. It relies on size separation and has been used to isolated dendrimer-supported species.[27]

Another liquid-liquid separation technique is the use of biphasic systems where the two liquid phases are chosen such that they have different densities (Figure 4). If this second approach were used for homogeneous catalysis, the catalyst would be chosen such that it was selectively soluble in one liquid phase with the products being soluble in the other liquid phase. Our group has emphasized the practicality of this approach using nonpolar/polar biphasic systems for catalyst recovery and recycling. Nonpolar/polar biphasic systems consist of a mixture of two solvents that are immiscible at room temperature and homogeneous when heat is applied. For example, heptane and DMF are biphasic at room temperature. When the mixture is heated above 70 ºC the solvent system becomes homogeneous. Then, the biphasic system is reformed when the system

is allowed to cool to room temperature. Other systems that have demonstrated to be promising in this area are $scCO_2$,[28] ionic liquids,[29, 30] water, and fluorous[31] based solvent systems.

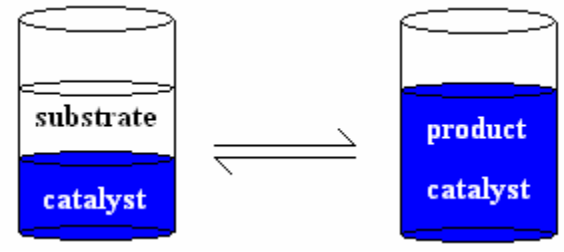
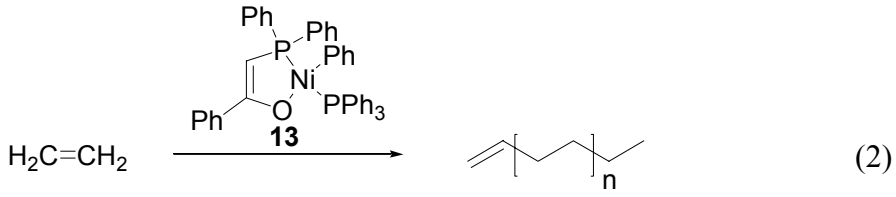


Figure 4. Liquid-liquid separation technique for soluble polymer supports separation.

This principle of catalyst recovery and recycling in a liquid-liquid biphasic system is not limited to polymers and is actually known as part of an industrial scale synthesis. An early example was its use in Shell's High Olefin Process (SHOP) in 1965.[32] The SHOP process consists of oligomerization of ethene to α-olefins using the P-O-chelated- Ni complex **13** as a catalyst (eq. 2). This process was discovered by mistake when the laboratory assistant, A. Nabong, used acetonitrile instead of toluene to carry out the reaction. At the end of the reaction, this scientist obtained two phases, one phase consisting only of α-olefins and the second phase of acetonitrile and the catalyst. Further studies to find a better solvent to perform the reaction using liquid-liquid biphasic catalysis eventually led to the use of 1,4-butanediol as the solvent. In this process, ethene and the catalyst were dissolved in 1,4-butanediol. After the reaction was

completed two phases were formed (Figure 5). The top phase contained the α-olefins and the bottom phase contained the 1,4-butanediol and catalyst. The two phases were separated and the catalyst containing phase was recycled.



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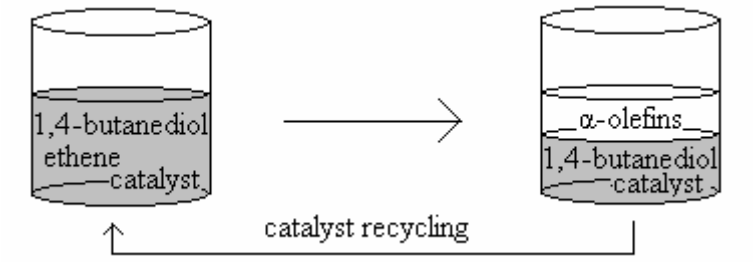


Figure 5. The SHOP production of α-olefins.

The Ruhrchemie/Rhône-Poulenc process is another example of industrial liquid-liquid biphasic catalysis.[33] The Ruhrchemie/Rhône-Poulenc process uses hydroformylation catalysis to transforms propene to *n*-butanal using a water soluble triarylphosphine Rh-catalyst in 9.2 million tons per year. The water soluble catalyst can be easily separated from butanal that composes the second phase of the biphasic system. This hydroformylation process is biphasic at all times, and only occurs if the reaction mixture is stirred vigorously.

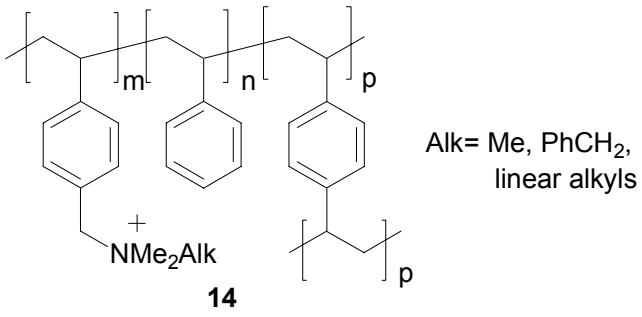
Any successful liquid-liquid biphasic process designed to simplify the catalyst recovery and recycling does have to meet some general criteria. The catalyst has to be designed to be soluble in only one phase of the biphasic system. Also, solvents need to be carefully chosen so that the catalyst is stable at the appropriate temperature. It is most useful if the substrate and catalyst are present in the same phase. If that is the case, the products need to be soluble in a phase different than the catalyst. Fortunately, soluble polymers that are to support a catalyst can be tuned and modified to have the desired solubility characteristics. Assuming the polymers impart these characteristics to a substrate or catalyst bound to them, soluble polymers and liquid/liquid separation schemes can be adapted to a variety of specific reactions and solvents.

Examples of Soluble Polymers as Catalyst Supports

Polymer supports in solid-liquid biphasic systems

The versatility of phase transfer catalysts (PTC) to undergo different organic transformations has contributed in the establishment of these catalysts as useful tools in organic synthesis. Phase transfer catalysts can be used in reactions such as nitrile, dicyclopropane, ether, and thioether formation, halogen exchange, dehalogenation of vicinal dibromides, oxidation of alcohols, and nucleophilic ring opening of epoxides. Regen[34] reported the first immobilized quaternary ammonium salt PTC catalyst in a crosslinked polystyrene divinylbenzene resin **14** and described its use in the conversion of 1-bromooctane to nonanitrile (eq. 3). However, the supported phase transfer catalysts showed lower activity compared with the activity of the low molecular weight analog.

This was explained by the diffusion of the substrate in and out of the polymer matrix that affects the catalyst's reactivity. An alternative strategy is to anchor the catalyst to a soluble polymer support with solubility properties suitable for catalyst recovery and recycling.



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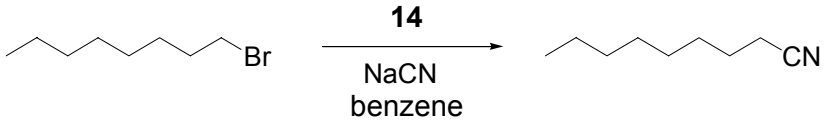


(3)

Recently, Benaglia and coworkers[35] have done this immobilization of a quaternary PTC salt on a modified poly(ethylene glycol) (PEG) polymer support. PEG is an inexpensive soluble polymer with functional groups that can be easily modified. The PEG- benzyl alcohol derivative was converted to the benzyl bromide in two steps. Then, tributylamine was reacted with the PEG-benzyl bromide to afford the PEG-quaternary ammonium salt **15**. This PEG supported phase transfer catalyst was used in a series of standard transformations (Figure 6). The results obtained were satisfactory with yields higher than 90% in most of the cases. The polymer supported catalyst was

recovered by solvent precipitation and filtration, and was reuse in three cycles without loss in activity.

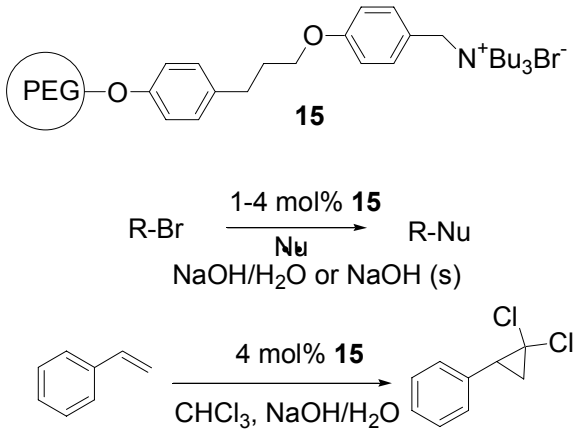


Figure 6. PEG-supported ammonium salt **15** used for phase transfer catalysis.

Carbon-carbon (C-C) bond formation is one of the most important transformations in organic synthesis. Carbon-carbon bond formation can be accomplished by many reactions. The Grignard reaction, Diels-Alder reaction, aldol reaction, and Michael addition reactions are examples of reactions used for C-C bond formation. Recently, there has been renewed interest in asymmetric C-C bond formation using chiral amines to activate ketones or aldehydes by an enamine formation. Aminocatalysis, or catalysis by enantiomerically pure amines, is of great interest due to the ready availability of the necessary amines in the chiral pool of natural products. Chiral amines react with the substrate, a ketone or an aldehyde, to form a reactive enamine intermediate. The enamine can be used in many different reactions for C-C bond formation, including Aldol, Michael, Mannich, and Diels-Alder reactions. Proline

has demonstrated to be one of the best organic catalysts for these reactions producing the desired product in high yield and high enantioselectivities.[36, 37]

Benaglia and coworkers described the immobilization of proline on PEG and its utility in Michael addition reactions.[38] Previously, List reported the proline catalyzed conjugated addition reaction of symmetric ketones to nitroalkanes.[39] The reaction of 2-nitrostyrene and cyclohexanone was carried out in DMSO for 24 h at room temperature in the presence of 0.15 mol eq. of proline. The proline activates the ketone by an enamine formation. The enamine reacts with 2-nitrostyrene to form the product in 94% yield, good *syn* diastereoselectivity (20/1 *syn/anti*), and modest enantioselectivity (23%). This same reaction was studied by Benaglia using PEG-supported proline.

Benaglia studied the conjugated addition reaction of cyclohexanone and 2-nitrostyrene using 0.15 mol eq. of PEG-supported proline **16** (Figure 7). The conjugated addition reaction was carried out in three different solvents- methanol, DMF, and DMSO for 24 h at room temperature. Methanol demonstrated to be the best solvent for this reaction allowing the isolation of the product in 60% yield, with *syn* diastereoselectivity (19/1 *syn/anti*), and 35% e.e. When DMF was used as the solvent, the product was obtained in 23% yield, 9/1 *syn/anti* diastereoselectivity, and 22% ee. Similar results were observed when DMSO was used, obtaining the product in 26% yield, with 7/3 *syn/anti* diastereoselectivity, and 15% e.e.

From these results it was concluded that PEG-supported proline **16** is less efficient than the non-supported proline in terms of chemical yields. However, PEG-supported proline produces products with improved diastereoselectivity and higher

enantioselectivity than the non-supported proline. PEG-bound proline was used to explore the possibility of catalyst recovery and recycling. PEG-bound proline was recovered by precipitation with diethyl ether followed by filtration, and recycled in three additional cycles. A decrease in chemical yield and enantioselectivity was observed for the second cycle. After the second cycle, reactions were performed with equal efficiency for two additional runs.

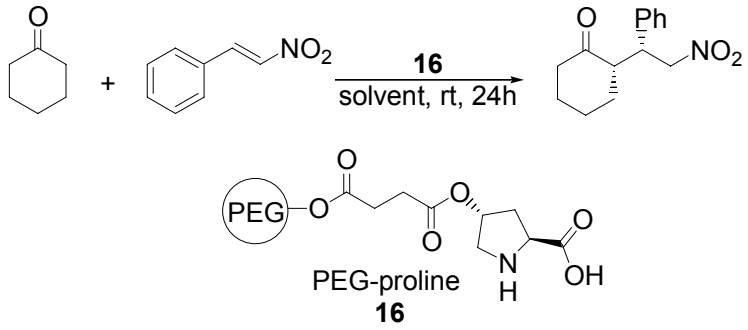


Figure 7. Michael addition reaction catalyzed by PEG-supported proline **16**.

Using a polymer support whose solubility depend on the temperature of the medium is another useful approach to carry out homogeneous reactions while being able to separate the polymer by a simple filtration or centrifugation. Polyethylene (PE) is a polymer that is insoluble in all organic solvents at room temperature, but is soluble in nonpolar solvents when the temperature is higher than 90 ºC (Figure 3a). Many groups have taken advantage of polyethylene's solubility properties and have attached many

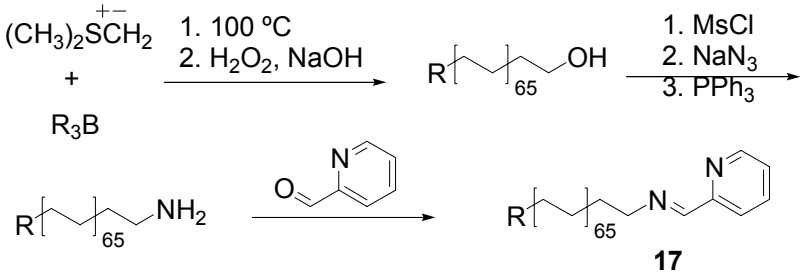
sorts of catalysts for different catalytic reactions.[8, 15, 40] For example, PE oligomers were used to attach copper(I) catalysts used in atom transfer radical polymerization.[14]

Atom transfer radical polymerization (ATRP) was discovered in 1995 and has been widely used for the synthesis of polymers with controlled molecular weights and narrow polydispersity index.[41] ATRP has not been widely adapted in industry for several reasons. One reason is because many of the early ATRP catalysts have low activity. This modest catalyst activity means that higher loadings of catalyst are necessary to carry out the polymerization. This problem may be solved in part by the introduction of newer catalysts with very high activity.[42] However, whether a high loading of a less active catalyst or a low loading of a more active catalyst is used, there is still interest in procedures that remove the catalyst from the product polymer. Whether it is the use of high loading catalysts or just the perception that the even 1-10 ppm of Cu needs to be removed from the product polymer, the post-polymerization purification steps necessary for this Cu recovery makes ATRP polymerization more expensive and less attractive as a route for commercial polymer synthesis. Thus, over the last decade, many different groups have worked on ways of addressing the catalyst recovery issue to make ATRP more attractive to the industry for commercialization.[43-46]

Brittain and coworkers used PE oligomers to attach a pyridyl ligated copper(I) catalyst and used it in atom transfer radical polymerization.[14] After a series of modifications (Scheme 2), the polymer bound pyridyl ligand **17** was obtained and used in the polymerization of methyl methacrylate. The PE-bound ligand **17**, CuBr, ethyl 2-bromoisobutyrate and methyl methacrylate were dissolved in toluene and heated to 100

ºC for 24 h (eq. 4). After completion of the polymerization reaction, the reaction mixture was cooled to 0 ºC. The PE-bound catalyst precipitated while poly(methyl methacrylate) (PMMA) remained dissolved in toluene. After centrifugation, the polymeric product was separated from PE by decantation, and then isolated by solvent precipitation in methanol. PMMA was obtained as a clear, colorless solution which required no other purification step than a simple decantation. PMMA was obtained with narrow PDIs (1.22-1.45), typical of atom transfer radical polymerizations.

Scheme 2. Synthesis of polyethylene supported pyridine ligand **17** for atom transfer polymerization.



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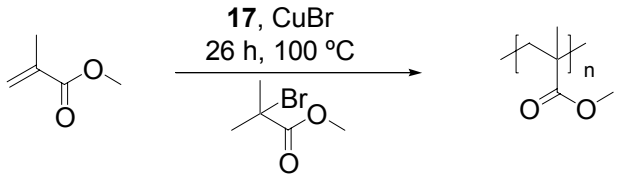


(4)

Brittain's studies demonstrated that PE is a suitable, recoverable, soluble support for ATRP of MMA. However, PE-supported copper bromide showed lower activity that the low molecular weight catalyst. While the molecular weights of PMMA achieved were close to the theoretical values, the polydispersities obtained were higher (1.2-1.45) than the PDIs obtained with the lower molecular weight catalyst (≤1.2). Later, Shen developed a new recoverable ligand attached to polyethylene-*block*-polyethylene glycol copolymer (PE-*b*-PEG) for ATRP of MMA.[15, 16] The results showed that the molecular weights of PMMA increased with conversion of the monomer, and that these molecular weights values were close to the theoretical values. The ATRP of MMA using PE-*b*-PEG was a controlled polymerization producing polymers with PDIs ≥1.2 below 70% conversion. The molecular weights and PDIs achieved with PE-*b*-PEG supported catalyst were similar to those obtained with the copper complexed to a small ligand. PE-*b*-PEG bound catalyst was recovered by centrifugation after the polymerization was completed and the reaction mixture was cooled to 0 ºC. The recovered catalyst was reused in a subsequent polymerization of MMA. PE-*b*-PEG supported copper bromide retained 90% of its fresh catalyst activity.

Polyethylene-supports have recently been described by DuPont as being suitable thermomorphic supports for catalysts used for chain transfer free radical polymerization or copolymerization of styrene or methacrylates.[47] The problem with using low molecular weight catalysts in this case is that the product polymer ends up with metal contamination. The presence of metal gives color to the resins that are to be used as additives in coatings. Dupont has shown that a soluble polymer like polyethylene

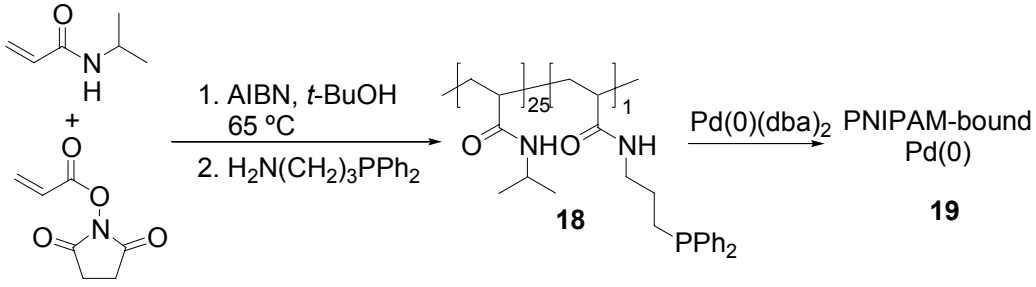
covalently linked to chelating ligands, including porphyrins, phthalocyanins, oximes, phosphines, and others, facilitates catalyst recovery and recycling. The PE-supported catalysts are homogeneous at the reaction temperatures and undergo phase separation upon cooling. The polymer-supported catalysts are recovered by filtration or centrifugation. The PE-supported catalysts used in Dupont' process produce metal and color free polymers, as well as polymers with controlled molecular weights. The chain transfer polymerization yields olefin terminated polymers, also known as macromonomers, which are used in further polymerization reactions to produce polymers with desired physical properties. The macromonomers obtained from the chain transfer polymerizations are lighter in color than the macromonomers obtained using analogous small homogeneous catalysts under the same reaction conditions. Such polymers are used in coatings, dispersants, binders, and other additives in automotive exterior paints.

While PE is a useful polymer support that can be easily isolated by a solid-liquid separation, it is not always desirable to carry out a reaction in a nonpolar solvent at high temperatures. Polymers that show inverse temperature dependent solubility are useful for solid-liquid biphasic separations at lower temperature and in other sorts of solvents (Figure 2b). Poly(*N*-isopropylacrylamide) (PNIPAM) has an LCST of 31 ºC in water, the temperature at which the polymer is insoluble in water. With a PNIPAM-supported catalyst, reactions can be carried out at room or colder temperatures, and separated and recycled by filtration or centrifugation upon heating to the LCST temperature.

Our group has reported the use of PNIPAM as an effective soluble polymer support for allylic substitution reactions, Heck reactions, and hydrogenation reactions.[48] The PNIPAM supported Pd(0) catalyst **19** was used for allylic substitution reactions.[22] The PNIPAM- bound phosphine ligated Pd(0) catalyst **19** was synthesized by the copolymerization of *N*-acryloxysuccinimide and *N*-isopropylacrylamide in the presence of AIBN at 65 ºC for 24 h (Scheme 3). Then, the active ester of the copolymer was allowed to react with 3-diphenylphosphinopropyl amine to afford the polymer bound phosphine ligand **18**. Then, ligand exchange with $Pd(0)(dba)_2$ afforded the PNIPAM-supported Pd(0) catalyst **19**.

The allylic substitution reactions[22] using PNIPAM- bound phosphine-Pd(0)-catalyst were carried out in water, or a mixture of water/EtOH, water/CH_3CN, and water/THF. When the reactions were carried out in water, reactions took longer due to the low temperature required to keep the polymer in solution. However, high yields averaging 89% were obtained and the polymer could be recovered quantitatively and reused in 15 cycles with modest loss in activity. The loss in activity was ascribed to adventitious oxidation of the phosphine ligand.

Scheme 3. Synthesis of PNIPAM-bound phosphine-Pd(0) catalyst **19**.



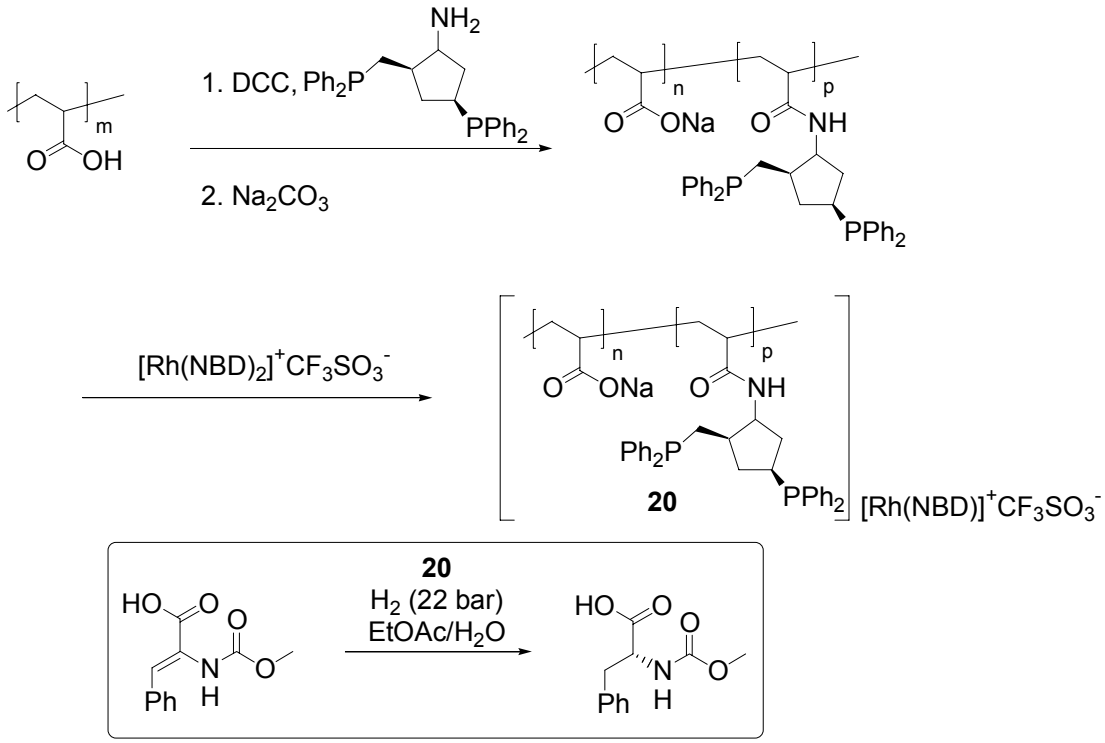
Aqueous biphasic systems

Catalysts that induce chemical transformations in water are of great interest because water is an environmentally benign solvent useful in green chemistry. Currently, low molecular weight ligands that are modified to increase their solubility in water are commonly used to make transition metal catalysts soluble in water. Polar polymers can also be designed to be soluble in water and serve as supports for catalysts and reagents. In such cases, liquid-liquid biphasic systems where one phase has an aqueous character can be designed and used in catalysis to separate catalysts and to take advantage of the low solubility of most organic materials in water. The concept consists of carrying out a reaction in the presence of an organic solvent and water. In classical aqueous biphasic catalysis, these two phases are immiscible at all time. In such cases, the reaction takes place at the interface of the organic and water phases. The catalyst remains in the water phase and is recovered by a simple liquid-liquid extraction. Poly(acrylic acid) and poly(ethylene imine) are common water soluble polymers used in aqueous biphasic systems.

Poly(acrylic acid) was used by Andersson as a support for catalytic asymmetric hydrogenation.[49] The poly(acrylic acid) supported Rh catalyst **20** was prepared following Scheme 4. The hydrogenation of α-acetoamidocinnamic acid was performed using 1.5 mM Rh using a biphasic mixture of H_2O and EtOAc. The polymer bound catalyst was recovered in the water phase after a liquid-liquid extraction. The catalyst was recycled after the addition of fresh EtOAc solution of the substrate α-acetoamidocinnamic acid. Products were obtained in 100% conversion and with an e.e

of 89% that was similar to that obtained with a structurally analogous low molecular weight catalyst.

Scheme 4. Synthesis of poly(acrylic acid) supported Rh catalysts **20** for the asymmetric hydrogenation of α-acetoamidocinnamic acid.



Fluorous polymer supports in liquid-liquid biphasic systems

Fluorous chemistry has been used as a simple way to carry out reactions under biphasic conditions with separation of catalysts from the products after the reaction is complete. The strategy involves the development of a catalyst with high solubility in perfluorinated solvents and little or no solubility in a conventional non-fluorinated organic solvent. The catalyst has to be selectively soluble to the fluorous phase and the

product to the organic phase to achieve the desired separation at the end of a reaction. The concept is based on using a mixture of a fluorinated solvent and an organic solvent that are immiscible at room temperature (Figure 8). Either a biphasic mixture is used (analogously to the aqueous biphasic system) or, when the mixture is heated to its upper critical solution temperature, miscibility of both phases is achieved. In the second thermomorphic case the reaction proceeds under homogenous reaction conditions. In the thermomorphic scenario, the mixture is allowed to cool to room temperature and the biphasic system reforms. In either case, the catalyst is recovered in the fluorinated phase after the reaction while the product stays in the organic phase. Then, the catalyst rich fluorous phase can be recycled by addition of fresh substrate in the organic solvent. Many examples of low molecular weight fluorinated catalysts have been reported.[31, 50, 51]

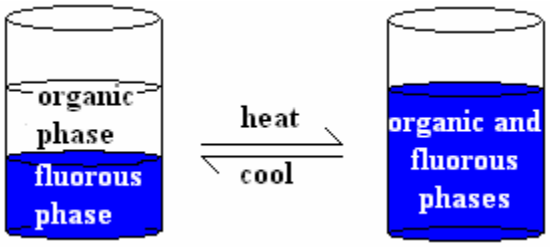
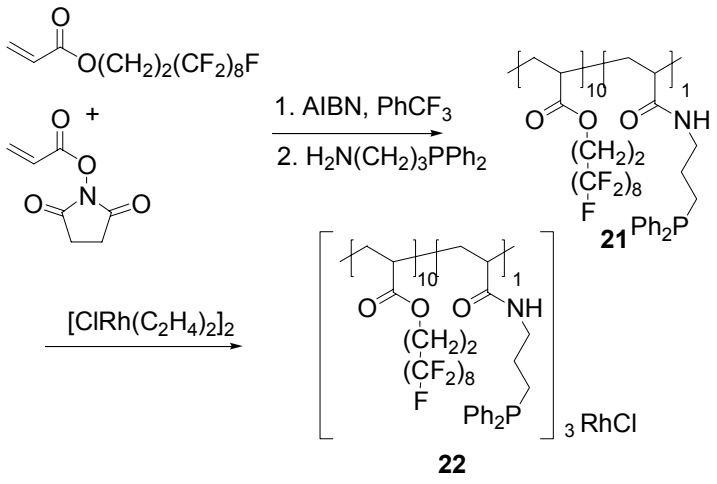


Figure 8. Fluorous liquid-liquid biphasic system.

While fluorous biphasic reactions normally employ non-polymeric fluorous ligands, our group was the first to report the use of fluorinated polymers for fluorous chemistry.[52] We subsequently reported the preparation of a fluorinated polyacrylate

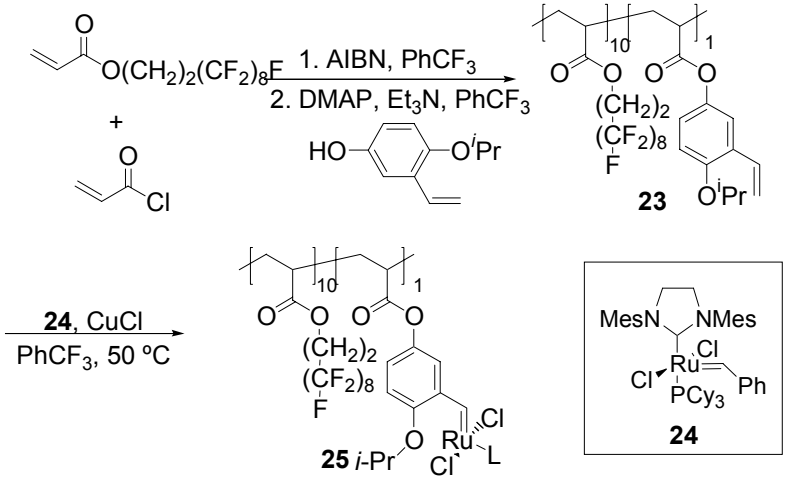
bound catalyst and described its use in Rh(I) catalyzed hydrogenation reactions.[53] The fluorinated polymer bound catalyst **22** was obtained after the copolymerization of the fluorinated acrylate ester and *N*-acryloxysuccinimide (NASI) (Scheme 5). Then, the aminolysis of NASI groups in the polymer with aminopropyl diphenylphosphine produced the desired fluorinated polymer bound ligand **21**. The polyacrylate supported Rh(I) **22** was successfully used in the catalytic hydrogenation of alkenes. In a typical experiment, 6 mol% of the polymer bound catalyst dissolved in 5 mL of FC-77 and 2 mmol of alkene were dissolved in THF and transferred to the hydrogenation vessel. The polymer bound catalyst was recovered by a liquid/liquid phase separation of the fluorous phase from the THF phase after completion of the reaction. Catalyst **22** was recycled for 15 times without any significant loss in activity.

Scheme 5. Fluorinate polyacrylate supported Rh(I) **22** for the hydrogenation of alkenes.



