Recoverable Catalysts for Asymmetric Organic Synthesis

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Introduction and Scope

Homogeneous asymmetric catalysis is one of the most important developments in chemistry in the past several decades.[1−4] Thousands of chiral ligands and their transition metal complexes have been reported,[5] and many of them are known to be highly effective in the asymmetric formation of C−H, C−C, C−O, and C−N bonds, etc. However, only a few examples have been developed into industrial processes. At present, most chiral synthons are still produced from natural chiral building blocks or through the resolution of racemic mixtures. The lack of application of homogeneous asymmetric catalysis is partly due to the problems of separation and recycling of the expensive chiral catalysts. To facilitate the separation of the chiral catalysts from the reaction mixture, methods for immobilizing the homogeneous catalysts have been pursued for decades.

Covalent immobilization of homogeneous catalysts to insoluble polymer supports has received considerable attention in recent years. The heterogenization facilitates the separation of the catalyst from reagents and products, simplifies the efficient recovery of the often expensive or toxic catalysts, and potentially allows the adaptation of the immobilized catalysts to continuous flow type processes. Unfortunately, the immobilization of chiral catalysts often results in lower activities and enantioselectivities as compared to those observed for their homogeneous counterparts.

Soluble polymers have been used as catalyst supports since the pioneering work of Bayer and Mutter in the early 1970s.[6] By using such catalysts, organic reactions can be carried out in a homogeneous manner and thus may have similar catalytic activity and stereoselectivity as the homogeneous parent system. When the reaction is completed, the catalyst can be separated by either solvent or heat precipitation, membrane filtration, or size-exclusion chromatography. The use of soluble polymers for traditional and combinatorial synthesis, and catalysis has been recently reviewed.[7,8]

Bayer and Schurig reported the first example of attaching a chiral ligand onto a soluble polymer support in 1976.[9] They prepared a linear polystyrene-supported DIOP ligand according to the procedure developed by Kagan and co-workers. The rhodium catalyst containing this polymeric DIOP ligand catalyzed the asymmetric hydroformylation of styrene with 95% regioselectivity for the branched aldehyde, albeit with only 2% ee. This work did not attract much interest, and in the following 20 years, the use of soluble polymer as chiral ligand or catalyst support has rarely been reported. In 1996, Janda and co-workers[10] reported an effective soluble

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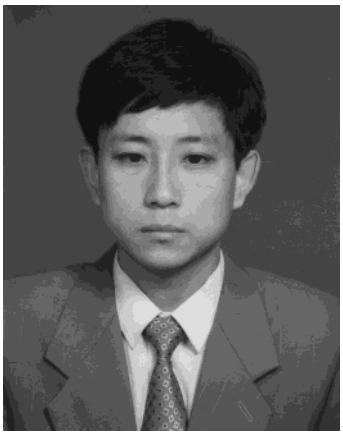


Dr. Yue-Ming Li was born in February 1966 in a small mountain village in Hebei Province, People's Republic of China. He started his university education in September 1981 in Nankai University, Tianjin, People's Republic of China, and got the bachelor degree in July 1985. He continued his post graduate and Ph.D. programs in the same university. Dr. Li received his Degree of Master of Science in July 1988 (under the supervision of Professor Shi-Xiong Tang) and the Ph.D. degree in June 1991 (under the supervision of Professor Ji-Tao Wang). He then worked in the chemistry department of Nankai University for four years, first as an assistant professor, then an associate professor. In 1993, Dr. Li received the Prize for Young Teachers from the Fok Ying Tung Education Foundation of the Ministry of Education of the People's Republic of China. From October 1995, Dr. Li started his new career in Dr. K. N. Ganesh's research group in National Chemical Laboratory, Pune, India, under the joint program of The Third World Academy of Sciences (TWAS, Italy) and Council of Scientific and Industrial Research (CSIR, India). After spending more than one year at the National Chemical Laboratory in India, Dr. Li joined the research group of Prof. Dr. Hartmut Laatsch in Institute of Organic Chemistry, University of Göttingen, Germany. Presently, Dr. Li is a Research Associate in Prof. Albert S. C. Chan's group in the Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University. Dr. Li's research interests are in the development of new methodologies for asymmetric organic reactions, the development of new process for the synthesis of chiral generic drugs, and the asymmetric synthesis of optically active organic compounds with biological activities.

Albert S. C. Chan received his B.Sc. from International Christian University in Tokyo, Japan, in 1975 and his Ph.D. from the University of Chicago (under the supervision of Professor Jack Halpern) in 1979. He joined the Central Research Laboratories of Monsanto Company in 1979 and worked there for 13 years through the ranks of Senior Research Chemist, Research Specialist, Senior Research Specialist, and Monsanto Fellow. In 1992–93, he spent a year as a Visiting Expert at National Taiwan University and six months as Reader at the Hong Kong University of Science and Technology. In 1994, he took up his current position at the Hong Kong Polytechnic University as Chair Professor and Head of the Department of Applied Biology and Chemical Technology. In 2001, he was elected to the Membership of the Chinese Academy of Sciences. His research interests are in asymmetric synthesis and catalysis, chemistry related to life sciences, and the development of new pharmaceuticals based on Chinese Herbal Medicines.

polymer-supported chiral catalyst for asymmetric synthesis and triggered increasing attention to the method.

Dendrimers are highly branched macromolecules having precisely defined molecular structures with nanoscale size. Complexes containing dendritic ligands are also soluble in many common solvents and can be separated from the products by precipitation, membrane or nanofiltration techniques. Since the pioneering work reported by Knapen et al. in 1994,[11] dendritic catalysts have been attracting increasing attention. The metallodendrimers and their catalytic applications have been frequently reported and reviewed.[12−16] Compared to the linear soluble polymeric chiral catalysts, the dendrimer architecture might offer better control of the disposition of the catalytic species than soluble polymer-based catalysts. Thus, it is possible to fine-tune the catalytic properties of the dendritic catalysts through the adjustment of their structure, size, shape, and solubility. Such novel class of catalysts may fill the gap between homogeneous and heterogeneous catalysis, which may combine the advantages of homogeneous and heterogeneous catalysts. The very first attempt to carry out asymmetric catalysis using chiral dendritic ligand was reported by Brunner's group.[17] In their first approach to dendritic catalyst, they designed a "dendrizyme" diphosphine ligand in which a dppe diphosphine core was surrounded by space-filling dendrimer substituents. The rhodium complex of this ligand was studied for the asymmetric hydrogenation of acetamidocinnamic acid which led to the product with essentially no optical induction (2% ee). Recently, chiral dendritic catalysts have been attracting much attention due to the excellent results obtained by the research groups of Seebach, Jacobsen, Togni, and Fan.

The practical application of asymmetric catalysis was sometimes limited by the fact that high enantioselectivities were often achieved in only a restricted range of solvents, many of which are environmentally hazardous. The use of supercritical fluids, such as supercritical carbon dioxide, as reaction media offers the opportunity to replace such organic solvents with environmentally less hazardous reaction medium, and control the solvent effect on the selectivity of the reaction. A unique and potentially advantageous characteristic of supercritical fluid solvents is that their density, polarity, viscosity, diffusivity, and overall solvent strength could be dramatically altered by changing a relatively small range of pressure and/or temperature. The relatively mild critical point of carbon dioxide (T_c = 31 °C, P_c = 72.9 atm) makes it particularly attractive for asymmetric synthesis. Supercritical carbon dioxide is nontoxic, nonflammable, easy to remove from the reaction system, and of low cost. Such special properties make supercritical carbon dioxide a favorable reaction medium of study.[18]

Over the past three decades, a number of methodologies and new concepts have been developed for immobilizing chiral catalysts. In general, there are three types of immobilized chiral catalysts: (1) insoluble chiral catalysts bearing stationary supports such as organic cross-linked polymers or inorganic materials; (2) chiral catalysts with "mobile carriers" such as aqueous phase, supercritical carbon dioxide ($ScCO_2$) or ionic liquid; and (3) soluble chiral catalysts bearing linear polymeric or dendritic ligands. Several previous reviews have summarized the historical context of the recent advances in asymmetric catalysis with different types of immobilized and recoverable catalysts.[16,19−25] In the present review, we attempt to summarize the very recently discovered immobilized chiral catalysts which showed good catalytic activity and enantioselectivity as well as recyclablility in asymmetric synthesis. This review will also focus on the development of new methodologies for recovering chiral catalysts with emphasis on their application in asymmetric synthesis. Literature data have been classified according to the type of reactions involved, as described above.

Metallic catalysts modified with chiral auxiliary, such as nickel catalyst modified with tartaric acid using bromide as co-modifier for the hydrogenation of β-ketoesters,[26] and the precious metal system (e.g., platinum) modified with cinchona alkaloids for the hydrogenation of α,β-diketones,[27] are not included in this review.

Another two types of heterogeneous asymmetric catalysis, aqueous micelle catalysis and phase transfer catalysis, also are not included in this review.[28,29] In most cases, catalyst recycling in these two systems is more difficult.

1. Asymmetric Hydrogenation

Since Knowles et al. developed the first commercial application of asymmetric catalytic reaction using a Rh(DIPAMP) catalyst around 30 years ago, most of the efforts in this area have been focused on the

application of such chiral phosphine ligand-containing catalysts. Thousands of chiral phosphine, phosphinite, or their hybrid ligands have been synthesized. High enantioselectivity and activity have been achieved using the Rh, Ru, and Ir complexes of these ligands in the asymmetric hydrogenation of a broad range of prochiral substrates. These ligands are usually expensive and air sensitive. It is difficult to recycle homogeneous phosphine-containing catalysts due to their low stability toward oxidation.

1.1. Insoluble Polymer-Supported Catalysts for Asymmetric Hydrogenation

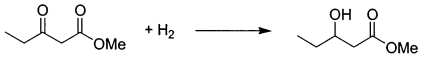
Inspired by the methodology for solid peptide synthesis developed by Merrifield in 1963,[30,31] the early efforts in the immobilization of chiral catalysts were focused on the attachment of chiral ligands onto cross-linked polystyrene beads. Kagan and co-workers reported the first example in 1973.[32] Chiral diphosphine-containing catalyst Rh(DIOP) was successfully attached to cross-linked Merrifield-type resin. The resulting catalyst was studied in the asymmetric hydrogenation of olefinic substrates and hydrosilylation of ketones, which, however, showed much lower efficiency than the soluble counterpart. Stille and others extended this approach to the copolymerization method.[33] In their study, insoluble polymer-supported catalysts were prepared through the copolymerization of a styrene monomer containing a chiral ligand, e.g., DIOP, with vinyl monomers. The copolymerization method provided better control of the distribution of the catalytically active sites. However, in most cases this type of polymer-supported chiral catalysts suffered from much lower catalytic activity and/or enantioselectivity than those of the corresponding homogeneous species, possibly due to the restriction of the polymer matrix. Moreover, these two approaches required additional modifications of the chiral ligands. Several other strategies such as adsorption, ion-pair formation, and entrapment[34] were further developed and applied in the immobilization of chiral catalysts. These strategies simplified the preparation of the heterogeneous chiral catalysts but were limited to several types of catalyst systems.

Pioneering work of asymmetric hydrogenation reactions carried out by Stille et al. involved the use of cross-linked polymer-supported chiral phosphine-containing catalysts. Such studies have been well documented and reviewed.[35,36] This section will summarize the most recent progresses in this fast growing area.

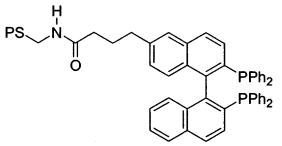
Bayston et al. reported a polymer-supported BINAP **1** which was used in the catalytic hydrogenation of β-ketoesters and dehydroamino acids.[37] They used polystyrene as the polymer support, and a C4-carboxylic acid moiety as the spacer. The spacer was first introduced to a BINOL derivative, followed by a routine BINAP synthesis. After the BINAP derivative was connected to the polystyrene support via an amide bond, the immobilized ligand was successfully used in the catalytic hydrogenation of a variety of substrates (Scheme 1).

Following the successful application of the Ru−BINAP−diamine system in the asymmetric catalytic hydrogenation of simple ketones, Noyori et al. further prepared an immobilized catalyst **2** for the same reaction.[38] While the conversion decreased slightly after more than 10 cycles of reuse, the enantioselectivity of the reaction remained almost unchanged, and the results compared favorably with the free BINAP catalyst system.

Scheme 1[a]



[a] 99% yield, 97% ee (homogeneous reaction: 100% yield and 99% ee).



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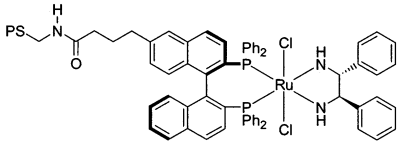
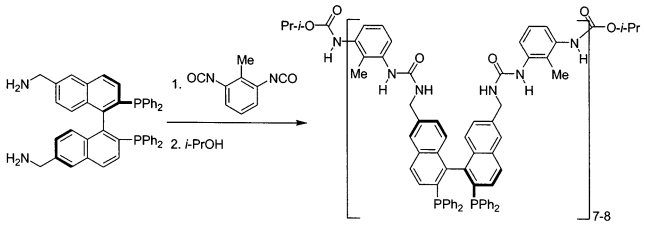


2

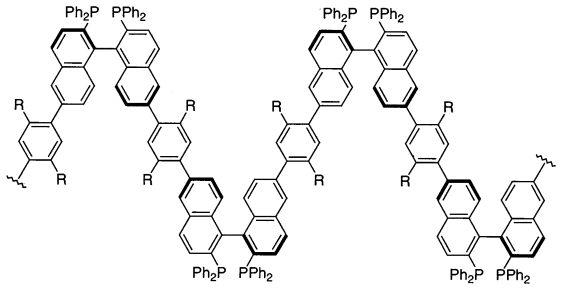
Lemaire et al. reported another different catalyst in which BINAP was incorporated into the polymer backbone.[39] At first, BINOL was brominated to form the dibromo-BINOL species followed by the substitution of the two bromo groups with two cyano groups. A standard BINAP synthesis procedure was then applied to this intermediate, giving a 6,6′-dicyano-BINAP. Lithium aluminum hydride reduction of this substituted BINAP gave 6,6′-di(aminomethyl)-BINAP, which polymerized with 2,6-toluene diisocyanate to give the final polymer (Scheme 2).

Scheme 2



Ruthenium complex of this polymer was used in the catalytic hydrogenation of β-ketoesters[40] and aryl ketones.[41] The results compared favorably with that from BINAP. Similar effects were observed in the catalytic hydrogenation of amidoacrylic acids.[42]

Pu et al. also reported the poly-BINAP ligand **3** which could be used for the hydrogenation of ketones.[43] In their catalyst, the chiral ligand BINAP was incorporated in a polyaryl polymer via Suzuki coupling reaction. While insoluble in methanol, this polymer was readily soluble in other common organic solvents such as methylene chloride, THF, chloroform, and toluene, thus making it very easy to separate the catalyst from the reaction system after the completion of the reaction.

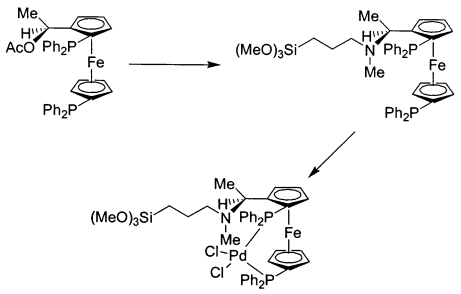


1.2. Inorganic Material Supported Catalysts for Asymmetric Hydrogenation

Inorganic materials have been used as alternative supports for the immobilization of homogeneous chiral catalysts since mid-1980s. Unlike polymers, inorganic solids prevent the intermolecular aggregations of the active species because of their rigid structure. Moreover, the inorganic materials often show higher stability under the catalytic conditions than the cross-linked polymers. Nagel and Kinzel reported the first example of using inorganic solid as chiral catalyst support in 1986.[44] In their study, the rhodium complex of 3,4-(*R*,*R*)-bis(diphenylphosphino)pyrrolidine was covalently bound to silica. The resulting heterogeneous catalysts were studied in the asymmetric hydrogenation of α-acetamidocinnamic acid and its methyl ester, giving the reduced products with over 99% ee. However, most of this kind of immobilized chiral catalysts also suffered from lowered catalytic activity and/or enantioselectivity due to the negative effect of the support on the chiral microenvironment around the active centers.

Raynor et al. reported a ferrocenyl phosphine ligand anchored inside the pore of MCM-41 (Scheme 3).[45] They first used dichlorodiphenylsilane to deac-

Scheme 3. Synthesis of the Ferrocenyl Precursor



tivate the outer wall to limit the immobilization to the inside of the pore.

For the purpose of comparison, the ferrocenyl precursor was also reacted with an incompletely condensed silsesquioxane cube to form a homogeneous model of the anchored catalyst. These two catalysts were then tested in the one-step hydrogenation of ethyl nicotinate to nipecotinate. While the free catalyst and the homogeneous silsesquioxane complex gave a racemic product, the MCM-41 anchored species catalyzed the reaction with 17% ee at 50% conversion

Jamis et al. reported a study of heterogenized catalyst in which a readily available hexagonal meso-

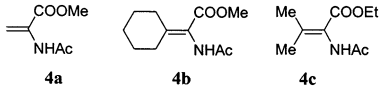
Table 1. Hydrogenation of Prochiral α-Enamide Ester Catalyzed by Immobilized and Free [(*R*,*R*)-Me-DuPHOS)Rh(COD)]OTf[a]

entry	substr	support	solvent	temp (°C)	anion	conv. (%)	ee (%)
1	**4a**	MCM-41	hexane	rt	OTf	>99	99
2	**4a**	none	hexane	rt	OTf	>99	87
3	**4a**	none	MeOH	rt	OTf	>99	>99
4	**4b**	MCM-41	hexane	rt	OTf	>99	98
5	**4b**	none	hexane	rt (50 psi)	BAr_F	92	93
6	**4b**	none	MeOH	rt (90 psi)	OTf	>99	96
7	**4c**	MCM-41	hexane	rt	OTf	>99	98
8	**4c**	none	hexane	rt (40 psi)	BAr_F	26	85
9	**4c**	none	MeOH	rt (90 psi)	OTf	99	96

[a] Except as noted, the reaction conditions are 20 mL of hexane, 8 psi H_2, and room temperature; reaction time for **4a**: 30 min; reaction time for **4b** and **4c**: 16 h.

porous silica (HMS) was used as the catalyst support.[46] The proper pore size was chosen to ensure that the chiral catalyst was tightly accommodated in the pore. The catalyst was retained in the host pore by van der Waals interactions, and was easier to prepare than the covalently bonded catalyst. Rh−(*S*,*S*)-BPPM and Ru−(*R*)-BINAP were chosen as the model catalysts and moderate results were obtained when the immobilized catalysts were used in aqueous phase asymmetric hydrogenation of sodium α-acetamidocinnamate (ca. 50% ee).

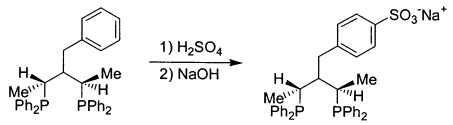
de Rege et al. reported the case of MCM-41 heterogenized $[(R,R)$-Me-DuPHOS)Rh(COD)$]^+$ catalyst for the asymmetric hydrogenation of amidoacrylic acids.[47] Mesoporous MCM-41 was frequently chosen as the catalyst support due mostly to its large, tailorable and well-defined pore structure, high surface area, and high area density of surface silanols. When MCM-41 was added to a CH_2Cl_2 solution of [(*R*,*R*)-Me-DuPHOS)Rh(COD)]OTf, the orange solution was rapidly decolorized, and the resultant functionalized MCM-41 could be used to catalyze asymmetric hydrogenation reactions. These results compared favorably with the free catalysts, and the reuse of the catalysts showed no loss of activity or enantioselectivity (Table 1).



4a **4b** **4c**

Bianchini et al. reported a different method to immobilize the catalysts onto the silica surface.[48] The sodium sulfonate ligand **5** prepared from sulfonation reaction was easily immobilized on silica surface via hydrogen bonding (Scheme 4). This process was quite

Scheme 4



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simple and efficient for catalyst immobilization, although the selectivity of the reaction was poor.

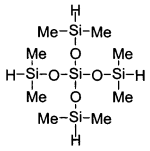
Augustine et al. reported another idea for anchoring the homogeneous catalysts.[49] They used heteropoly acids as the anchoring agents between the catalyst and the support materials such as alumina. DiPamp, ProPhos, Me-DuPHOS, BMMP, etc. were immobilized on alumina, and were used as catalysts in the hydrogenation of methyl 2-acetamidoacrylate. Several supports were tested: Montmorillonite K, carbon, alumina, and Lanthana. The alumina and Lanthana supported catalysts gave better enantioselectivity over the others.

Technical problems affecting the selectivity or activity of the catalysts included the preparation method, the pore size of the insoluble supports, or the choice of solvents for the immobilized organic polymer supports. Further, the catalyst loading on the supports also might play a crucial role in affecting the activity and/or selectivity. Pugin studied the site-isolation effect of the immobilized catalysts on the enantioselectivity of hydrogenation reactions[50] using several chiral phosphine ligands. In contrast to the free catalysts, the immobilized species had some sites close to each other to such extent that they interacted with each other while most other sites were completely isolated. The ligands sufficiently close to each other might be regarded as bis-ligands, and the formation of saturated inactive species was quite likely. In such case, the ratio of the active and inactive species could be controlled by the catalyst loading which consequently could affect the catalyst activity and/or selectivity.

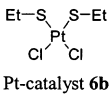
1.3. Chiral Membrane for Asymmetric Hydrogenation

The immobilization of catalyst on a membrane is a convenient way to separate the catalyst from the reaction mixture.

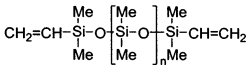
Poly(dimethylsiloxane) (PDMS) is the choice of membrane material as it is easy to prepare and is of low cost. Being the most hydrophobic polymer, its flexible siloxane chains provide a fast mass transfer through the membrane. PDMS polymer is generally prepared by mixing the cross-linker tetrakis(dimethylsiloxy)silane (**6a**) with a platinum complex *cis*-dichlorobis(diethyl sulfide)platinum(II) (**6b**), the vinyldimethyl terminated silicone polymer (**7**), and silica. By mixing the chiral phosphine−metal complex with the PDMS solution, the membrane with the occluded chiral catalyst might be obtained.



Crosslinker tetrakis(dimethylsiloxy)silane **6a**



Pt-catalyst **6b**



Vinyldimethyl terminated silicone polymer **7**

Vakelecom et al. reported the occlusion of Ru−BINAP on a membrane[51] to obtain a recoverable catalyst. The occluded Ru−BINAP showed lower catalytic activity and enantioselectivity (up to 70% ee) than the homogeneous analogue.

Comparing to the previously reported methods for catalyst immobilization, which involved the electrostatic interactions, covalent bonds, or coordinative bonds, the complex reported by Vankelecom et al. applied a very different strategy: the catalysts were trapped in the elastomer network through steric restriction.

The chiral catalytic membranes remained heterogeneous under a wide range of conditions and showed good to excellent activity and enantioselectivity in reactions.

The problem of leaching was avoided by using a solvent in which the complex was insoluble.[52] In such solvent system, no matter how large the membrane swelled, and how fast the transport of the reagents and products might be, the complex remained fixed. Aqueous solvent met this requirement, but the conversions and enantioselectivities were very low. Using other solvents such as glycerol, ethylene glycol and oligomeric ethylene glycol could dissolve the substrates and the products to some extent, and both the catalytic activity and the enantioselectivity were enhanced. Elevated reaction temperature further increased the rate of reaction without loss of enantioselectivity.

Tas et al. reported a bifunctional catalytic membrane for the asymmetric catalytic hydrogenation of methyl acetoacetate.[53] Both Ru−BINAP and *p*-toluenesulfonic acid were immobilized on the PDMS membrane by synthesizing the membrane in the presence of appropriate amounts of Ru−BINAP complex and the acid. The membrane had an average thickness of 0.2 mm, corresponding to a coverage of ca. 0.054 μmol cm^{-2} for the Ru−BINAP complex. The complex and the acid were both wrapped in the elastomer network and retained by steric interaction and van der Waals interactions.

The best result using the immobilized catalyst was 92% ee with turnover frequency of 41.6, which was very similar to those using the homogeneous Ru−BINAP catalyst (59.2 TOF and 96% ee). Catalyst leaching was not observed in all reported cases, as the ruthenium content of the reaction mixture was lower than the detection limit of 0.16 ppm of the instrument.

Vakelecom et al. also immobilized the Rh−MeDuPHOS via occlusion in poly(dimethylsiloxane) membranes (PDMS) for the asymmetric hydrogenation of methyl acetoacetate and obtained the hydrogenation product in over 90% ee.[54] Again, the immobilized catalyst showed no leaching in methanol. This allowed a facile recycling and reuse of the catalyst and thus making it possible to develop a continuous process. This immobilized Rh−DuPHOS was also studied in aqueous medium for the enantioselective

Table 2. Enantioselective Hydrogenation of Methyl 2-Acetamidoacrylate with Rh−MeDuPHOS Complex Occluded in PDMS Film[a]

entry	catalyst	solvent	sorption of the solvent in pdms	TOF (h^{-1})	ee (%)
1	homogeneous Rh−MeDuPHOS	MeOH		320	99.1
2	homogeneous Rh−MeDuPHOS	MeOH/H_2O[b]		210	99.0
3	Rh−MeDuPHOS/PDMS (10 wt % Si)	H_2O	0.035	9.9	93.1
4	Rh−MeDuPHOS/PDMS (15 wt % Si)	H_2O	0.037	10.6	92.8
5	Rh−MeDuPHOS/PDMS (20 wt % Si)	H_2O	0.049	12.6	96.9
6	Rh−MeDuPHOS/PDMS (20 wt % Si)[c]	H_2O	0.049	12.6	91.1

[a] Reaction conditions: 25 °C, 2 bar, 0.1 g of methyl 2-acetamidoacrylate, 10 μmol of catalyst, 15 mL of solvent. [b] 9 mL of MeOH and 9 mL of H_2O. [c] Reuse of the catalyst from previous entry.

hydrogenation of methyl 2-acetamidoacrylate. High enantioselectivity (up to 96.9% ee) was obtained (Table 2).

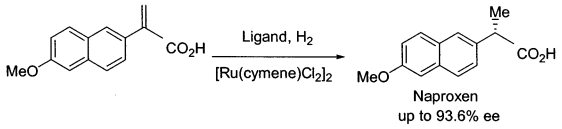
Wolfson et al. reported the aqueous phase enantioselective hydrogenation of methyl 2-acetamidoacrylate catalyzed by Rh−MeDuPHOS occluded in PDMS.[55] While homogeneous asymmetric hydrogenation of methyl 2-acetamidoacrylate in methanol gave 99.1% ee, reaction catalyzed by the occluded Rh−MeDuPHOS in water gave up to 96.9% ee.

1.4. Soluble Macromolecules for Asymmetric Hydrogenation

Besides the attachments of a chiral phosphine catalyst on an insoluble organic or inorganic support, a relatively new approach to solving the problem of catalyst separation and recycling while preserving enantioselectivity and activity involves the attachment of chiral phosphine catalysts to a soluble polymer.

BINAP was one of the most versatile and effective ligands for asymmetric hydrogenation,[56] and has been used as a standard ligand for developing new recoverable and soluble chiral catalysts. Chan and co-workers reported the synthesis of soluble chiral polyester-supported BINAP ligands and their application in the asymmetric hydrogenation of 2-(6-methoxyl-2-naphthyl)propenoic acid (Scheme 5).[57]

Scheme 5

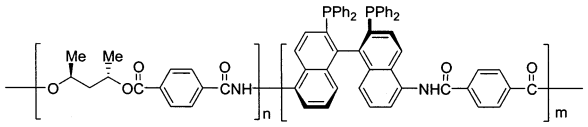


The polymeric ligand **8** was soluble in toluene, THF, and methylene chloride, and was quantitatively recovered by precipitation with methanol. In the presence of 0.5 mol % of Ru[(*R*)-**8**] catalyst in methanol−toluene (3:2, v/v) solvent system, under 69.0 kg cm^{-2} of hydrogen pressure at room temperature, the hydrogenation of 2-(6-methoxyl-2-naphthyl)-propenoic acid proceeded with 87.7% ee at 95.5% conversion in 4 h. Using methanol−toluene (9:1, v/v) solvent system, the same reaction under otherwise identical conditions gave only 37.5% conversion and 80.5% ee in 60 h. The profound solvent effect was due to the insolubility of the polyester-supported catalysts in the solvent system containing a high level of methanol. This demonstrated the importance of the soluble property of the polymeric catalyst under catalytic reaction conditions. More importantly, the soluble polymer catalyst was more active than the corresponding parent homogeneous catalyst while retaining similar enantioselectivity (Table 3). Moreover, the polymeric catalyst could be separated from the reaction mixture using solvent precipitation and was reused for 10 cycles without any loss of catalytic activity and enantioselectivity.

Table 3. Polymer Effect on the Asymmetric Hydrogenation of 2-(6-Methoxy-2-naphthyl)propenoic Acid[a]

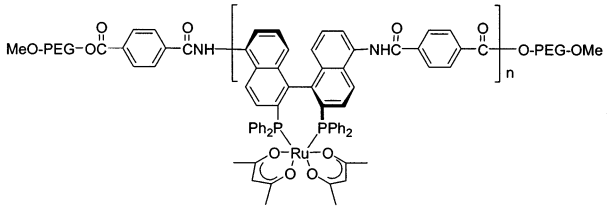
entry	catalyst (prepared in situ)	time, h	temp	conv., (%)	ee, (%)
1	(*S*)-BINAP + $[RuCl_2(cymene)]_2$	48	1∼2 °C	94.7	93.5
2	**8** + $[RuCl_2(cymene)]_2$	12	1∼2 °C	97.4	93.6
3	(*S*)-BINAP + $[RuCl_2(cymene)]_2$	4	rt	56.5	88.7
4	**8** + $[RuCl_2(cymene)]_2$	4	rt	95.4	87.7

[a] Reaction conditions: solvent = MeOH/toluene (2:3, v/v); sub./cat. = 200 (mol/mol); NEt_3/sub. = 1:1 (mol/mol); H_2 = 110 kg/cm^2 for entries 1 and 2, and 69 kg/cm^2 for entries 3 and 4.



8

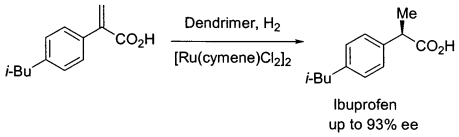
Fan et al. continued the study with a PEG-supported Ru(BINAP)$(acac)_2$ catalyst **9** which was soluble in methanol and could be quantitatively precipitated upon addition of diethyl ether.[58] This catalyst was also studied in the hydrogenation of 2-(6-methoxyl-2-naphthyl)propenoic acid in methanol and gave slightly higher catalytic activity and enantioselectivity (90% ee with 100% conversion in 10 min) than that of the parent homogeneous catalyst (89% ee with 98% conversion in 15 min). Enantioselectivity of up to 96% ee was observed when the reaction was carried out at lower temperature and higher H_2 pressure. The recovered catalyst was shown to maintain its efficiency in subsequent reactions.



9

Further studies by Fan et al. led to a series of soluble dendritic BINAP ligands with Fréchet-type polyether wedges (**10**) and their ruthenium complexes as catalysts in the asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid in methanol−toluene (1:1, v/v) at room temperature (Scheme 6).[59] It was found that the size of the

Scheme 6



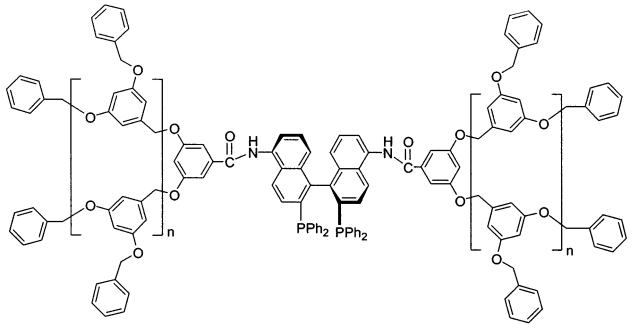
dendritic wedges influenced the reactivity of the ruthenium catalysts. The rate of the reaction increased with higher generation catalysts (Table 4).

Table 4. Activity and Enantioselectivity in Asymmetric Hydrogenation of 2-[*p*-(2-Methylpropyl)phenyl]acrylic Acid Catalyzed by Dendritic Ru(BINAP)[a]

entry	ligand	time, h	tof, (h^{-1})	conv., (%)	ee, (%)
1	(*S*)-BINAP	2	6.3	10.2	89.8
2	**10a**	2	6.5	10.4	91.8
3	**10b**	2	8.3	13.2	92.6
4	**10c**	2	21.4	34.3	91.6
5	**10c**	5	17.3	69.3	91.6
6	**10c** (cycle 1)	5	17.2	68.9	91.8
7	**10c** (cycle 2)	5	16.8	67.3	91.4
8	**10c** (cycle 3)	5	16.6	66.6	90.9

[a] Reaction conditions: solvent = MeOH/toluene (1:1, v/v); sub./cat. = 125 (mol/mol); NEt_3/sub. = 3:2 (mol/mol); H_2 = 80 atm.

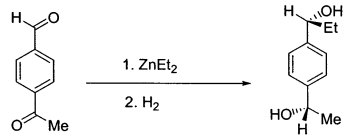
This effect was most pronounced when going from generation 2 to 3. The profound size effect was probably due to the steric bulk of the dendritic wedges which altered the dihedral angle of the two naphthalene rings in the Ru(BINAP) complex, and thus led to faster rate and/or better enantioselectivity of reaction. The catalyst could be quantitatively recovered by precipitation method and was reused for at least three cycles with similar activity and enantioselectivity.



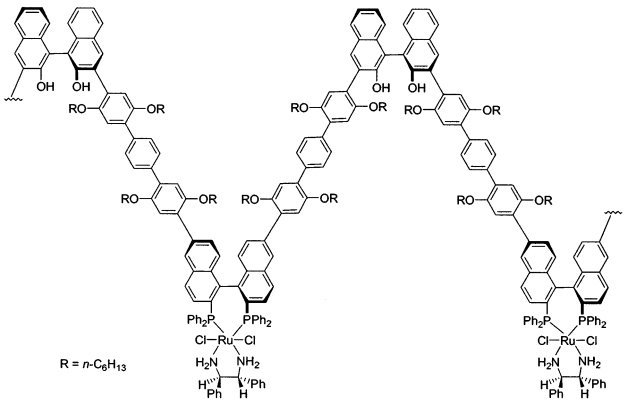
10a: n = 0, **10b**: n = 1, **10c**: n = 2

Pu and co-workers prepared a novel soluble bifunctional polymeric ligand (*R*,*R*)-**11** containing two distinctively different catalytic sites, BINAP and BINOL.[60] Its ruthenium diphenylethylenediamine complex (*R*,*R*)-**11**−Ru was used in the one-pot enantioselective diethylzinc addition and enantioselective hydrogenation of ketoarylaldehydes, giving products in high yields and high stereoselectivities (75−87% de, 92−94% ee) (Scheme 7). This bifunc-

Scheme 7

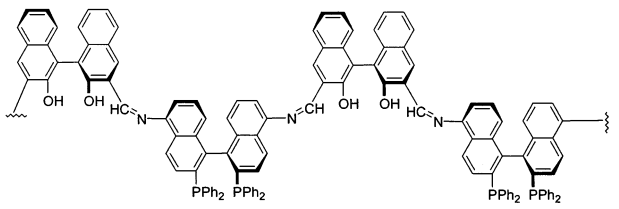


tional polymer catalyst could also be used as either BINAP or BINOL catalyst for individual asymmetric reactions. The catalyst (*R*,*R*)-**11**−Ru was studied in the asymmetric hydrogenation of acetophenone. In the presence of catalyst-to-substrate ratio of 1:4900, the hydrogenation was completed with >99% conversion and 84% ee. This soluble polymer catalyst showed higher reactivity and enantioselectivity than the insoluble polymer Ru(BINAP) catalysts reported by Lemaire, which gave 68% ee.[41]



11

Fan et al. also studied the soluble bifunctional polymeric ligand **12**, which was prepared via the direct condensation of (*R*)-3,3′-diformyl-1,1′-bi-2-naphthol with (*R*)-5,5′-diamino BINAP, for asymmetric hydrogenation and diethylzinc addition.[61] The feature of this polymer is that the different types of catalytic centers, BINOL and BINAP, were alternatively organized in a regular chiral polymer chain. Polymer **12** was found to be effective with high enantioselectivity either in the Ru(II)-catalyzed asymmetric hydrogenation of 2-arylacrylic acids (up to 88% ee) or diethylzinc addition to benzaldehyde (up to 84% ee).

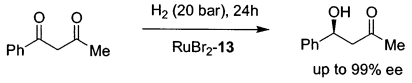


12

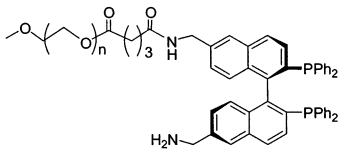
Guerreiro et al. also reported a PEG-supported BINAP ligand **13** for asymmetric hydrogenation. Polymer **13** was prepared by attaching BINAP ligand onto mono-PEG chain via an amide linkage at the 6-position of the naphthyl backbone.[62] The ruthenium

catalyst $RuBr_2$−**13** gave 99% ee in the enantioselective hydrogenation of methyl acetoacetate at 50 °C in MeOH and maintained the enantioselectivity at catalyst-to-substrate ratio of up to 1:10 000 (Scheme 8). The polymer catalyst was recycled four times and

Scheme 8



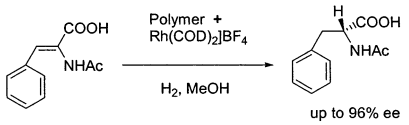
the recovered catalyst showed similar efficiency.



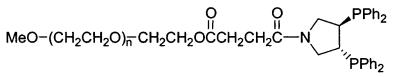
13

Besides the BINAP ligand, several other types of chiral diphosphine ligands were also used for developing soluble recoverable chiral catalysts for asymmetric hydrogenation. Fan et al. reported MeO−PEG-supported (3*R*,4*R*)-3,4-bis(diphenylphosphino)pyrrolidine **14** for asymmetric hydrogenation.[58] Polymer **14** was loaded with $[Rh(COD)_2]BF_4$ to afford the catalyst precursor, which was studied in the asymmetric hydrogenation of amidoacrylic acids (Scheme 9). Enantioselectivities in the range of 86−96% were

Scheme 9



achieved in the hydrogenation of α-acetamidocinnamic acid and the polymer catalyst was recycled at least three times without loss of enantioselectivity. In contrast, the insoluble polymer-supported catalyst significantly lost its catalytic activity in the second cycle.[63]

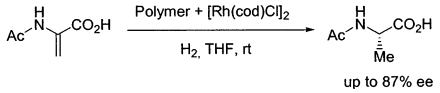


14

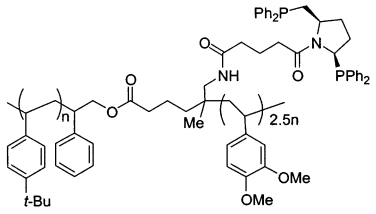
Pugin and co-workers employed a simple method to attach diphosphine ligands on the side chains of polymer supports.[64] Both polymers and chiral diphosphine ligands described in the patent contained hydroxyl or amino (primary or secondary) functionalities. For example, soluble polyphenoxy resin reacted with diisocyanate linker followed by reacting with chiral diphosphine PPM to form polyurethane or urea bridges, which provided distance from the polymer chain. The soluble polymeric Rh(PPM) complex was used to catalyze the asymmetric hydrogenation of methyl acetamidocinnamate with up to 95% ee.

Janda and co-workers also reported the soluble polymer-supported chiral diphosphine PPM ligand for asymmetric hydrogenation.[65] The catalyst support was synthesized through parallel polymer synthesis in which the preparation of libraries of block and graft copolymers were made from vinyl monomers by using a sequence of normal and "living" free radical polymerization. The feature of this kind of copolymers is their tunable solubility profiles and functional groups. As an example, polymeric ligand **15** was prepared and its Rh(I) catalyst was studied in the enantioselective hydrogenation of 2-*N*-acetamidoacrylic acid in THF under homogeneous conditions (Scheme 10). The observed enantioselectivity (87% ee) was

Scheme 10

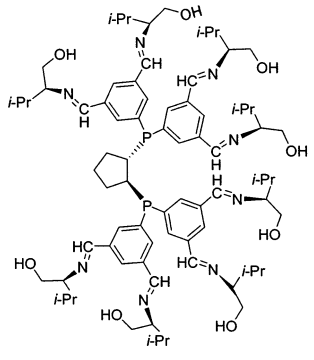


comparable to that observed with the corresponding monomer ligand. The polymer catalyst could be recovered by simple precipitation with methanol. The disadvantage is the low loading capacity of the new materials.

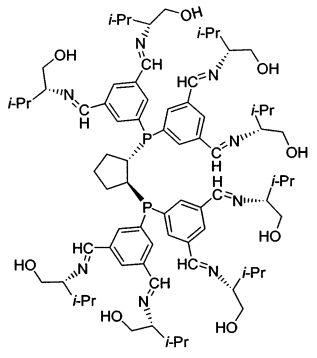


15

Brunner and co-workers pioneered the preparation and use of chiral dendritic ligands for asymmetric hydrogenation. Recently, they reported optically active dendritic chiral diphosphine ligands based on the *trans*-1,2-substituted cyclopentane skeleton **16**.[66] These ligands combined a chiral chelating core with the chiral dendritic extensions known from the first example of expanded ligands.[17] Dendrimers **16a** and **16b** were obtained by condensation of the aldehyde derivatives of chiral *trans*-1,2-bis(diphenylphosphino)cyclopentane with chiral amines and amino alcohols. The ligands were tested in Rh-catalyzed asymmetric hydrogenation of α-acetamidocinnamic acid with up to 96% ee, and the ligands (**16a** and **16b**) bearing opposite configuration of the periphery-substituted units gave almost the same enantioselectivity (**16a:** 93−94% ee versus **16b:** 96% ee). These results demonstrated that the orientation of induction was governed by the chiral cyclopentane core.



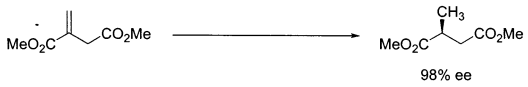
16a



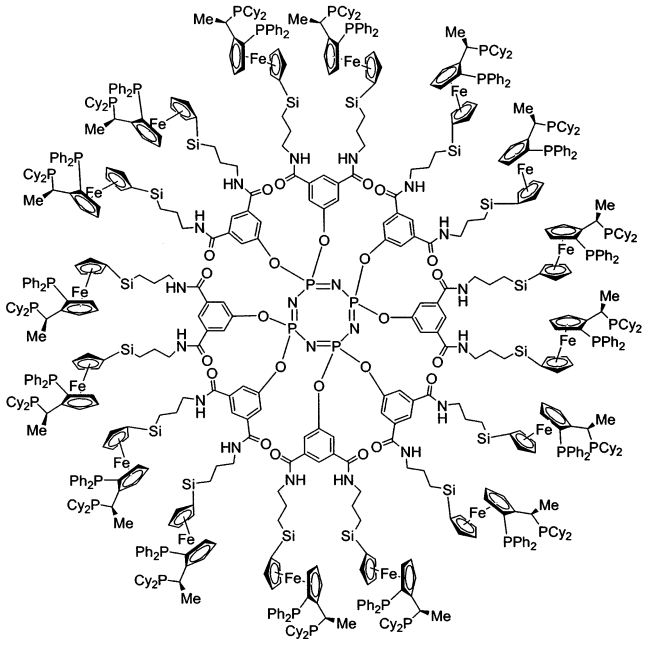
16b

Recently, Togni and co-workers reported a simple and efficient synthesis of dendritic chiral phosphine ligands **17** with 6-, 8-, 12-, and 16-peripheral Josiphos units, respectively.[67,68] The well-characterized dendrimers were used in the Rh-catalyzed hydrogenation of dimethyl itaconate, giving up to 98.6% ee (Scheme 11). This result was similar to that obtained with the

Scheme 11



monomeric Josiphos catalyst (99% ee). The dendritic catalysts could be separated from the reaction mixture through a nanofiltration membrane.



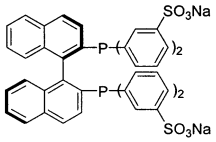
17

1.5. Biphasic Catalytic Systems for Asymmetric Hydrogenation

Since the first industrial application of rhodium-TPPTS [TPPTS = $P(C_6H_4$-*m*-$SO_3Na)_3$] system in Hoechst AG in Oberhausen, Germany, the idea of two-phase catalysis, which simplified the recovery of catalysts from products by phase-separation, has become a very active field of research.[69−71] In the case of asymmetric catalysis, substantial efforts have been made to prepare water-soluble chiral catalysts for biphasic applications. Most of the reported water-soluble chiral ligands were prepared by the incorporation of anionic groups such as sulfonate or carbonate, cationic groups such as quaternary ammonium ions, or neutral hydrophilic groups such as polyethers. Generally, chiral catalysts in aqueous or organic two-phase systems led to lower stereoselectivity and/or reactivity than in a homogeneous organic phase, due to several factors such as solvent effect, the reaction kinetics, and mass transport in the two solvents. Descriptions of water-soluble chiral ligands and their applications in aqueous biphasic catalysis were available in recent reviews.[72,73]

The industrial applications of homogeneous asymmetric catalysis have been pursued for many years. The concerns over hazardous waste generated during the catalytic reactions and separation increasingly led to the development of environmentally friendly processes. The potential benefits of systems using aqueous catalytic systems include easier product separation, decreased cost, and increased safety.

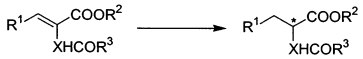
Wan et al. reported the asymmetric hydrogenation using a rhodium complex of sulfonated BINAP **18** as a water-soluble catalyst.[74] The reactions carried out in aqueous solution avoided the use of environmentally malign solvent systems, and some unexpected effects were observed using this polar protic solvent as a reaction medium.



18

In the preparation of the sulfonated phosphines, special care needed to be taken to minimize the possible phosphine oxidation and multisulfonation. The reaction could be controlled to take place only at the four phenyl rings by controlling the reaction conditions. The enantioselectivity of the asymmetric hydrogenation of 2-acetamidoacrylic acid and its methyl ester (Scheme 12) were carried out using the

Scheme 12



19a: R^1 = H, R^2 = H, R^3 = Me, X = N

19b: R^1 = H, R^2 = Me, R^3 = Me, X = N

19c: R^1 = Ph, R^2 = H, R^3 = Me, X = N

19d: R^1 = H, R^2 = H, R^3 = OH, X = CH

water-soluble rhodium complex (68−70%) was approximately the same as that using the unsulfonated complex in ethanol (67%) (Table 5).[75]

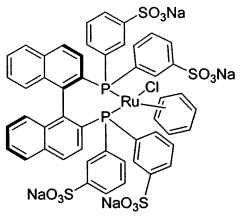
The reactions carried out in ethanol and methanol showed almost the same enantioselectivity; increasing the hydrogen pressure led to decreased enantioselectivity.

