PHASE SELECTIVELY SOLUBLE POLYSTYRENE-SUPPORTED ORGANOCATALYSTS

A Dissertation

by

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ABSTRACT

Alkane phase selectively soluble poly(4-alkylstyrene) supports have been developed. 4-Methyl-, 4-*tert*-butyl, 4-dodecyl-, and 4-octadecylstyrene were copolymerized with 5-10 mol % of 4-chloromethylstyrene to afford co- and terpolymers containing chloromethyl pendant groups so that a fluorescent dye can be attached. By varying the structure and the length of the alkyl groups, derivatives of these polymers with covalently coupled fluorescent dansyl groups as catalyst surrogates show a significant increase in phase selective solubility in thermomorphic and latent biphasic systems. The advantage of alkyl-substituted polystyrenes is that they are phase-selectively soluble which means that a polymer-bound catalyst can be separated from products in a biphasic separation that avoids a solvent-intensive precipitation process.

Coupling of a 4-dimethylaminopyridine (DMAP) analog, *Cinchona* alkaloid derivative or phosphine-ligated metal catalyst to the poly(4-alkylstyrene) supports was used to prepare alkylated-polystyrene-bound catalysts. The recycling of these polymer-supported catalysts was affected using a biphasic liquid/liquid separation step after a monophasic reaction.

Alkyl-substituted soluble polystyrene supports are found to be highly phase selectively soluble in heptane phase so that organo- and transition metal catalysts can be separated from products by thermomorphic or latent biphasic separations with minimum

loss of the catalyst in the polar phase, which was monitored by fluorescence spectroscopy or by inductively coupled plasma mass spectrometry (ICP-MS).

DEDICATION

This dissertation is dedicated to my parents and my husband, Douglas. Thanks to my parents and their strong belief in my capabilities. Thanks to my husband and his unconditional support and encouragement to achieve my goals while taking care of our twin boys.

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First and foremost I would like to offer my gratitude to my advisor, Dr. Bergbreiter, for giving me the opportunity to work in his laboratory when I decided to pursue graduate school in 2009. I want to thank him for being one of the toughest and the fairest teachers I have had the chance to meet. His mentoring was by no means sugarcoated but it helped me to develop a deep appreciation for science in general and chemistry in particular. Through his guidance, I was able to evolve as a scientist that I am now.

Secondly, I would like to I extend my thanks to the members of Bergbreiter research group, past and present. In my daily research, I have been very fortunate to have a friendly and very dynamic group of fellow students. In particular, I want to thank Dr. Yun-Chin Yang "Jeff", who gave me a tremendous amount of help in the lab and taught me a lot about research. Jeff was the sweetest, soft-spoken chemist with a brilliant mind who was always very encouraging and supportive. I would also like to thank Dr. Christopher Hobbs for his scientific knowledge and advice. I also would like to thank some of the students that I have had the honor to meet through the REU program or teaching the organic laboratory: Ashley, David and Mitchel. You made me realize the true meaning of teaching!

Last but not least, I would like to thank Dr. Melissa Grunlan, Dr. Daniel Singleton and Dr. Karen Wooley for taking the time to serve on my committee and their support throughout the course of this research.

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CHAPTER I

INTRODUCTION

A variety of research groups have designed and developed new types of ligands and catalysts to fulfill a synthetic chemist's tool box, thus desirable bond formations, functional group modifications and complex organic frameworks can be achieved. Concurrent with this work there has been the realization that recovery strategies for these ligands and catalysts have to be developed. Over the years, a variety of approaches to the design of effective catalytic systems that enable catalyst/product separation and catalyst recovery have been undertaken. A common method for recovery of precious catalysts and ligands is to use insoluble or heterogeneous polymer supports. Polymers have been used as solid supports for catalysis ever since the revolutionary work of Merrifield[1] and Letsinger[2] in solid peptide synthesis using cross-linked polystyrene resin. Cross-linked polystyrene is an inexpensive and chemically inert material, which offers an advantage in various synthetic schemes. Cross-linked polystyrene-supported ligands/catalysts have also an advantage as they can be separated from the product by simple filtration. The ease with which the products can be purified using cross-linked polystyrene opened the door to use other cross-linked polymeric materials whose swellability can be modified by changing the nature of the crosslinking agents. For example, more polar versions of the Merrifield resin such as TentaGel, *J*anda*J*el, and

ArgoGel have been developed that include polar oxygenated species such as poly(ethylene glycol) groups as shown in Figure 1.

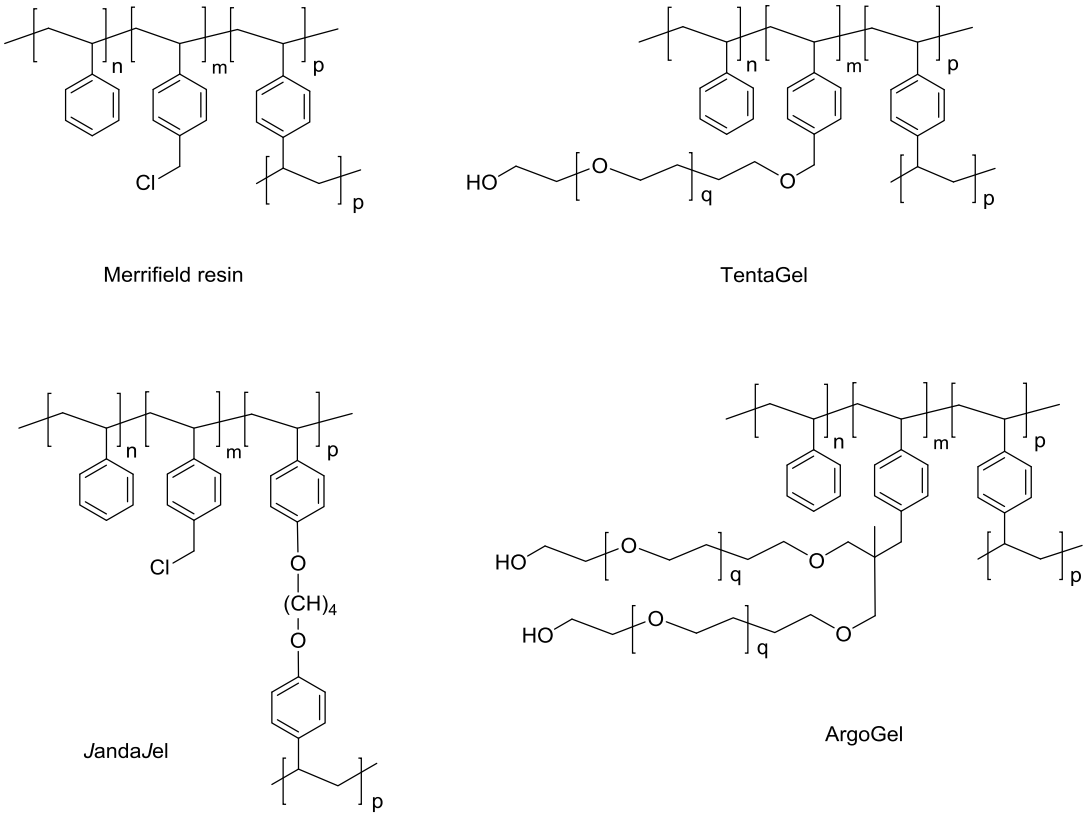


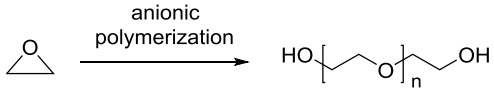
Figure 1. Cross-linked resins for polymer supports

However, there are disadvantages associated with using always insoluble polymer-bound species in synthesis. Characterization of ligands, catalysts or reagents

bound to the insoluble polystyrene supports by conventional solution state nuclear magnetic resonance (NMR) spectroscopy is difficult. Furthermore, the reactivity and selectivity of heterogeneous substrates bound to cross-linked polymers and the reactivity of ligands/catalysts bound to cross-linked polymers can be different from similar species used under homogeneous reaction conditions.

In order to keep the advantage of simple separation and to avoid the problem of different reactivity/selectivity arising from insolubility during a reaction, methods that use soluble polymers as reagent and catalyst supports have been developed.[3] A variety of different soluble polymers are utilized as supports. Poly(ethylene glycol) (PEG) is one of the oldest and commonly used soluble polymeric supports. PEG is an end-functionalized, linear polymer formed by the anionic ring-opening polymerization of ethylene oxide shown in Scheme 1.

Scheme 1. Anionic polymerization of ethylene oxide



The solubility of PEG and its derivatives in solvents such as DMF, CH_3CN, CH_2Cl_2 and water has shown to be useful for the development of more environmentally benign systems that use this polymer as a support. Moreover, although PEG derivatives are completely soluble in these solvents, they are insoluble in solvents such as hexanes,

heptane, diethyl ether and cold ethanol. This enables PEG's successful recovery and recycling using solvent precipitation as shown in Figure 2.

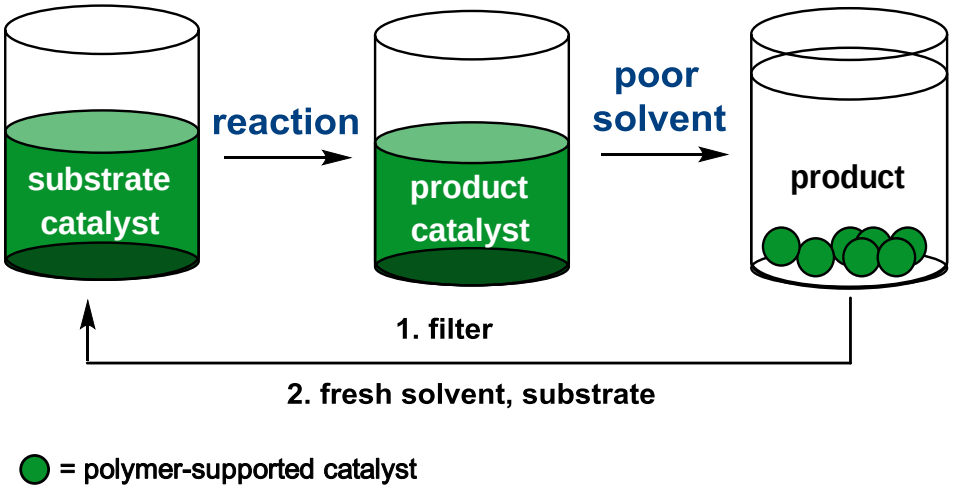
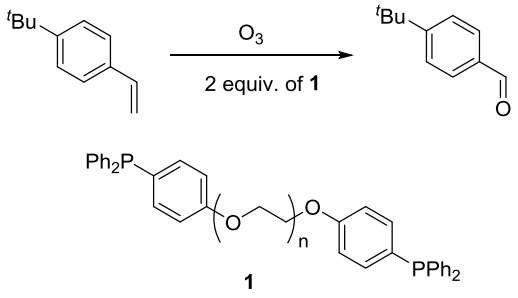


Figure 2. Liquid/solid separation of PEG supports

One of the earliest reports by Bayer described using PEG as a soluble support for solution-phase peptide synthesis.[4] Bayer and coworkers were able to successfully separate the peptide-containing PEG from the low molecular weight impurities using ultrafiltration, a type of membrane filtration in which a concentration gradient leads to the separation of high molecular PEG-supported peptide chains through a semipermeable membrane. This type of membrane filtration using soluble PEG supports offered an advantage of performing peptide synthesis under homogeneous conditions with an ease of separation.

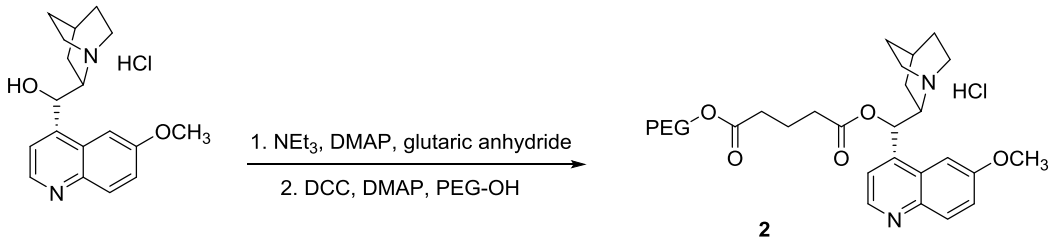
Since the original report by Bayer, membrane filtration methods have been utilized continueally as a separation method for wastewater treatment and catalysis.[5] Over the years, membrane filtration methods have become more practical due to the development of hybrid materials that improved membrane properties. Research shows that ultrafiltration membranes made of polymer-bound inorganic materials exhibit enhanced permeability, selectivity and improved stability with respect to mechanical, chemical and thermal stressors.[6] Work has continued investigating PEG supports for other uses since the original studies by Bayer. For example, Janda and coworkers have reported using PEG-supported phosphine **1** as a functional polymer-supported stoichiometric reagent in ozonide reduction as shown in Scheme 2.[7] In this work, a range of alkenes was treated with ozone at -78 ^{o}C in CH_2Cl_2 until a blue reaction mixture persisted. At this point ozone was removed and ozonides were decomposed to aldehyde products by addition of phosphine reagent.

Scheme 2. Ozonide reduction using PEG supported phosphine **1**



The isolation procedure for the PEG-supported phosphine involved a precipitation of the used reagent into diethyl ether. PEG supports also found utility in catalysis. For example, the Sharpless osmium-catalyzed asymmetric dihydroxylation (AD) reaction is one the most important catalytic oxidation reactions. There have been reports on the development of insoluble polymer-supported asymmetric dihydroxylation catalysts; however, the first soluble polymer support was the development of a PEG-supported *Cinchona* alkaloid **2** by Han and Janda.[8] PEG-bound *Cinchona* alkaloid was prepared using a linker to dihydroquinone (DHQD) as shown in Scheme 3. In the Sharpless AD reaction of various olefins, **2** afforded products in high ee (>88%) when compared to similar insoluble-supported systems.

Scheme 3. PEG-supported *Cinchona* alkaloid



PEG has proven to be an excellent support for catalyst/ligand immobilization; however, separation strategies of the PEG-supported species from reaction mixture can be impractical. The solvent precipitation of PEG-supports in excessive amounts of a

"poor" solvent that is most often used to recover the polymer-supported species, for example, generates significant solvent waste.

There are also other sorts of polymeric supports. One example from our group was the use of stimuli-responsive polymers as a support. Such polymers respond to external stimuli such as temperature, pH or ionic strength by undergoing solubility changes. These changes are apparent at the microscopic level as the polymer solution changes from clear to cloudy at the polymer's lower critical solution temperature (LCST). The LCST is an event at which the solvation entropy and solvation enthalpy terms of the Gibbs equation become equal. Poly(*N*-isopropylacrylamide) (PNIPAM) and its derivatives are well-known examples of such temperature-responsive polymer supports that have applications in drug delivery, photographic products, and optical filter agents.[9] PNIPAM also has attracted biochemical interest because its' changes in solubility closely mimic the protein conformational changes induced by salt co-solutes (the Hofmeister effect).[10]

Relevant to my work, there are also a growing number of research groups studying PNIPAM as supports for recovery of ligands and catalysts.[11] Taking advantage of the PNIPAM phase transition at different temperatures, a strategy has been developed that allows for separation of the PNIPAM-supported ligands/catalysts from the reaction mixture by precipitation above the LCST and successful recovery as shown Figure 3.[12]

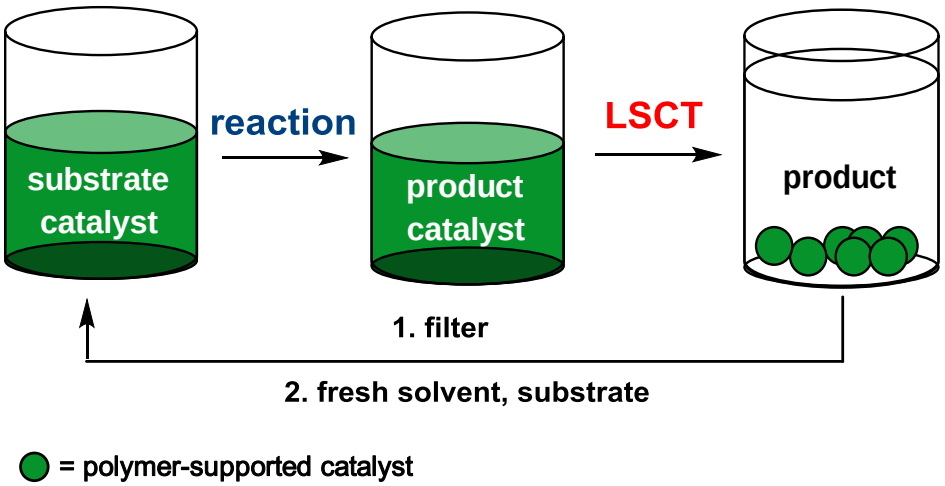
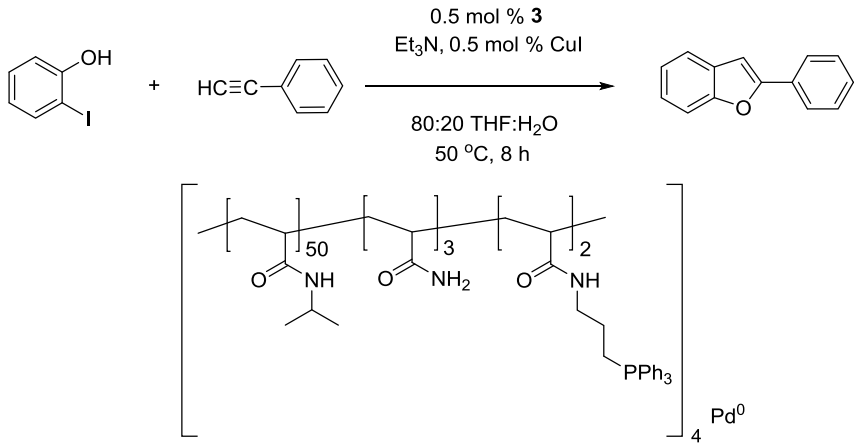


Figure 3. Liquid/solid separation of PNIPAM supports

Older work from our group described a PNIPAM-supported phosphine-ligated Pd(0) complex **3** that was successfully used in C-C cross coupling chemistry as shown in Scheme 4.[13] The catalyst **3** could be recovered either by heating above the LCST (in water) or by adding a "poor" solvent – hexane (in aqueous THF). While recovery of PNIPAM supports using the LCST is a convenient way to recover the polymer-supported catalysts, there is a major limitation to this system.

Scheme 4. C-C cross-coupling reaction using complex **3**



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Water is typically used as the solvent medium in which the LCST event occurs for PNIPAM; this dramatically limits the substrate scope for catalysis.

Polyethylene (PE) is another polymer with useful solubility changes that has been used as an alternative to PEG and PNIPAM. In this separation strategy, ligands and catalysts that are attached to PE can participate in catalysis at elevated temperature. On cooling the reaction solution to room temperature, the PE-supported ligand/catalyst precipitates out and can be filtered off as a solid polymer as shown in Figure 4. The solubility behavior seen in Figure 4 makes functionalized PE species appealing candidates as supports for catalysis. One of the earliest examples studied by our group was a PE-supported Rh(I) complex that was used in catalytic hydrogenation.[14]

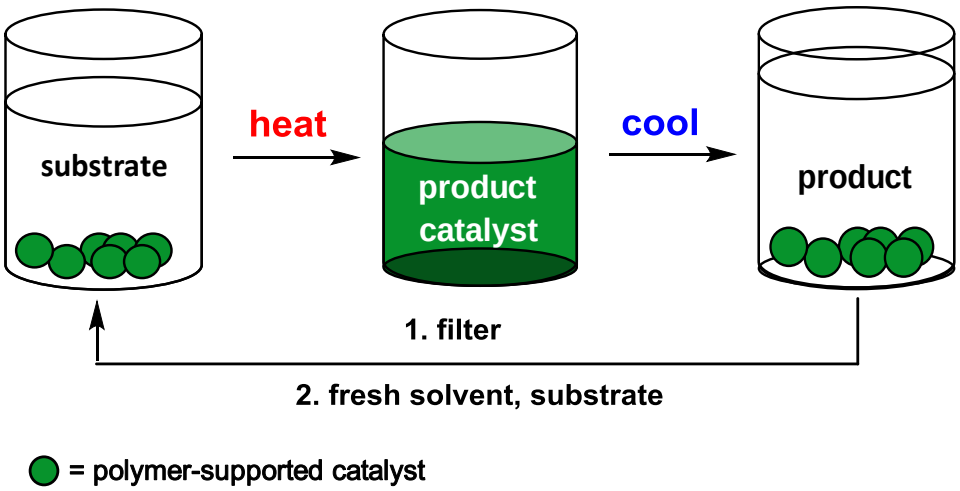
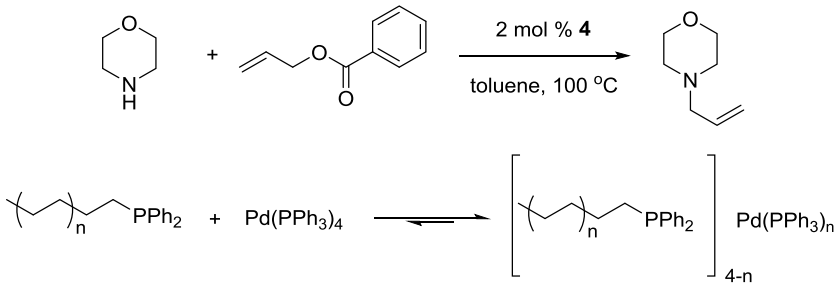


Figure 4. Thermomorphic liquid/solid separation of PE supports

In this chemistry, phosphine groups were introduced onto polyethylene oligomers and then exchanged with the triphenylphosphine groups of chlororhodium-(ethylene)triphenylphosphine complex to prepare a polyethylene oligomer-ligated rhodium(I) complex. This PE-supported Rh(I) complex showed good catalytic activity in hydrogenation of various alkenes at 90-110 ^{o}C and could be recovered by precipitation at 25^{o}C. Another example of a PE-supported catalyst is PE-bound Pd(0) complex **4** prepared using PE-supported phosphine ligands as shown in Scheme 5.[15] In this work, complex **4** was tested in the reaction of allyl benzoate and morpholine in toluene at 100 ^{o}C. At this temperature full conversion was achieved within 10 minutes and the PE-supported complex **4** was separated from the product by cooling to room temperature. The resulting solid PE-ligated Pd(0) catalyst was recycled up to ten times without

detectible metal leaching monitored by inductively coupled plasma-mass spectrometry (ICP-MS).

Scheme 5. PE-ligated Pd(0) catalyst **4** in cross-coupling reaction of allyl benzoate and morpholine



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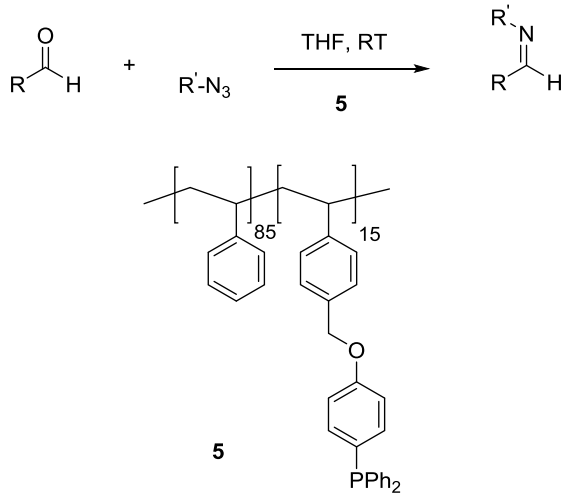
Another nonpolar polymer that was used even earlier as a support in catalysis is soluble linear polystyrene. Polystyrene has a high theoretical loading and it is soluble in a range of solvents at various temperatures. For these reasons, polystyrene is a versatile polymer support. While polystyrene exhibits solubility in various solvents such as chloroform, dichloromethane, THF, benzene, and toluene which allows for tuning the reaction conditions, it shows little solubility in solvents such as hexanes and methanol. Thus, the polystyrene-bound species can be separated by solvent precipitation methods.

Linear polystyrene has been used in peptide synthesis[16] as well as in catalysis.[17] For example, a linear polystyrene supported phosphine **5** has been synthesized and used to facilitate removal of the phosphine oxide by-product from a Staudinger/Aza-Wittig

reaction as shown in Scheme 6.[18] This polystyrene-bound phosphine **5** was prepared in three steps to produce a soluble polymer-bound reagent.

Scheme 6. Staudinger/Aza-Wittig reaction with polystyrene-supported phosphine **5**

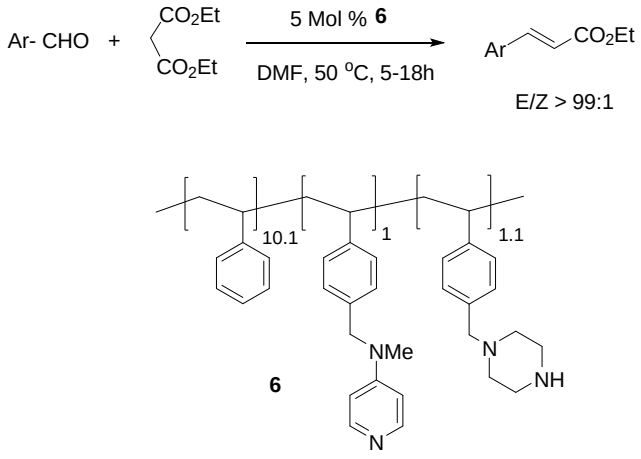


In this chemistry, tin chloride-mediated chloromethylation of polystyrene was the first step, followed by nucleophilic displacement with the cesium phenoxide derivative of *p*-hydroxyphenyldiphenylphosphine oxide gave the polymer-supported phosphine oxide. A subsequent reduction of phosphine oxide with trichlorosilane led to the polystyrene-supported phosphine **5**. In the aforementioned aza-Wittig chemistry, this phosphine reagent could be used in the synthesis of imines and showed reactivity that was higher than that seen when triphenylphosphine was used. In addition to higher reactivity, the by-product polymer-bound phosphine oxide was easily separated from the

imine products. At the end of the reaction, precipitation of the polymer support allowed for complete removal of phosphine oxide by-product.

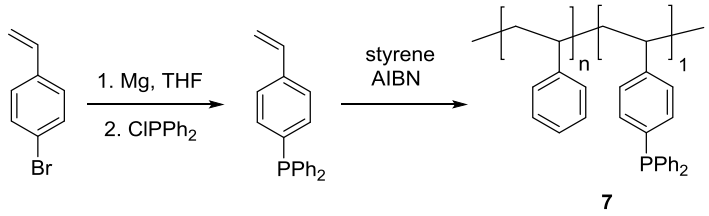
Catalysts bound to soluble linear polystyrene have also been reported. For example, Toy[19] prepared the styrene copolymer **6** containing dimethylaminopyridine (DMAP) and piperazine moieties. This bifunctional polymer was used as an organocatalyst in Doebner-Knoevenagel reactions as shown in Scheme 7. A variety of substrates were examined in these condensation reactions and in most cases good yields were obtained along with good *E/Z* selectivity. However, attempts to recover the catalyst **6** failed due to difficulty in precipitating **6** from the reaction mixtures.

Scheme 7. Doebner-Knoevenagel Condensation Reactions Catalyzed by **6**



Toy[20] also has shown that linear polystyrene-supported phosphine ligands could be prepared through the copolymerization of styrene and 4-styryldiphenylphosphine using AIBN to afford **7** as shown in Scheme 8. This polystyrene-supported phosphine was utilized as a polymeric reagent for the Mitsunobu reaction. At the end of the reaction, polystyrene-supported phosphine oxide was separated from the product using solvent precipitation into diethyl ether.

Scheme 8. Polystyrene-supported phosphine reagent **7**



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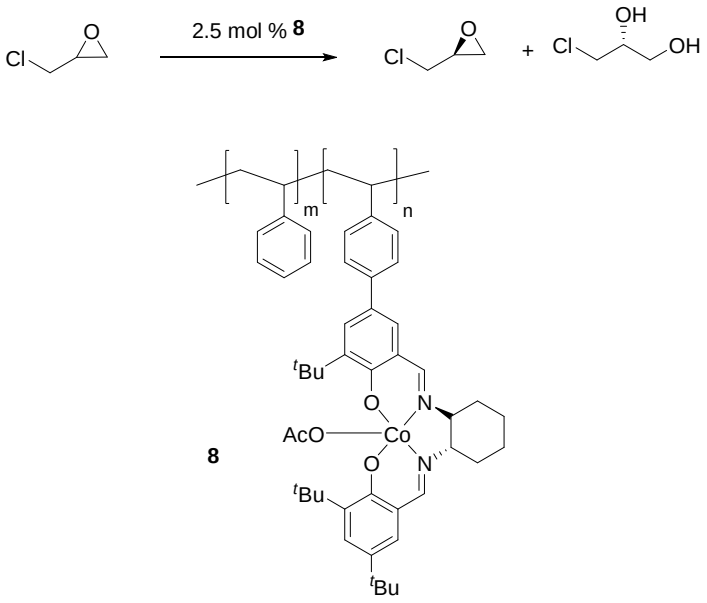
One of the main reasons to use linear soluble polymer supports is the expectation that reactivity and selectivity during homogeneous catalysis will consistently resemble that of a low molecular catalyst – a result that is less assured when insoluble supports are used. This selectivity is especially important in asymmetric catalysis; it is thus not surprising that extensive work has been done in the development of chiral ligands and catalysts. For example, Weck's group has shown that it is possible to use linear polystyrene as supports for chiral salen ligands.[21] Weck and coworkers demonstrated the first radical copolymerization of chiral salen monomer with styrene, chemistry that formed a polymer-supported salen ligand which then could be used to form the

cobalt(III) complex **8** as shown in Scheme 9. This complex **8** was then used as a recoverable catalyst in the hydrolytic kinetic resolution (HKR) of epichlorohydrin. The Co(III) complex **8** in the catalysis of the HKR of epichlorohydrin gave the ring opening product in 54% yield and >99% ee after 1 h. Complex **8** could be recovered by using a solvent precipitation method into diethyl ether and could be recycled up to four times.

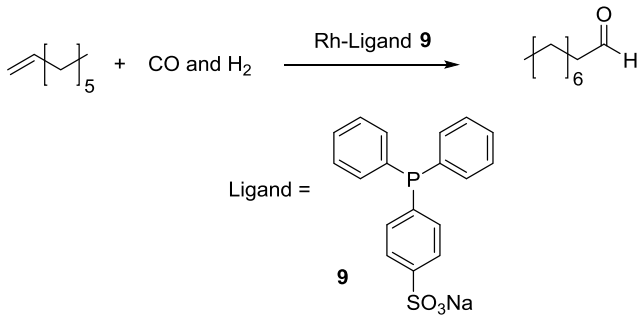
Scheme 9. Polystyrene-supported salen-Co(III) complex **8** in hydrolytic resolution of epichlorohydrin



Thus far, the examples of soluble polymer-supported catalysts depended on liquid/solid or solvent precipitation separation methods for the separation of the soluble polymer-supported catalyst from products or substrates at the end of a reaction. It is a common laboratory practice to use a simple organic/aqueous liquid/liquid extraction/separation to purify and separate compounds that have organic vs. aqueous solubility. The same strategy has been used in a variety of ways to recover catalysts from products or to recycle catalysts after a reaction. Some examples of these strategies are described below. Our group too has used liquid/liquid separations with phase selectively soluble polymers using systems containing a polymer-bound catalyst and product that are soluble in different phases of a biphasic solvent mixture. If these phase selectivities are high enough and if the two liquid phases have sufficiently different densities, effective separations can be achieved. Such solvent separation methods have been designed to allow a reaction to be performed homogeneously if a solvent mixture can be perturbed during workup to become biphasic.

An example of using a liquid/liquid separation after a homogeneous reaction phase would be the organic aqueous tunable solvent (OATS) system developed by Liotta.[22] In this chemistry, the separation is achieved by addition of modest pressure of CO_2 (50-60 bar) to the system, which splits the THF-water phase into two immiscible phases: the organic THF phase containing the hydrophobic product and the aqueous phase containing the hydrophilic catalyst. Liotta demonstrated the application of this solvent system in hydroformylation of 1-octene using a Rh(I) catalyst ligated by the phosphine ligand **9** as shown in Scheme 10.

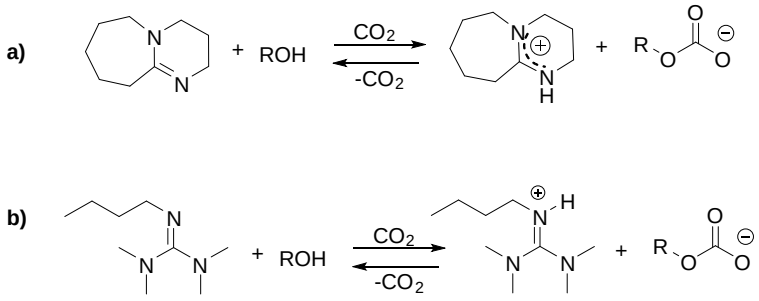
Scheme 10. Organic aqueous tunable solvent using ligand **9** in hydroformylation of 1-octene



In this chemistry, the conversion of 1-octene to aldehyde was carried out at 120 ^{o}C for 1 h and the catalyst was recycled three times. While OATS offers an effective recycling scheme, this system is limited since it is specifically designed for a water-stable hydrophilic catalyst.

