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Soluble Polymeric Ligands for Metal Complexation and Catalyst Recovery

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Summary: Soluble polymers that bind metals and that in turn can be separated from other components of a reaction mixture are described. The polymers used include derivatives of acrylamides, acrylates, polystyrene and other polymers. Both sequestration of trace metals and recovery of homogeneous catalysts is discussed. Separation methods using liquid/liquid mixtures that are monophasic during a reaction but biphasic during a separation are emphasized

Keywords: biphasic; catalysis; green chemistry; heck; ion exchange; latent biphasic; polymer; separation; thermomorphic

Introduction

Soluble synthetic polymers that bind metals have a variety of uses. As discussed below, such polymers can be used to sequester metals. The metals to be sequestered could be spent or recoverable catalysts.[1] They might be toxic metals in waste streams.[2] They could be metals that one wished to recover or sequester for any other reason.[3] Fortunately, simple complexation is easy to accomplish. However, polymers that bind metals can be especially useful when the soluble polymer-metal complex can be quantitatively separated and recovered. A variety of separation procedures have been used for such purposes. Figure 1 summarizes these approaches. As shown there are two general schemes that are typically used – liquid/solid separation (filtration, centrifugation) or liquid/liquid separation (membrane filtration, extraction). In this paper, we will focus on liquid/liquid separation schemes. We initially discuss metal complexation. This discussion is followed with some examples of catalyst recovery in a liquid/liquid regime using soluble polymer supports.

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Background

Removal and sequestration of metal ions is an old problem. While this paper is focused on polymers and on soluble polymers in particular, it is important to recognize that simple complexation of a metal by an organic ligand and extraction into an organic solvent like chloroform can work very well.[4,5] The formation of the complex provides the metal ion with organic solubility and, if the ligand is chosen correctly, the amount of the extracted species can be determined by photometric techniques.

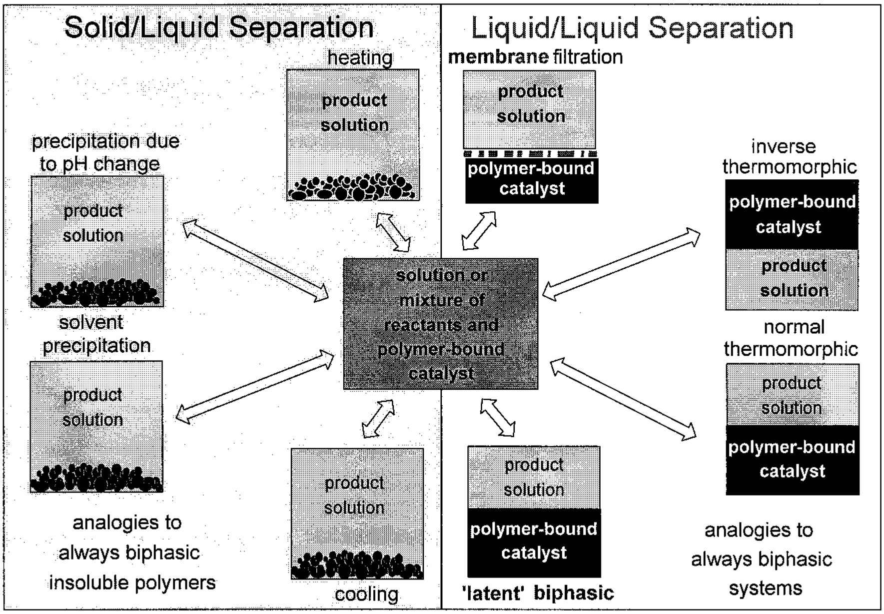


Fig. 1. Example of solid/liquid and liquid/liquid separation schemes applicable to soluble polymers and to soluble polymers that can be used to bind waste metals, toxic metals or recoverable catalysts.

Polymers like ion exchange resins (often in the form of crosslinked polystyrene) are an effective method of removing and sequestering metal ions.[6-8] Such resins are typically insoluble synthetic polymers. Biological polymers too can be used.[9] Soluble polymers too can be effective.[10,11] These soluble chelators are of interest as they help avoid some of the problems associated with resins. For example, slow diffusion of the metal species through the polymer matrix and detrimental interactions between the solid, hydrophobic polystyrene resin and the aqueous solution can be avoided using soluble polymers. Examples of these soluble polymeric chelators include poly(ethyleneimine), poly(vinyl alcohol), and poly(acrylic acid). The polymers can be efficiently recovered by membrane filtration in a pressurized system. When dissolved in a solution containing metal ions, the polymers coordinate to the ions to form soluble complexes. The polymer effectively increases the size of the metal ion, and both the metal and polymer are captured by the membrane. This purifies the solution and concentrates the volume of the material containing a potentially hazardous substance. This approach can be used in an industrial setting as was demonstrated in recovery of Zn from an electroplating bath.[12] The effluent from this operation typically contained 1000 L of water with an average Zn concentration of 60 ppm. The effluent was stirred with a proprietary soluble polymer and the system processed over a 5 h period. Analysis of the permeate showed that the concentration of Zn had been reduced to, on average, 200 ppb. This concentration was well below the discharge limit of 2 ppm. After the solution had been processed, the pH of the retained polymer solution was adjusted to release the bound Zn. Both the metal and chelating polymer could be recycled. The polymer was used almost 70 times over a two week period without any decrease in effectiveness.

Sequestration of Metals by Water-Soluble Polymers

Initially we investigated complexing and removing trace metal ions from aqueous solution. For this work, we used ligands attached to poly(*N*-isopropylacrylamide) (PNIPAM). This polymer is water soluble, but has the interesting characteristic of precipitating at elevated temperatures.[13] This inverse temperature dependent solubility is a product of the interactions between the hydrophilic backbone and hydrophobic side chain. Enthalpically, hydrogen bonding between water molecules and the amide backbone is favorable and provides solubility in water. However, formation of these hydrogen bonds requires organization of water molecules along the backbone of the polymer, an entropically disfavored arrangement. At a specific temperature, called the lower critical solution temperature (LCST), the enthalpy of dissolution can no longer compensate for the entropic requirement, and the polymer precipitates from solution. In essence, the hydrogen bonds are broken at the higher temperatures and the polymer is no longer solvated. The LCST of PNIPAM is about 31 °C but depends on subtle ways on the nature of the polymer support and other components that are present in the solution.[14,15]

For our work using PNIPAM-bound ligands, we synthesized a copolymer of NIPAM and an active ester *N*-acryloxysuccinimide (NASI), typically in a 10:1 ratio, respectively. This provides a polymer with solubility characteristics like PNIPAM and with reactive carbonyls that can be substituted with various ligands. Substitution by other groups or ligands can affect the polymer's solubility and LCST. We have shown that ligands can raise or lower the polymer's LCST depending on the hydrophilicity or hydrophobicity of the ligand.[16] This can be a problem if the polymer formed by ligand introduction is either insoluble in water or has an LCST above 100 °C. Such solubility would limit the utility of the support in an aqueous system. Fortunately, it is possible and even practical to control the solubility of the polymer by adjusting the amounts of ligand attached to the PNIPAM backbone (Figure 2). Instead of adding a full equivalent of the primary ligand, a lesser amount is used, and the solubility characteristics of the primary ligand are balanced by addition of a second ligand with opposing solubility. In this way, ligands of almost any solubility can be successfully attached to PNIPAM to obtain a polymeric ligand with a convenient LCST for use in aqueous media.

