

Soluble Polymers as Scaffolds for Recoverable Catalysts and Reagents

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Received April 10, 2002

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I. Introduction

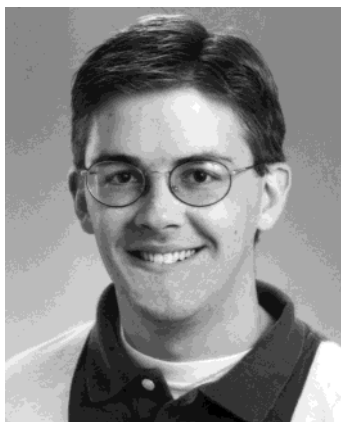
The use of polymeric supports in organic synthesis has become common practice, especially following the rapid development of combinatorial chemistry. Starting with the introduction of solid-phase peptide synthesis by Merrifield,¹ insoluble supports such as lightly cross-linked polystyrene have been implemented in a wide range of synthetic methodologies.^{2–4} Primarily, the uses of these polymers in synthesis have fallen into one of two areas: (A) the use of the polymer as a support for reactants or (B) the use of the polymer as a support for reagents and catalysts during a reaction. Both of these methods allow rapid product purification and the ability to drive a given reaction to completion through the use of an excess of reagents. However, despite the well-known advantages of insoluble supports, there are several short-

comings in the use of these resins due to the heterogeneous nature of the reaction conditions. Several laboratories have explored alternative methodologies to restore homogeneous reaction conditions resulting from a number of problems associated with insoluble polymer supports, including nonlinear kinetic behavior, unequal distribution or access to the chemical reaction, solvation problems associated with the nature of the support, and synthetic difficulties in transferring standard organic reactions to the solid phase. By replacing insoluble cross-linked resins with *soluble* polymer supports, the familiar reaction conditions of classical organic chemistry are reinstated, yet product purification is still facilitated through application of macromolecular properties. This methodology, termed liquid-phase synthesis, in essence avoids the difficulties of solid-phase synthesis while preserving many of its advantages.

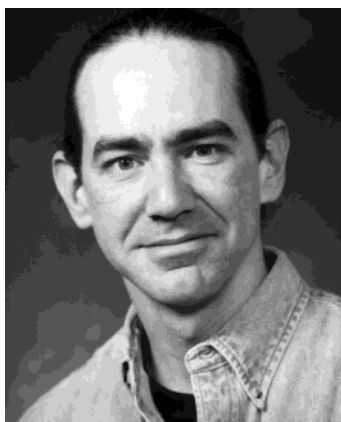
Initially, the term “liquid-phase” synthesis was used to contrast the differences between solid-phase peptide synthesis and a method of synthesis on soluble poly(ethylene glycol).^{5,6} Although “soluble polymer-supported” synthesis is less ambiguous than “liquid-phase” synthesis, the latter term is more prevalent in the literature. In keeping with previous reviews,^{7–12} the phrases “classical” or “solution” synthesis will be used to describe homogeneous reaction schemes that do not employ polymer supports while “liquid-phase” synthesis will be reserved for methodologies incorporating a soluble macromolecular carrier to facilitate product isolation.

In recent years, the use of soluble polymer-supported reagents and catalysts has gained significant attention as an alternative to traditional solid-phase synthesis. Inherent to library generation on solid support are two nondiversity-building steps, attachment and cleavage. Frequently, these procedures are not advantageous, and as a result, parallel libraries are commonly generated in solution. To facilitate synthesis, polymer-supported reagents and catalysts have found frequent use in the preparation and purification of these solution-phase libraries.^{13–17} However, the catalytic activity or stereoselectivity of these polymer-supported catalysts does not always correlate with their solution-phase counterparts. Subtle variations in the polymeric backbone can have profound implications in the activity of a support-bound catalyst. Also, in the case of solid-supported catalysts, many of the drawbacks of solid-supported organic synthesis are still present (e.g., inherent heterogeneity of reactions, inaccessibility of reagents

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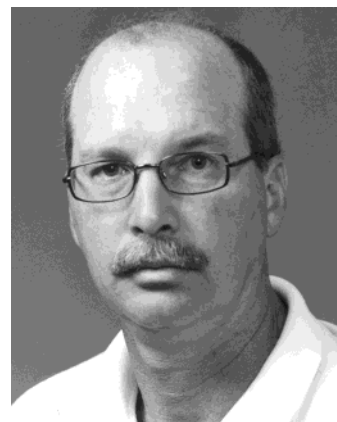
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to the catalyst). To combine some of the advantages of solution-phase chemistry with insoluble polymer-immobilized reagents and catalysts, soluble polymers have received significant attention as an alternative polymer support. This article will focus on the implementation of methodologies for soluble polymer-supported catalysts and reagents in organic synthesis.

II. Overview of Soluble Polymers in Organic Synthesis

A. Properties of Soluble Polymeric Supports

In order for a polymer to be useful as a soluble support for a catalyst or reagent, the polymer must (1) be commercially available or rapidly and conveniently prepared, (2) demonstrate good mechanical and chemical stability, (3) provide appropriate functional groups for easy attachment of organic moieties,



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and (4) exhibit high solubilizing power in order to dissolve molecular entities with low solubilities and permit the development of a general synthetic methodology independent of the physicochemical properties of target compounds.

Additionally, it should be realized that polymer supports purchased or prepared in the laboratory do not exist as one discrete molecular weight but instead consist of macromolecules with variable sizes. Polymer properties are known to vary with chain length, and as such, the molecular weight range of the support should be narrow; that is, the polydispersity should approach unity. Soluble supports in general should have molecular weights high enough to be solid or crystalline at room temperature and yet not excessively high that solubility and loading capacity are reduced to impractical levels.

Furthermore, the polymeric carrier must be robust enough to withstand the reaction conditions used in solution-phase synthesis. Consequently, most soluble supports used in liquid-phase synthesis possess hydrocarbon or alkyl ether backbone structures due to their inherent stability to standard reaction conditions. The properties of the macromolecular carrier, as well as the possible sites of attachment, are determined by variation of both the terminal and pendant functional groups of these two core backbone structures. If the conditions of polymerization and choice of monomer allow for suitable polymer functionalization, anchoring of the initial synthetic structure may be made directly to the support for liquid-phase synthesis. However, a linking group is often employed to impart anchor stability throughout synthesis, to improve accessibility to reagents, and to allow for product cleavage under specific, and generally orthogonal, conditions.

Polymers chosen for liquid-phase synthesis must also provide a reasonable compromise between load-

ing capacity and solubilizing power. The loading capacity of a polymer support is a measure of the number of anchoring sites per gram of polymer and is expressed in units of millimoles per gram. High loading capacities are advantageous to reduce the total expenditure for polymer supports and to allow manageable amounts of material in medium- or large-scale applications. Solubilizing power refers to the ability of the macromolecular carrier to maintain a homogeneous solution of the polymer-bound organic moiety; this property is especially important in cases where the unbound moiety is insoluble in the reaction medium. High solubilizing power is desirable to ensure homogeneous reactions and high yields throughout the synthetic scheme. Generally, solubilizing power decreases as loading capacity increases because as the polymer is further loaded, the solubility properties of the polymer-organic moiety conjugate are increasingly determined by the properties of the attached compounds. Thus, it is critical to achieve a balance between polymer loading and solubilizing power that limits solubility changes while still providing an economic and manageable synthesis.

Finally, polymers with a high loading capacity can experience complications due to the influence of neighboring anchoring sites. The presence of multiple compounds attached to a polymer support may result in nonequivalent reactivity of bound moieties due to unequal distribution along the polymer backbone. In some situations, excess reagents or longer reaction times may be required for reaction of attached compounds on heavily laden polymers; however, other reactions may require linkage exclusively to polymer termini to provide adequate accessibility to polymer-bound reagents or enzymes.

B. Methods for Separating Polymers from Reaction Mixtures

Traditionally, soluble polymers have received less attention as polymeric supports than their insoluble counterparts. A perceived problem with the use of soluble polymers rested in the ability to isolate the polymer from all other reaction components. Yet, in practice, this separation is not difficult and several methods have capitalized on the macromolecular properties of the soluble support to achieve product separation in liquid-phase synthesis. Most frequently the homogeneous polymer solution is simply diluted with an appropriate solvent that induces precipitation of the support. Analogous to solid-phase synthesis, the resulting heterogeneous mixture is filtered to isolate the polymer-product conjugate while excess reagents and impurities are rinsed away. Some polymers may be recrystallized to minimize the formation of inclusion complexes during precipitation, and the proper choice of solvents and temperature must be made to achieve satisfactory recovery and purification.^{18,19}

Although precipitation/crystallization is the fastest and most common mode of product separation, other methods have been used to isolate soluble polymeric supports from low molecular weight impurities. Dialysis using a semipermeable membrane has achieved polymer purification.²⁰ This methodology

becomes less time-consuming in ultrafiltration, also called diafiltration or membrane filtration, when pressure gradients speed the separation of polymer from the reaction supernatant using a membrane. Additionally, centrifugation methods allow convenient isolation of biomolecules and could be applied to more general polymer separations. Gel permeation chromatography and adsorption chromatography have also been demonstrated as means to remove excess reagents and byproducts away from polymeric products.⁹

These macromolecule-based purification methods isolate polymer-bound products from soluble impurities, but do not generally purify the product from other polymer-bound byproducts. Such byproducts arise from incomplete reactions or side reactions; and in classical solution chemistry, similar byproducts are removed during product purification at each step of a multistep synthesis. Support-based methodologies, while removing the multiple, laborious purification steps of a classical synthesis, generally do not provide a method for the purification of intermediates. Instead, these methodologies demand that reaction conditions be optimized such that reactions are driven to completion to avoid a complicated final mixture of products. However, some developed liquid-phase methods achieve high purity of products without quantitative reaction yields.²¹⁻²⁶

C. Analytical Methods in Liquid-Phase Synthesis

A frequent complication in the use of an insoluble polymeric support lies in the on-bead characterization of intermediates. Although techniques such as MAS ¹H NMR, gel-phase ¹³C NMR, and single-bead IR have had a tremendous effect on the rapid characterization of solid-phase intermediates,²⁷⁻³⁰ the inherent heterogeneity of solid-phase systems precludes the use of many traditional analytical methods. Liquid-phase synthesis does not suffer from this drawback and permits product characterization on soluble polymer supports by routine analytical methods including UV-visible, IR, and NMR spectroscopies as well as high-resolution mass spectrometry. Even traditional synthetic methods such as TLC may be used to monitor reactions without requiring preliminary cleavage from the polymer support.^{10,18,19} Moreover, aliquots taken for characterization may be returned to the reaction flask upon recovery from these nondestructive analytical methods. Chemical methods such as titration and derivatization can also be routinely performed and allow for subsequent characterization in the presence of the bound soluble support. Other traditional analytical methods used to monitor amide bond formation have been performed on poly(ethylene glycol);³¹ however, unreliable results have been demonstrated using certain methods.³² Circular dichroism (CD) measurements have also been shown to be feasible on poly(ethylene glycol)-bound peptides.³³ Two peptides, substance P and a hydrophobic peptide corresponding to myoglobin sequence 66-73, were synthesized and CD data reported the formation of secondary structures and the influence of peptide protecting groups on structure. The poly(ethylene glycol) support did not inter-

