Supported Chiral Catalysts on Inorganic Materials

Choong Eui Song* and Sang-gi Lee

Life Sciences Division, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul, 130-650, Korea

Received January 21, 2002 (Revised Manuscript Received June 10, 2002)

Contents

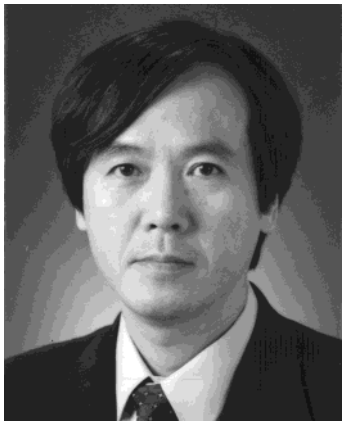
1. Introduction

For economic, environmental, and social reasons, the trend toward the application of optically pure compounds is undoubtedly increasing. Among the various methods to selectively produce single enantiomer, asymmetric catalysis is the most attractive method from the atom-economic point of view.[1,2] Over the last 30 years, numerous catalytic reactions allowing the enantioselective formation of C−H, C−C, C−O, C−N, and other bonds have been discovered. A number of homogeneous chiral catalysts have gained wide acceptance in terms of efficiency and selectivity, and some of them are even used on an industrial scale.[3] However, despite the huge amount of work devoted to this subject in both academic and industrial fields, the contribution of asymmetric catalysis in the overall production of chiral chemicals is much lower than originally expected. One of the major drawbacks of the homogeneous catalysis is the need for separation of the relatively expensive catalysts from the reaction mixture at the end of the process. An obvious solution to this separation problem is the use of heterogeneous catalysts, which can be recovered from the reaction mixture by filtration or centrifugation and then, potentially, be reused.[4−6] In addition to this separation advantage, the catalytic properties (e.g., stability and selectivity) of the heterogenized catalysts are sometimes improved compared to the homogeneous ones, which is ascribed to the contribution of the site-isolation[7] and constraint effects,[8,9] etc. Therefore, there is a continuing need to develop more efficient and practical immobilization methods for homogeneous chiral catalysts. Various methods are available for the heterogenization of homogeneous chiral catalysts. Generally, immobilization may be divided up into four distinct areas: (1) by formation of a covalent bond with the ligand, (2) by adsorption or ion-pair formation, (3) by encapsulation, and (4) by entrapment.

Binding of a ligand to a solid support via a covalent bond has become the most often employed method of heterogenization of an enantioselective catalyst. Clearly the supports and/or chiral catalysts must be functionalized in such a way as to be able to effect immobilization. However, the linking of the chiral auxiliary to the support modifies the conformational preference of the reactant-catalyst intermediates, which often leads to detrimental changes of catalytic properties. Immobilization without covalent bonds frequently avoids the chemical modification of the homogeneous chiral catalyst. There are several strategies for the immobilization of homogeneous catalysts without a covalent bond. The complex can be encapsulated within a pore of a zeolite or embedded into a

* Corresponding author. E-mail: s1673@kist.re.kr.

10.1021/cr0103625 CCC: $39.75
Published on Web 08/27/2002



Choong Eui Song was born in 1955 in Seoul, Korea. He received a B.S. in 1980 from Chungang University and obtained a Diploma (1985) and a Ph.D. (1988) at RWTH Aachen in Germany. Since 1989 he has worked as a Principal Research Scientist at the Korea Institute of Science and Technology (KIST). In 2001 he was appointed as the head of the National Research Laboratory for Green Chirotechnology in Korea. His research interests focus on the immobilization of chiral catalysts, ionic liquid chemistry, and the development of new pharmaceutically active compounds. He received the academic award from the KIST (2000) and the Scientist of the Month Award from the Ministry of Science and Technology in Korea (2002).

Sang-gi Lee was born in 1959 in Chilgok, Taegu Province, Korea. He received his B.E. degree in Industrial Chemistry from KyungPook National University in 1982 and M.S. degree from the Department of Chemistry at Korea Advanced Institute of Science and Technology in 1985. He then worked at the Korea Institute of Science and Technology as a research scientist until August 1990. Under the supervision Professor William H. Bunnelle (now in Abbott Lab, Chicago), he obtained his Ph.D. degree in 1994 at the University of Missouri–Columbia. Since 1994 he has worked as a principal research scientist at the Korea Institute of Science and Technology. From November 1997 to October 1998, he was a Postdoctoral associate with Professor John M. Essigmann at Massachusetts Institute of Technology. The research projects in his laboratory focus on the design and synthesis of novel chiral ligands and the study of their applications in areas such as asymmetric hydrogenations, allylic substitutions, hydrosilylations etc.

mesoporous silicate. It is also possible to immobilize a cationic or anionic complex by ion-pairing with an anionic or cationic solid. The chiral complex can also be immobilized by occlusion in a poly(dimethylsiloxane) membrane. Another strategy involves the use of a thin layer of a suitable solvent containing the homogeneous catalyst, supported onto a solid with a high surface area.

In any case of immobilization, the support materials need to be thermally, chemically, and mechanically stable during the reaction process. Moreover, the structure of the support needs to be such that the active sites are well dispersed on its surface and that these sites are easily accessible. Generally, this requires the support to have a reasonably high surface area (typically $>100\ m^2g^{-1}$) and appropriate pore size (i.e., >20 Å) to allow easy diffusion of the reactants to the active sites.[10] Inorganic supports[11] such as silica, zeolite, alumina, zirconia, ZnO, clay, etc., generally meet these requirements, although organic polymers[12,13] have been also extensively utilized. There are two classes of enantioselective catalysts heterogenized on inorganic supports. One is the chirally modified supported-metal catalyst, and the other is the immobilized homogeneous chiral catalyst. The former type of heterogeneous chiral catalyst is the most important class. Two of this types of chirally modified metal catalysts, first the Ni-tartaric acid system for the hydrogenation of β-ketoesters and second the cinchona alkaloids-modified Pt system for the hydrogenation of α-ketoesters, have reached a certain commercial importance. Recent review articles have covered this topic,[14−21] and thus, the supported metal catalysts will not be discussed in this review. In this review we will focus on immobilized homogeneous chiral catalysts on inorganic supports and their applications to asymmetric catalysis.

2. Asymmetric Reduction

2.1. Asymmetric Catalytic Hydrogenation of C═C Bond and C═N Bond

2.1.1. Immobilization via Covalent Attachment

Transition metal-catalyzed asymmetric hydrogenation of alkenes is one of the first and most important asymmetric catalytic reactions. An early example of silica immobilized chiral Rh catalysts **2** having different tether lengths between Si and P atoms was reported by Kinting et al. in 1985.[22] The silylated chiral monophosphines **1a**−**c** were anchored on silica (Kieselgel 100) first, and then the resulting phosphinated supports were subjected to reaction with $[RhCl(C_2H_4)_2]_2$ affording the immobilized catalysts **2a**−**c** (Figure 1).

These immobilized Rh complexes **2a**−**c** showed greater stability and selectivity than the homoge-

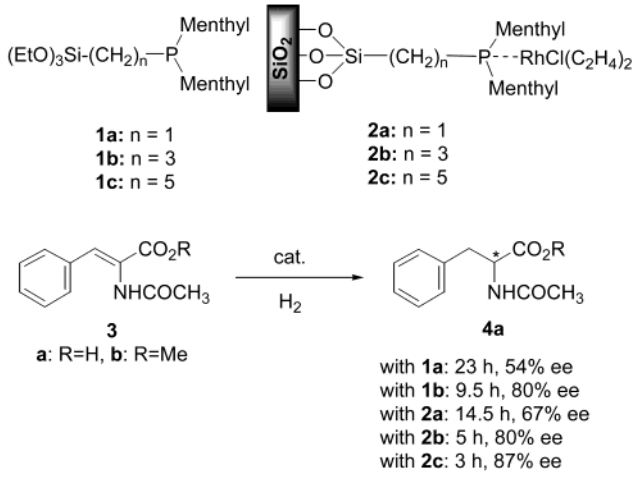


Figure 1.

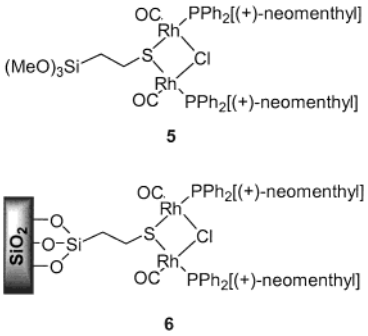


Figure 2.

neous counterparts Rh-**1** (see Figure 1). The instability of the homogeneous catalysts Rh-**1** may be due to the formation of mutinuclear complexes. The increased stability of catalyst upon immobilization can be ascribed to so-called site-isolation, i.e., attaching a catalyst to a support in such a way that catalytic sites can no longer interact with each other.[31] The length of the tether impacted on the selectivity and catalyst leaching. As the tether length increased, the enantioselectivity increased (from 67% ee with **2a** to 87% ee with **2c**) and leaching of catalysts decreased (for $n = 1$ the loss of Rh after three times reuse was more than 90%, while for $n = 5$ it was only 38%). It has been assumed that the use of the longer and more flexible tether encouraged the formation of Rh complexes bound in a bidentate fashion to the surface.

Immobilization of a homogeneous chiral catalyst sometimes affects the chirality of the products, as described by Blum et al.,[23,24] who immobilized the homogeneous di-Rh complex **5** on silica to give the heterogenized di-Rh complex **6** (Figure 2). In the hydrogenation of methyl (*Z*)-α-acetamidocinnamate (**3b**), the homogeneous catalyst **5** led to the formation of dextro-rotatory product, methyl α-acetamidodihydrocinnamate (**4b)**, while the silica-supported catalyst **6** gave levo-rotatory material. The difference in product chirality was assumed to be associated with the different orientations of the phosphine ligands in the homogeneous and immobilized catalyst, i.e., one side of the dirhodium complex in the immobilized complex could be blocked that may force the substrate to approach the metal from a different direction with homogeneous ones. The ee values of **4b** (up to 95% ee) obtained with the immobilized catalyst **6** are comparable with those (up to 97% ee) with homogeneous catalyst **5**, but the conversion yields were quite low in both homogeneous and heterogeneous catalytic systems (<15% conversion). Upon recycling the immobilized catalyst **6** in the hydrogenation, the enantioselectivity of the formation of **4a** gradually decreased.

In 1986, Nagel immobilized the highly effective C_2-symmetric chiral bisphosphine, 3,4-(*R*,*R*)-bis(diphenylphosphino)pyrrolidine (**7**, Pyrphos)[25] on silica gels to give silica-supported Pyrphos **9a**−**c** (Figure 3).[26] In the homogeneous hydrogenation of (*Z*)-α-acetamidocinnamic acid (**3a**) with the Rh−**7** complexes, the maximum ratio of substrate to catalyst was about 10 000, and the enantioselectivity in this case remained at 99% as long as the catalyst was active.[25]

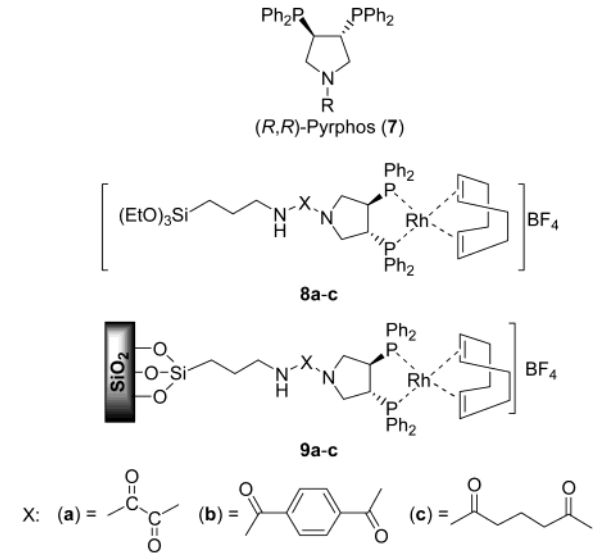


Figure 3.

For the immobilization of Pyrphos **7** on silicas with different pore sizes (4, 6, and 10 nm), the silylated Rh complexes **8a**−**c** bearing different tethers (**a**, **b**, and **c**) were prepared. In the hydrogenation of **3a** (up to 97% ee) and its methyl ester **3b** (up to 100% ee), the optical yields obtained with the immobilized catalysts **9a**−**c** were comparable to the homogeneous case using Rh−**7** complexes. The immobilized catalyst **9a** was reused 3 times for the hydrogenation of **3a**. However, in the third run the activity decreased considerably (from TON = 5 min^{-1} in the first run to 1−0.2 min^{-1}) with some loss of enantioselectivity (93% ee in the first run dropped to 87% ee in the third run), probably due to the oxidation of the complex. The pore size of the silica support greatly influenced selectivity of the hydrogenation of ester **3b**; this was not observed with the acid substrate **3a**. Thus, a 100% ee value for **4b** was achieved with **9b** on 4 nm pore size of silica, but this decreased to 89% ee with the same catalyst immobilized on 10 nm pore size of silica. This result showed that restricted conformational flexibility through geometrical constraint could provide a positive effect as described by Corma et al.[27−30]

Corma et al.[27−30] immobilized a number of proline derivatives on silica and modified USY zeolite (pore diameter 12−30 Å) (Figure 4). The homogeneous, silica-supported and modified USY zeolite-supported proline ligands **10**−**14** were used for the hydrogenation of various (*Z*)-α-*N*-acylcinnamic acid derivatives such as **3c** and **3d**. Some of the results are summarized in Table 1. For all the substrates tested using catalysts **10**, the enantioselectivity was higher with the zeolite-supported complex than with either the silica-supported or unsupported complexes (entries 1 and 2). The differences in enantioselectivity were greater for the less bulky *N*-acylderivatives of **3** (compare entries 1 and 2), suggesting an important role for the steric constraints imposed by the support as described above, especially in the zeolite case. It has been claimed that the zeolite-supported catalysts were reused several times with no loss of activity or rhodium content.[27] The other proline-derived Rh

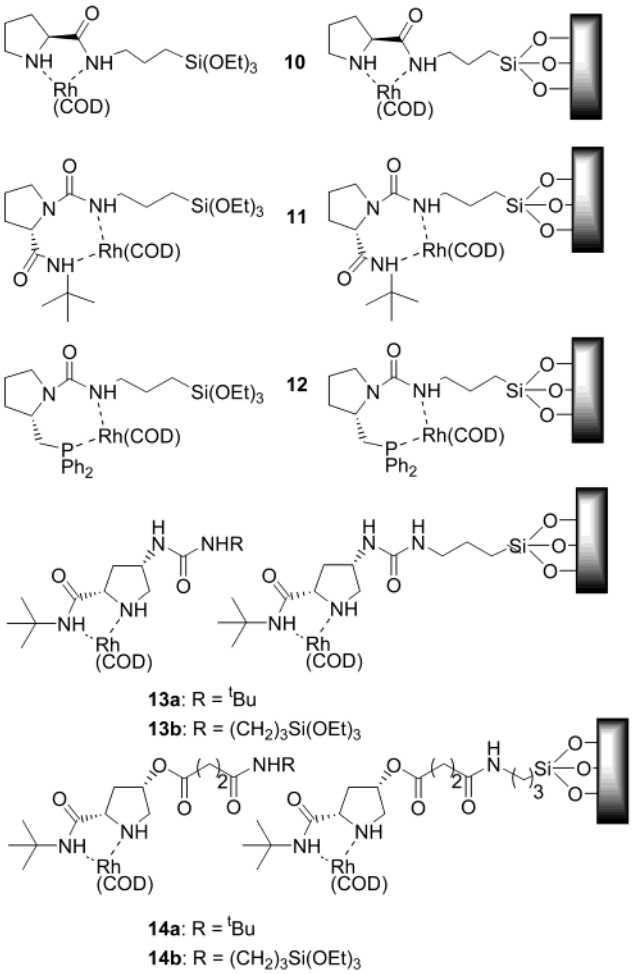
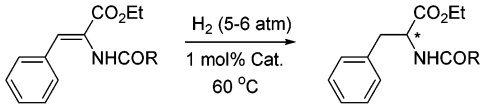


Figure 4.

Table 1. Asymmetric Hydrogenation of 3c,d Using 10−14 as Catalysts



			% ee		
entry	**3**	catalyst	homogeneous	silica	USY zeolite
1	**3c**	**10**	84.1	88.0	97.9
2	**3d**	**10**	90.3	93.5	96.8
3	**3c**	**12**	43.4	84.5	53.3
4	**3c**	**13**	34.5	29.9	46.9
5	**3d**	**13**	57.4[a]	54.3	62.3
6	**3c**	**14**	88.7[b]	76.1	55.1
7	**3d**	**14**	91.6[b]	87.6	84.1

[a] **13a** was used. [b] **14a** was used.

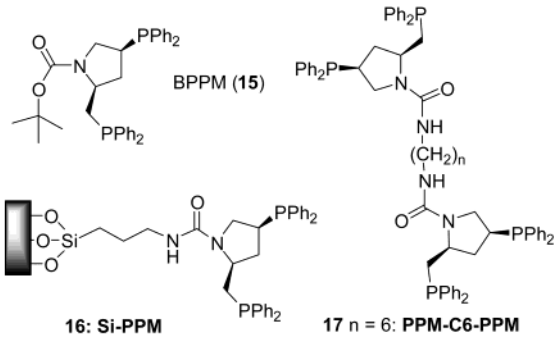
complexes **11**−**14** showed only moderate enantioselectivity (entries 3−7).[28−30]

As briefly described previously, immobilized catalysts on a rigid solid support can lead to so-called site-isolation.[31] The role of site isolation in catalytic hydrogenation has been investigated by Pugin et al.[32] To assess whether the possibility of dimer formation was detrimental to catalytic behavior, a series of PPM-type [PPM: 4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine] ligands, BPPM (**15**),

Table 2. Asymmetric Hydrogenation of Methyl *N*-Acetamidocinnamate 3b with PPM-Type Catalysts 15−18

entry	ligand	Rh	rate (min^{-1})	% ee
1	**16a**	$[Rh(cod)Cl]_2$	12.5	84.8
2	**16b**	$[Rh(cod)Cl]_2$	6.7	85.2
3	**16c**	$[Rh(cod)Cl]_2$	4.7	87.2
4	**16d**	$[Rh(cod)Cl]_2$	1.4	86.9
5	**16e**	$[Rh(cod)Cl]_2$	3.9	85
6	**16f**	$[Rh(cod)Cl]_2$	1.2	82.2
7	**16e**	$[Rh(cod)_2]BF_4$	13 (22)[a]	93.5 (94.5)[a]
8	**16f**	$[Rh(cod)_2]BF_4$	11 (19)[a]	91.2 (93.1)[a]
9	**15**	$[Rh(cod)Cl]_2$	9	93
10	**17**	$[Rh(cod)_2]BF_4$	18	94.8
11	**17**	$[Rh(cod)Cl]_2$	1.8	92.4
12	**17**	$[Rh(cod)_2]BF_4$	18	95.5
13	**18**	$[Rh(cod)Cl]_2$	3.9	92.6
14	**18**	$[Rh(cod)_2]BF_4$	18	95.5

[a] Results of 2nd run.



Ligand	Support	Loading (mmol ligand/g support)
16a: Si-PPM-1	Grace 332	0.016
16b: Si-PPM-2	Grace 332	0.058
16c: Si-PPM-3	Grace 332	0.092
16d: Si-PPM-4	Grace 332	0.19
16e: Si-PPM-5	Merk 100	0.11
16f: Si-PPM-6	Merk 100	0.20

Figure 5.

silica-supported ligands (Si−PPM, **16**), and the bis-PPM ligands (PPM-C6−PPM, **17** and PPM-C12−PPM, **18**) were tested in the Rh-catalyzed hydrogenation of methyl *N*-α-acetamidocinnamate **3b** (Table 2). The silica-supported ligands were prepared by grafting of a silylated monomer on two types of silica gel (Grace 332 and Merk 100) (Figure 5).

The activity and selectivity of the immobilized cationic Rh complexes of **16e** and **16f** prepared with $[Rh(cod)_2]BF_4$ were not significantly affected by catalyst loading (entries 7 and 8). In contrast to the cationic catalysts, the neutral catalysts prepared with $[Rh(cod)Cl]_2$ lost activity with increased loading (compare entries 1−4 and entries 5 and 6). Upon reusing the cationic Rh complexes of **16e** and **16f**, the reaction rate and enantioselectivity increased slightly (see entries 7 and 8). This is a quite rare case for immobilized catalysts. Similar enhancement of catalytic performances upon recycling of immobilized catalysts has been observed with heteropolyacid-modified inorganic supports, which will be discussed in a later part of this chapter.[33] The length of the tether in cationic Rh complexes of bis-PPMs **17** and **18**, had no effect on catalyst activity and selectivity (compare entries 12 and 14), whereas the catalyst

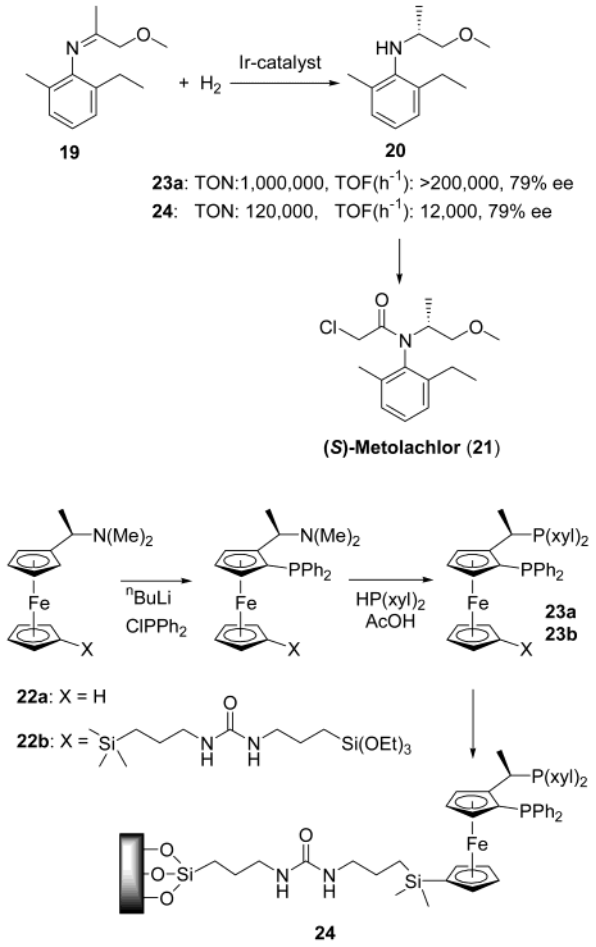


Figure 6.

activity of neutral Rh complexes was affected; thus, with an increase in the tether length, the activity also increased about 2-fold (entries 11 and 13). The neutral catalysts were about 2−3 times less active than the cationic catalysts. On the basis of these results it was concluded that cationic diphosphine−Rh complexes showed no tendency to interact with each other, whereas neutral Rh complexes interacted with each other in a way that was detrimental for their catalytic performance. Therefore, the immobilized cationic Rh complexes did not show as pronounced a site-isolation effect as that of the immobilized neutral analogues. The site-isolation effect was also observed in Ir-catalyzed enantioselective hydrogenation of the imine, *N*-(2-methyl-6-ethylphen-1-yl)methoxymethylmethylketimin (**19**). While the homogeneous Ir−BisPPM catalyst prepared with $[Ir(cod)Cl]_2$ was deactivated after 26% conversion, the immobilized catalysts were much more active and productive.[32] The fact that the activity (and also productivity) of the immobilized catalysts was increased with decreasing catalyst loading indicated that the formation of dimers could be prevented by immobilization.