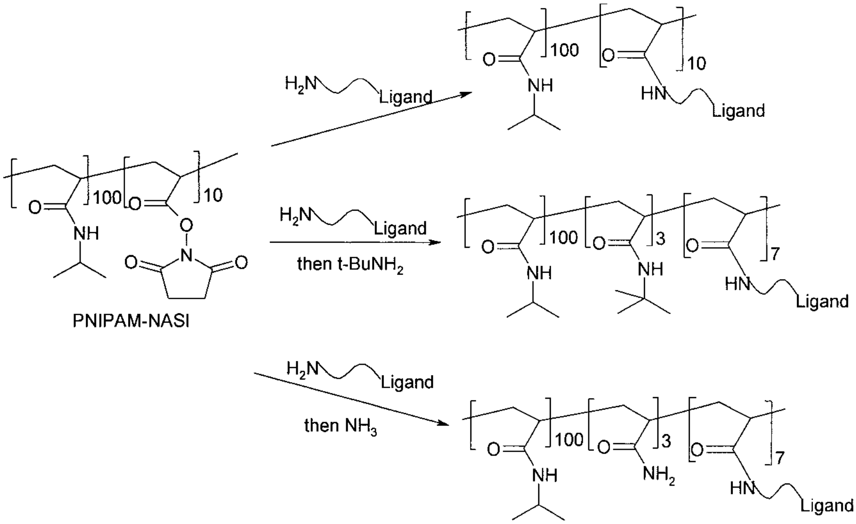


Fig. 2. PNIPAM-bound ligands with adjustments for the ligand's hydrophilicity.

We began our investigations into polymeric metal sequestrations by using a polymer-bound hydroxamic acid. Hydroxamic acids are known metal binders and have been applied in various systems to bind and extract metal ions.[17-22] A naturally occurring hydroxamic acid, deferoxamine, is a microbial transport agent for iron.[23] Hydroxamic acids also fortuitously form intensely red colored complexes with Fe. The red color provides a visual indication that a reaction has taken place and enables analysis by UV-Vis spectroscopy.

We synthesized a polymer bound hydroxamic acid starting from amino caproic acid (Figure 3). The amine was protected by reaction with di-*tert*-butyl dicarbonate, and the acid was coupled to *O*-benzyl hydroxylamine to give **1**. The Boc protecting group was removed with trifluoroacetic acid (TFA), and the benzyl group was cleaved by hydrogenolysis. The resulting amine terminated hydroxamic acid **2** was then attached to a PNIPAM-NASI copolymer to form polymer bound hydroxamic acid **4**. This polymer was water soluble and had an LCST of 31 °C, determined by observing a solution of the polymer as it was heated incrementally in a thermostated bath.

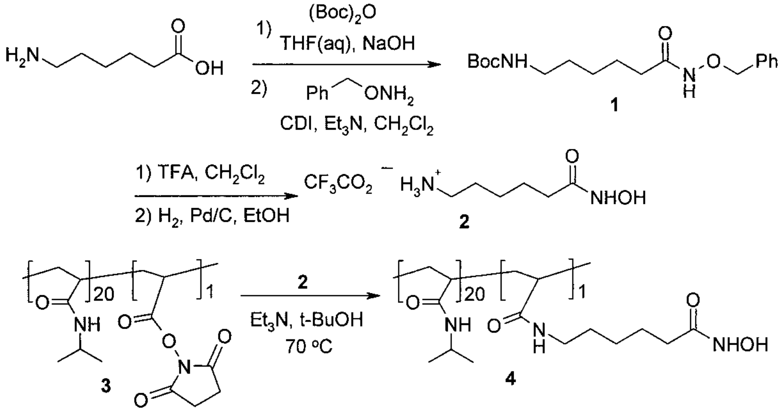


Fig. 3. Synthesis of PNIPAM-bound hydroxamic acid **4**.

When a solution of 200 mg of **4** in water was combined with an aqueous solution containing 15.5 ppm Fe^{+3}, a red solution formed. This red solution had an absorbance of 0.65 at 439 nm. Heating this solution above the LCST produced a red precipitate and a clear supernatant. The precipitate and supernatant were separated by centrifugation, and 5 mg of **2** were added to the supernatant. If any residual iron were present, the formation of an iron-hydroxamate complex would be detectable by UV-Vis and provide a measure of the remaining iron in solution. After addition of **2** to the supernatant, analysis by UV-Vis did not reveal any detectable color ($A<0.002$), indicating that the iron had been completely removed from solution. This conclusion was confirmed by inductively coupled plasma (ICP) spectroscopy, showing that the 15.5 ppm iron solution had been reduced in concentration to 116 ppb.

It is possible to regenerate the polymer-bound chelator. When a red solution of polymer-bound iron complex (A =0.62) was treated with disodium EDTA, the red color disappeared. Heating formed a white precipitate which was isolated, redissolved and precipitated from fresh water to removed any occluded EDTA. Dissolution of recovered **4** in fresh water and treatment with $FeCl_3$ gave the expected red solution having the same absorbance as the fresh polymer.

Another ligand we investigated was hydroxypyridinone. Like hydroxamic acids, hydroxyl-pyridinones form red-colored complexes with iron. This polymer-bound sequestering agent was synthesized from commercially available dihydroxy pyridinone and bromo ethyl acetate (Figure 4). After *N*-alkylation of the pyridine ring, the ester was trans aminated with ethylene diamine to produce the amine terminated hydroxypyridinone **6** which was attached to PNIPAM giving polymer **7**. When an aqueous solution containing 150 mg **7** was combined with a 14.4 ppm Fe solution, a red colored solution resulted having an absorbance of 1.1 at 578 nm. Precipitation of the polymer and separation of the clear supernatant was followed by addition of **6**. Analysis of the treated solution did not reveal an absorbance above 0.002, indicating an absence of iron in the solution.

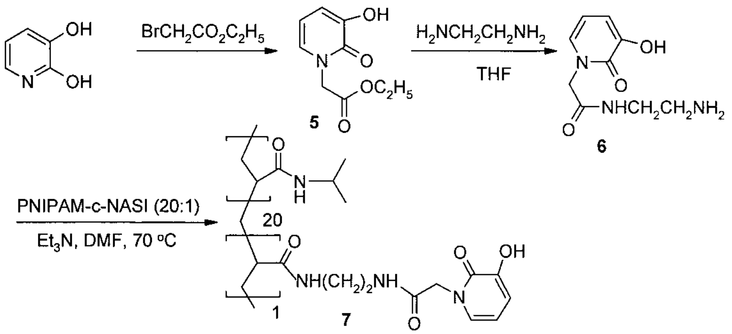
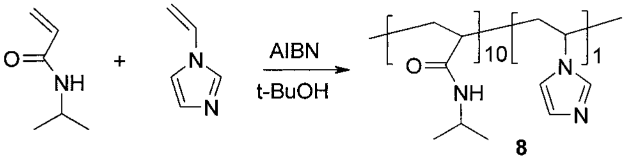


Fig. 4. Synthesis of PNIPAM-bound hydroxypyridinone 7.

In the same vein, a copolymer of NIPAM and vinyl imidazole was synthesized by radical polymerization (eq 1). Imidazole forms blue complexes with Cu^{II}, and we used this polymer to remove Cu^{II} from solution. Unfortunately, the absorbance of the copper-imidizole complex is much lower than that of the iron-hydroxamate, and higher polymer and metal concentrations must be used to obtain a distinct signal in the UV-Vis. A 1.23 g solution of **8** was mixed with a 269 ppm Cu^{II} solution, produces a blue-colored solution with an absorbance of 0.20 at 658 nm. Thermal precipitation separated the polymer from the supernatant. The supernatant was then concentrated by a factor of ten and methyl imidazole added. No absorbance > 0.002 due to the copper-imidazole complex was observed, indicating complete removal of the Cu^{II} contaminant.



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(1)

As part of our investigations of PNIPAM-bound catalysts, we demonstrated that when precipitated, these polymer-bound catalysts were inactive.[16] This indicates that while precipitated, the metal center is inaccessible to soluble species. Metal ions sequestered by PNIPAM-hydroxamic acid are also inaccessible to soluble ligands if the solvent's temperature stayed above the sequestration LCST. This was tested in an experiment where an aqueous solution of iron bound to **4** was precipitated, and the temperature of the mixture was maintained above the LCST. In this case, a low molecular weight hydroxamic acid (**2**) was added to the mixture. Ligand **2** dissolved, and the suspension stirred overnight. After this 18 h period, centrifugation separated the solid leaving a colorless supernatant. This shows that the precipitated polymeric ligand retains the bound metal even in the presence of soluble ligands so long as the polymer is precipitated.