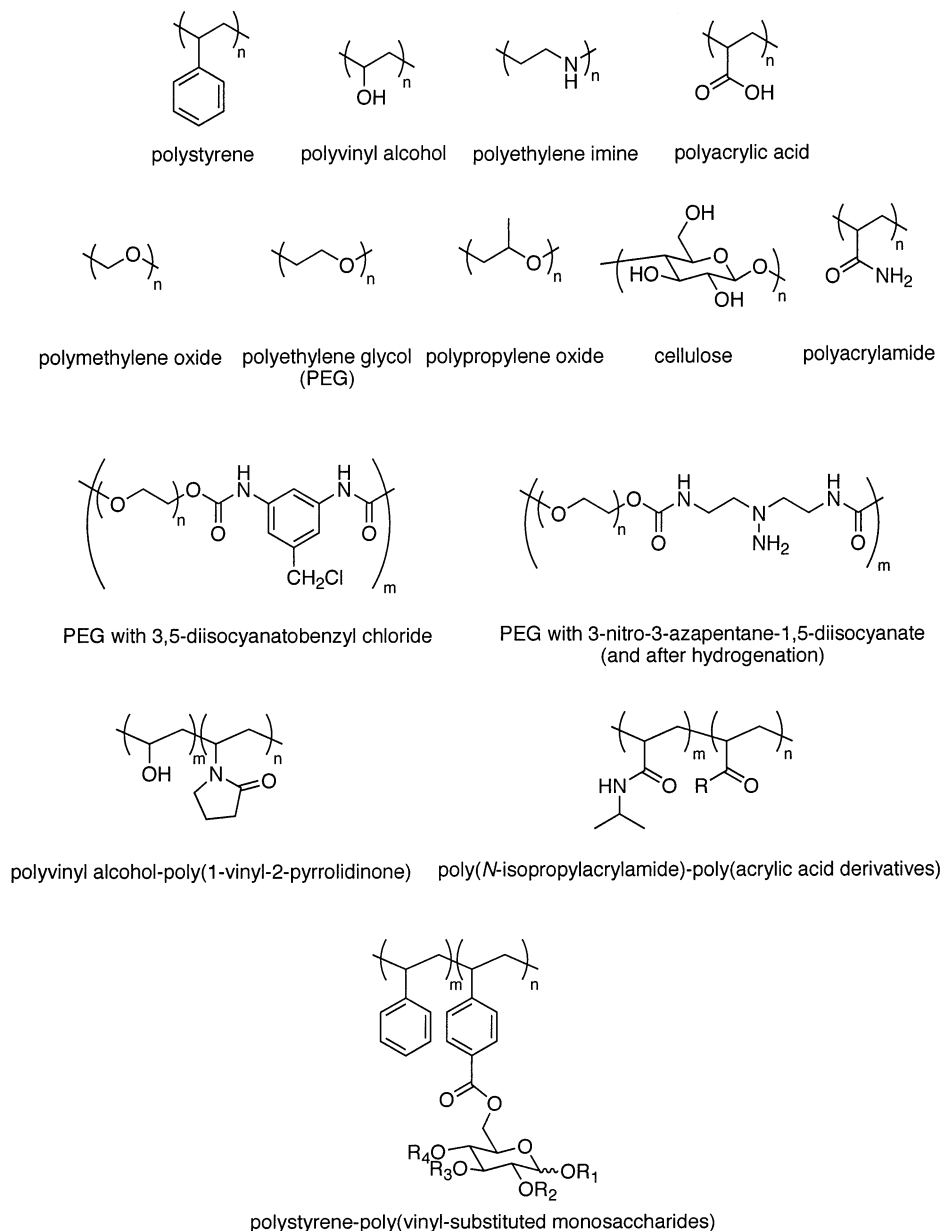


Figure 1. Soluble polymers used as supports for liquid-phase synthesis.

fere due to its UV cutoff at 190 nm, and the solubilizing power of the polymer support allowed solution measurements in solvents that the free peptide displayed limited solubility.

D. Listing of Polymers

Soluble polymers that have been used in liquid-phase methodologies are listed in Figure 1.^{3,7,8,34,35} Poly(ethylene glycol) and non-cross-linked polystyrene are some of the most often used polymeric carriers for organic synthesis and have found frequent use in the preparation of soluble polymer-supported catalysts and reagents; consequently, a brief discussion of these polymers is warranted.

i. Poly(ethylene glycol) (PEG)

Poly(ethylene glycol), poly(ethylene oxide) (PEO), poly(oxyethylene) (POE), and polyoxirane all refer to the linear polymer formed from the polymerization

of ethylene oxide. By convention, PEG usually indicates the polyether of molecular weight less than 20 000; PEO signifies polymers of higher molecular weights, and POE and polyoxirane have been applied to polymers of a wide range of molecular weights.¹⁹ Throughout this review, the term PEG will be used since poly(ethylene glycol)s of 2000–20 000 molecular weight are utilized as supports in organic synthesis. These limits have been set by the physical properties of the polymer; that is, within this molecular weight range PEG is both crystalline and has an acceptable loading capacity (1–0.1 mmol/g); lower molecular weight PEG exists as a liquid or wax at room temperature, and higher molecular weight PEG has a low loading capacity. Macromolecular size will be reported in this review using the notation PEG₆₀₀₀ to represent poly(ethylene glycol) of molecular weight 6000. It should again be emphasized that polymers do not exist as a singular molecular weight species, but as a distribution of molecular weights, although

the polydispersity of commercial PEG is reasonably narrow.¹⁹

Depending on polymerization conditions, PEG termini may consist of hydroxyl groups or may be selectively functionalized. Commercially available PEG is produced through anionic polymerization of ethylene oxide to yield a polyether structure possessing either hydroxyl groups at both ends or a methoxy group at one end and a hydroxyl group at the other. Further development of this method also allows the preparation of PEG that possesses a benzyl, *tert*-butyldimethylsilyl, or tetrahydropyranyl ether on one end and a free hydroxyl group at the other.³⁶ In this review, PEG will be used to represent poly(ethylene glycol) with hydroxyl functionalities at both ends. Similarly, poly(ethylene glycol) monomethyl ether (MeO-PEG) will indicate the polyether terminated by a methoxy group at one end and a free hydroxyl at the other. The polymer MeO-PEG is considered monofunctional because the methoxy group of MeO-PEG typically remains unchanged throughout chemical manipulations; and for identical chain lengths, the loading capacity of PEG is twice that of MeO-PEG as two hydroxyl groups serve as anchoring sites on PEG.

Employed as a protecting group, poly(ethylene glycol) exhibits solubility in a wide range of solvents including DMF, dichloromethane, toluene, acetonitrile, and water. PEG is insoluble in hexane, diethyl ether, *tert*-butyl methyl ether, isopropyl alcohol,³⁷ and cold ethanol, and these solvents have been used to induce PEG precipitation for purification. Careful precipitation conditions or cooling of polymer solutions in alcoholic solvents yields crystalline PEG due to the helical structure of the polymer that produces a strong propensity to crystallize.¹⁹ Purification by crystallization of the polymeric support is therefore feasible at each reaction step provided that the polymer backbone remains unaltered during the synthesis. Additionally, the solubilizing power of PEG not only permits homogeneous reactions conditions but also allows individual reaction steps to be monitored without requiring cleavage from the polymer support. The characterization of PEG-immobilized organic moieties is often identical to solution-phase small-molecule characterization as the polymer does not interfere with spectroscopic or chemical methods of analysis. In the case of MeO-PEG, the single methoxy group ($\delta = 3.38$ ppm; ethyl protons of PEG backbone $\delta = 3.64$ ppm in CDCl₃)³⁸ can be used as an internal integration standard, allowing for easy monitoring of chemical reactions by ¹H NMR spectroscopy.³⁹

ii. Non-Cross-Linked Polystyrene

Although poly(ethylene glycol) has found widespread use both in liquid-phase synthesis and as a scaffold for liquid-phase reagents and catalysts, it is not without drawbacks. Under standard low-temperature conditions used in synthesis (-78 °C in THF), PEG has very limited solubility. Additionally, PEG also poses a problem during the removal of excess organometallic reagents and inorganic materials due to its water solubility. Furthermore, the polyether backbone of PEG has known lability to strong base, complicating the use of organometallic reagents. To

compensate for this other polymeric supports, such as non-cross-linked polystyrene (NCPS), have been employed in liquid-phase methodologies. As is true for many other polymeric support-based methodologies, NCPS was first demonstrated to be useful in peptide synthesis.^{40,41} The utility has been further extended in a variety of publications detailing synthetic transformations of compounds immobilized on NCPS.^{42–48}

Non-cross-linked polystyrene is readily prepared from inexpensive materials using standard conditions and the functional group content of the polymer easily controlled by the stoichiometry of each monomer present in the monomer feed. As with PEG, the functional group content can be readily quantified using simple ¹H NMR analysis. The polymer has remarkable solubility properties that are extremely useful to organic chemists. It is soluble in THF, dichloromethane, chloroform, benzene, and ethyl acetate even at low temperatures (-78 °C) and is insoluble in water and methanol. It is this solubility profile that allows the implementation of solvent extraction techniques commonly used in classical organic synthesis.^{7,18,42–46} Consequently, after completion of a homogeneous reaction, the polymer-bound compounds can be diluted with dichloromethane or ethyl acetate and the organic layer subjected to an aqueous extraction. Methanol can then be used to precipitate the polymer and its uniquely bound compound as a solid, leaving behind any solution-phase products that can be separated by filtration. Finally, as NCPS is a soluble polymer, NMR analysis can be accomplished of any polymer-bound intermediates in a nondestructive manner^{42–48} without the need for specialized NMR techniques or equipment.

III. PEG-Supported Catalysts

Many different soluble polymers have been used as supports for catalyst immobilization. Since solvation of otherwise insoluble catalysts can frequently be accomplished by attachment to a soluble polymer, these supports have found significant use in the immobilization of classical solution-phase catalysts. Here, we will only survey PEG as a soluble polymeric support for catalysis. The use of other types of soluble polymers (e.g., polyethylene, non-cross-linked polystyrene) will be reviewed elsewhere in this issue.⁴⁹

A. Hydrogenation Catalysts

The earliest disclosure of a catalyst on a soluble polymer support was made by Bayer and Schurig, who reported the preparation of several soluble hydrogenation catalysts.⁵⁰ Although these catalysts included MeO-PEG-supported hydrogenation catalysts, only results using NCPS were described. Another early application of soluble polymers as a catalyst support was reported by Whitesides.⁵¹ Here, a series of water-soluble phosphines, including a MeO-PEG-supported bis(phosphine), were prepared for rhodium-catalyzed hydrogenation of various olefins in water. It was hypothesized that, by appending MeO-PEG onto the ligand, the solubility of the phosphine ligand would be increased. Water solubil-

ity was also achieved by forming various salts, and these proved more practical than the MeO-PEG catalyst since the observed number of turnovers (27) for the MeO-PEG bis(phosphine) was among the lowest reported in the series of catalysts surveyed.

