# Soluble Polymers as Tools in Catalysis

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ABSTRACT: Examples where soluble polymers have been used in homogeneous catalysis were first noted 50 years ago, but this role for soluble polymers remained relatively unexplored until the 1990s. Since then, the use of new polymers, new developments in polymer synthesis, new separation strategies, and the imaginative ways soluble polymers' structure and physical properties can be used to influence a covalent or ligated catalyst have led to increasing interest in soluble polymers as tools in catalysis.
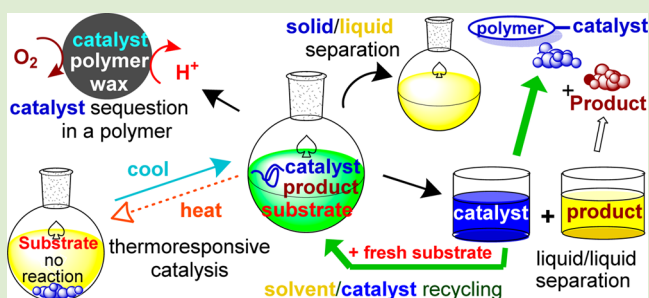
The pervasiveness of homogeneous catalysts in synthesis, interest in green chemistry and sustainability, and the ability to synthetically access polymers with tailored specific properties are driving forces in increasing interest in the use of soluble polymers as tools in catalysis. This increasing interest has included studies on more efficient catalyst/ligand recovery schemes as well on new ways soluble polymers can facilitate catalysis. This is in addition to designing soluble polymers or self-assemblies of soluble macromolecules to affect and effect catalysis. Coupling developments in polymer synthesis, functionalization, and self-assembly with the many types of catalysts in innovative ways have shown that the use of soluble polymers in catalysis will continue to grow.

Using soluble polymers as tools in catalysis is not new. The earliest examples date back to the decade after Merrifield reported using insoluble polymers as tools in peptide synthesis.[1−3] Those seminal studies emphasized catalyst cost as a justification for separating homogeneous catalysts from products. However, since then green chemistry and sustainability have not only heightened interest in recovering precious metal catalysts but also focused attention on other issues including the recovery and reuse of ever more costly sophisticated chiral and achiral ligands, the sustainability of many transition metals used in catalysis, and the toxicity of metals or ligands that requires quantitative separation of catalyst residues or ligands from products. Finally, the recognition of the precepts of green chemistry has focused attention on the ways separations are effected, on the efficiency of these separations, and on issues of solvent choice. These issues are leading chemists not just to focus on a catalyst's activity and selectivity but to also consider ways soluble polymers can separate, recover, and reuse catalysts and ligands after a reaction is complete or in other ways facilitate homogeneous catalysis.

The main application of soluble polymers in catalysis continues to be separation and recovery of catalysts and ligands (Scheme 1). Membrane filtration or solvent precipitation were the original approaches for separating polymer-bound catalysts and low molecular weight products. These