Togni and Spindler reported that ferrocenyl diphosphines (PPF, **23a**) are most effective chiral ligands for Ir-catalyzed hydrogenation of imines.[34] The asymmetric hydrogenation of **19** is important for the commercial production of (*S*)-metolachlor (**21**), which is biologically more active than the corresponding

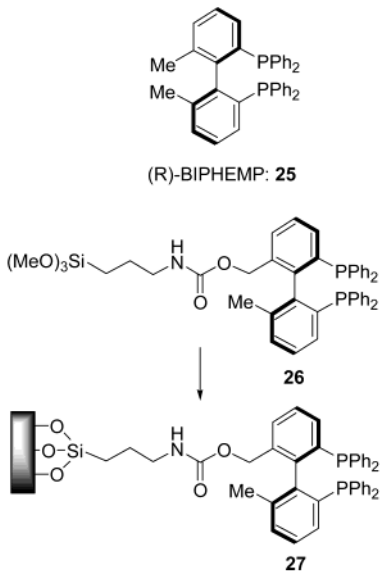


Figure 7.

racemic mixture. However, as observed by Pugin et al.,[32] due to formation of inactive chloride-bridged iridium dimers, the homogeneous **23a**−Ir complex tends to lose its activity during the hydrogenation reaction. To avoid such inactivation, researchers from Ciba-Geigy utilized the concept of site-isolation and thus immobilized the PPF ligand on silica (Figure 6). The immobilized PPF (**24**)−Ir catalyst displayed excellent catalytic performance (79% ee and up to 120 000 TON).[35] Unfortunately, the application of this immobilized catalyst to large scale production of (*S*)-metolachlor (**21**) was uneconomic since the catalytic performance of the homogeneous catalyst (TON = ca. 1 million) was so much better than the immobilized catalyst.

The immobilized chiral biphenyphosphine (BIPHEMP, **25**)[36] derivatives have also been made.[37] The silica-supported biphenylphosphine ligand **27**−Rh complex prepared by grafting of **26** on silica (Figure 7) hydrogenated (Z)-α-acetamidocinnamic acid methyl ester (**3b**) with 50% conversion and 39% ee.

The geometrical constraint sometimes has a positive effect on the catalytic performance compared to the homogeneous case as described by Corma et al.[27−30] for proline amide Rh complexes **10** (Figure 4). Thomas et al.[8,38] utilized the mesoporous channel of MCM-41 for the confinement of the substrate: this can lead to a large influence of the chiral directing group on the orientation of the substrate relative to the reactive catalytic center when compared to the situation in solution. The immobilized ligand **32** was prepared by modification of the bisphosphine **28** to the silylated **30** by reaction with aminosilane **29**, followed by formation of metal complex and grafting on MCM-41 (Figure 8). The constrained Pd catalyst **32** effected hydrogenation of ethyl 1,4,5,6-tetrahydronicotinate (**33**) to afford nipecotic acid ethyl ester (**34**) in 17% ee (TON = 291); the use of the homogeneous complex **31** resulted in racemic product (TON = 98). No metal leaching was observed. Although the results of this immobilized system are not satisfactory, this type of heterogeneous catalysts has considerable potential. Careful design of an active center and

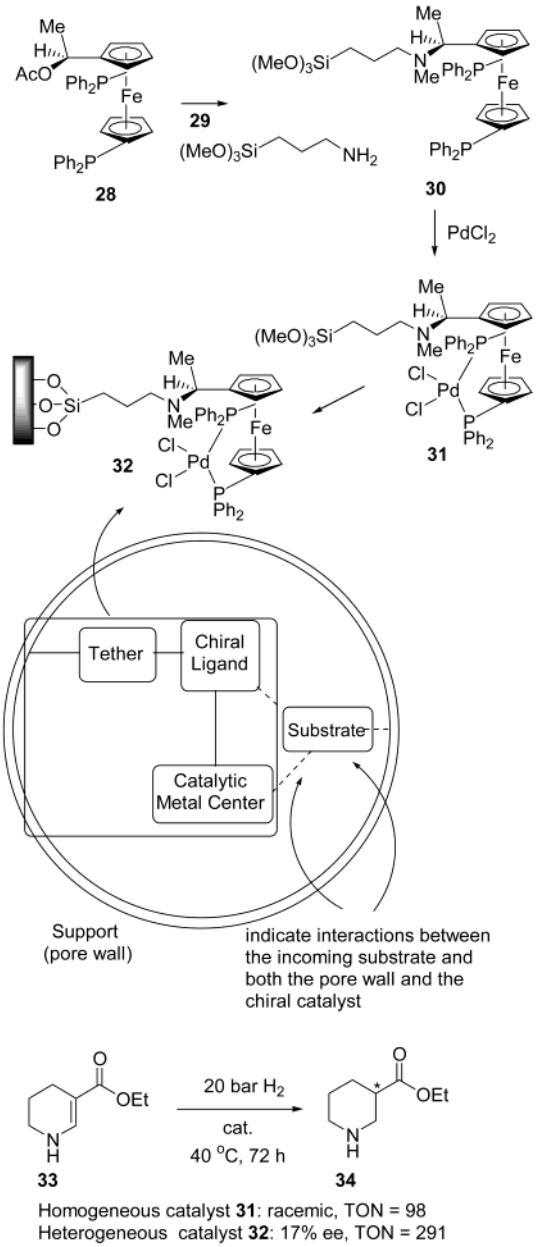
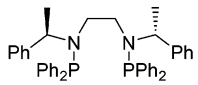


Figure 8.

control of pore size of supports will be necessary to develop more effective confined heterogeneous catalysts.

2.1.2. Immobilization via Ionic, Hydrophobic, and Other Interactions

A conceptually simple method for the immobilization of a variety of chiral ligands has been developed which takes advantage of the ionic nature of certain catalysts. For example, a cationic Rh complex can be fixed on a support containing anionic functional groups such as a sulfonate. Mazzei et al.[39] first applied this technique to the immobilization of the cationic Rh complex **35** (PNNP)[40] onto a series of mineral clays (hetorite, bentonite, montronite, halloysite). These mineral clays have a layer structure composed of alternate layers of cations and anionic silicate sheets. The interlayer distance between cationic and anionic silicate sheets could be increased (up to 100 Å) by swelling in either water or an alcohol, to allow the ion exchange of the large cationic Rh complex (about 2 nm)[26] into the intercrystal space. This clay-immobilized PNNP catalyst hydrogenated (Z)-α-acetamidocinnamic acid **3a** to furnish product (up to 72% ee). The activity and selectivity of the catalyst decreased upon reuse (72% ee of first run decreased to 47% ee in third run).



35 (PNNP)

Selke et al.[41] has immobilized a carbohydrate-based catalyst by ion-exchange. The cationic Rh chelates of 2,3-bis(*O*-diphenylphosphino)-β-D-glucopyranoside were immobilized on silica via ionic interaction. The silica-based cation exchangers (SiO_2)-O-Si$(CH_2)_3$O-$C_6H_4SO_3H$ **37** has been prepared by direct sulfonation of **36**. Two types of silica were used: Separon S56X (**A**−**H**) having a small particle diameter and exchange capacity (particle diameter: 55−65 μm; capacity: 0.58 mmol H^+g^{-1}) and Merck Kieselgel 100 having a large particle diameter and bearing a different exchange capacity (capacity: 0.88 mmol H^+g^{-1}, **B**$_1$−**H** or 1.08 H^+g^{-1}, **B**$_2$−**H**). Two possible routes for the preparation of the immobilized catalyst **40** were developed (Figure 9). One involved immobilization of the cationic Rh complex of Ph-β-glup **38** directly on the acidic support **37** (route 1). The other route was that support **37** was pretreated with alkali metal halide (MX) and then reacted with **39** to give the immobilized catalyst **40** (route 2).

The enantioselectivity for the hydrogenation of α-acetamidoacrylic acid ester **41b** with immobilized catalyst **40** was slightly higher (95% ee) than that obtained with homogeneous catalyst **38** (91% ee). The catalysts **40** immobilized via route 1 on different

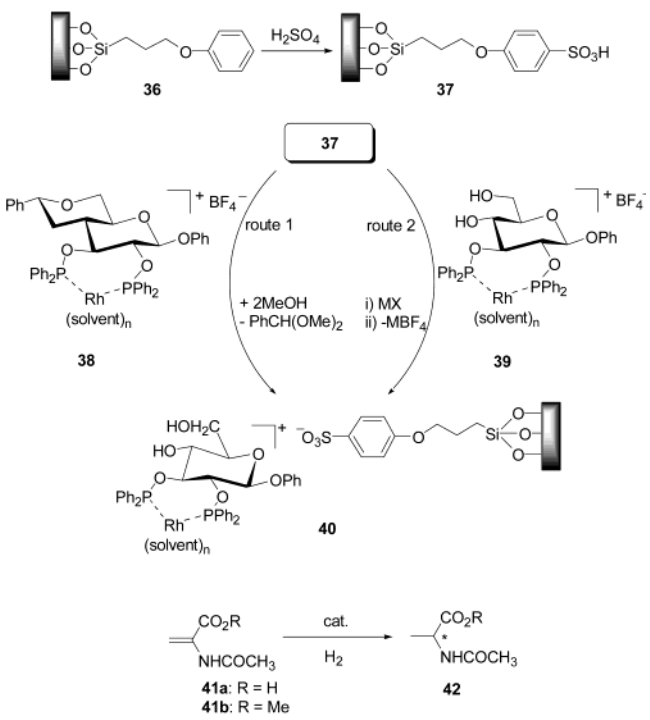
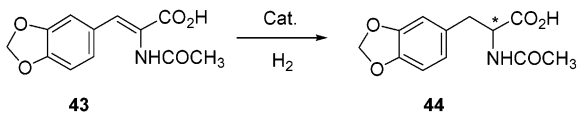
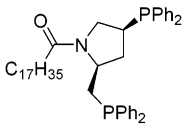


Figure 9.

silicas were recycled up to 20 times; the enantioselectivity was retained but appreciable amounts of Rh metal leached. However, supports preloaded with aniline minimized Rh leaching. The BPPM (**15**)[42]−Rh complex, [Rh(BPPM)(cod)]BF_4, was also immobilized on sodium-treated silica $\mathbf{B_2}$−Na: the enantioselectivity obtained with **41b** decreased upon recycling (91.7% ee to 86.8% ee after 7 times of recycling), but no Rh leaching was observed. The decreased catalyst leaching with the aniline preloaded or alkali metal treated supports could be explained by the increased ionic property of the supports leading to stronger ionic interactions between supports and catalysts. Similarly, the catalyst adsorption on hydrophobic supports was dependent on the hydrophobic interactions between the supports and the catalyst. Ishizuka et al.[43] carried out the asymmetric hydrogenation of 3,4-methylenedioxy-α-acetamidocinnamic acid (**43**), affording **44** in the presence of a chiral Rh complex of BPPM (**15**) adsorbed on hydrophobic silica gel in MeOH−H_2O solvents. Excellent conversions (100%) and a moderate optical yield (85%) were attained using [Rh(cod)BPPM]$^+ClO_4^-$ on methylated silica gel ($mSiO_2$). When recovered catalysts were reused three times, the optical yields decreased gradually from 85% to 69% ee. The adsorption of the complex was improved by introducing a stearoyl group (SPPM, **45**) instead of the butoxycarbonyl group of BPPM (**15**), but reactivity and enantioselectivity were lowered.



43 **44**



SPPM (**45**)

Recently, Bianchini et al. reported that phosphine ligands bearing sulfonate functional groups can be immobilized on porous silica through the ionic interactions between catalysts and the hydroxy groups on the silica surface.[44−46] This immobilization procedure involves a hydrogen-bonding interaction (denoted as supported hydrogen-bonded (SHB) catalysts) between the silanol groups of silica and sulfonate groups from the phosphine ligands and, possibly, also from the triflate counteranion, TfO^-. The Rh complexes, [((*R*,*R*)-$BDPBzSO_3$)Rh(nbd)], [(+)-DIOP−Rh(nbd)]OTf, and [(*S*)-BINAP−Rh(nbd)]OTf, of the three optically pure bisphosphines **46**,[47] **47**[48], and **48**[49] were immobilized on silica via hydrogen bonding, to give the supported hydrogen-bonded (SHB) catalysts **49**, **50**, and **51**, respectively (Figure 10).

The immobilized Rh complexes **49**−**51** were not extracted back into CH_2Cl_2 solution even after repeated washings. In contrast, stirring in MeOH or EtOH at room-temperature resulted in their complete tranfer into solution. No immobilization was observed when the triflate counteranion in either DIOP or BINAP was replaced by other counteranions such as

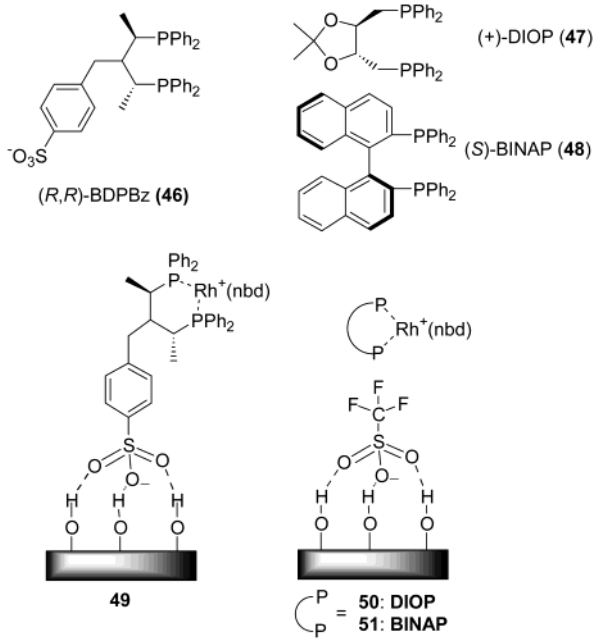


Figure 10.

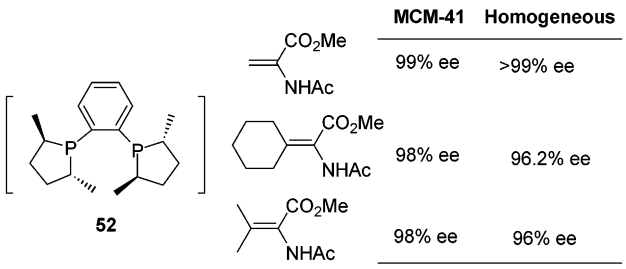


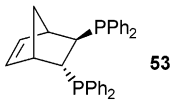
Figure 11.

BPh_4^- that are not capable of hydrogen bonding interactions with silica. Unfortunately, the enantioselectivities obtained for the hydrogenation of olefins with these immobilized catalysts were quite low (3−53% ee). Broene et al,[50] immobilized the cationic rhodium complex of Me−DuPhos (**52**),[51] [(*R*,*R*)-DuPhos−Rh]OTf, noncovalently on surface silanols of mesoporous MCM-41. In contrast to the results obtained by Bianchini et al.,[44] the catalytic activity and selectivities of the immobilized **52**−Rh complex on MCM-41 were equal to or greater than the homogeneous ones (Figure 11). Moreover, the catalysts were recyclable (4 times with no loss of activity) and did not leach. Here, too, the counteranion was very important for the successful immobilization of the catalyst onto MCM-41. Thus, whereas the DuPhos−Rh complex with triflate anion was effectively immobilized (6.7 wt % based on Rh), the analogous complex with the liphophilic BAr_F anion [BAr_F = B(3,5-$(CF_3)_2$−C_6H_3)] was not loaded onto the support. The mechanism of triflate binding is likely to be hydrogen bonding, similar to that demonstrated by Bianchini et al.[44] Advantages of this immobilization method are the simplicity and the fact that no catalyst modification is required; however, the number of the counteranions and solvents that can be used is limited.

Another type of immobilization involves physical entrapment of chiral catalysts in a sol−gel matrix. Compared to other solid support materials for cata-

lyst immobilization, inorganic sol−gel supports are superior in their thermal stability, inertness toward the entrapped molecules, high porosity (20−100 Å), and large surface areas (>100 m^2g^{-1}).[52] Shvo et al.[53] reported on the sol−gel entrapment of a cyclic dipeptide for hydrocyanation, and Shabat et al.[54] reported entrapment of a chiral antibody for heterogeneous aqueous catalysis. In 1999, Gelman et al.[55] reported entrapment of chiral DIOP (**47**)−Rh, BINAP (**48**)−Ru, and BPPM (**15**)−Rh complexes in sol−gel porous glasses and their utilization for the enantioselective hydrogenation of itaconic acid. The chiral catalysts were simply entrapped by stirring with tetramethoxysilane, $Si(OMe)_4$, until gelation occurred. No metal leaching into CH_2Cl_2 was observed from sol−gel entrapped catalysts. Asymmetric catalytic hydrogenation of itaconic acid using these sol−gel catalysts in water exhibited low to moderate optical yields (up to 78% ee). The catalysts were easily recovered (the entrapped catalysts were not soluble in water) and reused several times with decreased ee values. The major advantage of this sol−gel entrapment is the use of environmentally benign water as a solvent. Only a few reports[56−63] of asymmetric catalysis using water as solvent with inorganic supported chiral catalysts exist.

Brunner et al.[56,57] impregnated chiral Rh complexes of various phosphine ligands such as DIOP, Norphos **53**[64] and DuPhos on inorganic supports (e.g., $BaSO_4$, cellulose, silica gel, aluminum oxide, AgCl, and charcoal).



53

These catalysts hydrogenated (*Z*)-α-acetamidocinnamic acid **3a** in aqueous NaOH to give up to 79% ee of *N*-acetylphenylalanine **4a**. On repeated use of the immobilized catalysts, the catalytic activity declined.[56] In the hydrogenation of folic acid to 5,6,7,8-tetrahydrofolic acid, only low to moderate diastereoselectivities were obtained.[57]

Flach et al.[58] entrapped the Rh complex of BPPM (**15**) into surfactants immobilized on various supports, silica (**54** and **55**), alumina (**56**), and silica-based sulfonic ion-exchanger (**57**) (Figure 12). The enantioselectivities obtained from hydrogenation of methyl (*Z*)-α-acetamidocinnamate (**3b**) in water in the presence of the immobilized surfactants **55**-**57** (up to 93% ee) were comparable with those (up to 95% ee) obtained in the presence of the corresponding soluble surfactants. However, the same reaction in the presence of immobilized surfactant **54** exhibited lower enantioselectivity (78% ee). No metal leaching was observed, and the catalytic systems were reused up to 10 times without significant loss of enantioselectivity.

Wan and Davis[59−63] developed an interesting immobilization method for chiral catalysts, the so-called supported aqueous phase (SAP) system, which consists of a thin water film that lies on a high-surface-area hydrophilic inorganic support (a controlled pore glass) and contains the ruthenium complex of water

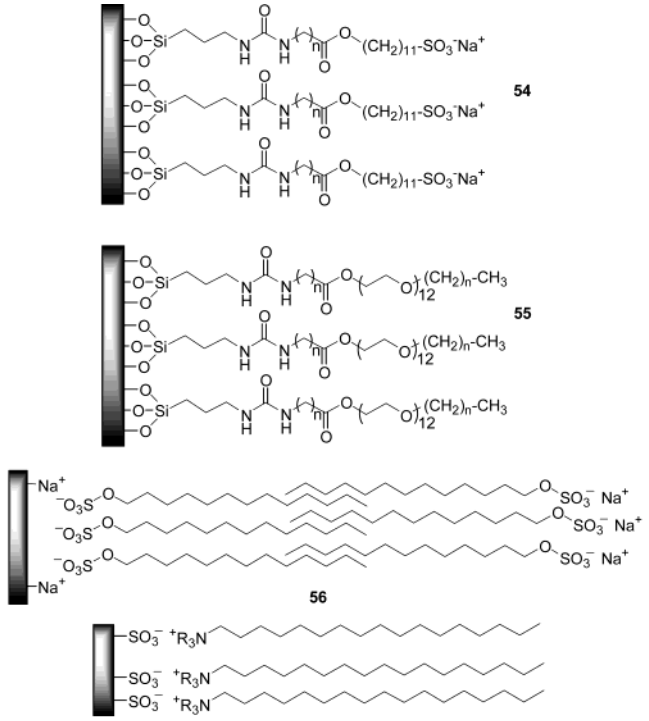
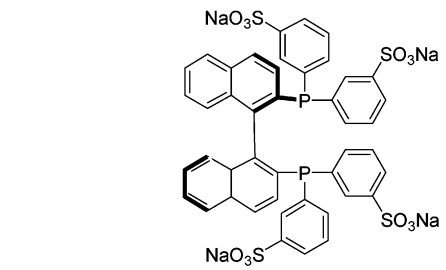
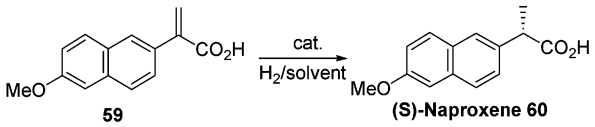


Figure 12.





