NEW MATERIALS AND TECHNOLOGIES: SUPPORTED CATALYSTS, SUPPORTS, SELF-SUPPORTED CATALYSTS, CHIRAL IONIC LIQUID, SUPERCRITICAL FLUIDS, FLOW REACTORS, AND MICROWAVES

CHAPTER 1

RECYCLABLE STEREOSELECTIVE CATALYSTS

CARLOS M. MONTEIRO, ALEXANDRE F. TRINDADE,
PEDRO M. P. GOIS, AND CARLOS A. M. AFONSO

1.1. INTRODUCTION

Asymmetric catalysis constitutes an important subject, generating thousands of published works every year. Still, the application of such methodologies in

the chemical industry is rather limited due to the high cost of the chiral ligands and/or noble metals used in such transformations. Additionally, sometimes the final products contain high levels of metal contamination derived from catalysts descomplexation or degradation phenomena, which can became a serious drawback if the metal is toxic, particularly for the pharmaceutical and food industries. For these reasons, there are still advantages to using the chiral building blocks readily available in nature or by applying resolution of optical isomers [1].

Stereochemical and chemical efficiency of a certain transformation are, in principle, better reproduced and predicted in homogeneous catalysis than in heterogeneous catalysis. The presence of the heterogeneous support in a reaction vessel can create, in some cases, unpredictable results (negative vs. novel positive effects) [2]. The choice of the heterogeneous support for the catalysis is a crucial decision. Some properties like high thermal, chemical and physical stabilities, chemical inertia, and homogeneous-like behavior are highly desirable. Furthermore, the catalyst is easily recovered using just filtration or extraction techniques that are impossible to be applied in homogeneous catalysis [3].

Amorphous and ordered silicas, clays, and highly cross-linked polymers are the standard supports to heterogenize a homogeneous catalyst. The principal immobilization mechanisms consist of ligand grafting, metal coordination, microencapsulation, electrostatic interactions, and ion exchange [3] (see also Chapters 3 and 4).

It is possible to combine the advantages of homogeneous and heterogeneous systems by running reactions with catalysts that have been chemically linked to soluble macromolecules like oligomeric and/or low cross-linked soluble polymers, poly(ethylene glycol) (PEG), and dendritic structures. The supported homogeneous catalyst can be precipitated at the end of the reaction by addition of a cosolvent and recovered like a heterogeneous system [3].

The reutilization of asymmetric catalysts and the reactions media was possible using greener solvents like water, ionic liquids (ILs), PEG, perfluorinated solvents, and supercritical CO_2 (scCO$_2$), which constitute alternatives to volatile organic solvents. Water appears as the cheapest solvent, bearing unique characteristics that differ from the others solvents: it is cheaper, most abundant in nature, and proven to have some unexpected beneficial effects in organic transformations [3, 4].

The need to transfer the asymmetric catalysis methodology to large-scale synthesis technology is a crucial goal for synthetic organic scientists worldwide. There are many contributions toward achieving this goal in the literature [2, 5]. In 2002, Chan et al. combined all these type of transformations or chiral ligands [6], or self-supported heterogeneous catalysts [7], or solvent-free transformations [8]. In 2009, Trindade et al. [3] updated the earlier Chan et al. work [2], covering a broader number of transformations and all type of catalyst recycling methodologies. Other reviews were published in the literature, where the majority focused on catalyst immobilization for both chiral and achiral

organic transformations, but they do not cover all types of reported catalysts immobilization processes [9]. From the reviews that focus only on enantiose-lective catalysis, some cover only one transformation performed with hetero-geneous catalysts [10].

This chapter provides an overview of our selection transformations and all types of catalyst (except organocatalysts) recycling methodologies described up to March 2010.

At the beginning of each paragraph, there is a small description of the ligand in question and its applications in asymmetric catalysis. In the text, maximum efforts were made to identify the best-reported catalyst recycle system using heterogeneous catalysts, homogeneous catalysts, and alternative reaction media. Also, the method for recovery, in terms of reactivity and enan-tioselectivity, will be highlighted, giving special attention to the recycling process. This recycling process will be analyzed both in terms of executability and efficiency. In terms of efficiency, at times the reader may encounter $Y_e(x) = \ldots$ % and $ee_e(x) = \ldots$ %. These percentages should be read as the yield (Y_e) or enantioselectivity (ee_e) erosion at run x. The percentages are calculated according to the following expressions:

$$Y_e(x) = \frac{Y(1) - Y(x)}{Y(1)} \quad ee_e(x) = \frac{ee(1) - ee(x)}{ee(1)}$$

1.2. CHIRAL PHOSPHINES

The wide synthetic applications of phosphine catalysts have motivated many investigations on enantioselective reactions, particularly hydrogenation, hydroformylation, cycloaddition, and allylic substitution. The search for new, particularly designed chiral phosphorus catalysts has become a goal of several research groups. Despite the high activity and enantioselectivity achieved by complexing these ligands with Ru, Rh, and Ir, their air sensitivity and high cost represent a drawback. To circumvent these limitations, more stable and recy-clable catalysts have been developed.

1.2.1. Hydrogenation

Rhodium(I) and chiral phosphine catalysts are widely used in asymmetric alkene hydrogenation due to their efficiency in the preparation of enantio-pure compounds with excellent atom economy. Generally, methyl α-acetamidoacrylate (MAA), methyl α-acetamido cinnamate (MAC), and dimethyl itaconate are the model substrates chosen by the authors to perform asymmetric hydrogenation reactions (Fig. 1.1).

Ding and Wang prepared a self-supported heterogeneous catalyst for enamines hydrogenation from an Rh complex [Rh(Cod)$_2$BF$_4$] and a bis-phosphoamidate derived from 1,1′-bi-2-naphthol (BINOL) (Monophos) **1**.
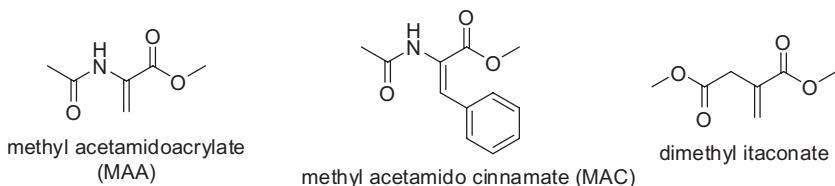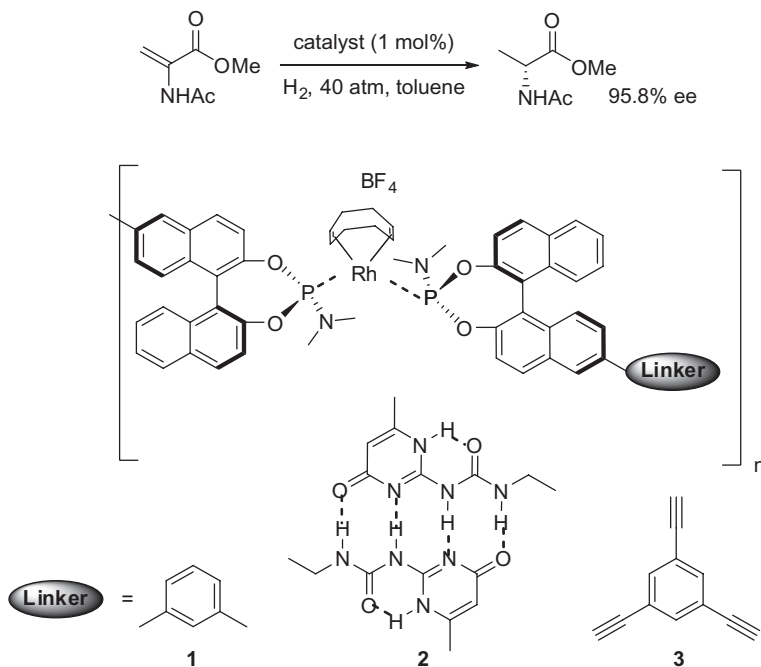
FIGURE 1.1. Main substrates used for asymmetric hydrogenation assays.

SCHEME 1.1. Hydrogenation reaction with self-supported heterogeneous catalyst.

Excellent enantioselectivities were obtained with aromatic and alkylic enamines with this heterogeneous catalyst (equivalent to a homogeneous ligand) (Scheme 1.1). The catalyst was recycled five times with a minimal 5% enantioselectivity erosion [11]. Two years later, Ding and Wang prepared a new self-supported polymer based on the same homogeneous catalyst (catalyst **2**). This polymeric complex proved to be an efficient heterogeneous catalyst for enamines hydrogenation reactions [substrate/catalyst (S/C) = 100, 40 atm H_2, 91%–96% enantiomeric excess (ee)]. It could be recovered by filtration and reused with minimal ee erosion [12].

More recently, the same authors developed a continuous-flow system using another self-supported catalyst **3** based on the same catalyst. Under experimental conditions (2 atm H_2), the α-dehydroamino acid methyl esters

could be continuously hydrogenated in >99% conversion (93–94 μmol/h) in 97% ee for a total of 144 hours and an overall yield of 2.52 g (15.75 mmol). The immobilized catalyst also showed high enantioselectivity (96%–97% ee) but was observed with lower reactivity in a batch recycling system during 10 cycles [13].

In 2000, de Rege et al. performed the heterogenization of a [((R,R)-Me-DuPHOS)Rh(COD)]+ catalyst in mesoporous crystalline material (MCM)-41. This heterogeneous catalyst proved to be as selective as the free catalyst (up to 99% ee) for the asymmetric hydrogenation of amidoacrylic acids and proved to be recyclable without loss of activity or enantioselectivity [14].

The chiral ligands (R)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) [15], (R,R)-Me-DuPhos [16] and (2S,4S)-BDPP [17], and carbon-activated [18] supports were studied under Augustine et al.'s immobilization methodology [19]. Generally, the heterogeneous catalysts were found to be less active than their homogeneous partners under batchwise conditions but provided comparable levels of enantioselectivities (generally above 90% ee). The high degree of recyclability of these catalysts was also demonstrated (up to 11 cycles).

Hutchings et al. showed that achiral [Rh(cod)$_2$]BF$_4$ could be immobilized in mesoporous MCM-41 by ion exchange, followed by chiral ligand coordination [(R,R)-Me-DuPhos]. Alternatively, they also immobilized directly the chiral rhodium complex. Both types of heterogeneous catalyst proved to be as efficient as their homogeneous analogs (up to 99% ee) and could be reused nine times without enantioselectivity erosion in methyl itaconate hydrogenation (S/C = 250, 80 psi H$_2$) [20].

Luna et al. grafted a Ru-(BINAP) (dpea) complex on the surface of amorphous AlPO$_4$ support to achieve its recycling. It was tested in the successive liquid-phase enantioselective hydrogenation of dimethyl itaconate, MAA, and MAC (in dichloromethane, S/C = 45.4, 6.8 atm H$_2$ at 50–70°C, Table 1.1). This heterogeneous catalyst **4** (Table 1.1) provided the respective products with excellent enantioselectivities (99% ee) over several days and worked continuously (up to 10 cycles) [21].

Other chiral phosphines immobilization in heterogeneous supports, such as acidic aluminosilacte (AlTUD-1) [22], phosphotungstic acid (PTA) on alumina [23], and carbon nanotubes [24], were reported. Excellent enantioselectivity (>96% ee) was obtained in this transformation, with good recyclability.

Fan et al. prepared and tested a chiral dendritic ligand **5** bearing a Pyrphos moiety linked to its core for the asymmetric hydrogenation of α-acetamido cinnnamic acid. After in situ catalyst formation [reaction between Rh(Cod)$_2$BF$_4$ and the dendritic ligand **5**, Fig. 1.2], it furnished phenylalanines with excellent ee's (>97% vs. 99% ee for nonsupported ligands) with all dendritic generations. The catalyst was recovered by filtration and reused with constant ee. However, the conversion decreased considerably upon recycling (run 1: 94%, run 2: 55%) [25]. Similar chiral dendritic ligand was tested with analogous results, but improving in terms of reutilization. A drastic decrease of conversion was only observed on the fourth cycle [26].

TABLE 1.1. Successive Hydrogenation Rates of Different Substrates

4
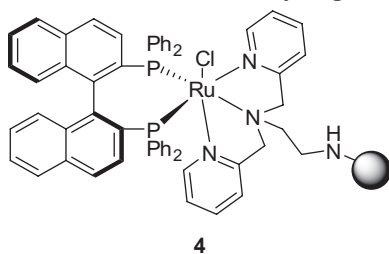
Run	Substrate	Temperature (°C)	Reaction Rate (μmol/s)	TOF (h^{-1})	Half Reaction Time (h)	Reaction Time (h)
1	Dimethyl itaconate	70.0	0.248	2.53	10.0	46.0
2	Dimethyl itaconate	55.0	0.062	0.63	76.0	144.0
3	Dimethyl Itaconate	70.0	0.023	0.24	96.0	216.0[a]
4	MAA	70.0	1.023	10.45	2.2	9.0
5	MAC	70.0	0.039	0.40	96.0	288.0

[a] After 1473 hours (2 months approximately) continuously working, TON = 408.

5
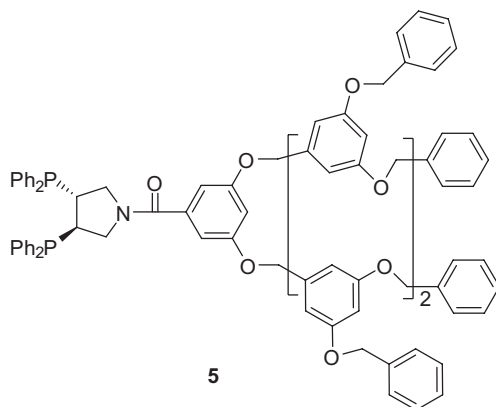
FIGURE 1.2. Structure of the dendritic ligand **5**.

Feng et al. reported the use of wet ILs as biphasic reaction media for MAA and MAC asymmetric hydrogenation [27]. The mixture of [omim]BF$_4$/water (2 mL of IL to 2–3 mL of cosolvent) proved to be the best reaction media for MAA, affording higher levels of enantioselectivity and conversion (up to >99% ee) than the traditional methanol/i-propanol system (catalyst loading of 1 mol%), for all ferrocene-containing catalysts (Fig. 1.3). This biphasic system proved to be very stable, and only at the sixth cycle was an extension on the reaction time required to always achieve complete conversion with a consistent 99% ee. For more apolar substrates such as MAC, the organic
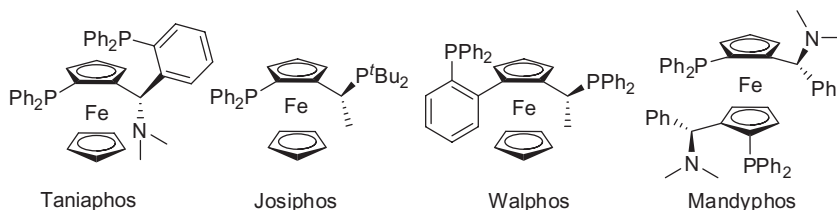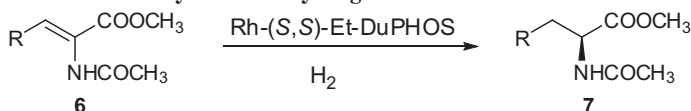
FIGURE 1.3. Chiral biphosphine ligands for asymmetric hydrogenation reaction in [omim]BF$_4$/water.

TABLE 1.2. Asymmetric Hydrogenation of Enamides

| Entry	Substrate (R)	Solvent	System (v/v)	ee (%)[a]
1	**6a** (C$_6$H$_5$)	PEG600/MeOH	(1:3)	97.6
2	**6a** (C$_6$H$_5$)	PEG600/MeOH	(1:4)	98.1 (98.6)
3	**6b** (3-Cl-C$_6$H$_4$)	PEG600/MeOH	(1:3)	97.0 (98.6)
4	**6c** (4-Cl-C$_6$H$_4$)	PEG600/MeOH	(1:3)	97.1 (98.8)
5	**6d** (4-CH$_3$O-C$_6$H$_4$)	PEG600/MeOH	(1:3)	98.6 (99.0)
6	**6e** (H)	PEG600/MeOH	(1:3)	98.2 (99.6)

[a] Data in parentheses were obtained by using MeOH as solvent under otherwise identical conditions.

cosolvent toluene was added to the wet IL in order to achieve high enantioselectivity.

Chan et al. showed that PEG could be added to methanol to conduct ruthenium- and rhodium-mediated hydrogenation of 2-arylacrylic acids and enamides (Table 1.2). This solvent mixture proved to be as efficient as the original solvent used in this transformation, providing excellent levels of enantioselectivity (quantitative yields, up to 98.6% ee). Furthermore, it added the possibility of recycling the homogeneous catalysts during nine efficient cycles [28].

Chiral phosphines also have a great potential for asymmetric hydrogenations and reductions of ketones (Scheme 1.2). Several chiral phosphines were described mixed with 1,2-diphenylethylenediamine (DPEN)-type ligands type with very good results. Some of the supported ligands provided excellent levels of chiral induction (up to 98% ee).

One of the most successful immobilizations techniques was carried out by Noyori et al. when they anchored a BINAP derivative to a polystyrene polymer. The ruthenium complex **8** (Fig. 1.4) with this ligand and DPEN were used to hydrogenate acetoacetates with 97% ee during 10 consecutive cycles.
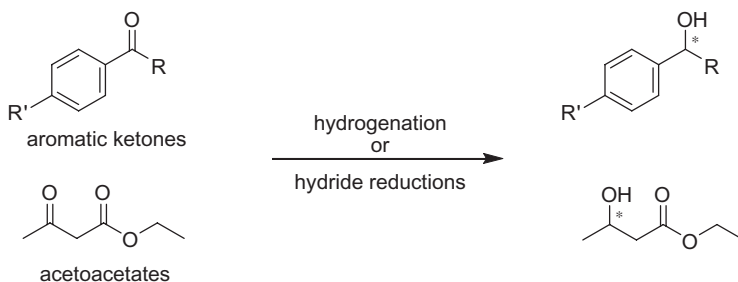
SCHEME 1.2. General substrates and methods for hydrogenation/reduction of ketones.
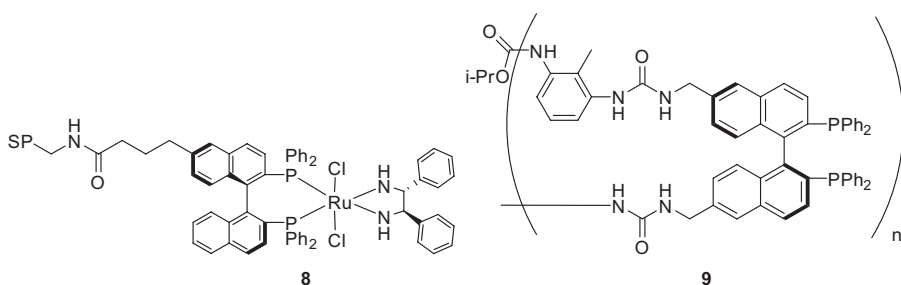

FIGURE 1.4. Structures of ruthenium complex **8** and ligand **9**.

Lemaire et al. immobilized diAm-BINAP in a polymer copolymer using di-isocyanates as the linker. The most rigid copolymer ligand **9** (Fig. 1.4) was used in ruthenium-mediated hydrogenation of acetoacetates with excellent performance and near-perfect selectivity (S/C = 1000, 40 atm hydrogen pressure, 50°C, 16 hours, 99% ee). This heterogeneous catalyst (in methanol) was reused three times without any change on its performance [29].

Lin et al. were interested in preparing hybrid materials containing organic linkers and metal nodes. The catalyst Ru(4,4′-(PO$_3$H$_2$)$_2$-BINAP) (DPEN)Cl$_2$ coordinated to a zirconium salt (ZrOt-Bu$_4$) was synthesized for such purposes. With this heterogeneous catalyst in hand, the hydrogenation of aromatic ketones was conducted with higher enantioselective than its homogeneous counterpart and achieved excellent performance (0.1 mol%, 700 psi of H$_2$, 20 hours to give up to 99.2% ee). Furthermore, the catalyst was reused seven times [30].

Bergens et al. reported the first polymeric asymmetric catalyst prepared by ring-opening metathesis polymerization (ROMP) of *trans*-RuCl$_2$(Py)$_2$((*R,R*)-Norphos)) and cycloctene. The living ends of the polymer were cross-linked with dicyclopentadiene and the pyridine ligands with chiral DPEN ligand and deposited on BaSO$_4$ (catalyst **10**). It was tested in 1′-acetonaphthone hydrogenation (S/C = 500, 4 atm H$_2$, Scheme 1.3), being reused up to 10 cycles with
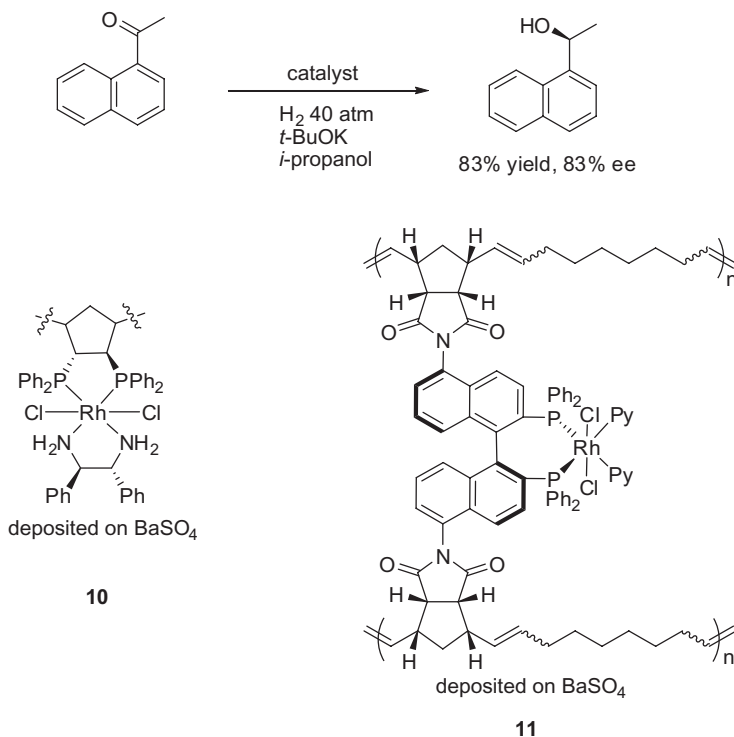
SCHEME 1.3. Hydrogenation of aromatic ketones using chiral Rh catalyst deposited in BaSO₄.

the activity reaching 100% and the optical yield maintaining above 80% ee. Despite this catalyst being less reactive than the homogeneous one, it proved to be by far more selective (83% vs. 48% ee) [31].

The enantioselectivity reached 95% ee when the bisphosphine ligand used was exchanged by a BINAP derivative **11**. Furthermore, this catalyst could be reused 25 times without any detrimental effect on the conversion and enantioselectivity using 0.1 mol% of catalyst [32].

Kantam et al. reported the application of nanocrystalline copper oxide/BINAP as a catalyst for asymmetric hydrosilylation of ketones in the absence of an inorganic base. The secondary alcohols can be obtained in very good yields and enantioselectivities after hydrolysis with tetrabutylammoniumfluoride (TBAF) (up to 99% ee). This heterogeneous catalyst was reused three times without any yield or enantioselectivity erosion [33].

For homogeneous ruthenium-mediated hydrogenation of acetoacetates, Guerreiro et al. presented a PEG-supported BINAP ligand. Excellent enantioselectivity (99% ee) was obtained with ligand **12** (Fig. 1.5) and was recycled four times with consistent efficiency [34].
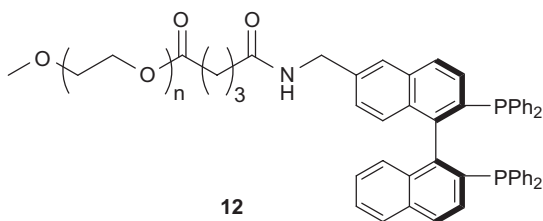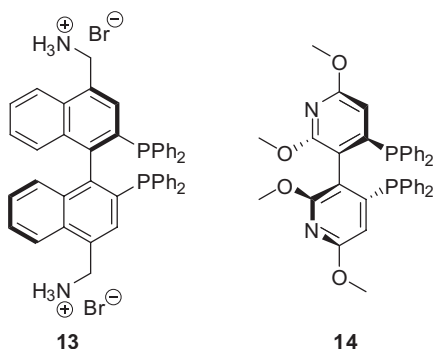
FIGURE 1.5. Structure of ligand **12**.

FIGURE 1.6. Structures of ligands **13** and **14**.

Zhu et al. prepared a new IL containing the *N*-n-butylpyridinium cation and the 1-carbadodecaborate anion ($BPCB_{10}H_{12}$). This new IL was applied in acetophenone and ethyl formate hydrogenation using a rhodacarborane as catalyst precursor and BINAP. Quantitative conversion was observed after 8 hours with high ee (>99%), turnover frequency (TOF) (>239/h) during six cycles [35].

Lemaire et al. applied BINAP ligand **13** (Fig. 1.6) and its 4,4′-analog in the ruthenium-mediated hydrogenation of acetoacetates (S/C = 1000 and 40 atm H_2). In a two-phase protocol, acetoacetates were added to an aqueous solution of the catalyst for hydrogenation to the respective alcohol in 99% ee (both ligands gave identical ee comparable to the original homogeneous protocol). At the end of each cycle, the product was extracted with pentane and the aqueous phase could be reused for at least eight cycles without any decrease of selectivity [36].

While looking for air-stable iridium catalyst for asymmetric imine reduction or hydrogenation, Chan et al. found that a complex with the ligand P-Phos **14** (Fig. 1.6) possessed those characteristics [37]. This catalyst was used to quantitatively hydrogenate quinolines in high enantioselectivities (90%–92% ee, 700 psi H_2, S/C = 200). To make the catalytic system more sustainable, the reaction was carried out in poly(ethylene glycol) dimethyl ether (DMPEG), providing the same levels of efficiency, especially for a biphasic mixture with
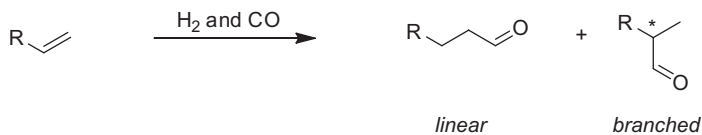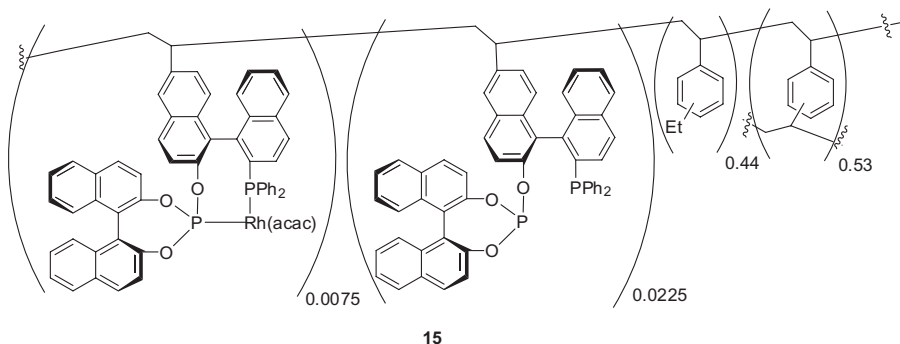
SCHEME 1.4. Hydroformylation reaction.