strategies are still used. Indeed, membrane filtration is industrially practiced as a separation method in catalysis.[4] While solvent precipitation and membrane filtration can effect a separation of a catalyst and products, more efficient separation strategies that minimize the use of extra solvent or that use a recyclable solvent have received more attention recently. Such strategies can advantageously involve soluble polymers. In such cases, separations rely on the phase-selective solubility of the polymer support. One approach is to use a soluble polymer that is selectively soluble in one phase of a solvent mixture that is monophasic during the catalytic reaction but is biphasic during workup. Efficient separations can be achieved in such cases when the product is largely or completely insoluble in the phase in which the polymer-bound catalyst is soluble.[5] Other separations have used soluble polymers that are soluble in a hot reaction solution but insoluble at lower temperature in solvents in which products remain dissolved.[6] Such supports quantitatively precipitate on cooling and can then be physically separated from a solution of the product. These approaches have been used with both transition metal and organocatalysts.
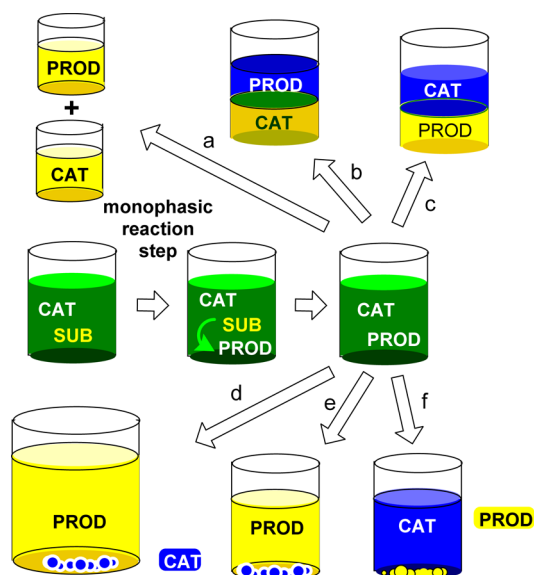
A variety of soluble polymers can be used to efficiently and quantitatively separate catalyst and product. This can involve modifying the termini of commercially available polyolefin starting materials to covalently bind catalysts or ligands. This has been done with terminally functionalized isobutylene, ethylene, and propylene (PIB, PE, and PP) oligomers.[5−8] While such polymers can be prepared by cationic or coordination polymerization with excellent control of end group functionality,[9,10] our group has focused on using commercial materials that we think will be more likely to be used by others.[11,12] Such materials can be converted into phosphine, bipyridine, N-heterocyclic carbine (NHC), or macrocyclic ligands in relatively short syntheses that can then be used to prepare conventional catalysts bound to the termini of these polyolefins.[5,6] The

Scheme 1. Biphasic Separation of a Soluble Polymer-Bound Catalyst (CAT) from Products (PROD) after a Monophasic Reaction with a Substrate (SUB) Using (a) a Membrane Separation of a Solution Containing a Polymer-Bound Catalyst from a Solution of a Low Molecular Weight Product, (b) a Liquid/Liquid Separation Where the Catalyst Partitions Selectively into the Polar Phase (Nonpolar Products), (c) a Liquid/Liquid (or Liquid/Solid) Separation Where the Catalyst (Polar Products) Partitions Selectively into the Nonpolar Phase That Is Isolated as a Liquid (or Solid if a Polyolefin Wax Is Used), (d) a Solid/Liquid Separation Where an Excess of a Poor Solvent Is Used to Precipitate a Soluble Polymer-Bound Catalyst, (e) a Solid/Liquid Separation Where the Catalyst Separates as a Solid after the Reaction and the Product Remains in Solution, and (f) a Solid/Liquid Separation Where the Catalyst Remains Soluble but the Product Itself Separates by Precipitation during the Reaction
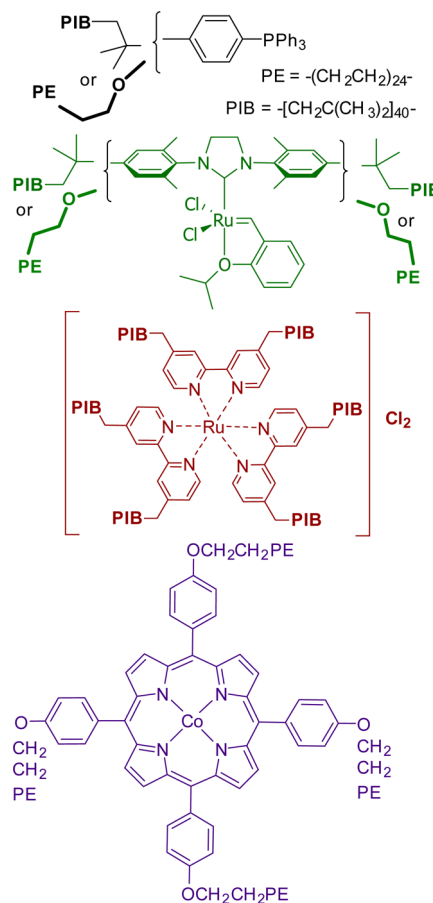

Figure 1. Polyolefin-supported phosphine, bipyridine, NHC, and porphyrin catalysts that are either phase-selectively soluble in the heptane phase of a biphasic heptane/polar solvent mixture at workup or that are thermomorphically soluble in conventional solvents (e.g., soluble hot and completely insoluble cold).

ligands and their transition metal complexes either exhibit high heptane solubility at 25 °C in biphasic heptane/polar solvent mixtures (PIB) or quantitatively precipitate from all solvents on cooling (PE) (Figure 1).