Another concept of separation using CO_2 was introduced by Jessop, who developed switchable polarity solvents (SPS)[23]- solvents that can replace a series of solvents of different polarity that might otherwise be used in one reaction for extractions or removal of waste. In collaboration with Eckert and Liotta at Georgia Institute of Technology, Jessop's group has accomplished this by using 1.8-diazabicyclo-[5.4.0]-undec-7-ene (DBU)/alcohol (a) and 2-butyl-1,1,3,3-tetramethylguanidine (TMBG)/alcohol (b) mixtures, whose properties can be reversibly changed by addition or removal of CO_2 as shown in Scheme 11.

Scheme 11. a) DBU/alcohol system and b) TMBG/alcohol system

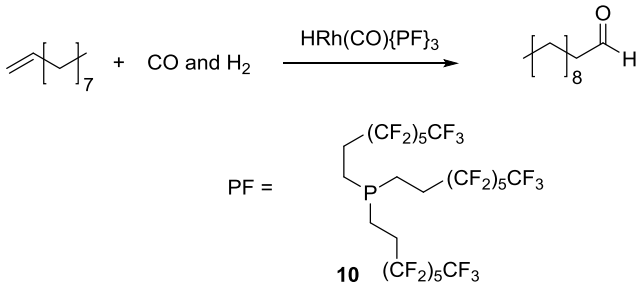


These mixtures produced a system that could switch from low-polarity non-ionic form to a high-polarity ionic form. The DBU- and TMBG alcohol systems have been tested in a number of reactions such as styrene polymerization and Claisen-Schmidt condensation.[24] In the case of a carbonyl condensation reaction, TMBG was used to which octane and then methanol was added. The enone product was isolated after the switchable solvent was converted into its ionic form. Even though DBU- or TMBG-alcohol switchable polarity solvent systems demonstrated their utility, they have limitations too. This is because of difficulties in maintaining the desired 1:1 ratio of the amidine and alcohol in these mixtures so that a change in polarity can be achieved.

An alternative system that addresses the problems of water sensitivity in OATS and the difficulty of the change in polarity in SPS is the fluorous biphasic solvent system concept.[25] It is known that perfluoroalkanes and related fluorous solvents produce biphasic mixtures with many organic solvents such as toluene, acetone and tetrahydrofuran at room temperature.[26] At elevated temperature, these fluorous/organic solvent mixtures become miscible. This phenomenon of two immiscible solvents

becoming miscible with the application of heat has been described by our group as thermomorphic behavior.[27] This solvent behavior combines the features of homogeneous reaction conditions with the simplicity of a gravity-based separation. A successful application of fluorous/organic thermomorphic conditions in catalysis was demonstrated by Horváth, who described a hydroformylation process for the conversion of 1-decene to undecanal.[28] In this example, perfluoromethylcyclohexane and toluene were used as solvents, and the hydroformylation of 1-decene was successfully completed at 100 ^{o}C as shown in Scheme 12. A modification of the phosphine ligand **10** with "fluorous ponytails" was used to increase the solubility of the catalytic system in the fluorous phase of the fluorous/organic solvent mixture. Cooling the reaction to room temperature produced a biphasic reaction mixture with the rhodium catalyst in the lower fluorous phase and the product in the upper toluene phase.

Scheme 12. Thermomorphic fluorous/organic hydroformylation of 1-decene



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While effective, fluorous/organic separation methods have significant limitations: fluorous solvents are costly and there have been questions about their environmental impact.[29] Environmentally benign alternatives to the fluorous/organic solvent system have been designed. These include latent biphasic separation[30] and thermomorphic[31] separation schemes that have been developed by the Bergbreiter group. For these two separation systems to be effective in a catalytic reaction and to make a process inexpensive and time-saving, a high differential solubility of the product and the catalyst must exist. A latent biphasic system involves at least one polar solvent and at least one nonpolar solvent that form a single phase mixture for a catalytic reaction. Such systems are then perturbed after the reaction by formation of a product or by-product or by addition of a perturbing agent such that they become biphasic. By employing a catalyst that is phase selectively soluble in a solvent phase in which the products are relatively insoluble, one can effect catalyst/product separation and recycle a stable catalyst.

An example of such a solvent mixture useful for homogeneous catalysis is a mixture of heptane and ethanol. When the system is perturbed by the addition of 5 vol % water, it separates into two phases: a polar ethanol phase containing the polar product, and the nonpolar heptane phase containing a nonpolar polymer-supported catalyst as shown in Figure 5.

The second approach for the development of a liquid/liquid separation scheme relevant to catalysis is a thermomorphic system that usually consists of a binary or ternary mixture of polar and nonpolar solvents that form a biphasic mixture on cooling

but form a single phase upon heating. In this system, by employing a catalyst that is phase selectively soluble in a solvent phase in which the products are insoluble, one can effect catalyst/product separation upon cooling after the monophasic reaction.

An example of one such system is a heptane/*N*,*N*-dimethylformamide mixture. When a hot thermomorphic system is cooled, it separates into two phases; a polar *N*,*N*-dimethylformamide phase containing the polar products and the nonpolar heptane phase containing the polymer-supported catalyst. A simple gravity separation can then separate the solution containing the catalyst from the solution containing the product (Figure 5).

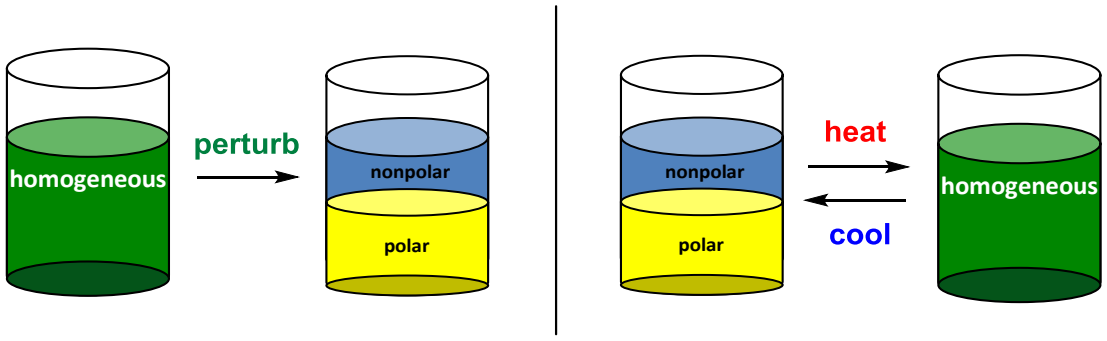


Figure 5. Latent biphasic (left) and thermomorphic (right) solvent systems

Our group and others have demonstrated that polymers can have high phase selective solubility in either a nonpolar or polar phase like the phases formed in the thermomorphic and latent biphasic systems.[32] Depending on the polarity of the product formed, ether nonpolar or polar polymer supports can be used to facilitate the recovery

of the polymer-supported catalyst after the monophasic reaction step. Examples of polymers that our group has used as supports to ensure high phase selective solubility include include poly(ethylene glycol) (PEG) **11**, polyisobutylene (PIB) **12**, polyethylene (PE) **13**, poly(4-*tert*-butylstyrene) (PTBS) **14**, poly(*N*-isopropylacrylamide) (PNIPAM) **15**, poly(*N*-octadecylacrylamide) (PNODAM) **16**, and poly(octadecyl acrylate) (PODA) **17** as shown in Figure 6. These polymers can be obtained commercially or prepared such that they have reactive terminal groups or reactive pendant groups for ligand/catalyst immobilization.

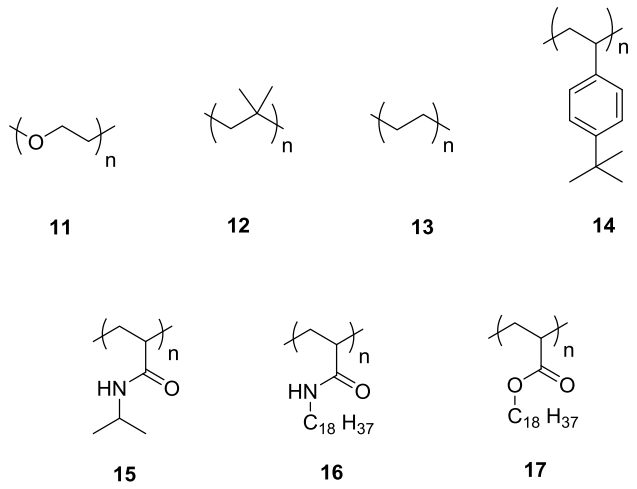


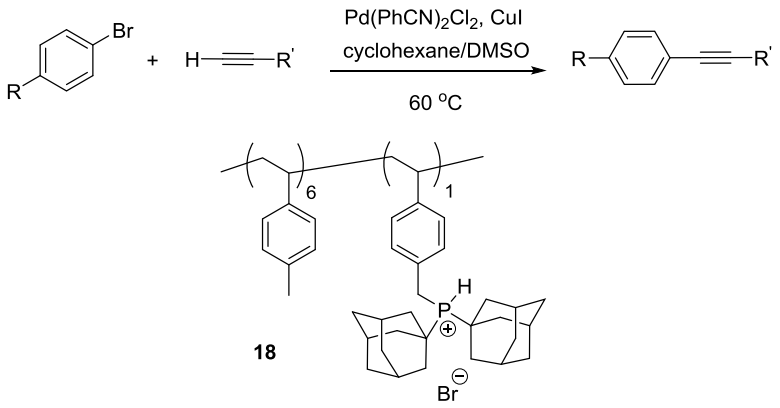
Figure 6. Common soluble polymer supports

There are several approaches utilized to determine a polymer's phase selective solubility. The ultimate test is of course running a reaction with a catalyst and determining the effectiveness of a polymer in separating the catalyst from product.

However, a polymer's phase selective solubility in biphasic solvent mixtures can be estimated without running a catalytic reaction using fluorescence or UV-vis spectroscopy. A polymer-bound dye as a surrogate of a polymer-bound catalyst is synthesized and a solution of this polymer supported dye is examined.[33] By measuring fluorescence or UV-visible absorptions of polymer-supported fluorophores or chromophores as catalyst surrogates in different solvent phases, a determination of the polymer's phase selective solubility in the two phases can be made. Several prior studies by our group illustrate the approach that can be used. In one case, we studied phase selective solubility of modified polyacrylamides where the isopropyl pendant alkyl groups were replaced with more lipophilic octadecyl groups. After dissolving these polymer-supported dyes in a mixture of toluene and 95% ethanol/water followed by addition of 5 vol% water, no detectable absorbance of the polymer bound UV-visible dye was found in the product phase. In this case, poly(*N*-octadecylacrylamide) (PNODAM) was shown to be a useful polymer support for catalysts with a phase-selective solubility for the nonpolar phase of >99.9%.

An alternative to using alkylated polyacrylamides is to use nonpolar alkyl-substituted polystyrenes. Plenio[34] described the polymerization of 4-methylstyrene to form catalyst supports that were soluble in cyclohexane and could be separated by liquid/liquid separation from dimethylsulfoxide. In this chemistry, Sonogashira coupling reactions of 4-bromoacetophenone and phenylacetylene were carried out. Poly(4-methylstyrene)-supported phosphine ligand **18** was used together with $Pd(PhCN)_2Cl_2$ as shown in Scheme 13.

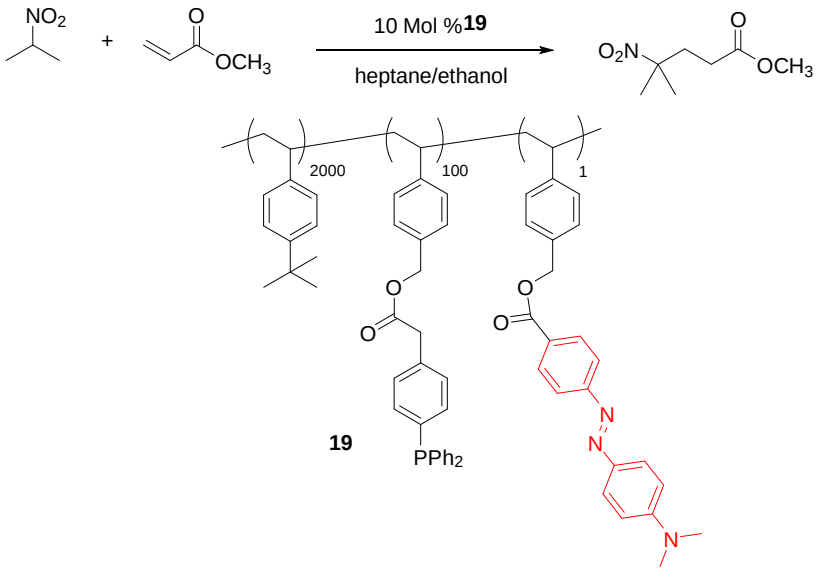
Scheme 13. Sonogashira coupling using poly(methylstyrene)supported phosphine **18**



In this example, the absence of significant leaching of the poly(4-methylstyrene)-supported Pd(0) catalyst is indicated by the high yields (over 90%) and constant turn over frequency (TOF) over the five reaction cycles. These alkyl-substituted polystyrene supports exhibited high solubility in alkane solvents. Concurrent to this work, Bergbreiter's group investigated the hydrocarbon phase-selective solubility of poly(4-*tert*-butylstyrene)-supported catalysts that can be prepared from commercially available 4-*tert*-butylstyrene. In this work, a dye-labeled poly(4-*tert*-butylstyrene)-supported phosphine or amine was prepared.[35] Alkyl-substituted polystyrene-supported catalysts containing low loading of the azo dye could quantify the efficiency of catalyst recycling through multiple cycles. In this work, we demonstrated that poly(4-*tert*-butylstyrene)-supported triphenylphosphine derivative **19** catalyzed the Michael addition of 2-nitropropane and methylacrylate under latent biphasic reaction conditions using heptane

and ethanol as shown in Scheme 14. In this chemistry, the catalyst could be recovered and recycled four times with no loss in product yield.

Scheme 14. Poly(4-*tert*-butylstyrene)-supported triphenylphosphine derivative **19** in Michael addition under latent biphasic conditions



The chemistry in our laboratory is mainly focused not on the development of new chemistry but on the development of new ways to use and improve existing chemical processes using thermomorphic and latent biphasic systems for catalyst recovery. In the chapters to follow, I will describe work where alkyl-substituted polystyrene supports are prepared and studied. I will also demonstrate how varying the alkyl chain on the polystyrene support can affect the phase-selective solubility. Lastly, I will present the

use of these alkyl-substituted polystyrenes as recoverable supports in catalysis using liquid/liquid biphasic separation strategies.

CHAPTER II

DESIGNING PHASE SELECTIVLY SOLUBLE ALKYLATED POLYSTYRENES

Introduction

Linear polystyrene is a useful polymer because it is a direct analog of the more widely used insoluble cross-linked polystyrene. Incorporating functionality into a soluble polymer support can be accomplished by copolymerization of chloromethylstyrene and styrene. This leads to the copolymers with reactive benzylic chloromethyl groups that can be substituted post-polymerization either with a catalyst or with a ligand that is then used to complex a catalyst. The extent of functional group loading can be adjusted by changing the ratio of co-monomers used in the polymerization reaction. The major advantage of soluble chloromethylated polystyrene is that a wide variety of functional groups can be introduced to the polymer. The products and the conversions of the starting material to product can also be analyzed using solution state NMR spectroscopy.

It is thus not surprising that linear polystyrene is widely used in chemistry as a recoverable polymer support for catalysts. Indeed, linear polystyrene was one of the original supports used in preparing soluble polymer bound catalysts.[36] The most common ways to recover the polystyrene supports are through solvent precipitation or membrane filtration. Unlike solvent precipitation that requires excessive amounts of solvent, membrane filtration is a more practical way to recover the polymer that does not

involve as much additional solvent. This separation is largely based on the size difference between the macromolecules (polymers) and micromolecules (substrate or product) in solution with a membrane being permeable to the smaller molecules.

While solvent precipitation and membrane filtration have been the general schemes used for separation of polymer-supported catalysts and reagents from products, other scheme are also possible. An alternative method that has been developed uses biphasic separation based on the phase selective solubility of polymer-bound ligands, catalysts and reagents. In this case a liquid/liquid separation can be achieved that effectively separates the polymer from the product and less or no added solvent is required. As described earlier, Plenio used this methodology to remove poly(4-methylstyrene)-supported catalyst that was phase selectively soluble in cyclohexane from the product of Sonogashira and Suzuki coupling reactions that were soluble in DMSO. This separation strategy does not require using a polymer support that undergoes a phase transition. It involves a solvent mixture that is monophasic when hot and biphasic when cold, a solvent mixture that becomes biphasic as a result of the addition or formation of perturbing agent, or addition of a second solvent at the end of a reaction that removes the products. While cyclohexane/DMSO biphasic separation was found to be an effective separation strategy in the particular example of poly(4-methylstyrene), it should be noted that the size, structure and polarity of the macromolecules and its substituents can affect the success of this separation technique.

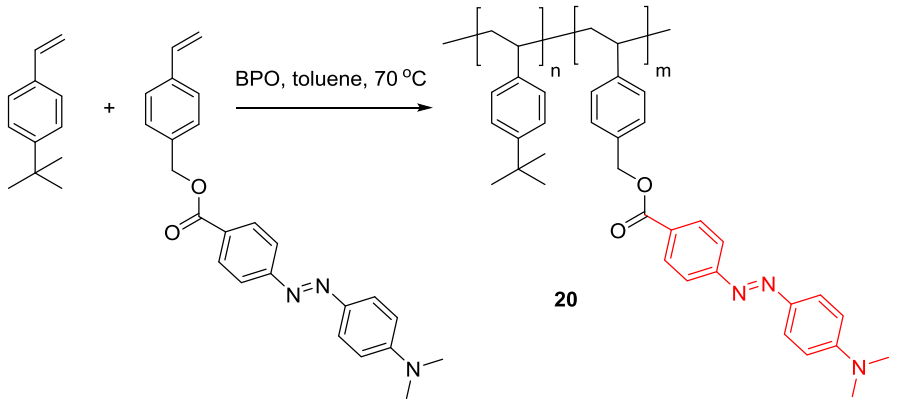
Bergbreiter's group has been a pioneer in developing alternative strategies to solvent precipitation or membrane filtration that allow the removal of phase selectively

soluble polymer-supported catalyst from product in a liquid/liquid separation.[3,37] The most important feature of this strategy is that the reaction takes place under homogeneous conditions and with a liquid/liquid biphasic separation that occurs at the end of the reaction. The most effective version of this approach to liquid/liquid separations requires the polymer-supported catalysts to be phase selectively soluble in a phase in which products are minimally soluble or insoluble. As a result, the Bergbreiter group has focused on polymer supports that are phase selectively soluble in a hydrocarbon solvent such as heptane, a nonpolar environmentally benign solvent. Unlike hexane, heptane is not a volatile organic compound (VOC) and does not present health concerns and can be used on a large scale. Unsubstituted polystyrene is however not a suitable polymer support to be used in this scenario because it is not soluble in heptane. Thus, the modification of polystyrene with alkyl functionality is achieved to improve the lipophilic property of the polymer support. Such alkyl-substituted polystyrenes are phase selectively soluble in heptane and in turn less soluble in polar solvents. This means that a polymer-bound catalyst can be separated from the product that is soluble in polar phase. Such biphasic separations avoid a solvent-intensive precipitation process.

The commercial availability of 4-methyl and 4-*tert*-butylstyrene makes soluble polymers derived from these monomers easily prepared. The synthesis of poly(4-alkylstyrene) supports that have greater solubility in heptane than unsubstituted polystyrene can be achieved. Previously, our group used commercially available 4-*tert*-butylstyrene as a monomer to prepare suitable heptane soluble polystyrene and the phase selective solubility of this polymer was tested using a 10:1 copolymer of 4-*tert*-

butylstyrene and 4-vinylbenzyl *p*-methyl red dye. This copolymer **20** was synthesized as shown in Scheme 15.[35]

Scheme 15. Synthesis of poly(4-*tert*-butylstyrene) with UV-visible dye

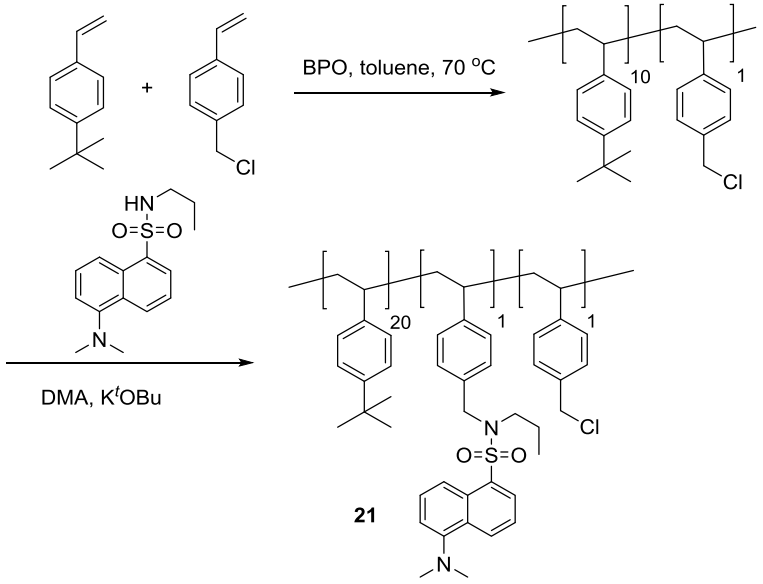


The UV-visible dye in this copolymer serves as a catalyst surrogate. It has an extinction coefficient of *ca.* 10^{-3} $M^{-1}cm^{-1}$ and a solution that is *ca.* 10^{-3} N has an absorbance that can be readily detected. For example, **20** was dissolved in heptane and then mixed with 90% aqueous ethanol to form a biphasic mixture. Heating this biphasic mixture to 70 °C produced a monophasic solution. Upon cooling to room temperature, this thermomorphic solution reformed a biphasic mixture. At this point, the two phases were separated using a gravity-based separation and analyzed by UV-visible spectroscopic analysis. The analysis showed no detectable (< 0.5%) dye in polar phase. The extent of this biphasic separation is sufficient for separation of common polar products and by-products from the polymer support. However, while the neutral dye

loaded polymer could be separated, a polymer that contained a more polar substituent – the protonated form of the *p*-methyl red dye – visually leached into the polar EtOH-rich phase.

Poly(4-*tert*-butylstyrene) polymers with fluorescent tags have also been prepared by nucleophilic substitution of the chloride of poly((4-*tert*-butylstyrene)-*c*-(4-vinylbenzyl chloride)). This chemistry used *N*-propyl-5-dimethylaminonaphthalene-1-sulfonamide as shown in Scheme 16.[33] In this work, the fluorescently labeled polymer **21** was used to probe the effect of solvents on a polymer-bound substituent. However, while this report did describe solubility of the dansyl-labeled polystyrene in various solvents and solvent mixtures and while the insolubility of this polymer in polar solvents was mentioned, the phase selective solubility of this polymer in biphasic systems was not explored.

Scheme 16. Synthesis of poly(4-*tert*-butylstyrene) with fluorescent dye



The limitation that poly(4-alkylstyrene) phase selective solubility can be affected by both polarity and the loading of the pendant groups is not unexpected but is a concern as evident from the colorimetric studies that showed visible leaching of the protonated azo dye labeled poly(4-*tert*-butylstyrene) into the polar phase at 10% loading.[33] Given that prior studies by our group have shown that longer alkyl groups on poly(*N*-alkylacrylamide)s can significantly improve phase selective solubility, I hypothesized that modification of polystyrene with different groups could lead to materials with much higher heptane phase selective solubility: phase selective solubility that would minimize leaching even when substituent group loading is increased or when substituents become more polar.[38] To explore possible modifications for the heptane soluble polystyrenes, I examined the effects of changing the 4-methyl or 4-*tert*-butyl

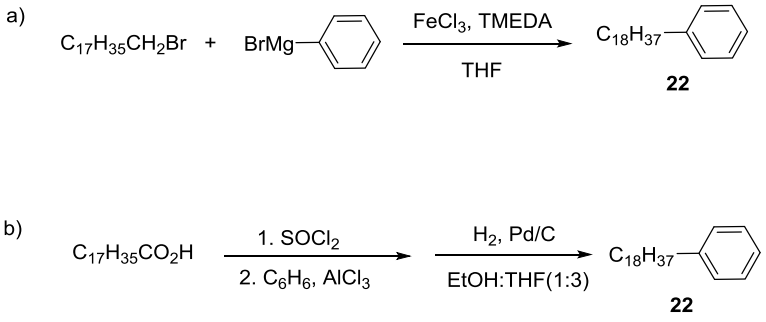
groups others used to make linear polystyrene so as to incorporate more hydrophobic alkyl groups. Various alkylstyrene monomers were prepared and copolymerized with 5-10 mol % of chloromethylstyrene monomer. Given that fluorescence is more sensitive than UV-visible spectroscopy, these syntheses were designed so that a dansyl dye could be attached to the new poly(4-alkylstyrene)s. The heptane phase selective solubility of these supports was examined in a variety of biphasic solvent systems including both latent biphasic and thermomosrphic solvent systems used previously in catalysis. The effects of these alkyl substituents on the phase selective solubility of polystyrene supports are described in this chapter.

Results and Discussion

While polystyrene and in particular divinylbenzene-crosslinked polystyrene has been used for decades to support catalysts,[39] there has been relatively little attention paid to soluble linear 4-alkyl-substituted polystyrene supports. Plenio's studies that used 4-methylstyrene based supports and our group's work with 4-*tert*-butylstyrene supported catalysts mentioned above are the only well described exceptions to this focus on simpler polystyrenes. However, as noted previously, while both of these supports can in some cases separate a catalyst from the polar phase, there is leaching of the soluble polymer into the polar phase during the liquid/liquid separation process. The extent of this leaching varies depending on the nature of the polar solvent and the substituents on the polymer. To test the hypothesis that increasing the lipophilicity of the 4-alkyl group of the poly(4-alkylstyrene) would afford more phase selectively soluble supports that could be more useful in catalysis, I prepared a variety of 4-alkylstyrenes.

4-Octadecylstyrene was of particular interest because of the hydrophobic nature of octadecyl groups. However, the precursor for this monomer, octadecylbenzene, is not commercially available. In order to prepare octadecylbenzene, two procedures were examined. In the first synthesis, the alkylation of benzene was accomplished through coupling of an aryl Grignard reagent to a primary octadecyl bromide using ferric chloride as a catalyst shown in Scheme 17 (a). This reaction worked; however, the modest yield of 54% and the presence of biphenyl by-product that is difficult to remove made this synthetic route impractical.

Scheme 17. Synthesis of 4-octadecylbenzene **22** by a) Fe-mediated coupling reaction or b) conventional acylation and catalytic reduction



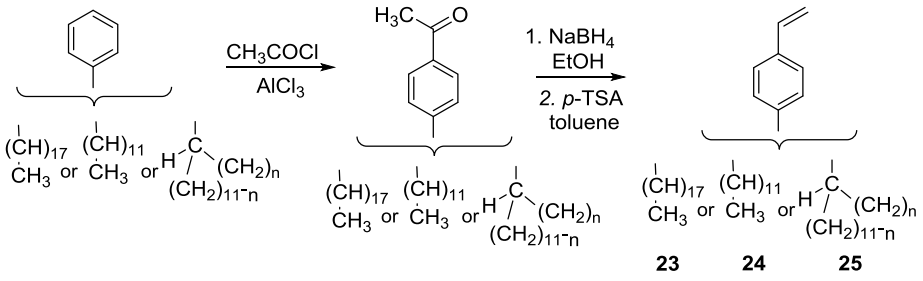
Since the chemistry shown in Scheme 17 a) turned out to be impractical on a multigram scale, so more classical synthesis shown in Scheme 17 b) that had been adopted from Laredo group was used.[40] This chemistry also has the advantage of using a

fatty acid, a readily available biomaterial. Such materials are of interest as sustainable alternatives to hydrocarbons derived from oil. In this case, stearic acid was converted to stearoyl chloride, which was then used as a reagent in Friedel-Crafts acylation with benzene in the presence of aluminum chloride catalyst. The product heptadecyl phenyl ketone was then reduced to form octadecylbenzene by hydrogenation with Pd/C. This synthesis was successful on the 5 g scale and provided a precursor octadecylbenzene that could be converted to 4-octadecylstyrene.

In addition to preparing octadecylbenzene, it was also possible to obtain alkyl benzenes containing dodecyl groups. These dodecylbenzenes contained both linear $C_{12}H_{25}$- groups and $C_{12}H_{25}$- groups that were mixtures of structural isomers.

All three types of alkylbenzenes could be converted to form 4-alkylstyrene monomers. In each case, this involved using the sequence of regioselective acylation with acetyl chloride, reduction, and dehydration as shown in Scheme 18.

Scheme 18. Synthesis of 4-alkylstyrenes **23**, **24**, and **25**



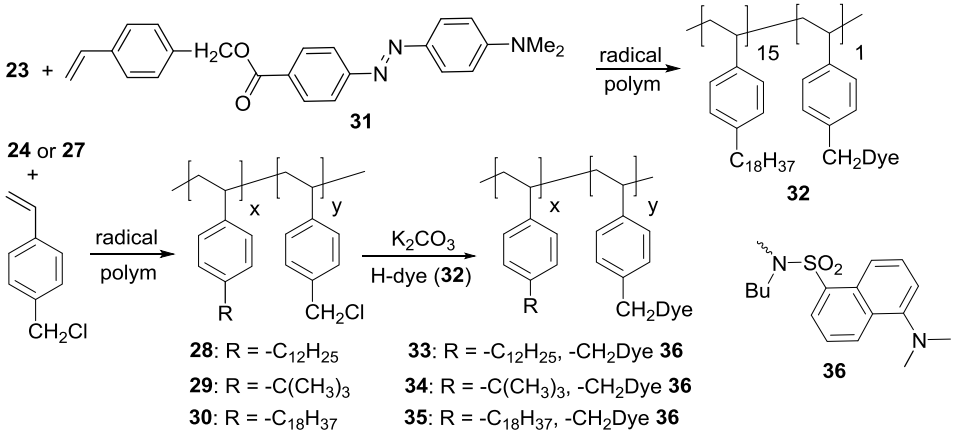
With several types of more lipophilic 4-alkylstyrenes available, I explored the synthesis of copolymers. The initial goal was to focus on polymerization of the least expensive monomer, 4-dodecylstyrene, which contained a mixture of isomeric dodecyl groups. Unfortunately, attempts to polymerize isomeric 4-dodecylstyrene monomer **25** by a conventional radical polymerization consistently led to formation of gels. The hypothesis for this is that gelation is a result of the chain transfer during the polymerization. This occurs when a radical abstracts the reactive benzylic hydrogen of the isomeric dodecyl group containing a tertiary carbon leading to a radical that produces branched polymers or that couples to other chains.

Thus, I focused my attention on polymers synthesized from monomers **23** and **24** containing linear octadecyl and dodecyl groups, where the benzylic carbon is secondary with less reactive benzylic hydrogens. As part of this work, the commercially available 4-methylstyrene **26** and 4-*tert*-butylstyrene **27** monomers were also used to prepare polymers by conventional radical polymerization or RAFT polymerization.

As mentioned above, dye-labeled polymers where a dye serves as a catalyst surrogate offer a convenient measure of polymer phase selective solubility in liquid/liquid separations.[41] These dyes can be incorporated into the product polymer in several ways. Using a 4-chloromethylstyrene comonomer as a method to incorporate a reactive group that can be transformed into a dye (or a ligand or a catalyst) was precedented and I used this approach as shown in Scheme 20. Using this scheme, I could prepare several types of polymers whose phase selective solubility could be examined qualitatively or quantitatively by labeling these polymers with dyes.

Copolymerization of these 4-alkylstyrenes **24** and **27** with 4-vinylbenzyl chloride was achieved using benzoyl peroxide as the radical initiator to produce the desired substituted polystyrene as shown in Scheme 19. In many cases, qualitative evidence that some polymer formed was readily apparent by changes in the properties of the reaction mixture. For example, in the preparation of 4-*tert*-butylstyrene copolymers, the reaction mixture turned into a solid. A more rigorous characterization of the product polymers involved gel permeation chromatography (GPC) and ^{1}H NMR spectroscopy. In the case of poly(4-dodecylstyrene) copolymer **28**, the molecular weight was determined to be a M_n 32000 Da with a PDI of 2.2, and the ratio of monomers in the product was determined to be 10:1 based on ^{1}H NMR spectroscopic analysis integrating the peaks at δ 2.47 for benzylic protons of 4-dodecylstyrene and at δ 4.45 for benzylic protons of 4-chloromethylstyrene. In case of poly(4-*tert*-butylstyrene) copolymer **29**, the molecular weight was determined to be a M_n 22000 Da with a PDI of 2.8, and the ratio of monomers was determined to be 11:1.

Scheme 19. Synthesis of dye-labeled poly(4-alkylstyrene)s **32**, **33**, and **34**



While a fluorescence assay is the most sensitive, visual assays using an azo dye are simpler. Thus, a typical initial experiment to test phase selective solubility used the azo dye labeled poly((4-octadecylstyrene)-*c*-(4-vinylbenzyl chloride)) copolymer **32** (x = 15, y = 1). As shown in Figure 7, these visual experiments showed that the dye-labeled polymer **32** was highly phase selectively soluble in the less dense heptane phase of a thermomorphic heptane/DMF solvent mixture that was monophasic at 90 ^{o}C and biphasic and room temperature. This solubility is opposite to that of *p*-methyl red dye, which was soluble in the DMF-rich phase as shown in Figure 7.