Cat	Ru-BINAP	Ru-58	Ru-SAP
MeOH	96% ee	96% ee	
H_2O/EtOAc			70% ee
Cyclohehane/$CHCl_3$			96% ee

Figure 13.

soluble BINAP−$(SO_3Na)_4$ **58**, [Ru(**58**)C_6H_6Cl]Cl (Figure 13). The hydrophilic interaction between the ligand and support was sufficient to maintain the immobilization. The catalytic activity of this SAP catalyst was examined for the hydrogenation of the alkene **59** to Naproxen **60**. Using a homogeneous Ru−BINAP (**48**), [Ru(**48**)C_6H_6Cl]Cl, and Ru−BINAP-$4SO_3Na$ (**58**), [Ru(**58**) C_6H_6Cl]Cl, in MeOH gave the product **60** in up to 96% ee. The reaction rate of SAP catalyst was 50 times greater than that with the H_2O/EtOAc biphasic homogeneous Ru−BINAP-$4SO_3Na$ (**58**) catalyst; however, it was still 7 times lower than that with the homogeneous [Ru(BINAP)C_6H_6Cl]Cl in MeOH. Unfortunately, the MeOH solvent cannot be used in the SAP-catalytic system since the catalyst leaches into alcohols. Thus, the reaction with SAP

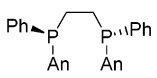
Table 3. Hydrogenation of Methyl 2-Acetoamidoacrylate Using Various Chiral Ligands Supported on PTA−Alumina

entry	ligand	use number	Immobilized rate[a]	Immobilized % ee	Homogeneous rate[a]	Homogeneous % ee
1	DiPamp	1	0.32	90	0.25	76
2		3	1.67	93		
3	Prophos	1	2.0	68	0.26	66
4		3	2.6	63		
5	Me-DuPhos	1	1.8	83	3.3	96
6		3	4.4	95		
7	BPPM	1	3.75	21	7.4	84
8		3	8.15	87		

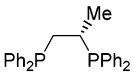
[a] Moles H_2/mol Rh/min.

catalyst in H_2O/EtOAc biphasic solvent system gave 70% ee of **60**. The lower enantioselectivity may be due to the presence of water, which is necessary to increase rotational mobility of the SAP catalyst but causes the loss of the Cl ligand through aquation of the Ru−Cl bond. Changing the hydrophilic phase from water to ethylene glycol and the organic phase from EtOAc to cyclohexane/$CHCl_3$, increased the enantioselectivity to 96% ee. In this SAP system, the Ru−Cl bond was expected to be left intact, but the overall activity was still lower than that of the homogeneous Ru−BINAP catalyst. The catalytic activity of the recovered SAP catalyst decreased, which may have occurred due to the significant solubility of ethylene glycol in the organic phase leading to leaching of the Ru complex.

Quite recently, Augustine et al.[33] immobilized various Rh complexes of the well-known bisphosphine chiral ligands such as DiPamp (**61**),[65] Prophos (**62**),[66] Me-DuPhos (**52**), and BPPM (**15**) onto heteropolyacid-modified inorganic supports such as montmorillonite K, alumina, carbon, and lanthna.



61:DiPamp



62: Prophos

In this new immobilization methodology, heteropolyacids (phosphotungstic acid (PTA), phosphomolybdic acid or silicotungstic acid) have been used as the anchoring agents to attach a complex to a support material via van der Waals forces or ion exchange forces between the support-anchor and anchor-metal.[67,68] Very interestingly, the reaction rates and enatioselectivities increased upon subsequent reuse (up to 15 times) of the recovered catalysts immobilized on PTA-modified supports. For example, in the hydrogenation of methyl 2-acetoamidoacrylate (**41b**) using Rh(DiPhamp)−PTA−montmorillonite K catalyst, the turnover frequency and enantioselectivity (0.18 min^{-1}, 67% ee) for the first run increased significantly (1.29 min^{-1}, 97% ee) after nine times of recycling. Enhanced catalytic performance of the recovered catalysts was also observed in other catalysts immobilized on PTA-modified supports. The results obtained with PTA-modified alumina are given in Table 3. A few other examples of such a positive influence on activity and selectivity for heterogenized catalysts have been described previously.[22,43] The reason for the increase in activity and selectivity upon reuse is not clear as yet. Elucidation of this interesting phenomena will provide a chance for the development of more efficient heterogenized catalysts. The generality of this immobilization technology has been proved by heterogenization of the BINAP (**48**)−Ru complex and achiral Wilkinson's catalysts, Rh(dppb) and other metal−ligand (phosphine, nitrogen) complexes. One of the advantages of this approach for immobilizing homogeneous catalysts is its simplicity and generality. A variety of preformed active homogeneous catalysts can be immobilized simply by mixing with a suspension of PTA-treated inorganic supports.

2.2. Asymmetric Catalytic Reduction of C=O Bond

2.2.1. Asymmetric Catalytic Hydrogenation

Chiral alcohols form an important class of intermediates for the pharmaceuticals, agrochemicals, flavors, and fragrances. The enantioselective synthesis of chiral secondary alcohols by catalytic reduction of the corresponding ketone is therefore an important transformation in organic synthesis. Numerous homogeneous rhodium and, to a lesser extent, ruthenium complexes chelated by chiral diphosphines have been developed for this purpose, and high enantiomeric excesses are achieved.[69] For heterogeneous asymmetric catalytic reduction of C=O bonds, there are two types of heterogeneous catalysts. One is chirally modified supported metals, and the other is the immobilized homogeneous catalyst. Many efforts on the development of heterogeneous catalysts for asymmetric hydrogenation of ketones have been focused on the former type of chiral heterogeneous catalyst.[14−21] In contrast, there are only a few reports of homogeneous chiral catalysts immobilized on inorganic materials.[70,72,73] In 1995, Carpentier et al.[70] reported the silica-immobilized chiral dirhodium (I) complexes **66a**−**c** of Cp,Cy−ProNOP (**67**)[71] (Figure 14).

Reaction of 1-amino-3-(triethoxysilyl)propane (**29**) with cyclic anhydride afforded the corresponding carboxylic acids **63a**−**c**. Formation of the Rh complex of **63a**−**c** with $[Rh(cod)(OMe)]_2$ followed by displacement of cyclooctadiene with ProNOP **67** gave the silylated dimeric complexes **65a**−**c**. The catalytic properties of the homogeneous (**65a**−**c**) and the silica-immobilized catalysts (**66b**−**c**) were examined for the hydrogenation of α-ketoesters such as ketopentolactone (**68**). For example, in the hydrogenation of **68** with silica immobilized catalysts **66**, the optical yields of the first run were comparable to the homogeneous cases, but upon recycling of the solid catalysts, the activity dropped significantly (see Figure 15). This could be attributed to the dimeric nature of **65**, for which only one unit might be immobilized on the silica, inducing leaching of both the rhodium and the ligand moiety.

Recently, the optically active biopolymer, chitosan, was immobilized on silica, and its Pd complex **70** was used for the hydrogenation of ketones (Figure 16).[72] Although it is not clear yet how the chitosan is immobilized on the silica surface, it seems the im-

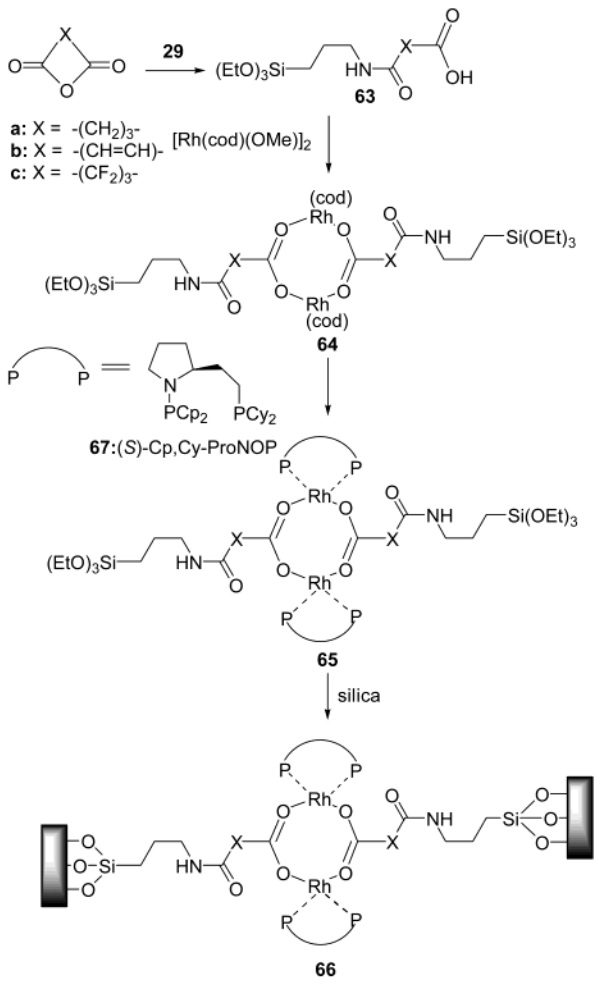


Figure 14.

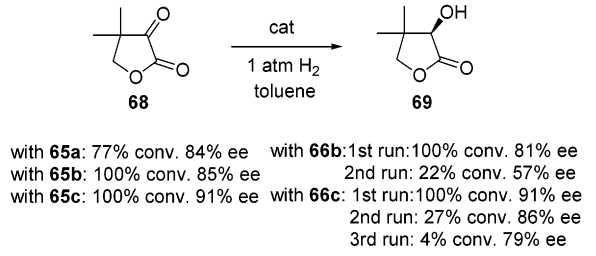


Figure 15.

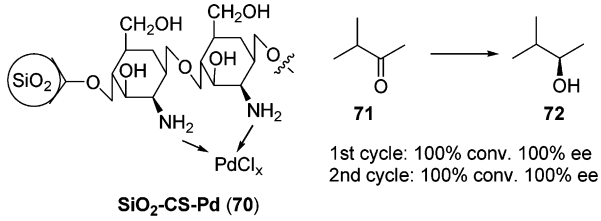


Figure 16.

mobilization may have occurred through ionic interactions. The immobilized chitosan−Pd complex **70** with 2.3:1 mole ratio of N:Pd hydrogenated a ketone **71**, 3-methyl-2-butanone, highly effectively (100% ee), and the catalytic properties were retained in a second cycle. However, the recyclability of **70** decreased (81.6% ee in second run, 77.3% ee in third run) on increasing the mole ratio of N:Pd to 4.7:1. At this time, it is hard to judge whether the Pd metal is

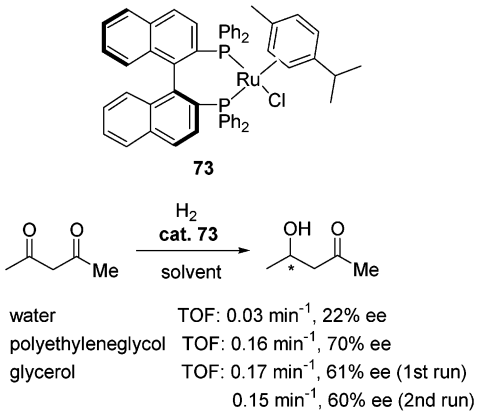


Figure 17.

bound in a bidentate fashion as shown in Figure 16. Other ketones such as acetophenone (99.1% ee), propiophenone (81.9% ee), and 4-methyl-2-pentanone (67.8% ee) were also reduced with moderate to high ees.

In 1996, Vankelecom et al.[73] reported a conceptually novel method for immobilization of catalysts within the apolar elastomeric framework of a polysiloxane membrane, where the unwanted interactions between the chiral catalyst and the support may be minimized. Thus, Ru−BINAP complex **73** was occluded in a poly(dimethylsiloxane) (PDMS) membrane and held in place merely by steric restrictions (van der Waals forces). Using this membrane-encapsulated Ru−BINAP catalyst, methyl acetoacetate was hydrogenated in poly(ethylene glycol) solvent with up to 70% ee (Figure 17). No metal leaching (>0.2%) was observed, and the recovered catalyst retained its catalytic activity. Although the results were inferior to the homogeneous Ru−BINAP system (>98% ee in MeOH), there might be a potential for the development of such membrane reactors.

2.2.2. Asymmetric Transfer Hydrogenation

Catalytic asymmetric transfer hydrogenation using either 2-propanol or formic acid/triethylamine as the source of hydrogen is a very attractive method for the synthesis of chiral secondary alcohols since it obviates the use of explosive hydrogen gas. Both mono and polynuclear Ru(II), Rh(I), and Ir(I) complexes with chiral phosphines and nitrogen ligands have been successfully employed as chiral catalysts for homogeneous enantioselective transfer hydrogenations.[74−78] However, examples of immobilized asymmetric transfer hydrogenation catalysts are still rare.[79−88] To date, only a few examples for immobilized catalysts on inorganic supports have been reported.[82−87]

Moreau et al.[82−84] reported the covalent immobilization of the silylated chiral diamines **74** and **75** into a sol−gel matrix to give **76** and **77**, respectively (Figure 18). The cohydrolysis of silylated chiral ligand−metal complex with tetraethoxysilane, $Si(OEt)_4$, allowed the immobilization of the chiral ligand−metal complex in a sol−gel matrix with a controlled surface area. The monosilylated Rh complex **74** was also grafted onto silica to give the silica-immobilized catalysts **78**.

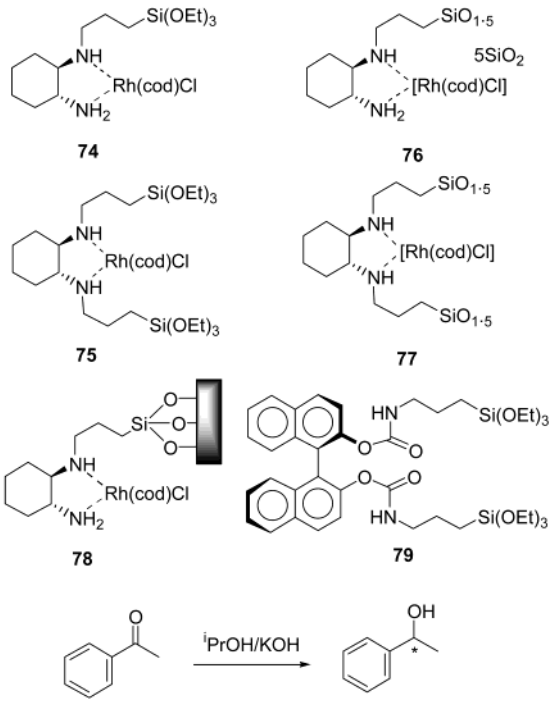


Figure 18.

In the 2-propanol-promoted transfer hydrogenation of aromatic ketones, all of the homogeneous catalysts **74**, **75**, and heterogeneous catalysts **76**−**78** showed extremely low activity. Moreover, most of the ketones examined was reduced to the corresponding alcohols with low to moderate enantioselectivities (14−80% ees). However, certain substrates showed excellent selectivity (98% ee for 2′-acetonaphthone, but the conversion was only 30% using catalyst **77**). Better enantioselectivities were found when the gels were prepared without $Si(OEt)_4$ such that the network consisted of only chiral diaminocyclohexane units linked by siloxane bridges. The secondary structure of the chiral 3D network may exert some influence on the selectivity. It has recently been found that the bis-silylated ligand **75** formed a helical morphology via H-bond mediated sol−gel hydrolysis.[85] The helicity was dependent upon the chirality of the cyclohexyldiamine. The silylated chiral binaphthol (**79**) was also immobilized in a sol−gel matrix, but the enantioselectivities in the Rh-catalyzed transfer hydrogenation of acetophenone were quite low (0−45% ee).[86] Although the enantioselectivities and reaction rates obtained from the chiral catalysts immobilized in a sol−gel matrix were not high, this immobilization method could have the potential to be a convenient technology for catalyst immobilization in the future.

Very recently van Leeuwen et al.[87] made the immobilized amino alcohol **84**, which was prepared by the reaction of (1*R*,2*S*)-(−)-norephedrine **80** with **83** or by direct grafting of silylated analogue **82** of the *N*-benzylated norephedrine ligand **81**[88] onto silica. A number of amino alcohols and a diamine were also immobilized on silica via solid-phase reaction with **83** to give a small library of immobilized amino alcohols **84**−**88** and **89a**,**b** (Figure 19). In 2-propanol-based (^{i}PrOH/^{t}BuOK) transfer hydrogenation of acetophenone, the homogeneous Ru−**82** com-

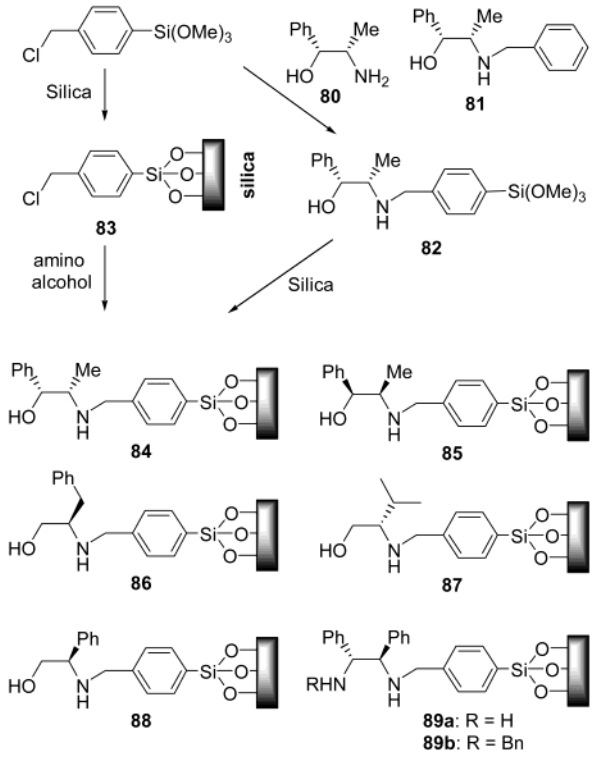


Figure 19.

plex showed higher activity and selectivity (81% conversion, 93% ee) than the heterogeneous Ru complexes (<88% ee). The catalytic activities of the immobilized catalysts **84**−**89** were retained upon recycling 2 times. Notably, the selectivity from the continuous reaction system increased up to 90% ee, where the catalytic efficiency was strongly dependent on the flow rate. As the flow rate increased, a better catalytic performance was observed. At a lower flow rate and hence a longer residence time of the product, equilibration becomes significant. Moreover, in a continuous reaction system, no catalyst deactivation occurred over a period of one week, a phenomenon ascribed to the effect of site isolation.

2.2.3. Asymmetric Hydrosilylation

Comparatively little work has been done in the area of asymmetric hydrosilylation with supported catalysts, and most of the efforts have been directed at hydrosilylation of ketones rather than olefins; the research has involved the use of organic polymeric supports (**90**) or silica (**91**) using DIOP as a chiral ligand.[89] Another silica-supported catalyst used in hydrosilylation of ketones was **92** (Figure 20).[90] In Rh-catalyzed hydrosilylation of acetophenone with diphenylsilane, all of these immobilized chiral catalysts exhibited low enantioselectivities (ca. 20% ee) and yields. The reason for the low enantioselectivities of these immobilized chiral catalysts may be due to the ineffectivity of the chiral phosphine ligand itself. For the homogeneous asymmetric hydrosilylation of ketones, many effective chiral phosphines and nitrogen ligands have been developed in recent years.[91] Immobilization of these effective chiral ligands will provide a chance for the development of efficient heterogenized chiral catalysts for hydrosilylation.

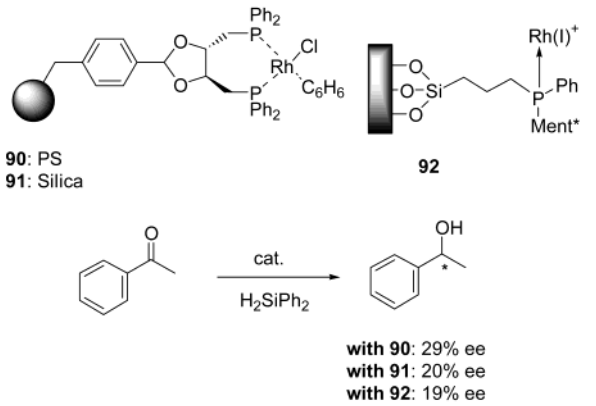


Figure 20.

2.2.4. Asymmetric Reduction Using Inorganic Hydrides as Reducing Agents

Chiral Co−salen complexes have been used for borohydride reduction of ketones under homogeneous conditions by Nagata et al.[92] The chiral (salen)metal complexes have been found to be highly enantioselective for the asymmetric epoxidation and epoxide ring-opening reactions. The immobilized metal salen complexes and their applications in oxidation reactions and epoxide ring-opening reactions will be discussed in the next chapter. An application of the immobilized Co−salen complexes in borohydride reduction of ketones has been reported by Kim et al.[93] 1,2-Diphenyldiamine and cyclohexyldiamine derived Co−salen complexes (**93** and **94**) were immobilized on MCM-41 to give **95** and **96**, respectively (Figure 21). In the asymmetric borohydride reduction of α-tetralone and acetophenone, the immobilized Co−salen complexes exhibited higher enantioselectivity than those of the homogeneous counterparts, but both the homogeneous and the immobilized catalysts exhibited only low to moderate enantioselectivities (15−73% ees). It has been claimed that the catalytic activity and selectivity of the Co-salen complexes immobilized on MCM-41 did not change substantially over several reuses. But no data for recycling experiments were reported.

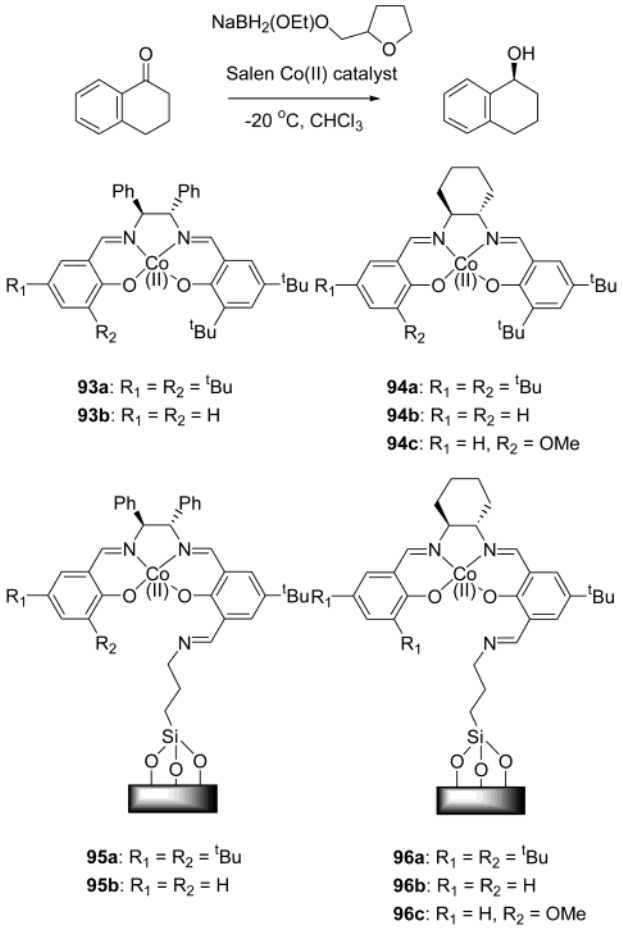


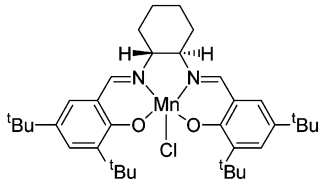
Figure 21.