Soluble polymers can also be synthesized such that they are phase-selectively soluble, and this phase-selective solubility can then be used to control the solubility of a supported catalyst. For example, hydrocarbon solvent solubility can be engineered into catalysts using polyolefin supports or by modifying other polymer supports by adding hydrophobic groups to existing materials as we and others have done with poly(N-alkylacrylamide)s or poly(4-alkylstyrene).[13−15] This can also be accomplished using newer polymer synthesis methodology. For example, chain walking polymerization forms a hyper-branched hydrocarbon copolymer that has been used to prepare heptane-soluble copolymers containing sulfur groups that self-support Pd(II) precatalysts for cross-coupling chemistry (Figure 2).[16]

Soluble polymers, particularly low molecular weight oligomers, also have a role in catalysis as solvents.[17] Poly(ethylene glycol) (PEG) has been used in many reactions as a solvent in catalytic reactions if the catalysts are not extracted by a solvent like heptane, diethyl ether, or scCO$_2$ that separates the products from the PEG solvent.[18,19] Polyolefin

oligomers too can be used as a solvent or cosolvent. When polyethylene waxes are used as a cosolvent, they can serve an additional role if the catalyst is a polyolefin oligomer bound catalyst in that they substitute for heptane in liquid/liquid separations leading to isolation of the catalyst in a polyethylene waxy solid (cf. Figure 1).[20]

Others have previously noted that catalyst decomposition or the absence of a stable resting state for a catalyst precludes any successful catalyst recycling scheme.[21] When a polyethylene wax is used as a solvent, the polyethylene wax does not just entrap, recover, and recycle the catalyst and itself as a solvent, but the solid wax phase also can also stabilize a recovered catalyst toward adventitious degradation by polar reagents. This is illustrated by the stability of PE-entrapped salen catalysts and PIB-bound azo dyes toward protonation by methanolic CF$_3$CO$_2$H.[22] Such effects are analogous to the stabilization of reactive species in paraffin[23] and could be of even more utility if polymer-bound catalysts and polymeric solvent systems could be devised that stabilize a recovered catalyst toward adventitious oxidation, a more common problem than adventitious reaction of a recovered catalyst with acidic or polar reagents.

While the principal role of soluble polymers in catalysis has focused on separations, soluble polymers can confer additional functionality onto catalysts. Polymers with lower critical solution state (LCST) behavior were first described in the
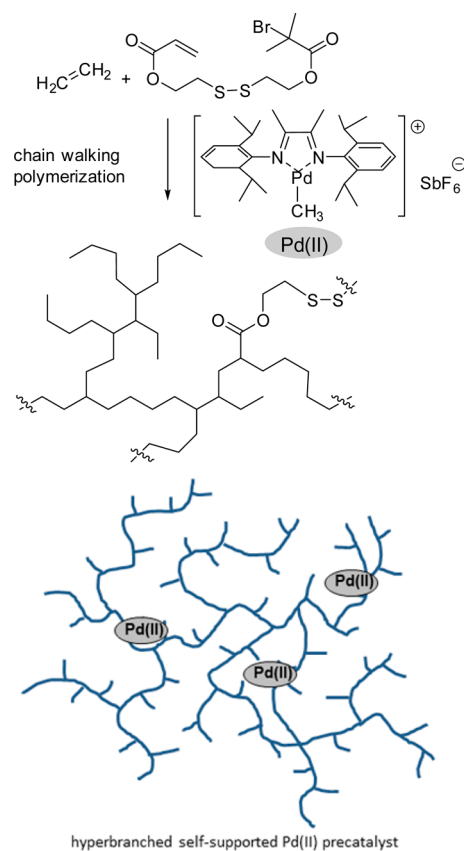
Figure 2. Hyperbranched polyethylene copolymer-supported Pd precatalysts that are phase-selectively soluble in the heptane phase of a biphasic heptane/polar solvent mixture at workup after Pd-catalyzed cross-coupling chemistry.