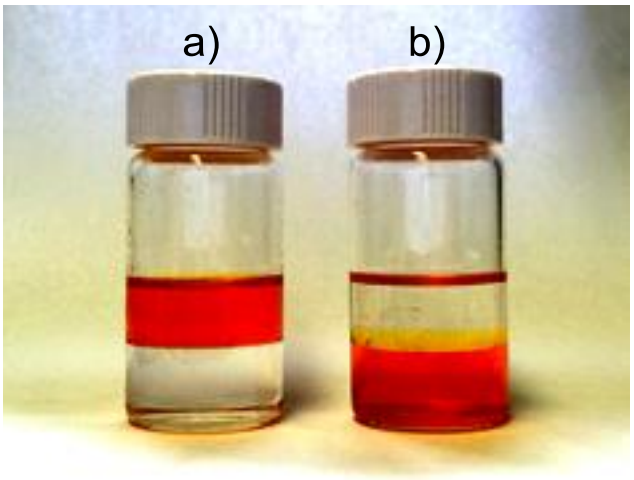


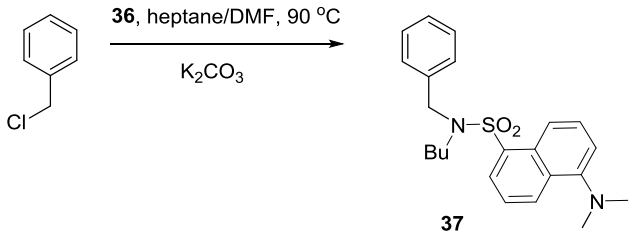
Figure 7. (a) Poly(4-octadecylstyrene)-supported methyl red dye in heptane phase of heptane/DMF solvent mixture and (b) low molecular weight methyl red dye in DMF phase of heptane/DMF solvent mixture

While using methyl red dye on poly(4-alkylstyrene)s such as poly(4-octadecylstyrene) allows for the qualitative analysis of phase selective solubility of the polymer support, the azo dye is not sensitive enough to distinguish subtle differences in phase selective solubility. Fluorescence is far more sensitive so a more sensitive dansyl label was incorporated for further studies. *N*-Butyl-5-dimethylaminonaphthalene-1-sulfonamide had previously synthesized and was attached to poly(4-*tert*-butylstyrene).[42] This synthesis was repeated using a nucleophilic substitution reaction with dansyl under thermomorphic conditions using a heptane/DMF solvent mixture at 90 ^{o}C to produce **33** and **34**.

To confirm that this dansyl probe has fluorescence that is linearly dependent on the concentration, I also prepared a benzyl substituted version of this tertiary

sulfonamide fluorescent dye by reaction of the sodium salt of butyl-5-dimethylaminonaphthalene-1-sulfonamide with benzyl chloride as shown in Scheme 20.

Scheme 20. Synthesis of *N*-benzyl-*N*-butyl-5-dimethylaminonaphthalene-1-sulfonamide **37**



While this dye is not remarkably soluble in heptane, it had sufficient solubility which allowed me to show that there is a linear relationship between fluorescence intensity and concentration at low concentrations (from μN to nN) as shown in Figure 8. The fluorescence intensity of this low molecular weight dye then was used to determine leaching of a similar dye labeled polymer. In these studies, I assumed that the fluorescence of the dye **37** was essentially the same as a similar dye on polystyrene.

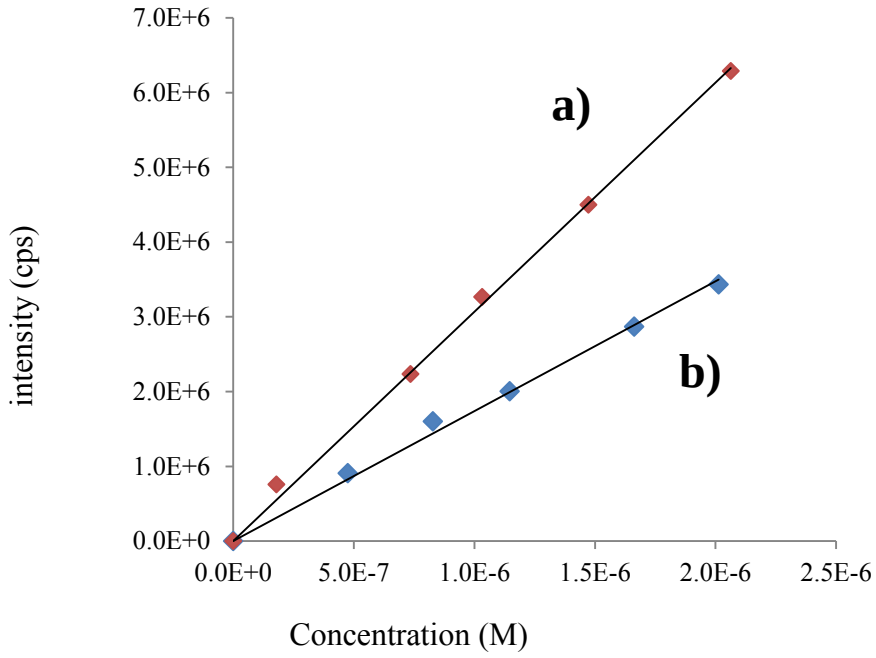


Figure 8. Calibration curve for *N*-benzyl-*N*-butyl-5-dimethylaminonaphthalene-1 sulfonamide **37** in (a) heptane and (b) acetonitrile. An R^2 value of 0.996 was obtained for both curves using the software in Microsoft Excel

Phase selective solubility studies of the dansyl-labeled poly(4-alkylstyrene) copolymers **33** and **34** were then carried out using a heptane/acetonitrile (2:1/v:v) mixture using fluorescence spectroscopy. In these studies, a heptane solution of fluorescently labeled copolymers **33** and **34** was prepared that was determined to be 1.3 mN according to the calibration curve. These heptane solutions were allowed to thoroughly mix with acetonitrile by manual shaking of the flask for 30 seconds. The heptane and acetonitrile phases were then allowed to separate and a 2.0 mL aliquot of more dense acetonitrile phase was transferred into a cuvette. The fluorescence (λ_{EX}=355 nm, λ_{EM}=500 nm) of this solution was measured. This mixing, separation and analysis

sequence was carried out four times for both **33** and **34**. The concentration of the extracted dansyl-labeled polymer in acetonitrile was then analyzed as shown in Figure 9. As the experiment progressed from cycle to cycle, the leaching of dye decreased. It is hypothesized that this reflects either the presence of some unreacted dye or, more likely, leaching of some small amount of lower molecular weight fractions of the polymeric support that have a lower phase selective solubility. The amount of leaching even in the first case is very low. In the case of the greatest leaching, only 0.68% of the dye labeled polymer was lost.

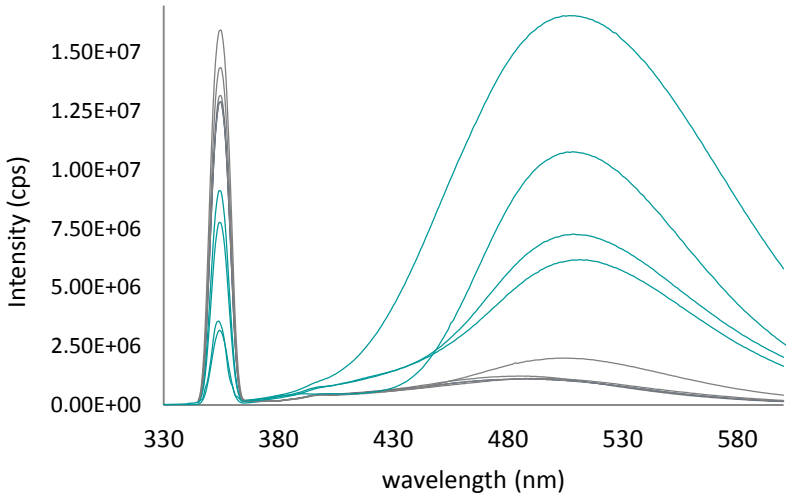


Figure 9. Fluorescence spectra of acetonitrile solutions for **34** (blue) and **33** (grey)

From the fluorescence studies, it was determined that the dansyl-labeled copolymers **33** and **34** exhibit high (> 99%) phase selective solubility in the heptane

phase. Analysis of the acetonitrile phase as seen in Figure 10 showed that only trace amounts of either copolymer leached into the acetonitrile phase and that the leaching of the copolymer containing the 4-dodecyl group is an order of magnitude less than that of the copolymer containing the *tert*-butyl group. This difference in phase selective solubility is attributed to the fact that the dodecyl group is more lipophilic making the poly(4-dodecylstyrene) polymer even more heptane soluble. This effect was later used as a tool in separation strategies with supported catalysts. When the phase selective solubility study was performed on copolymer **35** (x = 6, y = 1) and compared to **33**, it was shown that both copolymers exhibit similar (>99.9%) phase selective solubility in the heptane phase.

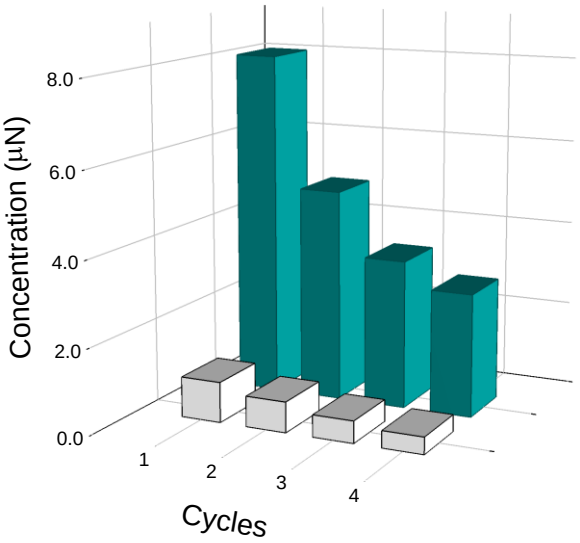


Figure 10. The concentrations for four consecutive cycles of the poly(4-dodecylstyrene) copolymer **33** (grey) and poly(4-*tert*-butylstyrene) copolymer **34** (blue) in acetonitrile phase

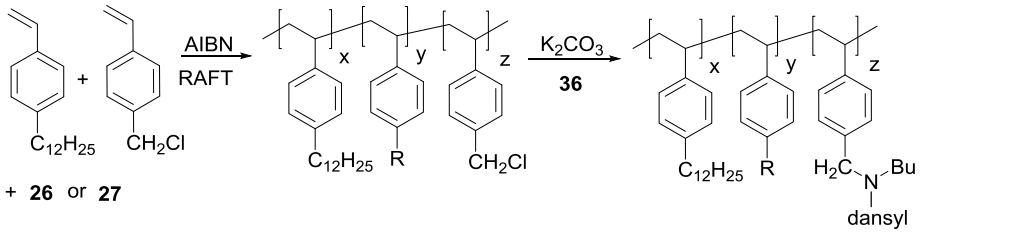
While using dodecyl groups in the polystyrene support gave excellent results, the dodecylstyrene monomer required multistep synthesis, which is time-consuming. In order to synthesize a polymer that would retain the lipophilic nature but avoid the need for the repetitive synthesis of the 4-dodecylstyrene monomer, several modifications to the polymer design were undertaken. This idea was based on earlier chemistry that suggested that a high loading of a lipophilic group is not always required to prepare a phase selectively soluble support. Thus, it might be possible to prepare copolymers of commercially available 4-methylstyrene or 4-*tert*-butylstyrene with only a fraction of dodecylstyrene.

To explore this, 4-dodecyl styrene was copolymerized with various amounts of commercially available 4-methyl or 4-*tert*-butylstyrene to yield soluble copolymer supports. The goal was to determine the minimum amount of 4-dodecylstyrene needed. In earlier studies, our group has shown that having 5-10 mol % of a more hydrophobic group in a polymer chain can significantly change a polymer's phase selective solubility.[42] A control radical polymerization was also incorporated so that polymers with uniform molecular weights could be obtained.

To carry out these studies, dansyl-labeled polymers were required. Thus, the polymerization included varying amounts of 4-methyl or 4-*tert*-butylstyrene, and 4-dodecylstyrene. These polymers were prepared by RAFT polymerization as shown in Scheme 21. The mole fraction of dodecyl groups was varied by gradually increasing the mole fraction of 4-dodecylstyrene monomer on a polymer chain. To test phase selective solubility, the synthesis was designed so that the terpolymers would contain 5-10 mol %

of benzyl chloride groups that could undergo a post-polymerization nucleophilic substitution reaction with *N*-butyl-5-dimethylaminonaphthalene-1-sulfonamide **36** to yield fluorescently-labeled terpolymers as shown in Scheme 21.

Scheme 21. Synthesis of terpolymers **38a**, **38b**, **38c**, **39a**, **39b**, **39c**, and **40**.



38a: R = -CH_3, x=28 mol%
38b: R = -CH_3, x=13 mol%
38c: R = -CH_3, x=0 mol%
40: x=90 mol%, y=0 mol%

39a: R = -$C(CH_3)_3$, x=28 mol%
39b: R = -$C(CH_3)_3$, x=9 mol%
39c: R = -$C(CH_3)_3$, x=0 mol%

The product polymers were analyzed by GPC and ^{1}H NMR spectroscopy. The ratio of monomers in the product was determined based on NMR spectroscopic analysis integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 4.45 (benzylic protons of 4-vinylbenzyl chloride). Phase selective solubility studies of the RAFT prepared dansyl-labeled poly(4-alkylstyrene) terpolymers **38a**, **38b**, **38c**, **39a**, **39b**, **39c**, and **40** were carried out using fluorescence spectroscopy employing a different solvent mixture than that previously mentioned. In this case, cyclooctane solutions of **38a**, **38b**, **38c**, **39a**, **39b**, **39c**, and **40** were prepared and mixed with DMF. These studies used DMF and cyclooctane because this solvent mixture is thermomorphic: it becomes a single phase on heating and returns to two phases on cooling. This ensures that the

mixing of the dye in the two solvents is complete. In these studies, *ca*. 4 mL of DMF was heated with 4 mL cyclooctane solution containing 1.3 mN of the fluorescently-labeled terpolymers **38a**, **38b**, **38c**, **39a**, **39b**, **39c**, and **40** for 5 minutes until the solution became a single phase. The approximate temperature at which miscibility was reached was *ca*. 80 ^{o}C. Once a homogeneous monophasic solution was formed, it was cooled to room temperature. The cyclooctane and the DMF phases were allowed to separate. A 2.0 mL aliquot of the DMF phase was then removed and transferred into a cuvette. The concentration of the extracted dansyl-labeled polymer in the DMF phase was then analyzed as shown in Figure 11.

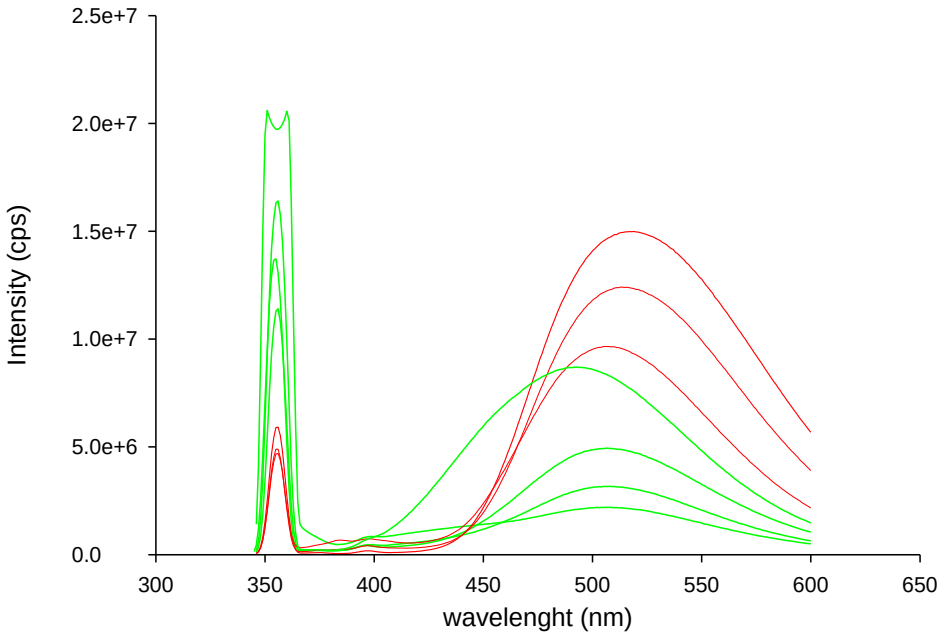


Figure 11. Fluorescence spectra of DMF solutions for poly(4-*tert*-butylstyrene)copolymer **39a**, **39b**, **39c**, and **40** containing 4-dodecylstyrene units (green), and for poly(4-methylstyrene) copolymer **38a**, **38b**, **38c** containing 4-dodecylstyrene (red). The fluorescence spectra for the first and third cycle for each of the polymers is omitted for clarity

This heating, cooling, separation and analysis sequence was carried out for three cycles using **38a**, **38b**, **38c**, **39a**, **39b**, **39c**, and **40** with high error bar indicating the first cycle and the low error bar indicating the third cycle as shown in Figure 12. While the amount of the polymer leaching into DMF phase was minimal for all of the terpolymers, the results clearly showed that leaching of poly(4-dodecylstyrene)-*c*-(4-*tert*-butylstyrene)-*c*-(4-cholomethylstyrene) terpolymer **39a** and **39b** was significantly less than leaching of poly(4-dodecylstyrene)-*c*-(4-methyl)-*c*-(4-cholomethylstyrene) **38a** and **38b**.

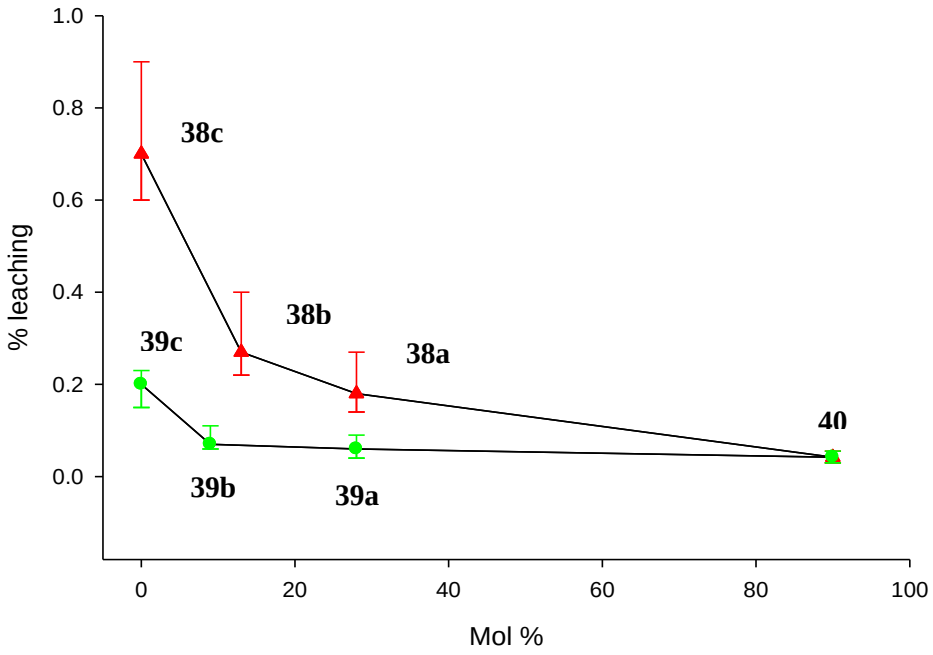


Figure 12. The concentrations of poly(4-*tert*-butylstyrene) terpolymer **39c, 39b, 39a** (green) copolymerized with 4-dodecylstyrene in 0 mol %, 9 mol %, 28 mol % or poly(4-methylstyrene) terpolymer **38c, 38b, 38a** (red) copolymerized with 4-dodecylstyrene in 0 mol %, 13 mol %, 28 mol % or terpolymer **40** containing 90 mol % of 4-dodecylstyrene in DMF phase

The percent leaching in each cycle for **38a**, **38b**, **38c**, **39a**, **39b**, **39c**, and **40** was calculated based on the initial concentration of the dansyl-labeled polymer. From Figure 12 it is evident as the mol percent loading of 4-dodecylstyrene on the polymer chain decreased, the leaching of the polymer into DMF phase increased. While both supports that contain approximately 10 mol % of 4-dodecylstyrene have high phase selective solubility, greater phase selective solubility for poly(4-*tert*-butylstyrene) containing 4-

dodecylstyrene was observed. When the phase selective solubilities of poly(4-dodecylstyrene)copolymer **33** prepared by conventional radical polymerization and poly(4-*tert*-butylstyrene)terpolymer **39b** containing only 9 mol % of dodecyl groups prepared by RAFT were analyzed, not surprisingly the results were comparable as shown in Figure 13. This result indicates that a highly phase selectively soluble polymer support could be synthesized largely based on the 4-*tert*-butylstyrene monomer with only a fraction of 4-dodecylstyrene monomer and used alternatively as an alkylated-polystyrene support for catalyst recycling in processes that involve a biphasic liquid/liquid separation.

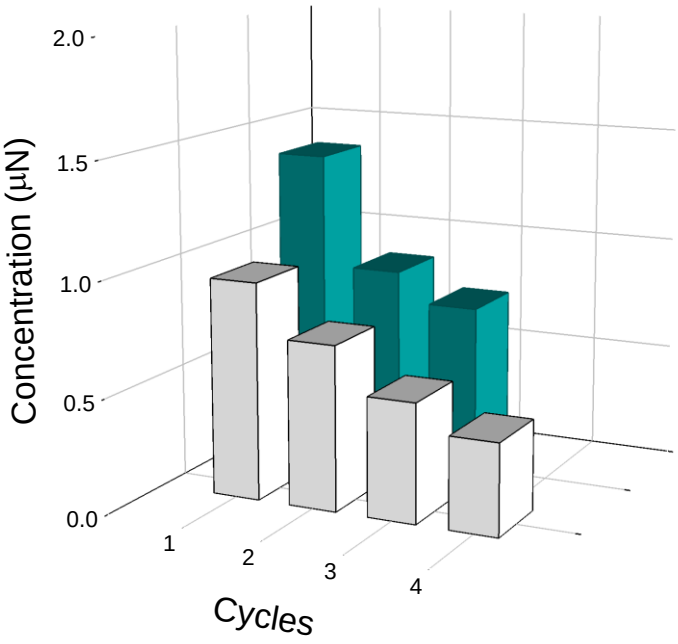


Figure 13. The concentrations for four consecutive cycles of the poly(4-dodecylstyrene)copolymer **33** (grey) and for three consecutive cycles of poly(4-*tert*-butylstyrene)terpolymer **39b** containing only 9 mol% of dodecyl groups (blue)

Phase selective solubility studies of polymers other than poly(4-alkylstyrene) have been reported.[33,43] In these studies, DMF and ethanol were used as the polar solvents to study the phase selective solubility of polyisobutylene with attached dansyl dye and poly(octadecyl methacrylate)s (PODMA) with supported methyl red dye. The results indicate that high phase selectively soluble alkylated polystyrenes are comparable, and in some cases even superior, supports in the heptane phase when using latent biphasic or thermomorphic systems as separation strategies.

Conclusions

A variety of syntheses of phase selectively soluble poly(4-alkylstyrene) co- and terpolymer supports have been developed. By varying the structure of the pendant alkyl group, an increase in nonpolar phase selective solubility is achieved as seen in the poly(4-*tert*-butylstyrene) and poly(4-dodecylstyrene) studies. Likewise, by modifying the design of the polymer support with respect to the ratio of 4-*tert*-butyl- or 4-dodecylstyrene monomers on the chain, a comparable phase selectively soluble polymer supports can be prepared. These supports contain chloromethyl groups that can be converted into dye labels. Nonpolar phase selective solubility can be measured with thermomorphic and latent biphasic systems either qualitatively by attaching a UV-visible methyl red dye or quantitatively by using fluorescence dansyl dye as a catalyst surrogate. The polymer supports based on 4-*tert*-butylstyrene monomers containing a fraction of 4-dodecylstyrene monomers can be expected to be useful in the recovery and recycling of catalysts or reagents in thermomorphic or latent biphasic systems where heptane is used as the nonpolar solvent for polymer recovery and separation.

CHAPTER III

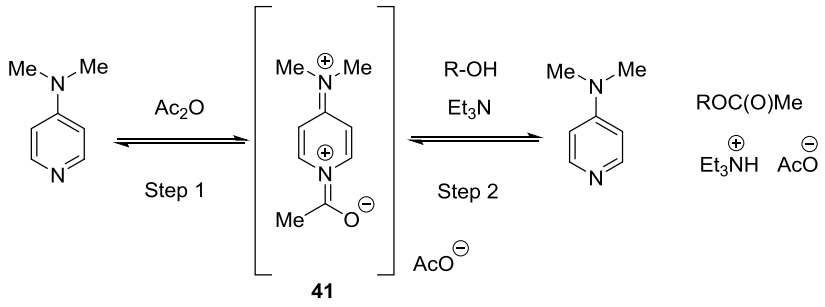
APPLICATIONS OF POLYSTYRENE-SUPPORTED DIMETHYLAMINOPYRIDINE AND CINCHONA ALKALOID ORGANOCATALYSTS

Introduction

The reaction of substrates such as alcohols, phenols and amines with acetic anhydride in the presence of pyridine as a base is a general acetylation method. In 1967, Litvinenko and Kirichenko reported the rates for the benzoylation of anilines using catalytic amounts of various pyridine-based catalysts. They observed that 4-dimethylaminopyridine (DMAP) accelerated the reaction rate by a factor of 10^4 when compared to pyridine.[44] A few years later, Vorbrueggen reported an analogous enhancement in yield and rate of acylation reactions of sterically hindered alcohols when using catalytic amounts of DMAP.[45] As a result of these and other similar observations, DMAP has become the catalyst of choice for a variety of fundamental chemical transformation, including acylations,[46] silylations[47] and synthesis of esters.[48] The increase of reported applications for DMAP and its availability in commercial quantities at reasonable prices continued to stimulate great interest in its use as a catalyst in the fields of organic, polymer, analytical[49] and biochemistry.[50]

The advantage of DMAP over other common organic acylation catalysts has been rationalized as shown in Scheme 22.[51] In a proposed mechanism the addition of acetic anhydride to DMAP forms a stable intermediate **41** in the first step.

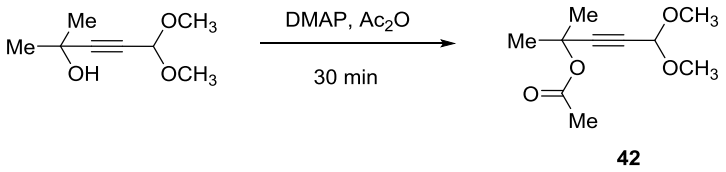
Scheme 22. Rationalization of DMAP Catalysis in Acylation Reactions



In the second step, the acetate counterion acts as a base to remove the proton from alcohol while the deprotonated alcohol acts as a nucleophile and forms a covalent bond with the acetyl group. The acetic acid formed by the proton removal from an alcohol then protonates DMAP. The catalytic cycle is complete when the auxiliary base such as triethylamine deprotonates the protonated DMAP and regenerates the catalyst.

One of the first reported acylation reactions catalyzed by DMAP was the acetylation of sterically crowded alcohols.[52] For example, formation of acetate **42** in 92% yield from the tertiary alcohol precursor was reported by Steglich as shown in Scheme 23.[53] In this chemistry, 4-dialkylaminopyridine was an especially useful catalyst in the acylation of acid-sensitive tertiary alcohols. When DMAP was used as a catalyst, yields and reaction times were generally improved versus those seen in the usual procedure where a tertiary alcohol is first converted into a sodium or magnesium alkoxide and then allowed to react with acid chloride.

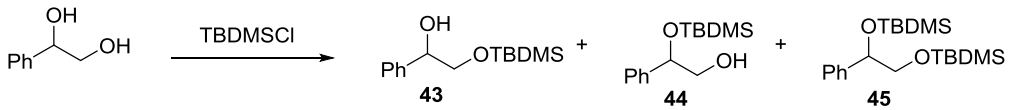
Scheme 23. Synthesis of acetate **42**



42

Silylation of a primary alcohol in the presence of a secondary one often presents a challenge as mixtures are formed when using imidazole as a basic catalyst. However, regioselective silylation of a primary hydroxyl group can be easily achieved when DMAP is employed as a catalyst as shown in Scheme 24.[47] In this chemistry, protection of the primary hydroxyl group of a dialcohol with *tert*-butyldimethylsilyl chloride (TBDMSCl) was carried out in the presence of DMAP and imidazole. The reaction with this 1,2-diol proceeded with dominant formation of the monosilyl ether **43** accompanied by a small amount of bis-silyl ether **44** when DMAP was used as a catalyst. A similar reaction using imidazole yielded a mixture of all three products with a slight preference for formation of **43**. The significant difference between the two reactions was the absence of the secondary silyl ether **44** formation when DMAP was employed.

Scheme 24. Silylation of primary alcohols

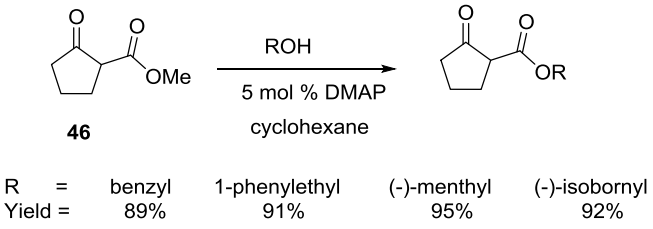


43 **44** **45**

DMAP, CH_2Cl_2, TEA, 15h, rt	95%	0%	5%
Imidazole, DMF, 15h, rt	59%	11%	30%

One of the most studied catalytic reactions that uses DMAP is transesterification, a process in which the alkoxy group of one ester is exchanged for the alkoxy group of an added alcohol. Transesterification is a reaction that is relevant to the development of sustainable fuels[54] and biodegradable polymers.[55] In general, the success of transesterification requires an excess of alcohol to favor the products because Le Chatelier's principle is what is used to drive the reaction. However, in one case as exemplified by Christoffers's work, transesterification of methyl β-ketocarboxylate **46** could be accomplished by using only one equivalent of alcohol in the presence of a catalytic amount of DMAP as shown in Scheme 25.[56]

Scheme 25. Transeserification of methyl β-ketocarboxylate **46**



Among nucleophilic catalysts, DMAP is certainly one of the most versatile nitrogen-based organocatalysts. Since its first use as a planar achiral acylation catalyst, there has been a growing interest in the design of planar-chiral DMAP derivatives that show utility for asymmetric catalysis.[57] Asymmetric organocatalysis, in which a chiral organic molecule catalyzes an enantioselective transformation, has become a growing field in recent years.[58] A variety of other organic nitrogen-based molecules have also

been employed as asymmetric nucleophilic organocatalysts. *Cinchona* alkaloids are one example of such asymmetric organocatalysts. Readily available, inexpensive *Cinchona* alkaloids possess a rich array of functionalities including five stereogenic centers, a secondary alcohol, a vinyl group and most importantly a quinuclidine moiety. These densely functionalized *Cinchona* compounds can engage in non-covalent interactions with other species making them extraordinary agents for molecular recognition as well as they are extensively employed as chiral catalysts (Scheme 26).

In 1949, Brown reported that tertiary amines that were part of a bridged structure, such as quinuclidine, had greater rate of addition to alkyl halides than non-bridged amines like triethylamine.[59] This was rationalized by the conformational constraints of bicyclic amines and thus the absence of steric hindrance at the nitrogen lone-pair of the bridged quinuclidine **50**. In 2003, Aggarwal examined the correlation between the Morita-Baylis-Hillman (MBH) reaction rate and pK_a of several nitrogen-based catalysts and observed a superior activity of quinuclidine when compared with more traditional catalysts such as DABCO and DBU.[60] Mayr rationalized this observation by obtaining kinetic and thermodynamic data of these classes of catalysts.[61] The nucleophilicity parameters *N* are shown in Figure 14 and can be compared with DMAP. Catalyst screening and experimental data led to the recognition of quinuclidine type compounds like *Cinchona* alkaloid as effective enantioselective catalysts.