More recently, Yao et al.[54] reported the use of a polymer supported ruthenium catalyst used in ring closing metathesis (RCM). The fluorinated polyacrylate bound ruthenium catalyst **25** was prepared using a similar procedure described above (Scheme 6). The fluorinated acrylate was copolymerized with acryloyl chloride in the presence of AIBN under heating in $PhCF_3$. The resulting acyl chloride containing copolymer **23** was coupled with the bidentate isopropoxystyrene ligand and then treated with Grubbs-type Ru catalyst **24** in the presence of CuCl. The fluorinated polymer support was obtained in a 90% conversion.

Scheme 6. Synthesis of a recyclable fluorous polymer bound Ru catalyst for ring closing metathesis



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The fluorous polymer supported Ru catalyst **25** was evaluated for the RCM of various dienes (Figure 9). Disubstituted dienes **26** and **27** underwent RCM in ≥ 94% yield in the presence of 0.5-1 mol% of catalyst **25** in $PhCF_3/CH_2Cl_2$ (1:19 v/v) solvent

mixture. The polymer bound catalyst **25** was recovered by a FC-72 extraction and reused in 20 cycles for diene **26** and 12 cycles for diene **27** without significant loss in activity. This catalyst was also successful in the RCM of tri- and tetrasubstituted dienes.

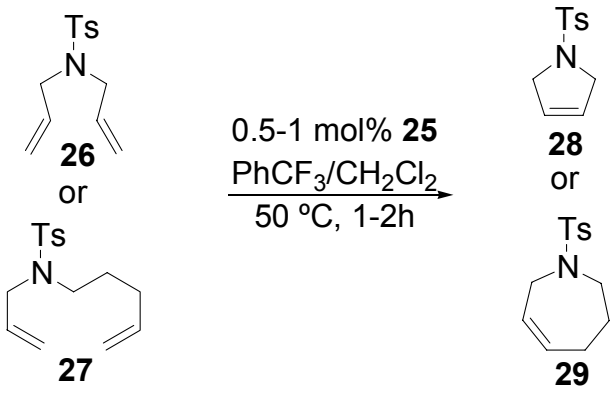


Figure 9. Ring closing metathesis of disubstituted dienes.

Polymer supports in liquid-liquid biphasic system

Most of the procedures used to date for the recycling of soluble polymer supports emphasize in liquid-solid separations. However, liquid-liquid separations like those describes above are actually used in industrial processes and such systems have proved to be very useful for polymer bound catalyst recovery and recycling too. Polymer supports that have phase selective solubility toward one phase of a nonpolar-polar thermomorphic system are the ones our group have used the most. These thermomorphic systems normally consist of a mixture of solvents that are immiscible at room temperature, but become miscible upon heating (Figure 10). In a thermomorphic system, this temperature induced miscibility change is reversible. Cooling of the hot

monophasic system induces phase separation of the solvents. Thus, if a polymer support can be designed to be phase selectively soluble in one phase of the biphasic mixture cold but soluble in the single miscible solvent mixture hot, catalytic reactions can be carried out under homogenous conditions, and the polymer bound catalyst can be separated when the biphasic system is reformed. Poly(ethylene oxide), PNIPAM, poly(octadecylacrylate), poly(*N*-octadecylacrylamide), poly(dimethylsiloxane), and poly(*tert*-butylstyrene) are examples of polymers that have been used in thermomorphic liquid-liquid biphasic systems. Poly(ethylene oxide) and PNIPAM are polar polymers that are isolated in the polar phase. Poly(octadecylacrylate), poly(*N*-octadecylacrylamide), poly(dimethylsiloxane), polyisobutylene, and poly(*tert*-butylstyrene) are polymers that can be recovered in the nonpolar phase.

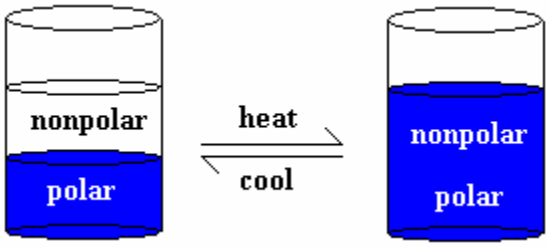


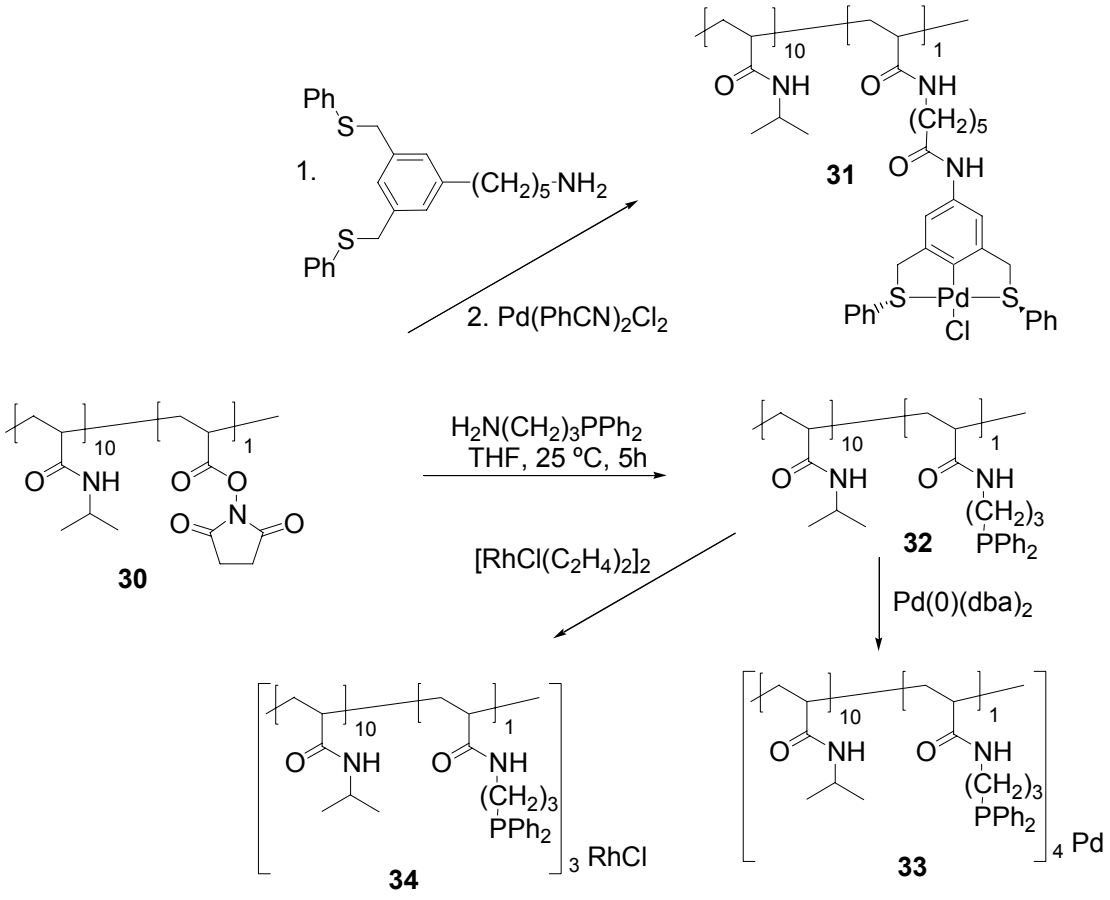
Figure 10. Thermomorphic liquid-liquid biphasic systems.

PNIPAM is a soluble polymer support that is ≥99.9% selectively soluble in the polar phase of a heptane-DMF, heptane-90% EtOH-H_2O thermomorphic systems. The utility of PNIPAM to catalyze reactions under biphasic conditions was tested with a series of catalysts. PNIPAM- SCS-Pd(II) **31**, PNIPAM-PPh_2-Rh **34**, PNIPAM-PPh_2-Pd(0) **33** were synthesized following Scheme 7.[21, 55] The polymer supported catalysts

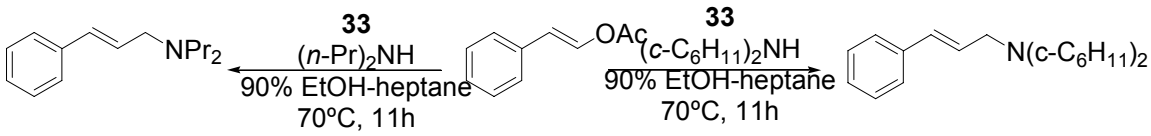
were obtained after the copolymerization of *N*-isopropylacrylamide and *N*-acryloxysuccinimide. Subsequent NASI substitution with the respective amine-ligands produced the polymer-supported ligands. The ligand exchange of the polymer supported ligands with $[RhCl(C_2H_4)_2]_2$ and $Pd(dba)_2$ gave the corresponding PNIPAM supported Rh(I) **34** and Pd(0) **33** complex, respectively. The precatalyst Pd(II) complex **31** was prepared either by metallation of the polymer or by addition of an amine-containing SCS-Pd(II) complex to the active ester-containing polymer **30**. The Heck reactions using Pd-complexes **33** and **31** in mixtures of heptane/90% EtOH-H_2O and heptane/DMA, respectively, were successful. In the case of the Heck reaction using **33,** yields of products isolated in the heptane phase ranged from 71 to >99%. The catalyst **33** was recycled 3 times by the recovering of the polymer-bound catalyst **33** in the ethanol phase. Catalyst **31** was also used in Heck reactions. Catalyst **31** was recovered in the polar DMA phase and reused in up to 4 cycles. The yields isolated from the heptane phase were from 10% for the first cycle to 90% for subsequent cycles. PNIPAM supported Pd(0) **33** was also tested in the allylic substitution reactions shown in Scheme 8. The allylic substitution reactions using catalyst **33** were carried out in heptane-85% EtOH-H_2O biphasic systems at 70 ºC. The polymer-bound Pd(0) catalyst **33** was recycled 4 times affording products in 73-91% yields. Catalyst **34** was used in the hydrogenation of 1-octadecene and 1-dodecene at 70 ºC in heptane-90% aqueous EtOH mixtures. The PNIPAM bound Rh(I) **34** was used in 4 cycles with no loss in catalytic activity. In all cases above, the yields increased form cycle 1 to cycle 2 and above due to the slight solubility of the products in the polar phase. As the polar phase

becomes saturated with product during cycle 1, apparent yields for cycle 2 improve significantly. In these cases, the actual yields are generally high in all cycles. The reported yields only refer to product isolation from the phase that does not contain the catalyst.

Scheme 7. Synthesis of different PNIPAM supported catalysts.



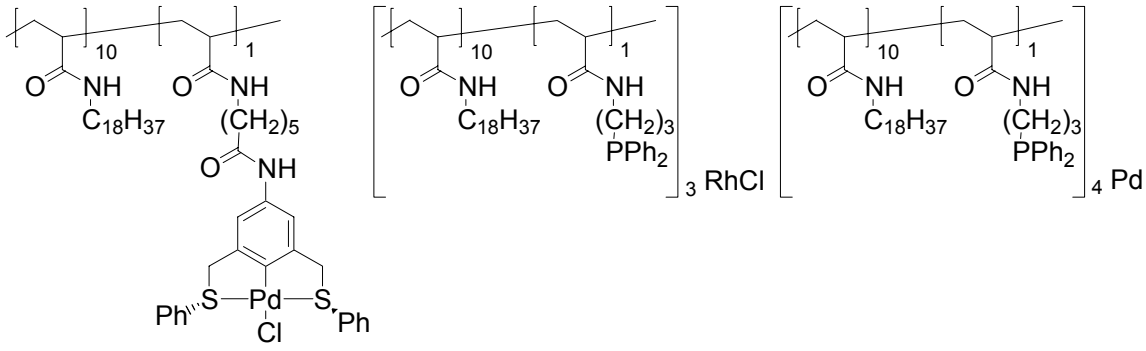
Scheme 8. Allylic substitution reactions using PNIPAM supported Pd(0) **33**.



Similar results to that of PNIPAM supported SCS-PdCl **31** were observed when using the same catalyst supported in PEG.[55] Both PNIPAM and PEG proved to be of great utility as soluble polymer supports. However, this chemistry is limited to reactions in where products and byproducts are soluble in the nonpolar phase. Many products and most of the byproducts formed in reactions have polar character. For example, the Heck coupling reactions produce salt byproducts that accumulate in the polar phase. In cases where byproducts accumulate in the polar, catalyst containing phase, the presence of byproducts could compromise the reaction. Nonpolar soluble supports can be design to overcome this problem.

Poly(*N*-octadecylacrylamide) (PNODAM) is a nonpolar soluble polymer support that is an alternative to PNIPAM. PNODAM can be quantitatively recovered in the nonpolar phase of a heptane/DMA and heptane-90% $EtOH_{(aq)}$ liquid-liquid biphasic systems.[56] The Heck reaction, allylic substitution reaction, and hydrogenation reaction that proved to work for PNIPAM were tested with PNODAM-supported systems.[57] [58] PNODAM- SCS-Pd(II) **35**, PNODAM-PPh_2-Rh **36**, PNODAM-PPh_2-Pd(0) **37**, were synthesized using the same procedure described for the synthesis of PNIPAM bound

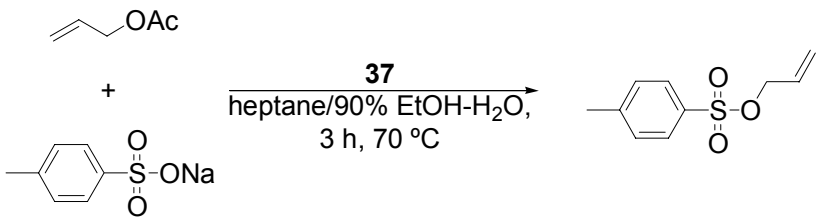
catalysts. PNODAM- SCS-Pd(II) **35** was air stable and active for the Heck reaction in a heptane/DMA thermomorphic biphasic system. The Heck reactions were carried out at 100 ºC using 0.2 mol% of the complex **35**. The complex **35** was used for up to nine cycles after the polymer recovery in the heptane phase of the thermomorphic heptane/DMA biphasic system. The isolated yields of the NMR pure products were 76-99%. PNODAM-PPh_2-Rh **36** was used for the hydrogenation reaction of polar alkenes. PNODAM-PPh_2-Pd(0) **37** was used in up to 5 cycles in the allylic substitution reaction shown in eq. 5 with an average yield of 85%. However, the reaction times gradually increased from cycle 1 to cycle 5 for the allylic substitution reactions, from 1-52 h, to achieve reaction completion. This is possibly due to the rapid oxidation of phosphine ligands in the presence of residual amounts of oxygen.



PNODAM-SCS-Pd(II) **35**

PNODAM-PPh_2-Rh(I) **36**

PNODAM-PPh_2-Pd(0) **37**



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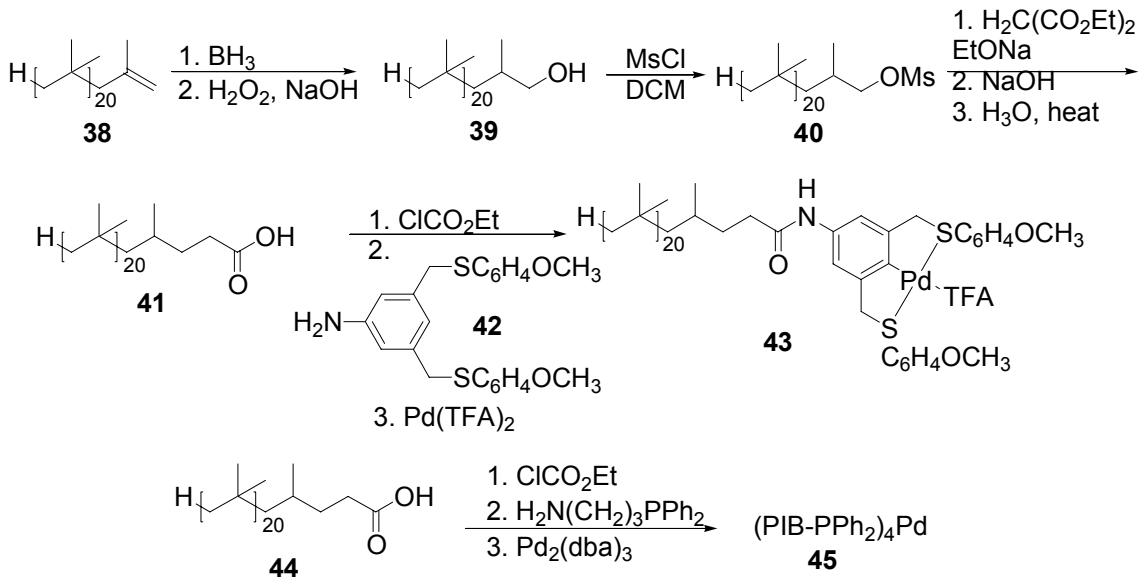
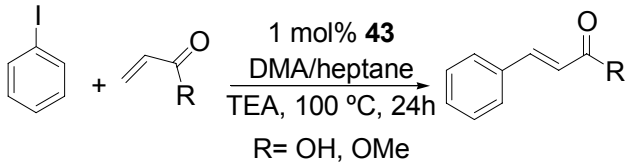
Polyisobutylene (PIB) is another example of a soluble polymer support that can be recovered in the nonpolar phase of a liquid-liquid biphasic system. PIB can be obtained from BASF with d.p. of *ca*. 20 or 40 with terminal vinyl groups. PIB can be easily modified and since catalysts attached would be present as end groups, the polymer's modification chemistry is much simpler to analyze than for polymers containing pendant groups. Two different PIB-bound catalysts, **43** and **45**, have been reported to be useful in a heptane-90% EtOH-H_2O thermomorphic system.[59]

PIB-supported catalysts were synthesized following a series of reactions described in Scheme 9. The PIB-supported SCS-Pd catalyst **43** was used to perform Heck chemistry. The Heck reactions were carried out using 1 mol% of the catalyst in heptane/DMA biphasic system at 100 ºC (eq. 6). The catalyst **43** was only effective in reactions using aryl iodides, affording products in 50-100% yields. The polymer supported catalyst **43** was recovered in the heptane phase after cooling the reaction mixture to room temperature, and used in three cycles without any detectable loss in activity.

Scheme 9. Synthesis of PIB-supported catalysts for Heck reactions, Sonogashira alkyne-arene couplings and allylic substitution reactions.

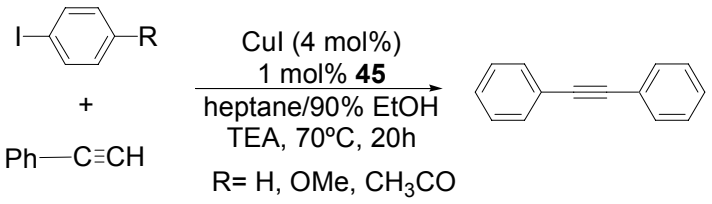




(6)

The PIB-supported phosphine-Pd(0) catalyst **45** was successful in the catalysis of Sonogashira alkyne-arene couplings and allylic substitution reactions, eq. 7 and eq. 8, respectively.[59] The reactions were carried out using heptane-90% EtOH-H_2O thermomorphic liquid-liquid biphasic systems. In the case of allylic substitution reactions, catalyst **45** was recovered in the heptane phase and reused in up to 4 cycles affording products in 78-100% isolated yields. Products formed from the Sonogashira alkyne-arene coupling reactions using catalyst **45** were isolated in 35% yield for the first

cycle to 100% yield for subsequent cycles. These yields represent products isolated from the aqueous EtOH phase and do not take into account products present in the nonpolar, polymer-supported catalyst containing phase. As the nonpolar phase gets saturated with product in the first cycle, yields improve for subsequent cycles. However, the recycling of the catalyst **45** requires more caution since presence of oxygen lead to the oxidation of the ligand and formation of Pd black having as a consequence a decreased in catalytic activity.



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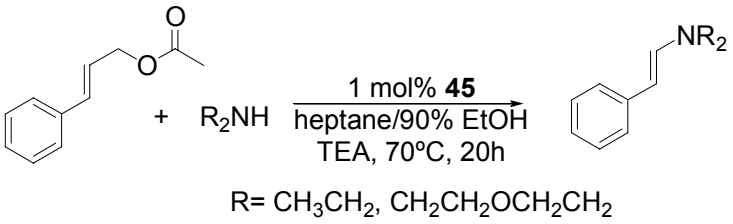


(8)

A different scheme for catalyst recovery in liquid-liquid biphasic systems would be to use latent biphasic systems.[60] Unlike thermomorphic systems, latent biphasic systems consist of a mixture of two solvents that are miscible, but are at the scope of immiscibility. A small perturbation can induce phase separation of the solvent mixture

(Figure 11). For example, a mixture of pure heptane and ethanol is homogeneous but after the addition of 10 vol% of H_2O a biphasic system is generated. The top phase corresponds to the heptane phase and the bottom phase consists of 90% EtOH-H_2O. Bergbreiter's group reported the use of polydimethylsiloxane as a soluble inorganic polymer support for an organocatalyst used in Michael addition reactions.[61] Polydimethylsiloxane is a commercially available, easy to modify polymer that proved to be selectively soluble to the nonpolar heptane phase of a heptane/DMF and heptane/90% EtOH-H_2O thermomorphic biphasic systems. Quinine **47** was immobilized on PDMS **46** through the vinyl groups using a Pt-catalyzed hydrosilylation procedure (Scheme 10). PDMS supported quinine **48** was also used for the Michael addition of thiols to α,β-unsaturated ketones and esters in a latent biphasic solvent mixture. In that case, the reactions were carried out a room temperature using 10 mol% of **48** as catalyst in 1:1 mixtures of heptane and ethanol. After the reactions were completed, 10 vol% of water was added to induce phase separation. The product was isolated in the EtOH-H_2O phase, while the polymer supported catalyst was recovered in the heptane phase. The catalyst was used in 5 cycles with no significant loss in activity.

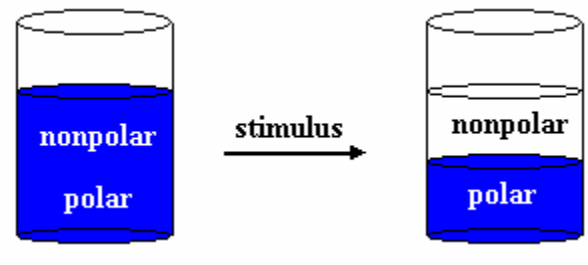
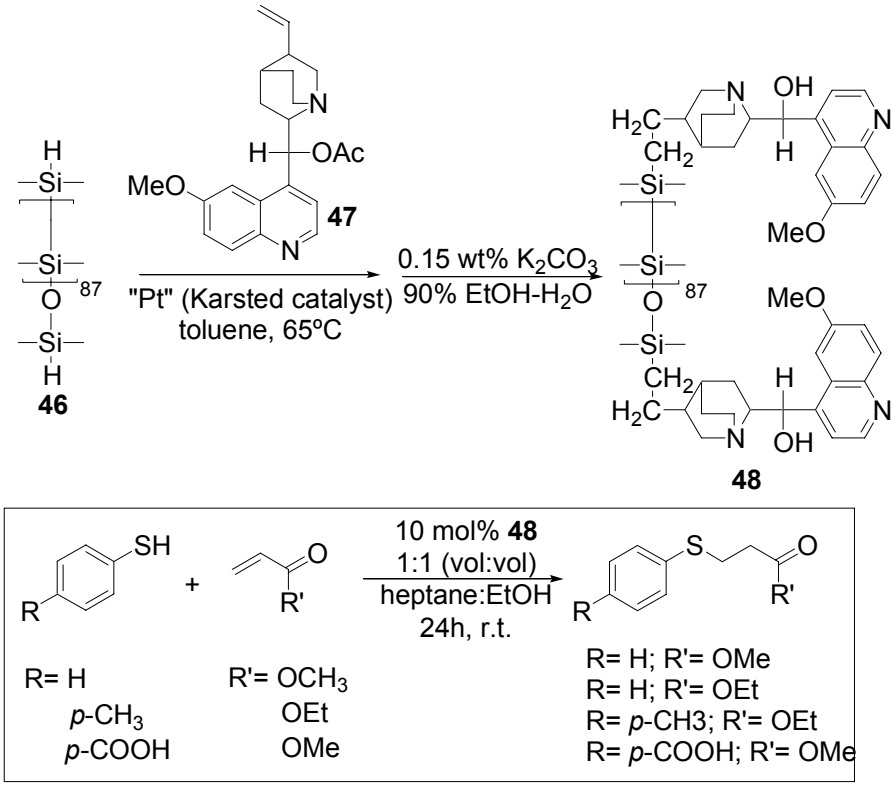


Figure 11. Latent liquid-liquid biphasic system.

Scheme 10. Synthesis of poly(dimethylsiloxane) supported quinine **48** for Michael addition of thiol to α,β–unsaturated esters.



Much of the work in our laboratory in recent years has focused on the use of thermomorphic and latent liquid-liquid biphasic systems for catalyst recovery. This work depends on developing and understanding polymer phase selective solubility and on the synthesis of new sorts of catalysts. Both sorts of chemistry are described in this dissertation. The design and synthesis of new, highly stable, and recoverable soluble polymer supports will be described first. The phase selective solubility of polymers like poly(octadecylacrylate)s and poly(*N*-alkylacrylamide)s are reported. Polymers

that are recovered in the nonpolar phase of liquid-liquid biphasic systems have proven to be useful as polymer supports. New examples of nonpolar phase selectively soluble polymer supported catalysts are also given.

CHAPTER II

PHASE SELECTIVE SOLUBILITY OF SOLUBLE POLYMER SUPPORTS

Introduction

Insoluble polymer supports have been the most common type of polymers used in polymer-facilitated organic synthesis thus far.[2, 62] These insoluble polymeric supports have the advantage of easy separation from soluble products using a simple filtration. However, such systems are biphasic both during and at the end of a reaction. The presence of more than one phase during the reaction introduces a kinetic barrier that may hinder the reaction. Such supports sacrifice a homogeneous activity for a simple separation. Soluble polymer supports on the other hand exhibit improved reactivity, selectivity, and more predictability in their chemistry.[18, 63] Also, soluble polymer supports can be easily modified[62] and characterized by the same analytical techniques everyday used in a synthetic laboratory.[18]

Two important factors must be taken into consideration when designing a soluble polymer support. The polymer support must be completely soluble to ensure that all the catalyst, reagent, sequestrant, or substrate bound to the polymer is available during the reaction. Also, the polymer support must be phase selectively soluble after the reaction in order to be able to completely separate the polymer from the products if a biphasic separation is used after the reaction.

Some common techniques used to recover soluble polymer supports are solvent precipitation and membrane filtration. Solvent precipitation involves the use of an excess amount of a "poor solvent" to precipitate the polymer support. The precipitated polymer is then filtered and washed with additional "poor solvent". Membrane filtration is a process that separates compounds of different sizes. Large macromolecules can be separated from low molecular weight substrates or products using membrane filtration. Solvent precipitation and membrane filtration are widely used for polymer recovery and recycling. However, the large amount of solvent required for such separations generates increasing amounts of waste solvents decreasing the overall efficiency of the processes. Also, membrane filtration is a very slow process. An alternative strategy is a separation based in the phase selective solubility of the polymer in a liquid/liquid biphasic system.[56, 64]

Soluble polymer supports are only useful if complete separation of the polymer from the products can be achieved. Phase selective solubility of polymers is a useful strategy when recovery and reuse of the polymer support is desired.[18, 31, 64-66] This technique requires the design of a polymer support that would be soluble in a solvent mixture containing the reactants, but that will selectively separate from the products in a latent or thermomorphic liquid/liquid biphasic system.[21, 31, 60]

While a variety of solvents can be used in liquid/liquid biphasic systems[31], our group has mainly used heptane/ethanol for latent biphasic systems, and heptane/ethanol/water or heptane/DMF solvent mixture for thermomorphic biphasic systems. In a latent biphasic system the solvent mixture is monophasic at rest and only a

small perturbation (<10 vol% of water) is enough to induce the formation of a biphasic system (Figure 12). Alternatively, thermomorphic systems that are biphasic at room temperature and homogeneous when heat is applied can be used (Figure 11). A mixture of heptane/DMF or heptane/ethanol/water (10:9:1) becomes reversibly miscible when the mixture is heated to 70ºC.[21] Once the homogeneous solution is allowed to cool to room temperature it separates back into two phases. An alternative thermomorphic system is a system that is biphasic at room temperature and monophasic when cold, e.g. triethylamine/water solvent system. The main advantage of using such latent and thermomorphic systems is that reactions can be performed under monophasic conditions, and at the same time complete separation of the soluble polymer support from the soluble products can be achieved without the addition of an extra solvent. Similar behavior is seen in other solvent mixtures such as fluorous/organic solvent mixtures, [53, 67] ionic liquids, and supercritical CO_2.[68, 69]

The phase selective solubility of different polymers has been studied by our group extensively. Soluble polymers such as poly(ethylene glycol),[70] poly(acrylic acid),[26] and poly(*N*-isopropylacrylamide)[18, 71] have been shown to be ≥ 99.9% selectively soluble in the polar phase of a heptane/DMF or heptane/ethanol/water solvent system. Poly(isobutylene),[59, 72] poly(*N*-vinyloxazoline)s,[73] poly(*tert*-butylstyrene),[74] poly(octadecylacrylate)s,[64] poly(*N*-octadecylacrylamide)s,[58] and poly(dimethylsiloxane)s[61] are examples of hydrophobic polymers that are ≥ 99.6% phase selectively soluble in the nonpolar heptane phase of these same solvent mixtures.