In 1993, Bergbreiter prepared two soluble polymer-supported phosphines that exhibited an inverse temperature-dependent solubility in water.⁵² Although PEG-supported phosphine undergoes a phase separation from water at 95–100 °C, the PEO–poly(propylene oxide)–PEO-supported catalyst was superior as it is soluble at low temperatures and phase-separates at a more practical 40–50 °C. Treatment of a diphenylphosphinoethyl-terminated PEO–PPO–PEO triblock copolymer with (Ph₃P)₃RhCl provided a catalyst that was used in the aqueous hydrogenation of allyl alcohol. This hydrogenation proceeded smoothly at 0 °C, but stopped upon warming to 40–50 °C and produced a dispersion of clear oily droplets. This effect was reversible, and cooling the reaction mixture allowed hydrogen uptake to continue. Furthermore, this behavior was observed through a series of four heating and cooling cycles. Bergbreiter termed these “smart ligands” since they control catalytic activity as a function of temperature.

Asymmetric hydrogenation catalysts such as BINAP have received significant attention, and MeO-PEG-supported (*R*)-BINAP and (3*R*, 4*R*)-Pyrphos ligands have also been prepared and shown to be effective in Ru^{II}- and Rh^I-catalyzed asymmetric hydrogenations.⁵³ High enantioselectivity was observed (86–96%), and furthermore, these catalysts were found to be easily recyclable with little loss of catalytic activity. A second approach to MeO-PEG-immobilized BINAP was reported by Guerreiro et al.⁵⁴ MeO-PEG₅₀₀₀ was treated with glutaric anhydride and then acylated with (*R*)-diaminomethyl-BINAP to afford a soluble chiral ligand. Treatment of the ligand with Ru(COD)(η³(CH₂)₂CCH₃)₂ in situ provided the active catalyst. Hydrogenation of methyl acetoacetate in methanol at 50 °C yielded the desired product in 99% ee, which could then be easily purified by precipitation of the catalyst from diethyl ether. This catalyst could be easily recycled for at least four times without any apparent loss of activity.

B. Chinchona Alkaloid Ligands for the Sharpless AD Reaction

The Sharpless osmium-catalyzed asymmetric dihydroxylation (AD) reaction^{55,56} has immense synthetic utility, and large efforts have been devoted toward the development of polymer-supported chinchona alkaloid ligands for this reaction.⁵⁷ The first use of a chinchona alkaloid ligand appended to a soluble polymeric support was demonstrated by Han and Janda in 1996.⁵⁸ MeO-PEG₅₀₀₀ was attached through a glutarate linker to dihydroquinidine (DHQD) via the chiral secondary alcohol to give ligand **1a** (Figure 2). In the Sharpless AD reaction of stilbene using *N*-methylmorpholine *N*-oxide as the stoichiometric oxidant, ligand **1a** gave higher ee's (88%) and similar yields (89%) compared to an insoluble polyacrylonitrile-supported DHQD (82% ee,

87% yield). Styrene, *trans*-β-methylstyrene, and *trans*-dec-5-ene were also epoxidized under the same conditions (Table 1). Precipitation allowed for excellent recovery, and five cycles of catalyst use and recovery were demonstrated with no apparent loss of activity. Importantly, this work showed that a chiral ligand could be immobilized onto a soluble polymer, giving rates similar to existing catalysts while allowing facile recovery of the catalyst.

This initial publication was rapidly followed by development of a second-generation catalyst **2** (Figure 2).⁵⁹ On the basis of an earlier report,⁶⁰ MeO-PEG-modified phthalazine [(DHQD)₂PHAL] ligand **2** was synthesized from MeO-PEG-NH₂ and found to be soluble in both *tert*-butyl alcohol/water and acetone/water mixtures, allowing for homogeneous AD reactions. Furthermore, in terms of time and enantioselectivity, the soluble polymer-bound catalyst was as efficient as the classical solution-phase alkaloid.

Han and Janda also took advantage of the solubility of PEG-supported catalyst **2** to perform *multi-polymer* AD reactions, effecting dihydroxylation on polymer-supported olefins.⁶¹ Four polymeric supports for the olefin were investigated—Tentagel-, Wang-, Merrifield-, and MeO-PEG-supported *trans*-cinnamic acid. The use of *N*-methylmorpholine *N*-oxide in *tert*-butyl alcohol/water gave excellent results for the Tentagel- and MeO-PEG-supported cinnamates, while K₃[Fe(CN)₆] in acetone/water was needed for the Wang- and Merrifield-supported cinnamates.

Soon after Janda's initial publication,⁵⁸ Bolm and Gerlach reported MeO-PEG-supported chinchona alkaloids for the Sharpless AD reaction.⁶² Two catalysts were described, MeO-PEG-supported diphenylpyrazinopyridazine (DPP) **3** and pyrimidine (PYR) **4** ligands using both DHQD and DHQ for the chiral ligand (Figure 2; only the DHQ derivative is shown). Enantioselectivity was observed comparable to that reported for the original DHQD and DHQ systems. Additionally, it was also noted that changing the linkage to the polymer from an ester to an ether eliminated hydrolysis of the ligand during the basic reaction conditions, allowing reuse of the catalyst without the loss of enantioselectivity observed with the pyridazine ester linkage.⁶³ A further improvement to this reagent using an anthraquinone core has also been reported.⁶⁴

The latest entry into soluble polymer-supported chinchona catalysts was a recent report by Zhang and co-workers.⁶⁵ Using MeO-PEG₅₀₀₀ as the soluble support, two different convenient two-step procedures to synthesize DHQD-PHAL-PEG-OMe **5** were developed to avoid the complicated synthetic manipulations in previous soluble polymer-bound chinchona ligands (Figure 2).^{59,62} This ligand gave >90% yields and 96–99% ee for the dihydroxylation of stilbene using K₃Fe(CN)₆ as the stoichiometric oxidant and was recycled six times without apparent loss of activity.

C. Phase-Transfer Catalysts

While poly(ethylene glycol) is well known for its ability to act as a phase-transfer catalyst⁶⁶ the first report of a derivatized PEG with quaternary am-

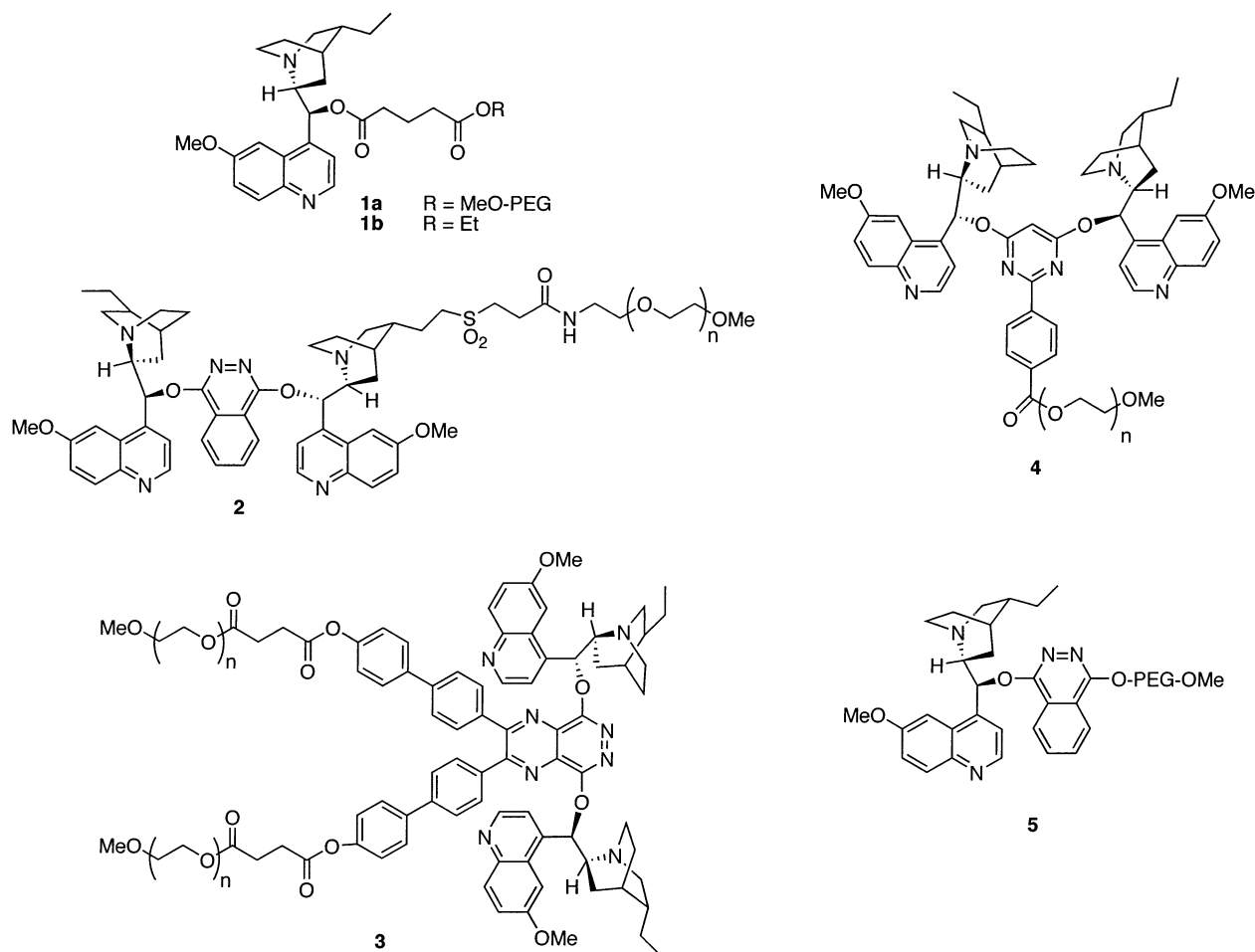


Figure 2. PEG-supported chinchona ligands.