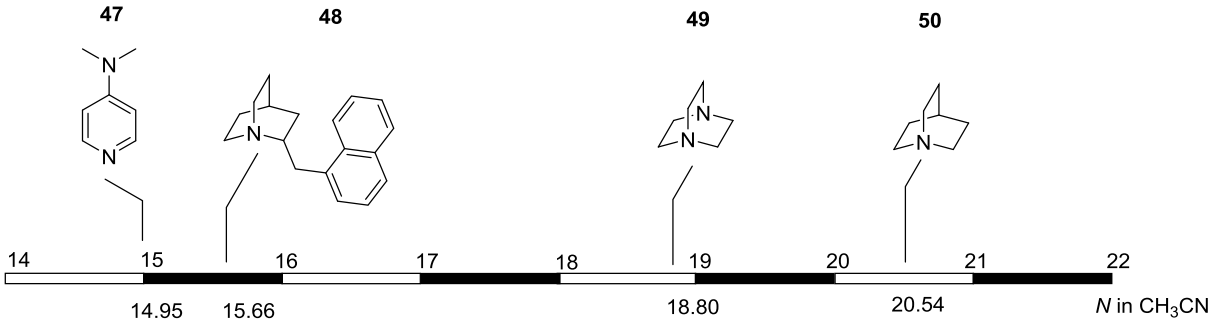
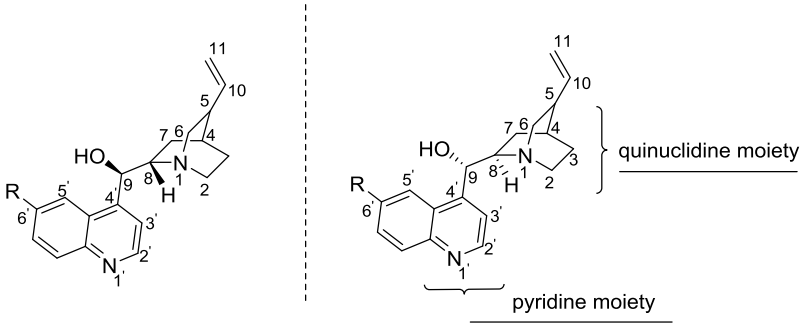


Figure 14. Nucleophilicity *N* in acetonitrile of DMAP **47**, benzylquinuclidine **48**, DABCO **49**, quinuclidine **50**

The presence of the quinuclidine functionality also makes derivatives of *Cinchona* alkaloids effective ligands for a variety of metal and metal free catalyzed processes. Of these processes, *Cinchona* alkaloid ligated osmium-catalyzed asymmetric dehydroxylation (AD) of olefins, developed by Sharpless has made the greatest impact in synthetic chemistry.[62] In addition to its utility for metal binding, the nucleophilic quinuclidine nitrogen can also be used as a reactive center in the development of enantioselective organocatalysis. As chiral catalysts, *Cinchona* alkaloids promote cyclization of ketenes with carbonyl compounds such as ketones and aldehydes.[63] Furthermore, the quinuclidine nitrogen can also be quaternized with benzyl halides to give ammonium salts that serve as useful asymmetric phase-transfer catalysts. This was shown by researchers at Merck, who reported the highly enantioselective alkylation of indanone derivatives in the presence of cinchonium salt.[64] Not surprisingly, *Cinchona* alkaloids containing a quinuclidine unit in their structure as shown in Scheme 26 drew

great attention as nucleophilic enantioselective catalysts and are considered "privileged ligands".[65]

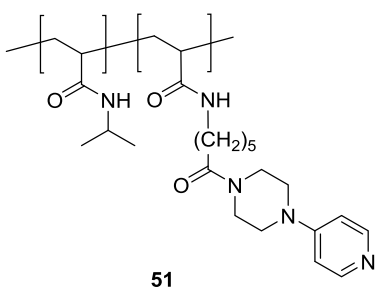
Scheme 26. Cinchona alkaloid derivative



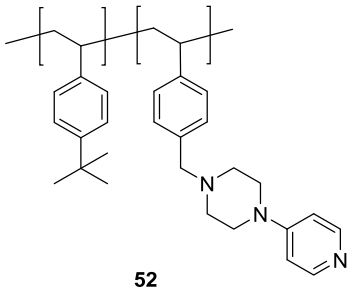
The use of achiral DMAP and chiral *Cinchona* alkaloid derivatives as effective organocatalysts for a variety of chemical transformations has long been recognized; however, their utility is often limited by the difficulty of separating the product from the catalyst.[66] With increasing demands for sustainable chemistry, factors such as catalyst recovery and recycling are also becoming very important. Because of the importance of feasible separation strategies for facile catalyst recovery, efforts have been undertaken to support 4-*N*,*N*-(dialkylamino)pyridine catalyst as well as *Cinchona* alkaloid catalysts on various organic and inorganic supports.[67-69] Polymers, dendrimers, and star copolymers have been studied as supports for this purpose.[19,35,70]

For example, cross-linked polystyrene-bound DMAP has been used by Toy as a heterogeneous catalyst in addition reactions of carbon dioxide to epoxides. While recyclable, this heterogeneous catalyst required filtration and washing with CH_2Cl_2 at the end of each cycle. This washing process is solvent-intensive and time consuming. Homogeneous polymer-supported DMAP catalysts have also been synthesized. Fréchet and coworkers prepared a dendritic dialkylaminopyridine catalyst and used it in acylation reactions of tertiary alcohols.[70] In this study, the dendrimer-supported DMAP was found to be a recyclable catalyst; however, the catalyst recovery required precipitating the catalyst in methanol. In order to facilitate the separation strategy and avoid a solvent-intensive precipitation procedure, our group has prepared polymer-bound versions of DMAP using poly(*N*-isopropylacrylamide) (PNIPAM) and poly(4-*tert*-butylstyrene) (PTBS) as polymer supports as shown in Scheme 27. Both the PNIPAM-supported DMAP **51** and PTBS-supported DMAP catalyst **52** showed activity similar to that of low molecular DMAP. Both catalysts were recycled using either liquid/liquid thermomorphic or latent biphasic separation strategies. In case of catalyst **52**, the phase selective solubility of poly(4-*tert*-butylstyrene) in heptane enabled recycling for 20 cycles. As mentioned before, while offering good heptane phase selective solubility, the ability of poly(4-*tert*-butylstyrene) to be separated is limited by both the polarity and the loading of the pendant groups. Therefore, a soluble polymer support with greater selectivity that could facilitate separation of polymer-supported DMAP catalyst from product is highly desirable.

Scheme 27. Polymer-supported DMAP using poly(*N*-isopropylacrylamide) (PNIPAM) **51** or poly(4-*tert*-butylstyrene) (PTBS) **52**



51



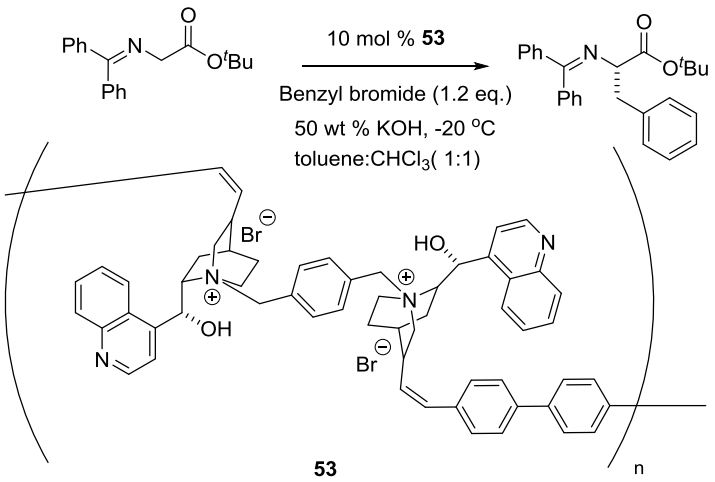
52

Cinchona alkaloids catalysts have also been immobilized on polymer supports.[71] The initial urgency for the development of polymer supported *Cinchona* alkaloid catalysts was primarily in conjunction with their use in asymmetric oxidation chemistry. However, the high cost of osmium metal along with the toxicity of osmium compounds was problematic. The polymer-supported *Cinchona* derivatives were found to bemore notable useful as recoverable catalysts for a variety of stereoselective C-C bond formations.[72] For example, Alvarez and coworkers were able to design a cross-linked polystyrene-supported *Cinchona* alkaloid catalyst and use it in asymmetric Michael reactions to obtain Michael adducts with 87% ee.[73] However, recycling experiments were not described.

Recently, Parvez reported the synthesis of *Cinchona* alkaloid-derived chiral polymers prepared by Mizoroki-Heck chemistry.[74] In this chemistry, the repetitive Mizoroki-Heck coupling reactions between the *Cinchona* alkaloid-derived dimer and diiodide afforded the chiral polymer catalyst which was used in asymmetric benzylation

reactions with high levels of enantioselectivity (95% ee) as shown in Scheme 28. In this work, the catalyst **53** demonstrated high level of catalytic activity and was recycled two times. Unfortunately, the details of recycling experiments were not provided.

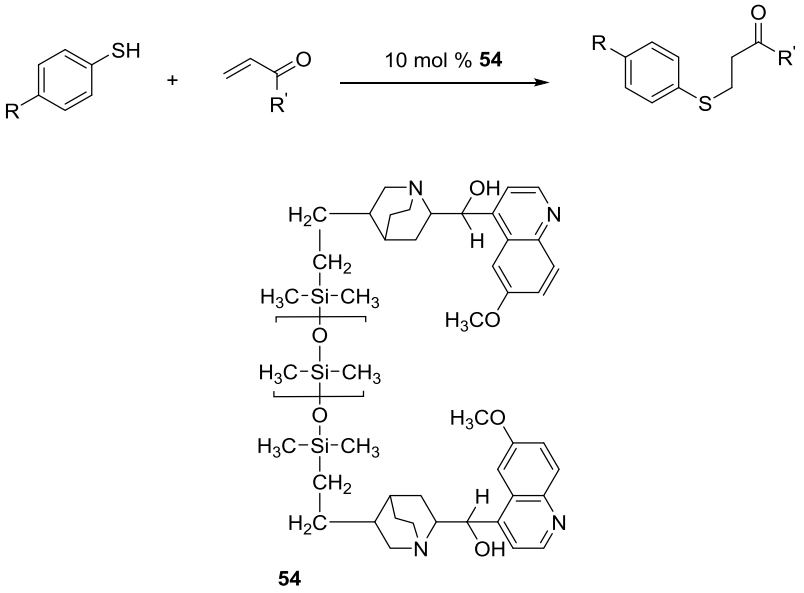
Scheme 28. Asymmetric benzylation using polymer-supported *Cinchona* alkaloid catalyst **53**



Our group has also made a polysiloxane-supported *Cinchona* derivative and has used it as a recyclable catalyst in Michael addition reactions with liquid/liquid separations to separate the catalyst and product.[75] This was an improvement over previous chemistry that required the use of solvent precipitation or membrane filtration to recover the catalysts bound to polysiloxanes.[76] In this improved chemistry, catalyst **54** was prepared and used as a recyclable Michael addition catalyst for thiol addition to α,β-

unsaturated ketones and esters as shown in Scheme 29. Using a latent biphasic separation, catalyst **54** was shown to be an effective catalyst for 5 cycles.

Scheme 29. Michael addition reaction using polysiloxane-supported *Cinchona* alkaloid catalyst **54**



54

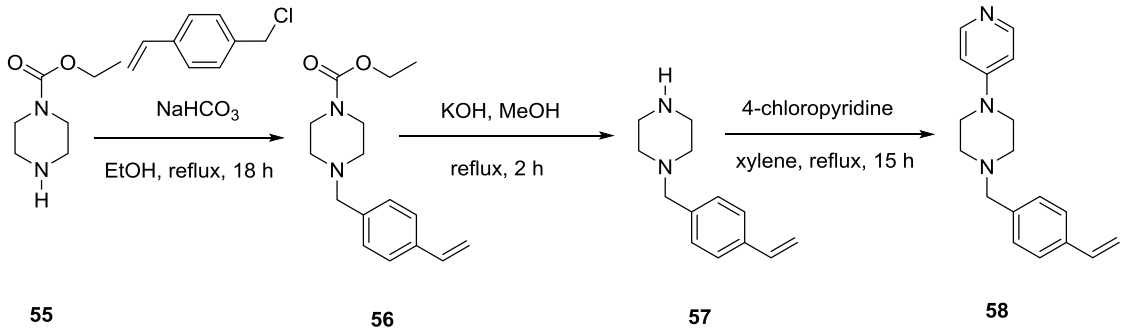
While polymer-supported DMAP and *Cinchona* alkaloids have been used as efficient catalysts for a variety of reactions, the strategies of separating the catalyst from the product at the end of reaction are still limited. Given the success of dansyl labeled poly(4-dodecylstyrene) polymers as highly phase selectively soluble supports in liquid/liquid separations, it was hypothesized that these polymers would be useful supports for DMAP and *Cinchona* alkaloid catalysts. In the work described below, polystyrene-supported quinidine, a *Cinchona* alkaloid derivative, was tested in

asymmetric Michael addition reactions using *trans*-4-methoxy-β-nitrostyrene and dimethyl fumarate as Michael acceptor. Poly(4-dodecylstyrene)-supported DMAP was also tested as a homogeneous catalyst in a variety of acylation type reactions. Both polymer-supported DMAP and *Cinchona* alkaloid catalysts were found to be recyclable using either latent biphasic or thermomorphic separation strategies. However, polymer-supported *Cinchona* alkaloid was not effective as an asymmetric catalyst.

Results and Discussion

The synthesis of poly(4-dodecylstyrene)-supported DMAP was accomplished as shown in Scheme 31.[77] In this chemistry, ethyl 1-piperazine carboxylate **55** was allowed to react with 4-chloromethylstyrene in the presence of solid sodium bicarbonate to form 1-carboxy-4-(4-vinylbenzyl) piperazine **56**. The resulting compound **56** was then deprotected in the presence of potassium hydroxide to yield (4-vinylbenzyl)piperazine **57**. Finally, compound **57** was allowed to react with 4-chloropyridine to afford DMAP analog **58** as shown in Scheme 30.

Scheme 30. Synthesis of DMAP monomer

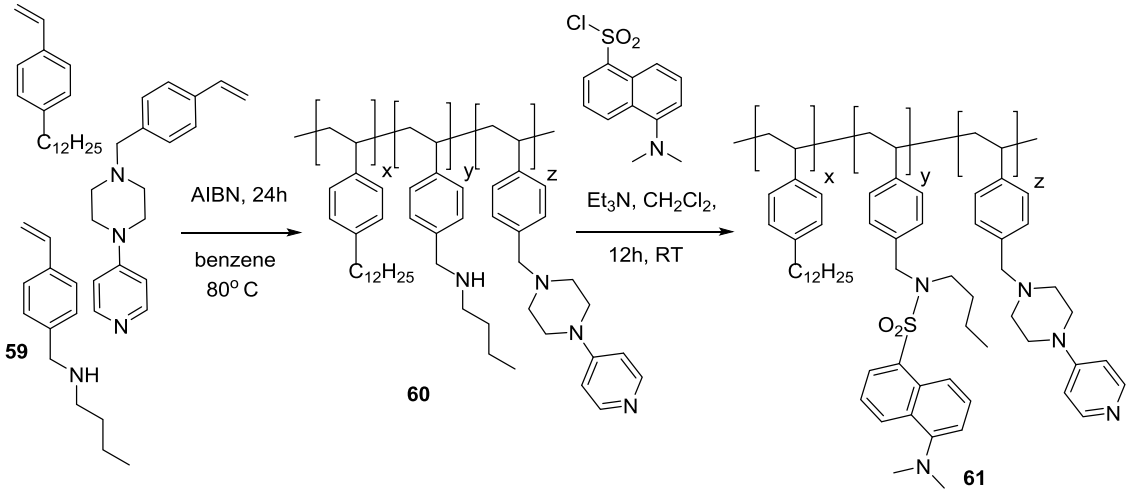


55 **56** **57** **58**

The DMAP analog **58**, vinylbenzylbutylamine **59** and 4-dodecylstyrene **24** were then copolymerized to form the poly(4-dodecylstyrene) terpolymer **60**. This poly((4-dodecylstyrene)-*c*-(DMAP)-*c*-(4-vinylbenzyl butylamine)) terpolymer was characterized by ^{1}H NMR spectroscopy and the ratio of 86:12:2 (mol:mol:mol) of the repeating units of 4-dodecylstyrene to DMAP to vinylbenzyl butylamine was determined by integrating the peaks at δ 2.47 (benzylic protons of 4-dodecylstyrene), δ 3.41 (benzylic protons of DMAP) and δ 3.67 (benzylic protons of 4-vinylbenzyl butylamine).

The synthesis of poly(4-dodecylstyrene)-supported DMAP catalyst was designed so that the catalyst would contain a fluorescent label. This was done so that the extent of the leaching of the polymer **61** could be monitored. This was accomplished by allowing the poly(4-dodecylstyrene)-supported DMAP catalyst **60** to react with dansyl chloride to form the fluorescently labeled terpolymer **61** as shown in Scheme 31. This terpolymer was designed to be an effective organocatalyst in a variety of acylation reactions using a monophasic solvent system that could be perturbed after reaction completion to form a biphasic liquid/liquid mixture. When using heptane as the nonpolar solvent, it was expected that the catalyst could be quantitatively recovered in this phase. If necessary, the product could also be extracted with a second polar solvent from the mixture containing **61**. In either case, the extent of the catalyst leaching could be determined by fluorescence spectroscopy.

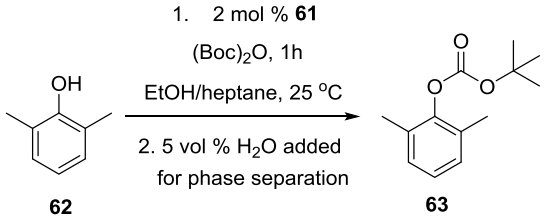
Scheme 31. Synthesis of poly(4-dodecylstyrene)-supported DMAP catalyst **61**[*]



After synthesis of the poly(4-dodecylstyrene)-supported DMAP **61**, its utility and recyclability were examined in acylation of 2,6-dimethylphenol **62** by Boc anhydride (Scheme 32). In this chemistry, 2 mol % of **61** was used to carry out synthesis of the Boc derivative of phenol in a monophasic heptane/ethanol solution.

[*] Khamatnurova, T. V.; Bergbreiter, D. E. *Polym. Chem.* **2013**, *4*, 1617. Reproduced by permission of The Royal Society of Chemistry.
http://pubs.rsc.org/en/content/articlelanding/2012/py/c2py20922e#!divAbstract

Scheme 32. Acylation of 2,6-dimethylphenol **62** with Boc anhydride using poly(4-dodecylstyrene)-supported DMAP **61**



The reaction could be monitored by the emission of CO_2 gas. When the evolution of CO_2 gas ceased, it was assumed that the reaction was complete and $(Boc)_2O$ was consumed. After the reaction was complete, 5 vol % of water was added to perturb the system. This water addition produced a biphasic heptane/ethanol mixture. The ethanol-rich product phase containing the Boc derivative of phenol **63** was separated from the heptane-rich phase containing the polymer-supported DMAP catalyst **61**. An ethanol solution of 2,6-dimethylphenol and $(Boc)_2O$ was added to the heptane solution containing **61** to effect another acylation reaction cycle. The poly(4-dodecylstyrene)-supported DMAP catalyst **61** was recycled twenty times. The ethanol phases from each of these cycles were combined and the acylated phenol **63** was isolated from this combined product mixture. The average yield of **63** was 91% per cycle.

The extent of leaching of **61** was analyzed in two ways. Qualitative visual analysis showed that the fluorescently-labeled **61** was not visually present in the ethanol-rich product phase as shown in Figure 15. The absence of leaching of **61** was

subsequently measured quantitatively by fluorescence spectroscopy. That analysis showed that an average of 0.09% of **61** per cycle leached into the ethanol-rich phase.

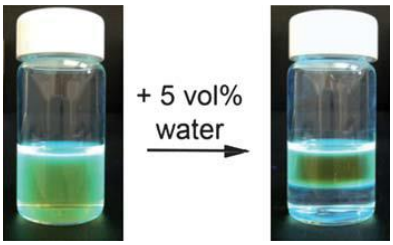
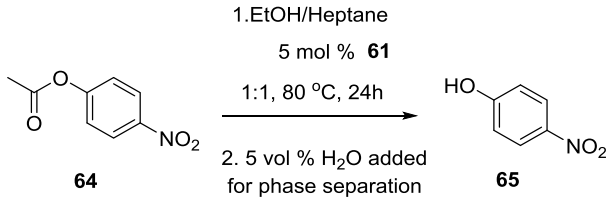


Figure 15. Photograph of the fluorescently-labeled poly(4-dodecylstyrene)-supported catalyst **61** in (a) a monophasic mixture of heptane-EtOH containing the polymeric **61** and the product **63** after Boc-protection of phenol or, (b) after addition of 5 vol % water to induce biphasic separation of **61** into the less dense heptane-rich phase

Next, I tested the utility of **61** as a transesterification catalyst using an ethanol-heptane biphasic solvent mixture at 80 ^{o}C as shown in Scheme 33. In this case, 5 mol % loading of organocatalyst, poly(4-dodecylstyrene)supported DMAP **61** was again recycled by cooling the reaction mixture to room temperature and adding 5 vol % of water to produce a biphasic mixture. The ethanol-rich phase containing 4-nitrophenol **65**

Scheme 33. Transesterification of 4-nitrophenyl acetate **64** using poly(4-dodecylstyrene)-supported DMAP catalyst **61**

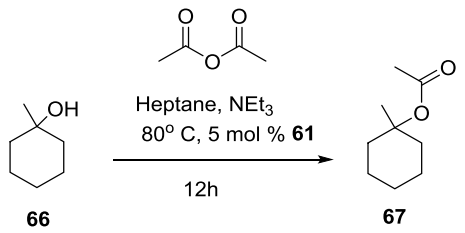


64 **65**

was separated from the heptane phase containing **61**. Subsequent cycles where **61** was used in successive transesterification reactions were carried out by adding fresh ethanol and 4-nitrophenyl acetate to the recovered heptane phase containing **61**. The poly(4-dodecylstyrene)-supported DMAP catalyst **61** was recycled twenty times with no loss of catalytic activity with an average isolated product yield of 92% per cycle (from the combined EtOH phases of all 20 cycles (*vide infra*)). Fluorescence analysis of the product phase showed that the catalyst leaching was only 0.002% of the charged catalyst. During these recycling studies, it was observed that the activity of **61** decreased in some reactions. It is believed that protonation of **61** by the relatively acidic 4-nitrophenol **65** product could deactivate the polymeric catalyst. When this problem arose, **61** could be reactivated by adding an ethanol solution of triethylamine to the heptane solution containing **61**. Subsequent addition of 5 vol % of water to the monophasic mixture induced a phase separation and the heptane phase yielded a regenerated polymeric catalyst **61**. The catalyst poly(4-dodecylstyrene)-supported DMAP regenerated in this fashion was equivalent in reactivity to the original **61** in further cycles of transesterification chemistry.

Next, I investigated the catalytic activity of **61** in acylation of a tertiary alcohol. In this chemistry, 1-methylcyclohexanol was allowed to react with acetic anhydride in the presence of auxiliary base and 5 mol % of **61** as shown in Scheme 34. The reaction

Scheme 34. Acylation of 1-methylcyclohexanol **66** with acetic anhydride using poly(4-dodecylstyrene)-supported DMAP catalyst **61**

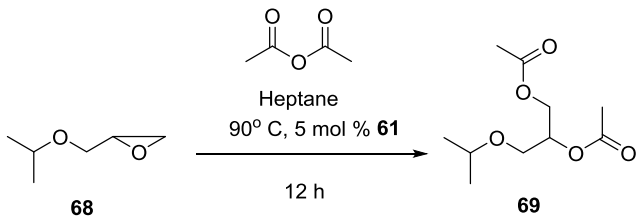


66 **67**

was carried out in 3 mL of heptane at 80 ^{o}C for 12 h. After cooling to room temperature, 3 mL of acetonitrile was added to extract the ester product **67** from the heptane phase containing **61**. The heptane phase containing the catalyst **61** was allowed to react with fresh substrate in a subsequent cycle. The catalyst was recycled twelve times with no loss of catalytic activity. The average isolated yield of **67** after removal of acetonitrile was determined to be 90% per cycle. The quantitative fluorescence analysis showed that only 0.015% of the catalyst leached into the acetonitrile phase.

A final reaction used to test the utility and recyclability of poly(4-dodecylstyrene)-supported DMAP catalyst **61** was the catalytic ring-opening of glycidyl isopropyl ether shown in Scheme 35. In this chemistry, glycidyl isopropyl ether was allowed to react with acetic anhydride in heptane at 90 ^{o}C for 12 h to form a diester **69**.

Scheme 35. Ring-opening of glycidyl isopropyl ether **68** using poly(4-dodecylstyrene)-supported DMAP catalyst **61**



When a reaction cycle was complete, the acetonitrile phase containing the product was separated from the heptane phase containing **61**. Each subsequent cycle was effected by adding fresh glycidyl ether to the heptane solution containing **61**. Eight cycles were carried out and the average isolated yield of diacetate product was 87% per cycle. Fluorescence analysis of the product phase for dansyl showed that the catalyst leaching was 0.005%.

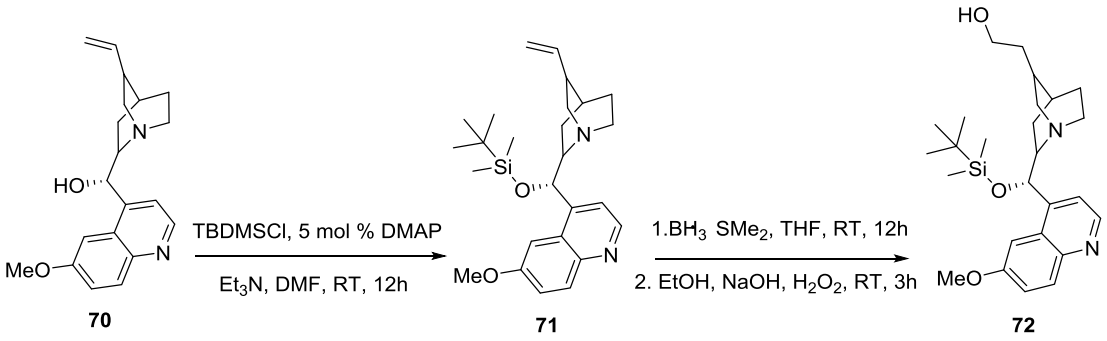
Based on the results shown above, excellent recyclability was obtained when poly(4-dodecylstyrene)-supported DMAP was used as a nucleophilic catalyst. Although the formation of an acidic environment could cause adventitious protonation of DMAP as was seen in the catalysis of 4-nitrophenyl acetate, washing the solution with triethylamine easily regenerated the catalyst without loss of catalytic activity.

I then turned my attention to the use of poly(4-alkylstyrene) supports for *Cinchona* alkaloid catalysts and investigated these catalysts' utility and recyclability in Michael addition reactions using liquid/liquid biphasic separation strategies. For these

studies, I selected quinidine, a *Cinchona* alkaloid derivative, as an organocatalyst to be immobilized on the poly(4-alkylstyrene) support.

Quinidine is equipped with a vinyl group, which is susceptible to chemical transformations and has been used as a chemical handle to attach these alkaloids to supports. I used several modifications of the quinidine ligand to facilitate its immobilization on a poly(4-alkylstyrene) polymer. Preparation of the desired *Cinchona* alkaloid catalyst began with a protection step as shown in Scheme 36.

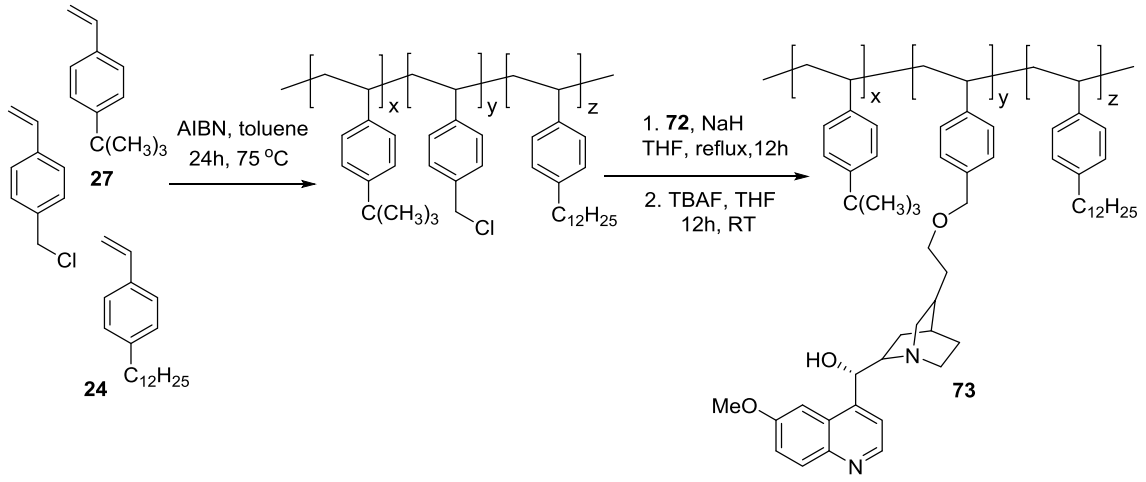
Scheme 36. Synthesis of *Cinchona* alkaloid **70**



In this chemistry, a bulky *tert*-butyldimethylsilyl chloride (TBDMSCl) was used to protect the hydroxyl group on quinidine **70** using 5 mol % of DMAP as a catalyst. The resulting protected quinidine **71** could then undergo a hydroboration reaction in the presence of $BH_3.SMe_2$ compound followed by the addition of EtOH, 4N of aqueous sodium hydroxide and hydrogen peroxide to give a hydroxyl-substituted quinidine **72**. Once the ligand **72** was prepared, it was attached to a poly(4-alkylstyrene) support using

the same type of post-polymerization modification described earlier in dye immobilizations from Chapter II. To use this chemistry to immobilize **72,** a terpolymer was prepared containing 4-dodecylstyrene **24**, 4-*tert*-butylstyrene and 4-chloromethylstyrene as shown in Scheme 37. Attachment of quinidine ligand **72** onto the polymer support then afforded a heptane soluble poly(4-alkylstyrene)-supported *Cinchona* alkaloid derivative. The resulting polymer-supported catalyst was then allowed to react with tetra-*n*-butylammonium fluoride (TBAF) to remove the silyl ether protecting group and to regenerate the hydroxyl group in polymer-supported quinidine **73** that was tested as a catalyst in Michael addition reactions. Regeneration of the hydroxyl group is essential to the catalysis since it engages in hydrogen bonding with the electrophile, hence increasing the reactivity and orienting it for nucleophilic addition.

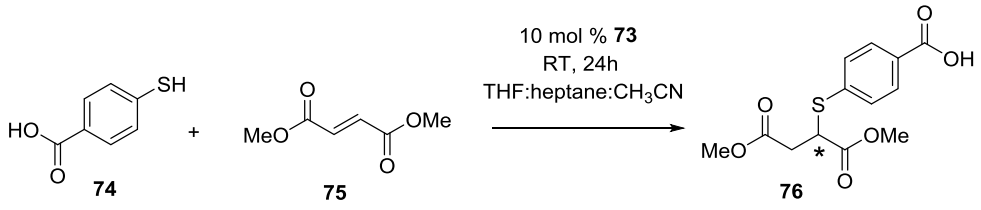
Scheme 37. Synthesis of poly(4-alkylstyrene)-supported *Cinchona* alkaloid derivative **73**



This poly((4-*tert*-butylstyrene)-*c*-(quinidine)-*c*-(4-dodecylstyrene)) terpolymer **73** was characterized by GPC and ^{1}H NMR spectroscopy and the ratio of 91:3:6 (mol:mol:mol) of the repeating units on the polymer chain was determined by integrating the peaks at δ 2.47 (benzylic protons of 4-dodecylstyrene), δ 8.75 (a proton next to the nitrogen atom on naphthyl group of quinidine). The molecular weight of the terpolymer **73** was determined to be 23 kDa with a PDI of 2.1.

Next, the catalytic activity and recyclability of poly((4-*tert*-butylstyrene)-*c*-(quinidine)-*c*-(4-dodecylstyrene)) terpolymer **73** was examined in Michael addition reactions using 4-mercaptobenzoic acid **74** as the Michael donor and dimethyl fumarate **75** as the Michael acceptor to form a Michael adduct **76** as shown in Scheme 38.

Scheme 38. Synthesis of Michael adduct **76** using poly(4-alkylstyrene)supported quinidine **73**



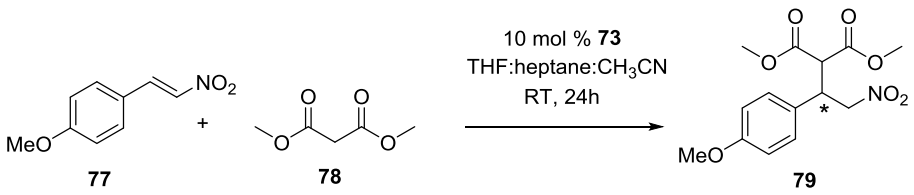
Initially, the conventional biphasic heptane-ethanol solvent mixture was selected to carry out the reaction. Testing the starting materials in the heptane-ethanol solvent mixture revealed that these substrates exhibit poor solubility in this solvent combination at room temperature, which would preclude homogeneous catalysis. A solution to this

problem was to use modified latent biphasic solvent mixture. A combination of three solvents THF:heptane:acetonitrile (3:1:1) yielded a monophasic solution mixture, which allowed for homogeneous catalysis to occur. Adding 5 vol % of water to this solvent mixture induced biphasic separation, which allowed for isolation of the polymer-supported catalyst from products at the end of the reaction. The ternary (THF:heptane:acetonitrile) solvent system that was found successfully dissolved the substrates and was discovered to be an excellent replacement for the heptane-ethanol biphasic mixture more often used by Bergbreiter's group. The Michael addition reaction was carried out for 24 h using 10 mol % of polymer-supported quinidine catalyst **73** in the aforementioned solvent mixture. After the reaction was complete, 5 vol % of water was added to the reaction mixture to perturb the system and induce biphasic separation. The THF-acetonitrile phase containing the product was removed from the heptane phase containing the polymer-supported quinidine catalyst **73**. Recycling of the catalyst was performed four times and the average isolated yield of the product for four cycles was determined to be 88%. The product from the first cycle was analyzed by high-performance liquid chromatography (HPLC) using a Chiralpak AD column and hexanes/isopropyl alcohol (60:40) as a solvent and was found to be achiral. The lack of enantioselectivity in this system is an obvious problem that has to be addressed in future work if these catalysts are to be useful. One of the possible approaches to achieve more acceptable enantioselectivity is to change the solvent from the ternary (THF:heptane:acetonitrile) mixture to THF or toluene. If this scenario is used, the separation of the polymer-supported *Cinchona* alkaloid catalyst **73** from Michael

addition products would require removing THF or toluene solvent at the end of the reaction. Next, adding a latent biphasic solvent mixture such as heptane/acetonitrile would be necessary so that the heptane soluble polymer-supported catalyst could be separated from the acetonitrile soluble Michael addition product. The recycling of the catalyst would require removing heptane solvent and redissolving the polymer-supported *Cinchona* alkaloid catalyst in THF or toluene for further reactions. This method of catalysis might improve the enantioselectivity but this would occur at the expense of a facile separation procedure. Another approach would be to incorporate a longer spacer between the polymer backbone and the quinidine catalytic site. In this scenario, the chiral moiety of the catalyst would be at a further distance from the polymeric matrix and more easily accessible for substrates; this allows for the immobilized catalyst to essentially perform comparably to a low molecular weight catalyst.

