Polymer-supported catalysis in synthetic organic chemistry

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Contents

1. Introduction

From the perspective of the organic chemist, the relevance of polymers has changed and evolved dramatically over the past half century. From their early use in peptide and oligosaccharide synthesis[1] to the more recent preparation of small, organic molecule libraries,[2] polymers have been used to aid in reaction manipulation and product isolation. Accordingly, the pharmaceutical industry has taken full advantage of this technology to expedite the identification of potential drug candidates. Since the preparation of compounds on solid support inherently requires two non-diversity-building steps (i.e. attachment and cleavage), it is sometimes preferable to prepare parallel libraries in the solution-phase. Nevertheless, polymers have still found a niche as supports for reagents, scavengers and catalysts to aid in the purification of solution-phase libraries.[3] This review will focus on the use of polymer-supported catalysts as applied to organic synthesis with emphasis given to the use of chiral catalysts to promote asymmetric reactions. A number of classes of organic transformations is presented, including oxidation, reduction, addition, cycloaddition, and transition metal-catalyzed carbon–carbon bond-forming reactions.

2. Oxidation catalysts

The growth of resin-bound oxidation catalysts has been tremendous in the past decade. This has provided the

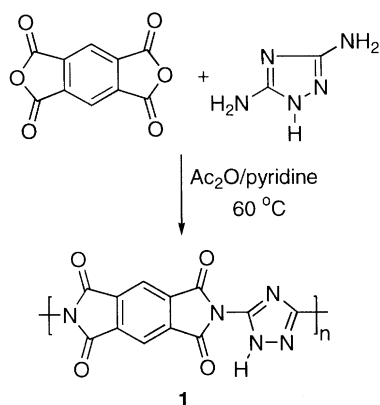* Corresponding author. Fax: +1-858-784-2595; e-mail: kdjanda@scripps.edu

Figure 1.

chemist with a vast array of new methodologies convenient for organic synthesis. This section will compile the many general oxidation catalysts that are available as well as the more recent development of chiral catalysts for asymmetric dihydroxylation and epoxidation.

2.1. General oxidation

Sherrington has utilized the suspension polycondensation technique to prepare functional polyimide beads that were used as supports for molybdenum alkene epoxidation catalysts.[4] Thus, reaction of pyromellitic dianhydride with 3,5-diamino-1,2,4-triazole produced the polyimide support **1** (Fig. 1). This was then loaded with Mo(VI) and utilized as a catalyst in the epoxidation of cyclohexene with *tert*-butyl-hydroperoxide (TBHP) as the oxidant. High yields (generally >80%) were obtained for cyclohexene oxide and the catalyst could be used for 10 cycles with little or no deactivation.

Another group has utilized a macroporous methacrylate-based resin, which contained pendant dithiocarbamate groups that coordinate vanadium, as a catalyst for the oxidation of phenols to quinones.[5] In the presence of TBHP, the polymer-bound vanadium complex forms a peroxo species that effectively carries out the transformation. 2-Methyl-and 2,6-dimethyl-phenol were converted into the corresponding benzoquinones in 75% and 70% yield, respectively, and the catalyst could be used for five cycles with only marginal reductions in yield (Fig. 2).

Ley and co-workers have developed a supported variant of the TPAP catalyst that is often used in synthetic ventures for the mild conversion of primary alcohols to aldehydes. The polymer-supported perruthenate (PSP) catalyst was
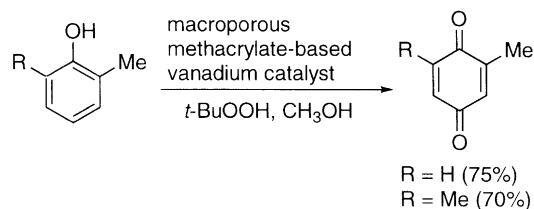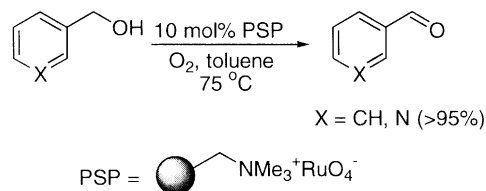

Figure 2.

Figure 3.

prepared by the reaction of Amberlyst A-26 resin with $KRuO_4$.[6] The use of the polymeric catalyst in combination with molecular oxygen as the stoichiometric oxidant is an excellent example of green technology and provided the expected products free of any contaminants. In this way, cinnamyl alcohol, benzyl alcohol, and 3-pyridine methanol were all oxidized to the corresponding aldehydes in greater than 95% yield (Fig. 3). The catalyst was also shown to be selective for the oxidation of primary alcohols in the presence of secondary alcohols.

Friedrich has used poly(4-vinylpyridine)-supported sodium ruthenate as a recoverable catalyst for alcohol oxidation chemistry.[7] Tetrabutylammonium periodate was found to be the most effective stoichiometric oxidant for this catalyst. Using this methodology, cinnamyl alcohol, crotyl alcohol, cyclohexanol, furfuryl alcohol, geraniol, 1-hexanol, 2-hexanol, and 4-nitrobenzyl alcohol were all oxidized to the expected aldehydes or ketones in 90% yield or greater (Fig. 4).

The use of a TEMPO–bleach combination has been shown to be highly effective for the large-scale oxidation
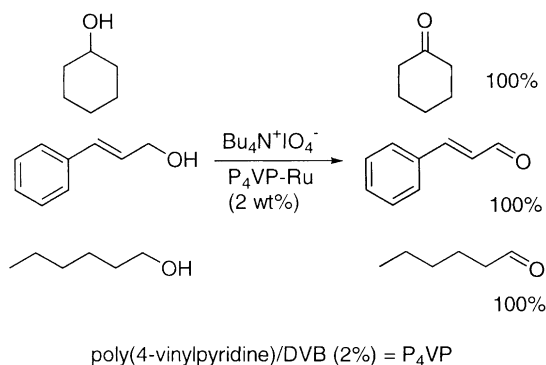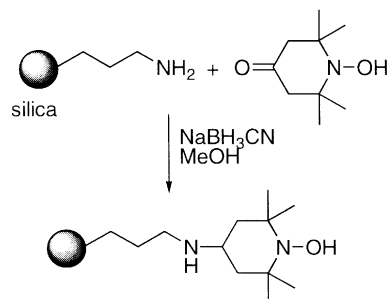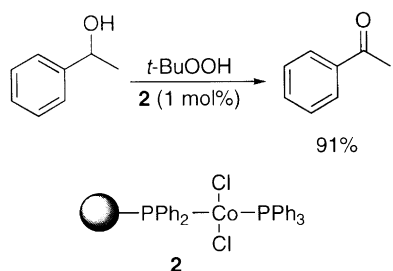

Figure 4.

Figure 5.

Figure 6.

of alcohols to carbonyl compounds. Bolm has prepared a supported version of TEMPO and used it for the oxidation of primary and secondary alcohols to aldehydes and ketones.[8] The catalyst was synthesized in one step by the reductive amination of aminopropyl-functionalized silica support with 1-hydroxy-4-oxo-2,2,6,6-tetramethyl piperidine (Fig. 5). The model oxidation of 1-nonanol to 1-nonanal proceeded in 85% isolated yield and remained constant over ten uses of the catalyst.

Two recent reports have described the use of polymer-supported triphenylphosphine (PS-PPh₃) as a ligand for metal-based oxidation catalysts. In one example, PS-PPh₃ was coordinated with a cobalt(II) source to form an immobilized complex **2** that was used for the oxidation of alcohols to carbonyl compounds.[9] The conversion of 1-phenylethanol to acetophenone occurred in 91% yield in the presence of TBHP and **2** and remained constant for five uses of the supported catalyst (Fig. 6). It was also shown that the complex is an effective catalyst for the preparation of anhydrides from acid chlorides and carboxylic acids.

Jun and co-workers have demonstrated the use of PS-PPh₃ in conjunction with RhCl₃ for the catalytic hydroacylation of terminal alkenes.[10] Reaction of benzyl alcohol with 1-hexene in the presence of RhCl₃ (5 mol%), PPh₃

(5 mol%), PS-PPh₂ (15 mol%), and 2-amino-4-picoline (1 equiv.) resulted in the formation of heptanophenone in 69% yield (Fig. 7). The catalyst, a polystyrene-based diphenylphosphine Rh(I) complex formed in situ, was used for three additional cycles with no loss of activity.

The preceding examples serve to highlight the general polymer-bound oxidation catalysts that have been developed in recent years. As these types of catalysts are generally not prohibitively expensive, the validation for their attachment to solid support lies in the simplified purification procedures and minimization of waste streams that are inherent with this chemistry. It seems likely that supported oxidation catalysts will see continued use in traditional synthetic organic chemistry as well as in high-throughput technologies.

2.2. Asymmetric dihydroxylation

The asymmetric dihydroxylation (AD) of alkenes catalyzed by OsO₄ and *Cinchona* alkaloid derivatives has proven to be a very important and effective method for the stereoselective incorporation of oxygen into organic molecules.[11] In an attempt to improve the convenience and economy of this reaction, efforts have been made by many to develop polymer-supported alkaloid ligands and osmium complexes, as these are the two most expensive components of the reaction. The examples described herein are not meant to be an exhaustive account of all the efforts put forth in this area but a compilation of some of the more important advances.[12]

Sharpless described the first example of a supported alkaloid ligand for asymmetric dihydroxylation.[13] The most effective catalyst proved to be the poly(acrylonitrile)-derived polymer **3** (Fig. 8) which afforded the diol of *trans*-stilbene in 96% yield and 87% enantiomeric excess (ee) (Fig. 9, entry 1) when potassium ferricyanide was utilized as a secondary oxidant with catalytic OsO₄.

Figure 7.

3
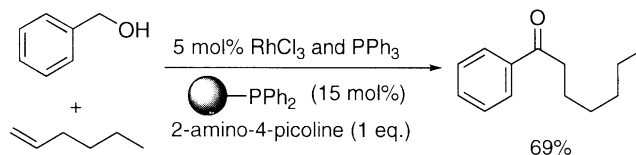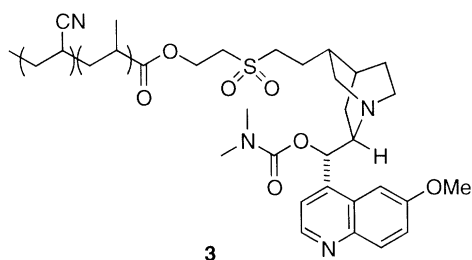
Figure 8.

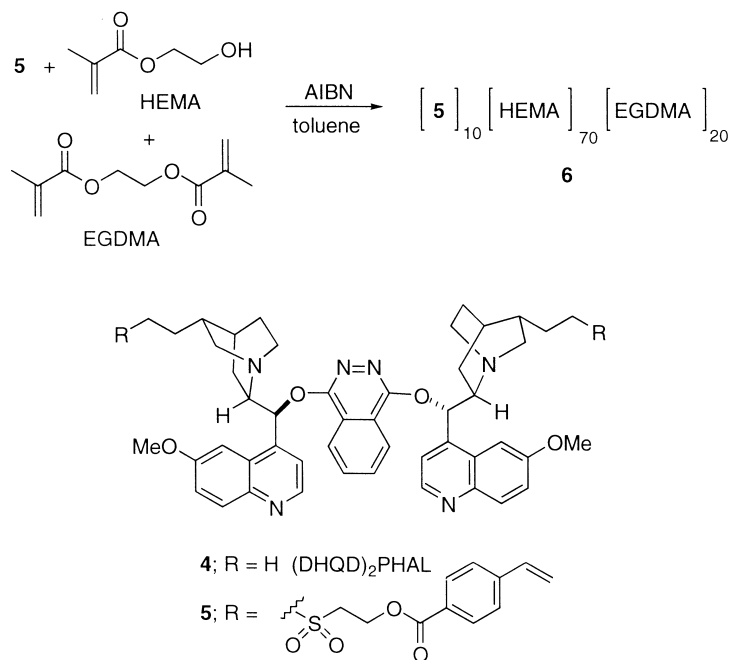| olefin	entry	polymeric alkaloid	isolated yield (%)	diol ee (%)
Ph〜Ph	1	**3**	96	87
	2	**6**	90	99
Ph〜	3	**6**	86	91
Ph⟨	4	**6**	88	94
Ph-⬡	5	**6**	85	97

Figure 9.

Figure 10.

Salvadori and co-workers have published a series of papers in which various features of the polymer-supported alkaloid ligand have been systematically optimized.[14] The most important aspects of the catalyst were found to be the nature of the polymer support, the distance of the ligand from the polymer backbone, and the substitution at the C-9 oxygen functionality.

Supports ranging from poly(acrylonitrile), polystyrene–divinylbenzene, and poly(hydroxyethyl methacrylate) (HEMA)– ethylene glycol dimethacrylate (EGDMA) were examined. The first two supports ultimately led to low or modest enantioselectivity in the dihydroxylation reaction. This was attributed to the poor swelling properties of the polymer in the reaction medium (an acetone/water or tBuOH/water mixture). The polymeric catalysts derived from the HEMA–EGDMA combination, however, swelled sufficiently under the reaction conditions due to the pendant alcohol groups, and use of this support generally gave the highest enantioselectivities. It was also discovered that a spacer group should be present between the alkaloid moiety and the polymer chain to allow free, unimpeded complexation of OsO_4 and alkene to the ligand. A chain of six or seven atoms was usually sufficient for this purpose. In the original report by Sharpless on solution-phase asymmetric dihydroxylation, the C-9 oxygen of the dihydroquinidine (DHQD) or dihydroquinine (DHQ) cinchona ligand was capped as its 4-chlorobenzoate ester. Since that time, over 300 different ligands have been screened as catalysts for the AD reaction. The ligand of choice that emerged from the early work by Sharpless contains two cinchona moieties linked by a central phthalazine (PHAL) unit and this core unit has also found success when bound to a polymer support. Thus, Salvadori prepared ligand **5**, which incorporates a polymerizable styrene unit linked to the alkaloid portion by a sulfone-containing tether (Fig. 10). Monomer **5** was co-polymerized with HEMA and EGDMA in a

10:70:20 molar ratio, respectively, to provide the desired polymer-supported ligand **6**.