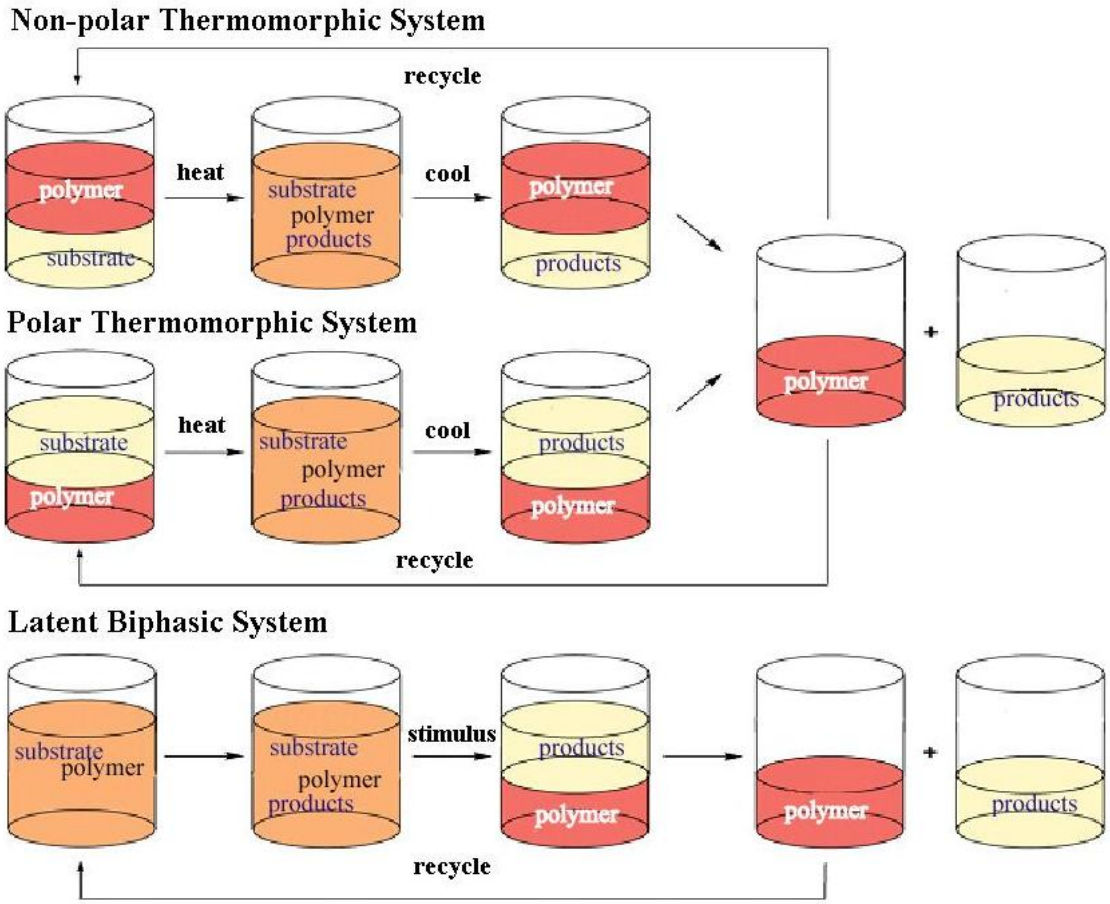


Figure 12. Thermomorphic and latent liquid/liquid biphasic systems.

Copolymers with pendant groups can also have good phase selective solubility in latent and thermomorphic systems. If a copolymer with pendant groups can be designed so that one of the components defines the phase selective solubility of the copolymer, an increased in catalyst loading may be possible. This chapter demonstrates that soluble polymer supports can be tailored to adjust their desired phase selective solubility using poly(octadecyl(meth)acrylate)s and poly(*N*-alkylacrylamide)s copolymers.

Results and Discussion

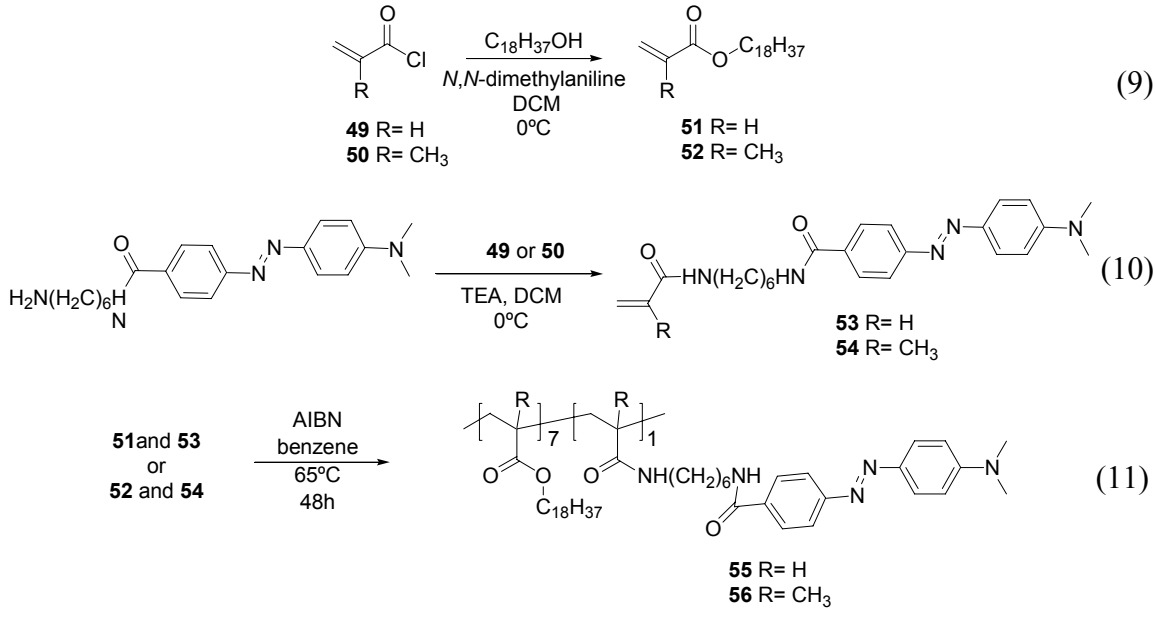
A broad range of studies by the Bergbreiter group has detailed many advantages for the use of soluble linear polymer supports as alternatives to insoluble resins. A key feature of much of this chemistry is that linear polymer supports can be designed to have high phase selective solubility in either polar or nonpolar solvent phases of a biphasic liquid/liquid mixture. This work has demonstrated that soluble polymer supported reagents, catalysts, or sequestrants can be simply and quantitatively separated from products in this way in thermomorphic or latent liquid/liquid biphasic systems.

We have reported polymers that are phase selectively soluble in either the polar phase or nonpolar phase of liquid/liquid biphasic systems. Using polymers that are phase selectively soluble to the polar phase is, however, only useful if the product is selectively soluble to the nonpolar phase of the biphasic system. Moreover, such systems are only useful if the reaction does not produce polar byproducts. Polar byproducts in such a system eventually hinder the reaction because they would accumulate during recycles of polymer containing polar phase. However, polymers that are recovered in the nonpolar phase of a liquid/liquid biphasic system do not have that problem. Nonpolar phase selectively soluble polymer-supported species are also more useful since most organic products and byproducts have polar character.

The Bergbreiter group has described a number of polymers that are phase selectively soluble in the nonpolar phase of a latent or themomorphic biphasic system. Polyisobutylene, polysiloxanes, poly(*tert*-butylstyrene), and poly(*N*-octadecylacrylamide) are some examples. Similar studies using poly(octadecylacrylate)

(PODA) and poly(octadecylmethacrylate) (PODMA) prepared according to eq. 11 have also been prepared. These polymers too are examples of nonpolar phase selectively soluble polymers.

To demonstrate that PODA and PODMA are phase selectively soluble in a nonpolar phase of a liquid/liquid biphasic system, dye labeled PODA and PODMA were prepared by the copolymerization of the appropriate acrylate monomer with a *p*-methyl red labeled acrylamide. The necessary acrylate monomers were obtained from the reaction of acryloyl chloride or methacryloyl chloride with octadecanol in the presence of *N*,*N*-dimethylaniline (eq. 9). A known similar procedure formed *p*-methyl red labeled acrylamide from the reaction of the amine-terminated methyl red with acryloyl chloride, or methacryloyl chloride (eq. 10). The monomers so formed were then copolymerized with the methyl red labeled (meth)acrylate to produce methyl red labeled PODA and methyl red labeled PODMA copolymers eq. 11.



Phase selective solubility studies of PODA and PODMA were performed using heptane/90% EtOH:H_2O and heptane/DMF thermomorphic systems. These solvent mixtures are miscible at 70 ºC and biphasic at room temperature. In a typical procedure, a dye-labeled polymer was added to a 1:1 (vol:vol) solvent mixture to create a solution that was 10^{-4} N in methyl red. Heating to 70 ºC then formed a homogeneous solution. Subsequent cooling to room temperature led to the reformation of a biphasic liquid/liquid mixture. Each phase of the resulting biphasic system was analyzed by UV-vis spectroscopy for methyl red (λ_{max} 415). The results of these studies are tabulated in Table 1. These studies show that PODA and PODMA are both phase selectively soluble on the heptane phase of the heptane/90% EtOH:H_2O thermomorphic system. The studies were less successful in the case of the heptane/DMF system though. In the case of the heptane/DMF biphasic system, PODA and PODMA precipitated out of the heptane phase after the solvent mixture reached room temperature. Evidently, while

Table 1. Phase selective solubility for poly(octadecylacrylate) and poly(octadecylmethacrylate).

Polymer	Polar solvent	Phase selective solubility in heptane (%)
PODA-MR	DMF	-[a]
PODA-MR	90% EtOH:H_2O	≥99.95
PODMA-MR	DMF	-[a]
PODMA-MR	90% EtOH:H_2O	≥99.95

Determined by using a Cary 100 scanning UV-vis spectrophotometer. [a] Could not be determined.

these polymers are soluble in heptane, small amounts of DMF present in the heptane phase make both polymers be insoluble in the heptane-rich phase that unavoidably contains some DMF.

The phase selective solubility of poly(*N*-alkylacrylamide) homopolymers were previously studied by our group.[56] Poly(*N*-alkylacrylamide)s that have *N*-alkyl substituent of 6 carbons or more showed a phase selective solubility of ≥80% to the heptane phase of a heptane/90% EtOH-water thermomorphic system. Alternatively, poly(*N*-alkylacrylamide)s that contain *N*-alkyl groups with 4 carbons or less have a phase selective solubility of ≥ 99.9% (Figure 13). While these studies of poly(*N*-alkylacrylamide)s could have involved multiple separate syntheses of dye-labeled polymers by multiple free radical polymerizations, a different strategy was used instead. These earlier studies of poly(*N*-alkylacrylamide)s[56] as well as other LCST[23] studies of poly(*N*-*i*-propylacrylamide) and poly(*N*-*n*-propylacrylamide) employed libraries of polymers that were prepared by a split-pool synthesis using an activated polyester-poly(*N*-acryloxysuccinimide) (PNASI) as the starting material (eq. 12). Such library syntheses of poly(*N*-alkylacrylamide)s using PNASI are attractive for several reasons. Such polymerization produces polymers with different substituents but which have the same polydispersity index and degree of polymerization.[23, 56] Libraries prepared in this way also have identical stereochemistry. Such similarities in library members can be assured so long as the reaction of the active ester is quantitative and so long as the preparation never involves a fractionation or precipitation step. I used a similar approach to prepare a library of poly(*N*-alkylacrylamide) copolymers that have polar and

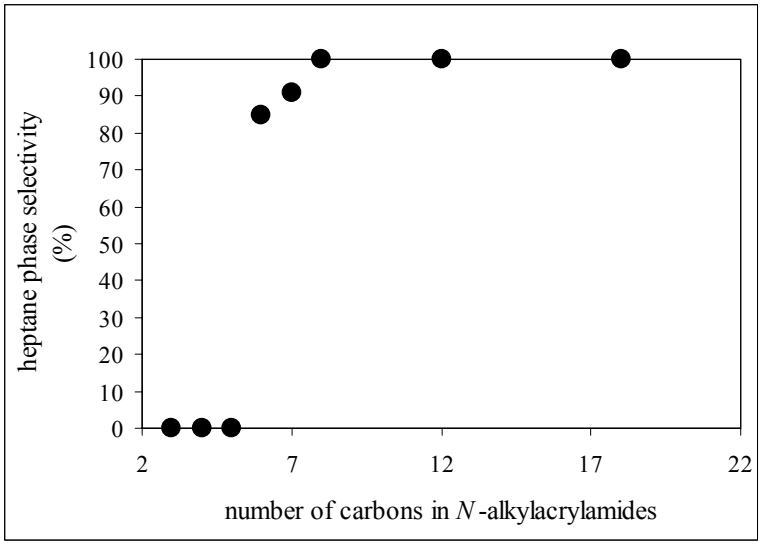
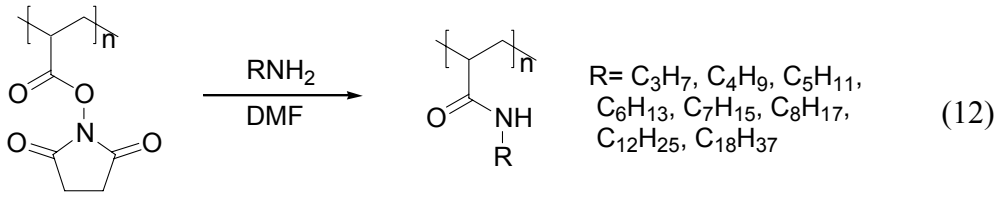


Figure 13. Phase selective solubility of poly(*N*-alkylacrylamide)s[56].

nonpolar pendant groups to understand the how such polar and nonpolar groups present in the same polymer affect their phase selective solubility.



(12)

The early approach using PNASI as the starting material works well in the synthesis of poly(*N*-alkylacrylamide) homopolymers[56] and polar copolymers like poly(*N*-*i*-propylacrylamide-*co*-*N*-*n*-propylacrylamide).[23] However, this methodology had problems when it was used to synthesize the copolymers I wanted to study. PNASI is only soluble in polar solvents such as DMF, DMA, and DMSO. For these reason,

PNASI cannot be used in the synthesis of copolymers containing nonpolar *N*-octadecyl groups that are not soluble in such solvents.

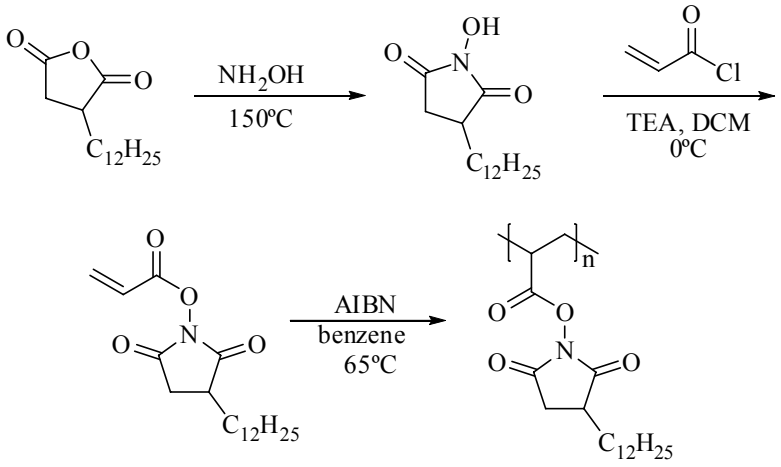
This limitation encouraged us to design a different version of PNASI that would have better solubility in the organic solvents I needed to use. This alternative active ester polymer was poly(*N*-acryloxy-2-dodecylsuccinimide) (PNADSI). PNADSI is soluble in many solvents including ethyl ether, chloroform, dichloromethane, benzene, dioxane, and THF. This greater solubility of PNADSI insures that all starting materials and products remain in solution during the synthesis of the copolymers.

Before using PNADSI, we first used PNASI for the synthesis of PNNODAM-PNNBuAM using DMF as the solvent. The result obtained was a library synthesis of copolymers with very low mol percentage of octadecylacrylamide compared to the mol percentage initially added to the reaction mixture. Octadecylamine does not have a good solubility in DMF. Thus, when a 60/40 ratio of octadecylamine to n-butylamine was used for the aminolysis of PNASI, only 21% of the *N*-alkyl substituents were octadecyl groups. Likewise, when 50, 60, 70, and 80% of octadecylamine was used for the reaction, only 30, 30, 42, and 36% of octadecylamine was attached to the polymer. Since the feed and product ratios in syntheses of poly(*N*-alkylacrylamide) were so disparate, we decided to use PNADSI as the starting polymeric material.

PNADSI **60** was synthesized following the procedure shown in Scheme 11. The monomer **59** was first synthesized starting with the commercially available dodecylsuccinic anhydride **57**. Dodecylsuccinic anhydride **57** was first allowed to react with hydroxylamine-hydrochloride at 140 ºC to produce *N*-hydroxy-2-

dodecylsuccinimide (NHDSI) **58**. This product, NHDSI, was then dissolved in CH_2Cl_2 in the presence of triethylamine. Then, acryloyl chloride was added slowly at 0 ºC. After 2 h the monomer *N*-acryloxy-2-dodecylsuccinimide (NADSI) **59** was obtained in 96 %yield. Subsequent free radical polymerization of NADSI using AIBN as the initiator produced the polymer PNADSI **60** after 3 d at 65 ºC.

Scheme 11. Synthesis of poly(*N*-acryloxy-2-dodecylsuccinimide) (PNADSI).

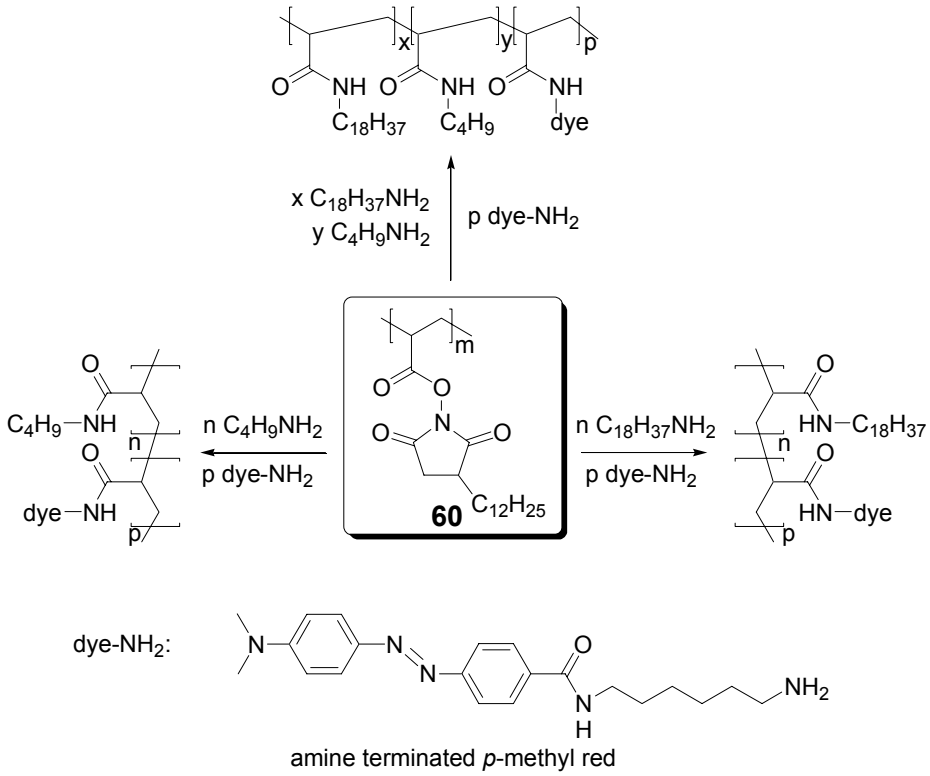


We know from previous work that poly(*N*-octadecylacrylamide) and poly(*N*-butylacrylamide) have opposite phase selective solubility. Poly(*N*-octadecylacrylamide) has a phase selective solubility of ≥ 99.9% in the nonpolar heptane rich phase of a heptane-90% ethanol-water thermomorphic system. Poly(*N*-butylacrylamide) is ≥ 99.9% selective to the 90% ethanol-water rich phase of the thermomorphic system described above. These earlier studies also demonstrate that polymers with *N*-alkyl groups larger than poly(*N*-butylacrylamide) dramatically affect the phase selective

solubility of a polymer in the nonpolar phase of these liquid/liquid biphasic systems. However, these studies did not show how a mixture of polar and nonpolar *N*-alkyl substituents in the same polymer will affect the polymer's phase selective solubility. This was of interest because if low loadings of nonpolar group were sufficient to determine phase selective solubility, we could prepare poly(*N*-octadecylacrylamide) containing polymers with high mol% loading of polar functionality that could be used for sequestration or as reagents or catalysts.

To understand the relative importance of the polar and nonpolar *N*-alkyl group in determining the phase selective solubility of the copolymer we created a library of *p*-methyl red labeled poly(*N*-octadecylacrylamide-*co*-*N*-butylacrylamide) (PNNODAM-PNNBuAM) copolymers with different ratios of *N*-octadecyl and *N*-butyl acrylamide groups. PNADSI **60** was used as the starting material to prepare this library of poly(*N*-alkylacrylamide) copolymers. To confirm that the aminolysis of PNADSI **60** produced polymers similar to those previously described, we first prepared poly(*N*-*n*-butylacrylamide) and poly(*N*-octadecylacrylamide) and studied their phase selective solubility. The phase selective solubility of the homopolymers prepared using PNADSI showed the same phase selective solubility as poly(*N*-*n*-butylacrylamide) and poly(*N*-octadecylacrylamide) prepared by previous methods. Subsequently we prepared several PNNODAM-PNNBuAM copolymers by allowing PNADSI to react with different ratios of octadecylamine, *n*-butylamine and *p*-methyl red in CH_2Cl_2 (Scheme 12). The average ratio of amines was 100:1 for octadecylamine/*n*-butylamine: *p*-methyl red. A 3.5 fold excess of amines was used to insure complete substitution of the activated esters.

Scheme 12. Split-pool synthesis of poly(*N*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers with different ratios of octadecylamine and *n*-butylamine.



Incomplete substitution of the PNADSI **60** had to be avoided because the active ester could later react with adventitious water to form acrylic acid groups that would affect the phase selective solubility of the copolymers. While the aminolysis of PNADSI allowed us to consume all the active ester groups and to form the copolymers, the product solution contains a mixture that needs to be purified. For example, since an excess of amines was used to avoid the presence of unreacted activated ester, unreacted amines are still present at the end of the reaction. Also, the amidation of the polymeric active ester produces *N*-hydroxy-2-dodecylsuccinimide as a byproduct. Techniques such as solvent

precipitation and membrane filtration would traditionally be used to purify these polymers. However, in our case, these techniques were excluded because they will fractionate the copolymers. That would produce product copolymers that would likely have different polydispersity, different degrees of polymerization, possibly different stereochemistry, and possibly different solubility. Therefore, we decided to purify the polymer products from contaminants using solid phase resin sequestrants that separate studies show are unreactive to the desired polyacrylamide products. Amberlyst 15 and Amberlite IRA 400 ($^-$OH form) resins were chosen for this purpose.

Amberlyst 15 is a very useful agent for amine sequestration. This sulfonic acid ion-exchange resin has been previously used by a number of groups to remove amines at the end of a reaction.[75, 76] It was also used to remove amines from *p*-methyl red labeled poly(*N*-alkylacrylamide) formed by the substitution reaction of PNASI.[56] UV-vis spectroscopic analyses also showed that Amberlyst 15 effectively removed amines from the polymer without sorbing polyacrylamides and changing the polyacrylamide concentration.

Hydroxy-2-dodecylsuccinimide was also removed from our final polymeric product in a similar way using an ion exchange resin. Amberlite IRA 400 ($^-$OH form) is a useful basic sequestering agent that we found could be used for the removal of *N*-hydroxysuccinimides. A literature survey showed that independent work had effected similar chemistry. Control experiments determined the efficiency of Amberlite IRA 400 ($^-$OH form) removing *N*-hydroxy-2-dodecylsuccinimide. In these experiments, different amounts of Amberlite IRA 400 ($^-$OH form) were added to different solutions containing

approximately 1.50 mmol of NHDSI. The results obtained were that approximately 2 equivalents of Amberlite IRA 400 ($^-$OH form) were required to completely sequester the NHDSI from the solution (Figure 14). Separates studies were done to determine whether or not the basic resin adsorbs the copolymer. The UV-vis absorption of *p*-methyl red labeled PNNODAM-PNNBuAM copolymers dissolved in CH_2Cl_2 was measured before and after their treatment with the resin. These UV-vis spectroscopic analyses established that the ammonium hydroxide resin, Amberlite IRA 400 ($^-$OH form), only sequesters low molecular weight products and that no detectable polymeric material was absorbed by the basic resin.

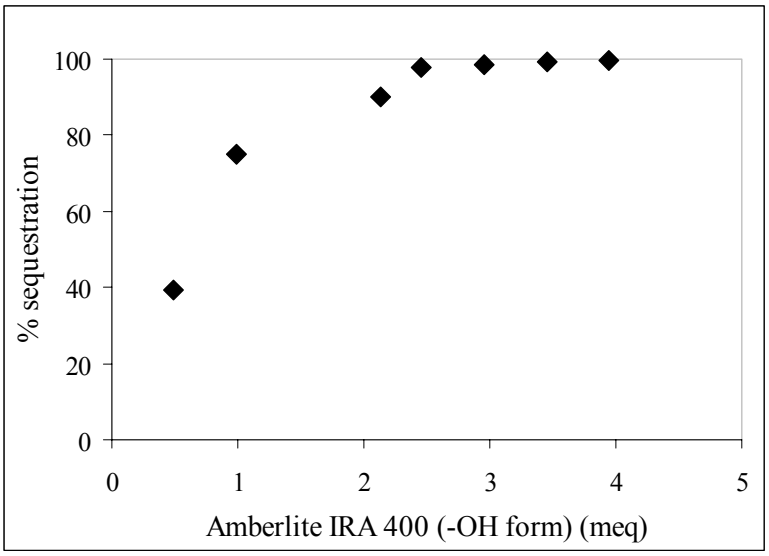


Figure 14. Sequestration of *N*-hydroxy-2-dodecylsuccinimide (1.5mmol) with Amberlite IRA 400 ($^-$OH) in CH_2Cl_2.

The PNNODAM-PNNBuAM copolymers prepared in these library syntheses were characterized by ^{1}H NMR spectroscopy and gel permeation chromatography. The ratio of octadecylamine and *n*-butylamine on PNNODAM-PNNBuAM copolymers was determined by ^{1}H NMR spectroscopy. The methyl groups of octadecylacrylamide and *n*-butylacrylamide have different shifts in the ^{1}H NMR spectroscopic data. The CH_3 group of octadecylacrylamide in the copolymer has a chemical shift of δ 0.88 ppm, and the CH_3 group of the *n*-butylacrylamide in the copolymer has a chemical shift of δ 0.92 ppm. As can be seen from Figure 15, the integrated signal for the CH_3 peak of the octadecylacrylamide increases when a higher amount of octadecylamine was used during the aminolysis of PNADSI. The integration of the methyl peaks clearly showed that octadecylamine and *n*-butylamine react at approximately the same rate with the activated polyester-PNADSI. Such analyses showed, for example, that when an 80:20 ratio of *n*-butylamine:octadecylamine was used to prepare a copolymer, that 25% of the alkyl groups in the polymer product were octadecylacrylamide groups. Similar results were observed for the other PNNODAM-PNNBuAM copolymers showing that library copolymer members prepared using PNADSI have a C_{18}/C_4 ratio that approximate the C_{18}/C_4 ratio of starting amines (Table 2).

Gel permeation chromatography (GPC) was used to determine the molecular weight and the polydispersity index for PNNODAM-PNNBuAM copolymers. The GPC instrument uses a fluorinated mixed bed column and light scattering, viscometry, and refractive index detectors. The fluorinated column was used to diminish sorption of the polyacrylamides seen with other columns. The data obtained from the GPC studies

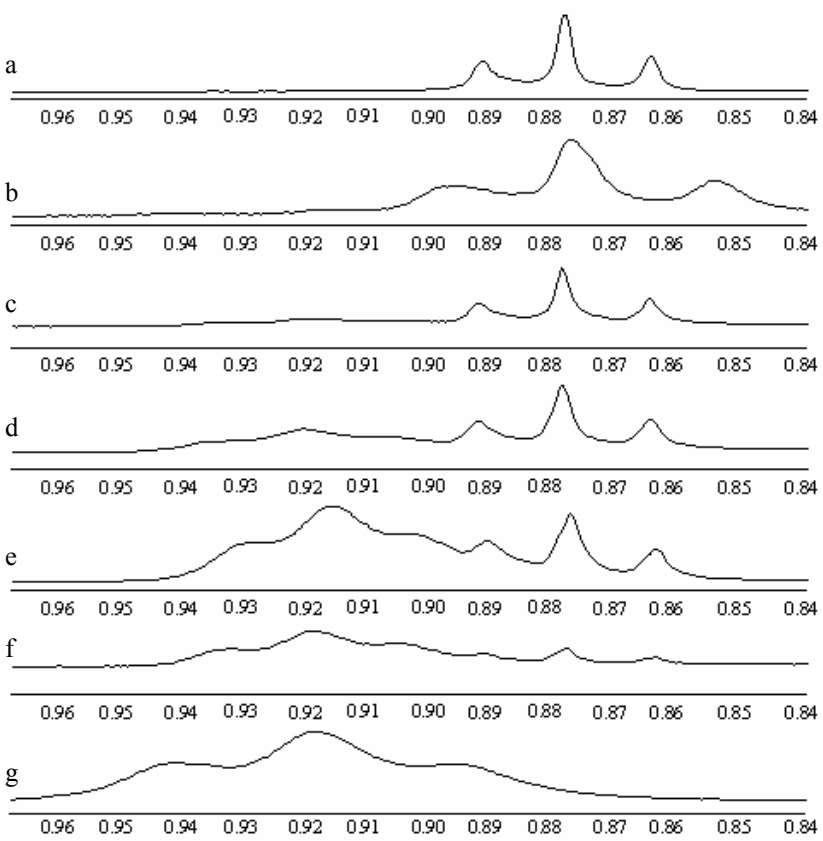


Figure 15. ^{1}H NMR (500 MHz, $CDCl_3$) spectroscopic analysis of the ratio of *n*-butyl/*n*-octadecyl groups in poly(*N*-*n*-octadecylacrylamide)-*c*-poly(*N*-*n*-butylacrylamide) copolymers using the integration of methyl groups to determine the mole percent of *n*-octadecyl groups in the copolymers: (a) 100 mol % octadecyl; (b) 86% mol % octadecyl; (c) 73 mol % octadecyl; (d) 57%; (e) 35 mol % octadecyl; (f) 25 mol %; (g) 0 mol % octadecyl.