3. Asymmetric Oxidation

3.1. Asymmetric Epoxidation

3.1.1. Asymmetric Epoxidation of Unfunctionalized Olefins

Catalytic asymmetric epoxidation of alkenes presents a powerful strategy for the synthesis of enantiomerically enriched epoxides. Among the several catalytic methods, asymmetric epoxidation of unfunctionalized alkenes catalyzed by chiral (salen)-Mn(III) complexes, developed by Jacobsen and coworkers, is one of the most reliable methods.[94−98] In particular, very high enantioselectivities are obtained for *cis*-disubstituted and *tri*-substituted olefins.

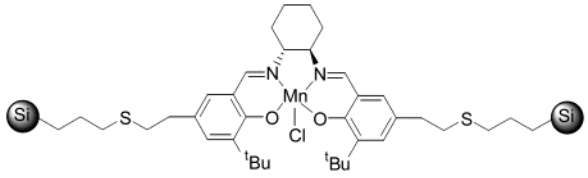


(*R*,*R*)-**97**

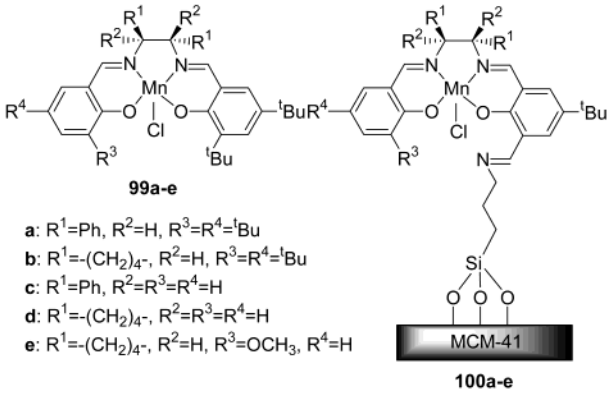
Although the typical Jacobsen-type catalysts such as **97** are cheap and easy to obtain, several attempts to immobilize Jacobsen's catalysts have been made.[99−123] Facilitation of catalyst separation, catalyst reuse, and an increase in stability of catalyst (e.g., minimization of the possibility of formation of inactive μ-oxo-manganese(IV) species[124]) are the main objectives of such research. Attempts to immobilize Jacobsen's catalyst have involved, until now, the covalent attachment of the complex to insoluble organic polymer[99−105] or inorganic supports,[106−108] the ion exchange of Mn(III) complexes into the intracrystalline space of zeolites or mesoporous materials,[109−114] the steric occlusion in the nanosized cages of zeolites using a "ship in a bottle methodology",[115,116] the physical entrapment in the poly(dimethylsiloxane) membrane,[73,117] and utilizing a fluorous biphasic system (FBS),[118,119] or room-temperature ionic liquids,[120] etc. Very recently, heterogenized Mn(salen) systems have been reviewed by Salvadori et al.[121]

To immobilize chiral (salen)Mn(III) complexes on inorganic supports, several different approaches have been attempted. In the first approach, chiral (salen)Mn complexes were heterogenized via a covalent link. First Salvadori et al. reported a covalently bound (salen)Mn(III) complex on silica gel

98.[106] This insoluble catalyst **98** exhibited high activity in the asymmetric epoxidation of some aromatic olefins (1,2-dihydronaphthalene, indene and 1-phenylcyclohexene) using mCPBA/NMO as the oxidant system in acetonitrile. For all substrates examined, the reaction was complete within 10 min at 0 °C. However, much lower ees (up to 58% ee for 1-phenylcyclohexene) were observed than those obtained in homogeneous reactions. Neither recycling experiments nor leaching studies were reported.



Kim et al.[107,108] described that the unsymmetrical chiral (salen)Mn(III) complexes **100a**−**e** immobilized by a covalent link to the siliceous MCM-41 displayed slightly improved enantioselectivities when compared with the homogeneous counterparts **99a**−**e** in the epoxidation of styrene and α-methylstyrene with mCPBA/NMO as the oxidant system. For example, using the insoluble catalyst **100a**, styrene (at 0 °C) and α-methylstyrene (at −78 °C) were epoxidized with 70% and 56% ee, respectively, whereas the homogeneous analogue **99a** gave the corresponding epoxides with 65% and 43% ee, respectively. However, the levels of asymmetric induction of these heterogenized catalysts are still far from satisfactory. It was also described that the catalytic activity and selectivity of the immobilized complexes were not changed after four times of reuse.[107] However, no data for recycling experiments were reported.



In addition to the above ways of heterogenizing chiral (salen)Mn complexes via a covalent link, a Cr−binaphthyl Schiff base (*R*)-**101** was immobilized by coordination to a terminal amino group **102** that had been attached covalently to the walls of a MCM-41 support (Figure 22).[122] Here again, the ee values obtained from the heterogenized catalyst **103** was slightly higher than those from the homogeneous analogue **101**. For example, with 4-chlorostyrene and cis-*β*-methylstyrene as substrates, the ee increased by as much as 17% and 19%, respectively, upon immobilization of **101** onto MCM-41. Epoxidation of 4-chlorostyrene and cis-*β*-methylstyrene with iodosylbenzene (PhIO) at 20 °C using the solid catalyst **103** gave (*R*)-4-chlorostyrene oxide and (1*R*,2*S*)-cis-*β*-methylstyrene oxide in 65 and 73% enantiomeric excess, respectively. This increase of chiral recognition was tentatively ascribed to an enhanced stability of the Cr complex upon immobilization or the spatial environment inside the channels of the support formed both by the chiral binaphthyl Schiff base ligand and the surface of the support. After four regeneration steps, both activity and ee value dropped significantly, even though only 2−3% of Cr had leached into solution.

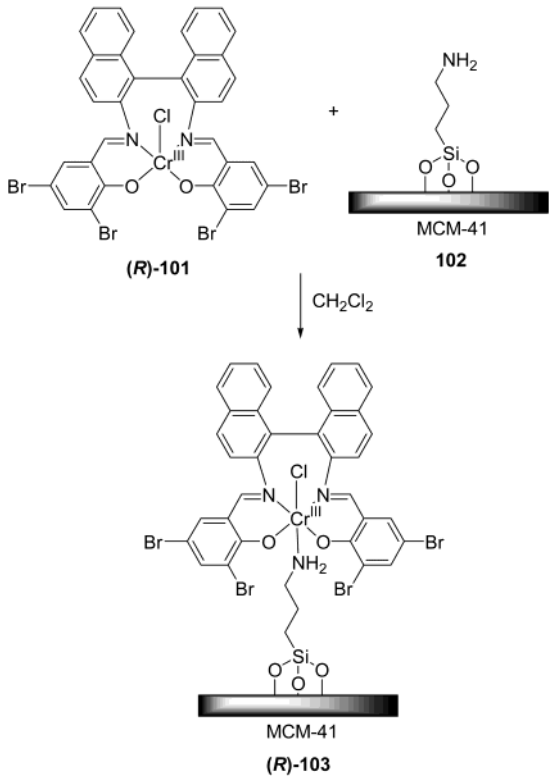


Figure 22.

Hutchings et al.[109−111] described another immobilization method for Jacobsen's (salen)Mn complex based on ion-exchange. Salen ligand, (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)cyclohexane-1,2-diamine (*R*,*R*)-**104**, was heated under reflux with a Mn-exchanged Al−MCM-41 in such a way that 10% of the Mn was ligated. The turnover frequency (26 h^{-1}) of this heterogeneous catalyst in the epoxidation of *cis*-stilbene using PhIO as oxygen donor was reported to be higher than the one (7 h^{-1}) for the homogeneous reaction. However, enantioselectivity (70% ee) was slightly lower than that (77% ee) obtained with the homogeneous system **97** (Figure 23). Moreover, immobilization of the chiral (salen)Mn complex **97** within Al−MCM-41 increased the cis:trans ratio of the epoxide product when compared to the non-immobilized complex under the same conditions. This indicates that the Mn−salen complex immobilized within the mesopores of Al−MCM-41 restricts the rotation in the radical intermediate, thereby decreasing the rate of formation of *trans*-epoxide. Although no leaching of Mn^{3+} was found in the reaction filtrate, the overall yield (18%) as well as ee value (30%) of epoxide obtained with the recovered catalyst dropped

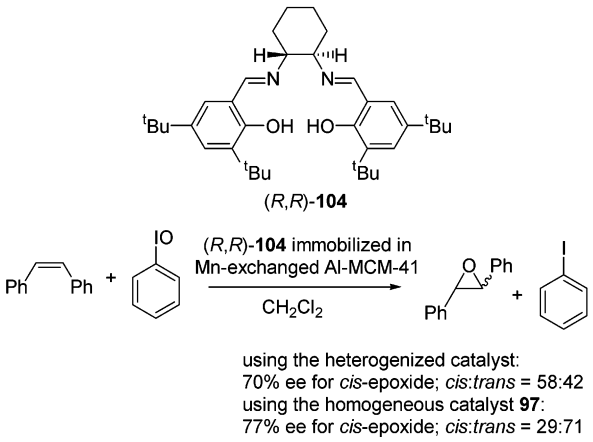


Figure 23.

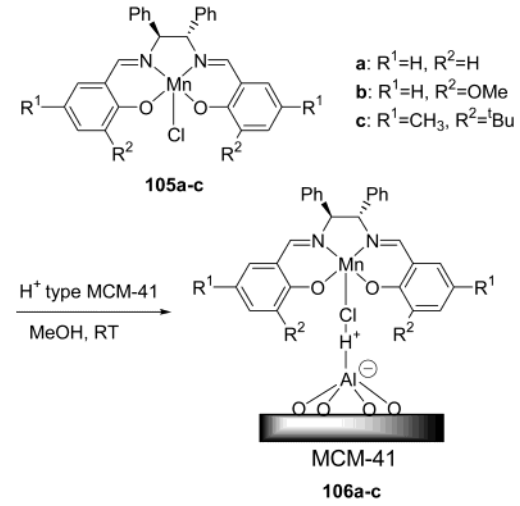


Figure 24.

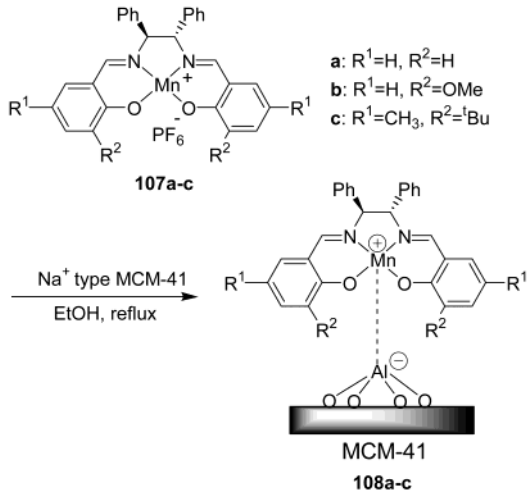


Figure 25.

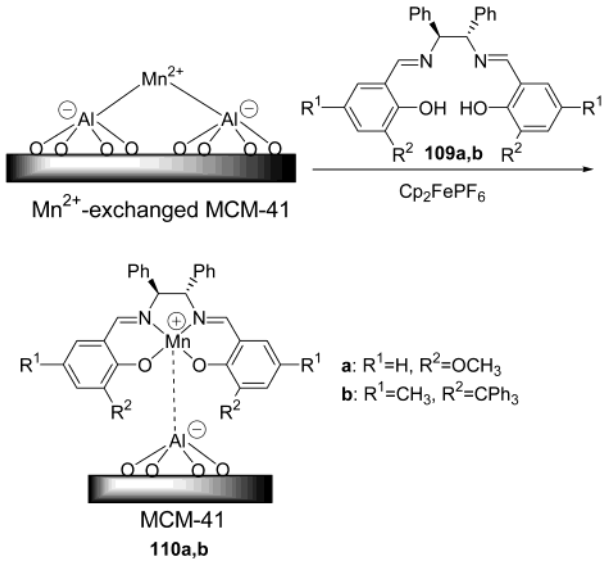


Figure 26.

significantly. It was assumed that the deposition of degradation product (iodobenzene) formed from iodosylbenzene on support surface led to a loss in catalytic efficiency of the recovered catalyst.

Contemporaneously, Kim et al.[112,113] also immobilized the chiral (salen)Mn complexes **105a**−**c** and **107a**−**c** by direct ion exchange with H^+-type MCM-41 (Figure 24) and Na^+-type MCM-41 (Figure 25), respectively, or by the reaction of the chiral salen ligand **109a**,**b** with Mn^{2+}-exchanged MCM-41, followed by oxidation with Cp_2FePF_6 (Figure 26). All heterogenized chiral (salen)Mn complexes **106a**−**c**, **108a**−**c**, and **110a**,**b** exhibited relatively high enantioselectivity for epoxidation of styrene and α-methylstyrene using mCPBA/NMO as the oxidant system as compared with the homogeneous counterparts. For example, using the insoluble catalysts **106c**, **108c**, and **110b**, styrene was epoxidized at 0 °C with 56%, 63%, and 66% ee, respectively, whereas the homogeneous analogues **105c** and **109b** gave the styrene oxide with 51 and 56% ee, respectively. This improvement of ee was explained by steric restriction of the olefin's approach to the catalytic site in the mesoporous zeolite system. Moreover, the immobilized (salen)Mn complexes were stable during the reaction without any leaching. The catalytic activity and selectivity of **110b** were not changed after three reuses in the epoxidation of styrene (1st run, 76% yield and 66% ee; 2nd run, 78% yield and 64% ee; 3rd run, 75% yield and 64% ee).

In connection with the above-mentioned contributions of Hutchings and Kim, the clay-supported catalyst was also prepared by direct ion exchange of the chiral (salen)Mn complex **97** on a synthetic Laponite.[114] After moderate enantioselectivities (32−34%) in the first epoxidation run with dihydronaphthalene and PhIO, a significant decrease of both activity and enantioselectivity was observed in subsequent runs.

Alternatively, Jacobsen's complex, (*R*,*R*)-**97**, was immobilized by simply embedding it into Al-substituted mesoporous silicates.[123] Guest/host interactions, mainly between the aromatic rings of the salen complex and the internal surface silanol groups on the walls of the mesopores, were found to be strong enough to prevent leaching of the complex. The embedded complex displayed nearly the same activity and enantioselectivity (55% ee) in the epoxidation of 1,2-dihydronaphthalene using NaOCl as compared with the homogeneous catalyst **97**. The similar catalytic activity and selectivity of the embedded complex compared with the free catalysts means that

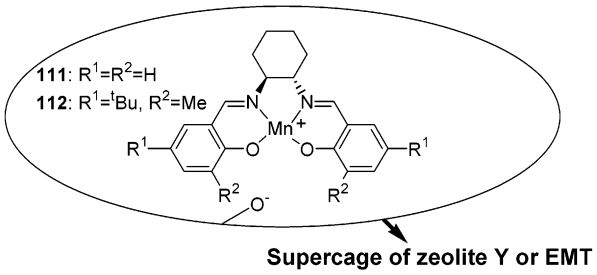
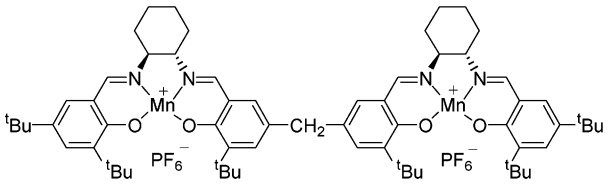


Figure 27.

the reactant molecules have free access to the embedded Jacobsen's catalyst. However regeneration experiments were not reported.

A "ship-in-a-bottle" approach to entrap the chiral (salen)Mn complexes **111** and **112** within the cages of zeolites was reported by two different research groups simultaneously.[115,116] The procedure comprised the stepwise treatment of the zeolite with the chiral diamine, a suitable salicylaldehyde (unsubstituted or 3-*tert*-butyl-5-methyl substituted), Mn(II) acetate and finally LiCl under aerobic conditions. The encapsulated catalysts (Figure 27) were used for the epoxidation of selected olefins, mostly with the CH_2Cl_2/NaOCl biphasic system. With the complex **111** encapsulated in zeolite Y,[115] both the activity and the selectivity were inferior to those obtained with the corresponding homogeneous system. Conversion values in the 5−40% range were achieved, together with 61−100% epoxide selectivity and ees of 5−58%. This low catalytic efficiency is probably due to problems related to diffusion of the substrate into the zeolite framework. However, with **112**-EMT,[116] having larger dimensions of supercages than those of zeolite Y, the enantioselectivity values were comparable to those with the soluble complex **112**. A remarkable ee of 88% for *cis*-*β*-methylstyrene was obtained. However, both activity (15−47% conversion) and chemoselectivity (58−87%) of the supported catalysts were significantly lower than with the homogeneous counterpart. Control experiments demonstrated that the catalytic property of both encapsulated catalysts was associated almost entirely with intrazeolite Mn(salen) chiral units.

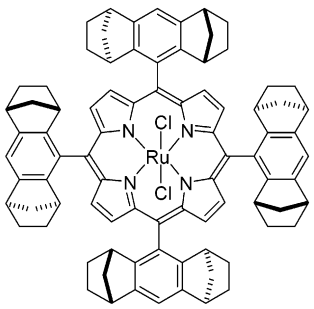
Finally, Vankelecom et al.[73,117] immobilized Jacobsen's catalyst **97** within the apolar elastomeric framework of a poly(dimethylsiloxane) (PDMS) membrane. As described in the previous chapter, this method of heterogenization presents the advantage of maintaining the structure of the chiral catalyst without any supplementary chemical bonding. The yields and enantioselectivities of this heterogenized system were comparable to those of the homogeneous monomer. However, unfortunately, severe leaching of the complex was observed during the epoxidation when the catalyst **97** was included in the membrane. For example, in the epoxidation of *trans*-*β*-methylstyrene using NaOCl as the oxidant in acetonitrile, 19.5% of the catalyst was leached out. To improve the retention of Mn(III)(salen)-type complexes in PDMS membranes, the same group synthesized a dimeric complex **113**. Although the dimeric complex **113** occluded in the membrane clearly leached less than the corresponding monomeric Jacobsen complex **97**, a remarkable leaching (8.7%) of dimer complex **113** was still found. Therefore, it seems not to be possible to achieve a complete regeneration of PDMS-included complex.



113

As described above, although chiral Mn(salen) catalysts are highly enantioselective for epoxidation for *cis*-disubstituted and *tri*-substituted olefins, the turnover numbers are low (<100) due to the instability of the catalysts under the oxidation conditions. On the contrary, matallophorphyrins are much more stable against various oxidants, especially when the ligand carries electron-withdrawing substituents.[125] High turnover number exceeding thousands has been realized in porphyrin-catalyzed epoxidation. For example, Collman and co-workers reported that a pseudo C_2-symmetric binaphthyl-strapped iron(III) porphyrin can effect enantioselective styrene oxidation with up to 5500 turnovers.[126] However, metalloporphyrins give rise to lower ees than the salen systems.

Recently, Che et al. heterogenized the chiral ruthenium porphyrin catalyst **114** in sol−gel matrix.[127] This sol−gel catalyst was prepared by hydrolysis and condensation of tetraethyl orthosilicate (TEOS) in the presence of **114** in an aqueous ethanol mixture. The sol−gel entrapped chiral ruthenium porphyrin catalyst was shown to be highly active toward asymmetric styrene epoxidation producing styrene oxide in 70% ee with up to 10 800 turnovers. However, a gradual decrease in catalytic activity over successive reactions was observed. At the fourth run, the sol−gel catalyst became inactive. The loss of activity of the Ru/sol−gel catalyst was ascribed to catalyst leaching and/or deactivation.



114

3.1.2. Asymmetric Epoxidation of Allyic Alcohols

Sharpless asymmetric epoxidation of allylic alcohols has become a benchmark classic in catalytic asymmetric synthesis[128,129] and is now used for some industrial applications.[130] A wide variety of primary allylic alcohols are epoxidized in excellent ees and yields using *tert*-butyl hydroperoxide (TBHP) as the

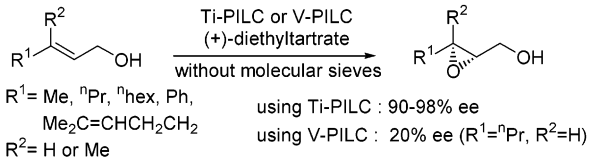


Figure 28.

oxygen donor and titanium isopropoxide-diethyl tartrate (DET) as the catalyst in the presence of 3 or 4 Å molecular sieves. In this catalytic reaction, the molecular sieves play a decisive role removing traces of water, which can deactivate the Ti−tartrate complex.[131,132] Although this catalytic process seems to be well understood, a heterogeneous system would be advantageous. It could avoid a complicated separation of product from catalyst, which can lead to decomposition of the epoxide formed.[130] However, only a few heterogeneous versions of this important reaction have been reported.[121,133−140]

In 1990, Choudary et al. reported that the heterogeneous chiral Ti catalyst immobilized on an inorganic support.[137] With the combination of a dialkyl tartrate and titanium-pillared montmorillonite (Ti−PILC) excellent ee values, in the 90−98% range, were achieved (Figure 28). Very interestingly, in contrast to the homogeneous conditions, this heterogeneous system was operational without the use of molecular sieves. However, no recycling experiment was reported. Distinct from Ti−PILC, the use of vanadium-pillared montmorillonite catalyst for the asymmetric epoxidation of (*E*)-hex-2-enol, however, led to only 20% enantiomeric excess.[138]

Quite recently, Basset et al.[139] prepared the silica-supported Ta- and Ti-alkoxides, and compared their catalytic properties in the asymmetric epoxidation of 2-propenol or *trans*-2-hexen-1-ol. As shown in Figure 29, silica-supported tantalum ethoxides **115** were prepared in two steps by grafting Ta(=CHCMe$_3$)-(CH$_2$CMe$_3$)$_3$ onto silica, followed by exchanging the alkyl and alkylidene ligands with ethanol. A titanium catalyst was similarly prepared from silica and Ti(O^{i}Pr)$_4$. Whereas the grafted titanium species led to a poorly active catalyst (17% conversion for 2-propenol) and exhibited almost no enantioselectivity, the silica-supported tantalum catalyst **115** showed good activity and excellent enantioselectivity, even without molecular sieves (see data in Figure 29). The tentative explanations of these results were as follows: grafted titanium species cannot provide all coordination sites for the ligands (a tartrate group chelating the metal through two σ-bonded oxygen atoms, an allyl alkoxy group, and a σ/π-coordinated *tert*-butyl peroxy group) because of the additional silica-O−Ti bond; on the other hand, the grafted group 5 metal such as tantalum can afford the potential of an active site. It was also found that molecular Ta(OEt)$_5$ did not lead to an active catalyst (0.5% conversion for 2-propenol) and, moreover, the opposite enantiomer was obtained predominantly. The higher activity of supported tantalum compared to the homogeneous tantalum may result from the presence of well dispersed monomeric tantalum species on the silica surface, which would lead to monomeric active sites. On the other hand, the molecular tantalum alkoxides, which are dimers in weakly polar solvents, would lead to dimers in the presence of tartrate and the reactants. These molecular tantalum dimers would be poorly active compared to Si-supported monomeric species. Moreover, the silica-supported Ta catalyst could be reused without adding tartrate after the reaction.

