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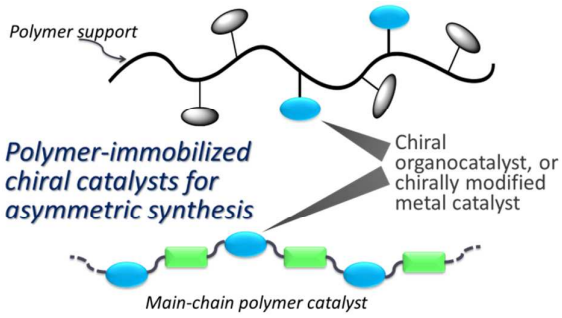

This review illustrates the current strategies and potential of polymer-immobilized chiral catalysts for highly enantioselective asymmetric synthesis.

Polymer-immobilized chiral catalysts

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Abstract:

Polymer immobilization of chiral catalysts has progressed extensively over the past years. Recent intensive development of chiral organocatalysts resulted in the identification of numerous highly active catalysts, which are, however, still far less effective than transition metal catalysts. Separation of relatively large amounts of organocatalysts from the reaction mixture causes problems during product isolation. In the case of chirally modified metal catalysts, recovery of the valuable metal species and suppression of metal leaching are perpetually important requirements in the design of environmentally friendly chemical processes. Various types of chiral organocatalysts and metal catalysts have been immobilized as pendant groups onto the side chains of polymer supports. Another important polymer immobilization technique is the incorporation of a chiral catalyst into its main chain, with several types of chiral catalyst monomers having been copolymerized with achiral monomers for their production. Recently, the synthesis of chiral main-chain polymeric catalysts has progressed extensively. Moreover, many examples of polymer-immobilized catalysts exhibited higher enantioselectivities in comparison to those of the corresponding low-molecular-weight catalyst. The development of these polymer-immobilized chiral

catalysts, which have largely been reported in the last five years, is reviewed in this article.

1. Introduction

Immobilization of chiral catalysts onto polymers for catalytic asymmetric reactions represents an attractive approach towards increased sustainability in organic synthesis. Compared to transition metal catalyzed reactions, a relatively large amount of organocatalyst is required for complete reaction, with at least 10 mol % of organocatalyst required in most cases. Separation of these catalysts is sometimes a troublesome process. Chiral quaternary ammonium salts are important organocatalysts in a variety of asymmetric transformations and their amphiphilic properties are essential for their ability to act as phase transfer catalysts.[1] However, the amphiphilicity of such catalysts usually hinders their separation from the reaction mixture. Polymer-immobilization of the organocatalyst is one efficient methodology to overcome such problems.[2] In such cases, almost perfect separation of the polymeric catalyst is achieved[3] and the recovered catalysts can be reused successfully many times.

Similar problems are encountered in asymmetric catalysis using chirally modified metal complexes. These species offer many inherent advantages, such as high selectivity, high catalytic activity, mild reaction conditions, and predictable behavior. However, difficulties associated with the recovery and recycling of the catalysts, as well as product contamination caused by metal leaching, significantly hinder their practical applications in the asymmetric synthesis of optically active compounds, particularly for pharmaceutical processes.[4] Polymer immobilization of such chirally modified metal catalysts offers significant advantages. However, insolubility of the crosslinked

polymeric catalysts sometimes lowers their catalytic activity and the enantioselectivity is usually decreased in comparison to the corresponding low-molecular-weight catalysts in solution systems. However, recently developed polymeric catalysts often show catalytic activity and enantioselectivity that is almost identical to the original unsupported catalyst. To understand the latest significant progress made in asymmetric polymer-immobilized chiral catalysis, we surveyed the literature published since 2010 in this area.

2. Asymmetric reactions using polymers containing catalysts in their side chain pendant group

Side chain functionalization of the polymer support, followed by modification with a chiral catalyst, has been extensively investigated for the preparation of polymeric chiral catalysts. The use of organocatalysts has been recognized as an essential method in the organic synthesis of chiral compounds. Recently, chiral organocatalysts have been developed extensively but, although some show high catalytic activity, in most cases chiral quaternary ammonium salts must be used to increase the rate of reaction due to their relatively low catalytic activity in comparison to transition metal catalysts. For the same reason, the use of over 10 mol % of the catalyst is usually required to effectively facilitate the reaction. Separation of the organocatalyst from the reaction mixture can also be problematic. Immobilization of such chiral organocatalysts onto polymers may solve these problems, as insoluble polymeric catalysts can be easily separated from the reaction mixture and reused many times. Different types of chiral organocatalysts have been attached onto the side chain of crosslinked insoluble polymers. The following is a description of recent developments in polymer-immobilization of chiral organocatalysts.

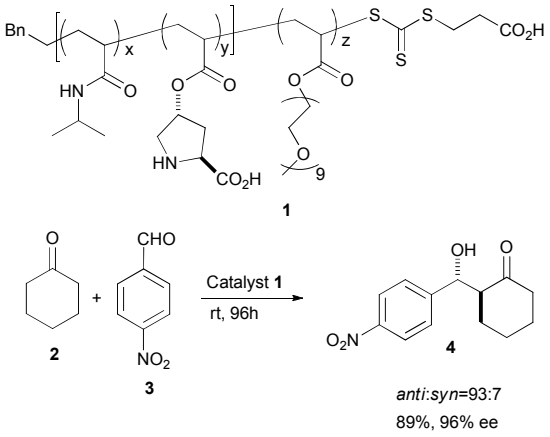
2.1 Polymer-immobilized chiral organocatalysts

Various types of chiral organocatalysts have been attached to the side chains of polymer supports. Several recent review articles related to this subject have been published.[2, 5,6,7,8,9,10] Most of these are focused on polymers that are covalently bonded to the chiral organocatalyst. A review of chiral organocatalysts that are linked to the support with a non-covalent bond is also available.[11] The recent examples of immobilized chiral organocatalysts include proline, its derivatives, other amino acids, peptides, imidazolidinones, BINOL derivatives, and cinchona alkaloids.

2.1.1 Immobilized proline-derived catalysts

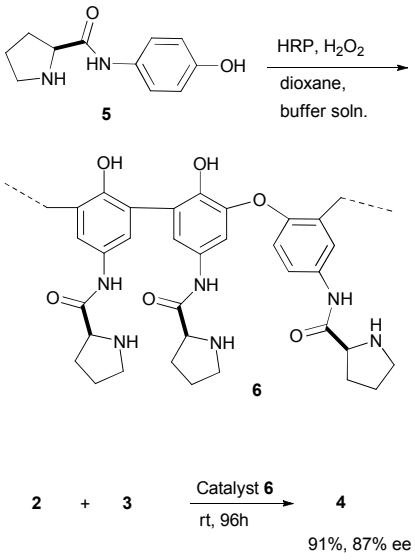
Proline and its derivatives are quite effective organocatalysts for a variety of asymmetric transformations. Polymer-immobilized proline derivatives have been developed and used as efficient catalysts for the asymmetric reactions described below.

Suzuki et al. recently reported the tethering of (*S*)-proline moieties on block copolymers (**1**) that consisted of thermoresponsive poly(*N*-isopropylacrylamide) and PEG-grafted polyacrylate blocks.[12] Aldol reactions between ketone **2** and aryl aldehyde **3** were then conducted in aqueous solution. The aldol product **4** was obtained in a high yield and with high diastereo- and enantioselectivity (96% ee) (Scheme 1).



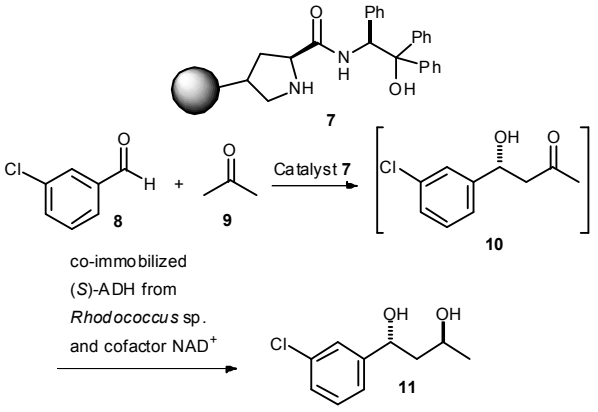
Scheme 1

Phenolic (*S*)-prolinamide **5** was enzymatically polymerized using horse radish peroxidase (HRP) to give the polymer-immobilized prolinamide **6**.[13] **6** was then used as a catalyst for the direct aldol reaction of **2** and **3** to give the aldol addition product **4** in a good yield and with high diastereoselectivity (up to dr 6:94) (Scheme 2).



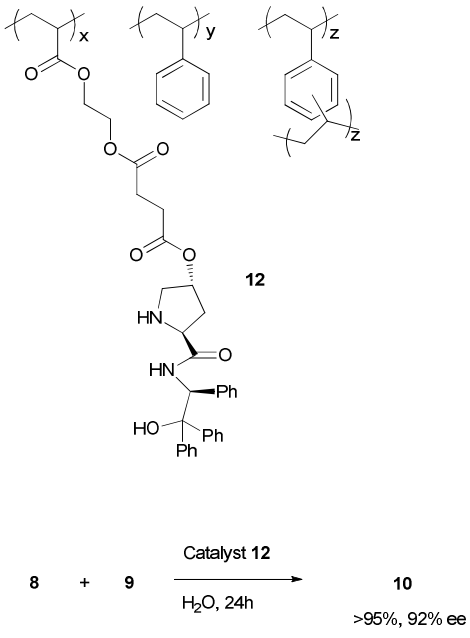
Scheme 2

An (*S*)-proline functionalized chiral amide alcohol was attached to a polymer to give **7**, which was used as a catalyst for the asymmetric aldol reaction of **8** and **9** to afford **10**, followed by its conversion to **11** (Scheme 3).[14]



Scheme 3

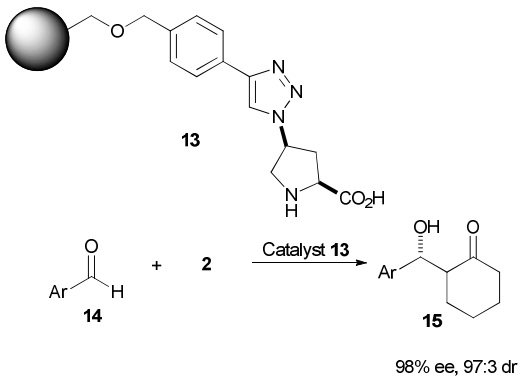
The hydroxy group of hydroxyl proline was used to attach a prolinamide structure onto a crosslinked polymer through an ester linkage. The resulting polymeric prolinamide alcohol **12** was used as a catalyst in the asymmetric direct aldol reaction of aldehyde **8** and acetone (**9**) to afford **10** (Scheme 4).[15]