Wan et al. also reported the supported aqueous-phase asymmetric hydrogenation of 2-(6′methoxy-2′-naphthyl)acrylic acid catalyzed by ruthenium com-

Table 5. Asymmetric Hydrogenation of Substituted Amidoacrylic Acids in the Presence of Ruthenium Sulfonated Phosphine Complexes

entry	catalyst	substrate	solvent	s/c	temp. (°)	ee (%)
1	[Ru(BINAP-4SO_3Na)Cl_2]	**19a**	MeOH	71	rt	84.2
2	[Ru(BINAP-4SO_3Na)Cl_2]	**19a**	H_2O	18	rt	68.5
3	[Ru(BINAP-4SO_3Na)Cl_2]	**19b**	H_2O	80	rt	75.9
4	[Ru(BINAP-4SO_3Na)Cl_2]	**19b**	H_2O	76	50	82.0
5	[Ru(BINAP-4SO_3Na)Cl_2]	**19b**	MeOH	75	50	85.2
6	Ru_2Cl_4(BINAP)$_2$(Et_3N)	**19a**	EtOH/THF (1:1)		35	76
7	[Ru(BINAP-4SO_3Na)Cl_2]	**19c**	MeOH	75	rt	81.3
8	[Ru(BINAP-4SO_3Na)Cl_2]	**19c**	EtOH	75	rt	80.1
9	[Ru(BINAP-4SO_3Na)Cl_2]	**19c**	H_2O	75	rt	87.7
10	Ru_2Cl_4(BINAP)$_2$(Et_3N)	**19c**	EtOH/THF (1:1)		35	86
11	[Ru(BINAP-4SO_3Na)Cl_2]	**19d**	MeOH	75	rt	81.1
12	[Ru(BINAP-4SO_3Na)Cl_2]	**19d**	EtOH	75	rt	90
13	[Ru(BINAP-4SO_3Na)Cl_2]	**19d**	H_2O	18	rt	50
14	Ru_2Cl_4(BINAP)$_2$(Et_3N)	**19d**	EtOH/THF (1:1)		35	88

plex of this sulfonated BINAP (Ru−SAP−BINAP, **20**).[76]



20 Ru-SAP-BINAP

Triethylamine had a significant effect on the reactivity and enantioselectivity. Both the reactivity and enantioselectivity were improved for the reaction carried out in neat methanol. The reaction carried out in methanol under 1230 psi of hydrogen pressure and with a substrate-to-catalyst ratio of 100:1 gave the best result (96.1% ee). The presence of water normally led to decreased enantioselectivity. This was possibly due to decomposition of the catalyst through hydrolysis of the Ru−Cl bond.[77] Reactions carried out in methanol−water mixture generally gave lower enantioselectivity than that in neat methanol. Adding triethylamine to the methanol−water reaction system resulted in the decrease of enantioselectivity.

When the two-phase catalysis was carried out in 1:1 ethyl acetate/water, lower reactivity was observed due to the low solubility of the substrate in water. Most of the reaction took place at the interface of the aqueous-water layers, and the reaction rate was limited by the interfacial surface area. An enantiomeric excess of 78% was observed in this two-phase reaction. The water-soluble catalyst was easily separated from the organic phase, and the recycled catalyst was reused without loss of enantioselectivity. Enantiomeric excesses ranging from 78 to 82% were observed in several recycles of the catalytic solution.

The highly effective heterogeneous enantioselective catalyst was prepared using the concept of "supported aqueous phase (SAP)". The supported Ru−SAP−BINAP complex was prepared by mixing an aqueous solution of Ru−BINAP complex with degassed CPG-240 (controlled-pore glass which bears an average pore size of 242 Å and 120/200 mesh in size) followed by vacuum-drying at 40−50 °C. The dry supported Ru−SAP−BINAP could be rehydrated via water-saturated organic phase treatment. Asymmetric hydrogenation of 2-arylacrylic acid carried out in the presence of supported aqueous-phase catalyst showed higher activity than the two phase system.

The larger interfacial surface area between the supported catalyst and the substrate was thought to be the cause of the high activity of this supported catalyst. The recovery of this supported catalyst seemed to be successful. Filtration of the reaction mixture yielded a colorless solution of product in ethyl acetate, and ruthenium leaching to the filtrate was below the instrumental detection limit.

The SAP catalyst was further improved by using ethylene glycol in place of the water film on the glass beads.[78] Enantioselectivity as high as 96% was reported for the asymmetric catalytic hydrogenation of 2-arylacrylic acid carried out in a mixture of chloroform/hexane (1:1) with a substrate-to-catalyst ratio of 300:1 and hydrogen pressure of 94−101 Mpa (Table 6).[77]

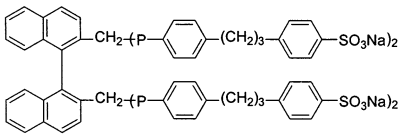
Table 6. Enantioselectivities of SAP−BINAP under Different Conditions

entry	catalyst	temp (°C)	solvent	ee (%)
1	heterogeneous	24	$CHCl_3$/cyclohexane 1:1	88.4
2	heterogeneous	3	$CHCl_3$/cyclohexane 1:1	95.7
3	heterogeneous	24	AcOEt	87.7
4	heterogeneous	3	AcOEt	94.8
5	homogeneous	4	MeOH	96.1

The advantage of this heterogeneous catalyst was that it facilitated the separation of the catalyst from the reaction system without the loss of catalyst to the organic phase. The presence of controlled pore glass is essential to get high conversion and enantioselectivity. Two experiments have been carried out using the ethylene glycol/tetrasulfonated catalyst system. One was carried out in the presence of controlled pore glass and another in the absence of it. The study showed that the reaction with controlled pore glass proceeded smoothly, whereas the control experiment showed less than 2% conversion. The CPG-240 collected after the reaction contained the ruthenium complex, whereas the organic solution was colorless.[77]

Kohlpaintner et al. claimed the use of amphiphilic phosphine ligands **21** and **22** for asymmetric hydrogenation and asymmetric hydroformylation.[79] The sulfonate groups were separated from phosphine

functional groups by spacer; this possibly reduced the negative influence of the electron-withdrawing sulfonates.



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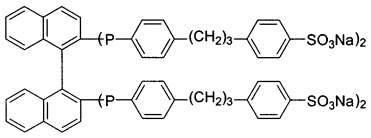

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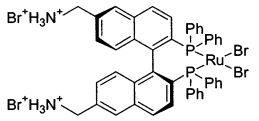
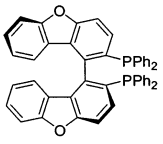
The asymmetric hydrogenation of acetophenone *N*-benzylimine was carried out in water under 1000 psi of hydrogen at 25 °C. Product was obtained in 98% yield with 56% ee. The asymmetric hydrogenation of acetamidocinnamic acid was less enantioselective, and only 16% ee was observed. Similarly, the hydrogenation of 2-(4-isobutylphenyl)propenoic acid gave the product in only 19% ee.

Lamouille et al. prepared 6,6′-(dimethylamino)-BINAP for asymmetric hydrogenation.[80] This diamino phosphine compound was first converted to the ammonium bromide **23** upon the addition of hydrobromic acid. The corresponding ruthenium complex was prepared using [Ru(η^3-2-methylallyl)$_2$(COD)] as a catalyst precursor. The asymmetric hydrogenation of ethyl acetoacetate was carried out with a substrate-to-catalyst ratio of 1000 to give complete conversion and high enantioselectivity (94% ee). Reuse of this water-soluble catalyst showed no loss of activity and enantioselectivity.



23

Gelpke et al. prepared the dibenzofuran-based diphosphine BIFAP **24** and its water-soluble sulfonated derivative BIFAPS **25** for asymmetric hydrogenation reactions.[81] The sulfonation using normal sulfuric acid was unsuccessful. The reactions carried out at room temperature could not be completed in more than 2 days. Elevating the reaction temperature gave complete sulfonation, but also caused the racemization of the ligand. The use of a stronger sulfonating reagent such as fuming sulfuric acid (containing 5% SO_3 in concentrated sulfuric acid) gave the sulfonated product in quantitative yield at room temperature.



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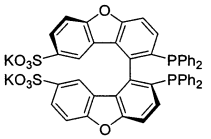

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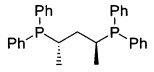
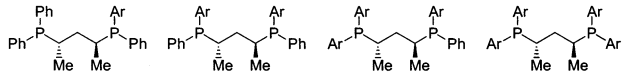
The ruthenium complexes of these two chiral phosphine ligands were used in a series of asymmetric hydrogenation reactions. In the presence of the sulfonated catalyst, (*Z*)-acetamidocinnamic acid was hydrogenated in methanol with quantitative conversion and 72% ee. The reaction carried out in H_2O/EtOAc mixed solvent gave similar enantioselectivity but a much lower rate.

Excellent results were obtained in the asymmetric hydrogenation of methyl acetoacetate carried out in methanol. In the presence of small amounts of an acid, 100% conversion and 100% ee were achieved in 2 h. The reaction carried out in water gave similar conversion but lower enantioselectivity (85% ee).

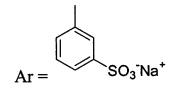
Most of the water-soluble phosphines were prepared by direct sulfonation of the phenyl groups, leading to the sulfonated products as a mixture. To investigate the influence of the degree of sulfonation on the enantioselectivity, Lensink et al. prepared a series of BDPP derivatives (**26b**−**26e**) by sulfonating the parent phosphine ligand (**26a**).[82] Controlling the extent of sulfonation introduced 1 to 4 sulfonate groups to BDPP, rendering the ligand soluble either in organic solvent or in water.



BDPP (26a)

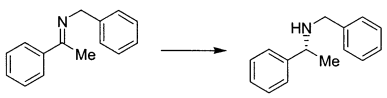


26b 26c 26d 26e

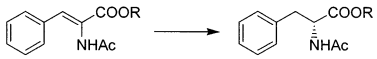


While the monosulfonated BDPP **26b** was soluble in organic solvent, disulfonated BDPP **26c** was water-soluble. Several substrates were subjected to asymmetric hydrogenation (Schemes 13−14 and 11),

Scheme 13



Scheme 14



and the rhodium complex of monosulfonated BDPP gave the highest ee's among all sulfonated catalysts (See Tables 7−9).

1.6. Carbohydrate-Type Chiral Catalysts for Aqueous Hydrogenation

Of the various strategies for water-soluble catalysts for asymmetric organic reactions, using a carbohy-

Table 7. Asymmetric Hydrogenation of *N*-Benzylimines

entry	ligands	solvent	pressure (bar)	conversion (%)	ee (%)
1	**26a**	MeOH	70	100	68
2	**26a**	EtOAc/H_2O	70		
3	**26b**	EtOAc/H_2O	70	100	94
4	**26c**	EtOAc/H_2O	70	100	2
5	**26d**	EtOAc/H_2O	70	100	3
6	**26e**	EtOAc/H_2O	70	100	63

Table 8. Asymmetric Hydrogenation of α-Acetamidocinnamic Acid and Its Ester[a]

entry	ligands	substrate (R)	solvent	ee (%)
1	**26a**	H	MeOH	96
2	**26a**	Me	MeOH	72
3	**26b**	H	EtOAc/H_2O	87
4	**26b**	Me	EtOAc/H_2O	74
5	**26c**	H	EtOAc/H_2O	83
6	**26c**	Me	EtOAc/H_2O	71
7	**26d**	H	EtOAc/H_2O	75
8	**26d**	Me	EtOAc/H_2O	59
9	**26e**	H	EtOAc/H_2O	65
10	**26e**	Me	EtOAc/H_2O	45

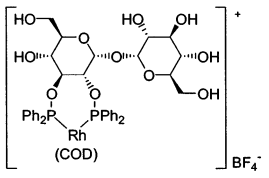
[a] Reaction pressure: 10 bar; 100% conversion in all cases.

Table 9. Asymmetric Hydrogenation of Dimethyl Itaconate

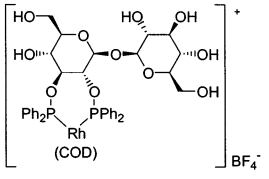
entry	ligands	solvent	pressure (bar)	conversion (%)	ee (%)
1	**26a**	MeOH	10	100	3
2	**26b**	EtOAc/H_2O	10	100	28
3	**26c**	EtOAc/H_2O	10	100	1
4	**26d**	EtOAc/H_2O	10	100	1
5	**26e**	EtOAc/H_2O	10	100	8

drate backbone as catalyst scaffolding has the advantage of its ready availability and its easily tunable chiral centers. The use of carbohydrate-derived catalyst for asymmetric catalytic reaction has been successfully developed by Shi et al. for the asymmetric epoxidation of unfunctionalized olefins[83] and by Selke et al. for asymmetric catalytic hydrogenations.[84]

Yonehara et al. reported the application of trehalose type diphosphinite ligand for the asymmetric catalytic hydrogenation of dehydroamino acids. Ligands with both α,α- and β,β-glycosideconnections (α,α-**27** and β,β-**27**) were obtained.[85]



α,α-**27**-Rh



β,β-**27**-Rh

The asymmetric hydrogenation was carried out in either water or aqueous organic biphasic system (Scheme 14, R = Me). While generally moderate ee's were observed in the asymmetric hydrogenation using Rh−(α,α-**27**) as catalyst (Table 10, entries 1, 3, 5, 7, and 9), the asymmetric hydrogenation in the presence of Rh−(β,β-**27**) gave significantly higher enantioselectivity (Table 10, entries 2, 4, 6, 8, and 10).

Table 10. Asymmetric Hydrogenation of Methyl Acetamidocinnamate Catalyzed by Rh−(α,α-27) and Rh−(β,β-27)

entry	solvent	catalyst	cat. (mol %)	time (h)	ee (%)
1	H_2O	Rh−(α,α-**27**)	5	6	55
2	H_2O	Rh(β,β-**27**)	5	6	88
3	H_2O	Rh−(α,α-**27**)	1	1	90
4	H_2O[a]	Rh(β,β-**27**)	1	1	99.9
5	H_2O/AcOEt (1:1)	Rh−(α,α-**27**)	2	1.5	68 (run 2: 66)
6	H_2O/AcOEt (1:1)	Rh(β,β-**27**)	2	1.5	87 (run 2: 85)
7	H_2O/MeOH/AcOEt (0.6:0.4:1)	Rh−(α,α-**27**)	1	3	76
8	H_2O/MeOH/AcOEt (0.6:0.4:1)	Rh(β,β-**27**)	1	3	98
9	H_2O/MeOH (3:2)	Rh−(α,α-**27**)	1	1.5	75
10	H_2O/MeOH (3:2)	Rh(β,β-**27**)	1	1.5	94

[a] Reaction carried out in the presence of surfactant SDS.

The asymmetric hydrogenation of other acetamidoacrylic acids (or esters) was also tested and excellent ee's were obtained in all cases. The enantioselectivity was improved to 99.9% by adding surfactant SDS into the reaction system. The high enantioselectivity resulted from β,β-trehalose compound was attributed to its high water solubility and its ability of effective micelle formation.

Using other anions such as OTf^- or D-camphor-10-sulfonate in place of BF_4^- decreased the enantioselectivity to 48%. Adding SDS again improved both the reactivity and the enantioselectivity (Table 11).[86]

Table 11. Asymmetric Hydrogenation of Methyl (*Z*)-α-Acetamidocinnamate Using Rh(α,α-27) as Catalyst in the Presence of Sulfonate Anions

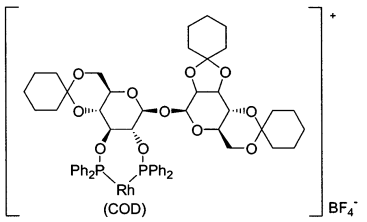
entry	anion	time (h)	ee (%)
1	OTf^-	6	48
2	D-camphor-10-sulfate	6	48
3	OTf^- + SDS (7.5×10^{-3})	1	81

Protecting the hydroxyl groups via ketal formation resulted in decreased water solubility of the complex (**28**), thus making it difficult for the reaction to proceed in water. Again, adding SDS to the reaction system facilitated the hydrogenation process (Scheme 16), and led to the product in high enantiomeric excess (94%, Table 12).

Table 12. Asymmetric Hydrogenation of Methyl (*Z*)-α-Acetamidocinnamate in Different Solvents Using Rh−28 as Catalyst

entry	solvent	ee (%)
1	$ClCH_2CH_2Cl$	95
2	H_2O	
3	H_2O + SDS (7.5×10^{-2} M)	94

In the process of preparing water-soluble carbohydrate based phosphinite ligands for asymmetric



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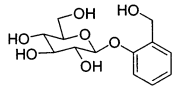
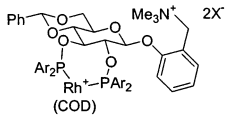
catalysis, Yan et al. obtained a series of chiral phosphinite ligands for the asymmetric hydrogenation of acetamidoacrylates.[87]

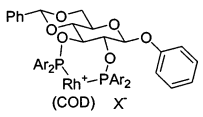
Starting from the natural carbohydrate compound salicin (**29**), a variety of chiral ligands were obtained.



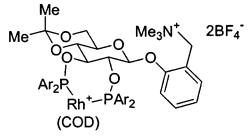
29 salicin



30a: Ar = Ph, **30b:** Ar = 3,5-dimethylphenyl

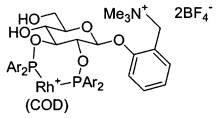


30c: Ar = Ph, **30d:** Ar = 3,5-dimethylphenyl



31a: Ar = Ph, **31b:** Ar = 3,5-dimethylphenyl,

31c: 3,5-di(trifluoromethyl)phenyl

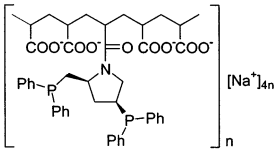


32a: Ar = Ph, **32b:** Ar = 3,5-dimethylphenyl, **32c:** 3,5-di(trifluoromethyl)phenyl

All these catalysts were tested in the asymmetric hydrogenation of acetamidoacrylates. While the reactions carried out in organic solvents showed quite high enantioselectivities, the reactions carried out in neat aqueous solution or biphasic medium normally gave lower enantioselectivities.

1.7. Water-Soluble Polymer-Supported Chiral Catalysts for Asymmetric Hydrogenation

In addition to direct modification, phosphines were also made water-soluble through the attachment to a hydrophilic polymer. Malmström et al. reported a poly(acrylic acid)-supported PPM (**33**) for asymmetric synthesis.[88] The catalyst was covalently linked to the polymer through an amide bond between the carboxyl groups in the polymer and the chiral ligand. Workup under basic conditions afforded the sodium salt of modified poly(acrylic acid). Increasing the catalyst loading lowered the water solubility of the modified catalyst, and a phosphine-to-carboxylate ratio of 1:5 was finally used to obtain a balance of phosphine loading and catalyst solubility.



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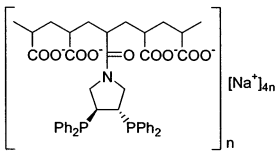
Reacting an aqueous solution of this supported PPM with $[Rh(NBD)_2]^+CF_3SO_3$ afforded the corresponding Rh-complex as an orange powder in its final form. The asymmetric hydrogenation of (*Z*)-acetamidocinnamic acid in the presence of this complex was carried out in different solvent systems. Over 97% yield was obtained in all the tested reactions with ee's ranging from 56 to 74%. Due to the low water solubility of the substrate, the reactions carried out in water proceeded rather slowly. The substrate could be dissolved in water by adjusting the pH value with sodium bicarbonate, but this resulted in a rather low reaction rate and low ee (56% ee). In biphasic water−ethyl acetate reaction system, the rate was comparable to that of the organic solvent system. The enantioselectivity was strongly dependent on the level of phosphine loading, and the polymer with 1% ligand loading gave the best results.[89] The asymmetric hydrogenation of acetamidocinnamic acid gave 89% ee with this ligand loading. Higher loading of phosphine ligand resulted in poor ligand separation and lower enantioselectivity.

The aqueous phase containing the catalyst was reused, after filtration and washing with degassed ethyl acetate to remove the organic components. Rhodium leaching was observed, and the analyses of the combined organic phases from two consecutive experiments of hydrogenation showed the loss of approximately 6.5% of the total amount of rhodium.

Similarly, another chiral ligand PyrPhos was connected to the poly(acrylic acid) backbone to give the supported ligand **34**.[90]



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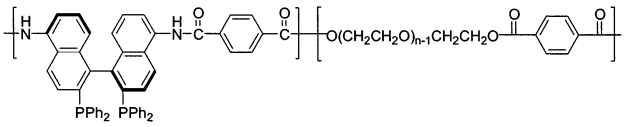
Polymers containing phosphine levels of 3.9, 1.6, and 0.95% were prepared and tested for the asymmetric hydrogenation of acetamidocinnamic acid. The hydrogenated product was obtained in 76 to 83% ee which were lower than the results from the use of the parent PyrPhos ligand.

Fan et al. reported an amphiphilic PEG-bound BINAP ligand **35** for the asymmetric hydrogenation of 2-arylacrylic acid.[91] The supported catalyst was prepared through the polycondensation of 5,5′-diamino-BINAP, poly(ethylene glycol) and terephthaloyl chloride in the presence of pyridine. The polymer

catalyst was found to be 30 times more active than the sulfonated Ru−BINAP catalyst, illustrating the advantage of the amphiphilic structure of the polymeric ligand.



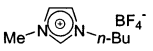
35

The homogeneous asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid carried out in methanol in the presence of 4-fold triethylamine gave the product with 86% ee, while the reaction carried out in the absence of triethylamine under otherwise identical conditions proceeded very slowly. The presence of water in the reaction system lowered the activity. The reaction in an aprotic solvent such as ethyl acetate was slower and gave lower enantioselectivity (67% ee). The reaction carried out in a two-phase system (ethyl acetate/water) showed higher reaction rate but lower enantioselectivity. Adding surfactant SDS produced little effect on the enantioselectivity of the reaction.

1.8. Asymmetric Hydrogenation in Ionic Liquid and Supercritical Carbon Dioxide

Over the past few years, room temperature ionic liquids (a salt mixture with a melting point below ambient temperature) have attracted renewed attention for a variety of reactions.[92] Ionic liquids are normally nonvolatile, nonflammable, and easy to recover, and are generally environmentally friendly for chemical reactions. In most cases, transition metal complexes are soluble in ionic liquids, while organic substrates are immiscible.

Monteiro et al. reported the asymmetric hydrogenation of 2-phenylacrylic acid in ionic liquid 1-*n*-butyl-3-methylimidazolium tetrafluoroborate molten salt (BMIM·BF_4, **36**).[93]



36

The reaction was carried out in BMIM·BF_4/2-propanol system with a ruthenium-BINAP catalyst immobilized in an ionic liquid phase. Under homogeneous conditions, the reaction in methanol gave a product in 82% ee. A two-phase reaction in 2-propanol/BMIM·BF_4 mixture gave the product in 2-propanol phase, and was separated by decantation. The recovered ionic liquid phase containing the catalyst was reused several times with ee's ranging from 68 to 84%. This catalyst system was also used for the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid to give naproxen in 80% ee.

Guernik et al. reported the asymmetric hydrogenation of methyl α-acetamidoacrylate and methyl α-acetamidocinnamate carried out in ionic liquid BMIM·PF_6^-. Rh−MeDuPHOS was used as catalyst, and the ionic liquid was found to provide additional stability to the air-sensitive chiral catalyst,[94] making it possible to recover and to reuse the highly air-sensitive catalyst Rh−MeDuPHOS. The hydrogenation of methyl α-acetamidocinnamate (Scheme 15) gave the product with 96% ee in 83% conversion. While the catalytic activity decreased gradually, successive reuse of the catalyst showed little decrease of enantioselectivity. The catalyst showed similar enantioselectivity (94% ee) in the fifth cycle even though the reaction was carried out after the heterogenized catalyst was exposed to air for 24 h (Table 13).

Scheme 15

Table 13. Asymmetric Hydrogenation of Enamides with Rh−MeDuPHOS in BMIM·PF_6/*i*-PrOH[a]

		R = H		R = phenyl	
entry	conditions	conv. (%)	ee (%)	conv. (%)	ee, (%)
1	homogeneous	100	97	100	99
2	homogeneous[b]	5	57		
3	heterogeneous (cycle 1)	100	93	83	96
4	heterogeneous (cycle 2)	100	80	64	96
5	heterogeneous (cycle 3)			62	95
6	heterogeneous (cycle 4)			60	94
7	heterogeneous (cycle 5)[c]			58	94

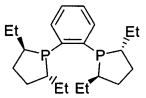
[a] Reaction conditions: for homogeneous catalyst, 25 °C, 2 atm H_2, 7 g of *i*-PrOH; reaction time = 5 min. In the heterogeneous system, 5 g of ionic liquid was added; reaction time = 20 min. [b] Catalyst prepared in an inert atmosphere and exposed to air for a few minutes. For entries 3−7, all manipulations were performed in air. [c] Left to stand in air for 24 h.

Burk et al. carried out the asymmetric hydrogenation of amidoacrylic acids (Scheme 16) in supercritical carbon dioxide using Rh−EtDuPHOS **37** (counterion = BARF or O_3SCF_3) as catalyst.[95] The reactions were also carried out in methanol or hexane for comparison. The enantioselectivities achieved in supercritical carbon dioxide were comparable to those achieved in conventional solvents (Table 14, entries 1−8).

Scheme 16

Table 14. Asymmetric Hydrogenation of Enamides in Different Solvents

	substrate			ee (%)		
entry	R^1	R^2	counter-ion	MeOH	hexane	supercritical CO_2
1	H	H	BARF	98.7	96.2	99.5
2	H	H	$CF_3SO_3^-$	99.4	99.1	99.1
3	Ph	H	BARF	97.5	98.3	99.1
4	Ph	H	$CF_3SO_3^-$	99.0	98.7	90.9
5	3,5-$(CF_3)_2$Ph	H	BARF	93.2	96.6	91.9
6	3,5-$(CF_3)_2$Ph	H	$CF_3SO_3^-$	99.1	98.6	94.6
7	Et	H	BARF	98.7	96.8	98.8
8	Et	H	$CF_3SO_3^-$	99.7	99.6	98.8
9	Me	Me	BARF	62.6	69.5	84.7
10	Me	Me	$CF_3SO_3^-$	67.4	70.4	88.4
11	-$(CH_2)_5$-		BARF	81.1	76.2	96.8
12	-$(CH_2)_5$-		$CF_3SO_3^-$	95.0	91.2	92.5

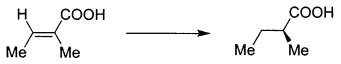


Et-DuPHOS **37**

The asymmetric hydrogenation of β,β-disubstituted α-enamide esters, which could not be hydrogenated with high enantiomeric excess under normal conditions, were also tested in supercritical carbon dioxide and good results were obtained (Table 14, entries 9−12).

Xiao et al. reported the asymmetric hydrogenation of α,β-unsaturated carboxylic acids (e.g., tiglic acid) using partially hydrogenated BINAP complex as catalyst (Scheme 17).[96] The hydrogenation of tiglic

Scheme 17



acid catalyzed by [Ru(OCOMe)$_2$((*S*)-H$_8$−BINAP)] with a substrate-to-catalyst ratio of 150 proceeded smoothly in supercritical carbon dioxide, giving the hydrogenated product in over 99% yield and up to 81% ee (Table 15). The reaction proceeded cleanly, and no

Table 15. Asymmetric Hydrogenation of Tiglic Acid in Supercritical Carbon Dioxide

entry	reaction medium	H_2 (atm)	yield (%)	ee (%)
1	Liq CO_2	30	0	
2	$ScCO_2$	33	99	81
3	$ScCO_2$	7	23	71
4	$ScCO_2$/R_FOH	5	99	89
5	MeOH	30	100	82
6	hexane	30	100	73

formic acid from carbon dioxide was detected. The addition of an alcohol increased the solubility of aromatic compounds in supercritical carbon dioxide, and adding fluorinated alcohol $CF_3(CF_2)_6CH_2OH$ to the reaction system increased both the conversion and enantioselectivity of the reaction.

Brown et al. reported the asymmetric hydrogenation of tiglic acid in a combined system of ionic liquid and supercritical carbon dioxide.[97] A ruthenium complex of Tol-BINAP was chosen as the catalyst. This complex was readily soluble in ionic liquid. The product was extracted from the ionic liquid by supercritical carbon dioxide, while the extraction of ruthenium complex was not observed. The catalyst contained in the ionic liquid can be reused for at least four more times without loss of enantioselectivity (Table 16).

Table 16. Asymmetric Hydrogenation of Tiglic Acid in Supercritical Carbon Dioxide

run	catalyst solution	ee (%)	conversion (%)
1	fresh	85	99
2	recycle from run 1	90	98
3	recycle from run 2	88	97
4	recycle from run 3	87	98
5	recycle from run 4	91	97

The asymmetric hydrogenation of 2-[4-(2-methylpropyl)phenyl]acrylic acid was also carried in ionic liquid. The reaction in wet ionic liquid was poor, but the reaction carried in the presence of methanol gave product with 85% ee under 100 bar of H_2.

2. Asymmetric Hydroformylation

2.1. Polymer-Supported Catalysts for Asymmetric Hydroformylation

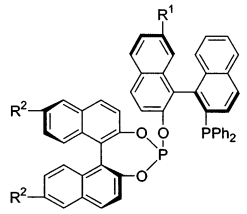
Hydroformylation, a reaction of an olefin with synthesis gas (carbon monoxide and hydrogen) to produce an aldehyde, has been extensively studied due to its high industrial potential. Asymmetric hydroformylation using polymer-supported catalyst was pioneered by Stille et al.[98]

The asymmetric hydroformylation of arylethylene, which may give key intermediates for some important nonsteroidal antiinflammatory drugs such as naproxen or ibuprofen, has also been extensively studied in the past decade. Among these studies, the asymmetric hydroformylation of arylethylene using chiral phosphine-phosphinite ligand has proved to be most successful.[99] Good results were achieved in the symmetric hydroformylation of styrene (Table 17).[100]

Table 17. Asymmetric Hydroformylation of Styrene

entry	catalyst	conversion	*i*/*n* (branched/linear)	ee%
1	free catalyst	98	84:16	92
2	polystyrene immobilized	75	85:15	91

Immobilized catalysts were also tested in this reaction.[101] Several different methods were devised to introduce the chiral ligand into the polystyrene support. In ligand **38b**−**38d**, R^1 or R^2 referred to the sites where the chiral ligand was connected to the support.

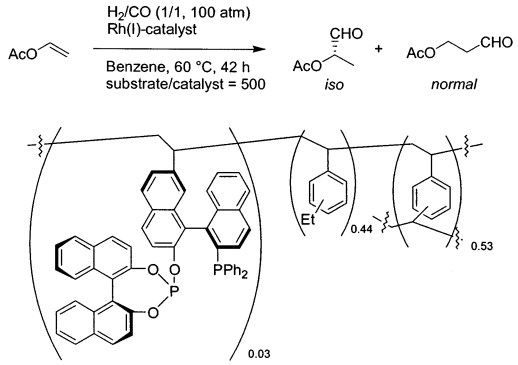


38

	R^1	R^2
38a	H	H
38b	-CH=CH$_2$	H
38c	H	-CH=CH$_2$
38d	-CH=CH$_2$	-CH=CH$_2$

When polymer-immobilized chiral phosphine−phosphite−Rh(I) (Rh-**39**) complexes were used, the asymmetric hydroformylation of styrene gave 2- and 3-phenylpropanals with iso/normal ratios from 84/16 to 89/11, and 2-phenylpropanal was obtained in 89% ee. The asymmetric hydroformylation of vinyl acetate, (*Z*)-2-butene, and 3,3,3-trifluoropropene were also successfully performed with the polymer-supported catalysts (Scheme 18).

Scheme 18. Asymmetric Hydroformylation of Vinyl Acetate

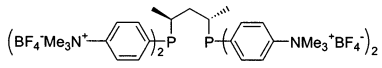


39

When the free catalyst was used, an iso-to-normal ratio of 84:16 was obtained at 98% conversion, and the enantiomeric excess for the iso-product was 92%; the immobilized catalyst **38c** gave an *i*/*n* ratio of 90:10 and 92% ee for the iso-product. The catalytic activity was lower: only 54% conversion was observed.

2.2. Water-Soluble Catalysts for Asymmetric Hydroformylation

Tóth et al. reported the quaternary aminophenyl derivatives of BDPP (**40**) for asymmetric hydroformylation.[102] Both the free and immobilized forms of the complexes Pt(Cl)($SnCl_3$)[(*S*,*S*)-BDPP-((*p*-NMe_3)(BF_4))$_4$] were prepared.



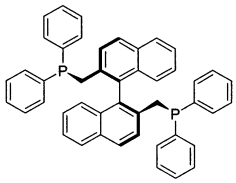
40

The $SnCl_2$ adduct was formed by treating the silica-supported $PtCl_2$[(*S*,*S*)-BDPP−((*p*-NMe_3)(BF_4))$_4$] with an organic solution of $SnCl_2$.

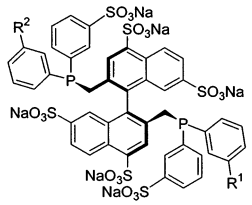
The asymmetric hydroformylation of styrene was carried out using this Pt/Sn complex as catalyst. The reaction carried out in two-phase gave low regioselectivity and stereoselectivity. The normal-to-branched ratio ranged from 1.4 to 1.9, and the highest ee for the branched product was only 14.1%.

Ligand **40** was also tested for rhodium complex-catalyzed hydrogenation of amidoacrylic acids. Using the same ligand, higher enantioselectivity was observed in the two-phase reaction than the homogeneous reaction. Recycling of the catalyst revealed that the complex was partially oxidized and deactivated.

Eckl et al. reported the use of sulfonated NAPHOS (**42a**−**42c**) for the asymmetric hydroformylation of styrene.[103]



41 NAPHOS



42

42a $R^1 = R^2$ = H BINAS-6

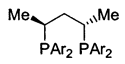
42b R^1 = H, R^2 = SO_3Na BINAS-7

42c $R^1 = R^2 = SO_3Na$, BINAS-8

(*S*)-BINAS with six sulfonate functional groups (**42a**) was used for a two-phase (toluene−methanol−water) asymmetric catalytic hydroformylation reaction. For comparison purpose, rhodium complex of (*S*)-NAPHOS (Rh−**41**) was also subjected to the same reaction in organic solution (toluene). The reaction in the presence of these complexes gave high percentage of iso-product, while the enantiomeric excess for the branched isomer remained low (32−34% for Rh−**41** and 18% for Rh−**42a**). For the two phase catalysis, catalyst recovery and recycling were easily achieved by phase separation. The reuse of recycled catalysts showed no significant loss of activity and stereoselectivity.

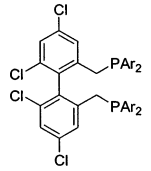
Miquel-Serrano et al. reported an aqueous phase asymmetric hydroformylation of styrene using rhodium complexes of tetrasulfonated CBD (**43**) or tetrasulfonated DBPP (**44**) as catalyst.[104] Branched aldehyde was obtained as the major product, but the enantiomeric excess was less than 17%.

43 (*R*,*R*)-CBDTS



44 (*S*,*S*)-BDPPTS

Rampf et al. reported the use of biphenyl type ligand **45a** for the rhodium-catalyzed asymmetric hydroformylation of styrene.[105] This compound was also sulfonated to give a water-soluble ligand **45b**. The asymmetric hydroformylation carried out at 40 °C using Rh−**45b** as catalyst showed 49% conversion with an iso-to-normal ratio of 4.5/1 and 15% ee for the branched product.



45a: BIPHLOPHOS Ar = Ph

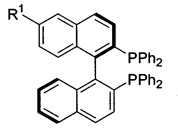
45b: Ar = -Ph-SO_3Na

3. Asymmetric Isomerization

The Rh−BINAP catalyzed asymmetric isomerization of diethylgeranylamine for the production of

optically pure (+)-citronella is an important industrial process. Studies have also been carried out using immobilized catalyst.

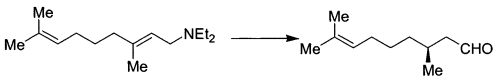
Chapuis et al. studied the activity of polymer-supported BINAP **46**.[106]



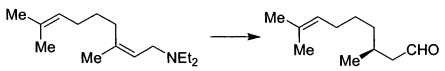
46 $R^1 = (CH_2)_3CO_2CH_2$-Polymer

Using triflate as the counterion, they found that the polymer-supported catalyst exhibited similar reactivity and selectivity as the Rh(BINAP) catalyst in the isomerization of diethylgeranylamine **47** and diethylnerylamine **48** (Scheme 19).

Scheme 19



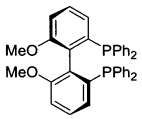
47 diethylgeranylamine



48 diethylnerylamine

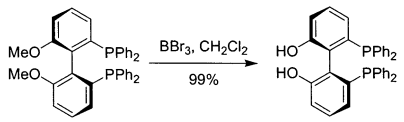
For the isomerization of **47**, the ratio of catalyst-to-substrate could be lowered to 0.1 mol % without adverse effect on either the conversion or the enantioselectivity of the reaction. The hydrolysis of the resulting enamine and bulb-to-bulb distillation afforded the (*S*)-(−)-citronellal in 98% ee at 95% isolated yield. The advantage of this polymer-supported ligand is its straightforward separation from the reaction system. The authors were able to recycle the immobilized catalyst for 37 times simply by decantation/filtration, and the recycled catalyst did not show any loss of reactivity and stereoselectivity.

Chiral ligand (*S*)-MeO−BiPHEP **49** is a special ligand that can be readily derivatized and immobilized by converting the methoxyl groups to hydroxyl groups flowed by appropriate treatments. In the presence of BBr_3 and dichloromethane,[107,108] **49** was successfully demethoxylated to afford the corresponding diphosphinobiphenyldiol **50** in almost quantitative yield (99%) without racemization (Scheme 20).



49 (*S*)-BiPHEP

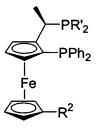
Scheme 20



50

Using either an ether or ester linkage, this new diol was attached to a solid support poly(ethylene glycol) (commercial name TantaGel).[109,110] In the asymmetric isomerization of diethylgeranylamine, ester linked catalyst gave 88% ee, and the ether linked catalyst gave 96% ee. These results were similar to those obtained by using MeO−BiPHEP, although the supported catalysts showed low reactivity.

A series of ferrocenylphosphine ligands in both homogeneous and immobilized form were also studied for this isomerization reaction. The immobilized ligands could be recycled by simple decantation/filtration. Generally, the reactivity was lower under heterogeneous conditions. The polymer-supported ligand (e.g., polymer-supported Josiphos) showed lower reactivity than the corresponding silica gel supported species. The silica gel-immobilized catalysts normally gave similar or better stereoselectivity as compared to the corresponding homogeneous analogues. For example, asymmetric isomerization of diethylgeranylamine and diethylnerylamine catalyzed by Rh−**51c** gave 83% ee and 88% ee, respectively, in comparison to 78% ee and 86% ee, respectively, from the use of the corresponding free catalyst. Similarly, Rh−**51d** gave 96% ee in the isomerization of both diethylgeranylamine and diethylnerylamine. In comparison, the free catalyst gave 92% ee and 97% ee, respectively, in these reactions.



51

	R^1	R^2
51a Josiphos	Cy	H
51b *t*-Bu-Josiphos	*t*-Bu	H
51c	Cy	$Si(Me)_2CH_2NHC(O)NH(CH_2)_3Si(OEt)(O_2Si)_n$
51d	*t*-Bu	$Si(Me)_2CH_2NHC(O)NH(CH_2)_3Si(OEt)(O_2Si)_n$
51e	Cy	$CH_2NHC(O)$NH-2,5-Tol-$NHC(O)NHCH_2$-4-Ph-Polymer

The polymer-supported catalyst failed to give exciting results. Both the selectivity and the reactivity were lower than the homogeneous analogue.

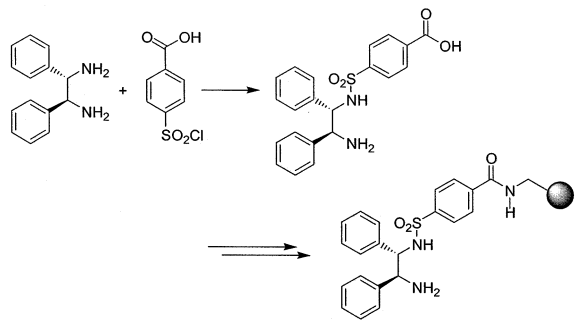
4. Asymmetric Reduction of Ketones

The reduction of ketones via hydrogen transfer can be regarded as an alternative for the asymmetric hydrogenation of ketones in the preparation of secondary alcohols. The difference between hydrogenation and transfer hydrogenation is obvious: the former applies dihydrogen as the hydrogen source, while the latter uses other hydrogen sources such as 2-propanol, formic acid, or formamide. Transfer hydrogenation is attractive, particularly in small scales, as it can avoid the inconvenience of handling hydrogen, sometimes under high pressure.[111]

4.1. Supported Catalysts for Asymmetric Transfer Hydrogenation of Ketones

Following Noyori's successful application of (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) complex as catalyst in asymmetric transfer hydrogenation reactions, efforts have been made to develop supported catalyst for this reaction. The advantages of using supported catalysts are the recovery of the often expensive ligands and the reuse of the potentially toxic transition metal species.[112] Two polymer supports, namely, polystyrene and poly(ethylene glycol) linked polystyrene, were chosen as the catalyst carriers (Scheme 21):

Scheme 21[a]



52

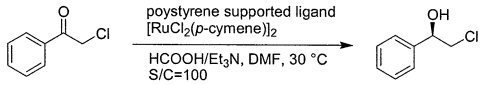
[a] **52a**: PS = polystyrene; **52b**: poly(ethylene glycol) linked polystyrene.

The effectiveness of the supported ligand (**52**) was assessed in the asymmetric transfer hydrogenation of acetophenone using 2-propanol or formic acid/triethylamine as the hydrogen source. In the case of 2-propanol as hydrogen source, poly(ethylene glycol) linked polystyrene supported catalyst (**52b**) gave 55.3% ee at 9% conversion, and the polystyrene supported catalyst (**52a**) gave 90.5% ee at 88% conversion. The latter result was comparable to that from the use of the corresponding free catalyst. The lower effectiveness of the polyethylene linked polystyrene supported catalyst may be due to the inaccessibility of the active sites. During the transfer hydrogenation process, the visual appearance of the polymer was unchanged with the beads remaining orange/red in color, and the catalyst was easily isolated from the reaction system by simple filtration under nitrogen atmosphere.

The use of a 5:2 formic acid/triethylamine azeotrope as hydrogen source showed promising results. While Ru−**52a** complex gave high ee (91.3%) but poor conversion (21%), Ru−**52b** complex gave (*S*)-1-phenylethanol in 97.6% ee at 96% conversion, a result comparable to that from using the homogeneous catalyst (98% ee at 99% conversion after 20 h with 0.5 mol % catalyst).

When using other solvents, such as CH_2Cl_2 or DMF, as cosolvent, the ruthenium catalyst containing ligand **52a** became more active and higher than 99% ee was observed. This ligand was also effective in the transfer hydrogenation of 2-chloroacetophenone; giving the desired product in 90% yield and 95.3% ee (Scheme 22).

Scheme 22

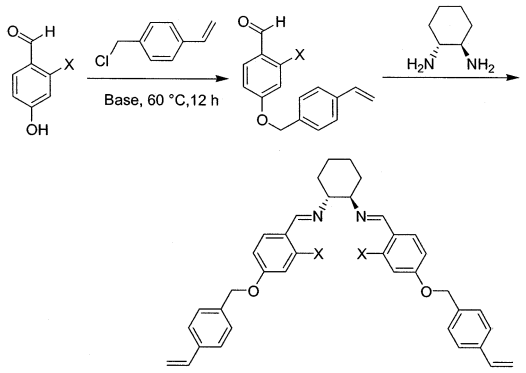


90% yield, 95.3% ee

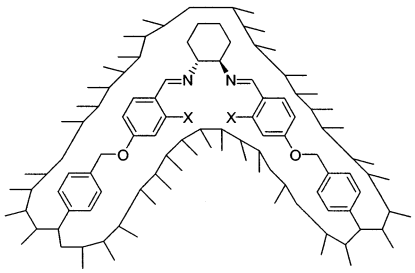
Similarly, ter Halle et al. prepared the linear and cross-linked polymer-supported (1*S*,2*S*)-TsDPEN ligand for Ir(I) and Ru(II) catalyzed asymmetric transfer hydrogenation of acetophenone.[113] Up to 94% ee was obtained in the transfer hydrogenation of acetophenone using an Ir-complex of the polymeric ligand as catalyst.

Breysse et al. reported the use of heterogenized dialdimine ligands (**53**) for the asymmetric transfer hydrogenation of acetophenone, as well as for the asymmetric epoxidation of styrene (Scheme 23).[114]

Scheme 23

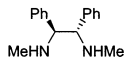


Enantioselectivities of up to 70% were obtained in the transfer hydrogenation reaction, and 15% ee was observed in the epoxidation of styrene.

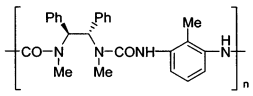


53 X=H or OH

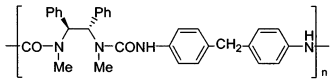
Locatelli et al. reported another method for the asymmetric transfer hydrogenation of acetophenone.[115] Initially Rh−(1*S*,2*S*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine (Rh−**54**, Rh:**54** = 1:2) was used as catalyst and the substrate was reduced in 3 to 7 days to give a product in 67% ee. Polyurea supported catalyst was studied for the same reaction, and the cross-linking of the polymer was found to be crucial for both catalytic activity and enantioselectivity (see the results of **55a**, **55b**, and **55c**).



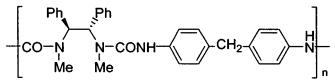
54 (1*S*,2*S*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine.



55a, polyurea based supported ligand. No crosslinking, 63% conversion after 17 days, 24% ee.

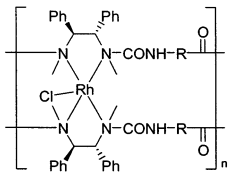


55b, no crosslinking, 97% conversion after 3 days, 39% ee.



55c, with crosslinking, 100% conversion in 1 day, 60 % ee.

It was speculated that the cross-linked polymer facilitated the formation of the active catalyst (**56**), hence enhancing both the reactivity and the stereoselectivity of the reaction.

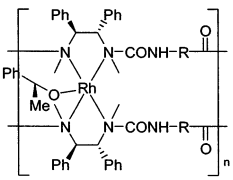


56

A heterogeneous catalyst was also prepared from a preformed catalyst rhodium(I)-(*N*,*N*-dimethyl-1,2-diphenylethane diamine)$_2$ (**57**) through the polyaddition with a mixture of di- and tri-isocyanate. Up to 47% ee was obtained in using this catalyst for the transfer hydrogenation.

The molecular recognition between enzymes and substrates and the subsequent catalytic transformations are largely controlled by precisely positioned functional groups within the protein cavities. The creation of such cavities in artificial catalysts is one of the challenges in designing such biomimetic catalysts. This may be realized through the introduction of the catalytically active species onto a host molecule such as cyclodextrin. Another alternative may be the application of the so-called imprinting technique to synthesize polymers with cavities of the molecular dimensions of the template.

