

Using Soluble Polymer Supports To Facilitate Homogeneous Catalysis

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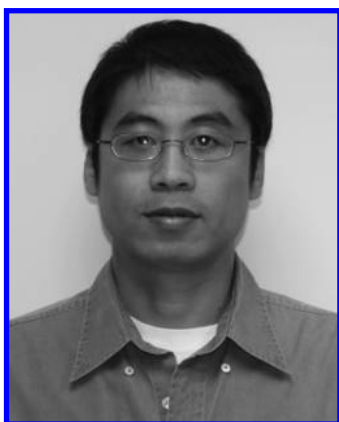
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David Bergbreiter's work at Texas A&M University since 1974 has involved studies in organic, polymer, and catalysis chemistry. In addition to work involving phase separable recoverable catalysts such as that discussed here, he and his group have studied asymmetric synthesis, polymer chemistry, and the design of new sorts of "smart" surfaces.



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1. Introduction

The most important application of polymers in synthetic chemistry is the use of cross-linked polymers in solid phase synthesis and in various sorts of "purifications". This is emphasized not only by chemistry discussed elsewhere in this issue of *Chemical Reviews* but also by an extensive array of other reviews and books over the past 40 years. However, while these cross-linked polymers that are insoluble before, during, and after a reaction have many applications, alternative approaches where polymers are used as soluble supports and then separated after the reaction have received increasing attention in recent years.

A key difference between a strategy that uses an insoluble cross-linked polymer and a strategy that uses a soluble polymer is that the latter strategy allows a catalytic reaction to be carried out under homogeneous conditions. In most cases where a cross-linked polymer is used to support a catalyst, the catalyst is necessarily separated before, during, and after the reaction because it is attached to an insoluble support. In the case of soluble polymers, the phase separation event can occur after the reaction. This phase separation can employ a permselective membrane, a solid/liquid separation after selective polymer precipitation, or a liquid/liquid separation of two different density liquid phases containing either a catalyst or product, respectively. The most common separation processes use solid/liquid or liquid/liquid separations. These processes are contrasted in Scheme 1. Processes that use soluble polymer-supported catalysts that are separated, recovered, and reused after a reaction by a solid/liquid or liquid/liquid separation are the focus of the following review.

Work on soluble polymer supports through 2001 has been reviewed.^{1,2} The discussion below is focused on work that has been reported since 2002. Other reviews since 2002 have also covered some of this material.³⁻⁶ Earlier reviews also emphasized the strategies for separation of soluble polymers. Those have not changed, so we have not exhaustively included each possible strategy in the discussion below. For example, we have not emphasized separations that use permselective membranes to effect a separation.⁷⁻¹⁰

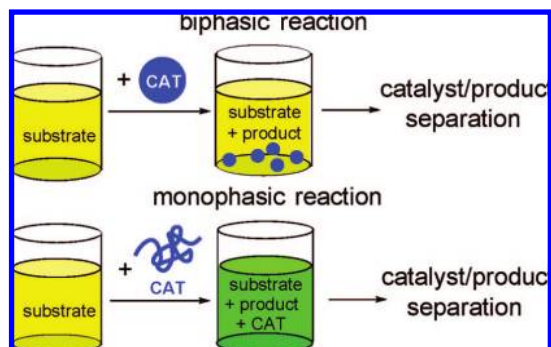
Instead, the discussion of soluble polymer-facilitated catalysis below is broadly divided based on whether a solid/liquid or liquid/liquid separation strategy was used to separate a catalyst from product. Within each of these discussions, we have further divided the discussion based either on the particular type of polymer used to facilitate a reaction or on the type of liquid/liquid separation used to recover, separate, or recycle the polymer-bound species.

2. Solid/Liquid Separations of Soluble Polymer-Bound Ligands and Catalysts

Solid/liquid separations are the general scheme used with cross-linked polymers and with reagents or catalysts that are immobilized on inorganic supports. Most commonly, separation only requires a filtration. In cases where the solids that form are not readily filtered, centrifugation is often effective in separating a solid from solution.

While the techniques of filtration or centrifugation are simple, carrying out a solid/liquid separation of a soluble polymer-bound catalyst after a homogeneous reaction requires a phase perturbation that induces the polymer-supported species to separate as a solid. This can involve a temperature change, as described below for thermomorphic

Scheme 1. Strategic Differences between Use of an Insoluble Cross-linked Polymer Supported Catalyst and a Soluble Polymer Supported Catalyst



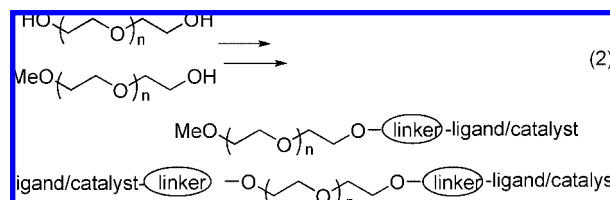
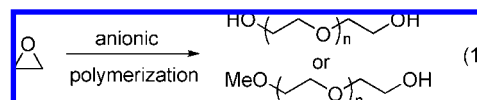
systems. In this case, no significant additions of solvent are required, and the separation can be carried out under reaction conditions. More commonly, a solid/liquid separation of a polymer-supported species from a product solution is effected by changing the solvent to one in which the polymer is not soluble. In either thermomorphic or solvent precipitation schemes, it is assumed that the products remain in solution. The significant additions of solvent required in solvent precipitation may be a problem in large scale processes. Nonetheless, solvent precipitation is the most general way to carry out a solid/liquid separation of a soluble polymer-bound catalyst and product after a homogeneous catalytic reaction.

2.1. Poly(ethylene glycol) (PEG)-Bound Ligands and Catalysts

Poly(ethylene glycol) (PEG) is a linear polymer formed from the polymerization of ethylene oxide. Along with polystyrene, it was one of the first soluble polymers used to facilitate catalysis and synthesis.^{2,11–13} PEG is a smaller version of poly(ethylene oxide) (PEO), a polymer with a $-\text{CH}_2\text{CH}_2\text{O}-$ repeating unit. PEG is the form of this polymer used in synthesis and catalysis because PEGs are polyethers with molecular weights of less than 20,000. With up to two terminal functional groups, polymers of this size have functional group loadings of at least 0.1 mmol/g. These polyether supports are most commonly recovered by solvent precipitation and filtration. PEG is insoluble in hexane, diethyl ether, *tert*-butylmethyl ether (TBME), isopropyl alcohol, and cold ethanol. These are the solvents usually used for the precipitation process.¹⁴ PEG is usefully soluble in a wide range of solvents including DMF, dichloromethane, toluene, CH_3CN , and water. This broad solubility facilitates the use of PEG-supported species under homogeneous reaction conditions. As a soluble linear polymer with a simple repeating unit that only obscures a small part of a typical ^1H NMR spectrum, the structure and loading of end groups can often be analyzed by solution-state ^1H NMR spectroscopy.

The commercial availability of many PEG derivatives with either two $-\text{CH}_2\text{OH}$ end groups or one $-\text{CH}_2\text{OH}$ end group makes it easy to prepare a variety of PEG supported ligands and catalysts. In addition, more complex functional derivatives of PEG are commercially available. If desired, PEG polymers can be prepared by anionic polymerization of

ethylene oxide.¹⁵ The free hydroxyl groups on the polymers that are purchased or prepared by eq 1 can be modified by simple organic reactions to form ligands or catalysts (eq 2). In the absence of branching, loading of ligands or catalysts is limited to one ($-\text{OCH}_3$, $-\text{OH}$ termini) or two (two $-\text{OH}$ termini) equivalents of ligand or catalyst per mole of polymer. Linkers as shown in eq 2 are not required but are sometimes used.

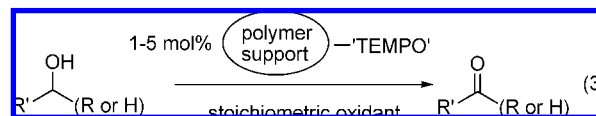


One of the original uses of PEG in synthesis was its use in liquid phase peptide synthesis.^{11,12} That sort of chemistry and chemistry where PEG's sole role is to modify the solubility of compound, for example where PEGs are used to increase the bioavailability of drugs,¹⁶ are not the focus of this review. Instead we have limited the discussion below to recent chemistry where PEG supports are used to facilitate catalysis.

2.1.1. PEG-Bound Organocatalysts

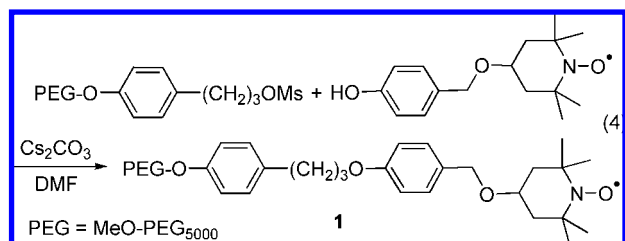
Organocatalysts are playing an increasingly important role in the field of catalysis. Interest in the field of organocatalysis has grown due to the advantages of performing catalytic reactions under metal free environments, which include working with wet solvents under aerobic conditions. As is true for transition metal catalysts, recycling of these homogeneous catalysts is an issue. Such recycling has been successful with a variety of polymers including PEG.³

TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy, is a commonly used organocatalyst for the selective oxidation of primary alcohols to aldehydes. Such reactions use NaOCl , 1,3,5-trichloro-2,4,6-triazinetrione (TCCA), or [bis(acetoxy)iodo]benzene (BAIB) as the stoichiometric oxidant in conversion of hydroxyl groups to carbonyl groups (eq 3). Such oxidations are attractive as metal-free oxidation processes that avoid the use of environmentally malign chromium oxidants. However, recovery and reuse of the TEMPO catalyst is still worthwhile and several groups have shown that soluble polymers such as PEG are useful in this regard.



Various strategies have been used to attach TEMPO oxidants to PEG. Benaglia and Pozzi immobilized TEMPO onto PEG using a trimethyleneoxy benzyl ether as a linker as shown in eq 4.¹⁷ The PEG-TEMPO (1) so formed proved to be an effective catalyst for oxidation of primary and secondary alcohols to aldehydes and ketones with stoichiometric oxidants such as BAIB, TCCA, and NaOCl in solvents

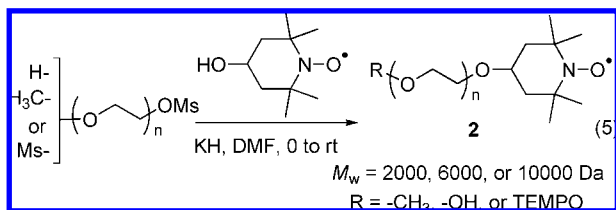
such as CH_2Cl_2 , $\text{CH}_3\text{CO}_2\text{H}$, and a biphasic mixture of $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ where **1** is soluble.



Typical yields were $>90\%$ using NaOCl as the terminal oxidant at $0\text{ }^\circ\text{C}$, and reactions were complete in 30 min using 1 mol % of **1** as a catalyst. However, **1** was inactive as a suspension in TBME. PEG is insoluble in TBME and as is true with other soluble polymers, polymer precipitation and the consequent heterogeneous reaction conditions often significantly decrease reaction rates.^{18–20} Benaglia's group also noted that **1**'s reactivity was not enhanced in acetic acid despite the remarkable accelerating effect this solvent showed in reactions with free TEMPO.²¹ This may reflect the known propensity of the multiple ether oxygen groups in the polymer backbone of PEG to hydrogen bond to $-\text{CO}_2\text{H}$ groups.²² The catalyst **1** was easily recovered by solvent precipitation with diethyl ether and recycled six times with no loss of catalytic activity.

Tsang and Hayes also tethered TEMPO directly to PEG using $\text{S}_{\text{N}}2$ chemistry as shown in eq 5.²³ PEG-bound TEMPO derivatives with a single TEMPO group with $M_w = 164$ or 5000 were prepared from 4-hydroxy-TEMPO.

In their work, they used a series of PEG samples with varying molecular weights and studied the reactivity of the product PEG-TEMPO **2** catalysts.

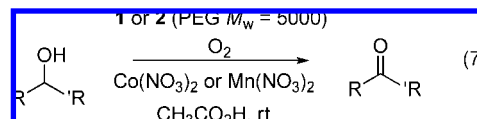


With the exception of TEMPO on $\text{PEG}_{10,000}$ ($R = -\text{OH}$), which had a turnover frequency (TOF) of 0.218 s^{-1} , the initial TOFs of oxidations with 1 mol % of the PEG-supported TEMPO catalysts with these various PEG supports were identical to the TOF reported for unsupported TEMPO (TOF of 0.333 s^{-1}). Recovery of **2** used solvent precipitation

with diethyl ether. Good results were only obtained if the PEG molecular weights were higher than 5000. The authors successfully recycled a $\text{PEG}_{10,000}$ -bound TEMPO four times. Slight decreases in catalytic activity were observed but were attributed to mechanical losses of the catalyst during the filtration process.

In extensions of their initial studies, Tsang and Hayes investigated branched PEG-supported TEMPO derivatives **3a** or **3b** that were prepared as shown in eq 6 (in Chart 1).²⁴ These branched PEG-supported TEMPO catalysts contained two (**3a**) or four (**3b**) TEMPO groups per polymer and possessed several advantages over TEMPO catalysts attached to the unbranched polymer **2**. First, the rate of oxidation of primary alcohols by **3** increased 4–5-fold vis-à-vis PEG-supported TEMPO **2**. This higher activity of **3** was attributed to intramolecular reoxidation of the intermediate hydroxylamine by a neighboring oxoammonium ion. The catalysts **3** were recycled by solvent precipitation with diethyl ether twice without any change in TOF.

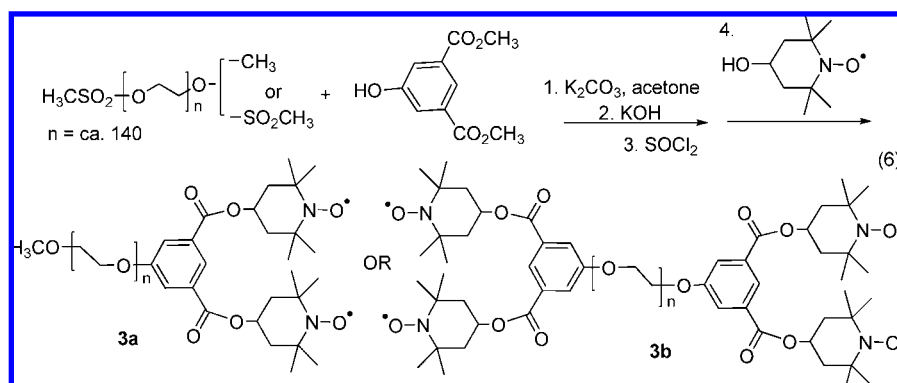
Pozzi investigated the effect of introducing a linker between PEG and TEMPO in aerobic oxidation of alcohols to carbonyl compounds with molecular oxygen as the penultimate oxidant using 5 mol % **1** or **2** along with 2 mol % $\text{Co}(\text{NO}_3)_2$ or $\text{Mn}(\text{NO}_3)_2$ as a cocatalyst (eq 7) ($R = -\text{C}_6\text{H}_5$, $\text{CH}_2\text{C}_6\text{H}_5$, $-4-\text{C}_6\text{H}_4\text{NO}_2$, $-(\text{CH}_2)_n\text{CH}_3$ ($n = 5, 6, 8, 9$); $R' = -\text{H}$, $-\text{CH}_3$).²⁵ PEG TEMPO derivatives **1** and **2** ($R = -\text{CH}_3$) were compared, and **1** was found to be more reactive than **2** based on slightly lower conversions with TEMPO **2** ($R = -\text{CH}_3$).



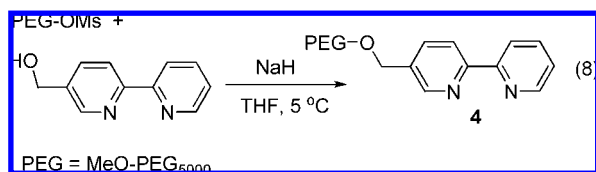
Both versions of the PEG-bound TEMPO were recovered and recycled by solvent precipitation in diethyl ether. Recycling did require fresh additions of the $\text{Co}(\text{II})$ or $\text{Mn}(\text{II})$ cocatalyst. The authors suggested that the presence of a spacer group minimized kinetic problems that might have arisen by hindrance of the active site on the polymeric structure as a result of coiling of the PEG polymeric backbone. This effect had been suggested by Tsang and Hayes to be the cause of the reduction in catalytic activity of certain linkerless PEG-TEMPOs.²³

In 2006, Toy described using multiple different polymer-supported ligands for selective aerobic alcohol oxidation.²⁶ In this work, Toy used two polymer-supported species, a PEG-bound 2,2'-bipyridine **4** as a ligand for $\text{Cu}(\text{II})$ (prepared

Chart 1

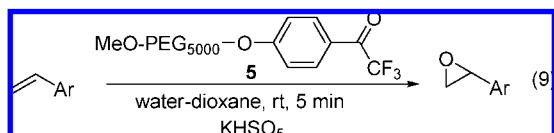


as shown in eq 8) and a PEG-TEMPO **2** ($M_w = 5000$, R = -CH₃), together to catalyze an aerobic oxidation process that converted primary alcohols into aldehydes.

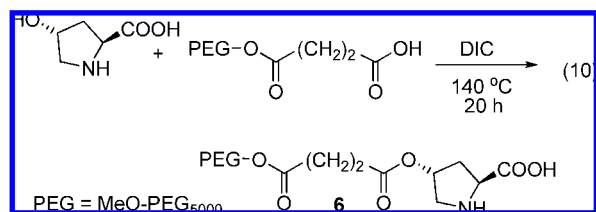


After an aerobic oxidation at 80 °C in CH₃CN/H₂O (2:1) using 5 mol % each of **4**, CuBr₂, and **2** and 10 mol % KOC(CH₃)₃, this mixture of **2** and **4** was separated from the carbonyl products by coprecipitating the PEG derivatives with diethyl ether. This mixed precipitate was recovered and successfully reused in subsequent oxidations without addition of more CuBr₂. The recovered **2** and **4** were reused four times. The isolated yield of aldehydes product decreased from 94% to 88% to 75% to 60% to 36% going from cycle 1 to 5. Addition of 1 mol % CuBr₂ did not alter the decreasing cycle to cycle yields.

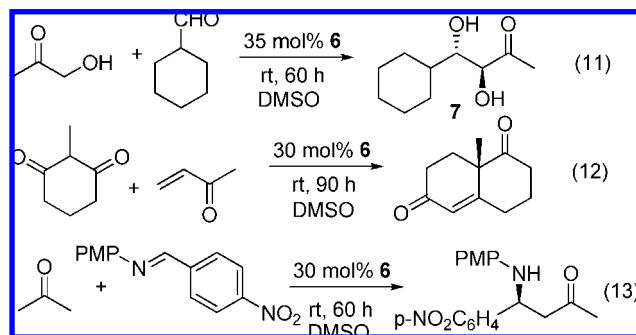
In 2004, Toy et al. immobilized α,α,α -trifluoroacetophenone onto PEG₅₀₀₀ through an ether bond by nucleophilic substitution of MeO-PEG₅₀₀₀-OMs using the Cs salt of 4-trifluoroacetylphenol.²⁷ The PEG-bound α,α,α -trifluoroacetophenone **5** so prepared was used to mediate epoxidation of alkenes using Oxone as the penultimate oxidant (eq 9). Yields of epoxides in 0.4 mmol scale reactions using mostly aryl-substituted alkenes ranged from 72–90%, and the PEG-bound catalyst **5** was recycled five times without affecting catalyst activity or yield.



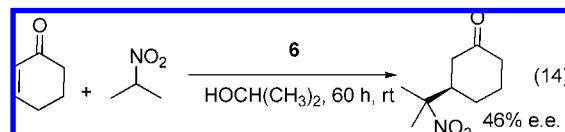
In 2002, Benaglia described a simple route to a PEG-supported proline **6** that his group subsequently used in a variety of proline-catalyzed organocatalytic reactions.²⁸ The PEG-bound catalyst was directly prepared from a succinic anhydride derivative and unprotected (2*S*,4*R*)-4-hydroxyproline (eq 10). This soluble PEG-proline derivative was successfully used as a recyclable catalyst in aldol, Michael, and iminoaldol reactions (eq 11–13).



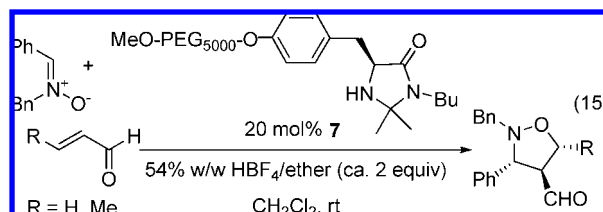
Aldol chemistry with hydroxyacetone derivatives required a 60 h reaction using high loadings of **6** and afforded the *anti* diastereomer of the aldol product **7** in 45% yield with 96% ee. By the third cycle, the synthetic yield dropped to 28% but the ee was unchanged. Catalyst **6** was also used to prepare the Wieland–Mischler ketone in 55% yield with 75% ee. Finally, **6** was effective in iminoaldol reactions such as eq 13. In this case, the synthetic yields were largely unchanged from 81% in cycle 1 to 64% in cycle 3 with constant ee values of 96%.



In 2003, Benaglia described using the PEG-supported proline **6** as a catalyst in enantioselective conjugate addition reactions.²⁹ In the best case, 15 mol % of **6** in MeOH at room temperature afforded Michael addition products of cyclohexanone with 2-nitrostyrene in 46% yield with 90% *syn* diastereoselectivity and 35% ee. Recycling this catalyst was not very successful, as both the chemical yields and ee values dropped into the 20% range during recycling. Other ketones such as cyclopentanone and acetone afforded product but with modest yields and low stereoselectivity. The authors then used Yamaguchi's method³⁰ and used the sodium salt of **6** to carry out Michael additions of 2-nitropropane. These reactions (eq 14) proceeded with 65% yield and 42% ee. Recovery and recycling of the sodium salt of **6** by diethyl ether precipitation was successful with yields (ee) of 65% (46% ee), 64% (38% ee), and 65% (32% ee) in cycles 2–4.

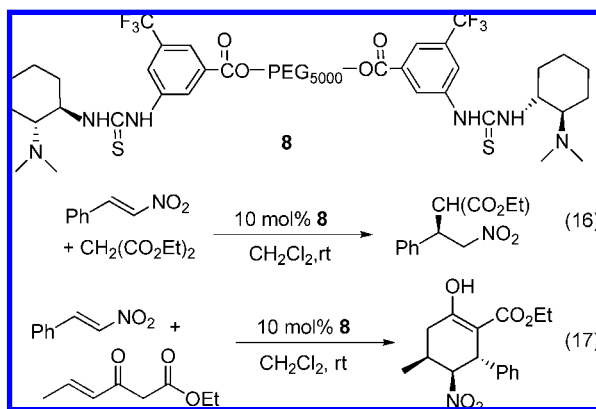


In 2004, Benaglia immobilized MacMillan's tyrosine-derived chiral imidazolidin-4-one catalyst on PEG₅₀₀₀ using chemistry like that shown in eq 4 above and used this catalyst (**7**) to catalyze 1,3-dipolar cycloadditions of unsaturated aldehydes with nitrones (eq 15).³¹ Reactions with 20 mol % catalyst in CH₂Cl₂ at room temperature afforded cycloaddition products in yields of 26–73%. Catalyst **7** was reused by first removing the reaction solvent and then dissolving the products in diethyl ether. The 80–95% of catalyst recovered in this way was then reused, allowing **7** to be recycled three times with nearly constant *trans/cis* ratios of as high as 94:6 and stereoselectivities in the range of 71–88% ee. The stereoselectivity of **7** was similar to that of its low molecular weight analog, but **7** afforded lower chemical yields. While the recycling experiments showed that the supported catalyst **7** could be recycled without affecting its stereochemical efficiency, synthetic yields decreased to less than 40% in the third cycle.

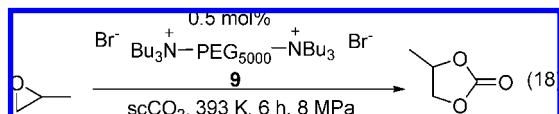


Thiourea catalysts anchored to PEG₈₀₀₀ (**8**) were prepared and compared to analogous DVB-cross-linked immobilized thiourea catalysts in work by the Takemoto

group.³² In reactions like eq 16, catalyst **8** could be recovered by precipitation with diethyl ether and reused once. Yields (stereoselectivity) through two cycles were 71% (86% ee) and 74% (90% ee) with **8** while yields were <40% in the first cycle with a DVB-cross-linked polystyrene thiourea. In the case of the cyclization in eq 17, insoluble thiourea catalysts like **8** formed product in <20% yield while the average yield using **8** was 63% through three cycles with an average ee of 77%.

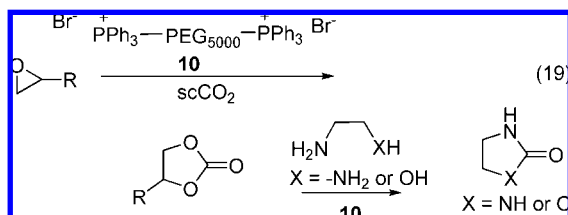


In 2005, He described using a PEG-supported quaternary ammonium salt **9** for solvent free synthesis of cyclic carbonates from carbon dioxide and epoxides under supercritical conditions.³³



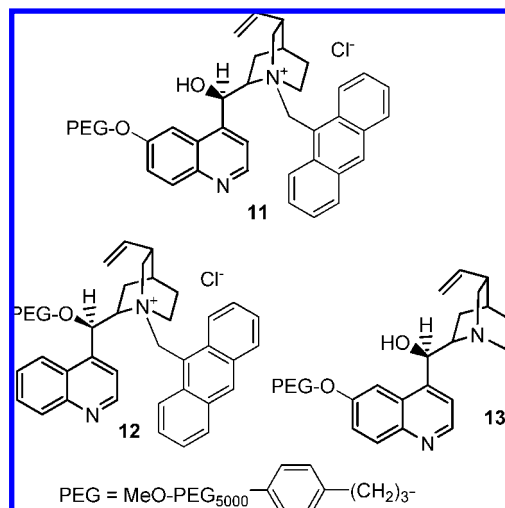
PEG-supported tributyl ammonium bromide salt **9** successfully converted various epoxides including propylene oxide to cyclic carbonates in high yields (92–98%) (eq 18). Catalyst **9** was recycled four times in the conversion of propylene oxide to propylene carbonate with very high yield (>98%). Recovery was achieved by simple filtration after the reaction was cooled down to room temperature.

Very recently, a phosphonium salt version of **9** was described by Bhanage and co-workers.³⁴ This phosphonium salt **10** catalyzed formation of cyclic carbonates just like **9**, but the intermediate cyclic carbonates could also be used without isolation as a phosgene-equivalent to form a structurally diverse group of 2-oxazolidinones or 2-imidazolidinones in 70–90% yield from 1,2-amino alcohols or 1,2-diamines (cf. eq 19). In these cases, the product was dissolved in EtOH and the catalyst **10** was recovered by precipitation using diethyl ether. Yields for cycloaddition of CO₂ and styrene oxide through five cycles were above 95%.

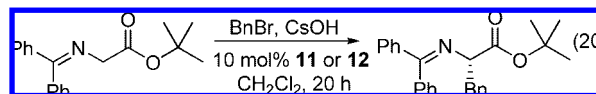


Salts of *Cinchona* alkaloids bound to PEG derivatives have been used as catalysts or ligands in various reactions.³⁵ The

use of PEG-bound *Cinchona* alkaloids as catalysts for alkylation of activated aminoacids and as catalysts for alkylation of thiophenols by enones was described by Benaglia's group. In this work, they prepared PEG-bound *Cinchona* alkaloid derivatives **11–13**. These catalysts were then used in benzylation of an activated glycine ester (eq 20) or to catalyze Michael additions of thiophenol to cyclohexenone.

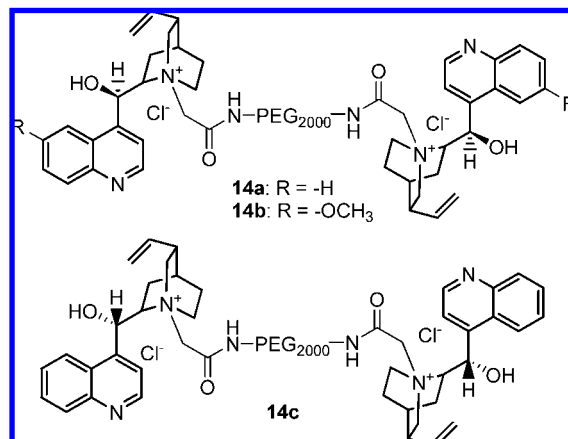


In the case of eq 20, 10 mol % of catalyst **11** or **12** afforded the *S* product in ¹H NMR or HPLC yields of up to 94%.



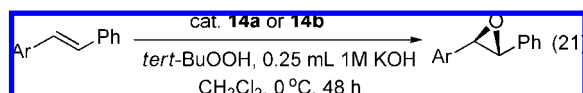
Stereoselectivity was generally modest with the best result being 64% ee. Catalyst recycling was precluded by decomposition of the catalysts **11** or **12** under the reaction conditions. This report also briefly described conjugate addition of thiophenol to cyclohexenone using 5 mol % of catalyst **13**. The β -thiophenoxycyclohexanone was obtained in 75% yield with 22% ee, but no recycling was described.

PEG-bound *Cinchona* ammonium salts have also been used as chiral phase transfer catalysts in both asymmetric epoxidation and asymmetric alkylation chemistry by the Wang group.^{36,37} These catalysts (**14a**, **14b**, and **14c**) were prepared from the corresponding cinchonidine, quinine, and

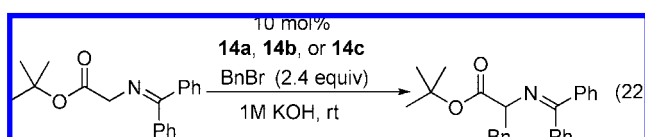


cinchonine alkaloids by *N*-alkylation using the bischloroacetamide of a diamino-PEG₂₀₀₀, ClCH₂CONH-PEG₂₀₀₀-

NHCOCH₂Cl. These amide bound *Cinchona* alkaloids were stable to the reaction media. The catalysts **14a** and **14b** were both used in chalcone oxidation (eq 21). While the crude NMR spectroscopic yields of the product in this chemistry were generally in the 80–95% range in 48 h epoxidation reactions carried out on a micromole scale, the ee was modest and was in most cases <60%. Three recycles with the catalyst **14a** consistently formed the epoxide product in reaction 21 (Ar = -Ph) in 90% yield with 86% ee.

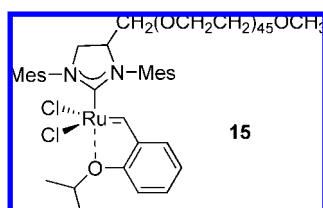


Asymmetric alkylation of the benzophenone imine of *tert*-butyl glycine using catalysts **14a**, **14b**, or **14c** was successful in small scale (0.2 mmol) reactions in water (cf. eq 22).³⁶ A variety of alkylating agents were used including benzylic bromides (R = -CH₂C₆H₅, -CH₂(*o*-CH₃C₆H₄), -CH₂(*m*-CH₃C₆H₄), -CH₂(*p*-CH₃C₆H₄), -CH₂(*o*-ClC₆H₄), -CH₂(*m*-ClC₆H₄), -CH₂(*p*-ClC₆H₄)), allyl bromide, or ethyl or methyl iodide. These alkylations afforded chiral amino acid derivatives in generally high yield with ee values that averaged about 90% ee. The limiting reagent in these aqueous phase alkylations was the amino acid Schiff base. The excess benzylic bromide presumably hydrolyzes. The product was the *S* amino acid derivative with catalysts **14a** and **14b**, but with the pseudoenantiomeric cinchonine derivative **14c**, the *R* product predominated. While similar catalysts had been reported earlier by the Cahard group,³⁸ those catalysts had not been efficiently recycled. The Wang group reported that, using 10 mol % catalyst **14b**, recycling was possible with yields that dropped slightly from 94% to 90% to 88% and ee values that were 82%, 80%, and 80% ee in cycles 1, 2, and 3, respectively. These recycling experiments were carried out on a 0.2 mmol scale reaction and involved extraction with 30 mL of CH₂Cl₂ and catalyst precipitation using 15 mL of diethyl ether.



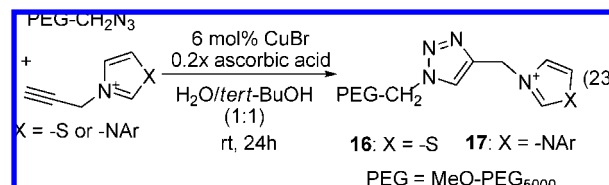
2.1.2. PEG-Bound *N*-Heterocyclic Carbene Ligand and Catalysts

N-Heterocyclic carbenes (NHCs) are attractive organocatalysts that have a long history and analogies to biological catalysts.^{39–42} As noted below, species like **15** have been immobilized on PEG for use in Ru-catalyzed metathesis chemistry.⁴³

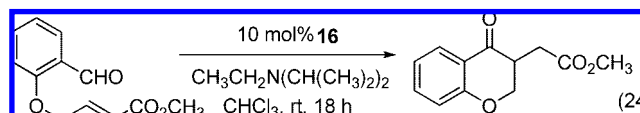


PEG-bound NHCs have also been prepared and used as organocatalysts in a variety of nucleophilic catalytic

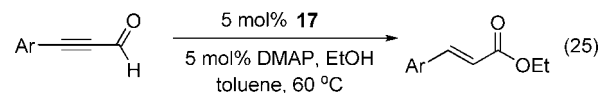
reactions.⁴⁴ In this case, the PEG-bound NHCs were prepared by a copper-catalyzed azide–alkyne cycloaddition reaction (eq 23). The resulting PEG-supported thiazolium derivative **16** was successfully used in intramolecular Stetter reactions of various substituted aryl aldehyde electrophiles in eq 24 (e.g., 4-Cl, 4-NO₂, 2-Cl, or 2-OCH₃) with isolated yields of chroman-4-one that typically exceeded 80%.



In this case, the main value of the PEG support was in simplification of product isolation in that the PEG-bound catalyst could be removed without need for column chromatography. Recycling of **16** was examined but was unsuccessful in CHCl₃. Some **16** could be recovered and reused when EtOH was used as the solvent though the synthetic yields of product in subsequent reactions catalyzed by **16** were below 50%.

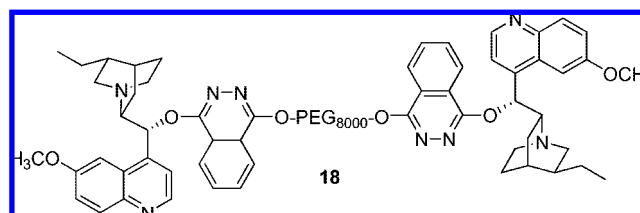


The PEG-bound carbene precursor **17** (Ar = 2,6-diisopropylphenyl) was also used in redox esterifications (eq 25). In this case, the reaction was successful with a variety of cinnamate analogs, affording 60–70% yields of isolated products. In this reaction, **17** could be recycled with yields of 83, 77, and 75% in cycles 1–3.



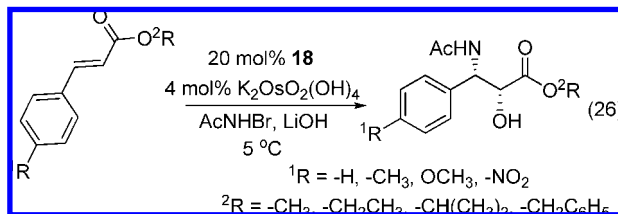
2.1.3. PEG-Bound *Cinchona* Alkaloid Catalysts

PEG-bound *Cinchona* alkaloids and their derivatives are widely used as chiral ligands for Sharpless asymmetric alkene dihydroxylation and aminohydroxylation reactions.⁴⁵ Xu and Lin recently described using PEG 4000, 6000, and 8000 immobilized *Cinchona* alkaloid ligands for the catalytic asymmetric aminohydroxylation of alkenes using K₂OsO₂(OH)₄ as a catalyst and AcNHBr as a nitrogen source.⁴⁶ In this case, the *Cinchona* alkaloid was first converted to a monosubstituted chlorophthalazine using 1,4-dichlorophthalazine. Then, the dilithium salt of a PEG diol was inserted to form the PEG derivative **18**.



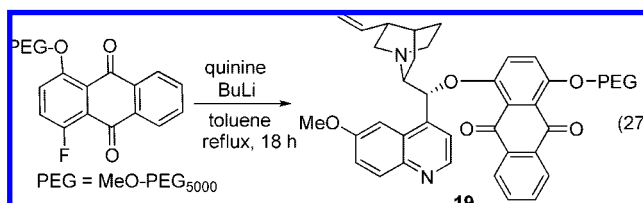
This PEG derivative **18** was then used in an asymmetric aminohydroxylation reaction. Various derivatives of *trans*-cinnamate were examined as substrates (eq 26).

The products' ee values were in the range of 74–99% ee, and the regioselectivity of the aminohydroxylation was >10:



1. The polymeric ligand **18** formed using PEG₈₀₀₀ was recovered by solvent precipitation and was reused with isopropyl *trans*-cinnamate with yields of ca. 90% and >95% ee in each of five cycles.