The second reaction that was used to test the utility of the poly(4-alkylstyrene)-supported quinidine catalyst **73** was a Michael addition reaction using *trans*-4-methoxy-β-nitrostyrene **77** as a Michael acceptor and dimethyl malonate **78** as Michael donor to afford Michael product **79** as shown in Scheme 39. Nitroalkenes such as *trans*-4-methoxy-β-nitrostyrene are commonly used as Michael acceptors in the field of organocatalysis because of their high electrophilicity originating from the strong electron-withdrawing and hydrogen bonding ability of the nitro group.[78] The ease of transformation of the nitro functionality into an amine or a carboxylic acid moiety provides potential for the synthesis of a wide range of compounds, which is important for synthetic chemists.

Scheme 39. Synthesis of Michael adduct **79** using poly(4-alkylstyrene)supported quinidine **73**



Based on the literature, THF and toluene were observed to be the optimal solvents for Michael addition reactions and are solvents that can be used to form products with good enantioselectivity.[79] However, in order to facilitate facile separation and recycling of the catalyst **73,** THF could not be used alone. Thus the modified latent biphasic solvent system containing THF-heptane-acetonitrile was selected as a solvent mixture to carry out the catalysis. In this case, the substrates were first dissolved in 3 mL of THF, then 1 mL of heptane solution containing the polymer-supported catalyst **73** and 1 mL acetonitrile were added. The reaction was allowed to run for 24 h at room temperature. After the reaction was complete, 5 vol % of water was added to the reaction solution to induce biphasic separation. The THF-acetonitrile phase containing the products could be separated from the heptane phase containing the catalyst **73**. A THF-acetonitrile phase containing fresh substrates was added to the heptane phase containing the catalyst **73** to effect a subsequent catalytic cycle. The polymer-supported quinidine catalyst **73** was recycled four times. The average isolated yield of the product after recrystallization in

methanol was determined to be 83% per cycle. Unfortunately, the HPLC analysis of the product from the first reaction cycle revealed that it too was achiral.

The absence of enantioselectivity could be attributed to several factors. As noted above, temperature is a parameter that can affect enantiselectivity, and it is common practice to lower the temperature in order to promote enantioselectivity. However, when an experiment was performed with 10 mol % of low molecular weight quinidine catalyst using a THF:heptane:acetonitrile solvent mixture at -20 ^{o}C, a dramatic decrease in conversion rate was observed: after 48 h only 15% of product formed. From this result it was evident that lowering the temperature would not be a practical way to recycle the polymer-supported quinidine catalyst. Secondly, solvent could also affect the enantioselective outcome. In the case of nitrostyrene **77** and dimethyl malonate **78**, toluene is the optimal solvent to use to obtain high enantioselectivity, whereas either acetonitrile or MeOH gives very poor (< 2%) enantioselectivity.[80] In order to facilitate biphasic separation at the end of the reaction, a combination of three solvents such as THF, heptane and acetonitrile had to be used, which could have contributed to the loss of enantioselectivity. This issue could be addressed by replacing a ternary THF:heptane:acetonitrile solvent mixture with a single solvent such as THF or toluene as was described earlier. However, carrying out recycling in a single solvent would affect the separation strategy. Lastly, the enantioselective outcome can be dramatically minimized if there is an inappropriate distance between the catalytic active site and the backbone of the polymer. Commonly, lengthy spacers or linkers containing five or more

carbons are used to extend the distance between the polymer backbone and the catalyst in other polystyrene-supported catalysts.[73]

While studying the recycling of polymer-supported catalyst **73** in the reaction to form Michael adduct **79**, it was also noted that the conversion decreased (~ 90%) for the fourth cycle. The decrease in conversion during recycling could be attributed to the catalyst acting as a polymerization initiator and therefore precluding the catalysis as was described by Barbas.[81] In his study, the Michael addition reaction of β-nitrostyrene with cyclohexanone in the presence of a catalytic proline derivative gave a solid polymerization by-product. He hypothesized that the anion intermediate derived from the addition of the amine catalyst to β-nitrostyrene is not stabilized and can initiate a polymerization, which would contribute to poor yields and enantioselectivity.

Conclusions

The recovery and recyclability of nucleophilic catalysts such as dimethylaminopyridine (DMAP) **61** and quinidine **73** can be facilitated with the use of soluble poly(4-alkylstyrene) supports as phase anchors for such ligands/catalysts. Using poly(4-alkylstyrene)-supported DMAP **61**, a variety of reactions including formation of Boc esters of phenols, acylation of hindered alcohols, acylation of hindered epoxides and transesterification of 4-nitrophenyl acetate were performed. Catalyst recyclability was monitored by incorporating dansyl groups into these polymer-bound catalysts and was consistently very high in a variety of recycling strategies where the soluble polymer-supported DMAP was separated from products using biphasic liquid/liquid separations. Poly(4-alkylstyrene) polymers containing 4-dodecyl groups were also prepared and used

as supports to immobilize quinidine, a *Cinchona* alkaloid derivative. In this case, the polymer-supported organocatalyst was tried in several asymmetric Michael addition reactions; however, only a moderate recyclability was observed with absolute loss of enantioselectivity.

These studies suggest that highly phase selectively soluble poly(4-alkylstyrene) polymers provide a class of efficient recyclable polymer supports when biphasic liquid/liquid separation strategies are utilized. They should have broad versatility as polymer supports for other catalyst when a biphasic nonpolar/polar solvent separation step is used to recover a homogeneous catalyst.

CHAPTER IV

APPLICATIONS OF POLYSTYRENE-SUPPORTED PHOSPHINE LIGATED Pd(0) CATALYST

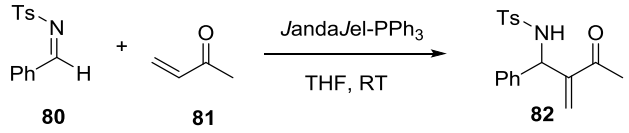
Introduction

The development of phosphine ligands has had a tremendous impact in palladium catalyzed chemistry including Sonogashira, Negishi, Kumada, Sizuki, and Heck cross-coupling reactions.[82-85]. These palladium catalyzed reactions, especially the Buchwald-Hartwig amination and the Suzuki-Miyaura cross-coupling reactions, have become common methods for the synthesis of aromatic amines, biphenyl derivatives and conductive polymers.[87-89] While other types of ligands can be used, the most common type of ligands for the Pd catalysts used in this chemistry are phosphine ligands. Since steric and electronic properties of phosphine ligands can be adjusted by modifying the structure of the alkyl or aryl groups on the phosphorus, fine-tuning of the ligand is possible allowing for selectively enhanced properties of the phosphine-metal complex. For example, by using sterically hindered phosphine ligands in conjunction with the metal source gives the access to highly active palladium complexes that increase the efficiency of various C-C and C-N couplings. However, the drawback of using these ligands is that they, like the Pd catalyst, need to be separated from the cross-coupling products after the reaction. This is in part because the toxicity of phosphine ligands or phosphine oxide byproducts can also pose health concerns.[90] Separation and recovery of

these ligands is also important in many cases because the ligands themselves are expensive.

These "green" chemistry issues led to the development of recovery strategies that facilitate product purification after reactions that use phosphine ligands as reagents or ligands for catalysts. These recovery strategies have used both soluble and insoluble polymer supports. For example, Toy and co-workers prepared insoluble polystyrene-supported triphenylphosphine and studied its catalytic activity in aza-Morita-Baylis-Hillman reaction[91] as shown in Scheme 40. In this chemistry, *J*anda*J*el-supported phosphine ligands were prepared at different loading ratios of phosphines (0.5, 1.5, and 3.2 $mmolg^{-1}$ of PPh_3) and examined in an aza-Baylis- Hillman reaction using *N*-benzylidene-4-methylbenzenesulfonamide **80** and methyl vinyl ketone **81** to form product **82**. The authors reused the catalyst multiple times to demonstrate recyclability.

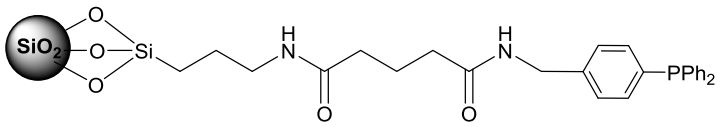
Scheme 40. Aza-Morita-Baylis-Hollman reaction using cross-linked polystryrene-supported phosphine ligand



Cross-linked polystyrene-supported phosphines have also been used in countless cases to prepare insoluble polymer bound versions of conventional homogeneous catalysts. These cases have included both simple phosphine ligated palladium complexes as well as Pd catalysts that use highly designed phosphine ligands.[92,93] For example, Buchwald and coworkers prepared Merrifield resin-supported hindered phosphine ligands and used them in palladium catalyzed amination and Suzuki cross-coupling reactions.[94] In this work, a resin-supported electron-rich phosphine ligand was prepared by reacting 2-dicyclohexylphosphino-2'-hydroxybiphenyl with Merrifield resin in the presence of sodium hydride. The polymer-supported ligand was used to form a ligand-palladium complex with $Pd(OAc)_2$ and was characterized by gel phase ^{31}P NMR spectroscopy and by phosphorus elemental analysis. This complex was successfully used at 2 mol % catalyst loading in palladium catalyzed Suzuki cross-coupling reactions with primary and secondary cyclic and acyclic amines and anilines with various activated and deactivated aryl halides. The catalyst was recycled multiple times. However, by the fourth cycle, the catalyst activity typically decreased. For example, in a reaction of bromobenzene and boronic acid that contained 2 mol % of the catalyst, conversion of bromobenzene to aryl boronic acid was complete in 24 h for cycle 1-3, but required 87 h in cycle 4. This loss in activity may be due to adventitious catalyst decomposition during the reaction.

Silica has also been widely used as an insoluble support for phosphine ligands. For example, Chen and coworkers prepared the silica-supported triaryl phosphine ligand **83** as shown in Scheme 41 and used it in Suzuki-Miyaura cross-coupling reactions.[95]

Scheme 41. Silica-supported phosphine ligand **83**



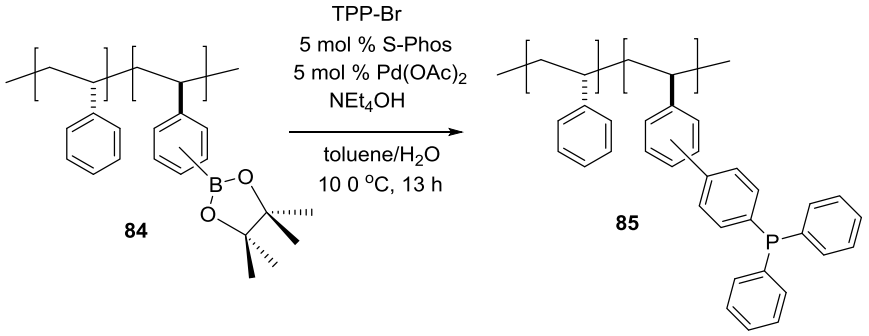
83

The chemistry involved in the synthesis of **83** is commonly utolized to prepare silica-supported phosphine ligands. In contrast to the chemistry used by Buchwald with cross-linked polystyrene resins where the resin contains a functional group for phosphine ligand attachment, silica has to first be functionalized. In the case of **83**, this aminopropyl functionalized silica gel was prepared by allowing silica gel to react with 3-aminopropyltriethoxysilane in refluxing toluene for 20 h. The resulting amino functionalized silica gel was subsequently allowed to react with glutaric anhydride in dichloromethane to form a carboxylic acid functionalized silica gel. Amide formation was then effected using a triarylphosphine containing a benzyl amine group. In this way the desired silica immobilized triarylphosphine ligand was formed. This supported phosphine ligand was then used to form a palladium complex with $Pd(OAc)_2$ that contained 0.118 mmol of Pd/g based on inductively coupled plasma atomic emission spectrometry (ICP-AES) and X-ray Diffraction (XRD) analysis that showed peaks corresponding to the typical structure of palladium particles. This catalyst was successfully used in cross-coupling chemistry with phenylboronic acids and 4-bromoanisole. Recycling involved separating the insoluble catalyst and product solution at the end of the reaction. Subsequent addition of fresh substrate allowed the catalyst to

be reused up to 10 times. Palladium leaching was analyzed by ICP-MS analysis and was discovered to be less than 0.3 ppm.

Soluble polymers such as linear polystyrene have also received attention as supports for catalysts. The Bae group synthesized linear syndiotactic polystyrene-supported triarylphosphine **85** and used it in palladium catalyzed Suzuki-Miyaura cross-coupling reactions.[96]

Scheme 42. Linear syndiotactic polystyrene supported triarylphosphine **85**

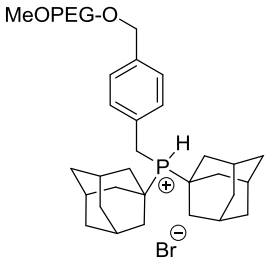


In this case, the syndiotactic linear polystyrene-supported phosphine ligand was synthesized using the Suzuki-Miyaura coupling reaction of (4-bromophenyl)diphenylphosphine (TPP-Br) and boron-functionalized polystyrene **84** as shown in Scheme 42. The polymer-supported ligand was characterized by ^{1}H and ^{31}P NMR spectroscopy and the phosphine loading was determined to be 0.71 mmol g^{-1}. The utility and recyclability of this ligand was examined in palladium-catalyzed Suzuki-Miyaura cross-coupling reactions of aryl halides and aryl boronic acid. The catalyst was

recycled five times; however, the conversion dramatically decreased to 66% for the fifth cycle. The catalyst was recovered by solvent-precipitation in methanol. Leaching studies were carried out by ICP-MS analysis and it was determined that an average of 46 ppm of palladium leached in each cycle.

While there are many examples of insoluble polymer-supported phosphine ligands for catalysis, there are limited studies where soluble polymers were used as phase handles to support phosphine reagents or catalysts during a homogeneous reaction with a biphasic separation.[3] One study where soluble PEG was used as a catalyst support was done by Plenio's group. PEG has a long history as a soluble polymer support. This polymer and its derivatives has the advantage of good solubility in many polar solvents such as DMF and EtOH and is typically recovered by solvent precipitation in diethyl ether. However, in Plenio's work biphasic conditions such as a DMSO/heptane solvent medium were used to separate PEG-supported phosphine ligand **86** that was used in palladium-mediated catalysis to form a Suzuki cross-coupling product.[97] This biphasic strategy avoids the solvent-intensive precipitation process and is considered a greener alternative to solvent precipitation.

Scheme 43. PEG-supported phosphine ligand **86**

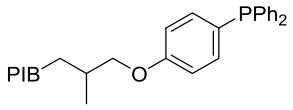


86

This recyclable PEG-supported ligand **86** was successfully used in cross-coupling reactions of aryl bromides and aryl boronic acids and exhibited high phase selective solubility (> 99.5%) in the DMSO phase of a DMSO/heptane solvent mixture.

Our group has also prepared PIB-supported triphenylphosphines such as **87** that can be useful as recyclable ligands,[98] reagents in aza-Wittig and Mitsunobu reactions,[99] and as additive ligands in carbon-carbon cross-coupling reactions using a palladium colloidal catalyst.[100] Biphasic solvent separation strategies are utilized in these examples. High phase selective solubility in the heptane phase allows PIB-bound phosphines and any phosphine oxide by-products to be easily separated from products by a liquid/liquid separation.

Scheme 44. PIB-supported phosphine ligand **87**



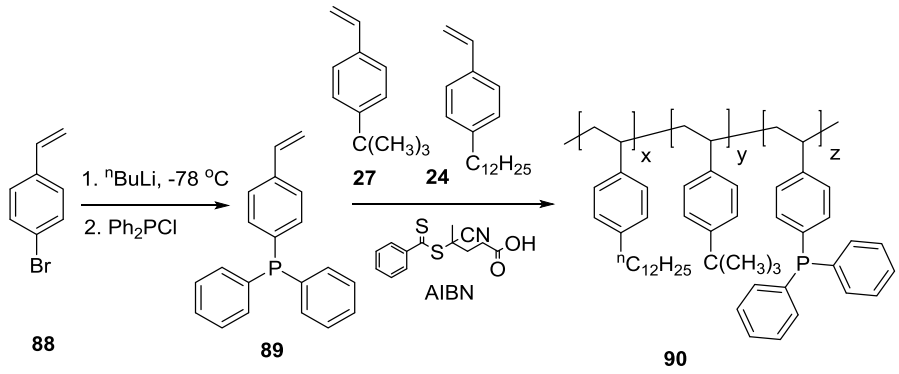
87

Given the success of poly(4-alkylstyrene) supports in separations and recycling of organocatalysts as well as the fact that hindered phosphines have previously been supported on cross-linked polystyrene, I examined the utility of poly(4-alkylstyrene) supports as tools to facilitate catalysis with phosphine-ligated Pd catalysts. The discussion below shows that both a simple triphenylphosphine ligand and a more hindered phosphine ligand can be immobilized on these polymers and that the Pd catalysts formed with these ligands are effective in catalysis.

Results and Discussion

In order to synthesize poly(4-*tert*-butylstyrene)-*co*-(4-dodecylstyrene)-supported phosphine ligands for palladium mediated cross-coupling reactions, I first prepared a simple triphenylphosphine analog. This involved the synthesis of diphenylstyrylphosphine monomer that could be used to prepare copolymers with 4-alkylstyrene as described in Chapter II. The monomer **89** was prepared by the reaction of 4-bromostyrene **88** with ^{n}BuLi at –78 ^{o}C followed by the addition of chlorodiphenylphosphine as shown in Scheme 43. The presence of the single peak in ^{31}P NMR at –6 ppm indicated the formation of **89**. The diphenylstryrylphosphine **89** was then copolymerized with 4-dodecylstyrene **24** and 4-*tert*-butylstyrene **27** to form the terpolymer **90**.

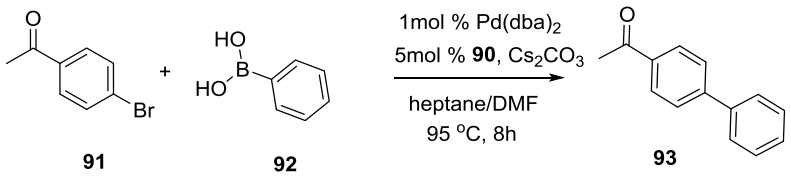
Scheme 45. Preparation of poly(4-alkylstyrene)-supported phosphine ligand **90**



The terpolymer **90** was characterized by ^{1}H NMR spectroscopy and GPC, and contained 12 mol % triphenylphosphine groups based on ^{1}H NMR spectroscopy analysis of the relative peaks at δ 2.47 for the benzylic protons of the 4-dodecylstyrene groups and at δ 7.37 for the biphenyl protons of the diphenylstyrylphosphine. The molecular weight of the terpolymer **90** was determined to be 17 kDa with a PDI of 1.2.

While the synthesis of the polymer was successful, the goal of this work was to use **90** as a ligand in homogeneous catalysis. For this chemistry, I prepared a Pd catalyst by reaction of **90** with $Pd(dba)_2$ and used the resulting complex to effect the Suzuki coupling of the activated aryl bromide **91** with phenylboronic acid **92** using cesium carbonate as a base. This reaction afforded the cross-coupling product **93** as shown in Scheme 44. Using a heptane/DMF mixture (2 mL:2 mL) at 95 ^{o}C, the reaction was monophasic. In a typical experiment, 5 mol % of the polymer-bound phosphine ligand was premixed with a 1mol % of $Pd(dba)_2$ in heptane at 95 ^{o}C for 1 h.

Scheme 46. Cross-coupling using poly(4-alkylstyrene)-supported phosphine ligand **90**



91 **92** **93**

Next, a solution of substrates and a base in DMF phase was added. After the reaction was complete, the reaction mixture was cooled and the solvent mixture separated into two phases. The lower DMF phase containing products was separated from the heptane phase containing **90** by forced siphon, and the residual heptane-rich phase containing the catalyst was recycled by addition of fresh substrate in DMF as shown in Figure 16.

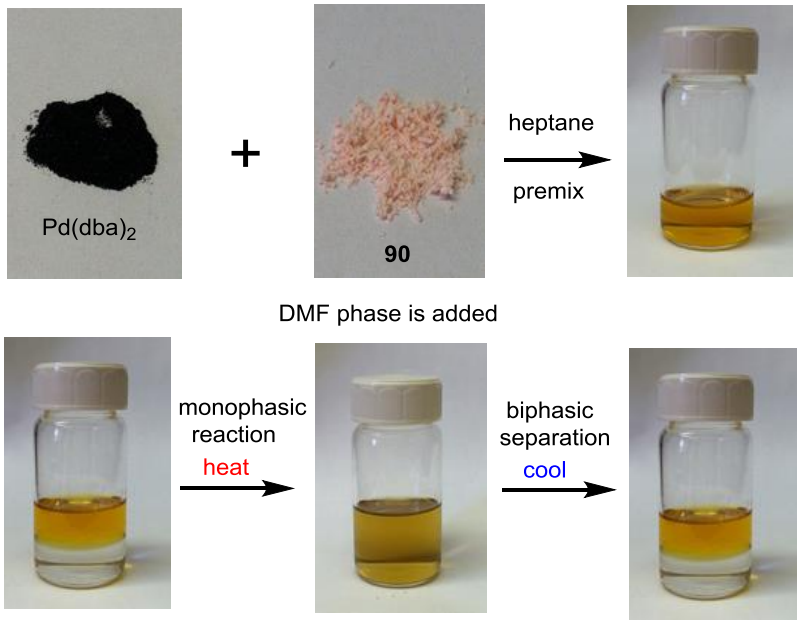


Figure 16. General scheme for biphasic homogeneous catalysis with a liquid/liquid biphasic catalyst/product separation using polymer-supported phosphine ligand **90**

The polymer-supported phosphine **90** was recycled for four cycles without the addition of palladium source. ICP-MS analysis of the DMF phase showed that the Pd content in the product-containing phase decreased with each subsequent cycle as shown in Table 1. This result can be attributed to the fact that initially lower molecular weight polymer chains containing the supported catalyst can leach into the polar DMF phase, but as the recycling progressed, the amount of shorter polymer chains decreased and the therefore the Pd content decreased as well. Table 1 also shows there was an increase in product yield with each cycle. This can be explained by the fact that the product initially partitions into the nonpolar heptane phase so the isolated yields of the product are lower in the first cycles. As recycling continued, the heptane phase became saturated with product and thus the product yield increased.

Table 1. ICP-MS leaching studies for cross-coupling reaction using **90**

cycle	yield (%)[a]	ppm
1	87	7.6
2	92	5.6
3	94	5.3
4	97	4.4

[a] Isolated yields

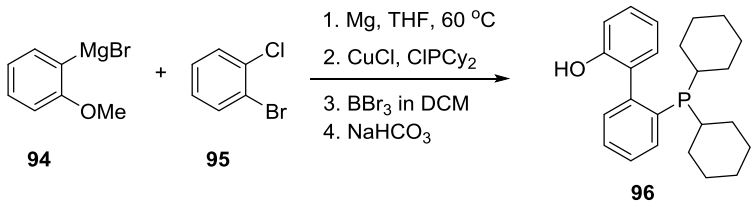
Next, the utility of polystyrene-supported **90** in palladium mediated Buchwald-Hartwig amination reaction using aryl bromide and morpholine was examined. Unfortunately, even after 48 h there was only 10% conversion of the product. This was

not surprising. Aryl amination typically proceeds well when more hindered phosphine ligands are used.

Buchwald's various dialkylbiarylphosphines such as RuPhos, XPhos, BrettPhos, and SPhos are among the most active ligands for Pd-catalyzed amination and Suzuki couplings. These ligands have several useful properties: they are electron-rich, good sigma donors, and sterically bulky. The first property, electron-richness, is advantageous because it enhances the rate of both the oxidative addition and reductive elimination processes in the catalytic cycle. Since these ligands are also sterically bulky, they assist in increasing the concentration of vacant coordination sites of Pd complexes. Both factors increase the reactivity of otherwise unreactive aryl halides toward the Pd catalyst.

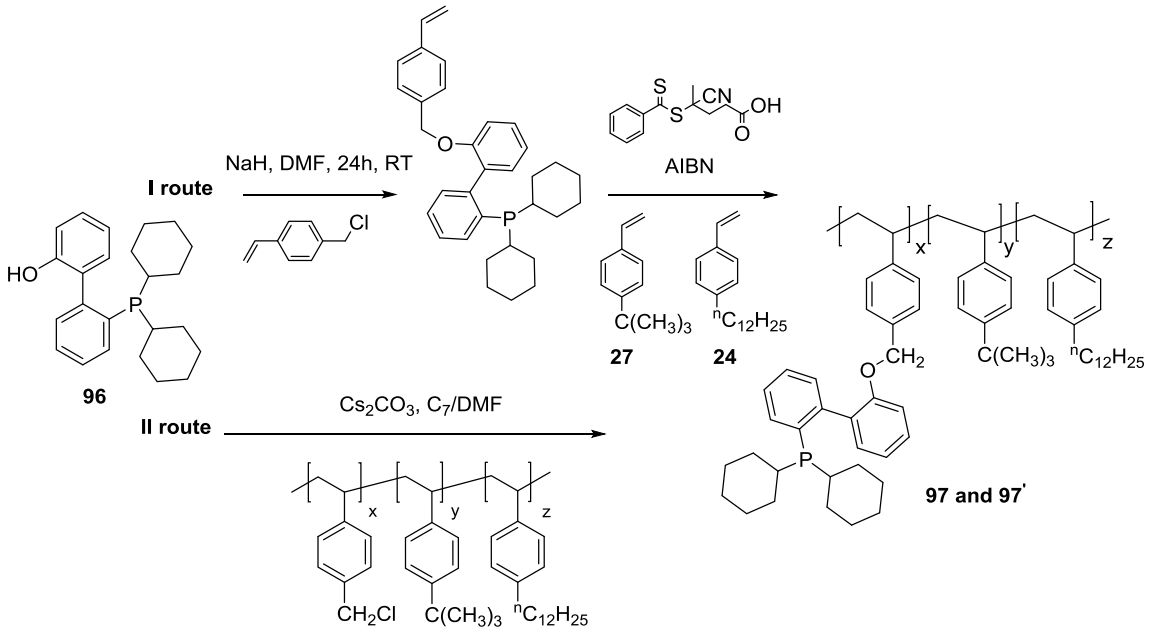
As noted above, Buchwald earlier immobilized one example of this type of ligand on cross-linked polystyrene. In this case, anchoring Buchwald's phosphine analog onto a soluble polymer support was accomplished by the preparation of a phosphine ligand having an aromatic hydroxyl group, which was then converted into a nucleophile as shown in Scheme 47.[94] To effect this chemistry, 2-methoxyphenylmagnesium bromide was allowed to react with 1,2-bromochlorobenzene in the presence of magnesium shavings. To the resulting slurry, copper (I) chloride was added, followed by the addition of chlorodicyclohexylphosphine to form methoxy-substituted dicyclohexyl biphenylphosphine ligand as a white solid. The resulting ligand could undergo dealkylation in the presence of BBr_3 to yield the hydroxyl-substituted dicyclohexyl biphenylphosphine **96**. Using this chemistry which was first repeated by Dr. Dongmae, the phosphine **96** could be attached to vinylbenzyl chloride.

Scheme 47. Preparation of phosphine ligand **96**



An alternative approach using this phenoxide in a post-polymerization modification with attachment of the hydroxyl-substituted phosphine ligand on the polymer support was also explored. Both approaches were successful yielding a poly(4-alkylstyrene)-supported electron-rich phosphine ligand as shown in Scheme 48.

Scheme 48. Synthesis of poly(4-alkylstyrene)-supported electron-rich phosphine ligand **97 and 97'**



When the phosphine ligand was prepared as a monomer, it was copolymerized with monomers **24** and **27** using reversible addition fragmentation (RAFT) polymerization to give **97'**. Meanwhile, the hydroxyl-substituted dicyclohexyl biphenylphosphine **96** could also react with benzyl chloride groups as shown in the second route under thermomorphic conditions using a heptane/DMF solvent mixture to yield polymer-supported phosphine **97**. Both terpolymers **97** and **97'** were characterized by GPC and ^{1}H and ^{31}P NMR. The terpolymer **97'** that was prepared using route I was used as a polymer-supported phosphine for palladium-mediated cross-coupling reactions; this ligand contained 8 mol % dicyclohexyl biphenylphosphine groups based on the ^{1}H NMR spectroscopy analysis of the relative peaks at δ 2.47 (benzylic protons of

the 4-dodecylstyrene) and δ 4.95 (benzylic protons of 4-vinylbenzyl-2-dicyclohexylphosphino-2'-biphenyl). The molecular weight of this terpolymer **97'** was determined to be 9000 kDa with a PDI of 1.2.

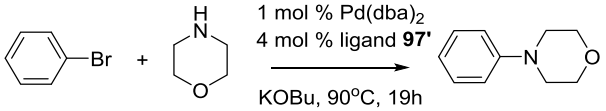
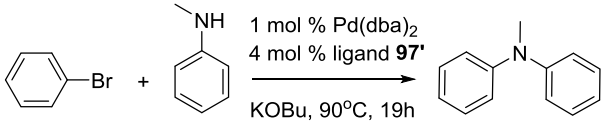
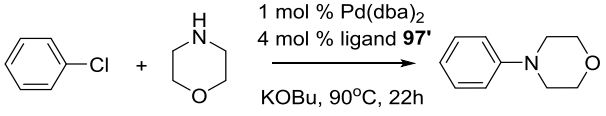
Next, the utility of **97'** as a polymer-supported phosphine ligand in palladium-mediated Buchwald-Hartwig amination reactions was tested. The initial goal of this recycling study was to carry out cross-coupling chemistry using poly(4-alkylstyrene)-supported phosphine ligated palladium complex under thermomorphic heptane/DMF conditions. Studies with polystyrene-supported dicyclohexylbiphenyl phosphine **97'** revealed that premixing of the catalyst with the Pd source is necessary for high catalytic activity. In palladium catalyzed Buchwald-Hartwig amination reactions, ligand **97'** was allowed to stir with $Pd(dba)_2$ in solvent at 60 ^{o}C for 30 min prior to addition of the substrates. The soluble polymer-supported electron-rich phosphine ligand **97'** was assumed to form an active catalytic system with the palladium source when a change of color from clear to sandy-yellow was observed. At this point the DMF phase containing the substrates and the base was added to the heptane phase containing the complex formed from **97'** and the palladium source. While this reaction was successful in forming an aryl amination product, a significant amount of color in the DMF phase was observed. After separation of the heptane catalyst-containing phase, it was then noted that the second cycle showed a dramatic decrease in conversion. The decrease in conversion from 99% to 63% was assumed to result from leaching of the catalyst in the DMF phase based on the change of color of the DMF phase. To address this problem, the thermomorphic heptane/DMF system was altered to use heptane as a single solvent

for the reaction. At the end of reaction, a polar solvent was required to extract the products. Several different solvents were tried to extract the products from the heptane phase such as acetonitrile and DMF; however, methanol was selected to be the optimal solvent for extraction. In these modified conditions, the ligand **97'** was premixed with the palladium source at 60 ^{o}C for 30 minutes. Then, a heptane solution containing the substrates was added. This chemistry used both aryl bromides and aryl chlorides with morpholine and *N*-methylaniline in the presence of an auxiliary base such as KOBu. The reactions were carried out in 3 mL of heptane in a sealed 10 mL graduated centrifuge tube for 19-22 h at 90 ^{o}C. After cooling to room temperature, 2 mL of degassed methanol saturated with heptane was added to the centrifuge tube via cannula. The graduated centrifuge tube was centrifuged for 3 minutes to simplify the biphasic separation. At this point the methanol phase was extracted from the heptane phase containing the catalyst. The heptane phase containing the catalyst was transferred to another sealed graduated centrifuge tube containing fresh substrates and base. The catalyst was recycled 5 times without loss of catalytic activity as summarized in Table 2.