Table 1. Comparison of Catalytic Asymmetric Dihydroxylation Using MeO-PEG-Supported Ligand **1a** and Solution Ligand **1b**

entry	ligand	olefin	reaction time (h)	yield (%)	ee (%)
1	1a	<i>trans</i> -stilbene	5	89	88
2	1b	<i>trans</i> -stilbene	5	89	88
3	1a	styrene	5	80	60
4	1b	styrene	5	80	60
5	1a	<i>trans</i> - β -methylstyrene	5	80	84
6	1b	<i>trans</i> - β -methylstyrene	5	80	85
7	1a	<i>trans</i> -dec-5-ene	10	62	42
8	1b	<i>trans</i> -dec-5-ene	10	65	43

monium end groups for phase-transfer catalysis was reported in 1991 by Grinberg and Shaubi.⁶⁷ Treatment of PEG-dibromide with tributylamine or tributylphosphine afforded the PEG-supported ammonium or phosphonium salts **6** and **7**, respectively. Hydroxyammonium PEG quaternary salts **8** and **9** also were prepared in a manner similar to what was reported to be monobrominated PEG (Figure 3). It should be noted that the conditions used to form the monobrominated PEG would be expected to produce a statistical mixture of monobrominated PEG (50%), dibrominated PEG (25%), and PEG-diol (25%), which is indistinguishable by ¹H NMR and elemental analysis from pure monobrominated PEG; however, this issue was not addressed. The catalytic activity of these compounds were then examined in the dehydrobromination of bromo(2-bromoethyl)benzene

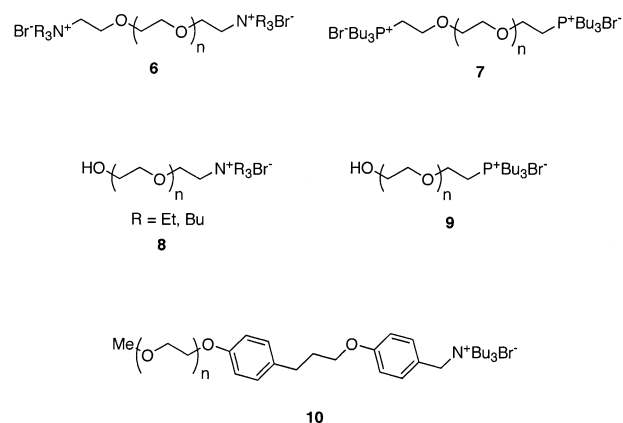


Figure 3. PEG-based phase-transfer catalysts.

and dibromo(2-bromoethyl)benzene to afford bromostyrene and dibromostyrene, respectively. While no mention was made of the catalytic activity of **7**, it was shown that the four remaining catalysts were more effective in dehydrohalogenation reactions than either PEG or tetrabutylammonium bromide alone, suggesting that both the polymer backbone and the covalently bound catalyst play a significant role in the observed catalysis. Additionally, the hydroxyammonium salt catalysts **8** and **9** were more effective than PEG-supported ammonium salt **6**.

In an extension of this work, the reuse of the polymeric catalyst was addressed and several new PE-poly(alkene) glycol copolymers were prepared.⁶⁸

Commercially available oxidized polyethylene (CO₂H terminated, both high and low molecular weight) was converted to the acid chloride and reacted with Jeffamine D or Jeffamine EDR and, subsequently converted to the tributylammonium bromide salt with butyl bromide. These new quaternary salts were shown to catalyze the nucleophilic substitution of 1,6-dibromohexane with sodium cyanide or sodium iodide. While none of the polymeric quaternary salts catalyzed the reaction as well as tetrabutylammonium bromide, the temperature-dependent solubility of the polymers allowed removal of the polymer by simple filtration.

In 2000, Benaglia and co-workers reported preparation of MeO-PEG supported quaternary ammonium salt **10** and examined the catalytic efficiency in a series of phase-transfer reactions (Figure 3).⁶⁹ The reactions occurred at lower temperatures and with shorter reaction times than with comparable insoluble 2% cross-linked polystyrene-supported quaternary ammonium salts, although yields varied with respect to classical solution-phase quaternary ammonium salt-catalyzed reactions. It was observed that yields dropped with a shorter linker and that PEG alone was not responsible for the extent of phase-transfer catalysis. While the catalyst was recovered in good yield by precipitation, it contained an undetermined amount of sodium hydroxide, although the presence of this byproduct was found to have no effect on the recyclability of the catalyst.

D. Epoxidation Catalysts

Soluble polymer-bound catalysts for epoxidation reactions have also been explored, with a complete study into the nature of the polymeric backbone performed by Janda.⁷⁰ Chiral (salen)-Mn complexes were appended to MeO-PEG, NCPS, *Janda.Jel*, and Merrifield resin via a glutarate spacer. It was found that for the Jacobsen epoxidation of *cis*- β -methylstyrene, the enantioselectivities for each polymer-supported catalyst were comparable (86–90%) to commercially available Jacobsen catalyst (88%). Both soluble polymer-supported catalysts could be used twice before a decline in yield and enantioselectivity was observed. However, neither soluble polymer support proved as suitable as the insoluble *Janda.Jel*-supported (salen)-Mn complex for the epoxidation due to residual impurities during precipitation and leaching of Mn from the complex, resulting in lowered yields.

Flood and co-workers utilized diamino-PEG₃₃₅₀-supported poly(L-leucine) to catalyze the Julia-Colonná asymmetric epoxidation of enones.⁷¹ Four catalysts were prepared with polyleucine content of 3.9, 7.5, 11.6, and 12.2 units long (average chain lengths). To measure the efficiencies of these catalysts, chalcone was epoxidized to chalcone epoxide using a THF solution of H₂O₂, giving the product in 95–98% ee. The conversion to chalcone epoxide was better for the catalysts containing 3.9 and 7.5 leucine units (80%) than the catalysts with longer leucine chains (11.6, 63%; 12.2, 58%). Finally, it was determined using FT-IR that these catalysts contain an α -helical structure and it is the nature of this secondary structure that

leads to the observed enantioselectivity. This was supported experimentally by the preparation of an additional catalyst containing an average of 1.8 leucine units that gave chalcone epoxide in only 5% ee.

E. Carbon–Carbon Bond-Forming Catalysts

Bis(oxazolines) have proven to be versatile ligands, and a MeO-PEG-supported bis(oxazoline) ligand **11** for a soluble copper (I) catalyst was reported by Glos and Reiser⁷² (Figure 4). The soluble polymer-sup-

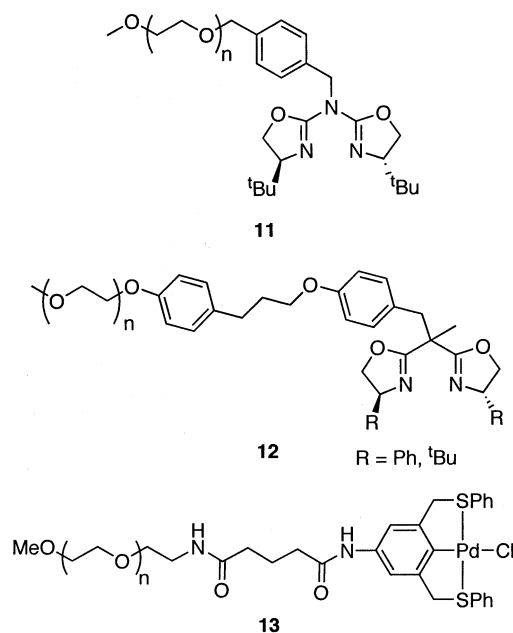


Figure 4. Bidentate ligands for carbon–carbon bond formation.

ported ligand was prepared by attaching an azabis(oxazoline) to MeO-PEG containing a benzylidene linker. The active copper(I) complex was generated in situ using copper(II) triflate (1 mol %), the ligand (2.2 mol %), and phenylhydrazine. This catalyst was used for the cyclopropanation of 1,1-diphenylethylene and gave higher yields and better enantioselectivities than the classical solution-phase analogues (78% yield, 90% ee for the MeO-PEG-bound catalyst versus 49% yield, 56% ee for a solution-phase ligand). The catalyst was reused in the cyclopropanation reaction nine times with nearly identical results before loss of activity was observed; however, the catalyst was regenerated by addition of phenylhydrazine to restore activity.

PEG-supported bis(oxazoline) ligands **12** were prepared and tested as ligands in homogeneous Cu-catalyzed asymmetric transformations (Figure 4).⁷³ The Diels–Alder reaction proceeded in poor ee, while cyclopropanation and ene reactions proceeded in good yield and good to excellent enantioselectivity, with ene reactions also displaying good diastereomeric excess as well. The catalysts were recovered by precipitation and regenerated, although a slight reduction in yield and ee was noted.

In conjunction with the development of low molecular weight “pincer”-type S–C–S tridentate ligands for Pd(II) catalyzed Heck reactions, the MeO-PEG-supported catalyst **13** was also prepared.^{74,75} The SCS

ligand was connected to MeO-PEG₅₀₀₀ via an aryl ether linkage. After treating the ligand with Pd-(PhCN)₂Cl₂, it was found that this catalyst slowly decomposed during the Heck reaction, giving a black precipitate of Pd⁰. Changing the aryl ether linkage to a more robust acetamido linker proved successful, and the new catalyst was shown to be stable and recyclable with no apparent loss of activity (Figure 4). Using 0.1 mol % of the catalyst with triethylamine in DMF at 115 °C, the Heck reaction of iodophenol and styrene to form stilbene and reaction of iodophenol with methyl acrylate to form methyl cinnamate went to completion within 7 h. Precipitation of the catalyst and extractive workup provided the pure Heck coupling products. The reactions were repeated three times with no deactivation of the catalyst observed.

Olefin metathesis has emerged as a powerful synthetic methodology, especially with the development of powerful catalysts such as the Schrock molybdenum alkylidene⁷⁶ and the Grubbs-type ruthenium alkylidenes.^{77–79} However, attempts to immobilize the Grubbs catalyst on insoluble polymers have been met with limited success.^{80–82} MeO-PEG₅₀₀₀ was coupled to a substituted styrene using a succinate linker to provide, after treatment with a ruthenium alkylidene, MeO-PEG-supported Grubbs-type catalyst **14** (Figure 5).⁸³ This catalyst was used

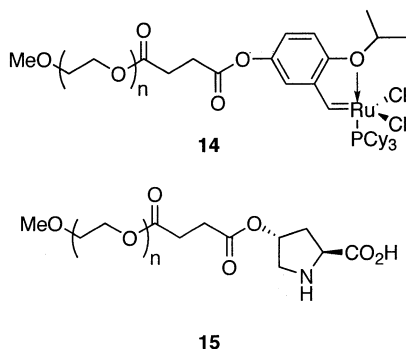


Figure 5. PEG-supported catalysts for carbon–carbon bond formation.

for the ring-closing metathesis reaction of a number of dienes and demonstrated excellent conversions (>92%) for all studied examples and only a slight decrease in catalytic activity after repeated use.