Mo(VI) complexes of chiral ligands derived from (2*S*,4*R*)-4-hydroxyproline were heterogenized onto a modified USY-zeolite by covalent bonding.[140] Interestingly, in the epoxidation of geraniol and nerol with TBHP as the oxygen source, the heterogenized cata-

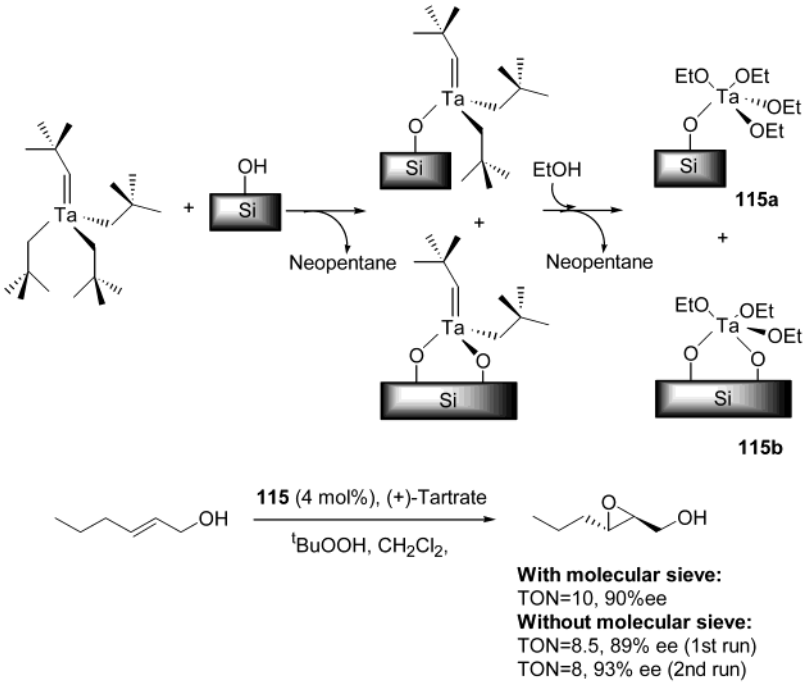
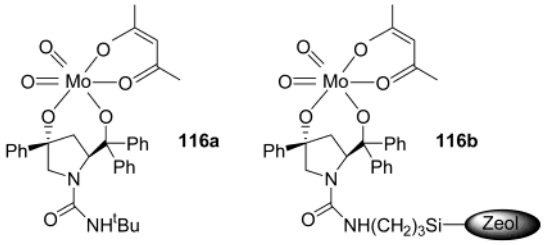


Figure 29.

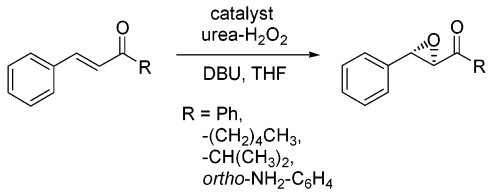
lyst **116b** exhibited much higher enantioselectivities (47% ee for geraniol and 64% ee for nerol) than those (up to 27.6% ee for geraniol and up to 10.4% ee for nerol) obtained with the homogeneous counterpart **116a**. The lifetime of the heterogenized catalyst was also examined by repeating the use of the catalyst **116b**; this showed similar rates and yields of epoxide, even after five runs. The enhanced stability of the heterogenized complex was ascribed to the stronger coordination of the dihydroxy-ligand to Mo than that of the acetylacetonate or hydroxyl group present on the substrate, *tert*-butyl alcohol or hydroperoxide. Dispersion of the catalyst molecules on the mesopores could also avoid dimerization and polymerization of Mo species.



3.1.3. Asymmetric Epoxidation of Enones

Polyamino acids such as poly-L-leucine or poly-L-alanine catalyze the asymmetric epoxidation of α,β-unsaturated ketones in organic solvent/alkaline hydrogen peroxide or in an organic solvent/peroxide donor (e.g., urea−hydrogen peroxide complex)/a organic base such as diazabicycloundecene (DBU).[141−143] However, the most serious problem of this reaction is the difficulty of recovery of gel- or paste-like catalyst. To overcome this problem, polyamino acids supported onto organic polymers[144−146] or inorganic materials[147−149] have been introduced. Roberts et al.[147−149] simply adsorbed polyamino acids (poly-L-(*neo*-pentyl)glycine (PLN), poly-L-leucine (PLL), etc.) onto several inorganic solid carriers, such as aluminum oxide, Celite, molecular sieve, zeolite TS1, silica gel 60, etc. Among these immobilized materials, the silica-adsorbed catalysts (e.g., PLN−Si, PLL−Si) were outstanding. Besides demonstrating an increased catalytic activity and enantioselectivity compared to nonadsorbed polyamino acids (see Table 4), the polyamino acid-on-silica catalyst could be very easily recovered by filtration making recycling of catalyst very simple. The recovered silica-adsorbed polyamino acid catalyst retained catalytic efficiency even after six runs. In addition of these advantages the catalyst exhibited extreme robustness. In contrast to unsupported polyamino acid, e.g., PLL, the catalytic activity of PLL−Si could be fully retained even after heating at 150 °C for 12 h under vacuum.

Table 4. Oxidation of Enones Using Polyamino Acids Adsorbed on Silica



substrate (R=)	catalyst	time (h)	conversion (%)[a]	%ee of epoxide[a]
Ph	PLL−Si	0.5	95 (90)	95 (95)
Ph	PLN−Si	0.5	95 (91)	>95 (>95)
$-(CH_2)_4CH_3$	PLL−Si	24	90 (45)	95 (95)
$-(CH_2)_4CH_3$	PLN−Si	24	100 (97)	97 (90)
$-CH(CH_3)_2$	PLL-Si	26	95 (47)	92 (92)
$-CH(CH_3)_2$	PLN−Si	26	95 (88)	95 (92)
ortho-$NH_2-C_6H_4$	PLL−Si	17	85 (49)	96 (94)
ortho-$NH_2-C_6H_4$	PLN−Si	17	100 (97)	97 (97)

[a] Conversions and ee values obtained in reactions with corresponding homogeneous polyamino acids are given in parentheses.

3.2. Asymmetric Dihydroxylation of Olefins

The cinchona alkaloid-based catalytic asymmetric dihydroxylation (AD) of olefins has become an most important process in organic chemistry for the synthesis of optically pure vicinal diols.[150−157] Since its discovery in 1988,[158] the alkaloid ligands and cooxidant/solvent systems have been optimized so that now almost all classes of olefins can be dihydroxylated with excellent enantioselectivity. Typical ligands are the bis-cinchona alkaloids bearing a pyridazine(PYRD), phthalazine(PHAL), diphenylphthal-

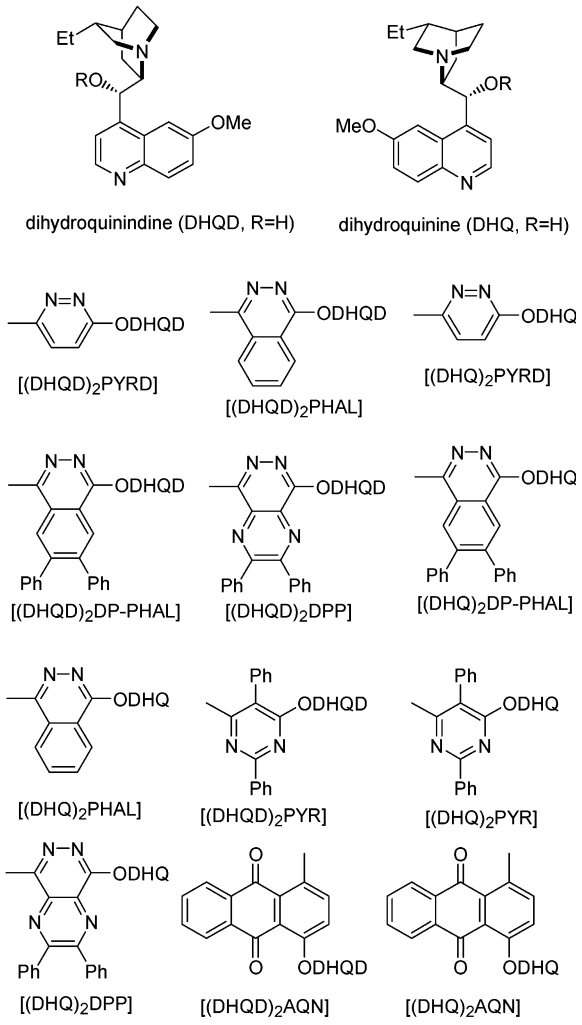
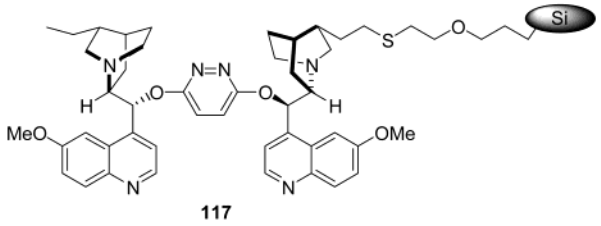


Figure 30. Structures of Cinchona Alkaloid Ligands and Their Abbreviations.

azine(DP−PHAL), diphenylpyrimidine(PYR), or anthraquinone(AQN) core, as shown in Figure 30.

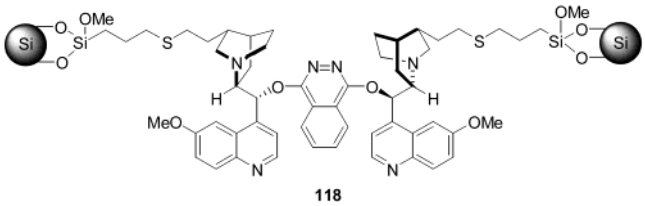
However, there are limitations to performing the catalytic AD reaction on a large scale due to the high cost and/or toxicity of osmium tetroxide and cinchona alkaloid ligands. Recently, to explore the possibility of the repetitive use of both components, alkaloid ligands have been incorporated into various insoluble[159−173] or soluble[174−178] organic polymers and onto inorganic supports.[179−184] Some reviews on this subject have recently been published.[121,185,186]

Immobilization of the alkaloid ligand ((DHQ)$_2$PYRD) on an inorganic support (silica gel) was reported for the first time by Lohray et al.[179] The use of the silica-anchored pyridazine-type ligand **117** led to a comparable reaction rate with that of the homogeneous system, but with significantly lower ees, especially for aliphatic mono- and disubstituted olefins. Using this insoluble ligand **117**, 3-hexene was dihydroxylated with only 45% ee, whereas the homogeneous analogue, (DHQ)$_2$PYRD, gave the dihydroxylated product with 93% ee. In addition, reuse of silica gel-bound ligand indicated appreciable leaching of OsO_4.



117

We[180] have also investigated the silica-supported version of the most effective ligand (DHQ)$_2$PHAL. The silica-attached phthalazine ligand **118** was prepared by the reaction of chiral monomer, 1,4-bis(9-*O*-quininyl)phthalazine [(QN)$_2$PHAL], with 3-mercaptopropylsilanized silica gel in the presence of AIBN as a radical initiator. The monomeric moiety, (QN)$_2$PHAL, could be obtained simply by the reaction of quinine with 1,4-dichlorophthalazine.



118

The silica-supported alkaloid **118** exhibited the same activity and enantioselectivity as the homogeneous phthalazine ligand in the ADs of *trans*-1,2-disubstituted alkenes and 1-phenylcyclohexene using $K_3Fe(CN)_6$ as the oxidant. Yields of between 88% and 95% and ees of greater than 92% were obtained in all cases. The observed results suggest that alkaloid moieties on silica gel remain highly exposed to the reactants and thus substrates can gain access to the catalytic sites easily. It could be also imagined that the alkaloid moiety on silica gel adopts a U-shaped conformation[187] favorable to the catalytic activity and selectivity. In addition, the silica-supported alkaloid **118** revealed a much greater binding ability for OsO_4 than that of its homogeneous analogue. In the

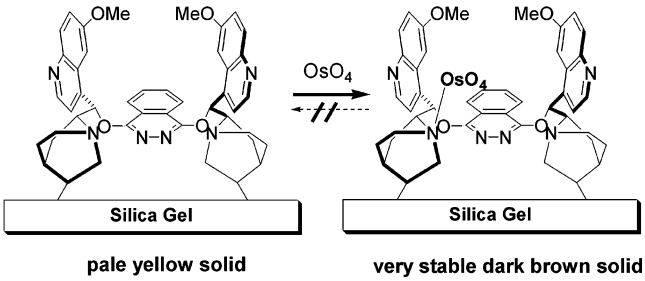
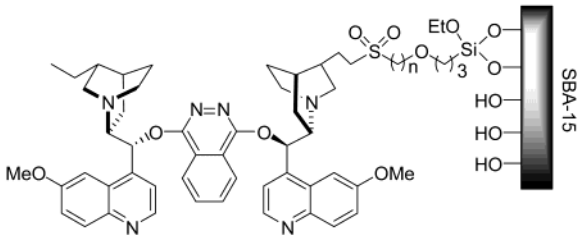


Figure 31. Irreversible Binding of **118** to Osmium.

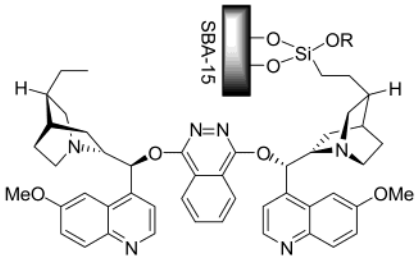
homogeneous solution, the complex formation of alkaloid and OsO_4 is in equilibrium. The binding constant K_{eq} for (DHQD)$_2$PHAL is 27.7.[188] Thus, the enantiomeric excess in the homogeneous reaction approaches the maximum value with increasing ligand concentration. Therefore, for the best results, the reaction usually requires an excess of the expensive alkaloid ligands over osmium. However, with the heterogeneous system **118**, an excellent ee was achieved with only an equimolar amount of ligand to osmium. According to UV analyses,[189] complex formation of the silica-attached ligand **118** with osmium seems to be irreversible (Figure 31). Moreover, in the conventional homogeneous process, there have been many problems due to the toxicity of highly volatile osmium tetroxide. However, formation of the highly stable Os complex of the heterogenized PHAL ligand **118** allowed long-term storage of these complexes without volatilization and decomposition of osmium tetroxide. After 3 months storage at ambient temperature, the SGS−(QN)$_2$PHAL−OsO_4 (1:1) complex exhibited almost the same catalytic activity and enantioselectivity. However, the repeated use of the silica gel supported alkaloid−OsO_4 complex indicated appreciable leaching of osmium.

Very recently, the PHAL ligands have also been successfully grafted on mesoporous silica (SBA-15) by two different research groups.[181,182] The supported ligands **119**[181] and **120**[182] yielded nearly equivalent enantioselectivity compared with that of the homogeneous system. The ligands were easily recovered after the reactions. Although the ligands were recovered unchanged and could be used multiple times, the Os was not retained on the surface and must be added prior to reuse of the ligands.

The DPP and PYR ligands were also immobilized by Bolm et al.[183] on differently functionalized silicas. High enantioselectivities (98% and 97% ee for styrene, respectively) were achieved especially with the ligands **121a**,**b** bearing ether and ester linkers. Lower asymmetric induction (90% ee for styrene) was observed with the amino-linked ligand **121c**. It has been proposed that residual amino groups on the silica surface or the amido linker may have a negative influence. Repeated use of the immobilized ligands was possible only after the addition of the osmium salt after each run; otherwise, a considerable decrease in the chemical yield was observed. The silica-supported alkaloid **121a** itself was used seven times in the AD of styrene without significant loss of enantioselectivity, while with **121b**, lower ees were obtained after each run. Presumably, part of the ligand **121b** was lost by ester hydrolysis under the



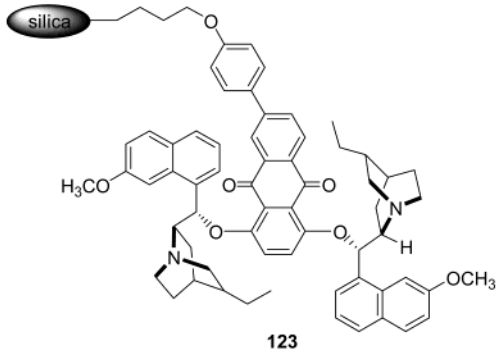
119 (n=2 or 6)



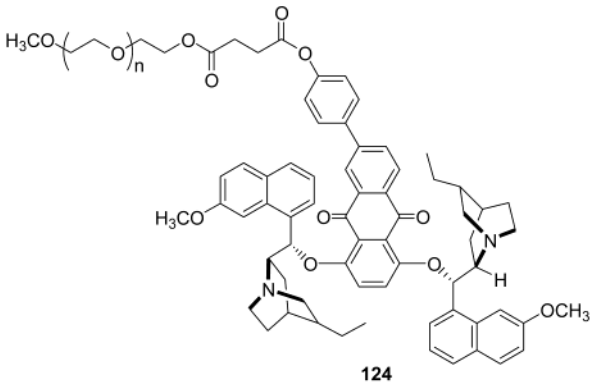
120

alkaline reaction conditions. In contrast to the results obtained with pyrazinopyridazine ligands **121**, ADs of dec-1-ene with the silica-supported pyrimidine-type ligands **122a** and **122b** afforded the corresponding diols only in moderate yield with enantiomeric excess of 84 and 61%, respectively.

The well-known alkaloid ligands with an anthraquinone core (AQN ligands) were also immobilized by covalent attachment to silica gel.[184] However, with the silica-anchored anthraquinone ligand **123**, the ADs of allyl iodide and indene gave greatly inferior results compared to those obtained with the homogeneous ligand ($(DHQD)_2AQN$). Under this heterogeneous conditions, allyl iodide and indene were dihydroxylated with 73% and 47% ee, respectively, whereas the homogeneous ligand gave the diols with 83% and 63% ee, respectively. On the basis of the results obtained using soluble polymeric analogue **124** giving comparable enantioselectivities with homogeneous conditions, the inferior ee values with silica supported alkaloid **123** can be ascribed to the particular character of this heterogeneous alkaloid carrier rather than wrong binding site or attachment type.

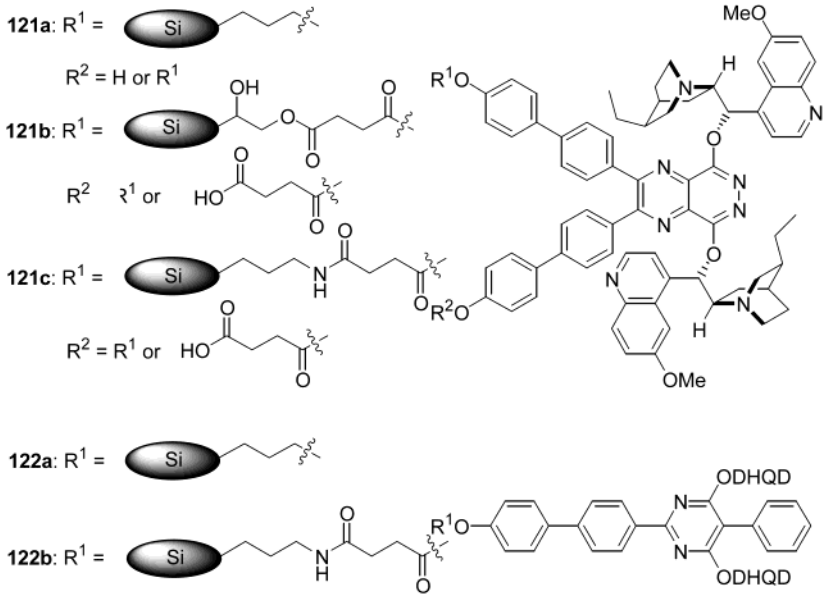


123



124

As described above, to the present day, there have been various successful protocols for ligand recovery. However, effective recovery of osmium has failed in all cases since the coordination of anchored ligands and osmium tetroxide is in equilibrium. To solve this problem, a different immobilization approach has been tried, i.e. immobilization of osmium tetroxide instead of chiral ligands. Kobayashi utilized the microencapsulation technique to envelop osmium tetroxide in the polymer capsules.[190−192] However, these polymer-based microencapsulated OsO_4 displayed relatively low catalytic activity (5 mol % of Os are needed to achieve reasonable reaction rate).



Very recently, the more active osmium catalysts were prepared by Choudary et al. from $K_2OsO_4 \cdot 2H_2O$ by simple ion-exchange technique on various supports such as LDH (layered double hydroxides), silica, and organic resin.[193] Among these three supported catalysts, the LDH−OsO_4 was superior in terms of activity. Especially, the LDH−OsO_4 catalyst is 30-fold more active than the Kobayashi's polymer-based microencapsulated catalyst in achiral dihydroxylation of trans-β-methylstyrene, and it also gave higher ee's in asymmetric dihydroxylation. The LDH−OsO_4 was recovered quantitatively by simple filtration, and the chiral ligand was also recovered by simple acid/base extraction (>95% recovery). The recovered catalyst along with the replenished chiral ligand was reused, and consistent efficiency was observed even after the fifth cycle. The leaching of osmium was not observed.

3.3. Asymmetric Aminohydroxylation of Olefins

Highly efficient methods for osmium-catalyzed asymmetric aminohydroxylation (AA) of alkenes in the presence of $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ ligand have been discovered by Sharpless and co-workers.[152] The resulting chiral β-amino alcohol unit obtained by AAs is an important structural element in many biologically active molecules as well as a starting point in the design of many chiral ligands. Initially, the catalytic AA reaction was exploited with TsNClNa (Chloramine-T) as the oxidant/nitrogen source.[194,195] Subsequent development of new procedures utilizing carbamate-[196] and amide-derived oxidants[197] allowed a great improvement of the substrate scope and selectivity. Up to 99% ee can be achieved with this system. In the absence of an alkaloid ligand, a large amount of diol was formed and the regioselectivity of the reaction decreased. Recently, Sharpless and co-workers reported that the use of AQN core instead of PHAL caused changes in regioselectivity in the AA of cinnamates.[198]

Heterogeneous versions for AAs have very recently been explored by us[199] using silica support and by two other research groups using polymer supports.[200,201] Using the silica-supported phthalazine ligand **118**, up to 99% ee was achieved in the AAs of *trans*-cinnamate derivatives using AcNHBr/LiOH as the oxidant/nitrogen source (Figure 32). Moreover, the dark brown-colored ligand **118**−Os complex was recovered by simple filtration after the reaction. Although XPS analysis showed clearly that these recovered complexes contained osmium, the osmium recovery was not high (<50%). The addition of small amounts of osmium to the recovered catalyst regenerated the optimum reaction conditions.