The use of **6** (25 mol%) in combination with potassium ferricyanide and OsO_4 (~1 mol%) in the dihyroxylation of a number of olefins provided very encouraging results. As indicated in Fig. 9, mono-, di-, and trisubstituted olefins underwent AD in good yield and with excellent enantioselectivity. Noteworthy is the >99% ee obtained for the dihydroxylation of *trans*-stilbene. These results could be duplicated for five cycles with fresh addition of a small amount of osmium before each catalyst reuse.

The progress in this area of research has been extraordinary. With the proper combination of polymer support and ligand structure, enantioselectivities equal to that of the soluble ligand can be obtained. Other important contributions to this area of research not included here, but still worthy of mention, include the soluble polymer-supported *Cinchona* ligands of Janda[15] and Bolm[16] and the use of microencapsulated osmium tetroxide by Kobayashi.[17]

2.3. Sharpless epoxidation

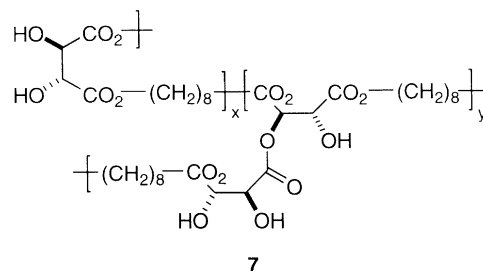Efforts have been undertaken to develop heterogeneous

Figure 11.

Figure 12.

Figure 13.

catalysts for the Sharpless asymmetric epoxidation reaction. Sherrington and co-workers have been the major contributors to this area and their efforts have focused on the incorporation of a chiral tartrate ester within a polymeric framework.[18]
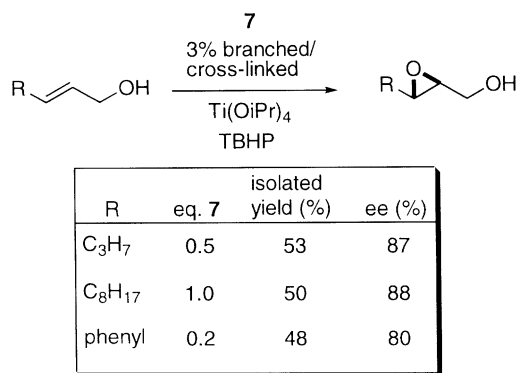
The motivation for this work lies mainly in the simplified isolation of the enantioenriched products free of the supported catalyst since, for this reaction, the chiral solution-phase catalysts (i.e. diisopropyl tartrate or diethyl tartrate) are relatively inexpensive.

The most effective polymeric tartrate derivative **7** is shown in Fig. 11 and was prepared by the reaction of L-(+)-tartaric acid with 20% excess 1,8-octanediol under p-toluenesulfonic acid (3 wt%) catalysis. The degree of branching varied with each preparation of **7** but generally ranged from 3% to 15%. This polymeric catalyst was not soluble in the reaction medium, CH₂Cl₂, and could be filtered to afford high recoveries.

The results in the epoxidation of three allylic alcohols utilizing **7**, Ti(O*i*Pr)₄, and *tert*-butylhydroperoxide are illustrated in Fig. 12.[18b] Each reaction was carried out at −20°C with reaction times ranging from 6 to 12 h. In some cases, excellent enantioselectivities of epoxide product were obtained, however, the isolated yields were fair to moderate. Additionally, high loadings of polymeric tartrate (20–100 mol%) were required and no discussion of its reuse was included.

2.4. Jacobsen asymmetric epoxidation

The Jacobsen epoxidation has recently emerged as a useful method for the asymmetric oxidation of unfunctionalized olefins, although the best results are usually achieved with *cis*-disubstituted alkenes.[19] Given the popularity of the reaction, a number of groups has examined methods of incorporating the active (salen)Mn(III) complex onto a heterogeneous organic polymer support as a means to recycle the chiral catalyst. Two strategies have emerged for the preparation of these polymer-bound catalysts: (1) co-polymerization of a functionalized salen monomer into an organic polymer; and (2) direct attachment or stepwise build-up of a salen structure to a preformed polymer. Although some success has been achieved in preparing active catalysts that deliver high enantioselectivities, problems associated with ligand decomposition have limited their recyclability.
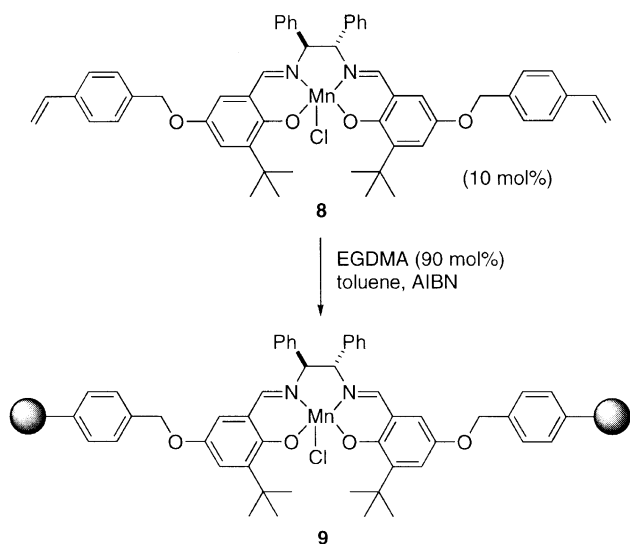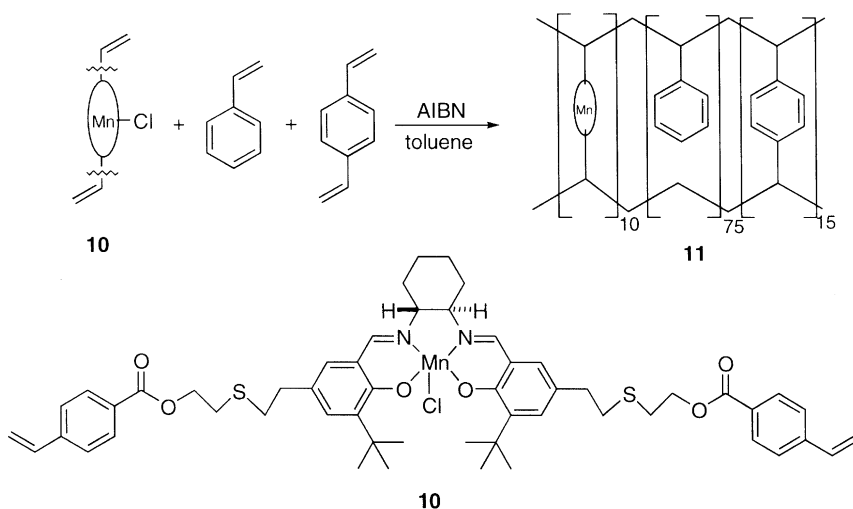

Figure 14.

In the first example of a polymer-supported Jacobsen catalyst, Dhal and co-workers polymerized salen monomer **8** with EGDMA in a ratio of 10:90 to give the functionalized macroporous polymer **9** (Fig. 13).[20] The use of **9** as a catalyst in asymmetric epoxidation reactions provided disappointing results. Although the chemical yields for epoxides were adequate (55–72%) for some substrates, the best ee obtained was 30% for dihydronaphthalene. The epoxidation of styrene gave nearly racemic styrene oxide. Nevertheless, the author indicated that the catalyst could be used for five cycles with only minor loss of activity.

After this first report, Salvadori and co-workers disclosed a similar approach in which monomer **10** was co-polymerized with styrene and divinylbenzene in a ratio of 10:75:15, respectively, to yield a macroporous polystyrene-based polymer **11** (Fig. 14).[21] It was anticipated that the greater conformational freedom of the salen moiety in **11** (as compared to **9**) as well as the different polymer matrix would result in greater enantioselectivity. Although styrene oxide was produced with an ee of only 16%, the epoxides of *cis-β*-methylstyrene and indene were formed in 62% and 60% ee, respectively. Also noteworthy is that reaction times were less than one hour in most cases and yields were usually greater than 90%.

These first two examples both utilize approaches in which the salen unit is localized at a cross-link. This may have an adverse effect on selectivity due to steric crowding and conformational rigidity. Therefore, Sherrington[22] and Laibinis[23] both independently described methods where a salen unit was constructed in a pendant, stepwise manner on a preformed polymer. In the work by Sherrington, the most effective polymer-supported catalyst was **12**, in which the support was a porous methacrylate-based resin (Fig. 15).[22a,c] In the asymmetric epoxidation of phenylcyclohexene, an ee of 91% was obtained. This value compares favorably with the 92% ee obtained using the analogous, soluble Jacobsen catalyst. The low loading (0.08 mmol/g) of manganese sites
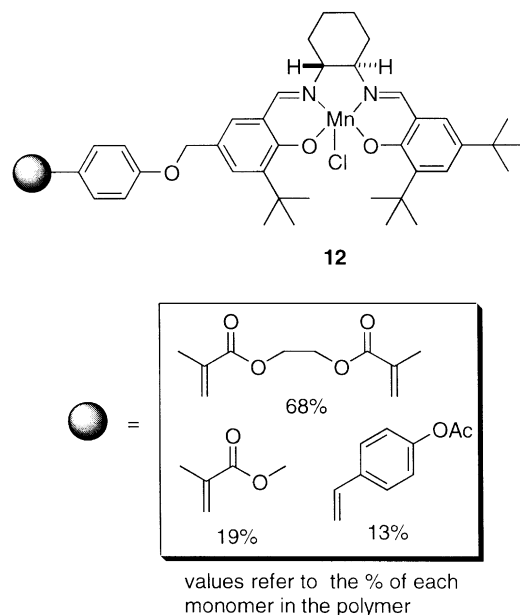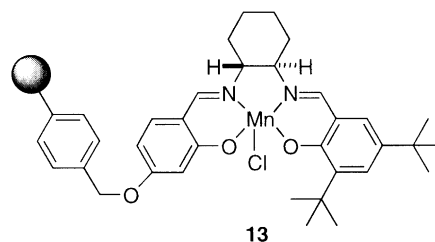

13

Figure 16.

as well as the high surface area of the resin was thought to be the key factors for this result. No discussion of the reusability of this catalyst was given in the paper.

As alluded to previously, Laibinis used a similar strategy for the preparation of the supported oxidation catalyst.[23] Thus, Merrifield resin was subjected to a four-step sequence to produce the supported catalyst **13** (Fig. 16). The asymmetric epoxidation was carried out under biphasic conditions using NaOCl as the oxidant. The isolated yield and enantiomeric excesses (ee's) for the epoxides of three substrates, styrene (7% yield, 9% ee), *cis-β*-methylstyrene (2% yield, 79% ee), and dihydronaphthalene (42% yield, 46% ee) were modest. It was also noted that reuse of the catalyst was unsuccessful as enantioselectivities dropped significantly upon catalyst recycle. A series of studies was undertaken by this group to determine the cause of catalyst deactivation. Attempted reloading of manganese to the ligand did not restore catalytic activity and it was ultimately found that fracture of the imine portion of the salen framework was at least partly responsible for its degradation.

In Janda's approach to a resin-bound (salen)Mn catalyst, an unsymmetrical salen ligand was attached to a polymer through a glutarate spacer to provide **14** (Fig. 17).[24a] In this instance, the polymer was prepared from styrene and a polytetrahydrofuran-derived cross-linker to form beads that swell to a great extent in common organic solvents.[24b] The five-carbon linker between the polymer and ligand was utilized to place the catalyst sufficiently away from the polymer backbone and allow unimpeded access of the olefinic substrate to the active metal center. When *m*-CPBA was employed as oxidant, the asymmetric epoxidation of styrene and *cis-β*-methylstyrene proceeded in good yield and with ee's (51% and 88%, respectively) nearly equivalent to those achieved using the commercial, homogeneous Jacobsen catalyst. This supported catalyst could be used up to three times without a significant loss of activity; however, as with the study by Sherrington[22] and Laibinis,[23] a gradual degradation of the salen ligand was unavoidable.
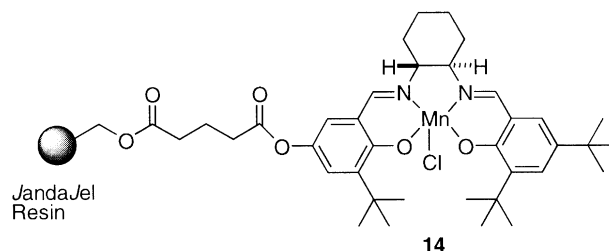

12

values refer to the % of each monomer in the polymer

Figure 15.

14

Figure 17.

Figure 18.

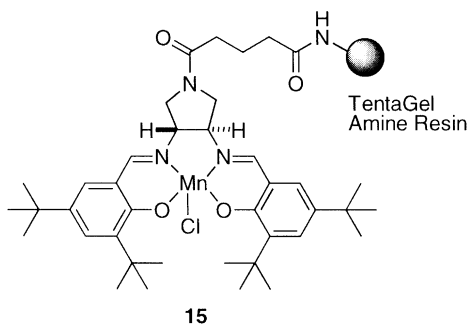**Figure 20.**

In a very recent report, Song has reported the preparation and use of the supported (pyrrolidine–salen)Mn complex **15** (Fig. 18).[25] The catalyst was linked to TentaGel resin through the nitrogen atom of the pyrrolidine ring. This allows both aromatic rings of the ligand to be fully substituted with *t*-butyl groups in the same manner as the solution-phase catalyst. Using *m*-CPBA or NaOCl as the oxidant and 4 mol% catalyst, 2,2-dimethylchromene, 6-cyano-2,2-dimethylchromene, and phenylcyclohexene all underwent asymmetric epoxidation in greater than 70% yield and with ee's of 92%, 86%, and 68%, respectively. No attempts to recycle the catalyst were reported; however, decoloration of the catalyst was taken as an indication of decomposition.