Recently, small organic molecule asymmetric catalysts have seen extensive use in synthesis. Primarily, these catalysts have used amine functionalities to impart either a lowering of the LUMO of one of the substrates⁸⁴ or nucleophilic catalysis mechanisms. Indeed, compounds such as proline catalyze a variety of processes including the aldol reaction via an enamine-based process.^{85–87} A soluble polymer-supported L-proline aldol catalyst was recently reported by Benaglia in which 4-hydroxyproline was attached to MeO-PEG₅₀₀₀ through a succinate spacer to generate catalyst **15** (Figure 5).⁸⁸ Catalyst **15** served as an efficient aldol catalyst for the reaction of acetone or hydroxyacetone with various aldehydes giving aldol addition products in yield and ee comparable to that of proline-catalyzed reactions. Reuse of the

catalyst was demonstrated, and after two cycles, only a slight loss of catalytic activity was observed, with no apparent reduction of enantioselectivity.

IV. Soluble Polymer-Supported Reagents

Soluble polymer-supported reagents have both advantages and disadvantages compared to insoluble macromolecular reagents. The most obvious advantage of either form of reagent is the ease of separation from solution-phase components. However, a potential disadvantage unique to soluble polymer-supported reagents derives from the higher molecular weight of the polymer relative to a traditional reagent. Essentially, the number of equivalents of reagent per gram of polymer can become a pronounced liability, especially when working with larger scale synthetic applications. A loading capacity in the range of 1–0.1 mmol/g may not provide the required number of equivalents of reagent without using extraordinary amounts of polymer-bound reagent. This drawback is not as prevalent with soluble polymer-supported catalysts as multiple equivalents of the catalyst are generally not required.

A. Phosphine Reagents

Soluble polymer variants of triphenylphosphine have found significant attention, and several applications of these reagents have been demonstrated. This reagent has widespread use in organic chemistry in reactions such as the Staudinger reduction, Mitsunobu reaction, Wittig reaction, and halogenation of alcohols. The key advantage to the use of these reagents is the ease in which they allow the phosphine oxide byproduct to be separated away from the rest of the reaction mixture.

The first publication of a soluble polymer-supported phosphine was reported in 1983.⁸⁹ In this work, non-cross-linked polystyrene was used as the polymeric support for the formation of poly(styryldiphenylphosphine) **16** with a loading of 2.7–3.0 mmol of phosphine/g of polymer (Figure 6). Interestingly, the efficiency of the soluble polymer-supported phosphine was found to be comparable to divinylbenzene cross-linked poly(styryldiphenylphosphine) in the formation of alkyl chlorides from an alcohol and carbon tetrachloride; however, upon prolonged storage, the polymeric reagent appeared to cross-link and become insoluble. The starting linear polystyrene was soluble under the reaction conditions, yet upon completion, the polymer precipitated allowing purification by filtration. It was postulated that the depleted polymeric reagent contained both the corresponding phosphine oxide and chloro- or dichloromethylphosphonium salts derived from the starting polymer. Through the use of a kinetic study of the conversion of benzyl alcohol or 3-phenylpropanol to the corresponding chlorides, Hodge demonstrated that the soluble polymer-supported phosphine was only slightly less reactive than a similar divinylbenzene cross-linked insoluble polymer-supported phosphine. A further refinement of a triphenylphosphine reagent on NCPS **17** has been reported for a Staudinger/aza-Wittig process with superior results observed relative

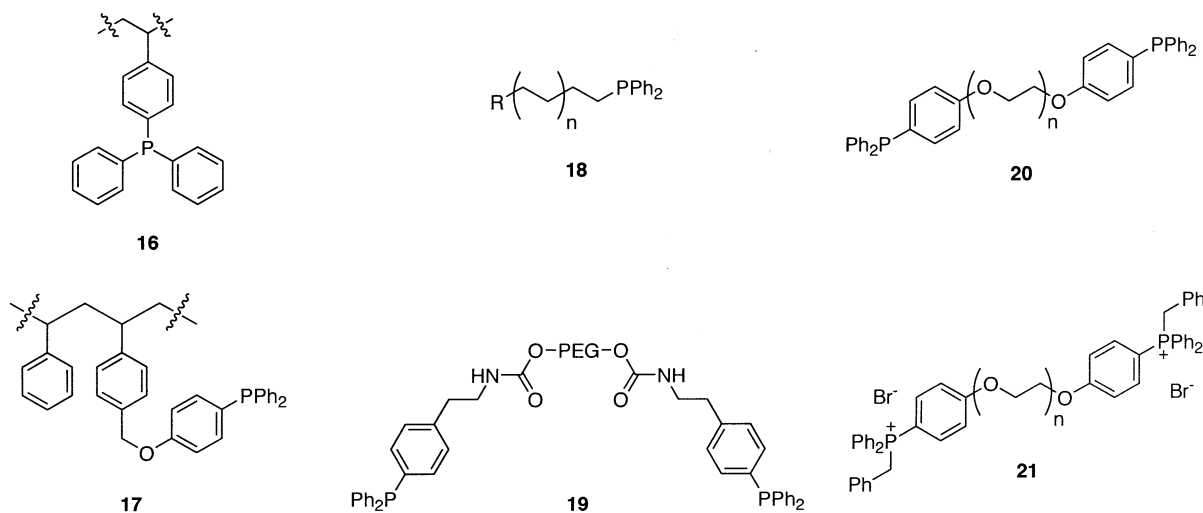


Figure 6. Soluble polymer-supported phosphine reagents.

to an insoluble-polymer variant of the reagent.⁹⁰ In a later study, this second-generation reagent was implemented in the Mitsunobu reaction and the synthesis of *E*-trisubstituted alkenes from Baylis-Hillman adducts via a highly regioselective S_N2' Mitsunobu reaction.⁹¹ Interestingly, the use of the soluble polymer-bound reagent showed significantly higher regioselectivity in this reaction as compared with triphenylphosphine, possibly due to increased steric bulk present in the NCPS-supported phosphine.

A polyethylene backbone has also been demonstrated as a suitable support for the immobilization of a diphenylphosphine reagent **18** (Figure 6).⁹² Here, linear polyethylene was prepared via an anionic polymerization process and the polymer capped with chlorodiphenylphosphine. This reagent also showed good activity in the synthesis of alkyl chlorides from alcohols, displaying results comparable to that of insoluble polystyrene-bound phosphine reagents. Furthermore, **18** could be recycled by reduction of any present phosphine oxide moieties with trichlorosilane, albeit with reduced activity. After one cycle of reaction and then regeneration, the recycled reagent only retained 65% of the activity of the fresh reagent. This is in agreement with previously observed results by Hodge in which insoluble divinylbenzene cross-linked diphenylphosphine only retained 40% of original activity upon regeneration using trichlorosilane. This reduction in the active reagent was hypothesized to be a result of reactions in which halogenated phosphonium salts form as unwanted and unreducible byproducts.⁸⁹

In 1997, Janda reported a poly(ethylene glycol) variant of soluble polymer-supported diphenylphosphine.⁹³ This reagent **19** (Figure 6) was synthesized on dihydroxy-PEG₃₄₀₀, and this support was found to satisfy two key requirements. The polymer was of low enough molecular weight to allow acceptable loading while still affording both excellent solubility in certain solvents (i.e., H₂O, DMSO, DMF, CH₂Cl₂, toluene, benzene, and warm THF) and high polymer recovery (>97%) when precipitated from an appropriate solvent. Synthetically, it was discovered to be advantageous to first synthesize the triarylphosphine derivative followed by loading of this molecule onto

the polymer since significant decomposition of the PEG support was observed if the synthetic steps were reversed. Polymer loadings were excellent (0.5 mmol of phosphine/g of polymer) and determined by both ¹H NMR spectroscopy and *p*-nitrophenol release during polymer loading.

The utility of the poly(ethylene glycol)-supported triarylphosphine reagent was shown in two reactions. First, the reagent was used in the chemoselective reduction of azides, the Staudinger reaction.^{94,95} Although the demonstration of a polystyrene-bound reagent in this reaction had been shown,⁹⁶ no soluble polymer approach has been disclosed. A variety of alkyl and aryl azides were subjected to the conditions of the Staudinger reaction using both the soluble polymer-supported phosphine and an insoluble polystyrene-bound phosphine. Reaction times were observed to be shorter in all cases for the PEG-supported reagent, and in one case, no reaction was observed for the polystyrene-supported phosphine, thus highlighting the importance of this liquid-phase methodology (Table 2).

The second reaction utilized with this reagent was the Mitsunobu reaction,⁹⁷ a reaction known to require chromatographic purification to obtain pure product due to the formation of side products. An insoluble polymer approach to this problem is known,⁹⁸ however, due to the nature of the support, the reaction is inherently heterogeneous (vide supra). The reaction between phenol and a series of alcohols in the presence of reagent **19** and diethylazodicarboxylate (DEAD) was performed, and each gave the respective Mitsunobu etherification product in excellent yield. As was observed for the Staudinger reductions, reactions using the soluble polymeric reagent proceeded faster than reactions using the corresponding insoluble polymer-supported triphenylphosphine. Furthermore, ether formation was observed in the case of benzyl alcohol only when the PEG-supported reagent was used.

In a continuation of their initial study, Janda and Wentworth disclosed an optimized version of the poly(ethylene glycol)-supported triarylphosphine reagent **20** (Figure 6).⁹⁹ In the previous report, the carbamate linkage used had known susceptibility to

Table 2. Comparative Staudinger Reactions Using **19 and Polystyrene-PPh₃ with the Listed Azides**

Azide	19		polystyrene-PPh ₃	
	Yield (%)	<i>t</i> (h)	Yield (%)	<i>t</i> (h)
	95	2	-	No reaction
	98	1.5	82	8
	91	4.5	95	11
	90	3	94	3.5

base, Lewis acid, and metalating agents. A more stable attachment was devised that would more closely resemble that of the polymer backbone. Here, the phosphine was attached to the polymer backbone using a more stable aryl ether linkage rather than a urethane linker. The reagent was prepared through a very concise synthesis starting from *p*-bromophenol in 85% yield over three steps. The unsupported reagent was then loaded onto PEG₃₄₀₀ via displacement of the mesylate moieties of the polymer. Interestingly, the preparation of the dimesylate was accomplished by heating PEG₃₄₀₀ in a neat solution of methanesulfonyl chloride without the need for a scavenger base. Upon generation of reagent **20**, it was determined by ³¹P NMR spectroscopy that less than 2% phosphorus oxidation had occurred. Furthermore, the reagent was found to be stable to air exposure for prolonged periods of time (2–3 weeks) with little oxidation of the phosphine moiety (<5%).