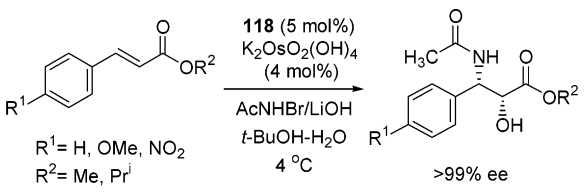
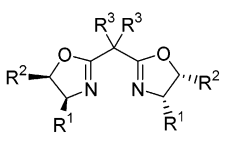


Figure 32.

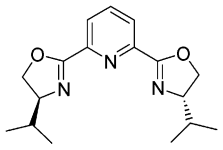
3.4. Asymmetric Aziridination of Olefins

Evans et al.[202,203] have shown that modification of the copper catalysts using chiral bis(oxazoline) ligands induced enantioselectivity in the aziridination reaction. High levels of enantioselection were observed in the aziridination of cinnamate ester derivatives (94−97% ee), although no other substrate classes have been demonstrated to undergo aziridination with synthetically useful levels of stereoinduction.

Hutchings et al.[204−208] immobilized chiral bis(oxazoline)s **125a**−**e** and **126** by electrostatic interaction on copper-exchanged zeolite Y (CuHY) and employed the resulting solid copper catalysts for the asymmetric aziridination of alkenes using two nitrene sources, [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (PhI═NTs) and [N-(*p*-nitrophenylsulfonyl)imino]-phenyliodinane (PhI:NNs). The effects of several factors on both the yields and enatioselectivity of aziridine formed have been examined.[207] It has been found that the ratio of nitrene donor to styrene is shown to be an important factor controlling both the yields and ee of aziridine formed. Moreover, the nitrene donor source also effected on the enantioselectivity. Thus, up to 95.2% ee with **125c** as a chiral ligand has been achieved in the styrene aziridination by using PhI:NNs as nitrene source with 1:1.4 mol ratio of styrene to nitrene donor in acetonitrile solvent. Particularly, the heterogeneous catalyst can give much higher enantioselection than the corresponding homogeneous catalyst for many bisoxazoline ligands. For example, the heterogenized **125b** exhibited 82% ee, whereas 43% ee has been achieved in homogeneous condition. The effect is considered to be due to the confinment of the catalyst within the micropores of the zeolite. Hutchings et al. also studied the stability of the heterogenized catalyst.[208] Under standard reaction conditions (25 °C, 10−24 h), 0.08−6.8% of the Cu present in CuHY were leached; thus, the filtrate obtained from the 24 h reaction catalyzed the aziridination in about 41% yield. However, using short reaction times (<2 h) minimized the leaching (no aziridine was formed by using the filtrate). The stability of the heterogenized catalyst can be also effected by the source of nitrene donor and structure of bisoxazoline ligands.[208] The amounts of leached copper when PhI:NNs (Ns = 4-$O_2NC_6H_4SO_2$) was used as a nitrene source was greater than that when PhI:NTs was used.



125a: R^1 = Ph, R^2 = H, R^3 = Me
125b: R^1 = ^{t}Bu, R^2 = H, R^3 = Me
125c: R^1 = Ph, R^2 = R^3 = H
125d: R^1 = ^{t}Bu, R^2 = R^3 = H
125e: R^1 = R^2 = Ph, R^3 = H



126

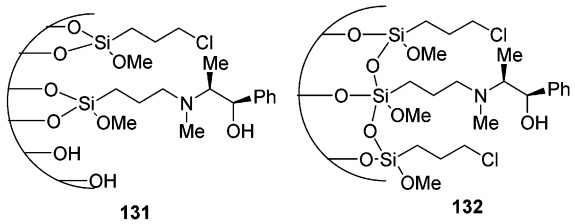
4. Asymmetric Carbon–Carbon and Carbon–Heteroatom Bond Formation

4.1. Enantioselective Addition of Dialkylzincs to Aldehydes

Enantioselective addition of dialkylzinc to aldehydes in the presence of a catalytic amount of chiral ligand is an important reaction for the formation of chiral secondary alcohols. Very high enantioselectivities have been achieved by using natural product-based chiral β−amino alcohols, e.g., ephedrine derivatives, dimethylaminoisoborneol, and proline derivatives. Some of synthetic catalysts such as Ti−TADDOLs, Ti−BINOLs, and chiral 1,2-disulfonamidocyclohexane−Ti complexes also revealed excellent enantioselectivity.[209−212]

Attempts have been made to immobilize the homogeneous catalysts on various supports.[209] Soai et al.[213] reported the use of silica gel or alumina as heterogeneous supports for chiral catalysts for the enantioselective addition of dialkylzinc to aldehydes. Chiral *N*-alkylnorephedrines (R = Me, Et, ^{n}Pr) **128** were immobilized on (3-chloropropyl)silyl-functionalized alumina or silica gel **127** via nucleophilic substitution (Figure 33). However, the catalytic activities and enantioselectivities of **129** were only moderate (24−59% ee) in comparison with those of homogeneous and polymer-supported counterparts. Ephedrine was also immobilized on silica gel coated with chloromethylated polystyrene (Figure 34). Using this hybrid organic/inorganic catalyst **130**, moderate ees (32−56%) were obtained in the alkylation of benzaldehyde and *n*-octanal. It was reported that the catalyst immobilized on silica gel coated with polystyrene **130** could be recycled without loss of enantioselectivity. However, no data for recycling experiments were reported.

Laspéras et al.[214−217] reported the immobilization of chiral ephedrine by covalent linkage to mesoporous templated silicates (MTS) or aluminosilicates (Al−MTS). On using these anchored catalysts for the addition of Et_2Zn to benzaldehyde, lower rates and enantioselectivities compared with homogeneous catalysis were obtained. All attempts involving changes in the pore size, the composition of the support, end-capping of the surface, and dilution of the catalytic sites failed to improve the ees significantly. These results indicate significant activity of the naked surface leading to the formation of racemic alcohols. Very recently, Laspéras et al.[217] tried to decrease the negative effects of the naked mineral surface by increasing the coverage with organic material. The heterogeneous catalyst **132** containing high surface densities of ephedrine ligand and chloropropyl group showed an enhanced rate ($k_{obs}h^{-1} = 0.55$) and ee (up to 64%) compared to those ($k_{obs}h^{-1} = 0.17$, 47% ee) obtained with the low-density solid **131**.



The well-known pyrrolidine methanol ligand was also immobilized covalently on mesoporous silicas by Kim et al. (Figure 35).[218,219] These supported catalysts **134a−c** were more efficient than ephedrine-based heterogeneous catalysts in the asymmetric addition of diethylzinc to benzaldehyde. However, to obtain higher ees, pretreatment of the catalyst with butyllitium was necessary. The highest ee value (75%) was obtained with TMS-capped SBA-15 based catalyst **134c** utilized after treatment with ^{n}BuLi. However, the ee values remained lower than those (93%) obtained under homogeneous conditions using the catalyst **133**. Moreover, the catalysts immobilized on other supports such as amorphous silica (**134a**) and MCM-41 (**134b**) exhibited a much inferior efficiency (see Figure 35). No studies concerning the reuse of the catalytic system were described.

Seebach et al.[220] linked the TADDOL ligand onto controlled-pore glasses (CPG) to prepare the solid-supported TADDOL−Ti catalyst **135**. This insoluble

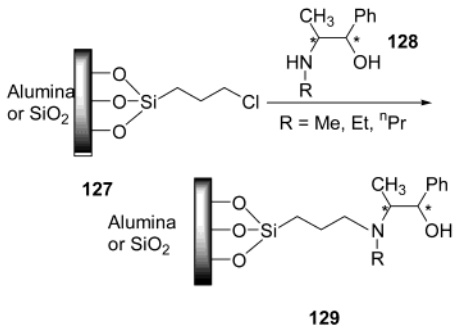


Figure 33.

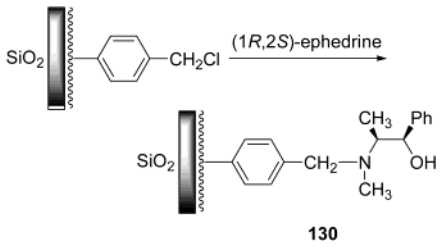


Figure 34.

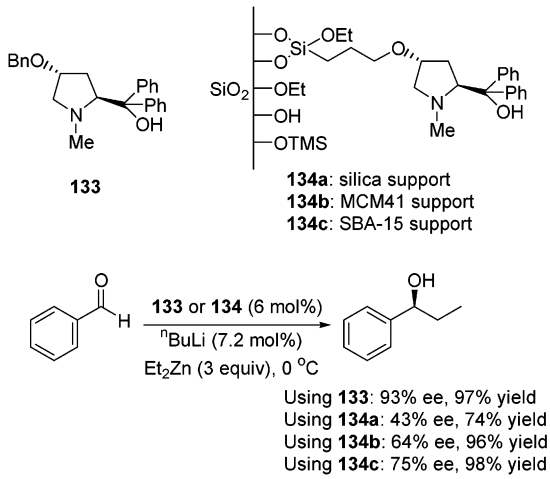


Figure 35.

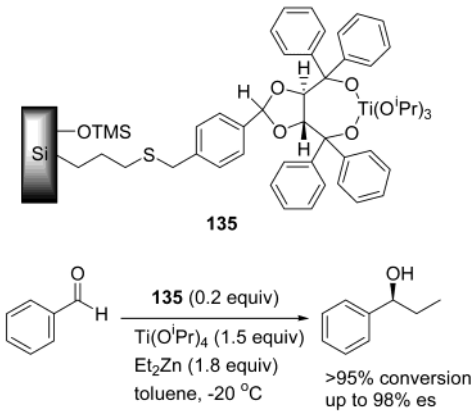


Figure 36.

material effectively catalyzed the Et_2Zn addition to benzaldehyde in toluene at −20 °C in the presence of excess $Ti(O^iPr)_4$ to give (*S*)-1-phenylpropanol with up to 96% ee and in >95% yield (Figure 36). The catalytic properties of this heterogeneous catalyst **135** were almost the same as those of its homogeneous analogue. Moreover, the immobilized TADDOL could be reused after washing with HCl/H_2O/acetone, drying, and reloading with titanate. For example, even after 20 catalytic runs, the enantioselectivities observed were as good as at those at the start.

4.2. Asymmetric Cyclopropanation

Asymmetric catalytic cycloaddition of electrophilic metal carbenes to prochiral olefins is a facile methodology for highly enantioselective cyclopropane synthesis. The method consists of the metal-catalyzed decomposition of substituted diazo compounds in the presence of various alkenes. The most successful catalysts are complexes of copper and rhodium.[221−223]

There are very few examples of chiral heterogeneous catalysts for cyclopropanation reactions. The first heterogeneous asymmetric cyclopropanation was reported by Matlin et al.[224] The homogeneous chiral ligand **136**, 10-methylene-3-trifluoroacetyl-(+)-camphor, was immobilized via silylated **137** on Hypersil 5 mm silica to give **138** (Figure 37). Residual silanol sites on the silica were capped using trimethylsilyl chloride. In the reaction of styrene with 2-diazodimedone **139**, the copper complex of the immobilized chiral *β*-diketone **138** exhibited comparable enantioselectivity (98.3% ee) with its homogeneous analogue (Cu^{2+} complex of **136**). Moreover, in a first run, the reaction proceeded 2.4 times faster than corresponding homogeneous reaction. However, due to the coating of polystyrene around the silica, recycling failed. The authors claimed that if olefins such as indene that were not polymerizable were employed, catalytic activity was retained. It was also reported that the Ni complex of **138** proved to be slightly more active than the Cu form and maintained its activity for at least three cycles.

Efforts have been made by Iglesias et al. to heterogenize copper[225,226] and rhodium complexes[28,226] of (*S*)-proline-derived ligands bearing a triethoxysilyl group, e.g., **141** and **143**, by a covalent link onto ultrastable Y-zeolite (Figure 38). The catalytic properties of the anchored complexes **142** and **144** in the

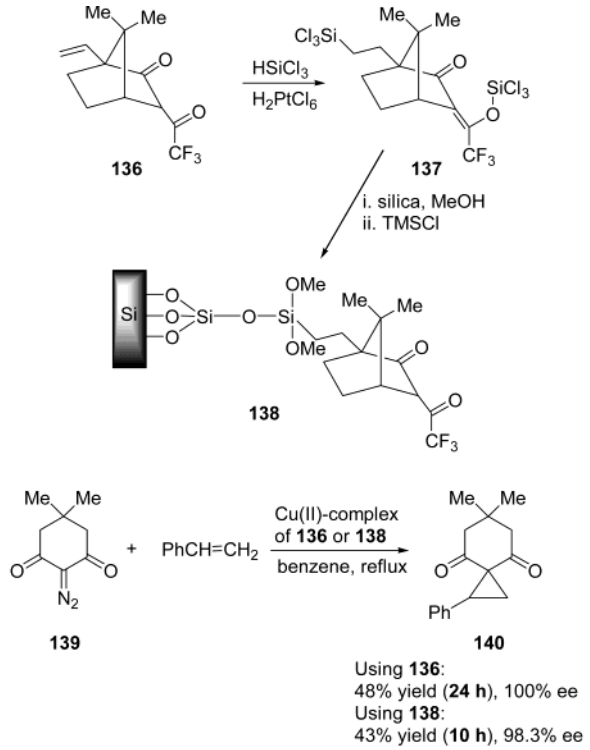


Figure 37.

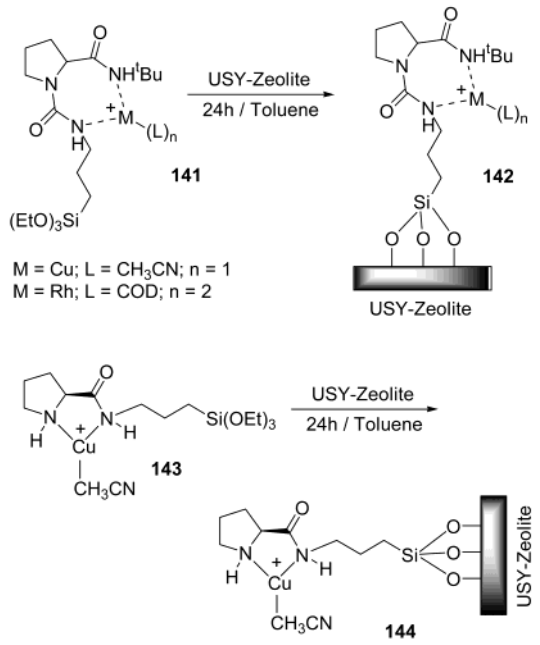
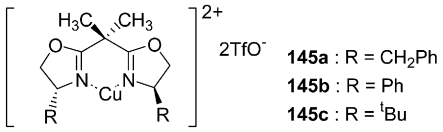


Figure 38.

cyclopropanation of styrene and dihydropyrane with alkyl diazoacetate were compared to those of their homogeneous counterparts. The chemical yields obtained with unsupported and zeolite-supported complexes were almost identical. However, both homogeneous and heterogeneous catalysts exhibited extremely low enantioselectivities (0−18% ee). The zeolite-supported complexes (**142** and **144**) induced a slightly higher proportion of cis ester than the soluble analogues due to steric factors.

Recently, Fraile et al.[227−230] reported that bis(oxazoline)−copper complexes **145** could be immobilized by electrostatic interaction with several anionic

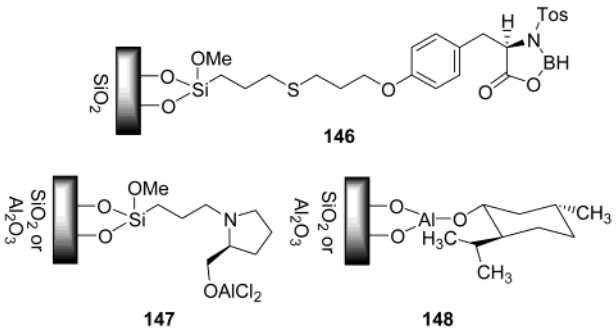
supports such as clays (Laponite, bentonite, K10 montmorillonite)[227,228] or Nafion−silica nanocomposite.[229,230] In these immobilized catalysts, the steric interactions between support counteranions and bis-oxazoline ligands could affect the catalytic efficiency; i.e., the activity and selectivity were dependent on the ligand substituent R in **145** and the nature of the anionic supports. For example, in the case of 2,2′-isopropylidene-[(4*R*)-4-phenyl-2-oxazoline] **145b**−copper complex, the Nafion−silica nanocomposite was the best support (57% ee for the *trans*-cyclopropanes and 46% ee for the *cis*-cyclopropanes) in the cyclopropanation of styrene with ethyl diazoacetate. The Cu(II) complex of 2,2′-isopropylidene-[(4*S*)-4-*tert*-butyl-2-oxazoline] **145c** led to better results (69% ee for the *trans*-cyclopropanes and 64% ee for the *cis*-cyclopropanes) when the complex was supported on Laponite. The recovered catalysts led to lower activity and enantioselectivity.



4.3. Asymmetric Diels−Alder Reaction and [3+2]-Cycloaddition

Diels−Alder reactions are usually catalyzed by Lewis acids, and several asymmetric versions of acid-catalyzed reactions have been reported.[231] However, often a large quantity (5 to over 100 mol %) of the chiral Lewis acid has to be employed. Therefore, immobilization and reuse of Lewis acid catalysts is potentially important. However, there are only a few reports on the use of supported chiral Lewis acids for enantioselective Diels−Alder cycloadditions.[105,232−241] Mostly, organic polymers have been utilized[105,232−239] and only a few examples of inorganic supported Lewis acid have been reported.[240,241]

Fraile et al.[240] studied a Diels−Alder reaction catalyzed by chiral Lewis acids immobilized on alumina and silica. (*S*)-Tyrosine, (*S*)-prolinol, or (−)-menthol were used as chiral auxiliaries. When these chiral auxiliaries were grafted on the support, the asymmetric induction decreased drastically. The silica-supported oxazaborolidone **146**, which was obtained by the reaction of BH_3 with *N*-tosyl-(*S*)-tyrosine anchored on functionalized silica showed no asymmetric induction for the reaction of methacrolein and cyclopentadiene. Anchored proline derivatives such as **147** also exhibited a very low ee (8%). End



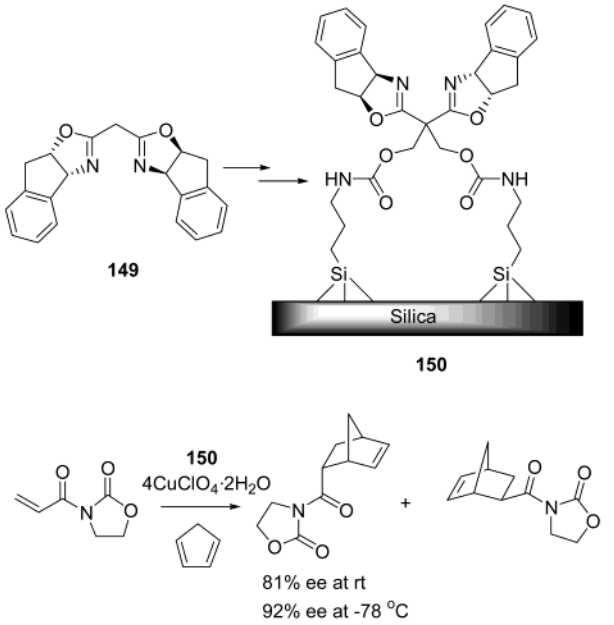


Figure 39.

capping of the unreacted surface silanol groups with hexamethyldisilazane (HMDS) did not improve the asymmetric induction. Slightly better results were obtained with the (−)-menthol-aluminum Lewis acid anchored on silica or alumina **148** (up to 31% ee).

Recently, Lemaire heterogenized the bis(oxazoline) ligand **149** by grafting onto silica surface to give **150**. The catalytic performance of the silica-grafted **150** was examined for asymmetric Diels−Alder reaction of 3-acryloyl-2-oxazolidinone with cyclopentadiene (Figure 39).[241] The heterogenized catalyst could be efficiently recycled when $Cu(ClO_4)_2 \cdot 6H_2O$ was used as the metal precursor. The catalytic activity did not diminish after four cycles. To obtain the best result, the silanol groups of this silica catalyst were protected by TMS groups, and thus 81% ee was obtained at room temperature and 92% ee at −78 °C. These

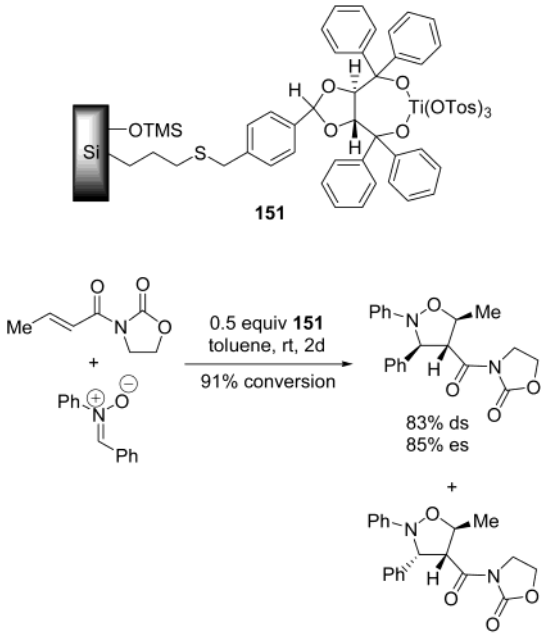


Figure 40.

results, although not quite as good as those (98% ee at −78 °C for the same reaction) of the homogeneous system **149**, are better than any achieved so far with heterogeneous bis(oxazoline) ligands for the Diels−Alder reaction. Moreover, this system has the advantage of being compatible with air humidity.

The TADDOL−Ti catalyst immobilized onto controlled-pore glasses (CPG) **151** induced [3+2]-cycloaddition of diphenylnitrone to *N*-crotonyl-1,3-oxazolidin-2-one with 66% de and 70% ee (Figure 40).[220] Under homogeneous conditions with a comparable TADDOL derivative, similar selectivities (70% de and 85% ee) were found. Good reproducibility was also possible when the catalyst was reused. Only a small loss of activity was observed after four runs.