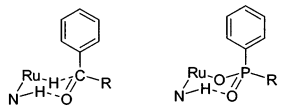
"Molecular imprinting effect" was explored in the synthesis of the polymerized catalyst. Optically pure 1-(*S*)-phenylethanol, the transfer hydrogenation product of acetophenone, was used as a template and diisocyanate and triisocyanate were added to a dichloromethane solution of bis(diamine)−Rh−phenylethanolate to form the solid catalyst.



57

As this template mimicked the reaction intermediate of the transfer hydrogenation, this type of polymer-supported catalyst was expected to give good results for the corresponding reaction. The stereoselectivity of the reaction catalyzed by the imprinted catalyst was generally higher than that without the imprinting technique.

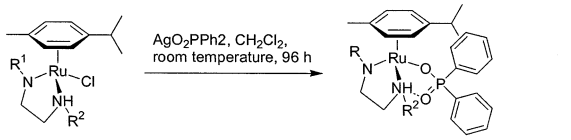
On the basis of the concept of molecular imprinting, Polborn et al. synthesized a ruthenium phosphinate species (**58**) as a pseudo substrate−catalyst complex for the transfer hydrogenation of acetophenone:[116, 117]



58

A ruthenium complex with a styrene side chain (**58**) was synthesized from the corresponding [(η^6-cymene)$RuCl_2$]$_2$ and the respective amine in the presence of NaOMe (1:2:2) (Scheme 24).

Scheme 24



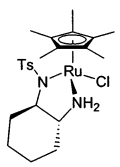
59a R^1 = *p*-vinylbenzenesulfonyl,

59b R^2 = H or *p*-vinylbenzenesulfonyl

This compound was copolymerized with ethylene glycol dimethacrylate (Ru:EGDMA = 1:99) in the presence of a porogen (chloroform) to give highly cross-linked jet porous polymer. The polymerization occurred under mild conditions using 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) as an initiator. After grinding and wet-sieving the polymer to a uniform particle size of 25−100 μm, the phosphinato ligand was selectively cleaved using methanolic $BnEt_3NCl$ to give the polymer containing the ruthenium complex.

The imprinted catalyst was five times more active than the nonimprinted analogue. This result was thought to be due to the reduced flexibility of the second-generation ruthenium complexes within the polymer cavity.

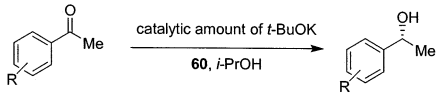
Polborn et al. also synthesized a Cp*Rh complex with chiral ligand for the asymmetric transfer hydrogenation reaction. The catalytic efficiency of free catalyst **60** was tested for comparison with the polymer-bound catalyst. [118]



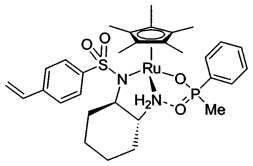
60

Several substrates were tested using 2-propanol as both the solvent and hydrogen donor, and over 90% ee was observed in the reduction of aryl methyl ketones (Scheme 25).

Scheme 25



Monomer **61** was used in the preparation of a polymer-bound catalyst using an imprinting technique.



61

The imprinted catalyst showed higher reactivity and stereoselectivity than the corresponding nonimprinted species (Scheme 26, Table 18).

Scheme 26

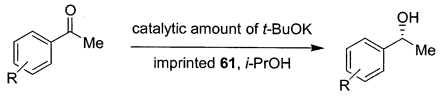


Table 18. Transfer Hydrogenation of Aromatic Ketones in the Presence of Imprinted Catalyst[a]

entry	ketone	time (h)	yield (%)	ee (%)
1	acetophenone	6	81(41)	95(93)
2	*p*-fluoroacetophenone	6	71(36)	93(90)
3	*o*-fluoroacetophenone	6	85(52)	84(76)
4	*m*-fluoroacetophenone	3	98(75)	94(92)
5	*m*-chloroacetophenone	3	98(69)	94(92)
6	1-acetonaphthone	6	52(24)	84(74)

[a] Data in parentheses are for the experiments using the control catalyst without imprinting.

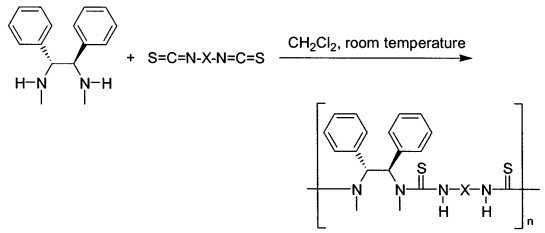
Touchard et al. reported a different chiral ligand in which the main chain of the chiral polymer itself worked as a ligand in the transfer hydrogenation reaction.[119]

As (1*R*,2*R*)-(+)-1,2-diphenylenediamine had been successfully used in a variety of asymmetric reactions including asymmetric transfer hydrogenation, one of its derivatives, (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenylenediamine, was chosen as the starting chiral compound to make the chiral polymer. Polythioureas was used as the main chain in the preparation of a series of polythioureas-bound amine ligands (Scheme 27).

The transfer hydrogenation of acetophenone using $[Ru(p\text{-cymene})Cl_2]_2$ or $[Ru(benzene)Cl_2]_2$ with **62e** (X = $-C_6H_4-$) gave 63% ee. A similar reaction using $[Ru(COD)Cl]_2$ as a catalyst precursor gave the product in poor ee.

When a ligand with a flexible alkyl linker (**62a**) was used, the transfer hydrogenation gave only 31% ee at 94% conversion after 2 days. Using pure aromatic linkage with 1,4-benzene-diyl or 1,3-benzene-diyl (**62e** or **62d**) improved the enantioselectivity to about 60%. Increasing the spacer length (biphenyl **62c**, for example) improved the enantioselectivity to 70%.

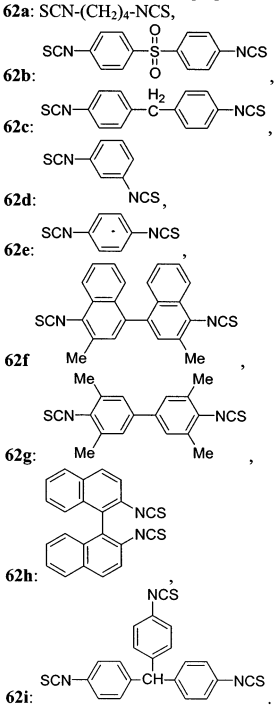
Scheme 27



62

SCN-X-NCS used for the preparation of **62a**-**62i**:

62a: SCN-$(CH_2)_4$-NCS,



The catalytic activity of polymer **62g**-bound catalyst in the transfer hydrogenation of acetophenone remained essentially unchanged, while the stereoselectivity decreased gradually in a series of recycles (Table 19).

Table 19. Reuse of the Recovered Catalyst 62g[a]

run	conversion (%)	ee (%)
1	92	70
2	98	67
3	99	66
4	99	63
5	98	61

[a] Reaction time, 1 day.

Other prochiral alkyl aryl ketones (RCOR′) were also subjected to the same reaction using **62g**, and up to 84% ee was observed (Table 20).

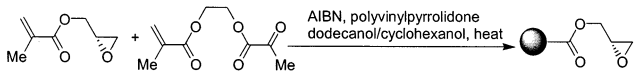
Table 20. Transfer Hydrogenation of Alkyl Aryl Ketones[a]

entry	R	R′	conversion (%)	ee (%)
1	Ph	Me	92	70
2	Ph	Et	95	80
3	Ph	*n*-Pr	90	76
4	Ph	*i*-Pr	87	84
5	Ph	*t*-Bu	85	78
6	1-naphth	Me	90	74

[a] Reaction time: 1 day.

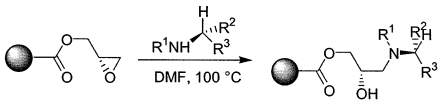
Poly(glycidyl methacrylate-*co*-ethylene glycol dimethacrylate), a copolymer of glycidyl methacrylate and ethylene glycol dimethacrylate, was also used as the polymeric chiral ligand. After copolymerization, the epoxy functional group was ready for further derivatization (Scheme 28).[120]

Scheme 28



The final polymer-supported chiral ligand (**63**) was obtained upon reacting the epoxy polymer precursor with a chiral amine (Scheme 29):

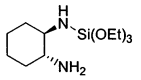
Scheme 29



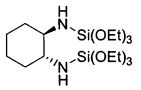
63

The best result from the asymmetric transfer hydrogenation of acetophenone was up to 70% ee at 94% conversion ($R^1 = R^2 = H$, $R^3 = Ph$).

Adima et al. reported two new alkoxysilylated derivatives of (−)-(1*R*,2*R*)-1,2-diaminocyclohexane: *N*-[(triethoxysilyl)propyl]-(1*R*,2*R*)-1,2- diaminocyclohexane (**64a**) and *N*,*N*′-bis[(triethoxysilyl)propyl]-(1*R*,2*R*)-1,2-diaminocyclohexane (**64b**).[121]



64a



64b

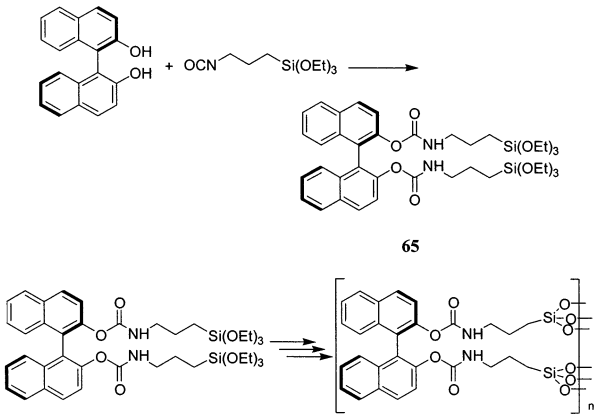
Their complexation with $[Rh(COD)Cl]_2$ in the presence of tetraethoxysilane followed by sol−gel hydrolysis−condensation afforded new chiral hybrid catalyst materials.

The N_2 sorption studies and BET analyses showed these solid gels to be in a wide range from nonporous to highly porous materials. The catalytic activities and selectivities of the solid materials were studied in the asymmetric transfer hydrogenation of prochiral ketones. The hybrid materials appeared to be interesting supports for enantioselective heterogeneous catalysis leading to chiral alcohols with up to 58% ee in the reduction of acetophenone and up to 98% in the case of the more hindered analogues.

Hesemann et al. prepared the polysilsesquioxane hybrid ligand containing binaphthyl moieties (**66**) via the coupling of (*R*)- or (*S*)-BINOL (2,2′-dihydroxy-1,1′-binaphthyl) with 3-(triethoxysilyl)propyl isocyanate and the subsequent hydrolysis polycondensation (Scheme 30):[122]

Hybrid gels containing rhodium could be obtained via hydrolysis of the BINOL precursor **65** in the presence of stoichiometric amount of $[Rh(COD)Cl]_2$. The different concentrations of the incorporated

Scheme 30



65

66

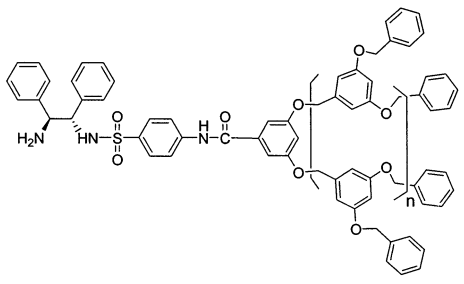
chiral organometallic moieties in the gel can be controlled by varying the amounts of tetraethoxysilane added to the hydrolysis polymerization system. The asymmetric transfer hydrogenation of acetophenone was tested and up to 45% ee was obtained.

Chen et al. designed the chiral dendritic TsDPEN-type ligands **67** by attaching the monomeric TsDPEN onto the focal point of the Fréchet-type dendrons.[123] The ruthenium complexes of up to the fourth generation were prepared in situ and were studied in the asymmetric transfer hydrogenation of acetophenone. Compared to the monomer catalyst, a slightly enhanced reactivity was observed for the dendritic catalysts with high enantioselectivity, in which the first and third generation catalysts possessed higher reactivity. Another feature of these dendritic catalysts was that they maintained the enantioselectivity with only slight loss of activity in successive applications (Table 21).

Table 21. Dendritic TsDPEN−Ru(II) Complex Catalyzed Asymmetric Transfer Hydrogenation of Acetophenone

entry	ligand	time (h)	conv. (%)	TOF/h^{-1}	ee(%)
1	**67a**	20	>99	11.9	96.6
2	**67b**	20	98	9.5	96.5
3	**67c**	20	>99	11.0	96.5
4	**67d**	20	98	9.6	96.5
5	**67d** (run 2)[a]	20	92		96.6
6	**67d** (run 3)[a]	25	87		96.8
7	**67d** (run 4)[a]	30	85		96.7
8	**67d** (run 5)[a]	40	73		96.3
9	**67d** (run 6)[ab]	40	52		87.0

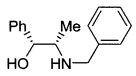
[a] Recovered catalyst was used. [b] Supplemented with additional $[RuCl_2(cymene)]_2$.



67

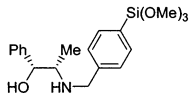
Ruthenium(II) complexes containing amino alcohol ligands are also good catalysts for the asymmetric

transfer hydrogenation of ketones. Sandee et al. reported an ephedrine derivative **68** which showed high ee in asymmetric transfer hydrogenation:[124]



68

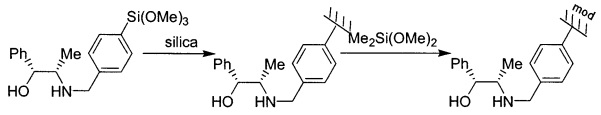
In the preparation of the immobilized version of the ligand,[125] ligand **69** (with trimethoxysilyl substitution) was prepared as the starting material.



69

Upon refluxing in toluene with a suspension of silica for 18 h, this precursor was immobilized on silica gel. The support could be further modified by reacting the thus formed supported catalyst with dimethyldimethoxysilane (Scheme 31). As a result of

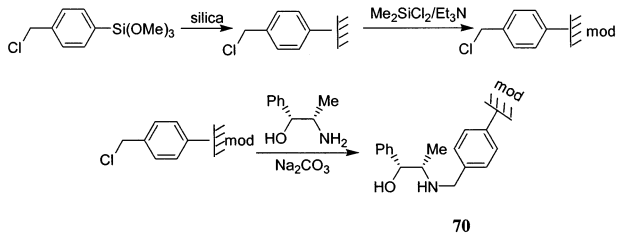
Scheme 31



this modification, the silanol hydroxyl groups on the silica support were protected as alkylsilanes.

Alternatively, the immobilized catalyst **70** can be prepared by the introduction of chloromethylphenyl groups on the silica followed by the capping of the silanol groups, and finally the introduction of the chiral amino alcohol moiety (Scheme 32).

Scheme 32



70

The ruthenium catalyzed asymmetric transfer hydrogenation resulted in 88% ee at 95% conversion. Recovery of the catalyst was investigated by performing subsequent batchwise reactions, and the enantioselectivity remained unchanged in most cases.

To obtain a more robust system for the asymmetric reduction of ketones with an immediate and straightforward separation of the product from the reaction system, a simple continuous flow reactor was designed. A small column equipped with a glass-filter was charged with freshly prepared Ru−**70** (one gram of catalyst containing 10−20 mg of ruthenium precursor). A homogeneous 2-propanol solution containing 0.01 M potassium *tert*-butoxide (*t*-BuOK) and 0.1 M of acetophenone was allowed to pass through the catalyst bed. At a flow rate of 1400 μL/h, acetophenone was reduced to phenylethanol in 90% ee at 95% conversion. The ruthenium leaching was less than 1% and the efficiency of this reaction system was virtually unchanged for one week.

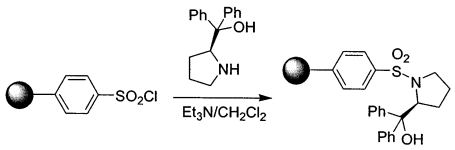
4.2. Supported Catalysts for the Enantioselective Borane Reduction of Ketones

The enantioselective reduction of ketones is also an important way to prepare optically active secondary alcohols, and a large number of reducing agents and/or chiral catalysts have been developed. One of the most successful reactions may be the oxazaborolidine mediated borane reduction, and chiral ligands such as chiral prolinol or ephedrine-type compounds proved to be very effective.

Fréchet demonstrated the first example of polymer-supported ligand for asymmetric hydride reduction of ketones. The polymer ligand gave lower enantioselectivity than the corresponding homogeneous counterpart. Better results were obtained later using polymer-supported amino alcohols as chiral ligands. The pioneering work has been well documented and reviewed.[126,127]

Hu et al. reported a polymer-supported CBS-type catalyst **71** for asymmetric borane reduction of prochiral ketones (Scheme 33).[128] The chlorosulfonation of a styrene-divinylbenzene cross-linked polymer gave the polymeric sulfonyl chloride. (*S*)-Diphenylprolinol was then attached to this functionalized polymer using Et_3N as a base to remove the hydrochloride.

Scheme 33



71

Up to 92.5% ee was obtained in the asymmetric reduction of acetophenone using $BH_3{\cdot}SMe_2$ as reducing agent. Other ketones were also used to evaluate the efficiency of the catalyst. Reduction of *p*-bromoacetophenone gave the corresponding product in 94.2% ee at 98% yield.

Hu et al. also used this type of catalyst in the $NaBH_4$ reduction of ketones in the presence of a Lewis acid (Me_3SiCl or $BF_3{\cdot}OEt_2$, Table 22 and Table 23).[129] In the reduction of β-acetonaphthone, the best ee reached 95.3% (at 99% conversion). In the reduction of acetophenone, 96% ee at 98% yield was observed as the best result. The recycled catalyst

Table 22. Asymmetric Reduction of Acetophenone under Different Conditions

			$NaBH_4/Me_3SiCl$		$NaBH_4/BF_3{\cdot}OEt_2$	
entry	chiral polymer (10 mol %)	temp (°C)	yield (%)	ee (%)	yield (%)	ee (%)
1	10	rt	99%	9.7	98	0
2	10	reflux	nd	nd	99	80.3
3	15	reflux	98	89.2	99	95.3
4	20	reflux	99	93.1	98	94.5
5	25	reflux	98	96.3	nd	nd
6	30	reflux	98	95.5	nd	nd

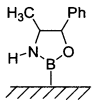
Table 23. Asymmetric Reduction of Ketones

		$NaBH_4$/Me_3SiCl		$NaBH_4$/$BF_3{\cdot}OEt_2$	
entry	ketone	yield (%)	ee (%)	yield (%)	ee (%)
1	acetophenone	98	95.7	98	95.1
2	acetophenone (run 2)	97	96.3	98	92.8
3	acetophenone (run 3)	98	95.4	97	94.6
4	*p*-bromoacetophenone	97	96.1	98	94.1
5	*p*-methoxyacetophenone	97	84.1	97	84.2
6	*p*-nitroacetophenone	99	96.6	98	96.0
7	α-chloroacetophenone	98	96.1	98	95.8
8	α-bromoacetophenone	99	96.6	98	94.0
9	α-tetralone	98	91.0	98	86.1
10	benzylacetone	97	65.1	98	64.5
11	1,1,1-triphenylacetone	96	89.5	95	87.0
12	1-cyclohexyl-1-propanone	95	71.1	96	69.8
13	2-butanone	91	50.6	92	47.5

showed similar activity and selectivity for acetophenone reduction (Table 23, entries 2 and 3).

Catalyst systems Ni/tartaric acid/NaBr developed by Izumi et al.[130] and cinchona-Pt/Al_2O_3 developed by Orito et al.[131] were highly effective in asymmetric catalytic hydrogenation. It was generally accepted that in these catalytic systems, the metal directly interacted with the chiral modifier. That is, the tartaric acid moiety was chemically bonded to nickel and did not leave the metal surface during the hydrogenation. In the case of cinchona-Pt/Al_2O_3 system, the aromatic π-system of the quinoline ring served as a binding site for the catalyst surface, and the enantioselectivity was determined mainly by the interaction of the quinoline N-atom with the substrate.

Molvinger et al. reported a similar catalyst system for both borane reduction and hydrogenation.[132] Upon addition of excess lithium borohydride, the surface part of the anhydrous nickel iodide was converted to nickel boride. The modification was accomplished after reacting the nickel boride with norephedrine to form the $NiB_{2-x}(oxaza)_x$ (**72**), whereas "oxaza" referred to the oxazaborolidine moiety possibly formed on the surface of the particle.



72

When the catalyst was used in the borane reduction of ketones, the product was obtained in up to 92% ee. The catalyst was also recycled and reused with slightly lower ee (90%).

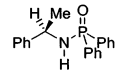
The authors also tried other substituted acetophenones, and the ee's were over 90% in all cases (Table 24).[133]

Table 24. Borane Reduction of Substituted Acetophenones Catalyzed by 72

entry	ketones	ee (%) first run	ee (%) second run	ee (%) third run	ee (%) fourth run
1	PhCOMe	94 (92)	91	91	90
2	4-MePhCOMe	95	93	91	90
3	4-FPhCOMe	92	91	91	92

Decreasing the acetophenone concentration gave better enantioselectivity, and the heterogenized catalyst gave better or similar ee as compared to the homogeneous analogue.[134,135]

Phosphinamides and related materials containing the N−P═O unit were also used in asymmetric borane reduction.[136] Cividino et al. used (*R*)-(+)-*N*-(1-phenylethyl)-*P,P*-diphenylphosphinamide (**73**) to dramatically accelerate the acetophenone reduction.

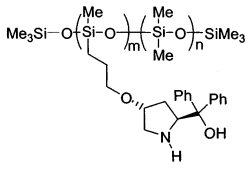


73

According to the authors, this compound was chemically adsorbed on NiB_2 through the strong interaction of the electron-rich oxygen atom with the boron atom. The asymmetric reduction of acetophenone was carried out using this immobilized phosphinamide as catalyst, and borane as reductant. The enantioselectivity of the catalyst was close to that of the homogeneous analogue. The study showed no free chiral ligand in the liquid phase after the reduction, indicating a strong binding between the chiral ligand and the NiB_2. The study also showed that the solid catalyst was easily recycled with retained activity and selectivity.[137−139]

4.3. Soluble Macromolecules for the Enantioselective Borane Reduction of Ketones

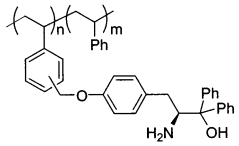
The oxazaborolidine-catalyzed reduction of ketones by borane is a widely used reaction that yields the corresponding chiral alcohols in high enantiomeric excess.[140] Owing to the existence of a competing uncatalyzed reaction, high catalyst concentration of about 1−20 mol % had to be applied to ensure high enantiomeric excess. The reuse of the valuable chiral amino alcohol ligand through special manipulation might be possible, but simple recycling of the catalyst was more desirable. Besides the insoluble polymer catalysts, soluble polymer catalysts were also developed. Wandrey and co-workers reported the synthesis of a polymer-enlarged homogeneous oxazaborolidine catalyst **74** and its use in the enantioselective borane reduction of ketones.[141] The enantioselective reduction of prochiral ketones such as acetophenone proceeded with enantiomeric excess of up to 98%, similar to that obtained with the homogeneous parent catalysts. The catalyst might be retained by a nanofiltration membrane and thus could be recovered after the reaction or used in a continuously operated membrane reactor.



74

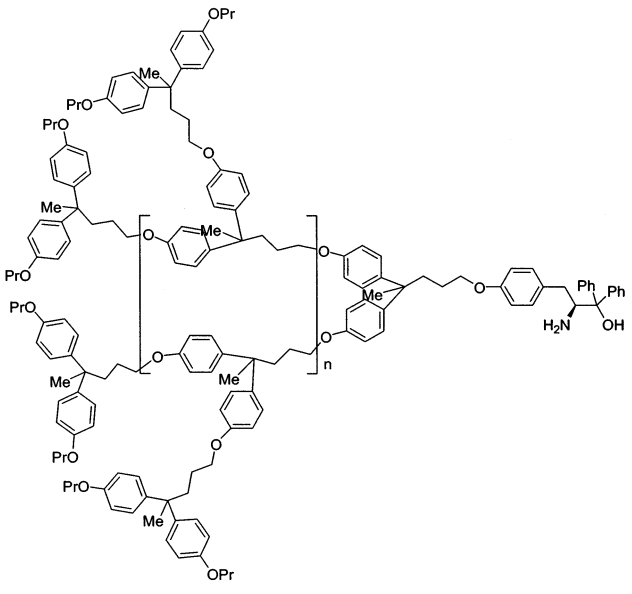
Giffels et al. also described a soluble polystyrene-supported oxazaborolidine **75** and pioneered the use of membrane separation in combination with soluble

polymer-supported ligands for the enantioselective reduction of ketones.[142] The reactions were carried out in a continuously operated membrane reactor equipped with a nanofiltration membrane. The mole ratio of chiral product-to-catalyst was increased from 10 to 560. The chiral alcohols were obtained in good to excellent ee and space-time yield (up to 99% ee and 1.4 kg/[$L_{\text{reactor volume}} \times$ day]. A comparison study on the enantioselective reduction of acetophenone catalyzed by polymer-bound oxazaborolidine catalyst and by dehydrogenase was performed in a continuously operated membrane reactor.[143] The chemical borane reduction gave (*R*)-phenylethanol in good enantiomeric excess with high space-time yields. An enzymatic reduction provided (*S*)-phenylethanol in excellent enantiomeric excess with low enzyme consumption.



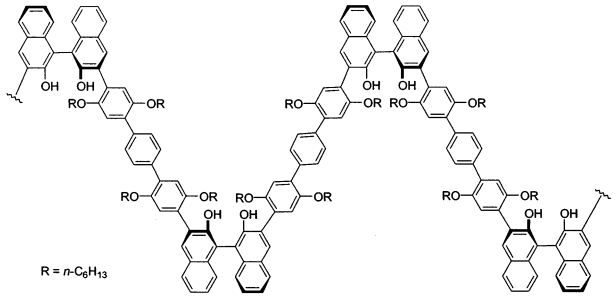
75

Bolm et al. described the use of chiral dendritic amino alcohol ligands **76** for asymmetric borane reduction of ketones.[144] Optically active amino alcohols were attached to the focal point of the Fréchet-type polyether dendrons. Compared to the parent catalyst (87% ee) slightly higher enantioselectivities (88−91% ee) and good yields were obtained using catalysts of various generations and using acetophenone as substrate. The highest enantioselectivity (up to 96% ee) in the reduction of *p*-chloroacetophenone was observed using the catalyst based on the first-generation ligand. Moreover, the enhancement of enantioselectivities comparing to the heterogeneous polymeric system (76% ee for acetophenone, 84% ee for *p*-chloroacetophenone) demonstrated the advantage of the dendrimer ligands.



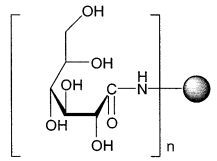
76

Huang et al. prepared polymeric BINOL **77** for asymmetric reduction of ketones. Using catecholborane as reducing agent the following compound induced up to 92% ee for the reduction of aryl ketones.[145]



77

Rico-Lattes et al. disclosed the preparation of amphiphilic dendrimers **78** which could be considered as rigid unimolecular micelles.[146,147] The glucose-persubstituted poly(amidoamine) dendrimers were found to induce chirality in the reduction of prochiral ketones by $NaBH_4$ under heterogeneous (THF) and homogeneous (water) conditions. Among these dendrimers, only the third-generation species ($n = 32$) gave good asymmetric induction under heterogeneous conditions (up to 100% ee). Even with substrates that were well-known to give poor results (especially linear ketones), good enantioselectivities were still obtained. Moreover, the dendrimer could be recovered, regenerated, and recycled (up to 10 times), leading to reproducible results in successive use. When this reaction was carried out in homogeneous manner in water, the best result was obtained by using the fourth-generation dendrimer ($n = 64$, up to 98% ee). Interestingly, the low generation dendrimers ($n = 8$ and 16) did not give any asymmetric induction in both cases. The architecture of the dendrimer was considered to dominate the selectivity.



gluconamide PAMAM dendrimers

78 (n = 8, 16, 32, 64)

5. Asymmetric Dihydroxylation and Related Reactions

Since its first discovery in 1988,[1] the cinchona alkaloid catalyzed asymmetric dihydroxylation has become one of the most general methods for the enantioselective functionalization of olefins. This method allows the olefin to be converted into optically active diols in one step in the presence of osmium oxide and cinchona alkaloid. Strong efforts have been made to optimize the reaction conditions such as the alkaloid ligands, oxidant, and solvent, and many reactions can be carried out with excellent enantioselectivity now.

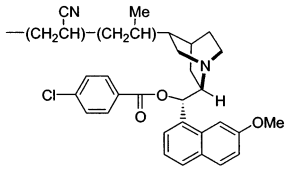
Due to the high cost of both osmium and the alkaloid-derived ligands and the toxicity of the metal, systems that can allow the facile and efficient separation of the catalyst from the reaction mixture are

highly desirable. This is particularly important for large-scale productions. Catalyst immobilization is a good way to solve such problems. The most commonly used methods for dihydroxylation catalysts involve the attachment of the alkaloids to a solid support such as an organic polymer or silica, or alternatively using the alkaloids that have been anchored to a soluble polymeric unit as catalyst. The former catalyst can be easily recycled after the catalytic reaction, and in the latter case the reaction is performed in a homogeneous fashion, and the ligand can be isolated by precipitation upon addition of another solvent.[21,148,149]

5.1. Insoluble Polymer-Supported Catalysts for Asymmetric Dihydroxylation

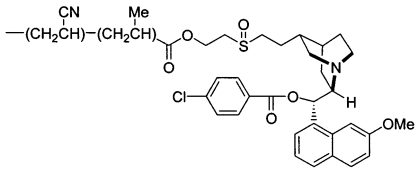
Kim and Sharpless reported the polymer-bound alkaloid derivatives for the asymmetric dihydroxylation of olefins.[150] Heterogeneous catalytic asymmetric dihydroxylation proceeded with good to excellent enantioselectivities in the dihydroxylation of *trans*-stilbene. It has also been shown that the OsO_4-polymer complex can be used for iterative processes.

The study was initiated with a copolymer **79** obtained by the copolymerization of 9-(*p*-chlorobenzoyl)quinidine with acrylonitrile.

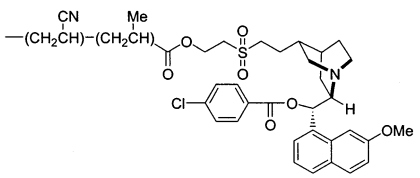


79

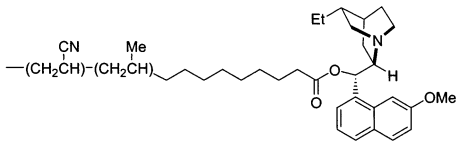
The asymmetric dihydroxylation catalyzed by the first generation catalyst **79** proceeded very slowly, which, according to the authors, may be resulted from the alkaloid being too close to the polymer backbone. To overcome this problem, catalysts with longer spacer groups (**80**, **81**, **82**) were prepared:



80



81

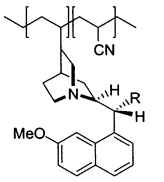


82

In the presence of $K_3Fe(CN)_6$ or NMO (*N*-methylmorpholino-*N*-oxide) as the secondary oxidant, the asymmetric dihydroxylation of *trans*-stilbene catalyzed by **80**, **81**, **82** proceeded smoothly, giving the corresponding diol in good yields (over 80% for most cases) and good ee (over 80% for most cases).

Modification of the catalyst system based on an understanding of the mechanistic features led to significant improvement in the osmium-catalyzed asymmetric dihydroxylation.[151]

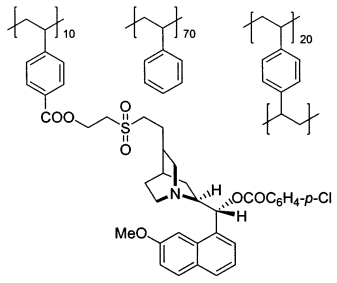
Pini et al. reported the asymmetric dihydroxylation using a copolymer containing 10 mol % of alkaloid as catalyst (**83**):[152]



83 R = H, *p*-ClPh, 3,5-$(MeO)_2$Ph

The asymmetric dihydroxylation of *trans*-stilbene to (*S*,*S*)-diphenyl-1,2-ethanediol proceeded readily with up to 86% yield and up to 46% ee. The OsO_4/polymeric alkaloid complex was simply and quantitatively recovered at the end of the reaction by centrifugation and was reused without loss of either reactivity or enantioselectivity.

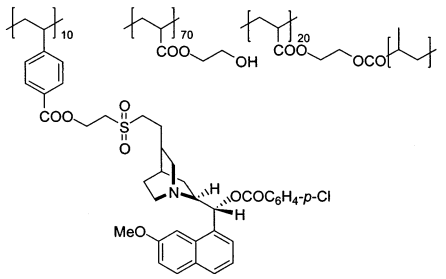
Pini et al. also reported a catalyst on a cross-linked polymer (**84**) which was prepared by the copolymerization of a chiral monomer containing the *p*-chlorobenzoic acid ester of quinine.[153] A spacer group was also introduced between the quinine derivative and the styryl group to allow the quinuclidinic moiety of the ligand not to be affected by the steric hindrance of the polymeric chain. To obtain a highly insoluble and easily filterable material, the chiral monomer was copolymerized with 70 mol % of styrene and 20 mol % of divinylbenzene to give the copolymer with 10 mol % of alkaloid. High levels of alkaloid incorporation were unfavorable because of possible inhibition of the asymmetric dihydroxylation.



84

When *trans*-stilbene was subjected to the asymmetric dihydroxylation reaction, the corresponding product was obtained in up to 87% ee at 85% yield.

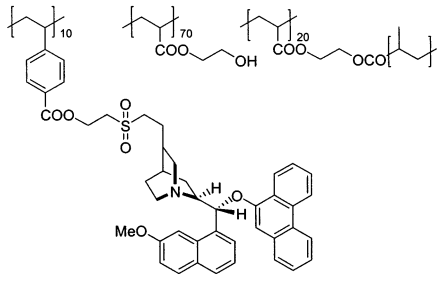
A polymer containing (4ClB)QN and alcoholic pendent groups (**85**) was also prepared.[154] The unreacted chiral monomer could be removed via filtration and thorough acetone extraction. This polymer was not soluble in any solvent and swelled very well in polar protic solvents:



85

In the presence of a secondary oxidant such as *N*-methylmorpholine-*N*-oxide in acetone/H_2O (10:1), the asymmetric dihydroxylation of *trans*-stilbene or styrene proceeded smoothly, providing the product with high chemical yield. Using potassium ferricyanide [$K_3Fe(CN)_6$] in *t*-BuOH/H_2O as a secondary oxidant resulted in a drop of yield. Both aliphatic and aromatic olefins were successfully dihydroxylated, and the ee's were up to 95%, a result comparable to those obtained with free alkaloid under similar reaction conditions.

Besides the modification of polymer backbone, Petri et al. also modified the alkaloid to get an optimal ligand for the dihydroxylation catalyst (**86**).[155] As the modification of the hydroxyl group at the 9-*O* position of the alkaloid is of great influence on the enantioselectivity of the reaction, a modified alkaloid in which the 9-position was derivatized with more bulky group was prepared.



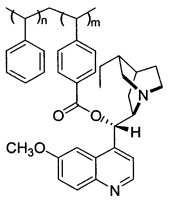
86

The catalyst containing hydroxyethyl methacrylate, ethylene glycol dimethacrylate and the phenanthryl ether of quinidine was also efficient for asymmetric dihydroxylation reactions, and up to 93% ee was obtained for the dihydroxylation of *trans*-stilbene.

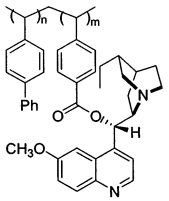
In the heterogeneous asymmetric dihydroxylation of olefins, using a suitable polymeric support and suitable substituent on the alkaloid 9-*O* position was important for higher enantioselectivity.[156]

Salvadori et al. concluded that the polyhydroxy methacrylic backbone offered a favorable microenvironment to the chiral catalytic sites, and once an appropriate support compatible with the reaction medium was chosen, the reactivity of using soluble or insoluble ligand was similar.[157]

Lohray et al. prepared a series of copolymers of dihydroquinidine (DHQD) 4-vinylbenzoate derivatives with styrene (**87**) and 4-phenylstyrene (**88**)[158] using the 9-*O* position of the alkaloid as a site of connection:



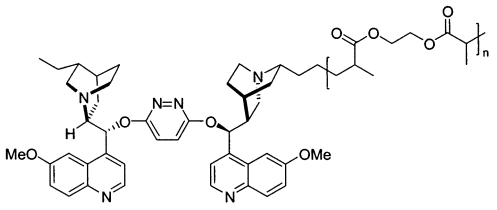
87



88

Among the polymers examined, the polystyrene with 10 mol % of dihydroquinidine or dihydroquinine and 1 mol % of osmium tetroxide proved to be the most effective. An increase of alkaloid on the polymer support led to an exponential decrease in the reactivity and stereoselectivity. Recycling of the polymer without any additional amount of OsO_4 resulted in slightly lowered yield and ee of the diol product, and the catalytic activity was regained by adding 0.1 mol % of OsO_4. It was concluded that leaching of the metal occurred during the product separation step. Phase transfer catalyst tetraethylammonium acetate (TEAA) had a deleterious effect on the reaction due possibly to the saponification of the chiral ligand from the polymer backbone. The saponificated dihydroquinidine is a poor ligand for the asymmetric dioxyosmylation reaction.

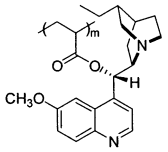
DHQ_2−Py, bearing two dihydroquinine molecules connected through 3- and 6- positions of pyridazine, showed great potential for asymmetric dihydroxylation. Lohray et al. connected this DHQ_2−Py to the polymer support of poly(ethyleneglycol dimethacrylate) (**89**), up to 99% ee was obtained with asymmetric dihydroxylation of *trans*-stilbene.[159]



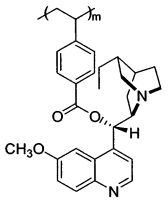
89

The polymer was prepared from 10 mol % of monomer and 90 mol % of ethylene glycol dimethacrylate. Radical initiated polymerization gave the corresponding polymer in almost quantitative yield. Polymers containing a higher percentage of monomer proved to be less reactive and selective. The polymers are mesoporous with large pore size, and are hydrophilic in general. This hydrophilicity facilitated the reactants to penetrate to the catalytic site and thus allowed the reaction to proceed smoothly and to give optimal results comparable to the use of the homogeneous catalysts.

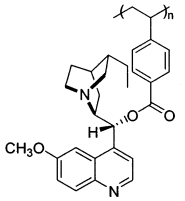
Song et al. reported some homopolymers (**90**, **91**, **92**) that gave good results in the asymmetric dihydroxylation of *trans*-stilbene or methyl cinnamate (up to 93% ee for *trans*-stilbene and 91% ee for methyl cinnamate).[160] The catalytic efficiency was largely dependent on the secondary oxidant and the solvent system. This might be due to the compatibility between the polymer support and the reaction medium.



90 Poly(DHQD acrylate)



91 Poly(DHQD 4-vinylbenzoate)

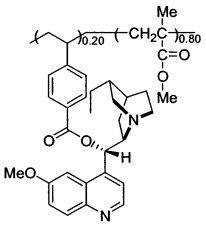


92 Poly(DHQN 4-vinylbenzoate)

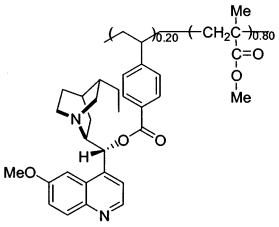
Comparing these two polymeric catalysts, the benzoate type catalysts (**91**, **92**) showed higher enantioselectivity than the arylate type catalyst and the catalytic reactivity and enantioselectivity of the poly(benzoate)−Os complex largely depended on the solvent system. For example, the asymmetric dihydroxylation of methyl cinnamate carried out in *t*-BuOH/H_2O using $K_3Fe(CN)_3$ as secondary oxidant could be completed after 18 h, giving the product in 91% ee, while the reaction carried out in acetone/H_2O using NMO as secondary oxidant proceeded very slowly, giving the product with much lower ee.

Song et al. pointed out that in acetone/H_2O (10:1 v/v) solvent system, the homopolymers (such as PolyDHQD or PolyDHQN) formed viscous lumps which might prevent the penetration of the substrate to the catalytic site. The substrate mostly stayed outside of the polymer and the concentration near the active site in the polymeric matrix was relatively low. In the *t*-BuOH/H_2O−$K_3Fe(CN)_3$ system, the polymeric catalysts swelled nicely, and this swelling might provide a chiral environment similar to that of the homogeneous system. The accessibility of the active site in polymer matrix depended mostly on the compatibility between the polymer support and the reaction medium, and the compatibility in a polar solvent would be improved by increasing the polarity of the polymer support.

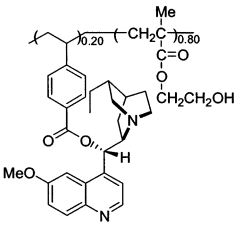
To evaluate the influence of the polarity of the polymer backbone on the compatibility with the reaction medium, several polymers with more polar backbone were prepared (**93**, **94**, **95**).



93 poly(DHQD 4-VB-*co*-MMA)



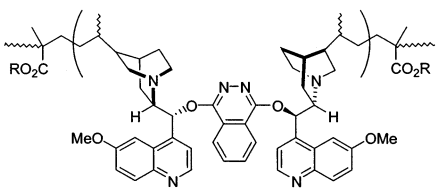
94 poly(DHQN 4-VB-*co*-MMA)



95 poly(DHQD 4-VB-*co*-HEMA)

With the polar polymer-supported alkaloids, the asymmetric dihydroxylation of the relatively less reactive substrate methyl *trans*-cinnamate proceeded smoothly, giving (2*S*,3*R*)-diol in up to 90% ee and over 80% yield. Recycling of the catalyst showed that the enantioselectivity of the polymer−OsO_4 complex was retained while the reactivity decreased, possibly due to the loss of OsO_4 during the workup.

$(DQH)_2$−PHAL has been extensively studied and has been found to be an excellent catalyst for asymmetric dihydroxylation reactions. Song et al. reported that via copolymerization with methyl methacrylate or 2-hydroxyethyl methacrylate, the alkaloid monomer was easily incorporated into the polar backbone, giving the corresponding polymer $(QN)_2$−PHAL-*co*-MMA (R = Me) **96** in nearly quantitative yield. The copolymerization of $(QN)_2$−PHAL with HWMA (R = CH_2CH_2OH) was not successful, and the polymer was obtained in only 7.1% yield.[161]

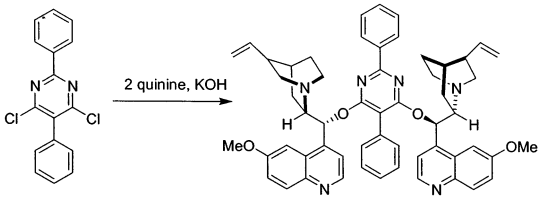


96 R = Me or CH_2CH_2OH

Substrates such as *trans*-stilbene and methyl *trans*-cinnamate were used to investigate the catalytic efficiency of these polymerized alkaloids. Using *t*-BuOH/H_2O (1:1) as the reaction medium and $K_3Fe(CN)_3$−K_2CO_3 as the secondary oxidant, the asymmetric dihydroxylation proceeded very fast at 10 °C, leading to the chiral diols with over 99% ee. The disadvantage of poly-hydroxyl catalyst $(QN)_2$−PHAL-*co*-HWMA might be the over-swelling, which led to difficulties in filtration.

Nandanan et al. also reported the preparation of some copolymers suitable for asymmetric dihydroxylation.[162] The condensation of 2,5-diphenyl-4,6-dichloropyrimidine with quinine gave monomer **97** in 78% yield (Scheme 34):

Scheme 34



97

The copolymerization of **97** with ethylene glycol dimethacrylate (EGDMA) or methyl methacrylate (MMA) in the presence of radical initiator such as AIBN gave the quinine incorporated copolymer, which was used as dihydroxylation catalyst. In the presence of the ethylene glycol dimethacrylate copolymer, the asymmetric dihydroxylation of olefins (e.g., *E*-ethylcinnamate) gave products with up to 84% ee.

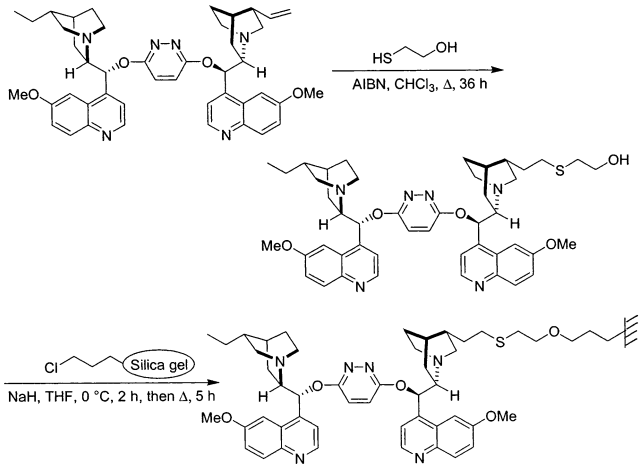
Canali et al. argued that the catalysts prepared by Song et al. or Nandanan et al. were not really the polymer-supported alkaloids, but possibly the physically trapped unreacted monomer precursor or physically adsorbed species.[163] They argued that significant polymerization occurred only with a highly electron deficient monomer such as acrylonitrile. They found that Song's polymer showed no nitrogen content after a prolonged Soxhlet extraction with ethanol, and concluded that direct free radical copolymerization of allyl groups containing alkaloids and other allyl substituted optically active ligands was not a general and simple option for the production of polymer-supported asymmetric catalysts.

5.2. Inorganic Material Supported Catalysts for Asymmetric Dihydroxylation

Due to the superior mechanical and thermal properties compared to organic polymer support, inorganic supports such as clay, zeolite, or silica gel are ideal candidates for catalyst for several reasons: (1) ready recoverability; (2) potential applications in flow processes; and (3) no need of extra solvent for catalyst precipitation. Insoluble organic polymers can be effective supports for catalyst immobilization, but the polymer has to be carefully designed and care has to be taken to ensure that the catalyst is chemically bound to and not occluded in the polymer support.

Lohray et al. immobilized 3,6-bis(9-*O*-dihydroquinyl)pyridazine and 3,6-bis(9-*O*-dihydroquinidyl)-pyridazine on silica gel (**98**).[164] In the presence of radical initiator azabisisobutyronitrile (AIBN), thioethanol was allowed to react with 6-(9-*O*-dihydroquinyl)-3-(9-*O*-quinyl)pyridazine, yielding a functionalized bisdihydroquinyl pyridazine derivative in 79% yield. This intermediate can be attached to silica gel through routine chemistry (Scheme 35):

Scheme 35

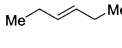
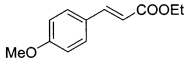


98

The advantage of using a silica gel supported catalyst over the organic polymer-supported analogue may be the better availability of the active sites. The binding of chiral ligand on the silica gel occurs on the surface and therefore makes it easier for the reactants to interact with the chiral ligands, while the chiral ligand may be well encapsulated in the polymer matrix in the case of an organic polymer-supported catalyst.