The examples illustrated here show the progression of ideas for the incorporation of salen catalysts into a polymer support. Although some high enantioselectivities have been realized, ligand degradation has limited their recycling. It is clear that there exists a delicate balance between reaction conditions and the structure of the polymer-supported catalyst. Further optimization of the polymer and catalyst structure as well as the epoxidation conditions are necessary for continued progress in this field.

Grubbs was one of the first to report the use of a polymer-supported catalyst for hydrogenation. Here, diphenylphosphinomethyl polystyrene was incubated with tris(triphenylphosphine)rhodium(I) chloride for 2–4 weeks to give the supported equivalent of Wilkinson's catalyst **16** (Fig. 19).[26] This was then used for the hydrogenation of a series of alkenes, providing reaction rates close to those seen in solution. In addition, the catalyst could be recovered and reused for at least ten reactions without loss of activity.

Stille and co-workers have also carried out much of the groundbreaking research of asymmetric hydrogenation and hydroformylation reactions using polymer-supported catalysts. Examples of some of the polymer-supported ligands, which are derived from various natural sources, are illustrated in Fig. 20.[27] These ligands (**17**–**19**) have been used in conjunction with an array of different metals and have been shown to effect a host of different reactions, including asymmetric reduction of dehydroamino acids to amino acids and α,β-unsaturated acids to acids as well as the hydroformylation of alkenes to chiral aldehydes. Stille has also demonstrated the benefit of having chiral pendant functionality within the polymer support of the catalyst to give improved enantioselectivity of products. This work has been reviewed in great detail and will not be discussed further.[28]

3. Reduction catalysts

3.1. Hydrogenation and hydroformylation

Reduction reactions and, more specifically, hydrogenation reactions often rely on the use of transition metal catalysts to effect their outcome. In addition, the ligands required to effect asymmetric versions of these reactions can be expensive to purchase or produce. Thus, many polymer-supported reduction catalysts that can potentially be recycled have been developed. Generally, these catalysts have been prepared by attachment of a ligand to the polymer followed by incubation of the supported ligand with an appropriate metal source.
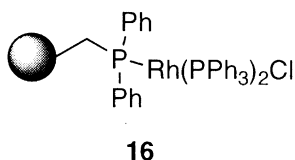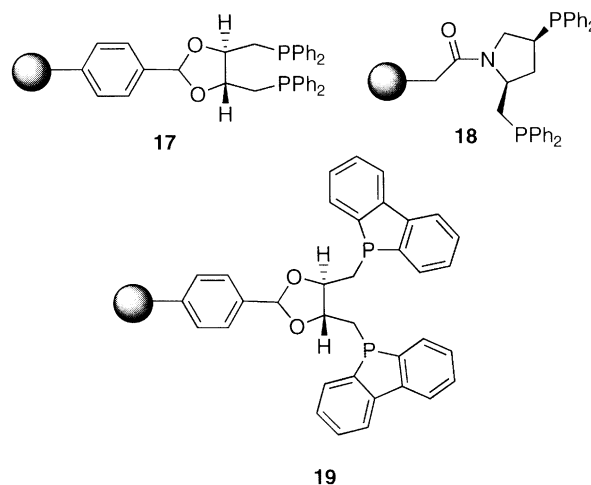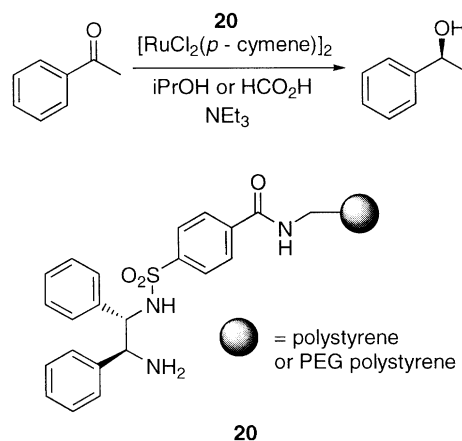

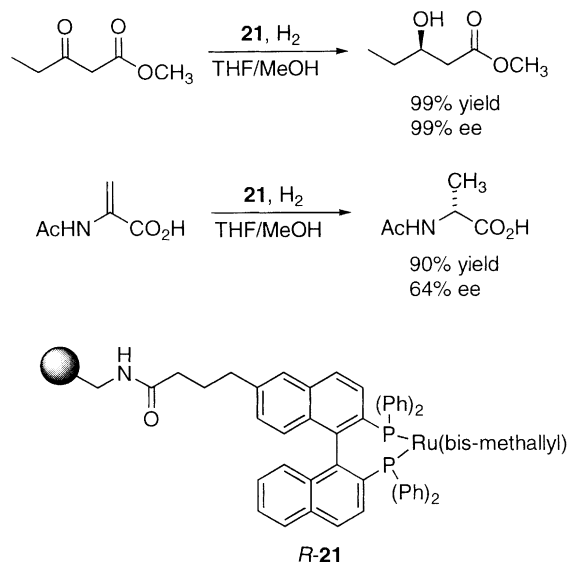**16**

Figure 19.

Figure 21.

Figure 22.

Nyori's chrial *N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenedi-amine ligand has seen great acclaim for the asymmetric reduction of aryl ketones, alkynyl ketones, and imines. Oxford Asymmetry International has recently reported the preparation of a polymer-supported version of Nyori's ligand and its subsequent application in the catalytic transfer hydrogenation of aryl ketones.[29] Here, the solution-phase sulfonamide ligand was attached to both aminomethyl poly-styrene and TentaGel to give the supported ligand **20** (Fig. 21). The active catalyst was then generated by incubation of the polymer-supported ligand with [RuCl$_2$(*p*-cymene)]$_2$. The transfer hydrogenation of acetophenone to 1-phenyl-ethanol using formic acid and triethylamine as solvent was used to establish optimum reaction conditions. It was found that the conventional polystyrene-supported catalyst required a co-solvent to give sufficient resin swelling to allow catalytic activity. Yields and ee's comparable to those achieved with the solution-phase catalyst were obtained. The catalyst was shown to be effective for three cycles, after which its activity decreased dramatically.

Oxford Asymmetry International has also reported the

synthesis and application of a polymer-supported BINAP hydrogenation catalyst.[30] A carboxylic acid-functionalized BINAP derivative was first linked to aminomethyl polysty-rene. Subsequent reaction with (COD)Ru(bis-methylallyl) and HBr in acetone provided the catalyst **21** (Fig. 22). The catalyst was shown to be highly effective for the asymmetric reduction of β-ketoesters to β-hydroxy esters and moder-ately selective for the reduction of dehydroamino acids to the saturated amino acid product. Each product was obtained in high yield with less than 1% contamination of leached ruthenium. Finally, catalyst reuse was successful with only slight loss of activity.

Chan has described the preparation of the soluble, linear polymeric BINAP derivative **22**, which was prepared from the condensation of 5,5'-diamino-BINAP, terphthaloyl chloride, and (2*S*,4*S*)-pentane diol.[31] The active catalyst was prepared in situ by mixing **22** with [RuCl$_2$(*p*-cymene)]$_2$. The utility of the catalyst was demonstrated in the asym-metric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid, the direct precursor to the anti-inflammatory drug Naproxen (Fig. 23). In the event, Naproxen could be obtained in nearly quantitative yield in up to 93% ee. The catalyst was recovered by precipitation of the reaction into methanol and reused for ten cycles with no loss of activity. Interestingly, this catalyst gave a superior rate of conversion compared to the conventional BINAP catalyst. This was attributed to the presence of large polyester chains on the BINAP ligand which alter its dihedral angle in such a way to increase reactivity.

Lemaire has also described the preparation of linear, poly-meric BINAP catalysts that were used in the asymmetric hydrogenation of ketones and α,β-unsaturated acids and esters.[32] Bis-aminomethylated BINAP was condensed with 2,6-diisocyanatotoluene to give the polymeric ligand. Incu-bation with a ruthenium(II) source gave the supported Ru–BINAP complex **23**, which was isolated before use (Fig. 24). The reduction of 2'-acetonaphthone occurred in 96% ee with 100% conversion.[32a] Additionally, dimethyl itaconate was reduced to the saturated product in 94% ee and 100% conversion.[32b]

Polymer-supported DMAP was shown to react with Rh$_6$(CO)$_{16}$ to form supported rhodium carbonyl clusters.[33]

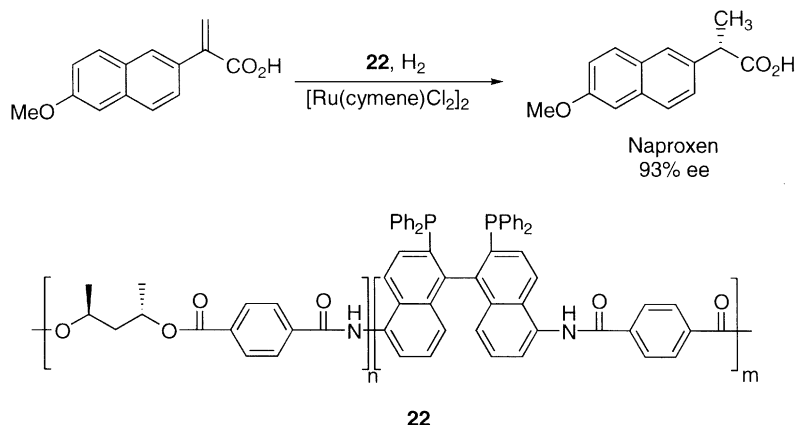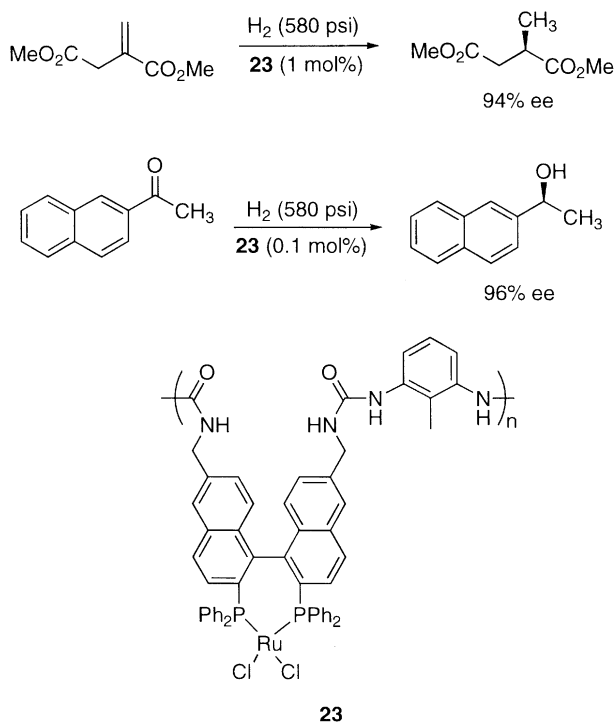**Figure 23.**

Figure 24.

Figure 25.

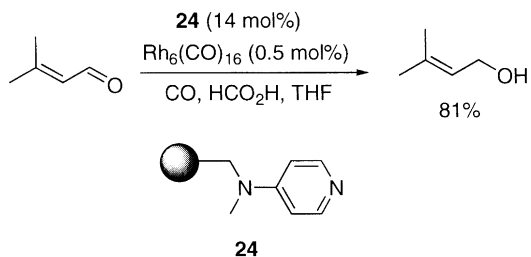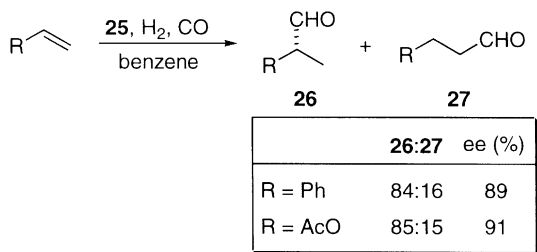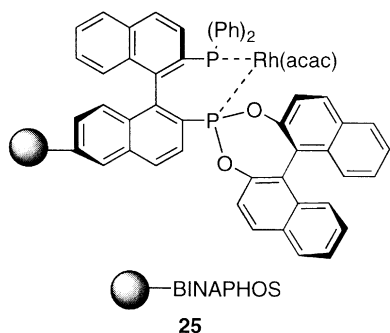|	26:27	ee (%)
R = Ph	84:16	89
R = AcO	85:15	91

Figure 26.

These were shown to be effective catalysts for the reduction of α,β-unsaturated aldehydes to the corresponding allylic alcohols. One particular example is shown in Fig. 25. Significantly, in this case, less than 1% of the saturated, over-reduced product was formed and the catalyst could be recycled for multiple uses.

Nozaki has recently reported a polymer-supported rhodium phosphine-phosphite (R,S)-BINAPHOS complex that was effective for the asymmetric hydroformylation of olefins.[34] A monomeric BINAPHOS was co-polymerized with 55% divinylbenzene/ethylstyrene to produce the highly cross-linked, functionalized polymer **25**. After conversion to the corresponding Rh(I)(acac) complex, the catalyst was used in the hydroformylation of styrene and vinyl acetate to produce the desired branched aldehydes in high ee and yield (Fig. 26). Nearly identical results were obtained when the catalyst was prepared by polymerization of a preformed Rh–BINA-PHOS monomer complex.