4.4. Asymmetric Conjugate Addition

Sanchez and co-workers[242] anchored the Ni complex of L-proline amide **152b** on USY zeolites or silica by a covalent link (Figure 41). Using the insoluble catalysts **153** and **154** the conjugate addition of $ZnEt_2$ to enones **155** took place more slowly than under homogeneous conditions. However, very interestingly, the ee values of the saturated ketones **156** were much higher with the zeolite-supported Ni complex **153** (91 and 95% ee, for R = Ph and Me, respectively) than those with the homogeneous counterpart **152a** (77 and 75% ee, for R = Ph and Me, respectively) or the silica-supported analogue **154** (34% ee, R = Ph). These enhanced enantioselectivities may result from the additional steric constraints imposed by the zeolite pores.

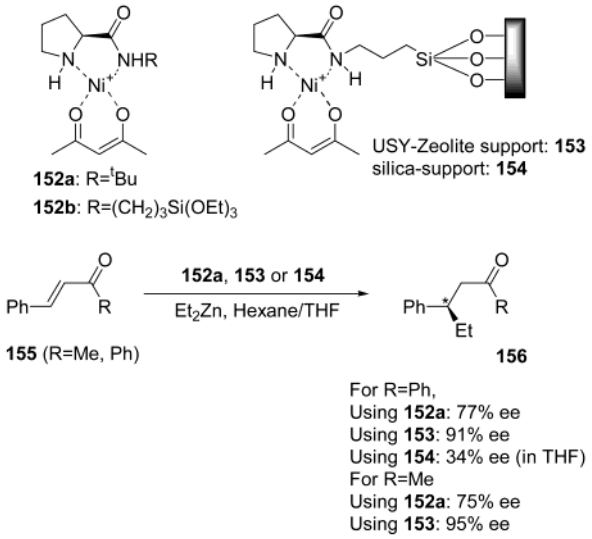
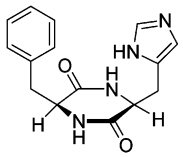


Figure 41.

4.5. Asymmetric Hydrocyanation

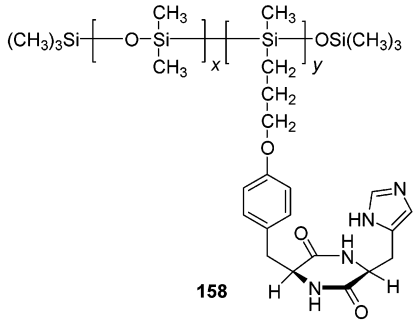
Optically pure cyanohydrins are versatile synthetic intermediates in the synthesis of a wide range of homochiral products such as α-hydroxy acids, *β*-hydroxy amines, and α-amino acid derivatives, etc. Many catalytic enantioselective hydrocyanations and silylcyanations of aldehydes and ketones have been reported.[243] In particular, the enantioselective hydrocyanation of aldehydes catalyzed by cyclic peptides, first reported by Inoue et al.[244,245] has been intensively studied; cyclo[(*S*)-phenylalanyl-(*S*)-histidyl] (**157**) proved to be a highly effective catalyst for the hydrocyanation of aldehydes giving (*R*)-cyanohydrins.



157

Shvo et al.[53] heterogenized the cyclic peptide catalyst **157** in a sol−gel matrix. The sol−gel entrapped chiral catalyst induced catalytic hydrocyanation of benzaldehyde to furnish (*R*)-mandelonitrile with up to 98% ee. However, the results from recycling the encapsulated catalyst were very disappointing. The enantioselectivity and activity dropped significantly in the second cycle.

Kim and Jackson[246] also made the insoluble polysiloxane catalyst **158**, in which the cyclic dipeptide was attached to a poly(hydrogen, methyl)(dimethyl)-siloxane copolymer via a C_3 spacer. However, this polysiloxane catalyst **158** gave a very low enantiomeric excess (10%) for the addition of HCN to 4-(4-allyloxyphenylcarboxy)benzaldehyde, whereas the use of the Inoue dipeptide **157** under similar conditions gave the cyanohydrin with 95% ee. The loss of enantioselectivity relative to the Inoue catalyst was attributed to the polysiloxane being formed through the para-position of the phenyl ring, which is the nearest site to the imidazole ring in the proposed active conformation of compound **157**. This may disrupt the conformation of the catalyst.



158

4.6. Pd-Catalyzed Asymmetric Allylic Substitutions

Pd-catalyzed asymmetric allylic substitution reactions are useful synthetic methods for asymmetric C−C and C−X bond formation. A number of homogeneous chiral ligands have been developed for this kind of reaction.[247,248] This catalytic enantioselective transformation has rarely been studied in its heterogeneous form.[9,249−253] Williams et al.[253] reported successful use of reverse phase silica in heterogeneous enantioselective allylic substitution reactions. The phosphino-oxazoline ligand **159**, simply incorporated into reverse phase silica, successfully catalyzed the reaction of allylic acetate **160** with sodium malonate,

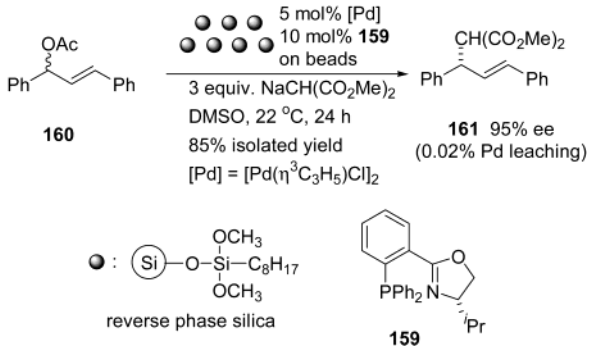
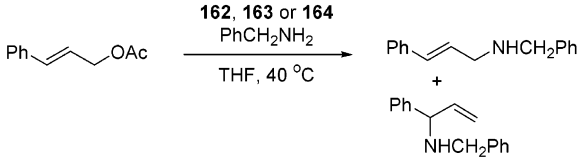


Figure 42.

Table 5. Catalytic Results



catalyst	conversion (%)	straight chain (%)	branched (%)	% ee
162 (*S*)	76	>99	–	–
163 (*S*)	98	98	2	43
164 (*S*)	>99	49	51	>99

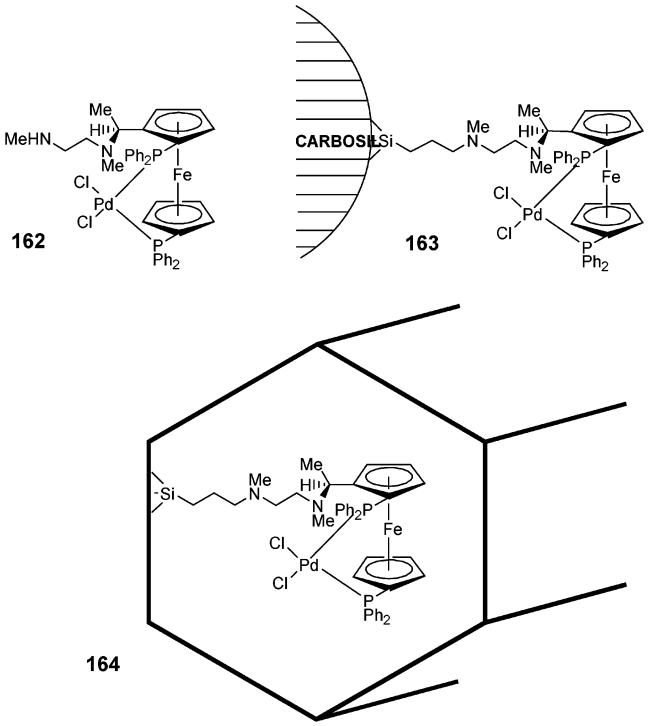
affording the malonate substituted product **161** in high yield and excellent ee (95%) (Figure 42). Moreover, the level of palladium leaching was very low (0.02%). This type of supported phase may have two important advantages: first, the mobility of catalyst can be retained, and so high enantiomeric excess can be achieved; second, the homogeneous chiral ligand **159** can be employed without any structural modification.

Immobilized ferrocenyl Pd-complexes **163** and **164** have been reported by Johnson et al.[9] In allylic amination of cinnamyl acetate, the catalyst **164**, immobilized on inner walls of the mesoporous MCM-41, exhibited superior catalytic properties compared to the catalyst **163** anchored on Carbosil (a non porous, high-area silica) or even the homogeneous catalyst **162**. As shown in Table 5, the catalysts **164** showed some degree of regioselectivity for the desirable branched product (51%) and extremely high enantioselectivity (>99% ee), whereas Carbosil immobilized catalysts **163** afforded the branched product in only 2% yield and with 43% ee. With the homogeneous catalyst **162** the reaction directed solely toward the straight chain product. These results can be a good example of the positive control effected by the surrounding support such as MCM-41.

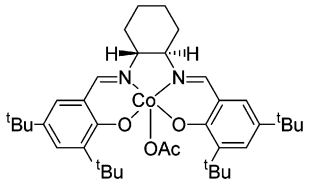
4.7. Asymmetric Ring-Opening Reactions of Racemic/Meso Epoxides

4.7.1. Hydrolytic Kinetic Resolution of Racemic Epoxides

Kinetic resolution (KR) can be highly effective strategy for the preparation of optically pure compounds, particularly if the corresponding racemates are readily available and a practical procedure for KR can be applied. In this light, the recently disclosed



hydrolytic kinetic resolution (HKR) reaction of epoxides catalyzed by chiral (salen)Co complex **165** constitutes a very attractive approach toward the preparation of enantiopure terminal epoxides.[254−256]



(*R*,*R*)-**165**

Silica-bound chiral (salen)Co complex **166** was used for the heterogeneous version of the hydrolytic kinetic resolution (HKR) of terminal epoxides, e.g., styrene oxide (Figure 43).[257] Enantiomeric excesses as high as those observed for homogeneous phase reactions were obtained. The enantioselective addition of phenols to terminal epoxides using this catalyst system **166** was also examined. The silica-bound catalyst was shown to be suitable for a continuous-flow system. Therefore, this catalytic system can provide a practical solution to certain technical difficulties associated with the isolation of reaction products such as epichlorohydrin from the HKR. For example, chiral epichlorohydrin can easily be racemized in the presence of the Co(salen) catalyst **165** during the isolation process by distillation.

The unsymmetrical chiral (salen)Co(III) complexes were also immobilized on a siliceous MCM-41 through multistep anchoring and used as catalysts in the hydrolytic kinetic resolution of racemic epoxides to diols.[258] The reaction using the immobilized Co−salen complexes **167** on MCM-41 gave the almost same enantioselectivity (up to 92 and 98% for epichlorohydrin and epoxystyrene, respectively) as compared to that of homogeneous salen catalysts. However, the

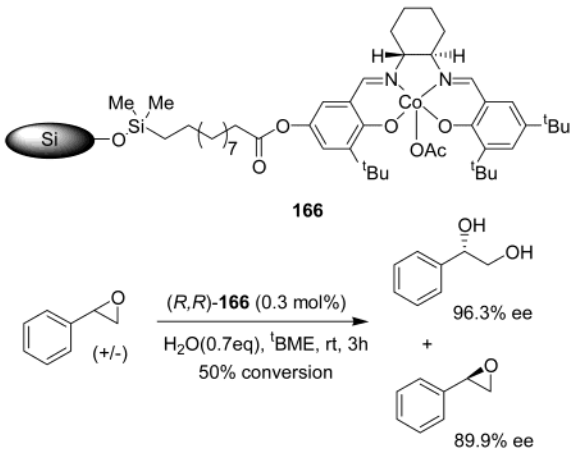
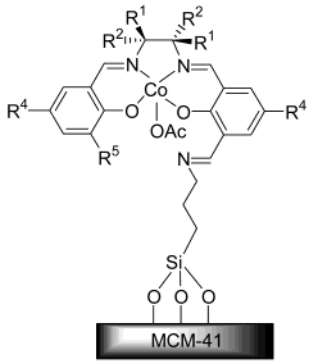


Figure 43.

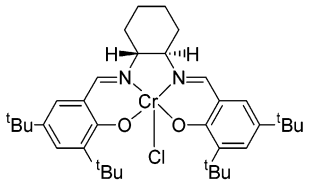
reaction rate was low, so that a prolonged reaction time was required.



167a: R^1=Ph, R^2=R^3=H, R^4=R^5=^{t}Bu
167b: R^1=-$(CH_2)_4$-, R^2=R^3=H, R^4=R^5=^{t}Bu
167c: R^1=-$(CH_2)_4$-, R^2=H, R^3=^{t}Bu, R^4=R^5=H
167d: R^1=-$(CH_2)_4$-, R^2=H, R^3=R^4=R^5=^{t}Bu

4.7.2. Asymmetric Ring Opening Reactions of meso-Epoxides With Trimethylsilyl Azide

Optically pure β-amino alcohols are important compounds, as intimated earlier. Among the many other methods, asymmetric ring opening reactions (ARO) of epoxides with $TMSN_3$, catalyzed by Cr(salen) complex **168**, has been recognized as an attractive approach to the synthesis of optically pure β-amino alcohols[254,255] particularly since the Cr(salen) catalyst exhibited an indefinite stability under the catalytic conditions which allowed for its repeated recycling. Jacobsen et al. reported that this reaction could be run without solvents and the catalyst could be recycled a number of times without loss of activity and enantioselectivity.[259] However, this catalyst recycling procedure involves the potentially hazardous distillation of neat azides and this factor may provide a limitation for large scale applications. Very recently, we reported a practical recycling procedure of Cr(salen) catalyst involving the use of air and moisture stable ionic liquids based on 1-butyl-3-methylimidazolium [bmim] salts.[260] However, only one heterogenized example of homogeneous Cr(III)-salen complex **168** has been reported so far.[261]



(*R*,*R*)-**168**

Chiral Cr(III)−salen complexes **169a**,**b** were incorporated with the cavities of zeolites Y, EMT and into the interlamellar region of K-10 montmorillonite (Figure 44).[261] Although these heterogenized catalysts were able to promote the asymmetric ring opening of epoxides with trimethylsilyl azide to afford chiral azido trimethylsilyl ethers and azido alcohols, the reaction times were markedly longer than those required with homogeneous catalysts. This can be attributed to restrictions imposed on the diffusion of reactants and products through the micropores of the zeolite lattice as compared to unrestricted diffusion in solution. Moreover, the enantioselectivity of the reaction leading to ring-opened azide was largely reduced with respect to that achieved with the unsupported complexes in the homogeneous phase. One of the reasons for the decreased enantioselectivity of the supported catalyst in the micropores of the zeolite may be a change from bimetallic to a single metallic reaction mechanism.

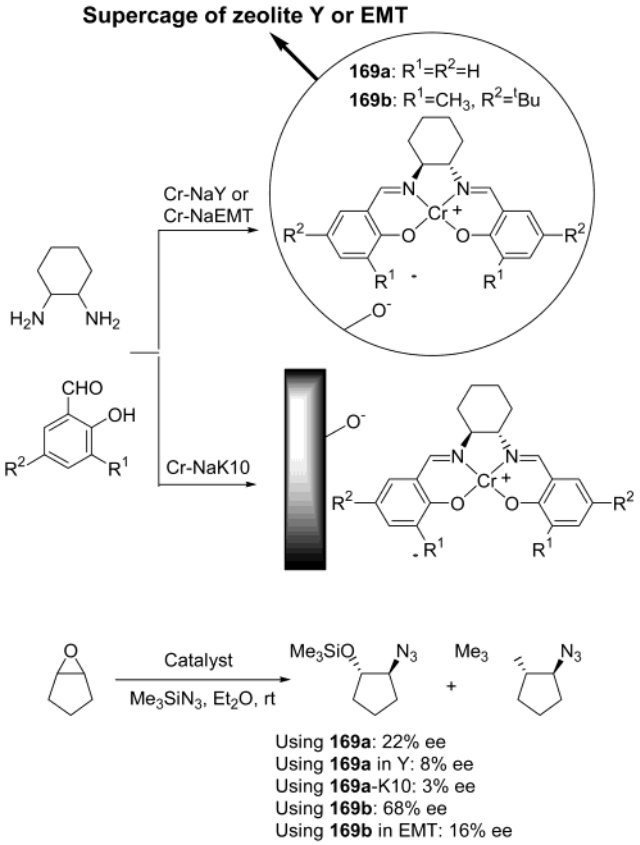


Figure 44.

5. Conclusion

This review has presented the current strategies for immobilization of homogeneous chiral catalysts

on inorganic supports. Because of their unique properties, such systems have received a great deal of attention in recent years. However, from a practical point of view, the results cited in this review are still far from satisfactory. Catalytic behaviors of the heterogenized catalysts are usually much more complex than their homogeneous ones, thereby often leading to unpredictable and undesirable changes of catalytic properties. However, some of recent results, where immobilization using inorganic supports positively influenced the catalytic properties (activity, selectivity and stability), are very promising. In some cases, the activity and selectivity rather increased upon subsequent reuses. More detailed understanding of such interesting phenomena should be addressed in future. Moreover, the studies on the influence of support materials on catalysis will also be very important for the development of more efficient and practical heterogenized chiral catalysts.

6. Acknowledgment

We are grateful to the National Program of the Ministry of Science and Technology in Korea and to the KIST for financial support.

7. References

(1) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. In *Comprehensive Asymmetric Catalysis I*−*III*; Springer-Verlag: Berlin, 1999.
(2) Ojima, I., Ed. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000.
(3) Collins, A. N., Sheldrake, G. N., Crosby, J., Eds. In *Chirality in Industry (I)*; John Wiley & Sons: New York, 1992. Collins, A. N., Sheldrake, G. N., Crosby, J., Eds. In *Chirality in Industry (II)*; John Wiley & Sons: New York, 1996.
(4) Pugin, B.; Blaser, H.-U. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, p 1367.
(5) Oehme, G. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, p 1378.
(6) Kragl, U.; Dwars, T. *Trends Biotechnol.* **2001**, *19*, 442−449.
(7) Song, C. E.; Lim, J. S.; Kim, S. C.; Lee, K.-J.; Chi, D. Y. *Chem. Commun.* **2000**, 2415.
(8) Raynor, S. A.; Thomas, J. M.; Raja, R.; Johnson, B. F. G.; Bell, R. G.; Mantle, M. D. *Chem. Commun.* **2000**, 1925.
(9) Johnson, B. F. G.; Raynor, S. A.; Shephard, D. S.; Mashmeyer, T.; Thomas, J. M.; Sankar, G.; Bromley, S.; Oldroyd, R.; Gladden, L.; Mantle, M. D. *Chem. Commun.* **1999**, 1167.
(10) Price, P. M.; Clark, J. H.; Macquarrie, D. J. *J. Chem. Soc., Dalton Trans.* **2000**, 101.
(11) Vankelecom, I. F. J.; Jacobs, P. A. In *Catalyst Immobilization on Inorganic Supports*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, 2000; p 19.
(12) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217.
(13) Bergbreiter, D. E. In *Organic Polymers as a Catalyst Recovery Vehicle* in *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, 2000; p 43.
(14) Blaser, H.-U.; Müller, M. *Studs. Surf. Sci. Catal.* **1991**, *59*, 73.
(15) Blaser, H. U. *Tetrahedron: Asymmetry* **1991**, *2*, 843.
(16) Webb, G.; Wells, P. B. *Catal. Today* **1992**, *12*, 319.
(17) Augustine, R. L.; Tanielyan, S. K.; Doyle, L. K. *Tetrahedron: Asymmetry* **1993**, *4*, 1803.
(18) Baiker, A. *J. Mol. Catal. A: Chem.* **1997**, *115*, 473.
(19) Blaser, H.-U.; Jalett, H. P.; Müller, M.; Studer, M. *Catal. Today* **1997**, *37*, 441.
(20) Wells, P. B.; Wilkinson, A. G. *Topics Catal.* **1998**, *5*, 39.
(21) De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds. In *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: New York, 2000; Chapters 6 (Wells, P. B.; Wells, R. P. K.), 7 (Baiker, A.), and 8 (Tai, A.; Sugimura, T.).
(22) Kinting, A.; Krause, H.; Čapka, M. *J. Catal.* **1985**, *25*, 152.
(23) Eisen, M.; Blum, J.; Schumann, H.; Gorelia, B. *J. Mol. Catal.* **1989**, *56*, 329.
(24) Eisen, M.; Blum, J.; Höhne, G.; Schumann, H.; Schwarz, H. *Chem. Ber.* **1989**, *122*, 1599.
(25) Nagel, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 435.
(26) Nagel, U.; Kinzel, E. *J. Chem. Soc., Chem. Commun.* **1986**, 1098.
(27) Corma, A.; Iglesias, M.; del Pino, C.; Sánchez, F. *J. Chem. Soc., Chem. Commun.* **1991**, 1253.
(28) Corma, A.; Iglesias, M.; del Pino, C.; Sánchez, F. J. *J. Organomet. Chem.* **1992**, *431*, 233.
(29) Carmona, A.; Corma, A.; Iglesias, M.; José, A. S.; Sánchez, F. *J. Organomet. Chem.* **1995**, *492*, 11.
(30) Corma, A.; Iglesias, M.; Mohino, F.; Sánchez, *J. Organomet. Chem.* **1997**, *544*, 147.
(31) Pugin, B.; Müller, M. *Stud. Surf. Sci. Catal.* **1993**, *78*, 107.
(32) Pugin, B. *J. Mol. Catal.* A.: *Chem.* **1996**, *107*, 273.
(33) Augustine, R.; Tanielyan, S.; Anderson, S.; Yang, H. *Chem. Commun.* **1999**, 1257.
(34) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.
(35) Pugin, B. WO 9632400 A1 (1996), WO 9702232 A1 (1997), European Patent 729969, 1996.
(36) Pugin, B.; Steiner, I.; Aufdenblatten, R. N.; Togni, A. European Patent 1002801, 1999.
(37) Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897.
(38) Thomas, J. M.; Maschmeyer, T.; Johnson, B. F. G.; Shephard, D. S. *J. Mol. Catal. A: Chemical* **1999**, *141*, 139.
(39) Mazzei, M.; Marconi, W.; Riocci, M. *J. Mol. Catal.* **1980**, *9*, 381.
(40) Fiorini, M.; Giongo, G. M. *J. Mol. Catal.* **1980**, *7*, 411.
(41) Selke, R.; Čapka, M. *J. Mol. Catal.* **1990**, *63*, 319.
(42) Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265.
(43) Ishizuka, N.; Togashi, M.; Inoue, M.; Enomoto, S. *Chem. Pharm. Bull.* **1987**, *35*, 1686.
(44) Bianchini, C.; Barbaro, P.; Dal Santo, V.; Gobetto, R.; Meli, A.; Oberhauser, W.; Psaro, R.; Vizza, F. *Adv. Synth. Catal.* **2001**, *343*, 41.
(45) Bianchini, C.; Burnaby, D. G.; Evans, J.; Frediani, P.; Meli, A.; Oberhauser, W.; Psaro, R.; Sordelli, L.; Vizza, F. *J. Am. Chem. Soc.* **1999**, *121*, 5961.
(46) Bianchini, C.; Dal Santo, V.; Meli, A.; Oberhauser, W.; Psaro, R.; Vizza, F. *Organometallics* **2000**, *19*, 2433.
(47) Bianchini, C.; Barbaro, P.; Scapacci, G.; Zanobini, F. *Organometallics* **2000**, *19*, 2450.
(48) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
(49) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori. R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
(50) De Rege, F. M.; Morita, D. K.; Ott, K. C.; Tumas, W.; Broene, R. D. *Chem. Commun.* **2000**, 1797.
(51) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653.
(52) Avnir, D. *Acc. Chem. Res.* **1995**, *28*, 328.
(53) Shvo, Y.; Becker, Y.; Gal, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2719.
(54) Shabat, D.; Grynszpan, F.; Saphier, S.; Truniansky, A.; Avnir, D.; Keinan, E. *Chem. Mater.* **1997**, *9*, 2258.
(55) Gelman, F.; Avnir, D.; Schumann, H.; Blum, J. *J. Mol. Catal. A.: Chem.* **1999**, *146*, 123.
(56) Brunner, H.; Bielmeier, E.; Wiehl, J. *J. Organomet. Chem.* **1990**, *384*, 223.
(57) Brunner, H.; Rosenboem, S. *Monatshefte Chem.* **2000**, *131*, 1371.
(58) Flach, H. N.; Grassert, I.; Oehme, G.; Capka, M. *Colloid Polym. Sci.* **1996**, *274*, 261.
(59) Wan, K. T.; Davis, M. E. *J. Catal.* **1994**, *148*, 1.
(60) Wan, K. T.; Davis, M. E. *Nature* **1994**, *370*, 449.
(61) Wan, K. T.; Davis, M. E. *J. Catal.* **1995**, *152*, 25.
(62) Davis, M. E.; Wan, K. T. U.S. Patent 5,736,480, 1998.
(63) Davis, M. E.; Wan, K. T. U.S. Patent 5,827,794, 1998.
(64) Brunner, H.; Pieronczyk, W.; Schönhammer, B.; Streng, K.; Bernal, I.; Korp, J. *Chem. Ber.* **1981**, *114*, 1137.
(65) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Commun.* **1972**, 10.
(66) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.
(67) Yin, M.-Y.; Yuan, G.-L.; Wu, Y.-Q.; Huang, M.-Y.; Jiang, Y.-Y. *J. Mol. Catal. A: Chem.* **1999**, *147*, 93.
(68) Nagata, T.; Sugi, K. D.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Catal. Surveys Jpn.* **1998**, *2*, 47.
(69) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; p 56.
(70) Carpentier, J.-F.; Agbossou, F.; Mortreux, A. *Tetrahedron: Asymmetry* **1995**, *6*, 39.
(71) Karim, A.; Mortreux. A.; Petit, et F. *J. Organomet. Chem.* **1986**, *312*, 375.
(72) Yin, M.-Y.; Yuan, G.-L.; Wu, Y.-Q.; Huang, M.-Y.; Jiang, Y.-Y. *J. Mol. Catal. A: Chem.* **1999**, *147*, 93.
(73) Vankelecom, I. F. J.; Tas D.; Parton, R. F.; Van de Vyver, V.; Jacobs, P. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1346.
(74) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.
(75) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
(76) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580.