The asymmetric dihydroxylation of a variety of olefins in *t*-BuOH/H_2O (1:1) using **98** as chiral ligand and $K_3Fe(CN)_6/K_2CO_3$ as co-oxidant proceeded readily at 20 °C, leading to the corresponding optically active diols in reasonable yields and ee's (Table 25).

Table 25. Asymmetric Dihydroxylation Using 98 as Chiral Ligand

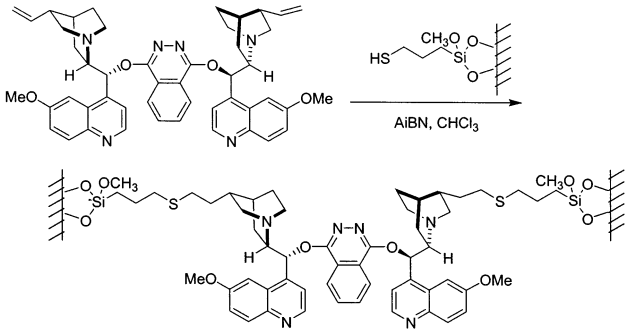
Entry	Alkene	Reaction time (h)	Yield (%)	ee (%)
1		24	96	80
2		15	92	56
3		15	86	64
4		15	90	52
5		15	83	22
6		15	83	22
7		36	69	97

According to the authors, the lower ee's might be due to the relatively small amount of the chiral ligand

comparing to the insoluble support and hence the ineffective binding of the substrate to the reaction pocket.

Following the disputed report of copolymer (copolymerization of $(QN)_2$−PHAL with methyl methacrylate or 2-hydroxyethyl methacrylate) supported catalyst for asymmetric dihydroxylation, Song et al. successfully attached their monomer $(QN)_2$−PHAL on silica gel (amorphous) to give catalyst **99** (Scheme 36):[165]

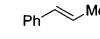
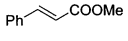
Scheme 36



99

Under standard conditions, the asymmetric dihydroxylation proceeded readily, giving chiral diol compounds in excellent yields and ee's. The results compared favorably to those obtained in homogeneous manner (Table 26).

Table 26. Asymmetric Dihydroxylation Using 99 as Chiral Ligand

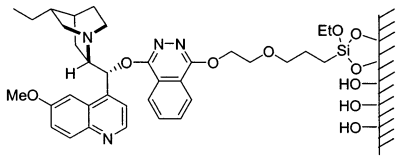
Entry	Olefin	Reaction time (h)	Yield (%)	ee (%)	Configuration
1		25	88	>99	*S,S*
2		15	92	96.5	*S,S*
3		20	93	95.2	2*R*,3*S*
4		15	96	96.2	*S,S*
5	 *	21	92	92.1	*S,S*

*: reaction carried out with reused silica gel supported catalyst without further addition of osmium tetroxide.

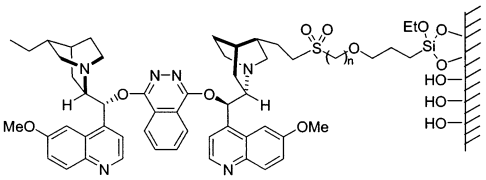
The authors suggested that the alkaloid moieties on silica gel remained highly exposed to the reactants and the catalytic sites were freely accessible, making the supported catalyst as powerful as the homogeneous analogues. The binding of OsO_4 to the supported alkaloid was stronger than to the corresponding homogeneous species, making it possible to recycle the costly alkaloid and the toxic osmium.

Lee et al. reported the preparation and application of alkaloid ligands immobilized on mesoporous silica.[166] Mesoporous silica has the advantage over organic supports with very high surface area and large pore size (> 2 nm), allowing for favorable reaction kinetics. The authors chose a mesoporous silica (with a uniform pore size of 7 nm) under the commercial name of SBA-15 as a catalyst support. The well-known dimeric ligand system, the cinchona-phthalazine system, was chosen as it was proved to be the most efficient species for asymmetric dihydroxylation.

Three different supported catalysts, namely, the mono-alkaloid **100**, and two dimers with different spacer lengths (**101**), were prepared and evaluated for their efficiency in catalyzing asymmetric dihydroxylation reaction.



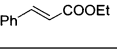
100



101a: n = 2, **101b**: n = 6

The transmission electron micrographs (TEM) and X-ray diffraction patterns showed that the regular arrangement of the uniform 7 nm pore size was preserved after the immobilization process. Using a standard protocol with 0.5 mol % of OsO_4, 1.0 mol % of the ligand and 300 mol % of $K_3Fe(CN)_6/K_2CO_3$ in *t*-BuOH/H_2O (1:1), a variety of substrates were dihydroxylated. The results showed that the supported monomer catalyst gave lower ee's compared to the dimeric homogeneous catalyst. Supported dimeric catalysts (**101a** and **101b**) induced much higher ee's in comparison to the supported monomeric species (**100**). A comparison of the two supported dimeric catalysts with different spacer lengths showed that the species with longer spacer (**100b**) gave higher ee, due possibly to the larger degree of freedom of the methoxyquinoline moiety provided by the longer spacer (Table 27).

Table 27. Asymmetric Dihydroxylation of Unfunctionalized Olefins

Entry	olefin	**100**	**101a**	**101b**	DHQ_2PHAL	DHQD-PCL
1		97	99	>99.5	>99.5	99
2		90	95	98	97	-
3		72	87	96	97	74
4		57	82	94	97	91
5		57	75	90	93	62
6		-	75	87	93	-
7		-	98	98	95	-

The recycle of the supported catalyst was achieved by filtration and washing (by water followed by ethyl acetate), and the mass change was negligible. Reuse of the recycled catalysts showed similar enantioselectivity but a decrease in reaction rate, indicating

the possible loss of osmium tetroxide during washing. Adding more OsO_4 before restarting the reaction gave a reasonable rate enhancement. In their recycling experiments, the authors reused the catalysts 5 times, and the reused species showed a small decrease in stereoselectivity (Table 28).

Table 28. Reuse of Catalysts 101a and 101b in the Asymmetric Dihydroxylation of *trans*-Stilbene

run	ee (%) for **101a**	ee (%) for **101b**
1	99	>99.5
2	96	94
3	96	96
4	85	94
5	93	92
6	88	92

Catalysts on amorphous inorganic supports, such as silica gel, are generally less effective, and significant tuning of both the support and the ligand is necessary to get satisfactory results.[167] In many cases, a longer spacer is required between the chiral ligand and the amorphous support to minimize the adverse influence of the solid support on the activity of the catalyst.

On the other hand, mesoporous solid support such as molecular sieves may offer a better catalytic environment. Such solid supports have well-defined nanometer-sized pores with a very narrow pore size distribution and may put the catalyst in an ordered microenvironment.

To evaluate the influence of ordered structures on the reactivity and stereoselectivity, Motorina et al.[167] grafted the dihydroxylation catalyst on both amorphous silica gel and mesoporous silica gel (SBA). The main differences between these two supports were that the pore size or shape of the former support was not uniform, and the surface area of the amorphous silica gel was only half of that of the mesoporous species.

A comparison of the catalytic activity and enantioselectivity of the three different kinds of catalysts, i.e., free catalyst, catalyst on amorphous silica, and catalyst on mesoporous silica, revealed that the catalyst on normal amorphous silica gel showed similar catalytic activity to the homogeneous species, while the catalyst on mesoporous silica gel showed somewhat higher activity (Scheme 37, Table 29).

Scheme 37

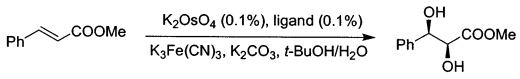
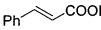
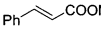
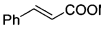


Table 29. Comparison of Catalytic Activity of Heterogeneous and Homogeneous Ligands

entry	ligand	loading (mmol/g)	conversion (%)
1	free catalyst	0.1%	44%
2	catalyst on mesoporous silica (SBA)	0.1%	54%
3	catalyst on normal amorphous silica	0.1%	46%

Further detailed studies on the influence of the solid supports on the enantioselectivity also showed that the ordered mesoporous silica was the better choice for catalyst immobilization. The cinchona alkaloid supported on ordered mesoporous silica (SBA) showed similar enantioselectivity to the homogeneous analogue, while the catalyst supported on amorphous silica gel gave lower enantioselectivity for all the substrates studied (Table 30).

Table 30. Asymmetric Catalytic Dihydroxylation of Unfunctionalized Olefins

Entry	Substrate	Ligand	Isolated yield (%)	ee (%)
1		$DHQD_2PHAL$	99	>99
2		Mesoporous support	97	>99
3		$DHQD_2PHAL$	-	97
4		Mesoporous support	67	98
5		Amorphous support	72	94
6		PEG-OMe	83	99
7		Mesoporous support	98	98
8		Amorphous support	85	96
9		$DHQD_2PHAL$	95	96
10		Mesoporous support	73	92
11		Amorphous support	85	87

Recycling of the catalyst was successful, although the osmium was not retained on the surface of the support and must be replenished prior to the reuse of the ligand. In the reuse of the catalyst, the enantioselectivity remained within 3% of the initial run, and the isolated yields were also similar (within a range of ± 5%).

5.3. Heterogenized Osmium Tetroxide for Asymmetric Dihydroxylation

The drawback of ligands supported on either organic polymers or inorganic materials in the asymmetric dihydroxylation of olefins is the leaching of osmium tetroxide, which has to be added prior to the reuse of the catalyst.

Kobayashi et al. used a different method to carry out the reaction.[168] While other chemists were trying to immobilize the chiral ligands on supports, Kobayashi et al. tried to trap the osmium tetroxide in a polymer capsule.

The preparation was quite straightforward. To a solution of polystyrene in cyclohexane was added 20% (w/w) of osmium tetroxide as a core (osmium tetroxide was dissolved). The mixture was slowly cooled to 0 °C after being stirred for 1 h at 40 °C. Coacervates (phase separation) were found to envelop the core dispersed in the medium. Methanol was used to harden the capsule walls. The unencapsulated OsO_4 was washed off with methanol at room temperature.

To examine the efficiency of this encapsulated OsO_4, the dihydroxylation of cyclohexene was carried out on a 10 mmol scale. Low yield was obtained when the reaction was carried out in H_2O/acetone or H_2O-*t*-BuOH, but the yield was enhanced by adding acetonitrile to the reaction mixture. The reaction

gave a lower yield using hydrogen peroxide or potassium ferricyanide as secondary oxidant. The encapsulated OsO_4 was also recycled several times with quantitative recovery yield.[169]

The investigators found poly(acrylonitrile-butadiene-styrene) (ABS) to be superior to the polystyrene polymer in the preparation of catalysts with higher activity, selectivity, and recoverability. Osmium tetroxide was encapsulated in the same way to give the so-called ABS-microencapsulated OsO_4 (ABS-MC-OsO_4).[170]

In the presence of ABS-MC-OsO_4, styrene was dihydroxylated in 93% isolated yield, and the ABS-MC-OsO_4 was quantitatively recovered by simple filtration. The recovered catalyst was used for several times without loss of activity. In such a manner, various olefins including cyclic and acyclic, terminal, mono-, di,- tri-, and tetra-substituted olefins were dihydroxylated, giving the corresponding diols in high yields. The authors also used 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine ((DHQD)$_2$PHAL) as chiral ligand to carry out the asymmetric dihydroxylation. *Trans*-methylstyrene was dihydroxylated in 84% ee at 88% isolated yield, and the osmium was quantitatively recovered by filtration. The chiral ligand (DHQD)$_2$PHAL was also recovered in over 95% recovery through acid/base extraction. The recovered catalyst and chiral ligand were reused without loss of activity and enantioselectivity (Scheme 38, Table 31).

Scheme 38

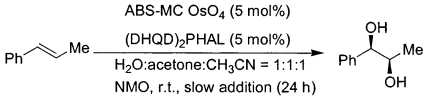


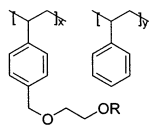
Table 31. Reuse of ABS-MC−OsO_4

run	yield (%)	ee (%)	recovery (of Os)
1	88	84	quantitative
2	75	95	quantitative
3	97	94	quantitative
4	81	96	quantitative
5	88	95	quantitative

The dihydroxylation of *trans*-methylstyrene on a 100 mmol scale was also carried out. In the presence of 1.0 mol % of ASB-MC-OsO_4, 2.0 mol % of (DHQD)$_2$-PHAL and 130 mmol of NMO, 100 mmol of *trans*-methylstyrene was dihydroxylated, giving the diol compound in 89% ee at 91% isolated yield.

Proton NMR study of the ABS−MC−OsO_4 using the swollen resin showed that the olefin moiety in the ABS polymer reacted with the microencapsulated osmium tetroxide, yielding some diol moieties which might be responsible for the effective two-phase dihydroxylation by rendering the support more hydrophilic.

Substituted ethoxymethyl-polystyrene (PEM-PS, **102a**: R = Ph, **102b**: R = Me) copolymers were also prepared for the encapsulation of osmium tetroxide.



102 (x = 0.05, y = 0.95)

The asymmetric dihydroxylation of styrene was studied to evaluate the recoverability of the polymer encapsulated osmium tetroxide. While polymer **102a** encapsulated osmium tetroxide showed good recoverability, **102b** was not effective. It appeared that the phenyl ether moiety in **102a** was required to get a good recovery of the encapsulated osmium tetroxide.

Other olefins were then subjected to the same reaction using (DHQD)$_2$PHAL as chiral ligand and $K_3Fe(CN)_6/K_2CO_3$ as secondary oxidant. Best results were obtained for the asymmetric dihydroxylation of *trans*-stilbene and ethyl *trans*-cinnamate, and ee's over 99% were observed.

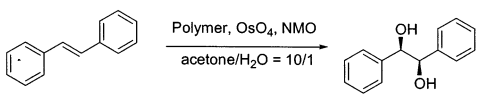
Choudary et al. used an ion-exchange method to immobilize osmium for asymmetric dihydroxylation.[171] Layered double hydroxides (LDH) consisting of alternating cationic $M(II)_{1-x}M(III)_x(OH)_2^{x+}$ (x = 0−1) and anionic $A^{n-}\cdot zH_2O$ were chosen as ion exchanger. The asymmetric dihydroxylation of olefins using ion exchanged osmate OsO_4^{2-} as oxidant was carried out using (QHQD)$_2$PHAL as chiral ligand and NMO as secondary oxidant. Best results were achieved in the asymmetric dihydroxylation of *trans*-stilbene, methyl *trans*-cinnamate, and ethyl *trans*-(4′-methoxy)cinnamate, and products with 99% ee and over 93% yield were obtained. The LDH−OsO_4 was quantitatively recovered by simple filtration, and iodometry tests showed no osmium in the filtrate. Consistent activity of the ion-exchanged osmate was still observed after the fifth recycle.

The high binding ability of the heterogeneous osmium catalyst enables the use of an equimolar ratio of ligand to osmium to give excellent enantioselectivity in asymmetric dihydroxylation reactions in contrast to the homogeneous system in which excess molar quantities of the chiral ligand are used.[172]

5.4. Soluble Macromolecules for Asymmetric Dihydroxylation

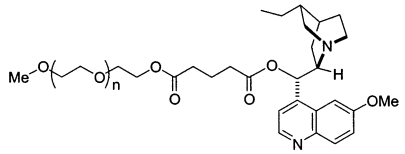
In heterogeneous catalyst systems for asymmetric dihydroxylation, the ligand resided in the insoluble phase while OsO_4 and the olefin are in solution. This feature of a heterogeneous catalyst resulted in a decrease in the reaction rate and caused diffusion problems. The conditions are thus less favorable than in homogeneous phase. An alternative method to the insoluble ligands is the soluble polymer-bound ligands and catalysts. Han et al. reported the soluble polymer-supported cinchona alkaloid ligand **103** for the ligand-accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reaction.[10] Dihydroquinidine was attached onto the end of MeO−PEG with glutarate linker. Polymeric ligand **103** was used in the osmium-catalyzed asymmetric dihydroxylation of different substrates in acetone/water solvent. Up to 88% ee was obtained in the dihydroxylation of *trans*-stilbene (Scheme 39). This result was similar to that from

Scheme 39



89% conv. 88% ee

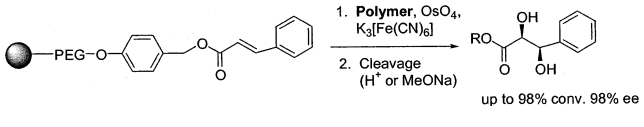
using the monomeric counterpart. A comparison between the soluble polymer **103** and an insoluble poly(acrylonitrile)-supported ligand[150] showed a slight increase in enantioselectivity but a big jump in catalytic activity for the former (5 h versus 48 h for the same conversion). After the reaction, the polymeric catalysts were recovered in up to 98% by precipitation with diethyl ether, and the recovered catalysts showed similar catalytic activity in at least five cycles.

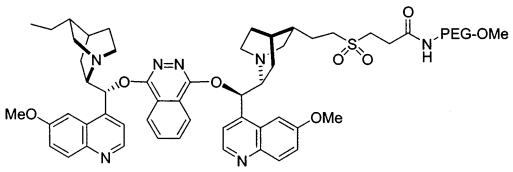


103

Han and Janda further prepared polymer **104** by attaching a better ligand, 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine ((DHQD)$_2$PHAL), to MeO-PEG-NH$_2$.[173] This soluble polymeric ligand gave high ee's (up to 99% ee) and comparable activities to those of the parent ligand, demonstrating that ligand-accelerated asymmetric catalysis could be fully maintained by attaching the ligand to a soluble polymer support. As an extension of this study, polymeric ligand **103** was also used in the asymmetric dihydroxylation involving both polymer-supported substrate and supported ligand. In this study, the substrate was supported on resins of various hydrophilicities and was tested with polymeric or free ligands.[174] With the free ligand, a soluble resin-supported substrate provided the best overall results (0.5 h, 10% OsO_4, 100% conversion and 99% ee), while an insoluble resin-supported substrate gave better results in the soluble polymer-bound catalyst system (Scheme 40).

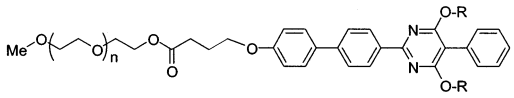
Scheme 40





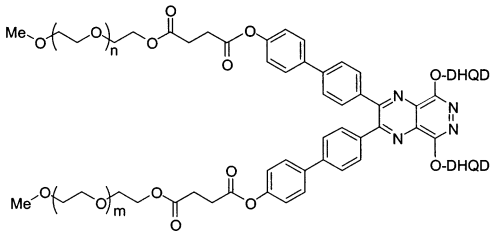
104

Bolm and Gerlach also developed the soluble PEG-bound cinchona alkaloid-type ligands (**105**, **106**) for asymmetric dihydroxylation.[175] The DHQ and DHQD ligands were attached to MeO−PEG via an aryl spacer such that the symmetries of the monomers were retained. These polymers remained soluble in the reaction mixture and consequently exhibited exceedingly high asymmetric induction in the asymmetric dihydroxylation of *trans*-stilbene (99% ee), styrene (98% ee), and 2-methylstyrene (95% ee), and fast reaction rate (for stilbene, 91% yield in less than 5 h). The asymmetric dihydroxylation of 1-decene and 3,3-dimethyl-1-butene using polymer **105a** provided the corresponding diols with 87% ee and 90% ee, respectively. These were likely the highest ee's in the dihydroxylation of aliphatic terminal monosubstituted olefins using polymer-supported alkaloid ligands. After the reaction, the polymer catalysts could be recovered in up to 98% yield by precipitation with *tert*-butyl methyl ether. In the repeated experiments, after constant ee's in the first four runs, a slight decrease of enantioselectivity was observed (run 1−4: 98% ee; run 5: 97% ee; run 6: 96% ee), which was due to a minor ester hydrolysis under the basic reaction conditions.



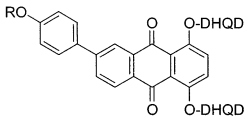
105a: R = DHQD

105b: R = DHQ

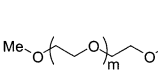


106

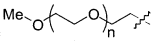
Bolm et al. further reported the immobilization of alkaloid-type ligands with an anthraquinone core by using soluble polymer or silica supports.[176] The anthraquinone ligands were attached to the supports using a remote position of the anthraquinone core (**107**) or using the double bonds of the naturally occurring alkaloid quinidine (**108**). The immobilized ligands were studied in the asymmetric dihydroxylation of two "difficult" substrates, allyl iodide and indene. Moderate to high enantioselectivities were observed (73−84% ee for allyl iodide and 47−57% ee for indene). No significant influence of the binding site or attachment type on the enantioselectivity of the asymmetric dihydroxylation was observed. After the reaction, the catalyst was recovered by precipitation with methyl *tert*-butyl ether and was reused in subsequent reactions (with the addition of 0.4 mol % osmium) without loss of catalytic efficiency. With the silica-supported ligands **107c**, the asymmetric dihydroxylation of allyl iodide gave almost identical results as those obtained under homogeneous conditions. Indene gave slightly lower enantioselectivity.



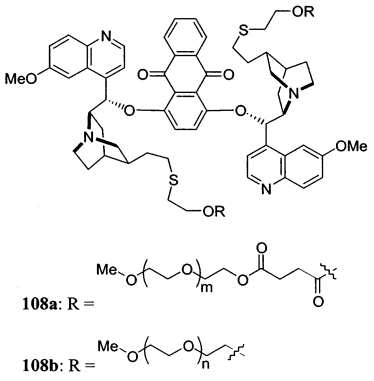
107a: R =



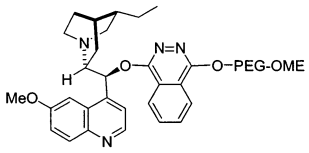
107b: R =



107c: R =



Kuang et al. recently reported a simple soluble polymer-supported alkaloid ligand.[177] 1,4-Dichlorophthalazine was used as the coupling reagent to connect dihydroquinidine and MeO−PEG, providing an aromatic group at the 9-O-position of dihydroquinidine. Ligand **109** was applied in the osmium-catalyzed asymmetric dihydroxylation of several *trans*-disubstituted olefins, giving products with high enantioselectivity (up to 98% ee). The repeated use of the polymer ligand showed essentially no change in ee values and yields in five runs.



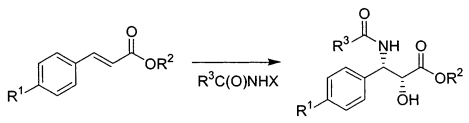
109

5.5. Asymmetric Aminohydroxylation

Following the study of asymmetric dihydroxylation, Song et al. reported the asymmetric aminohydroxylation of alkenes using silica gel supported bis-cinchona alkaloid (SGS−$(QN)_2$PHAL) as chiral ligand.[178]

A variety of cinnamates were subjected to the asymmetric aminohydroxylation reaction (Scheme 41). While the isolated yields varied from reaction to

Scheme 41



R^1 = H, R^2 = Me, R^3 = OEt

R^1 = OMe, R^2 = Me, R^3 = OEt

R^1 = NO_2, R^2 = Me, R^3 = OEt

R^1 = H, R^2 = *i*-Pr, R^3 = Me

R^1 = OMe, R^2 = *i*-Pr, R^3 = Me

30-80% yield, >99% ee for most reactions

reaction, high enantioselectivities were observed in most cases. The catalyst could be separated by simple filtration from the reaction mixture, and could be reused several times. Due to the possible leaching of osmium, the recovered catalyst showed a decrease in reactivity, but the enantioselectivity was preserved in all the studied cases. Adding a small amount of osmium tetroxide to the recovered catalyst regenerated the catalytic activity of the supported catalyst.

Table 32 summarizes the asymmetric dihydroxylation results catalyzed by both free catalysts and immobilized catalysts. The proper combinations of supports, linkers and catalyst structures would offer a favorable microenvironment to the chiral catalytic sites which again would result in high activity and enantioselectivity. Nevertheless, there is still no effective method to recycle both the chiral ligand and the osmium tetroxide so far.

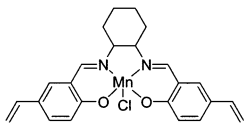
6. Asymmetric Epoxidation

Epoxides are versatile synthetic intermediates that can be readily converted into a large variety of useful compounds by means of regioselective ring opening. Hence, the asymmetric olefin epoxidation constitutes one of the most powerful methods in the synthesis of enantiomerically pure compounds.

The asymmetric epoxidation of unfunctionalized olefins catalyzed by chiral Mn−salen complexes was first reported more than 10 years ago, and excellent results have been achieved ever since. The commonly used oxidants in previous studies in asymmetric epoxidation are iodosylbenzene in organic solvents, or sodium hypochlorite in aqueous media. Excess of hydrogen peroxide was also used as an oxidant in aqueous media, but the presence of additional ligand is essential for an effective reaction. Molecular oxygen is the most economical and environmentally friendly oxidant and the studies of its application in epoxidation always attract interest.

6.1. Insoluble Polymer-Supported Catalysts for Asymmetric Epoxidation

De et al. reported the polymer-supported Mn−salen complex for the asymmetric epoxidation of unfunctionalized olefins.[180] The work started from the synthesis of appropriate vinyl monomer of salen via the reaction of 5-vinyl salicylaldehyde with 1,2-diaminocyclohexane. Reacting this salen monomer with $Mn(OAc)_2 \cdot H_2O$ in the presence of an excess amount of LiCl gave the corresponding complex **110** in good yield. Subsequent free radical polymerization with ethylene glycol dimethacrylate in toluene gave the desired macroporous polymer which was ground and thoroughly washed with ethanol to give the contaminant-free catalyst.



110

In the presence of this polymeric Mn−salen complex, the asymmetric epoxidation of prochiral olefin was carried out using iodosylbenzene as the oxidant. Compared to the homogeneous Mn−salen catalyzed reactions which can normally be completed in 1 h, the rate of the reactions catalyzed by the polymer-supported catalyst was much slower: 32 h were needed for the reactions to reach completion. The

Table 32. Comparison of Various Immobilized Ligands or Catalysts in the Asymmetric Dihydroxylation Reactions

		ee (%)			
catalysts	ligand	*trans*-stilbene	styrene	1-decene	ref
homogeneous catalyst		99	99	89	179
copolymer-supported catalyst	**88**	96 (87)[a]	95 (90)	24 (82)	159
copolymer with spacer supported catalyst		99 (90)	91 (86)		157
silica supported catalysts		99 (77)	98 (93)	84 (51)	176b
	98	99 (88)			165
	100b	>99.5 (quant.)	96 (quant.)	87 (quant.)[b]	166
		99 (97)	92 (73)		167
microencapsulated OsO_4^-		>99 (66)	78 (85)		170
heterogenization of OsO_4^- by ion-exchange		>99 (96)	95 (94)		171
soluble polymer-supported catalysts	**103**	99 (95)	98 (88)	97 (80)[b]	173
	104a	99 (91)	98 (92)	87 (86)	175

[a] Yields were given in parentheses. [b] 4-Decene was used.

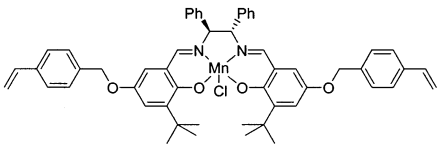
poor solubility of iodosylbenzene and the insolubility of the polymer-supported catalyst were likely the main reasons for the slow rate of reaction. The slow diffusion of substrates and reagents from the solution phase to the metal centers in the polymer matrix caused the drop of reaction rate. Compared to the soluble Mn−salen catalyzed epoxidation reaction, the reaction catalyzed by polymer-supported Mn−salen gave better chemoselectivity: the formation of byproduct decreased significantly, and epoxides were obtained as the only product for certain substrates (up to 90% yield).

The polymer-supported salen complex was recycled and reused at least 5 times without significant loss of catalytic efficiency.

Alternatively, the polymer-supported Mn−salen complex could also be prepared via the reaction of manganese acetate hydrate with the corresponding salen bearing functional polymer. The polymer-supported Mn−salen complex thus obtained was also used in the epoxidation of unfunctionalized olefins.[181]

A major limitation of low molecular weight metal−salen complexes as homogeneous catalysts is their tendency to degradation by oxidation and dimerization to μ-oxo-manganese (IV). Anchoring the small molecule Mn−salen complex to a solid support may result in the site isolation and thus may minimize the deactivating side reactions.[182]

De et al. also prepared the vinyl monomer **111** bearing an optically active Mn−salen moiety.



111

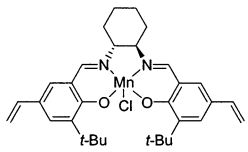
The polymer containing this chiral metal complex was obtained via the copolymerization of the monomer with ethylene glycol dimethacrylate. Thus, in the presence of free radical initiator AIBN, 10 mol % of Mn−salen monomer and 90 mol % of ethylene glycol dimethacrylate was copolymerized in toluene, which acted as both solvent and porogenic agent, giving the macroporous functional copolymer which was used for asymmetric epoxidation of olefins. Mercury porosimetry and scanning electron microscopy of this nonswellable, insoluble polymer revealed the macroporous amorphous property of this polymer. The polymer bore high surface area which allowed the easy access of the substrate to the catalytic sites during the reaction.

A series of olefins were subjected to epoxidation using this polymeric catalyst.[183] The conversions were normally satisfactory while the ee's of the products were lower than those from the corresponding homogeneous reactions. This was thought to be due to the steric reasons and/or certain microenvironmental effects associated with the macromolecular systems.

High cross-linking density of the polymer matrixes may bring about nonspecific catalytic sites. The bifunctional nature of the metal complexing monomer results in total cross-linking of the polymer, and this has been presumed by the authors as the reason for poor enantioselectivity.

Iodosylbenzene is a poor oxidant for the polymer-supported Mn−salen catalyzed epoxidation of olefins. Besides the poor solubility of this terminal oxidant, iodosylbenzene also undergoes a disproportionation reaction, giving a product $PhIO_2$, which is not soluble in all the tested solvent systems. It is very difficult to completely remove this insoluble material from the polymer, rendering the recycling of the supported catalyst very difficult.

Minutolo et al. reported another reaction using *m*-chloroperbenzoic acid (*m*-CPBA)/NMO as oxidants.[184] The supported catalyst was prepared via free radical initiated copolymerization of a monomer **112** with styrene and 1,4-divinylbenzene.



112

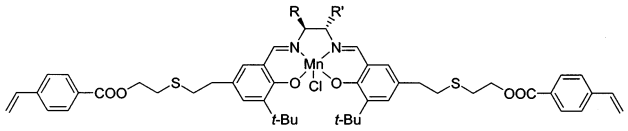
The epoxidation using *m*-CPBA/NMO as an oxidant proceeded very fast even at very low temperature with good chemoselectivity. No detectable amount of byproducts was present in the reaction mixture. In contrast to the homogeneous catalysis, noticeable degrees of cis-trans isomerization occurred during the epoxidation of cis-β-methylstyrene. Using magnesium monoperoxophthalate (MMPP) as an oxidant gave low ee (Table 33).

Table 33. Asymmetric Epoxidation of Styrene Compounds

substrate	oxidant	temp (°c)	time	conv. (%)	ee (%)
styrene	*m*-CPBA/NMO	0	30 min	96	14
styrene	*m*-CPBA/NMO	−30	1 h	84	15
styrene	MMPP(H_2O)	0	4 h	76	6
styrene	MMPP/NMO	0	22 h	74	8
(*Z*)-methyl styrene	*m*-CPBA/NMO	0	1 h	78	41
(*Z*)-methyl styrene	*m*-CPBA/NMO	−30	2 h	73	41
(*Z*)-methyl styrene	MMPP(H_2O)	0	7 h	67	8
(*Z*)-methyl styrene	MMPP/NMO	0	22 h	69	4

The reaction in dichloromethane was unsuccessful. At the end of the reaction, colloidal mixtures were formed and it was very difficult to recover the catalyst. The polymeric catalyst was insoluble in acetonitrile, and the recovery of the catalyst was easy and efficient. The recovered catalyst preserved the efficiency after five recycles.

These investigators further reported the supported catalyst containing a spacing group between the polymeric chain and the active metal site (**113**):[185]



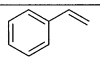
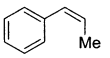
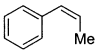
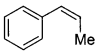
113a: R = R' = -$(CH_2)_4$-, **113b:** R = R' = Ph

Free radical induced copolymerization of these monomers with styrene and divinylbenzene gave the corresponding supported spaced catalyst. The catalytic epoxidation was carried out in acetonitrile at 0 °C using a combination of *m*-chloroperbenzoic acid and NMO as oxidant. Longer reaction time was required using iodosylbenzene as oxidant, and the formation of disproportionation product PIO_2 made the recovery of the catalyst rather difficult. When the oxidant system *m*-CPBA/NMO was used, the epoxidation was very rapid and the recovery of the catalyst was easy. The recovered catalyst could be used at least 5 times without loss of reactivity and stereoselectivity. IR analysis showed that the sulfur atom in the spacer group was not oxidized under the reaction conditions.

The catalysts with spacer groups gave higher ee's than those without spacer groups for all the substrates tested, indicating that when the catalytically active metal center was farther from the polymeric chain, the influence of the surrounding polymeric chain was reduced, making the microenvironment around the chiral complex more similar to the homogeneous systems (Table 34).

Having recognized the disadvantage of divinylbenzene-type copolymer-supported Mn−salen complex which led to low activity and stereoselectivity, Canali et al. concluded that some criteria had to be met in order for the immobilized catalyst to get satisfactory results:[186] (1) the local molecular structure of the Mn complex should mimic precisely the optimum structure of the Jacobsen catalyst; (2) the complex should be attached by a single flexible linkage to the polymer support to minimize the local steric restriction; (3) the complex should be attached to the polymer with sufficiently low loading to maximize site isolation of catalytic centers so that the formation of the inactive *oxo*-bridged dimer could be minimized; and (4) the morphology of the support should be made to allow all the active sites to be freely accessible.

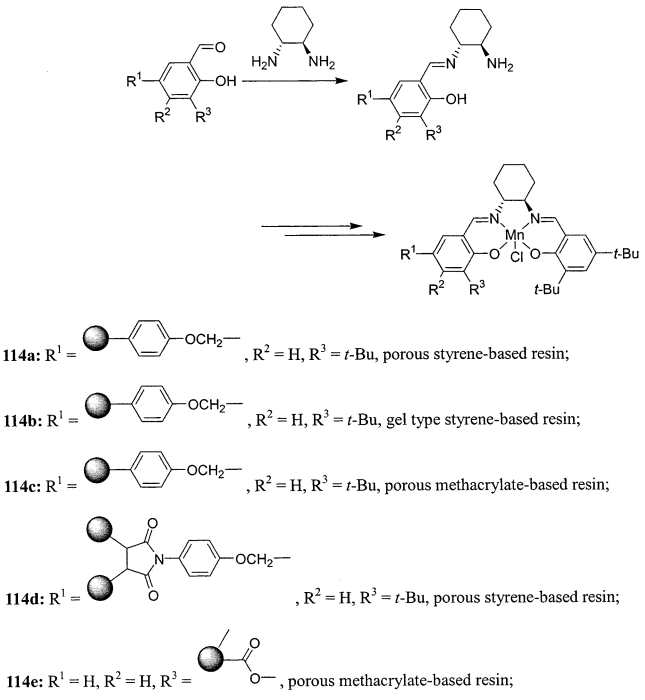
Table 34. A Comparison of the Asymmetric Epoxidation of Styrene Compounds with Different Catalysts

Entry	Substrate	Catalyst	Time (min)	Conv. (%)	ee (%)
1		p-**112**	30	96	14
2		p-**113a**	15	98	16
3		p-**113b**	15	99	26
4		p-**112**	60	78	41
5		p-**113a**	30	92	62
6		p-**113b**	30	99	56
7		p-**112**	30	95	10
8		p-**113a**	30	99	21
9		p-**113b**	30	98	37
10		p-**112**	30	91	27
11		p-**113a**	30	99	60
12		p-**113b**	30	99	46
13		p-**112**	30	67	21
14		p-**113a**	30	79	38
15		p-**113b**	30	99	42

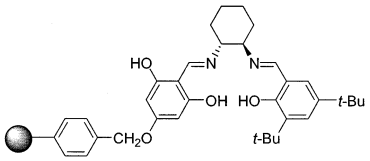
Following these criteria, a series of polymer-supported Mn−salen complexes **114a**−**114e** were prepared (Scheme 42).

The asymmetric epoxidation of 1-phenylcyclohex-1-ene was carried out in CH_2Cl_2 at 0 °C using *m*-CPBA/NMO oxidant system. The best result of 91% ee was obtained in the reaction catalyzed by Mn−salen attached to methacrylate-based resin (**114c**). The authors presumed that the methacrylate-based structure of **114c** bore a significantly higher polarity, and considerably improved the local mobility relative to a styrene-based analogue. Such factors combined with the rather low catalyst loading provided good reaction kinetics and stereoselectivity. The reaction catalyzed by **113e** gave poor yield and low ee, possibly due to the attachment of the catalyst to the polymer support at the position ortho- to the phenolic group, resulting in a highly congested structure which inhibited the approach of substrate to the Mn catalyst center.

Scheme 42



Angelino et al. also reported the Mn−salen catalyst immobilized on polystyrene (**115**) for the asymmetric epoxidation of unfunctionalized olefins.[187] The supported catalysts were prepared via the reaction of the corresponding substituted benzaldehyde with Merrifield peptide resin, followed by the reaction with a chiral diamine and another molecule of substituted benzaldehyde.



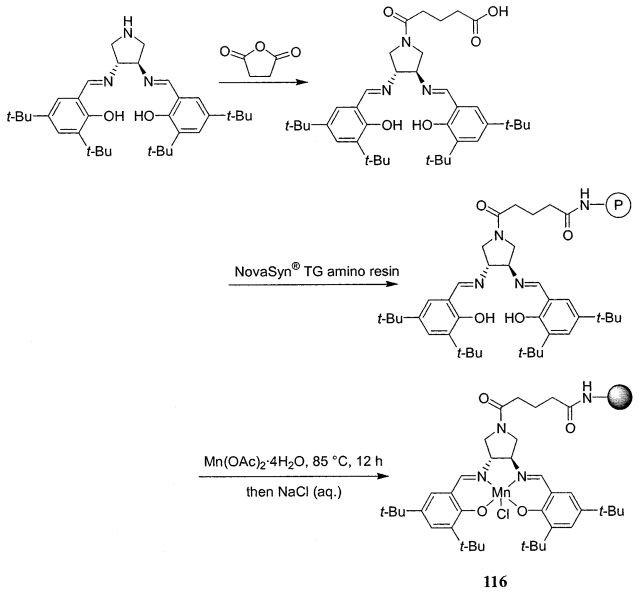
115

In the presence of this supported catalyst, the asymmetric epoxidation was carried out using NaOCl/PPNO as oxidant. The results were generally not as good as that catalyzed by the homogeneous Mn−salen complex. The catalyst was easily recovered and recycled. However, the performance of the recycled catalyst diminished after prolonged exposure to the oxidant.

Song et al. used the amido functionality to connect the catalyst to the polymer support.[188] In the presence of a spacer of proper length, this type of supported catalyst **116** is more similar to the homogeneous ligand (Scheme 43).

While the copolymers of styrene/bis-styrene showed steric restriction for complex formation and gave poor results for the asymmetric epoxidation of olefins, polymer-supported chiral Mn(III)(pyrrolidine salen) gave superior results. Attached to the polymer through single flexible linkage via the N-atom of the pyrrolidine moiety, this type of supported catalyst was easy to prepare and to handle.

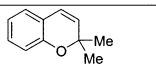
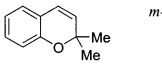
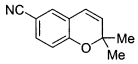
Scheme 43



116

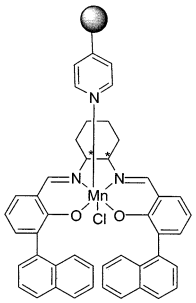
Using NaOCl/PPNO (4-phenylpyridine *N*-oxide) or *m*-CPBA-NMO as oxidant, the asymmetric epoxidation of olefins proceeded smoothly in the presence of 4 mol % of **116**, giving products with up to 92% ee (Table 35). In general, the reaction using *m*-CPBA as the oxidant proceeded faster than that using NaOCl as the oxidant. Although the recycling of the polymeric catalyst could be realized by simple filtration, partial decomposition under the epoxidation condition was observed for the supported Mn−salen complex. This tendency limited the successful recycling and reuse of the immobilized salen complexes.

Table 35. Asymmetric Epoxidation Using 116 as Chiral Ligand

Entry	Substrate	Oxidant system	Reaction time (h)	Yield (%)	ee (%)
1		NaOCl/PPNO	24	84	87
2		*m*-CPBA/NMO	1.5	85	92
3		NaOCl/PPNO	50	82	87
4		*m*-CPBA/NMO	1.5	72	86
5		NaOCl/PPNO	24	82	78
6		*m*-CPBA/NMO	2	76	68

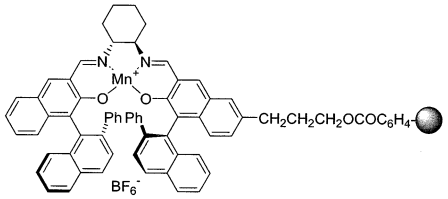
Kureshy et al. reported a polymer-based chiral Mn−salen complex via coordinative approach.[189] Copolymerization of styrene, divinylbenzene, and 4-vinylpyridine gave the highly cross-linked porous beads bearing pyridine as Mn−salen binding ligand. The supported catalyst was prepared by attaching the Mn−salen complex to the polymer beads in dichloromethane. The resulting catalyst (**117**) was employed in the epoxidation of styrene and 4-substituted styrene using iodosylbenzene as oxidant. The reaction carried out in dichloromethane at 4 °C gave the

product in 16−46% ee. The catalyst was recycled up to 10 times, indicating strong binding between manganese and pyridine in the polymer.



117

Smith et al. reported the preparation and application of Merrifield resin-supported Katsuki-type Mn(salen) complex **118** in the asymmetric epoxidation of olefins.[190] The catalytic activity and stereoselectivity of the immobilized catalyst were evaluated in the epoxidation of 1,2-dihydronaphthalene using NaOCl as oxidant and 4-PPNO as activator. The reaction gave 94% ee and 37% yield of the epoxide. Reuse of the catalyst showed no loss of enantioselectivity for the first three runs, while a little drop of enantioselectivity was observed from the fourth run and thereafter.



118

6.2. Inorganic Material Supported Catalysts for Asymmetric Epoxidation

To maintain the reactivity and stereoselectivity of the immobilized catalyst, it is essential that the immobilized catalyst preserves a similar microenvironment to that of the homogeneous species and allows for suitable site isolation and accessible catalytic sites.

The embedding of catalyst into the pore system of molecular sieves via host−guest interaction may well provide such a microenvironment, and the inclusion system is expected to result in easy recovery and/or continuous use of the catalyst.

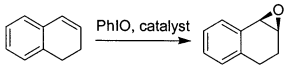
Frunza et al. reported a series of molecular sieves-included Mn(III) salen complexes, and their application in the asymmetric epoxidation of olefins.[191] Mesoporous Al-, Ga-, and Fe-substituted silicates related to MCM-41 were used as the host. A mixture of silica sol, water, cetyltrimethylammonium bromide, aluminum isopropoxide, sodium gallate, or iron sulfate in appropriate amounts was stirred to get a homogeneous solution. Hydrothermal treatment of this mixture at 150 °C for 3 days followed by calcination at 600 °C gave the mesoporous silicates ready for catalyst inclusion. A solution of 15 mg of Mn−salen in dichloromethane was added to 300 mg of molecular sieves, and the solvent was evaporated to give the molecular sieves-included Mn−salen. Thermoanalysis of the material showed that the complex was embedded into the mesopore rather than located outside, and the complex was not held by ionic interaction.

The epoxidation of 1,2-dihydronaphthalene was carried out to evaluate the catalytic properties of the immobilized Mn−salen complex. To avoid any free catalyst in the reaction system, the loaded samples were repeatedly washed with dichloromethane until the washing remained colorless. This step ensured that all the catalyst was located inside the zeolite and not on the external surface or in solution. Under identical conditions to the homogeneous asymmetric epoxidation system, similar catalytic activity and stereoselectivity were observed, indicating that the reactants had free access to the embedded salen complex. As suggested by the authors, the mechanism of the reaction with the embedded catalyst was the same as that with the free catalyst. Further, due to the strong guest/host interactions, the complex was stably bound and was hard to leach. This ensured the recycling and reuse of the embedded catalyst.

Piaggio et al. reported a different immobilization method.[192] They prepared the Mn exchanged molecular sieves Al-MCM-41, followed by refluxing the calcinated Mn−Al-MCM-41 with salen ligand (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene) to give the salen incorporated molecular sieves. The asymmetric epoxidation of (*Z*)-stilbene using this molecular-sieves supported catalyst in dichloromethane at 25 °C gave 70% ee. Leaching of metal was not observed and leaching of the ligand was thought to be the reason for the loss of activity of the reused catalyst.

Using ion exchange method, Fraile et al. successfully immobilized the Mn−salen complex on a series of supports, namely, the commercially available Laponite, Bentonite, and K 10-montmorillonite (K 10).[193] The immobilization was realized through two routes: (1) direct exchange of the Mn−salen complex, or (2) treating the Mn-exchanged clay with salen ligand. *N*,*N*′-Bis(salicylidene)ethylenediamine was chosen as the chiral ligand, and the asymmetric epoxidation of 1,2-dihydronaphthalene (Scheme 44)

Scheme 44



was chosen as the model reaction. Using iodosylbenzene as the oxidant, the turnover numbers obtained with the homogeneous and supported catalysts were essentially the same, while the enantioselectivity of the immobilized system was generally lower than the homogeneous counterpart (Table 36).

Using a "ship-in-bottle" method, Ogunwumi et al. reported an intrazeolite assembly of chiral Mn−salen complex in zeolite EMT for the asymmetric epoxidation of olefins.[194] Zeolite EMT has a hexagonal form faujasite structure. The hypercages of EMT are accessible through three 12-ring windows with a free dimension of 0.69 × 0.74 nm and two 0.74 nm circular apertures. This structural feature makes it

Table 36. Enantioselective Epoxidatyion of 1,2-Dihydronaphthalene Catalyzed by Clay-Supported Mn−Salen

entry	clay	axial ligand	runs	conv. (%)	yield (%)	TON	ee (%)
1				100	70	38.5	46
2	laponite		1	66	45	39.3	32
3	laponite		2	20	14	14.5	28
4		pyridine		100	74	40.7	36
5	laponite	pyridine	1	77	56	48.9	34
6	laponite	pyridine	2	31	18	18.1	1

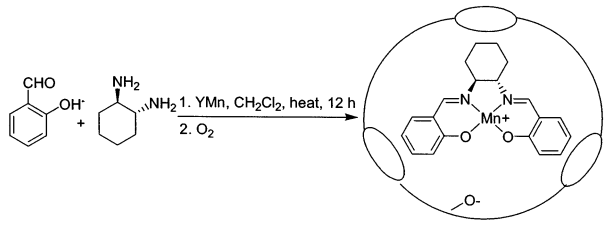
a good host for catalyst embedding. According to the authors, the micropore volume of degassed EMT is 0.325 mL/g before intrazeolite guest assembly. The chiral manganese complex has a dimension of ca. 1.5 nm. The escape of the assembled complex from the zeolite can thus be avoided.