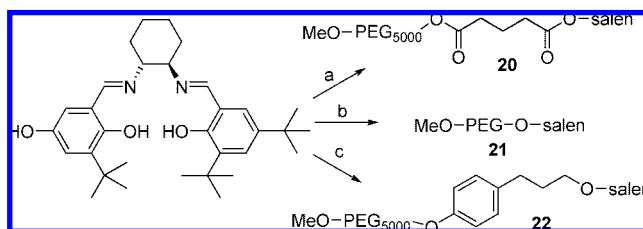
As noted above, PEG has been previously used to support ligands for Sharpless' asymmetric dihydroxylation reaction.² In 2005, Zhang described immobilization of *Cinchona* alkaloids with an anthraquinone core onto PEG₅₀₀₀ (eq 27).⁴⁷ This PEG-bound *Cinchona* alkaloid **19** was used in asymmetric dihydroxylation with various alkenes with high stereoselectivities (>80% ee) and high yield (>80%). The PEG-bound *Cinchona* alkaloid **19** was recovered by solvent precipitation with diethyl ether and recycled through five cycles with *p*-chlorostyrene as a substrate. The average yield of all five cycles was 93% with the minimum stereoselectivity of 96% ee.



2.1.4. PEG-Bound Salen Ligands

Venkataraman's group described the synthesis of three different types of PEG-supported salen ligands **20**, **21**, and **22** (Scheme 2) with or without linkers.⁴⁸ These chiral PEG-salen complexes were then used to catalyze the addition of diethyl zinc to aldehydes. In this chemistry, the PEG catalyst with a directly linked salen (**21**) yielded product in high yield but with lower stereoselectivity (32% ee) than an analogous low molecular weight salen ligand (82 ee). Since control experiments using a low molecular weight catalyst showed added PEG did not affect the stereoselectivity, the authors speculated that the PEG support in **21** interfered with the microenvironment of the catalyst. Thus, they examined the use of either a glutarate spacer or a phenoxypropyl spacer

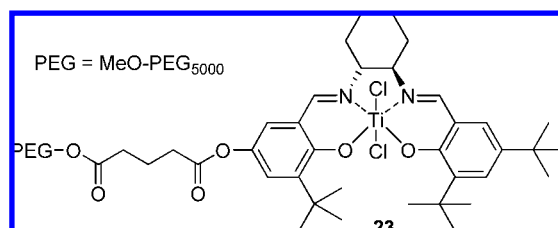
Scheme 2. Synthesis of PEG₅₀₀₀-Bound Salen Ligands with and without Linkers^a



^a Conditions: (a) (i) glutaric anhydride, DMAP, CH₂Cl₂, rt, 12 h and (ii) MeO-PEG₅₀₀₀-OH, DMAP, DCC, CH₂Cl₂, rt, 24 h; (b) MeO-PEG₅₀₀₀-OMs, Cs₂CO₃, DMF, rt, 24 h; and (c) MeO-PEG₅₀₀₀-OC₆H₄(CH₂)₃OMs, Cs₂CO₃, DMF, rt, 24 h.

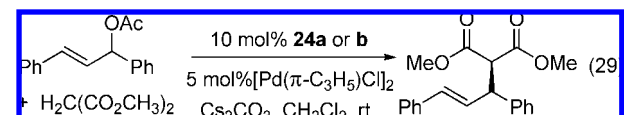
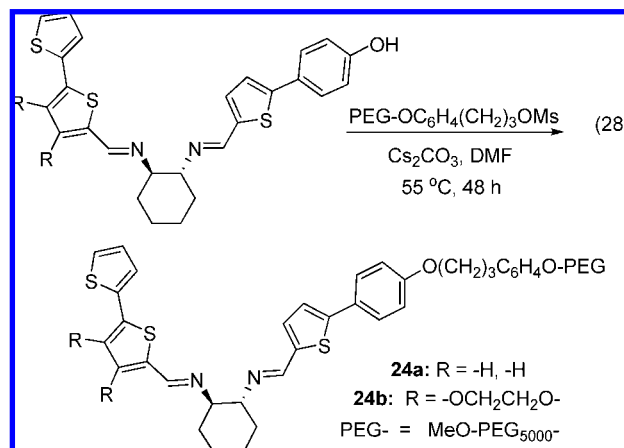
to tether salens to PEG (cf. **20** and **22**). The results showed PEG-salen **20** afforded an addition product with 82% ee and **22** afforded a product with 68% ee. Recycling was only studied with **20**, which was reused twice with high yields (>91%) and 82% ee. These results are consistent with the earlier studies of Hayes and Benaglia, who noted similar effects of tethering groups in PEG-supported TEMPO oxidations.

With the success of PEG-salen **20**, Venkataraman's group subsequently prepared a Ti(IV) salen **23** from **20** and used it for silylcyanation of benzaldehyde using equimolar amounts of trimethylsilylcyanide and 0.1 mol % of **23** in dichloromethane at room temperature for 24 h.⁴⁹ The PEG-bound Ti(IV) salen **23** was recovered and reused for four cycles without any loss in yield using a Soxhlet-dialysis apparatus. Typical yields were >95% with 84–86% ee.



2.1.5. PEG-Bound Diamino-oligothiophene Ligands

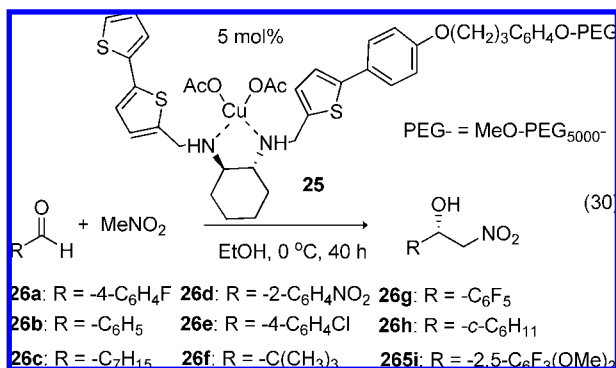
Diamino-oligothiophene ligands (DATs) are known to be effective ligands for Pd-catalyzed nucleophilic allylic alkylations.⁵⁰ In 2006, Bandini and Benaglia described the syntheses of PEG₅₀₀₀-bound DATs **24a** and **b** using eq 28 and used the PEG-bound catalysts for palladium promoted asymmetric alkylation of allylic esters with dimethylmalonate (eq 29).⁵¹



Of the two PEG catalysts prepared in eq 28, **24a** afforded a more active catalyst and it therefore was chosen for recycling experiments. The Pd-complex of ligand **24a** was recovered by solvent precipitation using diethyl ether and was reused for three consecutive runs. The 92–95% ee was

consistent run to run, and overall yields ranged between 84 and 91%, but only when an extra 5 mol % Pd was added in each cycle. Without additional Pd, yields and ee values significantly decreased by cycle 3.

In 2007, Bandini and Benaglia continued their investigation of PEG₅₀₀₀-DATs, synthesizing the Cu(II) PEG-DAT complex **25** and using it as a catalyst in an asymmetric nitroaldol reaction (eq 30).⁵² Reactions between various aldehydes and nitromethane were studied and the product yields ranged from 65 to 91% and the stereoselectivities were typically greater than 83% ee. Recycling was carried out by removing the solvent and washing the residue with diethyl ether. The ether-insoluble catalyst was recovered and reused 5 times in reaction of nitromethane with benzaldehyde. Reactions with the recycled catalyst proceeded without change in % ee, but the conversion decreased about 20% by the fifth cycle. A feature of this recyclable catalyst is that it could be used in successive reactions with different substrates (**26a–e**) without measurable cross-contamination. This idea has been used before with achiral soluble polymer-bound catalysts⁵³ and is an attractive feature of a recyclable chiral catalyst.

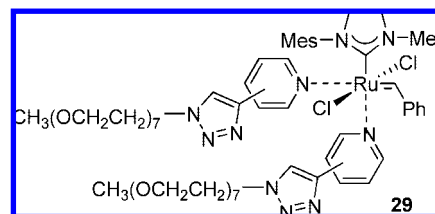


2.1.6. PEG-Bound Ruthenium Metathesis Catalysts

Ruthenium-catalyzed ring-closing metathesis, cross-metathesis, and ring-opening metathesis polymerizations are broadly useful methodologies that are equally useful in complex syntheses and in the formation of materials.^{54–56} However, as is true for other homogeneously catalyzed reactions, strategies to recover and reuse catalysts are of interest. This subject is addressed elsewhere in this issue of *Chemical Reviews*, so the use of soluble PEG derivatives in this context is only discussed briefly below.

PEG has been used to immobilize metathesis catalysts in several ways. One approach tried by several groups has been

to attach a benzylidene ligand of a precatalyst onto PEG. Various motifs have been used, as shown by **27** and **28** (Chart 2).^{57,58} The problem with this approach is that the active Ru species necessarily separates from the PEG support during the metathesis process. In these cases, catalyst recovery requires that the Ru alkylidene intermediate in the catalysis boomerang back onto a PEG-substituted styrene. Another approach using PEG-bound pyridine ligands **29** has also been described.⁵⁹

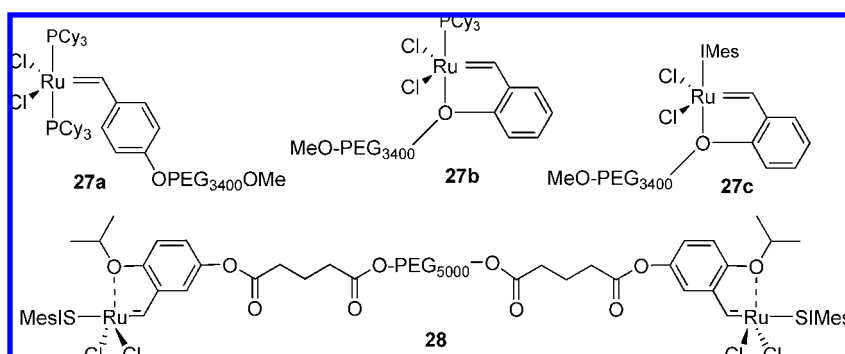


This issue was addressed by more recent work by Grubbs, who prepared PEG-substituted *N*-heterocyclic carbene-containing Ru complex **15**.^{43,60} Since NHC ligands are thought to remain attached to the Ru throughout the catalyst cycle, there is no need with **15** for a boomerang process or recoordination of a PEG-bound ligand for catalyst recovery.

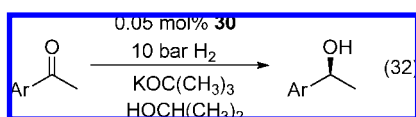
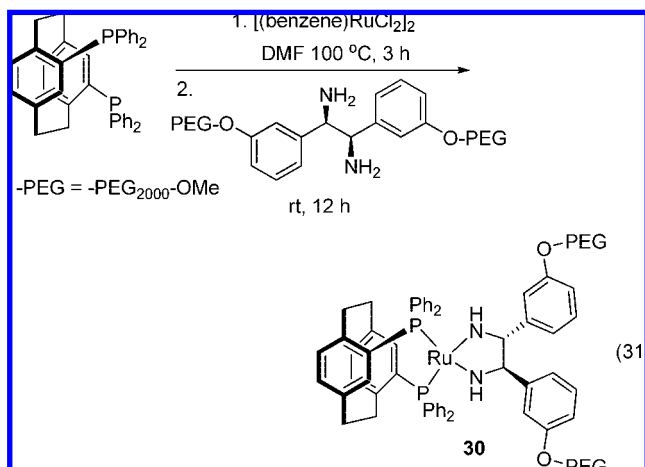
2.1.7. PEG-Bound Diphenylethylenediamine Ligands

Optically active 1,2-diphenylethylenediamine (DPEN) is a useful chiral ligand, and DPEN or its derivatives have been used as ligands for metals to generate highly enantioselective catalysts for many asymmetric organic transformations.⁶¹ In 2003, Xiao's group described a synthesis of a PEG-supported DPEN Ru(II) complex, **30** (eq 31), that was in turn used for asymmetric hydrogenation of ketones (eq 32).⁶² This PEG-DPEN-bound Ru(II) complex was effective in reduction of various aromatic ketones to alcohols with high conversion (>98%) and high stereoselectivity (>90% ee). For example, complex **30** was used to reduce 1- or 2-acetonaphthone, various *p*-substituted acetophenones, and propiophenone to the corresponding benzylic alcohols in >95% yield with >95% ee. Catalyst recovery was reported and variously involved precipitation with diethyl ether or removal of solvents and extraction of the catalyst residue by diethyl ether. The diethyl ether insoluble catalyst that was recovered was reused three times without any change in the yield or stereoselectivity for reductions like those in eq 32. Analysis for Ru leaching

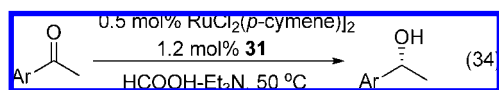
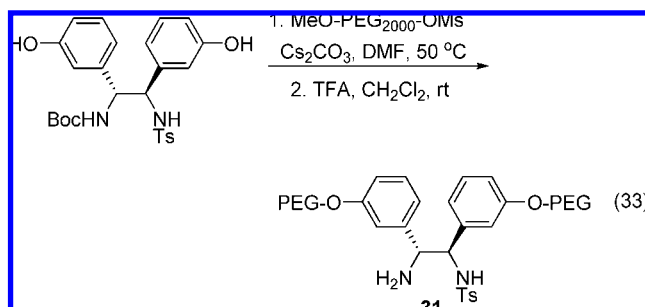
Chart 2



showed 2.7 ppm Ru in the diethyl ether washes—a concentration that could represent as much as 5–10% of the charged Ru.



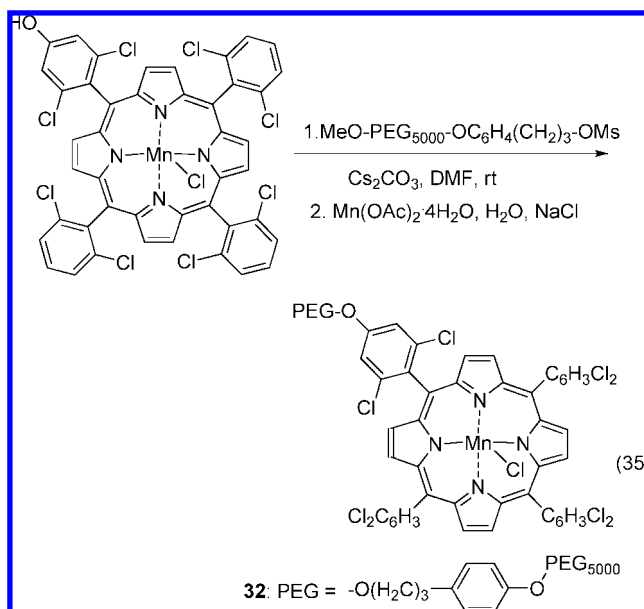
In subsequent work, a monotosylamide of a dihydroxylated DPEN was immobilized onto PEG₂₀₀₀ (eq 33) and the resulting PEG-bound species **31** was used as a ligand for Ru(II) in asymmetric transfer hydrogenation of aromatic ketones with ammonium formate as a hydrogen source (eq 34).⁶³ While high conversions (66–100%) and high ee's (87–95%) were seen in the first cycle, the conversions dropped to 56% and the ee dropped to 82% in the third cycle. Although ICP-MS analysis of the solution phase showed <0.7% of the ruthenium was lost by leaching, the stability of the ruthenium complexes was thought to be a possible problem affecting recycling.



2.1.8. PEG-Bound Porphyrin Ligands

Porphyrins are excellent ligands for many transition metals. However, metal porphyrin complexes not only contribute trace metals to products, they can affect things such as a product's visual appearance because they are such intense chromophores. Benaglia and Pozzi have described using PEG to prepare PEG-supported manganese porphyrin complexes such as **32** (eq 35). They studied the catalytic activity and recyclability of this complex in epoxidation of alkenes using H₂O₂ and PhIO as stoichiometric oxidants.⁶⁴ The yields of epoxide varied but were typically >80% for the first cycle

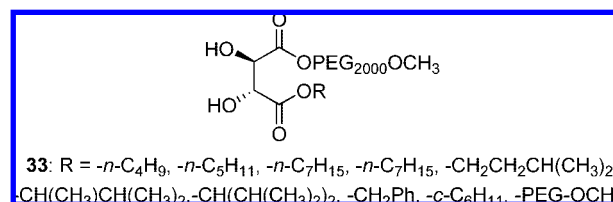
with PhIO as the oxidant. Monosubstituted alkenes were poorer substrates than disubstituted alkenes with conversions usually <50%. The oxidation of cyclooctene was studied most extensively and could be effected in 96% yield in the first cycle with as little as 0.01 mol % of **32**. Recycling studies showed that oxidations with 2 mol % of **32** could be carried out at least 7 times with a yield in the seventh cycle of 63%.



Complete catalyst recovery was evidenced by the almost complete absence of the peak at 478 nm for **32** in a UV–vis spectroscopy analysis of the product.

2.1.9. PEG-Bound Tartrate Ester Ligands

In 2003, Wang and Guo reported work on the use of PEG supports to prepare a tartrate ester ligand library that was used in an effort to probe the effect of tartrate structure on stereoselectivity in Sharpless asymmetric epoxidation of allylic alcohols.⁶⁵ This library synthesis used a mixture of hydroxyl-terminated PEG₂₀₀₀ methyl ether as one alcohol and a variety of other alcohols in an acid-catalyzed esterification of tartaric acid. The mixtures of diesters prepared (**33**) were then screened in epoxidation chemistry, with the best ligand being the tartrate formed from tartaric acid and a 4:1 mixture of 1-heptanol and the MeO-PEG₂₀₀₀-OH. That tartrate ester mixture with *tert*-butyl hydroperoxide, Ti(O*i*Pr)₄, and 4 Å molecular sieves epoxidized various allylic alcohols in modest yields that averaged ca. 50–60% with ee values that varied between 30 and 99%. That tartrate ester mixture was also examined as a recyclable catalyst. The authors described those results as unsatisfactory.

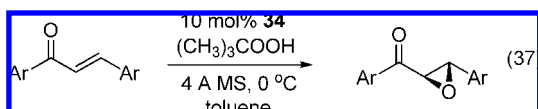
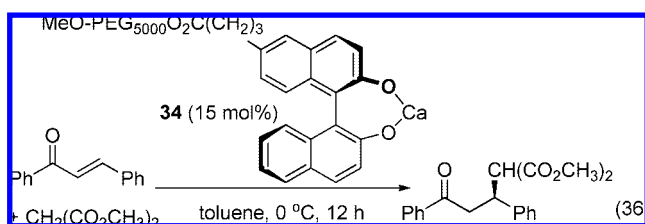


The PEG-supported Ti-tartrate complexes **33** used for Sharpless epoxidation were also used to catalyze the asymmetric oxidation of prochiral sulfides by the Wang group.⁶⁶

These reactions used cumyl hydroperoxide as the oxidant, and in the case of **33** with R = C₇H₁₅, the tartrate was precipitated with diethyl ether and recycled four times without affecting the ca. 64% yield of the *S*-sulfoxide product in the oxidation of thioanisole (95%, 94%, 93%, and 91% ee in cycles 1–4).

2.1.10. PEG-Bound BINOL Ligands

A PEG-bound BINOL calcium complex **34** was synthesized by Kumaraswamy and used in asymmetric Michael reactions of cyclopentenone or chalcone with dimethyl- or diethylmalonate or *tert*-butyl hydroperoxide epoxidation of chalcone or chalcone derivatives (eqs 36 and 37).⁶⁷

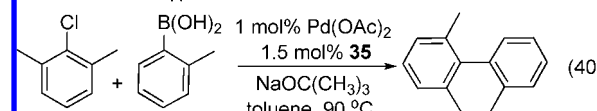
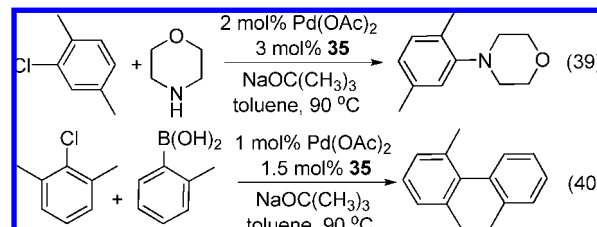
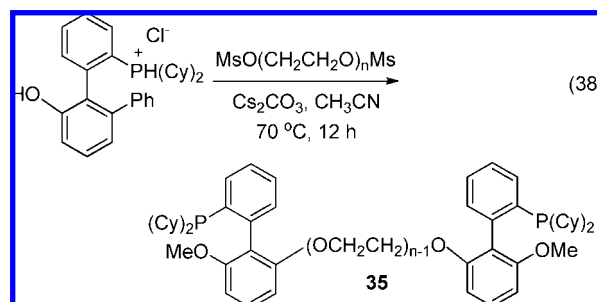


The catalyst **34** was separated from product by evaporating the toluene, redissolving the residue in CH₂Cl₂, and precipitating **34** using diethyl ether. In this way, **34** was successfully recycled three times. Excellent yields were observed with all substrates with little change in yield through three cycles. However, the asymmetric induction was typically only about 40%.

2.1.11. PEG-Bound Phosphine Ligands

PEG-bound phosphines were among the first soluble polymeric ligands. Since those initial reports in the 1960s,¹³ many other supported phosphines have been prepared. These were discussed in prior reviews.² More recently, interests have shifted to developing chemistry to support chiral phosphine ligands for asymmetric catalysis. A report by García's group of a PEG-supported SPhos phosphine that was used for Pd-catalyzed couplings of aryl chlorides is illustrative of this current interest.⁶⁸ In this case, a PEG-bound SPhos **35** derivative was prepared using the chemistry in eq 38 and was tested both in the Buchwald–Hartwig amination of aryl halides with secondary amines (eq 39) and in Suzuki couplings (eq 40). In this case, the authors compared this PEG-bound SPhos **35** with SPhos on a soluble non-cross-linked polystyrene support, on a cross-linked polystyrene support, and on SiO₂. In aryl amination of 2,5-dimethylchlorobenzene by morpholine, Pd ligated by **35** was the most reactive SPhos Pd catalyst with a TOF that was ca. 60-fold greater than that of a similar ligated Pd catalyst on cross-linked polystyrene and >1000-fold more reactive than a similar catalyst bound to SiO₂. In Suzuki coupling of 2,6-dimethylchlorobenzene and 2-methylphenylboronic acid, Pd ligated by **35** was also the most reactive and the SPhos Pd

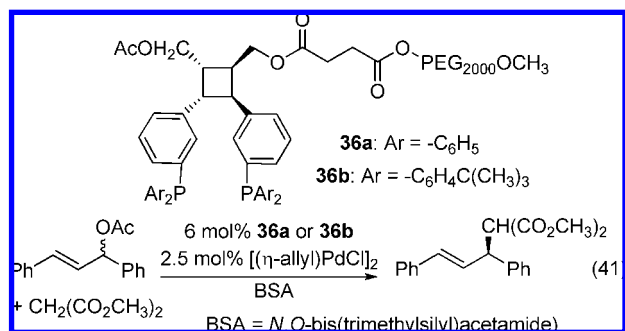
catalyst had a TOF that was 20-fold larger than that of a similar ligated Pd catalyst on SiO₂.



The PEG-bound SPhos **35** was recycled through eight cycles for the Buchwald–Hartwig amination reactions with a more reactive substrate such as 4-chloroacetophenone, but both in this case and other attempted recycling studies, notable decreases in yield and increases in reaction times were observed. While these phosphines are reportedly less sensitive to oxidation than other phosphines,⁶⁹ the general problem of phosphine oxidation that others have seen in Pd-catalyzed chemistry⁷⁰ remains a problem with **35**. This is evidenced by the results in this case where these authors found that, based on ³¹P NMR spectroscopy, the recovered PEG-supported ligands **35** were highly oxidized after the reaction. A further problem was that the conditions required for regeneration of the oxidized version of **35** by reduction detached the SPhos from the polymer.

Chiral bisphosphine ligands on a cyclobutane backbone that were developed by Ding's group for asymmetric allylic alkylation have been successfully attached to a PEG₂₀₀₀ polymer via a succinate linker.⁷¹ In this chemistry, the PEG₂₀₀₀ group served several functions. While the main purpose of the polymer was to recover a Pd catalyst, the PEG₂₀₀₀ also facilitated purification of the ligands during the synthesis. That chemistry used a dicyclohexylcarbodiimide and DMAP as reagents to couple the half acid formed from MeO-PEG₂₀₀₀-OH and succinic anhydride to one or the other enantiomer of a bisphosphine on a cyclobutane that had been previously resolved. This ester synthesis generated the desired products **36a** and **36b** along with unreacted starting material and dicyclohexylurea (DCU). While the DCU was insoluble in the CH₂Cl₂ solvent used in the esterification, the separation of the bisphosphine from starting materials might have, for example, required a column chromatography which would have possibly exposed the phosphines to oxygen and led to undesired phosphine oxides. In this case, this was avoided by evaporating the solvent from the solution of starting material and the PEG-bound bisphosphine and then simply washing away any diethyl ether-soluble starting materials or byproducts from the diethyl ether insoluble PEG₂₀₀₀-bound bisphosphine. Chiral bisphosphine ligands **36a** or **36b** so prepared contained either a bis(diphenylphosphinyl) or bis(4-*tert*-butyldiphenylphosphinyl) ligand and were successfully used to form a Pd-complex *in situ* using

$(\eta\text{-allylPdCl})_2$ and then used in an asymmetric allylic alkylation using dimethyl malonate (eq 41). Yields through 9 cycles with 2.5 mol % of Pd and 6 mol % of ligand **36b** in eq 41 varied from 99% (cycles 1–6) to 81% in cycle 9. Enantioselectivity was relatively constant at 91% ee \pm 3% through these 9 cycles.



2.2. Non-Cross-linked Polystyrene (NCPS)-Bound Ligands and Catalysts

Polystyrene is an attractive linear soluble polymer to use for supporting catalysts because the chemistry used to immobilize ligands and catalysts mirrors that used on the more common cross-linked polystyrene supports. Such chemistry has been extensively developed because of the importance of such supports in peptide synthesis and combinatorial chemistry during the past 30 years.¹³ In the case of linear polystyrenes, functionality to support ligands or catalysts can be introduced directly during a polymerization using an appropriate comonomer or postpolymerization by modification of the polymer. In many cases, a combination of steps is used. Control of the amount of functionality can be achieved by varying the amount of comonomer in a polymerization or by controlling reaction conditions in postpolymerization modification. Analyses of the amount of functionality (ligand or catalyst) can often be carried out by solution-state ¹H NMR spectroscopy though the background signals due to polystyrene's own NMR spectrum make some spectral regions essentially opaque. Polystyrene is usefully soluble in THF, dichloromethane, chloroform, benzene, and ethyl acetate. It is insoluble in hexane, methanol, and water.² Its insolubility in select solvents means that the polystyrene-bound ligands or catalysts can be recovered and recycled by the same type of solvent precipitation process used for PEGs. When such a precipitation works, it allows one to separate the polymer and solution phase products by simple filtration. While non-cross-linked polystyrene-bound catalysts have typically been recovered by solvent precipitation, substituted polystyrenes can be recovered using a liquid/liquid separation too.⁷²

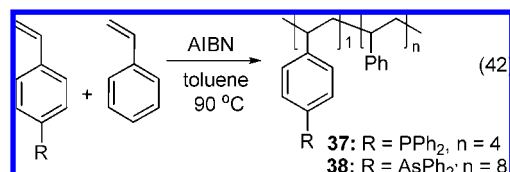
2.2.1. NCPS-Bound Phosphine and Arsine Ligands

Soluble polymer supported variants of triphenylphosphine such as the PEG-supported phosphine ligands discussed above were among the earliest examples of soluble polymeric catalyst ligands.¹³ Studies of these sorts of ligands and their close relative triarylsines have continued into the present because these species are both versatile tools for organic synthesis and useful as ligands. Separable soluble polymer-

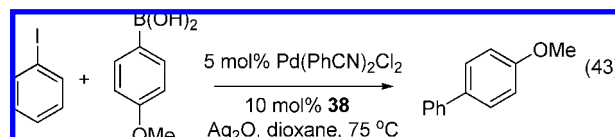
bound versions of these species simplify product purifications and facilitate catalyst recycling.

In 2003, Toy reported a simple synthesis of 4-styryl-diphenylphosphine and the radical copolymerization of it with styrene to form the polymeric phosphine **37** (eq 42).

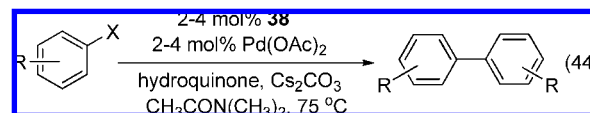
The ligand loading of **37** was determined by elemental analysis to be 1.5 mmol of PAR_3/g . The copolymer **37** was used successfully in Mitsunobu reactions, with a 1.5-fold excess of the polymeric phosphine affording products in yields that ranged from 65 to 83%.⁷³ Precipitation of **37** using cold diethyl ether separated the polystyrene-supported triarylphosphine from the product, and unlike the case with PPh_3 , the use of **37** yielded products without any trace of phosphine or phosphine oxide contamination.



Toy's initial success led to the development of an NCPS-bound triarylsine from 4-diphenylarsinostyrene by a polymerization like that used to prepare **37** (eq 42).⁷⁴ The ligand loading of **38** was determined by ¹H NMR spectroscopy after the oxidation of **38** by hydrogen peroxide to be 0.83 mmol AsAr_3/g . The product copolymer **38** was then used as a ligand for Pd in Suzuki cross-coupling reactions (eq 43).⁷⁵ These reactions afforded products in yields of 84–88%: yields like those obtained using AsPh_3 as a ligand for Pd. The authors noted that at 75 °C, the refluxing temperature of 1,4-dioxane, the recovered **38** was not contaminated with Pd black but that at 101 °C Pd black was formed. When the Pd catalysts formed with **38** were used at 75 °C, catalyst recycling by precipitation (MeOH) was feasible without any requirement for added Pd for four cycles.



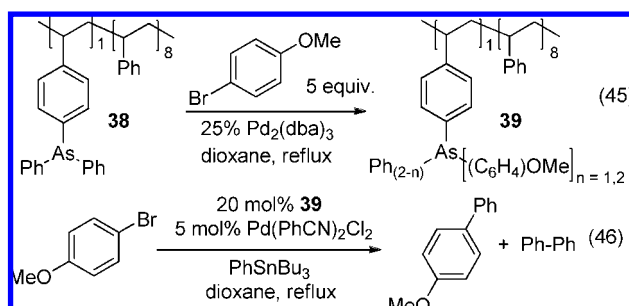
In 2005, Toy described Pd-catalyzed homocoupling of aryl halides (R = $-\text{NO}_2$, $-\text{CH}_3$, $-\text{H}$, $-\text{OCH}_3$) using **38** (eq 44).⁷⁶



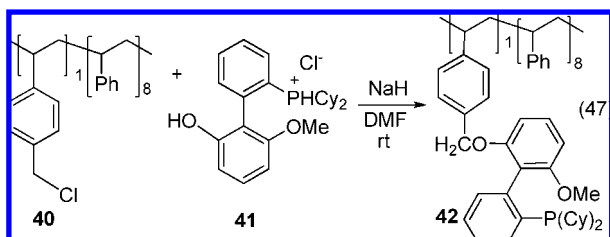
An unhindered aryl iodide formed product in high yield (90%), but the reaction time more than doubled and the yields decreased to 80% with similar aryl bromides. More hindered aryl halides had even longer reaction times and formed products in yields that were below 50%. No recycling experiments were described in this study.

In 2007, Chiu used **38** as a ligand for Pd-catalyzed Stille coupling.⁷⁷ In this report, the authors first showed that these polymer-bound triarylsines were effective ligands for Stille biaryl synthesis, ligands that were better than the corresponding phosphine ligand **37**. They also showed that

recycling of Pd catalysts ligated by **38** was practical. However, in these studies they also noted that the product mixture in later cycles using **38** as the initial Pd ligand had progressively more of the desired 4-methoxybiphenyl product vis-à-vis the undesired biphenyl side product. They showed this was due to aryl exchange of 4-bromoanisole with the polymeric arsine. This observation was then exploited to design a polymeric triarylsarsine that would minimize biphenyl byproduct formation. When they first treated **38** with 4-bromoanisole in the presence of Pd₂(dba)₃, they formed **39**, a version of **38** whose aryl groups are enriched with methoxyphenyl groups (eq 45). When the polymer-bound triarylsarsine **39** was used as a ligand in a Stille coupling of 4-bromoanisole with phenyltributyltin, the amount of biphenyl byproduct seen dropped to 15% (vs 34% using **38**) (eq 46). In this work, the NCPS-bound catalysts were recovered by concentrating the reaction mixture in THF and then using 20% diethyl ether in hexane to effect a precipitation of the NCPS-Pd complex.



As noted above, Sphos phosphine is an extremely good ligand for amination and Suzuki coupling of sterically hindered aryl chlorides and it has been successfully attached to both PEG and NCPS by the García group. This group synthesized the NCPS-bound Sphos **42** using the chemistry in eq 47 and used the product ligand for Pd-catalyzed coupling chemistry (cf. eq 39 and 40 above) of aryl chlorides.⁶⁸ As was true with PEG supports, Pd catalysts ligated by **42** were recoverable by solvent precipitation in cold diethyl ether. However, a Pd catalyst ligated by **42** was less reactive than its PEG analog and the reusability of the Pd catalysts was compromised by phosphine oxidation.



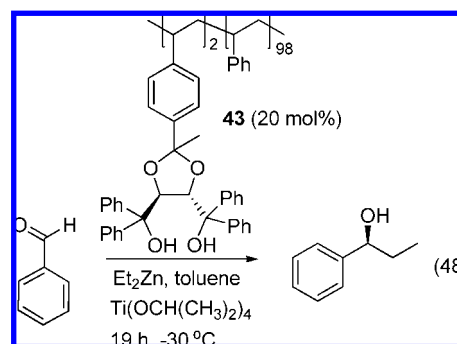
2.2.2. NCPS-Bound Phase Transfer Catalysts

Phase transfer catalysis (PTC), like other catalytic processes, benefits from separation and recovery of the catalysts.^{1,2} While most work with polymer-bound phase

transfer catalysts has involved insoluble supports, Chen and his group showed that a soluble NCPS-bound ammonium salt was effective in such chemistry and could be recovered.⁷⁸ In this work, Chen prepared the NCPS-bound ammonium catalyst either from a chloromethylstyrene–styrene copolymer or directly from chloromethylstyrene, styrene, and tributylamine. The polymeric ammonium salt so formed, like the well-known insoluble cross-linked polystyrene-bound onium salts used earlier,⁷⁹ was able to catalyze nucleophilic substitution reactions, halogen exchange reactions, cyclopropanations, and alkylations of phenols and thiophenols. This catalyst was found to be ca. 100-fold more reactive if microwave irradiation were used. The utility of microwave irradiation to enhance the rate of a polymer-supported reaction is very useful with insoluble polymer supported species but is less commonly used with soluble polymers (cf. the review by Sauer elsewhere in this issue). This report noted that the catalyst could be precipitated by solvent precipitation with cold diethyl ether but catalyst recycling was not described.

2.2.3. NCPS-Bound Chiral Diols as Ligands for Dialkylzinc Additions

The Rosling group successfully immobilized α,α',α'' -tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) on NCPS by copolymerization of a TADDOL functionalized styrene monomer with styrene.⁸⁰ The product, NCPS-bound TADDOL (**43**) was then used to catalyze the enantioselective addition of Et₂Zn to benzaldehyde as shown in eq 48.

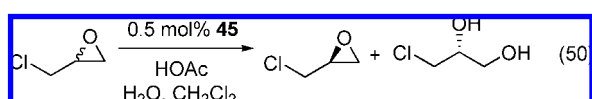
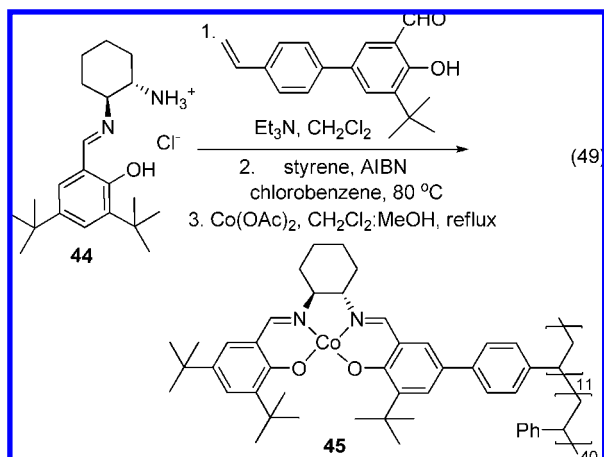


This NCPS-bound TADDOL was compared to a similar TADDOL ligand on another polymer—poly(*N*-isopropylacrylamide)—and afforded higher product yields. The NCPS-bound TADDOL (**43**) was recovered using a repetitive series of MeOH precipitations. The recovered **43**'s effectiveness (yield and % ee) in eq 48 was maintained for two more reaction cycles.

2.2.4. NCPS-Bound Salen Ligands

Salen ligands have been studied by chemists for over 60 years and are versatile achiral and chiral ligands in catalysis.⁸¹ Such ligands have typically been attached as pendent or terminal groups on a polymeric support. Recent work by the Weck group described a different synthetic approach that used free radical copolymerization of an unsymmetrical styrene-containing half-salen monomer **44** with styrene to form an NCPS-bound salen Co catalyst **45** that was then

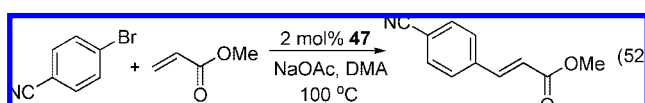
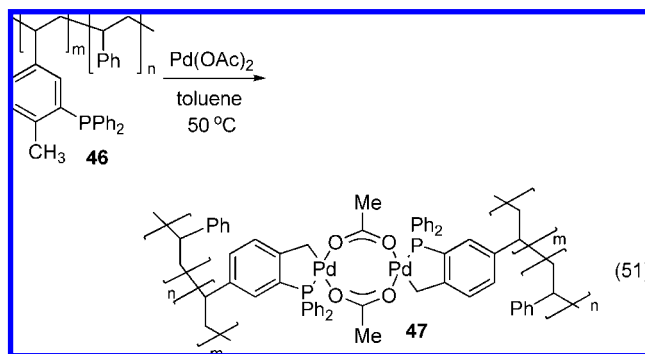
used in hydrolytic kinetic resolutions of epoxides (eq 49 and 50).⁸²



After copolymerization, the NCPS-bound chiral salen was metalated with $\text{Co}(\text{OAc})_2$ to form a Co-Salen complex. The product Co-salen was then successfully used in hydrolytic kinetic resolution of racemic epichlorohydrin. This kinetic resolution (eq 50) afforded starting material with >99% ee after the ring-opening reaction had proceeded to 54% conversion (1 h). Recycling of catalyst in three successive runs was successful but the reaction time in successive runs was longer, reportedly because of physical loss of catalyst during the diethyl ether precipitation/filtration process.