Table 2. Mol % of *N*-octadecylacrylamide obtained for PNNODAM-PNNBuAM.

amount of octadecylamine added (mol %)	amount of octadecyl obtained in the copolymer (mol %)
90	88
80	83
70	73
60	63
50	55
40	48
20	25
10	15

demonstrated that PNNODAM-PNNBuAM copolymers have similar degrees of polymerization and PDIs (Table 3). PNNODAM-PNNBuAM copolymers have a degree of polymerization of ca 200 ± 20 and a PDI of ca 2.1. Poly(*N*-octadecylacrylamide) showed a lower DP and an higher PDI than the other polymers in the table. Previously we have seen that polyalkylacrylamides have strong interactions with the column affecting the GPC analyses. We believe that the different PDI and DP of poly(*N*-octadecylacrylamide) measured in this analysis is caused by strong column-substrate interactions. What it is certain is that we obtained expected PDIs for the other polymers, PDIs that are consistent with conventional free radical polymerization that suggest no fractionation occurred since other studies have shown that fractionation of similar poly(*N*-alkylacrylamide)s significantly alters this PDI value. We also obtained similar degree of polymerizations for the polymers, which is consistent with the method used to prepare PNNODAM-PNNBuAM copolymers.

Table 3. Molecular weights, degrees of polymerization, and polydispersity indices for poly(*N*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers.

Octadecylacrylamide (mol%)	M_w	DP	PDI
100	143,820	143	3.12
58	94,120	228	2.11
48	79,300	213	2.08
0	57,410	180	2.5

The phase selective solubility of PNNODAM-PNNBuAM copolymers so formed were studied in a heptane/DMF thermomorphic liquid/liquid biphasic system. The polymers were first dissolved in either the polar or the nonpolar solvent so as to form solutions that have a concentration of 10^{-4} M of *p*-methyl red. Then the other solvent (heptane or DMF) was added and the thermomorphic system was then heated to 70 ºC to form a homogeneous solution. After allowing the mixture to cool to room temperature, a biphasic liquid/liquid system was formed. Each phase of the thermomorphic biphasic systems was then analyzed using a Cary 100 scanning UV/vis spectrophotometer. Figure 16 is a picture of the resulting thermomorphic biphasic systems obtained for each polymer. The results obtained from the spectroscopic analyses are tabulated in Figure 17 and in Table 4.

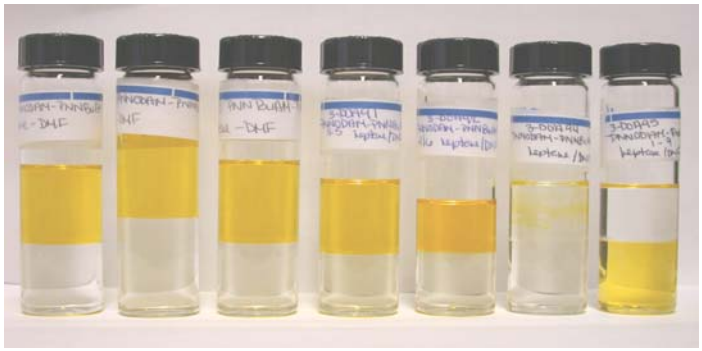


Figure 16. Heptane/DMF biphasic systems for poly(*N*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers.

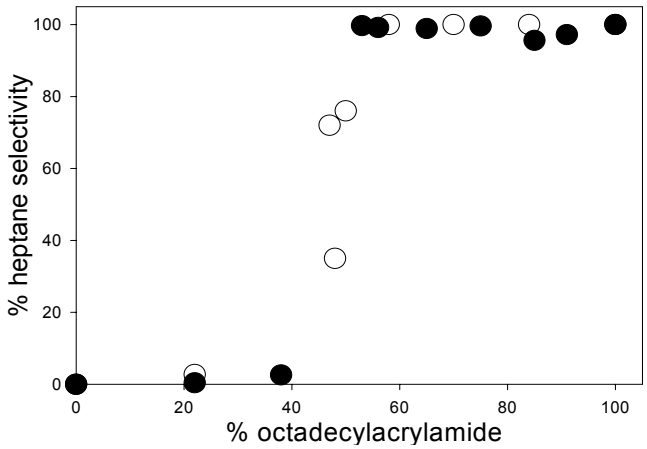


Figure 17. Heptane phase selective solubility of poly(*N*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers.

Table 4. Phase selective solubility of poly(*N*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers.

octadecyl content of copolymer (mol%)	solubility ratio (nonpolar:polar)	phase selective solubility in heptane (%)
100	>2000:1	99.99
88	>1000:1	99.9
84	>1000:1	99.9
75	>1000:1	99.6
70	>1000:1	99.9
65	>1000:1	99.8
58	>1000:1	99.9
56	780:1	99.2
53	>660:1	99.7
50	3.4:1	76
48	1:2	35
47	3:1	72
38	1:37	2.6
22	1:725	2.7
22	1:949	0.4
0	1:>1000	0.2

The results obtained for PNNODAM-PNNBuAM copolymers show that the hydrophobic octadecylacrylamide and the hydrophilic *n*-butylacrylamide group are of comparable importance in determining the phase selective solubility of these copolymers. As an example, a copolymer that contains 50% of octadecylacrylamide repeating unit has approximately 50% phase selective solubility in the heptane phase of the heptane/DMF liquid/liquid biphasic system. While we hoped that the hydrophobicity of poly(*N*-octadecylacrylamide) would dominate the solubility of the copolymer, the results suggest that at least in a mass sense the more hydrophilic groups are more important. These results are however understandable because polar-polar interactions are stronger than hydrophobic interactions. However, while we did not see the desired control of phase selective solubility, these studies of PNNODAM-PNNBuAM copolymers do show a dramatic change in the phase selective solubility in the nonpolar heptane phase with varying composition of *n*-butyl and *n*-octadecylacrylamide repeating units (Table 4). Indeed, going from 40 mol% octadecyl groups to 58% of octadecyl groups produces a ca. 10^5 –fold difference in phase selective solubility in the poly(*N*-alkylacrylamide) copolymers.

Earlier phase selective solubility studies of poly(*N*-alkylacrylamide)s clearly demonstrated that changing the *N*-alkyl substituents on the polymer can produce a dramatic change in the polymer's phase selective solubility. We also sought to determine if similar changes would be observed for tertiary poly(*N*,*N*-dialkylacrylamide)s in a number of different thermomorphic nonpolar/ polar solvent mixtures. However, in these cases the synthesis of poly(*N*-alkylacrylamide)s that

employed PNASI or PNADSI as the starting material could not be used to prepare tertiary polyacrylamides since secondary amines react significantly slower than primary amines. Studies using the aminolysis of PNASI to prepare tertiary polyacrylamides showed incomplete aminolysis often occurred. Since any unreacted reactive ester could easily hydrolyze to form carboxylic acid groups that would affect the phase selective solubility of the polymers, we had to separately polymerize poly(*N*,*N*-dialkylacrylamide)s without using the prior library synthesis if we wanted to analyze the effects of *N*-alkyl group size on the phase selective solubility of these polymers.

Poly(*N*,*N*-dialkylacrylamide)s were synthesized using the sequence shown in Scheme 13. This work was carried out with the assistant of an REU student- Ms. Nydea Avilés-Ramos. First, the monomers were obtained after the reaction of acryloyl chloride with the respective secondary amines. When excess amount of TEA was used in the reaction, the Michael addition byproduct was obtained. To minimize the formation of the Michael addition byproduct a 1:1.5 mixture of TEA: acryloyl chloride was used instead. Once pure monomers were obtained, polymerizations were carried out in dioxane using AIBN as the initiator at 65 ºC for 36h. A 3 mol% loading of *p*-methyl red was incorporated in the monomer feed so that a spectroscopic label would be present for the phase selective solubility studies. The tertiary polyacrylamides prepared included poly(*N*,*N*-dimethylacrylamide) **67**, poly(*N*,*N*-diethylacrylamide) **68**, poly(*N*,*N*-dipropylacrylamide) **69**, poly(*N*,*N*-dibutylacrylamide) **70**, poly(*N*,*N*-dihexylacrylamide) **71**, and poly(*N*,*N*-didecylacrylamide) **72**. These polymers do not have the same degree of polymerizations and are not as comparable as the polymers prepared using the

procedure of the aminolysis of PNADSI or PNASI. Molecular weights for poly(*N*,*N*-dialkylacrylamide)s ranged form 50,000-80,000 as can be seen in Table 5. Such molecular weights correspond to degrees of polymerization of 160-610. Also, these polymers had low PDIs that ranged from 1.13 to 1.67. These low PDIs were expected since the polymers were purify by a series of steps that could involve polymer fractionation.

Scheme 13. Synthesis of poly(*N*,*N*-dialkylacrylamide)s.

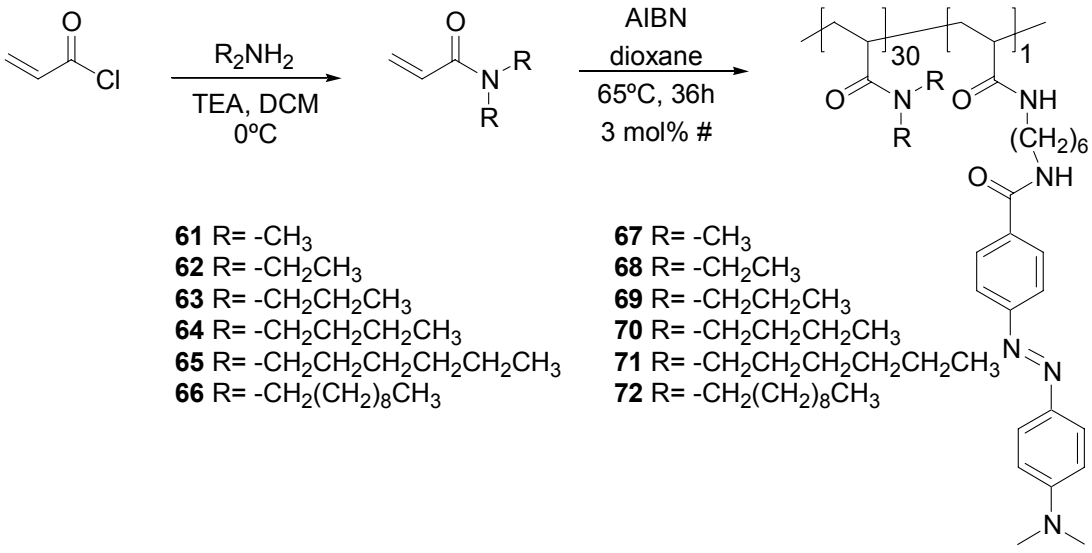


Table 5. Molecular weights, polydispersity indices, and degrees of polymerization for poly(*N,N*-dialkylacrylamide)s.

Polymer	M_w (Daltons)	PDI	DP
67	60,430	1.13	528
68	48,420	1.43	261
69	32,070	1.60	127
70	72,880	1.34	292
71	84,640	1.67	210
72	56,330	1.62	98

With a collection of poly(*N*,*N*-dialkylacrylamide)s in hand, phase selective solubilities of polymers **67-72** were carried out in four different thermomorphic liquid/liquid biphasic systems. The thermomorphic systems used were heptane/DMF, heptane/90% EtOH:H_2O, heptane/ethylene glycol diacetate, and heptane/dimethyl carbonate. In these studies, the polymer of interest was first dissolved in a solvent it will dissolve in so as to form a solution that was 10^{-4} N in terms of polymer bound spectroscopic label *p*-methyl red. Addition of an equal volume of the other polar or nonpolar solvent then produced a biphasic liquid/liquid mixture. After heating this biphasic system to 70 ºC, a clear homogeneous solution was obtained. The homogeneous solution was allowed to cool to room temperature at which point the original biphasic system reformed. The phase changes that occurred are illustrated in Figure 18.

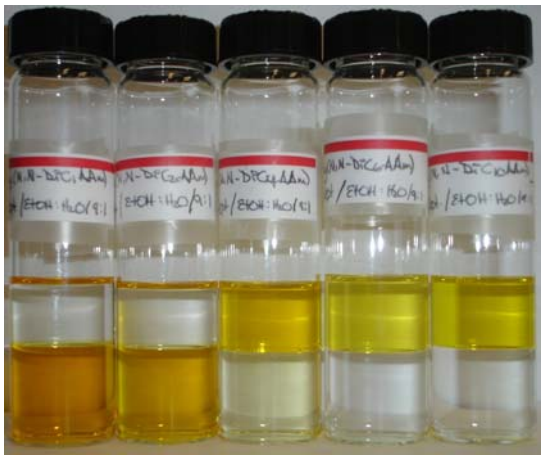


Figure 18. Heptane/90% EtOH-H_2O biphasic systems for poly(*N*, *N*-dialkylacrylamide)s.

The results of these studies shown in Table 6, and Figures 18 and 19 show that poly(*N*,*N*-dimethylacrylamide) **67**, poly(*N*,*N*-diethylacrylamide) **68**, poly(*N*,*N*-dipropylacrylamide) **69** were selectively soluble to the polar phase of the thermomorphic biphasic systems. Such polymers were ≥1000:1 selectively soluble in the ethanol-rich, DMF-rich, and dimethylcarbonate-rich phases. Poly(*N*,*N*-dialkylacrylamide)s containing 4 carbons or more in the *N*-alkyl substituent were selectively soluble to the nonpolar phase of the thermomorphic systems. Similar trends were seen in the four different thermomorphic systems. Only in the case of poly(*N*,*N*-dibutylacrylamide) was a modest phase selective solubility seen. In that case, a pentadecane/dimethylcarbonate liquid/liquid biphasic system, the poly(*N*,*N*-dibutylacrylamide) was not very soluble in either pentadecane or dimethylcarbonate.

Table 6. Phase selective solubility of poly(*N,N*-dialkylacrylamide)s in different thermomorphic solvent mixtures.

polymer	solvent mixture (50:50, vol/vol)	solubility ratio (nonpolar:polar)	phase selective solubility (%)
67	heptane-DMF	1:>678	0.15
68	heptane-DMF	1:>1000	0.1
69	heptane-DMF	1:>1000	0.07
70[b]	heptane-DMF	>50:1	98.0
71	heptane-DMF	>420:1	99.8
72[b]	heptane-DMF	>784:1	99.9
67	heptane-90% EtOH-H_2O	1:>1000	0.1
68	heptane-90% EtOH-H_2O	1:>1000	0.1
69	heptane-90% EtOH-H_2O	1:>1000	0.05
70	heptane-90% EtOH-H_2O	>1000:1	99.9
71	heptane-90% EtOH-H_2O	>525:1	99.8
72	heptane-90% EtOH-H_2O	>190:1	99.5
67	heptane-$AcOCH_2CH_2OAc$	1:>2000	0.05
68	heptane-$AcOCH_2CH_2OAc$	1:>2000	0.05
69	heptane-$AcOCH_2CH_2OAc$	1:2.7	27.0
70	heptane-$AcOCH_2CH_2OAc$	>1000:1	99.9
71	heptane-$AcOCH_2CH_2OAc$	>500:1	99.8
72	heptane-$AcOCH_2CH_2OAc$	>500:1	99.8
67	pentadecane-$CH_3OCOOCH_3$	1:>2000	0.05
68	pentadecane-$CH_3OCOOCH_3$	1>>2000	0.05
69	pentadecane-$CH_3OCOOCH_3$	1:>2000	0.05

Table 6. Continued.

polymer	solvent mixture (50:50, vol/vol)	solubility ratio (nonpolar:polar)	phase selective solubility (%)
70	pentadecane-$CH_3OCOOCH_3$	1:3	25
71	pentadecane-$CH_3OCOOCH_3$	> 513:1	99.8
72	pentadecane-$CH_3OCOOCH_3$	> 140:1	99.3

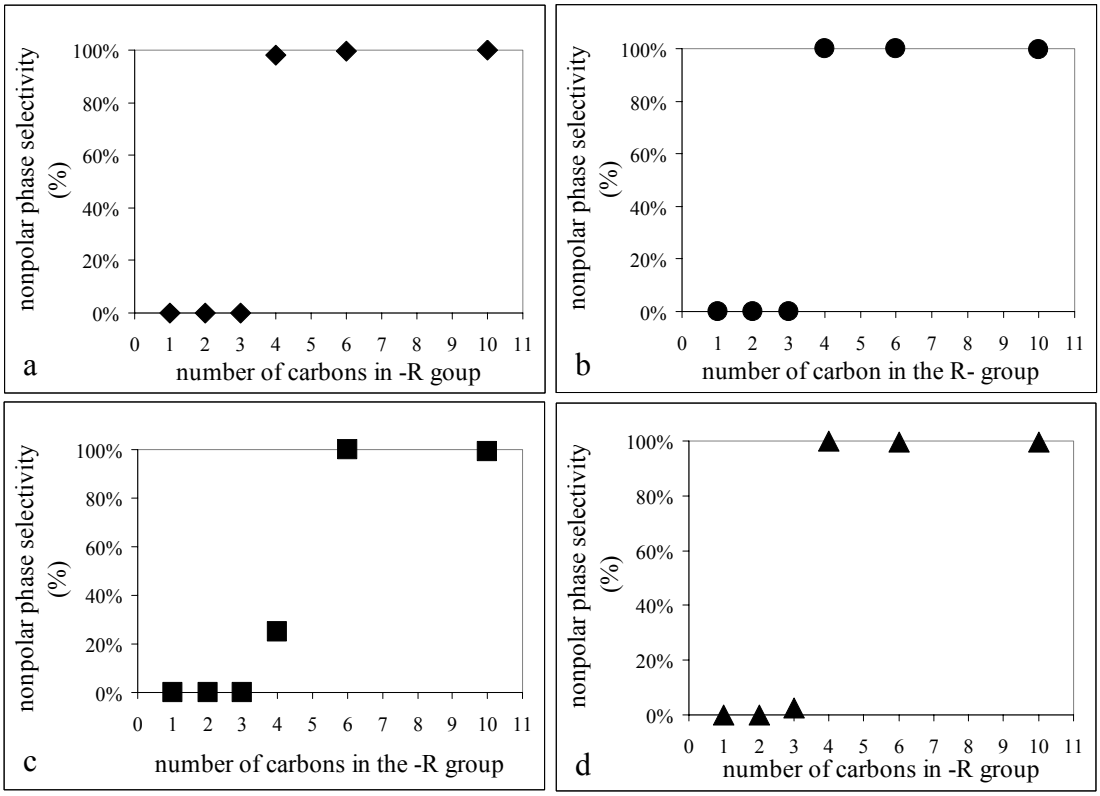


Figure 19. Nonpolar phase selective solubility of poly(*N,N*-dialkylacrylamide)s in a) heptane/DMF; b) heptane/90% EtOH:H_2O; c) heptane/ethylene glycol diacetate and; d) pentadecane/dimethyl carbonate.

Once again, dramatic changes in phase selective solubility like those seen in earlier work area are seen for both secondary poly(*N*-alkylacrylamide)s and tertiary poly(*N*,*N*-dialkylacrylamide)s with changes in their *N*-alkyl groups. The results obtained from the studies of poly(*N*,*N*-dialkylacrylamide)s show that the phase selective solubility of the polymers does not depend only on the size of the *N*-alkyl group. Changing from propyl to butyl groups in poly(*N*,*N*-dialkylacrylamide)s, a total of 6 to 8 carbons in the *N*-alkyl substituents, have similar effect in the phase selective solubility than changing from 5 to 6 carbons in the *N*-alkyl groups in poly(*N*-alkylacrylamide)s. This suggests that the total number of carbons in the substituents is more important than the length of the alkyl chain in the determination of the phase selective solubility of the polymers in liquid/liquid biphasic systems.

Conclusion

Soluble polymer supports can be design to have a phase selective solubility to the nonpolar or the polar phase of a thermomorphic or latent biphasic system. Poly(octadecylacrylate) and poly(octadecylmethacrylate) exhibit a phase selective solubility in the heptane phase of both heptane/90% EtOH: H_2O and heptane/DMF thermomorphic systems. PNADSI demonstrated to be a more useful precursor for the synthesis of poly(*N*-alkylacrylamide)s. Poly(*N*-alkylacrylamide)s synthesized using PNADSI can be easily purified using sequestering resins, Amberlyst 15 and Amberlite IRA 400 (-OH). The studies of the PNNODAM-PNNBuAM copolymers showed that both *n*-octadecylacrylamide and *n*-butylacrylamide groups are of comparable importance

in the determination of the copolymer's phase selective solubility. As it is true for poly(*N*-alkylacrylamide)s, poly(*N*,*N*-dialkylacrylamide)s exhibit a phase selective solubility that depends on the total amount of carbons in the *N*-alkyl groups. Poly(*N*-alkylacrylamide) with an *N*-alkyl group of six carbons is selectively soluble to the heptane phase of a heptane/DMF thermomorphic system. Likewise, poly(*N*,*N*-dibutylacrylamide) that have a total of 8 carbons in the *N*-alkyl group is selectively soluble to the heptane phase of the liquid/liquid biphasic system.

CHAPTER III

POLYISOBUTYLENE-SUPPORTED ORGANOCATALYSTS

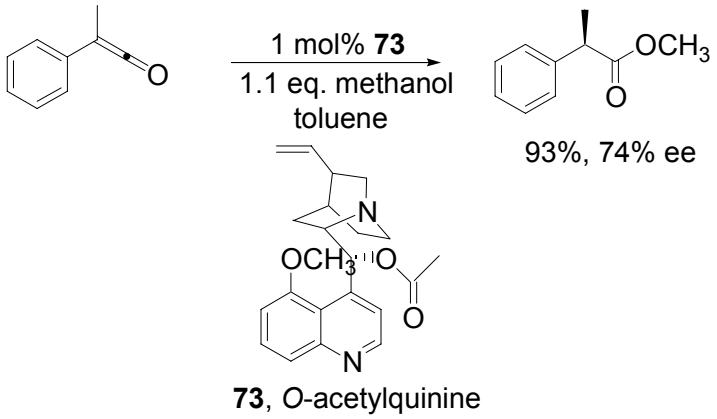
Introduction

Catalytic reactions for the enantioselective synthesis of organic molecules have mostly employed transition metal complexes and enzymes. In 2001, William S. Knowles and Ryoji Nojori were awarded the Nobel Prize in Chemistry for their work in catalytic asymmetric hydrogenation reactions. K. Barry Sharpless received a share of this prize for his work on chiral catalytic oxidation reactions. All three Nobel Laureates developed chiral transition metal complexes for these chiral hydrogenation and chiral oxidation reactions. Scientists used to believe that only transition metal complexes can usefully produce enantiomerically pure products when enzymes cannot. Recent advances in the field of catalysis have demonstrated that not only transition metal complexes and enzymes lead to products with high enantioselectivity. Organic catalysts too are effective.

An organic catalyst, also known as a metal-free catalyst, can be defined as a simple molecule capable of promoting a given transformation without the involvement of any metal in the catalytic reaction. The catalytic activity of an organocatalyst resides in the small molecule itself. Organic catalysts have several advantages over transition metal catalysts. Organocatalysts are usually robust, inexpensive, and readily available. Some organocatalysts can be found in nature and are ready to be used as is, e.g. proline, guanidine, and quinine. Because of its non-toxicity, an organocatalyst is ideal for the

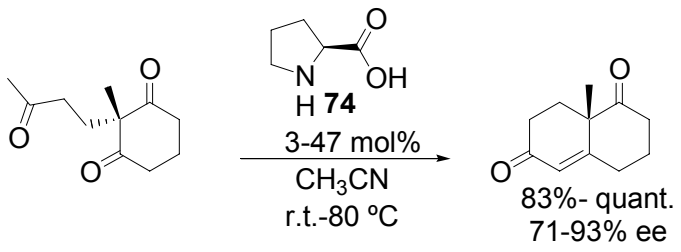
synthesis of products that are intolerant to metal contamination, such as drugs. Unlike transition metal complexes, organocatalysts are inert to moisture and oxygen so they can be used in wet solvents and under aerobic conditions.

Small organic molecules have been known to catalyze organic transformations for over 95 years. The first example known of a small organic molecule catalyzing a reaction was reported in 1912 by Bredig and Fiske.[7] Bredig and Fiske described the asymmetric addition reaction of HCN to benzaldehyde catalyzed by quinine and quinidine. The resulting cyanohydrins were optically active and had opposite chirality. Further studies of the use of quinine as an organocatalyst lead to the discovery of the asymmetric addition of methanol to ketenes. In 1960, Pracejus described the use of *O*-acetylquinine **73** as a catalyst for the addition of methanol to phenylmethylketene (eq. 13). The product from this reaction was obtained in 93% yield and 74 % ee.



(13)

The use of amino acids as catalysts for the asymmetric aldol reaction was first described by Fischer and Marschall in 1931.[77] In 1971, the Hajos-Parrish-Eder-Sauer-Wiechert reaction catalyzed by proline **74** was discovered.[78, 79] In this case, proline catalyzed the intramolecular asymmetric aldol reaction of a trione with the Weiland-Miescher ketone, an intermediate in steroid synthesis (eq. 14). The product ketone was obtained in 83%-quantitative yield and in 71-93% ee. However, in spite of this industrially practical success, proline was not further explored as an organocatalyst for the asymmetric aldol reactions until 2000.



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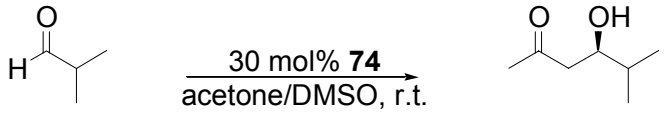
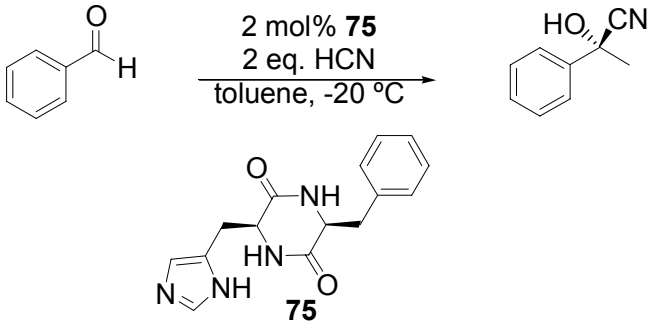
In 2000, List described the use of proline as a catalyst for the intermolecular aldol reaction of acetone to a variety of aldehydes.[39, 80] In an example, acetone was added to *iso*-butyraldehyde using 30 mol% of proline as the catalyst in DMSO (eq. 15). The aldol product was obtained in 97% yield and high enantiomeric excess (96% ee). Since the pioneering study of List, proline has been studied in many different sorts of reactions including the aldol, Mannich, Michael, Diels-Alder, and other reactions.



(15)

Interest in producing chiral compounds without using transition metal complexes or enzymes has led to the development of a variety of organic catalysts. For example, peptides and polyamino acids have been designed to catalyze specific reactions. The cyclic dipeptide catalyst **75** was used to catalyze the addition of HCN to benzaldehyde affording the cyanohydrin product in 90% ee (eq. 16).[81, 82] Also, a poly(*L*-alanine) was designed to catalyze the Juliá-Colonna epoxidation of chalcone (eq. 17).[83] The epoxide products were obtained in 85% yields and ee higher than 93%.



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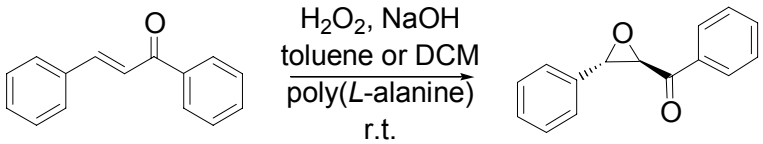
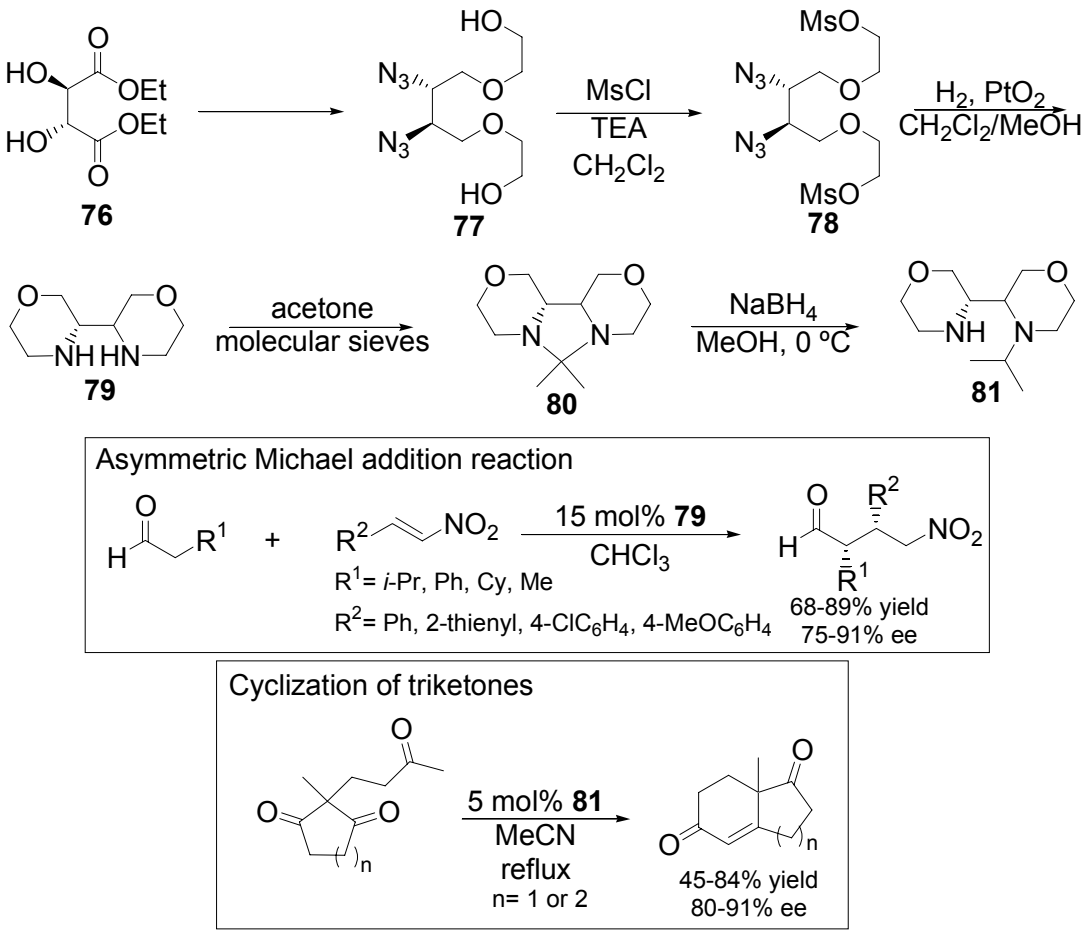


(17)

The ideal organocatalyst is a small, simple, and readily available compound such as proline. However, not all organocatalysts share proline's simplicity and efficiency. More complex organocatalysts are being developed too. Such complex catalysts can be useful if small catalysts are inefficient. Long and tedious synthetic processes required to make these catalysts do though lead to limitations and such complex organocatalysts should only be used if the catalyst displays exceptional catalytic activity and excellent chemical behavior, e.g. lower molar amounts of catalyst are needed, or higher enantioselectivity are obtained.