At first glance it may seem surprising that the PNIPAM-bound hydroxamic acid preferentially removes iron from solution even in the presence of soluble ligands. However, it is entropically favorable for the polymer to remove the soluble metal ions from solution since only one of the ligands coordinated to the metal needs to be polymeric.[24] In order for the metal to remain in solution, all the ligands surrounding it must be non-polymeric (Figure 5). In this experiment, **4** and Fe^{III} were dissolved in water and combined, forming the expected red solution. The absorbance of this solution was measured. The solution was heated and the polymer precipitated. Then the absorbance of the supernatant was measured. The polymer was allowed to redissolve, and a known amount of low molecular weight hydroxamic acid was added. The absorbance of the solution was again measured. Heating the solution precipitated the polymer.

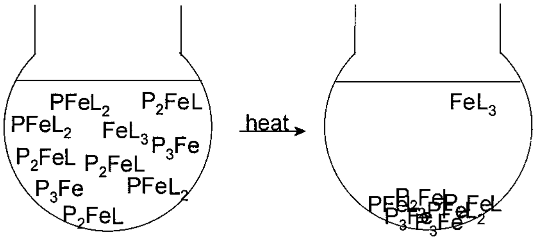


Fig. 5. Competition experiment between polymeric hydroxamate (P) and low molecular weight hydroxamate (L).

Now, any residual absorption in the supernatant indicates the amount of iron that was not precipitated with the polymer, i.e. it is a measure of the amount of the low molecular weight-iron complex. As seen in Figure 6, the absorbances in the supernatant are negligible until there is a greater amount of **2** than the polymeric ligand in the reaction. As the fraction of **2** is increased, the amount of the corresponding soluble complex increases slightly, but even at a 3:1 **2** to **4** ratio, the polymer still removes approximately 85% of the iron.

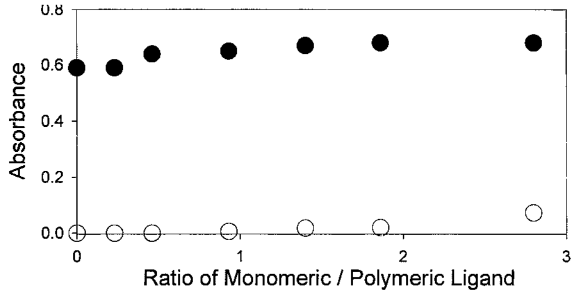
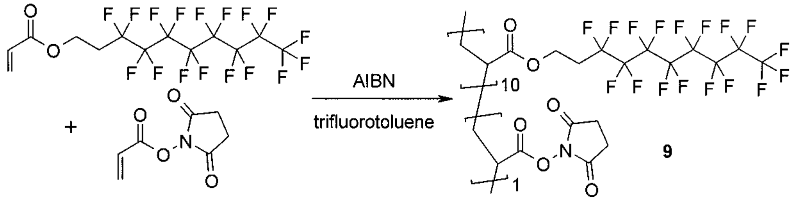


Fig. 6. Absorbances of a solution containing **4** and varying amounts of **2**. Closed circles represent absorbances of the solution when the polymer is dissolved. Open circles represent absorbances of the solution when the polymer is precipitated.

Sequestration of Metals from Organic and Fluorous Solvents

Besides metal sequestrations from aqueous solution, we have investigated sequestering and removing metals from organic solution. Rather than using a precipitation technique to isolate the polymer-bound metal, we investigated two biphasic separation techniques to effect the separation of the polymer from the metal containing solution.

The first is based on the fluorous biphasic separation reported by Horvath.[25] In his initial report, he used fluorinated phosphines and phthalocyanines to give the ligand and bound metal fluorous solubility. Rather than synthesize fluorinated ligands, we saw an opportunity for soluble polymers to fill the role of the fluorinated phosphines. Polymerization of the commercially available fluorous acrylate with *N*-acryloxysuccinimide (NASI) results in a fluorinated, substitutable support (eq 2). These supports are soluble in fluorinated solvents and insoluble in normal organic solvents.[26] The NASI residue provides an attachment point for non-fluorinated ligands. Thus, a fluorous-soluble ligand can be produced without special synthetic methods. The generalized polymer support acts as a fluorous handle for standard organic ligands. We and others have demonstrated that fluorinated acrylate polymers are useful supports for fluorous biphasic catalysis.[27-30]



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(2)

Fluorinated polyacrylate **9** was substituted with amine terminated hydroxamic acid **2**. This fluorous-soluble metal binder was dissolved in the perfluorinated solvent FC-77 and combined with a methanolic solution of Fe^{III}. The mixture was shaken for 15 min and then centrifuged, revealing a red fluorous layer. The methanol layer was removed, and **2** was added to it. Analysis by UV-Vis spectroscopy showed no residual color in the organic layer. Addition of the low molecular weight hydroxamic acid to the methanolic iron solution before extraction gave an absorbance of 1.02.

As was true for the PNIPAM-bound hydroxamic acid **4**, we were able to decomplex the iron from the fluorous polymer-bound hydroxamic acid and reuse the polymer. When a fluorous polymer-bound iron-hydroxamate complex was shaken with a methanolic solution of EDTA, a loss of color in the fluorous layer occurred. The layers were separated, and the fluorous phase was treated with fresh methanolic iron, reforming the red fluorous solution.

We were also interested in applying thermomorphic systems used in thermally reversible biphasic catalyst separations as a means of metal sequestration.[31] However, in those catalyst experiments, PNIPAM was used. PNIPAM is soluble in polar solvents like water and ethanol and insoluble in non-polar solvents like heptane and toluene. Metal ions are also soluble only in polar solvents, so a new polymer support was needed to successfully adapt thermomorphic separations to metal sequestration. A preferred support would need to be soluble in non-polar solvents and insoluble in polar solvents.

To produce a polymer with the required solubility, we applied the concept "like dissolves like." We synthesized an acrylamide monomer **10** from acryloyl chloride and octadecylamine. The extended length of the carbon side chain should increase the subsequent polymer's solubility in non-polar solvents while decreasing it in polar solvents. The monomer was recrystallized from acetone and copolymerized with NASI in benzene, forming polymer **11**. Simple solubility tests showed that the polymer was indeed soluble in heptane. In addition to heptane, it was soluble in chloroform, THF, and *t*-butanol. It was insoluble in polar solvents like methanol, dimethylformamide, dimethylacetamide, and acetonitrile. An azo dye, methyl red, was attached to the polymer via an amide linkage. The dye imparts an orange color to the polymer and enables analysis by UV-Vis. The polymer was dissolved in heptane and miscibilized with a 90% EtOH solution (Figure 7). After cooling and separation of the two layers, UV-Vis analysis showed that the polymer had a >99% preference for the heptane layer.

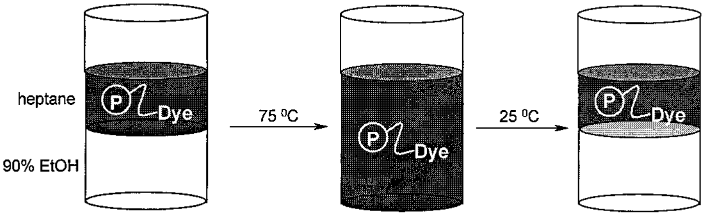


Fig. 7. Phase selectivity studies using PNODAM-methyl red.

In order to probe metal extraction using this thermomorphic approach, a PNODAM copolymer containing a hydroxamic acid moiety was synthesized (Figure 8). This polymer, **12**, (100 mg, 0.029 mmol) was dissolved in 10 mL of heptane and added to a 90% EtOH solution containing 0.0027 mmol $FeCl_3$ (15 ppm Fe^{III}). The mixture was heated to 80 °C and then cooled to 25 °C. The two layers reformed with the red color visibly in the top layer. No precipitation of the polymer was observed. The heptane layer had an absorbance of 0.59 at 448 nm while the ethanol layer, even after the addition of low molecular weight hydroxamic acid, had an absorbance <0.002. For comparison, 10 mL of 90% EtOH containing 0.029 mmol **11** and 0.0027 mmol $FeCl_3$ had an absorbance of 0.57 at 461 nm. Direct current plasma (DCP) spectroscopy showed that the 15 ppm Fe^{III} solution had been reduced to background levels of ~50 ppb.