2.2.5. NCPS-Bound Palladacycle Catalysts

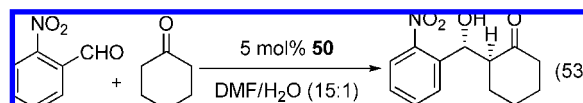
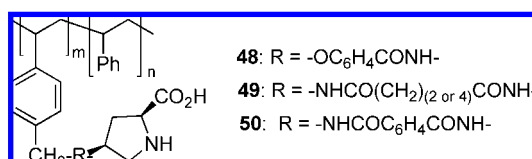
In 2005, Luo described using NCPS to support a palladacycle catalyst similar to one described earlier by Herrmann as being particularly effective for Heck and Suzuki reactions. This carboxylate-bridged palladacycle **47** was attached either by copolymerization of a palladacycle-containing styrene monomer with styrene or by metalation of a preformed phosphine-containing polymer, **46** (eq 51).^{83,84} This NCPS-bound Pd complex was then used in Heck and Suzuki chemistry (cf. eq 52).



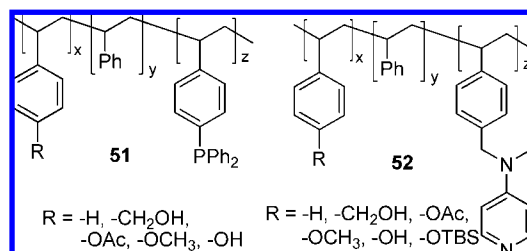
The catalyst **47** was successfully recycled four times with an isolated yield of a cinnamate product of more than 80% in the fourth cycle in Heck coupling chemistry. Recycling of a catalyst in a Suzuki reaction was not reported.

2.2.6. NCPS-Bound Organocatalysts

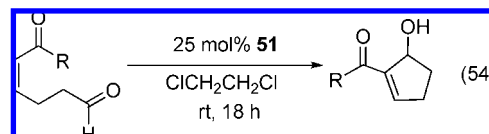
In 2007, Tao anchored L-proline to linear polystyrene using either an aliphatic diacid, terephthalic acid, or 4-hydroxybenzoic acid to form organocatalysts **48–50** that were used in aldol chemistry like that shown in eq 53.^{85,86} The catalysts **48–50** all afforded products in moderate yield (ca. 60–70%) with excellent ee values in the 90–98% range and served as recoverable catalysts for asymmetric aldol reactions. In studies with the aldol reaction shown in eq 53, Tao's group reported that the NCPS-bound proline catalyst **50** was recyclable five times with little or no effect on the initial 70% yield, 92:8 *anti/syn* diastereoselectivity, and 95% enantioselectivity.

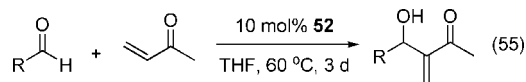


Toy and Shi prepared soluble NCPS-bound organocatalysts **51** and **52** as terpolymers by copolymerization of styrene, 4-acetoxy- or 4-trimethylsilyloxymethylstyrene, and an appropriately 4-substituted styrene derivative that contained a nucleophilic organocatalytic group.



These NCPS-bound nucleophilic catalysts were then used in intra- or intermolecular Morita–Baylis–Hillman reactions like those in eqs 54 and 55 (R = $-\text{Et}$, $-\text{Bu}$, $-\text{Ph}$, $-p\text{-ClPh}$, $-m\text{-MePh}$, and $-p\text{-MePh}$) and eq 55 (R = $-\text{Ph}$, $-p\text{-C}_6\text{H}_4\text{F}$, $-p\text{-C}_6\text{H}_4\text{Cl}$, $-p\text{-C}_6\text{H}_4\text{Br}$, $-o\text{-C}_6\text{H}_4\text{Cl}$, $-m\text{-C}_6\text{H}_4\text{NO}_2$, $-p\text{-C}_6\text{H}_4\text{NO}_2$, and $-2,4\text{-C}_6\text{H}_3\text{Cl}_2$).⁸⁷ Toy proposed that the hydroxyl group facilitated these reactions by hydrogen bonding with the α,β -unsaturated carbonyl Michael acceptor. Evidence for this was the fact that the best yields were obtained with phenol-containing terpolymers, more moderate yields with hydroxyl-containing terpolymers, and lowest yields with terpolymer without an H-bonding group.

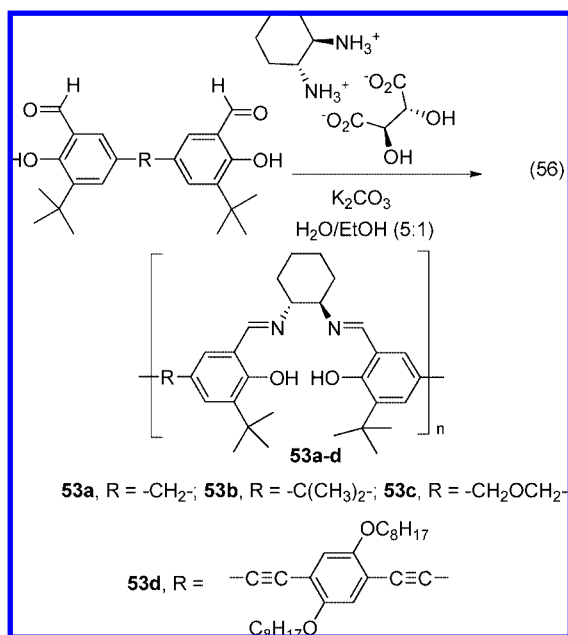




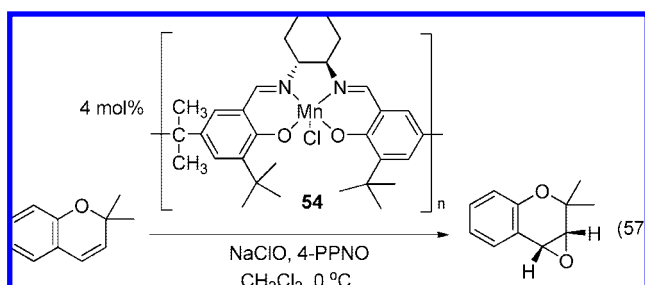
2.3. Soluble Polymeric Catalysts Containing Salen Monomers

As noted elsewhere, using polymers to support salen ligands is a common theme in catalysis because of the importance of these ligands and their metal complexes in modern chemistry. Most of these examples have salen units as pendant or terminal groups. An alternative approach for salen complex immobilization uses the salen groups as monomers to prepare homo- or copolymers.

The most general approach to synthesis of a soluble polymer with salen repeating units is based on Zheng's synthesis of polymeric salen ligands **53a–53d** from a bis(*o*-hydroxybenzaldehyde) and a diamine (usually *trans*-1,2-cyclohexanediamine) (eq 56).



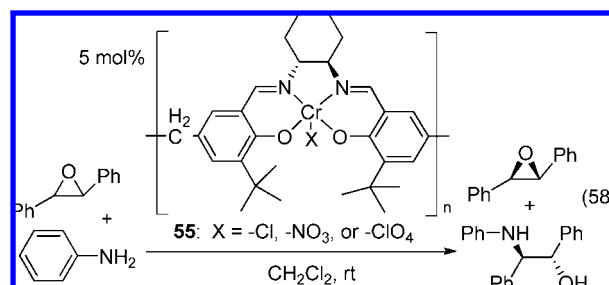
In 2002, Zheng described extensions of this original report that used a polymeric–salen Mn(II) complex **54** to catalyze asymmetric alkene epoxidation (eq 57).



The asymmetric epoxidation of 2,2-dimethylchromene (eq 57) using **54** as a catalyst using a 10:1 mixture of bleach and 4-phenylpyridine-*N*-oxide (4-PPNO) as the penultimate oxidants proceeded in 81% yield and 96% ee, forming the *R,S* epoxide. Zheng's results were very similar to the results they described earlier⁸⁹ and to what Jacobsen reported for a nonpolymeric salen (72% yield and 98% ee).⁹⁰ Catalyst **54** was recycled 4 times with the same yield and % ee by

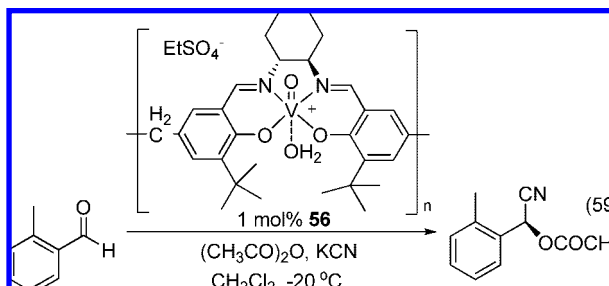
concentrating the reaction mixture and precipitating **54** with hexane and then isolating the recyclable catalyst by filtration.⁸⁸

Polymeric catalysts using polymers derived from **53a–d** have been used in a variety of other reactions. Kureshy described using chiral polymeric Cr(III) salen complexes for enantioselective aminolytic kinetic resolution (AKR) of epoxides.⁹¹ This work showed that a recyclable polymeric Cr(III) salen complex **55** containing Cl^- , NO_3^- , or ClO_4^- counterions had different activities, with the perchlorate complex being the most reactive but with the chloride complex being the most selective. The chloride complex was studied as a recyclable catalyst in the AKR reaction shown in eq 58. The 80% ee of the recovered epoxide and 87% ee of the product amino alcohol at 49% conversion changed slightly to 71% ee and 86% ee at 45% conversion in the fifth cycle with a slight increase in reaction times (14 to 20 h).



Kureshy's group extended this AKR chemistry using a microwave reactor using a 9:1 mixture of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ as the reaction solvent.⁹² With microwave irradiation, reaction times decreased from 14 h to 2 min. Recycling was as efficient as in the thermal process, but the % ee for both the recovered epoxide and the amino alcohol advantageously increased in the microwave process to ca. 90%.

Several reports describe recyclable polymeric salen complexes as catalysts in enantioselective additions of nucleophiles to aldehydes and ketones. Zheng first described a version of Belokon's chemistry wherein *O*-acetyl cyanohydrins are formed from a cyanide source and acetic anhydride (Ac_2O).⁹³ In that report, Zheng used a Ti(IV) complex formed from the salen polymer **53b**.⁹⁴ The soluble polymer-bound Ti(IV) catalyst was successful in that case, affording *S* product in 77% conversion with 47% ee. A V(V) complex of the salen polymer was also investigated and was far superior, affording addition product with various aldehydes in reactions at -42 °C that had >90% conversion with as high as 94% ee.⁹⁴ However, that V(V) salen polymer was not recyclable. A subsequent report by Khan described a V(V) complex (**56**) that could be used for the same reaction (eq 59).

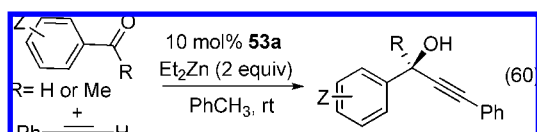


This V(V) salen polymer proved more useful in that it could be recycled by precipitation from the reaction mixture

(hexane addition) and reused, affording product in high ee and good conversions over multiple cycles (conversion (% ee) of 95 (91), 90 (91), 88 (91), 86 (91), and 84 (91) in 5 cycles).⁹⁵ Khan had earlier described chemistry similar to that in eq 59 using $(\text{CH}_3)_3\text{SiCN}$ to form *O*-trimethylsilyl cyanohydrins. That work used the same V(V) salen polymer **56** and afforded the *S* cyanohydrin TMS derivative from benzaldehyde in >94% conversion with an enantioselectivity of 96% ee for all four cycles.⁹⁶

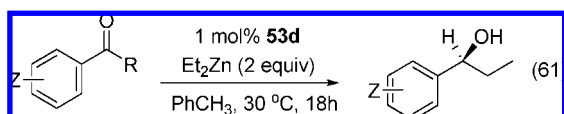
Abdi also described using a Zn salen complex formed *in situ* from Et_2Zn and **53a** for enantioselective addition of phenylacetylene to aryl aldehydes and aryl methyl ketones ($Z = -\text{H}$, *o*- CH_3 , *o*- OCH_3 , *m*- OCH_3 , *p*- CH_3 , *p*- OCH_3 , *c*- C_6H_{11} , $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, and naphthyl) (eq 60).

These additions afforded isolated yields of secondary alcohols that were typically in the 80–90% range with typical ee values of ca. 60%. Addition of phenylacetylene to methyl aryl ketones proceeded in ca. 10% lower yield but with similar enantioselectivity. The polymeric salen catalyst was reused four times in the reaction of phenylacetylene and acetophenone without affecting the yield or ee significantly.⁹⁷

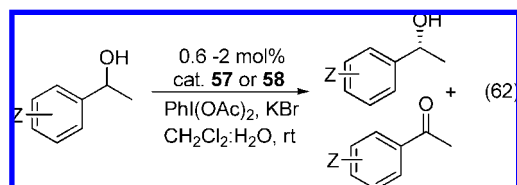


The salen polymer **53d** also formed a Zn-salen complex on treatment with Et_2Zn that catalyzed the Et_2Zn alkylation of benzaldehydes (eq 61) ($Z = -3\text{-NO}_2$, $-\text{H}$, -4-OCH_3).⁹⁸

Isolated yields of addition products were in the 70–80% range. Stereoselectivity was good, but the highest ee for the (*S*)-1-aryl-1-propanol product using this Zn derivative of the *R,R* salen complex **53d** as catalyst was only 70%. Precipitation using MeOH recovered the catalyst, which was reused once with the same yield and stereoselectivity.



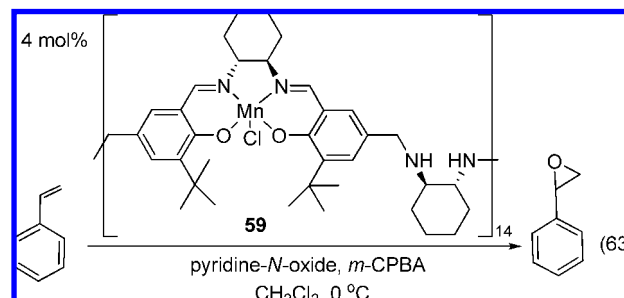
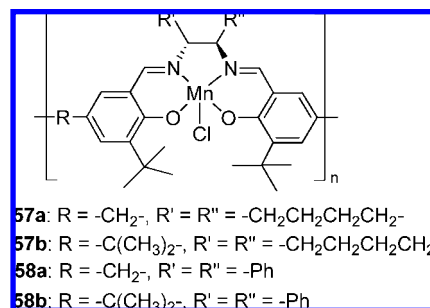
Salen polymer promoted oxidative kinetic resolutions of secondary alcohols have been described by the Kureshy and Sun groups.^{99,100} These groups used very similar polymeric salen catalysts **57a** and **57b** or **58a** and **58b** to selectively



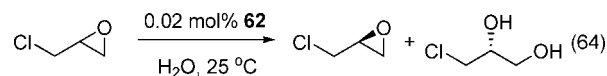
oxidize the *S* enantiomer of racemic mixtures of 1-arylethanol (eq 62). Both groups describe very successful kinetic resolutions leading to mixtures of the ketone and *R* alcohol starting material with >90% ee for the remaining alcohol at 50–60% conversion. Both groups found that bromide was a necessary additive, and both groups were able to successfully recycle the polymeric salen catalyst using hexane precipitation.

An alternative way to synthesize a polymeric chiral metal salen complex was described by Yu and Yin.¹⁰¹ In this case, the Mn(III) salen complex **59** was prepared using *trans*-1,2-

diaminocyclohexane and 3-*tert*-butyl-5-chloromethyl-2-hydroxybenzaldehyde as monomers. This polymerization could in principle form branched or cross-linked products, but Yu and Yin report isolating the linear polymer precursor of the Mn(III) complex **59** and described their work using it as a homogeneous catalyst for epoxidation of styrene (eq 63). While the first cycle afforded a 99% yield of product, the ee of 35% was modest and the yields dropped to 52% by the fifth cycle. The poor recyclability was ascribed to oxidative degradation of the salen complex based on differences in the UV–vis spectrum of fresh and used catalyst.



Weck's group has describe a third sort of polymeric salen complex containing salen groups as repeating units in the macrocyclic polymer chain formed by a ring expanding metathesis polymerization (Scheme 3).^{102,103} These macrocyclic salen polymers could be converted into cobalt salen complexes **62** that, like the cyclic oligomeric cobalt-containing salen complexes reported earlier by Jacobsen,¹⁰⁴ were very effective catalysts in HKR of racemic terminal epoxides (eq 64). Recycling of these catalysts by evaporation of the reaction products and addition of a fresh solution of starting materials was also carried out four times. No significant deactivation was observed.¹⁰³



2.4. Using Polymers Prepared by Ring Opening Metathesis Polymerization (ROMP) to Support Ligands and Catalysts

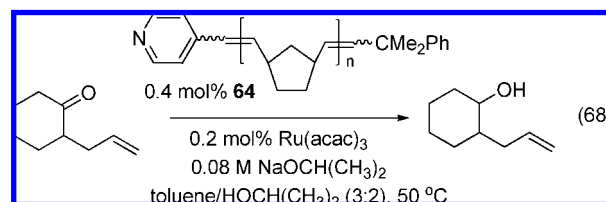
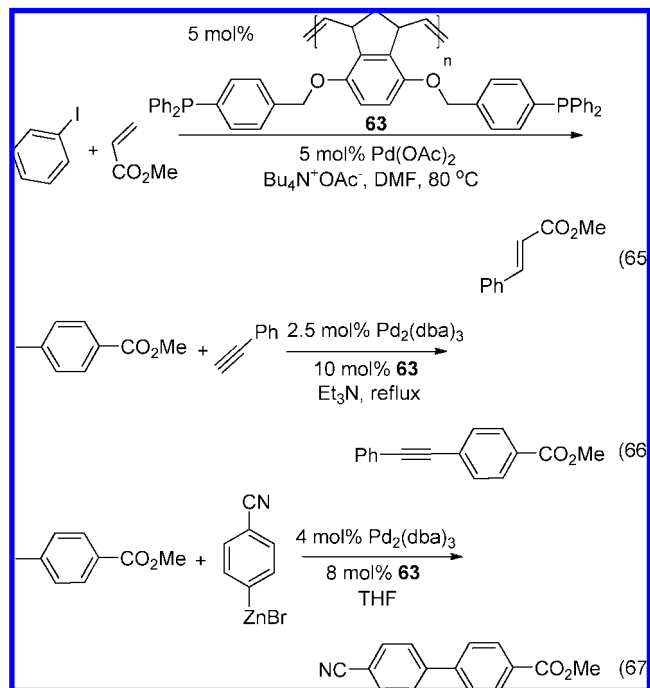
Ring-opening metathesis polymerization has provided chemists with a variety of soluble polymer supports that have been used to facilitate synthesis and catalysis.^{105–107} Such supports are useful in the synthesis of libraries of compounds of biological interest.¹⁰⁸ These sorts of supports generally are prepared using a norbornene-containing monomer. They continue to attract interest, as discussed below.

2.4.1. ROMP-Derived Polymer-Supported Phosphine Ligands

Luh and Yang reported the synthesis of polynorbornene-supported phosphine ligands **63** that were useful in Pd-catalyzed cross coupling chemistry (eqs 65–67).¹⁰⁹ The Pd catalysts formed with these ligands were all competent in the first cycle with aryl iodides, but the activity of the catalysts decreased cycle to cycle. In the case of the Heck coupling chemistry, the polymer-bound catalyst was soluble at 80 °C but was insoluble at room temperature. This thermomorphic system provided the most recyclable catalyst, with the initial 95% yield dropping to 85% in the fifth cycle. Catalysts that were recovered using solvent precipitation generally had larger decreases in activity cycle to cycle.

2.4.2. Polynorbornene-Supported Pyridine Ligands

Nomura and Kuromatsu reported using polynorbornene as a soluble support for various pyridine and bipyridyl ligands that were used as ligands for Ru in selective hydrogen transfer reduction of ketones.¹¹⁰ This polymeric ligand (**64**) was prepared by a living ring-opening metathesis polymerization using a Schrock type molybdenum-alkylidene initiator, and the bipyridine or pyridine was introduced onto the product polymer by a Wittig-like reaction with an aldehyde-substituted pyridine derivative. When Ru(acac)₃ was added to an *i*-PrOH/toluene solution of these ligands in the presence of NaOCH(CH₃)₂, cyclohexanone was reduced to cyclohexanol with TONs of ca. 250–300. Recycling was studied with the pyridine-terminated polymer (**64**). TON values for cyclohexanone reduction decreased by less than 5% cycle to cycle. Similar results were seen for the reduction of allylcyclohexanone in eq 68, where the first and second cycle TON values were both 125.



2.4.3. Polynorbornene-Supported Salen Ligands

Weck and Holbach described the use of ROMP chemistry with a third generation Grubbs catalyst as a route to

Scheme 3. Synthesis of Cobalt-Containing salen Polymers by a Metathesis Polymerization

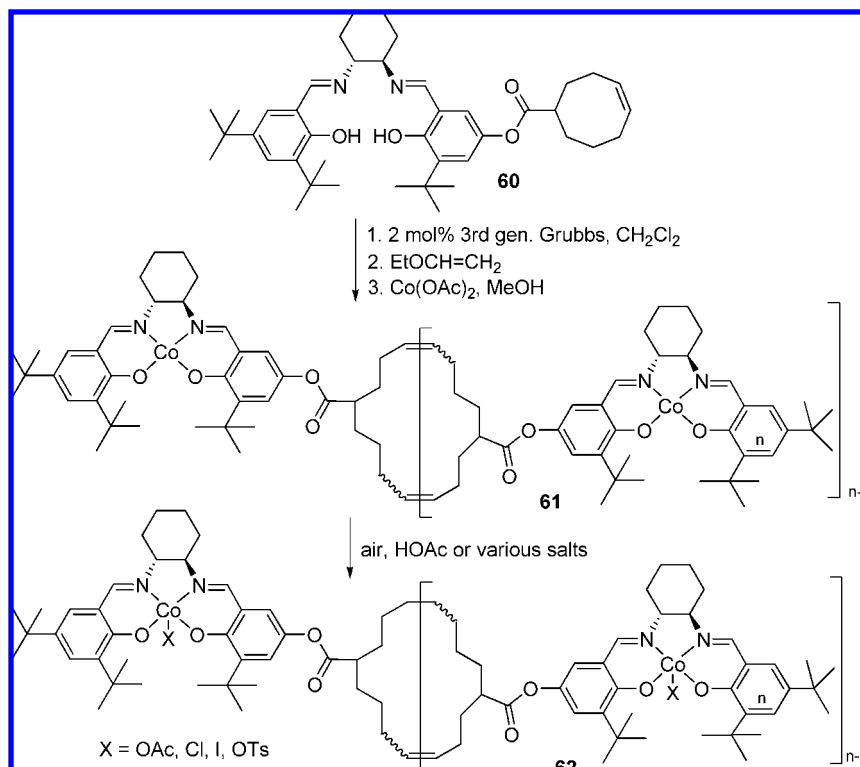
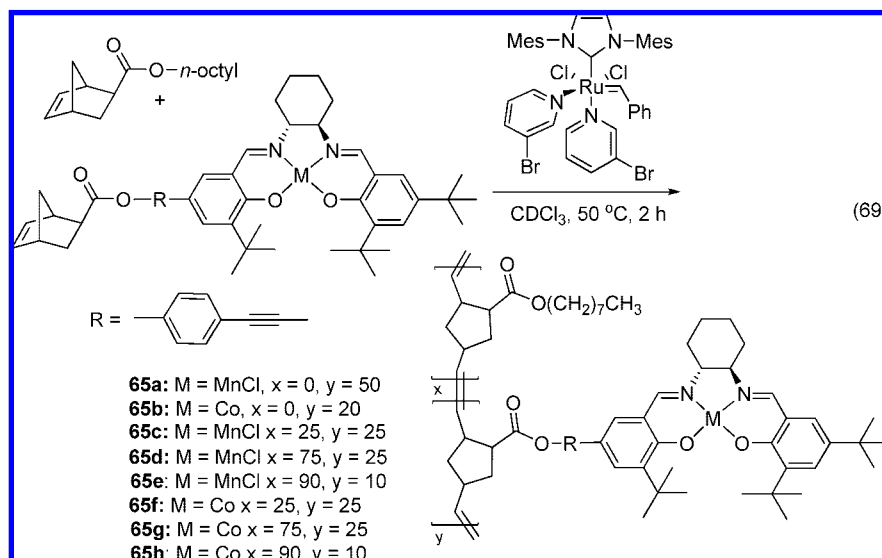
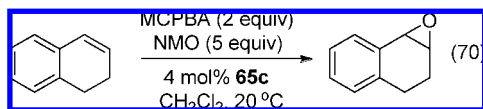


Chart 3



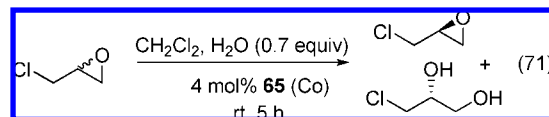
polynorbornene-supported salen catalysts where the concentration density of the metal salen complex in the polymer was controlled by the presence or absence of a comonomer (eq 69 in Chart 3).¹¹¹ Co(II) or Mn(III) complexes of a salen-bound to norbornene via an arylacetylene ester were found to be compatible with the ROMP chemistry. The comonomer was an octyl ester of the same norbornenyl acid used to bind the salen complex. Typical polymer degrees of polymerization (DP) were 50 or 100. Homopolymers of the Co-salen and the Mn-salen complexes (DPs of 20 and 50, respectively) were also prepared.

The polymer supported Mn-salen complexes **65a** and **65c–e** were used in the epoxidation of aromatic olefins. For example, the salen-containing copolymer **65c** at 4 mol % catalyst loading quantitatively oxidized 1,2-dihydronaphthalene, forming the epoxide with an enantioselectivity of 81%. The results obtained using **65c** as a catalyst were almost the same as those obtained when a low molecular weight salen-Mn(III) complex was used (88% ee). Recycling was examined in this reaction (eq 70). To recycle and recover the catalyst, the polynorbornene-supported **65c** was precipitated by adding the reaction mixture to a mixture of diethyl ether and methanol. However, while **65c** was recovered quantitatively, **65c** lost its activity and selectivity in recycling in that the conversions dropped to 85% and the product ee dropped to 6% in the third cycle from values of 100% conversion and 81% ee in the first cycle.



To examine these catalysts in hydrolytic kinetic resolution, the polynorbornene-supported salen Co(II) complexes **65b**, **65f**, and **65g** were oxidized to form Co(III) complexes using acetic acid and air. The Co(III) acetate salen complexes so formed selectively converted the *R* enantiomer of epichlorohydrin to the diol (eq 71). At 55% conversion, the unreacted *S* epichlorohydrin had an ee of 99%, a result that was very similar to that seen with the low molecular weight Co acetate salen catalyst (99% ee at 53% conversion).¹¹² Kinetic studies showed that the homopolymer catalyst derived from **65b** was slightly less reactive than a structurally

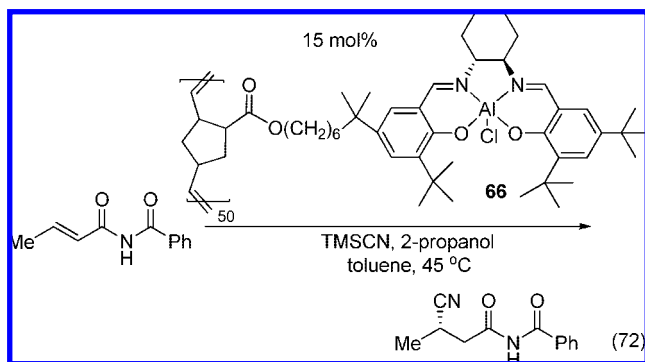
similar low molecular weight catalyst under solvent free conditions. However, by oxidizing the Co(II) salen **65b** with O₂ in the presence of *p*-CH₃C₆H₄SO₃H, it was possible to prepare a polymeric Co(III) tosylate that was more reactive, albeit slightly less selective.



Recycling of the polymeric Co complexes was possible using solvent precipitation by adding the reaction mixture to excess diethyl ether. The (*R*)-3-chloro-1,2-propandiol product was removed from this ether solution by extraction with water, leaving the pure *S*-chlorohydrins. However, the solubility of the recovered Co(III) acetate salen derived from **65b** significantly decreased cycle to cycle, and longer reaction times were required for the HKR of epichlorohydrin. Similar studies using a Co(III) tosylate salen derived from polymer **65b** showed that some degradation of the Co(III) salen polymer occurred based on the changes in the elemental composition of the recovered polymer. The solubility problems encountered with solvent precipitation could be avoided by using an alternative recycling strategy where the substrates were removed by fractional distillation and the catalyst-containing residue was reoxidized in acetic acid with oxygen. Using this method, the reaction time required to obtain the *S*-epichlorohydrin in 99% ee increased to ca. 11 h, but the aforementioned solubility problems were avoided.

Polynorbornene polymers with pendant Al-salen complexes have also been shown to be useful catalysts for asymmetric conjugate addition of CN to α,β -unsaturated imides (eq 72).¹¹³ In these reactions, the polymer was quantitatively recovered and reused five times without affecting the yield or ee of the product, both of which were >90%, so long as the α,β -unsaturated imides did not have a sterically cumbersome group at the β position.

The recycling procedures used in this example are effective, and the catalyst is robust. However, this report also illustrates two of the potential disadvantages of polymer-supported catalysts in general and solvent precipitation in particular as a catalyst recovery procedure.

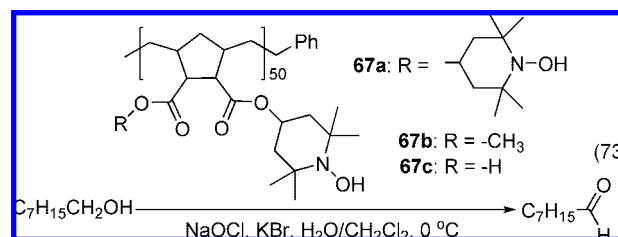


In this report, the examples where catalysts were recycled used 15 mol % catalyst (the authors did note that 5 mol % catalyst was equally effective). This mol % of catalyst coupled with the loading of catalyst on the polymer **66** means that the reactions use a mass of catalyst that is nearly equal to the mass of the substrate even though the polymer **66** has a pendant Al-salen group on every repeating unit of the polymer. Mass loading is an issue that is not often discussed with soluble or insoluble supported catalysts but is likely a concern if a reaction were to be run on a larger scale and is even more of a problem when the catalyst concentration on a polymer is diluted because it is present as a terminal group or present on a copolymer where its concentration is diluted with another monomer. Second, the workup procedure requires significant solvent to effect catalyst/product separation. In the workup described, the 160 μL of the reaction solvents toluene and isopropanol and the 4-fold excess of the toxic trimethylcyanide reagent are removed by evaporation. Then, 15 mL of ethyl acetate (EtOAc) was added to the residue to selectively dissolve the reaction products but not the polymeric catalyst. This process is repeated with four more 15-mL rinses of EtOAc. Overall, this corresponds to the use of 75 mL of solvent for a 0.26 mmol scale reaction. Finally, these recycling studies involved 36 h reactions. Since separate studies showed that the reactions with 15 mol % catalyst were complete in 6 h, these longer reaction times too make it impossible to rule out some catalyst deactivation.

2.4.4. Polynorbornene-Supported TEMPO

Polynorbornene has also been used to support TEMPO groups that can be used as recyclable catalysts in TEMPO catalyzed oxidation of primary alcohols to aldehydes (eq 73).¹¹⁴ Three sorts of catalysts were used, **67a**, **67b**, and **67c**. These polymeric TEMPO catalysts were prepared by ring opening polymerization of a reduced hydroxylamine TEMPO monomer derived from *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride. Each monomer unit contained $-\text{CH}_2\text{-OTEMPO-H}$ and a second $-\text{CH}_2\text{TEMPO-H}$, a $-\text{CO}_2\text{H}$, or a $-\text{CO}_2\text{CH}_3$ group. To avoid problems with the residual alkene groups that remain from the ROMP polymerization, the residual alkene groups of the polymeric catalysts were reduced with Pd/C and hydrogen. The oxidations were then carried out in a biphasic CH_2Cl_2 /aqueous system using NaOCl as the stoichiometric oxidant. The authors noted that the catalysts could be recycled for up to three runs with no drastic decrease in their activity from the 70–80% GC yield of aldehydes seen in the first cycle. The catalysts evidently partition into the CH_2Cl_2 phase of these biphasic reaction mixtures even though in one case the catalyst contains a

relatively polar $-\text{CO}_2\text{Na}$ group. After the oxidation, these catalysts could be separated from the aldehyde product-containing phase by solvent precipitation with diethyl ether.



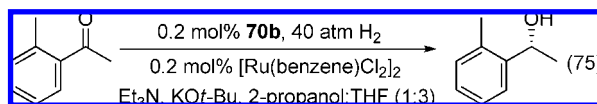
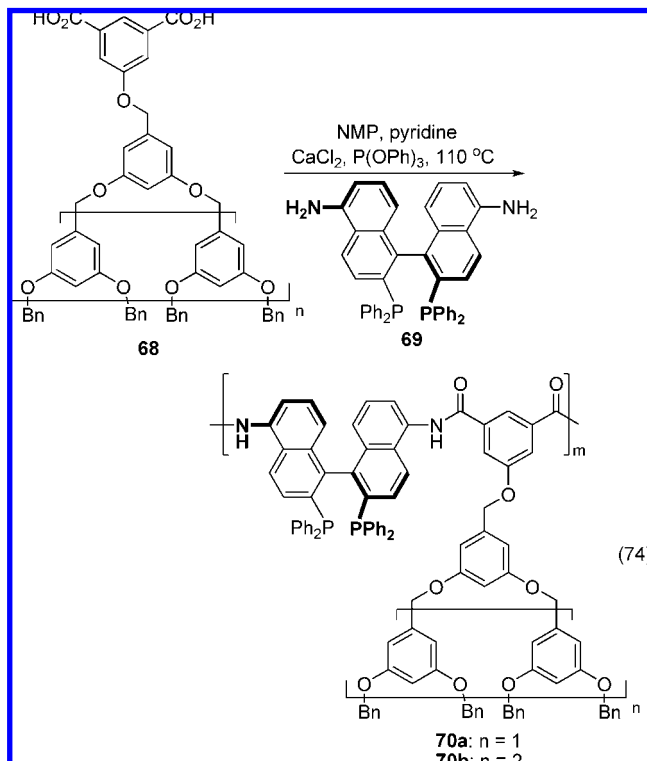
2.5. Solid/Liquid Separable Dendrimer-Supported Ligands and Catalysts

When they were first developed in the late 1970s, dendrimers attracted great interest as a new class of highly branched and well-defined macromolecules. Since then, dendrimers have mainly been the subject of extensive biology and materials science research. One of the promising applications of dendrimers is their use as a support for catalysts.^{115,116} As a soluble support for catalysts, dendrimers provide excellent handles for recovery and reuse of catalysts. They have the advantages of high catalyst loading, control of catalyst solubility by peripheral functionalization, and design flexibility that can be used to introduce variable numbers of active catalytic sites onto or into a single dendrimer.

Recovery of dendritic catalysts can be effected in several ways. Because of their shape, dendrimers are particularly amenable to separation by membrane filtration.^{7–10,117,118} However, they can be recovered by a liquid/solid separation after solvent precipitation too, as is illustrated in the discussion below.

2.5.1. Dendrimer-Supported BINAP-Ru Catalysts for Hydrogenation of Ketones and Carboxylic Acids

BINAP ligands are generally useful in asymmetric catalysis, and polymers containing BINAP ligands were successfully prepared from a first- or second-generation polyether dendrimer **68**, as shown in eq 74.¹¹⁹ The BINAP-modified polyamides **70a** and **70b** so formed contained pendant polyether and had M_n values of 20,500 and 26,070, respectively, with PDI values of 1.63 or 1.49. Such polymers were more soluble than a linear polyamide due to the presence of the polyether dendrons but could be quantitatively precipitated by solvent precipitation using methanol. Both dendronized poly(BINAP) polymers could be converted *in situ* into ruthenium catalysts by reaction with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$. The resulting Ru complexes were both effective catalysts in asymmetric hydrogenation of carbonyl compounds such as 2-methylacetophenone or of 2-arylacrylic acids such as 2-phenylacrylic acid to produce secondary or primary alcohol products with enantioselectivities that were typically greater than 80% (eq 75). Slightly higher enantioselectivities were observed for Ru complexes formed using **70b** (average of 85% ee) versus Ru complexes formed using **70a** (average of 82% ee). The catalyst formed with the dendronized polymer **70b** was chosen for the recycling experiment, and the recovered catalyst was recycled four times with 100% conversion/cycle with no changes in the product ee. No analysis for the Ru content in the product phase was reported.