FIGURE 1.7. Structure of catalyst **15**.

hexane. The immobilized catalyst was reused seven times without any negative impact on the reaction enantioselectivity. This protocol was also extended to other chiral diphosphine ligands [38].

1.2.2. Hydroformylation

The hydroformylation reaction constitutes one of the most successful organometallic reactions in organic synthesis history with high atom economy (Scheme 1.4). In 1993, Nozaki and co-workers [39] combined an unsymmetrical phosphine–phosphite ligand, (*R,S*)-BINAPHOS, and a rhodium (I) catalyst to afford chiral aldehydes with excellent enantioselectivities from prochiral olefins. Since then, these catalysts, (*R,S*)-BINAPHOS-Rh(I) (acac), became (and still are) the most potent catalysts for asymmetric hydroformylation. Several efforts have been made to make this reaction more sustainable via recycling approaches. However, the immobilized catalysts showed lower catalytic activity than the free catalyst.

In order to be used in continuous vapor-flow column reactors, Shibahara and co-workers packed the catalyst **15** (Fig. 1.7) together with sea sand in a stainless column. This column reactor was used to hydroformylate 3,3,3-trifluoropropene. The authors observed that high selectivities and enantioselectivities (iso/normal: 95:5, up to 90% ee), which characterize a homogeneous protocol, were maintained despite the TOF remaining at lower levels due to the aldehydes' strong affinity for the catalyst (9 vs. 64) [40] (see also Chapter 9).

The need to obtain a general protocol for the hydroformylation of gaseous, liquid, or solid olefins motivated the authors to apply $scCO_2$ as a solvent flow. Styrene was injected portionwise into the column reactor under the flow of syngas and $scCO_2$. When the styrene hydroformylation was carried out at a total pressure of 120 atm, selectivity, conversion, and ee's remained constant for seven reaction cycles [80% iso aldehyde, 90% conversion, 85% ee, $Y_e(7) = 11\%$, and $ee_e(7) = 0\%$)]. This last apparatus was successfully applied to synthesize a library of optically active aldehydes, using a sequential injection protocol, with similar results compared to a homogeneous procedure.
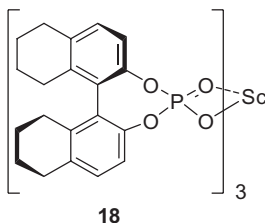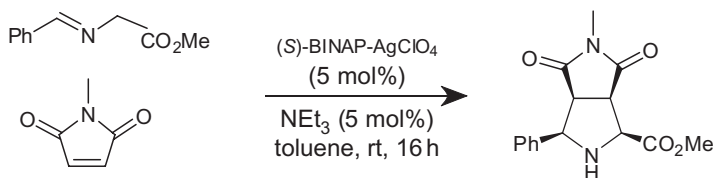
1.2.3. Cycloaddition

Metal-based asymmetric catalysts act as Lewis acids, activating the dienophile in cycloadditions reactions. The main strategies earlier developed relied on the direct ligand linkage with recoverable support, where the several Lewis acids could be coordinated.

Hoveyda et al. immobilized a chiral phosphinimine ligand in a Wang resin to achieve its recovery and recycling [41]. This ligand **17** was applied in Danishefsky's diene, and arylimines cycloaddition reaction was catalyzed by Ag(I)/ligand in air with undistilled tetrahydrofuran (THF) as the solvent. Using 5 mol% of catalyst, 96% yield and 86% ee were obtained, and ligand reutilization was achieved in five cycles. Under the same conditions, the non-supported protocol (ligand **16**) furnishes the respective arylenamine with 98% yield and 95% ee (Scheme 1.5).

Furuno et al. reported the use of new rare earth catalysts with chiral BINAP-type phosphorates [42]. The new catalysts showed enhanced solubility in dichloromethane (without the aid of any additive) and were tested in hetero

0.5 mol%, 98% yield, 95% ee   5 mol%, 96% yield, 86% ee
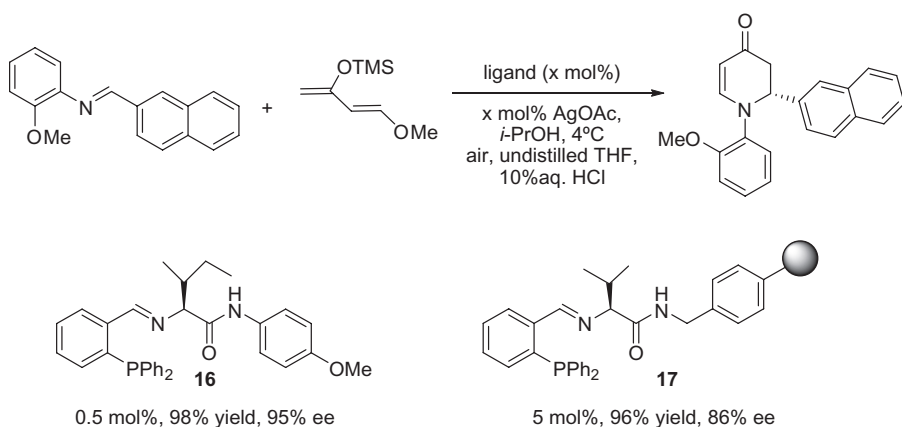
SCHEME 1.5. Asymmetric cycloaddition reactions promoted by chiral Ag–phosphinimine complex immobilized in Wang resin.

FIGURE 1.8. Structure of catalyst **18**.

SCHEME 1.6. Asymmetric cycloaddition reactions promoted by heterogeneous Ag–BINAP catalyst.
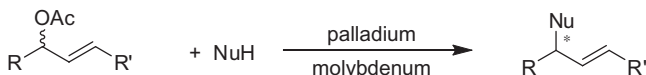
SCHEME 1.7. Asymmetric allylic substitution.

Diels–Alder reaction of Danishefsky's diene with aromatic aldehydes. Heavy lanthanides such as Yb and Er have a tendency to afford higher ee's (up to 98%) than lighter ones (up to 91%). The catalyst **18** (Fig. 1.8) proved to be the most robust combination and showed excellent performance (99% yield and 93% ee). It was also recovered by precipitation with diethyl ether and was reused up to three cycles with low yield (4%) erosion and ee (6%) erosion.

Nájera et al. discovered that the (*S*)-BINAP-AgClO$_4$ complex was insoluble in toluene, and it promoted the 1,3-dipolar cycloaddition reaction between azomethine ylides and maleimides (Scheme 1.6). The respective products were obtained in good-to-excellent yields (82%–90%), excellent *endo* selectivity (98:2), and excellent ee's (up to >99%). Due to its insolubility it was almost quantitatively recovered and could be reused efficiently up to five cycles [43].

1.2.4. Allylic Substitution

The asymmetric allylic substitution reaction (Scheme 1.7) constitutes an important tool to build chiral building blocks for several compounds with economical interest. This reaction is traditionally performed using palladium catalysts in the presence of expensive chiral mono- and bis-dentate phosphines.
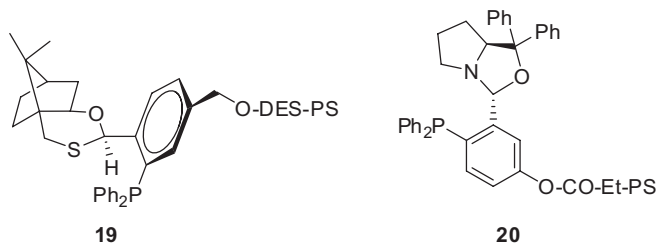
FIGURE 1.9. Structures of ligands **19** and **20**.

Owing to a heterogeneous approach, Nakano et al. grafted a chiral phosphinooxathiane ligand to a diethylsylilchloride polystyrene support. The ligand **19** (Fig. 1.9) promoted quantitative benzylamine condensation with allylic acetate in 99% ee. The heterogenous Pd/ligand complex was reused twice with 30 and 20% yield and enantioselectivity erosion, respectively [44].
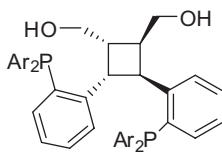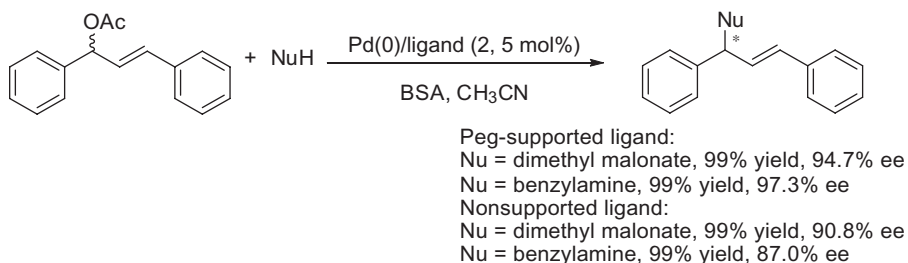
Better results for the alkylation of allylic acetate were obtained when a chiral phosphonioxazolidine ligand **20** (Fig. 1.9) was heterogenized using the same strategy. In this case, the best support was PS–Et–COOH, providing the respective product in a 99% yield and 99% ee. Unfortunately, if no palladium was added to the next run, a 57% yield and 33% enantioselectivity erosion were observed [45].

Ding et al. prepared a new type of C_2-symmetric bisphosphine ligand bearing a cyclobutane backbone and tested it on palladium-promoted allylic alkylation and amination reaction [46]. Due to the excellent results obtained with those new ligands, considerable efforts were made to link them to soluble PEG polymers in order to accomplish their recovery at the end of each reaction. In fact, one of those polymer-supported ligands (ligand **21**) was found to be more enantioselective than its nonsupported partner (ligand **22**) (Scheme 1.8).

The supported catalyst was quantitatively recovered by filtration and reused three times in allylic alkylation and eight times in allylic amination reaction, though with some yield (11%–18%) and ee (6%–8%) erosion.

Mino et al. attached two perfluoroalkyl chains on a diaminophosphine ligand to achieve its reuse together with the palladium catalyst (Scheme 1.9) [47]. The Pd/perfluoro ligand **23** complex was tested for the allylic alkylation reaction of racemic (E)-1,3-diphenyl-3-acetoxyprop-1-ene with dimethylmalonate, still proving some of the qualities of the parent nonfluorinated ligand **24**. The reaction became slower, requiring a higher temperature (30°C) to achieve quantitative conversion with 90% ee. Using 5 mol% of catalyst loading, it was possible to recycle both ligand and palladium efficiently, up to six cycles with a nearly unchanged outcome.

Herein, the main strategies for chiral phosphines catalyst recycling reported are ILs, perfluoruous techniques, and polymer-supported ligands (mainly heterogeneous). There is a tendency to use heterogeneous methods to the detriment of homogeneous methods, especially when the heterogenization

Peg-supported ligand:
Nu = dimethyl malonate, 99% yield, 94.7% ee
Nu = benzylamine, 99% yield, 97.3% ee
Nonsupported ligand:
Nu = dimethyl malonate, 99% yield, 90.8% ee
Nu = benzylamine, 99% yield, 87.0% ee

Ar = 4-t-BuC$_6$H$_4$

21
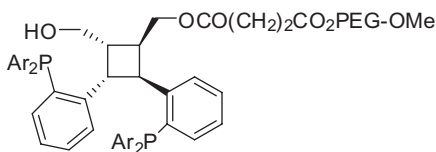
Ar = 4-t-BuC$_6$H$_4$

22

SCHEME 1.8. Palladium-catalyzed allylic alkylation promoted by C$_2$-symmetric bisphosphine ligand immobilized in PEG.
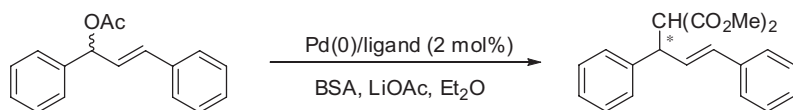
nonfluorinated ligand: −10ºC, 99% yield, 95% ee
fluorinated ligand: 30ºC, 96% yield, 90% ee
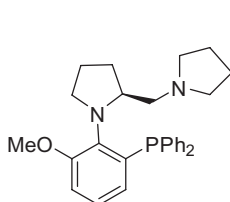
23
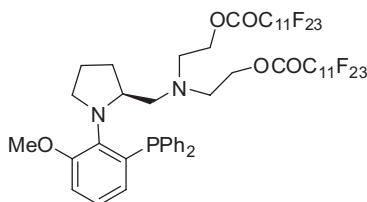
24

SCHEME 1.9. Asymmetric allylic alkylation promoted by Pd/perfluoro diaminophosphine complex.

does not involve the chiral ligand modification. Nevertheless, in some reactions the reutilization approaches still needs to be improved.

1.3. CHIRAL ALKALOIDS

Osmium-catalyzed asymmetric dihydroxylation (AD) of olefins is a robust methodology to conceive a wide range of enantiomerically pure vicinal diols
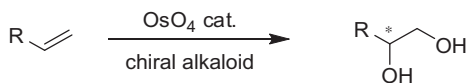
SCHEME 1.10. Asymmetric dihydroxylation reaction of alkenes.
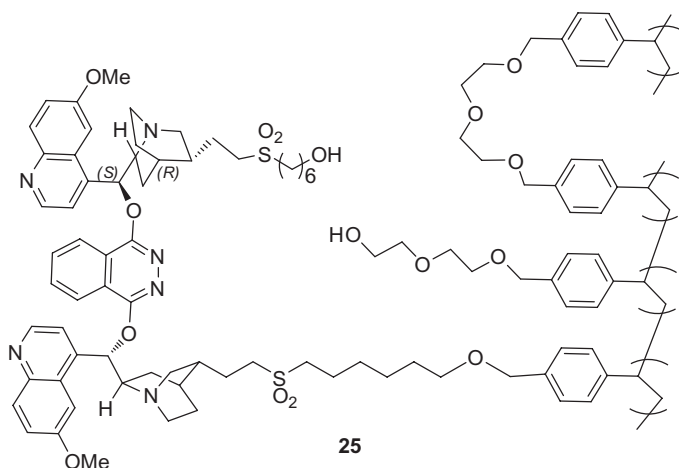
FIGURE 1.10. Structures of the supported ligand **25**.

[48]. This transformation became an enantioselective catalysis event when Markó et al. applied *N*-methylmorpholine-*N*-oxide (NMO) as a cooxidant, allowing osmium tetroxide (OsO$_4$) and a chiral cinchona alkaloid ligand to be used in catalytic amounts (Scheme 1.10) [49].

Although AD is a very important transformation, it uses expensive reactants (OsO$_4$ and a cinchona alkaloid) and a very toxic (and in some cases volatile) osmium component. To overcome these drawbacks, some alternatives have been developed, such as the use of K$_2$OsO$_2$(OH)$_4$ in place of OsO$_4$, and recovery and reuse of the Os ligand with high efficiency and without osmium contamination in the final product. Several strategies were developed for this purpose, namely by anchoring the ligand to a soluble or insoluble polymer matrix to an inorganic solid support (silica), or by immobilization of an osmium component through microencapsulation or ion exchange techniques [2–6c].

Salvadori et al. synthesized the supported ligand **25** (Fig. 1.10) with a copolymer architecture. When submitted to the same AD conditions it proved to be very efficient for typical substrates, with conversions up to 100% affording the respective diols in high ee's (87%–99%). Under recycle assays, using styrene as a starting material, a small amount of OsO$_4$ (0.35% mol) was added to account for losses during the recovery of the ligand at the beginning of each new cycle. The conversion and optical purity were analyzed at 1.5 hours of reaction time. The enantioselectivity fell in the 87%–91% range while the conversion fell in the 72%–94% range during 12 recycles [50].
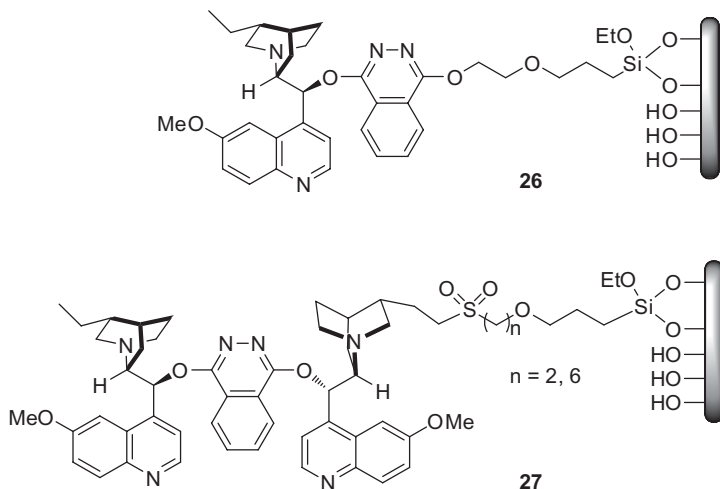
FIGURE 1.11. Structures of silica-supported *Cinchona* ligands **26** and **27**.
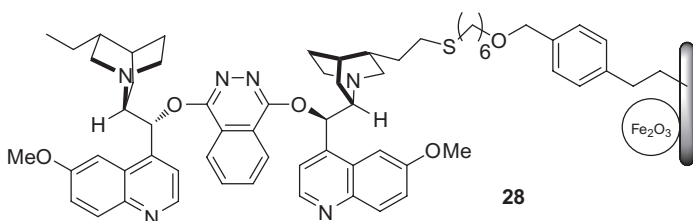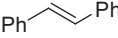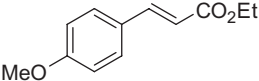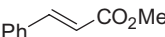
FIGURE 1.12. Structures of Fe_3O_4-supported $(DHQ)_2PHAL$ ligand **28**.

Silica was the preferred inorganic material used for this kind of *Cinchona* ligands immobilization. Lee and co-workers achieved high yields (up to 97%) and ee's (>99%) with catalysts **26** and **27** (Fig. 1.11) using *trans*-stilbene as a starting material; moreover, recycling experiments were successful for six runs [51].

Lee et al. prepared mesocellular silica foam with ordered mesoporous walls containing magnetic nanoparticles (γ-Fe_2O_3) and $(DHQ)_2PHAL$ ligand grafted in the pore surface (ligand **28**, Fig. 1.12) [52]. This ligand was tested for AD reaction using $K_3Fe(CN)_6$ as cooxidant (1 mol% catalyst). Several aromatic olefins were successfully dihydroxylated in high yields (up to 95%) and excellent ee's (up to 99.5%). At the end of each cycle, the supported ligand was separated by decantation with the aid of a magnet (magnetic separation) and reused seven times without any loss of efficiency. Unfortunately, it was necessary to add more osmium tetroxide at the end of each reaction to maintain a high level of conversion.

TABLE 1.3. AD Reaction with Heterogenized OsO_4

Olefin	$K_2OsO_4.2H_2O$-$Na_2WO_4.2H_2O$		LDH-OsW	
	Yield (%)	ee (%)	Yield (%)	ee (%)
Ph⌒⌒Ph	85	99	93	99
MeO—C₆H₄—CH=CH—CO_2Et	82	99	89	99
Ph⌒⌒CO_2Me	91	99	92	99

Following their work in ion exchange techniques with double-layered hydroxides, Choudary et al. designed a bifunctional catalyst composed of OsO_4^-–WO_4^- for one-pot synthesis of chiral diols via *N*-oxidation–AD reaction. This heterogeneous catalyst was found to be more active under AD conditions than its homogeneous analog, providing diols with comparable or even higher yields and ee's (*N*-methylmorpholine (NMM), Table 1.3). Furthermore, it provided the advantage of easy separation from organic products and uses lower amounts of the chiral alkaloid ligand (DHD)$_2$PHAL as well [53]. This methodology offers diols with higher yields and ee's than the Kobayashi PSresin-MC Os system [2, 54]. In addition, this system was easily recycled and reused for at least five cycles with minimal loss of activity and enantioselectivity [$Y_e(5) = 2\%$, $ee_e(5) = 0\%$].

Motivated by these results, the authors idealized and developed a trifunctional catalyst based on $PdCl_4^-$–OsO_4^-–WO_4^- for tandem Heck coupling–*N*-oxidation–AD reactions, using the same ion exchange technology. The desired diol was obtained in 85% yield with 99% ee. The LDH-PdOsW catalyst was recovered quantitatively by filtration, while the chiral ligand could be recovered (up to 95% recovery) by a simple acid/base extraction. The recovered catalyst was submitted to recycling assays without a significant drop in activity [$Y_e(5) = 3.5\%$] for at least five runs. To prove the synthetic utility of this trifunctional catalyst, the authors applied it in the synthesis of two well-known drugs, Diltiazem and Taxol side chain, minimizing in this way the number of unit operations needed in the process. The success of this kind of catalyst prompted the filing of several patents [55].

One of the major advantages of soluble polymer-bounded catalyst resides in the absence of diffusion problems of the reactants, which traditionally characterizes heterogeneous systems.

Bolm and Gerlach developed a hydroquinidinediether (DHQD) ligand attached to methoxy (MeO)-PEG via an aryl spacer (linked to 4,6-bis-(9-*O*-dihydrochininyl)pyrimidine (PYR) segment, **29**, Fig. 1.13) [56]. They successfully dihydroxylated several vinylic and aliphatic olefins in high yields and high
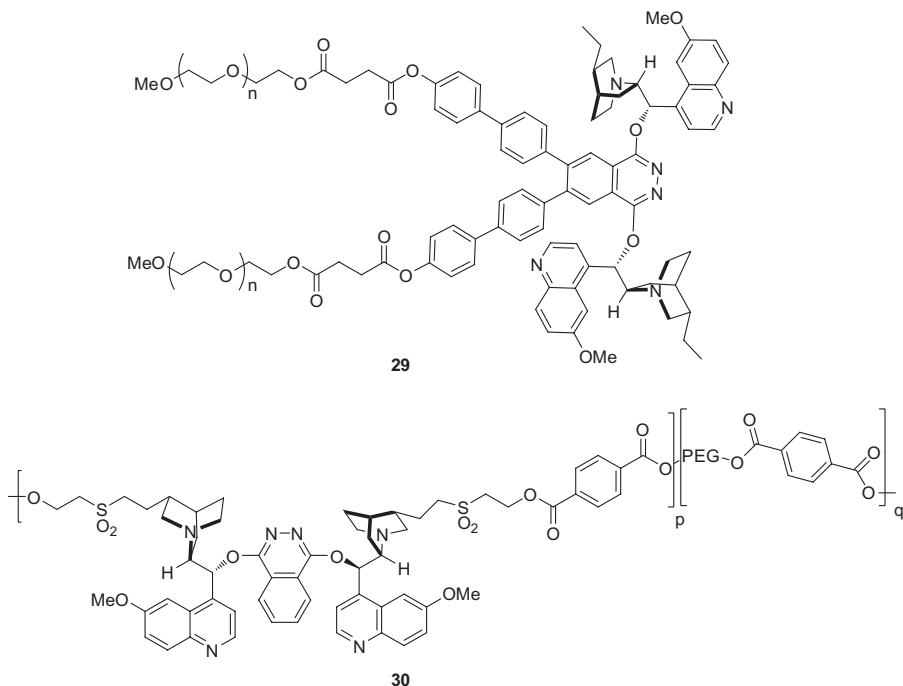
FIGURE 1.13. Structures of ligands **29** and **30**.
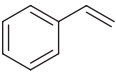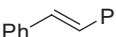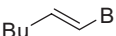
ee's—95%–99% and 87%–90% ee, respectively. This system was reused six times without a detrimental change on its enantioselectivity [$ee_e(6) = 2\%$].

Zhang et al. reported the immobilization of cinchona alkaloids in PEG-4000 [57] (Mw = 4000) instead of PEG-OMe [58] as reported in previous work [58]. The ligand **30** (Fig. 1.13) was always recovered in good yields (95%) and reused four times without changes on the activity (high yields up to 87%, up to 99% ee).

Taking advantage of greater affinity of the alkaloid-OsO_4 complex to the room temperature ionic liquids (RTILs) phase, Branco and Afonso started using RTILs to scope the substitution of the standard organic solvent (^{t}BuOH) used in AD reactions. In this way, they studied two different solvent systems: a biphasic RTIL/H_2O system and a monophasic RTIL/H_2O/^{t}BuOH system, using two different ligands [(DHQD)$_2$PHAL and (DHQD)$_2$PYR]. Using [bmim]PF$_6$, both systems gave similar or even higher results when compared with the traditional ^{t}BuOH/H_2O system [$K_2OsO_2(OH)_4$ (0.5 mol%), (DHQD)$_2$PYR/PHAL (1 mol%), $K_3Fe(CN)_6$ (3 eq), solvent, room temperature during 24 hours, Table 1.4] [59].

Once again, the use of $K_2OsO_2(OH)_4$ as oxidant proved to be less efficient, affording diols with lower chemical yield and ee's than OsO_4. The authors believe that this decrease was well compensated for by using a less toxic oxidant.

TABLE 1.4. Comparative Dihydroxylations Reactions Run in Different Reaction Media

Olefin	Ligand	^{t}BuOH/H$_2$O		RTIL/H$_2$O		RTIL/^{t}BuOH/H$_2$O	
		Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)
(styrene)	PHAL	88	97	87	62	86	94
	PYR	91	93	86	75	90	89
Ph⁀Ph	PHAL	89	96	87	98	92	99
	PYR	94	87	81	96	79	77
Bu⁀Bu	PHAL	94	94	69	87	96	92
	PYR	79	75	52	63	92	96

Both systems could be easily recycled as the products were extracted with diethyl ether. The biphasic system was efficiently reused for nine runs without loss of activity and enantioselectivity [$Y_e(9) = 10\%$, $ee_e(9) = 4\%$ and total turnover number (TON) = 1334], while the monophasic system proved to be a little more robust since it was successfully recycled 10 times [$Y_e(10) = 12.5\%$, $ee_e(10) = 9\%$ and total TON = 1720], affording higher yields. In all assays, the osmium content on the extracted phase was analyzed as being under 4% on average from its initial amount (0.5 mol%). Later, the authors achieved comparable results without the slow addition of olefin and a chiral ligand by using chiral ILs based on the combination of guanidinium cation and readily available chiral anion such as that derived from quinic acid and lactic acid [60].

Song et al. developed a simple method to achieve both ligand (QN)$_2$PHAL and osmium tetroxide recycling without the aid of any solid or polymeric support, nor with the use of an alternative reaction media such as ILs or perfluorophases [61]. In a simple and traditional homogeneous protocol, sucrose was added to the reaction media prior to the AD reaction. In the end, only the AD product could be extracted to an ethereal phase while the ligand and osmium products remained in the water phase. This retention was due to hydrogen bonding between the ligand and the sucrose (sugar, Fig. 1.14). It should be remembered that the applied ligand also undergoes AD and becomes more soluble in water. This system could be reused three times with an average activity erosion of 15%.

More recently, Kim et al. developed a similar strategy to recover the catalyst under traditional homogeneous conditions (Table 1.5) [62]. At the end of the reaction, osmium tetroxide was mainly in the organic phase (as neutral OsO$_4$) due to the large excess of cooxidant employed. Addition of a low-weight olefin like ethylvinylether returns the reduced specie (OsO$_4^{2-}$) to the aqueous phase, which will be retained when all the cooxidant is consumed. Solvent extraction allowed the immobilization of 89% of the osmium catalyst in water, which can be used in eight consecutive cycles with minimal yield erosion.
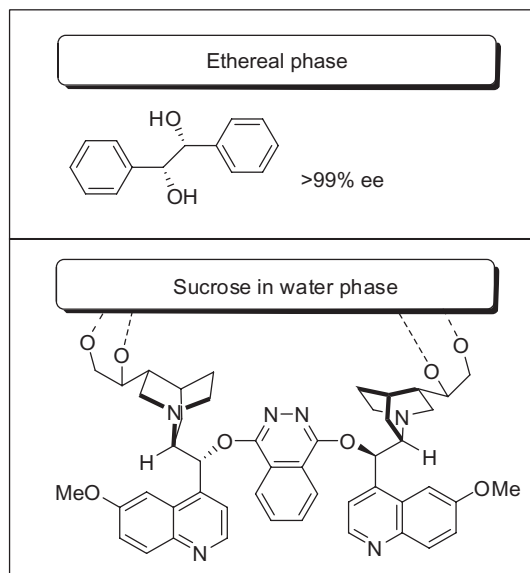
FIGURE 1.14. Catalytic system recycling mechanism.