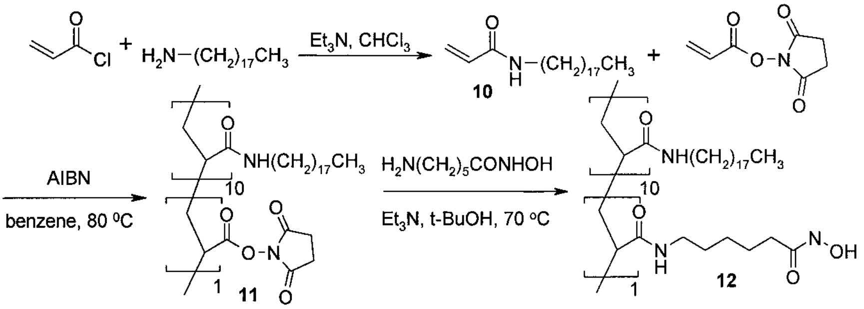


Fig. 8. Synthesis of PNODAM support and attachment of hydroxamic acid.

Simple shaking tests indicated that transfer of the iron from aqueous ethanol to the heptane soluble chelator was not as facile as that seen in the fluorous system. A series of vials containing $FeCl_3$ dissolved in aqueous ethanol were prepared. To each vial was added a heptane solution of PNODAM-bound hydroxamic acid. The vials were mechanically shaken and at different time intervals, one of the vials was removed, the aqueous ethanol layer separated, and low molecular weight hydroxamic acid **2** added to it. The ethanolic solution was then analyzed by UV-Vis spectroscopy for residual color. Over the course of 4 h, the concentration of iron in the aqueous ethanol decreases but is incomplete. As the iron is sequestered by the polymer, the more accessible sites are probably occupied first. As these accessible sites are filled, the rate of iron uptake slows. This implies that the PNODAM supported hydroxamic acid does not interact as well with alcoholic solutions as does its fluorous counterpart. This experiment illustrates the utility and advantages of a monophasic/biphasic scheme for metal sequestration (Figure 7).

In addition to iron, we investigated the utility of PNODAM-bound hydroxamic acid for sequestration of other metal ions. Hydroxamic acids are known to bind metal ions to varying degrees. We prepared solutions containing 9.4 ppm Cu^{II}, 6.7 ppm Cr^{III}, and 8.4 ppm Ni^{II}. These metals do not form colored complexes with hydroxamic acids, but they are still amenable to DCP analysis. Sequestration experiments like those for iron showed incomplete extraction for each of the metal ions. The Cu^{II} concentration was reduced to 2 ppm, Cr^{III} to 3.9 ppm, and the Ni^{II} concentration reduced to 1.4 ppm. A survey of the literature concerning hydroxamate complexes reveals that extraction efficiency for metal hydroxamates is pH dependant. At low pH, only iron is extracted from solution. As the pH is raised to a more neutral number, extraction of other metals becomes more efficient.[17,18,21] The pH of the solutions of Cu^{II}, Cr^{III}, and Ni^{II}, were 3.7, 2.5, and 5.3, respectively. It seemed reasonable that adjusting the pH higher would improve the extraction efficiency. However, there is a caveat; transition metals have a tendency to form insoluble hydroxides at higher pH's. In adjusting the acidity of the copper and chromium solutions, both became cloudy with addition of aqueous KOH, indicating precipitation of the metal. The nickel solution did not precipitate and the pH of that solution was successfully adjusted to 8.1. Subsequently, extraction of the adjusted solution with PNODAM-bound hydroxamic acid successfully removed all of the nickel. The 8.4 ppm Ni^{II} solution was reduced to background levels of about 50 ppb. This indicates that these polymer supported hydroxamic acid chelators would be useful sequestrants for many transition metals, if the conditions are adjusted properly.

A third ligand we have attached to the PNODAM support is 1,10 phenanthroline. Like hydroxamic acids, phenanthroline and its derivatives are widely investigated ligands for metals.[32] It has been used as a colorimetric indicator for Fe^{II}. In addition, phenantholine's complex with Fe^{II}, called ferroin, is a redox indicator. The orange-red color of the ferrous complex essentially disappeares if the iron is oxidized to Fe^{III}.

In order to prepare a phenanthroline derivative suitable for attachment to a polymer, phenanthroline was nitrated at the 5-position in refluxing sulfuric and nitric acid. The nitrophenanthroline was reduced to the corresponding amine by reduction with hydrazine in the presence of Pd/C. The amino phenanthroline was coupled to 6-phthalimide hexanoyl chloride to give amide **16**. The phthalimide protecting group was then removed with hydrazine in refluxing ethanol. The aminoamide-terminated phenanthroline was then attached to the PNODAM support, producing a heptane soluble sequestering agent (Figure 9).

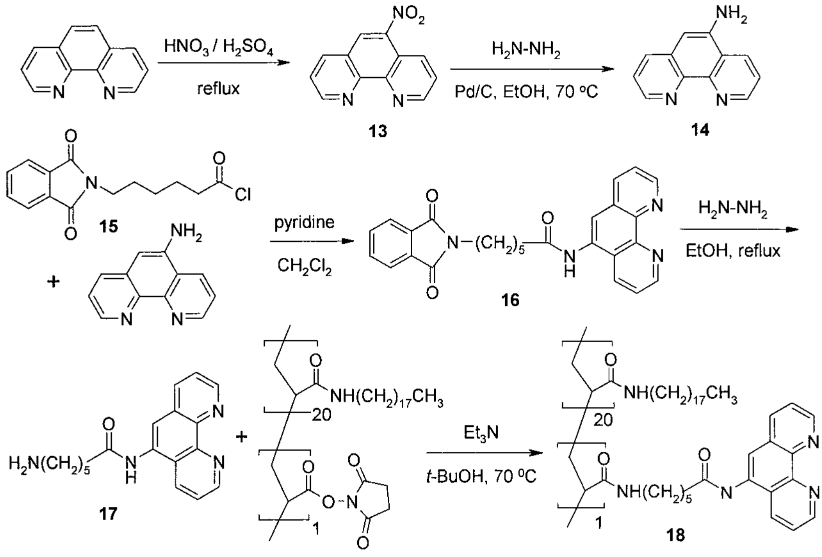


Fig. 9. Synthesis of amine terminated phenanthroline and attachment to PNODAM.

The PNODAM-phenanthroline polymer **18** was used in two extraction experiments. Two solutions were prepared. One contained 18 ppm Fe^{III}, and the other contained 20 ppm Cu^{II}. When combined with the polymer in a thermomorphic system, both metals were successfully removed from the aqueous ethanol. DCP analysis showed that the concentration of the iron solution had been reduced to 33 ppb and the concentration of the copper solution had beed reduced to 75 ppb. This chelator was useful for extracting copper from aqueous ethanol without adjustment of the solution conditions.

Polystyrene is another polymer we have investigated for thermomorphic extractions. This linear and soluble polymer is the counterpart to crosslinked, insoluble Merrifield-type resins. Polystyrene is not soluble in heptane, but soluble in toluene. We were interested in applying this support to a toluene/ aqueous ethanol thermomorphic system rather than the heptane/ aqueous ethanol previously described.

A substitutable polystyrene was synthesized according to Figure 10. Styrene and vinyl benzyl chloride, commercially available as a mixture of the 3 and 4 isomers, were radically polymerized to form **19**. The benzyl chlorides were substituted with p-hydroxy ethyl benzoate, and then the ester was hydrolyzed in aqueous THF. The resulting polymer-bound carboxylic acid was activated with DCC/NHS to give linear polystyrene **23** with an active ester like that on the previously described acrylamides.

Amine-terminated methyl red was attached to the polymer to assess its phase preference in a thermomorphic system containing toluene and a solution of 75:25 ethanol/water. Initially, a small amount of color was detected in the aqueous ethanol layer, indicating a 94% preference of the polymer for the toluene layer. Successive extractions of the toluene layer showed a decrease in the amount of color in the aqueous EtOH. The second and third extraction showed a 98.5% and 99.5% preference for the toluene layer, respectively. GPC analysis indicated that the polymer initially had a M_n of 14,400. After the third extraction the M_n had risen slightly to 21,000, indicating that lower molecular weight fractions were being removed in the extraction process.