A polymer containing dendritic phosphine appendages was also shown to be effective for the hydroformylation of styrene and vinyl acetate.[35] After complexation with a rhodium(I) source, the dendritic catalyst **28** was used in hydroformylation reactions. The branched aldehyde product was formed in good yield and with high selectivity over the linear product. The catalyst could also be used for five cycles with no drop in the conversion. The second-generation catalyst (**28**, eight phosphine ligands) (Fig. 27) was much more active than the first generation dendrimeric catalyst (four phosphine ligands). This was loosely attributed to better exposure of the catalytic sites and/or cooperativity
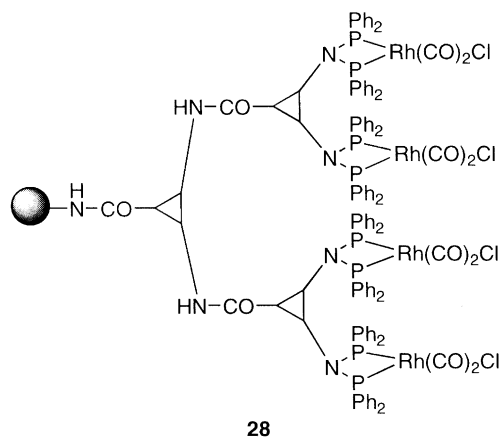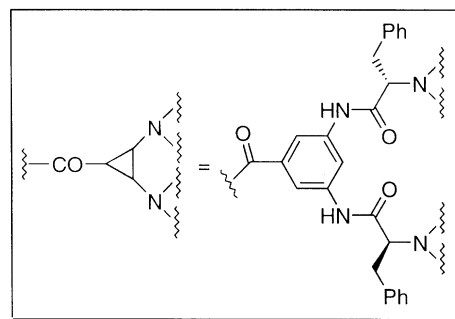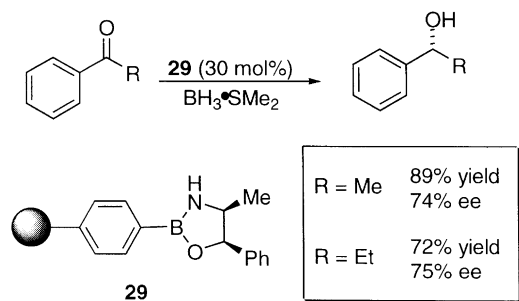

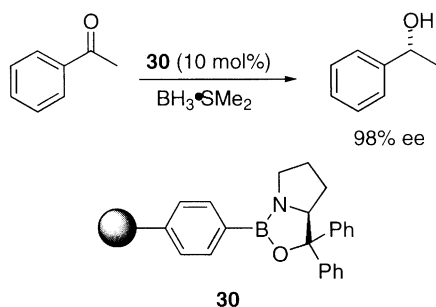**Figure 27.**

Figure 28.

Figure 29.

effects caused by the close proximity of the ligands on the dendrimer surface.

3.2. Oxazaborolidine catalysts

Caze, Hodge, and co-workers have reported the enantio-selective borane reduction of ketones in the presence of a polymer-bound oxazaborolidine catalyst.[36] The catalyst **29** was prepared by condensation of the known resin-bound boronic acid with a chiral 1,2-amino-alcohol. The reduction of acetophenone and propiophenone using borane–dimethylsulfide complex and **29** was investigated to establish optimum reaction conditions (Fig. 28). High yields and good ee's were obtained for the secondary alcohol products and the catalyst could be reused at least three times with no decrease in yield or enantioselectivity.

In related work, Franot and Stone utilized the oxazaboro-lidine catalyst **30** in the enantioselective reduction of aceto-phenone.[37] In the presence of borane–dimethylsulfide complex and **30**, the chiral secondary alcohol was obtained in high ee (Fig. 29). The catalyst provided consistent results in a second cycle; however, its third use led to an enantio-selectivity decrease of nearly 20%. This was attributed to the reaction quench process which was thought to partially hydrolyze the catalyst. In the work by Hodge and Caze, the quench was performed on the organic solution after fil-tration of the polymeric catalyst.[36] Therefore, the catalyst could be used for a longer period of time without under-going hydrolysis. Clearly, any comparison of results from different catalyst systems requires close examination of all the reaction parameters and details before meaningful conclusions can be drawn.
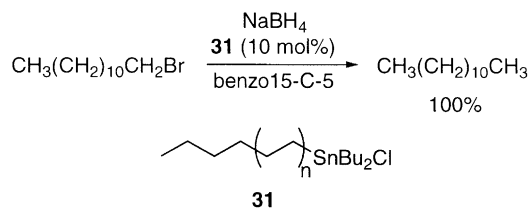

Figure 30.

3.3. Organotin catalysts

Organotin compounds are widely used for the conversion of alkyl halides to alkanes. These procedures, however, are complicated by the sometimes difficult removal of the highly toxic tin by-products after completion of the reaction. Several groups have addressed this issue by linking the tin species to a polymer to facilitate its removal and potential reuse.

Bergbreiter has prepared a soluble, linear polymer of ethyl-ene by butyllithium-initiated anionic polymerization.[38] The 'living' polymer was quenched with dibutyltin dichloride to provide the supported tin chloride catalyst **31**. In a typical reaction, 1-bromododecane was quantitatively reduced to dodecane in the presence of 10 mol% **31**, 20 mol% benzo-15-crown-5, and excess sodium borohydride (Fig. 30). Significantly, less than 0.03% of the tin reagent was found in the reaction filtrate after removal of the catalyst.

Enholm has utilized a similar approach where chloromethyl-ated linear polystyrene was converted to the supported tin chloride in a two-step procedure (Fig. 31).[39] Thus, displace-ment of the benzyl chloride with allyl alcohol followed by a photo-initiated hydrostannylation provided catalyst **32**. A range of aromatic and aliphatic halides were reduced in greater than 80% yield with 1–20% **32** and a slight excess of sodium borohydride. A few of the products were tested for tin contamination by ICP-MS and it was determined that the supported catalyst underwent less than 2% leaching of tin. It should be noted that the products were analyzed after purification by column chromatography and not as crude material.

The preparation of a tin reagent on macroporous resin beads has been reported by Deleuze and co-workers.[40] Thus, mono-mer **33**, *N*-phenylmaleimide (**34**), and bis-maleimide cross-linker **35** were co-polymerized with a *N*-methylformanilide/toluene mixture as the porogen to produce **36** (Fig. 32). The reduction of 1-bromoadamantane was carried out at 95°C in the presence of 10 mol% **36** and 5 equiv. of sodium boro-hydride. Over eight successive uses of the catalyst, the aver-age conversion to reduced product was 89% after 2 h. Over the course of these experiments, the total leaching of tin was estimated to be 20% of the initial loading.

4. Addition reaction catalysts

4.1. Diethylzinc addition to aldehydes

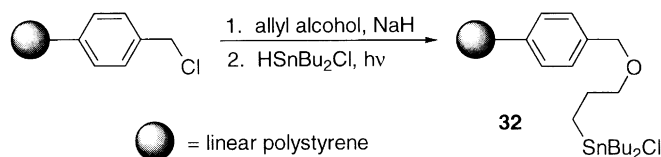The asymmetric addition of dialkylzinc species to aromatic
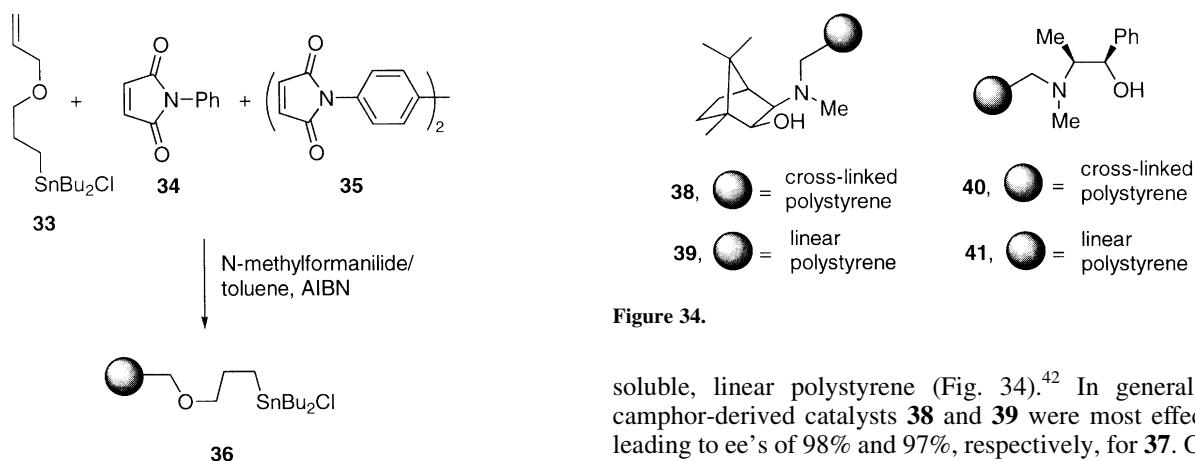
Figure 31.

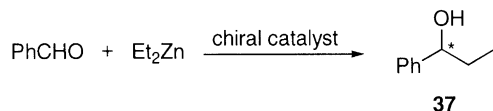**Figure 32.**

Figure 33.

Figure 34.

and aliphatic aldehydes has been extensively studied as a method for the preparation of optically active secondary alcohols. Wide ranges of chiral catalysts, most of which rely on a β-aminoalcohol functionality, have been developed for this purpose and enantioselectivities as high as 99% can be obtained. With the initial success of the solution-phase catalysts, extensive efforts have been made to develop a reusable polymer-bound catalyst that exhibits similar reactivity and stereoselectivity properties.

The addition of diethylzinc to benzaldehyde to produce 37 (Fig. 33) is the standard reaction by which most polymer-supported catalysts in this class are judged. In some of the earliest work in this area, Frechet utilized a polystyrene/divinylbenzene (PS/DVB) resin 38 functionalized with an amino-isoborneol moiety that catalyzed the formation of 37 in 91% yield and 92% ee.[41] The related β-aminoalcohol 40 was slightly less effective, producing 37 in 90% yield but only 80% ee (Fig. 34). One drawback to using these catalysts is the long reaction times (2.5–3 days) required as compared to the solution-phase counterpart (15 h).

Hodge has carried out an extensive study aimed at clarifying the most important factors that dictate the stereoselectivity of diethylzinc addition to benzaldehyde. Thus, the camphor and ephedrine-derived catalysts on cross-linked polystyrene (originally prepared by Frechet) were also synthesized on
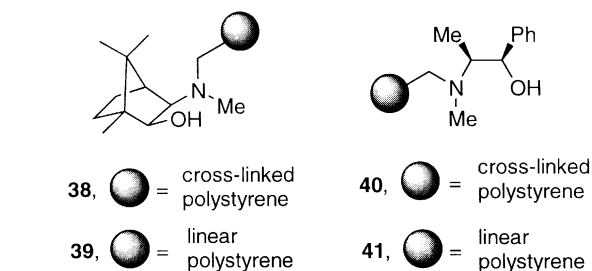
soluble, linear polystyrene (Fig. 34).[42] In general, the camphor-derived catalysts 38 and 39 were most effective, leading to ee's of 98% and 97%, respectively, for 37. Of the two ephedrine catalysts, the soluble-supported catalyst 41 was slightly better than insoluble catalyst 40. The most important factor for the success of these reactions was found to be the interaction of the polymer matrix with the solvent. Thus, toluene was the optimal solvent as it completely solubilized the linear polystyrene catalysts and effectively swelled the cross-linked polystyrene catalysts.

Frechet has also prepared polymer 44 derived from styrene, flexible cross-linker 42, and the chiral amino-alcohol monomer 43 (Fig. 35).[43] The primary amine functionality in this catalyst first forms a Schiff base with one equivalent of the aldehyde while a second equivalent undergoes addition by diethylzinc. With benzaldehyde as the substrate, the highest ee obtained was 86%. However, an ee of 99% was achieved for diethylzinc addition to 4-chlorobenzaldehyde.

Soai has been a major contributor to the field of polymer-supported catalysts for enantioselective addition of dialkyl-zincs to aldehydes.[44] For the model reaction of diethylzinc adding to benzaldehyde, catalyst 45, prepared from (−)-ephedrine and chloromethylpolystyrene (1% DVB), gave the highest selectivity (89% ee). When the substituent on the nitrogen of the catalyst was changed from methyl to ethyl, however, the ee fell to 41% (Fig. 36). Interestingly, if an aliphatic aldehyde such as nonanal was utilized, catalyst 46 proved to be the most effective, providing (+)-undecan-3-ol in 80% ee as compared to 48% ee for 45.

Soai has postulated that the lower enantioselectivities achieved from aliphatic substrates result from the limited mobility of the reactive site of the polymer-bound catalysts, which were attached directly to the chloromethylated benzene ring of the polymer backbone. To overcome this limitation, norephedrine-derived amino-alcohol 47, containing a six-carbon spacer between the catalyst and the polymer backbone as well as a butyl substituent on the nitrogen, was prepared (Fig. 37).[45] An ee of 69% was obtained in the
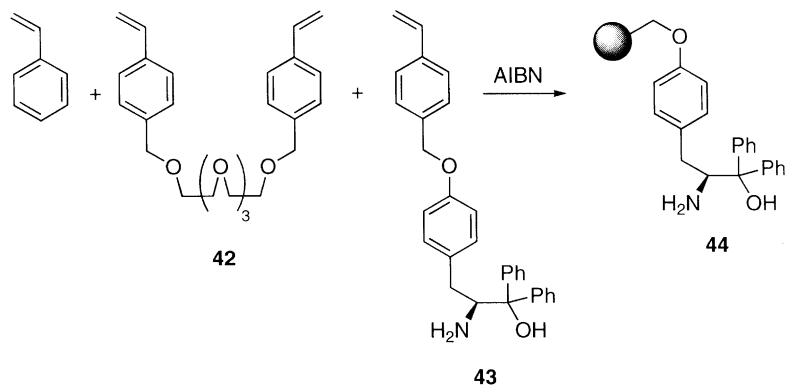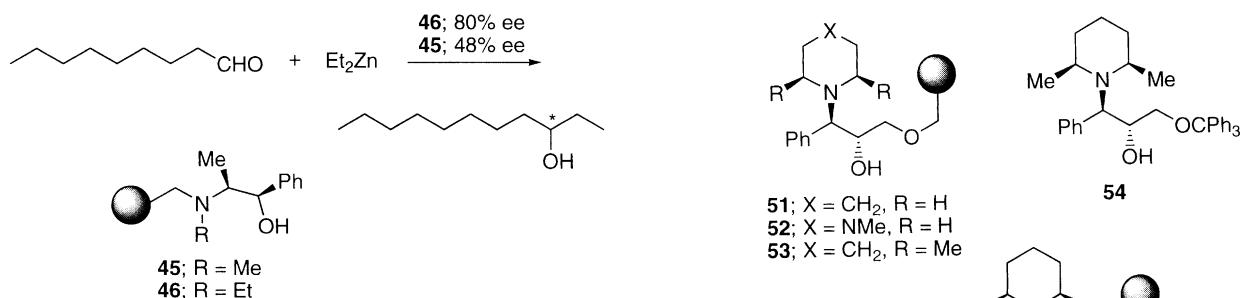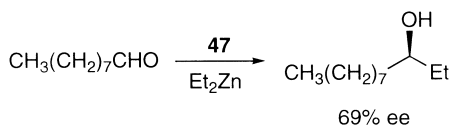
Figure 35.