When the polar methanol product phase from cycles one and three was analyzed by ICP-MS, the palladium content in the product phase was detected as slightly decreasing. The decrease in Pd content in the methanol product phase can be explained by the fact that lower molecular weight polymer chains containing the immobilized palladium catalyst can exhibit moderate solubility in the polar methanol phase and hence can contribute to some leaching. However, as the recycling continued, the leaching decreased because lower molecular weight polymer chains were extracted with methanol

leaving higher molecular weight polymers that are more selectively soluble in heptane. In this study, morpholine and *N*-methylaniline were successfully coupled with aryl halides to give good yields. Moreover, aryl chlorides, notoriously poor substrates, were also successfully used with the poly(4-alkylstyrene)-supported electron-rich phosphine ligated palladium complex as shown in Table 2, entry 3.

Table 2. Cross-coupling reactions using **97'**

entry	reaction	cycles	Average Isolated yield (%)	Pd leaching (ppm)
1		5	82	7.8 (1 cycle) 6.8 (3 cycle)
2		5	85	4.8 (1 cycle) 3.0 (3 cycle)
3		4	95	4.3 (1 cycle) 2.8 (3 cycle)

The lack of by-product formation allowed for facile recovery of the palladium complex containing poly(4-alkylstyrene)-supported phosphine ligand **97'**. It was noted, however, that the conversions of amination reactions decreased after the fifth cycle when

using aryl bromides as substrates and after the fourth cycle using aryl chlorides as substrates. This decrease in conversion could be attributed to the adventitious oxidation of the phosphine ligand, which could deactivate the palladium-phosphine complex and preclude the catalysis.

Conclusions

In summary, poly(4-alkylstyrene)-supported triarylphosphine ligand **90** and electron-rich dicyclohexylphosphine ligand **97'** were synthesized. The premixing of polymer-supported phosphine ligands **90** and **97'** with 1 mol % of $Pd(dba)_2$ in heptane at elevated temperature was a necessary step in order to form the catalysts to be used in Suzuki and Buchwald-Hartwig amination reactions.

The catalyst formed using poly(4-alkylstyrene)-supported phosphine ligand **90**, was found to be a recyclable catalyst in Suzuki cross-coupling chemistry. The high phase selective solubility of this catalyst in the heptane phase allowed its consecutive reuse for four cycles under thermomorphic heptane/DMF conditions. The Pd content in the DMF phase containing the product was found to be decreasing with each subsequent cycle.

In combination with $Pd(dba)_2$, poly(4-alkylstyrene)-supported phosphine ligand **97'** formed a catalyst that was effective in Buchwald-Hartwig amination reactions using both aryl bromides and aryl chlorides. In this chemistry, the heptane phase selectively soluble poly(4-alkylstyrene)-supported catalyst could be recycled up to five times with very low Pd leaching using added methanol phase to separate the product from the heptane solution of the catalyst.

CHAPTER V

USING THERMOMORPHIC SYSTEMS IN ATRP POLYMERIZATION

Introduction

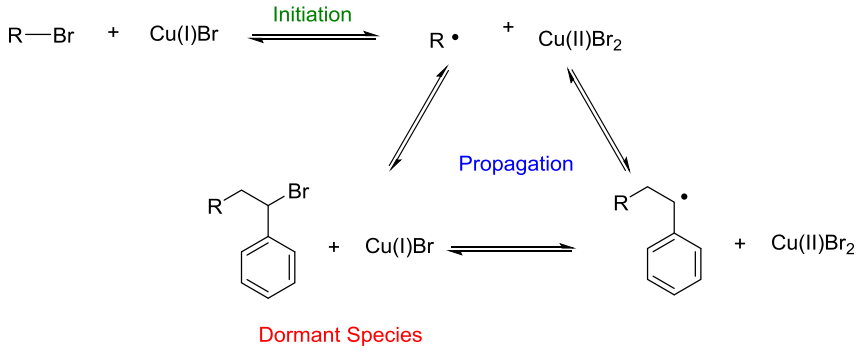
Atom transfer radical polymerization (ATRP) has developed into a common method of controlled radical polymerization since its initial discovery in 1995.[101] The number of publications dedicated to this subject is an indication of the broad interest in this chemistry. Like conventional radical polymerizations, this type of polymerization chemistry can be carried out with a variety of different solvents and conditions and is tolerant of most functional groups. This method makes it possible to synthesize polymer chains with a pre-definable molecular weight, a narrow molecular weight distribution and a reactive end-group functionality that can be exploited in further synthesis.

ATRP polymerization has opened new avenues to various advanced materials with precisely controlled architecture.[102] The capability afforded by ATRP to control different structural aspects of polymers allows for fine-tuning of a polymer's physical characteristics. ATRP can be used to graft polymers from surfaces of both organic and inorganic materials as well as nanoparticles. ATRP polymers as materials can be used in applications such as lubricants, membranes, electronics and drug delivery materials.[103]

The accepted mechanism for ATRP is shown in Scheme 49. In ATRP, radicals are produced by the reversible transfer of a radically transferable halogen atom from a monomeric or polymeric alkyl halide initiator to a transition metal complex in a lower

oxidation state. This forms an organic radical and a transition metal complex in a higher oxidation state.[104] In the case of Cu catalyzed polymerization, this typically involves a Cu(I) amine complex that becomes a Cu(II) species.

Scheme 49. Copper catalyzed transfer of a halogen atom to form active and dormant species in a typical ATRP reaction that proceeds through a copper(I)-copper(II) redox system



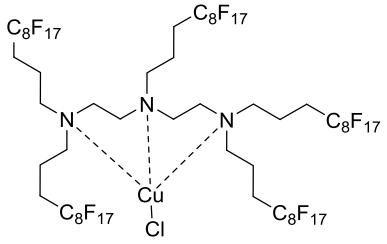
Typically all the polymer chains initiate at the same time and then react with initiator monomers in solution to form a growing chain. Since all polymer chains propagate at the same rate, a linear correlation between the monomer consumption and molecular weight is observed. An essential feature of ATRP is the presence of an equilibrium between a low concentration of active propagating species and a larger number of dormant chains via an inner sphere electron transfer process promoted by the transition metal complex. Therefore, if efficient initiation and propagation occurs, the molecular weights of the product polymer correlate to the predicted molecular weights.

Side reactions including termination reactions also occur in ATRP, mainly through radical coupling and disproportionation. However, the lower concentration of radical present slows this bimolecular process leading to a very small percentage of polymer chains undergoing termination in a well-controlled ATRP reaction.

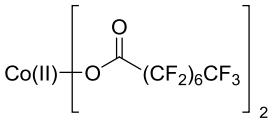
Despite being a powerful tool for polymerization, metal contamination remains an issue in some ATRP applications. Therefore, methods that reduce the amount of transition metal used in the process or that recycle the metal complex after the polymerization are desirable. One such method involves the liquid/liquid separation of the transition metal complexes from the product in an organic/aqueous solvent system. This biphasic separation involving toluene and water was investigated by Matyjaszewski.[105] Under these biphasic conditions, styrene and polystyrene are phase selectively soluble in toluene over water. The ATRP polymerization of styrene produced polystyrene with a molecular weight of 15 kDa and a PDI of 1.15. In this system a copper(I)halide/amine complex was used to effect the desired polymerization. This polar catalyst could therefore be easily removed in the aqueous phase of the reaction mixture and little contamination of metal content in the product polystyrene was measured (6 ppm residual Cu). While this system provides a facile way to separate the metal from the polymer product, it was limited because its biphasic nature and inhomogeneity. Thus, the formation of polystyrene with the same control over the final molecular weight could not be achieved. Moreover, the catalyst in this case cannot be easily recycled because it was concentrated in the polar phase.

Other biphasic systems such as fluorous thermomorphic systems described in earlier chapters have been investigated in ATRP chemistry. Unlike the aforementioned organic/aqueous system, a fluorous thermomorphic system offers homogeneous reaction conditions with a biphasic separation at the end of the reaction. This in principle would enable the formation of polymers with controlled molecular weights and allow for efficient separations of the active transition metal complex. A number of groups carried out the design of various fluorous ligands and complexes that are phase selectively soluble in fluorous solvents.

Scheme 50. Fluorous ligands for use in fluorous biphasic separations of active ATRP metal complexes from polymer product



Fluorous copper (I) ligand
98



Fluorous cobalt coplex
99

For example, Haddleton and coworkers investigated the use of a fluorous biphasic system as a medium for ATRP using ligand **98** as shown in Scheme 50.[106] In this approach, toluene was added to an equivolume solution of perfluoromethylcyclohexane containing catalyst **98**. While polymerization did occur upon addition of methyl

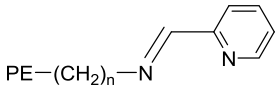
methacrylate and ethyl 2-bromoisobuterate as a polymerization initiator, this solvent system remained biphasic even at elevated temperature. As a result, polymerization in this fluorous biphasic system was even slower than a typical ATRP polymerization.

A second example using a fluorous system to carry out ATRP was described by Weiser.[107] In this work, the fluorous cobalt complex **99** was used in a homogeneous ATRP polymerization of styrene in a solvent mixture of toluene, cyclohexane, and perfluorodecalin (1:1:1). The catalysis occurred at 90 ^{o}C for duration of 4 h. At this temperature the ternary solvent mixture of toluene, cyclohexane and perfluorodecalin formed a monophasic solution allowing for homogeneous ATRP polymerization. After the reaction was complete, the reaction mixture was cooled to room temperature and resulted in a biphasic toluene-cyclohexane/perfluorodecalin system. The fluorous phase containing the cobalt catalyst was separated from the toluene-cyclohexane phase containing the product. In the fluorous biphasic ATRP process, both the perfluoroalkyl-tagged catalyst and perfluorinated solvent were found to be recyclable. However, the maximum molecular weight of 2500 Da that could be obtained for polystyrene was undesirable. The authors attributed the low degree of polymerization to the fact that higher molecular weight polymers were insoluble in the ternary toluene/cyclohexane/perfluorodecalin solvent mixture and therefore using this type of solvent mixture precluded the formation of higher molecular weight polymers.

To avoid these limitations, soluble polymer supports for ATRP have been investigated.[108] For example, polyethylene (PE) can be used as a soluble support based on the upper critical solution temperature. At elevated temperature, the **100**/copper

complex shown in Scheme 51 is completely soluble in reaction mixture. Upon cooling, the polymer-supported copper complex precipitates from the solution and can be recovered by filtration.

Scheme 51. PE-ligand **100**



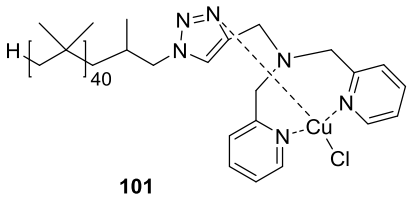
100

Using the ligand **100**/copper complex, ATRP of methyl methacrylate was performed in toluene at 100 ^{o}C. After the PE-functionalized ligand was precipitated, the Cu remained complexed with the ligand affording a clean and colorless poly(methyl methacrylate) solution. While the PE-supported **100**/copper complex is theoretically a recyclable catalyst, recycling studies using this complex were not described.

The phase selective solubility of polyisobutylene (PIB) in heptane has also been used as an advantage for ATRP by our group.[109] Given that polystyrene is insoluble in heptane and the catalyst **101** shown in Scheme 52 is soluble in heptane, this system was designed to self-separate after a reaction owing to the differential solubilities of the catalyst and the polymer product. In this study, polymerization was carried out in a heptane/styrene mixture at 110 ^{o}C. As polymerization proceeded, a viscous suspension was formed. At the end of the reaction, centrifugation produced a biphasic mixture where the colored catalyst was clearly present in the upper heptane phase and the white

polymer product was present in the bottom phase. UV-visible analysis showed no detectable PIB-bound copper complex in the product phase.

Scheme 52. Polyisobutylene-supported ATRP catalyst **101**



101

In this work, the polymer-supported copper complex was successfully separated from the polystyrene product and recycled 5 times giving a consistent molecular weight of the polymer product with a narrow PDI. When the product phase was analyzed by ICP-MS, it was revealed that only *ca*. 3% of the copper was present. This study also showed that use of solvent systems that contain a single solvent or a combination of solvents where the product and catalyst self-separate from one another is a useful approach to recover and recycle the catalyst.

While polymer-supported ATRP catalysts have shown promise as recyclable catalysts, there is a limitation of these polymer supported catalyst. They must be prepared, which adds extra cost to any process. As part of the work on synthesis of hydrophobic polymers, an alternative way to separate Cu species from these sorts of products was briefly explored. This chemistry was based on some of the original work in our group that used thermomorphic catalysts. That work used a polar polymer bound

catalyst in a binary solvent mixture that was thermomorphic. For example, a poly(*N*-isopropyl acrylamide) (PNIPAM) bound Rh(I) hydrogenation catalyst was prepared.[30] In heptane/aqueous EtOH it hydrogenated octadecene to form octadecane at 70 ^{o}C. Cooling formed a biphasic heptane/aqueous EtOH mixture with the catalyst in the polar phase and the octadecane in the heptane-rich phase. In this work, a thermomorphic biphasic solvent system was chosen to investigate ATRP polymerization with 4-alkylstyrenes and octadecyl acrylate. Depending on the monomers used, ATRP polymerization employs either nonpolar solvents such as anisole[110] and toluene[111] or polar solvents such as DMF[112] and dimethyl sulfoxide[113] (DMSO). Since DMF is a suitable solvent for an ATRP catalyst and could also form a monophasic reaction mixture with heptane at elevated temperature, I envisioned that this solubility would facilitate catalyst/polymer separation where the differential solubilities of poly(4-alkylstyrene) in the heptane phase and a typical low molecular weight copper-ligand complex in the DMF phase would enable the Cu catalyst to be recycled. This alternative solvent separation is in direct contrast to the traditional one with the nonpolar heptane phase containing the high molecular weight polymeric catalyst and the polar DMF phase containing the low molecular weight product as shown in Figure 17.

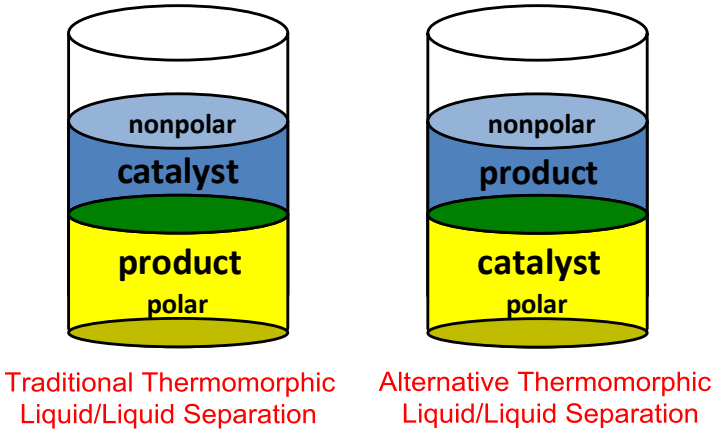


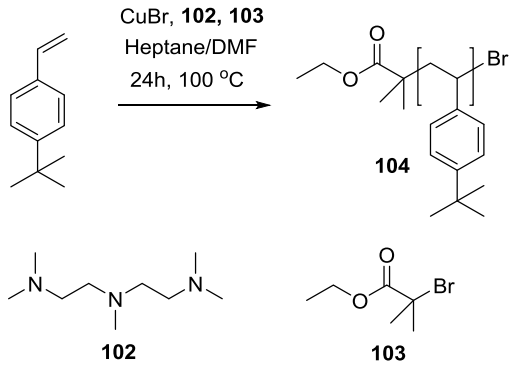
Figure 17. Traditional and alternative thermomorphic liquid/liquid separation systems

In the following work, some initial experiments where this strategy has been adapted for ATRP polymerizations using thermomorphic solvent mixtures, nonpolar monomers, and conventional polar low molecular weight ATRP catalysts are discussed. Not only would the alkylated polystyrene product be separated, the alkylated styrene monomer that typically remains after polymerization would be soluble in heptane and separable from the Cu-ligand species that would be sequestered in the DMF phase.

Results and Discussion

The first polymerization investigated used 4-*tert*-butylstyrene as a monomer as shown in Scheme 53.

Scheme 53. ATRP of 4-*tert*-butylstyrene using thermomorphic biphasic separation



N,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine (PMDETA) **102** was chosen as the amine ligand. PMDETA, along with copper(I)bromide and ethyl 2-bromoisobuterate **103** was dissolved in 1 mL of DMF and added to a 10-mL graduated centrifuge tube. To the resulting solution, a 1 mL solution of 4-*tert*-butylstyrene monomer in heptane was added to form a biphasic solvent mixture. The mixture was subjected to three freeze-pump-thaw cycles and then was allowed to warm to 100 ^{o}C in an oil bath. The reaction took place under monophasic homogeneous conditions for 24 h at 100 ^{o}C. Upon cooling the reaction mixture, a biphasic mixture formed consisting of a heptane-rich phase containing the polymer product **104** and a denser DMF-rich phase containing the catalyst complex as shown in Figure 18.

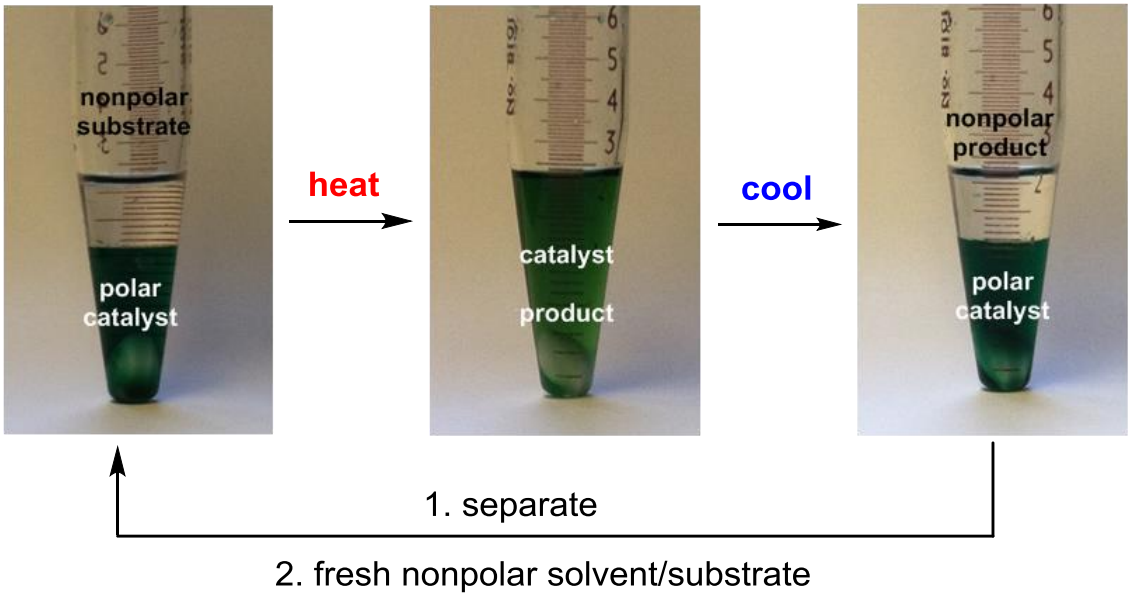


Figure 18. Thermomorphic liquid/liquid separation of ATRP

After cooling, the heptane phase could be separated from the DMF phase containing the catalyst complex. Addition of fresh substrate and more ethyl 2-bromoisobuterate initiator to the reaction flask followed by heating in an oil bath at 100 ^{o}C for 24 h provided a second batch of polystyrene product. Following this same procedure, four cycles were carried out to recycle the copper catalyst. The yields of these reactions were calculated based on the mass of 4-*tert*-butylstyrene used divided by the mass of recovered polymer after precipitation in methanol. The molecular weights were measured by gel permeation chromatography using polystyrene standards. The results for the ATRP polymerization of 4-*tert*-butylstyrene using this thermomorphic

liquid/liquid separation strategy can be seen in Table 3. The results show that this thermomorphic biphasic separation strategy could also be a suitable strategy to recycle

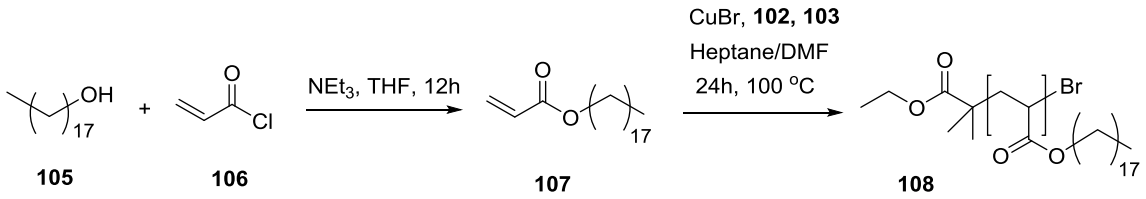
Table 3. ATRP polymerization of 4-*tert*-butylstyrene[a]

cycle	isolated yield %	M_n	PDI	Cu leaching (ppm)
1	82	9500	1.18	ND
2	84	8158	1.29	ND
3	89	6791	1.21	218.0
4	90	8190	1.30	123.4

[a]The ratio of monomer/initiator/CuBr/Ligand was 50/1/1/1.5
ND-not determined

polar low molecular weight catalysts from a nonpolar high molecular weight product. In order to see if this system is applicable for catalyst recovery with nonpolar polymer products, the ATRP polymerization of octadecyl acrylate was also studied. In this chemistry, octadecyl acrylate **107** was prepared from octadecyl alcohol **105** and acryloyl chloride **106** as shown in Scheme 54. Octadecyl acrylate **107** could now undergo ATRP polymerization to form polymer product **108** using similar conditions as those described in Scheme 51.

Scheme 54. ATRP polymerization of octadecyl acrylate **108** using thermomorphic biphasic separation



Poly(octadecyl acrylate) polymer **108**, a highly heptane phase selectively soluble polymer because of its lipophilic alkyl ester group, can be easily separated from the DMF phase containing a low molecular weight copper catalyst. As was the case with 4-*tert*-butylstyrene, the ATRP polymerization using monomer **108** was performed four times to recycle the catalyst. The results are summarized in Table 4.

Table 4. ATRP polymerization of octadecyl acrylate **108**[a]

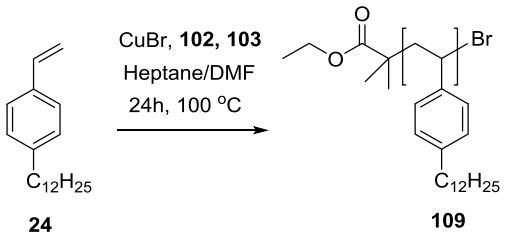
cycle	isolated yield %	M_n	PDI	Cu leaching (ppm)
1	80	9089	1.10	ND
2	83	8607	1.22	ND
3	87	9008	1.28	83.2
4	89	10207	1.52	72.5

[a]The ratio of monomer/initiator/CuBr/Ligand was 50/1/1/1.5
ND- not determined

The ease of separation and recyclability using thermomorphic liquid/liquid separation solvent system is a significant advantage for these low molecular weight copper catalysts. Traditionally used post-polymerization purification methods such as column chromatography are not required to isolate the polymer product.

Thermomorphic liquid/liquid separation was also tested in ATRP polymerization of 4-dodecylstyrene. Similar to the polymerization of 4-*tert*-butylstyrene or octadecylacrylate, the thermomorphic system was used to recycle the low molecular weight copper catalyst. In this case, 4-dodecylstyrene **24** was used to carry out homopolymerization to form **109** as described in Scheme 55.

Scheme 55. ATRP polymerization of 4-dodecylstyrene **24** using thermomorphic biphasic separation



24 **109**

The results for the ATRP polymerization of 4-dodecylstyrene using thermomorphic liquid/liquid separation strategy can be seen in Table 5.

Table 5. ATRP polymerization of 4-dodecylstyrene[a]

Cycle	isolated yield %	M_n	PDI
1	78	9800	1.07
2	83	8120	1.21
3	85	8700	1.13
4	87	11400	1.45

[a]The ratio of monomer/initiator/CuBr/Ligand was 50/1/1/1.5

The methodology envisioned for ATRP polymerization using a low molecular weight copper complex under homogeneous thermomorphic biphasic conditions has an advantage over the traditional ATRP polymerization because it allows ease of separation of the nonpolar polymer product from the copper catalyst at the end of the reaction. The polymers that were obtained had consistent molecular weights and narrow polydispersity indices. However, the initial ICP-MS data for poly(4-*tert*-butylstyrene) and poly(octadecyl acrylate) was not what was anticipated. A much higher than expected level of Cu contamination in the product was formed. In order to address this issue and lower the Cu contamination in the product phase several approaches could be used. One of the possible solutions is to lower the amount of catalyst used, which in turn would decrease the catalyst leaching into the product phase. To reduce the metal contamination in the product phase, "initiators for continuous activator regeneration" (ICAR) ATRP method is commonly used.[114] This method requires only a trace amount of copper catalyst (~100 ppm) and uses conventional radical initiators (e.g. azo or peroxides) to generate excess radical that reduces the Cu(II) complex to Cu(I). This technique provides an improvement in lowering the metal concentration in ATRP; however, control of the molecular weight is greatly reduced, because radical generated from

peroxide initiators can not only reduce Cu(II) to Cu(I) but also initiate new polymer chains. An improved approach to decrease the amount of catalyst used in ATRP is exemplified by "activators regenerated by electron transfer" (ARGET) machanism.[115] These systems, a small amount of copper catalyst is used in conjunction with a large excess of reducing agent. This allows for continuous regeneration of Cu(I) activators from Cu(II) deactivator formed through the radical-radical termination step. Implementing a reducing agent allows ATRP to be conducted with significantly lower concentrations of catalyst. A variety of reducing agents can be used including tin(II) 2-ethylhexanoate, ascorbic acid, and nitrogen containing ligands.[116] Since nitrogen containing *N*,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine (PMDETA) is used in ATRP under biphasic thermomorphic conditions, it is foreseeable that using a large amount of this ligand and replacing the CuBr species with a small amount of the $CuBr_2$ species would give an ARGET type ATRP polymerization with decreased metal contamination in the heptane product phase. Zerovalent copper metal as a reducing agent can also be used in ARGET ATRP. Utilizing Cu(0) was first demonstrated in 1997 and was shown to increase the rate of polymerization under various ATRP conditions.[117] Later, Matyjaszewski demonstrated a successful ATRP polymerization of methyl acrylate using ppm concentrations of a $CuBr_2$/PMDTA complex in the presence of copper powder or copper wire at room temperature.[118] Polymers prepared using $CuBr_2$/PMDTA/Cu(0) maintained excellent polydispersity indices with high molecular weights. Implementing ICAR or ARGET techniques with thermomorphic ATRP polymerization should ensure decrease of the catalyst leaching into the nonpolar heptane

phase and allow for recycling of the low molecular weight copper catalyst in the DMF phase.

Conclusions

ATRP is a robust tool for the synthesis of polymer materials with control over functionality and molecular weight. Catalysis using a thermomorphic biphasic solvent system provides a way to easily separate and recover a low molecular weight catalyst from a high molecular weight poly(4-alkylstyrene) or poly(alkyl acrylate) product. Upon heating, the thermomorphic heptane/DMF solvent system forms a monophasic solution that allows for homogeneous ATRP polymerization to occur. However, upon cooling, a biphasic separation is reformed where the heptane phase contains a highly phase selectively soluble polymer product and the DMF phase contains the low molecular weight copper catalyst. Once the heptane product-containing phase is removed, the DMF phase containing the copper-ligand complex is recyclable in further ATRP polymerization of alkylated monomers. While shown to be an efficient separation strategy, utilizing a thermomorphic biphasic solvent system leads to significant metal leaching into the heptane-rich product phase. If a thermomorphic ATRP strategy is used in the future, the metal leaching issue can be addressed by using ICAR ATRP or ARGET ATRP methods. In both techniques, the activator Cu(I) is regenerated through the reduction of accumulated Cu(II) species. Using these two methods would allow for a dramatic decrease in the catalyst loading and would ensure a decrease of metal leaching into the heptane product phase.

CHAPTER VI

EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial sources and used without further purification. The ^{1}H, ^{13}C and ^{31}P NMR spectra of the products of the catalytic reactions were identical to those in literature.[119-121] ^{1}H NMR spectra were recorded on Inova NMR spectrometer operating at 299.91 MHz. ^{13}C NMR spectra were recorded on Inova NMR spectrometer operating at 75.41 MHz. ^{31}P NMR spectra were recorded on Inova NMR spectrometer operating at 121.42 MHz using 85% H_2PO_4 as the standard. Chemical shifts are reported in parts per million (δ) relative to residual proton resonances in deuterated chloroform ($CDCl_3$). Coupling constants (*J* values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), and m (multiplet). Copolymers were analyzed by gel permeation chromatography in THF using a Viscotek I-MBMMW-3078 mixed bed column at 30 ^{o}C. The Viscotek instrument was equipped with a VE-3210 UV-visible detector, a 270 dual detector and a VE-3580 RI detector. The polymer molecular weights were calculated using OmniSEC software (v.4.6.1) and were based on polystyrene standards. A Fluorolog fluorometer was used for fluorescence studies. ICP-MS analysis was conducted by employing a NexION 300D ICP-MS spectrometer.

ICP-MS Digestion Procedure. The sample to be analyzed (30-70 mg) and 4 g of concentrated nitric acid were added to a glass vial and the mixture was heated to 120 ^{o}C until the sample was dissolved. Then the solution was cooled to room temperature and 4 g of concentrated sulfuric acid was added. The mixture was heated to 120 ^{o}C for 48 h. The solution was then allowed to cool to room temperature. At this point, the concentrated acid solution was diluted with 1% nitric acid solution and the diluted sample was analyzed by ICP-MS.

Octadecylbenzene (22). Stearoyl chloride prepared by a known procedure[122] was dissolved in benzene and added via an addition funnel to a reaction flask containing $AlCl_3$ in benzene. After 12 h at 25 ˚C, the reaction was concentrated under reduced pressure and then washed with H_2O (2 x 50 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed to yield 85% of octadecyl phenyl ketone. This ketone (3.0 g, 8.7 mmol) was then dissolved in 15 mL of a 3:1 (vol:vol) mixture of THF:EtOH and reduced using 14.3 psi of H_2 with 10 mol % of a Pd/C catalyst over 24 h. The Pd/C was removed from the reaction solution by filtration, the solvent was removed under reduced pressure using a rotary evaporator, and the residue was redissolved in hexane. This hexane solution was washed with H_2O, dried over Na_2SO_4 and the hexane solvent was removed to give 2.4 g of octadecylbenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.6 Hz, 3H), 1.16-1.49 (br m, 30H), 1.63 (m, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 7.21-7.30 (m, 5H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, multiple peaks between 29.3 and 29.8, 31.6, 32.0, 35.8, 125.5, 128.3, 128.5, 143.

4-Dodecylstyrene (24). 4-Dodecylstyrene was prepared from dodecylbenzene using the same sequence of reactions used by Overberger involving Friedel-Crafts acylation, reduction and dehydration.[123] The final product of this synthetic sequence could be prepared on a multigram scale and was purified by silica column chromatography (hexanes) to give a viscous liquid (4.9 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.20-1.35 (br m, 18H), 1.58 (m, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 5.18 (d, *J* = 11.1 Hz, 1H), 5.69 (d, *J* = 17.0 Hz, 1H), 6.68 (dd, *J* = 11.2, Hz, 17.0 Hz, 1H), 7.13(d, *J* = 8.3 Hz, 2H), 7.32(d, *J* = 8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, multiple peaks between 29.3 and 29.8, 31.5, 32.0, 35.8, 112.7, 126.1, 128.4, 135.1, 136.8, 142.7.

Poly((4-dodecylstyrene)-*c*-(4-vinylbenzyl chloride)) (28). 4-Dodecylstyrene (2.7 g, 9.9 mmol) and 4-chloromethylstyrene that had been passed through an aluminum oxide plug to remove inhibitor (0.15 g, 0.99 mmol) were added to a 50-mL Schlenk tube equipped with a stir bar. Benzoyl peroxide (0.031 g, 0.12 mmol) was added and the resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in an oil bath at 70 ^{o}C for 24 h. After cooling, the product was dissolved in 40 mL of chloroform and the resulting solution was slowly added to an excess of MeOH (400 mL) to precipitate the desired polymer product in 75% yield (2.40 g). The polymer was characterized by GPC and had a M_n of 32000 Da with a PDI of 2.22. The ratio of the monomers was determined as 11:1 based on ^{1}H NMR spectroscopic analysis integrating peaks at δ 2.47 (benzylic protons of the major species, 4-dodecylstyrene) and δ 4.45

(benzylic protons of 4-chloromethylstyrene). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (br t, 30H), 0.98-2.13 (br m, 233H), 2.47 (br s, 20H), 4.45 (br s, 2), 6.11-7.12 (br m, 44H).

Poly((4-*tert*-butylstyrene)-*c*-(4-vinylbenzyl dansyl)) (34). The copolymerization of 4-*tert*-butylstyrene and 4-chloromethylstyrene was carried out using a literature procedure.[69] The product was purified by two solvent precipitations using CH_2Cl_2 as the good solvent and methanol as a precipitation solvent. The polymer was characterized by GPC and ^{1}H NMR spectroscopy. GPC analysis showed that the polymer had a M_n of 22000 Da with a PDI of 2.86. This chloromethylated poly(4-*tert*-butylstyrene) copolymer was then allowed to react with *N*-n-butyl dansylsulfonamide. In this reaction N-*n*-butyl dansylsulfonamide (0.39 g, 1.27 mmol) was dissolved in DMF (50 mL) and allowed to react with K_2CO_3 (1.75 g, 12.70 mmol) for 1 h. Then, a 50 mL heptane solution of the chloromethylated copolymer (0.50 g, 0.26 mmol) was added dropwise. The reaction mixture was heated at 90 ^{o}C and was allowed to stir for 72 h. After the mixture was cooled to room temperature, the top heptane-rich layer was separated and washed with MeCN (25 mL x 3). The solvent was removed under reduced pressure. The resulting solid was redisolved in a minimum amount of CH_2Cl_2 and added to MeOH (50 mL) to precipitate the copolymer as a yellowish solid in 79% yield (0.44 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57-2.76 (br m, 168H), 2.89 (br s, 6H), 3.11 (br s 2H), 4.27 (br s, 2H), 6.11-7.12 (br m, 48H), 7.47 (br m, 2H), 8.19 (br s, 1H), 8.38 (br s, 1H), 8.52 (br s, 1H).