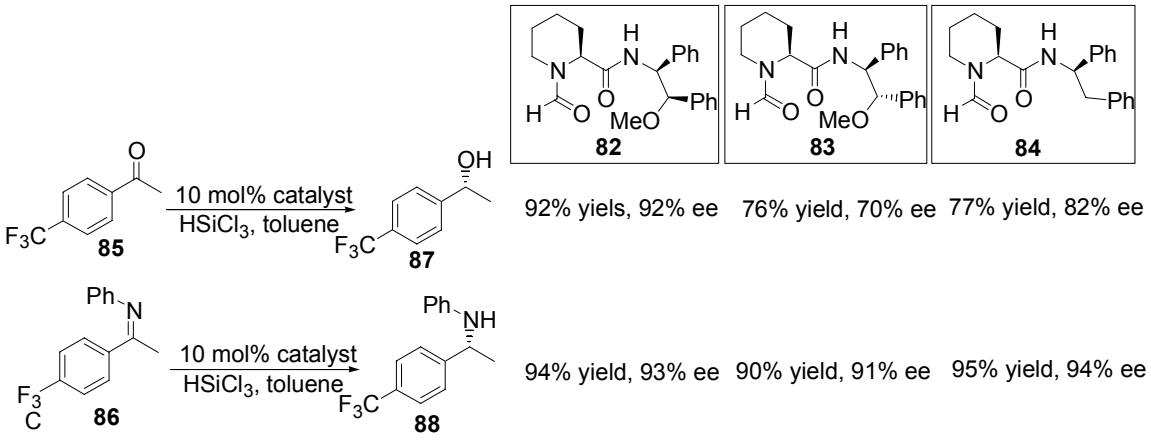
Recently, Alexakis and Kanger reported the synthesis and use of a new class of organocatalyst, 3,3'-bimorpholine derivatives.[84] The synthesis of the bimorpholine derived catalysts required 3 to 5 synthetic steps, as shown in Scheme 13. Bimorpholine **79** and **81** were used for the Michael addition reactions of ketones to nitrostyrene and for the cyclization of triketones, respectively. Such reactions produced products in good to high yields, and excellent enantioselectivities (up to 95% ee).

Scheme 13. Synthesis of 3,3'-bimorpholine derivatives for asymmetric Michael addition and cyclization of triketones.



The asymmetric reduction of ketones and imines is an important topic in organic synthesis. There are a variety of highly efficient catalysts for the reduction of ketones and imines. Most of these catalytic reactions involve the use of transition metal complexes. Recently, Sun and coworkers described the use of *L*-picolinic acid derived Lewis basic *N*-formamides in the asymmetric reduction of ketones and imines by $HSiCl_3$.[85] Catalysts **82**, **83**, and **84** reduced ketone **85** and imine **86** to the respective products, **87** and **88**, in excellent yield and with high ee (Scheme 14).

Scheme 14. The use of *N*-formamide derivatives as catalysts for the asymmetric reduction of ketones and imines.



The recycling of a catalyst has an important impact on the environment and on catalyst's costs, especially for catalysts that are produced in a multistep synthesis. Catalysts that require the use of expensive starting materials, and catalysts that are needed in large quantities are also good candidates for recycling. The major drives for immobilizing a catalyst onto a polymer support are to facilitate the recovery and recycle of any given catalyst and to decrease or eliminate any residual amount of catalyst in the product. In this chapter I am going to describe some success in the use of polyisobutylene (PIB) as a supports for an organic catalyst- *N*-oxide- used to catalyze the allylation of aldehydes. I will also describe some other incomplete work- work where I attempted to immobilize some H-bonding and proline like catalysts on polyisobutylene and polydimethylsiloxane. While those projects did not reach successful conclusions, the results are presented to aid others who may seek to effect similar chemistry.

Results and Discussion

PIB-supported thioureas

Lewis acid catalysts have been widely used as electrophiles to activate carbonyl compounds. Recently, there has been significant attention given to and remarkable advances in the design of organic catalysts that can activate carbonyl compounds. Nature often achieves the goal of activation of a carbonyl group to nucleophilic attack through the use of Lewis acid catalysis. The necessary Lewis acid can be a metal but is often a simple proton. While the proton is certainly the simplest and often one of the best carbonyl activators, not all reactions can tolerate the proton's presence since many nucleophiles rapidly deactivate under acidic conditions. This has led to interest in Bronsted acid catalysis where the proton activation of the carbonyl group involves hydrogen bonding. For example, thiourea derivatives and TADDOL derivatives are neutral catalysts that can activate carbonyl compounds by hydrogen bonding.[86]

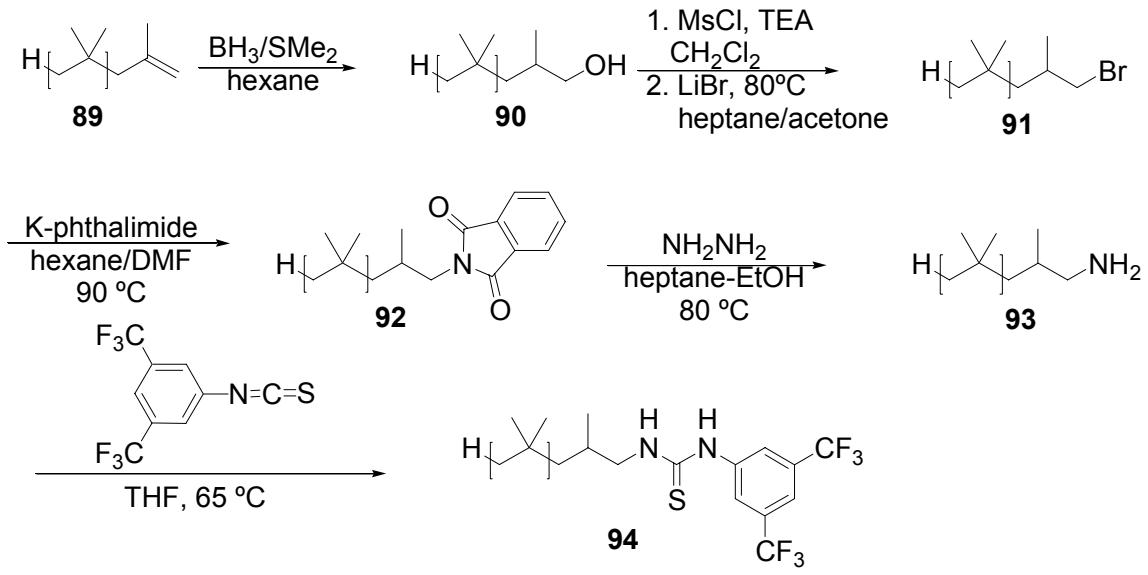
Thioureas have been extensively studied as organocatalysts since 1998 when Jacobsen reported the asymmetric hydrocyanation of imines using a thiourea derivative for the synthesis of amino acids.[87] Since Jacobsen's discovery, many groups have reported a variety of different thioureas that can be used as asymmetric catalysts for many sorts of reactions. Schreiner described the use of thioureas as catalysts for acetalization and Diels-Alder reactions. Wang reported the use of thiourea derivatives as catalysts for Michael addition reactions[88-90] and Morita-Baylis-Hillman reactions,[91] Deng described their use for Mannich reactions,[92] Soós examined them for the addition of

nitroalkanes to chalcones,[93] and Jacobsen noted their utility for the Michael addition,[94] Mannich,[95] Strecker,[96] and phosphorylation reactions.

Schreiner was able to catalyze the acetalization of a variety of aldehydes using *N*,*N'*-bis[3,5-bis(trifluoromethyl)phenyl] thiourea.[97] Schreiner acetalized a series of aromatic and aliphatic aldehydes in the presence of a trialkylorthoformate in ethanol using 1 mol% of *N*,*N'*-bis[3,5-bis(trifluoromethyl)phenyl] thiourea. Product acetals obtained from the acetalization of aldehydes were obtained in 65-99% yield. Therefore, we decided to study the utility of PIB-supported thiourea derivatives for the acetalization of aldehydes following Schreiner's procedures.

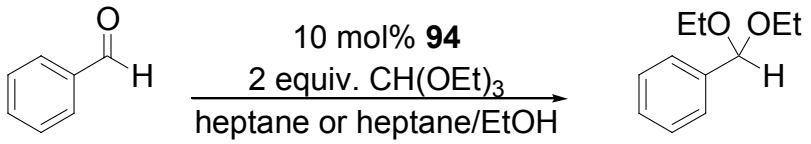
We synthesized PIB-supported thiourea **94** following Scheme 15. The synthesis started with the hydroboration of PIB-alkene **89** to form PIB-OH **90**. Then, the alcohol was converted to PIB-Br **91** in two steps: we first formed PIB-OMS, and secondly we treated the PIB-OMs with LiBr to form PIB-Br **91**. PIB-Br **91** was converted to PIB-phthalimide **92** after its treatment with potassium-phthalimide in a 1:1 vol:vol mixture of heptane/DMF at 90 ºC. PIB-phthalimide was reduced to PIB-NH_2 **93** with hydrazine hydrate in heptane-ethanol at 80 ºC. Finally, PIB-NH_2 **93** was allowed to react with 3,4-bistrifluorophenyl isothiocyanate in THF to form the PIB-supported thiourea catalyst **94**.

Scheme 15. Synthesis of PIB-supported thiourea for acetalization reactions.



PIB-supported thiourea **94** was utilized for the acetalization of benzaldehyde (eq. 19). The acetalization reactions were performed under different conditions. All the reactions were carried out using 1 mmol of benzaldehyde, 2 mmol of triethylorthoformate, and 0.1 mmol of PIB-supported thiourea **94**. I first tried two different reactions, one in heptane and other in a mixture of 4:1 heptane:ethanol at room temperature. The reason why we wanted to use heptane or a mixture of heptane/EtOH as solvents is to create homogeneous reaction conditions that can easily form biphasic systems at the end of the reaction by the addition of 90% EtOH-H_2O or H_2O, respectively. The formation of a biphasic system allows us to separate the catalyst from the product and to recycle the catalyst containing phase by the addition of fresh starting

materials. PIB-supported thiourea **94** was not successful catalyzing the acetalization of benzaldehyde under these reaction conditions. Then, I tried the same reactions but at a temperature of 75 ºC. These latter reactions were also not successful, and no acetal products were formed.



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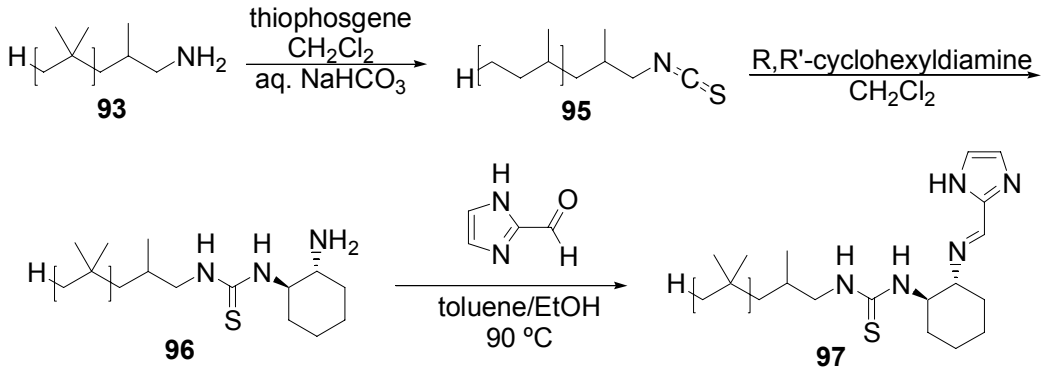
Schreiner examined the activity of several symmetrically substituted thiourea derivatives as catalysts for Diels-Alder reactions of cyclopentadiene with α,β-unsaturated carbonyl compounds.[98] Kinetic studies revealed that the rate acceleration of the Diels-Alder reactions with thioureas depends mostly on thiourea substituents rather than on reactants or solvent. Alkyl, cycloalkyl, phenyl, and aniline derived symmetrical thioureas were used in these studies. Results showed that alkyl substituted thioureas caused a minimal rate acceleration of the Diels-Alder reactions while the rate acceleration of the reactions were higher when thioureas bearing electron-withdrawing groups, including fluorophenyl and trifluoromethylphenyl substituted thioureas, were used to catalyze the Diels-Alder reactions. The complexation between thioureas and carbonyl compounds is endothermic by ca. 7 kcal/mol at room temperature in dichloromethane. This complexation is modestly strong and is thought to involve

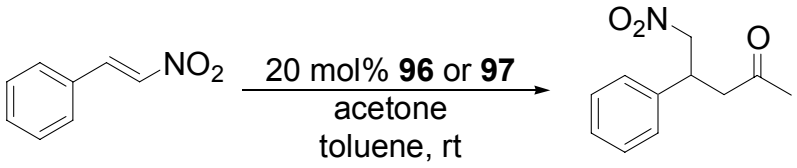
entropic effects that may exceed the binding exothermicities. This implies that the strength of the interactions between thioureas and carbonyl compounds largely depends on the rigidity of the catalyst. These observations indicate that thiourea catalysts need to be properly ordered for an effective interaction with the dienophile. Thus, interactions of alkyl substituted thioureas with dienophiles are entropically unfavorable because the free rotation of the alkyl groups does not allow the catalyst to acquire the required conformation to interact properly with the dienophile. These results could also explain why PIB-supported thiourea **94** is not an effective catalyst for promoting the acetalization of aldehydes.

Schreiner also studied the effect of solvent polarity on the acceleration of Diels-Alder reactions of methylvinyl ketone and cyclopentadiene catalyzed by thiourea derivarives.[98] Scheiner used cyclohexane, chloroform, and water in these studies. The studies revealed that reactions are accelerated to a greater extent in water than in cyclohexane and chloroform. While water can catalyze the Diels-Alder reactions, higher acceleration was observed when using the thiourea catalysts in water. An explanation for these observations is that nonpolar substrates interact more closely in aqueous solvents leading to acceleration in the reaction rate. This explanation can be used to explain the inefficiency of **94** to catalyze the acetalization of benzaldehyde. PIB-supported thiourea has a long alkyl chain that induces nonpolar character to the catalyst itself. This nonpolar character of the catalyst does not allow the polar reagents to interact appropriately with the catalyst thus the reaction cannot occur.

Other PIB-supported thioureas were also synthesized and studied as potential catalysts for the Michael addition reaction of acetone to nitrostyrene. PIB-supported thiourea catalysts **96** and **97** were synthesized following Scheme 16. Catalytic Michael addition reactions were carried out using 0.15 mmol of nitrostyrene, excess of acetone, and 20 mol% of the thiourea based catalyst (**96** or **97**) in 5 mL of toluene. After 48 or 72 h the toluene was removed under reduced pressure. Then, 5 mL of heptane and 5 mL of acetonitrile were added to the flask. The phases were separated and the heptane phase was concentrated under reduced pressure and dried under vacuum. The PIB-thioureas **96** and **97** were used in a second cycle of the Michael addition of acetone to nitrostyrene. PIB-supported thioureas **96** and **97** were successful in catalyzing the Michael addition of acetone to nitrostyrene. Catalyst **96** produced product in 89% conversion as determined by GC chromatography after 48 h. Catalyst **97** effectively catalyzed the reaction in 91% conversion after 72 h. However, while these catalysts were effective and while this methodology is feasible for the separation of catalysts from product, none of these catalysts were active in the second cycle of the Michael addition reaction. No conversion and no products were obtained in the second cycle with either **96** or **97**.

Scheme 16. Synthesis of PIB-supported thioureas for conjugated addition reactions.





(19)

To try to understand the failure of the recycling experiment, the heptane, catalyst- containing phase of each catalytic system was analyzed by ^{1}H NMR spectroscopy. In the case of catalyst **96**, it was observed some nitrostyrene derived species were present in the catalyst containing phase (Figure 20). While separate experiments showed nitrostyrene was itself not soluble in heptane, a nitrostyrene derivative of a PIB product would be soluble in heptane. Such a product could form by reaction of the amine group of the catalyst with nitrostyrene via a conjugate addition reaction. The addition of thiourea-amine to nitrostyrene could have happened as the reaction mixture was getting concentrated when toluene was being removed under reduced pressure and would have altered the catalyst and this may account for the failure in the recycling experiments.

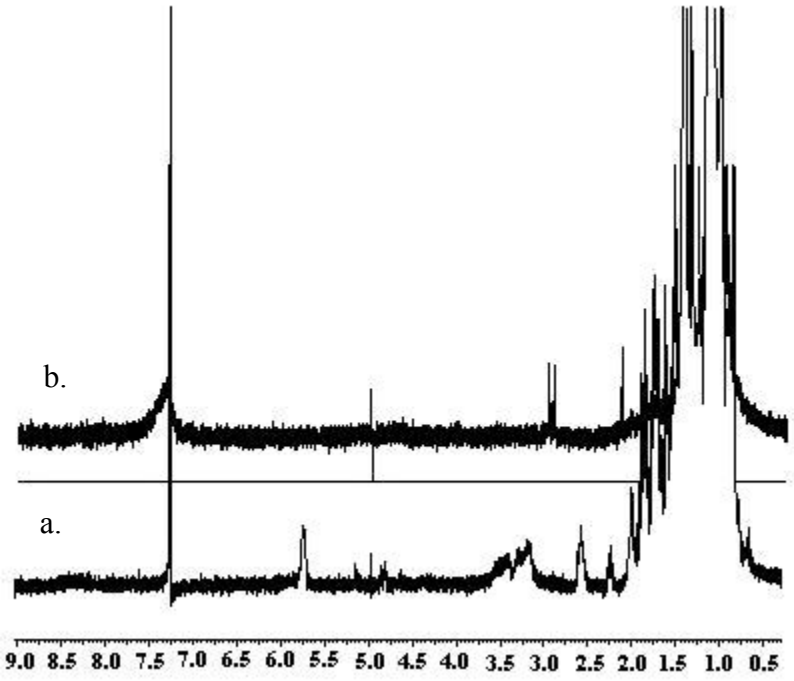


Figure 20. ^{1}H NMR spectrum of: a) PIB-supported thiourea **96**; b) PIB-supported thiourea **96** after Michael addition reaction of acetone and nitrostyrene.

Similar results were observed when catalyst **97** was used for the Michael addition reactions. In this case, ^{1}H NMR spectroscopy revealed that the imine group of the catalyst was not present in the recovered catalyst (Figure 21). Again, the ^{1}H NMR spectrum showed the presence of nitrostyrene derivatives in the catalyst containing phase. Recent publications have suggested that the catalysis of Michael addition reactions using bifunctional thiourea catalysts bearing an amine group proceeds via an enamine intermediate. If this were the case, water formed during the reaction could have hydrolyzed the imine group of the catalyst **97**. When the imine is hydrolyzed, catalyst **96** is formed and it can react as described above with nitrostyrene inhibiting the catalyst's activity.

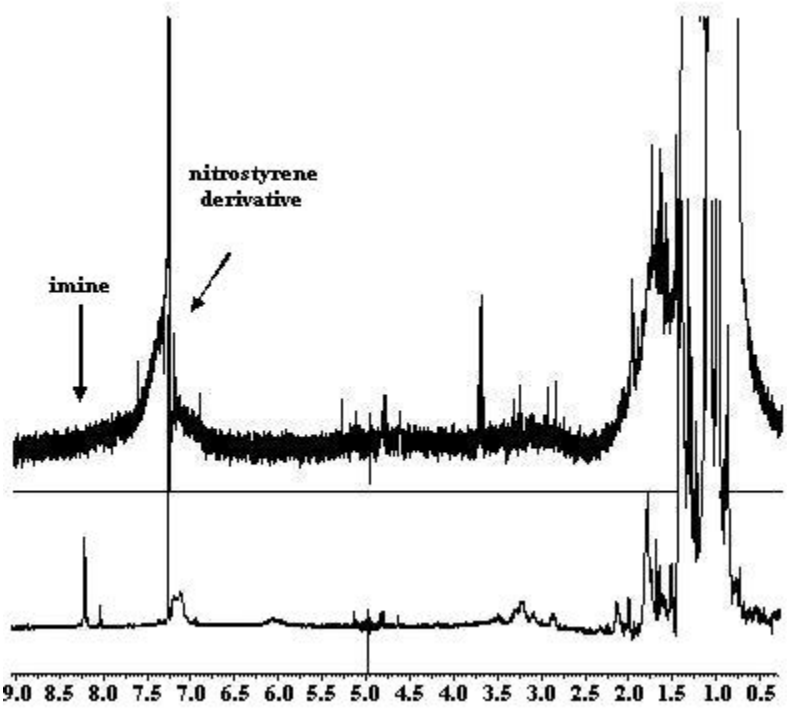


Figure 21. ^{1}H NMR spectrum of: a) PIB-supported thiourea imine **97**; b) PIB-supported thiourea imine **97** after Michael addition reaction of acetone and nitrostyrene.

Separate studies were therefore carried out to determine whether or not the imine group on PIB-supported thiourea **97** hydrolyzes in the presence of acetone. Catalyst **97** was treated with dry acetone in toluene for 72 h under the same reaction conditions described above. Then, the solvents were removed under reduced pressure. The ^{1}H NMR spectra (Figure 22) clearly showed that the starting imine decomposed when the catalyst was treated with acetone. This result agreed with hypothesis that the formation of water during the catalytic reaction could in fact hydrolyze the imine group on the catalyst **97** making these catalysts into reactants for the excess nitrostyrene and leading to catalyst decomposition.

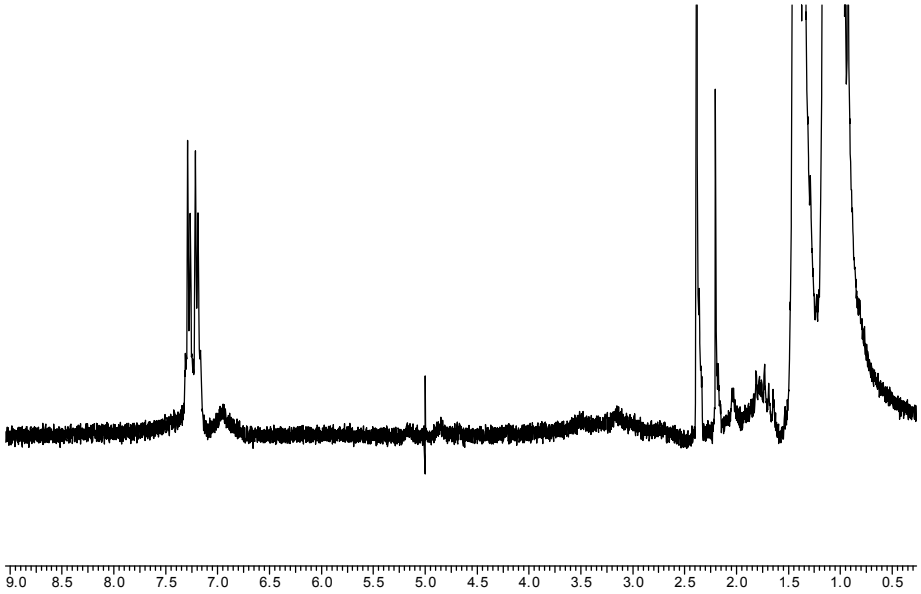


Figure 22. ^{1}H NMR spectra of PIB-supported thiourea **97** after its treatment with acetone in toluene.

Polymer-supported proline

Proline has been known to catalyze asymmetric reactions for over 30 years. Proline was the first enantioselective organocatalyst known to promote asymmetric aldol addition reactions. Proline is an aminocatalyst known to promote asymmetric addition reactions by formation of an enamine intermediate. Figure 23 in an example intermediate of proline catalyzed aldol reaction of acetone with benzaldehyde. The easy availability of both enantiomers in a chiral pool, low price, and its utility without derivatization make proline an ideal catalyst for asymmetric reactions. Currently, proline has been used as an enantioselective organocatalyst in a variety of reactions-aldol, Michael, Mannich, Diels-Alder, and other reactions. Also, many sorts of proline

derivatives have been designed in order to improve enantioselectivity in different reactions.[99-103]

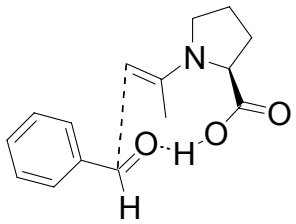
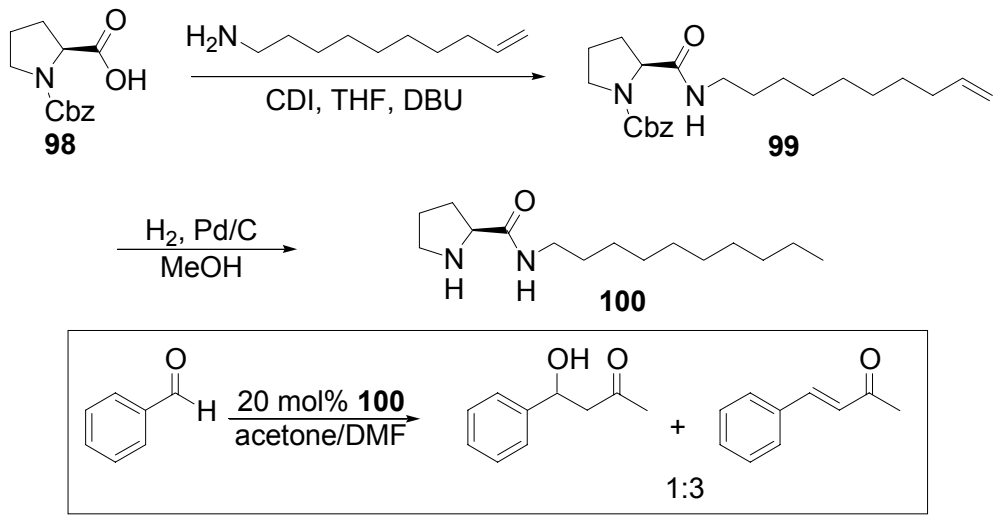


Figure 23. Transition state of the aldol reaction of acetone with benzaldehyde catalyzed by proline.

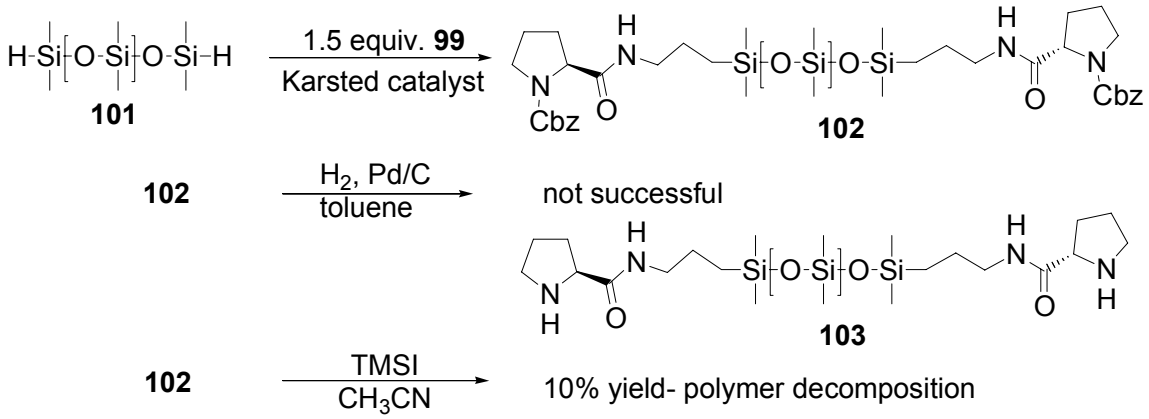
The great utility and efficiency of proline as an organocatalyst for many different reactions led us to design polymer-supported prolines and to study their utility in catalysis of aldol addition reactions. I first synthesized an *N*-Cbz-proline amide **99** following Scheme 17. Proline amide **99** was reduced and deprotected in a one-pot hydrogenation reaction. The product catalyst **100** was used in the aldol addition reaction of acetone and benzaldehyde. The proline amide **100** promoted the aldol reaction in 96% conversion as was determined by ^{1}H NMR spectroscopy. We then decided to support proline amide on polydimethylsiloxane (PDMS).

Scheme 17. Synthesis of proline amide and its utility in the aldol addition reaction.



PDMS-*N*-Cbz-proline amide **102** was synthesized following Scheme 18. A hydrosilylation reaction was performed to attach proline amide **99** on PDMS. The next step was the Cbz-deprotection of the proline catalyst. I first tried the Cbz-deprotection using a common hydrogenolysis reaction with H_2 and Pd/C, however, this reaction was not successful. Then, I tried the Cbz-deprotection using trimethylsilyl iodide following a procedure described by Alexander Katz for the deprotection of Cbz groups on mesoporous silica.[104, 105] While the deprotection of proline seemed to work, only 10% yield of the PDMS-supported proline amide was obtained suggesting that the polymer decomposed during the reaction. We then decided to attach proline to a more stable polymer- PIB.

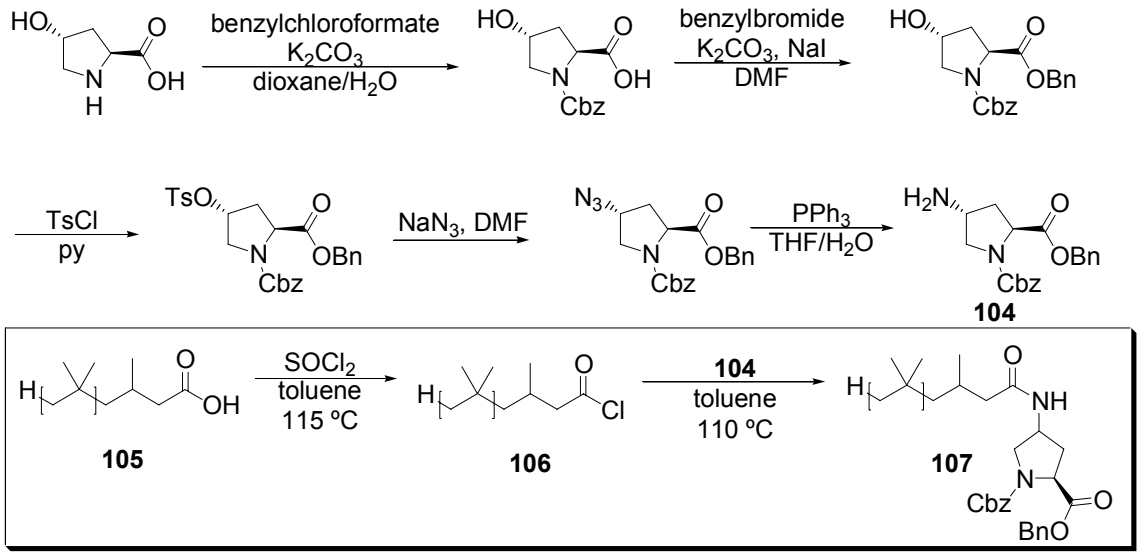
Scheme 18. Synthesis of PDMS-supported proline amide **103**.