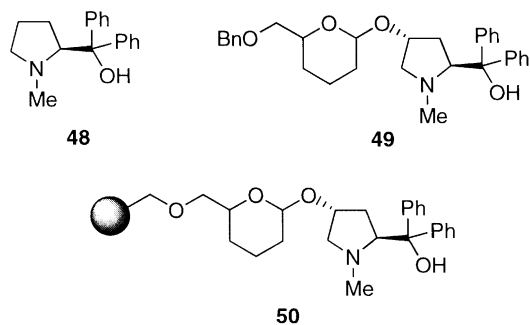**Figure 36.**

Figure 37.

Figure 38.

ethylation of undecanal and the authors attributed this increase to the freedom of the active amino-alcohol site.

A number of groups has used chiral β-amino-alcohol catalysts that are not derived from ephedrine or camphor.

Figure 39.

Ellman has developed a general synthesis of 2-pyrrolidine methanol ligands on solid-phase and studied their use as catalysts in diethylzinc addition reactions.[46] While this approach was developed to provide facile access to free, solution-phase ligands, amino-alcohol **50** bound to polystyrene via a tetrahydropyran (THP) linker was found to produce an ee of 89% for secondary alcohol **37** (Fig. 38). This compares favorably to the value of 94% obtained with structures **48** and **49** and demonstrates that the presence of either the 4-oxo group or the THP linker does not effect the enantioselectivity.

An exceptional study aimed at identifying optimal ligands and linking strategies to the polymer support was carried out by Pericas and Sanders.[47] They utilized chiral 1,2-amino-alcohols **51**–**53** (Fig. 39), resulting from the ring-opening of enantiomerically pure epoxides with piperidine or piperazine derivatives, as catalysts for the reaction shown in Fig. 33. Ligand **53** gave the best ee of 69%, compared to 36% and 39% for **51** and **52**. It was noted, however, that free ligand **54**, which differs from **53** only by the presence of a trityl functionality in place of the polystyrene resin, produced an ee of 95% for **37**. As this suggested that the polystyrene skeleton was perhaps not sufficiently bulky to allow high selectivities, polymer-bound catalyst **55** was prepared on the Barlos resin. This catalyst exhibited greatly enhanced selectivity, providing **37** with an ee of 94%. It also
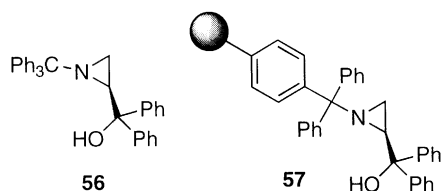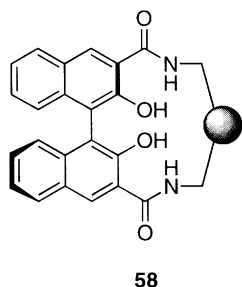
Figure 40.

Figure 41.

performed well with a number of substituted benzaldehydes, giving ee's ranging from 86% up to 98%.

Encouraged by the recent success of chiral aziridinylmethanol catalysts for diethylzinc addition to aldehydes, efforts

toward a polymer version of these compounds have been disclosed.[48] The *N*-trityl protected catalyst **56** has given excellent selectivity in the solution-phase so it was expected that polystyrene-bound catalyst **57** would behave similarly (Fig. 40). Indeed, a 96% ee of alcohol **37** was obtained if the solvent was a 50:50 toluene/CH$_2$Cl$_2$ mixture.

A recent disclosure by Wang and Chan has shown that a polystyrene/DVB supported BINOL ligand was highly effective in promoting asymmetric diethylzinc addition to benzaldehyde.[49] Using 1.8 equiv. of Ti(O*i*Pr)$_4$ and 20 mol% of supported catalyst **58**, alcohol **37** was obtained in 93% yield and 97% ee (Fig. 41). Carrying out the same transformation with commercial BINOL ligand afforded the product in 92% ee, which suggests that the polymer may have some subtle effects on enantioselectivity.

Two clever approaches to chiral catalysts incorporated at cross-links of a polymer have been recently reported. Kurth has described the preparation of the C$_2$-symmetric cross-linking monomer **59** derived from *trans*-1,2-diaminocyclohexane and its polymerization with styrene (Fig. 42).[50] When used as a catalyst for the model reaction, polymer **61** provided alcohol **37** in 82% yield and 98% ee. For a comparison, the monomer **60** containing a single vinyl group was also co-polymerized with styrene. The resulting polymer **62** contained a pendant catalyst as opposed to the previous cross-linked catalyst. Surprisingly, the 93% ee
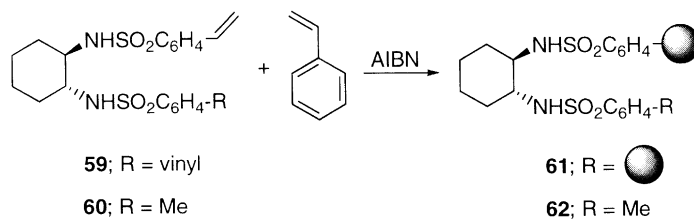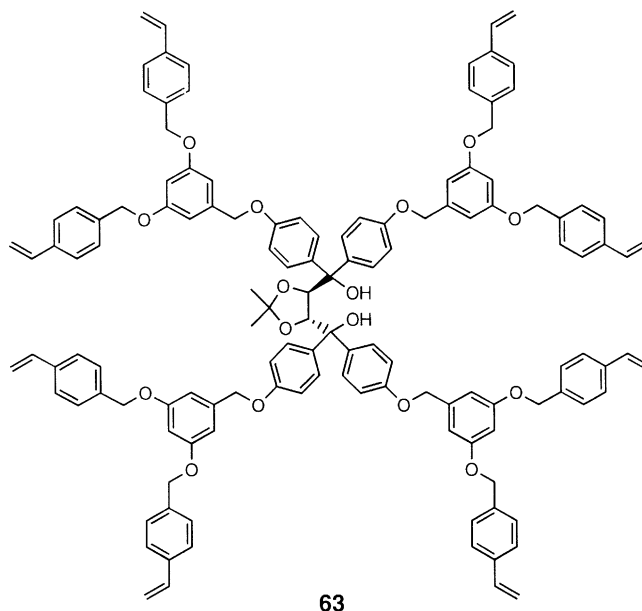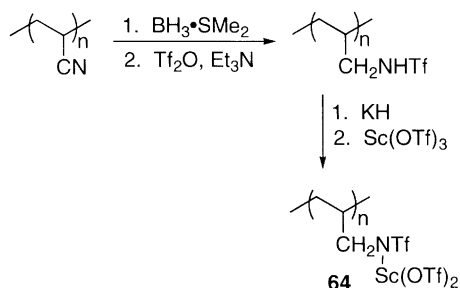

Figure 42.

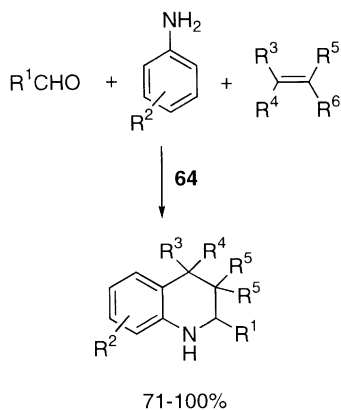**Figure 43.**

Figure 44.

Figure 45.

obtained with this catalyst was lower than that obtained with **61**, which indicates that access to the more sterically hindered cross-linked catalyst is not compromised.

Seebach has co-polymerized the dendritic TADDOL derivative **63** with styrene to produce a ligand which is highly effective in promoting asymmetric addition of diethylzinc to benzaldehyde (Fig. 43).[51] Complexation of the ligand with Ti(O*i*Pr)$_4$ produced the active Ti–TADDOLate catalyst which provided a 96% ee of alcohol **37**. A low loading (ca. 0.1 mmol/g) catalyst gave the best results and it was shown that the same catalyst could be used in 20 reactions with no decrease in enantioselectivity.

4.2. Miscellaneous addition reactions

Kobayashi has recently reported a three-component coupling strategy for the synthesis of quinolines which is catalyzed by lanthanide triflate. To aid in the preparation of libraries of potential therapeutic agents, a new polymer-bound scandium catalyst was synthesized. The supported Lewis acid (polyallyl)scandium triflyamide ditriflate (PA–Sc–TAD) **64** was prepared as shown in Fig. 44 and is partially soluble in the CH$_2$Cl$_2$–CH$_3$CN (2:1) solvent system employed for the reaction. After reaction completion, reisolation of the catalyst was accomplished by hexane addition and filtration. The general reaction sequence is shown in Fig. 45 and first involves the condensation of an aniline derivative and an aldehyde to form an azadiene which then undergoes a Diels–Alder cycloaddition.[52] A library of 15 quinoline analogs was prepared using this methodology.
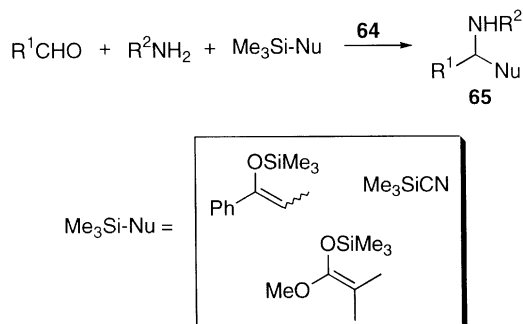

Figure 46.

Using the same catalyst, Kobayashi has also prepared libraries of compounds with the general structure **65** (Fig. 46).[53] These reactions proceed in a similar manner to those previously described wherein an aromatic amine first condenses with an aldehyde to generate an imine. These underwent addition in the presence of silylated nucleophile to form compounds such as **65** in excellent yield. The catalyst was found to be reusable for many cycles without loss of activity.

This catalyst was also found to catalyze the selective addition of silyl enol ethers to aldimines in the presence of aldehydes.[54] Thus, treatment of a 1:1:1 solution of **66**, **67**, and **68** with a catalytic amount of **64** produced β-amino ketone **69** with 99:1 selectivity over hydroxy ketone **70** (Fig. 47). If soluble Sc(OTf)$_3$ was used as the catalyst, the selectivity decreased to 4.5:1. The authors ascribe this difference to the greater stability of the aldimine/polymer-supported catalyst complex relative to the aldimine/non-polymer Lewis acid complex.

The supported π-allyl palladium catalyst **71**, derived from estrone, was used to catalyze the asymmetric allylation of imines by allyltributyltin.[55] The highest enantioselectivity was obtained for the reaction depicted in Fig. 48. While the yield of the homoallyl amine product was a reasonable 76%, the ee was only 42% and the reaction took six days to reach completion. Upon reuse, **71** gave consistent results with no significant decline in yield, ee, or reaction time.

Simoni has utilized polymer-supported 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (P-TBD) **72** to catalyze the addition of
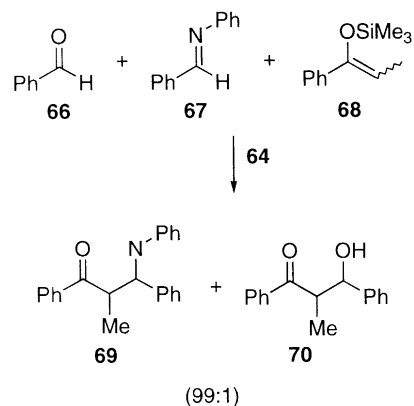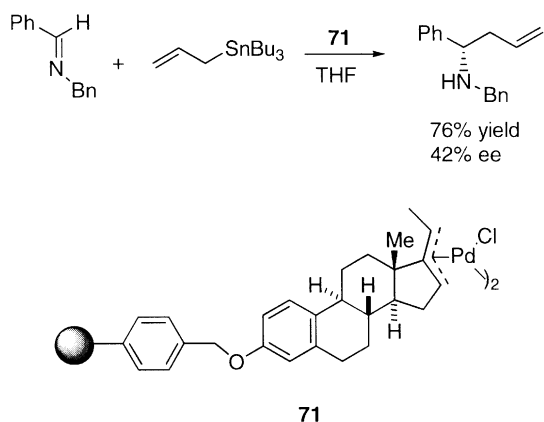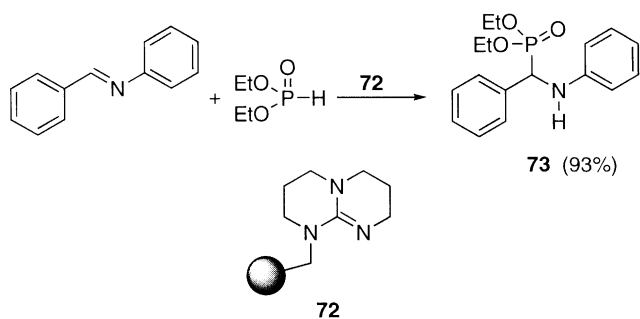

Figure 47.

Figure 48.

Figure 49.