The best ee of 88% was observed in the epoxidation of (*Z*)-PhCH=CHMe. Studies showed that smaller alkenes gave higher conversion, as bulky molecules such as cholesterol could not be epoxidized, indicating the encapsulated property of the Mn−salen complex.

Sabater et al. reported the preparation of manganese complex within Y-type zeolite.[195] The core structure of Y type zeolite consists of almost spherical 13 Å cavities interconnected tetrahedrally through smaller apertures of 7.4 Å. Molecular modeling indicates that both the *trans*-(*R*,*R*)-1,2-bis(salicylideneamino)cyclohexane ligand and its Mn complex can be accommodated inside the supercages of the Y-type zeolite, and Jacobsen's ligands/catalysts *tert*-butyl groups on the phenyl rings cannot fit into the supercage of Y-type zeolite.

A mixture of salicylaldehyde, (*R*,*R*)-1,2-diaminocyclohexane, and Y-type zeolite was heated in dichloromethane for 12 h, and subsequent oxidation of the Mn(II) to Mn(III) complex furnished the Mn−salen complex **119** in the supercage (Scheme 45).

Scheme 45



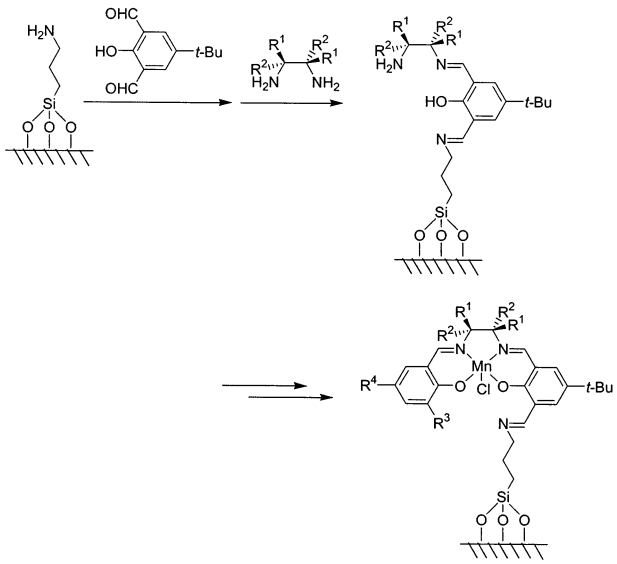
119

In the asymmetric epoxidation of prochiral olefins the enantioselectivity of this catalyst was found to be generally lower than that of the homogeneous counterpart.

To determine whether the reaction took place inside or outside the supercage, a bulky oxidant was used to carry out the reaction. Hydrolysis of [bis(trifluoroacetoxy)iodo]benzene gave a bulky iodosylbenzene moiety which, according to FABMS study, was an oligomer of iodosylbenzene. In the presence of a free catalyst, this bulky reagent gave results similar to those obtained from using NaOCl as oxidant. Using the same bulky oligomer as oxidant and the Y-type zeolite encapsulated complex as catalyst, no epoxide was observed. As the oligomeric iodosylbenzene could not freely travel through the 7.4 Å faujasite pore window, the result was consistent with the concept of encapsulated Mn−salen in the supercage, and no leaching of Mn ions from the interior of the zeolite to the solution occurred. In fact, no Mn ions were detected in the liquid phase after the reaction. As the epoxidation occurred inside the supercage, the external surface sites played a very minute role in the overall catalytic process.

Kim et al. reported a salen complex immobilized on the surface of mesoporous MCM-41 in a step by step manner.[196] Reacting (3-aminopropyl)trimethoxysilane with MCM-41 molecular sieves gave the modified MCM-41 with a free amino group which was used to connect the salen ligand. A multifunctional group aldehyde 2,6-diformyl-4-*tert*-butylphenol was attached to MCM-41 through imine bond formation. Subsequent routine chemistry furnished the immobilized salen complex **120** ready for epoxidation study (Scheme 46).

Scheme 46

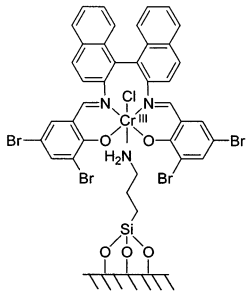


120

With different chiral diamine and different substituents on the benzene ring, a variety of Mn−salen complex attached to molecular sieves were prepared. In the asymmetric epoxidation of styrene at −78 °C (R^1 = Ph, R^2 = H, R^3 = R^4 = H) using *m*-CPBA/NMO as oxidant, the corresponding epoxide was obtained in 89% ee at 92% conversion after 4 h of reaction. In comparison, 84% ee at 97% conversion was observed when the homogeneous catalyst was used.

Zhou et al. reported another MCM-41 supported catalyst **121**. Their work included the synthesis of a salen-type ligand using 2,2′-diamino-1,1′-binaphthyl as the diamine backbone.[197] Modifying MCM-41 with (3-aminopropyl)trimethoxysilane provided some free amino groups which were used to anchor the Cr-salen complex on the surface of the molecular sieves.

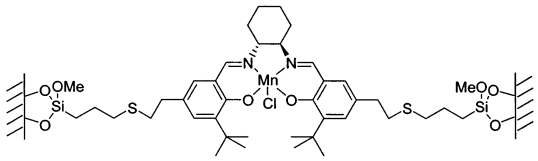
The anchored catalyst was studied in the epoxidation of a series of substituted styrenes. Using iodosylbenzene as the oxidant, 4-chlorostyrene was epoxidized to give the epoxide in 65% yield and 65%



121

ee. The catalyst was recycled 4 times without decrease in enantioselectivity. Under identical conditions, the heterogenized catalyst gave significantly higher enantioselectivity than the free catalysts. This may be attributed to the enhanced stability of the chromium complex upon immobilization or the unique spatial microenvironment constituted by both the chiral binaphthyl Schiff base ligand and the surface of the support.

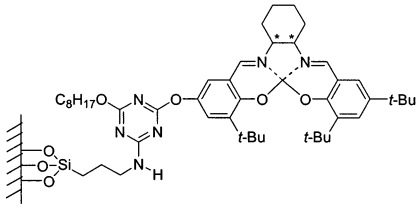
Pini et al. reported the immobilization of Mn−salen catalyst on silica gel surface (**122**)[198] with the same modified salen used for immobilization on the polymer support.



122

The silica gel with commercial name LiChrosper Si 100 was chosen as the catalyst support, and the spacer group -$(CH_2)_2S(CH_2)_3Si$- could be attached either on the surface of silica gel or connected to the salen benzene ring. The epoxidation of prochiral aromatic olefins was carried out using *m*-CPBA/NMO as oxidant. Good conversion was observed even at 0 °C and 53−58% ee were observed in the epoxidation of phenylcyclohexene. The choice of anchoring techniques, either the spacer group was attached on the silica gel surface or connected to the salen benzene ring, did not significantly affect the activity and stereoselectivity of the catalyst.

Bigi et al. reported the preparation and application of amorphous and MCM-41 silica-supported Mn−(salen) complexes (**123**) for enantioselective oxidation of olefins.[199] Up to 84% ee was achieved for epoxidation of 1-phenylcyclohexene using MCM-41-supported catalyst. Catalyst supported on amorphous silica showed similar enantiomeric excess, and a positive effect in the catalyst recycling.



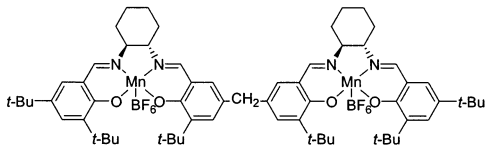
123

6.3. Chiral Membrane for Asymmetric Epoxidation

Vakelecom et al. reported a chiral membrane for the asymmetric catalytic epoxidation of olefins.[51] Reacting the prepolymer RTV-615A and cross-linker RTV-615 B for an hour followed by the addition of the Jacobsen Mn−salen complex furnished the PDMS membrane occluded the Jacobsen Mn−salen complex ready for asymmetric epoxidation reactions (Table 37). The recycled chiral membrane retained the reactivity and stereoselectivity, and manganese leaching was almost negligible.

Similar to its homogeneous counterpart, the chiral catalytic membrane is much more selective for cis-alkenes than for the trans-isomers.

To improve the retention of Mn−salen complex in a poly(dimethylsiloxane) membrane, Janssen et al. prepared a dimeric form of the Jacobsen catalyst **124**.[200]



124

The homogeneous epoxidation of a series of olefins using this dimeric Mn−salen as catalyst and NaOCl as oxidant showed that activity and enantioselectivity was comparable to its monomer. Under oxidation conditions, both the dimer and the monomer were highly resistant to degradation.

Pt catalyzed hydrosilylation between a prepolymer and a cross-linker gave the corresponding PDMS membrane. In making the occlusion catalyst, the complex was retained in the cross-linked membrane by steric interaction as well as physical interaction. The leaching of the complex depended on the swelling of the membrane and the solubility of the complex in the solvent system. For solvents which would cause a high degree of membrane swelling and could well dissolve the Mn complex, significant leaching (>80%) was observed. For solvents that could hardly cause membrane swelling but could still dissolve the complex well, a moderate degree (50−60%) of catalyst leaching was observed. The dimeric Mn−salen complex showed the same trends of leaching, but to a much lesser extent. Under reaction conditions, through the formation of a Mn−oxo species which was more polar and less soluble in apolar solvents, leaching was reduced significantly, particularly for the dimeric complex.

The dimeric catalyst occluded in the PDMS membrane showed slightly lower reactivity and stereoselectivity comparing to the PDMS membrane-occluded Jacobsen catalyst (Table 38).

For the Jacobsen catalyst occluded in PDMS, the excessive swelling of the membrane could be avoided by using a less polar solvent such as heptane.[201] No significant loss of enantioselectivity or activity was observed for the membrane occluded catalyst. Less than 1% of Mn was detected in the reaction mixtures after 24 h, indicating that the leaching of Mn^{3+} and/or catalyst was negligible. After regeneration, the

Table 37. Asymmetric Epoxidation of Olefins with NaOCl at 4 °C Catalyzed by Chiral Membrane[a]

entry	substrate	conversion (%)	epoxide selectivity (%)	TOF	ee (%)
1	styrene	84 (78)	80 (100)	0.0438 (0.0406)	52 (57)
2	styrene (run 2)	84	80	0.438	52
3	styrene (run 3)	84	80	0.438	52
4	*trans*-β-methylstyrene	13 (17)	80 (77)	0.0067 (0.0088)	18 (20)
5	*trans*-β-methylstyrene (run 2)	18	80	0.0067	18

[a] Data in parentheses refer to the results from using the corresponding homogeneous catalyst.

Table 38. PDMS-Occluded Dimer and PDMS-Occluded Jacobsen Catalyst for the Asymmetric Epoxidation of *trans*-β-Methylstyrene in Acetonitrile[a]

entry	substrate	yield (%)	ee (%)	TON
1	*trans*-β-methylstyrene	23 (64.0)	14.4 (20.5)	6.3 (17.4)
2	*trans*-β-methylstyrene (regeneration)	17 (27.6)	15.8 (10.6)	4.8 (7.5)

[a] Data in parentheses refer to results from PDMS-occluded Jacobsen catalyst.

catalyst was found to retain the original activity (Table 39).

Table 39. Epoxidation of Styrene Catalyzed by Homogeneous and Occluded Jacobsen Catalyst

entry	catalyst	TOF	ee (%)
1	homogeneous	~ 2.5	~ 42
2	PDMS−Mn−salen	~ 2.7	~ 45%
3	PDMS−Mn−salen (run 2)	~ 2.7	~ 45%
4	PDMS−Mn−salen (run 3)	~ 2.7	~ 45%

6.4. Soluble Macromolecules for Asymmetric Epoxidation

Reger and Janda reported the first soluble polymer-supported Mn(salen) catalysts (**125**) for asymmetric epoxidation and made a comparison between soluble and insoluble matrixes.[202] MeO−PEG and non-cross-linked polystyrene (NCPS) were used as soluble supports while JandaJel and Merrifield resins served as insoluble supports. Each polymer was linked to the salen catalyst through a glutarate spacer. The soluble catalysts were recovered by precipitation with a suitable solvent while the insoluble catalysts were simply filtered from the reaction mixture. The epoxidation of styrene, cis-β-methylstyrene, and dihydronaphthalene was studied and cis-β-methylstyrene gave the best result. The enantioselectivity obtained with each polymer-bound catalyst was similar to that achieved with the analogous unsupported Mn−salen catalyst (Scheme 47, Table 40). The soluble polymer-supported catalysts could be used twice before a decline in yield and enantioselectivity was observed and the JandaJel attached catalyst could be used for three cycles in some cases. The Merrifield-bound catalyst lost activity after each use.

Scheme 47

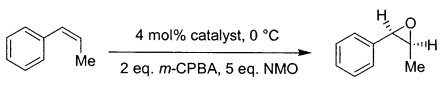
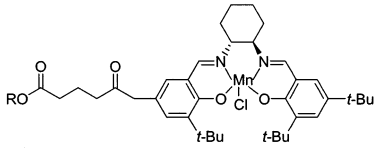


Table 40. Epoxidation of cis-β-Methylstyrene Catalyzed by 125a−125e

entry	catalyst	yield (%)	ee (%)
1	**125a**	79	88
2	**125b**	79	90
3	**125c**	77	88
4	**125d**	75	86
5	**125e**	80	87



125a: R =MeO-PEG$_{5000}$

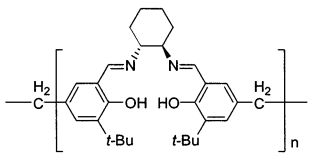
125b: R = NCPS

125c: R = JandaJel resin

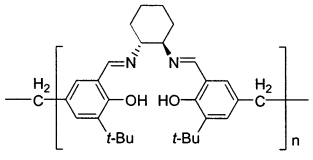
125d: R = Merrifield resin

125e: R = methyl

Zheng et al. disclosed a new approach to soluble linear polymeric salen ligands with main chain chirality which provided the advantage of maintaining the local C_2 symmetry in the individual salen units.[203] The chiral polymer ligands **126a** and **126b** were obtained by the polycondensation of a slight excess of (1*R*,2*R*)-diaminocyclohexane with the corresponding linked salicylaldehydes in ethanol. The structures of the resulting polymeric ligands, with average molecular weight of around 5400 (M_n = ~5400, n = ~12, based on VPO analysis), were confirmed by ^{1}H NMR and ^{13}C NMR. The polymeric salen-Mn complexes were employed in the enantioselective epoxidation of olefins under homogeneous conditions. Using NaOCl/4-phenylpyridine *N*-oxide and 3-chloroperbenzoate/*N*-methylmorpholine *N*-oxide as oxidants, the epoxidation of substituted styrenes and substituted 2,2-dimethylchromenes gave 30 to 92% ee. The catalyst was recovered and reused several times by a simple catalysis/separation method but the recovered catalyst was found to have lower enantioselectivity and activity after each cycle.

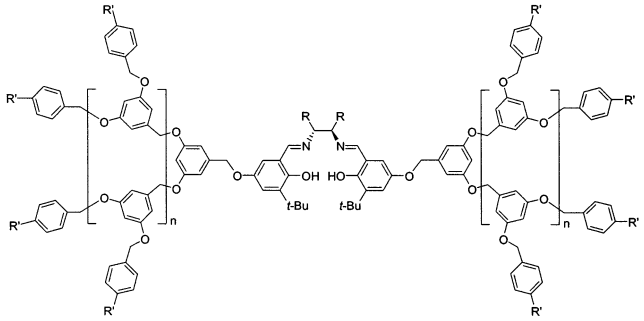


126a



126b

Recently, Seebach and co-workers reported a series of chiral dendritic salen ligands for the Mn complex catalyzed enantioselective epoxidation of unfunctionalized olefins.[204] The salen cores are either derived from (1*R*,2*R*)-cyclohexane diamine (**127a**, **128a**, **129a**) or from (1*R*,2*R*)-diphenylethylenediamine (**127b**, **128b**, **129b**). The dendritic wedges, Fréchet-type polyether dendritic benzyl bromides with or without peripheral vinyl groups, were attached with the salicylic aldehyde moieties via phenolic etherification or Sonogashira cross-coupling reaction. Polymer-supported salen ligands (p-**128a**, p-**128b**, p-**129a**, p-**129b**) were prepared by cross-linking radical suspension copolymerization of the peripherally styryl-substituted dendrimers (**128a**, **128b**, **129a**, **129b**) with styrene. Both the free dendritic salen ligands and the polymer-supported salens were studied in the Mn-catalyzed asymmetric epoxidation of phenyl-substituted olefins (*m*-CPBA/NMO system). In the former case, the enantioselectivities observed in homogeneous solution using dendritic salens **127a** and **127b** were similar to those reported for the classical Jacobsen catalyst. The second-generation salen gave, in general, similar results to the first-generation species. The best enantioselectivity (up to 92%) was obtained in the epoxidation of 1-phenylcyclohexene using the first-generation salen **127a** as ligand. In the case of the heterogeneous catalysis, most of the cross-linked polymer-supported salens gave similar conversions, albeit lowered enantioselectivities compared to the free dendritic catalysts or the original Jacobsen-Katsuki complexes. The polymer-supported Mn−salen, especially the acetylene-linked Mn(salen) polymers (**129a** and **129b**) were recovered via simple filtration and were reused for at least 10 times without loss of enantioselectivity or activity under the standard reaction conditions.

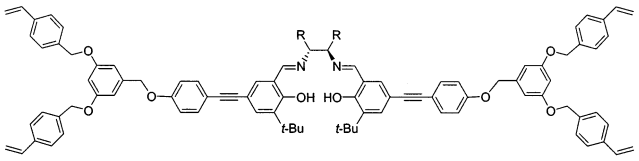


127a: R-R = -$(CH_2)_4$-, R' = H, n = 0 or 1

127b: R = Ph, R' = H, n = 0 or 1

128a: R-R = -$(CH_2)_4$-, R' = vinyl, n = 0 or 1

128b: R = Ph, R' = vinyl, n = 0 or 1



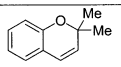
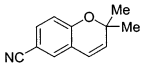
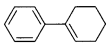
129a: R-R = -$(CH_2)_4$-

129b: R = Ph

6.5. Asymmetric Epoxidation in Ionic Liquid

Song et al. reported the Mn−salen asymmetric epoxidation in ionic liquid BMIM·PF_6.[205] The reactions were carried out at 0 °C using NaOCl as the oxidant. Good conversion and enantioselectivity were observed for a variety of substrates (Table 41).

Table 41. Mn−Salen Catalyzed Asymmetric Epoxidation in Ionic Liquid BMIM·PF_6

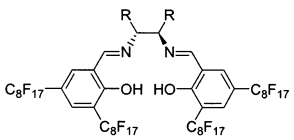
Entry	Substrate	Time (h)	Yield (%)	ee (%)	Config.
1		2	86	96	(3*R*,4*R*)
2		4	72	94	(3*R*,4*R*)
3		4	72	84	(1*R*,2*S*)
4		3	72 (*cis*/*trans* 3.7:1)	86	(1*R*,2*S*)
5		4	77	84	(*S*,*S*)

The epoxidation using the recovered catalyst showed gradually decreased enantioselectivity.

6.6. Asymmetric Epoxidation in Fluorous Biphase System

Perfluorocarbons are generally inert and immiscible with most of the organic solvents, and therefore were neglected for decades until Horváth and Rábai developed the fluorous biphase system (FBS).[206] Due to the immiscibility of perfluorocarbons with most of the organic solvents such as acetonitrile or toluene at ambient temperature and under atmospheric pressure, a biphase could easily be obtained, in which a catalyst soluble in perfluorocarbon could be separated from the reaction system. Perfluorocarbons have some special features, such as sharply increased miscibility with organic solvents upon increase of temperature or pressure, which makes one-phase reaction and two-phase separation possible. In addition, the unique solvation environment provided by perfluorocarbons might have some unforeseen beneficial effects on the selectivity of the reaction. For the reaction to be carried out in fluorous biphase system, the catalyst system should normally be modified with some perfluorous functional groups in order for the catalyst to be soluble in perfluorocarbons.

Perfluorocarbons can dissolve large quantities of molecular oxygen, and this property has been exploited in oxidation reactions. Pozzi et al. prepared the *n*-perfluorooctyl group substituted salen **130** for the asymmetric aerobic epoxidation of alkenes.[207]



130a: R = -$(CH_2)_4$-, **130b**: R = Ph

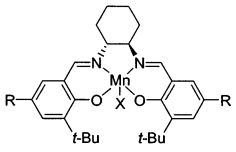
A variety of unfunctionalized olefin substrates were tested in Mn−salen mediated epoxidation using molecular oxygen dissolved in perfluorocarbons as oxidant. Good to excellent conversions of substrates were observed, providing epoxides in good yields, and in some cases also in good ee's (Table 42).

Table 42. Epoxidation of Unfunctionalized Olefins Catalyzed by 130a and 130b

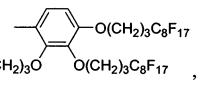
entry	catalyst	substrate	time (h)	conv. (%)	yield (%)	ee (%)
1	**130a**	indene	2	100	83	92
2	**130a**	1,2-dihydronaphthalene	8	85	70	10
3	**130a**	styrene	5	100	86	
4	**130a**	3-nitrostyrene	12	70	36	
5	**130a**	*trans*-β-methylstyrene	5	100	75	
6	**130a**	*trans*-stilbene	12	80	78	
7	**130a**	*cis*-stilbene	12	88	85	
8	**130b**	indene	3	100	77	90
9	**130b**	1,2-dihydronaphthalene	8	95	73	13
10	**130b**	styrene	5	100	81	

The perfluorocarbon phase was recovered by decantation and was reused without appreciable loss of activity.[208] Reaction using *m*-CPBA/NMO oxidant system proceeded rather slowly, probable due to the poor mass-transfer between the organic phase (CH_2Cl_2/$PhCF_3$) and the fluorous phase. Reactions carried out under homogeneous conditions were generally faster than those in fluorous biphase system, but the ee values were similar.

Several other Mn−salen complexes (**131**) bearing different perfluoroalkyl functional groups, or the second generation fluorous salen complexes, were synthesized and used in the same reaction.[209]



X = $C_7H_{15}COO^-$



131a: R = , **131b**: R = 3,5-di(perfluorooctyl)phenyl,

In asymmetric epoxidation reactions, these complexes gave much higher ee values than the first generation complexes. Reactions carried out at higher temperatures gave better enantioselectivity. The fluorous layer was easily separated upon cooling and was reused for up to three times without loss of enantioselectivity and activity. The catalytic activity generally decreased in the fourth run due to the oxidative decomposition of the catalyst (Table 43).

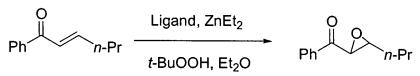
6.7. Asymmetric Epoxidation of α,β-Unsaturated Ketone

Pu and co-workers prepared a polybinaphthyl zinc catalyst for the asymmetric epoxidation of α,β-unsaturated ketones in the presence of *tert*-butyl hydrogen peroxide.[210] Up to 81% ee was obtained in the epoxidation of α,β-unsaturated ketones containing β-aliphatic substituents by using a binaphthyl polymer **132** in combination with diethylzinc. An interesting positive cooperative effect of the catalytic sites in the polymer chain, which led to increased enantioselectivity over the corresponding monomer ligand **133**, was observed (Scheme 48).

Table 43. Asymmetric Epoxidation of Olefins Catalyzed by 131a and 131b

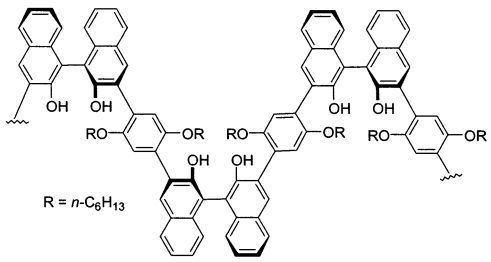
entry	catalyst	substrate	temp. (°C)	time (h)	yield (%)	ee (%)
1	**131b**	1,2-dihydronaphthalene	0	3	4.5	8
2	**131b**	1,2-dihydronaphthalene	20	3	46	26
3	**131b**	1,2-dihydronaphthalene	40	3	46	32
4	**131b**	1,2-dihydronaphthalene	70	2	74	42
5	**131b**	1,2-dihydronaphthalene	100	1	77	50
6	**131a**	1,2-dihydronaphthalene	100	1	68	50
7	**131b**	triphenylethylene	100	0.5	98	87
8	**131b** (run 2)	triphenylethylene	100	0.5	96	85
9	**131b** (run 3)	triphenylethylene	100	0.5	92	83
10	**131b** (run 4)	triphenylethylene	100	1	80	71
11	**131a**	triphenylethylene	100	0.5	98	80
12	**131b**	benzosuberene	100	0.5	92	68
13	**131a**	benzosuberene	100	0.5	84	69
14	**131b**	1-methylindene	100	0.5	98	77
15	**131a**	1-methylindene	100	0.5	96	70
16	**131b**	1-methylcyclohexene	100	0.5	91	58
17	**131a**	1-methylcyclohexene	100	0.5	95	52

Scheme 48

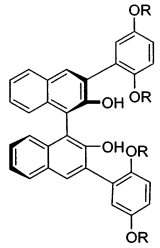


132: 76% ee, 92% conv.

133: 30% ee, 75% conv.



132



133

6.8. The Sharpless Epoxidation Catalyzed by Polymer-Supported Catalysts

Since its discovery, the asymmetric epoxidation of allylic alcohols has become one of the leading areas of investigation in synthetic organic chemistry. Efforts have been made to develop polymer-supported catalysts for the Sharpless epoxidation reaction. The main objective of the study is to facilitate the separa-

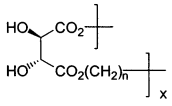
Table 44. Asymmetric Epoxidation of *cis*-Allylic Alcohols Using Heterogeneous Polymer/Ti as Catalyst

entry	R	ligand branch/ cross-linking	molar ratio substrate:Ti:tartrate	reaction time (days)	yield (%)	ee (%)
1	C_2H_5	10	100:100:200	7	51	86
2	C_2H_5	≫15	100:100:200	6	42	48
3	C_3H_7	10	100:200:400	6	48	80
4	C_3H_7	14	100:200:400	21	29	75
5	$PhCH_2OCH_2$	10	100:100:200	7	20	66
6	$PhCH_2OCH_2$	10	100:200:400	6	18	68
7	$PhCH_2OCH_2$	≫15	100:100:200	6	20	38

Table 45. Epoxidation of Homoallylic Alcohol Hex-3-en-1-ol

entry	ligand branch/cross-linking	substrate hex-3-en-1-ol (*Z*/*E*)	molar ratio substrate:Ti:tartrate	reaction time (days)	yield (%)	ee (%)
1	monomer dimethyl tartrate	E	100:100:200	10	58	29
3	monomer dimethyl tartrate	Z	100:100:200	6	15	28
3	no cross-linking	E	100:200:400	21	26	54
4	10% cross-linking	Z	100:200:400	21	20	51
5	8% cross-linking	E	100:200:400	5	45	54
6	13% cross-linking	Z	100:200:400	1	52	41
7	16% cross-linking	Z	100:100:200	13	33	41
8	13% cross-linking	E	100:200:400	1	75	38

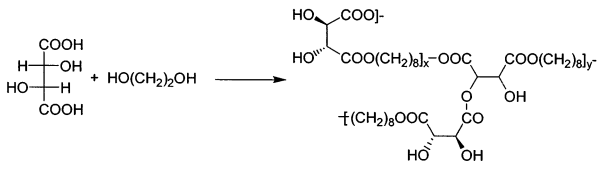
tion and purification of the enantio-enriched products from the reaction mixture because the homogeneous chiral catalysts are relatively inexpensive. Canali et al. reported the preparation of a class of linear poly(tartrate ester) ligands **134** and the use of them in Ti-catalyzed Sharpless epoxidation.[211] The polymer catalysts gave only moderate enantioselectivities (up to 79% ee) in the epoxidation of *trans*-hex-2-en-1-ol using Ti(O*i*-Pr)$_4$/*tert*-butyl hydrogen peroxide while L-(+)-dimethyl tartrate gave 98% ee in the same reaction (Scheme 50).



134

A branched poly(tartrate ester) ligand **135** was prepared via the reaction of L-(+)-tartaric acid with 20% excess 1,8-octanediol under polycondensation conditions with higher reaction temperature and longer reaction time (Scheme 49). The most effective

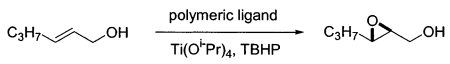
Scheme 49



135

polymer catalyst (3% branched) was found to be insoluble under the reaction conditions and afforded (2*S*,3*S*)-propyloxiranemethanol with improved enantioselectivity (87% ee, Scheme 50).[212] Both the soluble

Scheme 50



134: up to 79% ee

135: up to 87% ee

and insoluble polymer catalysts could be easily removed from the reaction mixture via solvent precipitation and filtration, respectively.

The study showed that the complexes formed by Ti(O*i*-Pr)$_4$ with the polymeric ligand were insoluble in CH_2Cl_2, and 70 to 100% of the polymer could be recovered from the reaction mixture by filtration.[213] An IR spectroscopic analysis showed that the recovered polymer had the same characteristic bands as the original species, indicating that this polymer ligand might in principle be reused.

When the polymer ligand was removed from the reaction mixture by filtration, 80% of the Ti bound to the polymer was recovered. The catalytic activity of the leached Ti was relatively low.

Under heterogeneous conditions, the epoxidation of cis-allylic alcohols (Scheme 51) proceeded more

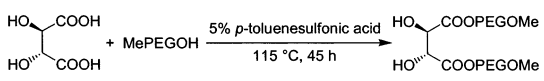
Scheme 51

slowly than the epoxidation of the trans-substrates.[214] Higher cross-linking resulted in decreased enantioselectivity (Table 44).

In the presence of properly cross-linked poly(tartrate ester), the epoxidation of homoallylic alcohols proceeded smoothly,[215] giving the corresponding epoxides with higher yield and ee than the corresponding homogeneous reactions (Table 45).

Guo et al. reported soluble polymer-supported tartrate **136** for asymmetric Sharpless epoxidation reactions (Scheme 52).[216] Tartaric acid was reacted

Scheme 52

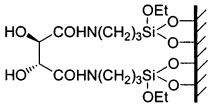


136

with poly(ethylene glycol) monomethyl ether to give the tartrate for allyl alcohol epoxidation. While dimethyl tartrate induced over 98% ee and 91% yield for the epoxidation of *trans*-hex-2-en-1-ol, the sup-

ported catalyst gave up to 93% ee for oxidation of the same substrate.

Xiang et al. reported asymmetric Sharpless reaction catalyzed by tartaric acid grafted on the surface of silica and mesoporous MCM-41 (**137**), up to 86% ee was obtained for the epoxidation of allylic alcohol.[217]



137

7. Asymmetric Ring Opening of Epoxides (Kinetic Resolution)

Epoxides are valuable intermediates for the stereocontrolled synthesis of complex organic compounds, and the asymmetric ring opening of such chiral epoxides extends their utilities.

Martínez et al. reported the recycle of Mn−salen complex **138** used for the asymmetric ring opening of epoxides.[218] The catalyst was recovered by distilling off the product, and the residue containing the Cr−salen complex was reused for the same reaction without obvious loss of catalytic activity (Scheme 53, Table 46).

Scheme 53

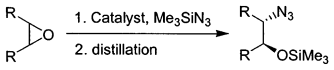
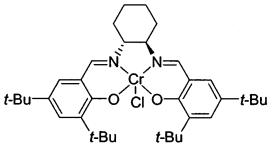


Table 46. Asymmetric Ring Opening of Epoxides Catalyzed by 138

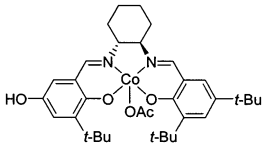
Cycle	Substrate	Time (h)	Isolated yield (%)	ee (%)
1		18	86	84
2		21	88	87
3		20	91	88
4		4	81	94
5		18	75	83



138

Allen et al. reported the use of polymer-supported Co−salen complex for the asymmetric ring opening of terminal epoxides.[219] A ligand/catalyst precursor **139** bearing a hydroxyl group was synthesized for immobilization.

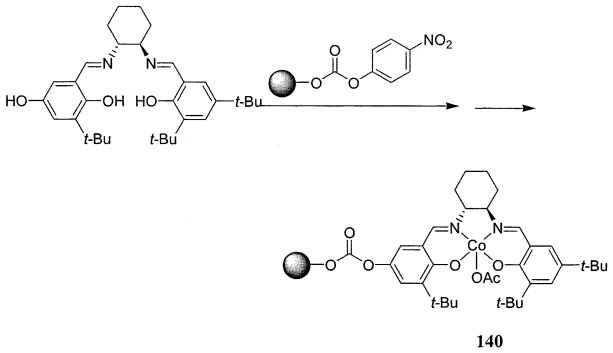
A commercially available polymer of hydroxylmethylpolystyrene was chosen as the catalyst support. It was first converted to 4-nitrophenyl carbonate, followed by the treatment with **139**. In the presence of diisopropylethylamine, transesterification



139

occurred to give the supported catalyst **140** in good yield (Scheme 54).

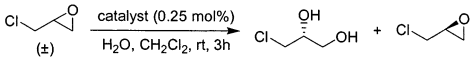
Scheme 54



140

The catalytic efficacy of this polymer bound catalyst was tested in the asymmetric ring opening of epichlorohydrin (Scheme 55). Complete consumption of

Scheme 55



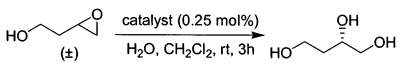
the reactive enantiomer occurred within 3 h in the presence of 0.25 mol % of catalyst. The catalyst was recovered by simple filtration and was reused without significant loss of activity and selectivity (Table 47).

Table 47. Recycle of Catalyst 140 in Asymmetric Ring Opening of Epichlorohydrin

cycle	conversion (%)	ee of epoxide (%)	ee of diol (%)
1	52	>99	92.4
2	51	>99	95.0
3	51	>99	93.6
4	51	>99	93.4
5	52	>99	93.0

The efficacy of this polymer-bound catalyst was also visualized by the asymmetric ring opening of 3,4-epoxy-1-butanol (Scheme 56). The ring opening prod-

Scheme 56

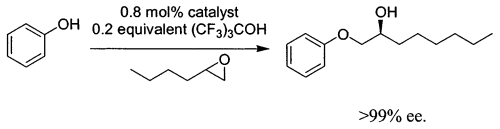


36% overall yield, 94.4% ee.

uct triol was a direct precursor to 3-hydroxytetrahydrofuran, a component of HIV protease inhibitor VX-478. Normal hydrolytic kinetic ring opening also provided such triol in high enantiomeric purity, but its isolation from the catalyst residue proved to be difficult due to the foaming problem upon distillation. A straightforward separation was achieved using the polymer-bound Co−salen as catalyst. Again, the supported catalyst was easily recovered and reused.

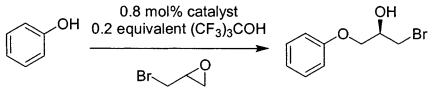
In addition to the hydrolytic kinetic ring opening reaction, this bound catalyst was also an efficient catalyst for the ring opening of terminal epoxides with phenols. Addition of tris(trifluoromethyl)methanol accelerated the reaction, presumably by helping the catalyst to stay in Co(III) state (Scheme 57).

Scheme 57



The ring opening of epibromohydrin by phenol (Scheme 58) in the presence of the supported catalyst

Scheme 58

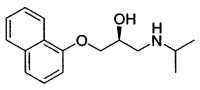


also proceeded smoothly, leading to the ring opening product bromohydrin in high ee (Table 48).

Table 48. Asymmetric Ring Opening of Epibromohydrin by Phenol

cycle	ee (%)
1	97.1
2	97.1
3	95.5
4	95.8
5	94.6

Upon addition of solid potassium hydroxide, the bromohydrin product could be quantitatively converted to the epoxide in over 99% purity and excellent enantiomeric excess without further purification. This reaction is commercially attractive as it may be used to make the important antihypertensive agent (*S*)-propranolol (**141**).



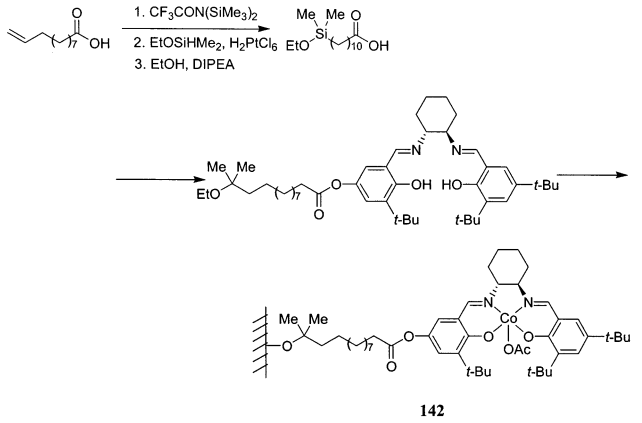
141

This Co(III)−salen complex was immobilized on silica to give catalyst **142**. Being inflexible and noncompressible, silica provides a stationary phase amenable to incorporation in continuous flow reactor. A bifunctional tether bearing one end for immobilization and the other for ligand attachment was synthesized (Scheme 59).

The catalytic efficacy of this silica supported catalyst was tested in the asymmetric ring opening of styrene oxide. In the presence of only 0.7 mol % of catalyst, the reactive enantiomer was converted to the corresponding ring opening product almost quantitatively after 3 h of reaction, giving the diol product in excellent ee (Scheme 60).

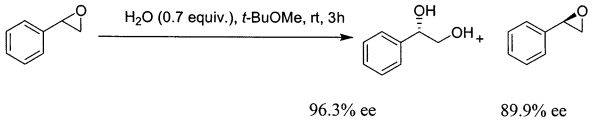
This silica-bound Co−salen catalyst was also used in a continuous flow system for the hydrolytic kinetic ring opening of epoxides (Figure 1). The reactivity and the selectivity of this catalyst were found to be

Scheme 59



142

Scheme 60



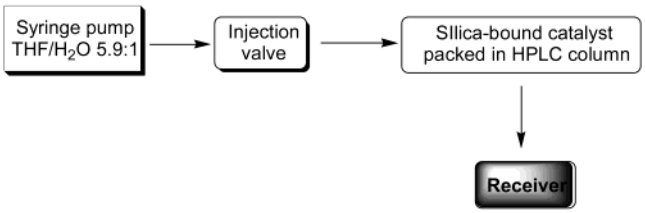


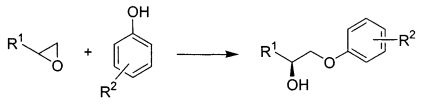
Figure 1.

comparable to those of the polystyrene-bound analogue in the ring opening of 3,4-epoxy-1-butanol.

The packed column was regenerated by elution with a small amount of acetic acid/toluene, and a second cycle of the same reaction gave the product with comparable yield and enantiomeric excess.

Peukert et al. extended the polymer-supported Co−salen catalyzed asymmetric ring opening reaction to the enantioselective parallel synthesis.[220] A variety of phenols were used as the nucleophiles, and ee's over 99% were observed (Scheme 61). By varying the

Scheme 61[a]

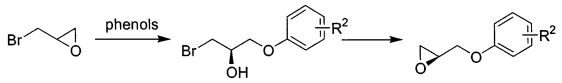


[a] R^1 = Et, $CH_2{=}CH(CH_2)_2$, *i*-$PrOCH_2$, $CH_2{=}CHCH_2OCH_2$, $CF_2HCF_2OCH_2$. R^2 = H, *p*-*t*-Bu, *p*-Ph, *p*-PhO, *p*-Br, *p*-CF_3, *m*-MeO, *m*-AcO, *p*-NO_2-*m*-Me.

structures of epoxide and phenol, a series of amino alcohols were obtained.

In the presence of 1.2 mol % of polymer-bound catalyst, epibromohydrin was subjected to asymmetric ring opening using a variety of phenols. Since epibromohydrin can undergo facile racemization, it is an ideal substrate for dynamic kinetic resolution. Under the ring opening conditions, the bromohydrin products underwent slow transformations to aryloxy epoxides, and potassium hydroxide was added to effect this conversion. The ee's of the epoxides were found to be over 98% in most cases (Scheme 62).

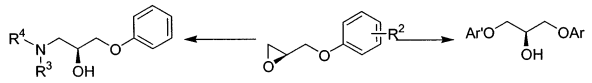
Scheme 62[a]



[a] R^2 = *p*-F, *o*-F, *o*-Cl, *m*-Me, *p*-CN, *p*-NO_2, *p*-CF_3O.

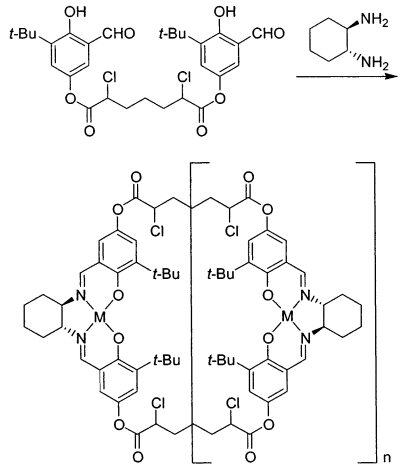
The aryloxy epoxides could be converted to either amino alcohols or aryl glycidyl ethers upon second ring opening with different nucleophiles. Determination of the enantiomeric excess of the amino alcohols or aryl glycidyl ethers showed that the second ring opening occurred without compromising the enantioselectivity of the starting epoxides. Enantiomeric excess of over 97.5% was observed for the amino alcohols, and most of the aryl glycidyl ethers were obtained in over 99% ee (Scheme 63).

Scheme 63



Ready et al. synthesized a series of Co−salen oligomer catalysts **143** on the basis of cooperative catalysis.[221] Such oligomers showed high activity for the asymmetric ring opening of epoxides (Scheme 64).

Scheme 64



143a: M = CoOTs, n = 1-5

143b: M = CoOCSA n = 1 – 3

143c: M = CoNBS, n = 1 – 3

The introduction of chlorine substitutent α- to the carbonyl group was based on an empirical screening that indicated the effect of electronic tuning of carboxylate-substituted ligands on the reactivity of the catalyst.

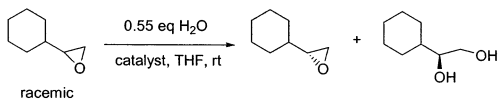
This oligomeric Co−salen complex was tested in asymmetric ring opening of cyclohexene oxide. Compared to the corresponding monomer, the oligomer showed higher catalytic activity and thus allowed the use of substantially lower catalyst loading. Improved enantioselectivity was also observed in many cases. In a large-scale reaction, 0.5 mol of epichlorohydrin was subjected to hydrolytic kinetic resolution under solvent free conditions. In the presence of only 50 mg of catalyst, 23 g of the recovered epoxide was obtained in over 99% ee after 11 h of reaction.

The drawback of this ligand was also associated with the chlorine substituent. Installation of the chlorine substituent at the α-position of the linker required very strict reaction conditions and only moderate yield was achieved.[222] Another disadvantage of the introduction of the chlorine substituent came from the activation of the adjacent carbonyl group which rendering the oligomer sensitive to decomposition under that epoxide ring-opening conditions. Further, the oligomer prepared is a mixture of over 1000 diastereomers which made it difficult to fully understand the high reactivity and high enantioselectivity originated from the catalyst. The authors then found that the electronic tuning was alternatively achieved by varying the ancillary ligands (counterion) of the complex. Changing from the current counterion "OTs" to more electron-withdrawing groups such as 10-camphorsulfonate and 3-nitrobenzenesulfonate gave complexes with comparable reactivity but slightly improved selectivity (**143**, M = CoCSA or CoNBS, n = 1−3). Such oligomeric salens were prepared on large scale under chromatography-free conditions from inexpensive components, and metal insertion followed by air oxidation in the presence of one equivalent of sulfonic acid provided the corresponding oligomeric catalysts (**143b**, **143c**). Catalysts **143b** and **143c** showed remarkable catalytic activity toward the hydrolytic kinetic resolution of terminal epoxides, and only 5 mg of **143c** catalyzed the resolution of 1.5 mol of styrene oxide in 24 h at 23 °C.

Angelino et al. also tested polystyrene-supported salen complex (Cr-**115**) in the asymmetric ring opening of epoxides.[223] At 0 °C with 1 mol % catalyst loading, the asymmetric ring opening of epoxyhexane, propylene oxide, and cyclohexene oxide gave the corresponding products with 34, 36, and 6% ee, respectively, and in 40−47% yield. The recycled catalysts were stable and were reused three times without loss of activity or enantioselectivity.

Breinbauer and Jacobsen reported the use of dendrimer-bound Co(salen) complexes for the asymmetric ring opening of epoxides and demonstrated the first positive "dendritic effect" in asymmetric catalysis.[224] The dendritic catalysts were prepared by covalently attaching Co−salen to NH_2-terminated PAMAM dendrimers. When using epoxyhexane as a standard substrate, the dendrimer Co−salen complexes **144** exhibited significantly higher catalytic activity in the hydrolytic kinetic resolution of terminal epoxides as compared to the monomer **145** or the dimer **146** complexes (Scheme 65, Table 49). The best

Scheme 65



results were obtained with the first generation (4-branch) metallodendrimer and the efficiency of catalyst on a per-metal basis was in the following order: 4-Co(salen)-PAMAM > 8-Co(salen)-PAMAM > 16-Co(salen)-PAMAM. This "dendrimer effect" was thought to arise from restricted conformation imposed by the

Table 49. Asymmetric Ring Opening of Epoxyhexane Catalyzed by 144−146

entry	catalyst	relative rate per Co(salen) unit	diol conv. (%)	diol ee (%)
1	**144** ($n = 4$)	24	42.8	99.2
2	**144** ($n = 8$)	15	40.1	99.4
3	**144** ($n = 16$)	11	39.8	99.3
4	**145**	7.1	37	99.2
5	**146**	1	29.1	98.2

dendrimer structure, which enhances the cooperative interactions between Co−salen units (Figure 2).

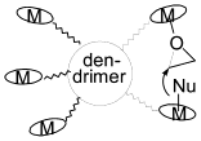
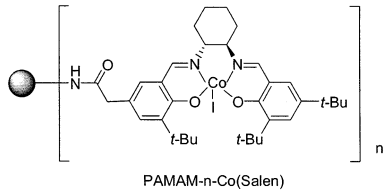
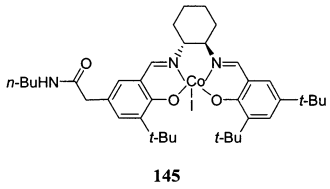
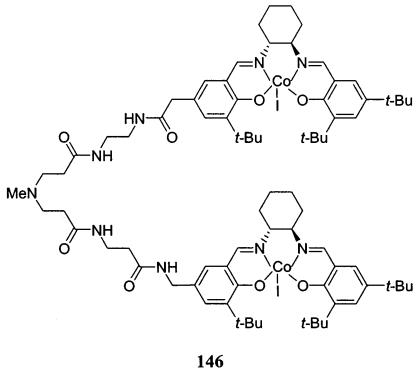


Figure 2. Cooperative Catalytic ARO with a Dendritic Framework.







Song et al. carried out the asymmetric ring opening reaction in ionic liquid using Cr−salen as catalyst.[225] Both the reactivity and the enantioselectivity were strongly influenced by the nature of the anion present in the ionic liquid, and BMIM·PF_6 gave the best result (94% ee) among other ionic ligands (Table 50).