Scheme 4

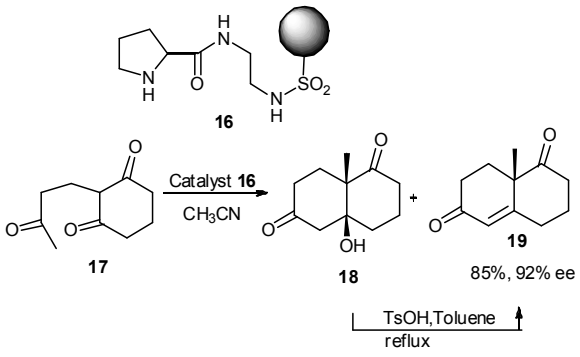
(*S*)-Proline moieties bound to a thermoresponsive polymer nanoreactor efficiently

directed the asymmetric aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in water with excellent yields and enantioselectivities.[16] An (*S*)-proline structure was attached to a crosslinked polymer using an azide-acetylene click reaction. The resulting polymeric proline **13** was used as a catalyst in the asymmetric aldol reaction between aromatic aldehyde **14** and **2** to form **15** in a flow system (Scheme 5).[17]



Scheme 5

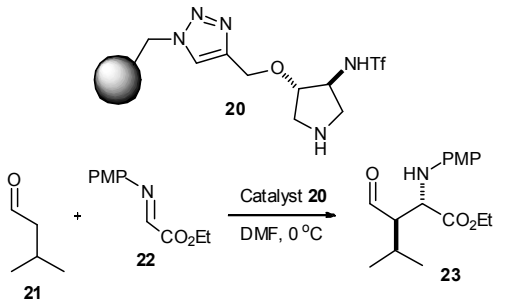
(*S*)-Prolinamide was attached to polystyrene through a sulfonamide linkage to give **16**, which was used as a catalyst for the asymmetric cyclization of triketone **17** to form **18** and **19** (Scheme 6).[18]



Scheme 6

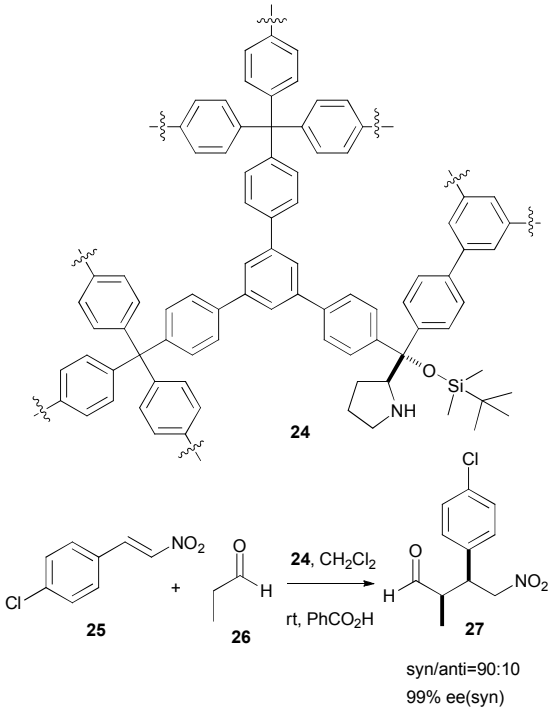
Polystyrene-immobilized chiral pyrrolidine **20** was used as a catalyst in the asymmetric Mannich reaction of aldehyde **21** and imine **22** to form **23**. High *anti* selectivity was

observed using this catalyst[19] and the enantioselectivity was higher when using **20** than when using the unsupported catalyst (Scheme 7). The immobilized catalyst was used in a continuous flow system. Proline-based monoliths were also prepared and used as catalysts for an asymmetric Mannich-type reaction.[20]



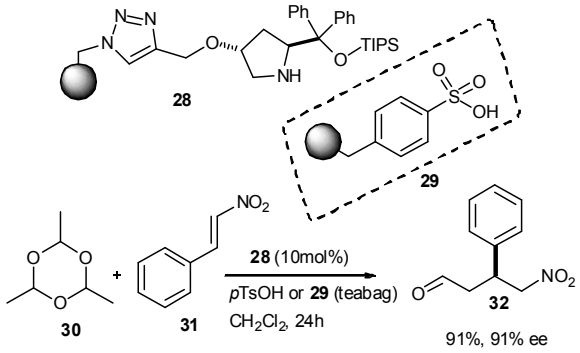
Scheme 7

Diarylprolinol silyl ethers, the so-called Jørgensen–Hayashi catalysts, have been immobilized onto polymers.[21,22, 22b] Wang et al. reported the bottom-up construction of chiral porous organic networks with an embedded asymmetric Jørgensen–Hayashi organocatalyst.[23] Michael addition to nitroalkenes **25** by aldehydes **26** in the presence of polymeric catalyst **24** gives the desired product **27** in excellent yield (99%), with high enantioselectivity (up to 99% ee), and high diastereoselectivity (dr 97:3) (Scheme 8).



Scheme 8

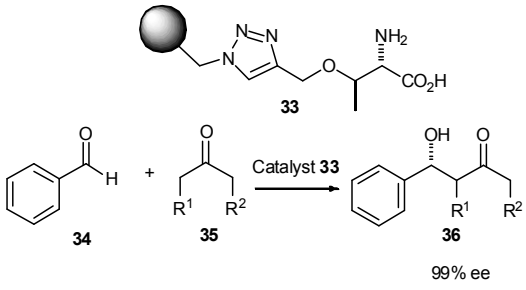
Chiral pyrrolidine catalyst **28** is effective for the Michael reaction of acetaldehyde and β-nitrostyrene (**31**). Since acetaldehyde is highly volatile and susceptible to oligomerization, it is best used by in situ generation with an acid catalyst. However, an acid catalyst cannot coexist with an amine catalyst as the catalysts will be deactivated. Pericas et al. proposed a new approach, using a tea bag to hold the polymer-immobilized sulfonic acid catalyst **29** in order to separate the acid from the chiral amine catalyst. With the polymeric sulfonic acid in the tea bag, trioxane **30** was easily decomposed to generate acetaldehyde, which participated in the Michael reaction with **31,** catalyzed by polymer-immobilized chiral amine catalyst **28** (Scheme 9).[24]



Scheme 9

2.1.2 Immobilized amino acid derivatives

In addition to proline and its derivatives, other amino acids have been used as chiral organocatalysts. One recent example is the use of L-threonine, whose hydroxy group enabled its linkage to the polymer side chain. The resulting polymeric L-threonine **33** acts as an readily recyclable, highly reactive, and stereoselective (up to 99% ee) catalyst for the aldol reaction of aromatic aldehyde **34** with ketone **35** to form **36** in an aqueous environment (Scheme 10).[25]



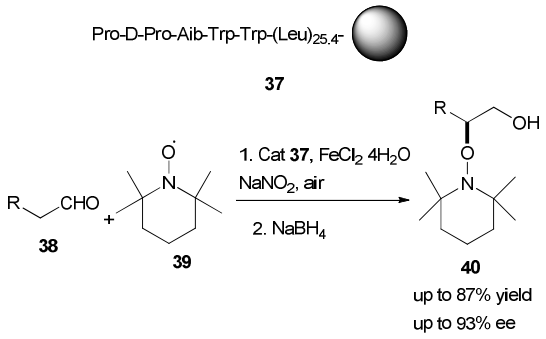
Scheme 10

2.1.3 Immobilized peptide catalysts

Peptides are also promising candidates for chiral organocatalysts.[26] Although most peptides have a dynamic structure in solution, some can adopt a stable secondary structure, depending on the amino acid sequence. From only 20 naturally occurring

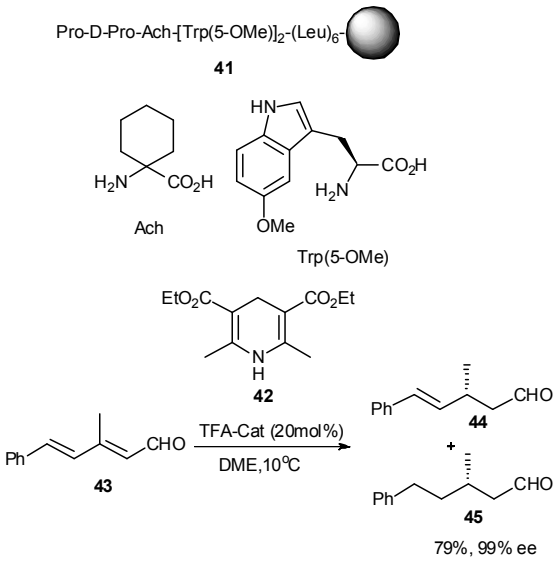
amino acids, there are many sequence combinations possible with, for example, 3.2 million different pentapeptide sequences available. Some of the peptides developed exhibited efficient catalytic activity in asymmetric reactions although their separation and recovery is sometimes difficult. Immobilized peptides have recently been prepared and used as catalysts for asymmetric synthesis. The following is a description of examples of peptide catalysts attached to the side chain of the polymer.

Kudo and Akagawa designed peptide catalyst **37** with a terminal five-residue Pro-D-Pro-Aib-Trp-Trp combined with polyleucine, which was attached to a polymer support. **37** was then used for the asymmetric α-oxyamination of aldehydes **38** with **39** to form **40** in aqueous media (Scheme 11).[27]



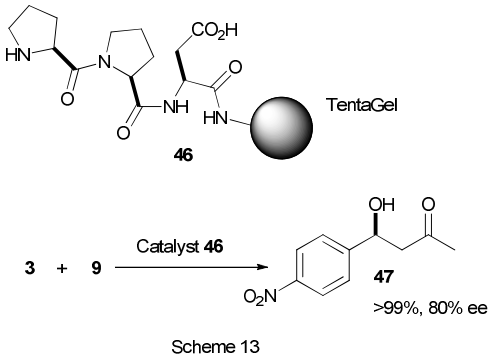
Scheme 11

The same group recently developed a similar peptide catalyst **41** and applied it to the asymmetric reduction of unsaturated aldehydes. By using the peptide polymer **41**, in combination with **42**, a highly regio- and enantioselective reduction of α,β,γ,δ-unsaturated aldehyde **43** to afford **44** and **45** was achieved (Scheme 12).[28]



Scheme 12

The most reactive peptidic organocatalysts developed to date for the aldol[29] and Michael addition[30,31] reactions were reported by Wennemers et al. A continuous flow process was also developed by using the polymer-immobilized Wennemers' tripeptide **46** for the synthesis of **47** (Scheme 13).[32]

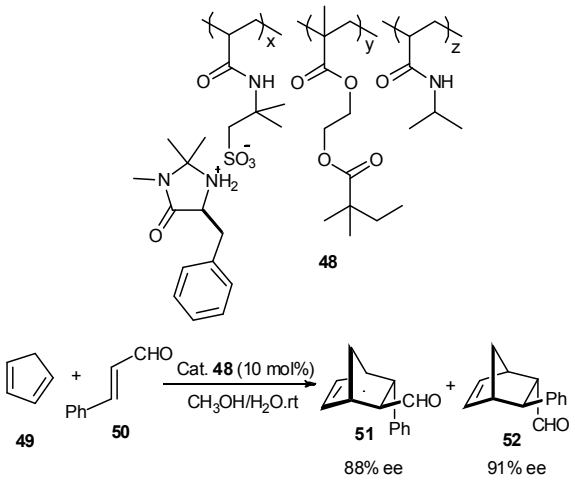


Scheme 13

2.1.4 Immobilized chiral imidazolidinone (MacMillan) catalysts

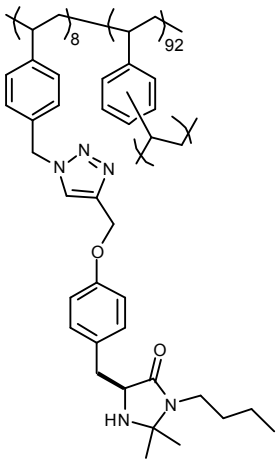
Chiral imidazolidinones are known as MacMillan catalysts. Several approaches for their immobilization make use of a covalent bond between the polymer support and the catalyst moiety. An alternative method is via ionic bond formation. Imidazolidinones

readily form its sulfonates allowing their immobilization through an ionic bond with the ammonium sulfonate structure. The immobilized imidazolidinone sulfonate **48** was successfully used to catalyze the asymmetric Diels–Alder reaction of cyclopentadiene (**49**) and cinnamaldehyde (**50**) to form **51** and **52** (Scheme 14).[33]