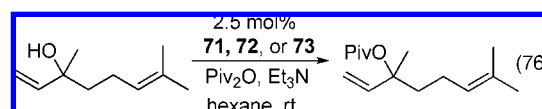
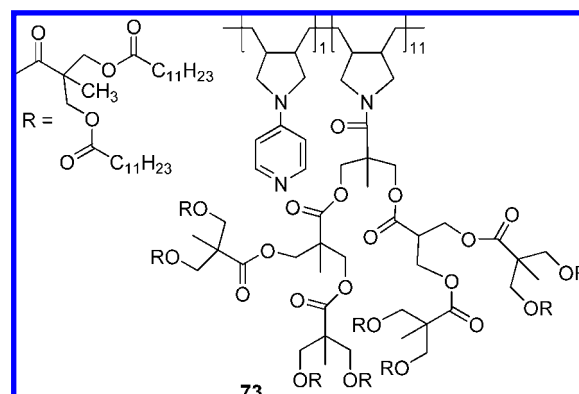
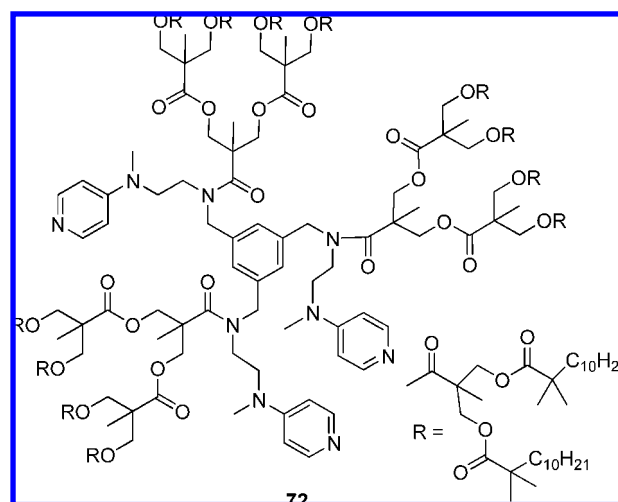
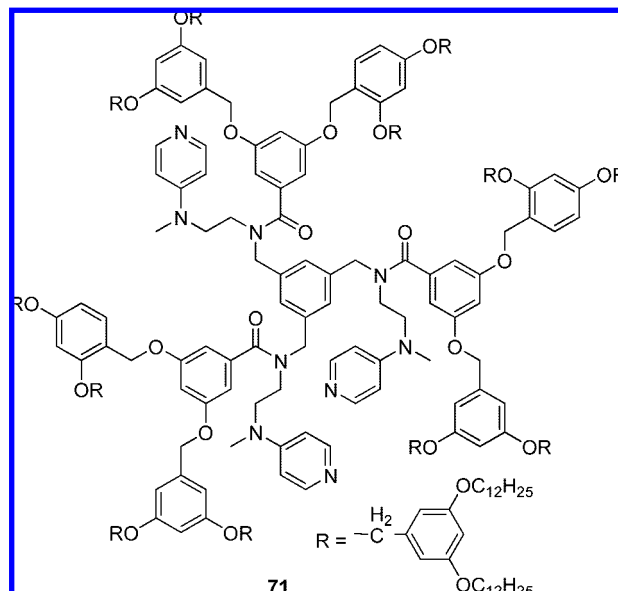


2.5.2. Dendrimer-Supported Organocatalysts

Dendrimer-bound organocatalysts are attractive alternatives to linear polymers in part because of their possible use as synthetic analogs of enzymatic catalysts.^{120,121} In 2005, Fréchet and Hawker studied the influence of polymer architecture and nanoenvironment on dendritic polymer-bound dialkyl(amino)pyridine catalysts.¹²² Their studies not only examined the recovery and reuse of these dendritic DMAP analogs, they also designed dendritic catalysts with a radial polarity gradient around a catalytic core to examine how nanoenvironment affected these dendritic organocatalysts. In order to achieve these goals, three polymeric DMAP analogs **71–73** were prepared.

Catalyst recycling with the dendronized linear polymer **73** that used solvent precipitation had been described previously.¹²³ Similar studies were carried out with dendrimers **71** and **72** using acetylation of 2-butanol with 5 mol % of **71** or **72** in the presence of triethylamine in hexane to probe the activity and recyclability of these dendrimer-bound catalysts. These dendritic analogs of DMAP were not as easily recovered as **73** because they did not precipitate as a solid. However, these dendrimer-bound DMAP analogs could be recovered after an initial water wash (to remove ammonium salt byproduct) followed by evaporation of all the volatiles by heating at $80\text{ }^\circ\text{C}$ for 24 h *in vacuo*. The recovered dendrimers **71** and **72** maintained their activity as acylation catalyst through four recycles with average yields of 83% and 90% for **71** and **72**, respectively.

The potential of using the architecture of the dendritic catalysts to affect catalyst efficiency was examined by comparing the reactivity of DMAP with **71**, **72**, or **73** in a more difficult acylation of a tertiary alcohol (eq 76).

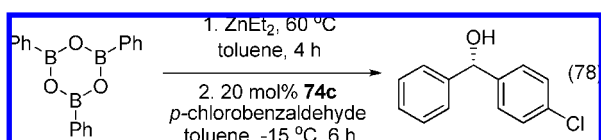
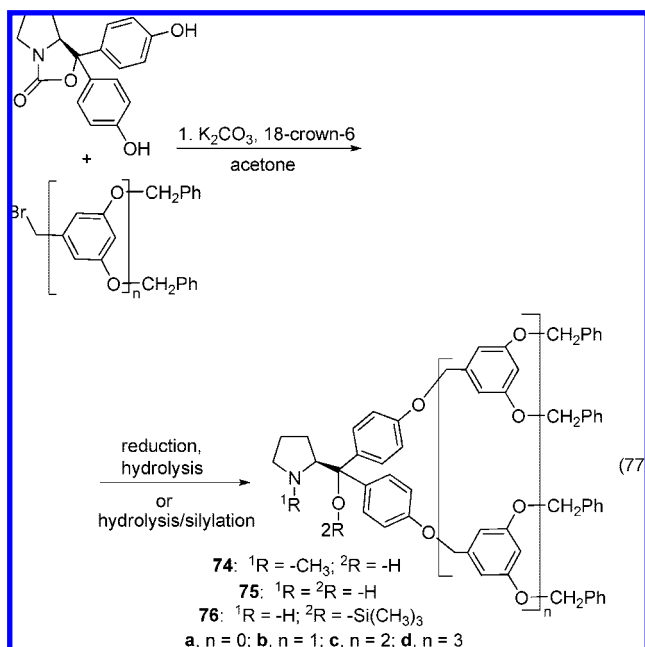


Pivalation of linalool was very slow with DMAP but was significantly faster with any of the dendritic catalysts. The dendronized polymer-bound DMAP analog **73** was marginally more reactive than **72**. Both in this reaction and in acetylation of 1-methylcyclohexanol, the differences in acylation rates were ascribed to differences in the nanoenvironment of the interior of dendrimers **71** and **72**. In both cases, the polyester-containing

dendrimer was more reactive. This was attributed to substrate preconcentration in the polar interior of the dendrimer catalyst, since these reactions were carried out in the nonpolar solvent hexane. However, other explanations for the enhanced reactivity of **72** based on transition state stabilization or dielectric effects were not excluded.

Proline and its derivatives are among the more commonly used organocatalysts and have been immobilized on many soluble polymers including dendrimers. Polyether dendritic proline derivatives such as **74**, **75**, **76**, or **77**, for example, have been used as separable, recyclable soluble polymeric catalysts in a variety of chemistry. In these studies, the dendritic proline derivatives have been recycled by adding MeOH to the reaction mixture to precipitate the dendrimer-bound proline catalyst. After filtration, the recovered catalysts were then reused.

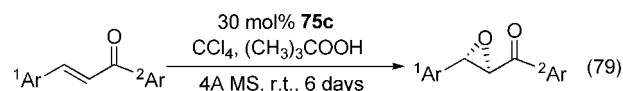
In their first report, Zhao and Zhu described the synthesis of the dendrimer-supported *N*-methyl prolinol **74** by alkylation of a bis(4-hydroxyphenyl) derivative of proline using eq 77, reducing the cyclic urethane to introduce the *N*-methyl group in **74**.¹²⁴ This dendrimer-bound *N*-methylproline derivative was then used as an organocatalyst in Bolm's enantioselective aryl transfer of arylboronic acid derivatives to aldehydes.¹²⁵ The second generation dendritic *N*-methyl prolinol **74c** was the best catalyst for the aryl transfer. Aryl groups with halogens, alkyl, alkoxy, and electron withdrawing $-\text{CF}_3$ groups could all be successfully transferred from arylboroxine $(\text{ArBO})_3$ substrates with typical yields of 95% and typical ee values for the product *S* alcohol of 95–98%. The asymmetric aryl transfer reaction of $(\text{C}_6\text{H}_5\text{BO})_3$ to *p*-chlorobenzaldehyde (eq 78) was used to test recycling.



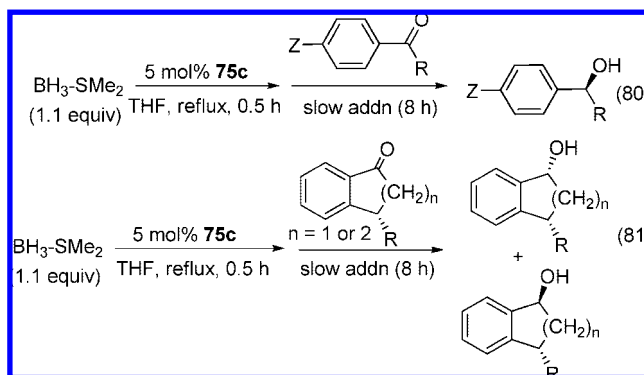
These reactions used 20 mol % of **74c** as the catalyst and were carried out on a small scale using 4.5 equiv of ZnEt_2 and 0.5 equiv of $(\text{C}_6\text{H}_5\text{BO})_3$ relative to the substrate aldehyde.

In these studies, The catalyst was quantitatively precipitated in methanol and reused throughout five cycles with yields of >91% and stereoselectivities favoring the *S*-configuration of the product that exceeded 95% ee in each cycle.

Zhao's group also described using **75c** for the enantioselective epoxidation of enones (eq 79).¹²⁶ In these studies, the catalyst **75c** was used as a catalyst for epoxidation of chalcone derivatives. Aryl groups with electron-withdrawing substituents could be used in place of the phenyl groups of chalcone ($^1\text{Ar} = ^2\text{Ar} = -\text{Ph}$). Enones with aryl substituents with electron-donating groups failed to react. Yields were typically around 90% with ee values that ranged from 84 to 93%, but the reactions were slow with most of the 0.1 mmol scale reactions taking 6 days. Recovery and reuse of the catalyst **75c** was tested using the epoxidation of chalcone as an example. Throughout five cycles, the yield was in the range of 80–84% with the enantioselectivity ranging from 72 to 74% ee. These successful recycling studies showed that this dendrimer-bound prolinol catalyst was stable to the excess *tert*-butyl hydroperoxide under the reaction conditions.



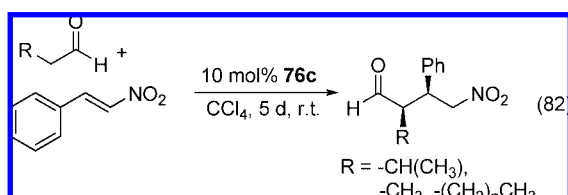
The prolinol dendrimer **75c** was also successfully used as a recyclable catalyst for enantioselective borane reduction of ketones. A variety of substrate ketones were studied (e.g., $\text{Z} = p\text{-NO}_2$, $-\text{H}$, $p\text{-OCH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, -2-pyridinyl , $p\text{-C}_6\text{H}_5$; $\text{R} = -\text{CH}_3$, $-\text{CH}_2\text{SO}_2\text{Ph}$, $-\text{CO}_2\text{CH}_3$) along with various indanone or tetralone derivatives ($\text{R} = -\text{CH}_3$, $-n\text{-C}_4\text{H}_9$, $-t\text{-C}_4\text{H}_9$, $-c\text{-C}_6\text{H}_{11}$, $-\text{C}_6\text{H}_5$, $-m\text{-C}_6\text{H}_4\text{F}$, $-p\text{-C}_6\text{H}_4\text{F}$, $-m\text{-C}_6\text{H}_4\text{Cl}$, $-p\text{-C}_6\text{H}_4\text{Cl}$, and $-2,3\text{-C}_6\text{H}_3\text{Cl}_2$) (eqs 80 and 81). Product yields in these reductions were generally 80–99%, and in most cases the product had ee values that exceeded 90%. Poorer ee values were seen for chalcone derivatives or for dialkylketones. Reduction of substituted indanone or tetralone derivatives could also be carried out in high yield but generally with poor diastereoselectivity for the *cis*- and *trans*-products. Formation of the *trans*-products occurred with higher enantioselectivity than that of the *cis*-products (*trans*-products were usually >90% ee).



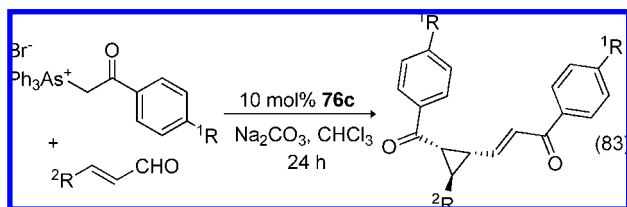
Recycling of the dendritic prolinol **75c** was studied in a 1 mmol scale reduction of *p*-nitroacetophenone (eq 80).¹²⁷ After the reduction was complete, the dendrimer-supported prolinol catalyst **75c** was precipitated by addition of MeOH to the reaction mixture, and it was then recovered by filtration. The recovered solid catalyst was reused through five cycles and formed the *R* secondary alcohol product with a constant ee of 96% and with yields that varied from 99% to 96%. When

this dendritic prolinol was used in reduction of the racemic tetralone ($R = 2,3\text{-C}_6\text{H}_3\text{Cl}_2$), recycling was equally effective in five cycles, forming a nearly 50:50 mixture of the *cis*- and *trans*-products with an average 97% yield and 97% (*cis*-) or 95% (*trans*-) stereoselectivity. In this case, the (*S*)-*trans* product was prepared on a 600 mg scale and subsequently converted into the antidepressant drug (+)-sertraline.¹²⁸

The trimethylsilyl ether of the dendritic prolinol (**76**) was successfully used as an organocatalyst in diastereo- and enantioselective Michael reactions (eq 82).¹²⁹ Catalyst **76c** was the best catalyst, forming predominantly *syn*-products with 70–80% stereoselectivity with ee values that were generally 99%. Recycling experiments using a 0.25 mmol scale 5-day reaction of 3-methylbutanal and nitrostyrene gave the product in yields that dropped from 81% (cycle 1) to 65% (cycle 5) with diastereoselectivity (*syn*-favored) that dropped from 62% to 50% but with ee values for the *syn*-product that were consistently 99%.



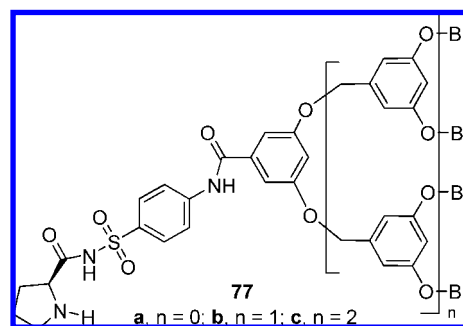
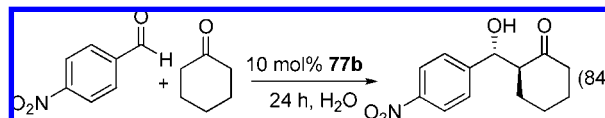
Zhao and Cao also used **76c** as a recoverable recyclable dendritic catalyst for enantioselective tandem cyclopropanation/Wittig reactions of α,β -unsaturated aldehydes using arsonium ylides (eq 83).¹³⁰ While high diastereoselectivity favoring the product shown was possible with ¹R = H and ²R = Ph in a 1 day, 0.2 mmol scale reaction, the yields of products were generally modest (in the 50–70% range). The diastereoselectivity varied significantly with changes in the substituents on the aryl rings. Recycling of the dendritic catalyst **76c** was successful after MeOH precipitation and filtration. Through four cycles of cyclopropanations with the acetophenone-derived ylide and cinnamaldehyde, the product yields were in the range of 55–60%. The diastereoselectivity dropped during this recycling from 98% to 84%, but the ee of the favored product shown was consistently greater than 96%.



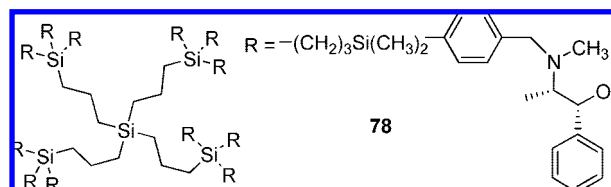
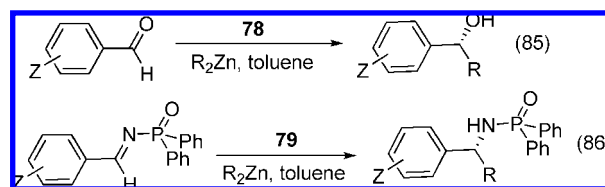
Efficient, reusable dendritic catalysts derived from *N*-prolylsulfonamide using polyether dendrons are also useful for the asymmetric aldol reactions in water.¹³¹ Using the reaction shown in eq 84, the dendritic catalysts **77a**, **77b**, and **77c** were compared one to another and to a low molecular weight *N*-prolylsulfonamide.

The dendritic catalysts generally gave higher yields of product with diastereo- and enantioselectivities that were equal to or better than those obtained using nondendritic *N*-prolylsulfonamide catalysts. Catalyst **77b** was the best dendritic catalyst, and its scope was studied in an aldol reaction of cyclohexanone and various substituted benzaldehydes. The products were obtained in good yield if the

aryl substituents were not electron-donating. The *anti/syn* stereoselectivity was uniformly greater than 90% and was in most cases greater than 95%. The ee values too were consistently >95%. This catalyst **77b** was also recycled. These recycling studies were carried out on a 0.5 mmol scale with 10 mol % catalyst, and the catalyst was recovered by adding 1.5 mL of a 1:1 (v/v) mixture of hexane and EtOAc to the 1 mL aqueous reaction mixture. Through four cycles, the yield, *anti/syn* ratio, and ee of product for *p*-nitrobenzaldehyde and cyclohexanone were 99%, > 99%, and an average of 96%, respectively.

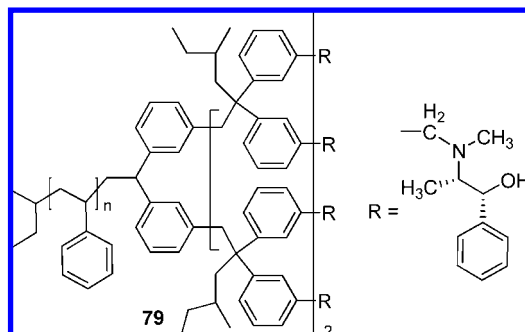


A variety of dendrimers or dendritic materials with chiral β -amino alcohols have been used as recoverable recyclable catalysts in the enantioselective addition of diethyl- or diisopropylzinc to aryl aldehydes or aryl *N*-diphenylphosphinylamines (eqs 85 and 86).



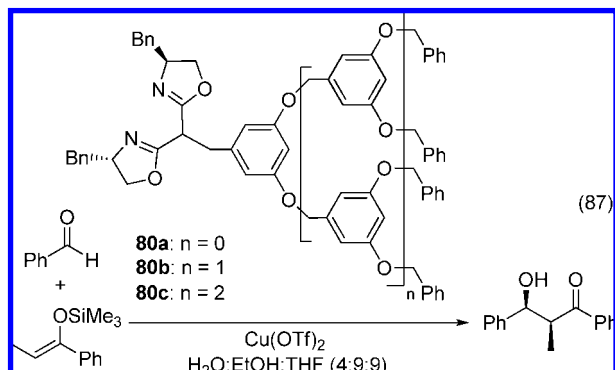
These include dendrimers containing carborane backbones like **78** that have a corona of chiral ephedrine moieties^{132–134} and polystyrene terminated with dendritic chiral ephedrine moieties (**79**).^{135,136} In these reports, recycling was not emphasized. Recycled catalysts were as effective as the starting catalyst, but only one recycle was described in either reaction 85 or 86. In the case of the carborane dendritic catalyst, the recycling procedure was not clearly described. Recycling of the polystyrene terminated with eight ephedrine moieties

(catalyst **79**) required silica gel chromatography and precipitation from a THF solution using MeOH and HCl in the case of Et₂Zn addition to the *N*-diphenylphosphinylimine of benzaldehyde. In the case of Et₂Zn addition to benzaldehyde, recycling required precipitation of the polymeric catalyst from a THF solution using a 4:1 mixture of MeOH-2 M HCl followed by freeze-drying of the polymer from its absolute benzene solution for 24 h.



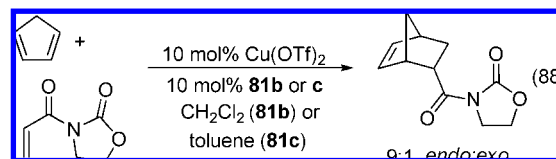
2.5.3. Dendrimer-Supported Cu(II) Catalysts

C₂-symmetric bis(oxazoline)s with Fréchet-type polyether dendrons have been successfully used to ligate Cu(OTf)₂, and the resulting complexes have been used as Lewis acid catalysts for enantioselective aldol reactions in a solvent mixture composed of H₂O/EtOH/THF (4:9:9).¹³⁷ Using benzaldehyde as the aldol acceptor and a trimethylsilyl enol ether as an enolate equivalent (eq 87), aldol product formed with ca. 2:1 *syn/anti* selectivity. However, even in one of the better examples using the dendrimer supported Cu(O₃SOCF₃)₂ complex **80b**, the results in the initial run (78% yield of 2.2/1 *syn/anti* 65% ee (*syn*)) dropped to 40% yield, 1.8/1 diastereoselectivity, and 25% ee in the third run.

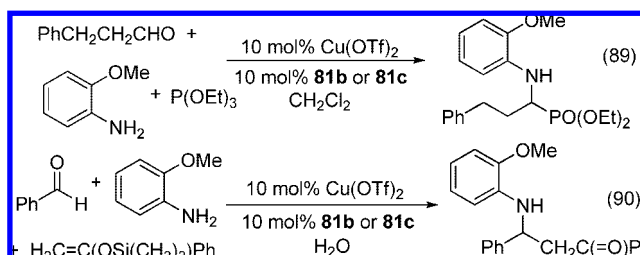
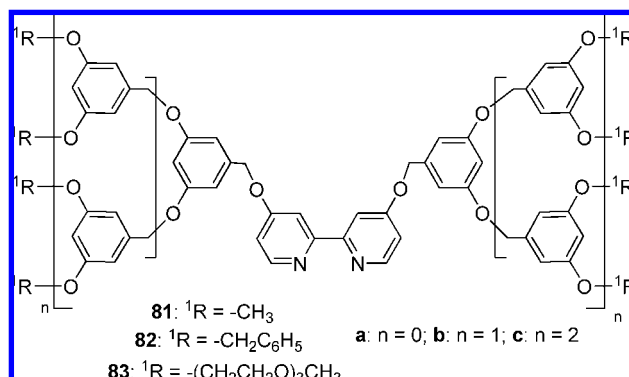


Fujita's group described the synthesis of dendritic 2,2'-bipyridine ligands **81**, **82**, and **83** for Cu(OTf)₂, that proved to be useful in Lewis acid-catalyzed Diels–Alder and three component condensation reactions.¹³⁸

In this work, the dendritic 2,2'-bipyridine ligand **81b** and Cu(OTf)₂ formed a competent catalyst for Diels–Alder reactions of cyclopentadiene, 1,3-cyclohexadiene, and 2,3-dimethylbutadiene with a variety of activated dienophiles (eq 88). Products were formed in yields that were in most cases >86%. Catalyst recycling involved pouring the reaction mixture into hexane. The precipitated catalysts **81b** and **81c** were successfully used five times. Essentially no change in yield was seen in these experiments.

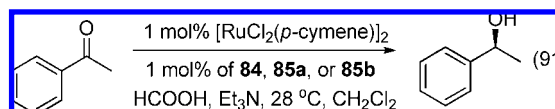


These dendritic bipyridine ligands and the Cu(II) Lewis acid Cu(OTf)₂ also were useful in three component condensation reactions of aldehydes, *o*-anisidine, and nucleophiles such as triethyl phosphite or trimethylsilyl enol ethers (eq 89 and 90). Synthetic yields of products in these cases were more modest (ca. 60–70%). In these cases, hexane precipitation produced a tarlike oil that was still separable from the product solution that could still be recycled. As was true for the Diels–Alder chemistry, catalysts **81b** and **81c** could be used five times without deactivation.



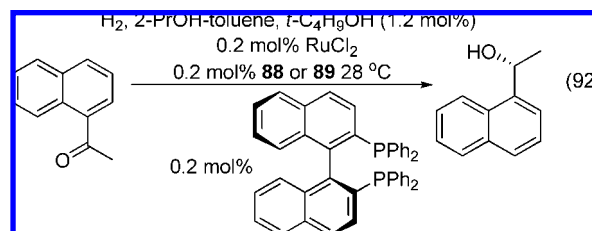
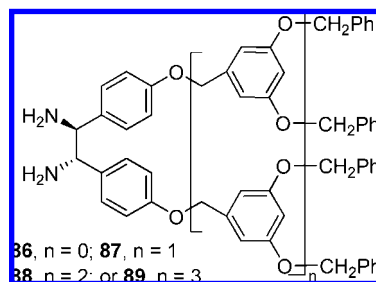
2.5.4. Dendrimer-Supported Diphenyldiamine Ligands

Asymmetric transfer hydrogenation of aryl alkyl ketones by dendrimer-bound derivatives of 1,2-diphenylethylenediamine was described originally by the Deng group in 2001.¹³⁹ In 2005, Chen and Deng expanded these studies, describing recyclable chiral hybrid dendrimer-bound diamines for asymmetric transfer hydrogenation.¹⁴⁰ These studies involved Ru complexes of 1,2-diphenylethylenediamine-containing dendrimers **84**, **85a**, and **85b** (Chart 4) that were prepared *in situ* by reaction of these diamine derivatives with [RuCl₂(*p*-cymene)]₂. Kinetic studies showed that catalysts prepared using dendrimers **85a** and **85b** were ca. 80–90% as active as a low molecular weight Ru(II) complex of (*R,R*)-*N*-(4-acetylamino phenylsulfonyl)-1,2-diphenylethylenediamine in transfer hydrogenation of acetophenone at 28 °C in CH₂Cl₂ using formic acid/Et₃N as the hydrogen source (eq 91).^{140,141}



The authors noted that the choice of solvent affected the reactivity of these dendrimer-bound catalysts much like solvent affects the reactivity of insoluble polymer-bound catalysts. For example, while CH_2Cl_2 and THF were good solvents affording 98–99% conversion in 20 h in this acetophenone reduction, conversions were only about 70% in DMF or CH_3CN under the same conditions. Recycling was studied in eq 91 by first removing the CH_2Cl_2 solvent and then precipitating the dendrimer-bound $\text{Ru}(\text{II})$ complex of **84**, **85a**, or **85b** with methanol. Recycling was modestly effective with the dendrimer **84**– $\text{Ru}(\text{II})$ complex. Excellent (>95% ee) stereoselectivity was maintained through five cycles, but by the sixth cycle, the ee dropped to 87% and the conversion was only 52%. The other two dendrimer– $\text{Ru}(\text{II})$ complexes formed from **85a** and **85b** were less recyclable. Both exhibited only 70% conversion in the second cycle and third cycle, while **85a**– $\text{Ru}(\text{II})$ had only 31% conversion. Attempts to recover reactivity for **84**– $\text{Ru}(\text{II})$ catalyst by $[\text{RuCl}_2(\text{cymene})]_2$ addition to the recovered ligand were unsuccessful, so these losses in activity were not simply due to Ru leaching. The authors speculated that a “dendritic effect” of the large polyether dendron was important in stabilizing the active $\text{Ru}(\text{II})$ complex.

The use of chiral dendritic 1,2-diamine ligands in conjunction with (*S*)-BINAP complexes of RuCl_2 in hydrogenation of aryl alkyl ketones such as acetophenone has also been described (eq 92).¹⁴² In these cases, all the diamines **86**–**89** ($n = 0, 1, 2,$ or 3) could be used to make catalysts that produced the *R* alcohol product in >99% conversion and >94% ee. Recycling of catalysts with **88** ($n = 2$) or **89** ($n = 3$) was possible and involved addition of MeOH to the reaction mixture after the reaction was complete (ca. 20 h). This additional MeOH precipitated the catalyst, which could be recovered by centrifugation. The recovered catalyst was then reused in two more cycles with no change in enantioselectivity. ICP analyses of the MeOH solution showed that 3.6% and 0.7% of the charged Ru leached using the ligands **88** ($n = 2$) and **89** ($n = 3$), respectively.

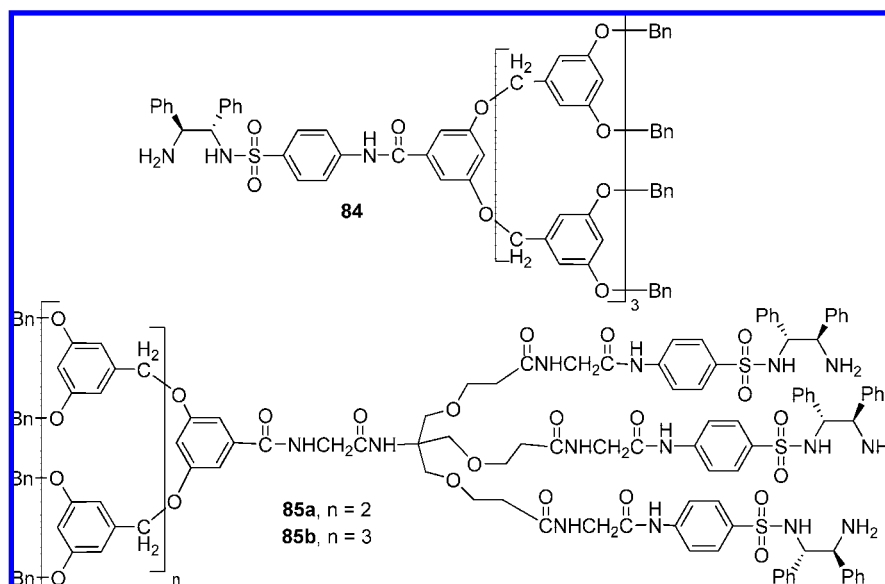


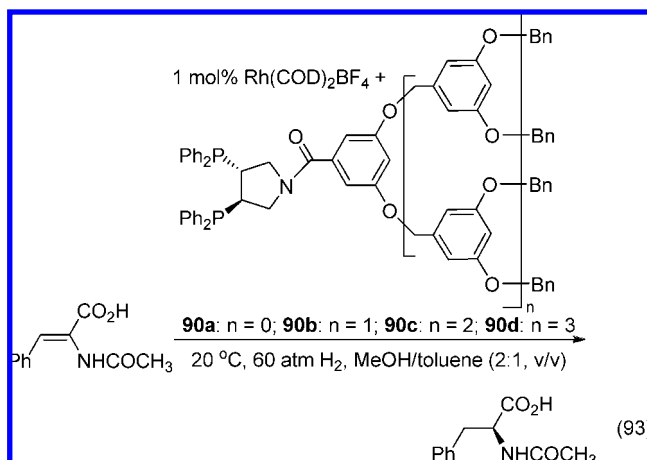
2.5.5. Dendrimer-Supported Phosphine Ligands

In 2003, Chan and Fan described the use of a Fréchet-type polyether dendron to prepare dendritic ligands that contained a chiral bisphosphine at the focal point of the dendrimer.¹⁴³ These dendrimer-bound pyrphos ligands **90a**–**d** were used to prepare recoverable reusable $\text{Rh}(\text{I})$ -catalysts for asymmetric hydrogenation of α -acetamidocinnamic acids (eq 93).

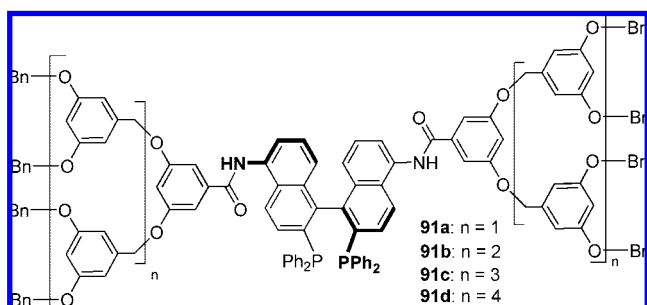
The primary objective of this study was to probe the effect of dendrimer structure and generation on the activity of a core-centered single site catalyst. However, a brief recycling study was also described with the cationic Rh complex formed from the dendrimer-bound pyrphos ligand **90c**. Catalyst recovery in these experiments was achieved by precipitation in methanol. The selectivity was >97% ee for all cycles, but the conversion dropped from 94% in the first cycle to 55% in the third cycle. While metal analyses of the supernatant MeOH phase were not described, some catalytic activity in that phase suggested some Rh leaching had occurred.

Chart 4

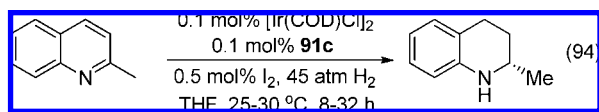




Recent reports have shown that BINAP-iridium complexes are effective in the asymmetric hydrogenation of imines.¹⁴⁴ However, the formation of an irreversible iridium dimer is a pathway for catalyst deactivation and leads to catalyst deactivation.¹⁴⁵ Based on the results with chiral diphosphine-cored dendrimer catalysts, Fan hypothesized that the encapsulation of a BINAP-Ir complex into a dendrimer framework of a Fréchet-type polyether dendron would reduce dimerization and enhance catalyst activity.¹⁴⁶ This hypothesis was tested by synthesis of all four generations of the dendritic BINAP ligand **91** and using these ligands to form an Ir catalyst *in situ* from [Ir(COD)Cl]₂ and using the Ir catalyst so formed to hydrogenate quinaldine (eq 94).



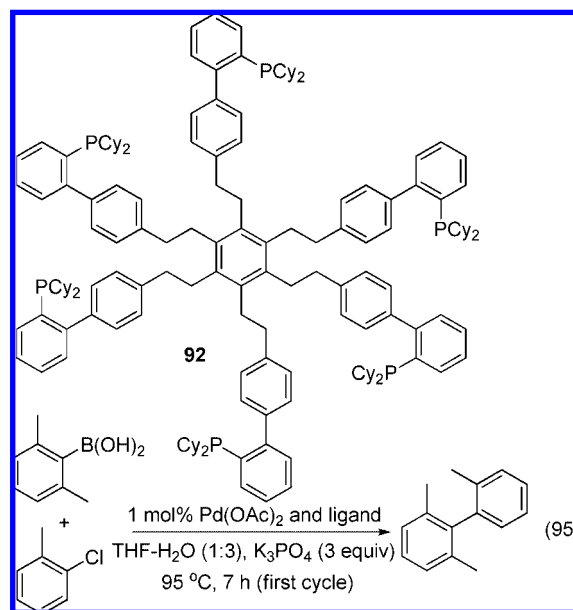
Ir catalysts from the various dendrimers were compared both in terms of reactivity and in terms of the % ee of the product in eq 94.



When 0.01 mol % of catalyst was formed using the various versions of **91**, **91a** had a TOF of 1000 h⁻¹ with 90% ee, **91b** had a TOF of 1500 h⁻¹ with 89% ee, **91c** had a TOF of 1589 h⁻¹ with 90% ee, and **91d** had a TOF of > 1900 h⁻¹ with 89% ee. A catalyst formed using **91c** was also compared to the low molecular weight Ir-BINAP catalyst. At 0.02 mol % catalyst, the TOF for a reaction using a catalyst formed from **91c** was 3450 h⁻¹ but was only 625 h⁻¹ for an Ir catalyst formed from a low molecular weight BINAP ligand, suggesting that the dendrimer does usefully encapsulate an Ir catalyst. Recycling of a catalyst prepared using **91c** in a quinaldine hydrogenation was also studied. In this work, the catalyst formed *in situ* from [Ir(cod)Cl]₂ and **91c** was precipitated

after a reaction by added hexane. The precipitate was recovered and used five more times with 85–57% ee and >95% conversion in the first four cycles. Conversions decreased to 80% in the fifth and sixth cycles. The leaching of iridium was measured by ICP-XRF (X-ray fluorescence) at the second cycle. Less than 0.024 ppm Ir was present in the supernatant.

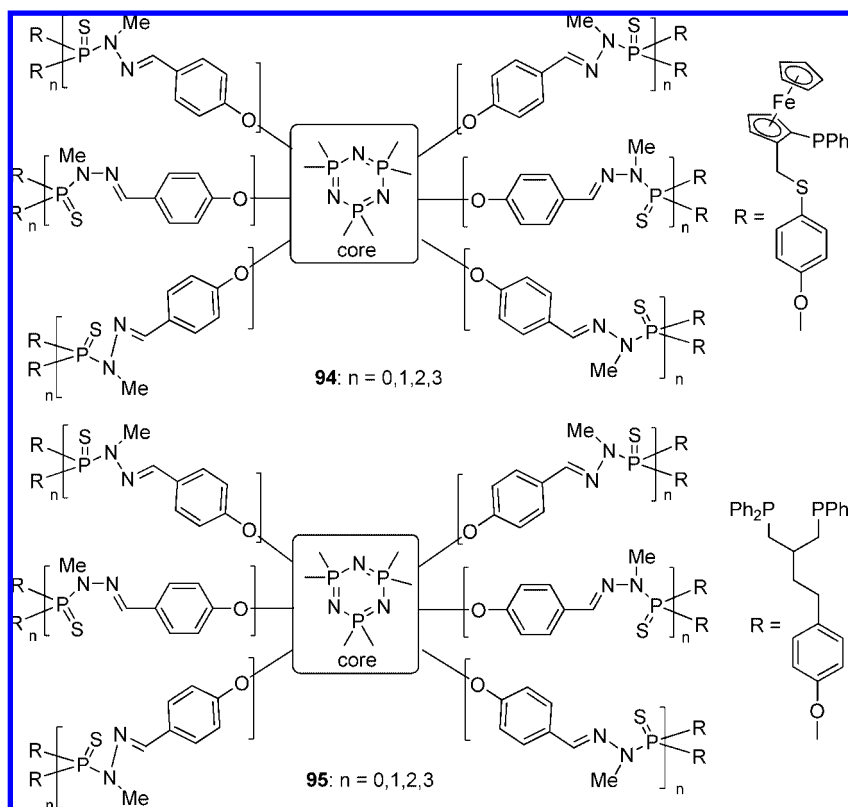
Dendrimers **92** containing hindered biarylphosphine ligands at the periphery have been prepared and used in Pd-catalyzed cross coupling chemistry.¹⁴⁷ Such phosphines are known to form more active Pd catalysts. Also, as noted above, these phosphines are reportedly more oxidation resistant,⁶⁹ and catalysts derived from them would presumably be more recyclable than Pd catalysts from more oxygen sensitive phosphines. This was tested by using the dendritic phosphine ligand **92** in Suzuki coupling reactions of hindered aryl chlorides and boronic acids (eq 95).