Poly((4-dodecylstyrene)-*c*-(4-vinylbenzyl dansyl))copolymer (33). N-*n*-Butyl dansylsulfonamide **36** (0.75 g, 2.4 mmol),[42] potassium carbonate (0.30 g, 2.4 mmol) and

DMF (30 mL) were added to a flame-dried, 3-necked 100-mL round-bottomed flask equipped with a stir bar. This mixture was stirred for 1 h under N_2 at which point a solution of copolymer **28** (2.1 g, 0.66 mmol) in heptane (30 mL) was added. The resulting biphasic mixture was heated to 90 ^oC in an oil bath to form a single phase mixture that was allowed to stir for 72 h. After cooling to ambient temperature, hexane (50 mL) was added to the reaction mixture. The hexane phase was separated from the DMF phase and was washed first with water (1 x 100 mL), then with 90% EtOH (2 x 50 mL) and finally dried over Na_2SO_4. After filtering, the solvent was removed under reduced pressure to give the product in 87% yield (1.92 g.). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.59 (br s, 3H), 0.91 (br t, 30H), 1.03-2.10 (br m, 237H), 2.47 (br s, 20H), 2.85 (br s, 6H), 3.09 (br s, 2H) 4.37 (br s, 2), 6.06-7.22 (br m, 45H), 7.47 (br m, 2H), 8.19 (br s, 1H), 8.38 (br s, 1H), 8.52 (br s, 1H).

Poly((4-dodecylstyrene)-*c*-poly(*tert*-butylstyrene)-*c*-poly(4-vinylbenzyl dansyl)) terpolymer (39b, 9 mol%). 4-Dodecylstyrene (1.7 g, 6.4 mmol), *tert*-butylstyrene (4.1 g, 25 mmol) and 4-vinylbenzyl chloride (0.48 g, 3.5 mmol) that had been passed through an aluminum oxide plug to remove any inhibitor were dissolved in 2 mL of 2-butanone and added to a 50-mL Schlenk tube equipped with a stir bar. RAFT reagent 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid (0.091 g, 0.32 mmol) and AIBN (0.0060 g, 0.037 mmol) were added to the flask and the resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in oil bath at 80 ^oC for 48 h. After cooling, the product was dissolved in 3mL of chloroform and this solution was slowly added to excess MeOH (300ml) to precipitate the desired polymer product in

70% yield (4.1 g). The product polymer was analyzed by GPC and had a M_n of 9000 Da with a PDI of 1.08. The ratio of monomers in the product was determined to be 9:1:1 based on NMR analysis integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 4.45 (benzylic protons of 4-vinylbenzyl chloride). The chloromethylated poly(4-dodecylstyrene)-*c*-poly(*tert*-butylstyrene) terpolymer was then allowed to react with *N*-n-butyldansylsulfonamide using a literature procedure[1]. In this reaction *N*-n-butyldansylsulfonamide (0.39 g, 1.3 mmol) was dissolved in DMF (50 mL) and allowed to react with K_2CO_3 (0.18 g, 1.3 mmol) for 1 h. Then a 50 mL heptane solution of chloromethylated terpolymer (0.40 g, 0.21 mmol) was added dropwise. The reaction mixture was heated at 90 ^oC and was allowed to stir for 72 h. After the mixture was cooled to room temperature, the top heptane-rich layer was separated and washed 3 times with MeCN. The solvent was removed under reduced pressure and the resulting solid was redissolved in a minimum amount of CH_2Cl_2 and added to MeOH (50 mL) to precipitate the copolymer as a yellowish solid in 82 % yield (0.38 g). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.59 (br s, 3H), 0.91(br t, 3H), 1.03-2.10 (br m, 134H), 2.47 (br s, 2H), 2.85 (br s, 6H), 3.09 (br s, 2H), 4.37 (br s, 2H), 6.06-7.22 (br m, 45H), 7.47 (br m, 2H), 8.19 (br s, 1H), 8.38 (br s, 1H), 8.52 (br s, 1H).

Poly((4-dodecylstyrene)-*c*-poly(*tert*-butylstyrene)-*c*-poly(4-vinylbenzyl dansyl)) terpolymer (39a, 28 mol %). 4-Dodecylstyrene (1.8 g, 6.4 mmol), *tert*-butylstyrene (2.0 g, 12 mmol) and 4-vinylbenzyl chloride (0.29 g, 1.91 mmol) that had been passed through an aluminum oxide plug to remove any inhibitor were dissolved in 2 mL of 2-butanone and added to a 50-mL Schlenk tube equipped with a stir bar. RAFT reagent 4-

cyano-4-(phenylcarbonothioylthio)pentanoic acid (0.050 g, 0.18 mmol) and AIBN (0.0030 g, 0.018 mmol) were added to the flask and the resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in oil bath at 80 ^{o}C for 48 h. After cooling, the product was dissolved in 3 mL of chloroform and this solution was slowly added to excess MeOH (300 mL) to precipitate the desired polymer product in 72% yield (3.6 g). The product polymer was analyzed by GPC and had a M_n of 7000 Da with a PDI of 1.10. The ratio of monomers in the product was determined to be 9:4:1 based on NMR analysis integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 4.45 (benzylic protons of 4-vinylbenzyl chloride). The chloromethylated poly(4-dodecylstyrene)-*c*-poly(*tert*-butylstyrene) terpolymer was then allowed to react with *N*-n-butyldansylsulfonamide using a literature procedure. In this reaction *N*-n-butyldansylsulfonamide (0.39 g, 1.27 mmol) was dissolved in DMF (50 mL) and allowed to react with K_2CO_3 (0.175 g, 1.27 mmol) for 1 h. Then a 50 mL heptane solution of chloromethylated terpolymer (0.6 g, 0.22 mmol) was added dropwise. The reaction mixture was heated at 90 ^{o}C and was allowed to stir for 72 h. After the mixture was cooled to room temperature, the top heptane-rich layer was separated and washed 3 times with MeCN. The solvent was removed under reduced pressure and the resulting solid was redissolved in a minimum amount of CH_2Cl_2 and added to MeOH (50 mL) to precipitate the copolymer as a yellowish solid in 79 % yield (0.51 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.59 (br s, 3H), 0.91 (br t, 12H), 1.03-2.10 (br m, 203H), 2.47 (br s, 8H), 2.85 (br s, 6H), 3.09 (br s, 2h), 4.37 (br s, 2H), 6.06-7.22 (br m, 57H), 7.47 (br m, 2H), 8.19 (br s, 1H), 8.38 (br s, 1H), 8.52 (br s, 1H).

Poly((4-dodecylstyrene)-*c*-poly(4-methylstyrene)-*c*-poly(4-vinylbenzyl dansyl) terpolymer (38b, 13 mol %). 4-Dodecylstyrene (1.0 g, 3.7 mmol), 4-methylstyrene (4.0 g, 34 mmol) and 4-vinylbenzyl chloride (0.30 g, 1.9 mmol) that had been passed through an aluminum oxide plug to remove any inhibitor were dissolved in 2 mL of 2-butanone and added to a 50-mL Schlenk tube equipped with a stir bar. RAFT reagent 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (0.050 g, 0.37 mmol) and AIBN (0.0060 g, 0.037 mmol) were added to the flask and the resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in oil bath at 80 ^{o}C for 48 h. After cooling, the product was dissolved in 3 mL of chloroform and this solution was slowly added to excess MeOH (300 mL) to precipitate the desired polymer product in 70% yield (4.1 g). The product polymer was analyzed by GPC and had a M_n of 14000 Da with a PDI of 1.15. The ratio of monomers in the product was determined to be 12:2:1 based on NMR analysis integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 2.32 (benzylic protons of 4-methylstyrene). The chloromethylated poly(4-dodecylstyrene)-*co*-poly(4-methylstyrene) terpolymer was then allowed to react with *N*-n-butyldansylsulfonamide using a literature procedure[1]. In this reaction *N*-n-butyldansylsulfonamide (0.39 g, 1.3 mmol) was dissolved in DMF (50 mL) and allowed to react with K_2CO_3 (0.18 g, 1.3 mmol) for 1 h. Then a 50 mL heptane solution of chloromethylated terpolymer (0.46 g, 0.22 mmol) was added dropwise. The reaction mixture was heated at 90 ^{o}C and was allowed to stir for 72 h. After the mixture was cooled to room temperature, the top heptane-rich layer was separated and washed 3 times with MeCN. The solvent was removed under reduced pressure and the resulting

solid was redissolved in a minimum amount of CH_2Cl_2 and added to MeOH (50 mL) to precipitate the copolymer as a yellowish solid in 80% yield (0.42 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.59 (br s, 3H), 0.91(br t, 6H), 1.03-2.10 (br m, 85H), 2.32 (br s, 36H), 2,47 (br s, 4H), 2.85 (br s, 6H), 3.09 (br s, 2H), 4.37 (br s, 2H), 6.06-7.22 (br m, 61H), 7.47 (br m, 2H), 8.19 (br s, 1H), 8.38 (br s, 1H), 8.52 (br s, 1H).

Poly(4-dodecylstyrene)-*c*-poly(4-methylstyrene)-*c*-poly(4-vinylbenzyl dansyl) terpolymer (38a, 28 mol %). 4-Dodecylstyrene (2.0 g, 7.4 mmol), 4-methylstyrene (3.5 g, 29 mmol) and 4-vinylbenzyl chloride (0.30 g, 1.9 mmol) that had been passed through an aluminum oxide plug to remove any inhibitor were dissolved in 2 mL of 2-butanone and added to a 50-mL Schlenk tube equipped with a stir bar. RAFT reagent 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (0.10 g, 0.34 mmol) and AIBN (0.0060 g, 0.037 mmol) were added to the flask and the resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in oil bath at 80 ^{o}C for 48 h. After cooling, the product was dissolved in 3 mL of chloroform and this solution was slowly added to excess MeOH (300 mL) to precipitate the desired polymer product in 74% yield (3.0 g). The product polymer was analyzed by GPC and had a M_n of 12000 Da with a PDI of 1.13. The ratio of monomers in the product was determined to be 12:5:1 based on NMR analysis integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 4.45 (benzylic protons of 4-vinylbenzyl chloride). The chloromethylated poly(4-dodecylstyrene)-*co*-poly(4-methylstyrene) terpolymer was then allowed to react with N-*n*-butyldansylsulfonamide using a literature procedure. In this reaction N-*n*-butyldansylsulfonamide (0.35 g, 1.14 mmol) was dissolved in DMF (50

mL) and allowed to react with K_2CO_3 (0.175 g, 1.27 mmol) for 1 h. Then a 50 mL heptane solution of chloromethylated terpolymer (0.42 g, 0.20 mmol) was added dropwise. The reaction mixture was heated at 90 ^oC and was allowed to stir for 72 h. After the mixture was cooled to room temperature, the top heptane-rich layer was separated and washed 3 times with MeCN. The solvent was removed under reduced pressure and the resulting solid was redissolved in a minimum amount of CH_2Cl_2 and added to MeOH (50 mL) to precipitate the copolymer as a yellowish solid in 80% yield (0.38 g). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.59 (br s, 3H), 0.91(br t, 9H), 1.03-2.10 (br m, 102H), 2.32 (br s, 30H), 2.47 (br s, 6H), 2.85 (br s, 6H), 3.09 (br s, 2H), 4.37 (br s, 2H), 6.06-7.22 (br m, 57H), 7.47 (br m, 2H), 8.19 (br s, 1H), 8.38 (br s, 1H), 8.52 (br s, 1H).

1-Carboxy-4-(4-vinylbenzyl) piperazine (56). Ethyl 1-piperazine carboxylate (29.20 g, 184.58 mmol) was dissolved in 60 mL of 90% EtOH and added to a 100-mL round-bottomed flask. Then, 4-chloromethylstyrene (28 g, 184 mmol) and solid sodium bicarbonate (32 g, 385 mmol) were added to the ethanol solution and the mixture was refluxed for 18 h. After cooling to room temperature, the ethanol was removed under reduced pressure. The residue was taken into water, and the aqueous mixture was extracted with diethyl ether. The organic phase was dried over Na_2SO_4 and the solvent was removed to give a colorless liquid in 95% yield (48.08 g) ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.4 Hz 3H), 2.37 (br, 4H), 3.37 (br, 4H), 3.38 (s, 2H), 4.07 (q, *J* = 7.1, 2H), 5.10 (d, *J* = 11.1 Hz, 1H), 5.62 (d, *J* = 17.0 Hz, 1H), 6.60 (dd, *J* = 11.2 Hz, 17 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 43.6, 55.8, 61.3, 62.8, 113.7, 126.2, 129.4, 136.5, 136.7, 137.4, 155.6.

(4-Vinylbenzyl)piperazine (57). 1-Carboxy-4-(4-vinylbenzyl) piperazine (48 g, 175 mmol) and solid potassium hydroxide (24 g, 429 mmol) were dissolved in 146 mL of methanol and added to a 2-necked 250-mL round-bottomed flask. The mixture was heated to reflux and the methanol was distilled off slowly during a 2 h period. The residue was then cooled to room temperature and treated with 75 mL of benzene and 100 mL of water. The aqueous mixture was extracted with two 100 mL portions of benzene. The benzene extract was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the product in 69% yield (24.88 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6 (s, 1H), 2.4 (br s, 4H), 2.89 (t, *J* = 5.2 Hz, 4H), 3.5 (s, 2H), 5.10 (d, *J* = 11.0 Hz, 1H), 5.64 (d, *J* = 17.0 Hz, 1H), 6.63 (dd, *J* = 11.0 Hz, 17.1 Hz,1H), 7.20 (d, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.12, 54.5, 61.8, 112.0, 126.0, 129.3, 136.2, 136.3, 137.8.

(4-Vinylbenzyl-4-pyridyl)piperazine (58). (4-Vinylbenzyl)piperazine (13.00 g, 63.11 mmol) and 4-chloropyridine (6.5 g, 57 mmol) were dissolved in 50 mL of xylene and added to a 100-mL round-bottomed flask equipped with a stir bar. The reaction mixture was heated to reflux for 15 h. After cooling, the xylenes solution of the product was filtered and the supernatant was evaporated to dryness to give a yellow solid, which was recrystallized from heptane to yield 87% of the product (14.11 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (t, *J* = 5.5 Hz, 4H), 3.37 (t, *J* = 5.5 Hz, 4H), 3.51 (s, 2H), 5.21 (d, *J* = 11.0 Hz, 1H), 5.67 (d, *J* = 17.0 Hz, 1H), 6.60 (d, *J* = 5.0 Hz, 2H), 6.65 (dd, *J* = 11.0 Hz, *J* = 17.0 Hz, 1H) 7.23 (d, *J* = 7.5 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 8.22 (d, *J* = 5.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 45.9, 52.6, 62.7, 108.5, 113.7, 126.1, 129.5, 136.4, 136.6, 137.3, 150.5, 154.9.

4-Vinylbenzylbutylamine (59).[124] 4-Chloromethylstyrene (5.0 g, 33 mmol) and *N*-butylamine (24 g, 328 mmol) were allowed to react with excess *N*-butylamine following a literature procedure to afford the benzylamine product that was obtained by column chromatography (hexanes: ethyl acetate: 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 5.6 Hz, 3H), 1. 20 (s, 1H), 1.27 (m, 2H), 1.40 (m, 2H), 2.60 (t, J = 6.6 Hz, 2H), 3.67 (s, 2H), 5.10 (d, J = 11.0 Hz, 1H), 5.63 (d, J = 17.2 Hz, 1H), 6.60 (dd, J = 11.0 Hz, 17.0 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 7.27 (d, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) 14.1, 20.5, 32.5, 49.2, 53.9, 113.5, 126.1, 128.4, 136.3, 136.7, 140.4.

Poly((4-dodecylstyrene)-*c*-(DMAP)-*c*-(4-vinylbenzyl butylamine)) terpolymer (60). 4-Dodecylstyrene (1.0 g, 3.8 mmol), 4-vinylbenzyl amine (0.030 g, 0.16 mmol) and DMAP (0.10 g, 0.35 mmol) were dissolved in 2 mL of benzene and added to a dry Schlenk tube. AIBN (0.01 g, 0.06 mmol) was added to the flask and then the flask was sealed. The mixture was degassed using 3 freeze/pump/thaw cycles. After warming the mixture to room temperature, the reaction was heated in oil bath at 70 ^{o}C for 24 h. After cooling, the reaction mixture and the polymer were precipitated into 200 mL of MeOH. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (br s, 213H), 0.98-2.13 (br m, 1650H), 2.47 (br s, 180H), 3.23 (br s, 40H), 3.40 (br s, 20H), 3.67 (br s, 2H), 6.06-7.10 (br m, 340H), 8.22 (br s, 20H).

Poly((4-dodecylstyrene)-*c*-(DMAP)-*c*-(4-vinylbenzyl dansyl)) terpolymer (61). 5-(Dimethylamino)naphthalene-1-sulfonyl chloride (dansyl chloride) (15 mg, 0.060 mmol)

was dissolved in 3 mL of dry CH_2Cl_2 and this solution was then added to a solution of triethylamine (0.15 mL, 1.1 mmol) and poly((4-dodecylstyrene)-*c*-(DMAP)-*c*-(4-vinylbenzyl butylamine)) terpolymer (0.16 g, 0.021 mmol) in dry CH_2Cl_2 (3 mL). The reaction mixture was stirred for 12 h and then evaporated to dryness to remove any excess triethylamine. The residue was dissolved in CH_2Cl_2 (3 mL) and filtered through Celite to remove the ammonium salt NEt_3•HCl. The resulting solution was washed with 0.1 M NaOH. The organic phase was passed through a Na_2SO_4 plug, and the solvent was removed under reduced pressure to yield a yellow viscous oil (67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (br s, 213H), 0.98-2.13 (br m, 1650H), 2.47 (br s, 180H), 2.90 (br s, 6 H) 3.23 (br s, 40H), 3.40 (br s, 20H), 4.45 (br s, 2H), 6.06-7.10 (br m, 341H), 7.50 (br m, 2H), 8.34 (br s, 21H), 8.41 (br s, 1H), 8.58 (br s, 1H).

Acylation of 2,6-dimethylphenol (63). The C_{12}PS-supported catalyst **61** (0.10 g, 0.050 mmol) was dissolved in 4 mL of heptane. Separately, 2,6-dimethylphenol (0.30 g, 2.4 mmol) was dissolved in 4 mL of EtOH that contained Boc_2O (0.54 g, 2.5 mmol). The two solutions were then combined and stirred. The reaction was monitored by IR spectroscopy following the disappearance of the phenolic –OH group at 3300 cm^{-1} and the appearance of the carbonate carbonyl group at 1748 cm^{-1}. When the reaction was complete, 0.4 mL of water was added to induce phase separation. The aqueous phase was concentrated under vacuum to isolate the product as a clear liquid. Twenty cycles were performed with an average isolated yield per cycle of 91% . ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6 (s, 9H), 2.3 (s, 6H), 7.06-7.08 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ

16.1, 27.7, 83.0, 125.9, 128.7, 130.3, 148.4, 151.4. IR (neat): 2980, 1748, 1473, 1361, 1252, 1132.

Transesterification of 4-nitrophenyl acetate (65). The C_{12}PS-supported catalyst **61** (0.060 g, 0.030 mmol) was dissolved in 4 mL of heptane and added to a solution of 4-nitrophenyl acetate (0.10 g, 0.55 mmol) in 4 mL of EtOH. The reaction mixture was heated for 24 h at 80 ^{o}C. After the completion of the reaction, the reaction mixture was cooled and 0.4 mL of water was added to induce phase separation. The aqueous phase was concentrated under vacuum to isolate a bright yellow solid. 20 cycles were performed and the average isolated yield was found to be 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.9 (d, J = 9.0 Hz, 2H), 8.20 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.8, 126.3, 141.6, 161.4. IR (neat): 2934, 1589, 1485, 1326, 1269, 1163, 1097, 837.

A control reaction using 4-nitrophenyl acetate (0.10 g, 0.55 mmol) in 4 mL of EtOH and 4 mL of heptane was heated for 24 h at 80 ^{o}C. Under these conditions only 4% transesterification occured.

Acylation of 1-methylcyclohexanol (67). The C_{12}PS-supported catalyst **61** (0.29 g, 0.13 mmol) was dissolved in 3 mL of heptane. 1-Methylcyclohexanol (0.30 g, 2.60 mmol), triethylamine (0.40 g, 3.9 mmol) and acetic anhydride (0.39 g, 3.8 mmol) were added to this solution and the reaction mixture was heated for 12 h at 85 ^{o}C. After cooling, 3 mL of acetonitrile was added to the reaction mixture to form a biphasic solution. The acetonitrile-rich phase was separated and the solvent was removed under reduced pressure to give a liquid product. The catalyst was recycled 12 times with an average isolated yield of the acetate product 90% per cycle. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 1.2-1.6 (m, 11H), 2.0 (s, 3H), 2.08-2.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 22.3, 25.3, 25.4, 36.5, 81.6, 170.4. IR (neat): 2938, 2864, 1717, 1558, 1357, 1237, 1151, 1012.

Acylation of glycidyl isopropyl ether (69). The C_{12}PS-supported DMAP catalyst **61** (0.14 g, 0.060 mmol) was dissolved in 4 mL of heptane. Glycidyl isopropyl ether (0.15 g, 1.3 mmol) and acetic anhydride (0.15 g, 1.4 mmol) were added to this solution and the reaction mixture was heated for 12 h at 90 ^{o}C. After the reaction was complete, 4 mL of acetonitrile was added. The acetonitrile-rich phase containing the products was separated from the heptane-rich phase containing **61**. The acetonitrile phase was concentrated under reduced pressure to yield a yellowish liquid. Eight cycles were performed and the average isolated yield of the product per cycle was 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.0 Hz, 6H), 2.04 (d, *J* = 5.2 Hz, 6H), 3.54-3.62 (m, 3H), 4.15 (dd, *J* = 3.0 Hz, 12.0 Hz, 1H), 4.32 (dd, *J* = 3.4 Hz, 12.0 Hz, 1H), 5.12-5.19 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.6, 21.6, 62.8, 65.9, 70.4, 72.1, 170.1, 170.4. IR (neat): 2969, 2864, 1748, 1442, 1364, 1217, 1118.

(1*S*,2*S*,4*S*,5*R*)-2-((*S*)-((tert-butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (71). Quinidine **70** (2.0 g, 6.2 mmol) was dissolved in DMF (10 mL) and added to a 50-mL round-bottomed flask. Then, triethylamine (2 mL, 14 mmol), *tert*-butyldimethylsilyl chloride (0.84 g, 5.6 mmol) and dimethylaminopyridine (0.040 g, 0. 31 mmol) were added to the DMF solution. The reaction was allowed to stir for 12 h at room temperature. After reaction was complete, 30 mL of toluene was added, and the reaction mixture was transferred to a separatory funnel. The organic phase was washed

with first with saturated $NaHCO_3$ and then with water (50 mL x 2). The organic phase was dried over Na_2SO_4 and the solvent was removed to give a liquid product. The product was purified by flash chromatography (Ethyl acetate:MeOH/ 9:1) to yield a yellow liquid in 92% yield (2.5 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ = -0.47 (s, 3H, minor rotamer), -0.37 (s, 3H, major rotamer), 0.07 (s, 3H, major rotamer), 0.14 (s, 3H, minor rotamer), 0.83 (s, 9H, minor rotamer), 0.96 (s, 9H, major rotamer), 1.41-1.52 (m, 2H), 1.61-1.86 (m, 3H), 2.24 (m, 1H), 2.58-2.73 (m, 2H), 2.88-2.94 (m, 1H), 3.09 (t, *J* = 12.0 Hz, 1H), 3.45-3.58 (m, 1H), 3. 89 (s, 3H, minor rotamer), 3.91 (s, 3H, major rotamer), 4.78-5.01 (m, 2H, major rotamer), 5.59 (d, *J* = 2.1 Hz, 1H), 5.63-5.72 (m, 1H, major rotamer), 5.84-5.92 (m, 1H, manor rotamer), 7. 10 (d, *J* = 4.2 Hz, 1H, minor rotamer), 7.17 (d, *J* = 4.0 Hz, 1H, major rotamer), 7.32-7.39 (m, 1H), 7.53 (d, *J* = 4.5 Hz, 1H, major rotamer), 7.85 (s, 1H, minor rotamer), 7.97 (d, *J* = 9.3 Hz, 1H, minor rotamer), 8.03 (d, *J* = 9.2 Hz, 1H, major rotamer), 8.63 (d, *J* = 4.5 Hz, 1H, minor rotamer), 8.75 (d, *J* = 4.5 Hz, 1H, major rotamer).

(1*S*,2*S*,4*S*,5*R*)-2-((*S*)-((tert-butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine ethan-1-ol (72). Compound **71** (1.8 g, 4.1 mmol) was dissolved in THF (20 mL) and added to a 50-mL round-bottomed flask. To this solution, $BH_3{\cdot}SMe_2$ (0.13 g, 1.7 mmol) was slowly added and the reaction was allowed to stir for 12 h at room temperature. After 12 h, the reaction mixture was cooled to 0 ^{o}C and 4 mL of EtOH and 2 mL of 4 N aqueous NaOH were added. Then 1 mL of 35 wt % of H_2O_2 was slowly added and the reaction mixture was allowed to stir for 3 h at room temperature. At this point the reaction mixture was transferred to a separatory funnel and 50 mL of

CH_2Cl_2 was added. The organic phase was washed with H_2O (20 mL x 2) and brine (20 mL), and then dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the product was dried under vacuum to yield 1.6 g of white solid (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = -0.44 (s, 3H), 0.09 (s, 3H), 0.86 (s, 9H), 1.04-1.31 (m, 2H), 1.61-1.86 (m, 4H), 2.03 (m, 2H), 2.45 (m, 1H), 2.83 (m, 1H), 3.09 (m, 3H), 3.45 (m, 1H), 3.69 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ = -5.2, -4.2, 18.0, 20.5, 25.7, 26.0, 28.3, 31.9, 38.1, 43.2, 55.9, 58.7, 60.4, 60.7, 72.5, 100.6, 118.7, 121.8, 126.2, 131.6, 144.2, 147.2, 148.2, 158.1.

Michael adduct (76). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.85 (dd, *J* = 5.3 Hz, 16.8 Hz, 1H), 3.08 (dd, *J* = 6.7 Hz, 16.7 Hz, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 4.25 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 8.07 (d, *J* = 7.8 Hz, 2H).

Michael adduct (79). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.6 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.83 (d, *J* = 9.2 Hz, 1H), 4.19 (m 1H), 4.86 (m 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H).

4-Styryldiphenylphosphine (89). 4-Bromostyrene (5.6 g, 31 mmol) was dissolved in THF (100 mL) at room temperature. Then n-butyllithium (1.6 M, 37 mmol) was added to this solution. The mixture was stirred for 30 min at -78 ^{o}C, and chlorodiphenylphosphine (8.1 g, 37 mmol) was added to this solution dropwise. After 3 h of stirring at -78 ^{o}C and 1 h at room temperature, saturated aqueous NH_4Cl was added to this mixture. The mixture was extracted with ethyl acetate (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine. The organic layer was dried over the anhydrous $NaSO_4$, filtered and the solvent was evaporated to give a crude product of

diphenyl(4-styryl) phosphine. The product was purified by recrystallization from hot methanol to give 86 % yield of a white solid (7.59 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.21 (d, *J* = 10.8 Hz, 1H), 5.74 (d, *J* = 17.6 Hz, 2H), 6.61(dd, *J* = 17.7 Hz, 10.8 Hz, 1H), 7.27 (m, 14H); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 114.4, 126.3, 128.5, 128.7, 133.6, 133.8, 134.0, 136.4, 137.2, 137.9; ^{31}P NMR ($CDCl_3$) δ = -5.7. Melting point is 78 ^{o}C.

Poly(4-dodecylstyrene)-*c*-poly(*tert*-butylstyrene)-*c*-poly(4-styryldiphenylphosphine) terpolymer (90). 4-Dodecylstyrene (2.7 g, 9.9 mmol), *tert*-butylstyrene (5.5 g, 34 mmol) and 4-styryldiphenylphosphine (1.4 g, 4.9 mmol) were dissolved in 5 mL of 2-butanone and added to a 50-mL Schlenk tube equipped with a stir bar. RAFT reagent 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (0.13 g, 0.47 mmol) and AIBN (0.008 g, 0.049 mmol) were added to the flask and the resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in oil bath at 80 ^{o}C for 24 h. After cooling, the product was dissolved in 3 mL of chloroform and this solution was slowly added to excess MeOH (300 mL) to precipitate the desired polymer product in 75% yield (5.9 g). The product polymer was analyzed by GPC and had a M_n of 17000 Da with a PDI of 1.2. The ratio of monomers in the product was determined to be 5:2:1 based on NMR analysis integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 7.31 (diphenyl protons of 4-styryldiphenylphosphine. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (br t, 6H), 1.03-2.10 (br m, 109H), 2.47 (br s, 4H), 6.06-7.22 (br m, 34H), 7.31 (br m, 8H). ^{31}P NMR ($CDCl_3$) δ = -6.26.

2-Dicyclohexylphosphino-2'-hydroxybiphenyl (96). Magnesium shavings (0.42 g, 17 mmol) were added to a 100-mL round-bottomed flask. Then, tetrahydrofuran (10 mL),

2-methoxyphenylmagnesium bromide (19 mL of a 1.0 M solution in THF) and 1,2-bromochlorobenzene (2 mL, 17 mmol) were added sequentially to the reaction mixture. The reaction mixture was allowed to reflux for 2.5 h. At that point, the reaction mixture was cooled to room temperature. Copper(I) chloride (2.0 g, 20 mmol) and then chlorodicyclohexylphosphine (4.5 mL, 20 mmol) were added to the reaction mixture and was allowed to stir at room temperature for 16 h. At this point, 10 mL of saturated aqueous ammonia solution was added to the reaction and allowed to stir for 2 h. Then, the reaction mixture was transferred to the separately containing 100 mL of diethyl ether and 100 mL of saturated aqueous ammonia solution. The layers were allowed to separate and the aqueous layer was further extracted with 50 mL of diethyl ether. The organic layers were combined and washed with a saturated aqueous ammonia solution (2 X 100 mL). Then the organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to give a white residue. Recrystallization of the residue in methanol provided the white crystals in 50% yield (3.3 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89-1.43 (m, 10H), 1.57-1.74 (m, 11H), 1.94 (m, 1H), 3.74 (s, 3H), 6.93 (d, J = 8.2 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 7.10 (dd, J = 7.3 Hz, 1.8 Hz, 1H), 7.23 (m, 1H), 7.33-7.45 (m, 3H), 7.60 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 26.6, 27.2-27.8 (4 resonances), 28.6 (d, J_{CP} = 6.9 Hz), 29.8 (d, J_{CP} = 12.8 Hz), 30.0 (d, J_{CP} = 18 Hz), 30.7 (d, J_{CP} = 18.3 Hz), 33.6 (d, J_{CP} = 15.9 Hz), 35.0 (d, J_{CP} = 16.2 Hz), 55.0, 110, 119.8, 126.5, 128.5 (d, J_{CP} = 1.2 Hz), 128.6, 130.2 (d, J_{CP} = 5.9 Hz), 131.8 (d, J_{CP} = 2.6 Hz), 131.9 (d, J_{CP} = 6.6 Hz), 134.4 (d, J_{CP} = 3.4 Hz), 135.4 (d, J_{CP} = 21.2 Hz), 146.9 (d, J_{CP} = 32.0 Hz), 156.4 (d, 1.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ -10.5.

Next, a 50-mL round-bottomed two-necked flask was charged with 2-dicyclohexylphosphino-2'-methoxybiphenyl (1.0 g, 2.6 mmol) and dichloromethane (9.0 mL). The solution was cooled to -78 ^{o}C, and a solution of boron tribromide in dichloromethane (5.2 mL of 1.0 M solution) was added dropwise over 5 min. The reaction mixture was stirred at -78 ^{o}C for 15 min. After this, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 16 h of stirring, 3 mL of saturated aqueous sodium bicarbonate was added to the reaction mixture. The mixture was transferred to a separatory funnel and diluted with 100 mL of ethyl acetate. At this point, the mixture was washed with water (2 X 30 mL) and brine (30 mL). The organic layer was separated and dried over sodium sulfate. The solvent was removed under reduced pressure to give a white solid in 72% yield (0.70 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89-1.43 (m, 10H), 1.46-1.94 (m, 11H), 2.11 (m, 1H), 5.14 (s, 1H), 6.98-7.08 (d, 2H), 7.11 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 7.27-7.38 (m, 2H), 7.41-7.53 (m, 2H), 7.60-7.72 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 27.2-27.8 (5 resonances), 28.6, 29.8-30.0 (2 resonances), 30.5 (d, J_{CP} = 14 Hz), 32.4 (d, J_{CP} = 10.8 Hz), 35.2 (d, J_{CP} = 14.6 Hz), 116.7, 120.5, 127.5, 129.2, 129.4, 130.0 (d, J_{CP} = 6.2 Hz), 131.6 (d, J_{CP} = 6.0 Hz), 131.9 (d, J_{CP} = 1.9 Hz), 133.0 (d, J_{CP} = 2.6 Hz), 135.0 (d, J_{CP} = 20.1 Hz), 145.2 (d, J_{CP} = 30.7 Hz), 151.6. ^{31}P NMR (121 MHz, $CDCl_3$) δ -9.31.