Scheme 14

Radical copolymerization of divinylbenzene and a chiral imidazolidinone monomer in a stainless steel column, in the presence of dodecanol and toluene as porogens, afforded **53**, comprising a MacMillan catalyst immobilized onto a monolithic reactor (Figure 1). By using **53**, the Diels–Alder reaction of cinnamaldehyde and cyclopentadiene was performed in a continuous flow system to give the chiral adduct with 90% ee. The same reactor was applied to the asymmetric 1,3-dipolar nitrone-olefin cycloaddition and a Friedel–Crafts alkylation.[34]



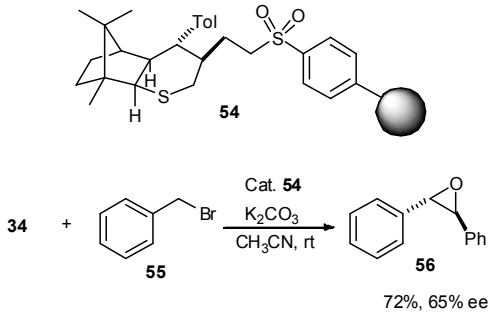
53

Figure 1

2.1.5 Immobilized chiral organocatalysts

As well as amino acids, peptides, and their derivatives, other chiral organocatalysts have also been attached to polymers. Some recent examples involving terpenes and cinchona alkaloids are listed below.

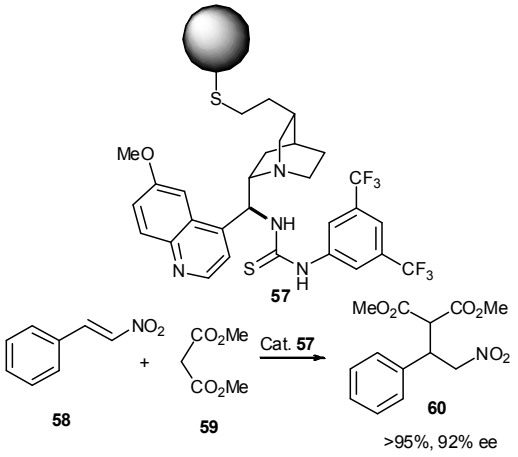
Polymer-immobilized camphor-derived sulfide **54** was used to catalyze the asymmetric epoxidation reaction of **34** and **55** to form **56** (Scheme 15).[35]



Scheme 15

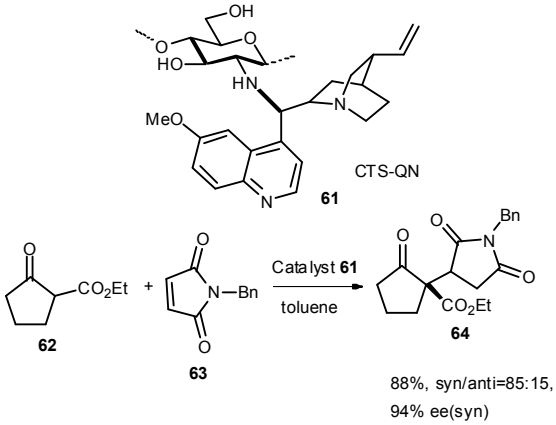
A mixture of an azo initiator, a polyfunctional thiol, a polyfunctional alkene, and a cinchona-derived organocatalyst in solvent was added to water and copolymerized

on heating via thiol–ene reactions. The obtained polymeric cinchona-derived organocatalyst **57** showed excellent catalytic activity in the Michael addition reaction of **58** and **59** to afford **60** (Scheme 16).[36]



Scheme 16

Instead of synthetic polymer supports, biopolymers such as chitosan were used for the immobilization of organocatalysts. Quinine was attached to chitosan through an amination reaction of quinine tosylate. Chitosan-immobilized quinine **61** was an efficient catalyst for the asymmetric Michael addition of 1,3-dicarbonyl compound **62** and maleimide (**63**) to give the chiral product **64** in 94% ee (Scheme 17).[37]



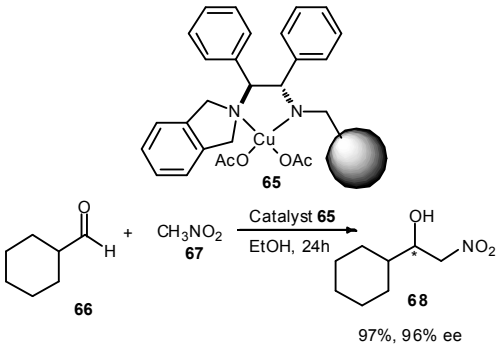
Scheme 17

2.2 Immobilized chirally modified metal catalysts

Chirally modified transition metal catalysts are a powerful tool for asymmetric synthesis due to their high catalytic activity. Immobilization of the transition metal species onto the polymers is a useful and effective technique to facilitate the recovery of the rare metal species and suppress leaching. Recent publications have demonstrated new developments in this field. In most cases, the chiral ligand molecule was attached to the side chain of the polymer.

2.2.1 Asymmetric Henry reactions

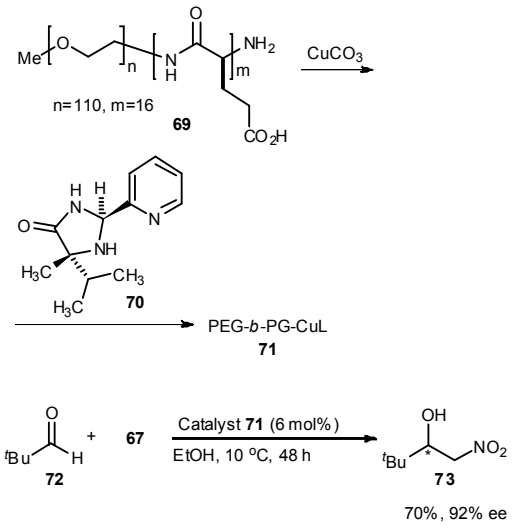
A chiral 1,2-diphenylethylenediamine derivative was attached to crosslinked polystyrene. The polymeric chiral diamine ligand was treated with $Cu(OAc)_2$ to give **65** and used for the catalysis of the Henry reaction, such as that of aldehyde **66** with nitromethane (**67**) in ethanol. The corresponding 2-nitroethanol **68** was formed in a quantitative yield at 20 °C with an ee values of 96% (Scheme 18).[38]



Scheme 18

The complex of block copolymer α-methoxypoly(ethylene glycol)-β-poly((*S*)- glutamic acid) (**69**) with (2*R*,5*S*)- or (2*S*,5*R*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidin-4-one (**70**) with Cu(II) to form **71**, was used as a catalyst for

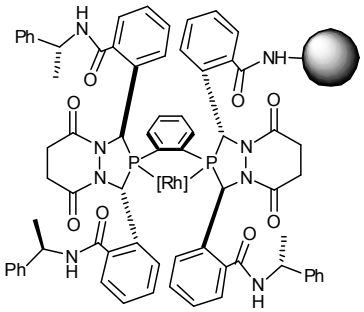
the reactions of substituted aldehydes **72** with nitromethane (**67**). A high yield of the chiral β-nitroalcohol **73** (70%) was obtained with high enantioselectivity (92% ee) using the polymeric catalyst (Scheme 19).[39]



Scheme 19

2.2.2 Asymmetric hydroformylation

Chiral bis-3,4-diazaphospholane (BDP) ligands were attached to an amine-functionalized polystyrene resin.[40] The immobilized BDP was treated with $Rh(acac)(CO)_2$ to prepare the polymeric Tentagel-immobilized bisdiazaphospholane rhodium catalyst **74**, which was used for the asymmetric hydroformylation of prochiral alkenes, such as the highly selective conversion of **75** to **76** and **77** (Scheme 20).[41]



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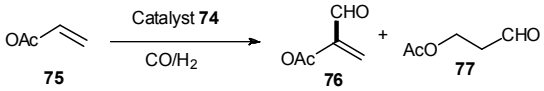


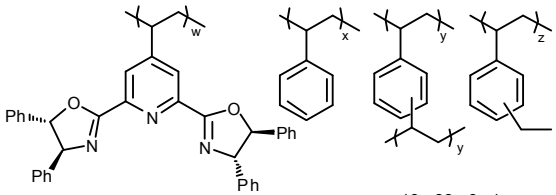
75 76 77

b:l=50:1, 92% ee

Scheme 20

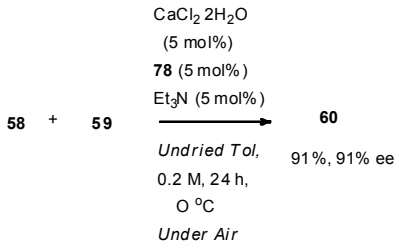
2.2.3 Asymmetric 1,4-addition reactions

Polymer-immobilized chiral pyridine bisoxazoline (Pybox) ligands **78** were treated with $CaCl_2$ to give the polymeric Pybox–Ca catalysts. The reaction of methyl malonate (**58**) with trans-β-nitrostyrene (**59**) proceeded smoothly in the presence of the polymeric catalyst to give the chiral γ-nitro carbonyl compound **60** with a high yield and high enantioselectivity (Scheme 21). The polymeric Ca catalyst was applied in a continuous flow system and showed a high TON.[42,43]