High yields were observed even with these rather unreactive substrates, just as is the case with similar nonpolymeric bisarylphosphine ligands.⁶⁹ Recycling was studied through five cycles. Recovery of the Pd-catalyst ligated by **92** was achieved by precipitation of the polymeric ligand catalyst complex using pentane. In the recycling studies, high product yields in the first three cycles (89–93%) dropped to 74% in the fourth cycle and 48% in the fifth cycle. No catalytic activity was seen in the sixth cycle even when fresh Pd(OAc)₂ was added. An increase in reaction times from 7 h in the first cycle to 96 h in the last cycle was also observed. Catalyst deactivation was also seen when fresh substrates were added to each reaction without separation of the products and catalysts. This gradual loss in activity and the increase in reaction times from 7 h in the first cycle to 96 h in the last cycle suggest Pd leaching or catalyst decomposition. Given that additional Pd did not restore activity and that ³¹P NMR studies showed new peaks that could be due to ligand degradation, phosphine oxidation or metalation seems a likely cause of the catalyst deactivation.

Phosphorus-containing dendrimers containing chiral monodentate phosphines at their periphery have been described by Majoral and Caminade and used to form Pd catalysts that can be recovered by solvent precipitation and reused.¹⁴⁸ These chiral dendritic phosphine ligands **93**

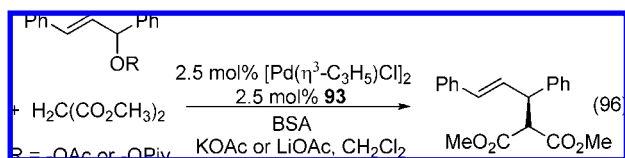
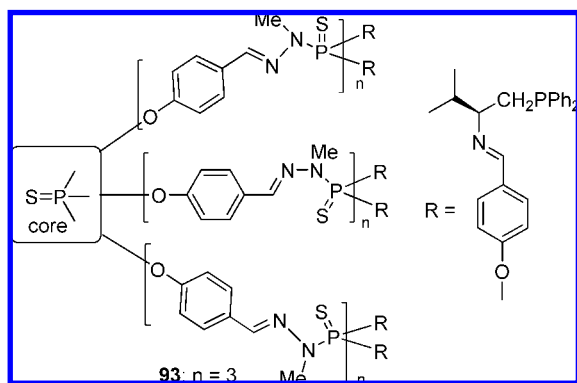
Chart 5



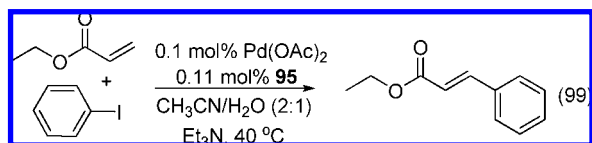
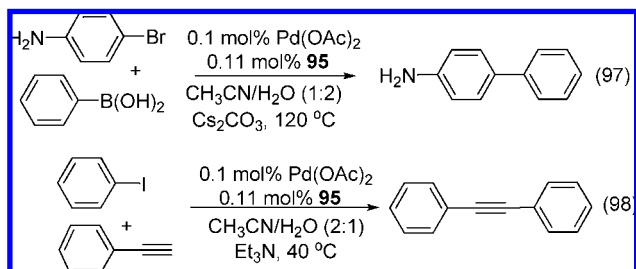
formed a Pd catalyst *in situ* with $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ that was recycled three times with yields (ee) of 97% (90%), 95% (82%), and 89% (82%) in cycles 1, 2, and 3 in allylic substitution (eq 96) with an acetate leaving group or with yields (ee) of 95% (95%), 93% (94%), and 87% (22%) in cycles 1, 2, and 3 in allylic substitution with a pivalate leaving group. A kinetic study of the acetate reaction showed that the catalyst in the three runs was kinetically equivalent throughout the course of the 24 h room temperature reaction.

Pd catalyst for Pd-catalyzed asymmetric allylic substitution *in situ* when treated with $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ in the presence of *N,O*-bis(trimethylsilyl)acetamide in an allylic substitution like that in eq 96 above, the attempts to recycle a fourth generation dendrimer-bound catalyst by pentane precipitation led to what were described as significant decreases in the catalytic activity and enantioselectivity.

While the ferrocenyl phosphine containing dendrimers were not recyclable, better results were obtained in Pd-catalyzed cross coupling chemistry with dendrimers **95** terminated with bis(diphenylphosphinomethyl)amino ligands.¹⁵⁰ These dendrimeric phosphine ligands formed Pd catalysts *in situ* that were used in Suzuki (eq 97) and in Sonogashira reactions (eq 98). The dendrimer bound catalysts in a $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ mixture were more active than a low molecular weight bis(diphenylphosphinomethyl)amino ligand derived from tyrosine. The only attempts at recycling involved the Heck coupling shown in eq 99. In that case, the products and any reactants were extracted from the reaction mixture with diethyl ether, which precipitated the polymeric catalyst. This catalyst was isolated and was then used in a second cycle. The results showed a drop in conversion from the first to second cycle. Using the non-dendritic tyrosine derived bis(diphenylphosphinomethyl)amino ligand, the initial 27% conversion dropped to 16% in this recycling in a 14 h reaction run at 40 °C in a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ mixture. Using the dendrimer **95** ($n = 1$), the conversion changed from 84 to 66%. Using the dendrimer **95** ($n = 3$), the conversion dropped from 44 to 32%. The origin of the loss in activity in the second cycle was not explained but is high enough to suggest that these catalysts at least under these conditions are not very recyclable.

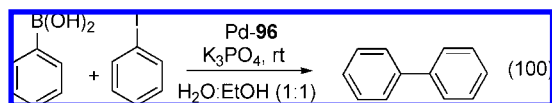


In 2007, another recyclable phosphorus-containing dendrimer-based Pd catalyst that contained chiral ferrocenyl phosphines on its periphery (**94**) was described.¹⁴⁹ However, while any generation 1–4 of **94** (Chart 5) formed an active



2.5.6. Dendrimer-Stabilized Nanoparticle Catalysts

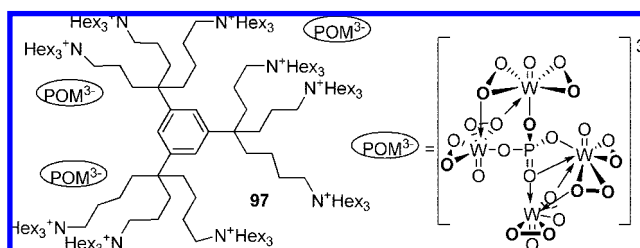
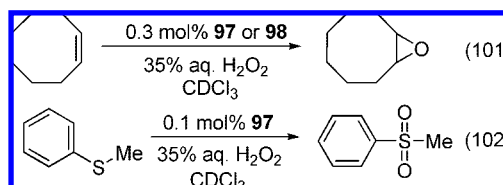
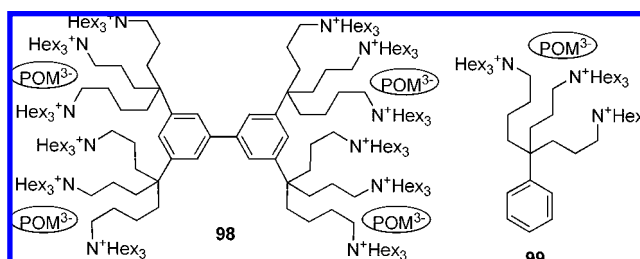
Dendrimers, like other polymers, can stabilize metal nanoparticles. Such catalysts have characteristics of both homogeneous and heterogeneous catalysts.¹⁵¹ Much of the work with such catalysts has focused on their extraordinary activity. For example, Astruc's group has noted that water-soluble sulfonated dendrimers formed by copper assisted azide alkyne coupling stabilize Pd nanoparticles that can be used at very low catalyst loading in hydrogenation of allyl alcohol and in Suzuki couplings.¹⁵² In a few cases, catalyst recycling has also been a focus of attention. Sometimes this involves a liquid/liquid separation of catalyst, and product and examples of this are discussed below. However, solid/liquid separation can be useful here too, as shown by a report by Fan's group.¹⁵³ In this work, a Fréchet-type polyether dendron with a benzylidiphenylphosphine group at the core was used to stabilize Pd nanoparticles which were used in Suzuki coupling (eq 100) and hydrogenation reactions. In this example, recycling was successful through eight runs where the yield of the biaryl product in a Suzuki coupling of 4-hydroxyphenyliodide and phenylboronic acid was maintained at >94% when a Pd nanoparticle catalyst stabilized by **96** (Chart 6) was quantitatively precipitated from the reaction solution by the addition of MeOH. However, an increase in the reaction time was required, and by the ninth cycle, the yield of product dropped to 75%. Whether this was due to phosphine oxide or Pd leaching was unclear. In these cases, some Pd leaching was detected by ICP-XRF analysis. In the second and third cycles, the Pd loss was found to be 0.84 and 0.37% of the charged Pd. However, this low level of Pd loss would not solely account for the doubling in reaction time and the decrease in yield in the ninth cycle.



2.5.7. Dendrimer Polyelectrolytes for Electrostatic Immobilization of Polyoxometalate Catalysts

Polyoxometalates (POMs) are charged assemblies of metal clusters that are useful as catalysts for various oxidations.¹⁵⁴ Such polyanions have been developed into recoverable catalysts by the Astruc group using polycationic dendrimers as a precipitable support. Two immobilization strategies have been developed. First, a supramolecular ionic assembly of the dendritic oxidation catalysts and POM trianions at the periphery of a dendrimer containing tetraalkylammonium

cations at the dendrimer surface was used (cf. **97** or **98**).¹⁵⁵ These dendritically modified POMs can be used in epoxidation of cyclooctene and in oxidation of a thiol using aqueous hydrogen peroxide in CDCl₃ (eq 101 and 102).

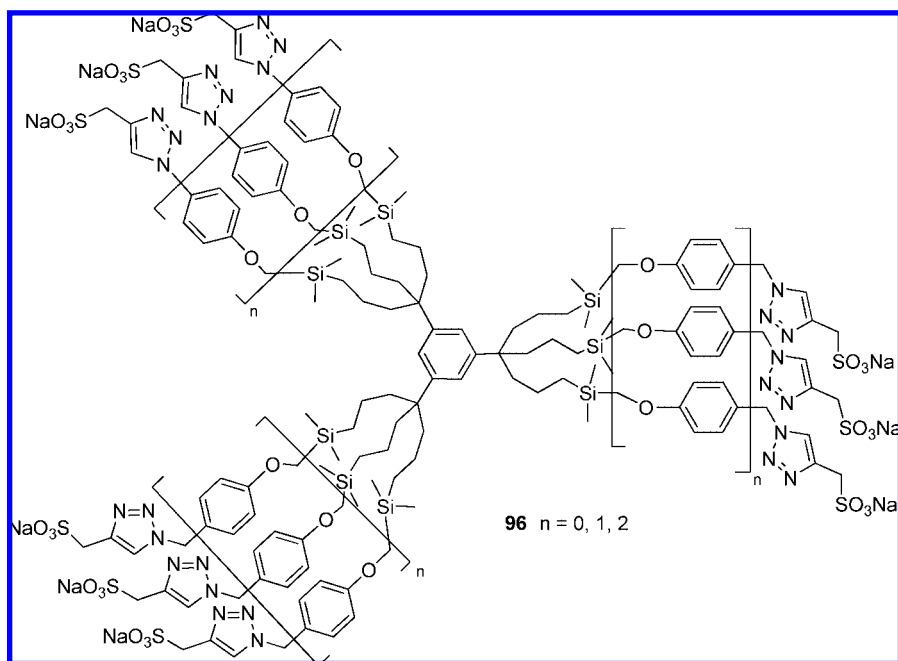


Both dendrimer-bound POMs **97** and **98** were as effective as catalysts as the low molecular weight analog **99**. However, only **97** and **98** could be recovered by pentane precipitation at the end of the reaction. The POM complexes **97** and **98** precipitated, leaving a clear solution, but the low nonpolymeric ammonium POM salt **99** formed a white colloidal solution. Thus, recovery of **97** and **98** and separation of these POM catalysts from products was facilitated. ³¹P NMR spectroscopic analysis of the recovered **97** and **98** showed no changes in the POM catalyst. However, when the catalyst **97** was recovered from a thioanisole oxidation and left in air for several days, **97**'s ³¹P NMR spectrum changed, indicating that degradation occurred. While these studies suggested recycling of catalysts **97** and **98** was possible, the number of cycles and the details of the recycled reactions were not reported.

An alternative to binding a POM at the periphery of a dendrimer is to locate the POM at the dendrimer core and to ionically assemble a dendrimer around the polyoxometalate. Astruc's group has described several examples of this strategy, preparing dendrimers like **100a**, **100b**, **101a**, **101b**, **102a**, and **102b** (Scheme 4).¹⁵⁶

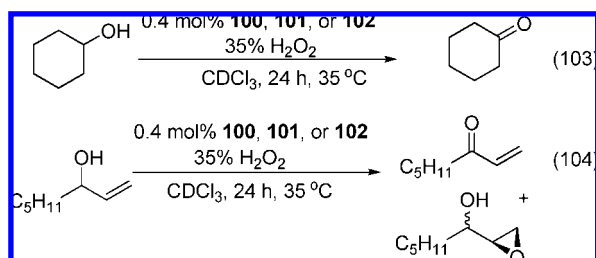
Initial studies of the catalytic activity of ionic dendrimers with POM cores used **100a** and **100b** in an aqueous/CDCl₃ biphasic epoxidation of cyclooctene and oxidation of thioanisole as shown in eqs 101 and 102 above. As was true for **97** and **98**, POM-cored ionic dendrimers **100a** and **100b** were recoverable by precipitation using pentane. The authors concluded that the bulk around the catalyst center increased the stability of these types of catalysts because unlike **97**, **100a** and **100b** were air stable and could be stored for several weeks in solution without degradation. Recycling of **100a** and **100b** was reported, but the details of the recycled reactions and the number of cycles were not described.

Chart 6



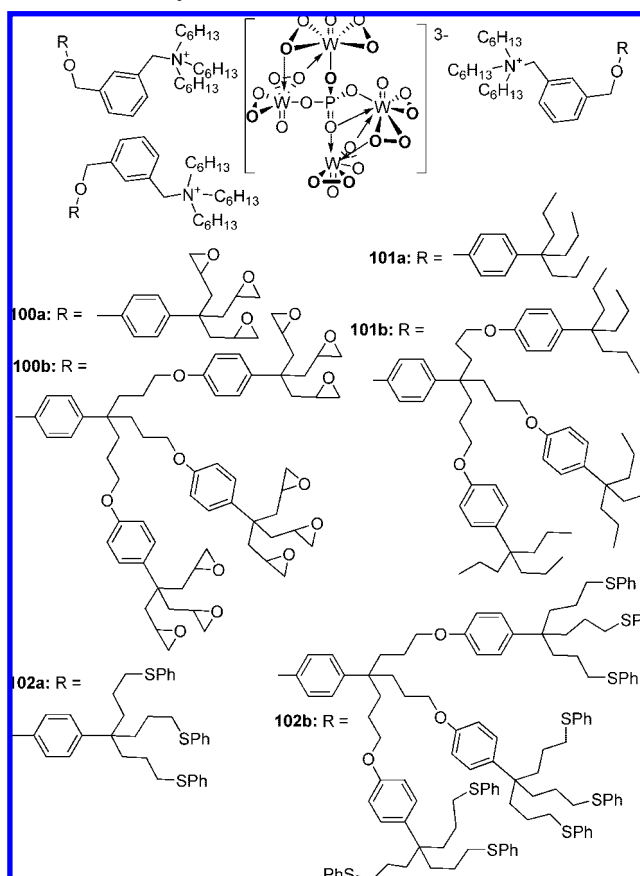
In 2006, Astruc's group expanded their investigations examining a broader collection of dendrimer-encapsulated POMs **101** and **102** using tetraalkylammonium dendrons with various degrees of branching and with various end groups.¹⁵⁷

These dendrimers, along with **100a** and **100b**, were then used as recyclable catalysts in the biphasic oxidation of cyclooctene, thioanisole, cyclohexanol, and 1-octen-3-ol (eqs 101–104).



The same experimental conditions were used for all reactions. Comparison of the results showed that the nine armed dendrimers **100a**, **101a**, and **102a** were generally kinetically slightly more reactive than their 27 armed counterparts though kinetic differences between different types of dendrimers were sometimes greater than differences between different sized dendrimers that had the same peripheral groups. Curiously, dendrimer **102a** or **102b** was competent in oxidation of thioanisole, but oxidation of the peripheral alkylphenyl sulfides of the dendrimer was not reported. Recycling was examined in the oxidation reactions shown in eqs 103 and 104 with POM-cored dendrimers **100**, **101**, and **102**. In each case, the POM-cored dendrimer catalysts were recovered by precipitation and checked by ¹H and ³¹P NMR spectroscopy before being reused. Two cycles with each dendrimer showed no change in the reactivity of the recycled catalyst. In the case of **100a** and thioanisole oxidation, reuse of the catalyst through eight cycles was successful. In contrast to these results, attempts to recycle lower molecular weight nondendritic POM catalyst by precipitation failed, showing that the dendrimer polymer usefully facilitates catalyst recovery and reuse of these oxidation catalysts.

Scheme 4. POM-Cored Ionically Assembled Dendritic Oxidation Catalysts

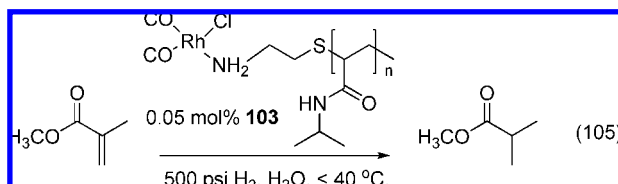


2.6. Other Polymer-Bound Catalysts and Ligands

2.6.1. Poly(*N*-isopropylacrylamide) (PNIPAM)-Bound Ligands and Catalysts

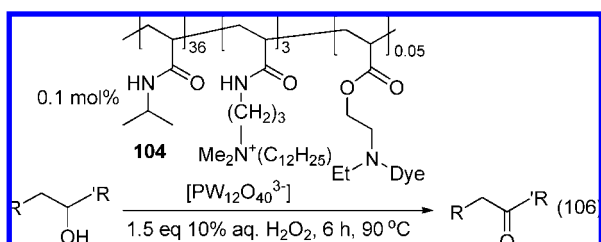
Stimulus sensitive soluble polymers are polymers that can change solubility in response to stimuli such as pH, light, or temperature. This property has been used both to regulate catalyst

activity and to recover catalysts in the past with polymers such as poly(alkene oxide)s or poly(*N*-alkylacrylamide)s.^{19,20} Poly(*N*-isopropylacrylamide) or PNIPAM is the best known example of this sort of material,¹⁵⁸ and its remarkable hydration–dehydration changes in aqueous solutions in response to relatively small changes in temperature, its so-called lower critical solution temperature (LCST) behavior, have been extensively studied.^{159–162} In 2005, Shaw reported using PNIPAM to prepare water-soluble polymeric ligands for a Rh(I) hydrogenation catalyst **103** that was recoverable on heating.¹⁶³ This report described hydrogenation of methyl methacrylate to 2-methyl propionate under 500 psi H₂ (eq 105) at 26 °C in water.



The conversion of the starting materials was complete in 12 h based on NMR spectroscopic analyses. In this case, the PNIPAM-bound catalyst **103** was recovered as a solid by heating the product solution to 40 °C. While prior groups have typically favored centrifugation and decantation to separate the product hydrogel-bound catalysts from products,^{19,164,165} in this case, simple filtration was reportedly effective. When the recovered polymer was redissolved, it exhibited renewed catalyst activity, supporting the notion that **103** was recyclable. Experiments with 3-buten-1-ol as a substrate showed that the TOF for this catalyst and this substrate was 3000 turnovers/Rh/h and that there was no catalytic activity in the filtrate (the precipitated solid did retain activity).¹⁶⁶ This further suggests that catalyst recovery is quantitative, but neither the number of times this catalyst could be recycled nor analyses for Rh leaching were reported.

A second example where PNIPAM-bound catalysts were recovered after a reaction was reported by the Ikegami group.¹⁶⁷ In this work they prepared a POM oxidation catalyst that was ionically bound to the PNIPAM terpolymer **104**. This polymeric catalyst was insoluble in a mixture of water and an alcohol substrate at room temperature. At 90 °C, this catalyst formed an oil in water emulsion where the discontinuous phase was substrate and **104**. The dye on the polymer facilitated these analyses of the phase behavior of **104**, but the dye is otherwise not involved in the catalysis. As an emulsion, the PNIPAM-bound POM catalyst converted a series of secondary alcohols (R, R' = -Ph, -Et; -Ph, -Me; -Bn, -Me; -*n*-C₆H₁₃, -Me) to ketones or primary alcohols (benzyl alcohol and 3-phenylpropanol) to carboxylic acids using aqueous hydrogen peroxide as the oxidant (eq 106).

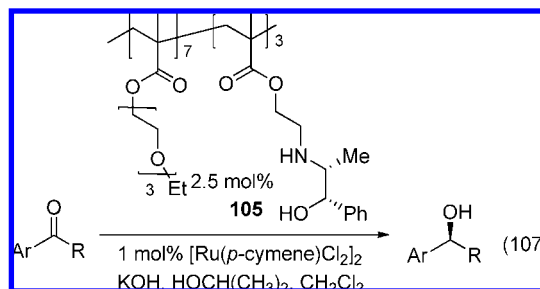


Recycling in a 10 mmol-scale reaction involved cooling the reaction mixture to room temperature and addition of 3–5 mL of diethyl ether to precipitate **104**. The organic and aqueous

phases were removed from **104**, and the recovered catalyst was washed and reused after drying. The reaction in eq 106 is one of the six examples where the catalyst **104** was successfully recycled three times. In this particular case, the yields of isolated products were 93, 93, and 89% in the three cycles.

2.6.2. Polymethylacrylate-Supported Norephedrine Ligands

In 2004, Wills described using poly(alkyl methacrylate) **105** as a polymer support for Ru(II) asymmetric hydrogenation catalysts.¹⁶⁸ Using established radical polymerization chemistry, a copolymer was prepared from monoethyl ether triethylene glycol methyl methacrylate and hydroxyethyl methacrylate. These authors used standard sorts of radical polymerization, but other controlled polymerization methods could also presumably be used to prepare similar polymers with defined molecular weights and narrower polydispersity. Once formed, the hydroxyl groups of the initial polymer were converted into tosylate groups and then directly to a derivative of (1*S*,2*R*)-norephedrine to form the polymer **105**.¹⁶⁸ This polymer was then used to complex Ru(II), and the product was used in asymmetric transfer hydrogenation of ketones. In this example, the structure of the poly(ethoxytriethyleneglycol methacrylate) copolymer was designed to incorporate a high 30% loading of catalyst.



Transfer hydrogenations of various aromatic ketones in eq 107 (Ar = -C₆H₅, -4-C₆H₄Cl, -4-C₆H₄NO₂, -4-C₆H₄F, -4-C₆H₄CN, -2-C₆H₄Cl, tetralone, naphthyl; R = -CH₃) using the Ru-complex **104** led to alcohol products with ee values in the 39–87% range. Isolated yields of alcohol product ranged from 52 to 99%. Catalyst separation was not described in this case, but recycling was evaluated by simply adding more substrate once the initial reaction ended. This sort of process provides some information about possible catalyst turnover but is not representative of the results one can expect in an experiment where recycling includes a catalyst separation step. Even in this oversimplified approach, this Ru catalyst was not very recyclable, as catalyst activity noticeably decreased in the third cycle.

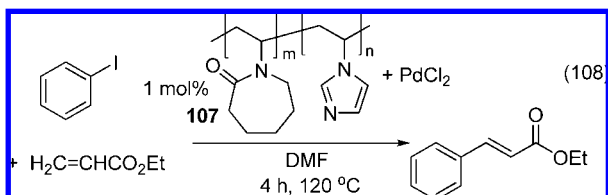
2.6.3. Polyester-Supported Bis-Cinchona Alkaloid Ligated Catalysts

While polymers with terminal or pendant groups are most commonly used to support catalysts, polymers with catalyst ligands incorporated into the polymer too are known.¹⁶⁹ An example of this approach is work by Zhang wherein a bis-Cinchona alkaloid phthalazine derivative of terephthalic acid was immobilized as a repeating unit within a polyester formed from terephthaloyl chloride and poly(ethylene glycol) (PEG₄₀₀₀).¹⁷⁰ The polymer-bound alkaloid ligand **106** (Chart 7) so prepared was used for an osmium-catalyzed asymmetric dihydroxylation. Asymmetric dihydroxylation reactions with six different alkenes were carried out in *tert*-BuOH/H₂O.

OsO₄ was used as a catalyst, and K₃Fe(CN)₆ served as the penultimate oxidant. The recovery of the Os-complex of **106** was achieved by solvent precipitation with diethyl ether. Yields of diol ranged from 78 to 87%, and ee values of 84–99% were obtained. This polyester catalyst **106** was recycled five times without further additions of OsO₄. However, no analysis for osmium in the leachate was reported.

2.6.4. Soluble Polymer Stabilized Pd Nanoparticle Catalysts

Palladium nanoparticles stabilized in or by dendrimers are discussed elsewhere in this review. Linear polymers too have been used in this regard, and the resulting supported Pd catalysts can be recovered by solvent precipitation in appropriate cases. This is illustrated by work by the Beletskaya group where poly(*N*-vinylimidazole) or poly(*N*-vinylimidazole-*co*-*N*-vinylcaprolactam) was used to support a recyclable catalyst for Pd cross-coupling chemistry.¹⁷¹ In this work, the copolymer-stabilized Pd colloid **107** prepared *in situ* from PdCl₂ was found to be the most effective catalyst in the Heck reaction shown in eq 108. In studies with either Pd colloids stabilized by **107** or the homopolymer poly(*N*-vinylimidazole), solvent precipitation of the polymer/copolymer Pd colloid catalyst was possible using diethyl ether. Washing the resulting solid followed by addition of fresh reagents provided a method to use these Pd catalyst five more times without any visible formation of palladium black and without any change in product yield.



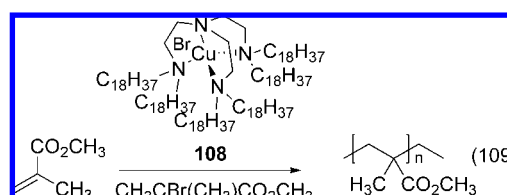
2.7. Saturated Hydrocarbon Oligomers as Supports for Recoverable Catalysts in Solid/Liquid Separations

About 20 years ago, we introduced the use of saturated hydrocarbon oligomers as catalyst supports.^{18,172,173} That work showed that polyethylene (PE) oligomers with a wide variety of terminal ligands could be prepared to function as thermomorphic supports for recoverable catalysts. These low molecular weight versions of polyethylene are useful because their phase behavior is profoundly affected by temperature. Below about ca. 50 °C, PE oligomers with an *M_n* of ca. 1200 are completely insoluble in all solvents. Above about 70 or 80 °C, they are quite soluble in nonpolar or slightly polar solvents such as toluene or dibutyl ether. Such supports can be separated as solids at room temperature by centrifugation or filtration, but during catalysis at elevated temperatures in

the appropriate solvents, they are soluble and behave like their low molecular weight counterparts.

2.7.1. Oligomeric Alkane-Supported Separable Catalysts for Polymerization Reactions

The use of polymeric or oligomeric alkanes as thermomorphic ligands for polymerization catalysts has a long history.^{173–175} This work was extended by the Vincent group in 2004 with their disclosure that multiple octadecyl groups on a CuBr-tren complex afforded an ATRP catalyst **108** that was both highly reactive and more stable to aerobic conditions. This complex exhibited the same thermomorphic solubility temperature behavior in 1,4-dioxane that had been seen for the larger oligomeric polyethylene oligomers studied by others in other solvents and served as a catalyst in a Cu(I) mediated polymerization of vinyl monomers (e.g., eq 109). These hexa(octadecyl) tren complexes were completely recoverable after a polymerization reaction by simply cooling the reaction mixture.¹⁷⁶

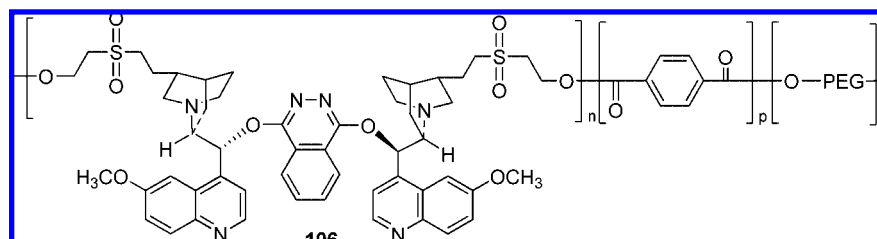


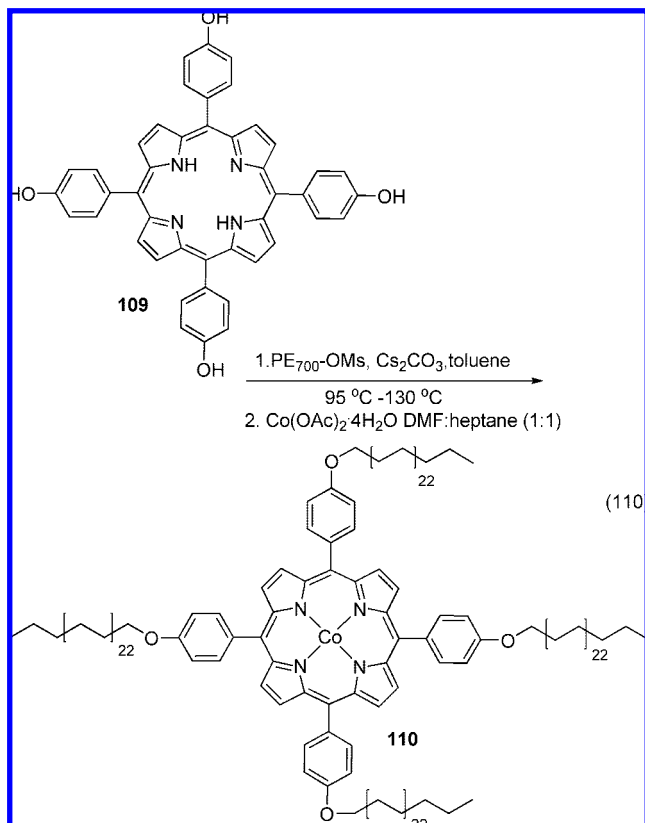
A more recent report on thermomorphic polyethylene supported porphyrins by DuPont suggests that the thermal responsive solubility of these polyethylene oligomers may afford catalysts that are commercially viable thermomorphic catalysts for free radical polymerization or copolymerization of styrene or methacrylates.¹⁷⁷ Such catalysts can be prepared using functional groups on the periphery of porphyrins such as **109** using commercially available polyethylene oligomers (eq 110). The resulting polyethyl-ligated catalysts **110** are not any more reactive than the porphyrin catalysts already used for this industrial process. However, unlike low molecular weight catalysts, the polyethylene-bound catalysts can be completely separated from the desired product. In this case, the polyethylene oligomer-supported porphyrins are soluble under the higher temperature used for the polymerization chemistry but quantitatively precipitate on cooling. They can then be removed by filtration or centrifugation. In the application described, these polyethylene-bound catalysts are used to prepare metal- and color-free polymer products with controlled molecular weights. The macromonomers produced in these processes are ultimately used in coatings (e.g., automotive paints), and these separable catalysts avoid problems with the color imparted by trace contamination from more conventional catalysts.

2.7.2. Oligomeric Alkane-Supported Separable Catalysts for Asymmetric Hydrogenation of Ketones

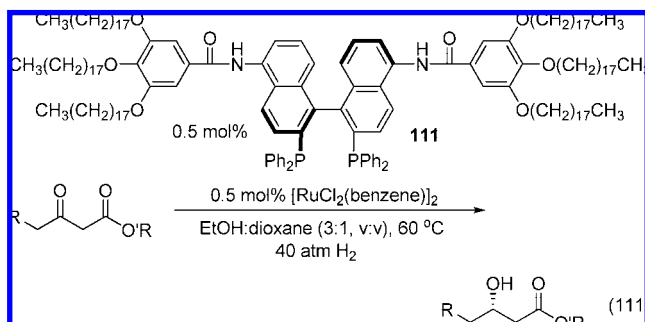
Fan and co-workers used multiple octadecyl groups to tag a BINAP ligand **111** and to thus immobilize a [RuCl₂(benzene)]₂

Chart 7





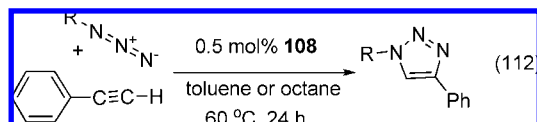
complex.¹⁷⁸ The resulting supported Ru catalyst possessed thermomorphic character due to the PE-like nature of the multiple C₁₈ chains. It was soluble and catalytically competent in a hot solution but recoverable at room temperature. In an optimized catalyst recycling protocol, this catalyst was used as a homogeneous solution in a mixture of ethanol and 1,4-dioxane (3/1, v/v) at 60 °C to catalyze the hydrogenation of substituted acetoacetates (eq 111). Cooling to 0 °C precipitated the catalyst, and it was recovered by filtration. This ruthenium catalyst demonstrated excellent enantioselectivity (>95% ee) in the asymmetric hydrogenation of β -ketoesters (R = -Me, -Ph, *p*-(C₆H₄)-F, *p*-(C₆H₄)-Cl, *p*-(C₆H₄)-OMe; R' = -CH₃, -CH₂CH₃, C(CH₃)₃), and it was reused for four cycles without any loss of enantioselectivity by simply redissolving the recovered solid in fresh solvent with fresh substrate. Slight decreases in conversion were, however, observed in the fourth cycle. ICP-MS analysis of the filtrate indicated that about 1.78% of the charged Ru leached into the organic product.



2.7.3. Oligomeric Alkane-Supported Separable Catalysts for Cu(I)-Catalyzed 1,3-Dipolar Cycloaddition of Azides and Alkynes

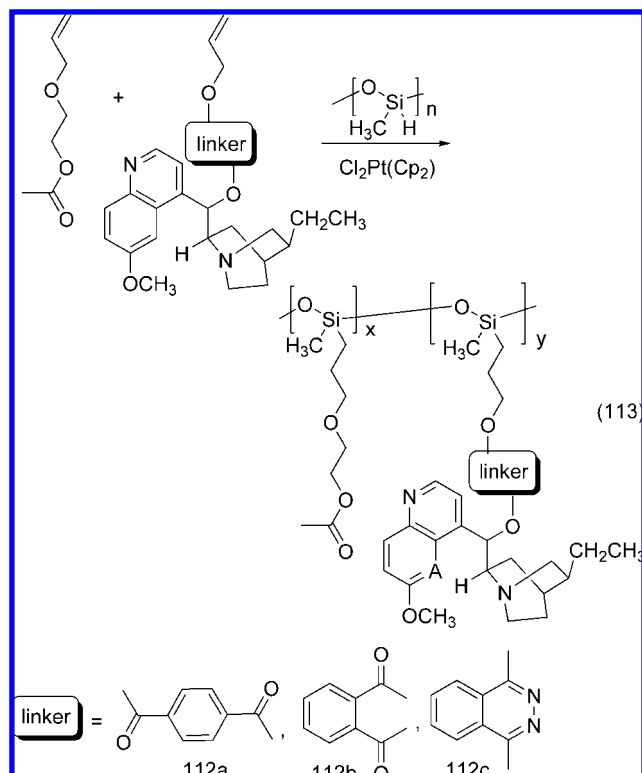
Copper(I)-tren complexes such as **108** containing six octadecyl groups have recently been shown to be useful as phase-separable catalysts for Cu-catalyzed “Click”

reactions of azides and alkynes (eq 112).¹⁷⁹ These complexes, like their counterparts that Vincent’s group used earlier as phase separable catalysts for atom transfer radical polymerization, separate readily from products simply by cooling and can be recovered by filtration and reused.