Figure 50.

which have been shown to have potential as anti-cancer agents.

Cave and D'Angelo have recently prepared polymer-supported *Cinchona* alkaloids for use in asymmetric Michael addition reactions.[58] Catalyst **76**, which contains a seven-atom tether between the polymer and the DHQ portion, was determined to give the best results. In the conjugate addition between 2-carbomethoxy-indan-1-one and methyl vinyl ketone catalyzed by 30 mol% **76**, the desired product **77** was obtained in 85% yield and 87% ee (Fig. 51). These results were superior to earlier efforts employing immobilized *Cinchona* alkaloids as Michael addition catalysts.

5. Cycloaddition reaction catalysts

There have been several reports of polymer-supported Lewis acid catalysts that promote the Diels–Alder reaction. Itsuno[59] and Luis[60] have independently described the preparation of complexes that are effective in catalyzing the asymmetric [4+2]-cycloaddition between cyclopenta-diene and methacrolein. In the first instance, Itsuno co-poly-merized the valine-derived styryl sulfonamide **78** with styrene and three different cross-linkers (**a–c**) (Fig. 52).[59] The resulting carboxylic acid sulfonamides were then converted to the active oxazaborolidinone catalysts **79a–c** by treatment with borane–dimethylsulfide complex. The use of catalysts **79a** and **79b**, derived from divinylbenzene
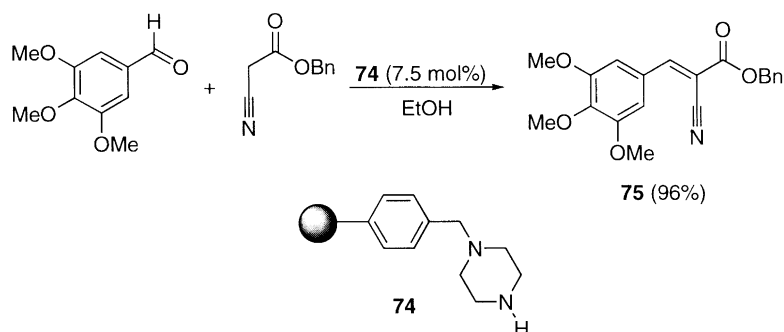
dialkylphosphites to imines, ketones, aldehydes, and esters.[56] In one example, diethylphosphite underwent addition to benzylidene aniline in the presence of **72** to provide the product **73** in 93% yield (Fig. 49). The reaction was very clean and required only filtration of the reaction mixture and evaporation to obtain pure product. Catalyst **72** was also efficient in promoting the Henry reaction between nitroalkanes and aldehydes.

The reaction of piperazine with Merrifield resin produced the supported piperidine equivalent **74**, which was used as a catalyst for the Knoevenagel reaction.[57] A range of benzaldehydes was heated in ethanol with a number of different β-cyanoesters in the presence of 7.5 mol% **74**. In a typical example illustrated in Fig. 50, the condensation product **75** was formed in 96% yield. This methodology was used to prepare a library of lipoxygenase inhibitors,
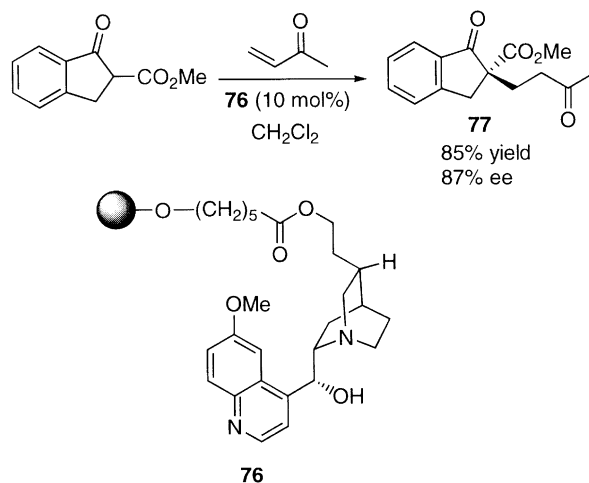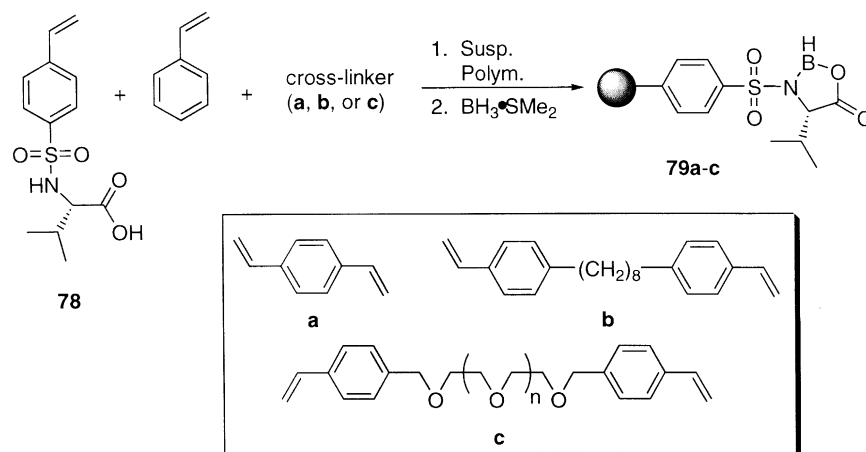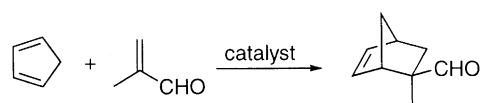

Figure 51.

Figure 52.

and bis-styryl octamethylene cross-linkers, respectively, provided the [4+2] adducts with comparable or slightly lower ee's than the solution-phase counterpart (Fig. 53, entries 1 and 2). The use of catalyst **79c** containing an oligo(oxyethylene) cross-linker, however, gave superior ee's compared to the unsupported catalyst (Fig. 53, entry 3). This result was loosely attributed to the ability of the oxygen atoms in the cross-linker to act as donor additives that can dissociate inactive aggregates of the catalyst. Furthermore, the catalyst was used successfully in a continuous flow reactor to allow for its repeated recycling.

As catalysts for the same transformation, the supported aluminum catalysts **80a–c**, derived from three cross-linkers (**a–c**), were prepared by Luis and co-workers (Fig. 54).[60] The divinylbenzene cross-linked catalyst **80a** was prepared by two different methods: (1) direct functionalization of Merrifield resin; and (2) co-polymerization of a functionalized monomer. In all cases, a supported prolinol moiety was treated with ethyl aluminum dichloride to give the active catalyst. For all the catalysts, the exo:endo of the products was 5.5:1 or greater. Additionally, the conversions were generally very high. Compared to the boron catalysts of Itsuno, however, the product ee's were very low (Fig. 53, entries 4–6). In particular, catalyst **80c**, which has a PEG-based cross-linker, provided disappointing results (2% ee of the Diels–Alder adduct). It was postulated that the oxyethylene units may interact with the aluminum, which would preclude its incorporation into the chiral prolinol fragment. This is in sharp contrast to Itsuno's work in which the catalyst derived from the poly(oxyethylene) cross-linker provided the best results.

Luis has also prepared a range of polymer-grafted Ti–TADDOL complexes and tested them in the Diels–Alder reaction between cyclopentadiene and 3-crotonyl-1,3-oxazolidin-2-one (Fig. 55).[61] Catalyst **81** was identified as giving the best results and was prepared by reaction of the supported TADDOL precursor with Ti(O*i*Pr)$_2$Cl$_2$. The desired product of the cycloaddition was formed with excellent conversion, however the ee and exo/endo ratio was poor to moderate. The analogous soluble catalyst **82** provided only slightly better results, suggesting that the

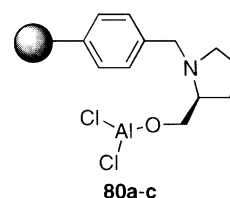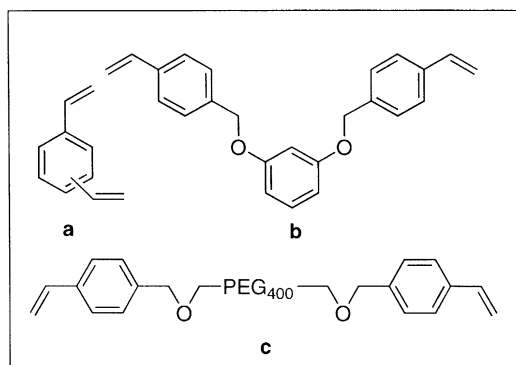| entry	catalyst	yield (%)	ee (%)
1	**79a**	87	65
2	**79b**	86	84
3	**79c**	88	95
4	**80a**	97[a]	25
5	**80b**	98[a]	11
6	**80c**	93[a]	2

a) conversion (%)

Figure 53.

80a-c

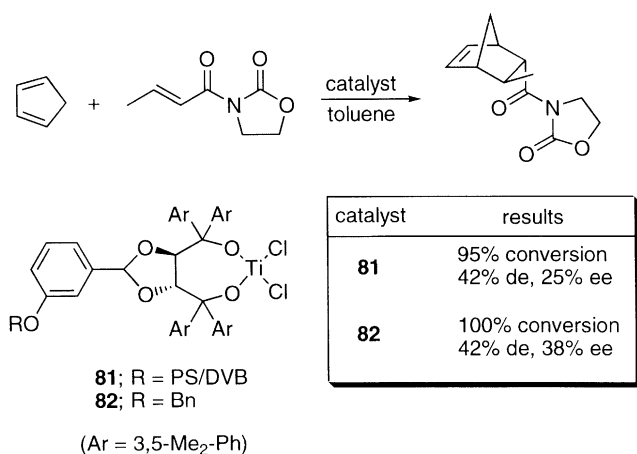Cross-linkers used for **80**

Figure 54.

Figure 55.

catalyst design should be altered to afford improved selectivities.

Kobayashi has recently described the optimization of asymmetric aza-Diels–Alder catalysts using both solid-phase and liquid-phase methods.[62] The complexes under investigation were zirconium complexes of 3,3′-disubstituted BINOL. A range of potential ligands bearing different aromatic substitution at the 3 and 3′ positions were screened on the solid-phase, and catalyst **83** bearing a 3-trifluoromethyl-phenyl substituent was found to be the most effective (Fig. 56). In the reaction of aldimine **84** with 1-methoxy-2-methyl-3-trimethylsilylsiloxy-1,3-butadiene catalyzed by **83**, the Diels–Alder adduct was formed in quantitative yield and in 91% ee.

Owing to the formation of two new bonds and its high regio- and stereoselectivity, the Diels–Alder reaction is among the most important synthetic methods. The use of Lewis acid catalysts has further improved the efficiency and utility of this reaction. The more recent development of effective polymer-supported chiral catalysts has without doubt advanced this area of research even further.
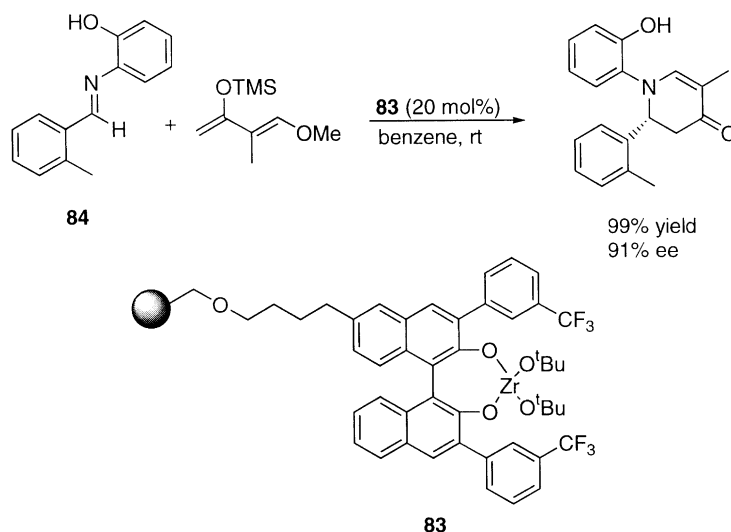
6. Transition metal-catalyzed reactions

Carbon–carbon bond formation is a fundamental reaction in organic chemistry. Many methods exist for achieving this, and catalytic procedures that facilitate transformation under mild reaction conditions are exceptionally useful and have received a great deal of attention. Not surprisingly, extensive efforts at preparing polymer-supported catalysts have been reported in order to aid in parallel synthesis and in the recovery and reuse of the valuable catalysts.

6.1. Palladium-catalyzed couplings

Tetrakis(triphenylphosphine)palladium(0) is routinely employed in many catalytic cross-coupling reactions. Trost reported one of the first uses of this catalyst supported on a polystyrene resin.[63] The reaction of chloromethyl polystyrene with lithium diphenylphosphide followed by a palladium source gave catalyst **85** (Fig. 57). The reaction of allylic acetate **90** with diethylamine in the presence of catalytic **85** provided the substitution product **91** with net retention of stereochemistry (Fig. 58). In contrast, the use of non-supported $(Ph_3P)_4Pd$ provided a 2:1 mixture of diastereomers **91** and **92**. This "steric steering" effect was attributed to the inability of the amine nucleophile to coordinate the supported palladium intermediate—a pathway that leads to products with inversion of configuration. It was also noted that the supported catalyst could be stored in the dry state for prolonged periods of time without undergoing decomposition.

Jang has shown the utility of the same catalyst **85** in effecting the Suzuki coupling of organoboranes with alkenyl halides and aryl triflates.[64] Two representative examples are illustrated in Fig. 59. In most cases, the yields of coupled products obtained using the supported palladium catalyst were superior to those obtained using the solution-phase catalyst. Additionally, the catalyst was used for ten cycles with no decrease in activity.