To test the ability of this second-generation reagent to perform as a substitute for triphenylphosphine, it was first used in the decomposition of ozonides. Triphenylphosphine is an important alternative to standard methods for the decomposition of these types of compounds as it is not only a very mild reaction but also avoids the use of malodorous reagents and high-boiling-point byproducts that are present in other methods.¹⁰⁰ Unfortunately, when triphenylphosphine is used in solution, the removal of excess reagent and triphenylphosphine oxide can cause significant problems. As an alternative, solid-supported triphenylphosphine has been reported as an acceptable alternative to PPh₃ in the generation of aldehydes.¹⁰¹ A series of alkenes were exposed to ozone and the resulting ozonides treated with PEG-supported triarylphosphine reagent **20**. For comparison, ozonides were treated with triphenylphosphine as well as a commercially available polystyrene-immobilized triphenylphosphine resin. Isolation of **20** following the completion of the reaction was performed by simple precipitation and consistently removed >99% of the polymer byproduct. Also, in

Table 3. Direct Comparison of Ozonide Hydrolysis between Solution-Phase, Solid-Phase, and Liquid-Phase Triphenylphosphine

entry	alkene	product	yield (%)		
			PPh	●PPh ₃	20
1			94	58	98
2			80	73	92
3			84	60	97
4			51	56	77
5			72	62	63

almost all studied cases, the produced aldehydes were obtained in highest yield with the soluble polymer reagent (Table 3). The regeneration of the phosphine reagent from the corresponding phosphine oxide was also studied.⁹⁹ A number of standard methods for the reduction of phosphine oxides were tested including poly(methylhydrosiloxane) (PMHS),¹⁰² trichlorosilane,¹⁰³ and alane (AlH₃).¹⁰⁴ Of the methods tested, only alane gave satisfactory results for the regeneration of **20** as determined by ³¹P NMR. Upon reduction, the polymer could be isolated in 75% yield by precipitation into degassed diethyl ether. The incomplete recovery of polymer was attributed to the presence of aluminum salts that could either prevent precipitation by complexing the polymeric support or cause hydrolysis of the polymer backbone during phosphine reduction.

The use of polymeric supports to aid in the Wittig olefination reaction is well-documented.^{105–110} Polymer-bound phosphonium salts have the advantage of being readily separated from a reaction mixture once converted to their respective phosphine oxides. Furthermore, these oxides can then be readily recycled by reduction of the phosphine oxide by standard methods. Divinylbenzene cross-linked polystyrene has been the most common polymeric carrier used, and there has been significant success in the use of these reagents. However, soluble polymers have also been shown useful as supports for Wittig reagents. Hodge reported the use of a diphenylphosphinylated non-cross-linked polystyrene support (*M*_w = 100 000) for use as a Wittig reagent.¹¹¹ This reagent contained approximately 2.7 mmol of phosphine/g of polymer and could be readily converted to the corresponding phosphonium salt via reaction with either benzyl chloride or 2-bromomethylnaphthalene. A series of ketones were tested as substrates for the soluble polymeric reagent, in addition to 1% and 8% divinylbenzene cross-linked polystyrene reagents. Since the

bases used in these experiments were only soluble under aqueous conditions, a phase-transfer catalyst was necessary in the case of the insoluble polymeric supports. However, no phase-transfer catalyst was necessary with the soluble polymeric reagent, reportedly due to the known ability of soluble polymeric supports to function as phase-transfer reagents.⁶⁶ Isolation of the alkene products from the soluble polymer was accomplished by precipitation of the linear poly(styryldiphenylphosphine oxide) using methanol.

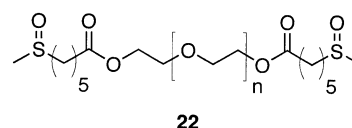
Organic chemistry performed in water has attracted significant effort in recent years due to both the ready availability and environmental compatibility of water relative to organic solvents.^{112,113} Examples of aqueous Wittig reactions are known;^{114,115} however, none of these employ polymeric reagents. The physical properties of the PEG backbone are such that a PEG-supported phosphonium reagent could have excellent solubility in water. Janda and Wentworth reported the preparation of poly(ethylene glycol)-supported phosphonium reagent **21** in 81% yield by a treating PEG-immobilized phosphine **20** with benzyl bromide (Figure 6).⁹⁹ Reagent **21** was used in the Wittig olefination to prepare a series of stilbene derivatives in aqueous sodium hydroxide solution. All products were obtained in good to excellent yield by partitioning the stilbene products into CH₂Cl₂, followed by precipitation of the polymer-bound phosphine oxide byproduct in diethyl ether. Furthermore, unlike previous reports, which stated the *E/Z* ratio could be affected byproduct isolation conditions,¹¹⁶ this methodology allows for full extraction of both isomeric stilbenes without concern for phosphine oxide contamination, which is removed by precipitation and filtration. The scope of this reaction was further explored by varying both the base strength and temperature of the reaction. It was found that, by increasing the base strength from 1 M to 2 M sodium hydroxide, neither the yield of stilbene nor the ratio of geometric isomers was affected. However, elevation of the reaction temperature did give improved reaction yields as well as an expected increase in the *E/Z* ratio.

B. Oxidants

A variety of groups have reported the preparation and use of oxidizing agents in which a polymeric backbone is used to either ionically or covalently bind the oxidant. Oxidation reagents that have been immobilized onto soluble polymeric supports have also been studied. For example, Schuttenberg reported the use of *N*-chlorinated nylon polymers as a soluble reagent for the oxidation of primary and secondary alcohols as well as the oxidation of sulfides to sulfoxides.¹¹⁷ These polymers contained a high loading of *N*-chloro moieties, facilitating the ability of the polymer to serve as a reagent. The oxidant was prepared by chlorination of linear polyamides using either *tert*-butyl hypochlorite, chlorine monoxide, or hypochlorous acid in carbon tetrachloride. Using Nylon 66 and *tert*-butyl hypochlorite as the oxidant, these reactions were complete in 3 h at 15 °C and converted 94% of the original N–H bonds to N–Cl

bonds. Interestingly, the new polyamide reagent had markedly different solubility properties relative to the parent polymer. Although the starting polyamide was relatively insoluble in many solvents, the new polymer was readily soluble in chloroform, benzene, and toluene. This new solubility was hypothesized to be due to diminished hydrogen bonding as most N–H hydrogen bond donors had now been converted to N–Cl bonds. When used as an oxidant, the polymeric reagent would then be converted back into the starting polyamide, which had poor solubility in the reaction solvent. Therefore, upon completion of the reaction, the reagent could be filtered away from the products and regenerated by treatment with *tert*-butyl hypochlorite or hypochlorous acid. A range of secondary alcohols were oxidized to the corresponding ketone at 35 °C, typically in 24 h using the nylon-based reagent, in good to excellent yield as measured by gas chromatography. A series of primary alcohols and sulfides were also oxidized; however, significant variability was seen in the products. Attempts at performing asymmetric oxidations of sulfides using a chiral *N*-chloro nylon derived from (–)-poly(*S*(–)-4-methylazetididin-2-one) were also described, but the sulfoxides obtained were optically inactive.

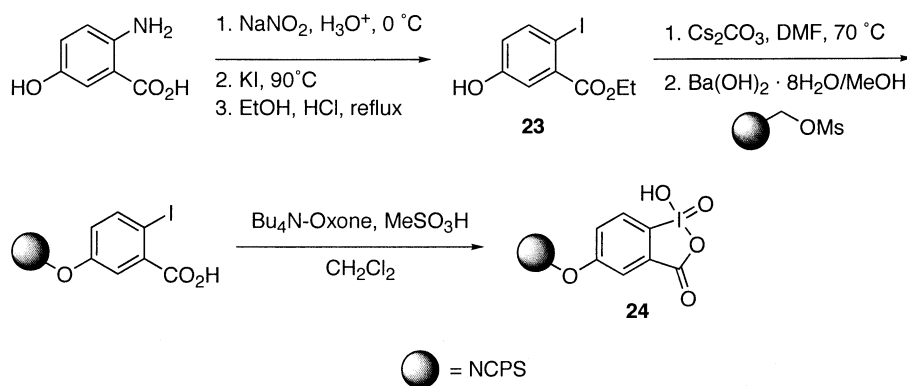
The Swern oxidation is among the most valuable and widely used reactions in synthetic organic chemistry.¹¹⁸ Although highly effective, its main drawback rests in the production of the noxious, volatile byproduct, dimethyl sulfide. A number of solutions to this problem have been reported, including the use of modified dimethyl sulfoxide reagents in the Swern oxidation.¹¹⁹ A soluble polymer approach to the Swern oxidation has also been reported.¹²⁰ Here, 6-(methylsulfinyl)hexanoic acid was attached to PEG₂₀₀₀ under standard conditions to allow for optimal loading while still retaining high polymer recoveries after precipitation of the reagent. The sulfinyl ether was then oxidized to the corresponding sulfoxide reagent **22** using sodium metaperiodate (Figure 7). Initial



22

Figure 7. PEG-supported Swern oxidant.

studies were conducted using insoluble polymeric supports such as Merrifield resin, but although the reagent performed acceptably, regeneration of the reagent was accompanied by a loss in oxidation capacity from 92% to 78%. A series of alcohols were explored and a comparison was made between the PEG-sulfoxide reagent, 6-(methylsulfinyl)hexanoic acid, and literature yields obtained under standard Swern conditions. In all tested cases, yields were comparable to both previously reported reagents demonstrating the utility of this reagent. The recyclability of the PEG-supported sulfoxide was also tested. After the oxidation of *endo*-borneol under limiting conditions using a slight excess of sulfoxide reagent was performed, the recovered reagent was reoxidized with sodium metaperiodate. The desired reagent was regenerated in excellent yield (91%) and

Scheme 1. Synthesis of NCPS-Supported IBX

reused for five oxidation/regeneration cycles with no apparent loss of oxidation capacity.

Hypervalent iodine reagents have become extremely valuable tools in organic chemistry.¹²¹ Reagents such as the Dess–Martin periodinane have received immense attention due to their efficiency and mild reaction conditions. The precursor to the Dess–Martin periodinane, *o*-iodoxybenzoic acid (IBX), has also become popular as a reagent and has been used in various synthetic methodologies.¹²² In some cases, IBX is a preferred reagent as it is shelf-stable, conveniently handled, and exhibits greater selectivity in its oxidation potential relative to the Dess–Martin periodinane.^{123,124} However, IBX is notoriously insoluble, and reactions that use IBX as an oxidant are frequently performed as heterogeneous slurries of the reagent. Insoluble polymer-supported hypervalent iodine species have been reported by Ley,¹²⁵ this reagent, polystyrene(diacetoxyiodo)benzene, was immobilized on divinylbenzene cross-linked polystyrene and successfully used in the oxidation of a variety of substrates. Recently, Janda and co-workers have reported a soluble polymer-supported version of IBX that has the advantage of being soluble in a greater range of solvents.¹²⁶ This reagent was prepared by first synthesizing the appropriate *m*-hydroxyiodobenzoic acid precursor **23** (Scheme 1). Loading of this compound onto NCPS, followed by ester hydrolysis and oxidation of the iodine from I(III) to I(V), led to NCPS-supported reagent **24**. Although PEG was also explored as a possible soluble support for this reagent, difficulties in purifying the PEG-immobilized reagent from Oxone salts led the researchers to drop this support from the study. Using 2 equiv of NCPS-supported IBX, it was demonstrated that the conversion of benzyl alcohol to benzaldehyde proceeded in quantitative yield after only 1 h in methylene chloride. In comparison, a macroporous polystyrene-supported IBX reagent required 4 h to achieve quantitative conversion, and a gel-type polystyrene-supported reagent only gave 75% conversion even after extended reaction times.