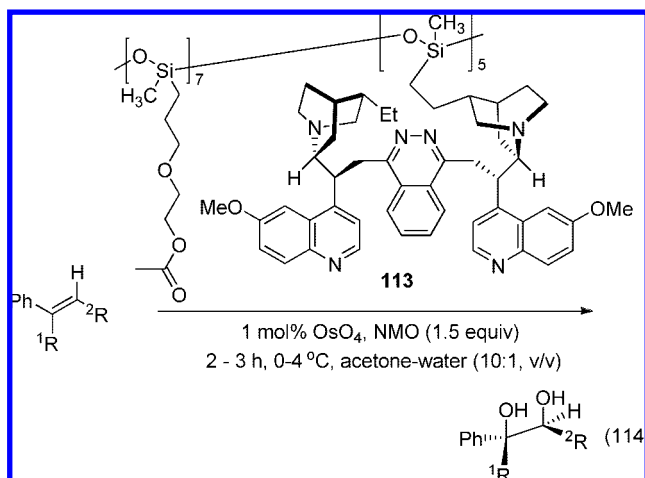
2.7.4. Polysiloxane-Supported Cinchona Alkaloid Ligands for Asymmetric Dihydroxylation

Polysiloxanes are widely used materials, but these polymers have received little attention as soluble polymer supports for the recovery and separation of catalysts. Prior reports have used membrane filtration to separate catalysts bound to these polymers.¹⁸⁰ More recently, Siegel’s group described using solvent precipitation as a recovery/separation method for supports.¹⁸¹ Siegel’s group showed polysiloxanes’ versatility as a scaffold for support of *Cinchona* alkaloids useful as ligands for Sharpless’ asymmetric dihydroxylation reaction. This work used commercially available poly(methylhydrosiloxane) and Pt-catalyzed hydrosilylation to prepare an array of polymer supports (eq 113), varying the ratio of comonomers to tune the solubility of the product siloxane and varying the mode of attachment of the *Cinchona*-containing ligand to tune the selectivity of the asymmetric dihydroxylation catalysts supported on these polysiloxane polymers.



A variety of linkers and copolymers were prepared to study the effect of loading and linker identity on the reactivity and selectivity of the supported ligand. While good results were obtained for aromatic linkers where the *Cinchona* alkaloid was attached via an oxypropylarene linker (cf. **112a**–**112c**) (average isolated yields of 82% and average ee values of

ca. 81%), even better results were obtained with another polymer **113**. In the case of **113**, a dimeric *Cinchona* ligand was coupled to the polymer via hydrosilylation of a vinyl substituent on the alkaloid. This polymeric ligand **113** at 5 mol % loading with 1 mol % of OsO₄ afforded chiral diol products from various styrene derivatives (¹R = -H, ²R = -C₆H₅; ¹R = -H, ²R = -CH₃; ¹R = -H, ²R = -CO₂Et; ¹R = -CH₃, ²R = -H) in isolated yields that averaged 90% with ee values that in most cases were in the 80 or 90% range (eq 114). However, while the polymeric ligand **113** could be effectively recycled by precipitation with water addition to reactions using acetone–water (*N*-methylmorpholine *N*-oxide as the penultimate oxidant) or *tert*-butanol–water (K₃Fe(CN)₆ as the penultimate oxidant) as reaction solvents, recycling the soluble ligand required additional OsO₄ in subsequent cycles. It was suggested that ultrafiltration might be a more suitable separation process in this instance.



3. Liquid/Liquid Separation of Polymer-Bound Ligands and Catalysts

Liquid/liquid separations are ubiquitous in chemistry. Indeed most organic reactions involve a gravity separation of two phases of different density and polarity in the workup steps. This same concept of separations also has precedent in homogeneous catalysis for separation of catalysts and products too.¹⁸² Processes like the SHOP process and later processes like the Ruhrchemie/Rhone–Poulenc (RCH/RP) oxo process commercialized in the 1980s^{182,183} advantageously immobilize a catalyst in one of the two liquid phases to facilitate catalyst recovery and reuse. More recent biphasic systems that use organic solvents,^{184,185} fluorosolvents,¹⁸⁶ ionic liquids,^{187,188} and supercritical fluids¹⁸⁹ have been developed and used in a variety of catalytic transformations over the past two decades. The use of soluble polymer supports to bind a catalyst and ensure high levels of catalyst and ligand recovery in liquid/liquid separations in biphasic liquid/liquid systems is a more recent concept.

When a liquid/liquid separation is used, the polymeric catalysts are isolated as a solution at the separation stage. As was true for solid/liquid separation strategies that used soluble polymer facilitated catalysis, catalytic reactions prior to the separation process often involve single phase conditions. However, sometimes reactions are carried out under biphasic conditions. In some of those cases, partial miscibilization occurs or the polymeric catalyst's phase selective solubility is different during the catalytic process. In cases where the reaction involves a single solvent, an extraction

is used to either remove the polymeric catalyst from the product or to remove the product from the catalyst. With systems containing mixed solvents, a perturbation induced by a temperature change (a thermomorphic effect),¹⁹⁰ a perturbation induced by addition of a small amount of a chemical perturbant (a latent biphasic system),¹⁹¹ or a perturbation induced byproduct formation (self-disassembly)¹⁹² can lead to liquid/liquid biphasic separation, which can be followed by a liquid/liquid separation of the polymer-bound catalyst and product phases. All liquid/liquid separations rely on a gravity based separation of two liquid phases to recover and separate the catalyst. All useful liquid/liquid separations require a soluble polymer-bound catalyst to have high phase selective solubility.

As is true in some solid/liquid separations, liquid/liquid separations of mixed solvent systems can often be carried out without exposing the catalyst mixture to air or water. This can be advantageous if the catalysts or their ligands are air or moisture sensitive because there is no need to open the reactor and transfer the reaction mixture to another container for a workup.

The choice of solvents and polymers for liquid/liquid separations is affected by the catalytic process of interest. First, solvents suitable for the catalytic process have to be used. Second, if miscible solvents are used, they can be miscible under the reaction conditions but it must be possible to perturb this mixture so that it is biphasic during the separation step. Third, if a thermomorphic, latent biphasic, or self-disassembling separation is used, it has to be experimentally practical to separate the two liquid phases. For example, formation of a biphasic with two solvents nearly equal in density will yield an emulsion whose separation will be difficult. Likewise, a liquid/liquid separation that only occurs far from ambient temperature would make a separation less practical. Fourth, the solvents used have to be acceptable. While equal volumes of Et₃N and water are miscible at 0 °C and immiscible at 25 °C,¹⁹³ Et₃N is noxious enough that it is unlikely that such separations would be widely used. Finally, liquid/liquid separations would not be feasible in some cases. For example, separation of heptane and aqueous ethanol is feasible in general, but it might be impractical if a particular product acted as an emulsifying agent for heptane and aqueous EtOH.

The nature of the polymer support is another consideration if liquid/liquid separations of a polymer-supported catalyst and product are to be effective. For a liquid/liquid separation using soluble polymer supports to be useful, the polymer-bound catalyst must preferentially dissolve in one of the two phases and products in the other. Thus, polar polymer-bound catalysts are more suitable for preparing nonpolar products and vice versa. A more subtle facet of this issue is that while a soluble polymer and hence the polymer-bound catalyst can have very high (>99.99%) phase selective solubility in one phase of a liquid/liquid biphasic system, low molecular weight products often have some solubility in both phases. Thus, some of the product is often “lost” to the catalyst-containing phase in the first few cycles of a liquid/liquid based recycling process involving a soluble polymer-bound catalyst. This “loss” of product can be mitigated by an extraction. It is also arguably less important when a catalyst is recycled numerous times.

In the discussion above, dendrimer-bound catalysts separable by solid/liquid separation were described and select examples in the section below describe liquid/liquid separa-

tions that use dendrimer bound catalysts too. Hyperbranched polymers are an alternative to dendrimers.⁷ However, while hyperbranched polymers and catalysts attached to them should be recoverable and separable from products by liquid/liquid separations, to date these polymers and catalysts attached to them have generally been separated from products by dialysis rather than by a solid/liquid or liquid/liquid separation.¹⁹⁵ Thus, only a few examples (e.g., polyethylene imine supported catalysts) are discussed in detail below.

3.1. Water/Organic Biphasic Systems

Water is generally considered to be the most environmental benign solvent. Many biphasic systems that include water as a solvent immobilize the catalyst in the aqueous phase.¹⁹⁴ Because many organic products are insoluble in water, complete separation of catalysts from products can be achieved easily. However, a biphasic catalytic process can introduce kinetic problems. In some cases, partial solubility of catalyst or substrate in the other phase or efficient mixing can alleviate these problems and reasonable reaction rates can be achieved. This is the case in the Ruhrchemie/Rhone-Poulenc (RCH/RP) oxo process for the production of butyraldehyde from propene, where a water soluble triphosphine ligated Rh(I) complex is used to catalyze the hydroformylation of alkenes.¹⁹⁶ However, such chemistry is often restricted to a few substrates. For example, in the RCH/RP process, other more lipophilic substrates, e.g. larger 1-alkenes, are not readily hydroformylated.

Many sorts of ionic or polar substituents can be used to make catalysts water soluble and thus amenable to aqueous biphasic catalysis. This topic is addressed by Shaughnessy elsewhere in this issue of *Chemical Reviews*.

Thus, the discussion below is brief and is focused on cases where water-soluble polymers are used to ensure that a catalyst is phase selectively soluble so that it can be separated and recovered by a liquid/liquid separation.

3.1.1. Thermoregulated Phase Transfer Catalysis

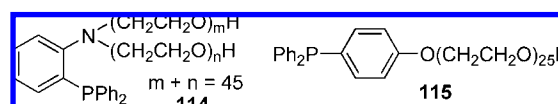
Poly(ethylene glycol)'s history as a soluble polymer support was discussed above. These polyether polymers, like the PNIPAM-supports described above, exhibit LCST (lower critical solution temperature) behavior. However, unlike PNIPAM, poly(alkene oxide)s often separate as an oil above their LCST. This LCST behavior of poly(alkene oxide)s in water has been used to design a process termed "thermoregulated phase-transfer catalysis" (TRPTC) by Jin's group.^{197–200} Rhodium catalysts attached to these sorts of polymers have been successfully used in hydroformylation of higher olefins which are not suitable substrates in RCH/RP processes using a biphasic liquid/liquid mixture of water and an organic solvent. In these TRPTC systems, the polymer-bound catalysts' inverse temperature dependent solubility makes them soluble in an aqueous phase at a temperature below their LCST. However, at their LCST, the polymer's solubility changes. Since poly(alkene oxide)s separate as an oil-in-water emulsion at their LCST, these polymers and catalysts bound to them can partition into the organic phase that is present. In cases where the substrate is present in that organic phase, the reaction does not occur to any appreciable extent below this LCST because the catalyst concentration is low. However, above the LCST, the catalyst concentration in the organic phase increases and reaction occurs. Cooling after the reaction is complete allows the

polymer-bound catalyst to partition back into the aqueous phase where it can be recovered.

An example of thermoregulated catalysis is the hydroformylation of 1-decene in a water/toluene system using the PEG-supported P,N-bidentate triphenylphosphine ligand **114**.²⁰¹ In this case, the catalyst was generated in situ by reaction of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ with **114**. Catalytic reactions were carried out using 0.1 mol % Rh catalyst at 120 °C, and under these conditions, essentially 100% conversion of alkene to aldehydes product was seen. A major difference with this system was that a lower *n/iso* selectivity in the range of 0.60–0.64 was observed. This difference was attributed to increased alkene isomerization at the 120 °C reaction temperature.

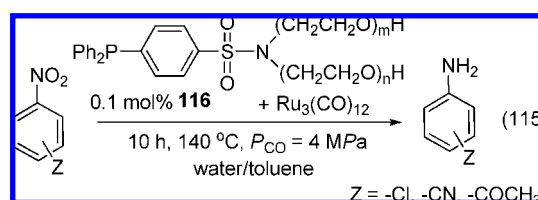
While the level of Rh leaching into the product phase was not measured, good recycling efficiency was evident from the fact that after 20 cycles the yield of aldehyde and the TOF number of the catalyst were 94.4% and 189 h⁻¹, as compared to 99% and 198 h⁻¹ in the first cycle. The high recyclability of the Rh catalyst in the water phase suggests both a high phase selective solubility for the catalyst and good catalyst stability, a stability that the authors attributed to P–N chelation of Rh by the ligand.

These recycling results suggest a high phase selective solubility for Rh complexes of the ligand **114** during the catalyst/product separation step. However, this successful hydroformylation could not be solely attributed to the ligands' LCST behavior. Specifically, the biphasic hydroformylation reaction still occurred below the LCST. When a Rh catalyst was prepared using **114** (LCST = 92 °C), a ca. 40% increase in conversion from ca. 65% conversion to ca. 85% conversion was seen as the biphasic toluene/water mixture of catalyst was heated through the LCST (i.e., from 90 to 100 °C).²⁰¹



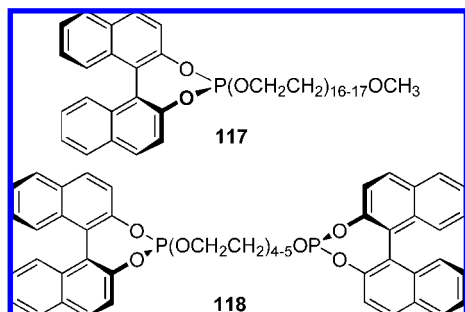
Further studies of hydroformylation using catalysts that have LCST behavior showed that even a very hydrophobic internal alkene, oleyl alcohol, afforded a good (81%) yield of aldehyde products that decreased minimally to 78% through four cycles using a very simple monovalent PEG-phosphine ligand **115**.²⁰²

A Ru complex of ligand **116** has also been used to reduce nitroarenes to aniline derivatives using CO as the reductant (eq 115).²⁰³ While no analyses for Ru were reported, only a slight loss of activity over four cycles was observed when recycling these catalysts.



Attempts at enantioselective hydroformylation of styrene under TRPTC conditions have been reported by Breuzard and co-workers.²⁰⁴ In this work, the catalysts were generated in situ by allowing a PEG-supported chiral phosphite ligand **117** or **118** derived from (*S*)-binaphthol to react with

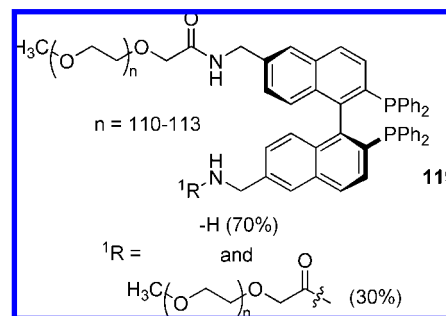
[Rh(cod)₂BF₄] in an aqueous solution. Very modest enantioselectivity, ca. 25% ee, was achieved using ligand **118**. Moreover, recycling was unsuccessful for either polymer-bound ligand. This might be attributed to the use of relatively short PEG chains in the ligand syntheses. Alternatively, there could have been some catalyst decomposition. ³¹P NMR spectroscopic studies of recovered catalyst/ligand or ICP analyses for Rh might have addressed this issue but were not reported.



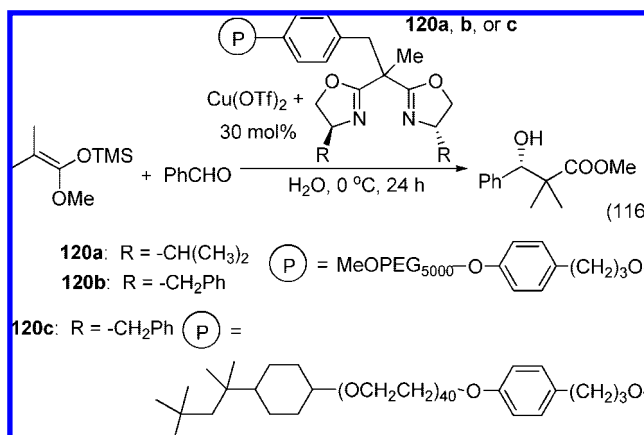
Smart catalyst that coupled a catalyst to a soluble responsive polymer were described by our group earlier in our efforts to develop recoverable catalysts.^{19,20,205} More recently, Davies and Stringer found that an aqueous solution of poly(alkene oxide)s (Ploxamers) can serve as a smart reaction medium that exhibits anti- or hyper-Arrhenius behavior.²⁰⁶ In these cases, the polymer was not used in a catalyst recovery step. Rather, the highly temperature dependent critical micelle concentration (cmc) of these polymers was used to design systems where reactions were turned ON or OFF above a particular temperature. For example, an exothermic reaction containing hydrophobic and hydrophilic reactants was turned OFF after all the hydrophobic reactant was transferred into the micellar pseudophase formed at higher temperature. It was turned back ON once the reaction mixture was cooled. More interestingly, hyper-Arrhenius behavior with a significantly accelerated reaction rate was seen in cases where the reactants and catalyst both partitioned into the micellar phase.

3.1.2. Aqueous Biphasic Catalysts Separable by Extraction

Saluzzo and co-workers reported another PEG-supported BINAP ligand **119** and its use in Ru-catalyzed aqueous biphasic asymmetric hydrogenation of ketones.²⁰⁷ The PEG-bound Ru catalyst was prepared in DMF by reaction of [RuCl₂(benzene)]₂ with **119**. Initial tests of this Ru catalyst under aqueous biphasic conditions were conducted with acetophenone as a substrate in the presence of (*S,S*)-diphenylethylene diamine. After a biphasic reaction and pentane extraction of the product, the aqueous phase containing the Ru-catalyst was reused. Recycling was evaluated in the hydrogenation of ethyl acetoacetate to form ethyl 3-hydroxybutanoate. The polymer-bound Ru catalyst could only be reused twice with a large decrease in conversion (from 100% in cycle 1 to 20% in cycle 2) and enantioselectivity (from 75% ee in cycle 1 to 56% ee in cycle 2).



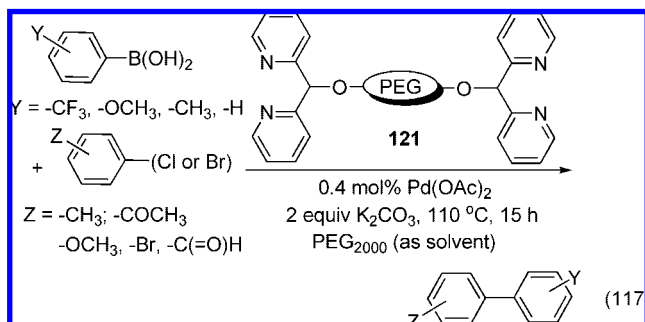
Another example of an aqueous biphasic system with PEG supports was described by Benaglia and co-workers.²⁰⁸ In their work, PEG-supported chiral bisoxazoline (Box) ligands **120a–c** were prepared and used in Cu(OTf)₂ catalyzed Mukaiyama aldol reactions between the trimethylsilyl ketene acetal of methyl isobutyrate and various aldehydes in aqueous media (eq 116).



Cu(II) catalysts ligated by either **120a** or **120b** showed that the reaction of the ketene acetal and benzaldehyde proceeded with the highest enantioselectivity (55% ee) with ligand **120b**, a result that was comparable to results reported by Kobayashi with unsupported ligands in aqueous media.²⁰⁹ However, poor water-solubility of the aldehyde electrophiles led to relatively low synthetic yields. The use of ligand **120c** slightly improved the enantioselectivity but did not affect the yield. Higher yields were only seen with more polar aldehydes such as 4-nitrobenzaldehyde, perhaps because of solubility. These more reactive aldehydes were used to study catalyst recycling. Catalyst recycling in this case involved separation of the organic product from the aqueous solution of the catalyst by extraction of the aqueous phase containing the catalysts was directly reused in a subsequent reaction cycle. These experiments showed that catalysts that used ligand **120c** could not be recycled (the ligand was partly soluble in diethyl ether). However, recycling Cu(OTf)₂ complexed by **120b** was successful with only modest decreases in yield (40–38%) and enantioselectivity (50–43% ee) through three cycles.

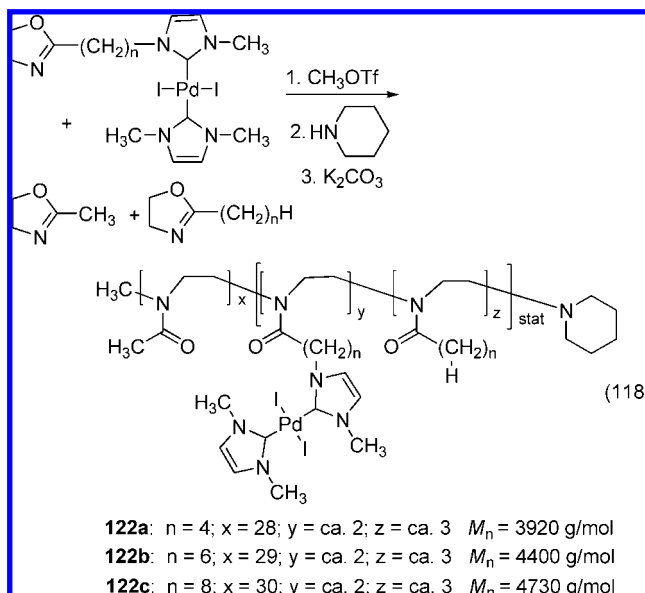
Gao used a similar approach in extracting products from a PEG-bound Pd catalyst prepared from the bis(pyridyl-methane) ligand **121** and Pd(OAc)₂ in studying cross-coupling reactions of aryl halides with either ArB(OH)₂ or sodium tetraphenylborate.²¹⁰ These reactions were carried out using either PEG₂₀₀₀ or a PEG₂₀₀₀–H₂O mixture as a

solvent. While the Pd catalyst ligated by **121** was successfully recycled six times using PEG₂₀₀₀ as solvent in cross-couplings with substituted aryl boronic acids after extracting the products with diethyl ether (eq 117), ligand **121** was evidently not effective in stabilizing the Pd(0) catalyst in the PEG–water mixture as Pd black formed in the second cycle when water was used as a cosolvent. This observation is not at all unique to this particular ligand. Adventitious catalyst decomposition or inherent catalyst instability frustrates many attempts to recycle homogeneous catalysts.

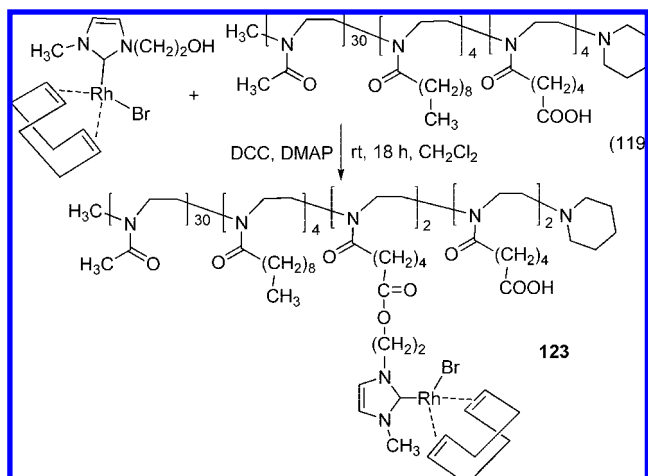


Aqueous biphasic catalysis and aqueous biphasic catalysis with polymer-supported catalysts are both successful strategies for separation of catalysts and products. However, satisfactory results with more hydrophobic substrates are problematic in either case. A possible solution to this problem is the use of amphiphilic block copolymer supports that contain a polar or hydrophilic block and a more nonpolar hydrophobic polymer block. This concept is illustrated by work where poly(2-oxazoline) copolymers were used to separate, recover, and recycle cross-coupling Pd catalysts^{211,212} or Rh hydroformylation and hydrogenation catalysts.^{213,214}

Poly(2-oxazoline) copolymer-bound palladium (**122**) and rhodium (**123**) catalysts were prepared as shown in eqs 118 and 119.^{213,215} In these examples, the metal ligation involved an *N*-heterocyclic carbene ligand and the polymers were prepared using a Pd-complex as a comonomer or by a postpolymerization coupling of a Rh complexed functional NHC ligand to a pendant -CO₂H group.



Unlike PEG, these amphiphilic block copolymer-supported catalysts were not completely soluble in water. Instead, these



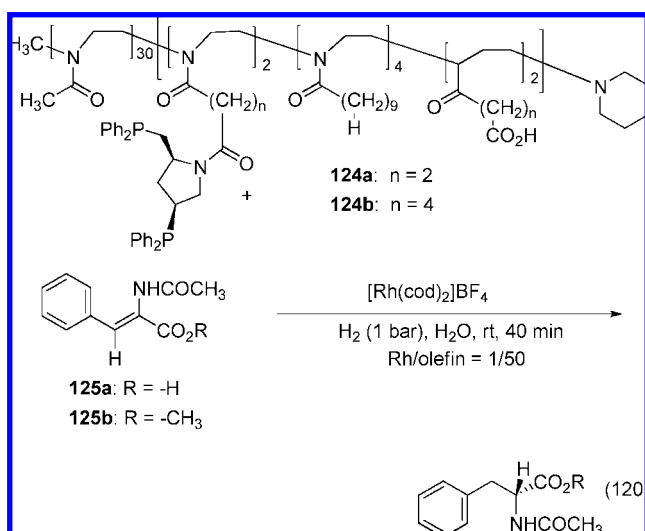
amphiphilic polymers formed micellar aggregates with a 15-nm hydrodynamic radius under the reaction conditions. The polymer-bound Pd catalyst **122a–c** showed good catalytic activity in the coupling of iodobenzene and styrene. For example, ca. 93% of *trans*-stilbene was obtained after 3 h at 90 °C using 0.67 mol % catalyst for **122a, b**, or **c**. In these cases, the spacer length affected the catalytic activity of the pendant polymer-bound catalysts. A minimum spacer length of six methylene groups was needed to reach the highest turnover frequency (TOF = 570 h⁻¹). This is consistent with NMR spectroscopic studies of pendant groups on other water soluble polymers that showed spaces of this size confer rotational freedom on attached groups.¹⁹ Recycling of catalyst **122c** was performed by a postreaction extraction with diethyl ether. The initial yield of 80% in the first cycle reduced somewhat to 68% in the third cycle. While the authors speculated that the lower activity might arise from residual diethyl ether left in the aqueous phase that prevented the solubilization of the substrates, other explanations for a decreased rate (catalyst decomposition, metal leaching) were not fully explored.

The same catalyst used in Heck couplings was also effective in the Suzuki coupling reactions between iodobenzene and phenyl boronic acid. The highest TOF number (5200 h⁻¹) was achieved by using 0.1 mol % of catalyst **122c** at 80 °C. In this case, no results on catalyst recycling were reported.²¹⁵

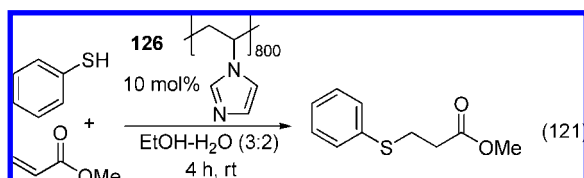
The rhodium catalyst **123** was successfully reused four times in hydroformylation of 1-octene under aqueous biphasic conditions using a mixture of water and 1-octene where the substrate 1-octene was the organic phase. The organic phase consisting of the aldehyde products was separated by decantation after the reaction, and the denser aqueous catalyst-containing phase was directly reused for the next cycle. Rh leaching into the product phase after the first cycle was measured by ICP-OES (inductively coupled plasma-optical emission spectroscopy). The TOF varied from 1100 to 2350 h⁻¹ in the third cycle to 2360 h⁻¹ in the fourth cycle. These TOF values were similar to those seen for an analogous low molecular weight analog in benzene (TOF = 2400 h⁻¹) measured in the same laboratory with a structurally similar Rh-carbene catalyst. The authors suggested that the initially lower TOF number in the first two cycles and variation of the *n*/*iso* ratio from 2.6 in the first cycle to 1.2 in the last two cycles were due to incomplete exchange of the bromide on rhodium for hydride in the initial cycles. Analyses for bromide in the recovered catalysts that would

have established this were not reported. The authors also noted some hydrolysis of the ester group that coupled the Rh-NHC complex to the polymer in **123** occurs over 18 h. This resulted in a calculated loss of 2.7% of the charged Rh in each 2 h reaction cycle.

Similar water-soluble poly(2-oxazoline)-bound chiral Rh catalysts ligated by the polymers **124a** and **124b** also have been used in asymmetric hydrogenation reactions.²¹⁴ Hydrogenation of the acid **125a** was less effective than hydrogenation of the ester **125b** (eq 120). Using **124a** as a ligand, 94% conversion and 85% ee was observed in 35 min with a Rh catalyst formed *in situ*. Using **124b**, the conversion was only slightly less (90%) with the same stereoselectivity with a similarly formed catalyst. Recycling was only studied for a catalyst ligated by **124b** and in hydrogenation of the ester **125b** and in this case only once. The only moderate conversions and no enantioselectivity seen with the acid **125a** was explained in terms of the possible micelles that this amphiphilic polymeric catalyst might form and the lower solubility of the more polar acid substrate in these micelles.

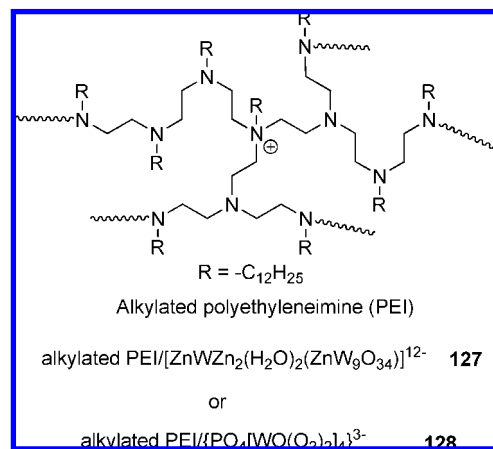


The use of poly(*N*-vinylimidazole) (PVI) (**126**) as a recyclable organocatalyst for thiol additions to α,β -unsaturated carbonyl compounds was recently described by the Beletskaya group.²¹⁶ In this reaction (eq 121), 10 mol % of PVI (75.3 kDa) in a EtOH–water mixture was used to quantitatively effect a Michael addition of thiophenol onto methyl acrylate. After the reaction, a diethyl ether extraction removed the product. Then additional water, EtOH, or reagents were added as needed. Through four cycles, the yield of thioether product was 100, 99, 100, and 100%.

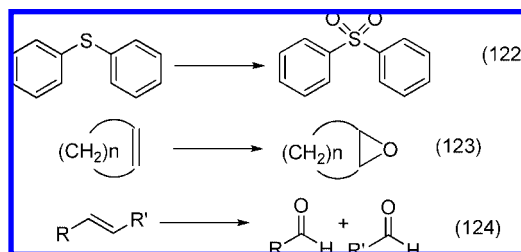


In general, polymer-supported catalysts are prepared from terminally functionalized or pendent group functionalized polymer supports. Recently, Neumann and co-workers described using the interaction between atoms on the main chain and metal ions to support a homogeneous catalyst.²¹⁷ In this research, polyethyleneimine (PEI, $M_w = 10,000$) was first alkylated with iodododecane and iodomethane using a ratio of substrate

PEI to alkylating agents of 10.5:1:7.4 (CH₂CH₂NH/C₁₂H₂₅I/CH₃I). The resulting alkylated PEI only contained tertiary amines and quaternary ammonium moieties based on ¹⁵N–¹H heteronuclear multiple bond correlation spectroscopy. Ionic immobilization of polyoxometalates such as Na₁₂[ZnWZn₂(H₂O)₂–(ZnW₉O₃₄)₂] and Na₃(PO₄[WO(O₂)₂]₄) onto these water-soluble, randomly alkylated PEI supports afforded catalysts **127** and **128**, respectively. Unlike unalkylated PEI-supported



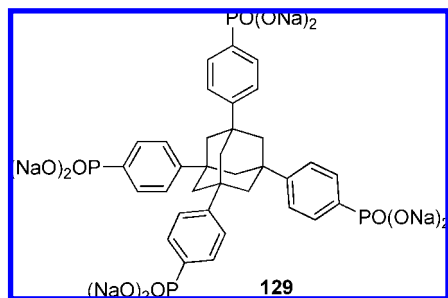
polyoxometalates, these amphiphilic catalysts **127** and **128** were very effective in many hydrogen peroxide mediated oxidation reactions with hydrophobic substrates in aqueous media, as shown in eqs 122–124. High conversions (>96%) were obtained in all these reactions. The recyclability of these catalysts was demonstrated in epoxidation of cyclododecene with **127**. No apparent decrease of activity was observed over three cycles though the details of the liquid/liquid separation technique used in this case were not discussed in detail.



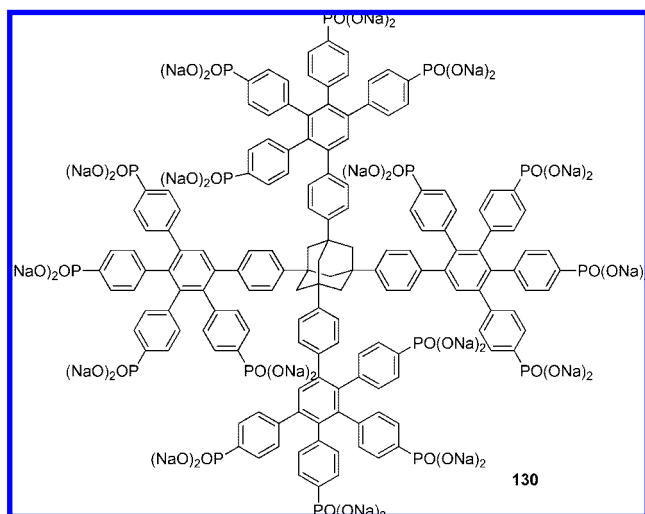
Men'shikov and co-workers reported a similar catalyst immobilization scheme in a study on aerobic oxidation of α -pinene with Co and Mo complexes.²¹⁸ In this work, polyvinyl alcohol was used to immobilize ammonium heptamolybdate via hydrogen bonding in an aqueous media. The resulting aqueous solution containing the polymer-supported catalyst was reused twice in an aqueous biphasic epoxidation of α -pinene, with catalyst recovery being effected by a simple liquid/liquid separation. No loss in catalytic activity was seen.

Water soluble dendrimers can also be used as phase tags to immobilize and recover peroxophosphotungstate catalysts in aqueous phases. For example, both a low molecular weight anionic dendritic ligand such as **129** and its higher molecular weight dendritic analog **130** react with tungstic acid (H₂WO₄) to generate *in situ* peroxophosphotungstate species that are active and selective catalysts for alkene epoxidation reactions in a mixture of 60% H₂O₂ and CH₃CN (1:2.5, v/v) at 70 °C.²¹⁹ In a model study with *E*-2-octene as substrate, a catalyst derived from ligand **129**

showed good activity (91% conversion) and selectivity (93%) in formation of the epoxide.



Lower conversion (62%) but higher selectivity (98%) to epoxide over aldehydes and acids was observed when ligand **130** was used. Recycling experiments were conducted with a tungstate catalyst bound to **129** with cyclododecene as the substrate. The product was separated from the aqueous phase by a postreaction extraction with ethyl acetate. The catalyst remained in the aqueous phase and was recycled three times with 93%, 92%, 95% conversion and >99% selectivity in each cycle.



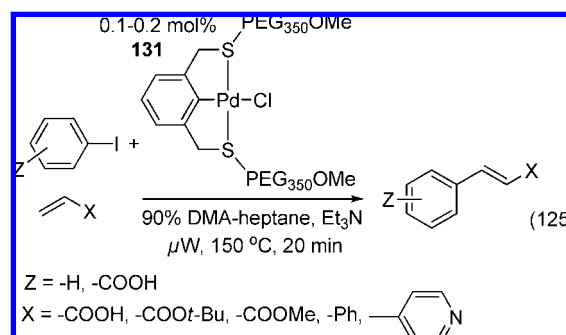
3.2. Organic/Organic Biphasic Systems

Most organic reactions are still carried out in organic media. Catalysts attached to phase selectively soluble polymer supports can be separated from products, recovered, and reused in these systems, just as they are in water/organic systems. Three general schemes are used. First, the reaction can be carried out in a mixture of immiscible organic solvents. If the polymer-bound catalyst were phase selectively soluble in a phase different than that favored by the product, the separation would just involve a gravity separation after the reaction. A second and possibly more useful scheme is to carry out a reaction under conditions where the solvent mixture used is a single phase. Then a phase separation could be triggered by addition of another solvent, addition of an additive, or a temperature change. Gravity separation would then serve to separate and recover the catalyst. Again, a phase selectively soluble polymer-bound catalyst would be required and the product would have to be preferentially soluble in the noncatalyst containing phase. Finally, a reaction can be run homogeneously in a single solvent. Extraction with an immiscible solvent can then remove the product or catalyst if the catalyst was phase selectively soluble in a solvent that

was not a good solvent for the product. Phase selective solubility of polymers in one or the other phase of an organic/organic biphasic system is required for any of the above schemes to be viable. Fortunately, polymers often have excellent phase selective solubility—phase selective solubility that is subtly dependent on polymer microstructure.^{220,221} Polymers can be molecularly engineered to be soluble only in a polar phase or only in a nonpolar phase. Thus, these organic/organic separation schemes can in principle be implemented in many if not most solvent mixtures.

3.2.1. Thermomorphic Polar Phase Selectively Soluble Polymers

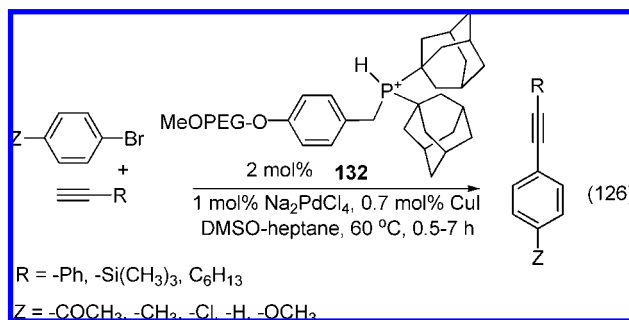
Thermomorphic separations using soluble polymers were first described by our group in 1998 using polar poly(*N*-isopropylacrylamide) (PNIPAM) polymer supports.¹⁹⁰ Subsequent to our initial work with PNIPAM-supported catalysts under thermomorphic conditions, we prepared both PEG and PNIPAM supported SCS-Pd complexes.^{222,223} The initial reports of their use in catalysis was discussed in our earlier review.¹ While later studies showed that these complexes are precatalysts and not catalysts for Pd-catalyzed cross-couplings,^{224–226} low loadings of Pd complexes can be used in catalytic reactions to form products with high levels of separation of Pd from the cross-coupling products. For example, the PEG-supported SCS-Pd complex **131** was used in 90% aqueous dimethylacetamide (DMA)/heptane (1:2, vol/vol) in cross-coupling chemistry (eq 125) under microwave conditions with reactions being complete in 10–30 min with as little as 0.01 mol % catalyst.²²⁷



In this reaction, microwave heating caused the initial thermomorphic biphasic mixture to become miscible. After the reaction, cooling re-formed the biphasic mixture. Separation of the polar phase recovered complex **131** and four recycles were carried out. Pd leaching into the nonpolar heptane phase was measured by ICP-MS, and in a reaction using ca. 3×10^{-4} M Pd, the amount of Pd lost was <0.5% of the charged Pd.