Poly(4-dodecylstyrene)-*c*-poly(4-*tert*-butylstyrene)-*c*-poly(2-dicyclohexylphosphino-2'-biphenyl) terpolymer (97). 4-Dodecylstyrene (2.0 g, 7.4 mmol), *tert*-butylstyrene (4.5 g, 28 mmol) and 4-vinylbenzyl chloride (0.50 g, 3.3 mmol) that had been passed through an aluminum oxide plug to remove any inhibitor were dissolved in 2 mL of 2-

butanone and added to a 50-mL Schlenk tube equipped with a stir bar. RAFT reagent 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (0.10 g, 0.32 mmol) and AIBN (0.0060 g, 0.037 mmol) were added to the flask and the resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in oil bath at 80 ^{o}C for 48 h. After cooling, the product was dissolved in 3 mL of chloroform and this solution was slowly added to excess MeOH (300 mL) to precipitate the desired polymer product in 70% yield (4.1 g). The ratio of monomers in the product was determined to be 11:2:1 based on NMR analysis integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 4.45 (benzylic protons of 4-vinylbenzyl chloride). The chloromethylated poly(4-dodecylstyrene)-*co*-poly(*tert*-butylstyrene) terpolymer was then allowed to react with 2-dicyclohexylphosphino-2$^{'}$-hydroxybiphenyl using a thermomorphic conditions. In this reaction 2-dicyclohexylphosphino-2$^{'}$-hydroxybiphenyl (0.080 g, 0.22 mmol) was dissolved in DMF (10 mL) and allowed to react with Cs_2CO_3 (0.070 g, 0.22 mmol) for 1 h. Then a 10 mL heptane solution of chloromethylated terpolymer (0.42 g, 0.21 mmol) was added via cannula dropwise. The reaction mixture was heated at 90 ^{o}C and was allowed to stir for 24 h. After the mixture was cooled to room temperature, the top heptane-rich layer was separated and washed 3 times with MeCN. The solvent was removed under reduced pressure and the resulting solid was redissolved in a minimum amount of CH_2Cl_2 and added to MeOH (50 mL) to precipitate the copolymer as a yellowish solid in 70% yield (0.34 g). The product polymer was analyzed by GPC and had a M_n of 8400 Da with a PDI of 1.2. The ratio of monomers in the product was determined to be 11:2:1 based on NMR analysis

integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 4.95 (benzylic protons of 4-vinylbenzyl-2-dicyclohexylphosphino-2'-biphenyl). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (br s, 6H), 1.03-2.10 (br m, 203H), 2.47 (br s, 4H), 4.95 (br s, 2H), 6.06-7.22 (br m, 64H). ^{31}P NMR (121 MHz, $CDCl_3$) δ -11.1.

Poly(4-dodecylstyrene)-*c*-poly(4-*tert*-butylstyrene)-*c*-poly(2-dicyclohexylphosphino-2'-biphenyl diphenyl) terpolymer (97)'. 4-Dodecylstyrene (0.14 g, 0.51 mmol), *tert*-butylstyrene (0.33 g, 2.1 mmol) and 4-vinylbenzyl-2-dicyclohexylphosphino-2'-biphenyl (0.13 g, 0.26 mmol) were dissolved in 1 mL of 2-butanone and added to a 10-mL Schlenk tube equipped with a stir bar. RAFT reagent 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (0.0070 g, 0.025 mmol) and AIBN (0.00050 g, 0.0030 mmol) were added to the flask and the resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in oil bath at 80 ^{o}C for 24 h. After cooling, the product was dissolved in 1mL of chloroform and this solution was slowly added to excess MeOH (30 mL) to precipitate the desired polymer product in 72% yield (0.44 g). The product polymer was analyzed by GPC and had a M_n of 9000 Da with a PDI of 1.2. The ratio of monomers in the product was determined to be 11:1:1 based on NMR analysis integrating peaks at δ 2.47 (benzylic protons of the 4-dodecylstyrene) and δ 4.95 (benzylic protons of 4-vinylbenzyl-2-dicyclohexylphosphino-2'-biphenyl). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91(br t, 3H), 1.03-2.10 (br m, 176H), 2.47 (br s, 2H), 4.95 (br s, 2H), 6.06-7.22 (br m, 68H). ^{31}P NMR (121 MHz, $CDCl_3$) δ -11.1.

General Procedure for Suzuki reaction

4-Acetylbiphenyl (93). The polymer supported ligand **90** (0.080 g, 0.050 mmol) was dissolved in 2 mL of heptane and added to a 10-mL graduated centrifuge tube, to which $Pd(dba)_2$ (0.0060 g, 0.010 mmol) was added and the premixing of the ligand **90** and $Pd(dba)_2$ continued for 1 h at 95 ^oC. At this point, the premixed ligand **90** was added to another 10-mL graduated centrifuge tube containing 4-bromoacetophenone (0.20 g, 1.0 mmol), phenylboronic acid (0.15 g, 1.2 mmol), Cs_2CO_3 (0.40 g, 1.2 mmol) and DMF (2 mL). The graduated centrifuge tube was sealed and the solution was degassed using 3 freeze-pump-thaw cycles. The reaction was then heated at 95 ^oC for 8 h. After the reaction was complete, the DMF phase was separated from the heptane phase containing the catalyst and the solvent was removed under reduced pressure to obtain the biphenyl product. The catalyst was recycled 4 times with an average isolated yield of the biphenyl product of 93 % per cycle. ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 3H), 7.40-7.54 (m, 3H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 8.06 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 127.2, 127.3, 128.3, 128.9, 129.0, 135.8, 139.8, 145.7, 197.7

General Procedure for Buchwald-Hartwig amination reaction

***N*-Phenylmorpholine (Table 2, entry 1).** The polymer supported catalyst **97'** (0.10 g, 0.040 mmol) was dissolved in 2 mL of heptane and added to a 10-mL graduated centrifuge tube with a stir bar, to which $Pd(dba)_2$ (0.006 g, 0.01 mmol) was added. The centrifuge tube was sealed and the solution was degassed using 3 freeze-pump-thaw cycles. After warming to RT, the premixing of the ligand **97'** and $Pd(dba)_2$ continued

for 30 min at 60 ^{o}C. At this point, the premixed ligand **97'** was added to another 10-mL graduated centrifuge tube containing previously degassed bromobenzene (0.16 g, 1.0 mmol), morpholine (0.12 g, 1.4 mmol), KOBu (0.17 g, 1.5 mmol). The reaction was then heated at 90 ^{o}C for 19 h. After the reaction was complete, degassed MeOH (2 mL) was added to the centrifuge tube and the test tube was centrifuged for 5 min. At this point, the MeOH phase containing products was extracted and the heptane phase containing the catalyst **97'** was added to the test tube containing fresh substrates. MeOH was removed under reduced pressure to give phenylmorpholine product. The catalyst was recycled 5 times with an average isolated yield of the biphenyl product of 82 % per cycle. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (t, *J* = 4.5 Hz, 4H), 3.90 (t, *J* = 4.5 Hz, 4H), 6.95 (m, 3H), 7.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.5, 66.9, 115.6, 120.0, 129.5, 151.2

***N*-Methyl-*N*-phenylaniline (Table 2, entry 2).** The polymer supported catalyst **97'** (0.10 g, 0.040 mmol) was dissolved in 2 mL of heptane and added to a 10-mL graduated centrifuge tube with a stir bar, to which $Pd(dba)_2$ (0.0060 g, 0.010 mmol) was added. The test tube was sealed and the solution was degassed using 3 freeze-pump-thaw cycles. After warming to RT, the premixing of the ligand **97'** and $Pd(dba)_2$ continued for 30 min at 60 ^{o}C. At this point, the premixed ligand **97'** was added to another 10-mL graduated centrifuge tube containing previously degassed bromobenzene (0.16 g, 1.0 mmol), *N*-methylaniline (0.15 g, 1.4 mmol), KOBu (0.17 g, 1.5 mmol). The reaction was then heated at 90 ^{o}C for 19 h. After the reaction was complete, degassed MeOH (2 mL) was added to the test tube and the test tube was centrifuged for 5 min. At this point, the MeOH phase containing products was extracted and the heptane phase containing the

catalyst **97'** was added to the test tube containing fresh substrates. MeOH was removed under reduced pressure to give *N*-methyl-*N*-phenylaniline product. The catalyst was recycled 5 times with an average isolated yield of the biphenyl product of 85 % per cycle. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (s, 3H), 6.99 (td, *J* = 8.0 Hz, 2.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 4H), 7.32 (t, *J* = 8.0 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.5, 120.7, 121.6, 129.3, 149.0

Octadecyl acrylate (108). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.89 (t, 3H, J = 6.2 Hz), 1.25-1.43 (br, 30 H), 1.70 (m, 2H), 4.19 (t, 2H), 5.84 (d, *J* = 18.2 Hz, 1H), 6.15 (dd, *J* = 8.1 Hz, 17.6 Hz, 1H), 6.43 (d, *J* = 18.0 Hz, 1H).

General procedure for ATRP polymerization. Octadecyl acrylate (0.50 g, 1.5 mmol), was dissolved in 1 mL of heptane and added to a 10-mL graduated test tube equipped with a stir bar. CuBr (0.0060 g, 0.030 mmol), PMDETA (0.0080 g, 0.050 mmol), and ethyl 2-bromoisobuterate (0.0060 g, 0.030 mmol) were dissolved in 1 mL of DMF and added to the heptane solution in the 10-mL graduated test tube. The resulting solution was subjected to 3 freeze-pump-thaw cycles. Then, the mixture was heated in an oil bath at 100 ^{o}C for 24 h. After cooling, the biphasic mixture reformed and the top heptane-rich layer was separated and transferred to a 20-mL disposable vial. The solvent was removed under reduced pressure and the resulting solid was redissolved in a minimum amount of CH_2Cl_2 and added to MeOH (4 mL) to precipitate the polymer as an off-white solid. The DMF phase containing the catalyst was transferred via cannula to another 10-mL graduated test tube containing fresh monomer and the initiator in deoxygenated heptane phase for further recycling studies

CHAPTER VII

SUMMARY

Research presented in this dissertation includes the development of phase selectively soluble poly(4-alkylstyrene) supports and their applications under homogeneous conditions. Chapter II of this dissertation outlines the variety of syntheses of phase selectively soluble poly(4-alkylstyrene) co- and terpolymer supports that have been developed. By altering the structure of the pendant from a small *tert*-butyl alkyl chain to a longer dodecyl alkyl chain, an increase in nonpolar phase selective solubility was achieved as seen in the poly(4-*tert*-butylstyrene) and poly(4-dodecylstyrene) studies. Likewise, by modifying the design of the polymer support with respect to the ratio of 4-*tert*-butyl- or 4-dodecylstyrene monomers on the chain, comparable phase selectively soluble polymer supports can be prepared. These supports were prepared so that they contained chloromethyl groups that can be later converted into dye labels. Nonpolar phase selective solubility could be measured either qualitatively by attaching a UV-visible methyl red dye or quantitatively by using fluorescent dansyl dye. Both act as catalyst surrogates in thermomorphic and latent biphasic systems. Polymer supports that are based on 4-dodecylstyrene monomers or containing a fraction of 4-dodecylstyrene monomers can be expected to be useful in the recovery and recycling of catalysts or reagents in thermomorphic or latent biphasic systems where heptane is used as the nonpolar solvent for polymer recovery and separation.

Chapter III of this dissertation demonstrates the applications of these alkylated polystyrene copolymers as supports for organocatalysts such as dimethylaminopyridine (DMAP) and *Cinchona* alkaloid (quinidine). The advantage of these organocatalysts is that nonpolar phase selective solubility of the alkylated polystyrenes facilitates the isolation and separation of products when traditional or modified latent biphasic solvent mixtures are used.

Polystyrene-supported DMAP catalyst could be recycled up to twenty times without any loss of catalytic activity. Catalyst recyclability was monitored by incorporating a dansyl dye into the polystyrene-supported catalyst. Recyclability was found to be uniformly very high in a variety of strategies where the soluble polymer-bound catalyst was separated from products using a biphasic liquid/liquid separation. In the case of polystyrene-supported *Cinchona* alkaloid, the results showed that the poly(4-alkylstyrene)-supported quinidine catalyst was a recyclable catalyst in several asymmetric transformations using *trans*-4-methoxy-β-nitrostyrene and dimethyl fumarate as Michael acceptors. Unfortunately, the optical activity was absent for both asymmetric Michael addition reactions yielding an achiral product. This issue could be addressed by replacing a ternary THF:heptane:acetonitrile solvent mixture with a single solvent such as THF or toluene as was described in Chapter III. However, recycling using a single solvent would affect the separation strategy. Another approach to improve the enantioselectivity is to use a linker or a spacer of appropriate distance between the chiral catalytic active site and the backbone of the polymer. Spacers or linkers

containing five or more carbons are reported to give products with good enantioselectivity and high yield.

Chapter IV of this dissertation describes the syntheses of different poly(4-alkylstyrene)-supported phosphine ligands and their applications in palladium-mediated cross-coupling catalysis. The results show that poly(4-alkylstyrene)-supported phosphine ligated Pd(0) catalysts generated *in situ* are efficient catalysts in Suzuki and Buchwald-Hartwig amination reactions. The poly(4-alkylstyrene)-supported triphenylphosphine ligand was found to be a recyclable ligand in Pd-catalyzed Suzuki cross-coupling chemistry. The high phase selective solubility of this catalyst in the heptane phase allowed its consecutive reuse for four cycles under thermomorphic heptane/DMF conditions. The Pd content in the DMF phase containing the product was found to decrease with each subsequent cycle.

In combination with poly(4-alkylstyrene)-supported electron-rich biphenyl dicyclohexyl phosphine ligand, Pd(dba) could form a catalyst that was utilized in Buchwald-Hartwig amination reactions using aryl halides with morpholine or *N*-methylaniline. The catalyst was recycled up to five times with very low Pd leaching when methanol was added to extract the product.

The application of thermomorphic systems in ATRP polymerization is described in Chapter V. The ease of separation and recyclability are significant advantages when using low molecular weight copper catalysts in thermomorphic liquid/liquid separation solvent systems. Traditionally used post-polymerization purification methods such as column chromatography are not required to isolate the polymer product. Unfortunately,

the metal leaching that was detected in the product phase is a concern. This issue can be addressed by employing ICAR or ARGET ATRP methods, where the activator Cu(I) is regenerated through a reduction process from accumulated Cu(II) species using a reducing agent.

REFERENCES

1. Merrifield, R. B. *J. Am. Chem. Soc*. **1963**, *85*, 2149.
2. Letsinger, R. B.; Mahadevan, V. *J. Am. Chem. Soc*. **1966**, *88*, 181.
3. Bergbreiter, D. E. *Chem. Rev*. **2002**, *102*, 3345.
4. Bayer, E.; Mutter, M. *Nature* **1972**, *237*, 512.
5. Mecking, S. in "Multiphase Homogeneous Catalysis", Cronils, B.; Herrmann, W. A.; Horvath, I. T.; Leitner, W.; Mecking, S.; Bourbigou-Olivier, H.; Vogt, D., Eds., Wiley-VCH, Weinheim, **2005**, 766.
6. Prince, J. A.; Bhuvana, S.; Boodhoo, K. V. K.; Anbharasi, V.; Singh, G. *J. Membrane Science* **2014**, *454*, 538.
7. Sieber, F.; Wentworth Jr., P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem*. **1999**, *64*, 5188.
8. Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632.
9. Taylor, L. D.; Cerankowski, L D. *J. Polym. Sci. Polym. Chem. Ed.* **1975**, *13*, 255.
10. Zhang, Y.; Furyk, S.; Sagle, L. B.; Cho, Y.; Bergbreiter, D. E.; Cremer, P. S. *J. Phys. Chem*. **2007**, *111*, 8916.
11. Wang, Y.; Zhang, J.; Zhang, W.; Zhang, M. *J. Org. Chem.* **2009**, *74*, 1923.
12. Bergbreiter, D. E.; Caraway, J. W. *J. Am. Chem. Soc.* **1996**. *118*, 6092.
13. Bergbreiter, D. E.; Case, B. L.; Liu, Y.-S.; Caraway, J. W. *Macromolecules* **1998**, *31*, 6053.
14. Bergbreiter, D. E.; Chandran, R. *J. Am. Chem. Soc.* **1987**, *109*, 174.
15. Bergbreiter, D. E.; Weatherford, D. A. *J. Org. Chem.* **1988**, *54*, 2726.
16. Ohkubo, K.; Fukimori, K.; Yoshinaga, K. *Inorg. Nucl. Chem. Lett.* **1979**, *15*, 231.
17. Schurig, V.; Bayer, E. *CHEMTECH* **1976**, *6*, 212.
18. Charette, A. B.; Boezio, A. A.; Janes, M. K. *Org. Lett*. **2000**, *22*, 3777.
19. Lu, J.; Toy, P. H. *Synlett*. **2011**, *12*, 1723.
20. Lau, K. C. Y.; He, H.-S.; Chiu, P.; Toy, P. H. *J. Comb. Chem.* **2004**, *6*, 955.

21. Zheng, X.; Jones. C. W.; Weck, M. *Chem. Eur. J.* **2006**, *12*, 576.
22. Pollet, P.; Hart, R. J.; Eckert, C. A.; Liotta, C. L. *Acc. Chem. Res*. **2010**, *43*, 1237.
23. Jessop, P. G.; Heldebrant, D. J.; Li, X.; Eckert, C. A.; Liotta, C. L. *Nature* **2005**, *436*, 1102.
24. Hart, R.; Pollet, P.; Hahne, D. J.; John, E.; Llopis-Mestre, V.; Blasucci, V.; Huttenhower, H.; Leitner, W.; Eckert, C. A.; Liotta, C. L. *Tetrahedron* **2010**, *66*, 1082. Blasucci, V. M.; Hart, R.; Pollet, P.; Liotta, C. L.; Eckert, C. A. *Fluid Phase Equilib.* **2010**, *294*, 1.
25. Horváth, I. T. *Acc. Chem. Res*. **1998**, *31*, 641.
26. Gladysz, J. A.; Curran, D. P.; Horváth, I. T. *Handbook of Fluorous Chemistry*; 1st Ed.; Wiley-VCH: Weinheim, Germany, **2004**.
27. Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. *J. Am. Chem. Soc*. **2001**, *123*, 11105.
28. Horváth, I. T.; Rábai, J. *Science* **1994,** *266*, 72.
29. Bergbreiter, D. E.; Osburn, P. L.; Smith, T.; Li, C.; Frels, J. D. *J. Am. Chem. Soc*. **2003**, *125*, 6254.
30. Bergbreiter, D. E.; Liu, Y. S.; Osburn, P. L. *J. Am. Chem. Soc*. **1998**, *120*, 4250.
31. Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc*. **2000**, *122*, 9058.
32. Bergbreiter, D. E.; Sung, S. D. *Adv. Synth. Catal*. **2006**, *348*, 1352.
33. Bergbreiter, D. E.; Sung, S. D.; Li, J.; Ortiz, D.; Hamilton, P. N. *Org. Proc. Res. Dev*. **2004**, *8*, 461.
34. Datta, A.; Plenio, H. *Chem. Commun*. **2003**, 150.
35. Bergbreiter, D. E.; Li, C. *Org. Lett*. **2003**, *5*, 2445.
36. Shemyakin, M. M.; Ovchinnikov, Y. A.; Kiryushkin, A. A.; Kozhevnikova, I. V. *Tetrahedron Lett*. **1965**, *27*, 2323.
37. Bergbreiter, D. E. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 2351.

38. Bergbreiter, D. E.; Aviles-Ramos, N. A.; Ortiz-Acosta, D. *J. Comb. Chem.* **2007**, *9*, 609.
39. Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev*. **2002**, *102*, 3325.
40. Lopez-Carrasquero, F.; Giammanco, G.; Diaz, A.; Davila, J.; Torres, C.; Laredo, E. *Polym. Bull*. **2009**, *63*, 69.
41. Bergbreiter, D. E.; Osburn, P. L.; Li, C. *Org. Lett*. **2002**, *4*, 737.
42. Yang, Y.; Mijalis, A. J.; Fu, H.; Agosto, C.; Tan, K. J.; Batteas, J. D.; Bergbreiter, D. E. *J. Am. Chem. Soc*. **2012**, *134*, 7378.
43. Bergbreiter, D. E.; R. Hughes R.; Besinaiz, J.; Li, C.; Osburn, P. L. *J. Am. Chem. Soc.* **2003**, *125*, 8244.
44. Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk SSSR* **1967**, *176*, 97.
45. Hoefle, G.; Steglich, W.; Vorbrueggen, H. *Angew. Chem.* **1978**, *90*, 602.
46. Held, I.; von den Hoff, P.; Stephenson, D. S.; Zipse, H. *Adv. Synth. Catal.* **2008**, *350*, 1891.
47. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett*. **1979**, *20*, 99.
48. Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl*. **1978**, *17*, 522.
49. van Wijk, A. M.; Beerman, B.; Niederlander, H. A. G.; Siebum, A. H. G.; de Jong, G. J. *Ana. Bioanal. Chem*. **2011**, *400*, 1375.
50. Tsotsoros, S. D; Bate, A. B.; Dows, M. G.; Spell, S. R.; Bayse, C. A.; Farrell, N. P. *J. Inorg. Biochem*. **2014**, *132*, 2.
51. Murugan, R.; Scriven, E. F. V. *Adrichimica Acta*, **2003**, *36*, 21.
52. Goe, G. L.; Huckstep, M.; Scriven, E. F. V. *Chem. Ind*. **1982**, 722.
53. Hoefle, G.; Steglich, W. *Synthesis* **1972**, 619.
54. Subramaniam, D.; Murugesan, A.; Avinash, A.; Kumaravel, A. *Renew. Sustainable. Energy Rev*. **2013**, *22*, 361.
55. Imre, B.; Pukanszky, B. *Eur. Polym. J*. **2013**, *49*, 1215.
56. Christoffers, J.; Önal, N. *Eur. J. Org. Chem*. **2000**, 1633.
57. Fu, G. C. *Acc. Chem. Res*. **2000**, *33*, 412.
58. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.

59. Brown, H. C.; Eldred, N. R. *J. Am. Chem. Soc*. **1949**, *71*, 445.
60. Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem*. **2003**, *68*, 692.
61. Baidya, M.; Kobayashi, S.; Brotzel, F.; Schmidhammer, U.; Riedle, E.; Mayr, H. *Angew. Chem. Int. Ed*. **2007**, *46*, 6176.
62. Wang, L.; Sharpless, B. *J. Am. Chem. Soc*. **1992**, *114*, 7568.
63. H. Wynberg. H.; Staring, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 166.
64. Dolling, U.-H.; Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.* **1984**, *106,* 446.
65. Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.
66. Marcelli, T.; Hiemstra, H. *Synthesis*, **2010**, *8*, 1229.
67. Deratani, A.; Darling, G. D.; Horak, D.; Frechet, J. M. J. *Macromolecules*, **1987**, *20*, 767.
68. Rubinsztajn, S.; Zeldin, M.; Fife, W. K. *Macromolecules* **1991,** *24*, 2682.
69. Besenius, P.; Cormack, P. A. G.; Liu, J.; Otto, S.; Sanders, J. K. M.; Sherrington, D. C. *Chem. Eur. J*. **2008**, *14*, 9006.
70. Helms, B.; Liang, C. O.; Hawker, C. J.; Frechet, J. M. J. *Macromolecules* **2005**, *38*, 5411.
71. Kuang, Y. Q.; Zhang, S. Y.; Wei, L. L. *Syn. Commun*. **2003**, *33*, 3545.
72. Onimura, K.; Matsuzaki, K.; Lee, Y. K.; Tsutsumi, H.; Oishi, T. *Polym. J*. **2004**, *36*, 190.
73. Alvarez, R.; Hourdin, M.-A.; Cavé, C.; d'Angelo, J.; Chaminade, P. *Tetrahedron Lett*. **1999**, *40*, 7091.
74. Parvez, M. M.; Haraguchi, N.; Itsuno, S. *Macromolecules* **2014**, *47*, 1922.
75. Grunlan, M. A.; Regan, K. R.; Bergbreiter, D. E. *Chem. Commun*. **2006**, 1715.
76. DeClue, M. S.; Siegel, J. S. *Org. Biomol. Chem.* **2004**, *2*, 2287.
77. Khamatnurova, T. V.; Bergbreiter, D. E. *Polym. Chem.* **2013**, *4*, 1617.
78. Tsogoeva, S. Eur. *J. Org. Chem*. **2007**, 1701.
79. Qin, Y.; Yang, G.; Yang, L.; Li, J.; Cui, Y. *Catalysis Lett*. **2011**, *14*, 481.
80. Gavin, D. P.; Stephens, J. C. *ARCIVOC*, **2011**, *9*, 407.

81. Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F.III *J. Am. Chem. Soc*. **2006**, *128*, 4966.
82. Gelman, D.; S. L. Buchwald, S. L. *Angew. Chem*. **2003**, *115*, 6175.
83. Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc*. **2004**, *126*, 13028.
84. Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc*. **2007**, *129*, 3844.
85. Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem.* **2006**, *118,* 3564.
86. Okano, K.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc*. **2006**, *128*, 7136.
87. Alici, B.; Oezdemir, I.; Guerbuez, N.; Cetinkaya, E.; Cetinkaya, B. *Heterocycles* **2005**, *65*, 1439.
88. Witker, D.; Reynolds, J. R. *Macromolecules* **2005**, *38*, 7636.
89. Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173.
90. Brautbar, N.; Howard, J. *Toxicol. Ind. Health* **2002**, *18*, 71.
91. Zhao, L.-J.; He, H. S.; Shi, M.; Toy, P. *J. Comb. Chem.* **2004**, *6*, 680.
92. Schweizer, S.; Becht, J.-M.; Le Drian, C. *Org. Lett*. **2007**, *9*, 3777.
93. Iwai, T.; Harada, T.; Hara, K.; Sawamura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12322.
94. Parrish, C. A.; Buchwald, S. L. *J. Org. Chem*. **2001**, *66*, 3820.
95. Chen, W.; Li, P.; Wang, L. *Tetrahedron* **2011**, *67*, 318.
96. Shin, J.; Bertoia, J.; Czerwinski, K. R.; Bae, C. *Green Chem*. **2009**, *11*, 1576.
97. an der Heiden, M.; Plenio, H. *Chem.-Eur. J.* **2004**, *10*, 1789.
98. Bergbreiter, D. E.; Li, J. *Chem. Commun*. **2004**, 42.
99. Bergbreiter, D. E.; Yang, Y.-C.; Hobbs, C. E. *J. Org. Chem*. **2011**, *76*, 6912.
100. Priyadarshani, N.; Suriboot, J.; Bergbreiter, D. E. *Green Chem*. **2013**, *15*, 1361.
101. Wang, J.-S.; Matyjaszewski K. *J. Am. Chem. Soc*. **1995**, *170*, 5614.
102. Matyjaszewski, K.; Tsarevsky, N. V. *Nat. Chem*. **2009**, *1*, 276.

103. Matyjaszewski, K.; Spanswick, J. *Mater. Today* **2005**, 26.

104. Hong, S.C.; Matyjaszewski, K**.** *Macromolecules* **2002,** *35,* 7592.

105. Sarbu, T.; Pintauer, T.; McKenzie, B.; Matyjaszewski, K. *J. Polym. Sci. Part A: Polym. Chem.* **2002**, *40*, 3153.

106. Haddleton, D. M.; Jackson, S. G.; Bon, S. A. F. *J. Am. Chem. Soc.* **2000**, *122*, 1542.

107. Weiser, M.; Mülhaupt, R. *J. Polym Sci. Part A: Polym. Chem*. **2005**, *43*, 3804.

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

109. Bergbreiter, D. E.; Hamilton, P. N.; Koshti, M. *J. Am. Chem. Soc*. **2007**, *129*, 10666.

110. Dong, H. C.; Matyjaszewski, K. *Macromolecules*, **2008**, *41*, 6868.

111. Even, M.; Haddleton, D. M.; Kukulj, D. *Eur. Polym. J*. **2003**, *39*, 633.

112. Muñoz-Bonilla, A.; León, O.; Cerrada, M. L.; Rodríguez-Hernández, J.; Sánchez-Chaves, M.; Fernández-García, M. *J. Polym. Sci. Part A: Polym. Chem*. **2012**, *50*, 2556.

113. Monge, S.; Darcos, V.; Haddleton, D. M. *J. Polym. Sci. Part A: Polym. Chem*. **2004**, *42*, 6299.

114. Mueller, L.; Jakubowski, W.; Tang, W.; Matyjaszewski, K. *Macromolecules* **2007**, *40*, 6464.

115. Jakubowski, W.; Matyjaszewski, K. *Macromol. Symp*. **2006**, *240*, 213.

116. Kwak, Y.; Matyjaszewski, K. *Polym. Int.* **2009**, *58*, 242.

117. Matyjaszewski, K.; Coca, S.; Gaynor, S. G.; Wei, M. L.; Woodworth, B. E. *Macromolecules* **1997**, *30*, 7348.

118. Kwak, Y.; Magenau, A. J. D.; Matyjaszewski, K. *Macromolecules* **2011**, *44*, 811.

119. Nakamura, K.; Nakajima, T.; Kayahara, H.; E. Nomura, E.; H. Taniguchi, H. *Tetrahedron Lett.* **2004**, *42*, 45.

120. B. Zeynizadeh, B.; Sadighnia, L. *Bull. Korean Chem. Soc*. **2010**, *31*, 2644.

121. Yadav, J. S.; Narsaiah, A. V.; Reddy, B. V. S.; Bazak, A. K.; Nagaiah, K. *J. Mol. Catal. A: Chem.* **2005**, *230*, 107.

122. Clawson, R. W. Jr.; Dacko, C. A.; Deavers, R. E. III; Akhmedov, N. G.; Söderberg, B. C. G. *Tetrahedron* **2005**, *65*, 8786.

123. Overberger, C. G.; Frazier, C.; Mandelman, J.; Smith, H. F. *J. Am. Chem. Soc*. **1953**, *75*, 3326.

124. Garcia-Con, L. M.; Whitcombe, M.; Piletska, E. V.; Piletsky, S. A. *Angew. Chem. Int. Ed.* **2010,** *49*, 4075.

APPENDIX

Table A1 Data for Figure 8: Calibration curve for *N*-benzyl-*N*-butyl-5-dimethyl aminonaphthalene-1-sulfonamide **37** in (a) heptane and (b) acetonitrile

a) heptane

entry	Concentration [N]	Intensity (cps)
1	1.79E-07	753982
2	7.36E-07	2233333
3	1.03E-06	3266667
4	1.47E-06	4500000
5	2.06E-06	6286667

b) acetonitrile

entry	Concentration [N]	Intensity (cps)
1	4.76E-07	9.07E05
2	8.29E-07	1.60E06
3	1.15E-06	2.00E06
4	1.66E-06	2.87E06
5	2.01E-06	3.43E06

Table A2 Data for Figure 10: The concentrations for four consecutive cycles of the poly(4-dodecylstyrene) copolymer **33** and poly(4-*tert*-butylstyrene) copolymer **34** in the acetonitrile phase. According to the calibration curve, the concentration of the original polymer in heptane was determined 1.3 mN for **33** and **34**

cycle	Concentration of **33** [μN]	Concentration of **34** [μN]
1	0.9500	8.100
2	0.7200	5.000
3	0.5200	3.500
4	0.4000	2.900

Table A3 Data for Figure 12: The concentrations of poly(4-*tert*-butylstyrene) terpolymer **39c, 39b, 39a** copolymerized with 4-dodecylstyrene and poly(4-methylstyrene) terpolymer **38c, 38b, 38a** copolymerized with 4-dodecylstyrene or terpolymer **40** containing 90 mol % of 4-dodecylstyrene in the DMF phase. The concentration of the original solution was 1.3 μN

polymer	% leaching 1 cycle	% leaching 2 cycle	% leaching 3 cycle
39c	0.2300	0.2000	0.1500
39b	0.1100	0.0700	0.0600
39a	0.0900	0.0600	0.0400
38c	0.9000	0.7000	0.6000
38b	0.4000	0.2700	0.2200
38a	0.2700	0.1800	0.1400
40	0.0550	0.0420	0.0300

Table A4 Data for Figure 13: The concentrations for four consecutive cycles of the poly(4-dodecylstyrene)copolymer **33** and for three consecutive cycles of poly(4-*tert*-butylstyrene)terpolymer **39b** containing only 9 mol% of dodecyl groups. The original concentration of the polymer was determined to be 1.3 μN

cycle	Concentration of **33** [μN]	Concentration of **39b** [μN]
1	0.9500	1.4000
2	0.7200	0.9000
3	0.5200	0.7800
4	0.4000	-