TABLE 1.5. AD Using Chemoentrapment Strategy

Entry	Olefin	Extracting Solvent	Yield (%)	ee (%)
1	Styrene	Ethyl acetate	97	96.2
2	Styrene	TBME	97	97
3	α-Methylstyrene	TBME	96	89.6
4	trans-Stilbene	TBME	96	>99.5
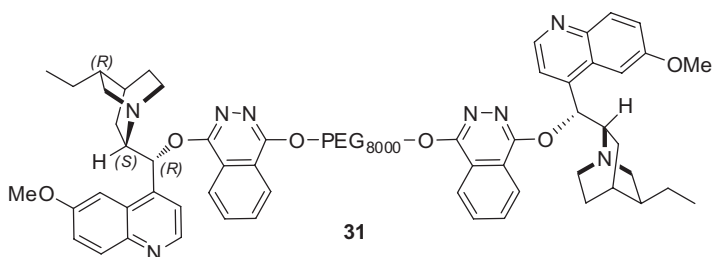
FIGURE 1.15. Structure of the PEG$_{8000}$-supported ligand **31**.

Xu et al. developed a methodology of preparing a family of new PEG-bound bis-cinchona alkaloid ligands. This new family was evaluated on cinnamic esters with amino-hydroxylation in order to achieve the ideal polymer length. The ligand that had the biggest polymeric chain (PEG$_{8000}$, ligand **31**, Fig. 1.15) behaved better in terms of efficiency (90% yield, 99% ee) and

allowed the capture of osmium during the recycling procedure (precipitation upon the addition of ethyl ether). Despite recyclability, it achieved five cycles, but decreasing reactivity in each run was observed [63].

In previous years, some of the methods for AD reactions had already afforded diols with excellent yields and enantiopurity. In this way, AD studies became more focused on obtaining the optimal method, where both the osmium and ligand can be recovered and reused with high efficiency. These efforts have been directed not only in terms of a large number of successful recycles, but also in lowering the catalyst systems loadings. In contrast, less extended approaches have been reported for the parent asymmetric amino-hydroxylation (AA) reaction.

1.4. BISOXAZOLINES

The bisoxazoline ligands (BOX ligands) rose as one of the most important family of ligands in asymmetric catalysis, which are easily synthesized to take advantage of the chirality nature of amino acids. Their principal role in catalysis is to act as a ligand for copper catalysts, being applied in a wide range of transformations in which it could behave as Lewis acids or as carbene generators [64]. Depending on the link between bisoxazoline rings, it is possible to have Aza-BOX (nitrogen), BOX (dimethyl methylene), Phe-BOX (phenyl), and Py-BOX (pyridine) ligand families. It is true that bisoxazolines are not as expensive as chiral phosphines; however, the reutilization of Cu-bisoxazolines catalysts can make their industrial application more viable and prevent high degrees of copper contamination on the final products.

1.4.1. Py-BOX Ligands

Regarding Py-BOX ligands, several methods were applied to achieve the recycling of the catalytic system. The main benchmark transformations used to test the efficiency of each system are alkyne addition to imines, ruthenium-catalyzed cyclopropanations, indium-catalyzed aldehydes allylation, and lanthanides-catalyzed silylcyanation of aldehydes.

Afonso et al. demonstrated that RTILs can be applied as solvent media for a Cu(I)-promoted phenylacetylene in addition to *N*-benzylidene-aniline. The transformation occurred with the same efficiency compared with toluene, but some trouble appeared when the catalytic system was recycled (Scheme 1.11) [65]. Hexane was not polar enough to fully extract the reaction product from the IL, while diethyl ether was able to accomplish such task. Unfortunately, 25% of catalyst was also extracted to the ethereal phase.

Li et al. achieved an identical recyclability when the same transformation was conducted in water in the presence of a surfactant (stearic acid, Scheme 1.11) [66]. Under certain conditions the hydrolysis of Py-BOX ligands in the presence of Lewis acids [Ce(OTf)$_4$] or in acidic conditions has been observed [67]. No signs of decomposition were reported on this example.
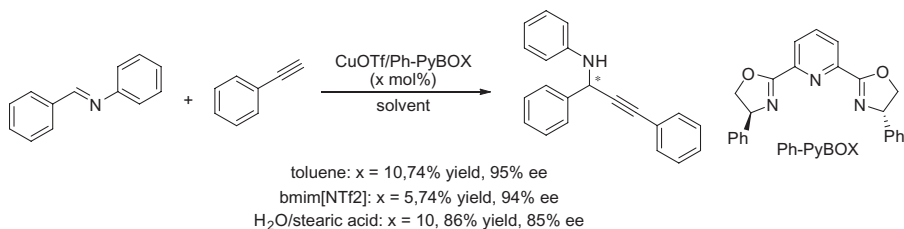
SCHEME 1.11. Asymmetric addition of alkynes to imines promoted by Cu-Ph-PyBOX complex in ILs and water/stearic acid medium.
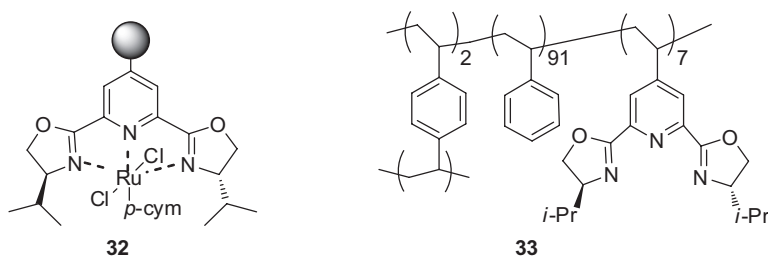
FIGURE 1.16. Structures of immobilized Ru-PyBOX catalyst **32** and polymeric ligand **33**.

Alternatively, O'Leary and co-workers immobilized a Cu(I)- and Cu(II)-Ph-PyBOX triflate complex on silica due to electrostatic interactions, but the catalyst's reusability was studied only during three cycles [68]. The immobilization of the Py-BOX ligand in a Wang resin did not provide a very recyclable system for the same transformation [69]. The reactions performed in IL provided the higher levels of enantiomeric induction, but the water/stearic acid system was more efficiently recyclable.

A series of works were conducted for the reutilization of a Py-BOX ligand with soluble and insoluble copolymers with high cross-linking. Mayoral et al. immobilized the Ru-PyBOX catalyst **32** (Fig. 1.16) to a polystyrene polymer by copolymerization. With this catalyst, the respective cyclopropanes (derived from styrene and ethyl diazoacetate) were isolated with high *trans* selectivity (85:15 *trans*/*cis*), in which the major diasteriomer was obtained in 85% ee's with 30% yields. The lack of reactivity could be explained by the presence of several inaccessible catalyst sites inside the polymer chains. In the third consecutive cycle, both activity and enantioselectivity dropped about 50% [70]. Recently, the authors prepared a monolithic polystyrene resin bearing the Ru-PyBOX to be used under continuous flow conditions [71].

The polymeric ligand **33** (Fig. 1.16) with a lower cross-linking degree provided an efficient catalyst (52%–70% yields, *trans*/*cis* selectivity of 90:10 and enantioselectivities of around 85%–91% for the *trans*-cyclopropanes) [72]. This catalytic system was reused consistently during four cycles;
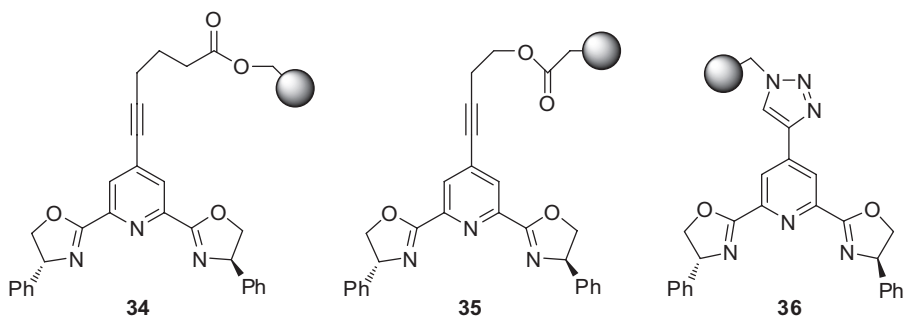
FIGURE 1.17. Structures of heterogeneous Ph-PyBOX ligands **34–36**.

however, the recovery protocol required inert conditions. Grafting the ligand in Merrifield resin proved slightly less efficient than catalysts prepared from copolymerization.

Although low cross-linking polymerization is the best method for the immobilization of the Ru-PyBOX system (when looking at the overall efficiency of the reaction: yield and enantioselectivity), microencapsulation appears as a competitive alternative since no ligand modification is required [73]. Both polystyrene and Ru-PyBOX are soluble in dichloromethane (the solvent used in the cyclopropanation reaction), but when hexane was added, the polymer has a tendency to microencapsulate the catalyst, precipitating together and allowing its recovery.

In(III)-PyBOX was used as a catalyst for allylation of ketones and aldehydes in a mixture of [hmim]PF$_6$/dichloromethane, and its reutilization was achieved up to four cycles with consistent yield and slightly decreasing ee [ee$_e$(4) = 12%] [74]. In 2003, the Ph-PyBOX ligand was immobilized to TentaGel resins. Both heterogeneous Ph-PyBOX ligands **34** and **35** (20 mol%) (Fig. 1.17) were tested in the catalytic asymmetric silylcyanation of benzaldehyde in the presence of 10 mol% of YbCl$_3$, being slightly less enantioselective than the homogeneous analog. Curiously, both polymeric ligands showed an outstanding lifetime since they can be used in 30 consecutive cycles without any change in the reaction outcome (enantioselectivity and conversion). However, the catalytic system (ytterbium/ligand complex) was only efficiently reused during four cycles, due to metal-leaching phenomena during the filtration procedures [75]. More recently, the same ligand was grafted to polystyrene resin, bearing an azide group via click chemistry [76]. Ligand **36** (Fig. 1.17) was tested in the cyanosilylation of aromatic aldehydes promoted by ytterbium and lutetium. High conversions (68%–87%) and high enantioselectivities (67%–78% ee) were obtained for this reaction in four consecutive cycles (10 mol% of catalyst, acetonitrile/dichloromethane 3:2) [77].

1.4.2. BOX Ligands

Cu-BOX catalysts have been addressed for recycling for cyclopropanation, carbonyl-ene, Mukaiyama aldol, and cyclo addition reactions. The enantiose-

lectivity of a cyclopropanation reaction catalyzed by Cu-BOX catalysts can be extremely sensitive to two parameters: the presence of halide and/or water impurities and the alterations of the bite angle in the BOX ligand. Davies et al. showed that the presence of 5% of halide impurities on an RTIL's phase was more than enough to deactivate completely the copper catalyst for cyclopropanation reactions [78]. Due to their synthesis strategy, RTILs in general can have halide impurities that could prevent a smooth cyclopropanation reaction in this media. Furthermore, since RTILs are in general hygroscopic, that limits their application in this transformation. It is known that a BOX bearing two methyl groups attached in the C-bridge atom provides cyclopropanes with higher enantioselectivities compared with BOX ligands bearing benzyl groups [64]. This is due to the alteration of the bite angle of the ligand.

The first studies for BOX ligand immobilization in polymeric structures were conducted using BOX ligands bearing two styril moyeties linked in the bridge carbon atom that could be polymerized and copolymerized with styrene (and cross-linker, ligands **37** and **38**, Fig. 1.18) [79]. The polymeric ligands were tested in the benchmark cyclopropanation reaction (styrene cyclopropanation with diazoacetate), affording the respective cyclopropanes with an efficiency similar to the one observed with homogeneous nonsupported ligands [37:63 *trans*/*cis* selectivity, 78%:72% ee (*trans*/*cis*)].

The rapid immobilization of such ligands in polystyrene was accomplished using only one flexible linker that separated the ligand from the polymer backbone (Scheme 1.12) [80]. Not only did the immobilization have a minor effect on the enantioselectivity of the reaction, but the polymeric catalyst (Cu/BOX **39**, Fig. 1.19) could be recycled four times without any efficiency erosion.
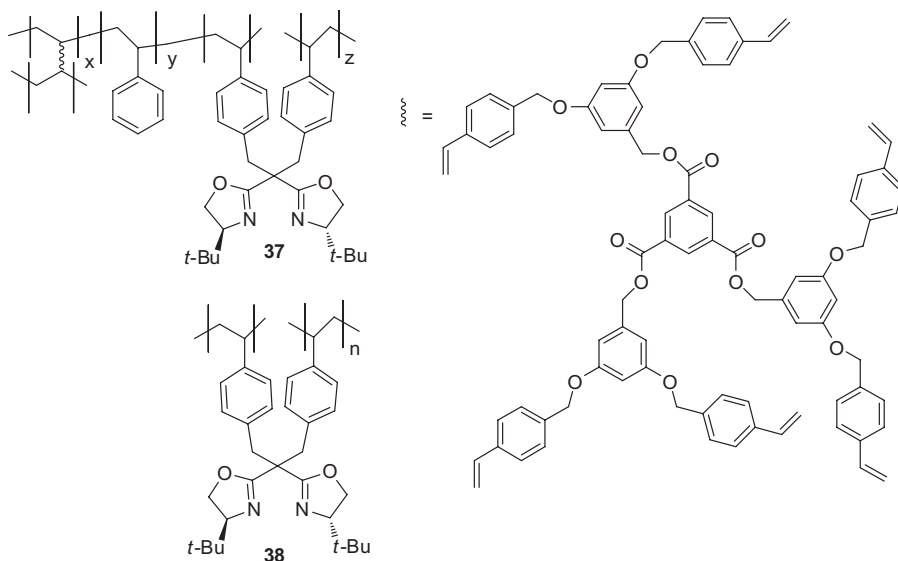
FIGURE 1.18. Structures of ligands **37** and **38**.

homogeneous: 61%, 29:71 *cis/trans*, 92%:94% ee (*cis/trans*)
heterogeneous: 60%, 33:67 *cis/trans*, 90%:93% ee (*cis/trans*)
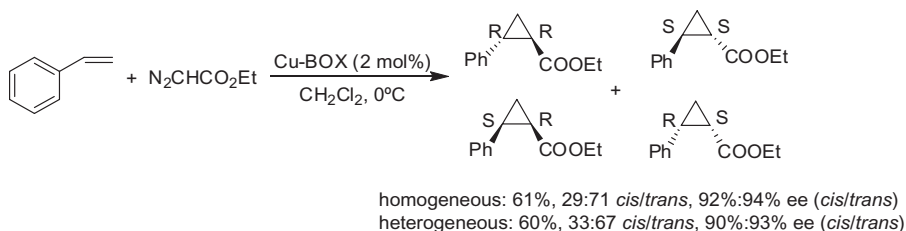
SCHEME 1.12. Benchmark cyclopropanation reaction promoted by copper/polymer-supported BOX complex.
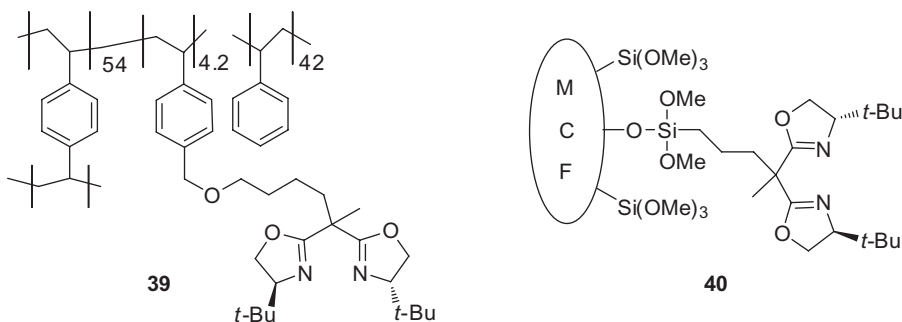
FIGURE 1.19. Structures of ligands **39** and **40**.

As an alternative to organic polymeric supports, Ying et al. grafted a chiral BOX ligand to the surface of siliceous mesocellular foams (MCFs) using only one silanized linker [81]. It was necessary to protect free silanols groups with trimethylsilane in order to achieve excellent enantioselectivities. The heterogeneous ligand **40** (Fig. 1.19) was applied in styrene cyclopropanation, providing cyclopropanes in 80% yield with excellent enatiomeric excesses (65:35 *trans/cis*, 95%:92% ee *trans/cis*, comparable with the homogeneous counterpart). The catalyst loading could be decreased to 0.2 mol% without compromising the reaction outcome. The Cu/ligand **40** was reused for 12 consecutive reactions without losing activity or enantioselectivity. Once again, monotethered Box ligands proved to be more selective than bis-tethered ones [82].

Sometimes, the immobilization of a catalyst can alter considerably the reaction selectivity compared with the one observed in homogeneous solution. This phenomenon revealed itself when a Cu-BOX complex was immobilized in laponite containing a supported IL film. This heterogeneous catalyst was tested in a benchmark styrene cyclopropanation reaction with diethyl diazoacetate. Despite the moderate success, a totally different *trans/cis* ratio was disclosed when compared with the same reaction run in IL media. It was also observed that the thickness of the film had a crucial influence on the selectivity [83].
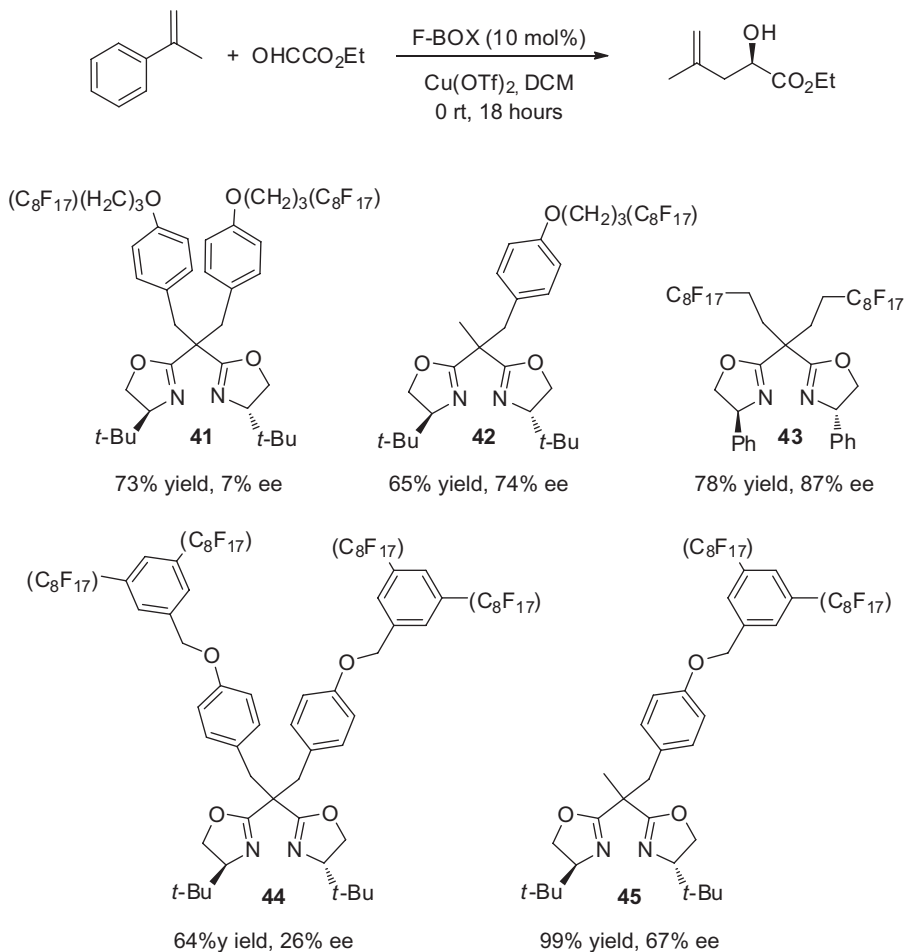
SCHEME 1.13. Asymmetric carbonyl-ene reaction promoted by Cu–perfluoroBox complexes.

The carbonyl-ene reaction catalyzed by copper-BOX complexes also proved to be considerably dependent on the BOX bite angle. In Scheme 1.13, it is possible to compare the evolution of enantioselectivity in the function of the fluorous tail linked to the BOX ligand [84].

The BOX **43** provided higher levels of enantioselectivity compared with other fluorinated BOX (**41–45**, Scheme 1.13). The catalyst was reused efficiently at least five times with the aid of fluorous reverse phase silica gel [85].

Kanemasa et al. attached the BOX ligand to gold nanoparticles. Despite the excellent enantioselectivities obtained during five cycles, the recovery protocol is rather complex, which could represent an important drawback [86].
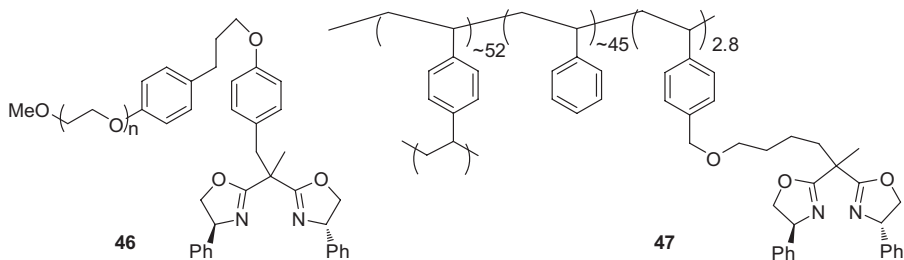
FIGURE 1.20. Structures of ligands **46** and **47**.

For this transformation, the best results were obtained when the BOX was grafted to PEG and copolymerized with styrene/divinylbenzene. The benchmark carbonyl-ene reaction between α-methylstyrene and glyoxylate afforded the respective product in 96% yield with 95% ee (10 mol% Cu/ligand **46**, Fig. 1.20). The supported catalyst was precipitated with diethyl ether and reused twice with marginal loss of efficiency [2]. The copolymer **47** (Fig. 1.20) in a 10 mol% loading provided 96% yield with 90% ee for the same reaction. In the recycling assays, consistent 90% ee was obtained during five cycles. However, the reaction time required to achieve high conversions increased gradually in each cycle [87].

Ligand **46** was studied in copper-catalyzed Mukaiyama aldol reactions in water (20 mol%). Low chemical yield was accounted for due to the low aldehyde solubility in water, but the enantioselectivity remained unchanged. The catalytic system could be 85% recovered with extractions and reused twice upon pretreatment [88]. Ligand **42** was tested for a Cu(II)-promoted Mukaiyama aldol reaction between silylketene and ethylglyoxalate and reused once [84b].

When the BOX ligand was immobilized on mesoporous silica SBA-15 (ligand **48**, Fig. 1.21) and in the core of dendritic structures (ligand **49**, Fig. 1.21), it proved to be at least as efficient as the nonsupported counterpart. The copper/**48** catalyst was easily recovered and reused five times for nitro-Mannich with gradual loss of enantioselectivity and diastereoselectivity. The catalyst heterogenization had a positive impact on the reaction enantioselectivity surpassing the homogeneous catalyst [89]. The copper/**49** catalyst proved to be more efficient than the nonsupported catalyst in the Mukaiyama aldol reaction, affording 1,3-dydroxyketone with 78% yield in 64% ee and 2.2:1 *syn/anti* selectivity (Scheme 1.14) [90].

In the following works, the application of IL enhanced ecyclability. It appears that ILs act as a protecting agent toward metal leaching that would lead to loss of catalytic activity.

Doherty et al. showed that ligand **50** (Fig. 1.21) provided the same levels of enantioselectivity (90% ee) in a Cu(II)-catalyzed Mukaiyama aldol reaction
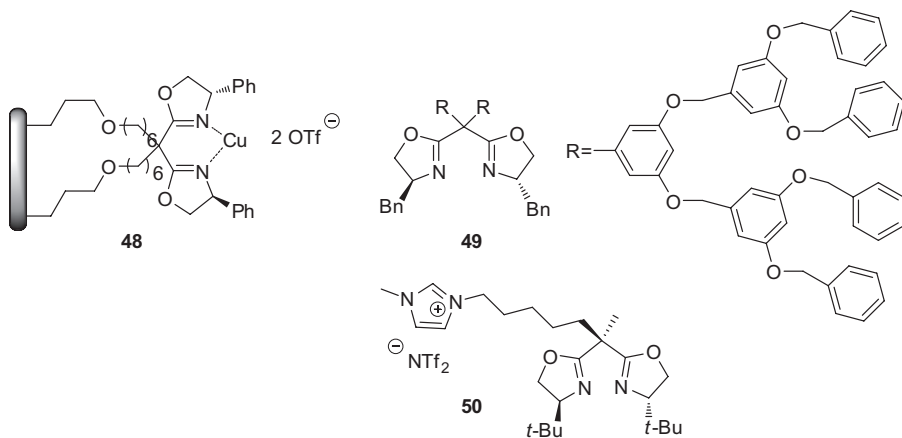
FIGURE 1.21. Structures of catalyst **48** and ligands **49** and **50**.
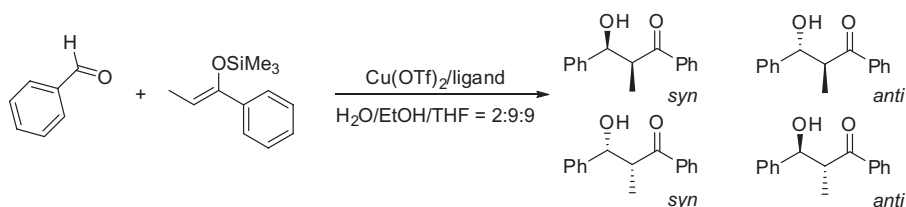
SCHEME 1.14. Mukaiyama aldol reaction catalyzed by copper in the presence of dendritic Box ligand.

between methyl pyruvate and 1-methoxy-1-trimethylsilyloxypropene in [emim]NTf$_2$ that are observed in dichloromethane at −78°C. The catalytic activity of this system was retained over three cycles. The electrostatic immobilization of the catalytic system was achieved when the silica treated with IL was used as an immobilizing agent. The reusability in this case reached eight cycles with excellent enantioselectivity [91].

The same ligand **50** was also explored in the copper-catalyzed Diels–Alder reaction between *N*-acryloyloxazolidinone and cyclopentadiene in [emim] NTf$_2$, providing identical levels of recyclability (nine cycles). An accelerating effect was observed that allowed more demanding substrates to be scoped [92].

Kim et al. observed that the same transformation catalyzed by Cu-Inda-BOX ligand can have its enantioselectivity enhanced up to 94% ee when run in [bmim]SbF$_6$ instead of in dichloromethane (8 mol% catalyst, 3°C, 10 minutes, Table 1.6). Furthermore, the authors show that the catalytic system and IL could be recycled 16 times with residual enantioselectivity erosion (88%–92% yields, 10 minutes) [93].