We decided to synthesize PIB-supported proline via an amide bond. I first synthesized benzyl *N*-Cbz-4-aminoprolinate **104** following a reported procedure illustrated in Scheme 19. Then, PIB-carboxylic acid **105** was treated with thionyl chloride to form PIB-acid chloride **106**. PIB-acid chloride **106** was allowed to react with benzyl *N*-Cbz-4-aminoprolinate in toluene in the presence of pyridine at 110 ºC to afford PIB-supported proline **107**. The synthesis of the final catalyst was then going to occur by the deprotection of the Cbz and benzyl group on proline. Different procedures were attempted in an effort to obtain the deprotected PIB-bound catalyst. Hydrogenation reactions were tried in different solvent systems- toluene, toluene/EtOH, THF, THF/EtOH. However, none of these reactions were successful in the deprotection of neither the Cbz nor the benzyl group. I then tried a catalytic transfer hydrogenation in cyclohexene and ethanol using Pd/C as the catalyst. The latter reaction was also not successful in the deprotection of proline. A possible reason for the failure in the

deprotection of PIB- and PDMS-supported prolinate could be that the heterogeneous nature of the catalyst, Pd/C, and the nonpolar character of the polymer supports do not allow close interaction or adsorption of the substrate with the catalyst surface. While our group has generally found that soluble polymer-bound species react like their low molecular weight analogs with low molecular weight substrates, reactions of a soluble polymer with another macroscopic reagent catalyst can be problematic.

Scheme 19. Synthesis of PIB-supported prolinate.

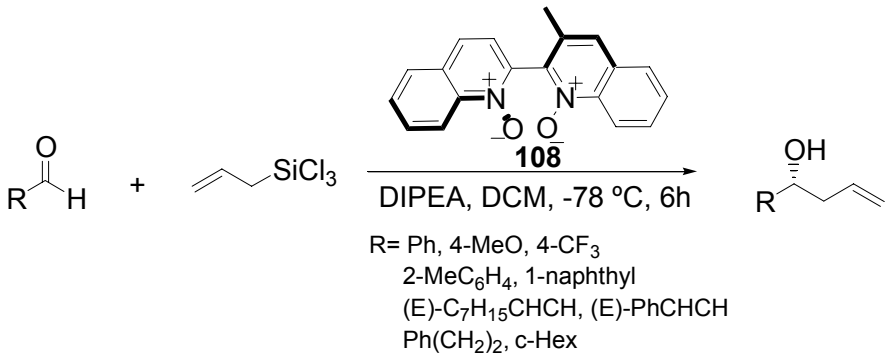


PIB-supported amine and pyridine N-oxides for the catalytic allylation of aldehydes

Allylation of aldehydes is another important C-C bond forming reaction. The unsaturated alcohols obtained from the allylation reaction of aldehydes are versatile precursors of many other molecules, and are useful in syntheses of natural products. There are a broad variety of catalysts that are known to catalyze the allylation of aldehydes. The most common approach is to use Lewis acid complexes.[106] However, the allylation of aldehydes can be performed using organic catalysts too. Common organic catalysts used for the allylation of aldehydes leading to the corresponding unsaturated alcohols are Lewis base catalysts such as phosphoramides,[107] formamides,[108, 109] and amine or pyridine *N*-oxides.

The use of chiral Lewis base catalysts for the allylation of aldehydes is one of the most efficient methods to prepare allylic alcohols from aldehydes. Nakajima discovered the use of amine *N*-oxides as suitable organocatalysts for the allylation of aldehydes in 1998.[110] Knowing that amine *N*-oxides exhibit great nucleophilicity toward silicon, Nakajima decided to study *N*-oxides' utility as catalysts for the allylation of aldehydes. Nakajima's group described the use of the chiral (S)-3,3'-dimethyl-2,2'-biquiniline *N*,*N*'-dioxide **108** in the allylation of a variety of substituted aldehydes with allyltrichlorosilane in the presence of diisopropylethylamine (eq. 20). Only 10 mol% of the catalyst **108** was needed to achieve homoallylic alcohol products in high yields and good enantioselectivities. In the case of aromatic aldehydes, alcohols were obtained in 68-91% yield and 71-92% ee. While the procedure was very efficient for aromatic aldehydes, the allylation of aliphatic aldehydes proved to be not very efficient in terms

of chemical yields and enantioselectivities affording the product alcohol in 27-30% yield and 7-28% ee.



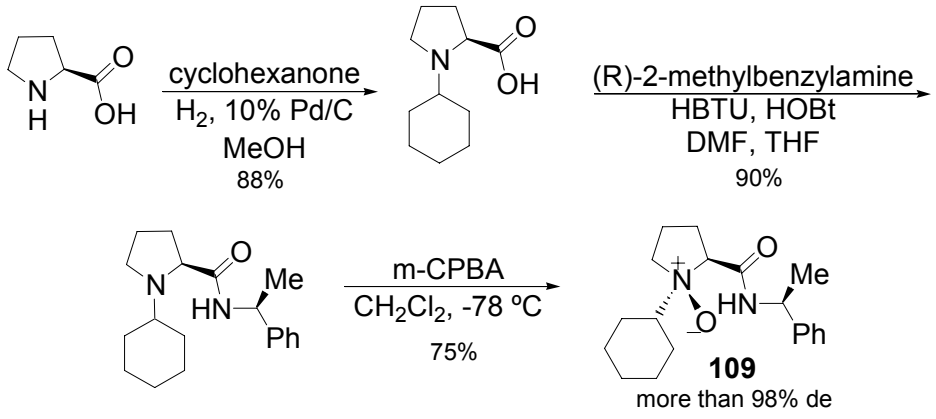
(20)

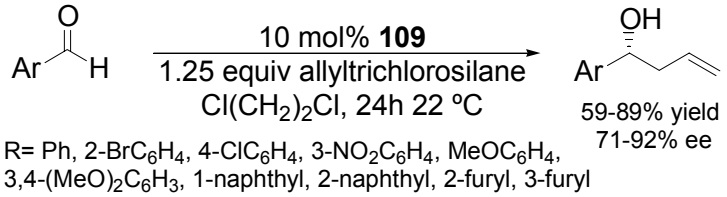
Currently, there are a wide variety of *N*-oxide organocatalysts known to catalyze the allylation reaction of allyltrichlorosilane with aldehydes.[111-118] However, most of the chiral *N*-oxide catalysts used so far have been prepared in long multistep syntheses. Amino acid-based *N*-oxides are attractive because of the availability of a variety of optically pure amino acids that can be easily modified to obtain the desired catalyst with optimal reactivity and selectivity. Recently, Hoveyda and Snapper reported the use of proline-based *N*-oxides for the enantioselective allylation of aldehydes with allyltrichlorosilane.[119]

Proline-based *N*-oxides are Lewis base catalysts that promote the allylation of aryl aldehydes and α,β-unsaturated aldehydes to form homoallylic alcohol products. Proline-based *N*-oxides can be prepared in three steps from optically pure proline without the need of purification by column chromatography. An example of the synthesis of the proline-based *N*-oxide **109** is shown in Scheme 20. A variety of

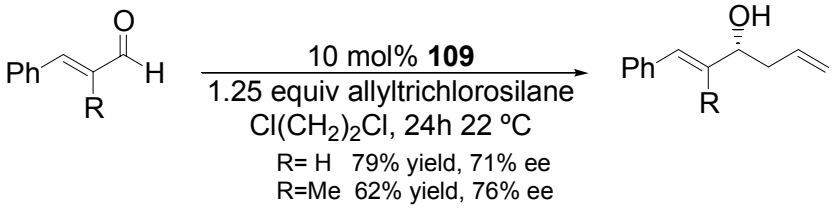
allylation reactions were performed to determine which proline-based *N*-oxides were the best catalysts at promoting the allylation of aldehydes. Proline-based *N*-oxides with different *N*-groups and amide substituents were synthesized and used in allylation reactions. The resulting studies indicated that the proline *N*-oxide bearing a cyclohexyl on the *N*-terminus and a (*R*)-α-methylbenzylamine on the *C*-terminus (e.g **109**) was the more efficient catalyst at promoting allylation of aldehydes with high conversions and good enantioselectivities. The allylation of aromatic aldehydes with allyltrichlorosilane using 10 mol% of **109** as the catalyst afforded homoallylic alcohols in 59-89% yield and 71-92% ee (eq. 21). Proline-based *N*-oxide **109** is not limited to use in the allylation of aromatic aldehydes. Proline-based *N*-oxide **109** also promoted the allylation of α,β-unsaturated aldehydes with good yields and ee (eq. 22).

Scheme 20. Synthesis of a chiral proline-based *N*-oxide catalyst.





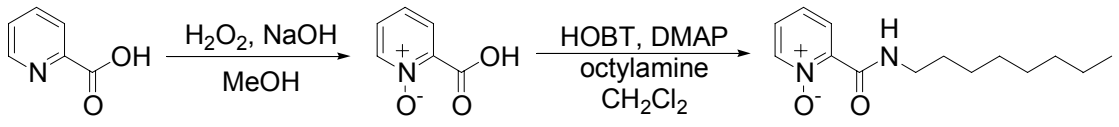
(21)



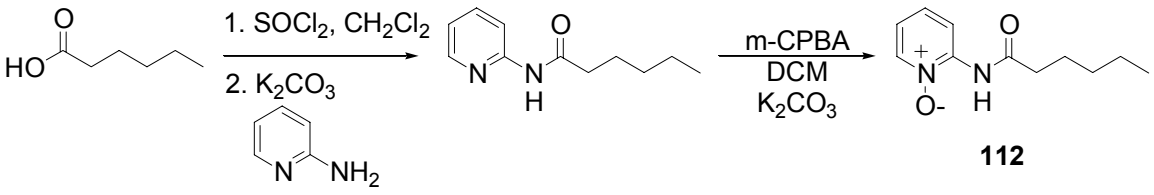
(22)

Since amine *N*-oxides are efficient catalysts for promoting the allylation of aldehydes, we decided to design a PIB-supported pyridyl *N*-oxide and utilize it in the allylation of several benzaldehydes. I first synthesized two low molecular weight amine *N*-oxide analogs- **111** and **112**- following Scheme 21 and 22. To examine the ability of catalysts **111** and **112** to promote the allylation of aldehydes, I first tried the allylation of benzaldehyde using 10 mol% of each of these catalysts. The reactions were carried out in 5 mL of CH_2Cl_2 at room temperature for 24 h. Catalysts **111** promoted the allylation of benzaldehyde in 52% conversion after 24 h. In contrast, catalyst **112** promoted this reaction in only 7% conversion after 24 h.

Scheme 21. Synthesis of picolinic acid octylamide *N*-oxide **111**.



Scheme 22. Synthesis of *N*-pyridine-2-yl hexanamide *N*-oxide **112**.



Previously, it was proposed that a six-membered ring transition state between the silane and aldehydes is involved during the allylation of the aldehydes with allyltrichlorosilane.[111, 116, 117, 119] The results obtained from the studies of catalyst **111** and **112** in the allylation of benzaldehyde also suggest that a six-membered ring transition state between the catalyst and the silane is also preferred (Figure 24). This hypothesis could in fact explain why catalyst **111** is more active than catalyst **112**.

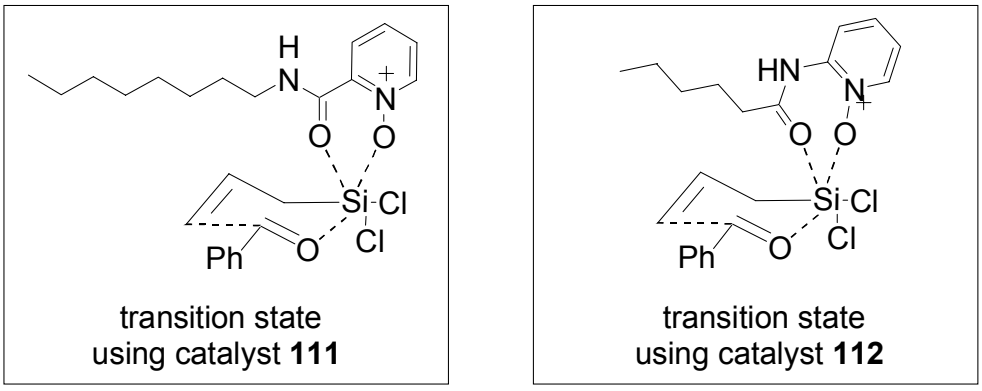
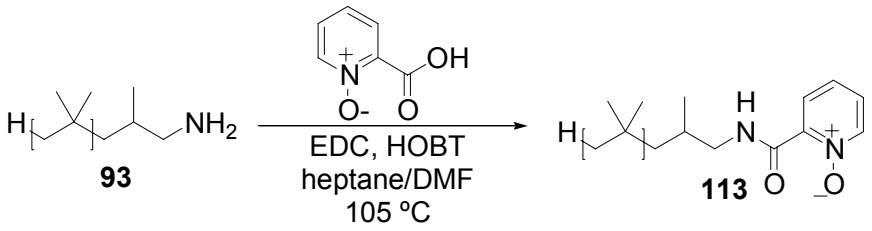


Figure 24. Proposed transition state model for the allylation of benzaldehyde with catalysts **111** and **112**.

Since catalyst **111** appeared to be more effective in promoting the allylation of benzaldehyde, we decided to test **111** in the allylation of other aromatic aldehydes. Catalyst **111** promoted the allylation of benzaldehyde and *p*-tolualdehyde in ≥99% conversion after 48 h. Catalyst **111** also promoted the allylation of *p*-fluorobenzaldehyde and *p*-nitrobenzaldehyde in ≥99% conversion after 24 h. After testing the low molecular weight catalyst's efficiency in the catalysis of the allylation of different aldehydes, we decided to synthesize PIB-pyridyl *N*-oxide and used it to catalyze the allylation of the same aromatic aldehydes used in with the low molecular weight catalyst.

PIB-supported pyridyl *N*-oxide **113** was synthesized starting from PIB-amine **93**. PIB-amine **93** was allowed to react with picolinic acid *N*-oxide in the presence of EDC and HOBT in a mixture of heptane-DMF (1:1 vol) at 105 ºC for 24 h (eq. 23). The product polymer was used as catalyst for the allylation of different benzaldehydes.



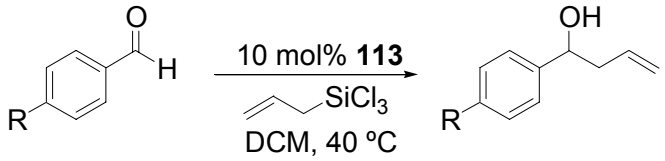
(23)

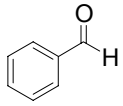
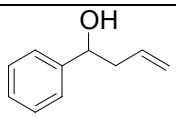
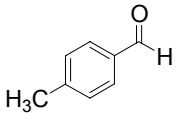
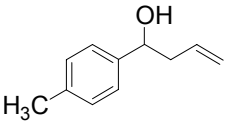
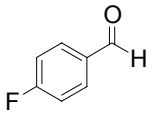
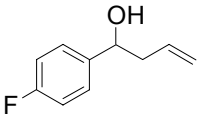
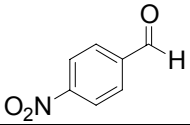
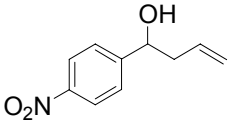
PIB-supported pyridyl *N*-oxide was used for the allylation of benzaldehyde, *p*-tolualdehyde, *p*-fluorobenzaldehyde, and *p*-nitrobenzaldehyde. The catalytic reactions were performed in a 1 mmol scale of the aldehydes. Catalyst **113** and the corresponding aldehyde were dissolved in 5 mL of dichloromethane. Then, 1.5 equiv. of

allyltrichlorosilane was added and the reaction mixture was stirred for the 24 h or 48 h. The reactions were quenched with 7 mL of saturated aqueous $NaHCO_3$. The solvents were removed under reduced pressure and the residues were dissolved in 10 mL of hexane and 10 mL of 90% EtOH-H_2O. The phases were then separated by a liquid-liquid extraction. The hexane phases were concentrated under reduced pressure and recycled. The isolated catalysts were used in 5 cycles. The ethanol phases were analyzed by GC chromatography to determine the amount of product isolated in such phases using decanol as the internal standard.

PIB-pyridyl *N*-oxide **113** is an efficient catalyst for the allylation of aromatic aldehydes. First, a control reaction using benzaldehyde under the same reaction conditions but without the catalyst was performed. The control reaction demonstrated that the allylation of benzaldehyde did not occur in the absence of the catalyst. The catalyst promoted the allylation of different benzaldehydes in good yields as shown in Table 7. Table 7 shows the product yields isolated in the ethanol phase. As can be seen from Table 7, the catalyst did not have any significant loss in activity for benzaldehyde and *p*-tolualdehyde. After the third cycle, the catalyst's activity drop in the case of *p*-fluoro and *p*-nitrobenzaldehyde. However, these studies demonstrated that PIB-supported pyridyl *N*-oxide can be easily recovered and recycled using a liquid-liquid biphasic system. It is worth mentioning that the yields noted here may have been lowered by inadvertent product loss during evaporative steps used in the workup.

Table 7. Allylation reactions catalyzed by PIB-supported pyridyl *N*-oxide **113**.



substrate	product	time (h)	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5
		48	45	66	60	65	57
		48	81	75	≥99	≥99	≥99
		24	78	52	58	47	37
		24	81	84	79	54	59

Conclusion

This chapter describes the attachment of different catalysts onto polyisobutylene. PIB-supported thioureas were synthesized and tested in a variety of reactions. PIB-supported thiourea **94** was not successful in promoting the acetalization of benzaldehyde probably due to the hydrophobic environment of the polymer supports. PIB-thiourea amine **96** and imine **97** were synthesized and examine in the catalysis of the Michael addition reaction of acetone and nitrostyrene. Catalysts **96** and **97** were effective in promoting the Michael addition of acetone to nitrostyrene. These catalysts were recovered in the nonpolar phase of a polar-nonpolar liquid-liquid biphasic system.

However, catalysts **96** and **97** were not successfully recycled. ^{1}H NMR spectroscopic studies of catalysts **96** and **97** suggested that side reaction occurred that can inhibit the catalysts activity. Also, PIB-supported benzyl *N*-Cbz-prolinate **107** was synthesized. However, deprotection of the PIB-supported prolinate **107** failed under several conditions. This failure suggests that a different route for the deprotection of proline would have to be pursued if such a catalyst were to be prepared. If the deprotection could be performed under homogeneous reaction conditions, the synthesis of PIB-supported proline might be more successful. For example, proline could be protected using Boc-protecting groups which could be easily cleaved under acidic conditions. Finally, PIB-supported pyridyl *N*-oxide **113** was synthesized and successfully utilized in the catalyzed allylation of aromatic aldehydes with allyltrichlorosilane. PIB-supported pyridyl *N*-oxide **113** was effective in promoting the allylation of benzaldehyde, *p*-tolualdehyde, *p*-fluorobenzaldehyde, and *p*-nitrobenzaldehyde with yields isolated in the ethanol phase ranging from 37 to ≥99%. Catalyst **113** was active through 5 cycles with some loss in activity after the third cycle for *p*-fluorobenzaldehyde and *p*-nitrobenzaldehyde. Having shown that this simple PIB-supported amine *N*-oxide is active in the allylation of aromatic aldehydes, a more complex, chiral amine *N*-oxide catalyst supported on PIB could be prepared in the future to test its effectiveness in the enantioselective allylation of different sorts of aldehydes.

CHAPTER IV

CONCLUSIONS

Soluble polymers are useful materials for catalyst recovery and recycling. The use of soluble polymer-supported catalysts enables using homogeneous reaction conditions akin to those used with small homogeneous catalysts. This avoids problems that occur when insoluble polymer supports are used. Soluble polymer supports can be designed to have a phase selective solubility such that they are selectively soluble in the nonpolar or the polar phase of a thermomorphic or latent biphasic system. Also, soluble polymer supports can be synthesized by a variety of methods. Poly(octadecylacrylate) and poly(octadecylmethacrylate) were synthesized by free radical polymerization using AIBN as the initiator. Poly(octadecylacrylate) and poly(octadecylmethacrylate) exhibit a phase selective solubility in the heptane phase of both heptane/90% EtOH: H_2O and heptane/DMF thermomorphic systems. Poly(*N*-alkylacrylamide)s were obtained by a nucleophilic substitution of an activated polyester. PNADSI demonstrated to be a more useful precursor for a combinatorial split-pool synthesis of these poly(*N*-alkylacrylamide)s since PNADSI exhibits better solubility in common solvents such as CH_2Cl_2 and THF than PNASI. Poly(*N*-alkylacrylamide)s synthesized using PNADSI can be easily purified using non-fractionating procedures. Poly(*N*-alkylacrylamide)s were purified using sequestering resins, Amberlyst 15 and Amberlite IRA 400 (-OH), to remove excess of amines and *N*-hydroxy-2-dodecylsuccinimide byproduct, respectively. The studies of the PNNODAM-PNNBuAM copolymers showed that both *n*-

octadecylacrylamide and *n*-butylacrylamide groups are of comparable importance in the determination of the copolymer's phase selective solubility. Poly(*N*,*N*-dialkylacrylamide)s were obtained by the free radical polymerization of the corresponding monomers. Poly(*N*-alkylacrylamide)s with different sized alkyl groups were also prepared. These poly(*N*,*N*-dialkylacrylamide)s too exhibit phase selective solubility that depends on the total amount of carbons in the *N*-alkyl groups. A poly(*N*-alkylacrylamide) with an *N*-alkyl group of six carbons is selectively soluble to the heptane phase of a heptane/DMF thermomorphic system. Likewise, a poly(*N*,*N*-dibutylacrylamide) that has a total of 8 carbons in the *N*-alkyl group is selectively soluble to the heptane phase of the liquid/liquid biphasic system. Poly(*N*,*N*-dialkylacrylamide)s containing a total of 6 carbons or less are selectively soluble to the polar phase of a nonpolar/polar liquid/liquid biphasic systems. Poly(*N*,*N*-dialkylacrylamide)s exhibit similar phase selective solubilities in heptane/DMF, heptane/90% EtOH-H_2O, heptane/ethylene glycol diacetate, and pentadecane/dimethylcarbonate thermomorphic systems.

Polyisobutylene (PIB) is a hydrophobic polymer that is ≥99.9% phase selectively soluble in the nonpolar phase of thermomorphic and latent biphasic systems. Polyisobutylene can be easily modified to a variety of end-functionalized PIBs. PIB-supported thioureas were synthesized and tested in a variety of reactions. PIB-supported thiourea **94** was not successful in promoting the acetalization of benzaldehyde probably due to the hydrophobic environment of the polymer supports. PIB-thiourea amine **96** and imine **97** were synthesized and examined as possible catalysts for the Michael

addition reaction of acetone and nitrostyrene. PIB-supported thioureas **96** and **97** were effective in promoting the Michael addition of acetone to nitrostyrene. These catalysts were recovered in the nonpolar phase of a polar-nonpolar liquid-liquid biphasic system. However, catalysts **96** and **97** were not successfully recycled. ^{1}H NMR spectroscopic studies of catalysts **96** and **97** suggested that side reaction occurred that can inhibit the catalyst's activity. Also, PIB-supported benzyl *N*-Cbz-prolinate **107** was synthesized. However, deprotection of the PIB-supported prolinate **107** failed under several conditions. This failure suggests that a different route for the deprotection of proline would have to be pursued if such a catalyst were to be prepared. If the deprotection could be performed under homogeneous reaction conditions, the synthesis of PIB-supported proline might be more successful. For example, proline could be protected using Boc-protecting groups which could be easily cleaved under acidic conditions. Finally, PIB-supported pyridyl *N*-oxide **113** was synthesized and successfully utilized in the catalytic allylation of aromatic aldehydes with allyltrichlorosilane. PIB-supported pyridyl *N*-oxide **113** was effective in promoting the allylation of benzaldehyde, *p*-tolualdehyde, *p*-fluorobenzaldehyde, and *p*-nitrobenzaldehyde with yields isolated in the ethanol phase ranging from 37 to ≥99%. Catalyst **113** was active through 5 cycles with some loss in activity after the third cycle for *p*-fluorobenzaldehyde and *p*-nitrobenzaldehyde. Having shown that this simple PIB-supported amine *N*-oxide is active in the allylation of aromatic aldehydes, a more complex, chiral amine *N*-oxide catalyst supported on PIB could be prepared in the future to test its effectiveness in the enantioselective allylation of different sorts of aldehydes.

EXPERIMENTAL

Materials

Dodecylsuccinic anhydride was obtained from TCI America. All other reagents were purchased from Aldrich Chemical Co. These and other commercial reagents were used without further purification.

Instrumentation

^{1}H NMR spectra were obtained using a Varian Mercury 300, Inova 500 or Inova 300 spectrometer at 300 or 500 MHz. ^{13}C NMR spectra were obtained using Mercury 300, Inova 500 or Inova 300 spectrometer at 75 or 125 MHz. The phase selectivity solubility studies were performed using a Cary 100 scanning UV/vis spectrophotometer using azo dye (*p*-methyl red) labeled polymers. The poly(*N*-alkylacrylamide)s and poly(*N,N*-dialkylacrylamide)s were analyzed by gel permeation chromatography using a Viscotek GPC instrument. The experiments were carried out using a Viscotek I-MBMMW-3078 mixed bed column, a triple detector system including a Model VE3580 RI detector, and OmniSEC software. Gas chromatography data were obtained using a Shimadzu GC-2010 instrument. The experiments were carried out using a ZB 5MS column with a serial number of 71822, an inner diameter of 0.25 μm, and a film thickness of 0.50 μm.

*General procedure for synthesis of octadecyl acrylates (**51** and **52**)*

A 500-mL three-necked round-bottomed flask with stir bar, addition funnel, and condenser was charged with octadecanol (31.427 g, 110.37 mmol), *N,N*-dimethylaniline

(10 mL, 86.32 mmol), and 60 mL of dichloromethane. The mixture was warmed to dissolve the alcohol, and a solution of acryloyl chloride (11 mL, 130 mmol) in 50 mL of dichloromethane was added dropwise. Following addition, the reaction was gently refluxed overnight. The mixture was cooled and alternately washed with water and 10% HCl. The organic phase was dried over $MgSO_4$, concentrated under reduced pressure, and dried in vacuo to give 35.09 g of **51** as a viscous oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.8 Hz, 3H), 1.25 (s, 28H), 1.55-1.75 (m, 4H), 4.14 (t, *J* = 6.9 Hz, 2H), 5.80 (dd, *J* = 1.8 and 10.5 Hz, 1H), 6.11 (dd, *J* = 10.5 and 17.4 Hz, 1H), 6.39 (dd, *J* = 1.8 and 17.4 Hz, 1H). Octadecyl methacrylate (**52**)^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, *J* = 6.6 Hz, 3H), 1.18 (s, 28H), 1.4-1.7 (m, 4H), 1.85 (t, *J* = 0.9, 1.5 Hz, 3H), 4.05(t, *J* = 6.9 Hz, 2H), 5.45 (q, *J*= 1.5, 1.8 Hz, 1H), 6.01 (dd, *J*= 0.9, 1.8 Hz, 1H).

Amine-terminated p-methyl red

p-Methyl red **(**7.89 g, 29.3 mmol) was suspended in 225 mL of dichloromethane. To this suspension was added carbonyldiimidazole (10.0 g, 61.67 mmol), resulting in a rapid emission of CO_2. The mixture was stirred at ambient temperature for 4 h, and the starting material was observed to dissolve to form a bright red homogeneous solution. This solution was transferred to an addition funnel and added dropwise over 3 h to a solution of 1,6-hexanediamine (13.6 g, 117 mmol) in 200 mL of dichloromethane. After the addition, the resulting solution was allowed to stir for 24 h at room temperature. The reaction was filtered, and the filtrate was washed with water (10 x 60 mL), dried over $MgSO_4$, and dried in vacuo to yield 8.57 g of amine-terminated methyl red as a red solid (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 4H), 1.60-1.67 (m, 4H), 2.69 (t, *J* = 6.6

Hz, 2H), 3.10 (s, 6H), 3.47 (q, J = 6.3 Hz, 2H), 6.21 (t, J = 6 Hz, 2H), 6.76 (d, J = 9 Hz, 2H), 7.86 (s, 4H), 7.89 (d, J = 9 Hz, 1H).

Synthesis of amine-terminated methyl red {2-[4-(Dimethylamino)phenylazo]benzoic acid} (3.90 g) and 100 mL of CH_2Cl_2 were added to an oven-dried flask and flushed with N_2. CDI (2.40 g) in 36.5 mL of CH_2Cl_2 was added by forced siphon with a cannula and the mixture was stirred vigorously under N_2. After stirring for 7 h, the solution was transferred by forced siphon with a cannula into an N_2-flushed flask containing 8.47 g of 1,6-hexanediamine in 85 mL of CH_2Cl_2. The methyl red solution was added dropwise for 1 h using an addition funnel. The mixture was stirred under N_2 flow overnight. The resulting orange mixture was filtered and a dark red solution was obtained. The solution was washed with H_2O, 3 x 150 mL, dried over Na_2SO_4, filtered and dried under reduced pressure. The residue was dried in vacuo and yielded 2.56 g (48%) of an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 (m, 6H), 1.7 (m, 4H), 2.6 (t, 2H), 3.0 and 3.1 (2s, 6H), 3.5 (q, 2H), 6.8 (d, 2H), 7.5 (m, 2H), 7.7-7.8 (m, 3H), 8.4 (m, 1H), 9.1 (br, 1H).