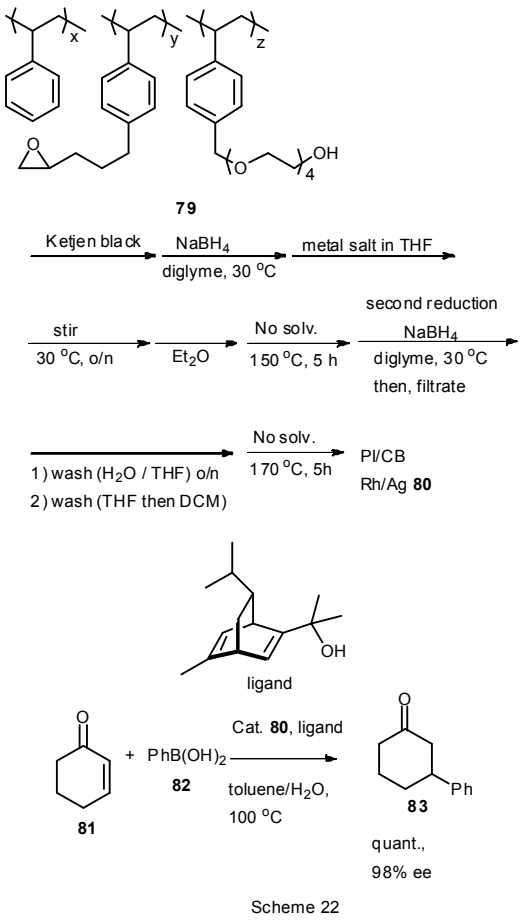
w :x : y : z = 13 : 83 : 3 : 1

78



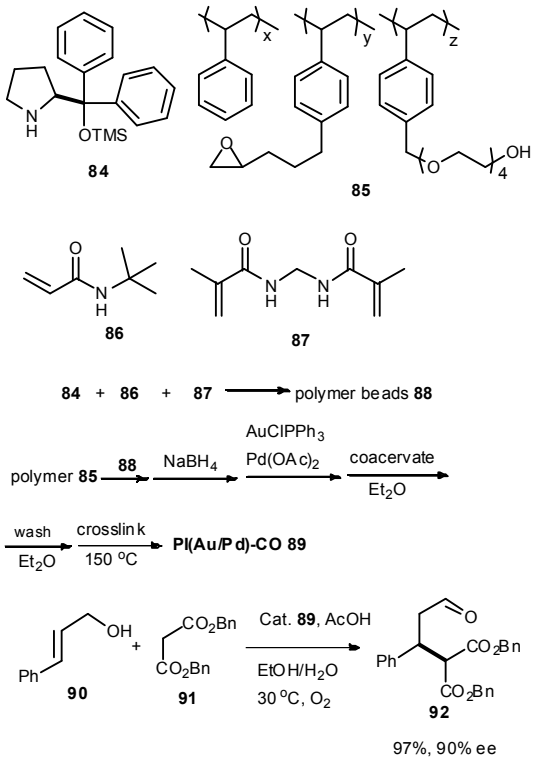
Scheme 21

79 reacted to form heterogeneous metal nanoparticle catalysts **80**, which comprise Rh or Ag on polymer-incarcerated (PI) carbon black (CB), as shown in Scheme 22 and **80** applied to the asymmetric 1,4-addition of arylboronic acid **81** to enone **82** to afford **83** without leaching of the metals.[44]



Scheme 22

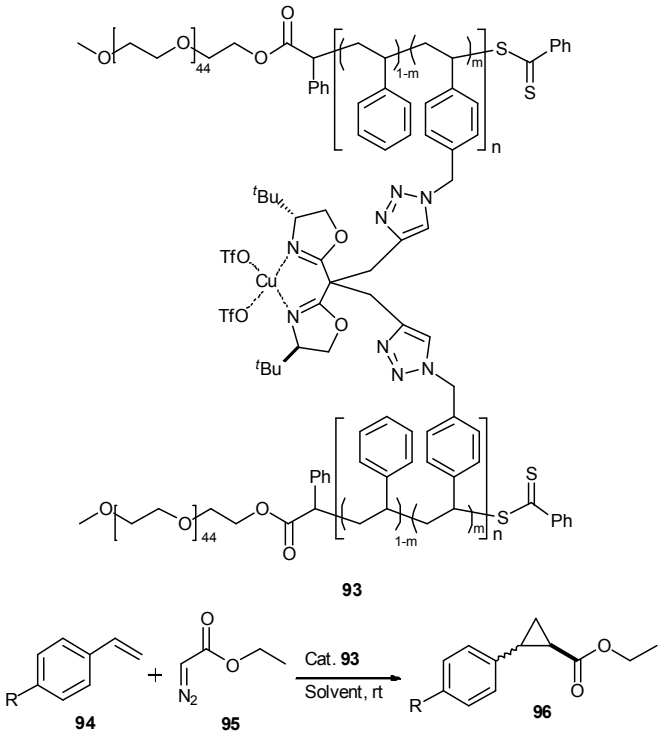
A heterogeneous bifunctional chiral catalyst for an asymmetric tandem oxidation process was developed.[45] In homogeneous catalysis, undesired interactions between catalysts may lead to their deactivation. The heterogeneous bifunctional catalyst overcomes this problem by site separation via immobilization. Such a polymeric catalyst, **89**, was prepared as shown in Scheme 23. By using this polymeric catalyst, the one-pot conversion of **90** and **91** to afford **92**, by aerobic oxidation followed by asymmetric Michael addition, proceeded smoothly to give the chiral product with high enantioselectivity (Scheme 23).



Scheme 23

2.2.4 Asymmetric cyclopropanation

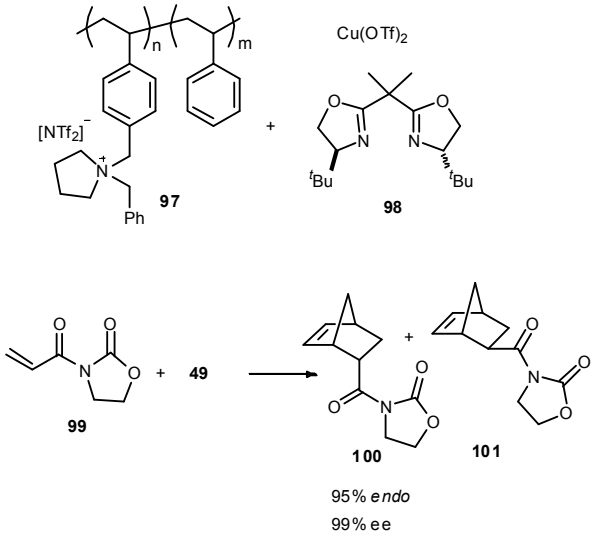
A copper-bisoxazoline catalyst was immobilized inside the polymeric membrane **93** for use as a catalyst for asymmetric cyclopropanation. In the presence of **93**, the reaction between **94** and **95** proceeded smoothly to give chiral cyclopropane derivative **96** (Scheme 24).[46]



Scheme 24

2.2.5 Asymmetric Diels–Alder reaction

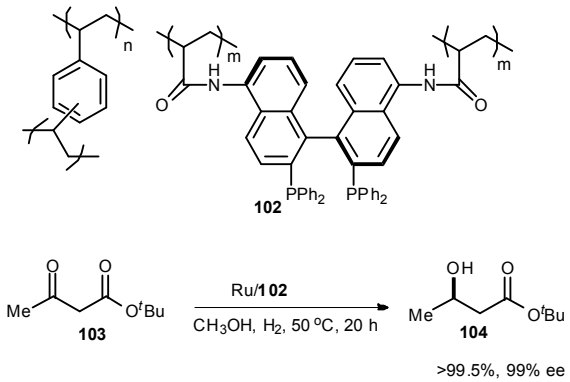
Polymeric ionic liquid **97** was used for the immobilization of the copper-bisoxazoline catalyst **98** for an asymmetric Diels–Alder reaction. The reaction of **99** and **49** gave **100** and **101** with higher *endo* selectivity and enantioselectivity than the corresponding homogeneous reactions (Scheme 25).[47]



Scheme 25

2.2.6 Asymmetric hydrogenation[48,49,50]

Copolymerization of divinylbenzene and a chiral BINAP monomer gave polymer-immobilized BINAP **102**. The Ru complex of **102** showed excellent catalytic activity in the asymmetric hydrogenation of β-keto ester **103** to give β-hydroxyester **104** with quantitative conversion and with high enantioselectivity (Scheme 26).



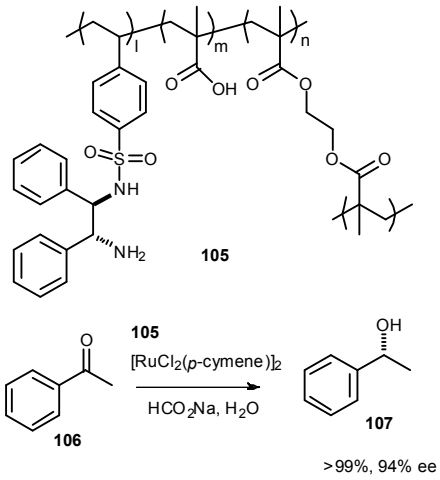
Scheme 26

2.2.7 Asymmetric transfer hydrogenation (ATH) of ketones

The catalytic ATH of ketones is a simple and mild procedure for chiral alcohol synthesis.

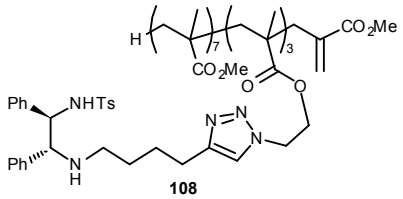
Various chiral catalysts, based on complexes of Ti, Ru, Rh, and Ir, have been developed for transfer hydrogenation. Among them, the most significant to date is the complex of Ru(II) with optically active N^1-*p*-toluenesulfonyl-1,2-diphenylethylene-1,2-diamine (TsDPEN), developed by Ikariya and Noyori's group.[51] The complex was immobilized on various support materials, such as sulfonated polystyrene,[52] PEG,[53] silica,[54,55] and phosphonate-containing polystyrene copolymers.[56] These immobilized catalyst complexes performed efficiently in aqueous medium.

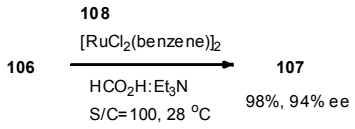
By precipitation polymerization of the TsDPEN monomer, styrene, and the crosslinking agent, narrowly dispersed polymer microspheres **105**, with diameters of sub μm to a few μm, were prepared. Core–shell type microspheres showed higher catalytic activity than the other microsphere catalysts for reduction of ketone **106** to form **107** with high enantioselectivity (Scheme 27).[57]



Scheme 27

A chiral diamine monosulfonamide ligand was attached to a soluble polymer through triazole linkage. The soluble polymeric chiral ligand **108** was used for complexation with Ru and then used as a catalyst for ATH (Scheme 28).[58]





Scheme 28

Soluble and surface-functionalized solid polymers were also used as supports for a modified tethered Rh(III)–TsDPEN complex **109** (Figure 2).[59] The polymeric catalysts were applied to the ATH of phenyl ketones in an aqueous solution of sodium formate. High enantioselectivities (up to 99%) and good activity were achieved.