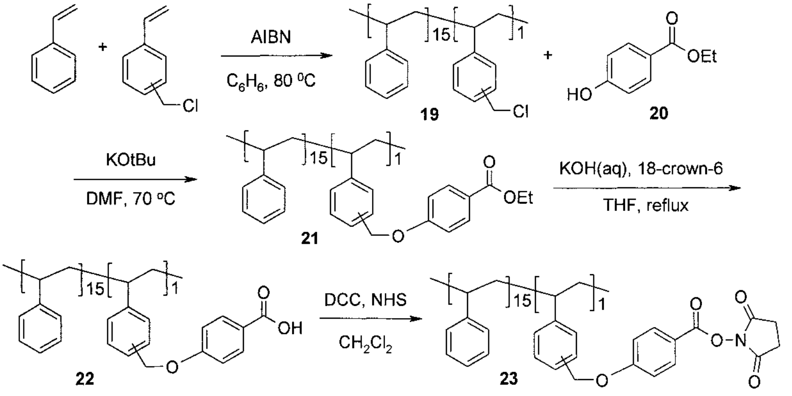


Fig. 10. Synthesis of linear polystyrene support.

To study this support's use as in metal sequestration, amine-terminated hydroxamic acid **2** was attached to the polystyrene backbone. This polymer was dissolved in toluene and combined with a 17 ppm Fe^{III} solution in aqueous ethanol. The alcohol layer was extracted by the polymeric chelator, then separated from the red toluene solution. The aqueous ethanol was then treated with **2** and analyzed by UV-Vis spectroscopy. The lack of color detected by spectroscopy indicated complete extraction of the iron.

We briefly investigated an imidazole ligand bound to soluble polystyrene. An amine terminated imidazole was synthesized from 6-aminohexanol. The amine group was protected, and then the alcohol was converted to the mesylate with methane sulfonyl chloride. Imidazole was added to tether **24** in the presence of KOtBu and 18-crown-6, and finally the Boc group was removed with TFA. The amine terminated imidazole **26** was attached to the polystyrene support through the NHS activated ester to form a toluene soluble chelator **27** (Figure 11).

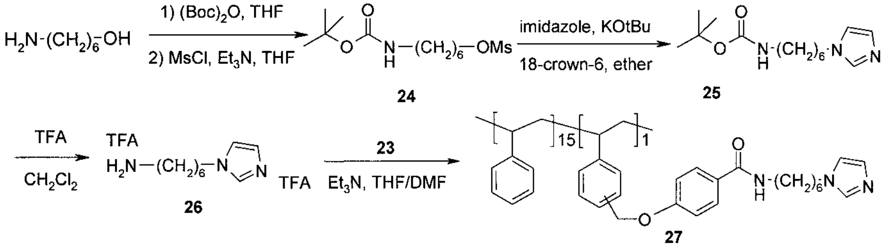


Fig. 11. Synthesis of tethered imidazole and attachment to a polystyrene support.

In a toluene/75% ethanol thermomorphic system, 60 mg of **27** was combined with a 16.5 ppm Cu solution, a 10:1 ratio of ligand to metal. After separation of the layers, the toluene layer was a light blue color. The aqueous ethanol was removed and analyzed by DCP. The concentration of the copper in the ethanol had been reduced to 1.6 ppm. While this extraction did not give complete removal of the copper, it still supports the use of soluble polymers in thermomorphic metal sequestration.

The work above illustrates that polymers can readily separate complexed metals under biphasic conditions after heat-induced miscibilization. Extractions of metal ions from water, organic, and mixed solvents are possible. While a number of different ligands effect binding of transition metals, the principles are broad. They are also generally applicable to catalysis and catalyst recovery as discussed below.

Homogeneous Catalyst Recovery from Thermomorphic Mixtures

The temperature dependent miscibility of compounds and solvents described above is a well known phenomenon and we recognized that it could be the basis of a general approach to homogeneous catalyst recovery using phase-selectively soluble polymers or phase-selectively soluble low molecular weight ligands.[1] Many binary and ternary solvent mixtures increase in miscibility with increasing temperature suggesting that this approach should be potentially quite useful.[33] While our group had limited experience in polymer synthesis, we had previously used the temperature dependent solubility of polymer supports to facilitate recovery of the polymer and bound ligands. Polyethylene supports[34-37] were designed to be soluble in a heated solution and insoluble when that solution is cold, whereas poly(*N*-isopropylacrylamide) (PNIPAM) supports were shown to be soluble in cool water and insoluble in heated aqueous systems.[16] With this history, the use of soluble polymer supported catalysts combined with solvents of reversible miscibility was developed into a general method for separating and recovering catalysts, an approach we have dubbed thermomorphic catalysis (Figure 12). Unlike the case with smart catalysts or the polyethylene bound catalysts,[34-39] the polymer would remain soluble whether the system is hot or cold, but the solvents would increase or decrease in miscibility as the system is heated or cooled. To be successful, the polymer support would need to have a strong phase preference for one of the two layers of the resting state.

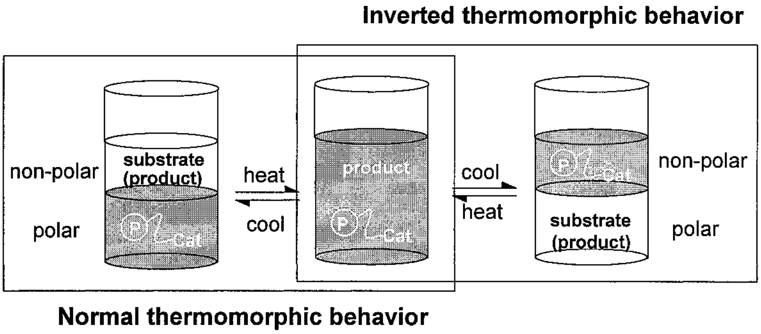


Fig. 12. Generalized examples of thermomorphic behavior.

Fortunately, phase selective soluble polymers are readily available. Our group had previously investigated biphasic systems composed of polar and nonpolar solvents like aqueous ethanol and heptane.[30,31] The polymers PNIPAM and polyethyleneglycol (PEG) showed strong phase preferences for the polar phase but remained soluble under heated, homogeneous conditions. Transition metal complexes supported by these polymers catalyzed hydrogenations, allylic substitutions, and Heck reactions and were successfully recycled. Since these polar polymers reside in the polar phase, products formed during the reaction are isolated from the nonpolar phase, constituting a normal thermomorphic system.

A potential limitation of this approach is that the products in a reaction must have at least partial solubility in the nonpolar phase in order to be isolated in a reasonable fashion. Polar products are more difficult to separate from the polar polymer. For example, salt by-products generated in the Heck reaction would accumulate in the polar phase. It was therefore desireable to develop a soluble polymer support that resided in the nonpolar phase of the biphasic mixture. To accomplish this, a poly(*N*-alkylacrylamide) similar to PNIPAM was synthesized. In this polymer, the *N*-alkyl group was changed from isopropyl to the more lipophilic octadecyl group as described above (Figure 8). As discussed above, this PNODAM-NASI was labeled with amine terminated methyl red to form PNODAM-MR. This red-colored polymer was dissolved in heptane and added to either a 9:1 ethanol/water solution or DMA as a general way to test PNODAM's nonpolar phase selective solubility.[40] In either case, a 2-layer system formed with t he color in the top layer. Heating the mixtures to 75°C formed homogeneous solutions with color distributed throughout. Cooling the solution returned the system to its original biphasic state with the color exclusively (>99.9%) in the nonpolar phase (Figure 7). With the polymer in the upper, non-polar phase, products formed in a reaction would be recovered from the lower, polar phase. This constitutes an inverse thermomorphic system.

We used the PNODAM support in catalyst recovery schemes using heptane/90% EtOH thermomorphic systems. PNODAM-NASI was allowed to react with the amine terminated phosphine, DPPA (Figure 13). The resulting polymer, PNODAM-DPPA was isolated by precipitation into methanol. Analysis by IR spectroscopy showed that the absorption peaks corresponding to carbonyl stretches of the NASI groups at 1812, 1783, and 1739 cm^{-1} had disappeared. The ^1H NMR spectrum also indicated that the NASI groups had been consumed since the peak for those methylenes (δ 2.9) had disappeared. Peaks in the aromatic region (δ 7.2-7.7) were present indicating the phosphine ligand had been bound to the polymer. In the ^{31}P NMR spectrum a broad peak at δ -16 for the free phosphine was observed along with a minor peak at δ 35 corresponding to the phosphine oxide (<10% of the phosphine peak).