1960s and used as soluble affinity supports or to control diffusion in instant film.[24] We reported in the 1990s that the reversible solubility of such polymers could be used to support catalysts that are soluble and active cold but insoluble and inactive hot. Such "smart" catalysts autonomously control exotherms in a reaction (Scheme 2).[25] In other cases, this phase

Scheme 2. Thermoresponsive Polymer-Bound Catalysts That Both Autonomously Regulate Exothermic Reactions of a Substrate (Sub) But That Can Also Be Used to Separate and Isolate Catalysts (Cat) and Products (Prod) after a Reaction
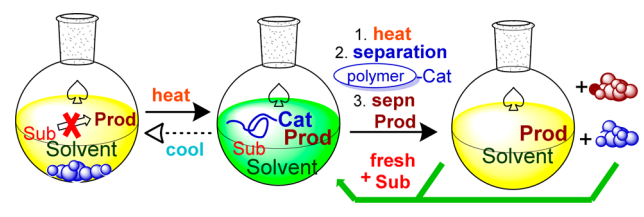
separation was used to make reactions actually faster or to recycle catalysts.[15,26] In still other cases, solubility changes alter the pK_a of pendant acidic or basic groups such that polymer-bound amphoteric groups have enhanced acidity or basicity much like catalytically important amphoteric groups at enzyme active sites.[27] Solubility behavior control can be designed into polymers using triggers other than temperature. Thus, polymers that have light-triggered solubility,[28] that have "thermo-

regulated solubility" in biphasic systems,[29] or that have solubility that is sensitive to formation of a product solute can all be used to affect reaction rates or separations.

Many polymers have chiral centers or intrinsic chirality. In pioneering work on soluble polymer-bound catalysts, Stille briefly investigated the effects of polystyrene chirality on asymmetric catalysts. While those studies showed minimal or no effect,[30] more recent work has shown that the effects of backbone polymer chirality on catalysis can be very significant. Such effects in some cases can afford both enantiomers from a single catalyst. Suginome's group first demonstrated this using solvent changes to change the helical chirality of a P-type (right-handed) helical polymer to form an M-type (left-handed) helical polymer (Figure 3).[31]
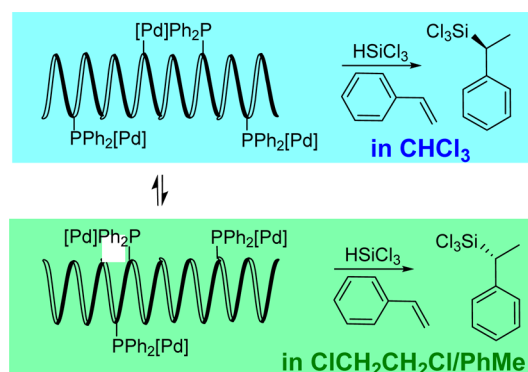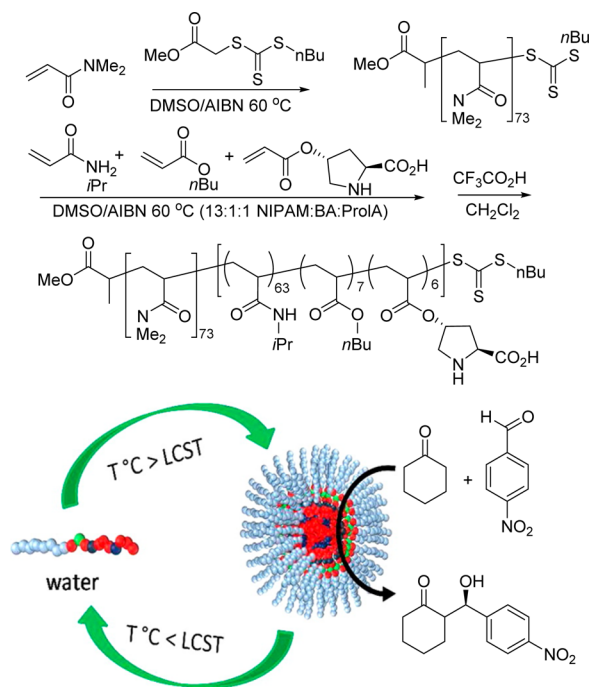

Figure 3. Soluble polymers' solvent-dependent switchable helical chirality and enantioselectivity in Pd-catalyzed hydrosilylation.