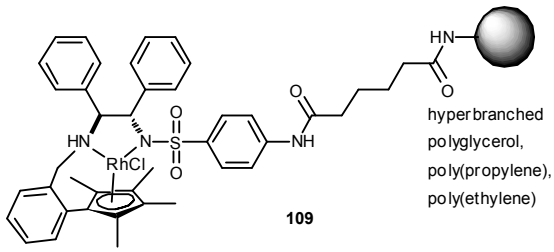
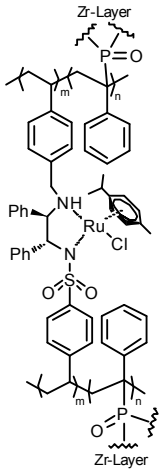


Figure 2

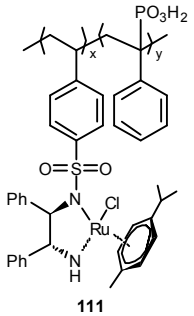
Phosphonate-containing polystyrene copolymers, containing an *N*′-alkylated TsDPEN and double-stranded polystyrene chains, were prepared. Through the coprecipitation of their supported ruthenium–polystyrene copolymers with NaH_2PO_4 and $ZrOCl_2$, pillared hybrid zirconium phosphate–phosphonate-anchored ruthenium catalysts **110** were obtained. In the aqueous ATH of aromatic ketones, the anchored Ru catalysts showed good catalytic activities, chemoselectivities (~100%), and enantioselectivities (up to 95.6% ee) (Figure 3).[60]



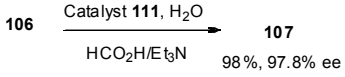
110

Figure 3

Similar polymers, phosphonate-containing copolystyrenes with a chiral TsDPEN ligand, were used as chiral polymeric ligands. The corresponding immobilized Ru catalysts **111** were used for the same reaction to give the secondary alcohol **107** in a high yield with high enantioselectivity (97.8% ee) (Scheme 29).[56]



111

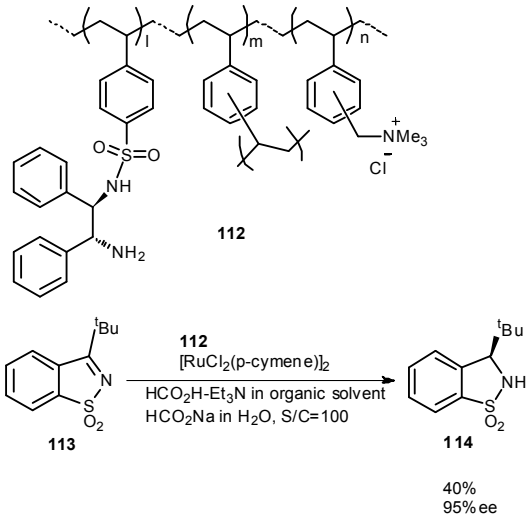


Scheme 29

2.2.8 Asymmetric transfer hydrogenation (ATH) of imines

ATH of cyclic sulfonimine **113** was conducted with a polymeric chiral

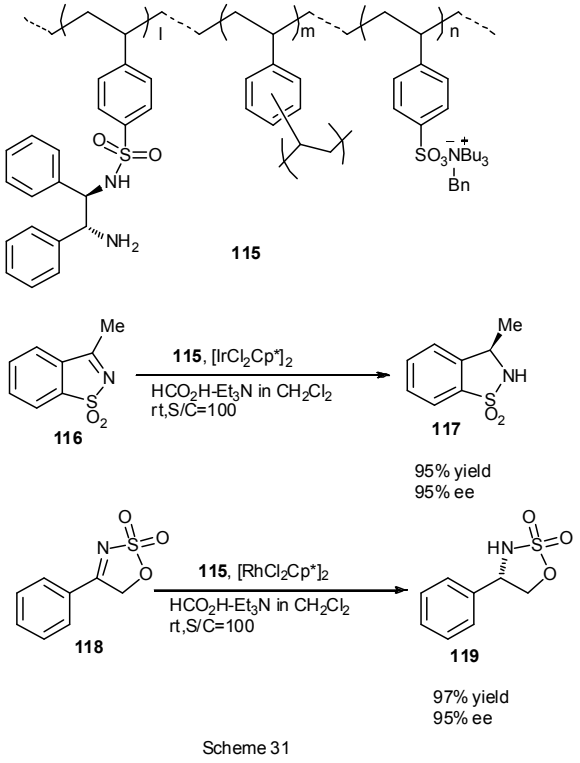
monosulfonamide ruthenium complex. Various polymers have been examined as supports. Polystyrene crosslinked with divinylbenzene showed the best performance for the ATH reaction in the organic solvent CH_2Cl_2. However, in the aqueous system, no reaction occurred with the polystyrene-based support due to its high hydrophobicity. The quaternary ammonium pendant group is important for the facilitation of this reaction in water. Therefore, by using the polymeric chiral ligand **112**, 95% ee was attained for the conversion of **113** to **114** in water (Scheme 30).[61]



Scheme 30

An Ir complex of the polymer-immobilized chiral 1,2-diphenyldiamine monosulfonamide **115** is an excellent catalyst for the asymmetric reduction of cyclic imine **116** to **117** (Scheme 31). Quaternary ammonium sulfonate pendant groups in the support polymer play an important role in achieving high catalytic activity in both organic and aqueous systems. In CH_2Cl_2 the reaction was complete within 1 h, even in a heterogeneous system with the polymeric catalyst. The Rh complex of the same polymer chiral ligand showed high catalytic activity in the reduction of cyclic sulfamidate imine **118** to the chiral cyclic amino alcohol sulfonamide **119**, which is an

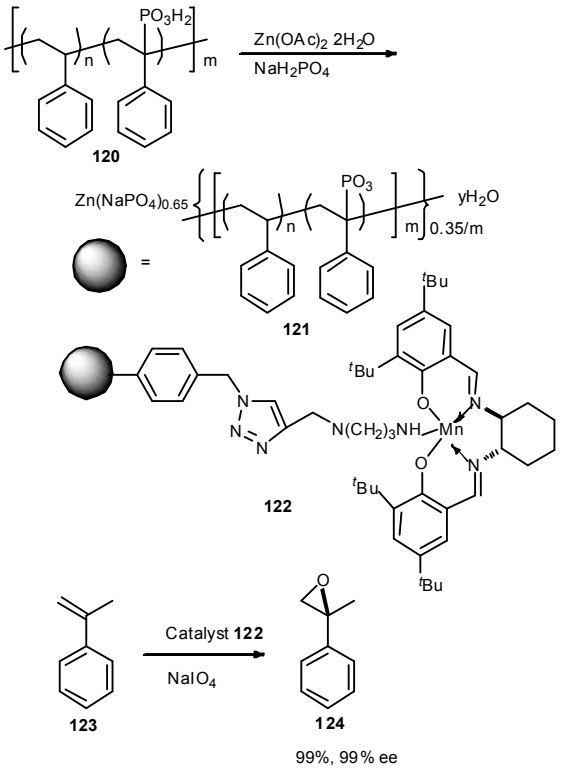
important precursor of chiral amino alcohols, in a high yield and with high levels of enantioselectivity (95% ee) (Scheme 31).[62]



Scheme 31

2.2.9 Asymmetric epoxidation[63,64,65,66,67,68,69]

Chemical modification of zinc poly(styrene-phenylvinylphosphonate)-phosphate[70] or zirconium poly(styrene-isopropenylphosphonate)-phosphate,[71,72] followed by attachment of a chiral manganese(III)–salen complex gave the polymer-immobilized catalyst **122**. **122** was used for the asymmetric epoxidation of unfunctionalized olefins, such as that of **123** to give **124** (Scheme 32). Higher catalytic activities than those of the corresponding homogeneous chiral manganese(III)–salen catalyst were achieved with the immobilized catalyst.

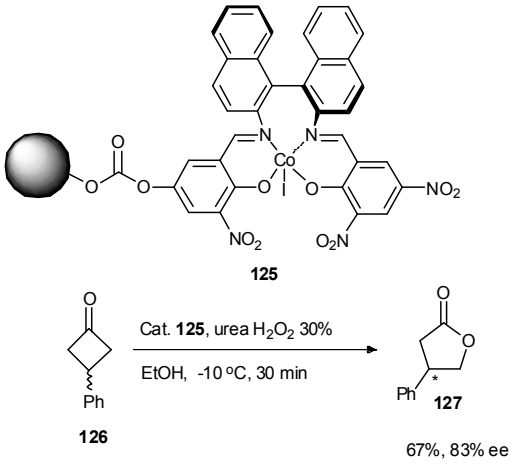


Scheme 32

Jacobsen's catalyst was also attached to a mesoporous phenolic polymer[73] and dendrimer,[74] which were then used as catalysts for asymmetric epoxidation reaction.

2.2.10 Asymmetric Baeyer–Villiger reaction

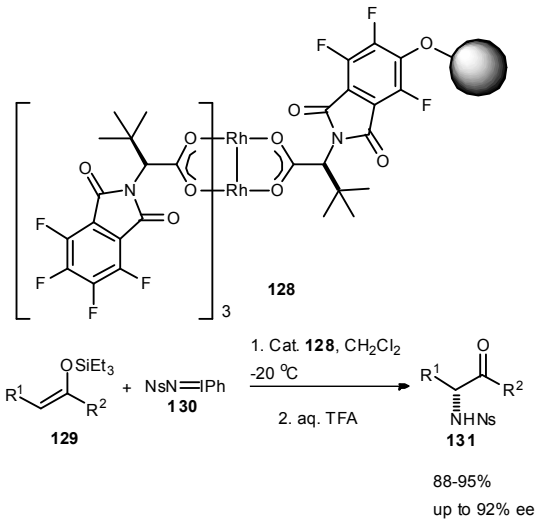
Enantioselective Baeyer–Villiger oxidation, mediated by polymer-immobilized chiral cobalt(II)–salen complex **125**, of 3-substituted cyclobutane **126** afforded chiral γ-butyrolactone **127** (Scheme 33).[75]



Scheme 33

2.2.11 Asymmetric amination

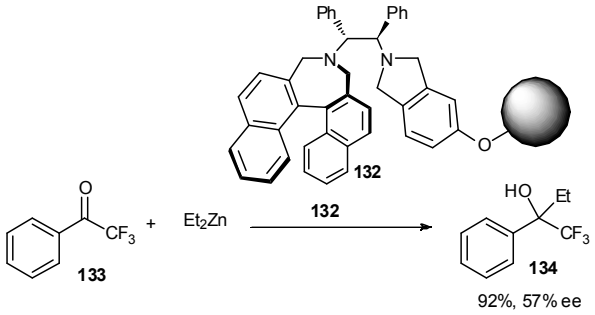
Polymer-immobilized chiral fluorinated dirhodium(II) complex **128** catalyzed the amination of silyl enol ethers **129** with [*N*-(2-nitrophenylsulfonyl)imino]phenyliodinane (NsN=IPh) (**130**) to provide α-amino ketones **131** in high yields and with high levels of enantioselectivity (up to 92% ee) (Scheme 34).[76]



Scheme 34

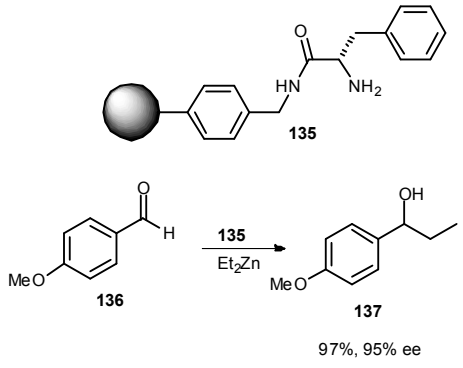
2.2.12 Asymmetric alkylation of aldehydes and ketones[77,78]

The polymer-immobilized (*R*,*R*)-1,2-diphenylethylenediamine derivative **132** mediated the addition reaction between $ZnEt_2$ and trifluoromethyl ketone **133** to afford the chiral alcohol **134** with moderate enantioselectivity (Scheme 35).