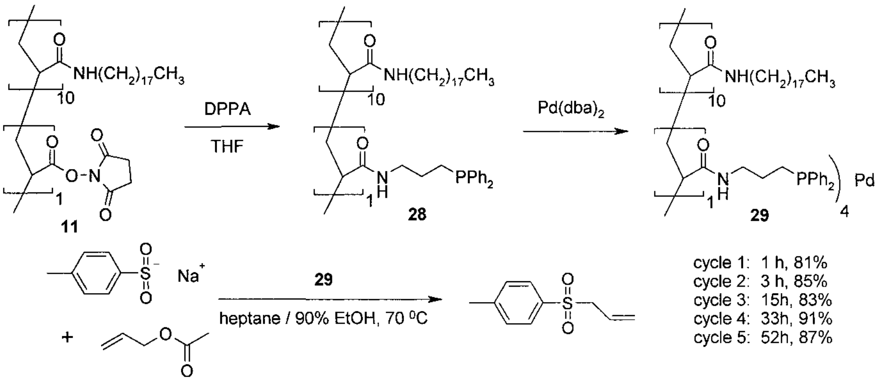


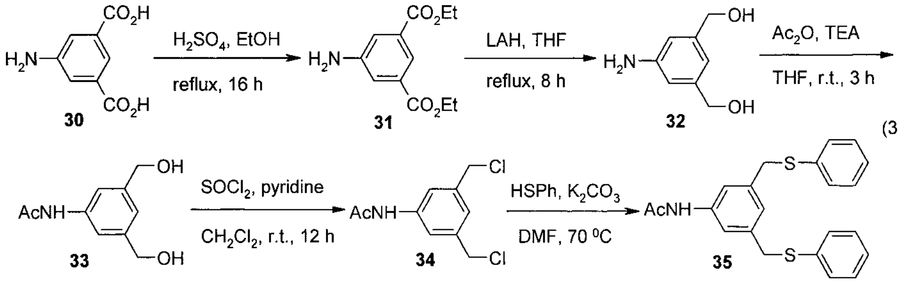
Fig. 13. Synthesis of PNODAM-DPPA and use in thermomorphic allylic substitutions.

To generate a polymeric catalyst, PNODAM-DPPA was dissolved in heptane and a purple THF solution of $Pd(dba)_2$ was added. The reaction was stirred for one hour, and the color changed from purple to a light yellow. The polymeric palladium complex was analyzed by ^{31}P NMR spectroscopy. Only broad resonances at δ –16 and δ 35 ppm were observed, probably due to rapid intramolecular exchange. This polymer-bound Pd(0) complex was used to catalyze an allylic substitution between allyl acetate and sodium *p*-toluenesulfinate (Figure 12). The reagents were dissolved in 90% ethanol, added to the heptane solution of catalyst. The reaction was heated at 75 °C and monitored by NMR spectroscopy. At the end of the reaction the system was cooled and the layers were separated. The aqueous ethanol layer was removed. Fresh reagents were dissolved in 90% EtOH and added to the catalyst for another cycle. A total of five cycles were completed and good isolated yields of the products were obtained. The activity of the catalyst did slowly decrease, probably due to adventitious oxidation. This deactivation was observed in the increasing reaction times and the appearance of a black precipitate of Pd(0). After recycling, the ^{31}P NMR spectrum confirmed the increase of phosphine oxide on the polymer.

Air sensitivity of phosphine-based catalysts limits their use to systems where rigorous exclusion of air is feasible. In recycling strategies, the inert atmosphere must be maintained in both the reaction and the recovery steps. This requirement can present a technically challenging obstacle to a successful recycling strategy, especially in batch processes. However, numerous reports have appeared in the literature concerning transition metal complexes that are stable to atmospheric oxygen.[41] Collectively, these pincer complexes form a family of metallocycles. These metallocycles are distinguished from typical transition metal coordination complexes by a covalent bond between the transition metal and the ligand, and chelating ligands composed of atoms like N, P, or S. A number of these complexes are active for the Heck and related reactions. These organometallic catalysts were attractive for our catalyst recycling studies as they obviated the need for an inert atmosphere during the reaction or recovery processes. The tridentate SCS-Pd(II) complexes were of particular interest to us as they are easy to prepare. These complexes have been known in the literature for some 20 years,[42] but their potential as catalysts had been largely uninvestigated. We first developed SCS ligands that included a means of attaching the ligand to a tether and ultimately to a polymer support.[43] As low molecular weight catalysts supported on a polar polymeric ligand like PNIPAM or PEG, these SCS palladacycles were shown to be competent, recyclable catalysts for the Heck reaction of aryl iodides and alkenes. In such cases the catalysts and polymers were recovered as a polar solution if a thermomorphic polar/nonpolar solvent mixture (e.g. heptane/DMA or heptane/aqueous EtOH) were used. However, as noted above, polar polymers have limitations, especially since most organic compounds are more soluble in polar solvents than in heptane. Thus, we eventually went on to explore less polar polymer supports for these SCS-Pd(II) catalysts.

The SCS ligands that we studied were synthesized from simple starting materials in a few steps. Commercially available 5-amino isophthalic acid was esterified and the resulting ester reduced using LAH, forming the amino diol. The NH_2 group was protected by treatement with acetic anhydride to provide an acetamido diol. The alcohols were changed to chlorides by stirring the diol with $SOCl_2$. Subsequent treatment of this dichloride with thiophenol and K_2CO_3 in DMF yielded the acetamido SCS ligand. If desired, this ligand could then be palladated by reaction with $Pd(NCPh)_2Cl_2$ to form an SCS palladacycle. To attach this ligand to a polymer support, the SCS ligand was further elaborated by first removing the acetamido group. The free aniline was then coupled to Boc protected 6-amino hexanoic acid. The Boc group was removed with TFA and the free amine was coupled to PNODAM-NASI forming a supported SCS ligand, PNODAM-SCS (Figure 14). As is generally true for soluble polymer-bound metal complexes, solution state NMR spectroscopy served to characterize the complex and ligand. In the ^1H

NMR spectrum, the benzyl protons of the SCS moiety were observable at δ 4.0 as well as broad aromatic signals in the δ 6.9-7.5 range. Analysis by ^{13}C NMR spectroscopy showed distinct signals in the aromatic region. However, we did not observe a distinct signal for the ipso carbon bonded to palladium (~δ 150 ppm) that was seen in the solution state ^{13}C NMR spectum of the PNIPAM analog of **40**. Fortunately, analysis by solid-state CP-MAS NMR showed a signal at 152.5 ppm that was not present in the solid-state NMR of the unpalladated ligand, indicating that a carbon-palladium bond had indeed formed.



(3)

We then used this polymeric catalyst (PNODAM-SCS-Pd) in thermomorphic systems consisting of heptane and DMA. The polymer (0.2 mol % in Pd) was dissolved in heptane and combined with an aryl iodide, an alkene, and triethylamine dissolved in DMA. The reaction was heated at 100 °C for 10-20h. After consumption of the aryl iodide, the system was cooled. The layers were allowed to separate and the lower DMA phase was removed. Fresh reactants in DMA were then added to the reaction. A few mL of heptane was also added to the reaction. Heptane has some solubility in DMA, and a portion of the nonpolar solvent is removed with the DMA. This loss must be replaced to maintain the two layer resting state.

Several Heck reactions were run with different aryl iodides and alkenes. Isolated yields of the products typically increased from the first cycle to the third cycle (Table 1). Conversions of the aryl iodide in each cycle were complete, but the product partitions itself in both the nonpolar and polar layers. Since only the DMA solution is removed, the product in the heptane is "lost." Therefore, isolated yields in the first cycle are lower than a reaction run in a single solvent. In subsequent cycles, the heptane becomes saturated with product and the isolated yields increase. The isolated yields in the first cycles using PNODAM as a support in an inverted thermomorphic system were usually higher than those obtained in a normal thermomorphic system. This stands to reason as DMA is usually a better solvent for organic materials than heptane. We were able to use the PNODAM-SCS-Pd catalyst in nine cycles for the formation of cinnamic acid from iodobenzene. In the ninth cycle, the GC conversion at 24 h was 90%, showing that these polymer-bound catalysts are very recyclable.