*General procedure for the synthesis of p-methyl red- labeled acrylamides (**53** and **54**)*

A solution of amine-terminated methyl red (1.82 g, 5 mmol) and triethylamine (2 mL, 14 mmol) in 50 mL of dichloromethane was added to a 100-mL round-bottomed flask. Acryloyl chloride (0.60 mL, 7.09 mmol) was then added dropwise via syringe. The reaction was allowed to stir for 24 h at room temperature before the mixture was transferred to a separatory funnel and the organic phase was washed with water. The organic phase was set aside, and the aqueous phase was washed with dichloromethane

until the dichloromethane was colorless. The organic phases were combined, washed with water (3 x 50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was dried in vacuo to give 1.95 g of **53** as a red solid (96.5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30- 1.7 (m, 8H), 3.11 (s, 6H), 3.34 (q, *J* = 6.6 Hz, 2H), 3.46 (q, *J* = 6.6 Hz, 2H), 5.61 (dd, *J* = 2.1 and 10.2 Hz, 1H), 5.8 (br t, 1H), 6.28 (dd, *J* = 2.1 and 17 Hz, 1H), 6.10 (dd, *J* = 10.2 and 17 Hz, 1H), 6.39 (br t, 1H), 6.76 (d, *J* = 9 Hz, 2H), 7.88 (m, 6H). Methyl red-labeled methacrylamide **54** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2-1.70 (m, 8H), 1.97 (s, 3H), 3.11 (s, 6H), 3.33 (q, *J* = 6.9 Hz, 2H), 3.48 (q, *J* = 6.3 Hz, 2H), 5.31 (s, 1H), 5.68 (s, 1H), 5.9 (br t, 1H), 6.40 (br t, 1H), 6.76 (d, *J* = 9.3 Hz, 2H), 7.88 (m, 6H).

*General procedure for the synthesis of methyl red- labeled poly(octadecyl acrylate)s (**55** and **56**)*

Benzene (50 mL) was added to a 100-mL three-necked round-bottomed flask and degassed by bubbling N2 for 3 h. The benzene was then cooled to -78 °C. Then **51** (2.50 g, 7.7 mmol), **53** (0.108 g, 1.26 mmol), and AIBN (0.0188 g, 0.114 mmol) were added to this solid, and any air that was introduced into the flask was removed under vacuum. The flask was flushed with N2, and the reaction mixture was allowed to warm and melt. The polymerization occurred when the mixture was heated to reflux with stirring over 48 h. After this period of time, the solution was concentrated under reduced pressure, and the residue was dissolved in 100 mL of hexane. The hexane solution was washed first with DMF until the DMF washings were no longer colored and finally with water (3 x 50 mL). The water-DMF phases were washed with hexane to remove any polymer. The

combined hexane phases were then concentrated under reduced pressure, and the resulting product was dissolved in a minimum amount of chloroform (approximately 10 mL). Addition of this solution to 400 mL of methanol precipitated the product polymer which was isolated by filtration and dried in vacuo to yield 0.7664 g of **55** as a bright yellow solid (31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.8 Hz, 90H), 1.25 (br s, 900H), 1.5-1.65 (br m, 60H), 3.10 (s, 6H), 4.03 (br t, 60H), 5.5 (br s, 1H), 6.18 (br s 1H), 7.9 (br s, 2H). GPC analysis was carried out in THF using polystyrene standards: *M*n= 8236, *M*w= 15157, PDI= 1.84. Methyl red-labeled poly(octadecyl methacrylate) (**56**) was prepared similarly. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J*= 6.5 Hz, 90H), 1.26 (br s, 900H), 1.61 (br s, 90H), 1.65-1.95 (br m, 60H), 3.10 (s, 6H), 3.92 (br t, 60H), 5.55 (br s, 1H), 6.1 (br s, 1H), 7.9 (br s, 2H). GPC analysis of **56** was carried out in THF using polystyrene standards: *M*n= 6668, *M*W= 12567, PDI= 1.88.

*Synthesis of N-hydroxy-2-dodecylsuccinimide (**58**)*

Hydroxylamine-hydrochloride (4.9 g, 69.3 mmol) was suspended in 25 mL of dioxane. The suspension was added to a 100-mL round-bottomed flask containing 18.6 g (69.3 mmol) of 2-dodecylsuccinic anhydride and stirred at 75 ºC for 20 h. After removing the dioxane at reduced pressure, the residue was dried at 140 ºC for 1 h under vacuo. The hot product was precipitated in 50 mL of hexanes with stirring. Complete precipitation occurred when the mixture cooled down to room temperature. The precipitate was filtered and recrystallized from diethyl ether. The reaction yielded 9.83 g (67%) of the desired product, m.p. 74-77 °C (lit m.p. 76 °C). IR (KBr pellet, cm^{-1}) 3123,

1774, 1716, 1678. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.881 (t, 3H, *J*= 7Hz), 1.29 (bs, 20H), 1.55 (m, 1H), 1.90 (m, 1H), 2.40 (dd, 1H, *J*= 3, 14 Hz), 2.84 (m, 2H), 8.14 (bs, 1H).

*Synthesis of N-acryloxy-2-dodecylsuccinimide (**59**)* *N*-

Hydroxy-2-dodecylsuccinimide (7.17 g, 25.3 mmol) was added to a 250-mL round-bottomed flask containing triethylamine (3.5 mL, 25.3 mmol) and 170 mL of CH_2Cl_2. Then, the solution was cooled with an ice/water bath to 0 ºC and acryloyl chloride (3 mL, 35 mmol) in 15 mL of CH_2Cl_2 was added dropwise over a period of 30 min using an addition funnel. After 1 h at 0 ºC, the solution was allowed to warm to room temperature and was washed 4 times with 150 mL of NH_4Cl, once with 150 mL of H_2O, and once with 150 mL of brine. The solution was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was dried *in vacuo* and yielded 7.84 g (92%) of product having m.p. 41-45 °C. IR (KBr pellet, cm^{-1}) 2910, 2840, 1775, 1740, 1624, 1453, 1418. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.882 (t, 3H, *J* = 7 Hz), 1.231-1.345 (bm, 21H), 1.41 (m, 1H), 1.64 (m, 1H), 1.95 (m, 1H), 2.52 (m, 1H), 2.95 (m, 2H), 6.16 (dd, 1H, *J* = 1, 10.5 Hz), 6.32 (dd, 1H, *J* = 10.5, 17 Hz), 6.69 (dd, 1H, *J* = 1, 17 Hz). **HRMS:** ($C_{19}H_{31}O_4NH^+$ ($M+H^+$)) 338.2331.

*Synthesis of poly(N-acryloxy-2-dodecylsuccinimide) (**60**, PNADSI)*

N-Acryloxy-2-dodecylsucc-inimide (14.42 g, 42.8 mmol) and AIBN (0.012 g, 0.07 mmol) were dissolved in 250 mL of benzene in a dry 500-mL round-bottomed flask equipped with a condenser and a magnetic stir bar. (While toluene could be used in place of benzene (as a less hazardous solvent), there is less chain transfer with benzene. The solution was degassed three times using freeze pump thaw procedure.) The solution

was heated to 65 ºC and stirred for 3 d to form the polymeric active ester poly(*N*-acryloxy-2-dodecylsuccinimide) which was isolated by removing the benzene under reduced pressure. The crude polymeric material was then dissolved in 50 mL of THF and the solution was added slowly to 500 mL of dry acetonitrile. A gum formed quickly. After centrifugation, the solvent was decanted from this gum and the gum was dried under vacuum to yield an amorphous polymer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.882 (t, 3H, J = 7 Hz), 1.29-1.37 (bs, 21H), 1.54 (bs, 1H), 1.90 (bs, 1H), 2.18 (bs, 1H), 2.43 (bs, 1H), 2.87 (bs, 2H), 3.3 (bs, 1H).

Synthesis of poly(N-alkylacrylamide) copolymers (PNNODAM-PNNBuAM).

Samples of same batch of PNADSI **60** (0.3 g, 0.89 mequiv) were dissolved in 5 mL aliquots of CH_2Cl_2. In separate 10-mL round-bottomed flasks, different mixtures of *n*-octadecylamine, *n*-butylamine, and a primary amine labeled derivative of *p*-methyl red were dissolved in 5 mL of CH_2Cl_2. The amine solutions were transferred to these PNADSI solutions. Each mixture used the same total amount of amines: 3 mmol of *n*-octadecylamine- *n*-butylamine, and 0.03 mmol of the amine terminated *p*-methyl red. The reaction mixtures were stirred at room temperature for 24 h and 2 g of Amberlyst 15 was added to remove the excess of amines. After shaking the suspension for 24 h, the solution was filtered and the filtrate was treated with 2 g of Amberlite IRA 400 (OH-form) for another 24 h to remove the byproduct *N*-hydroxy-2-dodecylsuccinimide. The resulting red suspensions were filtered to remove the resin and the solvent was removed under reduced pressure. Each product polymer was then dried under vacuum and analyzed by ^{1}H NMR spectroscopy. These ^{1}H NMR analyses were used to determine

the relative amount of octadecyl and butyl groups in the product copolymers using the NMR spectra shown in Figure 15. ^{1}H NMR spectra were obtained in a Varian Inova 500 MHz instrument. ^{1}H NMR experiments were carried out to determine T1 and d2 values. The experiments were carried out a room temperature in $CDCl_3$ with 1^{rst} pulse= 180 degree, 2nd pulse= 90 degrees, T1= 4, d2= 51.2, acquisition time of 2.892 sec, bs= 4, and nt= 16. The ratio of octadecyl- to *n*-butyl acrylamide was determined by peak integration at δ 0.88 ppm and δ 0.92 ppm, for octadecyl- and *n*-butylacrylamide respectively.

UV-visible analysis of the methyl red-labeled copolymers

The *p*-methyl red labeled PNNODAM-PNNBuAM copolymers formed above were then dissolved in either nonpolar (e.g. heptane) or polar (e.g. DMF) solvents so as to form a solution whose methyl red concentration was approximately 10^{-4} M. Then, an equal amount of the other solvent was added (e.g. the nonpolar solvent heptane was added to the polar DMF solution or the polar solvent DMF was added to the nonpolar heptane solution), and the biphasic system was heated to 70 ºC. This heating produced a clear, monophasic reddish solution. Then, the solution was allowed to cool to room temperature and the solution phase separated. Centrifugation of the product biphasic system using Jouan CT422 was used to insure complete phase separation. The phases were then separated and each was analyzed using a UV/vis spectrometer. The extinction coefficients were considered to be the same on each solvent.

*Synthesis of N,N-diethylacrylamide (**62**)*

Diethylamine (4.1 mL, 39.3 mmol) and triethylamine (5.5 mL, 39.5 mmol) were

dissolved in 263 mL of dichloromethane in a 500-mL round-bottomed flask. The solution was cooled to 0 ºC while being stirred and acryloyl chloride (3.32 mL, 39.2 mmol) in 50 mL of CH_2Cl_2 was added dropwise over a period of 1 h at 0 ºC using an addition funnel. The reaction mixture was stirred at 0 ºC for 1 h and 1 h at room temperature. The solution was then washed twice with 50 mL of NH_4Cl (sat), and twice with 50 mL of Na_2CO_3 (sat). It was then dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The product was dissolved in 30 mL of ethyl acetate and was washed with Na_2CO_3 (sat), 2 x 50 mL and twice with 50 mL of brine. Drying over Na_2SO_4 followed by filtration and concentration at reduced pressure yielded an oil that was distilled to yield 2.25 g (45%) of *N*,*N*-diethylacrylamide (b.p. ~58-59 ºC at 0.6 Torr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, 6H), 3.36 (m, 2H), 3.42 (m, 2H), 5.64 (dd, 1H, cis β-CH_2, *J* = 10.3, 2.0 Hz), 6.32 (dd, 1H, trans β-CH_2, *J* = 16.7, 2.0 Hz), 6.53 (dd, 1H, α-CH_2, *J* = 16.7, 10.3 Hz). In some cases, acrylic acid was present in the distillate. If this were the case, the product was then dissolved in 50 mL CH_2Cl_2 and washed with 3 times with 50 mL of 3M KOH. The CH_2Cl_2 solution was then dried over Na_2SO_4, filtered, and dried at reduced pressure. The residue was dried in vacuo and to yield the product as a colorless liquid product.

Synthesis of N,N-dipropylacrylamide ***(63)***

Dipropylamine (6.8 mL, 49.4 mmol) and triethylamine (6.9 mL, 49.4 mmol) were dissolved in 330 mL of dichloromethane in a 500-mL round-bottomed flask. The solution was cooled to 0 ºC while being stirred and acryloyl chloride (6.3 mL, 74.4 mmol) in 50 mL of CH_2Cl_2 was added dropwise over a period of 1 h at 0 ºC using an

addition funnel. The reaction mixture was stirred at 0 ºC for 1 h and 1 h at room temperature. The solution was then washed with 3 x 50 mL of NH_4Cl (sat), and 5 x 50 mL of 3M KOH. It was then dried over Na_2SO_4, filtered, and concentrated at reduced pressure. *N*,*N*-Dipropylacrylamide product was obtained in 58% yield (4.44 g) as a colorless liquid after distillation b.p. 58-59 °C at 0.6 Torr. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (dt, 6H, J = 2.7, 7.2 Hz), 1.5-1.66 (m, 4H), 3.24 (t, 2H, J = 7.8Hz, 3.32 (t, 2H, J = 7.5Hz), 5.62 (dd, 1H, cis β-CH_2, J = 10.2, 2.1 Hz), 6.31 (dd, 1H, trans β-CH_2, J = 16.5, 2.1 Hz), 6.52 (dd, 1H, α-CH_2, J = 16.5, 10.2 Hz).

*Synthesis of N,N-dibutylacrylamide (**64**)*

Dibutylamine (4.64 mL, 27.2 mmol) and triethylamine (3.82 mL, 27.4 mmol) were dissolved in 182 mL of dichloromethane in a 500 mL round-bottomed flask. The solution was cooled to 0 ºC while being stirred and acryloyl chloride (3.5 mL, 41.4 mmol) in 50 mL of CH_2Cl_2 was added dropwise over a period of 1 h at 0 ºC using an addition funnel. The reaction mixture was stirred at 0 ºC for 1 h and 1 h at room temperature. The solution was then washed with NH_4Cl (sat), 3 x 50mL and Na_2CO_3 (sat), 3 x 50 mL. It was then dried over Na_2SO_4, filtered, and concentrated at reduced pressure. *N*,*N*-Dibutylacrylamide was distilled in order to purify it (b.p. ~240ºC at 760 mmHg). The reduced boiling point obtained from distilling at reduced pressure (0.6 mmHg) was ~50ºC. The product was then dissolved in 50 mL of CH_2Cl_2 and washed with KOH 3M, 3 x 100 mL. The solution was dried over Na_2SO_4, filtered, and dried at reduced pressure. The residue was dried in vacuo and yielded 3.33 g (67%) of colorless liquid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 6H), 1.26 (m, 4H), 1.48 (m, 4H),

3.24 (t, 2H), 3.31 (t, 2H), 5.59 (dd, 1H, cis β -CH_2, *J* = 10.2 Hz and 2.2 Hz), 6.27 (dd, 1H, trans β -CH_2, *J* = 16.7 Hz and 2.2 Hz), 6.49 (dd, 1H, α -CH_2, *J* = 16.7 Hz and 10.2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) 13.790, 13.889, 20.023, 20.281, 29.947, 31.769, 46.388, 47.868, 127.452, 127.885, 165.817.

*Synthesis of N,N-dihexylacrylamide (**65**)*

Dihexylamine (5 mL, 20.9 mmol) and triethylamine (2.9 mL, 20.8 mmol) were dissolved in 140 mL of dichloromethane in a 250 mL round-bottomed flask. The solution was cooled to 0 ºC while being stirred and acryloyl chloride (2.65 mL, 31.3 mmol) in 50 mL of CH_2Cl_2 was added dropwise over a period of 90 min at 0 ºC using an addition funnel. The reaction mixture was stirred at 0 ºC for 1 h and 1 h at room temperature. The solution was then washed with NH_4Cl (sat), 3 x 50 mL and dried over Na_2SO_4. It was filtered and concentrated at reduced pressure. Excess starting material and other impurities were removed by carrying out column chromatography (normal phase silica gel, CH_2Cl_2: EtOAc/ 7:3). Fractions containing only *N*,*N*-dihexylacrylamide were combined and dried under reduced pressure. The product was then dissolved in 20 mL of CH_2Cl_2 and washed with Na_2CO_3 (sat), 2 x 50 mL. The solution was dried over Na_2SO_4, filtered, and dried at reduced pressure. The residue was dried in vacuo and yielded 4.09 g (82%) of colorless to yellowish liquid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 6H), 1.27 (m, 12H), 1.53 (m, 4H), 3.26 (t, 2H), 3.34 (t, 2H), 5.63 (dd, 1H, cis β -CH_2, *J* = 10.5, 2 Hz), 6.32 (dd, 1H, trans β -CH_2, *J* = 17, 2 Hz), 6.52 (dd, 1H, α -CH_2, *J* = 17, 10.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.98, 13.92, 22.52, 26.68, 27.72, 29.59, 31.43, 31.52, 31.57, 46.63, 48.08, 127.39, 127.84, 165.77.

*Synthesis of N,N-didecylacrylamide (**66**)*

Didecylamine (4.328 g, 14.5 mmol) and triethylamine (1.92 mL, 13.8 mmol) were dissolved in 95 mL of dichloromethane in a 250-mL round-bottomed flask. The solution was cooled to 0 ºC while being stirred and acryloyl chloride (1.8 mL, 21.3 mmol) in 50 mL of CH_2Cl_2 was added dropwise over a period of 1 h at 0 ºC using an addition funnel. The reaction mixture was stirred at 0 ºC for 1 h and 1 h at room temperature. The solution was then washed with NH_4Cl (sat), 3 x 50mL and dried over Na_2SO_4. It was filtered and concentrated at reduced pressure. The product was dissolved in 50 mL of CH_2Cl_2 and washed with 3 times with Na_2CO_3 (sat) and 3 times with 100 mL of 3 M KOH. The solution was dried over Na_2SO_4, filtered, and dried at reduced pressure. The residue was dried *in vacuo* and yielded 4.15 g (82%) of colorless to yellowish liquid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 6H), 1.26 (m, 28H), 1.56 (m, 4H), 3.27 (t, 2H), 3.35 (t, 2H), 5.64 (dd, 1H, cis β - CH_2, J = 10.3, 2.4 Hz), 6.33 (dd, 1H, trans β -CH_2, J = 16.6, 2.4 Hz), 6.53 (dd, 1H, α -CH_2, J = 16.6, 10.3 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.07, 22.64, 26.81, 27.08, 27.83, 29.25, 29.28, 29.42, 29.48, 29.51, 29.54, 29.56, 29.66, 31.84, 31.87, 46.68, 48.13, 127.39, 127.93, 165.82.

*Synthesis of poly(N,N-dimethylacrylamide) (**67**)*

In a 500 mL round-bottomed flask equipped with a condenser and a magnetic stir bar, *N*,*N*-dimethylacrylamide (2.00 g, 20.2 mmol), acrylamide-methyl red (0.28 g, 0.65 mmol), and AIBN (0.011 g, 0.07 mmol) were dissolved in 134.5 mL of benzene. The solution was degassed two times using the freeze pump thaw procedure. The solution was then stirred and heated for 36 hours at 65 ºC. The benzene was removed under

reduced pressure. The reaction product was dissolved in 10 mL of $CHCl_3$ and precipitated in 250 mL of hexane. It was dried under reduced pressure and then dissolved in 25 mL of THF and precipitated in 250 mL of hexane. This procedure was carried out three times. The residue was dried in vacuo and yielded 0.51 g (25%) of a hygroscopic orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 6H, J = 7.5 Hz), 1.25-1.41 (br m, 10H), 1.65 (s, 14H), 2.3-3.2 (br m, 28H), 6.75 (br s, 1H), 7.87 (br s, 1H). GPC analysis was carried out in THF using polystyrene standards: Mn = 53511, Mw = 60436, PDI = 1.13.

*Synthesis of poly(N,N-diethylacrylamide) (**68**)*

In a 500 mL round-bottomed flask equipped with a condenser and a magnetic stir bar, *N*,*N*-diethylacrylamide (2.00 g, 15.7 mmol), acrylamide-methyl red (0.22 g, 0.52 mmol), and AIBN (0.009 g, 0.05 mmol) were dissolved in 105 mL of dioxane. The solution was degassed two times using the freeze pump thaw procedure. The solution was then stirred and heated for 36 h at 65 ºC. The dioxane was removed under reduced pressure. The reaction product was dissolved in 25 mL of THF and precipitated in 250 mL of hexane three times. The residue was dried in vacuo and yielded 1.68 g (84%) of a hygroscopic orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.8-1.5 (br m, 8H), 1.72 (s, 2H), 2.52 (br s, 1H), 2.95-3.60 (br m, 4H), 6.76 (d, 0.11H), 7.9 (br s, 0.19H). GPC analysis was carried out in THF using polystyrene standards: Mn = 33838, Mw = 48417, PDI = 1.43.

*Synthesis of poly(N,N-dipropylacrylamide) (**69**)*

In a 500-mL round-bottomed flask equipped with a condenser and a magnetic stir

bar, *N*,*N*-dipropylacrylamide (2.00 g, 12.9 mmol), acrylamide-methyl red (0.1813 g, 0.43 mmol), and AIBN (0.0074 g, 0.045 mmol) were dissolved in 86 mL of dioxane. The solution was degassed twice using the freeze pump thaw procedure. The solution was then stirred and heated for 36 h at 40 ºC. The dioxane was removed under reduced pressure. The reaction product was purified by silica gel column chromatography using a 9:1 mixture of acetone:methanol. After removing the solvents under reduced pressure 1.28 g of product was obtained (68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.6-1.0 (br m, 6H), 1.0-2.0 (br m, 6H), 2-2.7 (br m, 1H), 2.8-3.8 (br m, 4H), 7.86 (m, 0.3H). GPC analysis was carried out in THF using polystyrene standards: M_n = 20054, M_w = 32071, PDI = 1.60.

*Synthesis of poly(N,N-dibutylacrylamide) (**70**)*

In a 250 mL round-bottomed flask equipped with a condenser and a magnetic stir bar, *N*,*N*-dibutylacrylamide (2.00 g, 10.9 mmol), acrylamide-methyl red (0.15 g, 0.36 mmol), and AIBN (0.006 g, 0.04 mmol) were dissolved in 73 mL of dioxane. The solution was degassed two times using the freeze pump thaw procedure. The solution was then stirred and heated for 36 h at 65 ºC. The dioxane was removed under reduced pressure. The reaction product was dissolved in 75 mL of heptane and extracted with DMF, 4 x 75 mL. Three phases formed and each was concentrated at reduced pressure. After viewing the NMR data, the DMF extract and the solid/emulsion extract were combined and washed with acetonitrile. The heptane/hexane extract was concentrated at reduced pressure and the acetonitrile washes were discarded. The residue was dried in vacuo and yielded 0.86 g (43%) of a clear orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ

0.92 (t, 6H, *J* = 7.5 Hz), 1.25-1.64 (br m, 8H), 2.5 (br s, 0.41H), 2.8-3.5 (br m, 2.34H), 7.9 (br s, 0.04H). GPC analysis was carried out in THF using polystyrene standards: *M*n = 54323, *M*w = 72883, PDI = 1.34.

*Synthesis of poly(N,N-dihexylacrylamide) (**71**)*

In a 100 mL round-bottomed flask equipped with a condenser and a magnetic stir bar, *N*,*N*-dihexylacrylamide (1.73 g, 7.24 mmol), acrylamide-methyl red (0.10 g, 0.242 mmol), and AIBN (0.004 g, 0.025 mmol) were dissolved in 48 mL of dioxane. The solution was degassed two times using the freeze pump thaw procedure. The solution was then stirred and heated for 36 h at 65 ºC. The dioxane was removed under reduced pressure. The reaction product was purified by column chromatography (normal phase silica gel, CH_2Cl_2:EtOAc. The residue was dried in vacuo and yielded 1.17 g (68%) of a clear orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (br s, 6H), 1.28 (s, 11H), 1.57 (s, 3H), 2.2-2.6 (br s, 2H), 2.85-3.39 (br m, 4H), 7.9 (br s, 0.06H). GPC analysis was carried out in THF using polystyrene standards: *M*n = 50653, *M*w = 84643, PDI = 1.67.

*Synthesis of poly(N,N-didecylacrylamide) (**72**)*

In a 250 mL round-bottomed flask equipped with a condenser and a magnetic stir bar, *N*,*N*-didecylacrylamide (2.00 g, 5.7 mmol), acrylamide-methyl red (0.08 g, 0.19 mmol), and AIBN (0.003 g, 0.02 mmol) were dissolved in 38 mL of dioxane. The solution was degassed two times using the freeze pump thaw procedure. The solution was then stirred and heated for 36 h at 65 ºC. The dioxane was removed under reduced pressure. Purification process consisted of extractions of 100 mL hexanes and extracted with acetonitrile until clear. The residue was dried in vacuo and yielded 1.36 g (68%) of

a clear orange solid. ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 6H), 1.26 (s, 24H), 1.60 (s, 4H), 2.4 (br s, 1H), 2.7-3.5 (br m, 3H). GPC analysis was carried out in THF using polystyrene standards: *M*n = 34703, *M*w = 56334, PDI = 1.62.

*Synthesis of PIB-OH (**90**)*

The vinyl-terminated PIB (44.18g, 44.18 mmol) was dissolved in 100 mL of hexane. BH_3-SMe_2 (7.36 mL, 14.7 mmol) was added to the PIB solution. The reaction mixture was stirred for 24 h at room temperature. Then, the mixture was cooled to 0 ºC and 12 mL of 4M NaOH and 40 mL of ethanol were added. Then, 8 mL of 30 % H_2O_2 were added dropwise. The oxidation was allowed to proceed for 2 h. Then, 300 mL of water was added and the phases were separated. The aqueous phase was washed with 3 x 100 mL of hexane. The combined hexane phases were washed with 100 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was dried under vacuum to afford 44.89g (105 % yield, possibly containing trace hexane) of **90**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76-1.49 (m, 180H), 3.31 (dd, 1H, *J*= 7.5, 10.2 Hz), 3.41 (dd, 1H, *J*= 5.4, 10.2 Hz).

*Synthesis of PIB-Br (**91**)*

PIB-OH **90** (10 g, 9.8 mmol) and TEA (4.3 mL, 31 mmol) were dissolved in 100 mL of CH_2Cl_2. The mixture was cooled to 0 ºC. MsCl (2.3 mL, 29 mmol) dissolved in 10 mL of CH_2Cl_2 was added dropwise to the PIB-OH containing solution. The reaction mixture was stirred for 6 h. Then, the solvent was removed under reduced pressure. To the residue were added 50 mL of heptane and 50 mL of acetone. LiBr (9 g, 103 mmol) was added and the reaction mixture was stirred at 80 ºC for 18 h. Then, the solvents

were removed under reduced pressure and 150 mL of hexanes was added. The hexane phase was washed 3 x 100 mL of 90% EtOH-H_2O and 1 x 50 mL of brine. The hexane phase was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was dried under vacuum to afford 10.58 g (100% yield) of **92**. The product polymer may contain residual amounts of hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76-1.49 (m, 180H), 3.27 (dd, 1H, *J*= 6.9, 9.6 Hz), 3.41 (dd, 1H, *J*= 4.8, 9.6 Hz).

*Synthesis of PIB-phthalimide (**92**)*

A mixture of **91** (4 g, 3.7 mmol) and potassium phthalimide (1.51 g, 8 mmol) dissolved in 50 mL of heptane and 50 mL of DMF was stirred at 90 ºC for 24 h. The reaction mixture was cooled to room temperature and 100 mL of hexane was added. The hexane phase was isolated and washed with 2 x 40 mL of 90% EtOH-H_2O and 1 x 40 mL of brine. The hexane phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product polymer was dried under vacuum affording 4 g of **92** (94% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76-1.49 (m, 180H), 3.49 (dd, 1H, *J*= 8.1, 13.4 Hz), 3.59 (dd, 1H, *J*= 6.6, 13.4 Hz), 7.68 (dd, 2H, *J*= 3.0, 5.4 Hz), 7.82 (dd, 2H, *J*= 3.0, 5.4 Hz).

*Synthesis of PIB-NH_2 (**93**)*

PIB-phthalimide **92** (4 g, 3.49 mmol) and hydrazine hydrate (4.8 mL, 154 mmol) were dissolved in 75 mL of heptane and 75 mL of EtOH. The reaction mixture was stirred at 80 ºC for 20 h. The reaction mixture was allowed to cool to room temperature and an additional 100 mL of hexane and 100 mL of water were added. The phases were separated and the nonpolar phase was washed with 2 x 50 mL of 90% EtOH-H_2O and 50

mL of brine. The nonpolar phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product polymer was dried under vacuum affording 3.61 g (> 100% yield) of **93**. The product may contain residual amounts of solvents. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76-1.49 (m, 180H), 2.41 (dd, 1H, *J*= 7.5, 12.4 Hz), 2.59 (dd, 1H, *J*= 5.4, 12.4 Hz).

*Synthesis of PIB-thiourea (**94**)*

PIB-NH_2 **93** (3.55 g, 3.5 mmol) was dissolved in 30 mL of dry THF. Isothiocyanate (0.70 mL, 3.83 mmol) dissolved in 50 mL of dry THF was added dropwise to the **93** containing solution. The reaction mixture was stirred for 18 h at 65 ºC. The solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in 125 mL of hexane and washed 3 x 50 mL of DMF, 2 x 50 mL of 90% EtOH-H_2O, and 50 mL of brine. The hexane phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was dried under vacuum to afford 3.7g of **94** (84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75-2 (m, 180H), 3.36 (br m, 1H), 3.6 (br m, 1H), 6.12 (br s, 1H), 7.74 (m, 3H), 7.94 (br s, 1H).

*Synthesis of PIB-isothiocyanate (**95**)*

PIB-NH_2 **93** (2.03 g, 2 mmol) was dissolved in 10 mL of CH_2Cl_2 and 10 mL of aqueous $NaHCO_3$(sat) was added. The flask was cooled in an ice-bath. Then, thiophosgene (0.2 mL, 2.66 mmol) was added via syringe. Rapid stirring was subsequently started and the reaction was maintained in the ice-bath for 3 h. The layers were separated. The aqueous layer was washed with 10 mL of dichloromethane. The

combined organic layers were dried over Na_2SO_2, filtered, and concentrated under reduced pressure. The residue was dried under vacuum affording 2.44g (115% yield) of **95**. The product contained residual amounts of solvent. IR (KBr plate, cm^{-1}). 1472.29, 2096.42 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.5-2.0 (m, 180H), 3.30 (dd, 1H, *J*= 6.9, 14.1), 3.40 (dd, 1H, *J*= 5.7, 14.1).