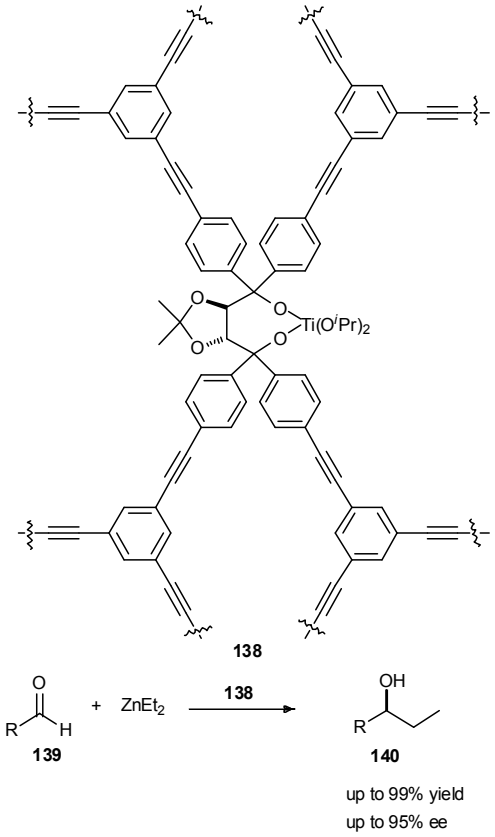
Scheme 35

Polymer-immobilized α-amino amides **135**, derived from natural amino acids, have been synthesized. Their chiral Zn(II) complexes catalyzed the enantioselective addition reaction between $ZnEt_2$ and aldehyde **136** to form chiral secondary alcohol **137** in a high yield and with an enantioselectivity of 95% (Scheme 36).[79]



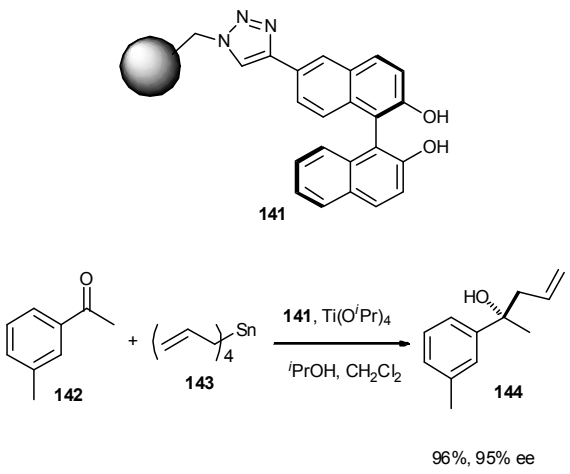
Scheme 36

The TADDOL (α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol) polymer was complexed with a titanium alkoxide to give **138**, which was used as a catalyst in the enantioselective addition between $ZnEt_2$ and aldehydes **139** to form **140**. High catalytic activity with high enantioselectivity were obtained with the polymeric catalyst (Scheme 37).[80]



Scheme 37

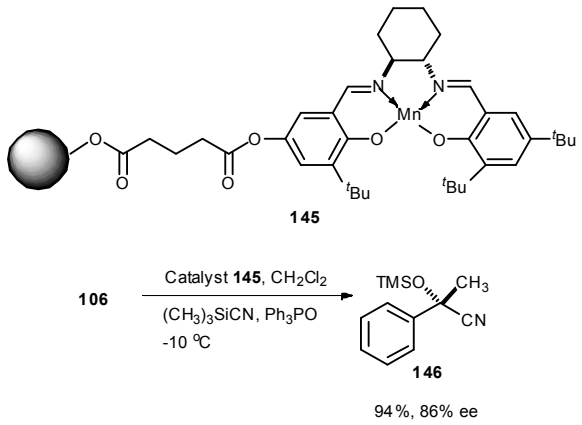
The BINOL moiety was attached to crosslinked polystyrene through a copper-catalyzed alkyne-azide cycloaddition reaction. The polystyrene-immobilized BINOL ligand **141** was converted into its diisopropoxytitanium derivative in situ and used as a catalyst in the asymmetric allylation of ketone **142** with tetraallyl tin **143** to afford **144** (Scheme 38).[81]



Scheme 38

2.2.13 Asymmetric cyanosilylation

Asymmetric trimethylsilylcyanation of ketone **106** with $(CH_3)_3SiCN$ proceeded in the presence of a JandaJel-immobilized chiral copper(II)– salen complex **145** as the catalyst and Ph_3PO to give optically active cyanohydrin trimethylsilyl ethers **146** in 83–96% yields with 52–84% ee at room temperature (Scheme 39).[82]

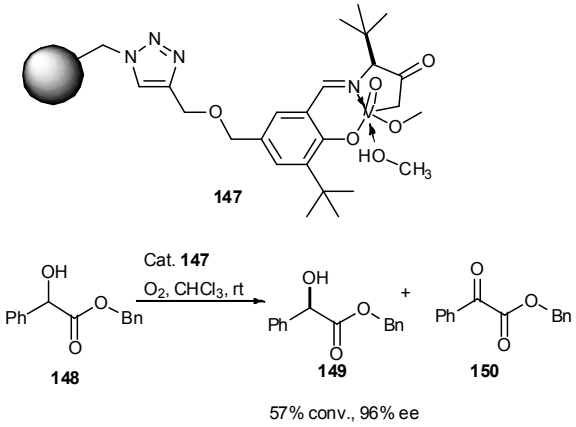


Scheme 39

2.2.14 Asymmetric aerobic oxidation of α-hydroxy acid

Chiral *N*-salicylidene vanadyl(V) *tert*-leucinates were immobilized onto

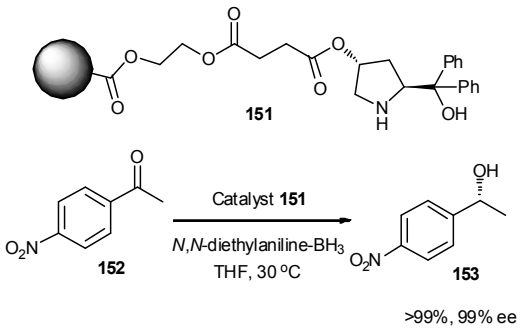
4-azidomethyl-substituted polystyrene through an alkyne-azide click reaction to give **147**, which promoted the asymmetric aerobic oxidation of α-hydroxy ester **148**, to form **149** and **150**, and amides with enantioselectivities of up to 99% ee (Scheme 40).[83]



Scheme 40

2.2.15 Asymmetric borane reduction

Chiral oxazaborolidine catalyzed borane reduction of ketone[84] was performed with a polymethacrylate support. 4-Hydroxy-α,α-diphenyl-(*S*)-prolinol was immobilized onto crosslinked polymethacrylate. The polymeric chiral amino alcohol **151** was used for the asymmetric borane reduction of ketones, such as the reaction of **152** to form **153**. High catalytic activity and enantioselectivities were obtained (Scheme 41).[85]



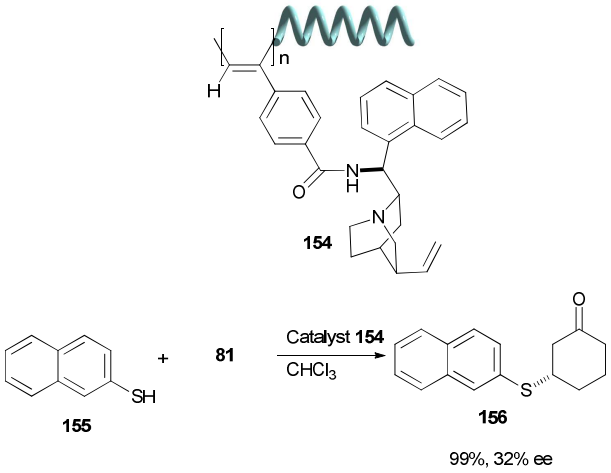
Scheme 41

3. Asymmetric reaction using helical polymers

The use of single-handed helical polymers as support materials is a new strategy for the immobilization of chiral catalysts. Some review articles in this area are available.[86,87,88] Recent developments in helical polymers for chiral catalyst application involve the use of helical poly(phenylacetylene)s as support of chiral catalysts. Helicity of the support polymer may effect on the catalytic activity of the pendant chiral catalyst. Another important approach to this field is the use of polyquinoxaline helical polymer. A very interesting phenomenon in this area is the switching of the helicity, depending on the solvent used, which results in a change in the sense of enantioselectivity for the asymmetric reaction.

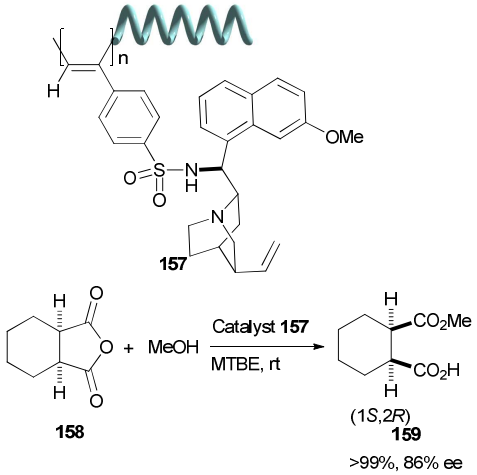
3.1 Helical poly(phenylacetylene)s bearing cinchona alkaloids

Helical poly(phenylacetylene)s bearing cinchona alkaloid derivatives as the pendant groups were synthesized. These helical polymers **154** catalyzed asymmetric conjugated addition and Henry reactions. The polymeric catalysts exhibited a higher enantioselectivity than those obtained through catalysis by their monomeric counterparts. For example, the reaction of **155** to form **156** (Scheme 42).[89]



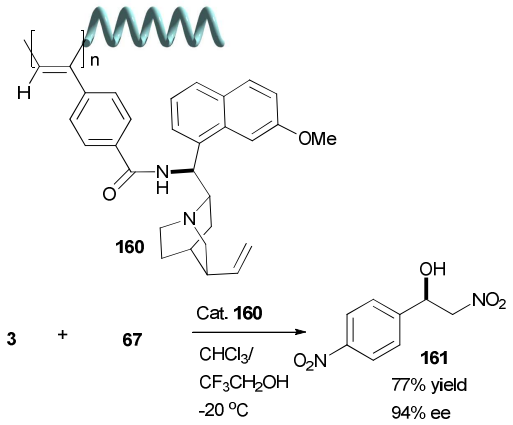
Scheme 42

Helical poly(phenylacetylene)s with amino-functionalized cinchona alkaloid pendant groups, connected to the phenyl rings through a sulfonamide linkage, were synthesized. These chiral polymers **157** were used as catalysts for the enantioselective methanolytic desymmetrization of cyclic anhydride **158** to afford **159** (Scheme 43) and the aza-Michael addition of aniline to chalcone.[90]



Scheme 43

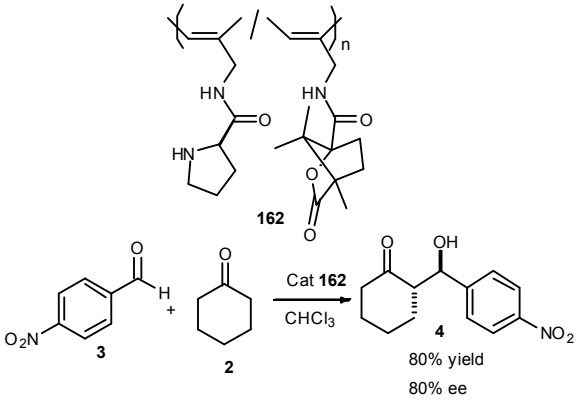
The side chains of the poly(phenylacetylene)s were easily modified to attach a chiral catalyst. These polymeric catalysts were used for asymmetric Henry reactions.[91] When a cinchona alkaloid catalyst was attached to the poly(phenylacetylene)s, the resulting polymeric catalyst **160** showed higher catalytic activity compared to the original monomeric catalyst. The formation of **161** is an example (Scheme 44).