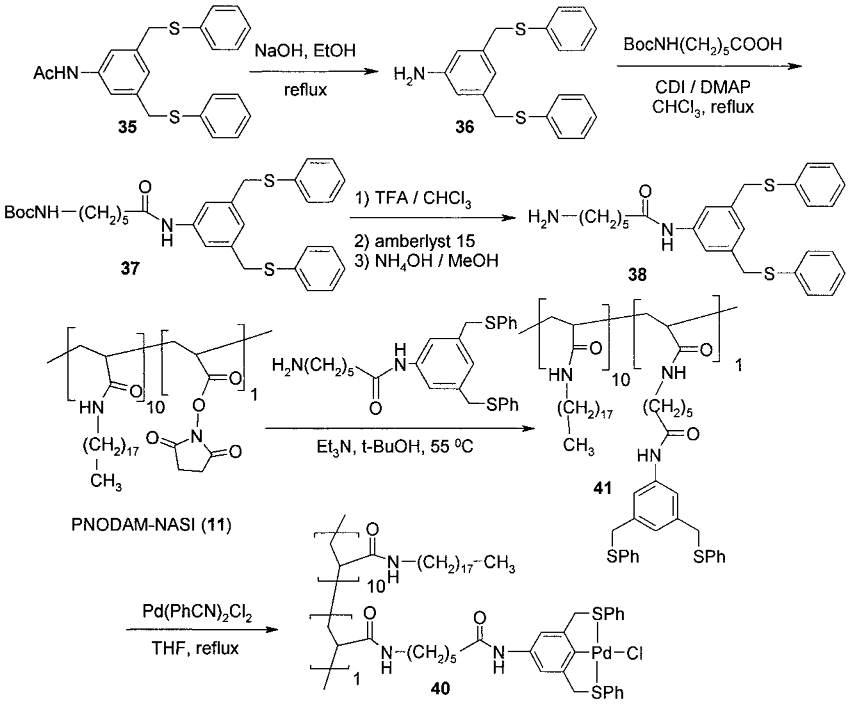
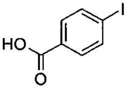
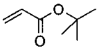
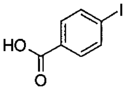
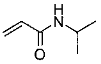
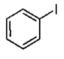
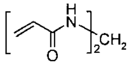
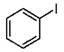
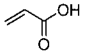
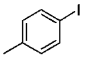
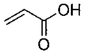
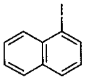
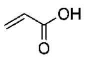


Fig. 14. Synthesis of a PNODAM-bound SCS catalyst.

In addition we have analyzed the DMA layers for leached palladium. While the polymer resides in the heptane layer, it is possible that the palladium center is being detached from the ligand and lost in the isolation steps. A Heck reaction of iodobenzene and methyl acrylate was performed using the PNODAM-SCS-Pd catalyst. Four cycles were completed and the polar layer saved for analysis. The reactions were run using 0.2 mol% catalyst, corresponding to a total of 42 ppm Pd. Analysis of the DMA layers for each cycle by DCP spectroscopy did not reveal any detectable palladium. Analyses of Pd samples were usually reliable down to the 0.5 ppm level indicating that palladium recovery is 98.8% or better.

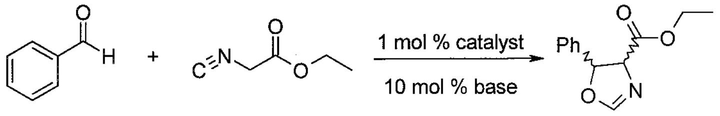
Table 1. Heck reactions in an inverted thermomorphic system.

Aryl Iodide	Alkene	1st cycle	2nd cycle	3rd cycle
		89	94	99
		76	85	83
		82	93	96
		96	99	99
		83	90	99
		88	99	--

Latent Biphasic Systems

Thermomorphic systems use a temperature change to alter the miscibility of solvents. In such systems, heating and cooling caused solvent mixtures to change between being miscible (monophasic) and immiscible (biphasic). However, temperature is not the only means available to change the miscibilty of a mixed solvent system. The composition of the solution could be modified by adding additional solvent or other solute like a salt (Figure 15). Such a perturbation could cause the system to convert from a monophasic solution to a biphasic state. Solvent mixtures that are by design on the cusp of immiscibility could then be induced to separate with a minimum of external influence. As in thermomorphic catalysis, soluble polymer supports with a strong phase preference for one of the layers in the biphasic state would afford a means of separating and recovering polymer-bound catalysts from organic reactions.[43-45]

A simple polymer-bound Lewis acid using Ag(I) was used to test the viability of latent biphasic systems for catalysis. It is generally recognized that a variety of transition metals are catalysts for the formation of oxazolines from aldehydes and isocyanoacetates (eq 4).[46-48] For example, a ferrocenylphosphine-gold(I) complex effectively catalyzes the aldol reaction of



(4)

methyl isocyanoacetate with benzaldehyde, forming the oxazoline products. Based on this, we performed simple experiments using silver acetate and triethylamine. This combination of Lewis acid and base converted benzaldehyde and ethyl isocyanoacetate to the oxazoline products in a latent biphasic mixture of heptane and aqueous ethanol. Encouraged by this result, we set out to synthesize a polymeric silver acetate analog suitable for recovery in heptane and use in a latent biphasic system.

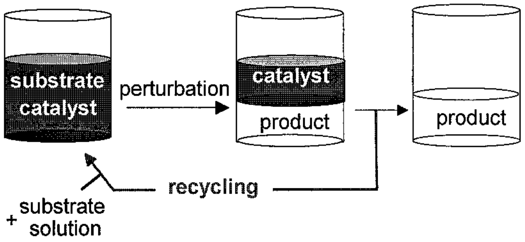
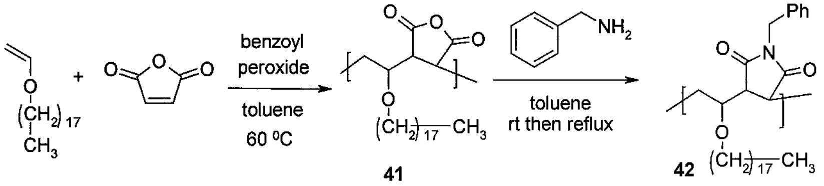


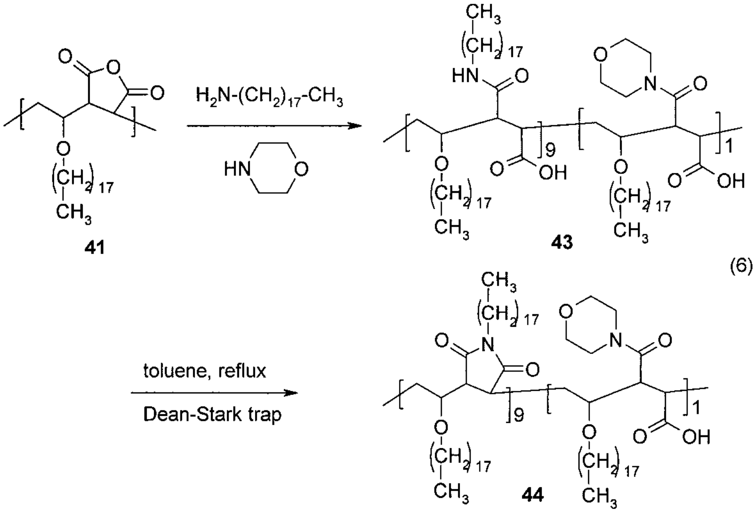
Fig. 15. Latent biphasic process with a reaction occurring under monophasic conditions and separation occurring under liquid/liquid biphasic conditions after some perturbatiseparation.