TABLE 1.6. Asymmetric Diels–Alder Reaction Between Cyclopentadiene and _N_-acryloyloxazolidinone with Recycled [Bmim]SbF$_6$ Containing IndaBOX–Cu Complex

Run	_Endo/Exo_	_Endo_ ee (%)
1	97:3	94
6	96:4	88
10	95:5	86
15	93:7	84
17	93:7	84
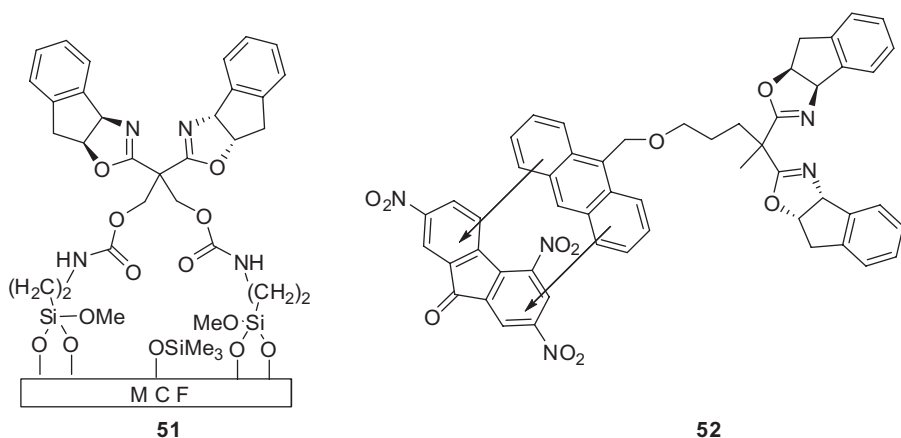
FIGURE 1.22. Structures of ligands **51** and **52**.

Other immobilization strategies were applied to the Cu-Inda-BOX catalyst, such as grafting in siliceous materials, copolymerization with methylene diphenyl isocyanate, and immobilization in MCFs [94]. The best results were obtained in the heterogenization on MCFs after capping the free silanols groups (ligand **51**, Fig. 1.22). The enantioselectivity of the Cu(II)-catalyzed cycloaddition of 3-cryloyl-2-oxazolidinone with cyclopentadiene reached 88% ee with quantitative conversion in 8 hours and 96% _endo_ selectivity. The catalyst was reused at least four times without any observable efficiency loss [95].

Chollet et al. reported a very peculiar way to recycle a Cu-Inda-BOX complex by preparing a charge transfer complex that could be recovered by precipitation. Ligand **52** (Fig. 1.22) was applied in Cu(II)-promoted cycloaddition of 3-acryloyl-2-oxazolidinone with cyclopentadiene, providing the respective product with quantitative conversion, 93% de, and 84% ee (Scheme 1.15). The system was reused with an extraordinary longevity (11 recycles). Surprisingly, the catalyst became more efficient as it was being reused since the reaction time reduced from 44 hours (run 1) to 0.5 hours (run 11) [96].
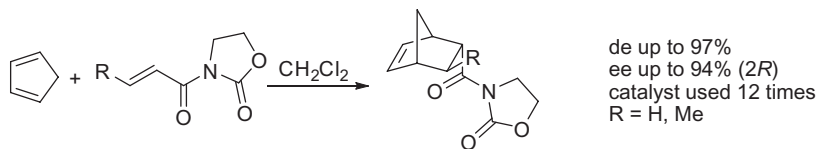
SCHEME 1.15. Asymmetric cycloaddition reactions promoted by Cu–Box complex immobilized in a charge transfer complex.
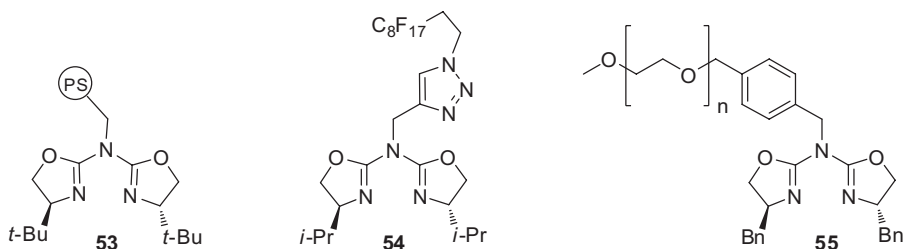
FIGURE 1.23. Structures of ligands **53–55**.

1.4.3. Aza-BOX and Phe-BOX Ligands

Several methods were reported in the literature to achieve the reutilization of Aza-BOX ligands. In a first method, polystyrene-bound Aza-BOX ligand **53** (Fig. 1.23) was prepared by grafting and copolymerization to be tested for Cu(I)-catalyzed cyclopropanations of styrene with ethyl diazoacetate [97]. The supported ligands derived from grafting proved to have a large number of catalyst active centers accessible to the substrate molecules, providing very active catalysts. The respective cyclopropanes were isolated in enantioselectivities comparable or even higher than those provided by homogeneous and nonsupported catalysts for several olefins (as an example, for styrene: 94%, 1 mol% catalyst, up to 99% ee). The catalyst could be recycled up to five cycles for reactive alkenes [98].

Alternatively, Cu-AzaBOX catalyst immobilization can be achieved by the following methods: electrostatic interactions in laponite (clay), nafion-silica [98, 99], retention in the [emim][OTf] phase, immobilization in PEG, and self-supported polymers. From these contributions, the highlights go to the immobilization IL, PEG, and in a self-supported polymer. The recyclability with IL strategy was considerably higher because the enantioselectivity of the isolated *trans* product remained at 90% ee during eight cycles [100, 101].

The MeO-PEG Aza-BOX ligand **55** (Mw = 5000) as a homogeneous-supported catalyst proved to be at least as efficient as its nonsupported analog in copper-catalyzed cyclopropanation of styrene and 1,1-diphenyl ethylene with ethyl diazoacetate. The enantioselectivity observed for the cyclopropanes
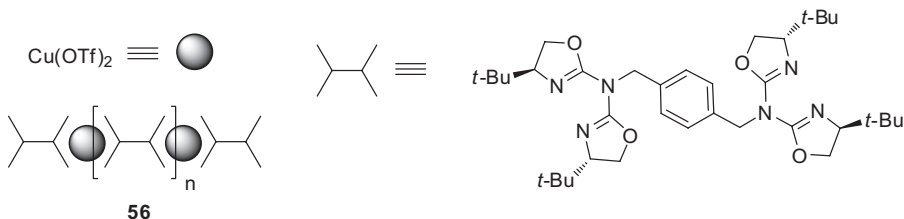
FIGURE 1.24. Structure of self-supported polymeric Aza-BOX catalyst **56**.
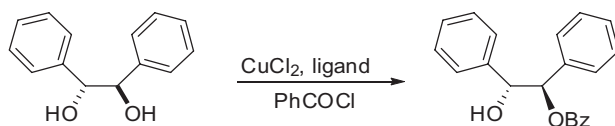
SCHEME 1.16. Desymmetrization of 1,2-diols with copper- and polymer-supported aza-BOX.

with this catalyst rose to 90% ee and its reutilization reached nine consecutive cycles [102].

In 2008, the application of the self-supported polymeric Aza-BOX catalyst **56** (Fig. 1.24) in the cyclopropanation of styrene (which curiously behaved as a heterogeneous and homogeneous catalyst) was reported. During the catalysis, the heterogeneous polymer becomes soluble, perhaps due to substrate-induced depolymerization and, at the end of the reaction, it precipitates. The recyclability of this catalyst was demonstrated during 14 cycles (>95% ee) [103].

The ligand **55** was also applied for the kinetic resolution (KR) of racemic 1,2-diols via copper-catalyzed benzoylation (Scheme 1.16) [104]. The product was obtained in 41% yield and >99% ee. The catalyst was recovered in high yields (>95%) and reused up to five cycles without efficiency variations. The nonsupported version of ligand **55** was also anchored to other supports like Merrifield resin, PEG chains, and superparamagnetic magnetite/silica nanoparticles using click chemistry developed by the Sharpless group [76]. From this list of supports, it was possible to achieve the same recyclability with only superparamagnetic magnetite/silica nanoparticles [105]. Recently, this ligand was also immobilized in a dendritic structure [106].

Interestingly, it was possible to recycle fluorous-tagged Aza-BOX **54** without the need to use perfluorous solvents. The homogeneous catalyst prepared with ligand **54** could be precipitated with diethyl ether (when dichloromethane is used as solvent) and recycled with similar efficiency as for **55** [107].

The Phe-BOX immobilization was conducted by Weissberg and Portnoy, via preparation of the Rh-Phe-BOX catalysts **57** (Fig. 1.25) by solid-phase synthetic chemistry. The preliminary results of the application of **57** in benz-aldehyde enantioselective allylation indicates that there is still room for improvement in the recovery and reutilization efficiency [108].
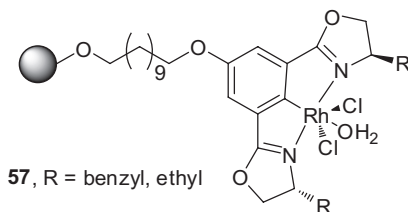
FIGURE 1.25. Structure of Rh-Phe-BOX catalysts **57**.

In conclusion, Phe-BOX ligands were considerably less studied for recycling strategies than BOX, Py-BOX, and Aza-BOX. There are several strategies to achieve the immobilization of the catalystic systems and their consequent reutilization. From such strategies in general the best results are obtained when the immobilization is done in a robust support that does not alter the nature of the catalyst. It is also noteworthy that for immobilization by electrostatic interaction, the utilization of ILs and an ionic-tagged catalyst provided excellent results when the BOX ligands are applied in Lewis acid catalysis.

1.5. SALEN-TYPE LIGANDS

The family of salen-based complexes has applications in several synthetic methodologies; however, the epoxidation of alkenes, KR of epoxides, and cyanosylilation of aldehydes are among the most well developed. The number of works based on catalyst reutilization with salen complexes is high. The aim of this section is to highlight some successful examples. For a more complete view on the topic, consult a recent review [2].

This section will be structured by reaction. In the asymmetric epoxidation of olefins, the main supports chosen to immobilize the catalyst are inorganic. The recycling of the catalytic system with this strategy was conducted by coordination of the support to the metal, grafting of ligand moiety, or electrostatic interaction.

Nguyen et al. prepared a coordination polymer by reaction of a [bis(catechol) salen]Mn(III) complex with several di- and trivalent metal ions. The polymer prepared with copper was found to be insoluble in several organic solvents and a good heterogeneous catalyst to perform the asymmetric epoxidation of 2,2,-dimethyl-2H-chromene with 2-(*tert*-butylsulfonyl)iodosylbenzene (79% yield, 76% ee). The catalyst **58** (Fig. 1.26) could be reused during 10 cycles with minimal yield erosion (10%) and constant enantioselectivity [109].

A series of works were published that used functionalized siliceous materials to which the Mn-salen complex could be coordinated. Li et al. grafted phenolic groups on the mesoporous surface of siliceous MCM-41 heterogeneous support [110]. The chiral Mn-salen complex was then anchored into this
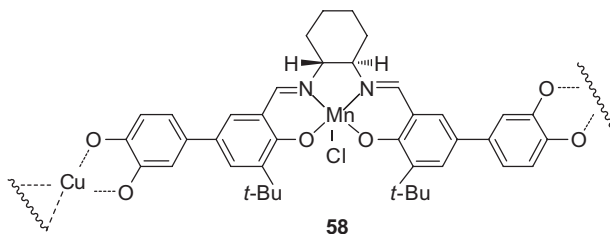
FIGURE 1.26. Structure of catalyst **58**.

run 1: 99% conversion, 70% ee
run 2: 99% conversion, 70% ee
run 3: 98% conversion, 73% ee
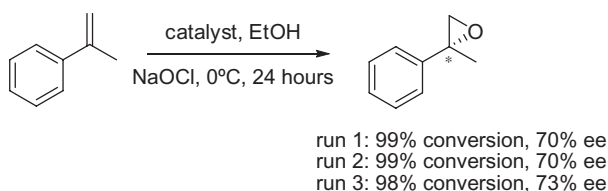
SCHEME 1.17. Recycling of Mn-salen catalyst anchored in modified MCM-41 (phenolic groups).

cis   +   *trans*

homogenous Mn(salen)Cl: *cis/trans* = 0.38
Mn(salen)/MCM: *cis/trans* = 17.6
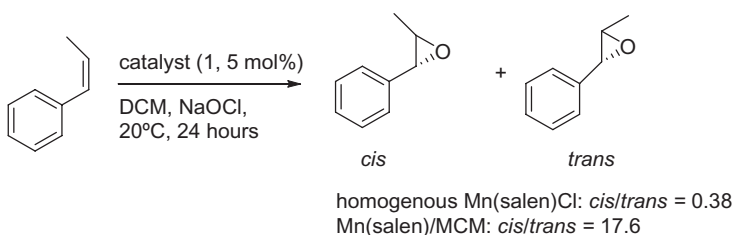
SCHEME 1.18. Pore effect in the selectivity of *cis-β*-methylstyrene epoxidation.

modified support through axial complexation of manganese on the phenoxy groups. This catalyst was tested for *α*-methylstyrene epoxidation and gave better results in terms of enantioselectivity (67%–73% ee) than the homogeneous Mn-salen complex (56% ee, Scheme 1.17). Interestingly, alkenes that do not fit inside the cavities (such as 1-phenylcyclohexene) were not epoxidized: a proof that all Mn-salen complexes were strongly anchored and behaved like a heterogeneous catalyst. The catalyst was reused three times without any loss of activity and enantioselectivity.

The same methodology was extended to create a monolayer of phenyl sulfonic groups on the surface of several inorganic supports (MCM-41, SBA-15, and activated silica) [111]. The same behavior in terms of enantioselectivity was detected. When the Mn-salen–silica catalyst was reused, consistent 76% ee was achieved during five cycles [$Y_e(5) = 30\%$]. Interestingly, when the olefin was changed to *cis-β*-methylstyrene, a curious selectivity behavior was detected with anchored Mn-salen catalysts. In fact, on going from homogeneous environment to low-sized pores, the *cis/trans* ratio changed from 0.38 to 17.6 (Scheme 1.18).

TABLE 1.7. The Recycles of Mn-Salen in the Asymmetric Epoxidation of α-Methylstyrene

Run	Time	Conversion (%)	ee (%)	TOF $\times 10^{-4}$(s^{-1})
1	24	>99	>99	2.31
5	24	96	>99	2.22
6	24	95	99	2.20
10	24	90	91	2.08
11	24	80	85	1.85

The supported catalyst was found to be more selective for *cis* epoxide than the homogeneous catalysts that showed a higher tendency to generate the *trans* isomer. The sulfonic and phenoxy groups were also prepared in the surface of highly cross-linked polystyrene resins [112] and phenoxy-modified zyrconiumpoly-(styrene-phenylvinylphosphanate)phosphate [113]. The first new catalysts proved to be easier to handle than the silica-based ones, providing the same results. Regarding the second family, the coordination of a supported amine to the Mn-salen allowed a recyclability of 11 cycles (99% ee) for epoxidation α-methylstyrene (Table 1.7) [114].

The authors found that the increase in enantioselectivity was due to a positive pore effect since catalysts anchored in the external surface did not provide enantioselectivities as high as those catalysts immobilized inside nanopores [115]. It was also reasoned that the inversion on the *cis-β*-methylstyrene epoxidation selectivity was due to the effect on the rotation motions necessary to achieve the *trans* transition state caused by the lack of space inside the nanopore. *N*-oxide groups were also scoped as ligands to anchor Mn-salen inside MCM-41 [116].

Chemical functionalization of silica with ligand moieties and functionalization of salen ligand with silanes were also tested to achieve recyclable systems. Kureshy et al. functionalized the surface of MCM-41 and SBA-15 with a reactive 3-aminopropyltriethoxysilane, allowing the salen complex to be grafted and therefore immobilized on the support [117]. Both heterogeneous catalysts **59** (Fig. 1.27) proved to be nearly as efficient as the nonsupported analog, and quantitative yields were achieved with good-to-excellent levels of enantioselectivities (chromenes, 5 mol%, up to 94% ee). Furthermore, they were successfully recycled with minimal yield erosion and consistent ee up to four cycles. In the case of styrene derivatives, the heterogenized catalyst provided the respective epoxides with higher enantioselectivity [118]. More recently, Liu et al. studied the pore effect for this type of immobilization. They observed that siliceous supports, with bigger pores, facilitated diffusion phenomena enhancing the reactivity, but with a penalty on the enantioselectivity of the epoxides [119].

The authors also studied the immobilization of Mn(III)-salen complex in MCM-48. The enantioselectivity and reactivity of the immobilized catalyst **60** (Fig. 1.27) sometimes surpassed those obtained with the homogeneous
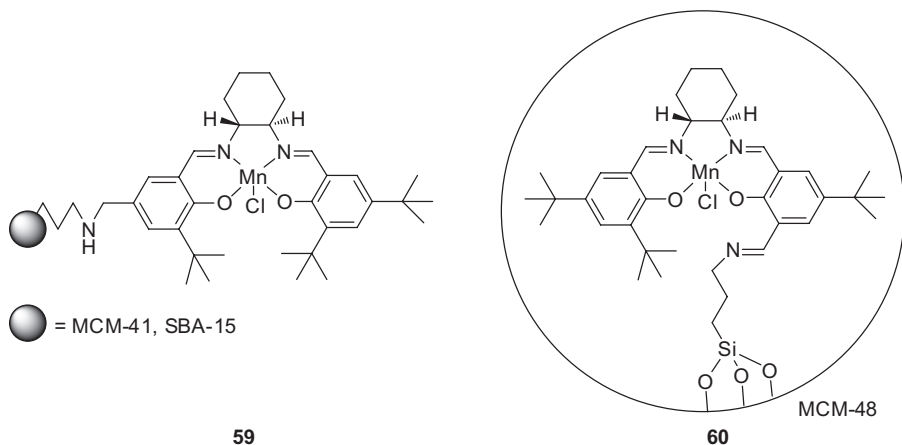
FIGURE 1.27. Structures of catalysts **59** and **60**.
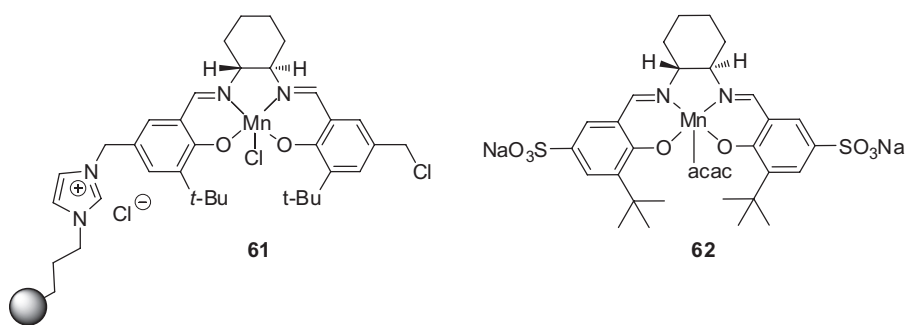
FIGURE 1.28. Structures of catalysts **61** and **62**.

complex, and it could be recycled up to three cycles [120]. A few years later, the authors anchored this ligand on several siliceous supports (MCM-41, SBA-15, amorphous silica, and MCM-48) using an ionic linker (imidazolium chloride salt). In this case, the catalyst **61** (Fig. 1.28) was recycled five times with success [121]. The immobilization of the Mn(III)-salen complexes in MCM-48 modified with imidazolium-based ILs units treated with [bmim]PF$_6$ was also analyzed. This heterogeneous catalyst was tested in asymmetric epoxidation of unfunctionalized olefins, where it was found to be stable, recyclable (three cycles), and exhibited comparable activity and considerable higher enantioselectivities than those obtained by the homogeneous counterparts (e.g., >99%, 92% ee for α-methylstyrene) [122].

Hydrotalcite-like materials [123, 124] and clays [125] were also used to immobilize the ionic Mn-salen complex by electrostatic interaction. In the work of Choudary et al., the catalyst **62** (Fig. 1.28) was immobilized on layered

double hydroxide (LDH) and cationic resin with beneficial effects on catalyst recycling, namely in terms of enantioselectivity (which remains unchanged up to five cycles). Epoxidation of cyclic olefins affords excellent levels of enantioselectivity (>94% ee), while acyclic ones like styrene were converted to the respective epoxide in moderate ee (48% ee) [126].

Liese et al. reported the application of a chiral Mn(III)-salen complex covalently anchored to a hyperbranched polyglycerol polymer as an efficient recyclable catalyst for asymmetric epoxidation of chromenes (96% conversion, 96% ee). Epoxidation of 6-cyano-2,2-dimethylchromene, using catalyst **63** (Fig. 1.29), was carried out in a continuously operated chemical membrane reactor for 20 residence times, and steady conversions up to 70% as well as steady ee's of up to 92% were achieved (total TON = 240) [127].

Seebach and co-workers prepared insoluble polymers using ligand **64** (Fig. 1.29) as a cross-linker. The application of this ligand in asymmetric epoxidation of styrene was successful, namely in terms of recyclability (it reached 10 cycles with consistent 77%–80% ee) [128].

Until now, all the methods described herein have a heterogeneous nature. The following contributions are in homogeneous catalysis. Kureshy et al. showed that dimeric Mn(III)-salen complexes **65** and **66** (Fig. 1.30) are able
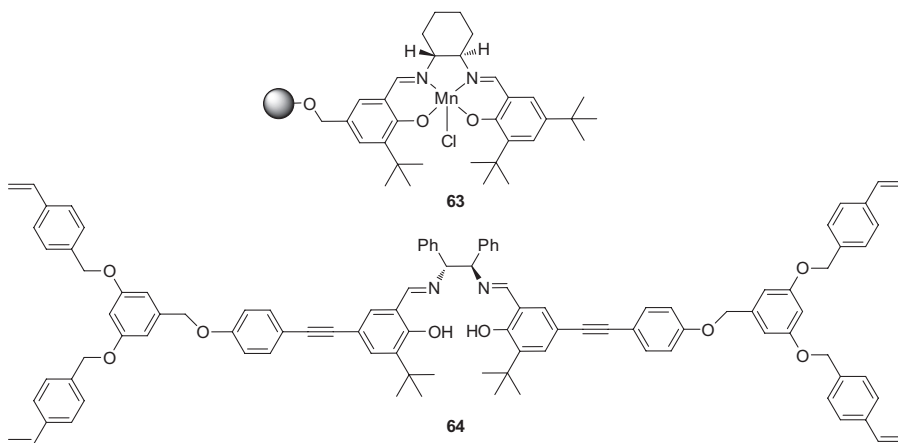
FIGURE 1.29. Structures of catalyst **63** and ligand **64**.
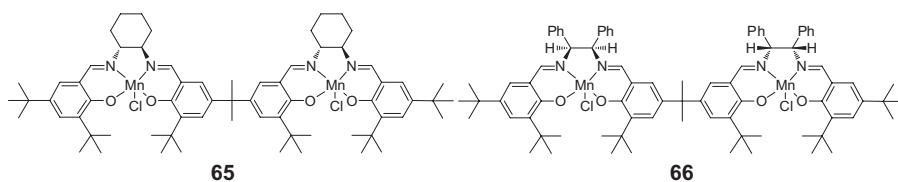
FIGURE 1.30. Structures of dimeric Mn(III)-salen complexes **65** and **66**.

to catalyze the epoxidation of several alkenes (in the presence of a 4-PhPy-oxide and NaOCl) with the same efficiency described for Jacobsen's catalysts; however, the first was recoverable by precipitation and reused for five cycles without any efficiency erosion [129]. Later, the authors described a greener protocol where urea hydrogen peroxide was substituted by NaOCl [130].

In 2004, the asymmetric epoxidation of dihydronaphthalene in the presence of a Mn–Katsuki-type salen catalyst in IL media ([bmim]PF$_6$, 2.5 mol%, 93% ee) was performed. The IL phase bearing the catalyst was reused eight times [$Y_e(9) = 25\%$, $ee_e(9) = 13\%$] [131].

The KR of epoxides was explored almost at the same time as the asymmetric epoxidation of alkenes. In this transformation, the synergetic effects of two near Co-salen units provide high levels of enantioselectivity and in principle should be taken into account when the catalyst is immobilized.

Yang et al. demonstrated for the first time that cooperative activation effect (between two metallic units) can be enhanced in the nanocage of mesoporous materials like SBA-16. The Co(III)-salen catalyst confined to nanocages exhibited a significantly higher activity and enantioselectivity for the resolution of racemic aromatic epoxides (S/C up to 12,000) compared with the homogeneous catalyst. Furthermore, the system retained its activity for more than eight cycles (with regeneration) [132]. Recently, a polymeric chiral Co-salen was anchored in the walls of SBA-15 pretreated with dimethylcarbonate. This heterogeneous catalyst proved to have an efficiency similar to the homogeneous version and was reused efficiently three times [133].

To take advantage of mechanism cooperativity of nearby Co-salen centers in dendritic structures, Weck and co-workers grafted dendrons to insoluble polystyrene resins. The heterogeneous catalyst **67** (Fig. 1.31) could be applied in hydrolytic kinetic resolution (HKR) of terminal epoxides with catalysts loadings as low as 0.04 mol% furnishing the respective products in 99% ee.
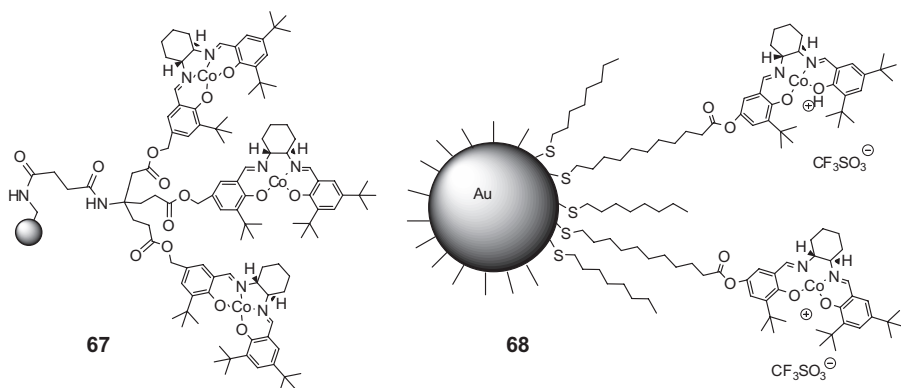
FIGURE 1.31. Structures of catalysts **67** and **68**.
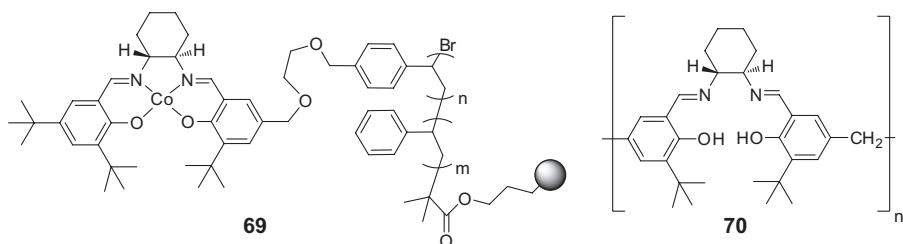
FIGURE 1.32. Structures of catalyst **69** and ligand **70**.

The efficiency of reutilization of the catalytic system was demonstrated during five cycles [134].

Jacobsen and Belser prepared gold colloids coated with a monolayer of *n*-octanethiolates and thiolates with a chiral Co(III)-salen catalyst and tested it as the catalyst for the HKR of hexene-1-oxide. Due to cooperative effects, the catalyst **68** (Fig. 1.31) exhibited a significant acceleration relative to the homogeneous system (>99.9% ee epoxide, 0.01% mol% catalyst). Recovery of the immobilized catalyst was possible by simple filtration, and after catalyst reoxidation, it was reused seven times without any loss of activity and enantioselectivity [135].