Scheme 44

Substituted polyacetylenes **162** having prolinamide pendant groups were

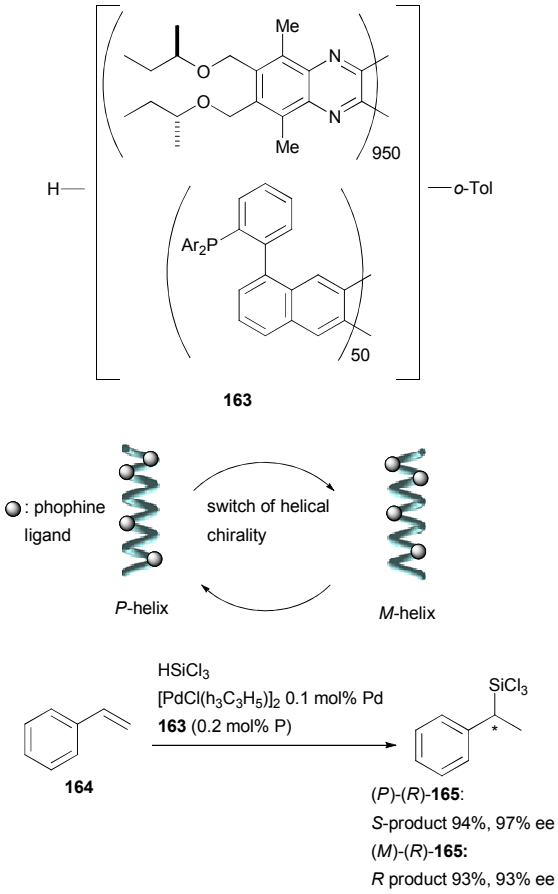
prepared.[92] The prolinamide moiety of the polymer catalyzed the asymmetric aldol reaction of *p*-nitrobenzaldehyde (**3**) and cyclohexanone (**2**) to yield the chiral aldol adduct **4** in 80% yield with 80% ee (Scheme 45).



Scheme 45

3.2 Polyquinoxaline helical polymer

Living aromatizing copolymerization of *o*-diisocyanobenzene monomers generated the polyquinoxaline-based helically chiral phosphine ligands.[93, 94, 95, 96] The chiral reaction environment of chiral polymer was created on the basis of its single-handed helical structure. Asymmetric hydrosilylation of styrene was conducted with the polymeric ligand **163**.[96] Interestingly, helicity of the polymer is switchable with the solvent. In the asymmetric hydrosilylation of **164**, (*P*)-(*R*)-**165** gave *S*-product while (*M*)-(*R*)-**165** yielded *R*-product in high enantioselectivities.



Scheme 46

4. Asymmetric reactions using polymers containing catalysts in their main-chain

A novel approach to the synthesis of chiral polymer catalysts is the preparation of polymers that incorporate the chiral catalyst molecules into their main chain. Polyaddition or polycondensation reactions of chiral catalyst molecules with other achiral monomers gave main-chain chiral polymeric catalysts. These have several advantages over conventional side-chain chiral polymers, such as stereoregular polymer structures, high loading of the chiral catalyst, precise control of the available microenvironment within the chiral polymer, fine tuning of catalytic performance with various polymer designs using achiral comonomers, and facile synthesis. Recent

developments of chiral main-chain polymers and their application to asymmetric catalysis are described below.

4.1 Asymmetric alkylation

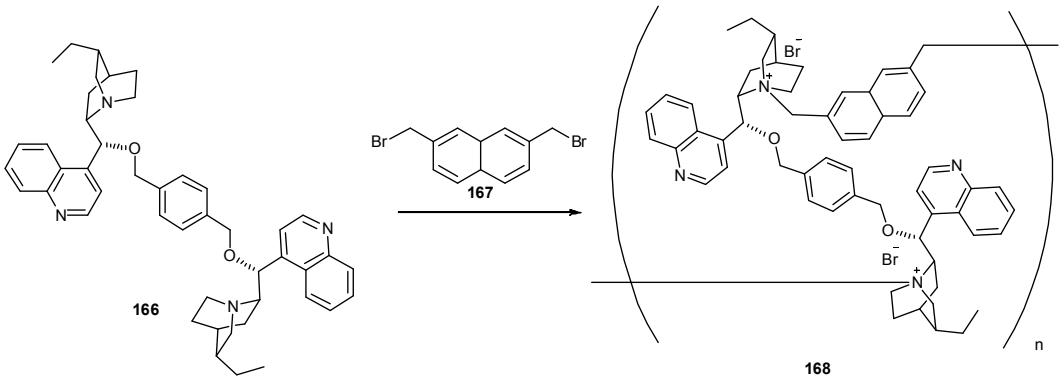
Quaternary ammonium salts of cinchona alkaloid derivatives have been efficient catalysts in the asymmetric alkyation of glycine derivatives, particularly *N*-diphenylmethylene glycine *tert*-butyl ester. This reaction is particularly useful for the synthesis of optically active α-amino acids. The amphiphilic quaternary ammonium structure is necessary as it acts as a phase transfer catalyst between the organic and aqueous phases. However, the amphiphilicity of the catalysts hinders their separation from the reaction mixture. Polymer immobilization of such catalysts is one of the most effective solutions to this problem and, for this purpose, a number of polymer-immobilized quaternized cinchona alkaloids have been developed. However, cinchona alkaloids covalently attached to the side chain of the support polymers showed lower catalytic activity and lower enantioselectivity in asymmetric reactions. Since cinchona alkaloids possess various functionalities, they can be utilized for the preparation of their dimers and polymers.

4.1.1 Chiral polyethers[97]

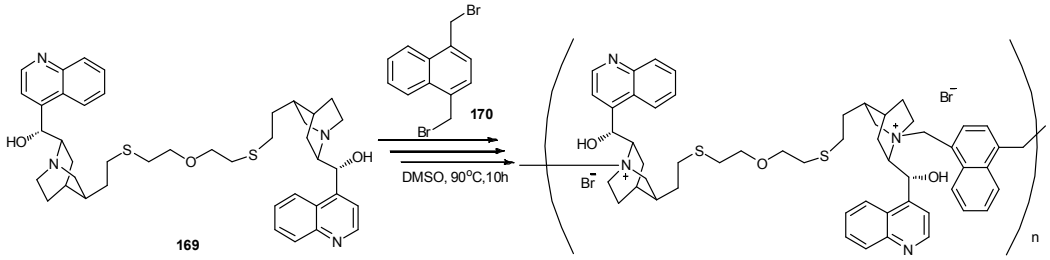
One simple method for the preparation of the chiral polymer of quaternized cinchona alkaloids is the polymerization of quaternized cinchona alkaloid dimers. For example, cinchonidinium dimers were polymerized with achiral dihalides by using the repeated etherification reaction.

4.1.2 Quaternization polymerization[98,99]

When the cinchonidine dimer **166** was prepared by the etherification reaction, the dimer could be polymerized by the quaternization reaction. The obtained chiral polymer structure was the same as that obtained from the etherification polymerization. The chiral polymer structures can be precisely designed by modification of the linker of the dimer and of the dihalides. Chiral dihalides **167** were also used to prepare the chiral cinchonidinium polymers **168** (Scheme 47). Since cinchona alkaloids possess a vinylic double bond, a thiol–ene reaction was also useful for the preparation of their dimers **169**. Thioetherified dimers were then readily polymerized by quaternization polymerization with dihalides **170** to afford **171** (Scheme 48).[100]



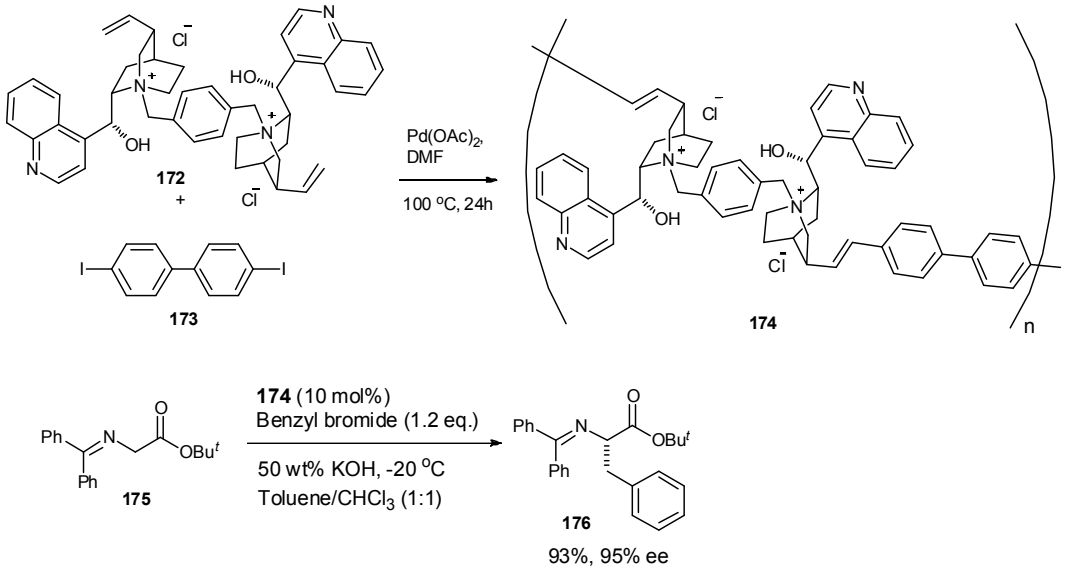
Scheme 47



Scheme 48

4.1.3 Mizoroki–Heck polymerization

The vinylic double bond of the cinchona alkaloid readily reacts with aromatic iodides in the presence of a Pd catalyst. The Mizoroki–Heck coupling was thus applied to the synthesis of chiral polymers containing the cinchonidinium salt structure in their main chain. For example, cinchonidinium dimer **172** and diiodide **173** reacted smoothly in the presence of $Pd(OAc)_2$ to afford the corresponding chiral polymer **174**, with a molecular weight higher than 30 000, in good yield.[101] **174** was then used to catalyze the asymmetric alkylation reaction of **175** to form **176**, as shown in Scheme 49. These chiral cinchonidinium polymers showed high catalytic activity with high enantioselecltivities for the alkylation reaction (Scheme 49).