*Synthesis of PIB-thiourea-NH_2 (**96**)*

PIB-isothiocyanate **95** (1 g, 0.98 mmol) was dissolved in 20 mL of anhydrous CH_2Cl_2. Then, *R,R'*-cyclohexyldiamine (0.22 g, 1.96 mmol) was added rapidly in one portion. The resulting solution was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was dissolved in 50 mL of hexane. The hexane solution was washed with 3 x 25 mL of 90% EtOH-H_2O and 25 mL of brine. The hexane phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was dried under vacuum affording 0.98 g (85% yield) of **96**. ^1H NMR (300 MHz, $CDCl_3$) δ 0.5-2.0 (m, 180H), 2.5-2.7 (m, 1H), 3.0-3.7 (m, 4H), 5.7-5.8 (m, 1H), 8.3 (br s, 1H).

*Synthesis of PIB-thiourea-imine (**97**)*

PIB-thiourea-NH_2 **96** (0.5 g, 0.43 mmol) and imidazole-2-carbaldehyde (0.05g, 0.53 mmol) were dissolved in 10 mL of toluene and 10 mL of EtOH in a pressure vessel. The reaction mixture was heated to 90 ºC and stirred of 18 h. Then, the solvents were removed under reduced pressure. The residue was dissolved in 20 mL of hexane and washed with 2 x 15 mL of acetonitrile. The hexane phase was concentrated under reduced pressure and dried under vacuum. The product **97** was obtained in 64% yield

(0.3461g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.5-2.0 (m, 180H), 2.8-3.6 (m, 4H), 5.9-6.2 (br s, 2H), 7.0-7.2 (m, 2H), 8.21 (s, 1H).

*Michael addition reaction using catalyst **96***

In a flame-dried round-bottomed flask were dissolved 15 mol% of catalyst **96**, 15 mol% of AcOH, nitrostyrene (2 mg, 0.14 mmol), and 0.27 mL of acetone in 5 mL of toluene. The reaction mixture was stirred at room temperature for 48 h. The toluene was removed under reduced pressure. The residue was dissolved in 5 mL of heptane and 5 mL of acetonitrile. The biphasic system was stirred vigorously and centrifuged. The phases were separated and the solvents were removed under reduced pressure. The reaction was converted in 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.95 (d, 2H, *J*= 6.9 Hz), 3.9-4.1 (m, 1H), 4.55-4.8 (m, 2H), 7.2-7.5 (m, 5H).

*Michael addition reaction using catalyst **97***

In a flame-dried round-bottomed flask were dissolved 20 mol% of catalyst **97**, nitrostyrene (2 mg, 0.14 mmol), and 0.27 mL of acetone in 5 mL of toluene. The reaction mixture was stirred at room temperature for 72 h. The toluene was removed under reduced pressure. The residue was dissolved in 5 mL of heptane and 5 mL of acetonitrile. The biphasic system was stirred vigorously and centrifuged. The phases were separated and the solvents were removed under reduced pressure. The reaction was converted in 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.95 (d, 2H, *J*= 6.9 Hz), 3.9-4.1 (m, 1H), 4.55-4.8 (m, 2H), 7.2-7.5 (m, 5H).

*Synthesis of N-carbobenzyloxy-N'-(9-decenenyl) proline amide (**99**)*

Cbz-proline (3.19 g, 12.8 mmol) and CDI (2.09 g, 12.9 mmol) were dissolved in

100 mL of dry THF. The solution was stirred at room temperature for 30 min, and refluxed for 1 h. The reaction mixture was allowed to cool to room temperature. The 9-deceneamine was dissolved in 30 mL of THF and was added to the reaction mixture. After 10 min, DBU (2 mL, 13 mmol) was added to the reaction mixture. The solution was refluxed for 18 h. Then, the mixture was allowed to cool to room temperature and poured into 500 mL of water. The aqueous phase was extracted 5 x 100 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was further purified by silica gel column chromatography using CH_2Cl_2/EtOAc (4/6) as the eluent to obtain 2.57g (52% yield) of **99** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20-1.46 (m, 12H), 1.8-2.42 (m, 6H), 3.20 (m, 2H), 3.52 (m, 2H), 4.32 (m, 2H), 4.97 (m, 2H), 5.17 (m, 1H), 5.80 (m, 1H), 6.7 (br s, 1H), 7.36 (m, 5H).

*Synthesis of N-carbobenzyloxy-N'-(9-decyl) proline amide (**100**)*

Proline amide **99** (0.49 g, 1.27 mmol) was dissolved in 10 mL of methanol. To this solution was added Pd/C. The solution was stirred for 18 h under H_2 at 1 atm. Then, the solution was filtered through celite and concentrated under reduced pressure to afford **100** in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, 3H, *J*= 7.2 Hz), 1.19 (br s, 14H), 1.4 (m, 2H), 1.55-1.6 (m, 2H), 1.68-1.9 (m, 1H), 2.0-2.15 (m, 1H), 2.75-2.85 (m, 1H), 2.90-3.0 (m, 1H), 3.15-3.22 (m, 2H), 3.66 (dd, 1H, *J*= 6, 12 Hz),7.57 (br s, 1H). ^{13}C NMR (300 MHZ, $CDCl_3$) δ 14.03, 22.6, 26.11, 26.85, 29.22, 29.47, 29.59, 30.70, 31.81, 38.82, 47.19, 60.52, 174.92.

*Synthesis of PDMS-supported N-Cbz proline amide (**102**)*

PDMS (2.88 g, 0.88 mmol) and proline amide **99** (0.53 g, 1.36 mmol) were dissolved in 30 mL of toluene in a pressure vessel. The vessel was purged by bubbling N_2 through the solvent. The Karsted catalyst was then added and the reaction mixture was purged again. The pressure vessel was closed and the reaction mixture was stirred for 18 h at 105 ºC. At this point, the IR spectra showed reaction completion. Then, the toluene was removed under reduced pressure. The residue was purified through a silica gel column chromatography using a 2:1 mixture of DCM:EtOAc to remove the "Pt" catalyst. The solvents were removed under reduced pressure and the residue was dissolved in 20 mL of heptane. The heptane was washed with 3 x 50 mL of 50% MeOH-H_2O. The heptane phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2.78g (78% yield) of polymer product **102**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00-0.89 (m, 464H), 1.25-1.46 (m, 35H), 1.60 (s, 4H), 1.89 (br m, 4H), 2.17 (m, 2H), 2.39 (m, 2H), 3.20 (m, 4H), 3.53 (m, 4H), 4.32 (m, 2H), 5.17 (m, 4H), 5.90 (br s, 1H), 6.70 (br s, 1H), 7.32 (m, 10H).

*Synthesis of PIB-proline (**106**)*

PIB-COOH (2.44 g, 2.30 mmol) was dissolved in 100 mL of toluene. Thionyl chloride (3.43 mL, 47 mmol) was added and the reaction mixture was stirred at 115 ºC for 18 h. Then the solvent was removed under reduced pressure and the residue was dried under vacuum for 4 h. Benzyl *N*-Cbz-4-amino prolinate (1.26 g, 3.54 mmol) was dissolved in 50 mL of toluene and 1 mL of pyridine. This solution was transfer to the flask containing PIB-COCl using a cannula. The resulting solution was stirred for 18 h

at 110 ºC. The reaction mixture was allowed to cool to room temperature and the toluene was removed under reduced pressure. The residue was dissolved in 80 mL of hexane and washed with 3 x 50 mL of 90% EtOH-H_2O. The hexane phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The polymer was dried under vacuum affording 1.78 g (55% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79-2.00 (m, 337H), 2.45-2.46 (m, 1H), 3.53-3.71 (m, 2H), 4.46 (dd, 1H, *J*= 9.9, 20 Hz), 4.62-4.68 (m, 1H), 5.0-5.3 (m, 4H), 7.13-7.36 (m, 10H).

*Synthesis of picolinic acid N-oxide (**110**)*

To a solution of picolinic acid (25 g, 0.20 mol) in 140 mL of MeOH was added NaOH (8.20 g, 0.20 mol). The solvent was removed under reduced pressure and the remaining solid was dissolved in 120 mL of acetic acid. Then, 24 mL of 30% $H_2O_{2(aq.)}$ was added and the mixture was heated to 80 ºC and stirred for 3 h. Additional 20 mL of 30% $H_2O_{2(aq.)}$ was added and the reaction mixture was stirred at 90 ºC for 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in water and the pH was adjust to pH=1 by the addition of conc. HCl. The precipitate was filtered and washed with copius amounts of water. The product **110** was obtained in 74% yield (20.68 g) after drying the white solids under vacuum. m.p. 157-161 ºC. ^{1}H NMR (300 MHz, DMSO) δ 7.9 (m, 2H), 8.29 (m, 1H), 8.73 (m, 1H). ^{13}C NMR (300 MHz, DMSO). 128.65, 130.11, 132.85, 135.97, 139.03, 160.95.

*Synthesis of picolinic acid octylamide N-oxide (**111**)*

Picolinic acid *N*-oxide (1 g, 7.2 mmol), EDC (3.04 g, 16 mmol), and HOBT (2.14g, 16 mmol) were dissolved in 20 mL of CH_2Cl_2. Then, octylamine (2.62 mL, 15.8

mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 24 h. The CH_2Cl_2 solution was washed 3 x 20 mL of 1M HCl, 3 x 20 mL of saturated aqueous Na_2CO_3, and 20 mL of brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dried under vacuum to afford 1.65 g (92% yield) of product. ^{1}H NMR (300 MHz, $CHCl_3$) δ 0.85 (t, 3H, *J*= 6.6 Hz), 1.19-1.44 (m, 10H), 1.57-1.69 (m, 2H), 3.42-3.49 (m, 2H), 7.32-7.46 (m, 2H), 8.21-8.24 (m, 1H), 8.41 (dd, 1H, *J*= 2.4, 8.7 Hz). ^{13}C NMR (300 MHz, $CHCl_3$) δ 14.02, 22.57, 27.07, 29.12, 29.20, 31.74, 39.68, 127.02, 127.07, 128.81, 140.47, 140.76, 159.45.

*Synthesis of 2-hexaneamido pyridine N-oxide (**112**)*

Hexanoic acid (1 g, 8.6 mmol) was dissolved in 10 mL of CH_2Cl_2. Thionyl chloride (1 mL, 13.7 mmol) was added and the mixture was stirred for 1 h at room temperature. Then, the volatiles were removed under reduced pressure. 2-Amino pyridine (1.62 g, 17 mmol) was dissolved in 20 mL of CH_2Cl_2 and was added dropwise to the hexanoic acid chloride. Then, 1.82 g of K_2CO_2 was added and the mixture was stirred for 3 h. Then, 10 mL of water was added and the phases were separated. The organic phase was washed with an additional 10 mL of water. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using diethyl ether as the eluent to obtain 0.70 g (42% yield) of 2-hexaneamide pyridine. ^{1}H NMR (300 MHz, $CHCl_3$) δ 0.89 (t, 3H, *J*= 6.9 Hz), 1.27-1.40 (m, 4H), 1.66-1.75 (m, 2H), 2.38 (t, 2H, *J*= 7.2 Hz), 7.00-7.05 (m, 1H), 7.67-7.73 (m, 1H), 8.22-8.26 (m, 2H), 8.81 (s, 1H). ^{13}C NMR (300 MHz,

$CHCl_3$) δ 13.79, 22.28, 24.98, 31.25, 37.49, 114.45, 119.45, 138.42, 147.31, 151.87, 172.15. 2-Hexaneamide pyridine (0.70 g, 3.65 mmol) and 1.51 g of K_2CO_3 were suspended in 20 mL of CH_2Cl_2 and cooled to 0 ºC. Then, *m*-CPBA (2.45 g, 11 mmol) was added at once and the reaction mixture was stirred for 2 h at 0 ºC, and for 18 h at room temperature. Then, the mixture was filtered through celite. The solvent was removed under reduced pressure and the product was purified through silica gel column chromatography using CH_2Cl_2 and then a mixture of CH_2Cl_2-MeOH (9:1) as eluents. The product was obtained in 87 % yield. ^{1}H NMR (300 MHz, $CHCl_3$) δ 0.87 (t, 3H, *J*= 7.2 Hz), 1.28-1.40 (m, 4H), 1.64-1.80 (m, 2H), 2.48 (t, 2H, *J*= 7.5, 15.3 Hz), 6.92-6.98 (m, 1H), 7.30 (td, 1H, *J*= 1.5, 7.5, 8.7 Hz), 8.19-8.22 (m, 1H), 8.40-8.44 (m, 1H), 10.11 (s, 1H). ^{13}C NMR (300 MHz, $CHCl_3$) δ 13.80, 22.26, 24.76, 31.16, 37.80, 114.62, 118.35, 128.17, 136.96, 144.09, 172.06.

*Synthesis of PIB-pyridyl-N-oxide (**113**)*

PIB-NH_2 **93** (1.48 g, 1.45 mmol) and **110** (0.4g, 2.9 mmol) were dissolved in 15 mL of heptane and 15 mL of DMF. Then, EDC (1.26 g, 6.38 mmol) and HOBT (0.86 g, 6.38 mmol) were added to the solution. The reaction mixture was stirred at 110 ºC for 24 h. Then, the mixture was allowed to cool to room temperature and the phases were separated. The heptane phase was washed with 2 x 15 mL of 90% EtOH-H_2O. The heptane phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dried under vacuum to obtain 1.34 g (81% yield) of **113**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.5-2.0 (m, 180H), 3.21-3.26 (m, 1H), 3.41-3.46, (m, 1H), 7.37 (td, 1H, *J*= 2.5, 6.5 Hz), 7.44 (td, 1H, *J*= 1.5, 8 Hz), 8.25 (dd, 1H, *J*= 5, 6 Hz), 8.45 (dd, 1H,

J= 2, 8.5 Hz), 11.35 (s, 1H).

General procedure for the allylation of benzaldehydes

PIB-*N*-oxide **113** (0.11g, 0.1 mmol) and benzaldehyde (1 mmol**)** were dissolved in 5 mL of CH_2Cl_2. Then, allyltrichlorosilane (0.23 mL, 1.5 mmol) was added and the reaction mixture was stirred at 40 ºC for the time specified on Table 7. The reaction was quenched by the addition of 7 mL of aqueous $NaHCO_{3(sat.)}$. The solvents were removed under reduced pressure. Then, 10 mL of heptane and 10 mL of 90% EtOH-H_2O was added and the resulting mixture was stirred vigorously. The resulting triphasic system (2 liquid phases and 1 solid phase) was centrifuged and the phases were separated. The heptane phase was concentrated under reduced pressure and recycled by addition of fresh CH_2Cl_2-substrate. The ethanol phase was analyzed by gas chromatography.

1-Phenyl-but-3-ne-1-ol

Yields: 45, 66, 60, 65, 57%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.4 (br s, 1H), 2.46-2.56 (m, 2H), 4.72 (q, 1H, *J*= 5.5, 7.5 Hz), 5.12-5.2 (m, 2H), 5.76-5.86 (m, 1H), 7.15-7.35 (m, 5H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 43.69, 73.22, 118.24, 125.75, 127.43, 128.30, 134.385, 143.78.

1-(4-Methylphenyl)-but-3-ne-1-ol

Yields: 81, 75, ≥99, ≥99, ≥99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (s, 3H), 2.76-2.94 (m, 2H), 4.9 (t, 1H, *J*= 7.2 Hz), 5.08-5.17 (m, 2H), 5.70-5.84 (m, 1H), 7.17 (d, 2H, *J*= 8.3 Hz), 7.29 (d, 2H, *J*= 8.3Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.14, 44.04, 62.71, 118.11, 126.91, 129.27, 134.11, 138.17.

1-(4-Fluorophenyl)-but-3-en-1-ol

Yields: 78, 52, 58, 47, 37%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (br s, 1H), 2.43-2.5 (m, 2H), 4.69 (t, 1H, *J*= 6.9 Hz), 5.11 (t, 1H, *J*= 1.2 Hz), 5.14-5.18 (m, 1H), 5.70-5.84 (m, 1H), 6.98-7.05 (m, 2H), 7.26-7.33 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 43.82, 72.59, 114.97, 115.26, 118.53, 127.35, 127.46, 134.10, 139.49, 139.53, 160.45, 163.69.

1-(4-Nitrophenyl)-but-3-en-1-ol

Yields: 81, 84, 79, 54, 59%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35-2.60 (m, 2H), 2.67 (br s, 1H), 4.83 (q, 1H, *J*= 5, 7 Hz), 5.09-5.15 (m, 2H), 5.69-5.80 (m, 1H), 7.49 (d, 2H, *J*= 9 Hz), 8.14 (d, 2H, *J*= 9 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ 43.67, 72.10, 119.28, 123.44, 126.47, 133.14, 146.97, 151.84.

REFERENCES

1. Merrifield, R. B. *Science* **1966,** *152*, 1735.
2. Letsinger, R. L.; Mahadeva, V. *J. Am. Chem. Soc.* **1966,** *88*, 5319-5324.
3. Merrifield, R. B. *Angew. Chem., Int. Ed. Engl.* **1985,** *24*, 799-810.
4. Baxendale, I. R.; Ley, S. V. *Curr Org Chem* **2005,** *9*, 1521-1534.
5. Kupchan, S. M.; Dasgupta, B.; King, M. L.; Fujita, E. *Tetrahedron* **1963,** *19*, 227-232.
6. Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Edit.* **2000,** *39*, 1279-1281.
7. Berkessel, A.; Groger, H. *Asymmetric Organocatalysis- From Biomimetic Concepts to Applications in Asymmetric Synthesis*. Weinheim, Wiley-VCH, Great Britain, 2005.
8. Bergbreiter, D. E.; Chandran, R. *J. Am. Chem. Soc.* **1987,** *109*, 174-179.
9. Phelps, J. C.; Bergbreiter, D. E.; Lee, G. M.; Villani, R.; Weinreb, S. M. *Tetrahedron Lett.* **1989,** *30*, 3915-3918.
10. Bergbreiter, D. E.; Weatherford, D. A. *J. Org. Chem.* **1989,** *54*, 2726-2730.
11. Bergbreiter, D. E.; Chen, L. B.; Chandran, R. *Macromolecules* **1985,** *18*, 1055-1057.
12. Bergbreiter, D. E.; Walker, S. A. *J. Org. Chem.* **1989,** *54*, 5138-5141.
13. Bergbreiter, D. E.; Morvant, M.; Chen, B. *Tetrahedron Lett.* **1991,** *32*, 2731-2734.

14. Liou, S.; Rademacher, J. T.; Malaba, D.; Pallack, M. E.; Brittain, W. J. *Macromolecules* **2000,** *33*, 4295-4296.

15. Shen, Y. Q.; Zhu, S. P. *Macromolecules* **2001,** *34*, 8603-8609.

16. Shen, Y. Q.; Zhu, S. P.; Pelton, R. *Macromolecules* **2001,** *34*, 3182-3185.

17. Lavastre, O.; Bebin, P.; Marchaland, O.; Dixneuf, P. H. *J. Mol. Catal. A: Chem.* **1996,** *108*, 29-34.

18. Bergbreiter, D. E. *Chem. Rev.* **2002,** *102*, 3345-3383.

19. Bergbreiter, D. E.; Chen, B. *J. Chem. Soc., Chem. Commun.* **1983**, 1238-1239.

20. Bilgrien, C.; Davis, S.; Drago, R. S. *J. Am. Chem. Soc.* **1987,** *109*, 3786-3787.

21. Bergbreiter, D. E.; Liu, Y. S.; Osburn, P. L. *J. Am. Chem. Soc.* **1998,** *120*, 4250-4251.

22. Bergbreiter, D. E.; Liu, Y. S. *Tetrahedron Lett.* **1997,** *38*, 7843-7846.

23. Mao, H. B.; Li, C. M.; Zhang, Y. J.; Furyk, S.; Cremer, P. S.; Bergbreiter, D. E. *Macromolecules* **2004,** *37*, 1031-1036.

24. Furyk, S.; Zhang, Y. J.; Ortiz-Acosta, D.; Cremer, P. S.; Bergbreiter, D. E. *J. Polym. Sci., Part A: Polym. Chem.* **2006,** *44*, 1492-1501.

25. Zhang, Y. J.; Furyk, S.; Bergbreiter, D. E.; Cremer, P. S. *J. Am. Chem. Soc.* **2005,** *127*, 14505-14510.

26. Bergbreiter, D. E.; Liu, Y. S. *Tetrahedron Lett.* **1997,** *38*, 3703-3706.

27. Berger, A. K. G., R.J.M.; van Koten, G. . *Top. Organomet. Chem.* **2006,** *20*, 1-38.

28. Leitner, W. *Acc. Chem. Res.* **2002,** *35*, 746-756.

29. Picquet, M.; Poinsot, D.; Stutzmann, S.; Tkatchenko, I.; Tommasi, I.; Wasserscheid, P.; Zimmermann, J. *Top. Catal.* **2004,** *29*, 139-143.

30. Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chem.* **2002,** *182*, 419-437.

31. Behr, A.; Henze, G.; Schomacker, R. *Adv. Synth. Catal.* **2006,** *348*, 1485-1495.

32. Keim, W. *Green Chem.* **2003,** *5*, 105-111.

33. Cornils, B.; Kuntz, E. G. *J. Organomet. Chem.* **1995,** *502*, 177-186.

34. Regen, S. L. *J. Am. Chem. Soc.* **1975,** *97*, 5956-5957.

35. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Org. Lett.* **2000,** *2*, 1737-1739.

36. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001,** *123*, 5260-5267.

37. Tanaka, F.; Thayumanavan, R.; Barbas, C. F. *J. Am. Chem. Soc.* **2003,** *125*, 8523-8528.

38. Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *J. Mol. Catal. A: Chem.* **2003,** *204*, 157-163.

39. List, B. *Tetrahedron* **2002,** *58*, 5573-5590.

40. Doyle, M. P.; Eismont, M. Y.; Bergbreiter, D. E.; Gray, H. N. *J. Org. Chem.* **1992,** *57*, 6103-6105.

41. Matyjaszewski, K.; Xia, J. H. *Chem. Rev.* **2001,** *101*, 2921-2990.

42. Tsarevsky, N. V.; Braunecker, W. A.; Tang, W.; Brooks, S. J.; Matyjaszewski, K.; Weisman, G. R.; Wong, E. H. *J. Mol. Catal. A: Chem.* **2006,** *257*, 132-140.

43. Matyjaszewski, K.; Pintauer, T.; Gaynor, S. *Macromolecules* **2000,** *33*, 1476-1478.

44. Honigfort, M. E.; Brittain, W. J.; Bosanac, T.; Wilcox, C. S. *Macromolecules* **2002,** *35*, 4849-4851.

45. Faucher, S.; Okrutny, P.; Zhu, S. P. *Macromolecules* **2006,** *39*, 3-5.

46. Faucher, S.; Zhu, S. P. *J. Polym. Sci., Part A: Polym. Chem.* **2007,** *45*, 553-565.

47. Bryndza, H. E.; Grady, M. C.; Kristjansdottir, S. S.; Older, C. M.; Page, M. A.; Ritter, J. C.; Tam, W. Recoverable polymer-bound homogeneous catalysts for catalytic chain transfer processes. Eur. Pat. Appl. WO2007024634, March 1, 2007.

48. Zhao, M. Q.; Zhou, Y. F.; Bruening, M. L.; Bergbreiter, D. E.; Crooks, R. M. *Langmuir* **1997,** *13*, 1388-1391.

49. Malmstrom, T.; Andersson, C. *J. Mol. Catal. A: Chem.* **1999,** *139*, 259-270.

50. Horvath, I. T. *Acc. Chem. Res.* **1998,** *31*, 641-650.

51. Juliette, J. J. J.; Rutherford, D.; Horvath, I. T.; Gladysz, J. A. *J. Am. Chem. Soc.* **1999,** *121*, 2696-2704.

52. Bergbreiter, D. E.; Franchina, J. G. *Chem. Commun.* **1997**, 1531-1532.

53. Bergbreiter, D. E.; Franchina, J. G.; Case, B. L. *Org. Lett.* **2000,** *2*, 393-395.

54. Yao, Q. W.; Zhang, Y. L. *J. Am. Chem. Soc.* **2004,** *126*, 74-75.

55. Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000,** *122*, 9058-9064.

56. Bergbreiter, D. E.; Hughes, R.; Besinaiz, J.; Li, C. M.; Osburn, P. L. *J. Am. Chem. Soc.* **2003,** *125*, 8244-8249.

57. Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. *Adv. Synth. Catal.* **2005,** *347*, 172-184.

58. Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. *J. Am. Chem. Soc.* **2001,** *123*, 11105-11106.

59. Bergbreiter, D. E.; Li, J. *Chem. Commun.* **2004**, 42-43.

60. Bergbreiter, D. E.; Osburn, P. L.; Smith, T.; Li, C. M.; Frels, J. D. *J. Am. Chem. Soc.* **2003,** *125*, 6254-6260.

61. Grunlan, M. A.; Regan, K. R.; Bergbreiter, D. E. *Chem. Commun.* **2006**, 1715-1717.

62. McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002,** *102*, 3275-3299.

63. Bergbreiter, D. E. *J. Polym. Sci., Part A: Polym. Chem.* **2001,** *39*, 2351-2363.

64. Bergbreiter, D. E.; Sung, S. D.; Li, J.; Ortiz, D.; Hamilton, P. N. *Org. Process Res. Dev.* **2004,** *8*, 461-468.

65. Zhou, M.; Sivaramakrishnan, A.; Ponnamperuma, K.; Low, W. K.; Li, C. M.; Liu, J. O.; Bergbreiter, D. E.; Romo, D. *Org. Lett.* **2006,** *8*, 5247-5250.

66. Bergbreiter, D. E.; Koshti, N.; Franchina, J. G.; Frels, J. D. *Angew. Chem. Int. Edit.* **2000,** *39*, 1039-1042.

67. Chen, W. P.; Xu, L. J.; Xiao, J. L. *Chem. Commun.* **2000**, 839-840.

68. Liu, F. C.; Abrams, M. B.; Baker, R. T.; Tumas, W. *Chem. Commun.* **2001**, 433-434.

69. Ladnak, V.; Hofmann, N.; Brausch, N.; Wasserscheid, P. *Adv. Synth. Catal.* **2007,** *349*, 719-726.

70. Bergbreiter, D. E.; Furyk, S. *Green Chem.* **2004,** *6*, 280-285.

71. Bergbreiter, D. E.; Case, B. L.; Liu, Y. S.; Caraway, J. W. *Macromolecules* **1998,** *31*, 6053-6062.

72. Li, J.; Sung, S. N.; Tian, J. H.; Bergbreiter, D. E. *Tetrahedron* **2005,** *61*, 12081-12092.

73. Engstrom, J. U. A.; Helgee, B.; Sung, S. D.; Bergbreiter, D. E. *Macromol. Chem. Physic* **2006,** *207*, 1062-1069.

74. Bergbreiter, D. E.; Li, C. M. *Org. Lett.* **2003,** *5*, 2445-2447.

75. Liu, Y. S.; Zhao, C. X.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998,** *63*, 3471-3473.

76. Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997,** *38*, 3357-3360.

77. Fischer, F. G.; Marschall, A. *Berichte Der Deutschen Chemischen Gesellschaft* **1931,** *64*, 2825-2827.

78. Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem. Int. Edit.* **1971,** *10*, 496-497.

79. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974,** *39*, 1615-1621.

80. List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000,** *122*, 2395-2396.

81. Oku, J. I.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229-230.

82. Oku, J.; Ito, N.; Inoue, S. *Makromolekulare Chemie-Macromolecular Chemistry and Physics* **1982,** *183*, 579-586.

83. Julia, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317-1324.

84. Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Synthesis* **2007**, 1729-1732.

85. Zhou, L.; Wang, Z.; Wei, S.; Sun, J. *Chem. Commun.* **2007**, 2977-2979.

86. Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006,** *348*, 999-1010.

87. Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998,** *120*, 4901-4902.

88. Wang, J.; Li, H.; Zua, L. S.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2006,** *348*, 2047-2050.

89. Wang, J.; Li, H.; Zu, L. S.; Jiang, W.; Xie, H. X.; Duan, W. H.; Wang, W. *J. Am. Chem. Soc.* **2006,** *128*, 12652-12653.

90. Wang, J.; Li, H.; Duan, W. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005,** *7*, 4713-4716.

91. Wang, J.; Li, H.; Yu, X. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005,** *7*, 4293-4296.

92. Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006,** *128*, 6048-6049.

93. Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005,** *7*, 1967-1969.

94. Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N. *Angew. Chem. Int. Edit.* **2006,** *45*, 6366-6370.

95. Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** *124*, 12964-12965.

96. Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** *124*, 10012-10014.

97. Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006,** *62*, 434-439.

98. Wittkopp, A.; Schreiner, P. R. *Chem.- Eur. J.* **2003,** *9*, 407-414.

99. Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004,** *346*, 1141-1146.

100. Zu, L. S.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006,** *8*, 3077-3079.

101. Chowdari, N. S.; Barbas, C. F. *Org. Lett.* **2005,** *7*, 867-870.

102. Bellis, E.; Vasilatou, K.; Kokotos, G. *Synthesis* **2005**, 2407-2413.

103. Tang, Z.; Jiang, F.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *Proc. Natl. Acad. Sci. U. S. A.* **2004,** *101*, 5755-5760.

104. Katz, A.; Davis, M. E. *Nature* **2000,** *403*, 286-289.

105. Defreese, J. L.; Katz, A. *Microporous Mesoporous Mater.* **2006,** *89*, 25-32.

106. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993,** *93*, 2207-2293.

107. Denmark, S. E.; Fu, J. P. *Chem. Commun.* **2003**, 167-170.

108. Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998,** *39*, 2767-2770.

109. Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999,** *55*, 977-988.

110. Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998,** *120*, 6419-6420.

111. Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Org. Chem.* **2006,** *71*, 1458-1463.

112. Kina, A.; Shimada, T.; Hayashi, T. *Adv. Synth. Catal.* **2004,** *346*, 1169-1174.

113. Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron-Asymmetry* **2004,** *15*, 1373-1389.

114. Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2000,** *48*, 306-307.

115. Hrdina, R.; Valterova, I.; Hodacova, J.; Cisarova, I.; Kotora, M. *Adv. Synth. Catal.* **2007,** *349*, 822-826.

116. Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kocovsky, P. *J. Mol. Catal. A: Chem.* **2003,** *196*, 179-186.

117. Pignataro, L.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Chirality* **2005,** *17*, 396-403.

118. Chelucci, G.; Belmonte, N.; Benaglia, M.; Pignataro, L. *Tetrahedron Lett.* **2007,** *48*, 4037-4041.

119. Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005,** *7*, 3151-3154.

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