Alternatively, it is possible to have identical efficiency if the catalyst is immobilized in polymeric units with considerable flexibility. Co-salen with a flexible pendant group was immobilized in a polystyrene residue anchored in silica. Catalyst **69** (Fig. 1.32) was applied efficiently during five cycles in the resolution of epichlorohydrin. The respective epoxide was isolated in 99% ee after a consistent conversion of 55% [136]. Recently, silica has been substituted by a magnetic nanoparticle with the same success [137].

Kwon and Kim tested a family of polymeric (linear and cross-linked) salen ligands for Co(II)-mediated KR of terminal epoxides [138]. Using 0.5 mol% of Co/salen **70** (Fig. 1.32), racemic epoxides were resolved with excellent enantioselectivity (>99% ee for both diol and epoxide). The counteranion played an important role in the efficiency of this immobilized catalyst, allowing its recyclability (tetrafluoroborate and hexafluorophosphate were the best). These catalysts were reused up to seven cycles with extraordinary consistency (44% yield and 99% ee for all cycles) without any need for reactivation at the end of each reaction. Recently, Kim et al. showed that group 13 salts (AlCl$_3$, GaCl$_3$, and InCl$_3$) can enhance the catalytic and enantioselectivity of polymeric Co(III)-salen catalysts [139].

Song et al. showed that KR of terminal alkylic epoxides (with water) could proceed smoothly in the presence of poly-salen-Co(III) complexes to furnish excellent conversions (>49%) and high enantioselectivities (up to 98%, Scheme 1.19) [140]. HKR of more reactive epoxides such as epychlorohydrin featured a different behavior with the formation of a unique phase. The free terminal amine from the catalyst **71** probably reacted with the epoxide, improving

conversion >49%, 97% epoxide ee, 94% diol ee
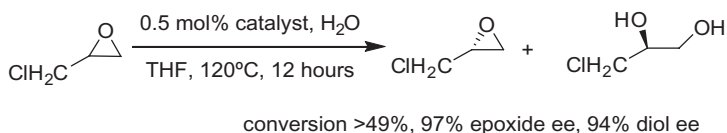
SCHEME 1.19. Racemic epichlorohydrin resolution with polymeric Co-salen catalyst.
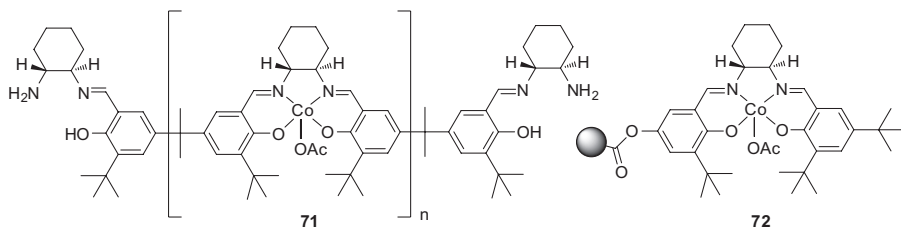
FIGURE 1.33. Structures of catalysts **71** and **72**.

its solubility in water, allowing an easier way to achieve the catalyst recovery. The recovered polymer catalyst **71** (Fig. 1.33) showed good activity and selectivity.

Weberskirch et al. built a self-assembled nanoreactor to perform the HKR of aromatic epoxides in pure water. The Co(III)-salen complex was anchored to an amphyphilic copolymer that formed micellar structures in water. The local high concentration of catalyst and the reasonable low concentration of water inside the micellar reactor allowed for the resolution of several types of aromatic epoxides with excellent enantioselectivitites (up to 51% conversion, 99% ee of epoxide, 96% ee of diol). The polymeric catalyst **72** (Fig. 1.33) could be separated and reused in four consecutive cycles without loss of enantioselectivity. The increase of the reaction time is due to incomplete regeneration of the catalyst [141].

Song et al. performed the HKR of racemic epoxides with water in the presence of a Jacobsen catalyst (Co-salen) in a mixture of IL and tetrahydrofuran ([bmim]PF_6/THF:1:4) [142]. The KR of epichlorohydrins in water was achieved with excellent enantioselectivities (>99% ee for the epoxide and 92% ee for the diol with 0.1 mol% of catalyst). Furthermore, the authors disclosed that the catalyst did not follow deactivation to cobalt (II) species, which is a characteristic of these reactions when run in organic media. In addition, the catalyst was found to be retained in the ionic phase during product removal procedures (distillation and water/IL extraction), allowing its recyclability and reutilization (up to 10 cycles with consistent activity and enantioselectivity with consecutively faster reactions). When the reaction was run in pure IL, the use of an additive (p-nitrobenzoic acid) was necessary in order to have an active catalyst for asymmetric aminolytic KR of terminal epoxides [143]. In the end of the reaction, no further additive was required to maintain an active catalytic system during seven cycles.

Homogeneous protocols have a tendency to afford equivalent results compared with traditional protocols, while heterogeneous- or macromolecules-supported catalysts should be aware of mechanistic evidence (synergistic effects by two near metal units) in its design so as to achieve higher levels of efficiency (compared with traditional method) and recyclability. Interestingly, in general, the procedures described uses at least identical (if not lower) amounts of catalyst loading compared with traditional homogeneous reactions. This is outstanding because traditionally the immobilization, especially in heterogeneous supports, required the application of higher levels of catalyst loading to achieve the same reactivity. Perhaps the supports tend to enhance the number of synergetic interactions improving the reactivity. In case of epoxidation reactions, the pore effect can be considered an important discovery in this field.

In case of the silylcyanation of aldehydes, Corma and collaborators described a very interesting study by comparing different protocols in order to achieve VOsalen catalysts reutilization. The first contribution focuses on the immobilization of the catalyst in the walls of a structured inorganic mesoporous materials by a postsynthesis treatment [144]. However, the immobilization proved to be detrimental for the ee of benzaldehyde silylcyanation. One year later, VOsalen was immobilized by five distinct methods: by covalent bonding to an ionic moiety (catalyst **73**), by grafting in silica (catalyst **74**), in single-wall nanotubes (catalyst **75**), in activated carbon (catalyst **76**) (Fig. 1.34), and finally, by retention in an IL phase ([beim]PF_6 and [emim]PF_6) [145]. The catalyst **74** and VOsalen in the IL ([emim]PF_6 or [beim]PF_6) afforded higher enantioselectivities (85% and 89% ee, respectively) [146]. In the case of catalyst **75** and catalyst **76**, the low enantioselectivity observed could be due to achiral interference of the solid support. The homogeneous VOsalen catalyst immobilized in IL presented a higher recyclability performance [Ye(5) = 2%] [146, 147].
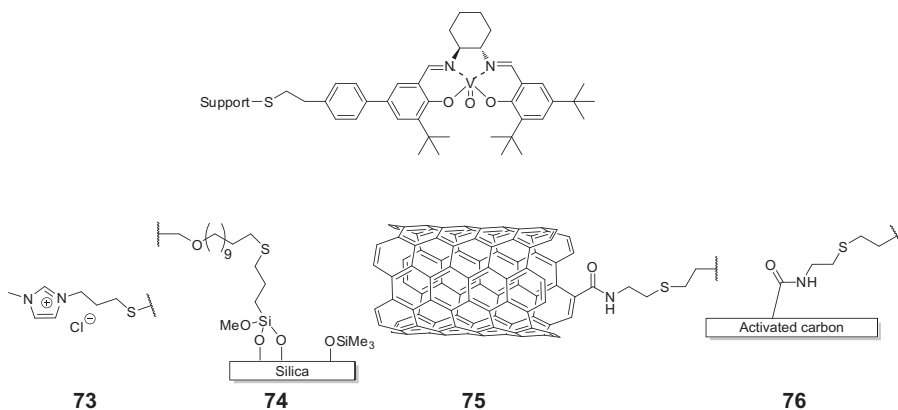
FIGURE 1.34. Structures of catalysts **73–76**.
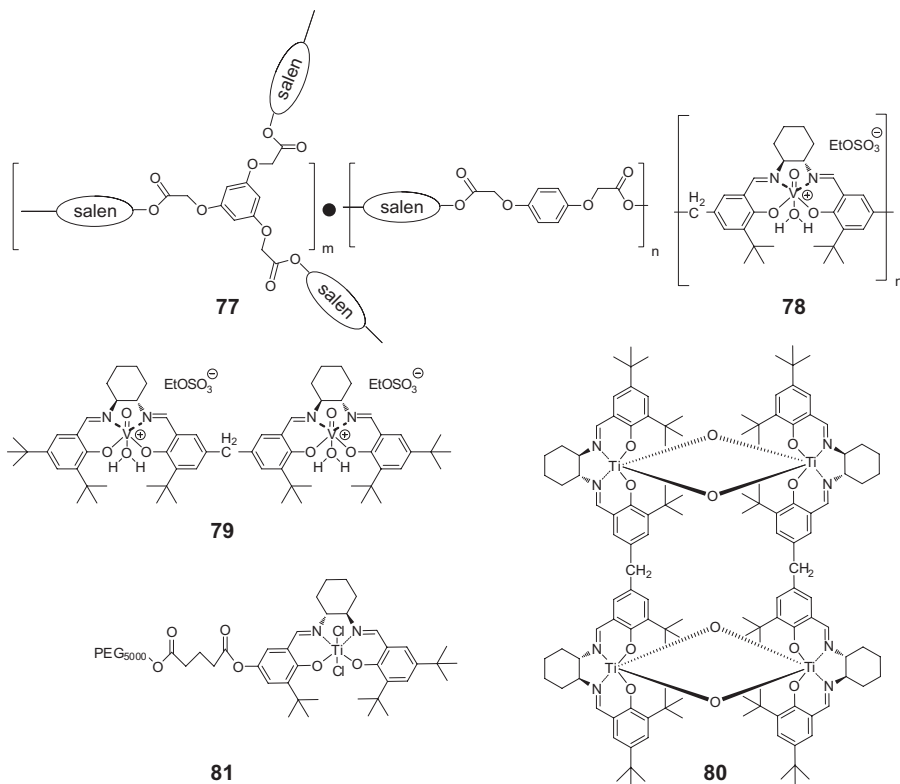
FIGURE 1.35. Structures of catalysts **77–81**.

Polymeric supports and dimeric catalysts were also studied in this transformation, and those that are homogeneous relied on the precipitation to achieve the reutilization. Zheng et al. prepared a polymeric Ti(IV)salen catalyst **77** (Fig. 1.35) for the synthesis of the *O*-acetylcyanohydrins from KCN, Ac$_2$O, and aldehydes. The polymeric catalysts were prepared from copolymerization of a di- or tribenzaldehydes with a chiral diamine to obtain supported catalysts with several degrees of cross-linking [148]. The polymeric ligand with a cross-linking ratio of 25:100 was reused six times with minimal conversion [run 1: 99%, Ce(7) = 4%] and ee erosion [run 1: 80% ee, ee$_e$(7) = 7%]. The lower observation arises from the difficulty of the catalyst to form titanium oxo-bridges between two near units due to a high cross-linking degree.

Khan et al. prepared a linear polymeric VOsalen possessing a methylene group as spacer (tri/di ratio of 0:100). The catalyst **78** (Fig. 1.35) proved to be as reactive as the previous catalysts and provided higher levels of enantioselectivity (97% yield and 94% ee). Furthermore, it tends to precipitate in apolar solvents, allowing its reutilization (up to four efficient cycles) [149].

The dimeric VOsalen and Ti(IV)salen catalysts were also studied under identical conditions. Both catalysts showed improved efficiency, where conversions up to 99% with enantioselectivities up to 96% were obtained for several benzaldehydes. Furthermore, catalysts **79** and **80** (Fig. 1.35) were recovered by precipitation (with hexane) and reused up to four cycles with consistent enantioselectivity [150].

It is known that the strategies based on catalyst immobilization in soluble macromolecules require precipitation techniques to achieve their recovery. In some cases, those techniques do not furnish the immobilized catalyst in quantitative yields. An example of such complex catalysts are those immobilized in PEG. Anyanwu and Venkataraman showed that a PEG-supported Ti-salen complex **81** (Fig. 1.35) could be recovered and reused for silylcyanation of benzaldehyde (0.1 mol% of catalyst) at least five times without any loss of activity (95% conversion, 86% ee) [151]. These results are comparable with those obtained with the nonsupported catalyst analog. The recovery process involved a Soxhlet-dialysis protocol, where the Soxhlet chamber was refilled with fresh dichloromethane every 20 minutes. After 38 hours, about 98% of cyanohydrins were separated from the PEG-supported Ti-salen complex.

Besides the reactions already addressed in this section, where salen ligands are involved, it is possible to apply this ligand in a Diels–Alder reaction, with the resolution of secondary alcohols and Michael additions. The following examples constitute highlights of the reutilization of salen complexes in these transformations.

Schulz and co-workers applied a distinct immobilization technique to recycle a Cr-salen catalyst based on induced electropolymerization. The resulting polymer **82** (Fig. 1.36) was then applied to the hetero Diels–Alder reaction [152] between Danishefsky's diene and heptanal and the Henry reaction [153]. In both cases, the catalyst immobilization proved to be a bit detrimental for the reaction enantioselectivity. The authors showed that despite some yield fluctuation, this system was very robust and achieved a recyclability of 20 cycles in the cyclization reaction [154].

Heckel and Seebach immobilized the Cr-salen complex in a pore-controlled glass silica gel support and tested it in a hetero Diels–Alder reaction of Danishefsky's diene with caproaldehyde ($HOCC_5H_{11}$) [155]. The supported
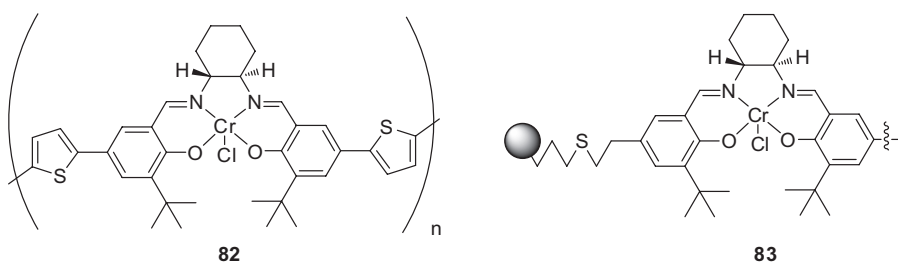
FIGURE 1.36. Structures of catalysts **82** and **83**.

catalyst **83** (Fig. 1.36) proved to be almost as efficient as Jacobsen's catalyst, yielding the respective cycloadduct in 91% conversion and 80% ee (vs. 97% conversion with 83% ee). The catalyst could be recovered by filtration and reused up to 10 cycles, and while the conversion showed some fluctuations (91%–55%), the enantioselectivity increased with the number of runs up to a certain level (84%).

Madhavan and Weck tested AlCl(salen) immobilized in a poly(norbonene) polymeric matrix with a relatively flexible linker in the asymmetric addition of cyanide to α,β-insaturated imides (Scheme 1.20). The homogeneous polymeric catalyst **84** (Fig. 1.37) provided the respective products in excellent enantioselectivities during four cycles. Kinetic studies indicated that the activity of the polymeric catalyst is significantly higher than that of the unsupported analog, suggesting an enhancement effect of the bimetallic pathway due to the catalytic sites' proximity [156].

cycle 1: 96% yield 98% ee
cycle 5: 95% yield 96% ee
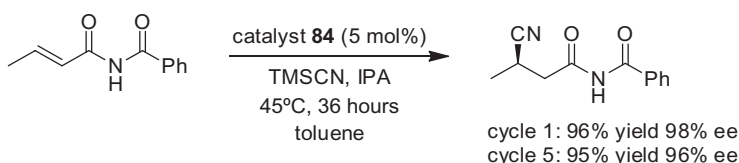
SCHEME 1.20. Asymmetric Michael addition catalyzed by AlCl(salen) anchored to polynorbonene resin.
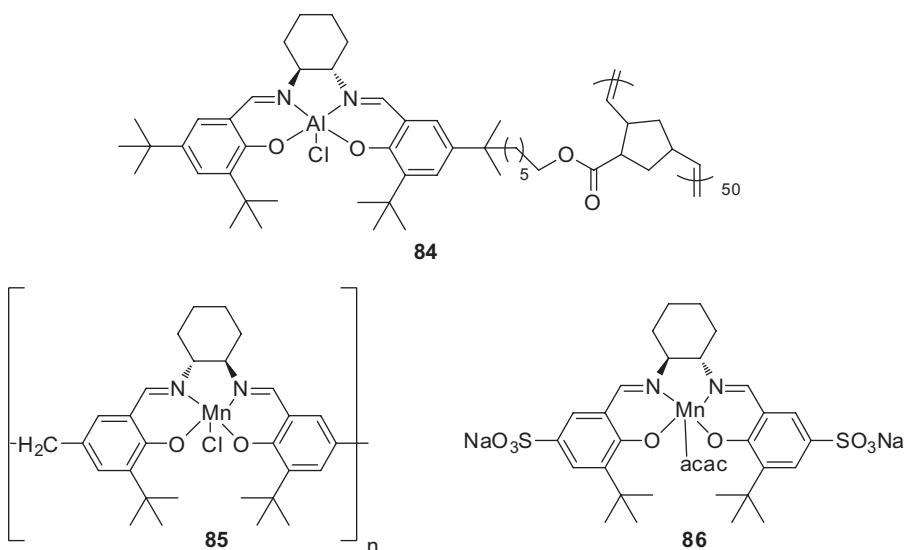
FIGURE 1.37. Structures of catalysts **84–86**.

Kureshy et al. used a chiral Mn(II)-salen polymer to separate a mixture of racemic secondary alcohols by oxidation in the presence of PhI(OAc)$_2$ and KBr (dichloromethane/water 1:2). The complex selectively oxidizes one enantiomer to the respective ketone, furnishing enantiopure unreacted alcohol (>99%). The catalyst **85** (Fig. 1.37) could be recovered by precipitation and reused. Its activity slowly decreased over five runs [Ye(5) = 18%], while the alcohol was always isolated with high enantioselectivity (95%–96% ee) [157]. Kantam et al. immobilized a sulfonate derivative of Mn-salen catalyst **86** (Fig. 1.37) in resin-bearing tetraalkyl ammonium groups, which could be used with identical efficiency during four cycles [158].

There are already a few works on the immobilization of chiral vanadyl and titanium salen complexes for cyanosilylation reported so far. The catalysts supported on polymers (by grafting or polymerization) have some tendency to perform better than those supported on inorganic materials.

1.6. ENZYMES

Enzymes are an important and versatile class of asymmetric catalysts (see also Chapter 12). They have an important role in organic synthesis when it comes to asymmetric induction or resolution of racemic compounds, namely sulfoxides, alcohols, and amines in mild and nonaqueous conditions. For industrial scale applications, the immobilization of enzymes has normal advantages since there is a control of the active site, and it allows reutilization of the catalyst or its application in a continuous process [159].

The KR of racemic alcohols and amines has one limitation: 50% is the maximum yield. In this way, dynamic kinetic resolution (DKR) allows total conversion of a racemic mixture to only one optical isomer using the resolving catalyst and a new catalyst that will racemize the remaining alcohol. Both DKR catalysts are extremely expensive, and therefore highly desirable recycling protocols should be developed (Scheme 1.21) [160].
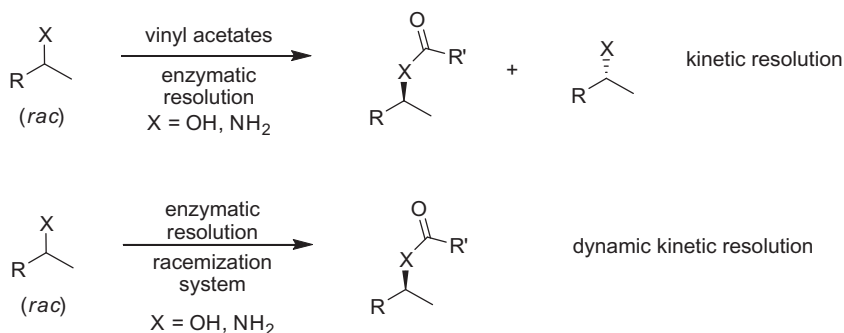
SCHEME 1.21. KR versus DKR of alcohols and amines.

Since the pioneering work by Allen and Williams [161], Pamies and Bäckvall envisaged the possibility of performing the reutilization of the catalytic system used in alcohol DKR [162]. *Candida antarctica* lipase B was recovered by filtration and recycled more than three times in the KR of β-hydroxynitriles (providing enantioselectivities up to >99% and 50% conversion). The racemization ruthenium catalyst (4 mol%) was also reused three times. Unfortunately, the recovered enzyme from the DKR did not retain any activity when tested under KR conditions. Therefore, the catalytic system could only be recycled in a two-step manner (KR followed by racemization) instead of one-pot DKR, which is limited by several purifications tasks.

Kim et al. reported the first ionic liquid-coated enzyme (ILCE) for secondary racemic alcohol resolution in the presence of *Pseudomonas cepacia* lipase (CPL). The enzyme was coated into [PPMIM]PF$_6$ [PPMIM = 1-(3′-phenylpropyl)-3-methylimidazolium], which becomes liquid above 53°C. The catalyst preparation protocol was very simple. The powder enzyme was added to the liquid [PPMIM]PF$_6$ and stirred until a uniform heterogeneous solution was formed, then it was cooled down to room temperature. The resulting solid was broken down to small-sized particles and used to resolve several secondary alcohols. The ILCE provided higher enantioselectivities than the native enzyme (twofold enhancement, Scheme 1.22) [163].

The authors observed that fresh ILCE showed reduced activities in the first cycle due to some diffusion difficulties, which were relieved in the second cycle when the particle size was decreased (100% relative activity of native enzyme is achieved). After five cycles, 93% of the native enzyme activity was retained.

Iborra et al. tested the possibility of having a flow system for 1-phenylethanol racemic resolution. The main idea consisted of immobilizing an enzyme (*C. antarctica* lipase B) in an IL that acted as a stationary phase, and a racemic mixture could be flown through the biocatalyst using $scCO_2$ as the mobile phase [164]. More polar IL such as [emim]NTf$_2$ tended to give higher selectivity (86.3% vs. 84.8%) and half-life time (24 vs. 22 cycles) when compared with the less polar [bmim]NTf$_2$. The (*R*)-1-phenyl ethyl propionate was always obtained in conversions higher than 35% and 99.9% ee's (Table 1.8). The use of IL as the stationary phase provided a protective effect to the biocatalyst; therefore, higher lifetimes are observed (about twofold) when compared with enzyme adsorbed on celite.

	ee$_s$	ee$_p$	E
native	54.5%	98.7%	265
ILCE	29.5%	99.5%	532
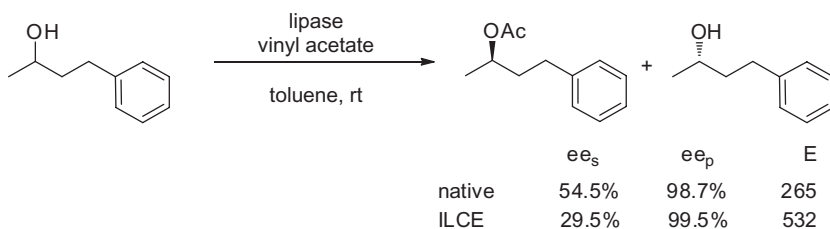
SCHEME 1.22. KR of secondary alcohols with IL-coated *P. cepacia* lipase.

TABLE 1.8. Activity and Operational Stability Parameters of Free *C. antarctica* Lipase B Dissolved in ILs for Continuous (R)-1-Phenylethyl Propionate Synthesis in scCO2 at 15 MPa

IL	Temperature (°C)	Specific Activity (U/mg Enz.)	Selectivity (%)	ee (%)	Half-Life Time (cycles)
[EMIM]	50	1.6 ± 0.3	86.3 ± 1.3	>99.9	24
[Tf$_2$N]	100	1.1 ± 0.1	95.2 ± 1.5	>99.9	16
[BMIM]	50	1.7 ± 0.2	84.8 ± 3.2	>99.9	22
[Tf$_2$N]	100	0.6 ± 0.1	88.1 ± 4.6	>99.9	8
None	50	0.2 ± 0.02	81.5 ± 2.9	>99.9	10

R= H, Me   **87**
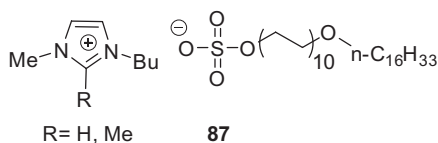
FIGURE 1.38. Structure of IL **87**.

Matsuda et al. applied the same flow methodology reported by Iborra et al [164], but did not use IL to immobilize *C. antarctica* Novozym 435 [165]. The KR of racemic 1-phenylethanol was conducted with this technology for more than 3 days of operation under supercritical condition (12.9–13 MPa of CO_2 at 42°C) and resulting in quantitative transformation of 221 g to (*S*)-1-phenylethanol with 99% ee and (*R*)-(1-phenylethyl) acetate with 99% ee using 1.73 g of the immobilized enzyme. This new flow system proved to be much more efficient than the batch protocol.

Itoh et al. showed that [bdmim]BF$_4$ was a suitable reaction media to perform the enzymatic resolution of 5-phenyl-1-penten-3-ol and methyl mandelate alcohols with Novozym 345. The products and acetaldehyde could be efficiently separated from the IL phase and enzyme, allowing its reuse up to 10 cycles [166]. In 2006, the authors described the application of several types of imidazolium-type ILs derived from poly(oxyethyleneglycol)alkyl sulfate **87** (Fig. 1.38) as an additive or coating material for lipase (*Burkholderia cepacia* lipase and *C. rugosa* lipase). It was disclosed that this material accelerated the enzymatic resolution of about 500- to 1000-fold, maintaining excellent levels of enantioselectivity (up to 99% ee). Both stabilized enzymes were reused four times without loss of activity [167].

Lourenco and Afonso developed a new method to achieve the separation of both enantiomers of racemic mixtures of secondary alcohols without application of laborious chromatographic separations. The separation was accomplished by using an ionic acylating agent that remains in the IL medium ([bmim]PF$_6$) while the unreacted *S*-enantiomer was removed by extraction.
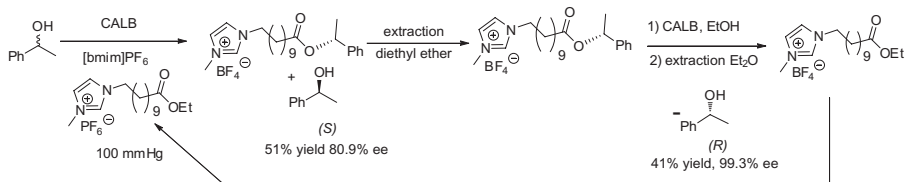
SCHEME 1.23. Protocol for separation of secondary alcohols enantiomers without using any chromatography separation.

Next, the reacted *R*-enantiomer as ionic ester was transesterified with ethanol by the same enzyme to be also removed by extraction. This protocol could be used for four consecutive cycles for secondary alcohol resolution (Scheme 1.23) [168]. Later, the same authors performed the same approach using ethyl myristate as an anchoring agent and reaction medium and isolation of each enantiomer by distillation without the need of an organic solvent for the overall process [169].