The study showed that BMIM·BF_4 and BMIM·OTf^- immobilized the catalyst more efficiently although the reaction hardly occurred in them. Mixed ionic liquids containing both BMIM·PF_6 and BMIM·OTf^- were found to immobilize the catalyst more efficiently than BMIM·PF_6 alone, and the catalyst was recovered almost quantitatively. The reuse of the recovered catalyst in the asymmetric ring opening of cyclopentene oxide showed no loss of enantioselectivity after several recycles (Table 51).

Table 50. Cr-Salen Catalyzed Ring Opening of Epoxides Carried out in Ionic Liquids

Entry	Substrate	Ionic liquid	Time (h)	Yield (%)	ee (%)
1		BMIM·BF_6	28	76	94
2	"	BMIM·SbF_6	28	75	87
3	"	BMIM·BF_4	28	5	3
4	"	BMIM·OTf^-	28	trace	-
5		BMIM·BF_6	18	86	85
6		BMIM·BF_6	18	74	97

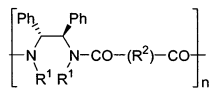
Table 51. Asymmetric Ring Opening Reactions of Cyclopentene Oxide Carried out in Mixed Ionic Liquid of BMIM·PF_6 and BMIM·OTf^-

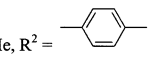
run	yield (%)	ee (%)
1	68	94
2	72	93
3	85	93
4	75	94
5	76	93

8. Asymmetric Allylic Substitution

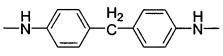
8.1. Insoluble Polymer-Supported Catalysts for Asymmetric Allylic Substitution

Gamez et al. synthesized some pseudo C_2 polyamide and polyurea compounds (**147**) as ligands for asymmetric allylic substitution reactions.[226]





147a: R^1 = Me, R^2 = ;



147b: R^1 = Me; R^2 =

In Pd-catalyzed allylic substitution [Scheme 66, Nu

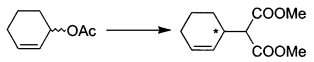
Scheme 66

= -CH(COOMe)$_2$], polyamide compound **147a** induced higher ee (80% ee) than the corresponding polyurea **147b** did (38% ee).

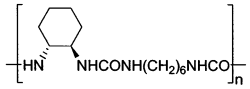
The catalyst could be separated from the reaction mixture by filtration.

Another polyurea **148** with a flexible backbone was tested and 25% ee was observed in the substitution of cyclohex-2-en-1-yl acetate (Scheme 67).[227]

Scheme 67

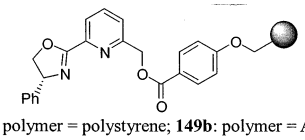


80% conversion, 25% ee

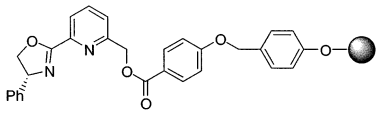


148

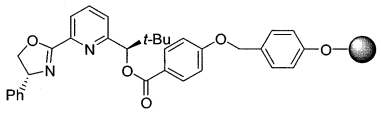
Hallman et al. prepared several polymer-supported oxazolylpyridine compounds **149a**−**h** for palladium-catalyzed enantioselective allylic alkylation.[228]



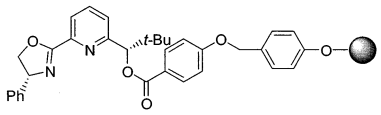
149a: polymer = polystyrene; **149b**: polymer = ArgoGel



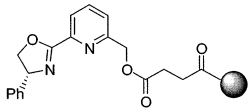
149c: polymer = ArgoGel



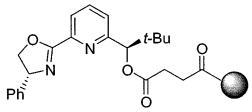
149d: polymer = ArgoGel



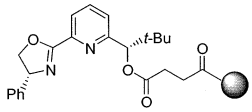
149e: polymer = ArgoGel



149f: polymer = TentaGel

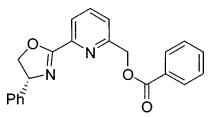


149g: polymer = TentaGel



149h: polymer = TentaGel

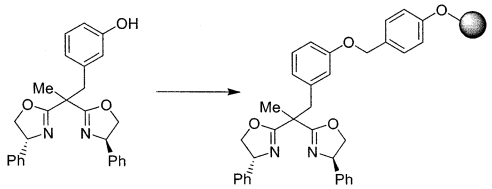
Ligands **149f**, **149g**, and **149h** were subjected to the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate [Scheme 66, Nu = $-CH(COOMe)_2$]. While ligand **149f** induced product with 80% ee in 60−100% yield, ligands **149g** and **149h** induced product in less than 4% yield. The unsupported catalyst **150** gave product with 77% ee in 76−98% yield.



150

Hallman et al. also prepared the ArgoGel bound bis(oxazoline) **151** and carried out a series of asymmetric reactions using this bound chiral ligand (Scheme 68).[229]

Scheme 68



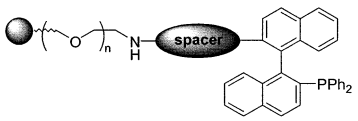
151

Pd-complex catalyzed allylic substitution [Scheme 66, Nu = $-CH(COOMe)_2$] was carried out in the presence of 2 mol % of bis[(π-allyl)palladium chloride] and 6 mol % of this bound ligand. The yields varied from time to time, whereas the enantioselectivity remained essentially constant (94−95% ee).

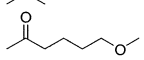
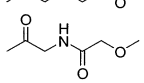
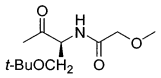
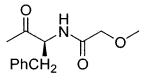
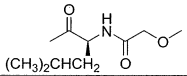
As palladium(0) could precipitate during the reaction, the recycling of the catalyst was troublesome. Removing the palladium with saturated potassium cyanide in DMSO facilitated the recycling, and the recycled catalyst was used 5 times without any loss of enantioselectivity.

8.2. Amphiphilic Catalysts for Asymmetric Allylic Substitution

Uozumi et al. reported the amphiphilic resin-supported MOP ligands **152a**−**f** for asymmetric allylic substitution.[230] The MOP moiety was connected to polystyrene-poly(ethylene glycol) resin through different spacers derived from carbamide (**152a)**, 5-hydroxyl pentanoic acid moiety (**152b**), or amino acid derivatives (**152c**−**152f**).

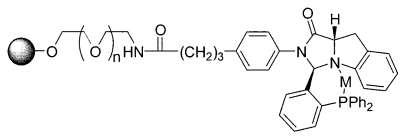


152

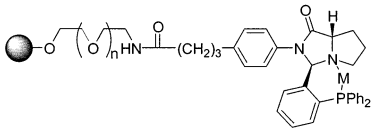
	Spacer
152a	
152b	
152c	
152d	
152e	
152f	

Treating these amphiphilic resin supported MOP ligands with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in dichloromethane at ambient temperature for 10 min gave the corresponding supported catalysts. Up to 84% ee was obtained by using these catalysts in the asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate with 3-methyl-2,4-pentanedione.

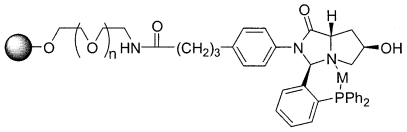
Several other amphiphilic resin-supported complexes **153**−**155** (M = PdCl(η^3-C_3H_5)) were also reported for asymmetric allylic reaction.[231] Being amphiphilic, these catalysts could be used in aqueous reactions, and the best ee of 98% was observed in the asymmetric allylic substitution of cyclohept-2-en-1-yl acetate.



153-Pd



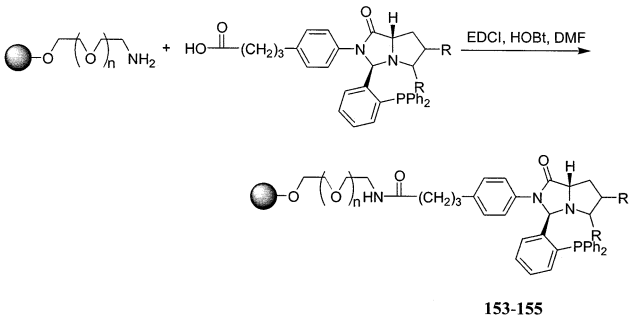
154-Pd



155-Pd

The supported chiral ligands were prepared by reacting the functionalized polystyrene-poly(ethylene glycol) resin (PS-PEG-NH_2) with the functionalized ligand monomer (Scheme 69):

Scheme 69



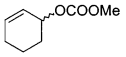
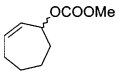
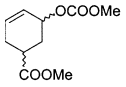
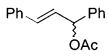
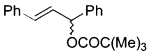
153-155

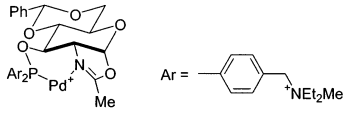
Mixing [PdCl(η^3-C_3H_5)]$_2$ with this polymer-supported ligand in toluene at ambient temperature for 10 min furnished the supported catalyst in quantitative yield. The study showed that when complex **153**−Pd was used as catalyst and dialkyl malonate as nucleophile, high stereoselectivity was achieved in water (Table 52).

The catalyst was separated from the reaction system by filtration. While the enantioselectivity remained essentially unchanged, the activity of the recovered catalyst decreased slightly.

Hashizume et al. reported an amphiphilic chiral ligand (**156**) derived from D-glucosamine.[232] The palladium complex of this ligand was used as catalyst in asymmetric allylic substitution in either aqueous or organic medium. The complex was made soluble by introducing quaternary ammonium into the phosphine phenyl ring. Glucosamine was first converted to an oxazoline derivative, and phosphinite formation provided the desired bidentate ligand **156** for asymmetric allylic substitution.

Table 52. Asymmetric Allylic Substitution Catalyzed by 153−Pd, 154−Pd, and 155−Pd

Entry	Substrate	Nucleophile	Catalyst	Yield (%)	ee (%)
1		$CH_2(COOMe)_2$	**153**-Pd	68	92 (*S*)
2	"	$CH_2(COOEt)_2$	**153**-Pd	67	92 (*S*)
3		$CH_2(COOMe)_2$	**153**-Pd	71	89 (*S*)
4	"	$CH_2(COOEt)_2$	**153**-Pd	78	89 (*S*)
5		$CH_2(COOMe)_2$	**153**-Pd	84	97 (*S*)
6	"	$CH_2(COOEt)_2$	**153**-Pd	94	98 (*S*)
7		$CH_2(COOMe)_2$	**153**-Pd	71	90 (*S*)
8	"	$CH_2(COOEt)_2$	**153**-Pd	80	90 (*S*)
9	"	"	**154**-Pd	55	23 (*S*)
10	"	"	**155**-Pd	44	32 (*S*)
11		$CH_2(COOMe)_2$	**153**-Pd	86	91 (*S*)
12		$CH_2(COOMe)_2$	**153**-Pd	50	94 (*S*)



156-Pd

Two-phase asymmetric allylic substitution of 1,3-diphenyl-3-acetoxypropyl-1-ene (Scheme 66) was carried out with this catalyst in an aqueous medium, giving the product in high yield and high ee (Table 53).

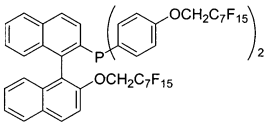
Table 53. Asymmetric Allylic Substitution of 1,3-Diphenyl-3-acetoxypropyl-1-ene Catalyzed by 156-Pd

Entry	Solvent	Base	NuH	**156**-Pd (mol%)	Time (h)	Yield (%)	ee (%)
1	MeCN	BSA+KOAc		1	1	95	92
2	$MeCN/H_2O$ (4:1)	K_2CO_3		5	48	0	-
3	$MeCN/H_2O$ (4:1)	K_2CO_3		5	3	85	83
4	$MeCN/H_2O$ (4:1)	K_2CO_3		5	12	66	77
5	$Toluene/H_2O$ (1:1)	K_2CO_3		5	24	51	80
6	$MeCN/H_2O$ (4:1)	K_2CO_3	$PhCH_2NH_2$	4	5	80	84
7	H_2O	K_2CO_3	$PhCH_2NH_2$	4	18	73	85

After the completion of the reaction, the catalyst present in the organic medium was extracted into an acidic aqueous phase in the form of ammonium salt, thus allowing a simple separation of the catalyst from the reaction system. The acidified catalyst in aqueous phase was neutralized and was re-extracted by an organic solvent. The recovered catalyst generally showed lower activity, while the enantioselectivity remained essentially unchanged.

8.3. Asymmetric Allylic Alkylation Using Light Fluorous Phosphine Ligand

Cavazzini et al. prepared a chiral "light fluorous" phosphine ligand **157**, and carried out the Pd-complex catalyzed allylic alkylation.[233]



157

This ligand showed a certain affinity for organic solvents due to the relatively low fluorine contents and its aromatic backbone. The asymmetric allylic alkylation was carried out in the presence of a palladium complex of this "light fluorous" ligand. Good to excellent enantioselectivities were observed (Scheme 66, Table 54). Extracting the reaction mixture with *n*-perfluorooctane allowed the complete recovery of the catalyst, but the reuse of this recycled fluorous catalyst was not successful.

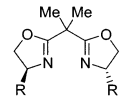
Table 54. 157−Pd Catalyzed Asymmetric Allylic Alkylations

entry	nucleophile	temp (°C)	time (h)	yield (%)	ee (%)	config
1	$CH_2(COOMe)_2$	25	36	99	81	*R*
2	$CH_2(COOMe)_2$	25	25	88	87	*R*
3	$CH_2(COOMe)_2$	0	48	95	99	*R*
4	$CH_2(COMe)_2$	25	1	100	85	*R*
5	$MeCH(COMe)_2$	25	48	7	76	*S*
6	$MeCH(COMe)_2$	50	48	69	44	*S*
7	$AcNHCH(COOEt)_2$	50	25	67	85	*S*

9. Asymmetric Cyclopropanation

Cyclopropane subunits have been found in many important natural and synthetic compounds, and the development of new catalysts for asymmetric cyclopropanation reactions is a subject of high interest. Among the reported chiral catalysts, the chiral bis(oxazoline)-Cu complexes are the most extensively used catalysts.

Fraile et al. exchanged the cationic copper complex of bis(oxazoline) **158** with several types of clay leading to supported bis(oxazoline) complexes for asymmetric cyclopropanation.[234] Stirring a suspension of the nonactivated clay in a solution of bis(oxazoline)-Cu^{II} complex in methanol or nitroethane gave the clay-catalysts ready for asymmetric cyclopropanation.

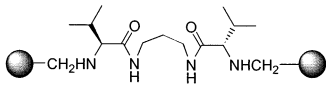


158 (R = *t*-Bu, Ph or CH_2Ph)

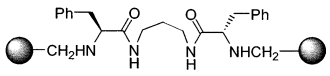
Different types of clay such as Laponite, bentonite, or K10 montmorillonite were tested as the catalyst support for the asymmetric cyclopropanation of styrene with ethyl diazoacetate. The results depended on the nature of the support, the chiral ligand, and the catalyst precursor and solvent used to carry out the ion exchange. Catalysts supported on Laponite gave better results over the others. The exchanged catalysts were generally recoverable with leaching of complex and a loss of catalytic activity and enantioselectivity.

Fraile et al. also immobilized the bis(oxazoline)-Cu complexes on Nafion and Nafion-silica nanocomposites.[235] Comparing to Laponite, Nafion was a better support due to its weaker electrostatic interaction with bis(oxazoline)-Cu complex. Nafion-silica nanocomposite gave the best results for asymmetric epoxidation of styrene, possibly due to the high surface area. In such cases, 58% ee was obtained for the trans-product and 47% ee for the cis-product, and the recovered catalyst showed essentially the same catalytic performance.

Adrián et al. reported the use of supported copper complexes **159** and **160** for asymmetric cyclopropanation reactions.[236] Amino acid derivatives were grafted on solid polystyrene-poly(divinylbenzene) support to give polymer-supported chiral amide moieties for asymmetric cyclopropanation reaction, but the catalyst was found to be ineffective.



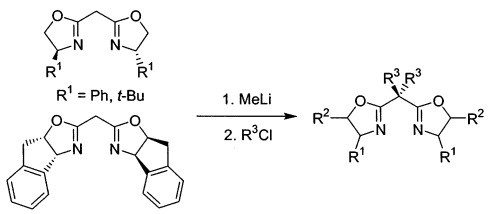
159



160

Burguete et al. connected bis(oxazoline) compounds onto polystyrene.[237] Double alkylation of the methylene bridge of the bis(oxazoline) produced the functionalized bis(oxazoline) compounds as a precursor of the supported catalyst (Scheme 70).

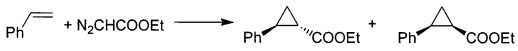
Scheme 70[a]



[a] R^3 = $PhCH_2$, *p*-CH_2=$CHPhCH_2$

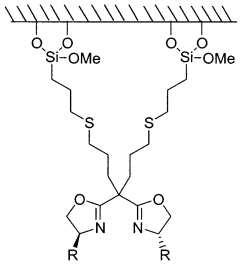
This precursor could either be self-polymerized or copolymerized with styrene to give several polymer-supported bis(oxazoline) compounds. The asymmetric cyclopropanation of styrene was carried out in the presence of these polymer-supported catalysts, giving the corresponding cyclopropane compounds as a mixture of cis- and trans-isomers (Scheme 71).

Scheme 71

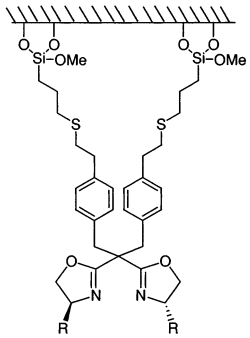


The study showed that the best results were obtained with the homopolymers. In homogeneous reaction, the cis-isomer was the dominant product, while the use of supported catalysts gave more trans-isomer. The authors concluded that the substitution in the methylene bridge position had a noticeable influence on the stereochemistry of the reaction. Being insoluble in the reaction system, this type of catalysts could be easily recovered, and the reuse of the catalysts did not show any loss of enantioselectivity.

Functionalized bis(oxazoline) ligands were also immobilized on silica via mercaptopropyl group to give chiral ligands **161** and **162**.[238]



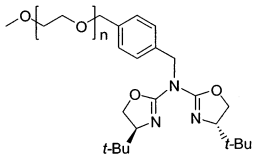
162 (R = Ph, $PhCH_2$, or *t*-Bu)



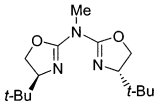
162 (R = Ph, $PhCH_2$, or *t*-Bu)

Asymmetric cyclopropanation in the presence of copper(II) complex of such ligand gave product in up to 65% ee.

Recently, Glos and Reiser introduced a new class of aza-bis(oxazoline) ligands for asymmetric cyclopropanation.[239] These ligands could be easily attached to poly(ethylene glycol) monomethyl ether (MeO−PEG, Mw 5000), leading to the immobilized aza-bis(oxazoline) **163** for homogeneous reactions. The active copper(I) catalyst was prepared in situ by mixing **163**, $Cu(OTf)_2$, and phenylhydrazine and was used for the asymmetric cyclopropanation of styrene and 1,1-diphenylethene with methyl diazoacetate. Products with high enantioselectivities and high yields were obtained. The asymmetric cyclopropanation of 1,1-diphenylethene gave a product with 90% ee at 78% yield, a result superior to that of using the corresponding unsupported catalyst **164**. Moreover, after the reaction, the polymer catalyst could be precipitated by adding diethyl ether. Without further addition of copper salt and phenyl hydrazine, such recovered catalyst was reused for at least nine cycles.



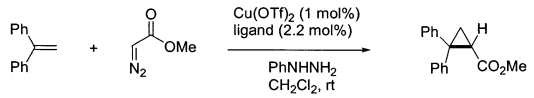
163



164

Annunziata et al. reported two types of poly(ethylene glycol)-supported chiral bis(oxazoline) **165a** and **165b** for the asymmetric C−C bond formation reactions.[240] Such catalysts were also effective for asymmetric cyclopropanations. The active catalyst generated in situ from **165b**, $Cu(OTf)_2$ and phenyl hydrazine in dry CH_2Cl_2 was used to catalyze the cyclopropanation of styrene with ethyl diazoacetate. The resulting cyclopropane adducts were obtained in 45% yield as a trans:cis (70:30) mixture with 87% ee of the major isomer. Cyclopropanation of 1,1-diphenylethylene under the same condition gave the corresponding product in 45% yield and 93% ee, a result comparable to that using structurally related, nonsupported ligands (Scheme 72).

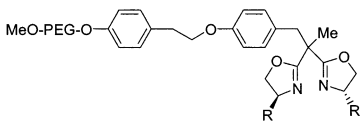
Scheme 72



165b: 93% ee

163: 90% ee, **164**: 83% ee

Insoluble ligand: 78% ee



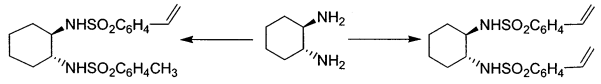
165a: R = Ph

165b: R = *t*-Bu

Halm et al. prepared polymer-supported disulfonamides **168** by reacting (*R*,*R*)-1,2-cyclohexanediamine

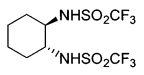
with styrenesulfonyl chloride (Scheme 73) followed

Scheme 73



166

by the copolymerization of the monomers thus obtained with styrene.[241]



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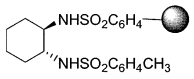
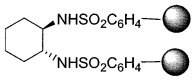


168a



168b

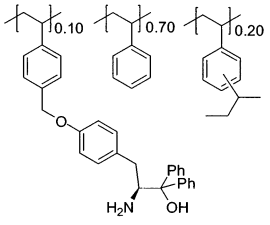
These catalysts were used in the asymmetric cyclopropanation of allyl alcohols with $ZnEt_2/CH_2I_2$. The supported sulfonamides gave cyclopropane with ee's comparable to those obtained using the corresponding homogeneous control ligand **167**.

10. Asymmetric Diels–Alder Reaction

10.1. Insoluble Supported Catalysts for Asymmetric Diels–Alder Reaction

Homogeneous Lewis acid-catalyzed asymmetric Diels–Alder reaction has been extensively studied, and various chiral Lewis acids containing aluminum, titanium, or boron and chiral ligands such as chiral amino alcohols, diols, *N*-sulfonylamino acids, bissulfonamide, or α-hydroxy acid as chiral ligands have been used as catalysts. Efforts were also made in heterogeneous diastereoselective Diels–Alder reactions, and several review articles well summarized such work.[242,243]

Itsuno et al. reported the preparation of polymer-supported chiral Lewis acids (**169**–**72**) and their application in Diels–Alder reactions.[244] The monomeric precursors were derived from readily available chiral sources such as amino acids or tartaric acid, and the copolymerization of these precursors with styrene produced the polymer-supported chiral ligands.



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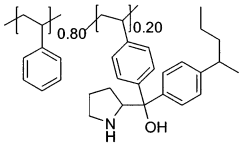

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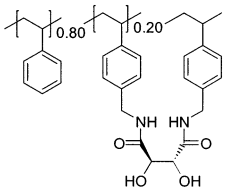

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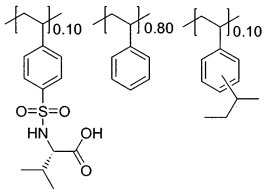


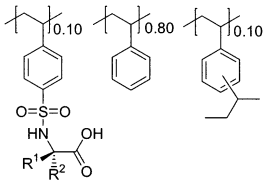
172

Upon reaction with borane, these polymer-supported chiral auxiliaries were converted to oxazaborolidines which were used to facilitate the Diels–Alder reaction between cyclopentadiene and methacrolein.

Among these four catalysts, the valine derivative proved to be the most regioselective. Higher than 99% diastereoselectivities (exo/endo > 99:1) were observed in all the examined cases, and the highest ee for the exo-isomer reached 65%.

To modify the Lewis acidity of the polymeric catalyst, bromoborane was used in place of borane.[245] While the oxazaborolidine prepared from chiral polymeric ligand and borane did not show high activity, the same reaction proceeded smoothly in the presence of the oxazaborolidine prepared from the chiral polymer and bromoborane, giving high regioselectivity (exo/endo = 96:4), and the highest ee was 54% (Scheme 74, Table 55).[246]

Other chiral amino acids were also attached to polystyrene, and up to 65% ee was observed in using valine derivative **173a** in the reaction.



173a: $R^1 = H$, $R^2 = i$-Pr

173b: $R^1 = H$, $R^2 = s$-Bu

173c: $R^1 = Ph$, $R^2 = H$

173d: $R^1 = H$, $R^2 = CH(OH)Me$

Higher loading of chiral catalyst in the polymer resulted in lower exo-selectivity and enantioselectivity, possibly due to the formation of highly associated structure. The addition of a donor solvent such as THF inhibited such an association and increased the

Scheme 74

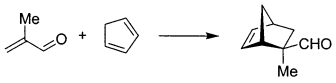


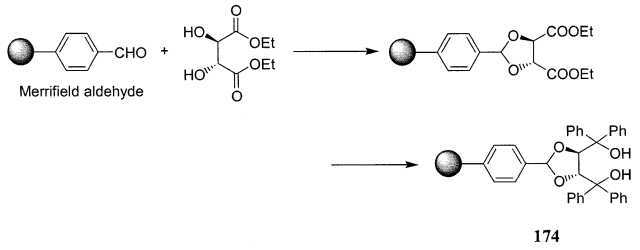
Table 55. Asymmetric Diels−Alder Reaction of Cyclopentadiene with Methacrolein Using Polymeric Catalysts

entry	polymer	borane	solvent	yield (%)	endo: exo (%)	ee (%) for exo
1	**169**	BH_2Br	CH_2Cl_2	96	8:92	16
2	**169**	BH_3	CH_2Cl_2			
3	**169**	BR_3	CH_2Cl_2	100	0	0
4	**170**	BH_2Br	CH_2Cl_2	98	4:96	25
5	**170**	BBr_3	CH_2Cl_2	97	5:95	54
6	**171**	BH_2Br	CH_2Cl_2	88	11:89	17
7	**172**	BH_2Br	CH_2Cl_2	99	<1:99	44
8	**172**	BH_3	CH_2Cl_2	95	<1:99	57
9	**172**	BH_3	CH_2Cl_2/THF	89	<1:99	65
10	**172**	BH_3	CH_2Cl_2/THF	93	<1:99	65

enantioselectivity. After the Diels−Alder reaction was completed, the polymeric catalyst was recovered by filtration, and the recovered polymer showed no loss in reactivity or selectivity.

Altava et al. reported a polymer-supported Ti-TADDOL complex (**174**−Ti) either from a Merrifield aldehyde or from a Merrifield polymer (Scheme 75).[247]

Scheme 75

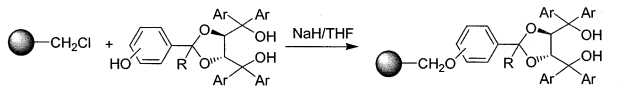


174

The polymeric TADDOL prepared with this method was contaminated by the presence of magnesium salts deposited in the inner cavity of the polymer beads and attempts to eliminate these contaminants resulted in the hydrolysis of the ketal group.

Another method involved a two-step synthesis, that is, the synthesis of functionalized TADDOL followed by its connection to the Merrifield resin via ether bond formation (Scheme 76):

Scheme 76



175a: R = H, Ar = Ph

175b: R = H, Ar = 3,5-Me_2-Ph

175c: R = H, Ar = 2-Naphthyl

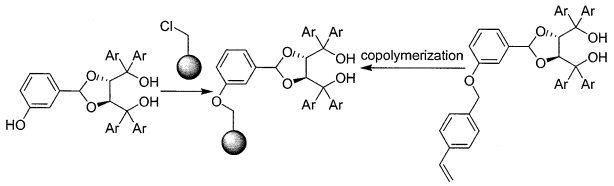
175d: R = H, Ar = *p*-MeOPh

175e: R = Me, Ar = *p*-MeOPh

All the catalysts showed good activity in the asymmetric Diels−Alder reaction of cyclopentadiene with 3-crotonoyl-1,3-oxazolidin-2-one. Unfortunately, the regioselectivity and stereoselectivity were lower than the corresponding homogeneous reactions.

Altava et al. prepared the supported TADDOL compounds **175** through the copolymerization of the TADDOL precursor with divinylbenzene (DVB/monomer = 60/40), and through a grafting method using a Merrifield type resin as support (Scheme 77).[248]

Scheme 77



175

A monolithic column with appropriate porosity was obtained via bulk polymerization of the precursor, and the desired morphology and properties were obtained using 40% of monomers and 60% of porogenic mixture (9 wt % of 1-dodecanol in toluene). The corresponding Ti-TADDOL moiety was obtained through the reaction of this monolithic TADDOL with $TiCl_2(O\textit{i}\text{-}Pr)_2$, and quantitative loading of Ti on the monolithic column was observed. The activity of such catalyst could be maintained for several months simply by keeping the monolithic column closed under an argon atmosphere.

While 2-naphthyl TADDOL catalyst (**175c**) produced via grafting or polymerization gave similar results, 3,5-xylyl TADDOL catalyst produced through different routes gave very different results, and the stereoselection was reversed (Scheme 78, R = Me,

Scheme 78

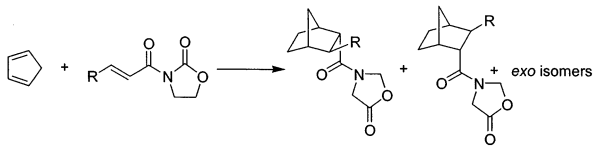


Table 56). The results were thought to be due to the presence or absence of π-stacking effect between one of the 3,5-xylyl groups with the acetal phenyl. For polymers produced through grafting, more flexible networks were used and the functionalization usually took place at the more accessible less cross-linked regions. Therefore, the π-stacking for homogeneous or grafted polymers existed to some extent, while for the monolithic catalyst, a very rigid, cross-linked matrix increased the steric crowding and made the π-stacking more difficult.

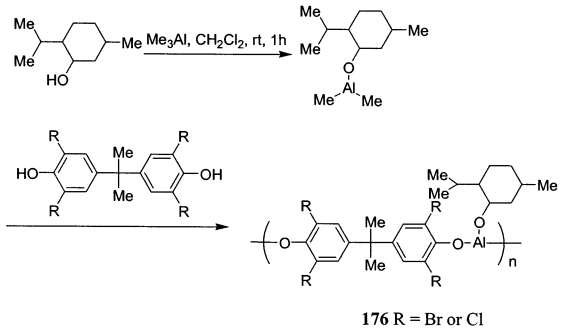
Nagasawa et al. reported a solid catalyst for asymmetric Diels−Alder reaction.[249] The chiral solid catalyst **176** was prepared from the reaction of (+)- or (−)-menthol with trimethylaluminum in CH_2Cl_2 followed by the reaction with tetrachlorobisphenol or tetrabromobisphenol (Scheme 79).

In the asymmetric Diels−Alder reaction of cyclopentadiene with methacrolein, increasing the amount of catalyst significantly improved the enantioselec-

Table 56. Asymmetric Cycloaddition Catalyzed by 175c Prepared through Different Immobilizaiton Method

entry	TADDOL	Ar	conversion (%)	endo:exo	ee (%) of endo
1	solution (monomer)	3,5-$(Me)_2C_6H_3$	100	71:29	38(2*R*,3*S*)
2	grafting	3,5-$(Me)_2C_6H_3$	99	71:29	17(2*R*,3*S*)
3	copolymerization	3,5-$(Me)_2C_6H_3$	100	80:20	18(2*S*,3*R*)
4	grafting	2-naphthyl	50	83:17	40(2*S*,3*R*)
5	copolymerization	2-naphthyl	96	79:21	40(2*S*,3*R*)

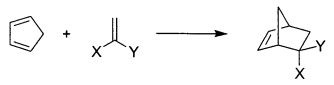
Scheme 79



176 R = Br or Cl

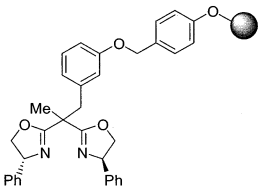
tivity, and 70% ee at 93% yield was obtained (R = Cl and (−)-menthol was used in the catalyst, Scheme 80).

Scheme 80



The recycled solid catalyst could be reused without loss in yield and enantioselectivity.

Hallman et al. tested the efficacy of the polymer-bound bis(oxazoline) **177** for asymmetric Diels−Alder reaction (Scheme 78, R = H).[229]



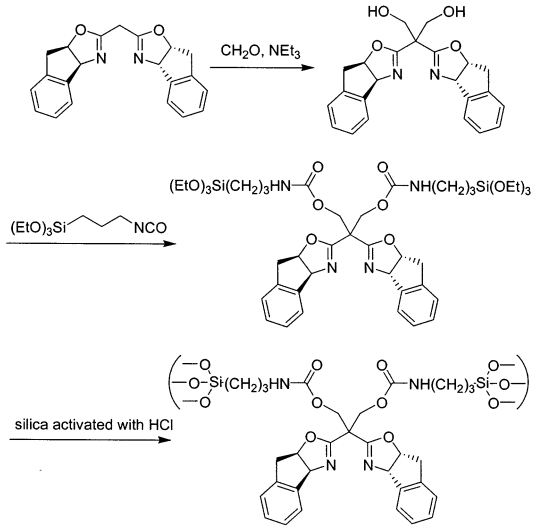
177

Treating 10 mol % of zinc iodide with 11 mol % of bound ligand and 20 mol % of $AgSbF_6$ in dichloromethane at ambient temperature gave the polymer bound catalyst in situ. The Diels−Alder reaction carried out at −78 °C proceeded very slowly, and only a trace of product was formed after 48 h. The supported catalyst induced no stereoselectivity at room temperature. It was also not possible to separate the salts from the supported catalyst via simple filtration (Scheme 80).

Rechavi et al. reported the grafting of bis(oxazoline) on silica (**178**).[250] The reaction of the functionalized bis(oxazoline) with 3-(isocyanatopropyl)triethoxysilane gave the bis(oxazoline) with spacer groups. The grafting was accomplished via the reaction of the modified bis(oxazoline) with activated silica (Scheme 81).

The catalyst was prepared by mixing the silica-grafted ligand with $Cu(OTf)_2$ in CH_2Cl_2 and the Diels−Alder reaction of 3-acryloyl-1,3-oxazolidin-2-

Scheme 81



178

one with freshly cracked cyclopentadiene using this catalyst gave a product in 65−73% ee for the first three reaction cycles. The enantioselectivity dropped on the fourth reaction cycle.

The decrease of enantioselectivity was attributed by the authors to the high water sensitivity of the catalyst and the highly hygroscopic nature of silica. Changing the catalyst precursor from $Cu(OTf)_2$ to $Cu(ClO_4)_2 \cdot 6H_2O$, which was not sensitive to water, improved the enantioselectivity of the reaction. Without taking special care, the catalyst was recycled 4 times without diminishing the enantioselectivity.

To overcome the problem of water sensitivity of the catalyst system, the authors protected the silanol groups of the silica support with trimethylsilyl groups. The modified supported catalyst gave improved results (92% ee at −78 °C, Table 57). In comparison,

Table 57. Diels-Alder Reaction of 3-Acryloyl-1,3-oxazolidin-2-one with Cyclopentadiene Catalyzed by Protected and Unprotected 178

entry	catalyst	temp (°C)	time (h)	endo (%)	ee (%)
1	grafted, unprotected	rt	1	85	65
2	grafted, protected	rt	1	86	81
3	grafted, protected	−78 °C	1	86	92

the homogeneous reaction using a similar catalyst gave 98% ee.

Using the cationic exchange method, Fraile et al. immobilized a series of bis(oxazoline) complexes of Cu(II), Mg(II), and Zn(II) on anionic solids Laponite clay and Nafion-silica nanocomposite.[251] The asymmetric Diels−Alder reaction of cyclopentadiene with (*E*)-3-butenoyl-1,3-oxazolidin-2-one was carried out

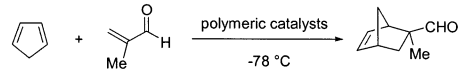
in the presence of these exchanged bis(oxazoline) complexes to give the product in 11% ee.

10.2. Soluble Macromolecules for Asymmetric Diels–Alder Reaction

Annunziata et al. also used their PEG-supported bisoxazolines (**165**) for the copper-catalyzed asymmetric Diels–Alder cycloaddition.[240] Using a catalyst prepared from **165b** and $Cu(OTf)_2$ in the enantioselective Diels–Alder cycloaddition of cyclopentadiene with *N*-acryloyloxazolidinone, up to 45% ee was obtained. The result was much inferior to that of using the corresponding monomeric catalysts (Scheme 78, R = H). The negative "polymer effect" was not clear at this stage.

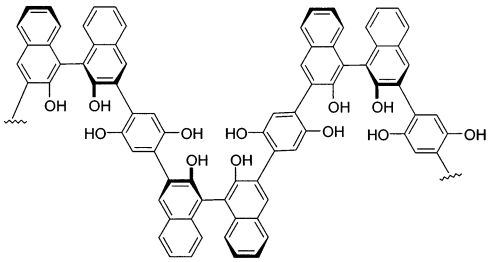
Pu and co-workers reported the use of rigid chiral polymer catalysts for asymmetric Diels–Alder reaction. Polymers **179** and **180** were loaded with $B(OMe)_3$ in the presence of 4 Å MS to generate the polymeric borate catalysts for the enantioselective Diels–Alder reaction of cyclopentadiene with methacrolein.[252] Up to 99/1 exo/endo ratio and 88% ee (exo) was observed using polymer **180** as chiral ligand (Scheme 82).

Scheme 82

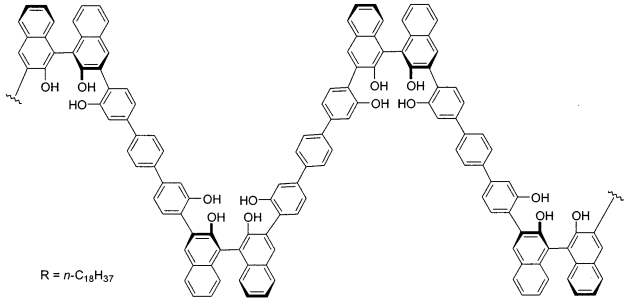


179: *exo*/*endo* = 94/6, 22% ee (*exo*)

180: *exo*/*endo* = 99/1, 88% ee (*exo*)



179

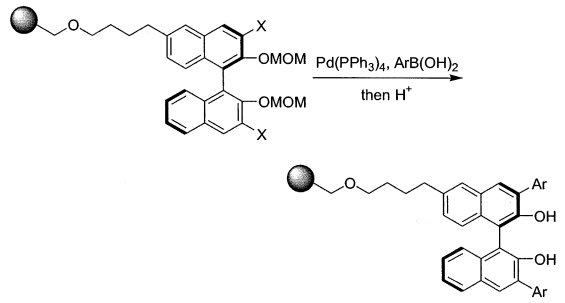


180

10.3. Immobilized Catalysts for Asymmetric Hetero-Diels–Alder Reaction

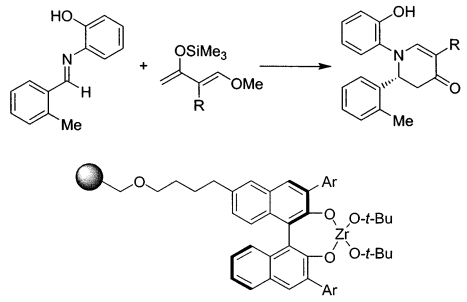
Kobayashi et al. reported a group of supported BINOLs for Zr catalyzed asymmetric aza-Diels–Alder reactions.[253] The immobilization started from the protection and functionalization of BINOL, followed by the reaction with Merrifield resin to connect the functionalized BINOL to the polymer (X = Cl or Br). Aryl groups were introduced to the binaphthyl rings via Suzuki coupling reaction (Scheme 83).

Scheme 83



Treating the supported BINOL with $Zr(Ot\text{-}Bu)_4$ furnished the supported catalyst **181** which was used for the asymmetric aza-Diels–Alder reaction of Danishefsky's diene (Scheme 84, R = H).

Scheme 84



181

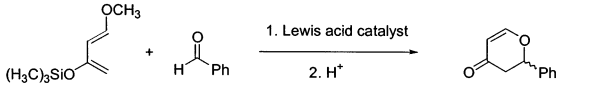
The product was obtained in 80% yield and up to 83% ee (Ar = 4-FPh). The ligand was recovered by filtration and was reused without loss of activity and selectivity (Scheme 84, R = Me, Table 58).

Table 58. Recycle of Catalyst 181

run	yield (%)	ee (%)
1	99	91
2	97	90
3	97	90

Schurig and co-workers reported a soluble polymer-supported chiral Lewis acid catalyst for hetero-Diels–Alder reactions.[254] A dimethylpolysiloxane chain and Lewis acid catalyst (1*R*)-(+)-oxovanadium(IV) bis[3-heptafluorobutanoylcamphorate] were covalently connected at the C-10 position of the camphor moiety, yielding the polymeric catalyst **182a** that was studied in the hetero-Diels–Alder reaction of *trans*-1-methoxyl-3-trimethylsilyloxy-1,3-butadiene with benzaldehyde (Scheme 85). Compared to the monomeric catalyst **183a**, polymer **182a** gave 2-phenyl-2,3-

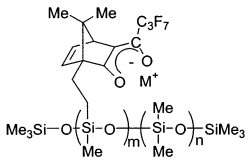
Scheme 85



182a: (+) 40.5 % ee; **182b**: (-) 43.0 % ee

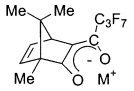
183a: (-) 59.0% ee; **183b**: (-) 42.0% ee

dihydro-4*H*-pyrone with similar enantiomeric excess, but in opposite configuration. The results demonstrated that the microenvironment of the active site of the catalyst was changed when the complex was connected to a polymeric chain. In contrast to the oxovanadium(IV) catalyst **182a**, the europium(III) catalyst **182b** gave the product with similar enantioselectivity and the same configuration as those obtained using the unsupported catalyst **183b**. These polymer catalysts were separated and reused in subsequent catalytic reactions with the same catalytic efficiency.



182a: M = $VO_{1/2}$

182b: M = $Eu_{1/3}$

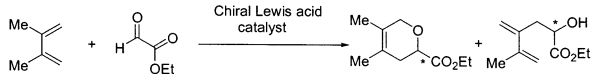


183a: M = $VO_{1/2}$

183b: M = $Eu_{1/3}$

Johannsen et al. disclosed chiral polybinaphthylaluminum complexes for enantioselective hetero-Diels−Alder reaction. Polymer **184** and **185** were loaded with Me_3Al or Me_2AlCl to generate the corresponding polymeric chiral aluminum catalysts in situ for the hetero-Diels−Alder reaction of 2,3-dimethyl-1,3-butadiene with ethyl glyoxylate (Scheme 86).[255] The soluble polymer catalyst derived from **185**

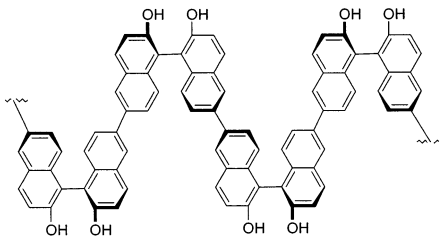
Scheme 86



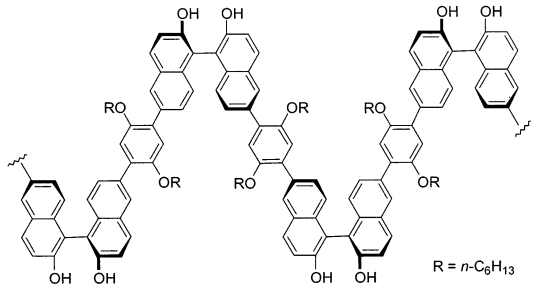
184: up to 46% ee, 2:1~3:1 (chemoselectivity)

185: up to 95% ee, 2:1~5:1 (chemoselectivity)

catalyzed the reaction under homogeneous condition with up to 95% ee, a result similar to that using the monomeric catalyst. Using the catalyst prepared from the insoluble chiral polymer **184** and Me_3Al, however, led to low enantioselectivity (up to 46% ee). In both cases, the ene reaction product was obtained as the byproduct. The polymeric **185**−AlMe catalyst was recovered by precipitation with methanol and was reused without significant loss in yield, chemoselectivity, and enantioselectivity.



184



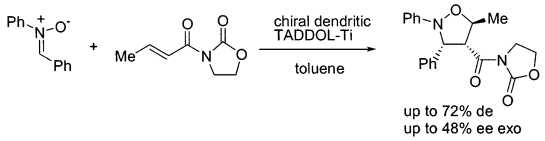
185

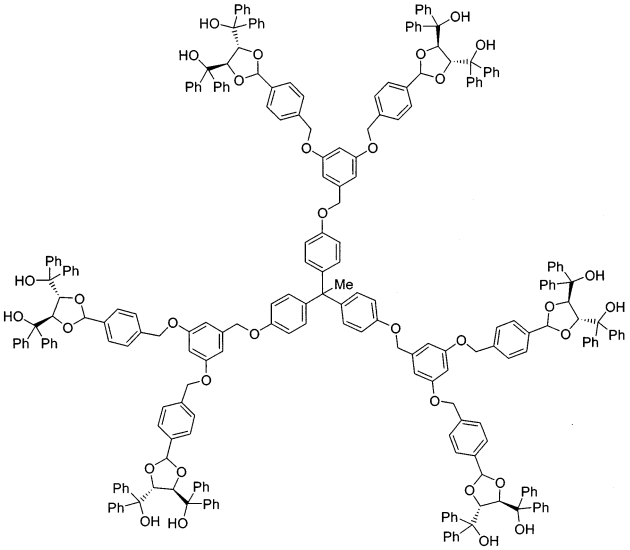
10.4. Immobilized Catalysts for Asymmetric 1,3-Diplolar Cycloaddition

Recently, the asymmetric 1,3-dipolar cycloadditions between nitrones and alkenes have been extensively studied.[256]

Seebach and co-workers reported the first example of 1,3-dipolar cycloaddition reaction of nitrones with electron-deficient alkenes catalyzed by chiral dendritic catalysts.[257] Dendrimers with chiral TADDOL moiety on the periphery (e.g., **186**) were loaded with $TiCl_2(O\textit{i}\text{-}Pr)_2$ to generate the active catalysts for 1,3-dipolar cycloaddition reaction of crotonoyl-oxazolidinone with nitrone (Scheme 87). The dendritic catalysts gave moderate selectivities (up to 72% de and 48% ee for the exo adduct), which were similar to those observed in using the corresponding parent monomeric catalysts.

Scheme 87

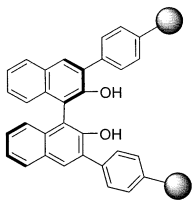




186

BINOL-polymer **187** from copolymerization of 3,3-distyryl-substituted BINOL with styrene was also tested for aluminum-mediated cycloaddition of diphenyl nitrone with alkyl vinyl ethers.[258] Products with an exo/endo ratio > 92:8 and enantioselectivity > 95% for the exo product were obtained. However, the poly-

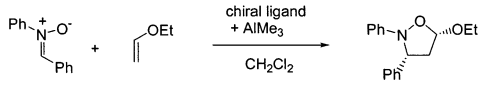
mer catalyst was not effective in further catalytic cycles.