C. Reducing Agents

Polymer-bound reducing agents have received significantly less attention, presumably due to the predominance of main group metal hydride complexes as reducing agents. However, there have been a few approaches to soluble polymer-supported re-

ducing agents. One example of a soluble polymeric metal hydride is linear poly(vinylpyridine) used as a matrix to bind borane.¹²⁷ This polymer–borane complex was shown to behave much like pyridine–borane in the reduction of carbonyl moieties to hydroxyl groups. Compounds such as benzaldehyde, *p*-chlorobenzaldehyde, and cyclopentanone were shown to be reduced to the corresponding alcohols by the polymeric reagent in a yield comparable to that of pyridine–borane. Furthermore, in the case of benzophenone, the alcohol product was obtained in 40% yield with the polymeric reagent, while pyridine–borane showed no visible reduction of the ketone functional group.

Radical anion species derived from the reaction of an alkali metal with aromatic moieties have been reported on insoluble polymeric supports.^{128,129} Similar soluble polymer-based reagents have also been developed using either poly(vinylanthracene) or polyacenaphthalene as the polymeric support.¹³⁰ Alkali metal derivatives of poly(vinylanthracene) were reported to include the dilithium salt, sodium salt, and potassium salt. Each was prepared by reaction of a solution of the soluble polymer with the appropriate alkali metal at room temperature for 24 h. The polymeric lithium derivative was found to quantitatively react with organic halides such as benzyl chloride, butyl bromide, and allyl chloride. However, it displayed no reaction with iodobenzene or other halogenated arenes or with cyclohexyl chloride. This discrepancy in reactivity was hypothesized to be due to the cyclic structure of the failed substrates. Presumably, this results in steric hindrance with the naphthalene-based backbone. Yet, reagents derived from a polyacenaphthalene did react with these cyclic halides and this was rationalized as being a result of the greater flexibility and resultant diminished steric hindrance of the naphthalene groups in the polymeric backbone. It is difficult to assess whether this is a general phenomenon with soluble polymer-supported alkali radical anions as a thorough study of the poly(vinylanthracene) support was not conducted.

An atypical approach to the use of a soluble polymeric reducing agent was described by Smith for the generation of colloidal dispersions of red, amorphous selenium.¹³¹ An aqueous solution of poly(acrylic acid) was treated with hydrazine hydrate followed by selenious acid to yield stable red disper-

sions of amorphous selenium. These reactions are performed at sufficiently dilute concentrations such that each polyacrylate is viewed as discrete and noninteracting. As a solution of selenious acid is added to the polymer, the selenious acid molecules that are spatially close to a given hydrazonium polyacrylate macromolecule are reduced to selenium atoms. These atoms were reported to aggregate in a single hydrophobic particle that remains bound to the acrylate backbone. Importantly, only 75% of the pendant acid groups were neutralized by added hydrazine to ensure that the polymeric reagent would contain a small amount of residual acid. These acidic moieties presumably serve to catalyze the reduction of the selenious acid by the polymeric reagent.

D. Microgel-Supported Reagents

The use of microgel-supported reagents for organic synthesis has unique advantages not present for other soluble polymeric reagents. Microgels are intramolecularly cross-linked molecules that form a stable solution in many solvents. Analogous to soluble polymers, microgel polymers are soluble in THF, toluene, methylene chloride, and DMF but insoluble in hexane and methanol. Unlike soluble polymers, however, microgel solutions also possess low viscosity even at high concentrations of polymer.¹³² Explorations into the uses of microgels in organic synthesis have only started,^{133,134} however, it is anticipated that they will offer many of the advantages of soluble polymeric reagents without suffering from low loading capacities. Currently, these polymers are not commercially available but their preparation is readily accomplished with minimal effort.

Many soluble polymeric reagents suffer from low loading capacities relative to insoluble supports due to the nature of their backbone structures. For example, in the range of usable molecular weights (*vide supra*), poly(ethylene glycol) has a maximum loading capacity of approximately 1.0 mmol/g as the only sites of functionality are the two ends of the linear polymer chain.¹³⁵ However, microgel-based reagents would not suffer from this drawback as they can be prepared at loadings identical to that of insoluble polymer-bound reagents.

Janda and co-workers recently reported the preparation and use of two microgel-supported reagents, a polyamine-based scavenging reagent and borohydride reducing agent.¹³⁶ These polymers are prepared in a manner similar to insoluble cross-linked polystyrene resins; however, monomers are held at very low concentrations and consequently the polymerization must be performed over extended periods of time. Both reagents were prepared from a chloromethyl-functionalized microgel using previously reported conditions for insoluble polymeric reagents. The effectiveness of the polyamine reagent (loading level = 0.84 mmol of amine/g) was demonstrated in the scavenging of excess phenyl isocyanate from the reaction of the isocyanate and *sec*-butylamine. Upon addition of a slight excess of the reagent and precipitation of the microgel with methanol, the desired product was obtained in quantitative yield and 97% purity. For a similar reaction using an insoluble

polymer-supported reagent, not only were more equivalents of reagent necessary but also longer reaction times.¹³⁷ The borohydride reagent (loading level, 0.44 mmol of borohydride/g) was explored in the context of the reduction of 4-chlorobenzaldehyde to the corresponding alcohol. Using an excess of borohydride reagent (1.1 equiv), complete reduction of the carbonyl moiety was observed and the spent reagent precipitated from the reaction mixture using hexane. Further explorations into the utility of microgels as scaffolds for polymer-supported reagents is clearly needed as these polymers display many of the advantages of liquid-phase chemistry while limiting its shortcomings.

E. Miscellaneous Reagents

A variety of synthetically useful soluble polymer-supported reagents have been developed to capitalize on the inherent advantages of liquid-phase synthesis. One example of this is the MeO-PEG-immobilized version of the Burgess reagent¹³⁸ reported by Wipf in 1996.¹³⁹ The Burgess reagent (methyl *N*-(triethylammoniumsulfonyl)carbamate) **25** has been shown to be extremely useful in the preparation of varied heterocyclic structures such as oxazolines and thiazolines with high stereochemical purity^{140,141} (Figure 8). However, the reagent has known susceptibility to

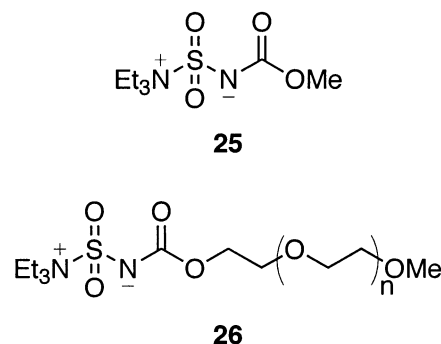


Figure 8. Burgess reagent and PEG-supported Burgess reagent.

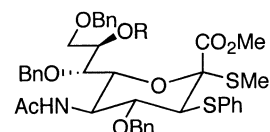
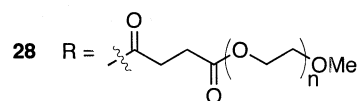
oxidation, moisture, and temperature. Even with appropriate precautions taken, the reagent still possesses a limited shelf life and should be freshly prepared for each use. Wipf successfully coupled chlorosulfonyl isocyanate with either dry MeO-PEG₇₅₀ or MeO-PEG₂₀₀₀ followed by treatment with triethylamine to generate PEG-bound reagent **26** (Figure 8). Interestingly, prior attempts to couple the reagent to modified Merrifield resin failed. Cyclodehydrations proceeded smoothly and in superior yields with PEG-supported Burgess reagent **26** (Table 4) compared with **25**. Furthermore, considerable reactivity was retained even after extended storage of the reagent at or below room temperature. Upon completion of the reaction, the polymer was readily removed by filtration through a plug of silica gel. When chiral substrates were used for cyclodehydration reactions, little epimerization or elimination was observed, and furthermore, it was demonstrated that the reaction was stereospecific. In a remarkable example of the utility of this reagent, sensitive oxazolines could be

Table 4. Cyclodehydration of Hydroxyamides and Thioamides with Polymeric Burgess Reagent **26**

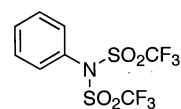
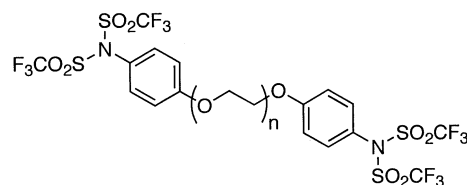
Entry	Hydroxyamide	Azole	Yield (%)
1	Cbz-Phe-Ser-OMe		88
2	Cbz-Val-Thr-OMe		90
3	Cbz-Pro-Thr-OMe		85
4	Cbz-Aib-Thr-OMe		88
5	Cbz-Val-αThr-OMe		76
6			80
7	Cbz-Phe-ψ(CSNH)Ser-OMe		98

generated in high yields (88%) using the MeO-PEG₂₀₀₀-supported reagent, whereas the reported maximum yield for this reaction was nearly 3-fold less. A further Burgess example of the utility of PEG-supported Burgess reagent has been shown in the cyclodehydration of a range of substituted 1,2-diacylhydrazines.¹⁴² Using reagent **26** in conjunction with single-mode microwave heating, 1,3,4-oxadiazoles were provided in excellent yields (>70%) and purity (>89%) as determined by HPLC. It was also discovered that transformations involving protected threonine, tyrosine, and serine derivatives required a larger excess of reagent, longer irradiation times, and addition of the reagent in two lots.

Soluble polymeric reagents for use in carbohydrate chemistry have also been developed. Sialic acid (NeuAc) is frequently found as a nonreducing end terminal residue in oligosaccharides, and a MeO-PEG₅₀₀₀-immobilized reagent has been synthesized to facilitate its introduction into a growing oligosaccharide chain.¹⁴³ To guarantee nearly complete stereocontrol over the glycosylation reaction independent of reaction conditions, thioglycoside **27** was chosen as a suitable auxiliary in the preparation of reagent **28** (Figure 9). Model glycosylations were performed with a galactose derivative using standard conditions for thioglycoside activation, and the desired disaccharide product was obtained in good yield (65–70%) after cleavage from the soluble polymer. A less reactive glycoside acceptor was also investigated and yielded the desired disaccharide product, albeit in reduced yield (50–60%).

**27** R = H**28** R = $\text{-(CH}_2\text{CH}_2\text{O)}_n\text{-CH}_2\text{CH}_2\text{O-}$ **Figure 9.** PEG-supported thioglycoside for carbohydrate synthesis.