De Vos et al. immobilized a palladium catalyst in alkaline-earth supports and found that this catalyst could also promote racemization of chiral amines. Combined with Novozym 435, achiral benzylic and alkylic amines were resolved in excellent yields (64%–98%) with near-perfect enantioselectivity (99% ee, Pd/BaSO₄ 5 mol%, 100 mg/mmol enzyme). The one-pot heterogeneous catalytic system was reused twice without efficiency erosion. The support for the palladium catalyst proved to have an important role in controlling the formation of by-products [170]. Recently, the authors discovered that microwave irradiation could be used to accelerate the racemization rate without affecting the catalytic activity of Novozym 345 [171].

Meanwhile, the same authors discovered that the Raney Ni catalyst can be used to replace palladium as the racemization agent. In the case of aliphatic amines, racemization and enzymatic resolution could be combined in one pot, resulting in an efficient DKR. However, to achieve efficient DKR for benzylic amines, it was required that the racemization and resolution reactions be physically separated [172].

Leaching problems due to desorption events could be an important issue when working with adsorbed catalysts in oxidation of sulfides. Therefore, Strukul et al. immobilized chloroperoxidase (CPO) in a microporous silica gel cage to prevent leaching events and catalyst deactivation with hydrogen peroxide (Scheme 1.24). Two distinct samples were prepared [173]. Sample A has 3.7 CPO units per 0.3 g of catalyst and gave lower enantioselectivity (73%–92% ee) than sample B, which has 123 CPO units per 0.3 g (>99% ee) (Scheme 1.24).

In terms of reactivity, sample B reacted faster despite not always giving higher conversions. Sample A failed to be reused in a second cycle (dramatic drops on reactivity and enantioselectivity were detected), while sample B was
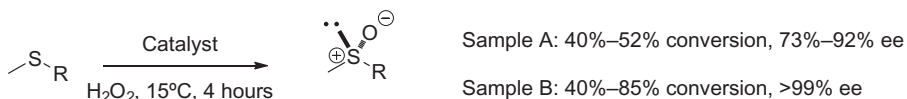
R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, and 2-pyridil

SCHEME 1.24. Asymmetric sulfide oxidation in the presence of CPO immobilized in silica cages.

efficiently applied in four consecutive cycles affording chiral sulfoxides in >99% ee with only 6% yield erosion.

As mentioned before, the CPO desnaturation promoted by hydrogen peroxide together with the known low solubility of organic compounds in water constitutes the most important drawbacks of CPO utilization in industrial applications. To overcome this limitation, Spreti et al. reported the utilization of PEG polymers on CPO-catalyzed asymmetric sulfide oxidation [174]. The addition of PEG to the reaction mixture solves both of these problems: They increase the solubility of organic substrates in water and allow the enzyme to retain more of its initial activity. Under optimized addition of oxidant, it was possible to achieve 100% yield with >99% ee (in the case of thioanisole oxidation). Unfortunately, the chemical yield dropped about 15% on each recycle.

Wang et al. reported for the first time the performance of immobilization of CPO in magnetic nanoparticles with an iron oxide and polymer shell in the sulfoxidation of thioanisole. The covalently bound CPO with a long spacer showed the sulfoxidation activity and enantioselectivity identified as those observed for free CPO. The thick polymer shell significantly increased the stability of the nanobiocatalyst. A great improvement was achieved when compared with CPO on other solid supports, giving excellent enantioselectivity (99% ee) and no loss of activity after recycling 11 times [175].

Enzymes showed to be an excellent catalyst in KR and asymmetric oxidation. The immobilization and use of alternative media represent the main approach for reutilization in batch or continuous systems.

1.7. CHIRAL DIAMINES, DIOLS, AND AMINOALCOHOLS

In this part, the goal is to provide insights in how chiral diamines, 1,2-amino alcohols, and diols can be recovered and reused together with the metal catalyst.

1.7.1. TsDPEN-Type Ligands

In the family of chiral diamine ligands, (1S,2S)-(+)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) appears as one of the most well-known ligands that are applied for the reduction of ketones and imines [176]. This ligand was recycled with the aid of several types of homogeneous and heterogeneous supports and alternative reaction media.
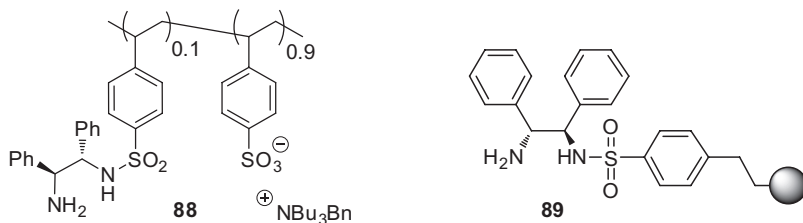
FIGURE 1.39. Structures of ligands **88** and **89**.
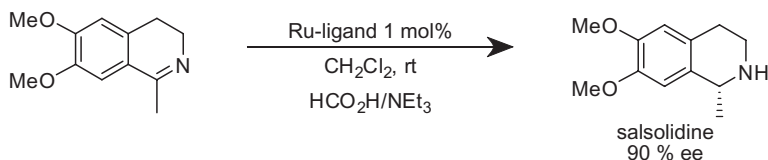
SCHEME 1.25. Reduction of aromatic imines in the presence of RuTsDPEN catalyst immobilized in silica.

In case of heterogeneous systems, the immobilization of TsDPEN ligand in polystyrene was conducted by grafting [177] and copolymerization [178]. Both methods did not have a negative impact on the reaction efficiency. However, the copolymerized ligand **88** (Fig. 1.39) provided a more recyclable system for the ruthenium-mediated reduction of acetophenone in water. The presence of a styrene derivative monomer bearing a sulfonic group in the polymer structure proved to be crucial for the polymer swelling in water and to obtain 98% ee. This heterogeneous catalyst was recycled up to five cycles with the same outcome of enantioselectivity.

Alternatively, it was demonstrated that it is possible to have active ruthenium catalysts anchored in amorphous silica gel, MCM-41, SBA-15, modified silica [179], functionalized SBA-16 [180], and MCFs [181] (ligand **89**, Fig. 1.39). All supports performed well in the recycling tests, with the best being amorphous silica gel (10 cycles), followed by silica MCFs (six cycles), and functionalized SBA-16 (six cycles). Recently, magnetic MCFs were used as support, allowing a recyclability of nine cycles [182].

Shortly after, the authors showed that ligand **89** anchored in silica gel can be applied in the reduction of aromatic ketones in water in the presence of TBAB as an additive and sodium formate. Curiously, the water induced an acceleration effect on this transformation, and the high degree of reusability was conserved [183].

Another application of TsDPEN ligand **89**, anchored in siliceous MCFs, is the reduction of salsolidine to prepare 1-substituted 1,2,3,4-tetrahydroisoquinolines (applied in the treatment of Parkinson's disease). The product was obtained in high yields (95%–100%) and consistent 90% ee over six consecutive cycles (Scheme 1.25).
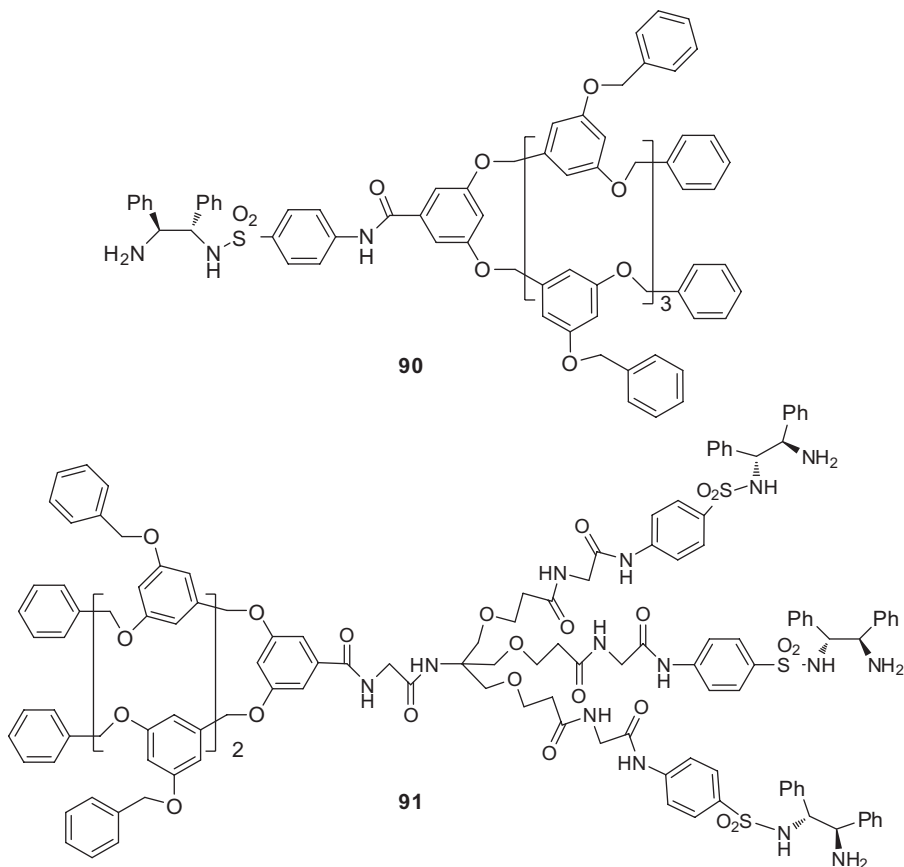
FIGURE 1.40. Structures of ligands **90** and **91**.

Regarding homogeneous catalysis, the ligand was linked to dendritic structures and to PEG polymers. Chen et al. showed that rhodium/ligand **90** (Fig. 1.40) can induce excellent levels of enantioselectivity in the reduction of aromatic ketones in water. The recyclability achieved five cycles with 25% yield erosion [184].

The authors also studied the effect of having the ligand anchored in the periphery of the dendrimer in ruthenium-mediated reduction of acetophenones [185]. This catalyst proved to be as selective as the nonsupported one (97.7% ee), but it was difficult to achieve an effective recycling. To overcome this limitation, the authors prepared a hybrid dendrimer (ligand **91**, Fig. 1.40) that was recycled twice [186]. Higher recyclability (14 and 7 cycles) were observed when the two TsDPEN-PEG ligands **92**[187, 188] (Table 1.9) and **93** [189] (Fig. 1.41), respectively, were studied using sodium formate as the hydride source in water.

TABLE 1.9. Asymmetric Transfer Hydrogenation of Ketones With Ru-PTsDPEN by HCOONa in Water

Ketone	Temperature (°C)	Time (h)	Conversion (%)	ee (%)
Acetophenone (acp)	22	8	>99	93
2'-chloro-acp	22	13	>99	91
3'-methoxy-acp	22	18	98	90
4'-methyl-acp	22	18	>99	86
1'-acetonaphthone	22	36	85	88
2'-acetonaphthone	22	36	>99	94
2-acetylfuran	22	18	98	91
1-tetralone	22	18	>99	94
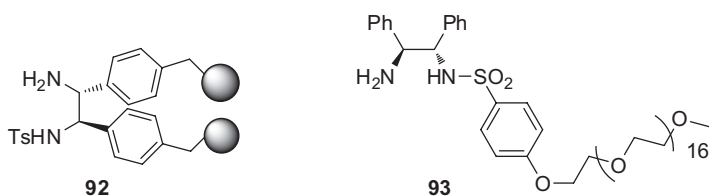
FIGURE 1.41. Structures of ligands **92** and **93**.
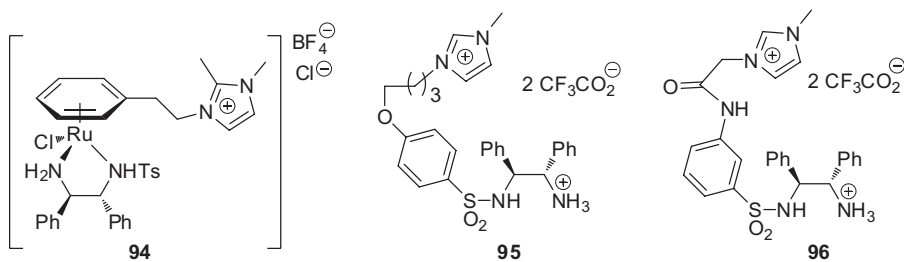
FIGURE 1.42. Structures of catalyst **94** and ligands **95** and **96**.

Another possibility is to attach ionic tags to the ligands such as imidazolium rings (catalyst **94** [190], ligand **95** [191], and ligand **96** [192]), or hydrophilic sulfonic groups (ligand **97**) [193] (Fig. 1.42). However, better results were described when surfactants or PEG were applied as additives for aqueous phase reactions. Zhu et al. disclosed a biphasic system (water/dichloromethane) that enables the Ru-TsDPEN catalyst recovery and recycle, with aid of a mixture of surfactants (sodium dodecyl sulfate (SDS)/cetyl trimethylammonium bromide (CTAB): 2:1). This system allowed an increase of activity, chemoselectivity, and enantioselectivity (S/C = 100, up to 99%) in aromatic

TABLE 1.10. Asymmetric Hydrogenation of Ketones Catalyzed by Ru-TsDPEN with HCOONa in PEG-H$_2$O

Entry	Ketone	Time (h)	Conversion (%)	ee (%)
1	Acetophenone	3	98	95
2	4′-methoxy-acp	8	91	94
3	1′-acetonaphthone	8	99	93
4	1-Indanone	6	99	95
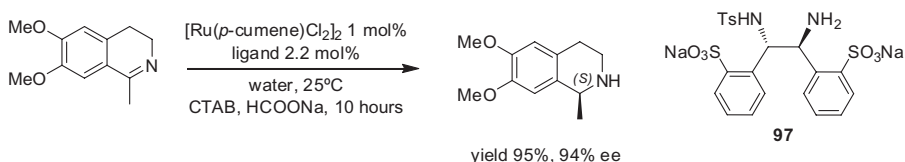
SCHEME 1.26. Reduction of aromatic imines in water/surfactant media.

ketones reduction with sodium formate. The hydrophobic catalyst remained inside the micelles while the products were found mainly in the dichlorometane phase. The aqueous phase was efficiently reused six times in this transformation [194]. Chan and co-workers showed that a solvent mixture of PEG$_{400}$/water (3:1) was a suitable media to efficiently run reduction of aromatic ketones with sodium formate in the presence of RuTsDPEN (S/C = 100) (Table 1.10). The reaction products were extracted with hexane and the catalyst could be reused up to 15 cycles with consistent enantioselectivity (95% ee) [195].

The use of surfactants in water was also explored in salsolidine synthesis. Working above the micellar critical concentration of CTAB, it was possible to enhance the enantioselectivity of the reaction [196]. A large number of arylimines were quantitatively reduced with excellent enantioselectivity (S/C = 100, generally above 95% ee, Scheme 1.26). At the end of the reaction, the products were extracted with a diethyl ether/hexane (1:1) mixture, leaving the catalyst Ru/ligand **97** in the aqueous phase. The catalytic system could be reused over eight consecutive times with consistent 94% ee, though with some yield erosion [Y$_e$(8) = 9%].

The TsDPEN ligand has high reliability and efficiency in enantioselective reductions of ketones and imines which lead to several reutilization studies.

1.7.2. Chiral Aminoalcohols

An important class of chiral ligands are 1,2-aminoalcohols that can be prepared from the respective amino acid. Two of the most important applications of these ligands are in boranes-mediated reduction of ketones and the alkylation of aldehydes.
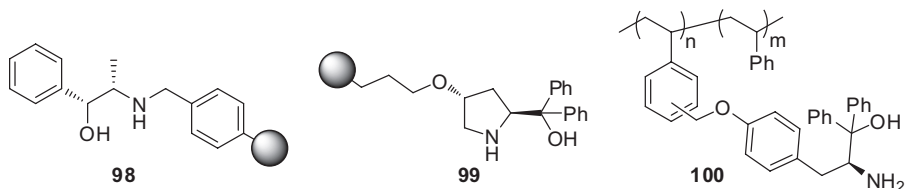
FIGURE 1.43. Structures of 1,2-aminoalcohol ligands **98–100**.
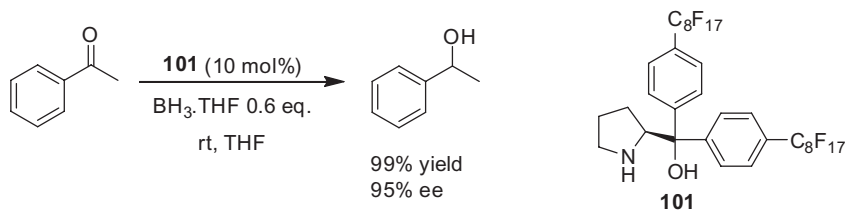
SCHEME 1.27. Reduction of aromatic ketones with borane in the presence of a perfluorinated-diphenylprolinol catalyst **101**.

Starting with borane reductions, Sandee et al. applied a heterogeneous ruthenium catalyst as the solid phase of a flow reactor for the reduction of acetophenone. The immobilization of an ephedrine derivative **98** (Fig. 1.43) in a silica support allowed the efficiency of the system to be retained after 1 week of work (95% conversion, 90% ee) [197].

Meanwhile, ligands **99** [198] and **100** [199] (Fig. 1.43) were immobilized in silica and polystyrene, respectively. The respective oxazaborolidine were reused, taking advantage of nanofiltration technology for the asymmetric reduction of acetophenone. In the case of ligand **100**, the reactions were carried out in a continuously operated membrane reactor equipped with a nanofiltration membrane. The chiral alcohols were obtained in good-to-excellent ee and space–time yield [up to 99% ee and $1.4 \text{kg}/(\text{L}_{\text{reactor volume}} \times \text{day})$].

Soós et al. studied the possibility of applying extraction techniques of perfluorous compounds. The authors synthesized a prolinol catalyst bearing two perfluoroalkyl chains (ligand **101**, Scheme 1.27). It was coordinated in situ to BH_3. THF promoted the reduction of aromatic ketones. Using only 10 mol% of catalyst with 0.6 eq. borane, quantitative yields were achieved with an excellent 95% ee for the acetophenone reduction. The perfluorinated ligand (not the oxazaborolidine) was quantitatively recovered with a solid–liquid extraction methodology and reused up to three cycles without any yield and ee erosion [200].

Dialkyl zinc addition to aldehydes was, in the past, one of the most explored reactions under the umbrella of recyclable stereoselective catalysts. A considerable number of strategies were tested and a representative fraction of those works are described here.
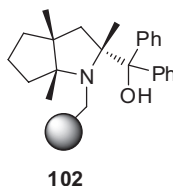
FIGURE 1.44. Structure of heterogeneous polymeric ligand **102**.
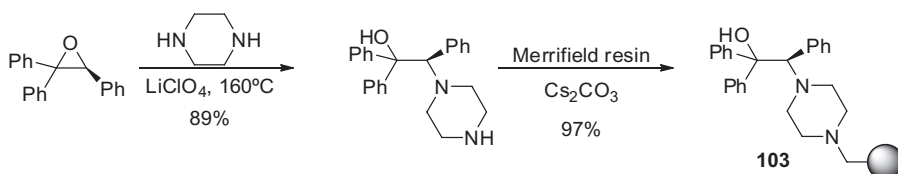
SCHEME 1.28. Preparation of (*R*)-2-piperidino-1,1,2-triphenylethanol anchored in a Merrifield resin.

Martens and co-workers immobilized a chiral amino alcohol by two different strategies in polystyrene polymers (grafting or copolymerization) [201]. The second immobilization strategy provided the heterogeneous polymeric ligand **102** (Fig. 1.44). The appropriate polymerization conditions provided a monolith with the desired morphology and properties that could be applied in a stationary monolithic column. This feature allows the design of a continuous-flow system where the reaction mixture is continuously passed through the monolith for 24 hours. This new protocol provided (*R*)-1-phenylpropanol in 85% with 99% ee in the first cycle. Further reutilization up to four cycles showed no loss of activity and enantioselectivity. A continuous-flow system is a very appealing solution for industrial application because the need for catalyst separation was suppressed, and the products can be easily isolated just by removing the solvent, thereby increasing the overall efficiency.

Pericàs et al. reported in 2003 the synthesis of (*R*)-2-piperidino-1,1,2-triphenylethanol covalently bonded to polystyrene polymeric support (five steps) [202]. More recently, Castellnou et al. [203] reported a simplified procedure for such supported ligand synthesis (Scheme 1.28). The supported ligand **103** was tested in the direct diethylzinc addition to benzaldehydes, where 94%–95% ee were obtained in high yield using only 2 mol% of catalytic resin at 0°C after 4 hours. The catalyst could be recovered and reused efficiently in five consecutive batches (resin 4 mol%, toluene, 0°C). Recently, such polymeric ligand was efficiently applied under a continuous-flow process. The high catalytic activity of this system allowed complete conversion of substrates with the use of stoichiometric reagent ratios and unprecedented short residence times (less than 3 minutes) [204].
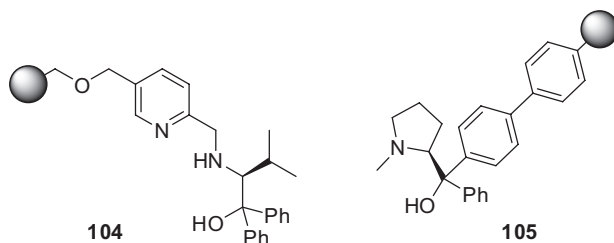
FIGURE 1.45. Structures of heterogeneous polymeric ligands **104** and **105**.
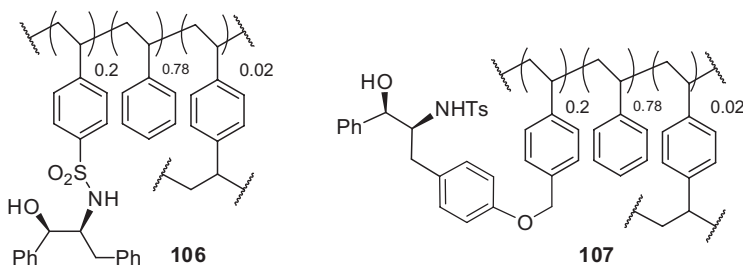
FIGURE 1.46. Structures of ligands **106** and **107**.

The first examples described proved to be very efficient, and their applications in flow reactors were accomplished. The next five examples were studied under batch conditions. Gros et al. described the application of a pyridine-based tridentate chiral ligand in enantioselective direct addition of diethylzinc to benzaldehydes supported on a Merrifield resin. This heterogeneous ligand **104** (Fig. 1.45) provided the respective phenylpropanols with excellent levels of enantioselectivities (up to 93% ee) and proved to be fully recyclable during five cycles [205]. Hodge et al. applied an *N*-methyl-diphenylprolinol grafted in polystyrene beads as catalyst for alkylzinc addition to benzaldehydes. Despite the high levels of catalyst loading required to obtain levels of enantioselectivities comparable with the homogeneous system (78%–94% ee), catalyst **105** (Fig. 1.45) was recycled efficiently nine times [206].

Gau et al. copolymerized a chiral styrene-substituted *N*-sulfonylated amino alcohol with styrene and divinylbenzene to achieve its recycling. The Ti/ligand **106** (Fig. 1.46) complex was tested in the diethyl zinc addition to aldehydes, which resulted in excellent levels of enantioselectivity. The ligand, recovered by filtration, was reused several times with a small erosion of enantioselectivity in each cycle (about 3%) [207]. Recently, the authors described the ligand **107** (Fig. 1.46) that is more reactive and more reusable than **106** (nine efficient recycles) [208].

Xu et al. immobilized *N*-sulfonylated amino alcohols in the amorphous silica to be used in titanium-mediated ethyl zinc addition to aldehydes. In the first tests, it was discovered that it was necessary to pretreat the free silinols
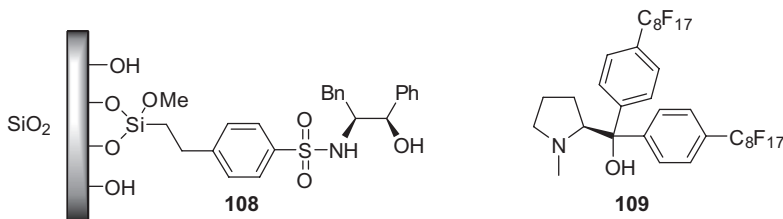
FIGURE 1.47. Structures of ligands **108** and **109**.
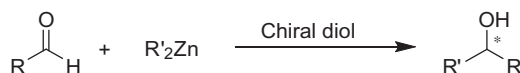
SCHEME 1.29. Asymmetric dialkylzinc addition to aldehydes.

with titanium isopropoxide to achieve any reaction (98% yield, 80% ee, substrate: benzaldehyde). The catalyst **108** (Fig. 1.47) showed an impressive recycling ability, since it was reused nine times without any significant decrease of reactivity and enantioselectivity [209].

Heterogeneous supports furnished a more robust catalyst than those prepared for homogeneous catalysis, in which soluble polystyrene polymers [210] and dentritic [211, 212] structures were examined as supports. However, when dealing with homogeneous catalysis it is crucial to highlight the work of Kim et al. In this work was described a method for the modification of pyrrolidinylmethanol derivatives to be applied in asymmetric addition of diethyl zinc to aldehydes [213]. Under biphasic conditions (FC-72/hexane, 40°C), the desired product was obtained in 92% ee. The ligand was recovered by lowering the temperature phase to 0°C, where a phase separation occurred. The authors claimed that stable **109** Li Et$_2$Zn (Fig. 1.47) forced the ligand to stay in the FC-72 phase. This protocol allows the catalytic system to have a long lifetime (about nine runs), affording (S)-1-phenylpropanol with high ee's.

As was observed in the previous section, a considerable amount of work has been described for dialkyl zinc additions to aldehydes from which very good results were highlighted in this section.

1.7.3. BINOL-Type Ligands

Over the past 20 years, BINOL ligands have become some of the most broadly used ligands in catalytic asymmetric reactions, such as the formation of new carbon–carbon bonds or on oxidation reactions. Mainly, they act as a ligand in titanium-promoted (Lewis acid) catalysis.

The asymmetric dialkylzinc addition aldeydes can be conducted in Ti/BINOL complexes (Scheme 1.29). BINOL can be immobilized in soluble and insoluble polymers with considerable success in this transformation. Several

polymeric ligands provided high levels of enantioselectivity (up to 98% ee) and proved to be recyclable [2].

An organosilane substituted (*S*)-BINOL was anchored in the surface of two siliceous materials, MCM-41, MCF, and SBA-15 by Abdi et al. [214]. These heterogeneous catalysts were applied to a Ti(IV)-mediated diethyl zinc addition to aldehydes where MCF readily proved to be the most efficient support. In the preliminary results, low enantioselectivities were observed caused by free silinol groups present in the supports, which interact with titanium. When those groups were protected with tetramethylsilane, enantioselectivities increased to 94% ee (comparable with free BINOL). The ligand **110** (Fig. 1.48) was recovered by simple filtration and reused up to four efficient cycles with some yield (27%) and enantioselectivity (9%) erosion before regeneration.

Ma et al. prepared Frechet-type dendritic BINOL ligands to be applied in titanium-promoted diethylzinc addition to benzaldehydes. Excellent yields and enantioselectivities were achieved with this ligand **111** (Fig. 1.48), sometimes surpassing the nonimmobilized BINOL system (up to 89% ee). Ligand **111** could be recovered by precipitation with methanol addition and reused twice without yield and enantioselectivity erosion [215].