187

Pu and co-workers reported a polymer-catalyzed highly diastereoselective and enantioselective 1,3-dipolar cycloaddition of electron-rich alkenes with nitrones.[259] The rigid and sterically regular binaphthyl polymers **185** and **77** were used as chiral ligands. The active aluminum catalyst generated in situ from **77** and $AlMe_3$ was used to promote the reaction between *N*-phenyl nitrones and vinyl ethers, up to 97% yield of product with high diastereoselectivity (up to 96% de) and enantioselectivity (up to 99% ee) was obtained (Scheme 88). The use of the 6,6′-linked

Scheme 88



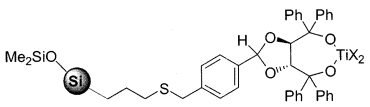
133: 96% de, 99% ee for *exo*

185: 50% de, 23% ee for *exo*

77: 96% de, 99% ee for *exo*

polymer (**185**) catalyst under the same conditions gave the isoxazolidine product with a 75:25 exo:endo ratio and a significant decrease in enantioselectivity (23% ee for the exo product). Polymeric catalyst **77**−AlMe showed similar selectivity and enantioselectivity and only slightly lower activity than those observed in using the monomeric catalysts **133**−AlMe. Both of these polymeric catalysts were superior to the BINOL-AlMe catalyst, which gave less than 5% ee. Moreover, the polymer catalyst could be quantitatively precipitated in methanol and could be successfully reused in at least four consecutive reactions. Both reaction yield and enantiomeric excess of the exo product showed only a slight decrease after the fourth recycle.

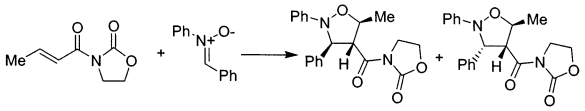
Heckel et al. reported the immobilization of TADDOL on CPG (**188**), the controlled-pore glass, and carried out the asymmetric [3+2] cycloaddition of diphenylnitrone to *N*-crotonoyl-1,3-oxazolidin-2-one.[260] The surface of the glass bead was first made hydrophobic and then was connected to a TADDOL moiety.



188

The conversion rate, diastereoselectivity, and enantioselectivity for the CPG-bound TADDOLates were similar to those in the homogeneous reactions (Scheme 89). Higher loading of TADDOL on CPG did not have a negative effect on the selectivity. The material could

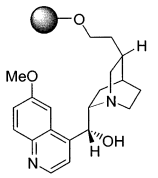
Scheme 89



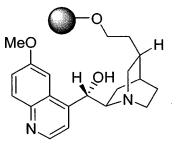
be washed with HCl/H_2O/acetone, dried, and reloaded with titanate, and the observed selectivities after 10 or even 20 catalytic runs were as good as they were in the beginning.

11. Asymmetric 1,4-Conjugate Addition

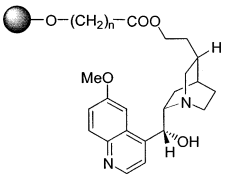
Alvarez et al. prepared supported cinchona alkaloids (**189a**−**189f**) for asymmetric 1,4-conjugate addition reactions.[261] A variety of Merrifield resin supported quinines and quinidines were prepared. Using different chemistry, the alkaloids could be attached to the resin either directly or through different spacers such as ω-hydroxy alkanoic acid or hydroxybenzoic acid.



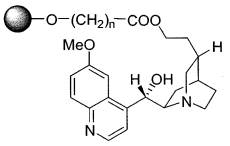
189a



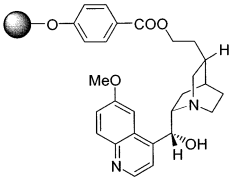
189b



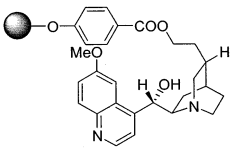
189c



189d n = 3, 5, 9



189e



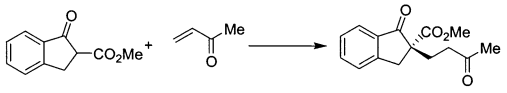
189f

Table 59. Asymmetric 1,4-Conjugate Addition Catalyzed by 190

entry	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%)	ee (%)
1	homogeneous, M = H (10)	THF	0	45	53	85
2	supported, M = H (20)	THF	rt	72	45	66
3	supported, M = H (50)	DME	rt	87	56	78
4	supported, M = ZnEt (20)	THF	rt	45	72	66

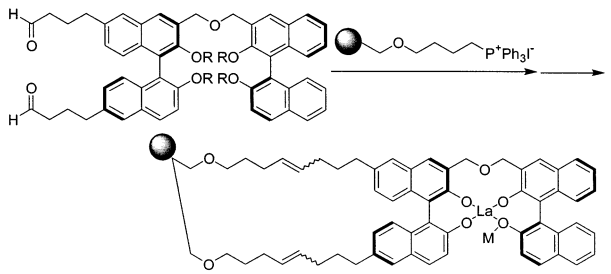
The asymmetric 1,4-conjugate addition was carried out in the presence of these supported alkaloids, and the best result was achieved when the quinine was linked to the resin through 6-hydroxyhexanoic acid. The product was obtained in 85% yield and 87% ee. The reactivity and selectivity were sensitive to the length of the spacer (Scheme 90).

Scheme 90



Matsunaga et al. reported the use of supported BINOL **190** for asymmetric 1,4-conjugate addition (Scheme 91).[262] The synthesis of a novel BINOL

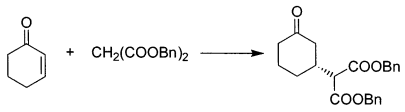
Scheme 91



190

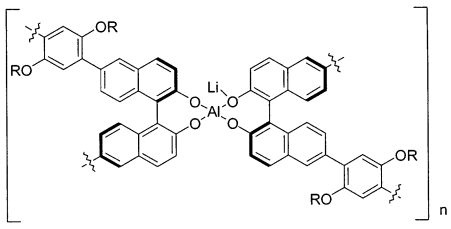
moiety in which two BINOL molecules were connected together followed by Wittig reaction using a reagent generated from Merrifield resin furnished the final chiral ligand. The results of using this ligand in asymmetric 1,4-conjugate addition reaction (Scheme 92) are summarized in Table 59.

Scheme 92



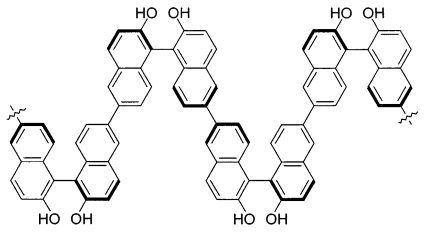
Using DME as solvent gave better enantioselectivity but resulted in a drop of activity of the supported catalyst possibly due to insufficient swelling of the polymer bead. Introducing Zn to the heterobimetallic system enhanced the activity of the catalyst.

Heterobimetallic multifunctional catalysts are a new type of catalysts, and can be used as highly efficient catalysts for asymmetric reactions.[263] Arai et al. prepared a variety of polymeric BINOL derivatives (**192**), and obtained the corresponding bimetallic catalysts **191** upon the reaction of these polymeric derivatives with lithium aluminum hydride.

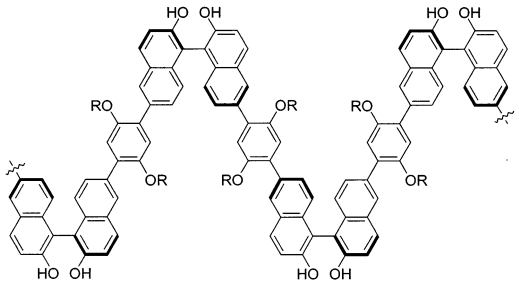


191

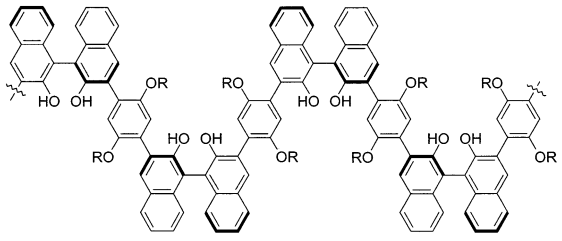
Three types of polymeric BINOLs were synthesized:



192a



192b



192c

Heterobimetallic compounds obtained through the reaction of polymeric BINOLs with $LiAlH_4$ gave the corresponding poly-ALB compounds (**191**). The asymmetric 1,4-conjugate addition (Scheme 76) using **192b** as catalyst was carried out at room temperature, giving product with up to 85% ee at 69% yield (**192b**). Adding butyllithium to the poly-ALB significantly enhanced the activity as well as the selectivity (93% ee at 78% yield). After the reaction was quenched with hydrochloric acid after 48 h of reaction, the

chiral catalyst was recovered in the form of polymeric BINOL. Both the activity and stereoselectivity decreased gradually in using the recycled catalyst. The activity and selectivity could be partially regained upon addition of basic agents such as butyllithium (run 6) (Table 60).

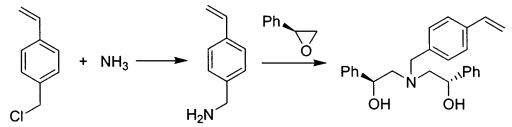
Table 60. Reuse of Immobilized Poly-ALB (192b)

run	yield (%)	ee (%)	recovery of catalyst (%)
1	78	93	quantitative
2	66	89	98
3	68	88	97
4	56	76	95
5	51	73	95
6[a]	83	85	93

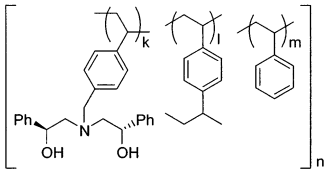
[a] The activity and selectivity were partially re-gained upon addition of basic agents such as butyllithium.

Sundararajan et al. reported the synthesis of a multifunctional amino alcohol ligand for heterobimetallic catalysis (Scheme 93).[264]

Scheme 93



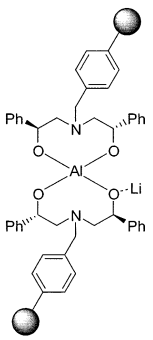
Copolymerization of this precursor with styrene/divinylbenzene produced the polymeric amino alcohols **193**. Different supported chiral ligands were obtained by varying the ratio of styrene/divinylbenzene in the copolymerization.



193a: k:l:m=1:1:4

193b: k:l:m = 1:1:8

Under an inert atmosphere, treating excess amount of the polymeric amino alcohol with lithium aluminum hydride gave the heterobimetallic catalyst **194**.

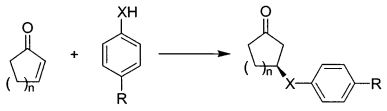


194

When ligand **193a** was used in the 1,4-conjugate addition of nitromethane to chalcone, up to 51% ee was obtained.

Polymeric alcohol **193b** was also tested in the 1,4-conjugate addition of thiols to cycloalkenones (Scheme 94). It was somewhat surprising that the supported

Scheme 94



catalyst generally gave better results than the homogeneous counterpart (Table 61).

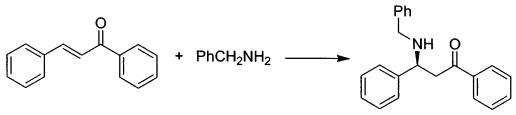
Table 61. Use of Ligand 193b in 1,4-Conjugate Addition of Thiols to Cycloalkenones[a]

entry	substrate (*n*)	R	X	yield (%)	ee (%)
1	1	H	S	95	41 (32)
2	2	H	S	90	57 (45)
3	1	Me	S	90	52 (26)
4	2	Me	S	90	33 (40)
5	1	H	CH_2S	85	52
6	2	H	CH_2S	90	76

[a] Data in parentheses refer to the results obtained using the unsupported catalyst.

The 1,4-conjugate addition of benzylamine to chalcone (Scheme 95) using LiAl-**193a** as catalyst gave

Scheme 95. The 1,4-Conjugate Addition of Benzylamine to Chalcone



81% ee. Adding neodymium isopropoxide resulted in some increase in yield but had no effect on enantioselectivity. The addition of molecular sieves had no influence on the rate and enantioselectivity of the reaction.

The recovered polymer could be reactivated upon addition of lithium aluminum hydride, and could be reused with decreased enantioselectivity. One disadvantage of these polymers was the easy breakage of the beads into powders on stirring and caused difficulty in recycling.

12. Asymmetric Aldol Reaction

The Aldol reaction is one of the most efficient methods for extending the carbon framework of an organic synthon. Since the discovery of the Lewis acid-catalyzed asymmetric aldol reaction with enolsilanes by Mukaiyama, numerous extensions of this type of reaction have been reported. Some efforts have also been devoted to the development of polymer-supported chiral ligands and catalysts.

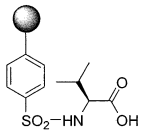
12.1. Insoluble Material Supported Catalysts for Asymmetric Aldol Reactions

Kiyooka et al. prepared the polymeric amino acid sulfonamides (**195a** and **195b**) from valine and glutamic acid and used them in oxazoborolidinone promoted Mukaiyama type aldol reaction.[265]

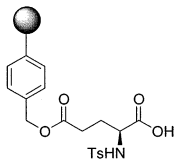
Table 62. Asymmetric Mukaiyama-type Aldol Reaction of Benzaldehyde with Silyl Ketene Acetal Catalyzed by 195a and 195b

entry	ligand (loading mmol/g)	solvent	temp (°C)	yield for **196** (%)	ee for **196** (%)	yield for **197** (%)	ee for **197** (%)
1	**195a** (0.69)	CH_2Cl_2	−78	68	63	13	26
2	**195a** (0.72)	CH_2Cl_2	−78	66	54	26	34
3	**195a** (0.92)	CH_2Cl_2	−78	56	44	40	30
4	**195a** (3.43)[a]	CH_2Cl_2	−78	25	18	75	10
5	Mono-val	CH_2Cl_2	−78	60	95	24	93
6	**195a** (0.44)	THF	−78	24	58		
7	**195a** (0.69)	THF	−78	28	76		
8	**195a** (0.77)	THF	−78	28	90		
9	Ts-val	THF	−78	72	90		
10	**195a** (0.77)	THF	−10	70	69		
11	**195a** (0.83)	CH_2Cl_2	−78	32	23	29	8
12	Ts-Glu	CH_2Cl_2	−78	70	74	25	70
13	**195b** (0.83)	THF	−78	10	52		
14	**195b** (0.83)	THF	−10	40	67		

[a] Homopolymer.



195a

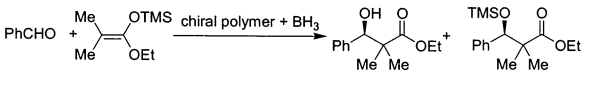


195b

The active promoter was prepared in situ via the reaction of **195a** or **195b** with borane. The aldol reactions of benzaldehyde with silyl ketene acetal were carried out in the presence of either supported chiral boranes or the corresponding monomeric species.

THF solvent enhanced the enantioselectivity dramatically, and 90% ee was observed (although with low yield) (Scheme 96, Table 62).

Scheme 96



196 **197**

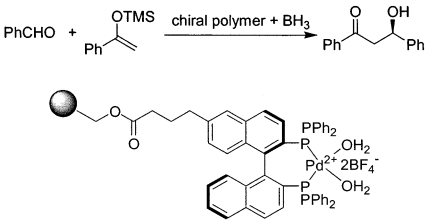
The recovered chiral copolymers were reused several times without reducing the enantioselectivity.

Fujii et al. reported the preparation of poly-BINAP−Pd complex and the application of such complex in Mukaiyama type aldol reaction and Mannich type reactions.[266]

Treating the commercially available polystyrene supported BINAP with $[Pd(MeCN)_4]^{2+}(BF_4^-)_2$ in wet acetone gave the polymeric BINAP−Pd complex **198** which was used in a Mukaiyama-aldol reaction (Scheme 97).

In comparison to the monomer BINAP−Pd complex which gave 74% ee and 65% yield, the polymer-supported palladium complex showed similar enantioselectivity (76% ee) but lower reactivity (35% yield). The yield was increased to 94% upon addition of 0.2 equivalent of water.

Scheme 97

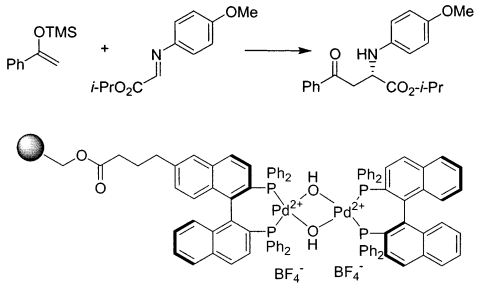


198

The addition of a small amount of water accelerated the reaction, but had no significant effect on the enantioselectivity. The catalyst was recovered by filtration, washed with THF and acetone, and dried under vacuum. The reuse of the recovered catalyst showed decreased reactivity and enantioselectivity.

The complex poly-BINAP−Pd−BINAP **199** was prepared and used in an asymmetric Mannich type reaction (Scheme 98).

Scheme 98



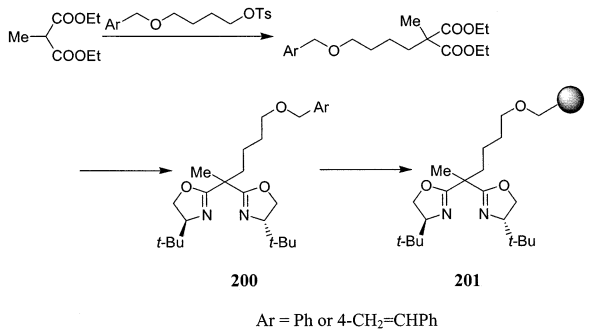
199

The reaction proceeded smoothly in DMF at room temperature to give the desired product in 95% yield and 81% ee. After the reaction, the resin was separated from the reaction mixture by filtration and washed with dry THF. Treating the recycled catalyst with a base regenerated the active catalyst which gave the product in 72% yield and 71% ee. The base treatment was essential for the activation of the catalyst. Catalyst without the base treatment gave only 25% ee in the same reaction.

Orlandi et al. carried out the Mukaiyama aldol reaction using polymer-supported bis(oxazoline)

ligands (**201**) prepared from the copolymerization of bis(oxazoline) monomer and styrene/divinylbenzene (Scheme 99).[267]

Scheme 99



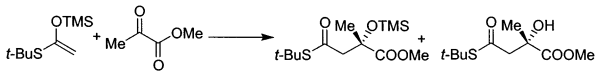
200 **201**

Ar = Ph or 4-CH_2=CHPh

The active catalyst was prepared in situ using Cu(OTf)$_2$ as catalyst precursor, 3 Å molecular sieves was added to remove the water in the reaction system.

Both the reaction using control bis(oxazoline) ligand **158** and that using the monomer ligand proceeded very fast, and were completed in 15 min, giving the desired product in 94% ee and 92% ee, respectively. In the presence of polymeric bis(oxazoline) ligand **201**, the reactions proceeded at a slower rate as compared to the homogeneous counterparts, but 90% yield could still be obtained in 1 h. Recycling of the polymeric bis(oxazoline) was quite simple. Both the polymeric ligand and molecular sieves were separated from the reaction mixture by simple filtration. The separated materials were washed with dichloromethane and dried in vacuo, and were reused in successive reaction. The same amount of Cu(OTf)$_2$ was added to the recovered materials to maintain the rate of the reaction. Without further addition of the precatalyst Cu(OTf)$_2$, the supported catalyst showed a slight increase of ee but lower activity (recycles 6 and 7) (Scheme 100, Table 63).

Scheme 100



202 **203**

Table 63. Reuse of Catalyst 201 in Mukaiyama-Type Aldol Reaction

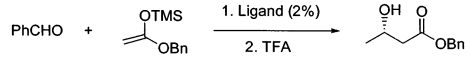
recycle	ligand (mol %)	time (min)	**202** + **203** (%)	(*S*)-**203** ee (%)
	158 (7.7)	15	100	94
	200b (monomer 7.7)	15	100	92
0	**201** (12.4)	60	90	90
1[a]	**201** (12.4)	60	85	91
2[a]	**201** (12.4)	60	86	89
3[a]	**201** (12.4)	60	81	88
4[a]	**201** (12.4)	60	52	91
5[a,b]	**201** (12.4)	60	96	89
6[b,c]	**201** (12.4)	120	97	93
7[b,c]	**201** (12.4)	240	97	93

[a] Supported ligand from the previous run, new Cu(OTf)$_2$ added. [b] Fresh molecular sieves were added. [c] Supported copper complex from the previous run without the addition of Cu(OTf)$_2$.

12.2. Macromolecules for Asymmetric Aldol Reaction

Mandoli et al. prepared the soluble branched polymer **204** via copolymerization of styrene, divinylbenzene, and the enantiomerically pure salicylaldimine ligand.[268] In the Ti(IV)-catalyzed Mukaiyama aldol reaction, the active Lewis acid catalyst prepared from **204** and Ti(O*i*-Pr)$_4$ afforded benzyl (*R*)-3-hydroxy-3-phenylpropanoate with 26% ee at 32% conversion in 36 h (Scheme 101). The enantioselectivity

Scheme 101

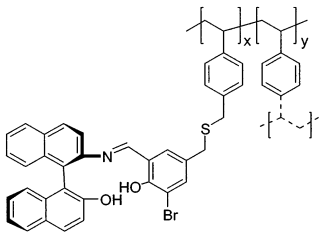


204: 26% ee

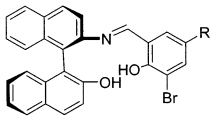
205a: 96% ee

205b: 53% ee

and activity were lower compared to those using the corresponding homogeneous counterparts **205a** and **205b** which gave 96% ee at over 95% conversion in 4 h and 53% ee at 48% conversion in 19 h, respectively. The relatively low efficiency observed in ligand **205b** might be due to the negative influence of the sulfur atom on the ligand.



204

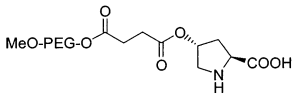


205a: R = *t*-Bu

205b: R = CH_2SCH_2Ph

The direct catalytic aldol reaction did not require a preconversion of a ketone or ester moiety into the more reactive species such as enol silyl ether or a ketene silyl acetal and thus simplified the operation. It was found recently that proline was an active chiral auxiliary which promoted the enantioselective aldol condensation of acetone or hydroxyacetone with various aldehydes. Cozzi and co-workers studied the immobilization of this chiral ligand.[269] The soluble poly(ethylene glycol) monomethyl ether (MeO−PEG) was used as a soluble support. (2*S*,4*S*)-4-hydroxyproline was attached on MeO−PEG (molecular weight 5000) through a succinate spacer. The resulting polymer catalyst **206** was used to catalyze the aldol condensation of acetone with benzaldehyde, 4-nitrobenzaldehyde, and 4-bromobenzaldehyde, affording the corresponding products in 59, 77, and 63% ee, respectively. These results were comparable to those using the corresponding homogeneous unsup-

ported catalyst. The reaction was extended to aliphatic aldehyde substrates to give products with high enantioselectivity. The polymer catalyst was also used to promote the condensation between hydroxyacetone and cyclohexane carboxaldehyde with high diastereoselectivity (anti/syn ratio > 20/1) and high enantioselectivity (>98% ee). The supported catalyst was recovered by precipitation and filtration, and could be reused two times with only marginal loss of activity and no loss of enantioselectivity.



206

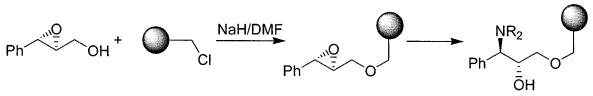
13. Asymmetric Carbonyl Alkylation

13.1. Insoluble Polymer-Supported Catalysts for Enantioselective Addition of Organozinc to Aldehydes

Since the first report of enantioselective addition of diethylzinc to benzaldehyde catalyzed by (*S*)-leucinol in 1984,[270] studies on homogeneous and heterogeneous catalytic enantioselective addition of organozinc compounds to aldehydes have attracted great attention.[271] Chiral β-amino alcohols are effective ligands in the enantioselective addition of diethylzinc to aldehydes. The attachment of these ligands to polymer supports offers the advantages of easy separation and reuse of the catalysts in successive reactions.

Vidal-Ferran et al. anchored some chiral amino alcohol ligands on polystyrene resins, and found them to be highly effective in the asymmetric nucleophilic addition of diethylzinc to carbonyl compounds.[272] Reacting a chiral epoxy alcohol with a Merrifield resin followed by ring opening of the chiral epoxide produced the supported chiral amino alcohol in good yield (Scheme 102).

Scheme 102[a]



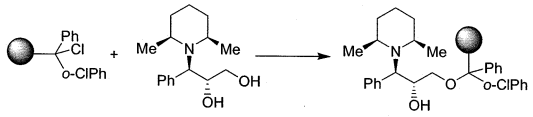
[a] NR_2 = piperidino, 4-methylpiperazin-1-yl, *cis*-2,6-dimethylpiperidino.

Varying the secondary amine or the Merrifield resin produced a variety of supported amino alcohols. The asymmetric nucleophilic addition of diethylzinc to benzaldehyde in the presence of these supported amino alcohols gave product α-phenylpropanol in up to 69% ee.

Barlos resin was also used as a support to take advantage of the fact that a sufficiently bulky substituent adjacent to amino alcohol induced higher enantioselectivity. This commercially available resin was also polystyrene-based, but used 2-chlorotrityl chloride instead of benzyl chloride as the site of anchoring. Reacting chiral amino alcohol with Barlos resin produced the polymeric chiral ligand (Scheme 103).

The enantioselective addition of diethylzinc to benzaldehyde in the presence of supported amino alcohol **207** gave the desired product in up to 94% ee (Table 64).

Scheme 103



207

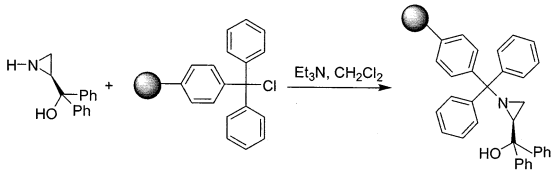
Table 64. Enantioselective Addition of Diethylzinc to Benzaldehyde in the Presence of 207

entry	mmol ligand/ g of resin	ligand (mol %)	temp (°C)	ee (%)
1	0.9	4	RT	79
2	1.1	5	RT	92
3	1.1	5	0	93
4	1.2	5	0	94

The efficacy of this supported amino alcohol was also examined in the enantioselective addition of diethylzinc to other aldehydes. Excellent conversion rates and enantioselectivity were observed in all cases.

ten Holte et al. attached an aziridinyl(diphenyl)-methanol on Barlos type resin (**208**) through *N*-trityl connection (Scheme 104).[273]

Scheme 104



208

The addition of diethylzinc to benzaldehyde in the presence of 10 mol % of polymer-supported catalyst gave the corresponding (*S*)-alcohol in high yield (92%) and high ee (96%). The solvent system affected both the activity and the enantioselectivity of the reaction, and the best solvent system proved to be a mixture of toluene and dichloromethane (1:1 v/v). Aliphatic aldehydes such as cyclohexane carboxaldehyde was also ethylated with excellent ee (97%) (Table 65).

Table 65. Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of 208

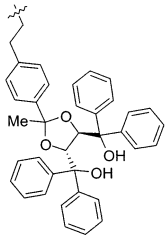
aldehyde	solvent (toluene/CH_2Cl_2)	yield (%)	ee (%)
PhCHO	100/0	88	93
PhCHO	72/25	91	96
PhCHO	50/50	92	96
PhCHO	0/100	72	91
p-ClPhCHO	50/50	88	96
p-MeOPhCHO	50/50	88	95
c-C_6H_{11}CHO	50/50	90	97
Isovaleraldehyde	50/50	77	81
Undecylic aldehyde	50/50	80	77

The recycled catalyst was found to be reasonably effective in the reaction: the second reaction cycle gave 95% ee, and the third run gave 94% ee for the α-phenylpropanol product.

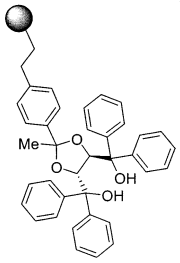
The architecture and properties of the polymeric support play an important role in the performance of the catalyst. The most common polymeric supports are cross-linked polystyrene beads prepared by suspension copolymerization of a ligand precursor with styrene and a proper cross-linker such as divinylbenzene. Alternatively, one can graft the chiral ligands to existing cross-linked polystyrenes such as Merrifield or Barlos resins.

The degree of cross-linking and the structure of the cross-linked polystyrene supports strongly influence the activity and selectivity of the catalyst. Practical drawbacks of cross-linked polystyrene supports are their low mechanical strength. Most of the polystyrene beads are not sufficiently stable to withstand stirring over a long period of time, and their breakdown to fine powder severely limits their handling during the separation and recycling process. Grafting functionalized ligands to functionalized resin often results in undesired side reactions and incomplete grafting. Therefore, the development of new approaches for facile grafting of chiral ligands on mechanically stable, inert polymeric supports is of special interest.

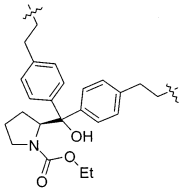
Degni et al. immobilized a variety of chiral ligands on chemically inert, mechanically stable polyethylene fibers by electron beam induced preirradiation grafting using styrene as a comonomer.[274] Several monomeric ligands, such as TADDOLs, and amino alcohols, have successfully been grafted.



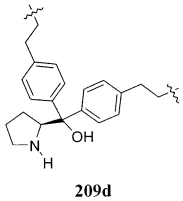
209a



209b (grafted through normal copolymerization)



209c



209d

The titanium tetraisopropoxide mediated enantioselective addition of diethylzinc to benzaldehyde, the fiber-supported TADDOL **209** gave results comparable to those by using regular copolymerized ligand. Reuse of this catalyst showed similar stereoselectivity with somewhat decreased activity in the third run (Table 66).

Table 66. Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of a Variety of Supported Chiral Ligands

entry	ligand	PhCHO (mmol/mL of toluene)	polymer (g)	catalyst loading (mmol/g of polymer)	conv (%)	ee (%)
1	TADDOL	0.13			100	98
2	**209a**	0.06	1.0	0.15	100	94
3	**209a** (run 2)	0.06	0.8	0.15	99	92
4	**209a** (run 3)	0.06	0.7	0.15	89	94
5	**209b**	0.15	0.25	0.6	100	94
6	**209b** (run 2)	0.15	0.23	0.6	90	94

Compared to the normal copolymerized ligand, the fibrous TADDOL generally showed a lower reaction rate, which might be attributed to different swelling characteristics, different ligand loading, and different accessibility of the active sites.

The supported proline type ligand **209d** was also tested and was found to give lower yield and lower enantioselectivity (24% ee). The supported ligand could be reused with the same levels of activity and stereoselectivity.

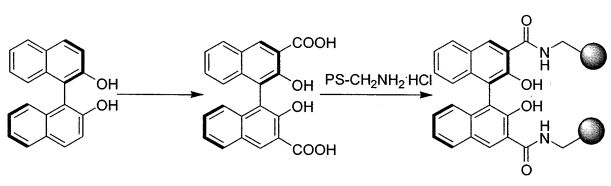
An even more dramatic decrease in enantioselectivity was observed in the borane reduction of acetophenone. Whereas the homogeneous reaction provided products with high enantioselectivity (>90% ee), the fibrous ligand showed almost no stereoselectivity.

The fiber-supported ethyl carbamate ligand was further tested in titanium-catalyzed addition of diethylzinc to benzaldehyde. Both the fibrous and the homogeneous ligands showed moderate enantioselectivities (24 and 48% ee, respectively).

Axial chiral ligand 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) and its derivatives have found extensive applications in asymmetric catalysis.[275] In 1997, Chan and Nakai independently reported the use of titanium complex of BINOL for the diethylzinc addition to aldehydes.[276]

Yang et al. reported the synthesis of a polymer-supported BINOL ligand **210** by connecting the functionalized BINOL to Merrifield type resin through amide bond and its application in titanium-catalyzed diethylzinc addition to aldehydes (Scheme 105).[277]

Scheme 105



210

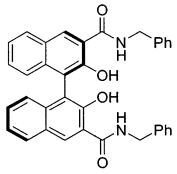
Under ordinary conditions, the enantioselective addition of diethylzinc using this catalyst proceeded with high yield and high ee. A total of 19 aromatic and aliphatic aldehydes were tested in the reaction, and up to 97% ee was observed (Table 67). This result

Table 67. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by 210[a]

entry	RCHO	time (h)	yield (%)	ee (%)
1	Ph	15	93 (93)	97 (63)
2	3-ClPh	24	89 (92)	94 (94)
3	Ph-CH=CH-	20	97 (89)	93 (36)
4	Piperyl	20	89 (87)	65 (36)

[a] The reactions were carried out at 0 °C; data in parentheses refer to the results using the control ligand.

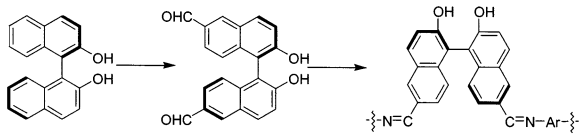
was better than that obtained from the corresponding homogeneous BINOL catalyzed reactions. The control ligand **211** generally showed lower stereoselectivity than the polymeric analogue possibly due to the lower rigidity of the free control.[278]



211

Dong et al. prepared the polymeric BINOLs **212** in which the BINOL moieties were connected through imine bonds.[279] The polymeric ligands were prepared by reacting a BINOL derivative bearing aldehyde carbonyl groups with *o*- or *p*-phenylenediamine furnished (Scheme 106).

Scheme 106

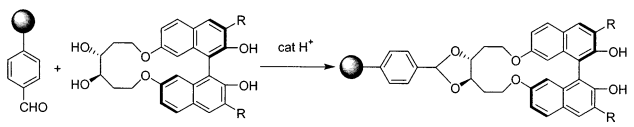


212 Ar = *o*- or *p*-phenylene

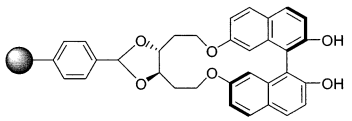
The enantioselective addition of diethylzinc to aromatic aldehydes was carried out using **212** as a chiral auxiliary. Moderate to good enantioselectivities (70−80% ee) were observed in most cases. Reuse of the recovered catalyst showed no loss of catalytic activity or enantioselectivity.

Lipshutz et al. described another type of polymer-supported BINOLs.[280] The BINOL and substituted BINOLs tethered at 7 and 7′ positions (i.e., cyclo-BINOL) were attached via the linkage to polystyrene resins using simple acetalization (Scheme 107). The

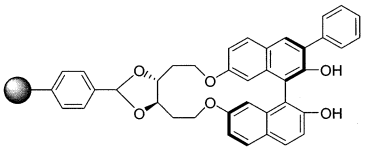
Scheme 107



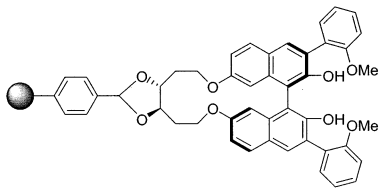
resulting PS-cyclo-BINOLs were allowed to react with Ti(O*i*-Pr)$_4$ to give the catalyst for the enantioselective addition of diethylzinc to aldehydes. For the reaction of benzaldehyde, polymer **213a** gave the product in 92% ee, 3-phenyl-substituted PS-cyclo-BINOL (**213b**) gave the product in over 92% yield and over 95% ee. Polymer **213c** showed high efficiency in the same reaction even in the absence of Ti(O*i*-Pr)$_4$, and the product α-phenylpropanol was obtained in 82 to 98% ee. Catalyst **213c** was recycled at least three times with the same results.



213a



213b



213c

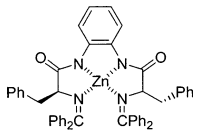
Halm et al. used their polymer-supported disulfonamides **168** in the titanium-catalyzed enantioselective addition of diethylzinc to aromatic aldehydes, and the results were comparable to those obtained from the corresponding homogeneous reactions (Table 68).[241]

Table 68. Enantioselective Addition of Diethylzinc to Aromatic Aldehydes Catalyzed by 166−168

entry	Ar in ArCHO	ligand	yield (%)	ee (%)
1	Ph	**167**	98	98
2	PhCH=CH	**167**	98	85−99
3	*p*-ClPh	**167**	95	98
4	Ph	**166**	96	98
5	PhCH=CH	**166**	98	70
6	*p*-ClPh	**166**	92	85
7	Ph	**168a**	82	98
8	PhCH=CH	**168a**	80	63
9	*p*-ClPh	**168a**	85	83
10	*p*-MeOPh	**168a**	75	70
11	*o*-ClPh	**168a**	85	56
12	*p*-MePh	**168a**	71	56
13	Ph	**168b**	73	93

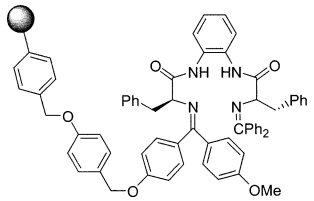
The reaction was sensitive to the choice of solvents. Reactions carried out in a better swelling solvent such as toluene gave better results, while reactions carried out in a poor swelling solvent such as hexane gave low yields.

Dangel et al. prepared several tetradentate ligands from amino acids such as valine, alanine, and phenylalanine.[281] Treating these ligands with diethylzinc produced the zinc complex **214** which was used in the enantioselective addition of diethylzinc to benzaldehyde to give a product in 86% ee.



214

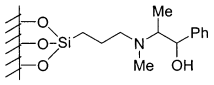
Other aldehydes were subjected to the same reaction, and excellent enantioselectivity was observed in all cases. Chiral ligands from alanine and valine were also effective for this type of reaction; similar enantioselectivities were observed. When the immobilized ligand **215** was used, the yields were only slightly diminished relative to the use of the unsupported catalyst, and the enantioselectivity was much lower. Reuse of this supported catalyst gave enhanced enantioselectivity, and the enantioselectivity was further improved at elevated temperature. This was thought to be due to the increased swelling and uncoiling of the polystyrene backbone at higher temperature.



215

13.2. Inorganic Material Supported Catalysts for Enantioselective Addition of Diethylzinc to Aldehydes

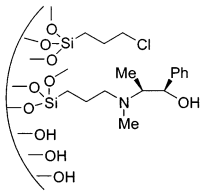
Laspéras et al. reported the addition of diethylzinc to benzaldehyde catalyzed by MCM-41 supported ephedrine **216** with low enantioselectivities (30−40% ee).[282] The low enantioselectivity was thought to be due to the interference by the free silanol groups present on the surface of the molecular sieve support. However, protecting the free silanol groups with ethyltrimethoxysilane before or after ephedrine grafting did not give too much difference in enantioselectivity.[283]



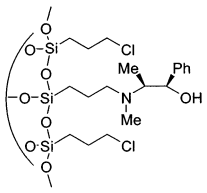
216

To improve the activity or stereoselectivity of the silica supported ligand, several issues were taken into consideration: (1) selection of a more effective ligand; (2) suppressing the undesired catalytic activity of the free silanol groups; and (3) selection of silica with appropriate pore size.[284]

To eliminate the influence of the MCM-41 surface on the enantioselectivity of the reaction, Abramson et al. prepared another supported catalysts using a different silanol protection method.[284] Two mesoporous aluminosilicates with different mean initial pore diameter were used as support. The surface was treated with 3-chloropropyltrimethoxysilane under either an anhydrous condition or sol−gel condition before the introduction of the chiral ligand.



217a, pore diameter 3.6, prepared anhydrously



217b, pore diameter 3.6, prepared through sol-gel method

218, pore diameter 8.3, prepared through sol-gel method

The protection of the molecular sieves seemed to enhance the stereoselectivity of the reaction and the addition of diethylzinc to benzaldehyde using these catalysts gave up to 64% ee (Table 69).

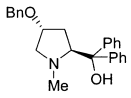
Table 69. Influence of Protection of the Solid Support Source on the Enantioselectivity of Diethylzinc Addition to Benzaldehyde

entry	catalyst	(−)-ephedrine loading (%)	rate constant k (h^{-1})	ee (%)
1	(−)-ephedrine	8.5	0.53	65
2	(−)-*N*-propyl-norephedrine	8.5	0.68	76
3	**217a**	13.6	0.17	47
4	**217b**	15.4	0.11	54
5	**218**	16.8	0.55	64

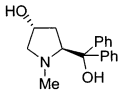
A comparison of the results from using **217a**, **217b**, and **218** as catalyst indicated that the enantioselectivity depended on the inner pore size as well as the method of preparation.

To eliminate the adverse effect of the silanol groups present on the silica surface, Bae et al. treated the catalyst with butyllithium prior to the reaction.[285]

Two types of mesoporous silica, MCM-41 and SBA-15, were chosen as catalyst supports, and prolinol (**219**) was chosen as the catalyst precursor.

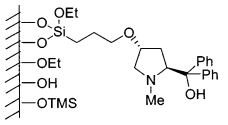


219a



219b

Chloropropyl linkers were grafted on the walls of mesoporous silica by treating the silica with $(EtO)_3SiCH_2CH_2CH_2Cl$ in refluxing toluene. Reacting this chloropropyl derivatized silica with the corresponding hydroxy-prolinol furnished the supported catalyst. Any remaining silanol groups might be capped with trimethylsilyl group.



a: amorphous silica, **b**: MCM-41, **c**: SBA-15.

220: supported prolinol without capping, **221:** supported prolinol with silanol hydroxyl groups capped.

The supported catalyst might be used directly in the reactions or alternatively might be pretreated with butyllithium before its application.

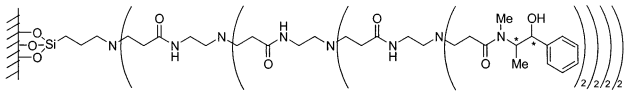
The experimental results revealed that the amorphous silica supported catalyst offered the lowest enantioselectivity, while the SBA-15 supported catalyst gave the best result. The catalyst pretreated with butyllithium always gave better results than the untreated catalyst (Table 70).

Table 70. Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by 219, 220, and 217[a]

entry	catalyst	yield (%)	ee (%)
1	**219a**	97	90
2	**220a**	89 (69)	16 (41)
3	**220b**	79 (84)	24 (26)
4	**220c**	95 (97)	29 (52)
5	**221a**	78 (74)	37 (43)
6	**221b**	77 (96)	36 (64)
7	**221c**	96 (98)	45 (75)

[a] Results obtained from BuLi treated catalysts are shown in parentheses.

Chung et al. reported a silica-supported chiral dendrimer **222** for enantioselective addition of diethylzinc to benzaldehyde; the product was obtained in 60% ee.[286]

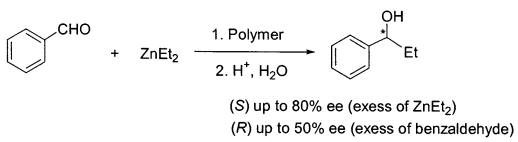


222

13.3. Soluble Macromolecules for Enantioselective Addition of Dialkylzinc to Aldehydes

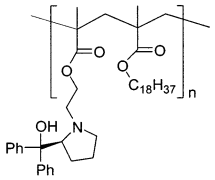
Kragl and co-workers reported the use of soluble polymer-supported α,α-diphenyl-L-prolinol for the addition of diethylzinc to aldehydes.[287] The polymer ligand **223** was a copolymer of octadecyl methacrylate and 2-hydroxyethyl methacrylate. The enantioselectivity in the diethylzinc addition to benzaldehyde strongly depended on the initial substrate/catalyst ratio. An excess of diethylzinc gave (*S*)-1-phenylpropanol in up to 80% ee, while an excess of benzaldehyde led to (*R*)-1-phenylpropanol in up to 50% ee (Scheme 108). This phenomenon was also observed in the study of other aldehydes in this reaction

Scheme 108



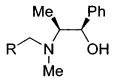
(*S*) up to 80% ee (exess of $ZnEt_2$)
(*R*) up to 50% ee (exess of benzaldehyde)

system. The polymeric ligand **223** was further used for the continuous addition of diethylzinc to benzaldehyde in a membrane reactor.[288] Coupling of the catalyst to the polymer prevented the loss of the catalyst from the reactor and provided a soluble feature under the reaction conditions. The total turnover number for **223** was raised from 50 to 500 by extending the duration of the continuous operation. However, the conversion rate and the enantioselectivity were not high enough for practical applications.



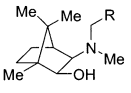
223

Hodge and co-workers reported the insoluble and soluble polymer-supported ephedrine or camphor derivatives for the enantioselective addition of diethylzinc to benzaldehyde with an aim at identifying the crucial factors for the success of using polymer-supported catalysts for such reactions. The ephedrine- or camphor-derived catalysts supported on cross-linked polystyrene and on soluble linear polystyrene (**224**, **225**) were prepared.[289] It was found that the most important factor was the interaction of the polymer matrix with the reaction solvent to allow the easy access of the reactant to the catalytic sites. Accordingly, the soluble polymer catalysts, which catalyzed the reaction in homogeneous manner, gave higher enantioselectivity. For the reaction of benzaldehyde with diethylzinc, using the best linear polystyrene-supported ephedrine derivatives gave 1-phenylpropanol in 83−88% ee, and the best linear polystyrene-supported camphor derivative gave the alcohol in up to 98% ee. When using the best cross-linked polystyrene-supported ephedrine or camphor derivatives, enantioselectivities in the range of 78−81% and 97%, respectively, were obtained.



224a: R = cross-linked polystyrene

224b: R = soluble linear polystyrene

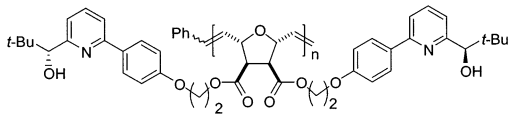


225a: R = cross-linked polystyrene

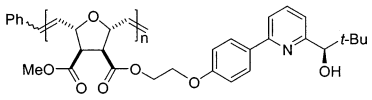
225b: R = soluble linear polystyrene

Recently, Bolm and co-workers applied a novel approach to polymeric multivalent chiral catalysts based on ring opening metathesis polymerization of strained bicyclic olefins.[290] The resulted polymer ligands **226** and **227**, which were soluble in organic solvents, were studied in the asymmetric diethylzinc addition to benzaldehyde. Enantioselectivities in the

range of 71−73% were obtained by using these polymer ligands. In comparison, the monomeric ligands gave higher catalytic activity and enantioselectivity (up to 87% ee).



226

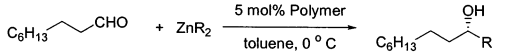


227

Pu and co-workers developed a class of main chain chiral polymers based on chiral binaphthyl for the enantioselective addition of organozinc reagents to aldehydes.[291] Such polymeric chiral catalysts with the catalytic sites organized in a sterically regular and inherently chiral polymer chain provided the potential for the systematic modification of the structure and function of the catalysts. The chiral major-groove polybinaphthyls **184** and **185** were studied in the asymmetric addition of diethylzinc to benzaldehyde.[292] The soluble polymer **185** showed higher asymmetric induction (40% ee) than the insoluble polymer **184** (13% ee). Polymer **185** was further used to catalyze the diethylzinc addition in the presence of Ti(O*i*-Pr)$_4$. The reactions were carried out at 0 °C for 5 h in toluene by using 20 mol % of **185** and 1.4 equiv of Ti(O*i*-Pr)$_4$. The reaction of benzaldehyde with diethylzinc gave 86% ee, and reaction of 1-naphthaldehyde gave 92% ee. The catalytic properties of this polymer were found to be similar to those of the corresponding BINOL catalyst.