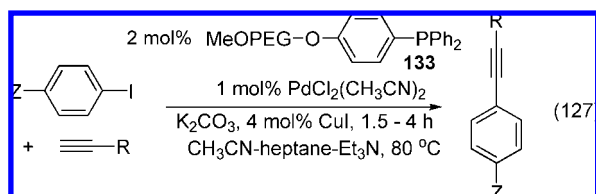
While the polar polymer-bound Pd complex **131** is effective in cross-couplings of aryl iodides and acrylates, the use of less expensive aryl bromides as substrates for C–C coupling reactions is more attractive. Hindered phosphine-ligated Pd catalysts are efficient in this process²²⁸ because the concentration of more coordinatively unsaturated Pd complexes is larger.^{229,230} This aspect of homogeneous Pd chemistry has been extended to thermomorphic polymeric systems using the PEG-supported hindered phosphine **132** to form a Pd catalyst for Sonogashira coupling reactions conducted in DMSO/heptane (eq 126).²³¹

Unreactive aryl bromides were suitable substrates with this more hindered polymer-bound phosphine ligand. This polymer-



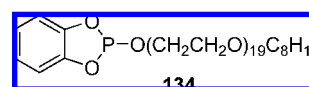
bound catalyst was successfully recycled through five cycles with overall yields > 90%. However, poor recyclability was seen when an aliphatic alkyne was used in place of phenyl acetylene in eq 126. The studies of recyclability of PEG-bound Pd catalyst were more thorough than most such studies. First, the kinetics were examined for three bromoarene substrates—4-bromoanisole, bromobenzene, and 4-bromoacetophenone. The TOF in the first cycles were 336, 440, and 1150 h⁻¹ versus a TOF of 252, 312, and 880 h⁻¹ in the fifth cycles for these three substrates, respectively. These differences were attributed in large part to oxidation of the Cu(I) cocatalyst to Cu(II), since the TOF values increased when fresh CuI was added to the reaction mixture. Second, leaching of **132** or Pd into the heptane phase was negligible based on the absence of the characteristic resonance for the CH₂O- group of PEG in ¹H NMR spectra of the nonpolar phase and analysis by X-ray fluorescence (XRF) for Pd. Based on the sensitivity of the XRF analysis, the retention of both the palladium and copper species in the DMSO phase was estimated to be >99.995%.

Plenio's group has also reported using the PEG-supported phosphine ligand **133** in Pd-catalyzed biphasic Sonogashira coupling reactions in a thermomorphic solvent mixture of a 5:2:5 (v/v/v) of CH₃CN, Et₃N, and heptane.²³¹ In coupling of aryl iodides and acetylenes catalyzed with a catalyst derived from **133**, they noted that added Et₃N affected the temperature-induced miscibility between CH₃CN and heptane. By introducing 20 vol % Et₃N, full miscibility was achieved by heating to 80 °C. In the absence of this additive, CH₃CN and heptane do not achieve full miscibility at this temperature. However, while this strategy worked to make two otherwise immiscible solvents miscible, this initial miscibility could not be replicated in recycling experiments because of the formation of ammonium salt, an effect noted previously in other systems.¹⁹¹ In this case, Plenio's group simply added a stronger inorganic base, K₂CO₃, that would serve to deprotonate the ammonium salt as it formed. Using this idea, this group was able to recycle a Pd catalyst formed from ligand **133** five times with excellent overall yields (83–96%) with a variety of aryl iodides (Z = -CH₃, -OCH₃, or -Cl) and alkynes (R = -C₄H₉ or -SiEt₃, -Ph) (eq 127).

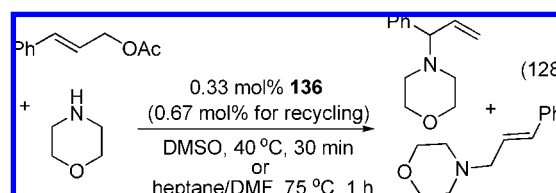


Recently, Wang and co-workers have reported a new thermomorphic system composed of PEG₄₀₀₀, toluene, and heptane as a solvent mixture for the hydroformylation of

p-isobutylstyrene by a rhodium catalyst.²³² In this system, the temperature at which miscibility is achieved is tunable by changing the weight ratio of the components. For example, a biphasic PEG₄₀₀₀/toluene/heptane solvent system with a 2/3/1 ratio of components formed a monophasic at 110 °C. Good yields (96%) and TOF numbers (384 h⁻¹) were achieved at 120 °C when using a rhodium catalyst formed *in situ* from RhCl₃·3H₂O and the PEG-phosphite derivative **134**. This PEG-phosphite-bound rhodium catalyst formed using a 1/2000 ratio of Rh/olefin was recycled seven times by thermomorphic phase separation. ICP-OES analysis of the upper phase revealed about a third of the charged rhodium was leached into the product phase over the first three cycles. Leaching then dropped to 3% in each of the subsequent cycles. The origin of this leaching was not determined. It is possible that this higher metal leaching in the first several cycles might be a result of the polydispersity of the PEG used to prepare ligand **134**, since others have shown that the molecular weight of a polymer support can affect its phase selective solubility in thermomorphic separations.^{223,233} Such effects can be minimized if the polymer or the polymer-bound catalyst is first exhaustively purified using a continuous liquid/liquid extractor.²²³



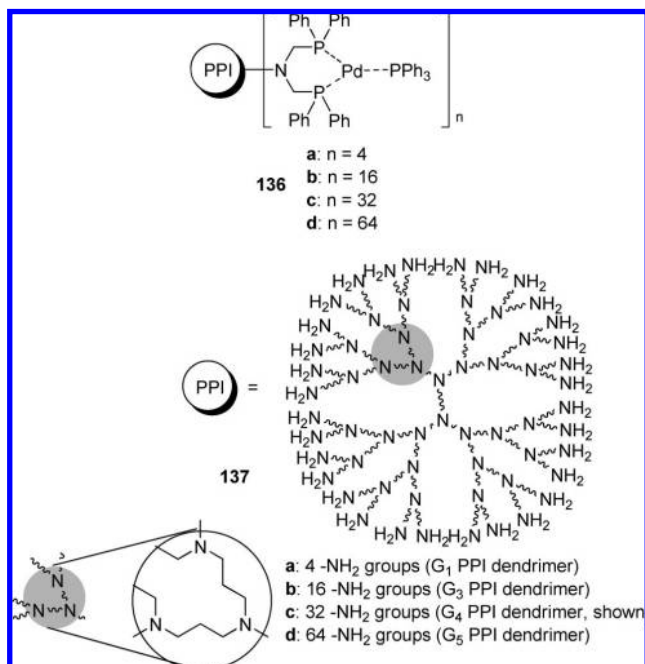
In a follow up paper, this group described using a more PEG phase selectively soluble ligand P[(OCH₂CH₂)₈OCH₃]₃ (**135**).²³⁴ In a study with the same solvents at 110 °C but without Rh present, 0.4% of the charged ligand **135** leached into the nonpolar phase. This was a lower ligand leaching value than that found for ligand **134** (2.2%). When a Rh catalyst was formed with the PEG derivative **135**, it could be reused for nine cycles without any measurable decrease in activity. As was true for a catalyst ligated by **134**, rhodium leaching decreased after the first few cycles, eventually stabilizing at ca. 1% leaching per cycle. These results suggest that Rh leaching in these systems is not solely due to ligand loss.



To further decrease rhodium leaching into the product phase of these thermomorphic hydroformylation reactions, a series of solvent mixtures were tested to determine which solvent mixture has the least ligand leaching using the PEG-bound phosphite ligand **135**.²³⁵ A mixture of PEG₄₀₀ and heptane (3 g each) was used as the solvents along with a series of organic cosolvents. The best results for a thermomorphic system were seen when 3.15 g of 1,4-dioxane was used as a cosolvent. In that case, a thermomorphic system using ligand **135** showed only 0.05 mol % ligand was leached into the heptane phase under the conditions used for the hydroformylation reaction.

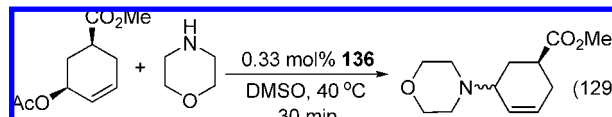
The recycling efficiency of this optimized thermomorphic system was examined in the hydroformylation of 1-dodecene using ligand **135** with a 1/1000 ratio of Rh/olefin. After 23 cycles, a catalytic system containing PEG-supported ligand **135** and Rh in a mixture of PEG₄₀₀, heptane, and 1,4-dioxane still had high activity (94% yield). Metal analysis of the

product phase using ICP-AES showed that though 1.1% of Rh leaching was detected in the first cycle, the average metal loss for the rest of the cycles was about 0.65%, much less than seen previously. However, while these results are much improved, the overall loss of Rh through 23 cycles would still be ca. 15%.

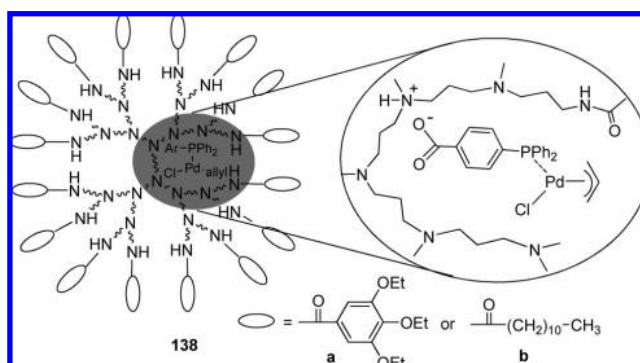


Dendrimer-bound catalysts have typically been recovered and reused by membrane filtration or other processes.^{236,237} However, such catalysts can be separated from products and reused using a thermomorphic system too, as shown by the Kaneda group. This group prepared a series of periphery functionalized dendritic phosphine ligands through double phosphinomethylation of primary amino groups on different generation polypropylene imine (PPI) dendrimers **137**.²³⁸ Coordination of $\text{PdCl}_2(\text{PhCN})_2$ to these covalently immobilized phosphines followed by hydrazine reduction formed dendrimer-bound $\text{Pd}(0)$ catalysts **136** that were successfully used in allylic substitution of *trans*-cinnamyl acetate by morpholine (eq 128), affording product in 99% yield with 9/1 (linear/branched) regioselectivity when reactions were carried out in DMSO for 30 min.

Unlike core functionalized dendritic palladium catalysts reported by van Leeuwen and co-workers,²³⁹ catalysts **136** of different generation afforded similar 9:1 linear/branched regioselectivity. However, when using *cis*-3-acetoxy-5-carbomethoxycyclohex-1-ene as a substrate (eq 129), higher stereoselectivity for the *cis* product was observed with higher generation dendritic catalysts **136**. This effect was attributed to the increased steric congestion on the surface of higher generation dendrimers. The excellent solubility of the catalysts in DMF allowed recycling to be easily performed in a thermomorphic system composed of DMF and heptane. The catalyst was reused four times. The products were isolated in the heptane phase in 66% yield in the first cycle and 99% yield in the second through fourth cycles. The low yield in the first cycle presumably reflects some product partitioning into the DMF phase. ICP analysis of the heptane phase did not find detectable Pd leachate based on the detection limit (0.1 ppm).



Kaneda's group has also described using dendrimer-encapsulated Pd catalysts **138** in cross-coupling and allylic substitution chemistry.²⁴⁰ In this chemistry, a third generation PPI dendrimer **137b** whose peripheral amine groups were acylated with 3,4,5-triethoxybenzoyl or decanoyl chloride was used to ionically anchor 4-diphenylphosphinobenzoic acids internally in the dendrimer. Earlier work had shown that ionically anchored triarylphosphine ligands could form palladium complexes.²⁴¹ These Pd dendrimers were effective in Heck couplings and in allylic substitution chemistry. When PPI dendrimers had been modified with aryl amides, the dendrimer-bound catalysts were insoluble in heptane and the catalysts could be recycled in a thermomorphic system using heptane and DMF for the allylic amination of cinnamyl methyl carbonate with piperidine. Catalyst **138a** was reused through four cycles.

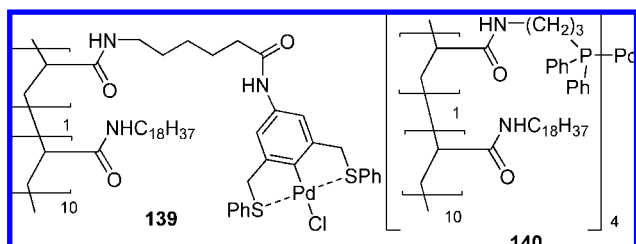


3.2.2. Thermomorphic Nonpolar Phase Selectively Soluble Polymers

The thermomorphic separations using soluble polymers first described by our group used polar polymers such as PEG and PNIPAM. However, polar polymer-bound catalysts in thermomorphic separations have an inherent problem in that both the products and byproducts of most reactions often preferentially accumulate in a polar phase. This affects the conditions necessary for miscibility in a recycling experiment. It also makes catalyst/product separation more problematic. Thus, as our group continued to explore the idea of thermomorphic separations, we focused most of our attention on nonpolar polymers for separation of catalysts and products.

An advantage of poly(*N*-alkylacrylamide) supports is their phase selective solubilities are tunable by changing the structure of the alkyl substituents on the nitrogen atom.^{220,221} For example, in contrast to PNIPAM, poly(*N*-octadecylacrylamide) (PNODAM) is a lipophilic polymer that has heptane solubility. We prepared PNODAM-supported phosphine and SCS ligands using a procedure like that used earlier to prepare PNIPAM derivatives. Metalation with $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ and $\text{Pd}(\text{dba})_2$ in refluxing THF then led to the Pd complexes **139** and **140**, which had high nonpolar phase solubility. The SCS-Pd complex **139** could be used in Heck reactions just like earlier PNIPAM-bound complexes. While the actual catalyst has subsequently been shown to not be the SCS-Pd complex,²²⁴ reactions using **139** to form cinnamic acid from iodobenzene and acrylic acid could be repeated multiple

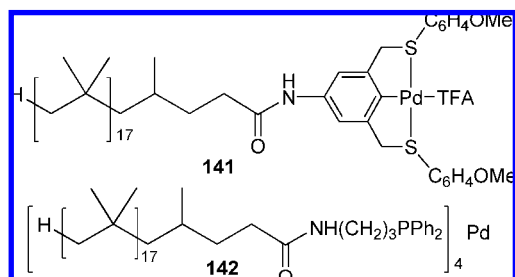
times without any additional Pd source. For example, after nine cycles, conversion was still 90%.²⁴²



Allylic substitutions that used the Pd(0) catalyst **140** were also reported. While five cycles with this catalyst were successful, gradual deactivation of the catalyst was observed based on the increase in reaction times from 1 h in cycle 1 to 52 h in cycle 5. In this case, the use of a soluble polymer allowed us to examine the catalyst after the reaction. This ³¹P NMR spectroscopy analysis showed that oxidation of phosphine ligands during the reaction was the proximate cause of the catalyst deactivation.

As noted above, nonpolar polyolefin supports such as polyethylene (PE) are readily recyclable. However, their insolubility in polar solvents and their complete insolubility at room temperature in any solvent limited their further use in catalytic processes. More recently, our group has begun to explore polyisobutylene (PIB) as an alternative to these PE supports. Vinyl terminated PIB is commercially available,²⁴³ and its vinyl end groups can easily be modified.²⁴⁴ More usefully, these PIB oligomers are soluble in many nonpolar organic solvents at room temperature. Studies on phase selective solubility using methyl red and dansyl labeled PIB oligomers in a biphasic system consisting of 90% aqueous ethanol and heptane revealed that these PIB derivatives are selectively soluble in the heptane phase of these thermomorphic solvent mixtures to an extent of more than 99.6%.^{185,244}

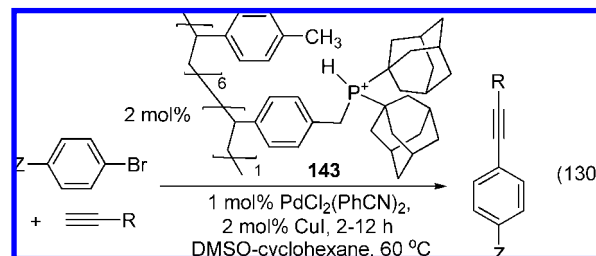
The utility of PIB oligomers as nonpolar soluble supports was first demonstrated in the thermomorphic systems using Pd catalyzed cross-coupling reactions. Both an SCS ligand and a phosphine ligand were attached to the terminus of a PIB oligomer, and these PIB ligands were used to prepare the Pd species **141** and **142**.^{226,245} Like other supported SCS-



Pd(II) species, the PIB-SCS-Pd precatalyst **141** was only effective for aryl iodides as substrates in Heck chemistry that was carried out at 100 °C. In these cases, an equivolume mixture of heptane and DMA was used as solvent. This solvent mixture was miscible under the reaction conditions but immiscible at room temperature, and the Pd in the heptane phase was separated and reused for three cycles without observable loss of activity. Similar results were achieved in a Sonogashira reaction conducted at 70 °C in a

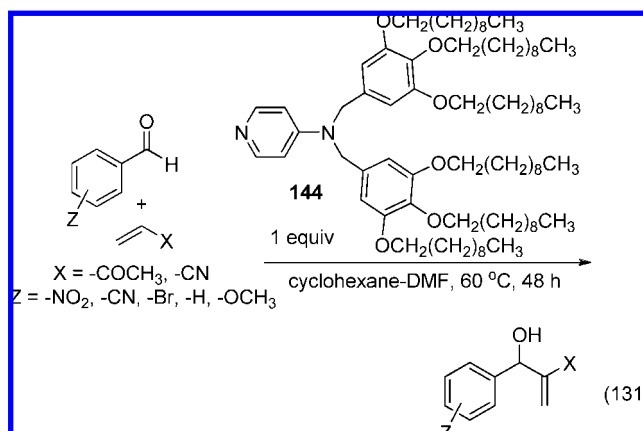
monophasic 90% aqueous ethanol and heptane mixture using the Pd catalyst **142** formed from a PIB-bound phosphine and Pd₂(dba)₃.

Plenio's group has also reported using nonpolar linear polystyrene bound hindered phosphines **143** to form recoverable Pd catalysts.^{246,247} This polymeric ligand was used in mixtures of DMSO or nitromethane with cyclohexane (eq 130) for Sonogashira chemistry or Suzuki couplings.



In the Sonogashira chemistry, the aryl bromide substrates included -COCH₃, -CH₃, -Cl, -H, and -OCH₃ substituents, and phenylacetylene or 1-octyne were used as the alkynes. In the Suzuki chemistry, Pd(OAc)₂ was used as the Pd source, K₃PO₄ as the base, phenylboronic acid, and aryl bromides and chlorides with -COCH₃, -H, -CN, and -OCH₃ substituents. In either case, the Pd catalyst ligated by the poly(4-methylstyrene)-bound hindered phosphine could be recovered in the cyclohexane phase. Five cycles were carried out. The loss of Pd into the polar phase in either example was less than 0.2% of the charged Pd based on XRF and UV spectroscopic analysis.

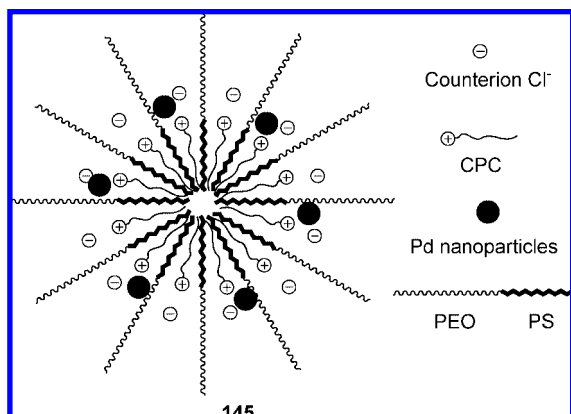
Yang and co-workers also reported a recyclable core-functionalized dendritic catalyst that was useful in Baylis–Hillman reactions using aromatic aldehydes and methyl vinylketone or acrylonitrile (eq 131).²⁴⁸ This dendritic form of 4-(*N,N*-dimethylamino)pyridine (DMAP) **144** was 97.5% phase selectively soluble in cyclohexane in a thermomorphic system formed from a DMF–cyclohexane solvent mixture. Thus, it could be recovered and reused. However, in recycling using 4-nitrobenzaldehyde and methyl vinyl ketone, reaction yields dropped from 92.3% to 47.6% after two cycles. Treatment of the deactivated catalyst with 2 M NaOH at 60 °C for 2 h regenerated the catalyst, so the observed deactivation was likely due to formation of pyridinium salts. Five reaction cycles were reported with yields of >90% per cycle when the catalyst was regenerated by treatment with base.



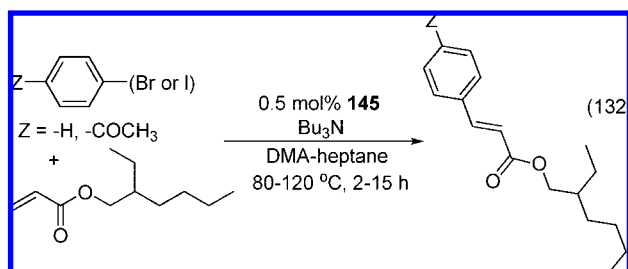
3.2.3. Polymer Stabilized Nanoparticles

Many palladium mediated cross-coupling reactions are now thought to involve actual catalysis by traces of palladium(0) formed *in situ*.^{151,249–251} Amphiphilic block copolymers containing heteroatoms such as nitrogen have long been known as agents that stabilize nanoparticles including catalytic Pd particles.^{252,253} Linear copolymers and dendrimers have more recently been used both to stabilize these sorts of particulate catalysts and to facilitate their separation, recovery, and reuse. This has included using such polymers to carry out liquid/liquid separations to recover and reuse these catalysts, as discussed below.

An apt example of how the linear copolymers can be used to facilitate the recovery and reuse of nanoparticle catalysts is work by the Beletskaya group.²⁵⁴ This group described recyclable amphiphilic PS-PEO block copolymer suspensions of Pd(0) nanoparticles that were effective in catalysis of Heck coupling reactions and other Pd(0)-catalyzed reactions. These Pd nanoparticles **145** stabilized in a dendrimer-like polymeric micelle were similar to those described earlier by Fox and Whitesell,²⁵⁵ but the Beletskaya group's work has demonstrated these catalysts' recyclability.

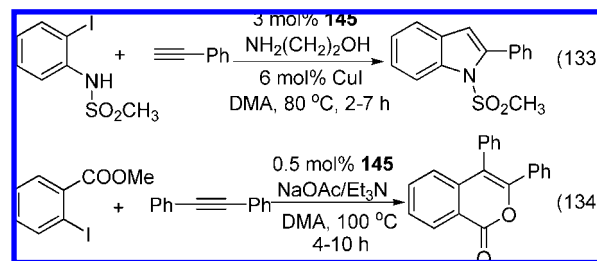


In the Russian work, the catalyst system was prepared in water and the palladium nanoparticles were generated *in situ* within micelles formed by the PS-PEO block copolymer that contained a cationic cetylpyridinium chloride (CPC) surfactant that sorbed into the hydrophobic micellar core. The resulting poly(ethylene-oxide-Pd stabilized colloidal catalysts (PEO-PS-Pd(0)) could be stored for one year without change. These polymer stabilized Pd colloids were used in Heck couplings (eq 132) with activity comparable to that of a low molecular weight palladium complex ($\text{PdCl}_2(\text{CH}_3\text{CN})_2$).

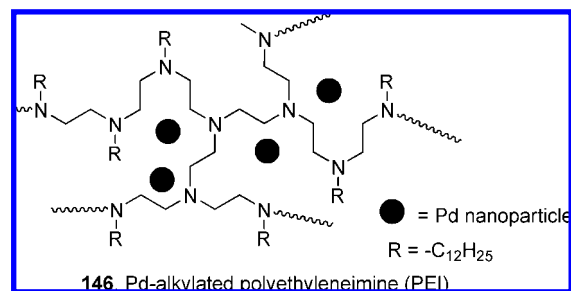


These (PEO-PS-Pd(0)) colloids **145** could be used in a thermomorphic mixture of 90% aqueous DMA/heptane (1/2; v/v) three times with yields of 90, 86, and 94%. Heck chemistry with aryl bromides worked, but longer reaction

times and higher temperatures were required. These (PEO-PS-Pd(0)) colloids were also used and recycled in *N*- or *O*-heterocyclization reactions (eq 133 and 134). In reaction 134, 0.5 mol % of (PEO-PS-Pd(0)) afforded the alkyne cycloaddition product in an average 70% yield over three catalytic cycles. Similar chemistry with an acetonitrile or triphenylphosphine complex of PdCl_2 required 5–6 mol % of a nonrecyclable catalyst to achieve a similar result.



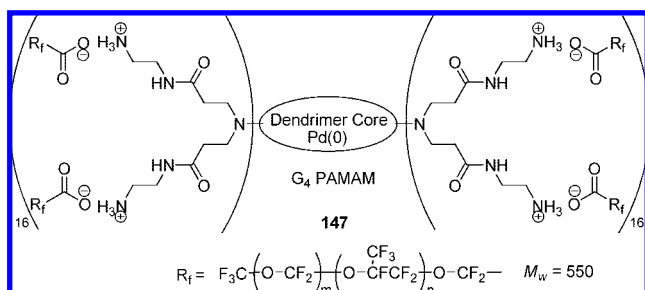
Use of 1-iodododecane to alkylate PEI ($M_w = 60,000$) led to a PEI derivative that could stabilize Pd nanoparticles in aqueous solution. Such PEI-stabilized Pd nanoparticles **146** were successfully used for hydrogenation of alkenes.²⁵⁶ In these catalysts, the primary amino groups in the original PEI polymer were completely alkylated by 1-iodododecane. Analysis by ^{15}N - ^1H heteronuclear multiple bond correlation spectroscopy showed that only secondary and tertiary amine groups remained in the alkylated PEI support. Under identical reaction conditions, higher reaction yields (>99%) and faster reaction rates were obtained in the hydrogenation of 1-octene with Pd nanoparticles stabilized by the amphiphilic alkylated PEI in an aqueous biphasic system than were seen with Pd nanoparticle catalysts stabilized by unalkylated PEI. The alkylated-PEI-Pd nanoparticles also showed significant chemoselectivity in competition reactions between 1-octene and 2-methyl-2-heptene or in reactions of 3-methylcyclohexene and 1-methylcyclohexene where only the less hindered substrates were hydrogenated. Recovery and recycling of the alkylated-PEI-Pd nanoparticles was also possible. In these cases, recycling simply involved decantation of the less dense alkane product phase from the aqueous phase. Over five reaction cycles were reported with 1-octene as substrate, and >99% yield was obtained in each cycle.



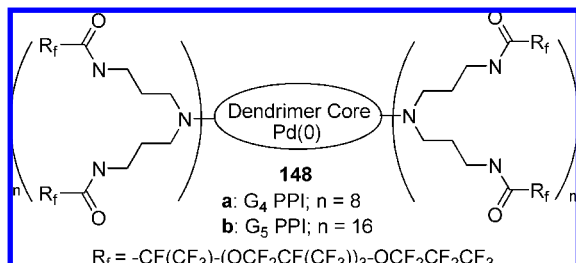
Crooks' group was the first to describe a recyclable dendrimer-encapsulated Pd nanoparticle catalyst for hydrogenation of alkenes in a fluororous biphasic system.^{257,258} In this case, a poly(amidoamine) (PAMAM) was used as the host for the stabilized Pd nanoparticle catalyst. This dendrimer-supported catalyst was made fluororous phase soluble by ionically binding perfluoropolyethers ($M_w = 550$) containing $-\text{CO}_2\text{H}$ groups to the peripheral amine groups of PAMAM. Hydrogenations were run at room temperature in a toluene/perfluoro-2-butyltetrahydrofuran emulsion formed

through vigorous stirring. The fluoros dendrimer-bound Pd catalyst **147** was recovered after the reaction by stopping the stirring and separating the heavier catalyst-containing fluoros phase. This Pd catalyst was reused 12 times, and no leaching of the brownish Pd catalyst into the organic phase was observed visually.

Recently, West and co-workers reported the use of this same fluoros phase soluble PAMAM-Pd catalyst **147** for hydrogenation of allyl alcohol in a CO₂ fluoros mixture.²⁵⁹ In this system, the allyl alcohol and the fluoros catalyst phase become miscible at room temperature upon addition of gaseous CO₂ (5.55 MPa). A higher TOF value (1858 h⁻¹) was observed in this system compared to that observed under biphasic conditions using allyl alcohol and FC-40 (95% perfluorotributylamine) (1093 h⁻¹).

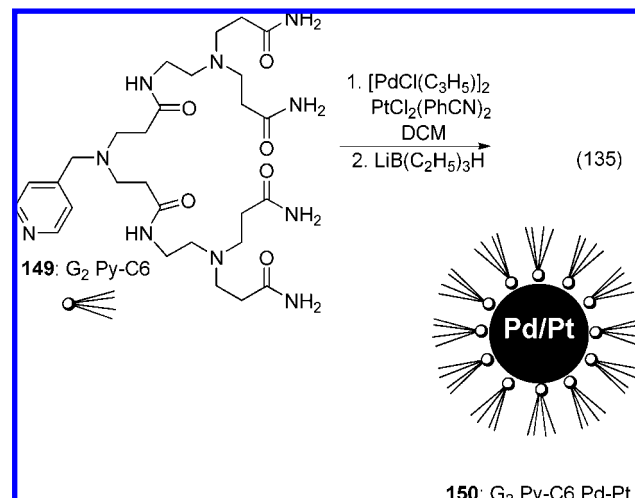


Other fluoros dendrimer-encapsulated Pd catalysts **148a** (G₄) and **148b** (G₅) derived from fourth and fifth generation PPI, respectively, were also reported by Crooks' group.²⁶⁰ In this case, the fluoros tags were connected to the dendrimers through covalent bonding, allowing the catalysts to be used at higher temperature. Catalytic activity and recyclability of catalysts **148a** and **148b** were investigated in Heck coupling reactions in the same fluoros biphasic system as above at 90 °C. The coupling reactions were conducted under homogeneous conditions, and moderate yields of the cross-coupled products were obtained using both aryl bromides and aryl iodides. No activity was observed with aryl chlorides. Catalyst recycling was accomplished using a liquid/liquid separation at room temperature. These catalysts were successfully recycled. However, the modest 38% yield (based on ¹H NMR) with 3–5 mol % Pd using iodobenzene and *tert*-butyl acrylate in the first cycle dropped to 27% in the second cycle. No Pd black was observed during the reaction. The organic phase showed <0.01 ppm Pd species based on direct current plasma (DCP) analysis.



Several groups have used the unique properties of dendrimers to prepare mixed metal nanoparticles including mixed metal clusters that are active in catalysis.^{261–263} The Kaneda group has shown that thermomorphic conditions can be used to recycle these materials when they are used as catalysts. In this example, Pd–Pt bimetallic nanoparticles solvated with dendrimers were prepared by self-assembly of dendrons **149** on mixed metal

nanoparticles formed by hydride reduction of a mixture of soluble Pt and Pd salts (eq 135).²⁶⁴



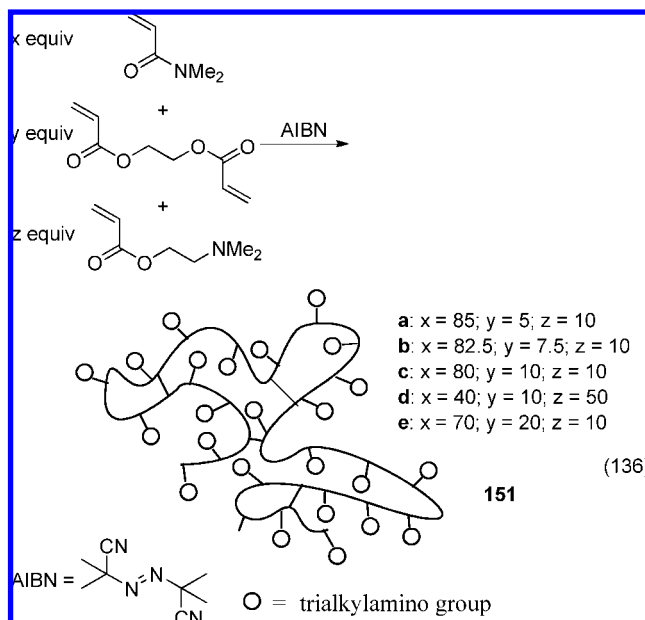
The dendrimer-solvated mixed metal nanoparticles **150** (G₂-Py-C6[Pd(0)–Pt(0)]) so formed were characterized by dynamic light scattering, transmission electron microscopy, and X-ray energy dispersive spectroscopy that together showed that the mixed metal particles were formed with a monolayer of dendrons around the bimetallic core. These bimetallic nanoparticles were then used in a hydrogenation of 1,3-cyclooctadiene to cyclooctene at 65 °C in a thermomorphic system consisting of DMF and heptane. As was true in the other examples above, these dendrimer-solvated nanoparticles were preferentially soluble in DMF. After cooling this thermomorphic mixture, liquid/liquid separation permitted them to isolate the DMF solution of the catalyst **150** and reuse it in four subsequent cycles without loss in activity.

The use of soluble microgels that stabilize metal nanoparticles has recently been reported.^{265–271} Such microgels can be prepared from acrylamides and/or acrylates and other functional vinyl monomers as soluble, intramolecularly cross-linked, globular-shaped macromolecules that are 10–100 nm in diameter. They dissolve in water or organic solvents such as DMF, chlorinated hydrocarbons, CH₃CN, acetone, EtOAc, THF, or toluene to form low-viscosity stable solutions. Like other functionalized polymers, microgels have pendent groups and can thus support reagents or catalysts. Such microgels are often recovered from solution and separated from products by ultracentrifugation, or ultrafiltration. A recent study has also shown that microgel-stabilized metal nanoparticles can be separated, recovered, and reused using liquid/liquid biphasic systems too.

In this recent work, Biffis' group showed that, in a biphasic mixture of water and CH₂Cl₂, pH-responsive microgel-stabilized Pd and Au nanoparticles selectively dissolve to the extent of >99% in either the aqueous phase or CH₂Cl₂ phase depending on pH. These microgel-stabilized metal nanoparticles were prepared from *N,N*-dimethyl acrylamide (DMAA; 40 mol %) and *N,N*-dimethylaminoethyl methacrylate (DMAEMA; 10 mol %) and ethylene dimethacrylate (EDMA, 50 mol %) using the metal salts Pd(OAc)₂ or AuCl₃, respectively (cf. eq 136).²⁷² Similar switchable phase affinity was also observed for these microgel-stabilized metal nanoparticles in organic/fluoros biphasic systems using the addition of perfluorooctanoic acid or triethylamine.

The Biffis group also successfully recycled microgel-stabilized Pd nanoparticles catalysts.²⁷³ In this case, a series

of microgels (**151a–e**) formed by copolymerization of differing amounts of the monomers DMAA, EDMA, and DMAEMA was used to complex $\text{Pd}(\text{OAc})_2$. Subsequent NaHBET_3 reduction of the microgel-bound $\text{Pd}(\text{II})$ salt yielded Pd nanoparticles that were stabilized inside of the microgel framework. The average size of the microgel-stabilized Pd nanoparticles was found to be ca. 1.9–2.8 nm based on transmission electron microscopy. These soluble polymer-stabilized nanoparticles were shown to be useful catalysts for an aqueous phase oxidation of 1-phenylethanol to acetophenone by molecular oxygen. They showed higher or comparable activity (100% yield, 6 h, 1 mol % Pd) than Pd nanoparticles entrapped in aluminum hydroxide (90% yield, 6 h, 1 mol % Pd) or Pd nanoparticles supported on hydroxyapatite (>99% yield, 24 h, 0.04 mol % Pd). Separation of these microgel-supported Pd nanoparticles from product and recycling was accomplished by a postreaction extraction of the aqueous reaction media with diethyl ether. The activity through three cycles (100%, 82%, 17%) using Pd catalysts stabilized by microgel **151b** showed a large decrease due to Pd metal precipitation in the third cycle.