Such polymers with pendant phosphine ligands complexed to Pd(II) were used in hydrosilylation reactions of styrene with $HSiCl_3$ to form the S product with the P-type polymer and the R product with the M-type polymer. Suginome has subsequently shown that the environment generated by these sorts of polymers can also alter catalyst activity.[32] It might also be possible to design chiral photoswitchable polymers as candidates for photoswitchable asymmetric catalysts.[33]

Organocatalysts too can be recycled as soluble polymer-supported species, and designed soluble polymers can be used to influence the reactivity of organocatalysts in interesting ways.[34] This is illustrated by recent papers that used polymer self-assembly to develop new sorts of organocatalysts from soluble polymers.[35,36] The O'Reilly and Monteiro groups did this by using controlled radical polymerization to prepare functional block copolymers containing a water-soluble poly-(N,N-dimethylacrylamide) block and a second random block containing poly(N-isopropyl-acrylamide) (PNIPAM), a butyl acrylate, and a proline organocatalyst (Scheme 3). This diblock soluble polymer-bound proline catalyst reversibly assembled into a polymeric micelle due to PNIPAM's LCST behavior, isolating the proline in a more hydrophobic region where it was very effective as an aldol catalyst, forming aldol products with excellent conversion and stereoselectivity with a turnover frequency (TOF) of ca. 2 s^{-1}.[35] These catalysts were also recyclable because the aldol product was insoluble, though catalyst activity decreased significantly after five reaction cycles

The Meijer group has shown that random terpolymers prepared by a controlled radical addition−fragmentation termination (RAFT) polymerization that contain chiral benzene-1,3,5-tricarboxamide groups for self-assembly along

Scheme 3. Soluble Polymer-Bound Organocatalyst (Prepared by a Controlled Radical Polymerization Using Azoisobutyronitrile (AIBN) as an Initiator) That Self Assembles to Form Polymeric Micelles Where the Catalyst Has Enhanced Activity Due to the Soluble Polymer's Lower Critical Solution Temperature (LCST)

Scheme 4. Soluble Polymer-Bound Organocatalysts That Self-Assemble to Generate Catalysts with Enzyme-Like K_m and k_{cat} Values for Aldol Chemistry

with pendant PEG groups for solubility and a proline residue can effect aldol reactions in water analogous to those seen in the O'Reilley/Monteiro work with a slightly greater TOF of 5 s^{-1}.[36] These reactions only occur with the folded polymer and appear to require polymers with substituents that fold on cooling to create active sites for the polymer-immobilized proline organocatalyst. Studies of aldol reactions of cyclohexanone and a reactive 4-nitrobenzaldehyde substrate were shown to have enzyme-like Michaelis−Menten kinetics with a k_{cat} of 0.053 s^{-1} and a K_m of 5.26 mM (Scheme 4). The catalysts were recyclable three times. Earlier work by this group showed similar effects of polymer folding on a Ru transfer hydrogenation catalyst. This intriguing enzyme-like behavior for a simple polymer is notable though a comparison with Nature's aldolase[37] whose k_{cat} and k_{cat}/K_m values are 48 s^{-1} and 1.6×10^7 M^{-1} s^{-1}, which shows that these synthetic polymers are best considered "models" of enzymes.