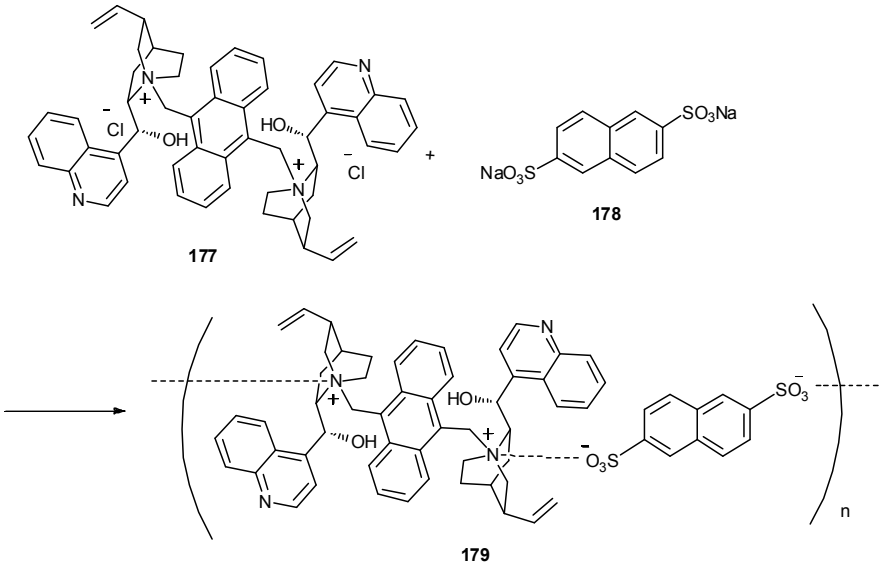
Scheme 49

4.1.4 Ion exchange polymerization[102,103]

The halide anion of the quaternary ammonium salt can be replaced with other anions such as hydroxide or sulfonate. In particular, the quaternary ammonium sulfonates of cinchona alkaloid derivatives are stable enough to be used for polymer synthesis. For

example, the ion exchange reaction between the cinchonidinium halide dimer and disulfonate proceeded smoothly to give the corresponding polymer in quantitative yield. Although these chiral ionic polymers are insoluble both in organic solvents and water, the asymmetric alkylation reaction was efficiently catalyzed to give the enantioenriched product in a high yield and with a high level of enantioselectivity.

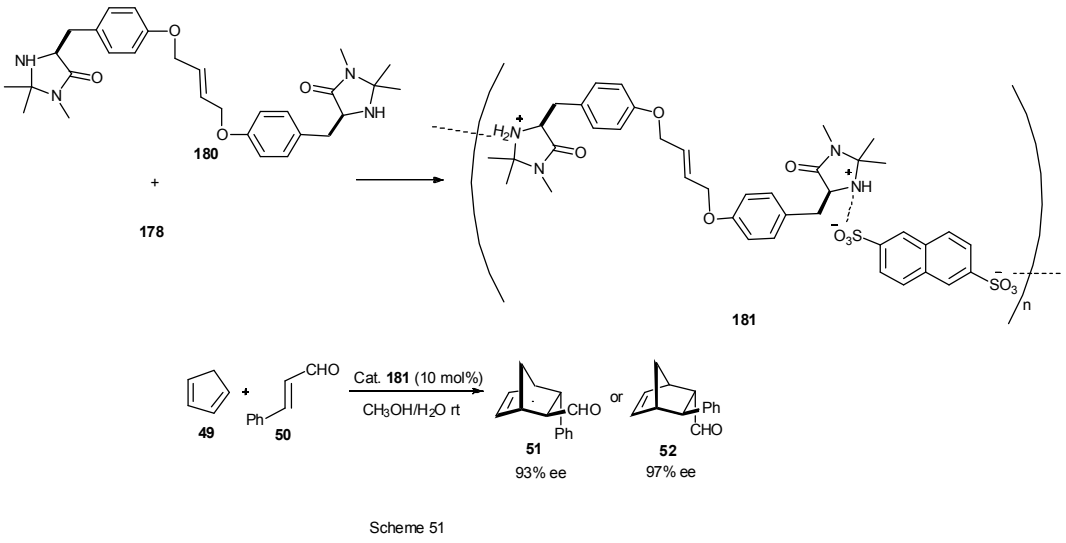
A methanol solution of cinchonidinium dimer **177** was allowed to react with an aqueous solution of naphthalene disulfonate **178** to give the corresponding chiral ionic polymer **179**. In the presence of **179**, the asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester (**175**) proceeded smoothly to give **176** in a high yield and with high enantioselectivity (Scheme 50).[104]



Scheme 50

4.2 Asymmetric Diels–Alder reactions

The series of chiral imidazolidinones, known as MacMillan catalysts comprises some of the most powerful and applicable organocatalysts. Chiral imidazolidinone hydrochloride was used as a catalyst for the Diels–Alder reaction of cyclopentadiene and cinnamaldehyde to prepare the chiral cyclic adduct. The sulfonate salt of the imidazolidinone was also an effective catalyst for the same reaction. Reaction between imidazolidinone dimer **180** and disulfonate **178** proceeded smoothly to give insoluble polymers **181**. In the presence of the polymeric catalyst **181**, the Diels–Alder reaction of **49** and **50** proceeded to give the chiral adducts **51** and **52** with high levels of enantioselectivity (Scheme 51).[105]

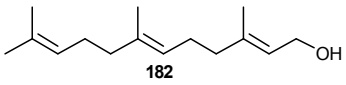


Scheme 51

4.3 Epoxidation[106]

Selective epoxidation of farnesol (**182**) at the 6,7-position, remote from the hydroxyl directing group is catalyzed by **183**.[107] A number of resin-immobilized peptide analogues were examined to reveal the importance of the four *N*-terminal residues (Scheme 52). Although the enantioselectivity at the 6,7-position is low (10% ee), it is an

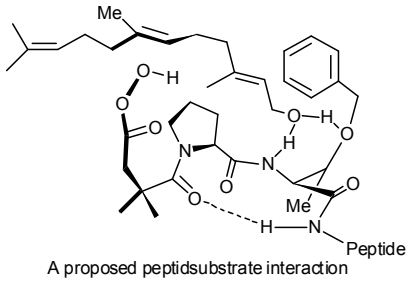
important example of remotely directed peptide catalysis.



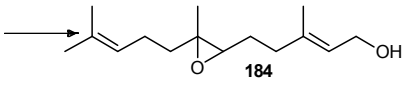
182

Boc-Asp-D-Pro-Thr(Bn)-Asn(Tri)-Tyr(^{t}Bu)-Gly-OMe

183



A proposed peptidsubstrate interaction



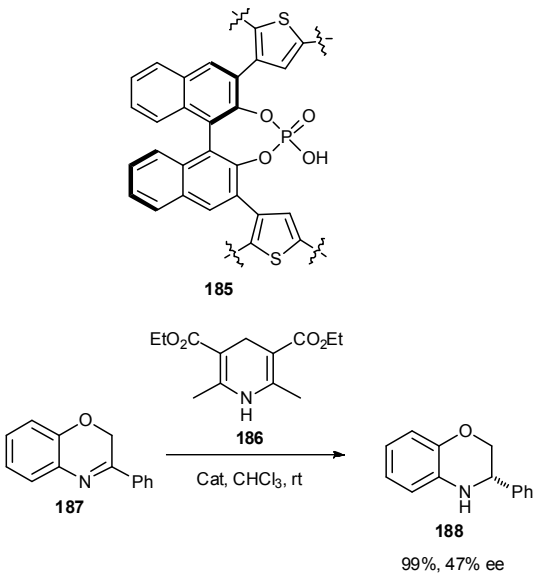
184

major product

Scheme 52

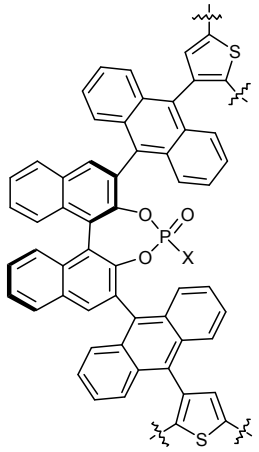
4.4 Heterogeneous organocatalysts containing BINOL

BINOL-derived phosphoric acids are important catalysts for various asymmetric transformations. Heterogeneous organocatalysts containing **185**, the BINOL-derived phosphoric acid structure, were prepared by polymerization with thiophene substituents. **185**, in the presence of **186**, catalyzed the asymmetric reduction of cyclic imine **187** to chiral amine **188** as shown in Scheme 53.[108]

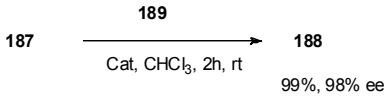


Scheme 53

BINOL-derived phosphoric acid catalysis[109,110] has been applied successfully for many asymmetric reactions. Thiophene units attached to BINOL were easily coupled under mild oxidative coupling conditions using $FeCl_3$. The resulting polymeric catalysts **189** were highly active and selective in asymmetric organocatalytic reactions, such as transfer hydrogenation, aza–ene-type reactions, and the asymmetric Friedel–Crafts alkylation of pyrrole. This polymeric catalyst also showed high catalytic activity in the asymmetric reduction of **187** (Scheme 54).[111]



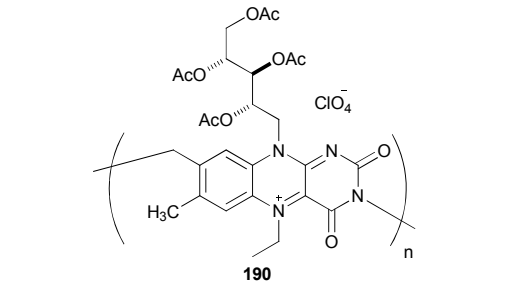
189



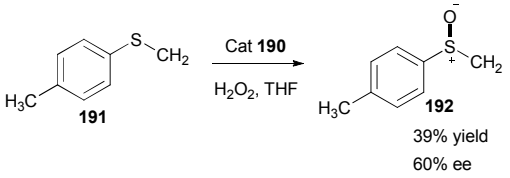
Scheme 54

4.5 Chiral riboflavin polymer

Main-chain optically active riboflavin polymer was synthesized from naturally occurring riboflavin (vitamin B_2).[112] The riboflavin residues of the polymer were converted to 5-ethyl rivoflavinium salts **190**, which could be reversibly transformed into the corresponding 4a-hydroxyriboflavins through hydroxylation/dehydroxylation reactions. The optically active polymer **190** efficiently catalyzed the asymmetric organocatalytic oxidation of sulfides with hydrogen peroxide, yielding optically active sulfoxides with up to 60% ee. This enantioselectivity obtained with the polymeric catalyst was higher than that catalyzed by the corresponding monomeric catalyst (30% ee).



190



191 192

39% yield
60% ee

Scheme 55

4.6 Metal-containing main-chain chiral polymers

An important series of main-chain chiral polymers are the chiral binaphthyl derivatives.[113] These chiral polymers were treated with various metals to form polymeric chiral catalysts. Applications of such chiral polymeric catalysts were reviewed in the literature.[114] Another strategy for the immobilization of chiral metal complexes in the polymer main-chain is the formation of self-supported chiral catalysts. Metal-containing chiral catalysts were polymerized to give homochiral metal–organic polymers for heterogeneous catalysis in asymmetric reactions. These self-supported chiral catalysts were reviewed in the literature.[115]

5. Conclusions and outlook

Developments in polymer-immobilized catalysis are mainly focused on their separation and recycling. However, as shown in this article, many examples demonstrate that polymeric chiral catalysts can give higher enantioselectivities compared with those obtained from the original low-molecular-weight catalyst in solution. Helical polymers provide a suitable microenvironment for asymmetric reactions. Fine-tuning of the

microenvironment of the main-chain chiral polymers is easily achieved by the modification of the linker chiral dimers and achiral comonomers. Precisely designed chiral polymer catalysts for each asymmetric reaction may provide a tailor-made catalyst. Some of the polymeric chiral catalysts have been used in a continuous flow system, which is necessary for the further development of automated synthesis of fine chemicals.

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