Moreau et al. immobilized BINOL derivates for titanium-promoted ethyl zinc addition to benzaldehyde in an IL [216]. The immobilized ligand **112** (Fig. 1.48) proved to be as effective as the BINOL itself, affording (*S*)-1-
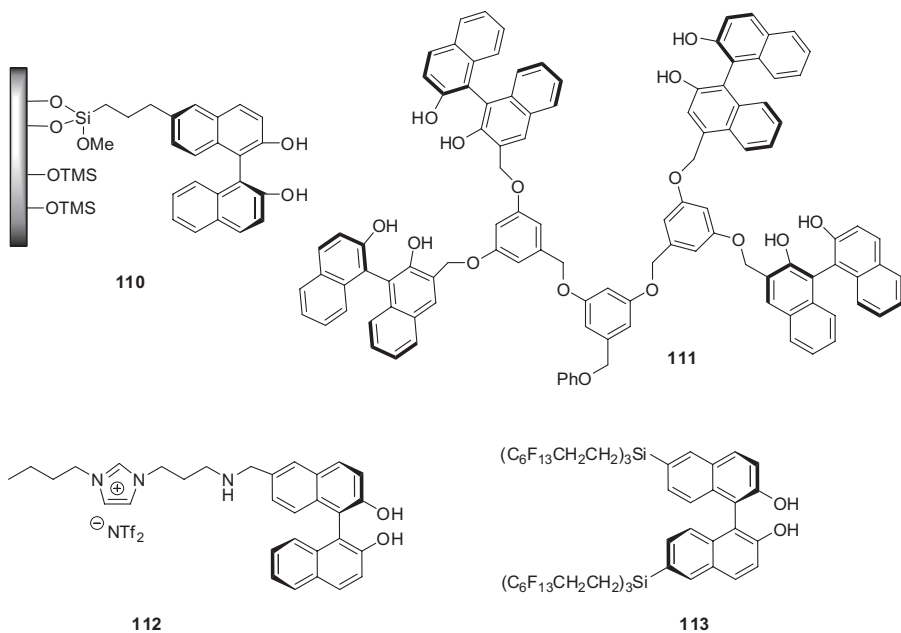
FIGURE 1.48. Structures of BINOL-type ligands **110–113**.

phenylpropanol with 82% ee's. Its recovery was achieved by extractions and filtration. It was reused three times with constant enantioselectivity (81%–82% ee's).

Curran et al. reported in a previous work that the ligand **113** (Fig. 1.48) with a fluorine content of 61.2% provided results comparable to the original system (81%–89% and 80%–83% ee vs. 97% and 85% ee) in titanium-promoted diethylzinc addition to aldehydes using a biphasic solvent system of toluene/hexane/FC-72. Despite its fluorine content, it was not possible to prevent some leaching to the organic phase during the liquid–liquid extraction. The reutilization problems were solved by using a solid-phase extraction technique. The reaction mixture was passed through a fluorous reverse-phase silica-gel column and eluted with acetonitrile. The retained ligand **113** was recovered using FC-72 and was reused up to four cycles without any efficiency loss [217].

The carbonyl-ene coupling mediated by a titanium or copper catalyst allows the formation of a new C–C bond with a high level of enantioselectivity. Titanium-based catalysts applied in this chemistry use BINOL-type ligands, which are quite expensive. Therefore, it is necessary to achieve reutilization of such catalysts to boost their industrial application.

Sasai et al. reported the first example of a chiral self-assembled structure, formed through the self-assembly of chiral multidentate ligands with a metal. This polymer acted as an asymmetric catalyst in carbonyl-ene reactions providing high enantioselectivities (20 mol%). The catalyst 114 (Fig. 1.49) was tested for enantioselective carbonyl-ene reaction of ethyl glycoxalate and prop-1-en-2-ylbenzene, affording the respective product after 98 hours in 88% yield with 88% ee. While the enantioselectivity remained unchanged for more than four cycles, the reactivity suffered a considerable decrease [218].

Wang et al. showed that the enantioselectivity could be increased to 95% ee using only 1 mol% of catalyst 115 (Fig. 1.49), if it does not have an oxo-bridge between the two titanium centers. Further ligand derivatization allowed the discovery of a new insoluble polymeric catalyst that provided quantitative yields with 97% ee. This new catalyst was also reused four times, but in this case both yield (19%) and enantioselectivity (27%) decreased [219].

Using the same polymeric-catalyst approach, Sasai et al. reported the first example of a chiral self-assembled structure, formed through self-assembly of chiral multidentate ligands with a aluminum instathat that acted as an asymmetric catalyst for Michael additions in high enantioselectivity [218].

This insoluble polymeric catalyst **116** (Fig. 1.49) showed a similar performance (Scheme 1.30) to the homogeneous monomer ALB [Al-Li-bis(binaphthoxide), 12 hours, quantitative yield, 97% ee]. At the end of the fourth cycle, significant erosion on the activity (~30%) and enantioselectivity (~20%) was observed.

Loh et al. performed the cycloaddition of acroleins with butadienes and cyclopentadiene in [bmim]PF$_6$ in the presence of (*S*)-BINOL-In(III) and allyltributyl stannane. This system performed better in terms of yields (78%–92%) in the IL media than in dichloromethane and furnished excellent

114

115

116
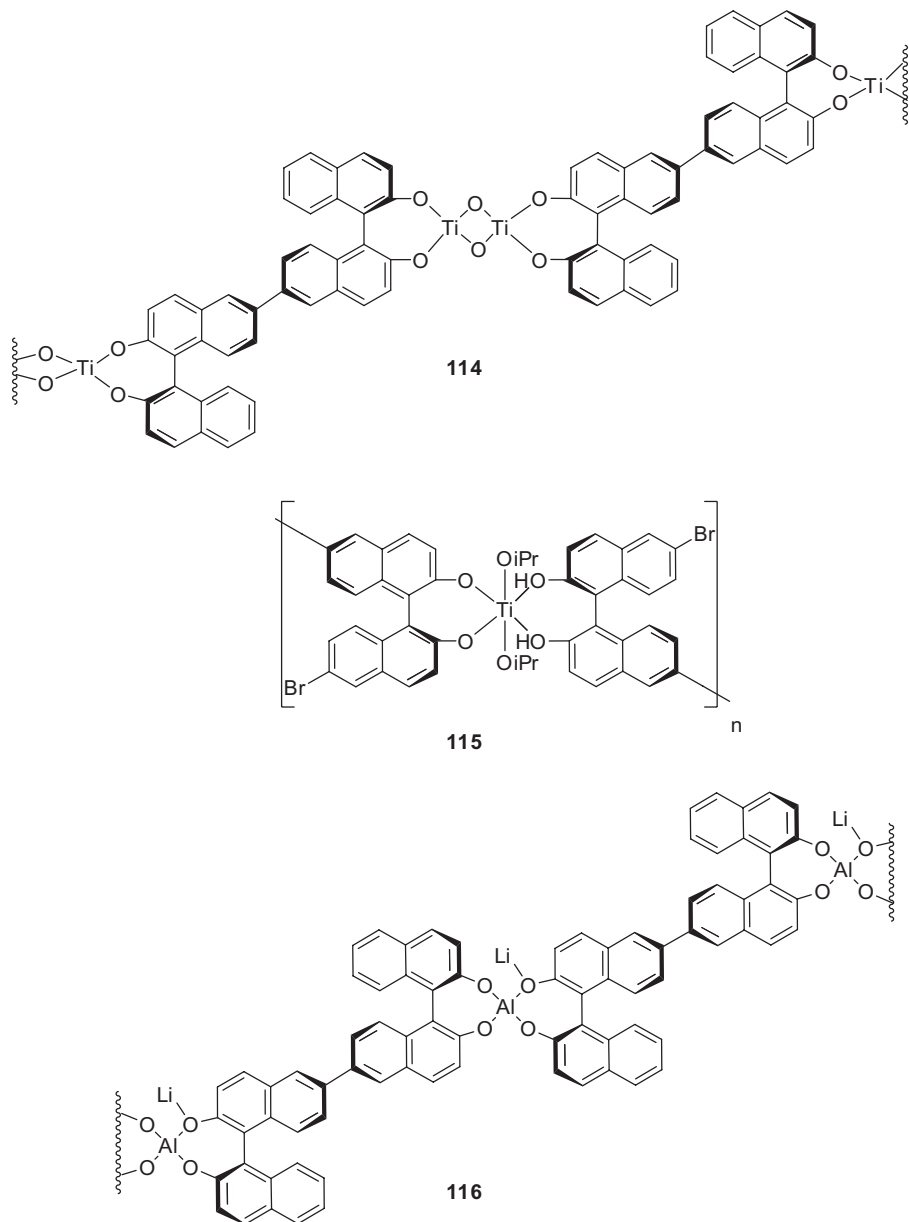
FIGURE 1.49. Structures of catalysts **114–116**.

48 hours, 86% yield, 96% ee
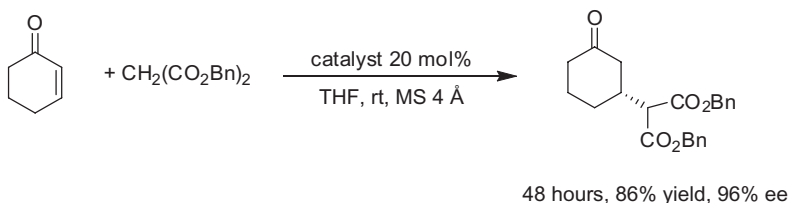
SCHEME 1.30. Asymmetric Michael addition catalyzed by insoluble self-assembled catalyst.
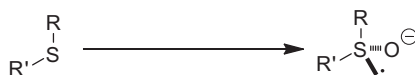
SCHEME 1.31. Asymmetric sulfide oxidation to sulfoxides.

117
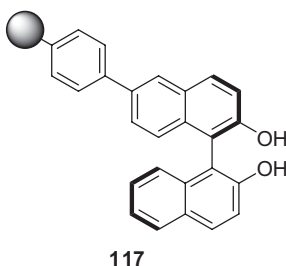
FIGURE 1.50. Structure of polymeric BINOL ligand **117**.

enantioselectivities (up to 98% ee). Furthermore, the catalytic system remained in the IL while the products were extracted enclosing the reutilization. In the seventh cycle, the yield eroded 5% while the enantioselectivity fell 12% [220].

The reutilization of BINOL catalysts was also described in asymmetric allylation [221], aldol-type reactions [222], or in Claisen–Schmidt condensation [223], but the results were not competitive with other approaches.

Several methodologies have been applied for the oxidation of the sulfide moiety to chiral sulfoxides (Scheme 1.31), from which the highlight here goes to the Ti/BINOL system.

Hodge et al. disclosed a straightforward method to immobilize a BINOL unit in polystyrene beads via a Suzuki coupling. Such heterogeneous ligands were coordinated to titanium tetraisopropoxide and tested in oxidation of prochiral thioethers (10 mol% titanium loading, ee up to 91%). The authors observed that retreatment of polymeric BINOL **117** (Fig. 1.50) with a titanium complex achieved four runs with consistent enantioselectivities [224].

Sahoo et al. immobilized chiral Ti/BINOL onto IL-modified SBA-15. The immobilized catalyst presented a high enantioselectivity in oxidation of

thioanisole (99.2% and 62% yield). The supported catalyst was recycled seven times without any loss of enantioselectivity [225].

A wide range of protocols and reactions were explored using BINOL systems. Generally, BINOL complexes give good-to-excellent enantioselectivities and conversions. Furthermore, several efficient immobilization and polymerization approaches were shown. However, more effort should be made in the area of reutilization since some protocols showed low recyclability and erosion of efficiency through cycles.

1.8. CONCLUSIONS

In the past several years, remarkable progress has been observed in the development of efficient asymmetric synthetic methodologies that allow catalyst reuse for a diverse range of organic reactions under homogeneous or heterogeneous conditions, or by using alternative reaction media such as water, ILs, perfluorinated solvents and catalysts, supercritical CO_2, and membrane separation technology. This area has been established as one of hottest areas in organic chemistry. However, at this stage, the following directions may be considered:

(1) the development of more efficient protocols that allow less leaching of precious (as well as toxic in many cases) metals, minimal use of volatile organic solvents, and the use of water as reaction media;

(2) more developments on the less explored methodologies based on the use of microreactors and membrane-based technologies;

(3) exploration of efficient methodologies for catalyst reuse for some (bio) catalysts.

One of the most important parameters that help to identify the limitations and potentialities of a recycling protocol using organometallic catalysis is the degree of metal leaching. This phenomenon is the main cause for the decrease of reactivity upon recycling in most of the protocols described herein, and this parameter is not always determined.

REFERENCES

[1] (a) Breuer, M., Ditrich, K., Habicher, T., Hauer, B., Kesseler, M., Sturmer, R., Zelinski, T. (2004). Industrial methods for the production of optically active intermediates. *Angew. Chem. Int. Ed.*, *43*, 788–824; (b) Ikunaka, M. (2003). A process in need is a process indeed: scalable enantioselective synthesis of chiral compounds for the pharmaceutical industry. *Chem. Eur. J.*, *9*, 379–388; (c) Hawkins, J. M., Watson, T. J. N. (2004). Asymmetric catalysis in the pharmaceutical industry. *Angew. Chem. Int. Ed.*, *43*, 3224–3228; (d) Cole-Hamilton, D. J. (2003).

Homogeneous catalysis—new approaches to catalyst separation, recovery, and recycling. *Science*, *299*, 1702–1706.

[2] Fan, Q. H., Li, Y. M., Chan, A. S. C. (2002). Recoverable catalysts for asymmetric organic synthesis. *Chem. Rev.*, *102*, 3385–3465.

[3] Trindade, A. F., Gois, P. M. P., Afonso, C. A. M. (2009). Recyclable stereoselective catalysts. *Chem. Rev.*, *109*, 418–514.

[4] Lindstrom, U. M. (2002). Stereoselective organic reactions in water. *Chem. Rev.*, *102*, 2751–2771.

[5] (a) Benaglia, M., Puglisi, A., Cozzi, F. (2003). Polymer-supported organic catalysts. *Chem. Rev.*, *103*, 3401–3429; (b) Corma, A., Garcia, H. (2003). Lewis acids: from conventional homogeneous to green homogeneous and heterogeneous catalysis. *Chem. Rev.*, *103*, 4307–4365; (c) Dickerson, T. J., Reed, N. N., Janda, K. D. (2002). Soluble polymers as scaffolds for recoverable catalysts and reagents. *Chem. Rev.*, *102*, 3325–3343; (d) Bergbreiter, D. E. (2002). Using soluble polymers to recover catalysts and ligands. *Chem. Rev.*, *102*, 3345–3383; (e) McMorn, P., Hutchings, G. J. (2004). Heterogeneous enantioselective catalysts: strategies for the immobilisation of homogeneous catalysts. *Chem. Soc. Rev.*, *33*, 108–122; (f) Bell, A. T. (2003). The impact of nanoscience on heterogeneous catalysis. *Science*, *299*, 1688–1691; (g) Rolison, D. R. (2003). Catalytic nanoarchitectures—the importance of nothing and the unimportance of periodicity. *Science*, *299*, 1698–1701.

[6] (a) Xia, Q. H., Ge, H. Q., Ye, C. P., Liu, Z. M., Su, K. X. (2005). Advances in homogeneous and heterogeneous catalytic asymmetric epoxidation. *Chem. Rev.*, *105*, 1603–1662; (b) Baleizao, C., Garcia, H. (2006). Chiral salen complexes: an overview to recoverable and reusable homogeneous and heterogeneous catalysts. *Chem. Rev.*, *106*, 3987–4043; (c) Kobayashi, S., Sugiura, M. (2006). Immobilization of osmium catalysts for asymmetric dihydroxylation of olefins. *Adv. Synth. Catal.*, *348*, 1496–1504.

[7] Ding, K. L., Wang, Z., Wang, X. W., Liang, Y. X., Wang, X. S. (2006). Self-supported chiral catalysts for heterogeneous enantioselective reactions. *Chem. Eur. J.*, *12*, 5188–5197.

[8] Walsh, P. J., Li, H. M., de Parrodi, C. A. (2007). A green chemistry approach to asymmetric catalysis: solvent-free and highly concentrated reactions. *Chem. Rev.*, *107*, 2503–2545.

[9] (a) Pozzi, G., Shepperson, I. (2003). Fluorous chiral ligands for novel catalytic systems. *Coord. Chem. Rev.*, *242*, 115–124; (b) Muzart, J. (2006). Ionic liquids as solvents for catalyzed oxidations of organic compounds. *Adv. Synth. Catal.*, *348*, 275–295; (c) Afonso, C. A. M., Branco, L. C., Candeias, N. R., Gois, P. M. P., Lourenco, N. M. T., Mateus, N. M. M., Rosa, J. O. N. (2007). Efficient catalyst reuse by simple dissolution in non-conventional media. *Chem. Commun.*, 2669–2679; (d) Parvulescu, V. I., Hardacre, C. (2007). Catalysis in ionic liquids. *Chem. Rev.*, *107*, 2615–2665; (e) Chen, J., Spear, S. K., Huddleston, J. G., Rogers, R. D. (2005). Polyethylene glycol and solutions of polyethylene glycol as green reaction media. *Green Chem.*, *7*, 64–82; (f) Andrade, C. K. Z., Alves, L. M. (2005). Environmentally benign solvents in organic synthesis: current topics. *Curr. Org. Chem.*, *9*, 195–218; (g) Song, C. E. (2004).). Enantioselective chemo- and bio-catalysis in ionic liquids. *Chem. Commun.*, 1033–1043; (h) Song, C. E., Yoon, M. Y., Choi, D. S. (2005). Significant improvement of catalytic efficiencies in ionic liquids. *Bull. Korean Chem. Soc.*, *26*, 1321–1330; (i) Jain, N., Kumar, A., Chauhan, S., Chauhan,

S. M. S. (2005). Chemical and biochemical transformations in ionic liquids. *Tetrahedron*, *61*, 1015–1060; (j) Lee, S. G. (2006). Functionalized imidazolium salts for task-specific ionic liquids and their applications. *Chem. Commun.*, 1049–1063; (k) Corma, A., Garcia, H. (2006). Silica-bound homogenous catalysts as recoverable and reusable catalysts in organic synthesis. *Adv. Synth. Catal.*, *348*, 1391–1412; (l) Mery, D., Astruc, D. (2006). Dendritic catalysis: major concepts and recent progress. *Coord. Chem. Rev.*, *250*, 1965–1979; (m) Helms, B., Frechet, J. M. J. (2006). The dendrimer effect in homogeneous catalysis. *Adv. Synth. Catal.*, *348*, 1125–1148; (n) Bergbreiter, D. E., Sung, S. D. (2006). Liquid/liquid biphasic recovery/reuse of soluble polymier-supported catalysts. *Adv. Synth. Catal.*, *348*, 1352–1366; (o) Cozzi, F. (2006). Immobilization of organic catalysts: when, why, and how. *Adv. Synth. Catal.*, *348*, 1367–1390; (p) Benaglia, M. (2006). Recoverable and recyclable chiral organic catalysts. *New J. Chem.*, *30*, 1525–1533.

[10] Heitbaum, M., Glorius, F., Escher, I. (2006). Asymmetric heterogeneous catalysis. *Angew. Chem. Int. Ed.*, *45*, 4732–4762.

[11] Wang, X. W., Ding, K. L. (2004). Self-supported heterogeneous catalysts for enantioselective hydrogenation. *J. Am. Chem. Soc.*, *126*, 10524–10525.

[12] Shi, L., Wang, X. W., Sandoval, C. A., Li, M. X., Qi, Q. Y., Li, Z. T., Ding, K. L. (2006). Engineering a polymeric chiral catalyst by using hydrogen bonding and coordination interactions. *Angew. Chem. Int. Ed.*, *45*, 4108–4112.

[13] Shi, L., Wang, X. W., Sandoval, C. A., Wang, Z., Li, H. J., Wu, J., Yu, L. T., Ding, K. L. (2009). Development of a continuous-flow system for asymmetric hydrogenation using self-supported chiral catalysts. *Chem. Eur. J.*, *15*, 9855–9867.

[14] de Rege, F. M., Morita, D. K., Ott, K. C., Tumas, W., Broene, R. D. (2000). Noncovalent immobilization of homogeneous cationic chiral rhodium-phosphine catalysts on silica surfaces. *Chem. Commun.*, 1797–1798.

[15] Augustine, R. L., Tanielyan, S. K., Mahata, N., Gao, Y., Zsigmond, A., Yang, H. (2003). Anchored homogeneous catalysts: the role of the heteropoly acid anchoring agent. *Appl. Catal. A*, *256*, 69–76.

[16] Brandts, J. A. M., Berben, P. H. (2003). Application of immobilized rhodium catalyst precursors in enantio- and chemoselective hydrogenation reactions. *Org. Process Res. Dev.*, *7*, 393–398.

[17] Zsigmond, A., Undrala, S., Notheisz, F., Szollosy, A., Bakos, J. (2006). Substituent effects in enantio selective hydrogenations catalyzed by immobilized Rh complexes. *Appl. Catal. A*, *303*, 29–34.

[18] (a) Augustine, R. L., Goel, P., Mahata, N., Reyes, C., Tanielyan, S. K. (2004). Anchored homogeneous catalysts: high turnover number applications. *J. Mol. Catal. A Chem.*, *216*, 189–197; (b) Barnard, C. F. J., Rouzaud, J., Stevenson, S. H. (2005). Straightforward preparation of highly enantioselective anchored chiral homogeneous catalysts. *Org. Process Res. Dev.*, *9*, 164–167.

[19] Augustine, R., Tanielyan, S., Anderson, S., Yang, H. (1999). A new technique for anchoring homogeneous catalysts. *Chem. Commun.*, 1257–1258.

[20] Hems, W. P., McMorn, P., Riddel, S., Watson, S., Hancock, F. E., Hutchings, G. J. (2005). Asymmetric hydrogenation using chiral Rh complexes immobilised with a new ion-exchange strategy. *Org. Biomol. Chem.*, *3*, 1547–1550.

[21] Bautista, F. M., Caballero, V., Campelo, J. M., Luna, D., Marinas, J. M., Romero, A. A., Romero, I., Serrano, I., Llobet, A. (2006). Heterogeneization of a new

Ru(II) homogeneous asymmetric hydrogenation catalyst containing BINAP and the N-tridentate bpea ligand, through covalent attachment on amorphous AlPO4 support. *Top. Catal.*, *40*, 193–205.

[22] Simons, C., Hanefeld, U., Arends, I., Sheldon, R. A., Maschmeyer, T. (2004). Noncovalent anchoring of asymmetric hydrogenation catalysts on a new mesoporous aluminosilicate: application and solvent effects. *Chem. Eur. J.*, *10*, 5829–5835.

[23] Simons, C., Hanefeld, U., Arends, I., Maschmeyer, T., Sheldon, R. A. (2006). Comparison of supports for the electrostatic immobilisation of asymmetric homogeneous catalysts. *J. Catal.*, *239*, 212–219.

[24] Xing, L., Xie, J. H., Chen, Y. S., Wang, L. X., Zhou, Q. L. (2008). Simply modified chiral diphosphine: catalyst recycling via non-covalent absorption on carbon nanotubes. *Adv. Synth. Catal.*, *350*, 1013–1016.

[25] Yi, B., Fan, Q. H., Deng, G. J., Li, Y. M., Qiu, L. Q., Chan, A. S. C. (2004). Novel chiral dendritic diphosphine ligands for Rh(I)-catalyzed asymmetric hydrogenation: remarkable structural effects on catalytic properties. *Org. Lett.*, *6*, 1361–1364.

[26] Yi, B., He, H. P., Fan, Q. H. (2010). Synthesis and application of peripherally alkyl-functionalized dendritic pyrphos ligands: homogeneous-supported catalysts for enantioselective hydrogenation. *J. Mol. Catal. A Chem.*, *315*, 82–85.

[27] Pugin, B., Studer, M., Kuesters, E., Sedelmeier, G., Feng, X. (2004). Mixtures of ionic liquids and water as a medium for efficient enantioselective hydrogenation catalyst recycling. *Adv. Synth. Catal.*, *346*, 1481–1486.

[28] Zhou, H. F., Fan, Q. H., Tang, W. J., Xu, L. J., He, Y. M., Deng, G. J., Zhao, L. W., Gu, L. Q., Chan, A. S. C. (2006). Polyethylene glycol as an environmentally friendly and recyclable reaction medium for enantioselective hydrogenation. *Adv. Synth. Catal.*, *348*, 2172–2182.

[29] Saluzzo, C., Lamouille, T., Herault, D., Lemaire, M. (2002). Polymer-supported catalysts: enantioselective hydrogenation and hydrogen transfer reduction. *Bioorg. Med. Chem. Lett.*, *12*, 1841–1844.

[30] Hu, A. G., Ngo, H. L., Lin, W. B. (2003). Chiral porous hybrid solids for practical heterogeneous asymmetric hydrogenation of aromatic ketones. *J. Am. Chem. Soc.*, *125*, 11490–11491.

[31] Ralph, C. K., Akotsi, O. M., Bergens, S. H. (2004). A reusable polymeric asymmetric hydrogenation catalyst made by ring-opening olefin metathesis polymerization. *Organometallics*, *23*, 1484–1486.

[32] Ralph, C. K., Bergens, S. H. (2007). A highly reusable catalyst for enantioselective ketone hydrogenation. Catalyst-organic frameworks by alternating ROMP assembly. *Organometallics*, *26*, 1571–1574.

[33] Kantam, M. L., Laha, S., Yadav, J., Likhar, P. R., Sreedhar, B., Choudary, B. M. (2007). Asymmetric hydrosilylation of prochiral ketones catalyzed by nanocrystalline copper(II) oxide. *Adv. Synth. Catal.*, *349*, 1797–1802.

[34] Guerreiro, P., Ratovelomanana-Vidal, V., Genet, J. P., Dellis, P. (2001). Recyclable diguanidinium-BINAP and PEG-BINAP supported catalysts: syntheses and use in Rh(I) and Ru(II) asymmetric hydrogenation reactions. *Tetrahedron Lett.*, *42*, 3423–3426.

[35] Zhu, Y. H., Carpenter, K., Bun, C. C., Bahnmueller, S., Ke, C. P., Srid, V. S., Kee, L. W., Hawthorne, M. F. (2003). *R*)-Binap-mediated asymmetric hydrogenation with a rhodacarborane catalyst in ionic-liquid media. *Angew. Chem. Int. Ed.*, *42*, 3792–3795.

[36] Berthod, M., Saluzzo, C., Mignani, G., Lemaire, M. (2004). 4,4′ and 5,5′-DiamBINAP as a hydrosoluble chiral ligand: syntheses and use in Ru(II) asymmetric biphasic catalytic hydrogenation. *Tetrahedron Asymmetry*, *15*, 639–645.

[37] Xu, L. K., Lam, K. H., Ji, J. X., Wu, J., Fan, Q. H., Lo, W. H., Chan, A. S. C. (2005). Air-stable Ir-(P-Phos) complex for highly enantioselective hydrogenation of quinolines and their immobilization in poly(ethylene glycol) dimethyl ether (DMPEG). *Chem. Commun.*, 1390–1392.

[38] Chan, S. H., Lam, K. H., Li, Y. M., Xu, L., Tang, W., Lam, F. L., Lo, W. H., Yu, W. Y., Fan, Q., Chan, A. S. C. (2007). Asymmetric hydrogenation of quinolines with recyclable and air-stable iridium catalyst systems. *Tetrahedron Asymmetry*, *18*, 2625–2631.

[39] Sakai, N., Mano, S., Nozaki, K., Takaya, H. (1993). Highly enantioselective hydroformylation of olefins catalyzed by new phosphinephosphite-Rh(I) complexes. *J. Am. Chem. Soc.*, *115*, 7033–7034.