A final role of soluble polymers is nanoparticle solubility control. Nanoparticles and polymers have comparable masses, and polymers that either encapsulate a nanoparticle or that are grafted to nanoparticles not only can provide nanoparticles with the same sorts of solubility behaviors discussed above but also can in some cases be used to control nanoparticle aggregation or structure. There are numerous examples of the former effect mostly using polymers to render nanoparticles soluble or solvent miscible. One example would be magnetic nanoparticles that have polymers or oligomers grafted to them to render them soluble during a reaction.[38] Another example would be the use of polymers that serve as nanoparticle supports. Crooks' group pioneered this latter chemistry,[39] showing that soluble dendritic polymers can be used to not only control the types of
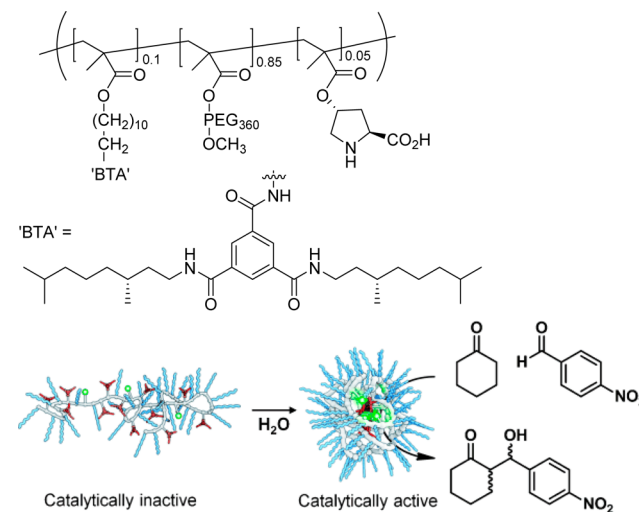
nanoparticles that form within a dendrimer core but also solubilize and recover catalytically active nanoparticles.

Using any sort of polymer support for catalysis of course has its own set of issues and problems—issues and problems that are not always explicitly stated. Adopting soluble polymer supports for real industrial processes also has other issues such as changing a process or changing the way a process is run which can introduce extra costs—costs that might not be justified if a soluble polymer-supported catalyst were replacing an existing catalyst. Nonetheless, some reports indicate that soluble polymer-bound catalysts are "commercially viable" for commodity products like polyacrylates used in paints.[6b] Other batch-type processes that use far more expensive catalysts or that produce more expensive products like fine chemicals or pharmaceutical agents should thus be candidates for such strategies particularly when the catalyst and ligands can be separated as stable species.

Nonetheless, it has to be recognized that there are extra costs and additional difficulty associated with synthesis of a polymer-supported ligand and catalyst. For example, soluble polymeric supports containing ligands typically have to be prepared, often by groups with little experience or interest in synthesis of a polymer. In contrast, a wide array of conventional ligands are commercially available. This is a barrier to using soluble polymers in catalysis because groups interested in using catalysts do not want to learn how to make or modify polymers or to make ligands. This problem is exaggerated too because of the general interest in varying ligand structure to optimize catalyst activity. The commercial availability of a variety of low molecular weight ligands makes it relatively easy to optimize catalyst selectivity in high-throughput assays. It is less well appreciated that soluble polymer-supported ligands and catalysts, while not commercially available, most often have chemistry that is an accurate mimic of that of their low molecular weight counterpart when the ligands are attached to the termini of polymers. This has been demonstrated in several studies with terminal ligands on PEG or PIB oligomers.[40] Soluble polymers like polystyrene with pendant catalyst groups too can have solution-like activity and selectivity equivalent to that of a low molecular weight ligand if the ligand and catalyst are attached via spacer groups. Thus, it should be possible to

prepare soluble polymer equivalents of an optimized low molecular weight ligand though there are still costs associated with the time and effort needed to synthesize the polymer-supported ligand—costs that might increase if a polymer supports' solubility requires alteration of the synthetic schemes used in synthesis of the optimum type of ligand. For example, a synthesis that uses acetonitrile could not be used as is for synthesis of a PIB-supported ligand because the PIB support is insoluble in acetonitrile.

In summary, the solubility properties of polymers, the functionality that can be molecularly engineered into these soluble polymers, and the ways these macromolecules can be separated from products of reactions make soluble polymeric tools for catalysis an avenue for research in both industry and academia. Such work not only can lead to new practical catalytic processes with facile catalyst/ligand/product separation but also can either facilitate existing catalysis or lead to new sorts of chemistry.

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Notes
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