(77) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J.-W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2000**, *6*, 2818.
(78) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466.
(79) Bein, T. *Curr. Opin. Solid State Mater. Sci.* **1999**, *4*, 85.
(80) Breysse, E.; Pinel, C.; Lemaire, M. *Tetrahedron: Asymmetry* **1998**, *9*, 897.
(81) Bayston, D. J.; Travers, C. B.; Polywka, M. E. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2015.
(82) Adima, A.; Moreau, J. J. E.; Wong Chi Man, M. *J. Mater. Chem.* **1997**, *7*, 2331.
(83) Adima, A.; Moreau, J. J. E.; Wong Chi Man, M. *Chirality* **2000**, *12*, 411.
(84) Bied, C.; Gauthier, D.; Moreau, J. J. E.; Wong Chi Man, M. *J. Sol-Gel Sci. Technol.* **2001**, *20*, 313.
(85) Moreau, J. J. E.; Vellutini, L.; Wong Chi Man, M.; Bied, C. *J. Am. Chem. Soc.* **2001**, *123*, 1509.
(86) Hesemann, P.; Moreau, J. J. E. *Tetrahedron: Asymmetry* **2000**, *11*, 2183.
(87) Sandee, A. J.; Petra, D. G. I.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 1202.
(88) Petra, D. G. I.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Van Loon, A. M.; de Vries, J. G.; Schoemaker, H. E. *Eur. J. Inorg. Chem.* **1999**, *12*, 2335.
(89) Čapka, M. *Collect. Czech. Chem. Commun.* **1977**, *42*, 3410.
(90) Kolb, I.; Cerny, M.; Hetlejs, J. *React. Kinet. Catal. Lett.* **1977**, *7*, 199.
(91) Nishiyama, H. In *Hydrosilylation of Carbonyl and Imino Groups*, in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 1, p 267.
(92) Nagata, T.; Sugi, K. D.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Catal. Surveys Jpn.* **1998**, *2*, 47.
(93) Kim, G.-J.; Shin, J.-H. *Catal. Lett.* **1999**, *63*, 205.
(94) Jacobsen, E. N.; Wu, M. H. Epoxidation of Alkenes Other than Allylic Alcohols. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 649.
(95) Katsuki, T. Asymmetric Epoxidation of Unfunctionalised Olefins and Related Reactions. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 287.
(96) Jacobsen, E. N. Asymmetric Catalytic Epoxidation of Unfunctionalised Olefins. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; p 159.
(97) Katsuki, T. *J. Mol. Catal. A* **1996**, *113*, 87.
(98) Jacobsen, E. N. Transition Metal-Catalysed Oxidations: Asymmetric Epoxidations. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, E., Eds.; Pergamon: New York, 1995; Vol. 12, p 1097.
(99) Canali, L.; Cowan, E.; Deleuze, H.; Gibson, C. L.; Sherrington, D. C. *Chem. Commun.* **1998**, 2561.
(100) Angelino, M. D.; Laibinis, P. E. *Macromolecules* **1998**, *31*, 7581.
(101) Kim, G.-J.; Shin, J.-H. *Tetrahedron Lett.* **1999**, *40*, 6827.
(102) Pini, D.; Mandoli, A.; Orlandi, S.; Salvadori, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3883.
(103) Song, C. E.; Roh, E. J.; Yu, B. M.; Chi, D. Y.; Kim, S. C.; Lee, K.-J. *Chem. Commun.* **2000**, 615.
(104) Yao, X.; Chen, H.; Lü, W.; Pan, G.; Hu, X.; Zheng, Z. *Tetrahedron Lett.* **2000**, *41*, 10267.
(105) Sellner, H.; Karjalainen, J. K.; Seebach, D. *Chem. Eur. J.* **2001**, *7*, 2873.
(106) Pini, D.; Mandoli, A.; Orlandi, S.; Salvadori, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3883.
(107) Kim, G.-J.; Park, D.-W.; Ha, J.-M. *Korean J. Chem. Eng.* **2000**, *17*, 337.
(108) Kim, G.-J.; Shin, J.-H. *Tetrahedron Lett.* **1999**, *40*, 6827.
(109) Piaggio, P.; McMorn, P.; Murphy, D.; Bethell, D.; Page, P. C. B.; Hancock, F. E.; Sly, C.; Kerton, O. J.; Hutchings, G. J. *J. Chem. Soc., Perkin Trans 2* **2000**, 2008.
(110) Piaggio, P.; Langham, C.; McMorn, P.; Bethell, D.; Page, P. C. B.; Hancock, F. E.; Sly, C.; Hutchings, G. J. *J. Chem. Soc., Perkin Trans 2* **2000**, 143.
(111) Piaggio, P.; McMorn, P.; Langham, C.; Bethell, D.; Page, P. C. B.; Hancock, F. E.; Hutchings, G. J. *New J. Chem. Soc.* **1998**, 1167.
(112) Kim, G.-J.; Kim, S.-H. *Catal. Lett.* **1999**, *57*, 139.
(113) Kim, G.-J. *React. Kinet. Catal. Lett.* **1999**, *67*, 295.
(114) Fraile, J. M.; García, J. I.; Massam, J.; Mayoral, J. A. *J. Mol. Catal. A: Chem.* **1998**, *136*, 47.
(115) Sabater, M. J.; Corma, A.; Domenech, A.; Fornes, V.; Garcia, H. *Chem. Commun.* **1997**, 1285.
(116) Ogunwumi, S. B.; Bein, T. *Chem. Commun.* **1997**, 901.
(117) Janssen, K. B. M.; Laquiere, I.; Dehaen, W.; Parton, R. F.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3481.
(118) Pozzi, G.; Cinato, F.; Montanari, F.; Quici, S. *Chem. Commun.* **1998**, 877.
(119) Cavazzini, M.; Manfredi, A.; Montanari, F.; Quici, S.; Pozzi, G. *Chem. Commun.* **2000**, 2171.
(120) Song, C. E.; Roh, E. J. *Chem. Commun.* **2000**, 837.
(121) Salvadori, P.; Pini, D.; Petri, A.; Mandoli, A. In *Catalytic Heterogeneous Enantioselective Dihydroxylation and Epoxidation* in *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: New York, 2000; p 235.
(122) Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Che, C.-M.; Li, S.-G.; Li, L.-S. *Chem. Commun.* **1999**, 1789.
(123) Frunza, L.; Kosslick, H.; Landmesser, H.; Hoft, E.; Fricke, R. *J. Mol. Catal. A: Chem.* **1997**, *123*, 179.
(124) Srinvasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.
(125) Dolphin, D.; Traylor, T. G.; Xie, L. Y. *Acc. Chem. Res.* **1997**, *30*, 251.
(126) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M. *J. Am. Chem. Soc.* **1999**, *121*, 460.
(127) Zhang, R.; Yu, W.-Y.; Wong, K.-Y.; Che, C.-M. *J. Org. Chem.* **2001**, *66*, 8145.
(128) Katsuki, T. Epoxidation of Allylic Alcohols. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 621.
(129) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 231.
(130) Shum, W. P.; Cannarsa, M. J. Sharpless Asymmetric Epoxidation: Scale-up and Industrial Production. In *Chirality in Industry II*; Collins, A. N., Shedrake, G. N., Crosby, J., Eds.; John Wiley & Sons: New York, 1996; p 363.
(131) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
(132) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(133) Canali, L.; Karjalainen, J. K.; Sherrington, D. C.; Hormi, O. E. O. *Chem. Commun.* **1997**, 123.
(134) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1563.
(135) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2019.
(136) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 3895.
(137) Choudary, B. M.; Valli, V. L. K.; Prasad, A. D. *J. Chem. Soc., Chem. Commun.* **1990**, 1186.
(138) Choudary, B. M.; Valli, V. L. K.; Prasad, A. D. *J. Chem. Soc., Chem. Commun.* **1990**, 721.
(139) Meunier, D.; Piechaczyk, A.; de Mallmann, A.; Basset, J.-M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3540.
(140) Corma, A.; Fuerte A.; Iglesias, M.; Sanchez, F. *J. Mol. Catal. A: Chem.* **1996**, *107*, 225.
(141) Aggarwal, V. K. Epoxide Formation of Enones and Aldehydes. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 679.
(142) Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J. *Tetrahedron* **1984**, *40*, 5207 and references therein.
(143) Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3501.
(144) Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047.
(145) Cappi, M. W.; Chen, W.-P.; Flood, R. W.; Liao, Y.-W.; Roberts, S. M.; Skidmore, J.; Smith, J. A.; Williamson, N. M. *Chem. Commun.* **1998**, 1159.
(146) Boulahia, J.; Carrière, F.; Sekiguchi, H. *Makromol. Chem.* **1991**, *192*, 2969.
(147) Dhanda, A.; Drauz, K.-H.; Geller, T.; Roberts, S. M. *Chirality* **2000**, *12*, 313.
(148) Geller, T.; Roberts, S. M. J. *Chem. Soc., Perkin Trans. 1* **1999**, 1397.
(149) Carde, L.; Davies, H.; Geller, T. P.; Roberts, S. M. *Tetrahedron Lett.* **1999**, *40*, 5421.
(150) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation-Discovery and Development. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 357.
(151) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; p 227.
(152) Bolm, C.; Hildebrand, J. P.; Muniz, K. Recent Advances in Asymmetric Dihydroxylation and Aminohydroxylation. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 399.
(153) Markó, I. E.; Svendsen, J. In *Dihydroxylation of Carbon-Carbon Double Bonds*, in *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 714.
(154) Beller, M.; Sharpless, K. B. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: 1996; Vol. 2, p 1009.

(155) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(156) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317.
(157) Waldmann, H. *Nachr. Chem. Technol. Lab.* **1992**, *40*, 702.
(158) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
(159) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3003.
(160) Pini, D.; Petri, A.; Nardi, A.; Rocini, C.; Salvadori, P. *Tetrahedron Lett.* **1991**, *32*, 5175.
(161) Lohray, B. B.; Thomas, A.; Chittari, P.; Ahuja, J. R.; Dhal, P. K. *Tetrahedron Lett.* **1992**, *33*, 5453.
(162) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2351.
(163) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron Lett.* **1994**, *35*, 6559.
(164) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron* **1994**, *50*, 11321.
(165) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron Lett.* **1995**, *36*, 1549.
(166) Song, C. E.; Roh, E. J.; Lee, S.-g.; Kim, I. O. *Tetrahedron: Asymmetry* **1995**, *6*, 2687.
(167) Petri, A.; Pini, D.; Rappaccini, S.; Salvadori, P. *Chirality* **1995**, *7*, 580.
(168) Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S.-g. *Tetrahedron: Asymmetry* **1996**, *7*, 645.
(169) Herrmann, W. A.; Kratzer, R. M.; Blumel, J.; Friedrich, H. B.; Fischer, R. W.; Apperley, D. C.; Mink, J.; Berkesi, O. *J. Mol. Catal. A: Chem.* **1997**, *120*, 197.
(170) Nandanan, E.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1997**, *38*, 2577.
(171) Salvadori, P.; Pini, D.; Petri, A. *J. Am. Chem. Soc.* **1997**, *119*, 6929.
(172) Canali, L.; Song, C. E.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1029.
(173) Petri, A.; Pini, D.; Rapaccinni, S.; Salvadori, P. *Chirality* **1999**, *11*, 745.
(174) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632.
(175) Han, H.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 1527.
(176) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546.
(177) Bolm, C.; Gerlach, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 741.
(178) Kuang, Y.-Q.; Zhang, S.-Y.; Wei, L.-L. *Tetrahedron Lett.* **2001**, *42*, 5925.
(179) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron: Asymmetry* **1996**, *7*, 2805.
(180) Song, C. E.; Yang, J. W.; Ha, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 841.
(181) Lee, H. M.; Kim, S.-W.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1537.
(182) Motorina, I.; Crudden, C. M. *Org. Lett.* **2001**, *3*, 2325.
(183) Bolm, C.; Maischak, A.; Gerlach, A. *Chem. Commun.* **1997**, 2353.
(184) Bolm, C.; Maischak, A. *Synlett* **2001**, 93.
(185) Salvadori, P.; Pini, D.; Petri, A. *Synlett* **1999**, 1181.
(186) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21.
(187) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579.
(188) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.
(189) Our unpublished results.
(190) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094.
(191) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229.
(192) Kobayash, S.; Ishida, T.; Akiyama, R. *Org. Lett.* **2001**, *3*, 2649.
(193) Choudary, B. M.; Chowdari, N. S.; Kantam, M. L.; Raghavan, K. V. *J. Am. Chem. Soc.* **2001**, *123*, 9220.
(194) Li, G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451.
(195) Li, G.; Sharpless, K. B. *Acta Chem. Scand.* **1996**, *50*, 649.
(196) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813.
(197) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483.
(198) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507.
(199) Song, C. E.; Oh, C. R.; Lee, S. W.; Lee, S.-g.; Canali, L.; Sherrington, D. C. *Chem. Commun.* **1998**, 2435.
(200) Nandana, E.; Phukan, P.; Pais, G. C. G.; Sudalai, A. *Indian J. Chem.* **1999**, *38B*, 287.
(201) Mandoli, A.; Pini, D.; Agostini, A.; Savadori, P. *Tetrahedron: Asymmetry* **2000**, *11*, 4039.
(202) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742.
(203) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744.
(204) Langham, C.; Taylor, S.; Bethell, D.; McMorn, P.; Page, P. C. B.; Willock, D. J.; Sly, C.; Hancock, F. E.; King, F.; Hutchings, G. J. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1043.
(205) Langham, C.; Piaggio, P.; Bethell, D.; Lee, D. F.; D.; McMorn, P.; Page, P. C. B.; Willock, D. J.; Sly, C.; Hancock, F. E.; King, F.; Hutchings, G. J. *Chem. Commun.* **1998**, 1601.
(206) Langham, C.; Bethell, D.; Lee, D. F.; D.; McMorn, P.; Page, P. C. B.; Willock, D. J.; Sly, C.; Hancock, F. E.; King, F.; Hutchings, G. J. *Appl. Catal. A: General* **1999**, *182*, 85.
(207) Taylor, S.; Gullick, J.; McMorn, P.; Bethell, D.; Page, P. C. B.; Hancock, F. E.; King, F.; Hutchings, G. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1714.
(208) Taylor, S.; Gullick, J.; McMorn, P.; Bethell, D.; Page, P. C. B.; Hancock, F. E.; King, F.; Hutchings, G. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1724.
(209) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.
(210) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 911.
(211) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
(212) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.
(213) Soai, K.; Watanabe, M.; Yamamoto, A. *J. Org. Chem.* **1990**, *55*, 4832.
(214) Lasperas, M.; Bellocq, N.; Brunel, D.; Moreau, P. *Tetrahedron: Asymmetry* **1998**, *9*, 3053.
(215) Bellocq, N.; Abranson, S.; Laspéras, M.; Brunel, D.; Moreau, P. *Terahedron: Asymmetry* **1999**, *10*, 3229.
(216) Abramson, S.; Bellocq, N.; Laspéras, M. *Top. Catal.* **2000**, *13*, 339.
(217) Abramson, S.; Laspéras, M.; Galarneau, A.; Desplantier-Giscard, D.; Brunel, D. *Chem. Commun.* **2000**, 1773.
(218) Bae, S. J.; Kim, B. M.; Kim, S.-W.; Hyeon, T. *Chem. Commun.* **2000**, 31.
(219) Kim, S.-W.; Bae, S. J.; Hyeon, T.; Kim, B. M. *Micropor. Mesopor. Mater.* **2001**, *44*−*45*, 523.
(220) Heckel, A.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 163.
(221) Pfaltz, A. Cyclopropanation and C-H Insertion with Cu. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 514.
(222) Lydon, K. M.; McKervey, M. A. Cyclopropanation and C-H Insertion with Rh. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 539.
(223) Charette, A. B.; Lebel, H. Cyclopropanation and C-H Insertion with Metals Other Than Cu and Rh. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 581.
(224) Matlin, S. A.; Lough, W. J.; Chan, L.; Abram, D. M. H.; Zhou, Z. *J. Chem. Soc., Chem. Commun.* **1984**, 1038.
(225) Carmona, A.; Corma, A.; Iglesias, M.; Sánchez, F. *Inorg. Chim. Acta* **1996**, *244*, 79.
(226) Alcón, M. J.; Corma, A.; Iglesias, M.; Sánchez, F. *J. Mol. Catal. A: Chem.* **1999**, *144*, 337.
(227) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Tarnai, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2089.
(228) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Tarnai, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3997.
(229) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Tarnai, T.; Harmer, M. A. *J. Catal.* **1999**, *186*, 214.
(230) Fernandez, M. J.; Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Burguete, M. I.; Garcia-Verdugo, E.; Luis, S. V.; Harmer, M. A. *Top. Catal.* **2000**, *13*, 303.
(231) Evans, D. A.; Johnson, J. S. Diels-Alder Reactions. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, p 1177.
(232) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710.
(233) Itsuno, S.; Kamahori, K.; Watanabe, K.; Koizumi, T.; Ito, K. *Tetrahedron: Asymmetry* **1994**, *5*, 523.
(234) Kamahori, K.; Tata, S. Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2547.
(235) Kamori, K.; Ito, K.; Itsuno, S. *J. Org. Chem.* **1996**, *61*, 8321.
(236) Fraile, J. M.; Mayoral, J. A.; Royo, A. J.; Salvador, R. V.; Altava, B.; Luis, S. V.; Burguete, M. I. *Tetrahedron* **1996**, *52*, 9853.
(237) Altava, B.; Burguete, M. I.; Escuder, B.; Luis, S. V.; Salvador, R. V.; Fraile, J. M.; Mayoral, J. A.; Royo, A. J. *J. Org. Chem.* **1997**, *62*, 3126.
(238) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. *J. Org. Chem.* **2001**, *66*, 3160.
(239) Hallman, K.; Moberg, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1475.
(240) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Royo, A. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2263.
(241) Rechavi, D.; Lemaire, M. *Org. Lett.* **2001**, *3*, 2493.
(242) Corma, A.; Iglesias, M.; Martin, M. V.; Rubio, J.; Sanchez, F. *Terahedron: Asymmetry* **1992**, *3*, 845.
(243) North, M. *Synlett* **1993**, 807.
(244) Oku, J.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229.
(245) Oku, J.; Ito, N.; Inoue, S. *Makromol. Chem.* **1982**, *183*, 579.
(246) Kim, H. J.; Jackson, W. R. *Tetrahedron: Asymmetry* **1992**, *3*, 1421.

(247) Trost, B. M.; Lee, C. B. Asymmetric Allylic Alkylation Reactions. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 593.
(248) Hayashi, T. Asymmetric Allylic Substitution and Grignard Cross-Coupling. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; p 325.
(249) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919.
(250) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8303.
(251) Hallman, K.; Moberg, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1475.
(252) Hallman, K.; Macedo, E.; Nordström, K.; Moberg, C. *Tetrahedron: Asymmetry* **1999**, *10*, 4037.
(253) Anson, M. A.; Mirza, A. R.; Tonks, L.; Williams, J. M. J. *Tetrahedron Lett.* **1999**, *40*, 7147.
(254) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.
(255) Jacobsen, E. N.; Wu, M. H. Ring Opening of Epoxides and Related Reactions. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, p 1309.
(256) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.
(257) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147.
(258) Kim, G.-J.; Park, D.-W. *Catal. Today* **2000**, *63*, 537.
(259) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.
(260) Song, C. E.; Oh, C. R.; Roh, E. J. Choo, D. J. *Chem. Commun.* **2000**, 1743.
(261) Gigante, B.; Corma, A.; Garcia, H.; Sabater, M. J. *Catal. Lett.* **2000**, *68*, 113.

CR0103625