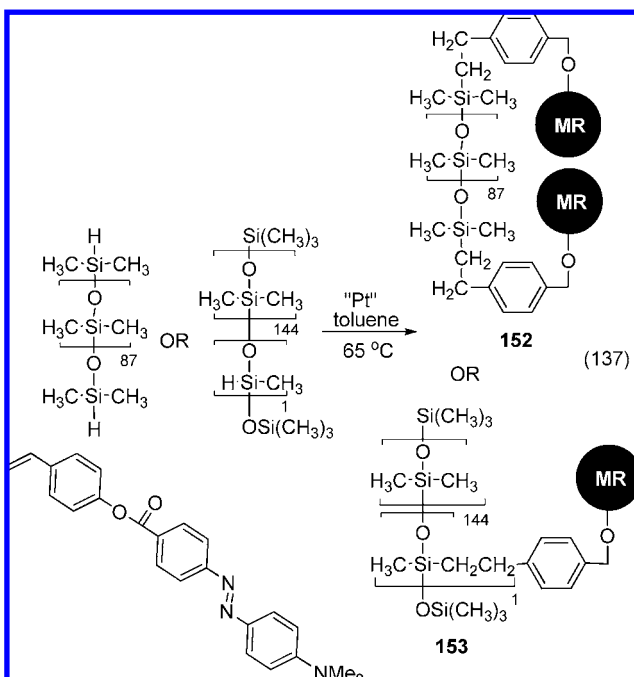


Microgel-stabilized Pt and Au nanoparticles could also be prepared, but these stabilized nanoparticles had limited activity in a similar aerobic oxidation of 1-phenylethanol (12% and 13% yields in 24 h, respectively). The authors attributed the lower activity of these nanoparticles to the size of the metal nanoparticles. These larger nanoparticles were in part the result of using DMAEMA as a monomer. The tertiary amines present in microgels that contain DMAEMA were thought to reduce AuCl_3 spontaneously even in the absence of NaHBET_3 . This problem was addressed by substituting vinylpyridine for DMAEMA. Since pyridine cannot reduce AuCl_3 , the resulting pyridine-coordinated Au ions in the product microgel were stable. In this case, subsequent NaHBET_3 reduction formed 2.4-nm-diameter Au nanoparticles that could catalytically oxidize 1-phenylethanol (100% yield in 24 h).²⁷⁴ Recycling of these more active gold catalysts was not described.

3.2.4. Latent Biphasic Separations

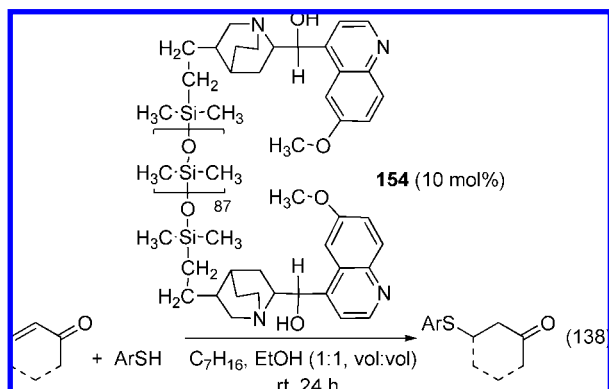
The use of temperature as a trigger to induce phase separation of solvents in a mixed solvent system is not always necessary. Product formation or small amounts of additives can have a similar effect, and this strategy has been used to advantage with several sorts of soluble polymer-supported catalysts.

Polysiloxanes have been used as supports for the recovery of catalysts but are usually recovered by membrane filtration or solvent precipitation.^{181,275} Liquid/liquid phase separations are an alternative to this approach for separation/recovery/reuse of polysiloxane-bound catalysts. The viability of this approach was demonstrated by the synthesis of several dye-labeled polydimethylsiloxanes **152** and **153** (eq 137).²⁷⁶ The feasibility of liquid/liquid biphasic separation for both **152** and **153** was studied using either a thermomorphic mixture of heptane and DMF or a latent biphasic mixture of heptane and EtOH. In these experiments, a heptane solution of the dye-labeled polymer was mixed with an equal volume of DMF or EtOH. Heating in the first case generated a monophasic solution that on cooling had 97.6% (**152**) or 99.5% (**153**) of the dye in the heptane phase. In the heptane/EtOH mixture, addition of 20 vol % water produced a biphasic mixture with 99.6% (**152**) or 99.5% (**153**) of the dye in the heptane phase.

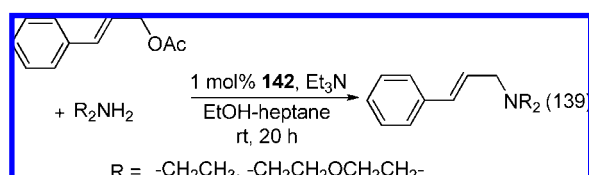


Based on these results, a silane-terminated poly(dimethylsiloxane) was used to hydrosilate a *Cinchona* alkaloid.²⁷⁶ The product immobilized quinine derivative **154** was then used to catalyze Michael additions of thiophenols to α,β -unsaturated ketones and esters (eq 138) in an equivolume of EtOH and heptane. Recycling simply involved water addition followed by separation of the catalyst containing heptane phase. This recycled heptane phase containing the polymer-bound quinine **154** afforded 80–100% yields of products for each cycle through five cycles. No effort was made to optimize this chiral catalyst, and only modest enantioselectivity was observed.

A polyisobutylene-bound Pd catalyst **142** was also successfully used in allylic substitution of cinnamyl acetate by secondary amines in a latent biphasic system (eq 139). In

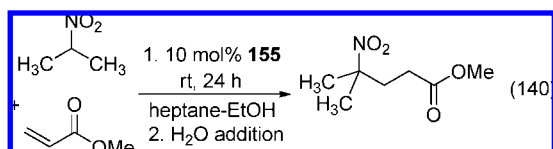


this case, a mixture of EtOH and heptane was used as a solvent at 25 °C and the separation was effected by addition of 10 vol % water. This allylic substitution catalyst was successfully recycled five times.²⁴⁵

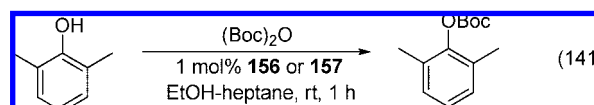
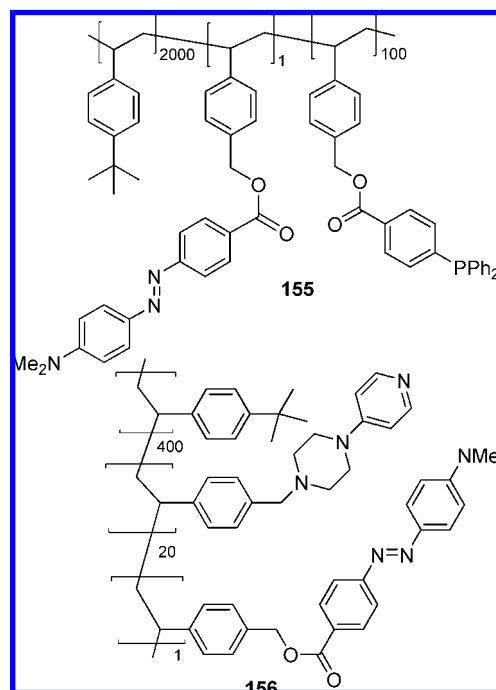


As noted above, polystyrene is an attractive soluble polymer to use to support catalysts because of the many examples that use cross-linked polystyrene as a support for catalysts, reagents, and sequestrants. However, while linear polystyrene or poly(4-methylstyrene) can be used in some liquid/liquid separations, modified polystyrenes with larger *p*-alkyl groups are more suitable because they have greater phase selective solubility. This is illustrated by work that used poly(4-*tert*-butylstyrene) (PtBS) as a support. This polymer, unlike polystyrene itself, is very soluble in heptane supports. This was shown with the dye-labeled polymers **155** and **156**. UV–visible spectroscopy showed that polymers with ca. 95 mol % *tert*-butylstyrene groups were 99.5% phase selectively soluble in mixtures of heptane and polar solvents in thermomorphic or latent biphasic systems.⁷²

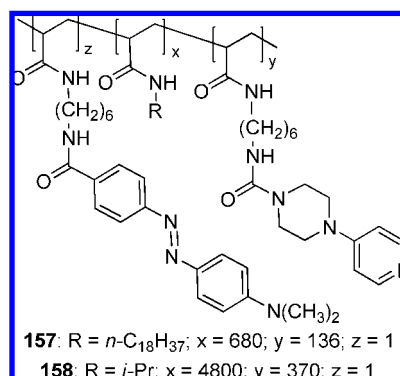
The use of PtBS in catalysis was demonstrated by the use of **155** and **156** as nucleophilic organocatalysts. When 10 mol % **155** was added to an equivolume mixture of heptane and EtOH containing 2-nitropropane and methyl acrylate, a Michael addition product formed. After the reaction was complete, addition of <10 vol % water induced biphasic separation (eq 140). All of the catalyst **155** separated into the heptane phase based on visual absence of dye in the polar phase. In recycling, this heptane solution was separated and a fresh EtOH solution of nitropropane and methyl acrylate was added. Five cycles in total were carried out. The yields of product in cycles 3, 4, and 5 were 69, 72, and 71%, respectively. These yields are similar to those seen with a nonrecyclable catalyst triphenylphosphine.



A second example of recyclability of a PtBS-bound catalyst was the use of **156** in formation of a *t*-Boc derivative of 2,6-dimethylphenol (eq 141).

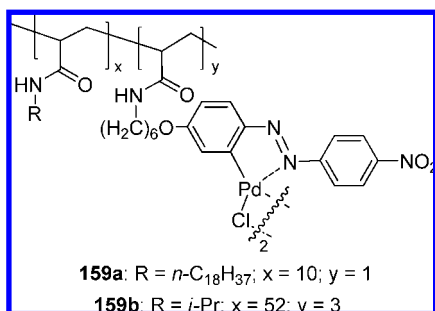


In this case, an equivolume mixture of EtOH and heptane was again used and phase separation was effected by adding a small amount of water (ca. 10% of the amount of EtOH). This polymer-bound DMAP analog was reused through 20 cycles with an average isolated yield of product of 93%/cycle. Other nonpolar polymers can be equally effective as supports for recoverable DMAP catalysts under latent biphasic conditions. The PNODAM-supported DMAP catalyst **157** for example was used and recycled six times for acylation of 2,6-dimethylphenol by $(Boc)_2O$. Recycling of the catalyst was conducted in a 1:1 heptane–EtOH solvent system at 25 °C with water addition used to perturb the system. A thermomorphic system (heptane–DMF) could also be used to recover this catalyst.¹⁹¹ Likewise, the PNIPAM supported DMAP catalyst **158** is also recoverable and reusable in systems where reversed phase selective solubility is desired in the catalyst/product separation step (**158** is polar phase soluble).

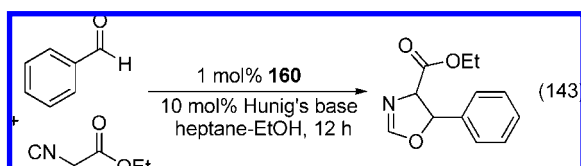
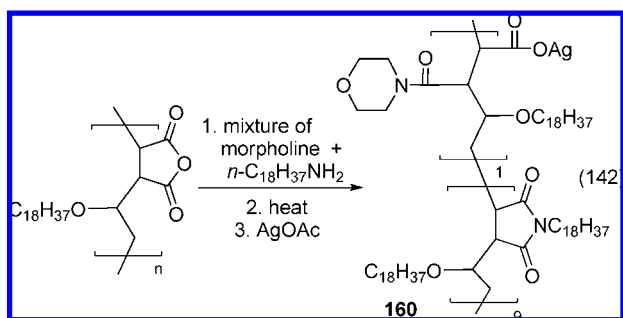


Polymer-supported palladium catalysts **159a** and **159b** were both successfully used in Heck reactions. These

polymeric Pd catalysts were designed to be recoverable in either a nonpolar or polar phase, respectively, and incorporated a colorimetric ligand to facilitate visual analysis of catalyst recovery/separation efficiency. While visual analysis of this colored Pd catalyst separation is possible, catalyst decomposition (Pd black formation) was observed during a Heck catalysis, which makes these Pd complexes less useful in cross-coupling than others.²⁷⁷



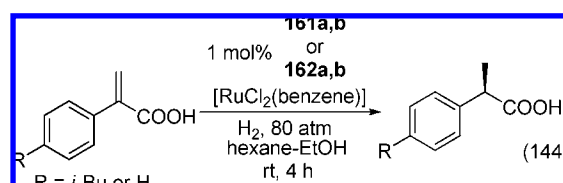
Another example where a latent biphasic system with heptane phase recovery of a catalyst after addition of a small amount of water was used effectively is the atom efficient formation of an oxazoline from ethyl isocyanoacetate and benzaldehyde. This process was catalyzed both by the silver carboxylate catalyst **160** and by the SCS-Pd complex **139**.¹⁹¹ Catalyst **160** was supported on a readily available alternating copolymer derived from maleic anhydride and an alkyl vinyl ether (eq 142). In this example, a phase selectively soluble hydrocarbon polymer was obtained by using octadecylvinyl ether as one monomer and by treating the maleic anhydride groups with a mixture of octadecylamine and morpholine. The amic acid derived from the primary amine could be imidized on heating, and the amount of morpholine could be controlled to set the amount of -CO₂H groups in the product, which determined the loading of Ag(I) in the eventual catalyst. Recycling of catalyst **160** was successful in eq 143 in a latent biphasic system of heptane and EtOH with an average loss of <0.15% of the starting Ag(I)/cycle over five cycles.



The use of **139** as a Pd source was also successful in a latent biphasic system containing DMA and heptane (1:1, vol). In this case, the phase separation was effected automati-

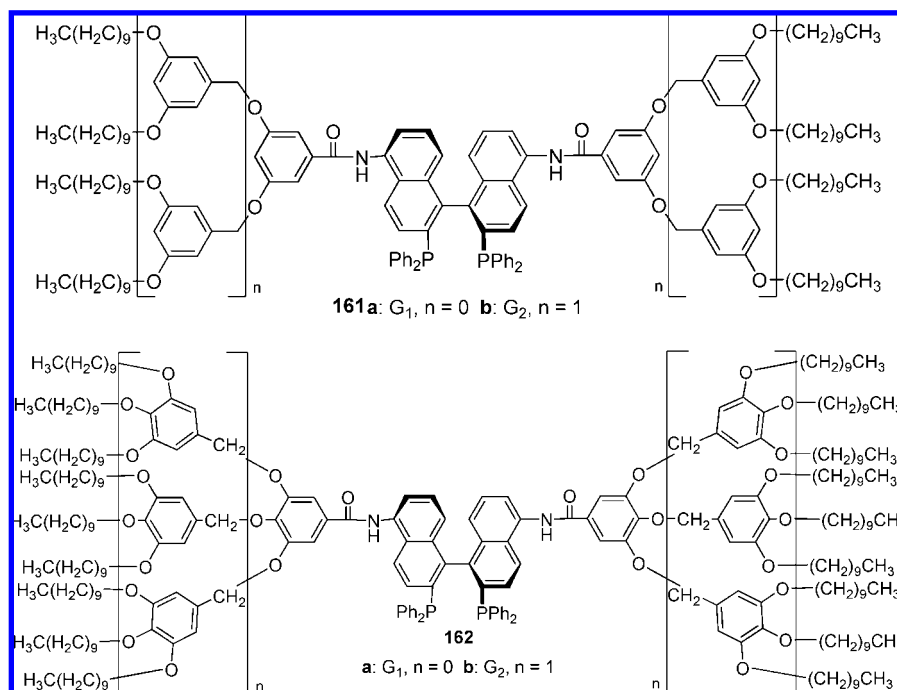
cally at room temperature by the formation of triethylammonium iodide byproduct.¹⁹¹ In this example, the byproduct formation advantageously effected the desired catalyst separation. However, it also illustrates the fact noted in several examples in this review that byproducts not only have to be removed from a product, they can also affect the practicality of catalyst recovery efforts that depend on a phase separation event.

Phase selectively soluble dendrimer-supported catalysts can also be recovered and recycled in latent biphasic systems. In a recent example reported by Fan and Chan, a (*R*)-BINAP ligand was incorporated into a Fréchet-type dendrimer which was peripherally functionalized with decyl groups.²⁷⁸ The resulting dendritic BINAP ligands **161a**, **161b**, **162a**, and **162b** (Chart 8) were each allowed to react with [RuCl₂(benzene)] in DMF at 100 °C for 20 min to generate dendritic BINAP-Ru catalysts that had good nonpolar phase selective solubility (>99% of **161b** or **162b** was partitioned into the hexane phase in a hexane/97.5% EtOH biphasic system). The catalytic activity and enantioselectivity of these dendritic Ru catalysts was then evaluated in the asymmetric hydrogenation of 2-arylacrylic acids (eq 144) in a single phase solution formed from an equivolume mixture of hexane and EtOH. Under these conditions, these catalysts showed excellent activity (100% conversions in 4 h, 1 mol % Ru, *P*_{H₂} = 80 atm) and good enantioselectivities (84–90% ee), which were comparable to the results obtained with an unsupported (*R*)-BINAP-Ru catalyst (100% conversion, 87–89% ee). Recovery and recycling of these supported catalysts was accomplished by adding a small amount of water (2.5 vol %) to the miscible solvent mixture to induce phase separation. In the case of **162b**, the dendritic catalyst was recovered in the nonpolar phase and was reused for four cycles with only a slight drop in conversion (72% in cycle 1 to 68% in cycle 4) and enantioselectivity (84% in cycle 1 to 82% in cycle 4). While no analysis for metal in the EtOH product-containing phase was reported, the authors did note that no catalytic activity was present in this phase, suggesting little if any catalyst leached into the EtOH phase.

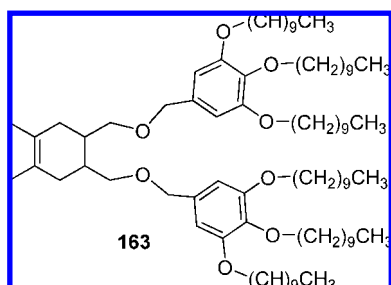


Another successful example where dendritic catalysts were recycled using a latent biphasic system was described by Yang and Fan.²⁷⁹ They tried several strategies to use dendritic ligands to recover osmium catalysts for dihydroxylation of alkenes. Their first attempt used osmium tetroxide (OsO₄) formed *in situ* in a mixture of *tert*-BuOH and hexane (2:1, v/v) that was ligated by 1.2 equiv of ligand **144**, a pyridine-containing dendrimer. In this case, the osmium dendrimer complex could be separated into the hexane phase but only by addition of a large amount of water. While the dendritic OsO₄ catalyst was effective in dihydroxylation of cyclohexene, these separation problems led them to explore other solvents. A new latent biphasic system consisting of *tert*-BuOH, CH₃CN, hexane, and water (2:1:1:0.2, v/v) was designed. Unlike the original hexane and *tert*-BuOH mixture where phase separation had to be effected by addition of a large amount of water (150 vol %), this new quaternary solvent mixture only required addition of ca. 20 vol % of

Chart 8



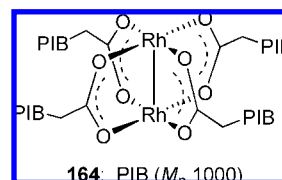
H_2O to induce phase separation. However, recycling of the dendritic OsO_4 catalyst in this solvent system proved to be problematic, since the reaction yield dropped gradually from 88% to 22% over four reaction cycles. The authors suggested that the competing coordination to Os by *N*-methylmorpholine, the reduced product of NMO, may have formed a low molecular weight Os species with high polarity that partitioned into the polar phase, causing the loss of catalyst during the recycling.



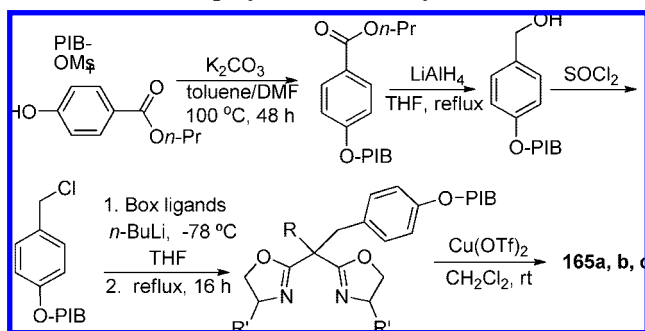
To address this problem, a more stable immobilized OsO_4 catalyst was prepared by allowing ligand **163** to react with OsO_4 . The osmate ester formed in this reaction was then oxidized with NMO. Osmate(VI) esters formed in the reaction of OsO_4 with a tetrasubstituted olefin such as **163** are more stable toward hydrolysis than osmate esters formed from other alkenes. These osmate esters can be reoxidized to form an Os(VIII) complex, and this complex can be used in alkene dihydroxylation.²⁸⁰ These factors allowed the osmium complex formed from dendrimer **163** to be successfully reused over 10 times in dihydroxylation of cyclohexene in the quaternary solvent system discussed above. Yields of diol product in this latent biphasic system ranged from 83% to 94%. ICP analysis showed only 5 ppm of Os in the product, which corresponded to Os leaching of <0.1% of the charged metal in each cycle.

3.2.5. Catalyst Separation and Reuse by Extraction

Whether a thermomorphic or latent biphasic scheme is used, the common feature of the above reactions is that mixed solvents are used. An alternative is to carry out a reaction in a single solvent and to rely on a soluble polymer's phase selective solubility in a subsequent extraction to separate the product from catalyst or catalyst from product. The use of this approach was demonstrated with PIB-bound Rh(II) carboxylate catalysts such as **164** that catalyze olefin cyclopropanation.²⁸¹ In this example, the catalysis was carried out in heptane. Then a polar solvent such as CH_3CN or ethyleneglycol diacetate (EGDA) was used to extract the cyclopropane products. The residual heptane solution of Rh catalyst was then reused with fresh substrates for nine cycles. Good activity was seen for cyclopropanation of styrene, with the PIB-bound catalyst **164** exhibiting reactivity and stereoselectivity that was comparable to that of analogous low molecular weight Rh carboxylate catalysts. ICP-MS analyses showed that ca. 1.8% of Rh ion leached into the EGDA phase in each cycle. When CH_3CN was used as the extraction solvent, Rh leaching was 2.3%. This was attributed to the better coordination by CH_3CN to Rh(II).

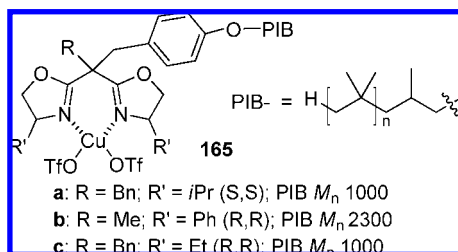


In addition to rhodium catalysts, PIB-ligands also were used to support and recover chiral copper catalysts **165a–c**. These catalysts were used in asymmetric cyclopropanation of styrene using heptane as a reaction solvent. The products in each cycle were extracted with EGDA. The copper catalysts **165a–c** all demonstrated moderate catalytic activity (50–60% yields) and were reused through five to six cycles. The enantioselectivities of these polymer-bound catalysts

Scheme 5. Multistep Synthesis of Catalysts **165a–c**^a

^a In each step, the PIB-bound intermediates were separable from other polar products by a liquid/liquid separation where the PIB products were isolated in a heptane phase.

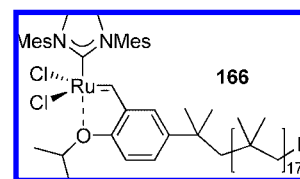
were the same or better than those of similar low molecular weight analogs in CH_2Cl_2 . For example, for **165b**, 92% ee and 68% ee were obtained for the *trans*- and *cis*-products, respectively, while a low molecular weight catalyst with similar chiral centers in the ligand ($\text{R}' = -\text{C}_6\text{H}_5$) afforded these products with 60% and 51% ee.²⁸² The deficiency of these recyclable copper catalysts is that the ligand represented a significant fraction of the molecular weight of the polymer. This is a problem because the relatively large size of the polar ligand compared to the nonpolar PIB backbone decreases the nonpolar phase selective solubility of the catalysts. This led to higher metal leaching, with 5% loss of copper being observed in cycle 3 and even higher catalyst/ligand leaching in cycles 1 and 2. Presumably this problem could be solved by using a larger PIB polymer or by incorporating multiple PIB chains on the catalyst.



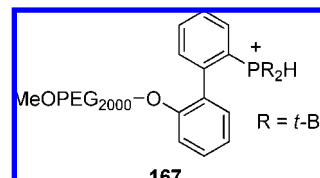
In the examples above, the phase selective solubility of the PIB group not only was useful in catalyst recovery, it simplified the multistep ligand synthesis. In the reactions in Scheme 5, the various PIB-derivatives could be separated from byproducts or excess polar reagents easily because of the PIB group's heptane solubility.^{244,281}

PIB has also been used as a polymer to support a second generation Hoveyda–Grubbs catalyst **166**.²⁸³ While a review elsewhere in this issue discusses metathesis chemistry in more detail, it is worth noting in the context of this review and this section of this review that extractable PIB ligands proved quite useful in recovery and recycling of this soluble ring-closing metathesis catalyst **166** too. Using the same approach described above, the products of a metathesis reaction that used **166** were extracted with acetonitrile. Experiments showed good activity and recyclability for **166**. In all five cases studied, the substrates were completely converted to corresponding cycloalkene products by ring-closing metathesis (RCM). Catalyst **166** was recycled at least five times. The efficiency of this recycling was evaluated in RCM of 2,2-diallyl diethylmalonate. An average of 3% metal leaching was observed in the polar phase in each cycle. The

inefficiencies of recapturing the active Ru-methylidene catalyst generated from **166** were believed to be the main reason for the loss of Ru.



Polymer-bound hindered phosphine ligands **132** and **167** are useful for Pd-catalyzed coupling chemistry. They can be recycled both in a thermomorphic system, as discussed above, or by selective product extraction. Both ligands were most effective in Pd catalysis when the coupling of an aryl halide and phenylboronic acid was carried out in pure DMSO.²⁸⁴ While this single polar solvent phase gave the best yield in this cross-coupling chemistry, the use of a single solvent precludes a thermomorphic separation. These PEG-containing ligands might have been recoverable by solvent precipitation. However, Plenio's group found that these catalysts could be efficiently recycled through three to six cycles by selective extraction of the products with heptane. High yields were achieved for both aryl bromides and aryl chlorides. Kinetic data were obtained in catalytic reactions using ligand **132**. Aryl bromides were more reactive with TOFs of 500–1200 h^{-1} that were dependent on the aryl halide substituents. TOF numbers for aryl chlorides were less than 100 h^{-1} in most cases. After five or six cycles, slight decreases in TOFs were seen. The leaching of Pd in the product phase was below the detection limits of a colorimetric 4,4'-bis(dimethylamino)thiobenzophenone-based UV analysis for Pd.



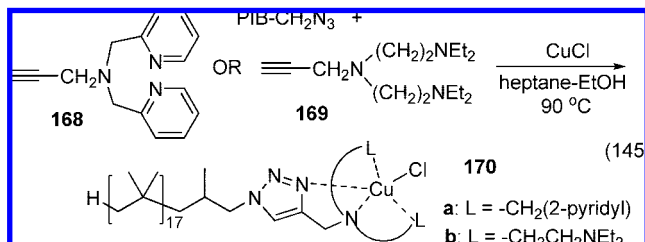
Most examples of soluble polymer-bound catalysts that are recoverable involve batch type reactions. An exception to this is the use of either **132** or **143** as a ligand for Pd in Sonogashira couplings (eqs 126 and 130 above). Both of these ligands have been used in a continuous reactor where solvent extraction served to separate a nonpolar product from a polar polymer-bound catalyst or vice versa. This liquid/liquid separation relied on density differences between the phase containing a polar polymer-bound Pd catalyst or a nonpolar polymer-bound Pd catalyst and the product phase to effect a continuous separation. In these two cases, the reactant was added in a nonpolar or polar phase and the product was continuously recovered from the upper less dense or lower more dense phase.²⁴⁶

3.2.6. Catalyst Recovery in Self-Separating Systems

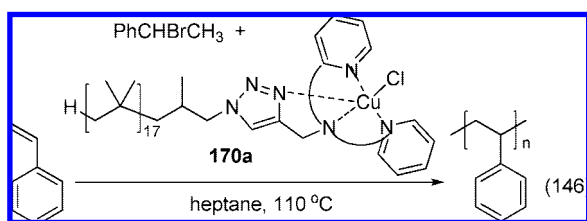
A third general way to use soluble polymers to facilitate catalyst recovery in liquid/liquid separations is similar in concept to latent biphasic chemistry. The difference is that, rather than perturbing a mixed solvent system with an additive, the formation of the products induces liquid/liquid biphasic formation. This is actually an old strategy that was

successfully used in the SHOP process.¹⁸² A recent report from our group where a soluble polymer is usefully used in this way is the use of the PIB-bound Cu(I) complexes in ATRP polymerization of styrene.²⁸⁵

In this report, the properties of the PIB polymer facilitate catalyst separation in two ways. First, the PIB-bound triazole catalyst was prepared in a mixture of heptane and EtOH from an azide-terminated PIB and an alkyne containing a chelating group for copper (**168** or **169**) using Cu catalysis (eq 145).²⁸⁶



After this copper assisted alkyne azide cyclization was complete, cooling produced a biphasic mixture and the polymer-bound chelated copper complex **170a** or **170b**. This copper complex was isolated as a heptane solution, and the heptane solution of **170a** was then used directly in a ATRP polymerization of styrene. This polymerization was carried out using an equimolar mixture of heptane and styrene with 1-bromo-1-phenylethane serving as an initiator (eq 146).



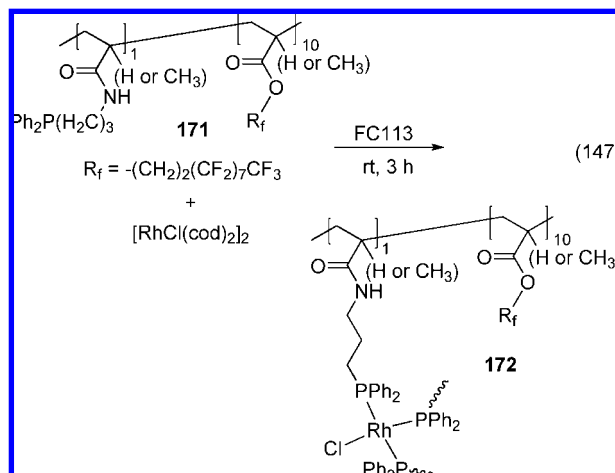
In this second polymerization step of this catalytic cascade process, the miscibility of this heptane/styrene solvent mixture changed as polystyrene formed because polystyrene is insoluble in heptane. Thus, when a polymerization like eq 146 was carried out at 110 °C to ca. 50% conversion and cooled, two phases formed, with the Cu catalyst **170a** being in the upper heptane phase and the colorless polystyrene being in the lower phase. Using this approach, catalyst **170a** was successfully recycled five times in a styrene polymerization. An average of 50% conversion achieved for each cycle with only ca. 3% of copper loss in the product was detected by ICP-MS. These results suggest that these copper catalysts and this approach should be useful in the synthesis and modification of other sorts of polymers if contamination of products by catalyst residue is of concern.

3.3. Fluorous/Organic Biphasic Catalysis

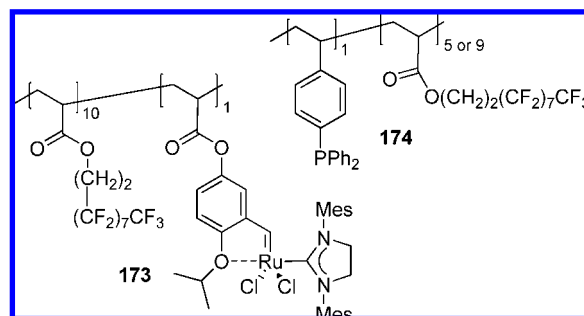
The concept of fluorous biphasic catalysis (FBS) was introduced by Horvath in 1990s²⁸⁷ and has become an attractive strategy to facilitate synthesis, as evidenced by several reviews in this issue of *Chemical Reviews*. Since this topic is being separately addressed, we have only briefly noted a few recent examples where soluble polymer-supported species are used to advantage in this sort of solvent system.

The attachment of phosphine ligands onto fluorinated polymer supports had previously been used in the synthesis of easily separated Rh catalysts for fluorous biphasic

catalysis.^{288,289} Similar fluoroacrylates containing alkyl-diarylphosphines bound as carboxamides (e.g., **171**) have also been used to form Rh complexes *in situ* [RhCl(cod)₂] in the fluorinated solvent FC113 to form the Rh catalyst **172** (eq 147). This catalyst was then used in hydroformylation and hydrogenation of alkenes in scCO₂.^{290–294} Catalyst recycling proved possible in this system, and a total of 20 cycles were carried out for the hydrogenation of 1-octene. No Rh was detected in the octane product by neutron activation analysis.



A second example where fluorinated polymer supports have facilitated catalyst reuse and separation is their use in olefin metathesis. Yao's group prepared a metathesis catalyst **173** with a Grubbs–Hoveyda Ru complex as a pendant group on a fluorinated acrylate similar to **171**. They then used the polymer-bound catalyst **173** in ring closing metathesis of 1,6- and 1,7-diene substrates in a mixture of PhCF₃ and CH₂Cl₂ (1:19, v/v) at 50 °C.²⁹⁵ They noted that this catalyst could be completely recovered by a postreaction extraction with a fluorinated solvent (FC72) due to its excellent solubility in fluorous solvents. High conversions and recyclability of **173** through 20 reaction cycles were observed.



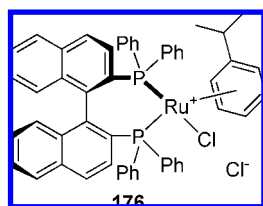
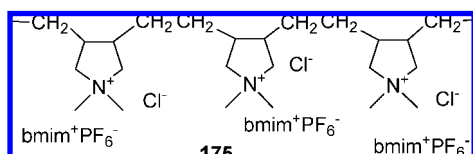
Fluorinated polymers containing a phosphine ligand have also been directly prepared by free radical copolymerization of styryldiphenylphosphines with fluoroacrylate monomers.²⁹⁶ When the product polymer **174** was allowed to react with [Rh(CO)₂(acac)] in a hexane–toluene–perfluoromethylcyclohexane (40:20:40, vol) solvent mixture, a Rh(I) catalyst that was formed *in situ* was then used in hydroformylation. In this case, the reaction was carried out under monophasic conditions at 50 °C. Cooling separated the fluorous catalyst phase and organic product phase. This sort of thermomorphic approach to fluorous catalysis was first noted by Horvath in his original description of fluorous chemistry.²⁸⁷ Compared

to other aqueous soluble polymer supported Rh catalysts, higher activity (TOF 136 h⁻¹) and regioselectivity (99%) were observed in the hydroformylation of 1-decene using a Rh catalyst ligated by the polymeric phosphine ligand **174**. However, catalyst recycling in this case proved to be problematic. These problems arose not because of catalyst loss or deactivation but mostly because of the continuous loss of the fluoruous phase into the organic solvents over three cycles.

3.4. Polymer-Supported Catalysts in Ionic Liquids

Ionic liquids (ILs) are of increasing interest as alternative solvents for chemical reactions in both academia and industry.^{187,188,297} These interesting materials have been used since the 1990s in commercial processes because they facilitate product catalyst separations.²⁹⁸ Soluble polymeric materials have been used in this context too.

The most common use of higher molecular weight materials in ILs chemistry is their use as insoluble supports for supported ionic liquid phases (as SILs).^{299–304} However, soluble polymers have attracted some attention too. An example of this is work by Wolfson and co-workers where a polymer supported IL-phase was formed by mixing an IL (1-butyl-3-methylimidazoliumhexafluorophosphate, $\text{bmim}^+\text{PF}_6^-$) with a soluble polyelectrolyte, poly(diallyldimethylammonium chloride).³⁰⁵ Hydrogenations of 2-cyclohexen-1-one and 1,3-cyclooctadiene with $(\text{PPh}_3)_3\text{RhCl}$ under biphasic conditions with this mixed ionic liquid **175** were faster (TOF = 9 and 14 h⁻¹, respectively) than analogous hydrogenations with the same catalyst using a biphasic mixture of $\text{bmim}^+\text{PF}_6^-$ and diethyl ether (TOF = 2.7 and 5.9 h⁻¹, respectively). Asymmetric hydrogenation of methyl acetoacetate with BINAP-Ru catalyst (**176**) likewise was faster too. A biphasic mixture of *i*-PrOH and the polymer-supported IL **175** containing the Ru catalyst formed product with 97% ee and with a TOF of 29 h⁻¹ while the same BINAP-Ru catalyst only had a TOF = 16 h⁻¹ with $\text{bmim}^+\text{PF}_6^-$ alone. In both cases, catalysts in the reactions using the ionic liquid phase **175** were reused twice with no change in activity or stereoselectivity. Atomic absorption spectroscopic analyses did not detect any leached rhodium or ruthenium in the organic product phases.



4. Conclusions

Soluble polymer supports are becoming more commonly used in catalysis. A variety of liquid/solid and liquid/liquid techniques can be used with soluble polymer-supported

species to facilitate the recovery, separation, and reuse of homogeneous catalysts. While leaching is still a problem in many cases, the best cases show by detailed analyses that it is possible to effect essentially quantitative catalyst recovery of a catalyst with a soluble polymer support. Soluble polymer-bound analogs of low molecular weight catalysts often have the same reactivities and selectivities as their low molecular weight counterparts. Most types of ligands and many types of catalysts have also been attached to one or another type of polymer. Future work should extend the scope of such processes such that soluble polymers will be able to be used to facilitate any sort of homogeneously catalyzed process. However, while there has been considerable progress in this area, some general problems remain. First, while separation processes exist for most soluble polymer supported catalysts, these processes are not always efficient in terms of the amount of solvent used or in terms of the mass of catalyst used relative to the mass of product formed. Second, while separation processes can be designed that recover a soluble polymer-bound catalyst or ligand, catalyst or ligand degradation that is not apparent in a single catalyst cycle often is a problem in multiple catalyst cycles. Third, while much is known about how a soluble polymer might or might not affect a catalyst's activity, the effects of temperature and solvent on catalyst reactivity still can vary depending on the polymer in ways that are still not completely understood. Fourth, most of the work to date has focused on a relatively small number of polymers and a limited number of ligands. Other polymers and other metal binding schemes merit more study, since such studies could easily make separations more economical, make catalysts more robust, or minimize the effects of metal leaching. Finally, relatively little effort has been made to employ the properties of a polymer to affect a reaction. Polymers have been mostly used as phase anchors for a catalyst or ligand, and clever ways to use a polymer's solubility, polyvalency, or properties should also be useful in facilitating catalytic reactions.

5. Acknowledgments

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