As an improvement upon solution-phase triflating agent **29**, PEG derivative **30** was reported by Janda and Wentworth for use in the high-throughput synthesis of aryl and enol triflates¹⁴⁴ (Figure 10). Aryl

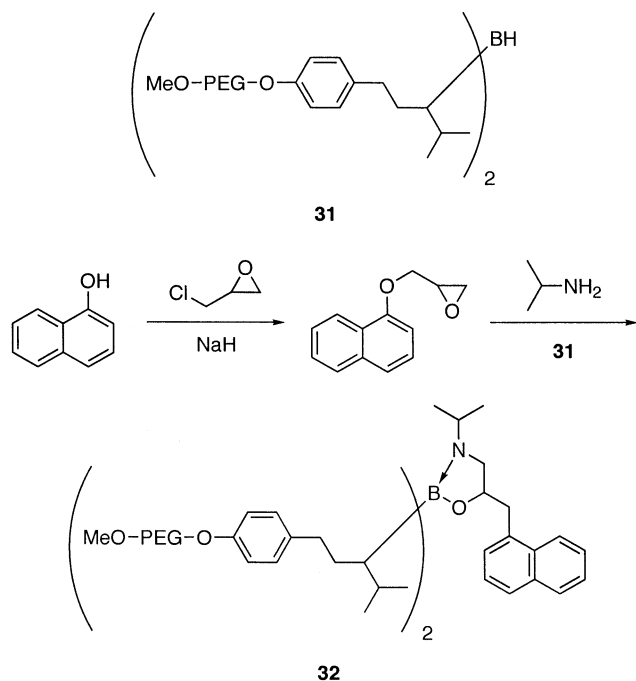
**29****30****Figure 10.** Classical triflimide reagent and corresponding PEG-based triflimide.

and enol triflates have been utilized in a variety of organometallic cross-coupling reactions; however, triflates are inherently unstable and the preparation of these types of compounds can be complicated by classical solution-phase purification techniques. Soluble polymer-supported reagent **30** was synthesized from PEG₃₄₀₀-dimesylate in greater than 98% yield over three steps. Loading of the reagent was determined to be quantitative (~0.6 mmol of triflate/g of polymer) by ¹H NMR, and purity of the bis(*N*-triflimide) was determined by ¹⁹F NMR. As was previously observed with the PEG-Burgess reagent,¹³⁹ **30** was found to be very stable on standing in air, unlike the corresponding classical solution-phase reagent. A range of aromatic alcohols was subjected to standard triflate formation conditions, and all products were formed in excellent yields and purity. Furthermore, the soluble polymeric reagent was also used in the trapping of kinetic enolates to form vinyl triflates in a yield superior to the classical triflimide reagent. The ability of **30** to be recycled was also examined, and it was found that the triflimide reagent could be quantitatively recovered and regenerated with no apparent loss of activity.

In a soluble polymer strategy comparable to resin capture,¹⁴⁵ Janda reported a MeO-PEG₅₀₀₀-supported dialkylborane reagent **31** that was used in the purification of a solution-phase library of β-amino alcohols.¹⁴⁶ Purification was achieved by simply adding **31** to the crude reaction mixture followed by

subsequent precipitation of the polymer with diethyl ether to give polymer-supported 1,3,2-oxazaborolidine **32** (Scheme 2). The β -amino alcohol product could

Scheme 2. PEG-Supported Boranes for β -Amino Alcohol Purification



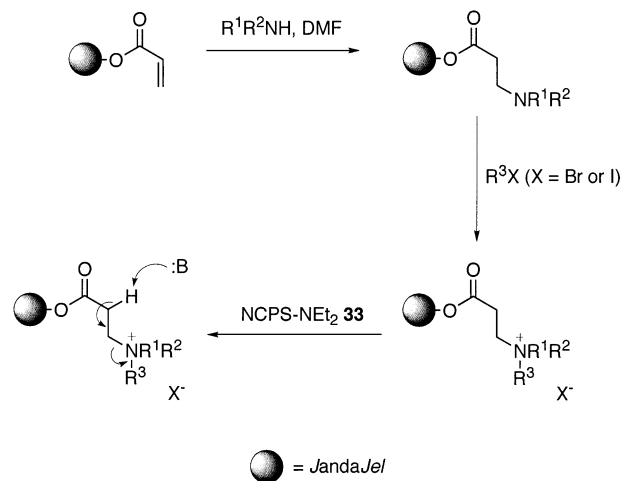
then be released from the soluble support by treatment with acid. In a two-step synthetic strategy that is readily amendable to automation, the isolation of a small library of β -amino alcohols was accomplished with all compounds obtained in >80% purity.

Thioacetals and thioketals have significant synthetic potential for use in organic chemistry but are often neglected due to their unpleasant odor. A polymeric reagent for the preparation of ketones via 1,3-dithianes has been reported using NCPS as a soluble support.¹⁴⁷ Using this reagent, a number of aldehydes were converted to the 1,3-dithane-immobilized compound in the presence of boron trifluoride etherate. These types of compounds have umpolung reactivity as a carbanionic species and can be readily generated and then alkylated with alkyl halides to produce ketones. Treatment of the polymer-supported 1,3-dithanes with *n*-butyllithium followed by treatment with various alkyl halides generated polymer-bound thioketals, which could be released upon oxidative treatment with either periodic acid or mercury(II) perchlorate trihydrate. These reagents were further studied, and a series of six polymers were synthesized ranging in amount of dithiol monomer from 10% to 50% to determine whether each new polymer could serve as an acceptable reagent for dithiane formation.¹⁴⁸ The six polymers were compared in the alkylation of a dithiane resulting from benzaldehyde. Polymers with lower contents of the active monomer showed identical yields of 1-phenyl-1-heptanone while soluble polymers with higher proportions of active monomer (i.e., 40–50%) showed a slightly decreased yield of product. On the basis of this decreased yield, the authors proposed a 1:1

mixture of active monomer and styrene in the monomer feed as an upper limit for the formation of usable reagent.

In an interesting multipolymer application of a regenerated Michael acceptor (REM) resin, Janda reported the use of NCPS-supported soluble reagent **33** to cleave tertiary amines from an insoluble support (Scheme 3).¹⁴⁹ This type of resin was developed

Scheme 3. Multipolymer Approach to Cleavage of REM Resin



by Rees and co-workers and has been used in the preparation of tertiary amines by sequential Michael addition, quaternization, and resin cleavage processes.¹⁵⁰ In the initial reports demonstrating the use of REM resins, purification of the amine products required either liquid–liquid extraction techniques or chromatography. Therefore, the use of a polymeric cleavage reagent in conjunction with the insoluble REM resin would allow the rapid synthesis and purification of a variety of tertiary amines. Previous multipolymer strategies are known for cleavage of REM resins using a basic ion-exchange resin.¹⁵¹ However, the insoluble nature of the cleavage reagent precluded the recycling of the REM resin as the two insoluble polymers could not be separated. In Janda's approach, the NCPS-supported reagent **33** was used to cleave a small library of tertiary amines from a JandaJel-REM resin in modest to good yield and in high purity (Scheme 3). Furthermore, **33** could be recovered and recycled after use by precipitation of the polymer from methanol.

Organostannane reagents have found widespread use for the free radical formation of carbon–carbon bonds. An allylstannane reagent synthesized on a soluble NCPS support has been developed and utilized in the formation of carbon–carbon bonds with alkyl halides.¹⁵² The reagent **34** was prepared by derivatization of a chloromethyl-functionalized NCPS soluble polymer and high loadings (up to 3.3 mmol of stannane/g of polymer) were achieved (Figure 11). It was found that, above 3.3 mmol/g loading, the polymer became gelatinous and no longer readily precipitated from cold methanol. A series of structurally diverse alkyl halides were tested with allylstannane reagent **34**, and all gave the desired allyl

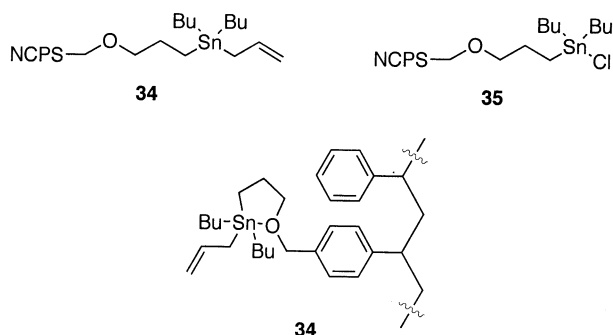


Figure 11. NCPS-supported stannane reagents.

products in modest to good yields. Interestingly, a hindered tertiary bromide did not react with allyltributyltin but does react with NCPS reagent **34**. Furthermore, regioselectivity was observed in the allylation of dihalides, with a strong preference for an electron-deficient radical. This type of regioselectivity is unparalleled among other allylstannane organometallic reagents. Presumably, this preference is due to chelation to the oxygen of the linker (Figure 11), causing the allylstannane to become electron rich and have a marked preference for electron-poor radicals. Enholm later reported another organotin reagent on NCPS **35** for use in the reduction of alkyl halides (Figure 11).¹⁵³ Typically, insoluble polymer-supported organotin reagents require multiple equivalents of reagent and prolonged reaction times when reducing alkyl halides due to the heterogeneous nature of the reaction. In this report, a variant of the procedure developed by Corey and Suggs for catalytic use of a tin reagent in the presence of sodium borohydride was used.¹⁵⁴ A NCPS-supported dibutyltin chloride was prepared and used in the reduction of a variety of alkyl halides. Reductions were successfully accomplished in good yield with primary, secondary, and tertiary halides with most reactions going to completion within 2.5 h. Furthermore, many reactions could be performed using only 0.01 equiv of the polymer-bound reagent and excess sodium borohydride.

V. Conclusions

The use of soluble polymers provides an alternative platform for organic synthesis by incorporating beneficial aspects of both solution-phase and solid-phase chemistry. By establishing homogeneous reaction conditions while still facilitating product separation, soluble polymer-supported methodologies have demonstrated utility in a variety of areas including peptide synthesis, small-molecule organic synthesis, polymer-supported reagents, and polymer-supported catalysts. Although great strides have been made in the use of soluble polymers as supports for recoverable reagents and catalysts, considerable research remains to be done.

It has been recognized that the nature of the macromolecular support plays a significant role in solid-phase organic synthesis.¹⁵⁵ Compatibility problems between reagent or substrate and the polymer support can greatly limit the applications of a given support. To overcome these limitations, soluble poly-

mer-supported reagents and catalysts have been utilized. Furthermore, in the case of substrates that possess limited solubility, covalent attachment to a soluble support would allow their use in a previously inaccessible range of synthetic applications. The refinement of current liquid-phase methodologies coupled with the development of new soluble polymeric supports tailored for organic synthesis combine to make soluble polymers an increasingly valuable tool for synthetic chemists.

VI. Acknowledgments

This work was supported in part by the National Institutes of Health (GM-56164), The Scripps Research Institute, and The Skaggs Institute for Chemical Biology.

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CR010335E