To avoid the use of large amounts of Ti(O*i*-Pr)$_4$, the chiral minor-groove polybinaphthyl **132** was synthesized by using the 3,3′-positions of binaphthol monomer as connection points.[293] Polymer **132** was soluble in common organic solvents such as toluene or dichloromethane. The transformation of a broad range of aldehydes to chiral alcohols using this ligand gave excellent enantioselectivity (up to 94% ee) and complete chemical selectivity without the addition of Ti(O*i*-Pr)$_4$. The chiral polymer was easily separated from the reaction mixtures by simple precipitation, and the recycled polymer showed the same enantioselectivity. Compared with the monomeric ligand **133**, polymer **132** still gave lower enantioselectivity in the asymmetric addition of diethylzinc to aldehydes, especially to *ortho*-substituted benzaldehydes as well as aliphatic aldehydes. The observed differences in enantioselectivity might be due to the interference between the two neighboring centers. To overcome this problem, polymer **77** with the binaphthyl units separated by a much longer rigid phenylene linker was prepared.[145,294] This polymer exhibited excellent enantioselectivity (91−98% ee) in the reaction of diethylzinc or dimethylzinc with a broad range of aldehydes (Scheme 109), and the results were similar to those from using the corresponding monomeric catalyst.

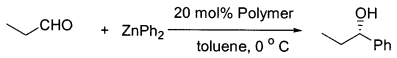
Scheme 109



R = Et: 85% conv., 97% ee
R = Me: 78% conv., 89% ee

Polymer **77** was also used to catalyze the addition of diphenylzinc to aldehydes. For example, the reaction of diphenylzinc to propionaldehyde in the presence of 20 mol % of **77** gave (*S*)-1-phenylpropanol with 82% yield at 85% ee. The result was similar to that from using the monomeric ligand **133** (90% yield and 87% ee, Scheme 110).[295] Moreover, after the

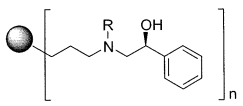
Scheme 110



85% ee, 82% yield

reaction, the polymer ligand could be easily recovered with the retention of the catalytic activity and selectivity.

Meijer reported the use of chiral dendritic amino alcohol ligand **228a** and **228b** in the asymmetric addition of diethylzinc to benzaldehyde.[296,297] Dendrimers **228** were prepared by reacting (*R*)-styrene oxide with amine-functionalized poly(propylene imine) dendrimers. These dendritic ligands were found to be effective in the asymmetric addition of diethylzinc to benzaldehyde with high yields of 1-phenylpropanol. In both cases, only moderate enantioselectivities were obtained for the small size catalysts and the ee's decreased with increasing generation number (for example, the ee decreased from 36% for the monofunctional catalyst to 7% for the fifth-generation dendrimer when using **228** as ligand). This negative "dendritic effect" was thought to be due to the dense packing of the chiral end groups at the periphery, leading to "frozen-in" conformations and resulting in increasing difficulty for all end groups to adopt their preferred conformation in the catalytic reaction.



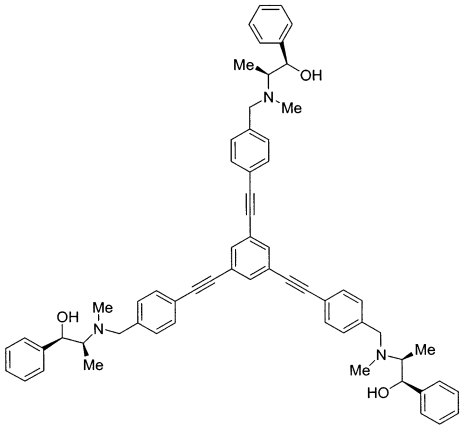
Poly(propylene imine) dendrimers

228a: R = H (n = 4, 8, 16, 32, 64)

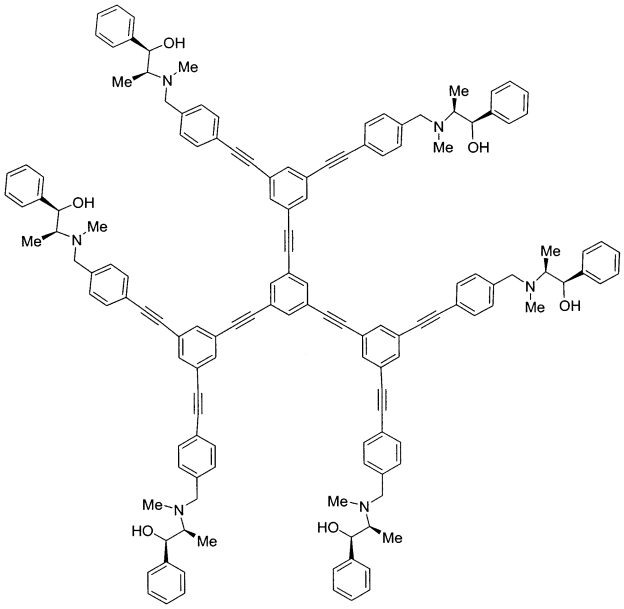
228b: R = Me (n = 4, 8, 16, 32, 64)

Recently, Soai and co-workers employed two chiral dendritic β-amino alcohol ligands **229a** and **229b** bearing rigid branches for dialkylzinc addition reactions.[298] It was found that both dendrimers showed high enantioselectivity (up to 86% ee) in the addition of dialkylzinc to aromatic aldehydes. Moreover, catalyst **229a** could be recovered and reused without any loss of enantioselectivity. The enantioselectivities were lower than those using the corresponding monomer (1*R*,2*S*)-*N*-benzylephedrine (e.g., 78% ee versus 92% ee in the addition of diethylzinc to benzaldehyde).

Bolm and co-workers disclosed another type of chiral dendritic pyridyl alcohol ligands for enantioselective addition of diethylzinc to aldehydes. Den-

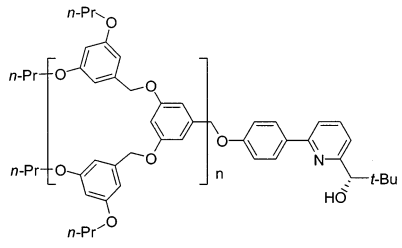


229a



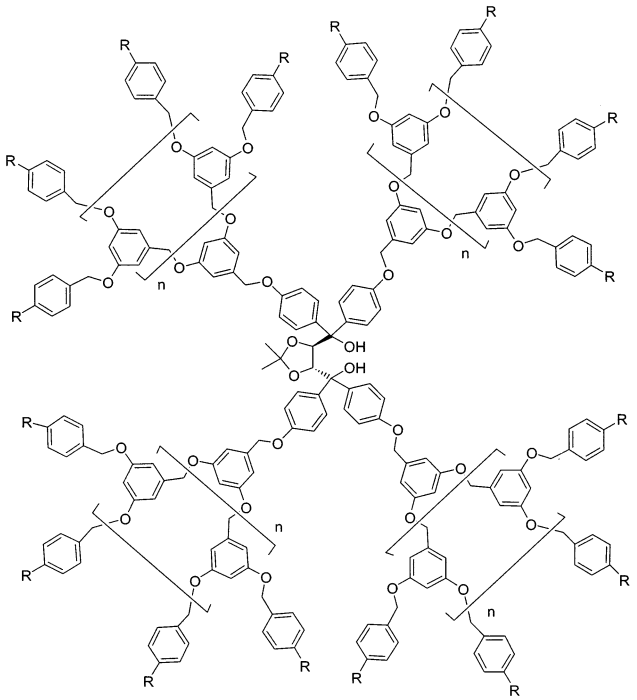
229b

drimer **230** was prepared by attaching a pyridyl alcohol to Fréchet-type dendrons at the focal point. Three dendritic generations gave similar enantioselectivity (up to 85%) in the addition of diethylzinc to benzaldehyde, a result slightly inferior to that of the corresponding parent catalyst (88% ee).[299]



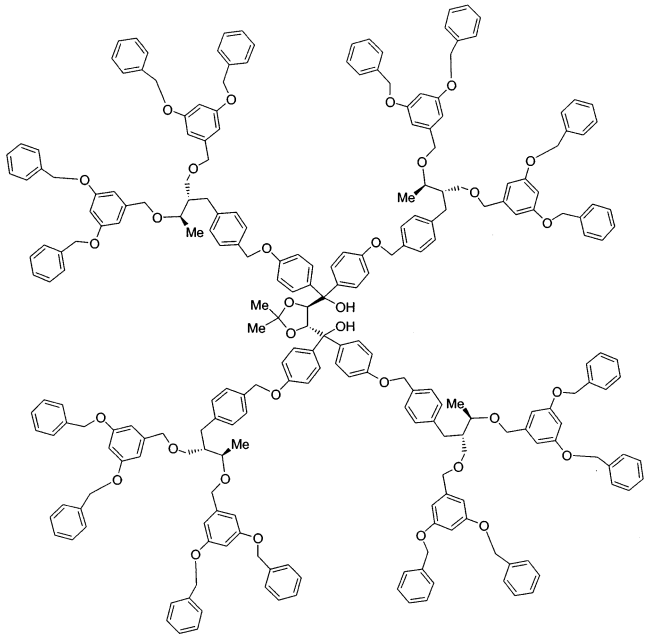
230 (n = 0-2)

Seebach and co-workers reported a series of dendritic TADDOL derivatives for the asymmetric organozinc addition. Initially, 3- and 6-branch (**186**) dendrimers were linked to TADDOL on the periphery.[300] These dendrimer ligands gave the same high enantioselectivity (up to 98% ee) in the Ti-catalyzed asymmetric addition of diethylzinc to benzaldehyde as the corresponding monomeric chiral catalyst. TADDOL was also attached to the core of the Fréchet-type dendrimers, giving compounds **231** and **233**.[301,302] These dendrimers were converted to Ti-TADDOLates and were employed as catalysts for the enantioselective addition of diethylzinc to benzaldehyde. The stereoselectivities and the reaction rates observed with these dendrimer catalysts up to the second generation were comparable with those of the corresponding homogeneous Ti-TADDOLate. The rates did not decrease up to the third generation but the enantioselectivity decreased slightly from generation 2 to 3 and 4. Both dendrimers **233a** and **233b** gave very similar enantioselectivities, although the configurations of the chiral centers in the dendritic wedges were inverted. These results demonstrated that the asymmetric induction was provided by the TADDOL core rather than the dendritic wedges. Similar results were observed by Brunner in the hydrogenation reaction by using the expanded diphosphine ligands. To increase the efficiency and the ease of separation of catalyst from the reaction mixture, Seebach and co-workers further synthesized dendritic TADDOL derivatives **232a** and **232b** with styryl groups on the periphery, which could be used as cross-linkers in polymers. Copolymerization of **232** with styrene gave the polymer-supported dendritic TADDOLs p-**232**.[303,304] The resulting polymerized dendrimers were loaded with Ti(O*i*-Pr)$_4$ to generate polymer beads incorporated with Ti-TADDOLates for the enantioselective diethylzinc addition to benzaldehyde. Compared to conventional insoluble polymer-supported Ti-TADDOLate catalysts, these heterogeneous dendritic catalysts gave much higher catalytic activities with the turnover rates close to that of the soluble analogues and more reactive than that of the corresponding dendrimer catalysts **232**−Ti. The polymer-supported dendritic TADDOLs could be

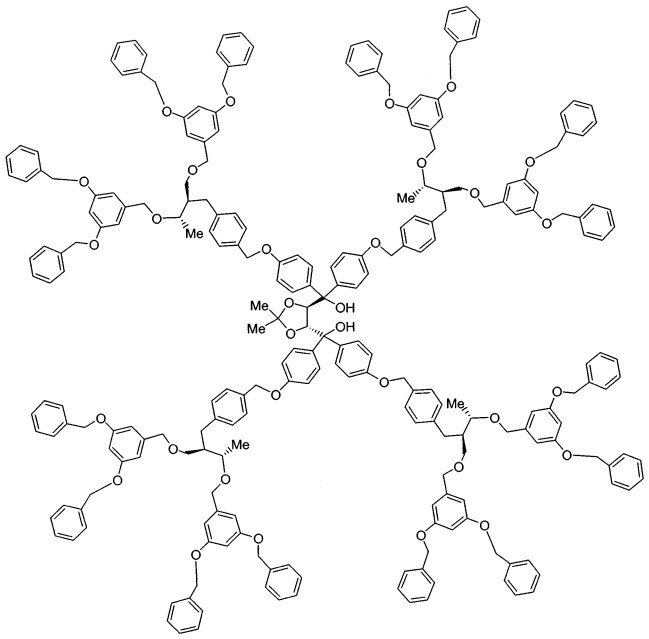


231 R = H (**231a**: n = 0, **231b**: n = 1, **231c**: n = 2, **231d**: n = 3)

232 R = CH=CH$_2$ (**232a**: n = 0, **232b**: n = 1)



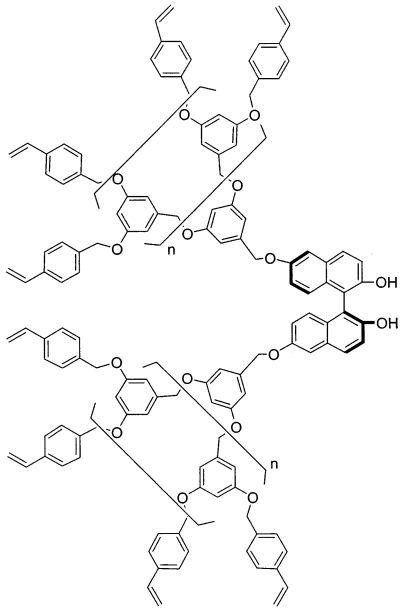
233a



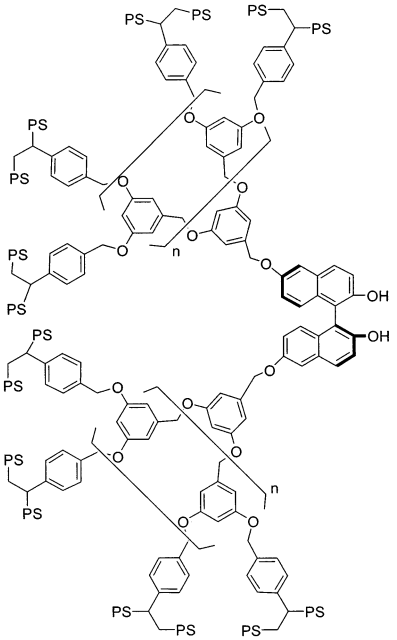
233b

recovered by simple phase separation and were reused for at least 20 runs with similar catalytic efficiency.

More recently, Seebach and co-workers reported a series of homogeneous and heterogeneous chiral dendritic BINOLs using an approach similar to that employed in the dendritic TADDOLs.[305] Chiral BINOL derivatives **234** with periphery styryl-substituted Fréchet-type wedges were synthesized and were used as cross-linkers for copolymerization with styrene, giving the polymer-supported dendrimer ligands **235**. The resulting free dendrimer and polymeric dendrimer BINOL ligands were loaded with $Ti(O\textit{i}\text{-}Pr)_4$ to afford catalytically active BINOLate-type catalysts for the enantioselective addition of diethylzinc to benzaldehyde. The enantioselectivities (up to 93%) and conversions obtained with the polymer-supported dendritic catalysts were in most cases identical to those obtained with the free dendritic BINOL or BINOL itself under homogeneous conditions. Moreover, the polymer-supported dendritic catalysts could be recovered by simple phase separation and reused in up to 20 consecutive catalytic runs, with the best polymer dendrimers showing no or only minor loss of enantioselectivity.



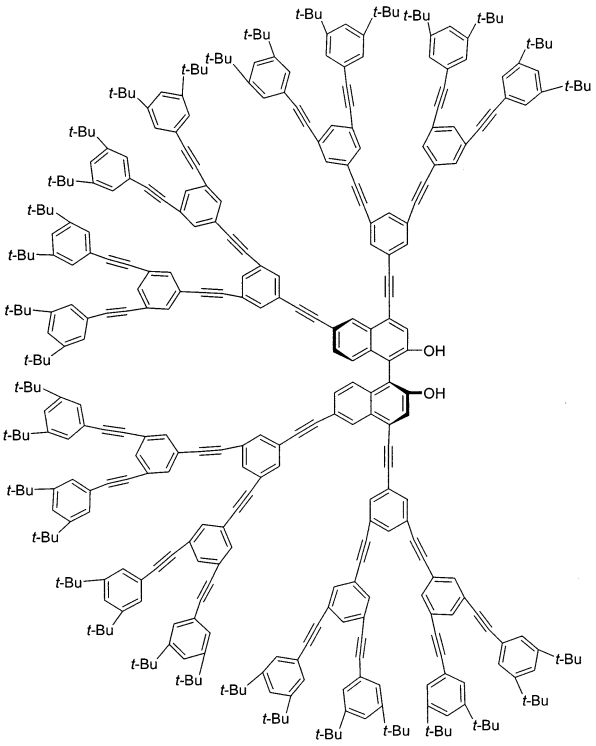
234 (**234a**: n = 0, **234b**: n = 1)



235 (**235a**: n = 0, **235b**: n = 1), PS = polystyrene

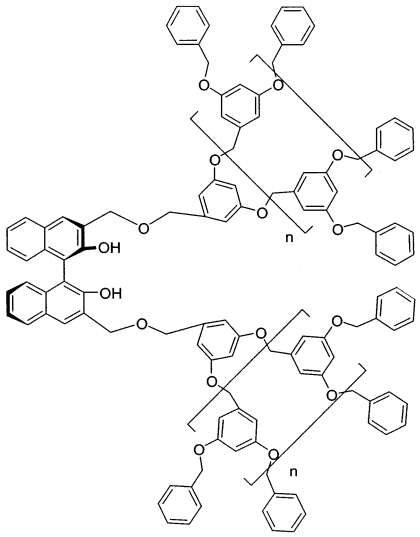
Pu and co-workers disclosed a rigid binaphthyl-based chiral dendrimer for the enantioselective addition of diethylzinc to benzaldehyde. Dendrimer **236** was synthesized by coupling phenylacetylene-based dendrons with an optically pure diacetate of 4,4′,6,6′-tetrabromo-1,1′-bi-2-naphthol.[306] This dendrimer showed much higher catalytic activity than BINOL

and also gave the opposite enantiomeric product in the absence of Ti(O*i*-Pr)$_4$. This "dendritic effect" was thought to be due to the formation of zinc complex from the reaction of BINOL with diethylzinc in aggregate form through intermolecular Zn−O−Zn bonds and thus greatly reduced the Lewis acidity of the active centers. Such aggregation was not formed in the case of dendrimer due to the large dendritic wedges. In the presence of Ti(O*i*-Pr)$_4$, the dendrimer was found highly enantioselective and up to 90% ee was obtained, which was very similar to that of BINOL in the presence of Ti(O*i*-Pr)$_4$. The dendritic BINOL could be easily recovered by precipitation with methanol.



236

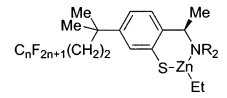
Fan et al. also reported dendritic BINOLs **237** for the enantioselective addition of diethylzinc to benzaldehyde.[307] Dendrimers were synthesized through the coupling of MOM-protected 3,3′-dihydroxymethylbinaphthol and Fréchet-type polyether dendritic benzyl bromide followed by the deprotection of MOM groups by TsOH. The proximity of the dendritic wedges to the catalytic center provided some different catalytic properties from BINOL. In the absence of Ti(O*i*-Pr)$_4$, the dendritic chiral BINOL ligands showed much higher catalytic activity and enantioselectivity than BINOL. For example, in the presence of 20 mol % of (*R*)-**237** in toluene, 97.5% conversion and 61.9% ee were observed in 7 h at 0 °C, and only 19% conversion and 4.6% ee were observed under the same conditions when BINOL was used. This "dendritic effect" was probably due to the existence of the oxygen atom on the linkage between the dendritic wedges and the binaphthyl backbone. The coordination of such oxygen atoms to zinc species might have afforded more active catalytic zinc species. In the presence of Ti(O*i*-Pr)$_4$, the dendritic chiral BINOL ligands showed lower enantioselectivity than those of the corresponding monomer and BINOL. The enantioselectivity decreased with increased generation in both cases. The advantage of the dendrimer over BINOL was its easy recovery and reuse in the subsequent catalytic cycles with the same catalytic efficiency.



237 (**237a**: n = 0; **237b**: n = 1; **237c**: n = 2)

13.4. Enantioselective Addition of Diethylzinc to Aldehydes in Fluorous Biphase System

Kleijin et al. reported the use of zinc complexes **238** containing fluoroalkyl substituted amino thiol as chiral catalysts in the enantioselective addition of diethylzinc to aldehydes.[308]

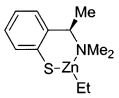


238a: R = Me, n = 6, **238b**: R = Me, n = 10, **238c**: R = -(CH$_2$)$_4$-, n = 10.

The study showed that the fluorinated chiral catalyst had higher activity and enantioselectivity than its parent catalyst **239** (Table 71).

Table 71. Enantioselective Addition of Diethylzinc to Benzaldehydes Catalyzed by 238 and 239

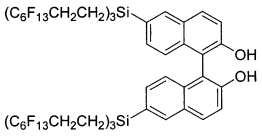
entry	catalyst	conversion (%) after 6 hours	ee (%)
1	**238a**	94	87
2	**238b**	90	82
3	**238c**	100	94
4	**239**	81	72



239

The reactions were also carried out in fluorous biphase system, and the catalysts were reused several times. The enantioselectivity decreased gradually.

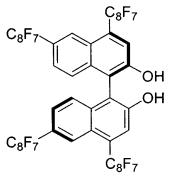
Nakamura et al. reported a fluorous binaphthol **240** for the enantioselective addition of diethylzinc to aromatic aldehydes in a fluorous biphase system.[309]



240

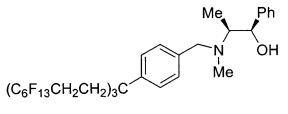
The catalyst was reused five times, and the product was obtained in over 80% yield and an average ee of 82%. In the recovery of the catalyst, about 10% of catalyst was found in the organic phase in every experiment, but the significant loss of enantioselectivity was not observed. Comparison experiments showed that reaction carried out in fluorous biphase system gave somewhat higher enantioselectivity than that carried out in toluene solution.

Tian et al. reported a multi-fluoroalkyl substituted BINOL **241** and the application of its fluorous biphase system in the enantioselective addition of diethylzinc to benzaldehyde.[310] The organic layer was withdrawn for analysis, and the product was obtained in 69% yield and 54% ee. The fluorocarbon layer was reused by adding titanium tetraisopropoxide and up to nine cycles of the reaction were performed without significant loss of catalyst activity or enantioselectivity. Other substituted benzaldehydes gave similar results.

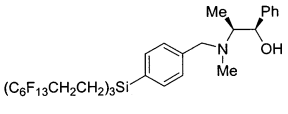


241

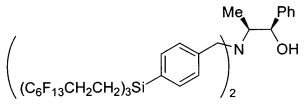
Substituted β-amino alcohols **242a**−**242c** were also tested in the enantioselective addition of diethylzinc to aldehydes.[311]



242a



242b



242c

Benzaldehyde was first chosen as a model substrate. The reactions were carried out in organic solvents at either 0 °C or ambient temperature to give moderate to good enantioselectivities (Table 72).

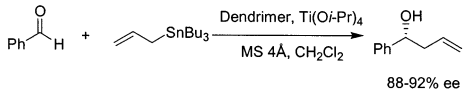
Table 72. Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by 242a−242c

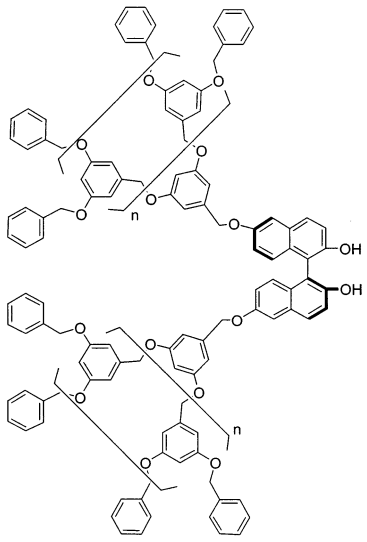
entry	catalyst	solvent	temp (°C)	time (h)	yield (%)	ee (%)
1	**242a**	hexane	rt	18	93	75
2	**242a**	toluene/hexane (2:1)	rt	20	90	83
3	**242a**	toluene	rt	20	87	83
4	**242a**	hexane	0	20	78	78
5	**242a**	toluene/hexane (2:1)	0	20	62	85
6	**242b**	toluene/hexane (2:1)	rt	20	91	83
7	**242c**	BTF/hexane (2:1)	rt	20	54	25

The reactions carried out at a low reaction temperature gave higher enantioselectivity but a lower rate of reaction. The chiral ligand was recovered via filtration through fluorous reverse phase silica gel. Successive washing of the silica with acetonitrile and FC-72 gave over 97% of recovered ligand that gave essentially the same activity and enantioselectivity in subsequent reactions. Other substituted benzaldehydes were also tested for the same reaction with ee's ranging from 70 to 84%.

Yoshida and co-workers prepared chiral dendritic BINOLs via the reaction of 6,6′-dihydroxy-2,2′-binaphthol with Fréchet-type dendritic benzyl bromides.[312] The dendrimers **243** were loaded with Ti(O*i*-Pr)$_4$ to afford BINOLate-type catalysts for the enantioselective addition of allyltributylstannane to benzaldehyde (Scheme 111). High enantioselectivity (up to 92% ee) was obtained, and the result was comparable to that of using BINOL as ligand.

Scheme 111

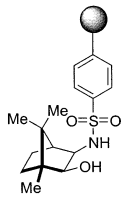




243 (n = 0-3)

The enantioselective addition of allylborane reagents to imines or aldehydes gave homoallyl alcohols or homoallylamines in good yields and enantiomeric excesses.[313]

Several cross-linked polymer-supported chiral *N*-sulfonamide alcohols were prepared via suspension polymerization of the corresponding monomers.



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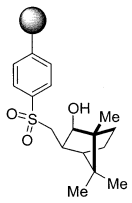

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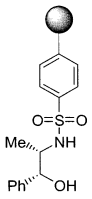

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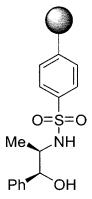
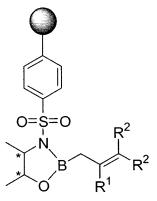


247

Treating these supported *N*-sulfonamides with triallylborane gave the polymeric chiral allylboron reagent (**244**-B − **247**-B) which could undergo nucleophilic addition to imines or aldehydes.



244-B – **247**-B: a: $R^1 = R^2 = H$, b: $R^1 = Me$, $R^2 = H$, c: $R^1 = H$, $R^2 = Me$.

The asymmetric allylation of benzaldehyde using this method gave 1-phenylbut-3-en-1-ol in high yield (Scheme 112). Similar to the homogeneous system, this reaction was temperature dependent, and higher ee's were obtained at lower reaction temperature. The supported boron reagents showed stereoselectivity similar to the homogeneous counterpart. The polymer was separated from the reaction mixture by filtration, and the recovered polymer was reused with similar reactivity and enantioselectivity (Table 73).

Scheme 112

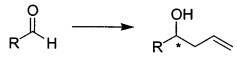


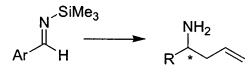
Table 73. Asymmetric Allylation of Aldehydes Using 239−242 as Allylboron Reagents[a]

entry	polymer	aldehyde	solvent	temp (°C)	yield (%)	ee (%)
1	**246b**	PhCHO	ether	−78	93	75 (73)
2	**247**	PhCHO	ether	−78	93	75
3	**244**	PhCHO	THF	−40	91	65
4	**244**	PhCHO	THF	−78	94	78 (74)
5	**244**	PhCHO	THF	−100	96	88
6	**244**	PhCHO	ether	−78	92 (89)	74 (71)
7	**244**	PhCHO	toluene	−78	91	72
8	**244**	PhCHO	ether	−78	93 (90)	85 (81)
9	**244** (recycled)	PhCHO	ether	−78	93	85
10	**244**	MeCHO	ether	−78	51	92
11	**239**	*t*-BuCHO	ether	−78	84	84

[a] Data in parentheses refer to the results from the homogeneous catalyst system.

The allylation of *N*-silylimine using these polymeric boron reagents gave the corresponding homoallylic amines in similar yields and enantioselectivities as those from the homogeneous system. For example, the allylation of *N*-silyl phenylimine in ether at −100 °C gave the corresponding homoallylamine 92% yield and 94% ee, a result comparable to those from the homogeneous reaction (80% yield and 96% ee) (Scheme 113).

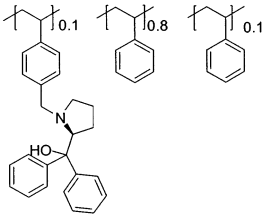
Scheme 113[a]



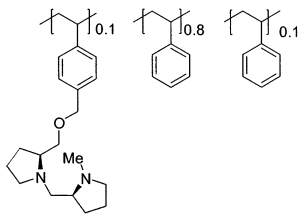
[a] a: Ar = Ph, b: Ar = *p*-ClPh, c: Ar = *p*-MeOPh, d: Ar = *p*-MePh.

Other allyl-boron reagents also gave excellent yields in the allylation of *N*-silylamines. For example, polymeric methallylboron gave the corresponding homoallylamine in 90% yield and 95% ee, which is similar to that from the homogeneous reaction (94% yield and 96% ee).

Itsuno et al. reported the enantioselective addition of butyllithium to imine compounds in the presence of polystyrene supported chiral ligands **248** or **249** prepared via the copolymerization of functionalized ligand monomer with styrene/divinylbenzene.[314]



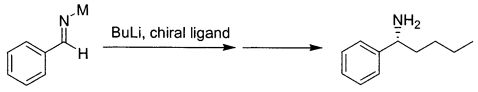
248



249

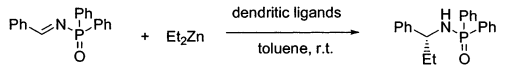
In the presence of a homogeneous catalyst such as (−)-sparteine, the reaction at −78 °C gave up to 74% ee, while the reaction using the supported ligands gave up to 44% ee (Scheme 114).

Scheme 114



Soai and co-workers reported the preparation of chiral dendritic amino alcohol ligands by attaching an ephedrine derivative onto the periphery of PAMAM. Dendrimers **250** were used as chiral ligands for the enantioselective addition of diethylzinc to *N*-(diphenylphosphinyl)imines (Scheme 115).[315] Enantio-

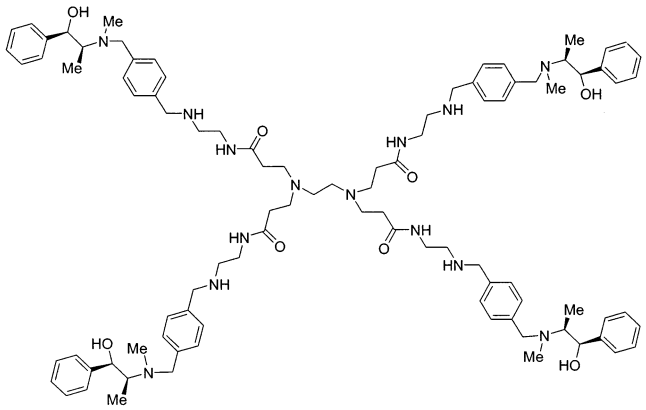
Scheme 115



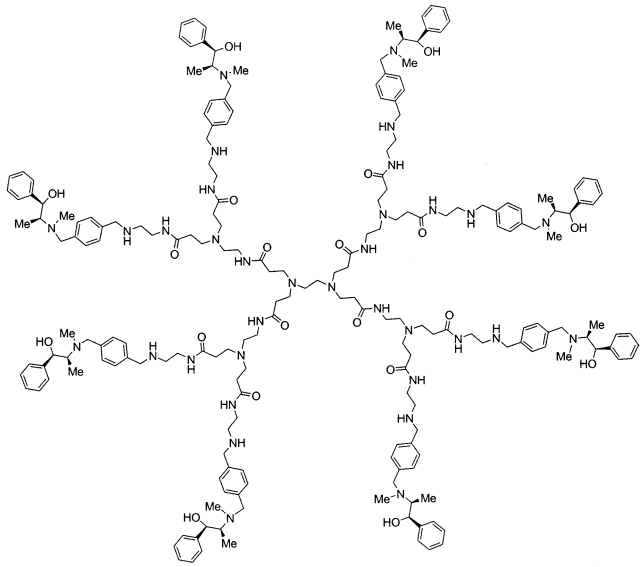
250a: 40% ee; **250b**: 30% ee;

229a: 89% ee; **229b**: 87% ee.

selectivities in the range of 30−43% were obtained, which were much lower than those obtained from using the corresponding monomeric ligands (up to 93% ee). The reaction rates using the dendritic ligand were also lower. This negative "dendritic effect" was probably due to the intramolecular interaction between the active centers on the periphery of the dendrimer. Soai and co-workers also synthesized similar ligands **229** which were linked to a more rigid dendrimer in place of PAMAM. In **229**, the ephedrine units were effectively separated by the rigid backbone, which provided the dendrimer with independent catalytic sites.[316] The dendrimer gave enantioselectivities up to 94%, which were similar to the parent ligand in the reaction.

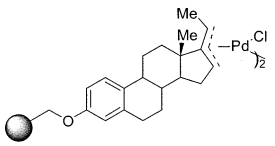


250a



250b

Bao et al. reported an interesting polymer-supported Pd complex **251** using a Merrifield type resin as support and estrone as chiral source.[317] The polymeric estrone was subjected to Wittig reaction to give an estrone derivative bearing an allyl moiety ready for palladium coordination.

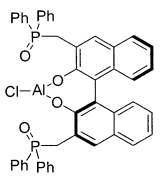


251

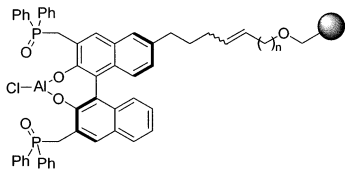
The palladium complex thus obtained was used as catalyst for the asymmetric allylation of imines using allyltributylstannane. The rate of reaction was very slow, and the selectivity was less than 42%.

The polymer was separated by filtration, and the recovered catalyst showed no loss of activity or enantioselectivity.

Following the successful application of bifunctional catalyst 252 in asymmetric Strecker type reaction,[318] Nogami et al. immobilized the catalyst on Merrifield (253a) and Janda*J*EL (253b) resins.[319]



252



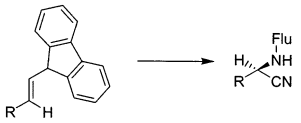
253

Table 74. A Comparison of the Efficacy of 252, 253a, and 253b

		time (h)			yield (%)			ee (%)		
entry	imine (R)	**252**	**253a**	**253b**	**252**	**253a**	**253b**	**252**	**253a**	**253b**
1	Ph	44	64	60	92	86	98	95	78	87
2	*p*-MePh			64			100			83
3	*p*-ClPh	44	85	59	92	74	98	92	80	85
4	*p*-MeOPh	44	85	41	93	85	98	93	62	83
5	3-furyl	44	64	66	92	81	97	92	76	86
6	(*E*)-PhCH−CH	41	86	66	80	55	96	80	53	83

Comparing to Merrifield resin, Janda*J*EL bearing flexible tetrahydrofuran moiety could be swollen more easily, rendering the catalytic sites more accessible. A comparison of the efficacy of **252**, **253a**, and **253b** is shown in Table 74 (Scheme 116).

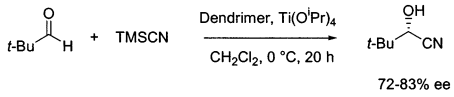
Scheme 116



Catalyst supported on Janda's resin was also recovered and reused 5 times with a gradual decrease of catalytic activity and stereoselectivity.

Seebach and co-workers employed polymer-supported chiral dendrimer **235a** for the asymmetric cyanosilylation of aldehyde.[305] The complex of **235a** with Ti(O*i*-Pr)$_4$ (20 mol % Ti−BINOLate) was used for the trimethylsilylcyanation of pivalaldehyde (Scheme 117). In the first run, the enantioselectivity

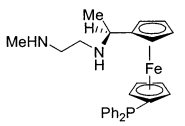
Scheme 117



was 72%, which was similar to that found in the homogeneous reaction. Interestingly, the enantioselectivity increased gradually during the following catalytic runs to reach a value of 83% after five runs.

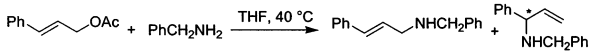
14. Recoverable Catalysts for Other Asymmetric Reactions

Johnson et al. reported the immobilization of chiral ferrocenyl phosphine ligand dppf on the inner walls of mesoporous silica MCM-41.[320] Under nondiffusive conditions, MCM-41 was treated with dichlorodiphenylsilane to deactivate the exterior walls of the material. The inner wall was derivatized with 3-bromopropyltrichlorosilane **254** to give the activated MCM-41. For preparation purpose, dppf was also anchored on the surface of cabosil, a silica closely related to MCM-41.



254

Scheme 118

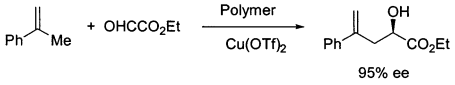


The allylic amination of cinnamyl acetate was carried out using benzylamine as nucleophile and palladium complexes of the supported and unsupported ferrocenyl phosphines as catalysts (Scheme 118).

The free catalyst gave solely the straight chain compound, and the cabosil-surface supported catalyst gave only 2% of branched product in 43% ee. The MCM-41 cavity confined catalyst gave very different result: 50% of branched product with up to > 99% ee.

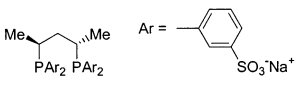
Cozzi and co-workers reported poly(ethylene glycol)-supported chiral bis(oxazoline) **165a** and **165b** for asymmetric C−C bond forming reactions.[240] The active polymer catalyst, which was generated in situ from **165b** and Cu(OTf)$_2$, was studied in asymmetric ene reactions. The reaction of α-methylstyrene (1 mol equivalent) with ethyl glyoxylate (10 mol equivalent) in CH_2Cl_2 in the presence of 10 mol % catalyst afforded the desired product in 96% yield and 95% ee (Scheme 119). The enantio-

Scheme 119

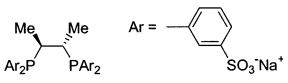


selectivity was comparable to that from using the unsupported catalyst under similar conditions. The polymer ligand was readily recovered by precipitation with diethyl ether and was reused twice with marginal loss in catalytic activity enantioselectivity.

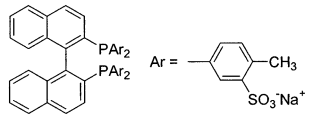
Hamed et al. reported the asymmetric Wacker oxidation of olefins in H_2O-THF mixed solvents using palladium complexes of BDPP, Chiraphos, Tol-BINAP, and their sulfonated counterparts as catalysts.[321]



255



256



257

In general, the catalysts containing sulfonated ligands gave lower ee's than their unsulfonated counterparts (Scheme 120, Table 75).

Scheme 120

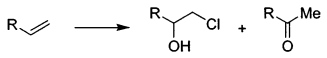
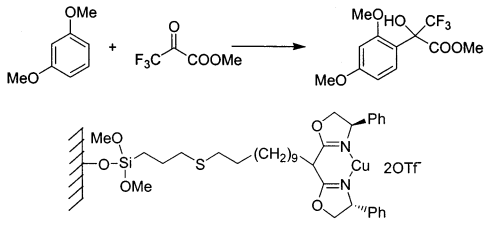


Table 75. Asymmetric Wacker Oxidation of Olefins Catalyzed by Palladium Complexes of 255, 256, and 257

entry	substrate	ligand	H_2O/THF	chlorohydrin/ketone	ee (%)
		Sulfonated			
1	propene	(*S*,*S*)-**255**	4/1	12	28
2	propene	(*S*,*S*)-**256**	4/1	12	46
3	propene	(*R*)-**257**	4/1	12	44
4	CH_2=CHC(O)Me	(*S*,*S*)-**256**	4/1	> 95	64
5	CH_2=CHC(O)Me	(*R*)-**257**	4/1	> 95	76
6	CH_2=$CHCH_2OPh$	(*R*)-**257**	3/2	> 95	68
		Unsulfonated			
7	propene	(*R*)-**257**	1/2	5.5	56
8	CH_2=CHC(O)Me	(*R*)-**257**	1/2	> 95	82
9	CH_2=$CHCH_2OPh$	(*R*)-**257**	1/2	> 95	80

Corma et al. reported a chiral copper(II) bisoxazoline covalently anchored to silica and mesoporous MCM-41 (**258**) as heterogeneous catalyst for the enantioselective Friedal-Crafts hydroxylation reaction. Up to 92% ee was obtained for reaction of 1,3-dimethoxybenzene with methyl 3,3,3-trifluoropyruvate (Scheme 121).[322]

Scheme 121



258

Van Veldhuizen et al. reported a recyclable chiral ruthenium complex **259** for enantioselective olefin metathesis, up to over 98% ee was observed (Scheme 122, Table 76),[323] and the catalyst was recovered through column chromatography.

Scheme 122

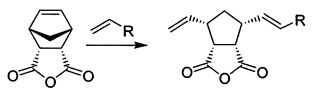
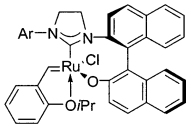


Table 76. Ruthenium Complex 259 Catalyzed Olefin Metathesis Reaction

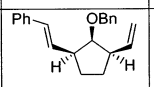
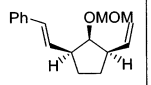
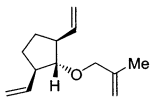
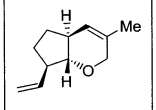
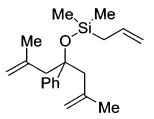
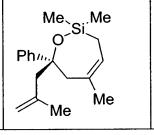
entry	R	trans/cis	ee (%)
1	Ph	> 98:2	80
2	n-C_5H_{11}	> 98:2	> 98
3	Cy	> 98:2	> 98



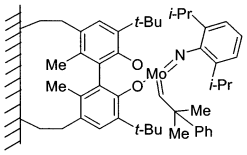
259 Ar = 3,4,6-mesityl

Hultzsch et al. reported the polymer-supported catalyst **260** for enantioselective olefin metathesis.[324] Biphenol compound was first functionalized to introduce the styrene moiety and the copolymerization of the functionalized biphenol with styrene provided the polymer-supported ligand which was subsequently converted to the molybdenum catalyst for olefin metathesis reaction. Up to 98% ee was obtained for metathesis of a variety of substrates. Reuse of the recovered catalyst showed similar enantioselectivity but a drop of catalytic activity (Table 77).

Table 77. Olefin Metathesis Catalyzed by 260[a]

Entry	Substrate	Product	Yield (%)	ee (%)
1			92 (89)	98 (> 98)
2			89 (88)	95 (> 95)
3			41 (84)	93 (> 98)
4			92 (97)	81 (93)

[a] Data in parentheses refer to the result from using the corresponding homogeneous catalyst.



260

Conclusion and Prospects

As enantioselective synthesis has progressed and parallel synthesis and combinatorial chemistry have emerged as new synthetic paradigms, in an atmosphere of increasingly stringent environmental and economical requirements, the field of asymmetric heterogeneous catalysis has become more attractive. Various approaches have been used to pursue high enantioselectivity and catalytic activity, as well as facile separation and recycling of the chiral catalysts. Among these approaches, the use of insoluble polymer-supported chiral catalysts represented the larger part of this field. Although the polymer-supported catalysts have shown high enantioselectivity and/or activity, and in some cases were even superior to the parent homogeneous systems, most catalysts supported on highly cross-linked polymer beads suffered from diminished activity compared to the homogeneous analogues because of reduced accessibility of the active sites. The proper combinations of polymer

supports, linkers, and catalyst structures might offer a favorable microenvironment to the chiral catalytic sites which might result in high reactivity and stereoselectivity. Subtle changes in any of these parameters could significantly influence the enantioselectivity of the polymer-supported chiral catalysts. Besides the chemical bonding onto the insoluble polymer supports, chiral catalysts could also be immobilized via encapsulation. The chiral membrane reported by Vakelecom,[51−54] and the microencapsulated chiral catalysts prepared by Kobayashi[168−170] represented the excellent examples of such variations. It is reasonable to expect that the development of new techniques will continue. In addition, combinatorial approaches for the acceleration of the discovery of chiral catalyst, and the use of polymer-supported chiral catalysts for library synthesis in combinatorial chemistry will attract more attention soon. In contrast to the polymer support, inorganic materials such as Zeolites and silica gel are rigid and unswellable. Similarly, lowered enantioselectivity and/or reactivity has been found due to mass transport problems. With the development of mesoporous molecular sieves or other silica with well-defined structures, chiral catalysts supported onto inorganic supports achieved high enantioselectivity and reactivity, and some were even higher than those of the homogeneous parent systems. The more recent developments of effective inorganic solid or organic and inorganic hybrid-supported chiral catalysts are important advancements in this area of research.

Biphasic catalysis represents another area of progress in this field and has provided an alternative to facilitate the catalyst separation and recovery. The novel concept of supported aqueous-phase catalysis, which is the combination of solid-supported catalysis and biphasic catalysis, has been demonstrated to be an attractive approach to chiral catalyst immobilization. The emergence of new "mobile" carriers such as supercritical fluid, fluorous solvents, and ionic liquid has been attracting increasing attention in this field. Biphasic asymmetric catalysis in supercritical CO_2, ionic liquid, and fluorous biphase system meet the criteria of "green chemistry", facilitating the separation and recycling of the chiral catalysts, and therefore will be actively studied.

Using soluble polymer or dendrimer as chiral catalyst support is a relatively new approach to the problem of catalyst separation. Such catalysts behave like homogeneous catalysts during the reaction and can be easily separated by precipitation method upon the completion of the reaction. Consequently, the attachment of chiral catalysts to soluble polymers, particularly dendritic polymers, offers a potential combination of the advantages of homogeneous and heterogeneous asymmetric catalysis. Excellent catalytic efficiency has been achieved by using the soluble polymer catalysts. The interplay between dendrimer and insoluble polymer-supported asymmetric catalysis, as reported by Seebach, seems to be a promising new approach to prepare polymer-bound chiral catalysts of high stability and performance for multiple uses. A membrane reactor incorporating chiral catalysts with linear polymeric or dendritic ligands facilitates the separation and recycling of the chiral catalysts. Dendrimers are particularly suitable for this type of reactor because of their globular morphology. In addition, it is possible to systematically fine-tune the structure, size, shape, and solubility of dendrimers and metallodendrimers at will and to locate catalytic species at the core or at the periphery. Some chiral dendritic catalysts have shown a positive "dendritic effect" in asymmetric catalysis. Catalysts combining the advantages of homogeneous and heterogeneous catalysts fill the gap between homogeneous and heterogeneous catalysis, and are expected to have a promising future.

To date, no example of successful industrial application of supported chiral catalyst has been reported. A large number of different types of immobilized chiral catalysts have been developed, and most of them were employed as chiral catalysts for asymmetric hydrogenation, dihydroxylation, epoxidation, and addition of diethylzinc to aldehydes. Finding a more general method to prepare enantioselective catalysts with broad applicability, high enantioselectivity and activity, and the capability for recycle and reuse remains an important challenge.

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