Soon after this report, Le Drian disclosed related results on Suzuki reactions catalyzed by supported palladium complexes.[65] A strong emphasis was placed on addressing
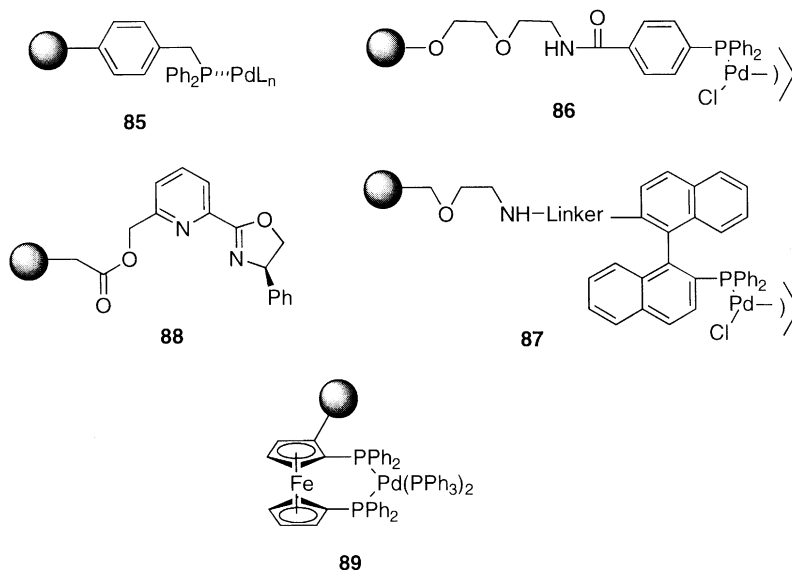
Figure 56.
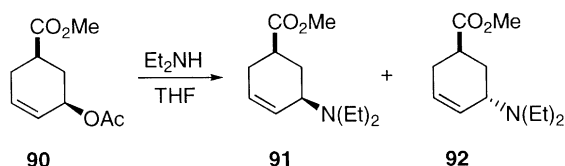
Figure 57.

Figure 58.

the optimal palladium source for the supported catalyst as well as the ideal Pd/P ratio in the catalyst. Using the coupling of phenyl boronic acid with 4-bromopyridine as the standard test reaction, the authors found that $(Ph_3P)_4Pd$ was the optimal source for introducing palladium to the polymer and that altering the Pd/P ratio of the catalyst had little effect on the outcome of the reaction.

Uozomi has prepared the π-allyl palladium(II) catalyst **86** on a polystyrene–polyethylene glycol composite ArgoGel resin.[66] This was used as a catalyst for Suzuki coupling reactions carried out in aqueous media. The coupling of aryl halides with three boronic acids provided the expected biphenyls in high yield (Fig. 60). The use of soluble $(Ph_3P)_4Pd$ under the same reaction conditions did not provide any coupled product; **86** and the related ArgoGel-

Figure 59.

Figure 60.

Figure 61.

Figure 62.

supported catalyst **87** were also effective in promoting the arylation of allylic acetates and the asymmetric allylic substitution of acetates by malonate esters.[66b]

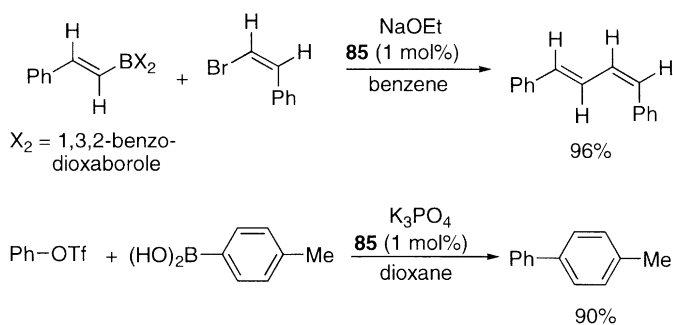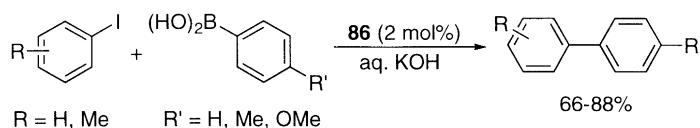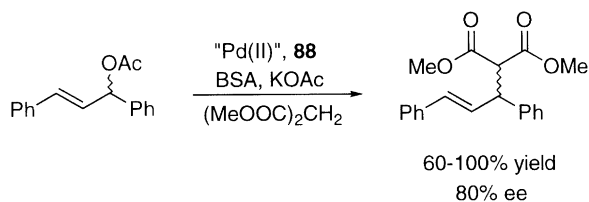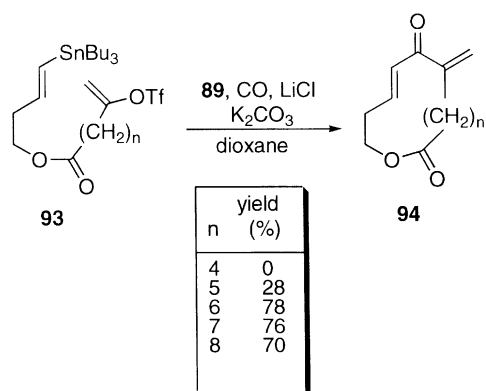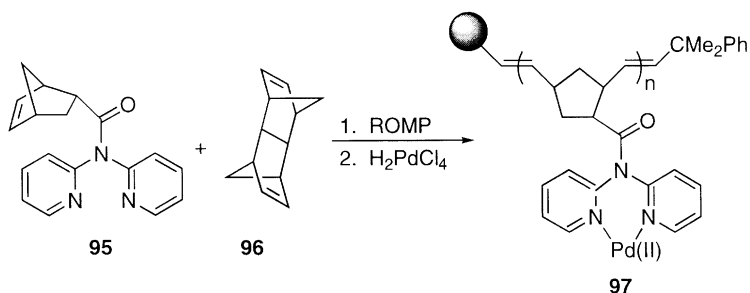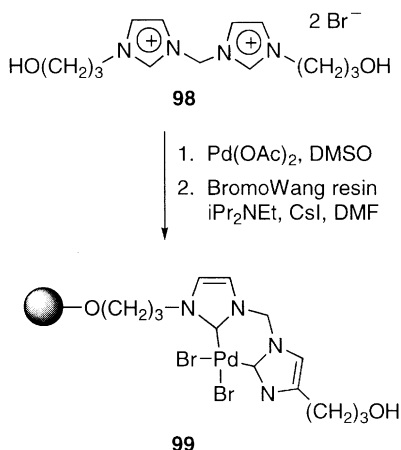Moberg has described the preparation of ligand **88** and its use in catalyzing the asymmetric substitution of allylic acetates.[67] Thus, racemic 1,3-diphenyl-2-propenyl acetate was reacted with dimethyl malonate in the presence of 6 mol% **88** and 2 mol% [(η^3-C$_3$H$_5$)PdCl]$_2$ (Fig. 61). The yield of the desired product varied considerably (60–100%) from run to run; however, the enantioselectivity was a reproducible 80%. Furthermore, this reaction required seven days for completion and no mention of catalyst reuse was made.

Stille, Hegedus, and co-workers have successfully used the supported bis[(diphenylphosphino)ferrocene]-derived catalyst **89** for the synthesis of large-ring keto lactones by the intramolecular carbonylative coupling of vinyl triflates with vinyl stannanes.[68] The use of the supported catalyst was warranted in this case as a result of the failure of traditional solution-phase palladium catalysts to effect the desired reaction in reasonable yield and purity. Catalyst **89** was prepared on a highly cross-linked polymeric support and with low functional group loading to achieve site isolation of the catalytic units. The use of **89** for the carbonylative intramolecular coupling of substrate **93** was effective for the preparation of 14, 15, and 16-membered keto lactones **94**

Figure 63.

Figure 64.

(Fig. 62). A severe darkening of the catalyst during the reaction was noted and this precluded its reuse.

Buchmeiser utilized the Schrock molybdenum catalyst to promote the ring-opening metathesis polymerization of the functionalized norbornene **95**.[69] Cross-linker **96** was then added to the mixture to provide a polymer in which the functional groups are located on tentacles emanating from the polymer core (Fig. 63). Incubation with a palladium(II) source generated the supported bipyridyl palladium(II) catalyst **97**. The catalyst was very effective in promoting the Heck coupling of aryl halides with styrene or ethyl acrylate (generally 80–90% yield). Additionally, the catalyst was used in the amination of aryl bromides, although the product yields were substantially lower. In all cases, the catalytic activity of the supported catalyst was superior to that of the corresponding solution-phase catalyst and **97** could be reused for three cycles with no decrease in yield.
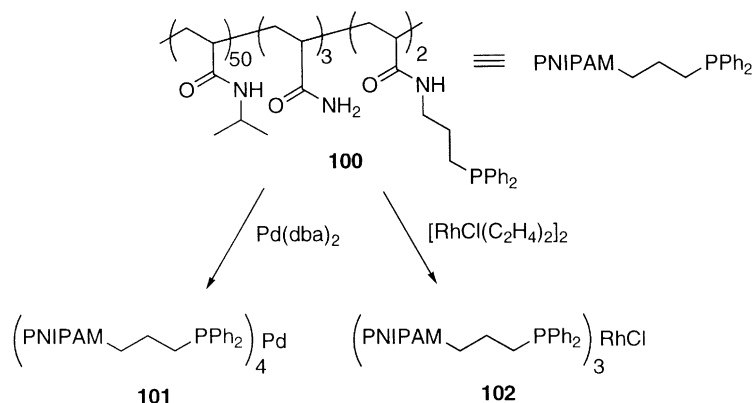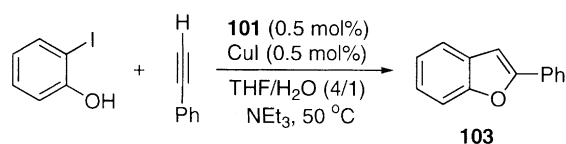
Figure 65.

Figure 66.

The polymer-supported palladium carbene complex **99** was prepared as shown in Fig. 64 and was utilized as a catalyst for the Heck reaction.[70] The diamidazoline species **98** was treated with Pd(OAc)$_2$ and the resulting complex was linked to bromo-Wang resin through an ether linkage to provide **99**. In the reaction of bromobenzene with butyl acrylate or styrene, the Heck products were obtained in 82% or 61% yield, respectively, after two days. The catalyst was effective for four uses before a decline in yield was observed.

Bergbreiter and co-workers have explored the use of linear poly(N-isopropylacrylamide) (PNIPAM) polymers, which are soluble in cold water but insoluble in hot water.[71] Thus, polymer precipitation is accomplished by heating an aqueous solution of the polymer or, alternatively, by the addition of a solvent such as hexane. It has been demonstrated that the phosphine-containing PNIPAM support **100** is a versatile precursor to transition metal complexes. Reaction with Pd(dba)$_2$ provided the supported Pd(0) catalyst **101** while reaction with [RhCl(C$_2$H$_4$)$_2$]$_2$ gave **102**, the polymer-bound equivalent of Wilkinson's catalyst (Fig. 65).

Catalyst **101** was effective for the reaction of 2-iodophenol with phenylacetylene to provide benzofuran **103**, as shown in Fig. 66. The product was obtained in 78% yield and the catalyst was used up to 15 times with minor loss of activity. Additionally, the rhodium catalyst **102** was an effective catalyst for the hydrogenation of allyl alcohol.

6.2. Cyclopropanation

Glos and Reiser have recently reported preparation of aza-bis(oxazoline) **104** for use in asymmetric cyclopropanation reactions.[72] The soluble poly(ethylene glycol) monomethyl ether was used as the polymeric support so as to allow for homogeneous reaction conditions. The active copper(I) catalyst was generated in situ from **104**, Cu(OTf)$_2$, and phenylhydrazine and was used to promote the reaction between 1,1-diphenylethene and methyl diazoacetate (Fig. 67). The cyclopropane product **105** was formed in 78% yield and 90% ee. The catalyst was recovered by precipitation into ether and recycled effectively without the further addition of copper salts.

Leadbetter and co-workers have shown that the supported ruthenium(II) complex **106** is capable of catalyzing the cyclopropanation of styrene derivatives by ethyl diazoacetate.[73] Styrene and 4-methylstyrene underwent cyclopropanation to provide the products **107** and **108** in 68% and 70% yield, respectively. Additionally, **106** was shown to catalyze the formation of enol formate **109** from phenylacetylene and
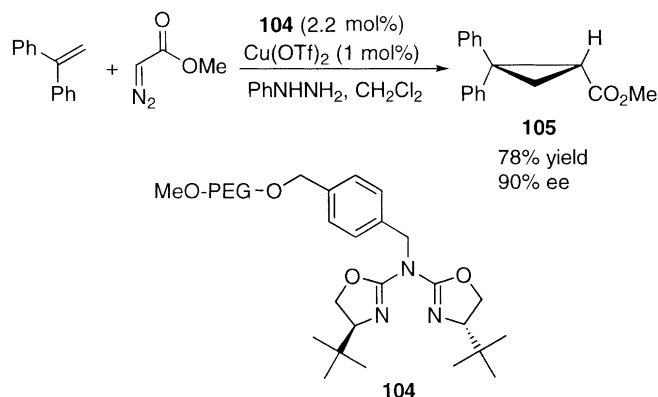

Figure 67.

formic acid in 73% yield (Fig. 68). The catalyst was reported to be air-stable and could be reused without loss of activity.

6.3. Olefin metathesis

The ring-closing metathesis (RCM) between two tethered alkenes and the ring-opening metathesis polymerization (ROMP) of cyclic alkenes are two reactions that have been extensively utilized in recent years. Many of the advances in this area of research have come from the Grubbs laboratory, and in 1995 this group introduced some poly-mer-supported ruthenium metathesis catalysts.[74] The ruthe-nium alkylidene **110** underwent ligand exchange with dicyclohexylphosphine-functionalized polystyrene resin to provide the supported catalysts **111** and **112** (Fig. 69). The reactivity of the immobilized catalysts was judged by their use in the acyclic olefin metathesis of *cis*-2-pentene and the ROMP of norbornene. The metathesis rates were much slower than those using the solution-phase analog but the catalysts could be recycled for a limited time. Additionally, the polydispersity index of the polymer products was much higher when the supported catalysts were used.