We chose a support similar to the polymer Gantrez, commercially available from ISP. Gantrez is an alternating copolymer of methyl vinyl ether and maleic anhydride. For our purposes, we synthesized an analogous polymer by substituting octadecyl vinyl ether for methyl vinyl ether, improving the resultant polymer's solubility in nonpolar solvents. Maleic anhydride and octadecyl vinyl ether were radically polymerized in toluene (eq 5) using benzoyl peroxide as an initiator.[44,49] The resulting polymer was isolated by precipitation into methanol. IR analysis showed anhydride peaks at 1859, 1781, and 1724 cm^{-1}. The product **42** formed by dehydration was analyzed by GPC, giving an M_n of 730,000 versus polystyrene standards.



(5)

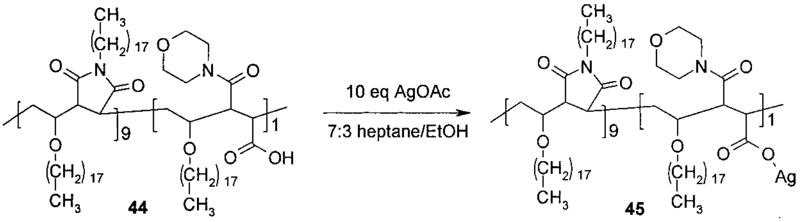
To prepare a catalyst, polymer **41** was loaded with a small amount of the amine terminated dye, then treated with two equivs each of octadecyl amine and morpholine. The less active secondary amine would form a smaller number of amide bonds than the more reactive primary amine. After the anhydrides had been consumed, the reaction was shaken with amberlyst-15 to remove the excess amines. The polymer was then dissolved in toluene and brought to reflux in the presence of a Dean-Stark trap (eq 6). In this reaction, conversion of adjacent amide/acid fuctionalities to imides would only occur where primary amines had reacted. The carboxylic acids adjacent to the tertiary amides would not form imides and therefore could be used as ligands for a silver catalyst. IR spectroscopy of the subsequent polymer showed peaks at 1772 and 1700 cm^{-1} indicating that an imide had formed. From NMR analysis, we estimated that the ratio of imide to carboxylic acid was 9:1. The product polymer was soluble in heptane. A solution formed from 500 mg of this polymer in 15 mL heptane was combined with 7.5 mL EtOH to give a homogeneous solution. Addition of 10 drops of water induced a phase separation. The upper layer had a absorbance of 1.04 @ 416 nm while the lower layer had an absorbance <0.005 indicating a >99.5% phase selective solubility for the polymer for the heptane layer.



(6)

The next step was to coordinate the silver to the carboxylic acids on the polymer. This was accomplished by stirring the polymer with an excess of silver acetate (eq 7). In the first attempt,

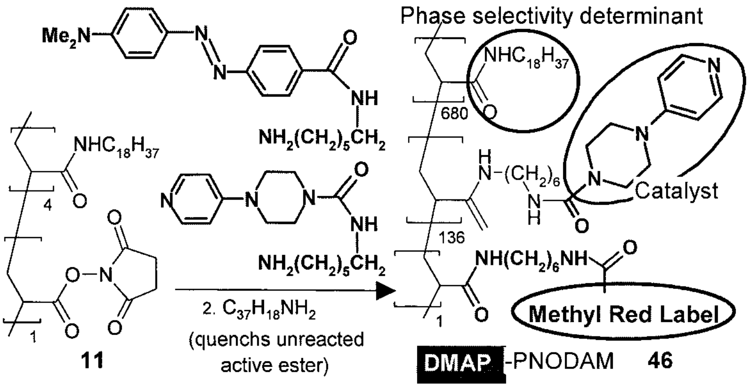
CH_2Cl_2 was used as a solvent. The polymer was dissolved in CH_2Cl_2 and 10 equivalents of silver acetate were added as a solid. The mixture was stirred overnight. The reaction was filtered to remove the insoluble material and the polymer was precipitated into methanol. Analysis by IR spectroscopy did not show a carboxylate peak. Evidently, silver acetate is not soluble enough in CH_2Cl_2 to interact with the polymer. To solve this, the polymer was dissolved in a latent biphasic system of 7:3 heptane/ethanol. Again, silver acetate was added as a solid and the reaction stirred at room temperature. After 48 h, water was added to separate the layers. The lower layer was removed, and the heptane layer was filtered to remove any remaining insolubles. This time IR analysis did show a carboxylate peak at 1585 cm^{-1}, indicating that the silver ion had been exchanged onto the polymer.



(7)

The polymeric catalyst was then used in a latent biphasic system to catalyze the formation of oxazolines. The polymeric catalyst (1 mol% in Ag) was dissolved in 20 mL of heptane. Separately, benzaldehyde, ethyl isocyanoacetate, and 10 mol% Hunig's base were dissolved in 10 mL EtOH. The two solutions were combined, forming a homogeneous solution. The reaction was stirred in the dark at room temperature. A control reaction using the analogous non-silver containing polymer was also prepared. After stirring overnight, GC analysis showed that the silver-catalyzed reaction was complete. The control reaction had reached only 25 % conversion. Water was added to the reaction (15 drops, ~2% of the total volume) to separate the system into two layers. The lower layer was removed. Fresh reagents were dissolved in 10 mL EtOH and added to the reaction along with 5 mL of heptane. Heptane does have some solubility in the aqueous ethanol, and it was necessary to add heptane at the beginning of each recycle to return the system to a homogeneous state. In all, five cycles were performed, each complete in under 18 h. On average, the 215 ppm Ag solution lost <0.15 mol% Ag to the polar phase. The process by which this silver was lost is not clear however. The varying amounts of Ag from cycle to cycle might be due to contamination of the products by anionic surfactants from ordinary glassware.

Latent biphasic catalysis works equally well with organic catalysts.[44] Indeed, the generality of this latent biphasic approach in homogeneous catalyst recovery was aptly shown using the polymer-bound trifunctional base catalyst **46**.[50,51] This soluble polymeric analog of 4-dimethylaminopyridine (DMAP) was prepared using the PNODAM polymer according to eq 8 and then used in acylation of 2,6-dialkylphenols by $(Boc)_2O$ in either a 1:1 heptane-aqueous EtOH system (eq 9). Yields in this chemistry gradually increased from cycle to cycle as the heptane-rich phase became saturated in the product carbonate. Yields through 6 cycles for R = -H were 59%, 80%, 95%, 99%, 99%, and 99% and for R = $-CH_3$ were 35%, 66%, 89%, 99%, 99%, and 99% when a heptane/ethanol system was used. In both cases, the initially monophasic reaction mixture was perturbed to be biphasic by the addition of 10 vol% H_2O. The heptane phase so formed was then recycled by addition of fresh EtOH, substrate and $(Boc)_2O$. Heptane was added as needed to replace heptane lost in the EtOH-rich phase. In both series, the polymeric catalyst used was labeled with a methyl red label. The absence of detectable dye-labeled polymer in any of the cycles in the polar EtOH-rich phase indicated quantitative separation of the catalyst into the nonpolar heptane-rich phase.



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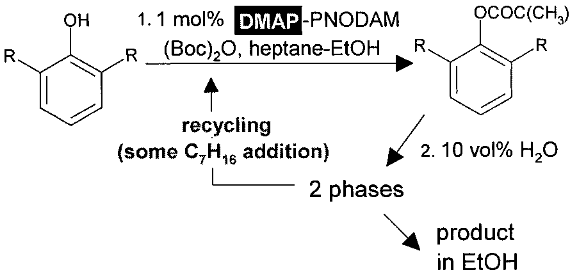

(9)

Conclusions

The work in this chapter demonstrates that soluble polymer are effective catalyst supports in biphasic separations. The solubility of the polymer can be designed to fit the requirements of the solvent system. Adjusting the alkyl side chain of a poly(acrylamide) support to the lipophilic octadecyl group produced a polymer that was soluble in nonpolar solvents. The support was useful for catalysis in thermomorphic systems, expanding the utility of that approach. Out of our work in thermomorphic catalysis we developed a different approach to inducing phase separations. This latent biphasic separation strategy was based upon the small perturbations of near-immiscible solvent systems. The recycling stragtegy was shown to be effective for separating polymer supports and recycling catalysts.

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