Barrett and co-workers have made a significant contribution to the area of supported metathesis catalysts.[75] Their second-generation polystyrene-bound alkylidene **113** was made by reaction of vinyl polystyrene with the correspond-ing non-supported ruthenium carbene containing an active 'IMes' ligand.[75b] This and related complexes have been termed 'boomerang' catalysts since the active alkylidene is released into solution and then recaptured by the support upon reaction completion. The RCM of two typical bis-alkenes is shown in Fig. 70. Quantitative conversion to the cyclic alkene products was observed for three catalyst uses. At that point, however, catalyst activity was retarded to the point of negligible conversion by the sixth catalyst use. It was also noted that only 0.25 mol% catalyst loading was required to achieve the quantitative ring-closure.

6.4. Other C–C bond formations

The construction of cyclopentenone derivatives by the cobalt carbonyl-mediated annulation of an alkene, alkyne, and carbon monoxide is a powerful synthetic method. Comely has recently reported the first supported cobalt complex to effect this transformation, the Pauson–Khand reaction.[76] Thus, **114** was prepared by heating $Co_2(CO)_8$ with PS-PPh₃. The cyclization of ene-ynes **115** and **116** was accomplished with 5 mol% **114** under 1 atm. of CO. The bicyclic cyclopentenones **117** and **118** were isolated in reasonable 61% and 49% yield, respectively (Fig. 71). This work is significant due to the increased stability of the immobilized cobalt complexes.

The Kumada cross-coupling involves the reaction of Grignard reagents with aryl and alkenyl halides under nickel catalysis. A polymer-supported nickel complex was prepared in situ by the reaction of the immobilized chiral phosphine **119** with NiCl₂ and then used in asymmetric coupling reactions.[77] Thus, secondary, benzylic magnesium chlorides underwent reaction with vinyl bromide to provide the chiral products **120** and **121** in good yield
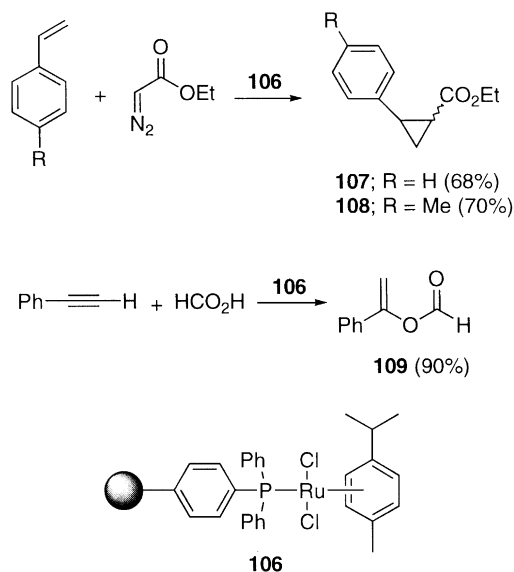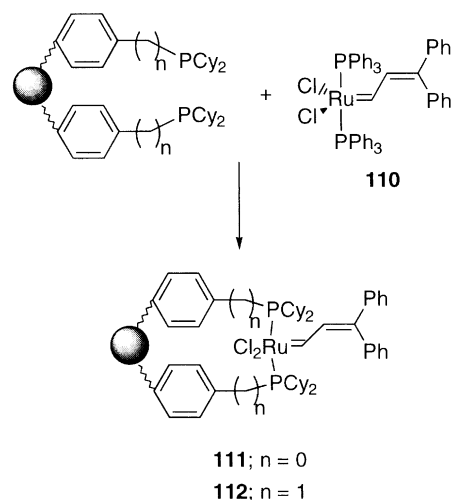

107; R = H (68%)
108; R = Me (70%)

109 (90%)

106

Figure 68.

110

111; n = 0
112; n = 1

Figure 69.

R = C(CO₂Et)₂ (100%)
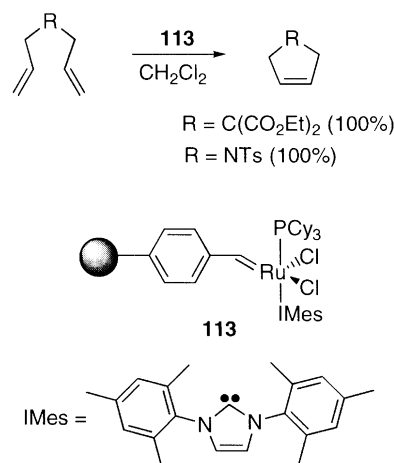R = NTs (100%)
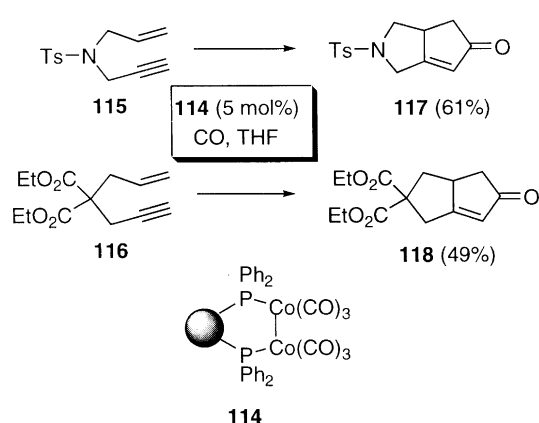
113

IMes =

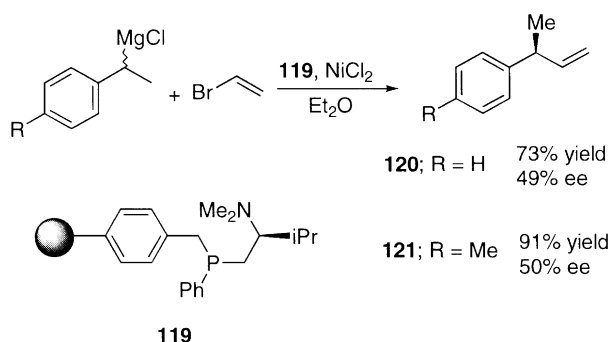**Figure 70.**

Figure 71.

Figure 72.

and with modest enantioselectivity (Fig. 72). Although the reaction times ranged from 2 to 7 days, the supported ligand could be reused with no loss of catalytic activity or stereoselectivity.

7. Miscellaneous reactions

Jacobsen has demonstrated the utility of the supported Co(salen) complex **122** as a catalyst for the kinetic resolution

of terminal epoxides by the addition of water or phenols.[78] Thus, the reaction of phenol with racemic epibromohydrin in the presence of 1 mol% **122** gave the bromohydrin product **123** in 97% ee (Fig. 73). After five catalyst uses, **123** could still be obtained in 95% ee, indicating that the catalyst does not lose a substantial amount of selectivity upon recycling. This methodology has been utilized in a parallel synthesis approach to prepare libraries of enantio-pure 1-aryloxy-2-alcohols.[78b]

Stannety has used PS-PPh$_3$ as a catalyst for the isomeri-zation of (E/Z)-nitro olefin mixtures into the pure E-isomer.[79] The E/Z mixtures were prepared by the aldol condensation of nitroalkanes with aldehydes. In one example, a 55/45 mixture of E/Z-nitro olefins **124** was treated with 10 mol% PS-PPh$_3$ for 20 h to produce exclusively the E-product in quantitative yield (Fig. 74).

Supported catalysts have also found use in protecting-group chemistry. Li and Ganesan have successfully employed poly(4-vinylpyridinium) p-toluenesulfonate (polyPPTS) **125** for the deprotection of THP ethers to the corresponding free alcohols.[80] As shown in Fig. 75, a range of alcohols was cleanly deprotected in high yield. Product isolation involved only filtration of the catalyst and evaporation of solvent. Acidic ion exchange resins such as Dowex or Amberlyst had some limitations as deprotection catalysts as they could not be used in the presence of acid-sensitive func-tional groups.

Masaki has reported the co-polymerization of EGDMA with the dicyanoketene acetal monomer **126** to provide the polymer-supported π-acid **127** (Fig. 76).[81] This was then used as a catalyst for the deprotection[81a] or monothio-acetalization[81b] of acetals. Thus, benzaldehyde dimethyl acetal reacted with a catalytic amount of **127** to provide benzaldehyde in 82% yield. Alternatively, a similar reaction in the presence of thiophenol provided the mixed acetal **128** in 83% yield (Fig. 77). In every case, catalyst recovery and reuse was very efficient. The catalyst was also shown to be effective for the deprotection of silyl ethers[81a] and for promoting the addition of silyl enol ethers to aldimines.[81c]
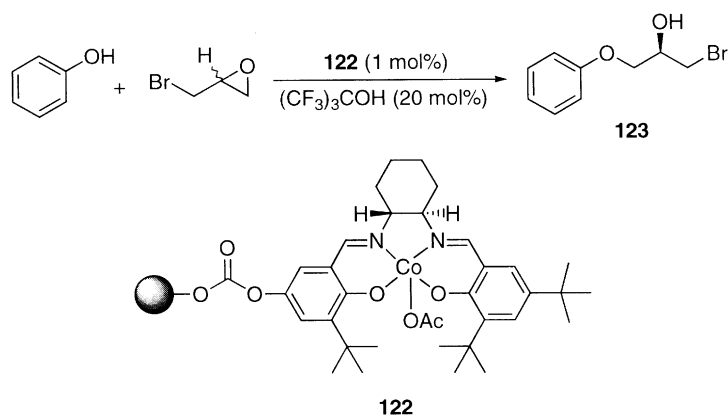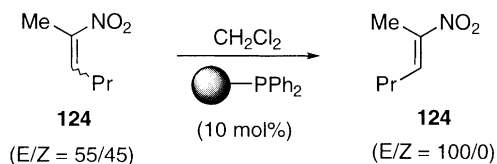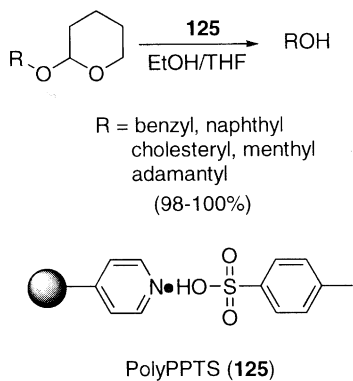

Figure 73.

Figure 74.

R = benzyl, naphthyl
cholesteryl, menthyl
adamantyl
(98-100%)

PolyPPTS (**125**)

Figure 75.

Figure 76.

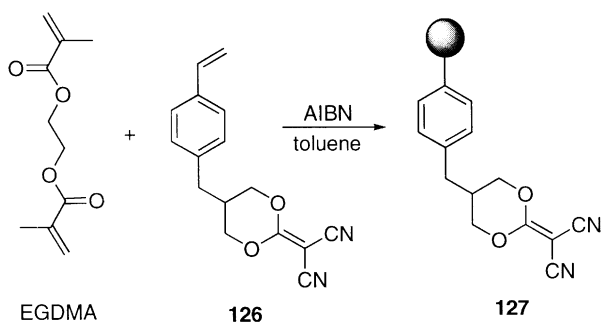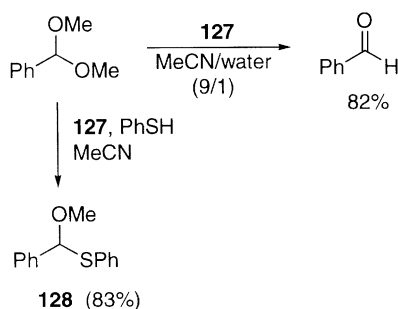**Figure 77.**

8. Conclusion

The renewed interest in the development of polymer-supported catalysts directly coincides with the emergence of parallel synthesis and combinatorial chemistry as new synthetic paradigms. In many cases, established solution-phase catalysts are linked to a polymeric support to allow

for recovery and reuse by simple filtration procedures. It is apparent, especially in asymmetric catalysis, that the catalytic activity and/or stereoselectivity found in the solution-phase does not always correlate to that in the solid-phase. Consequently, new combinations of catalyst structures, polymer supports, and linkers are under investigation. As seen in some of the examples described herein, subtle changes in any of these parameters can significantly affect the outcome of reactions under polymer-supported catalysis. Clearly, the adaptation of solution-phase techniques to the solid-phase is not always a smooth and straightforward process. Nevertheless, the design and synthesis of new supported catalysts will surely continue. The application of reusable polymer-bound catalysts in synthetic ventures is a clear example of 'green' chemistry in which the waste streams and depletion of resources associated with transition metals is minimized. As we begin the next millennium, this fact should be inspiration enough for further progress in polymer-supported catalysis.

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Thomas S. Reger, originally from Pennington, NJ, received his B.A. degree in chemistry from Colgate University (1994) and his Ph.D. in organic chemistry from Emory University (1999), where he worked with Professor Albert Padwa on the development of tandem reactions for the synthesis of heterocyclic compounds. He is currently a postdoctoral research associate with Professor Kim D. Janda at The Scripps Research Institute, where he is developing new methodologies for solid-phase organic synthesis involving polymer-supported catalysts and reagents.

Kim D. Janda obtained his B.S. degree in clinical chemistry from the University of South Florida (1980) and his Ph.D. in organic chemistry from the University of Arizona (1984). He joined The Scripps Research Institute in 1985 as a postdoctoral fellow and, in 1987, was promoted to the faculty, where he is currently the Ely R. Callaway, Jr. Professor of Chemistry. His research interests include catalytic anitbodies, polymer-supported methodologies, combinatorial chemistry, combinatorial phage display systems, immunopharmacotherapy for the treatment of drug abuse and cancer, and enzyme mechanistic studies. He is the recipient of an Alfred P. Sloan fellowship (1993–1995) and an Arthur C. Cope Scholar award (1999). He is a co-founder of the companies CombiChem, Inc. (now DuPont Pharmaceuticals) and Drug Abuse Sciences.