[40] Shibahara, F., Nozaki, K., Hiyama, T. (2003). Solvent-free asymmetric olefin hydroformylation catalyzed by highly cross-linked polystyrene-supported (*R,S*)-BINAPHOS-Rh(I) complex. *J. Am. Chem. Soc.*, *125*, 8555–8560.

[41] Josephsohn, N. S., Snapper, M. L., Hoveyda, A. H. (2003). Efficient and practical Ag-catalyzed cycloadditions between arylimines and the Danishefsky diene. *J. Am. Chem. Soc.*, *125*, 4018–4019.

[42] Furuno, H., Kambara, T., Tanaka, Y., Hanamoto, T., Kagawa, T., Inanaga, J. (2003). Highly enantioselective homogeneous catalysis of chiral rare earth phosphates in the hetero-Diels-Alder reaction. *Tetrahedron Lett.*, *44*, 6129–6132.

[43] Nájera, C., de Gracia Retamosa, M., Sansano, J. M. (2007). Recoverable (*R*)- and (*S*)-Binap-Ag(I) complexes for the enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides. *Org. Lett.*, *9*, 4025–4028.

[44] Nakano, H., Takahashi, K., Suzuki, Y., Fujita, R. (2005). Polymer-supported chiral phosphinooxathiane ligands for palladium-catalyzed asymmetric allylations. *Tetrahedron Asymmetry*, *16*, 609–614.

[45] Nakano, H., Takahashi, K., Fujita, R. (2005). Polymer-supported chiral phosphinooxazolidine ligands for palladium-catalyzed asymmetric allylic alkylations and Diels-Alder reactions. *Tetrahedron Asymmetry*, *16*, 2133–2140.

[46] Zhao, D. B., Sun, J., Ding, K. L. (2004). New types of soluble polymer-supported bisphosphine ligands with a cyclobutane backbone for Pd-catalyzed enantioselective allylic substitution reactions. *Chem. Eur. J.*, *10*, 5952–5963.

[47] Mino, T., Sato, Y., Saito, A., Tanaka, Y., Saotome, H., Sakamoto, M., Fujita, T. (2005). Synthesis, reaction, and recycle of fluorous palladium catalysts for an asymmetric allylic alkylation without using fluorous solvents. *J. Org. Chem.*, *70*, 7979–7984.

[48] Kolb, H. C., Vannieuwenhze, M. S., Sharpless, K. B. (1994). Catalytic asymmetric dihydroxylation. *Chem. Rev.*, *94*, 2483–2547.

[49] Jacobsen, E. N., Markó, I., Mungall, W. S., Schroder, G., Sharpless, K. B. (1988). Asymmetric dihydroxylation via ligand-accelerated catalysis. *J. Am. Chem. Soc.*, *110*, 1968–1970.

[50] Mandoli, A., Pini, D., Fiori, M., Salvadori, P. (2005). Asymmetric dihydroxylation with recoverable cinchona alkaloid derivatives: a warning note and an improved, insoluble polymer-bound ligand 5 architecture. *Eur. J. Org. Chem.*, 1271–1282.

[51] Lee, H. M., Kim, S. W., Hyeon, T., Kim, B. M. (2001). Asymmetric dihydroxylation using heterogenized cinchona alkaloid ligands on mesoporous silica. *Tetrahedron Asymmetry*, *12*, 1537–1541.

[52] Lee, D., Lee, J., Lee, H., Jin, S., Hyeon, T., Kim, B. M. (2006). Filtration-free recyclable catalytic asymmetric dihydroxylation using a ligand immobilized on magnetic mesocellular mesoporous silica. *Adv. Synth. Catal.*, *348*, 41–46.

[53] Choudary, B. M., Chowdari, N. S., Madhi, S., Kantam, M. L. (2003). A trifunctional catalyst for one-pot synthesis of chiral diols via Heck coupling-N-oxidation-asymmetric dihydroxylation: application for the synthesis of diltiazem and Taxol side chain. *J. Org. Chem.*, *68*, 1736–1746.

[54] Kobayashi, S., Endo, M., Nagayama, S. (1999). Catalytic asymmetric dihydroxylation of olefins using a recoverable and reusable polymer-supported osmium catalyst. *J. Am. Chem. Soc.*, *121*, 11229–11230.

[55] (a) Choudary, B. M., Chowdary, N. S., Madhi, S., Kantam, M. L. (2003). US6780810; (b) Choudary, B. M., Chowdary, N. S., Kantam, M. L., Raghavan, K. V., Reddy, C. V. (2002). US6387033 B1; (c) Choudary, B. M., Chowdary, N. S., Madhi, S., Kantam, M. L., Jyothi, K. (2004). US6706901 B1.

[56] Bolm, C., Gerlach, A. (1998). Polymer-supported catalytic asymmetric sharpless dihydroxylations of olefins. *Eur. J. Org. Chem.*, 21–27.

[57] Kuang, Y. Q., Zhang, S. Y., Wei, L. L. (2003). A soluble block copolymer-supported bis-cinchona alkaloid ligand for the asymmetric dihydroxylation of olefins. *Synth. Commun.*, *33*, 3545–3550.

[58] Cheng, S. K., Zhang, S. Y., Wang, P. A., Kuang, Y. Q., Sun, X. L. (2005). Homogeneous catalytic asymmetric dihydroxylation of olefins induced by an efficient and recoverable polymer-bound ligand QN-AQN-OPEG-OMe. *Appl. Organometallic Chem.*, *19*, 975–979.

[59] Branco, L. C., Afonso, C. A. M. (2002). Catalytic asymmetric dihydroxylation of olefins using a recoverable and reusable OsO_4 in ionic liquid [bmim] [PF_6]. *Chem. Commun.*, 3036–3037.

[60] Branco, L. C., Gois, P. M. P., Lourenco, N. M. T., Kurteva, V. B., Afonso, C. A. M. (2006). Simple transformation of crystalline chiral natural anions to liquid medium and their use to induce chirality. *Chem. Commun.*, 2371–2372.

[61] Kwueon, E. K., Choi, D. S., Choi, H. Y., Lee, Y. J., Jo, C. H., Hwang, S. H., Park, Y. S., Song, C. E. (2005). Osmium tetroxide-(QN) (2)PHAL-sugar: a new recyclable catalyst system for asymmetric dihydroxylation of olefins. *Bull. Korean Chem. Soc.*, *26*, 1839–1842.

[62] Lee, D., Lee, H., Kim, S., Yeom, C. E., Kim, B. M. (2006). A novel chemoentrapment approach for supportless recycling of a catalyst: catalytic asymmetric dihydroxylation. *Adv. Synth. Catal.*, *348*, 1021–1024.

[63] Yang, X. W., Liu, H. Q., Xu, M. H., Lin, G. Q. (2004). A highly efficient and practical new PEG-bound bi-cinchona alkaloid ligand for the catalytic asymmetric aminohydroxylation of alkenes. *Tetrahedron Asymmetry*, *15*, 1915–1918.

[64] Desimoni, G., Faita, G., Jørgensen, K. A. (2006). C2-Symmetric chiral bis(oxazoline) ligands in asymmetric catalysis. *Chem. Rev.*, *106*, 3561–3651.

[65] Rosa, J. N., Santos, A. G., Afonso, C. A. M. (2004). Enantioselective addition of alkynes to imines in ionic liquids. *J. Mol. Catal. A Chem.*, *214*, 161–165.

[66] Liu, J. T., Liu, B., Jia, M., Li, X. S., Chan, A. S. C. (2007). Asymmetric addition of alkynes to imines in water catalyzed with a recyclable Cu(I)-bis(oxazoline) and stearic acid system. *Tetrahedron Asymmetry*, *18*, 396–399.

[67] Loh, T.-P., Zhou, J.-R. (1999). An enantioselective allylation reaction of aldehydes in an aqueous medium. *Tetrahedron Lett.*, *40*, 9115–9118.

[68] McDonagh, C., O'Conghaile, P., Gebbink, R., O'Leary, P. (2007). Electrostatic immobilisation of copper(I) and copper(II) bis(oxazolinyl)pyridine catalysts on silica: application to the synthesis of propargylamines via direct addition of terminal alkynes to imines. *Tetrahedron Lett.*, *48*, 4387–4390.

[69] Weissberg, A., Halak, B., Portnoy, M. (2005). The first solid-phase synthesis of bis(oxazolinyl)pyridine ligands. *J. Org. Chem.*, *70*, 4556–4559.

[70] Cornejo, A., Fraile, J. M., Garcia, J. I., Garcia-Verdugo, E., Gil, M. J., Legarreta, G., Luis, S. V., Martinez-Merino, V., Mayoral, J. A. (2002). The first immobilization of pyridine-bis(oxazoline) chiral ligands. *Org. Lett.*, *4*, 3927–3930.

[71] Burguete, M. I., Cornejo, A., Garcia-Verdugo, E., Gil, M. J., Luis, S. V., Mayoral, J. A., Martinez-Merino, V., Sokolova, M. (2007). Pybox monolithic miniflow reactors for continuous asymmetric cyclopropanation reaction under conventional and supercritical conditions. *J. Org. Chem.*, *72*, 4344–4350.

[72] Cornejo, A., Fraile, J. M., Garcia, J. I., Gil, M. J., Luis, S. V., Martinez-Merino, V., Mayoral, J. A. (2005). A flexible and versatile strategy for the covalent immobilization of chiral catalysts based on pyridinebis(oxazoline) ligands. *J. Org. Chem.*, *70*, 5536–5544.

[73] Cornejo, A., Fraile, J. M., Garcia, J. I., Gil, M. J., Martinez-Merino, V., Mayoral, J. A. (2005). Reversible microencapsulation of pybox-Ru chiral catalysts: scope and limitations. *Tetrahedron*, *61*, 12107–12110.

[74] (a) Lu, J., Ji, S. J., Loh, T. P. (2005). Enantioselective allylation of aldehydes catalyzed by chiral indium(III) complexes immobilized in ionic liquids. *Chem. Commun.*, 2345–2347; (b) Lu, J., Ji, S. J., Teo, Y. C., Loh, T. P. (2005). Highly enantioselective allylation of aldehydes catalyzed by indium(III)-PYBOX complex. *Org. Lett.*, *7*, 159–161; (c) Lu, J., Ji, S. J., Teo, Y. C., Loh, T. P. (2005). Asymmetric allyltributylstannane addition to ketones catalyzed by chiral PYBOX-In(III) complex immobilized in ionic liquid. *Tetrahedron Lett.*, *46*, 7435–7437.

[75] Lundgren, S., Lutsenko, S., Jonsson, C., Moberg, C. (2003). Polymer-supported pyridine-bis(oxazoline). Application to ytterbium-catalyzed silylcyanation of benzaldehyde. *Org. Lett.*, *5*, 3663–3665.

[76] Kolb, H. C., Finn, M. G., Sharpless, K. B. (2001). Click chemistry: diverse chemical function from a few good reactions. *Angew. Chem. Int. Ed.*, *40*, 2004–2021.

[77] Tilliet, M., Lundgren, S., Moberg, C., Levacher, V. (2007). Polymer-bound pyridine-bis(oxazoline). Preparation through click chemistry and evaluation in asymmetric catalysis. *Adv. Synth. Catal.*, *349*, 2079–2084.

[78] Davies, D. L., Kandola, S. K., Patel, R. K. (2004). Asymmetric cyclopropanation in ionic liquids: effect of anion and impurities. *Tetrahedron Asymmetry*, *15*, 77–80.

[79] (a) Burguete, M. I., Fraile, J. M., Garcia, J. I., Garcia-Verdugo, E., Luis, S. V., Mayoral, J. A. (2000). Polymer-supported bis(oxazoline)-copper complexes as

catalysts in cyclopropanation reactions. *Org. Lett.*, *2*, 3905–3908; (b) Diez-Barra, E., Fraile, J. M., Garcia, J. I., Garcia-Verdugo, E., Herrerias, C. I., Luis, S. V., Mayoral, J. A., Sanchez-Verdu, P., Tolosa, J. (2003). Polymer immobilization of bis(oxazoline) ligands using dendrimers as cross-linkers. *Tetrahedron Asymmetry*, *14*, 773–778; (c) Burguete, M. I., Diez-Barra, E., Fraile, J. M., Garcia, J. I., Garcia-Verdugo, E., Gonzalez, R., Herrerias, C. I., Luis, S. V., Mayoral, J. A. (2002). Improvement of ligand economy controlled by polymer morphology: the case of polymer-supported bis(oxazoline) catalysts. *Bioorg. Med. Chem. Lett.*, *12*, 1821–1824.

[80] Mandoli, A., Orlandi, S., Pini, D., Salvadori, P. (2003). A reusable, insoluble polymer-bound bis(oxazoline) (IPB-box) for highly enantioselective heterogeneous cyclopropanation reactions. *Chem. Commun.*, 2466–2467.

[81] Lee, S. S., Hadinoto, S., Ying, J. Y. (2006). Improved enantioselectivity of immobilized chiral bisoxazolines by partial precapping of the siliceous mesocellular foam support with trimethylsilyl groups. *Adv. Synth. Catal.*, *348*, 1248–1254.

[82] Lee, S. S., Ying, J. Y. (2006). Siliceous mesocellular foam-supported chiral bisoxazoline: application to asymmetric cyclopropanation. *J. Mol. Catal. A Chem.*, *256*, 219–224.

[83] Castillo, M. R., Fousse, L., Fraile, J. M., Garcia, J. I., Mayoral, J. A. (2007). Supported ionic-liquid films (SILF) as two-dimensional nanoreactors for enantioselective reactions: surface-mediated selectivity modulation (SMSM). *Chem. Eur. J.*, *13*, 287–291.

[84] (a) Annunziata, R., Benaglia, M., Cinquini, M., Cozzi, F., Pozzi, G. (2003). Synthesis of perfluoroalkyl-substituted bis(oxazolines) as ligands for catalytic enantioselective reactions. *Eur. J. Org. Chem.*, 1191–1197; (b) Simonelli, B., Orlandi, S., Benaglia, M., Pozzi, G. (2004). New perfluoroalkyl-substituted bisoxazolines as chiral ligands in asymmetric Cu-II-catalyzed reactions. *Eur. J. Org. Chem.*, 2669–2673.

[85] Kolodziuk, R., Goux-Henry, C., Sinou, D. (2007). Recyclable copper catalysts in the enantioselective glyoxylate-ene reaction catalyzed by chiral fluorous-tagged bis(oxazolines). *Tetrahedron Asymmetry*, *18*, 2782–2786.

[86] Ono, F., Kanemasa, S., Tanaka, J. (2005). Reusable nano-sized chiral bisoxazoline catalysts. *Tetrahedron Lett.*, *46*, 7623–7626.

[87] Mandoli, A., Orlandi, S., Pini, D., Salvadori, P. (2004). Insoluble polystyrene-bound bis(oxazoline): batch and continuous-flow heterogeneous enantioselective glyoxylate-ene reaction. *Tetrahedron Asymmetry*, *15*, 3233–3244.

[88] Benaglia, M., Cinquini, M., Cozzi, F., Celentano, G. (2004). Enantioselective catalysis in water: Mukaiyama-aldol condensation promoted by copper complexes of bisoxazolines supported on poly(ethylene glycol). *Org. Biomol. Chem.*, *2*, 3401–3407.

[89] Lee, A., Kim, W., Lee, J., Hyeon, T., Kim, B. M. (2004). Heterogeneous asymmetric nitro-Mannich reaction using a bis(oxazoline) ligand grafted on mesoporous silica. *Tetrahedron Asymmetry*, *15*, 2595–2598.

[90] Yang, B. Y., Chen, X. M., Deng, G. J., Zhang, Y. L., Fan, Q. H. (2003). Chiral dendritic bis(oxazoline) copper(II) complexes as Lewis acid catalysts for enantioselective aldol reactions in aqueous media. *Tetrahedron Lett.*, *44*, 3535–3538.

[91] Doherty, S., Goodrich, P., Hardacre, C., Parvulescu, V., Paun, C. (2008). Efficient heterogeneous asymmetric catalysis of the Mukaiyama aldol reaction by silica- and ionic liquid-supported Lewis acid copper(II) complexes of bis(oxazolines). *Adv. Synth. Catal.*, *350*, 295–302.

[92] Doherty, S., Goodrich, P., Hardacre, C., Knight, J. G., Nguyen, M. T., Parvulescu, V. I., Paun, C. (2007). Recyclable copper catalysts based on imidazolium-tagged bis(oxazolines): a marked enhancement in rate and enantioselectivity for Diels-Alder reactions in ionic liquid. *Adv. Synth. Catal.*, *349*, 951–963.

[93] Yeom, C. E., Kim, H. W., Shin, Y. J., Kim, B. M. (2007). Chiral bis(oxazoline)-copper complex catalyzed Diels-Alder reaction in ionic liquids: remarkable reactivity and selectivity enhancement, and efficient recycling of the catalyst. *Tetrahedron Lett.*, *48*, 9035–9039.

[94] (a) Rechavi, D., Lemaire, M. (2002). Enantioselective catalysis of Diels-Alder reactions by heterogeneous chiral bis(oxazoline) catalysts. *J. Mol. Catal. A Chem.*, *182*, 239–247; (b) Rechavi, D., Albela, B., Bonneviot, L., Lemaire, M. (2005). Understanding the enantioselectivity of a heterogeneous catalyst: the influence of ligand loading and of silica passivation. *Tetrahedron*, *61*, 6976–6981; (c) Tanaka, S., Tada, M., Iwasawa, Y. (2007). Enantioselectivity promotion by achiral surface functionalization on SiO$_2$-supported Cu-bis(oxazoline) catalysts for asymmetric Diels-Alder reactions. *J. Catal.*, *245*, 173–183.

[95] Lancaster, T. M., Lee, S. S., Ying, J. Y. (2005). Effect of surface modification on the reactivity of MCF-supported IndaBOX. *Chem. Commun.*, 3577–3579.

[96] (a) Chollet, G., Rodriguez, F., Schulz, E. (2006). A new method for recycling asymmetric catalysts via formation of charge transfer complexes. *Org. Lett.*, *8*, 539–542; (b) Chollet, G., Guillerez, M. G., Schulz, E. (2007). Reusable catalysts for the asymmetric Diels-Alder reaction. *Chem. Eur. J.*, *13*, 992–1000; (c) Chollet, G., Didier, D., Schulz, E. (2010). Reusable chiral bis(oxazoline)-copper complexes immobilized by donor-acceptor interactions on insoluble organic supports. *Catal. Commun.*, *11*, 351–355.

[97] Werner, H., Herrerias, C. I., Glos, M., Gissibl, A., Fraile, J. M., Perez, I., Mayoral, J. A., Reiser, O. (2006). Synthesis of polymer bound azabis(oxazoline) ligands and their application in asymmetric cyclopropanations. *Adv. Synth. Catal.*, *348*, 125–132.

[98] Fraile, J. M., Perez, L., Mayoral, J. A., Reiser, O. (2006). Multipurpose box- and azabox-based immobilized chiral catalysts. *Adv. Synth. Catal.*, *348*, 1680–1688.

[99] (a) Fernandez, M. J., Fraile, J. M., Garcia, J. I., Mayoral, J. A., Burguete, M. I., Garcia-Verdugo, E., Luis, S. V., Harmer, M. A. (2000). Enantioselective cyclopropanation reactions promoted by immobilized bis(oxazoline)-copper complexes. *Top. Catal.*, *13*, 303–309; (b) Fraile, J. M., Garcia, J. I., Herrerias, C. I., Mayoral, J. A., Reiser, O., Socuellamos, A., Werner, H. (2004). The role of binding constants in the efficiency of chiral catalysts immobilized by electrostatic interactions: the case of azabis(oxazoline)Copper complexes. *Chem. Eur. J.*, *10*, 2997–3005; (c) Fraile, J. M., Garcia, J. I., Herrerias, C. I., Mayoral, J. A., Harmer, M. A. (2004). Bis(oxazoline)-copper complexes supported by electrostatic interactions: scope and limitations. *J. Catal.*, *221*, 532–540.

[100] Fraile, J. M., Garcia, J. I., Herrerias, C. I., Mayoral, J. A., Gmough, S., Vaultier, M. (2004). Comparison of the immobilization of chiral bis(oxazoline)-copper complexes onto anionic solids and in ionic liquids. *Green Chem.*, *6*, 93–98.

[101] Fraile, J. M., Garcia, J. I., Herrerias, C. I., Mayoral, J. A., Reiser, O., Vaultier, M. (2004). The importance of complex stability for asymmetric copper-catalyzed cyclopropanations in [emim][OTf] ionic liquid: the bis(oxazoline)-azabis(oxazoline) case. *Tetrahedron Lett.*, *45*, 6765–6768.

[102] Glos, M., Reiser, O. (2000). Aza-bis(oxazolines): new chiral ligands for asymmetric catalysis. *Org. Lett.*, *2*, 2045–2048.

[103] García, J. I., López-Sánchez, B., Mayoral, J. A. (2008). Linking homogeneous and heterogeneous enantioselective catalysis through a self-assembled coordination polymer. *Org. Lett.*, *10*, 4995–4998.

[104] Gissibl, A., Finn, M. G., Reiser, O. (2005). Cu(II)-aza(bisoxazoline)-catalyzed asymmetric benzoylations. *Org. Lett.*, *7*, 2325–2328.

[105] Schätz, A., Hager, M., Reiser, O. (2009). Cu(II)-Azabis(oxazoline)-complexes immobilized on superparamagnetic magnetite@silica-nanoparticles: a highly selective and recyclable catalyst for the kinetic resolution of 1,2-diols. *Adv. Funct. Mater.*, *19*, 2109–2115.

[106] Gissibl, A., Padie, C., Hager, M., Jaroschik, F., Rasappan, R., Cuevas-Yanez, E., Turrin, C. O., Caminade, A. M., Majoral, J. P., Reiser, O. (2007). Synthesis and application of phosphorus dendrimer immobilized azabis(oxazolines). *Org. Lett.*, *9*, 2895–2898.

[107] Rasappan, R., Olbrich, T., Reiser, O. (2009). Combining fluorous and triazole moieties for the tagging of chiral azabis(oxazoline) ligands. *Adv. Synth. Catal.*, *351*, 1961–1967.

[108] Weissberg, A., Portnoy, M. (2003). Unprecedented preparation of pincer bis(oxazolinyl)phenyl ligands on solid support and their use in the first heterogeneously-catalyzed enantioselective allylation of aldehydes. *Chem. Commun.*, 1538–1539.

[109] Cho, S. H., Gadzikwa, T., Afshari, M., Nguyen, S. T., Hupp, J. T. (2007). [Bis(catechol) salen]Mn-III coordination polymers as support-free heterogeneous asymmetric catalysts for epoxidation. *Eur. J. Inorg. Chem.*, 4863–4867.

[110] (a) Xiang, S., Zhang, Y. L., Xin, Q., Li, C. (2002). Enantioselective epoxidation of olefins catalyzed by Mn (salen)/MCM-41 synthesized with a new anchoring method. *Chem. Commun.*, 2696–2697; (b) Zhang, H. D., Xiang, S., Xiao, J. L., Li, C. (2005). Heterogeneous enantioselective epoxidation catalyzed by Mn(salen) complexes grafted onto mesoporous materials by phenoxy group. *J. Mol. Catal. A Chem.*, *238*, 175–184.

[111] (a) Zhang, H. D., Xiang, S., Li, C. (2005). Enantioselective epoxidation of unfunctionalised olefins catalyzed by Mn(salen) complexes immobilized in porous materials via phenyl sulfonic group. *Chem. Commun.*, 1209–1211; (b) Zhang, H., Li, C. (2006). Asymmetric epoxidation of 6-cyano-2,2-dimethylchromene on Mn(salen) catalyst immobilized in mesoporous materials. *Tetrahedron*, *62*, 6640–6649.

[112] Zhang, H. D., Zhang, Y. M., Li, C. (2005). Asymmetric epoxidation of unfunctionalized olefins catalyzed by Mn(salen) axially immobilized onto insoluble polymers. *Tetrahedron Asymmetry*, *16*, 2417–2423.

[113] (a) Ren, W. S., Fu, X. K. (2009). Chiral Mn (III) salen complexes covalently bonded on zirconium oligostyrenylphosphonate-phosphates as catalysts for enantioselective epoxidation of nonfunctionalized alkenes. *J. Mol. Catal. A*

Chem., *312*, 40–47; (b) Ren, W. S., Fu, X. K., Bao, H. B., Bai, R. F., Ding, P. P., Sui, B. L. (2009). Enantioselective epoxidation of unfunctionalized olefins catalyzed by chiral salen Mn(III) catalyst immobilized on zirconium oligostyrenylphosphonate-phosphate. *Catal. Commun.*, *10*, 788–793; (c) Zou, X. C., Fu, X. K., Li, Y. D., Tu, X. B., Fu, S. D., Luo, Y. F., Wu, X. J. (2010). Highly enantioselective epoxidation of unfunctionalized olefins catalyzed by chiral Jacobsen's catalyst immobilized on phenoxy-modified zirconium poly(syrene-phenylvinylphosphonate)phosphate. *Adv. Synth. Catal.*, *352*, 163–170.

[114] Gong, B., Fu, X., Chen, J., Li, Y., Zou, X., Tu, X., Ding, P., Ma, L. (2009). Synthesis of a new type of immobilized chiral salen Mn(III) complex as effective catalysts for asymmetric epoxidation of unfunctionalized olefins. *J. Catal.*, *262*, 9–17.

[115] Zhang, H. D., Zhang, Y. M., Li, C. (2006). Enantioselective epoxidation of unfunctionalized olefins catalyzed by the Mn(salen) catalysts immobilized in the nanopores of mesoporous materials. *J. Catal.*, *238*, 369–381.

[116] Kureshy, R. I., Ahmad, I., Khan, N. U. H., Abdi, S. H. R., Singh, S., Pandia, P. H., Jasra, R. V. (2005). New immobilized chiral Mn(III) salen complexes on pyridine *N*-oxide-modified MCM-41 as effective catalysts for epoxidation of nonfunctionalized alkenes. *J. Catal.*, *235*, 28–34.

[117] Kureshy, R. I., Ahmad, I., Khan, N. H., Abdi, S. H. R., Pathak, K., Jasra, R. V. (2005). Encapsulation of a chiral Mn-III(salen) complex in ordered mesoporous silicas: an approach towards heterogenizing asymmetric epoxidation catalysts for non-functionalized alkenes. *Tetrahedron Asymmetry*, *16*, 3562–3569.

[118] Kureshy, R. I., Ahmad, I., Khan, N. H., Abdi, S. H. R., Pathak, K., Jasra, R. V. (2006). Chiral Mn(III) salen complexes covalently bonded on modified MCM-41 and SBA-15 as efficient catalysts for enantioselective epoxidation of nonfunctionalized alkenes. *J. Catal.*, *238*, 134–141.

[119] Yu, K., Gu, Z., Ji, R., Lou, L. L., Ding, F., Zhang, C., Liu, S. (2007). Effect of pore size on the performance of mesoporous material supported chiral Mn(III) salen complex for the epoxidation of unfunctionalized olefins. *J. Catal.*, *252*, 312–320.

[120] Yu, K., Lou, L. L., Lai, C., Wang, S. J., Ding, F., Liu, S. X. (2006). Asymmetric epoxidation of unfunctionalized olefins catalyzed by Mn(III) salen complex immobilized on MCM-48. *Catal. Commun.*, *7*, 1057–1060.

[121] Lou, L. L., Yu, K., Ding, F., Peng, X. J., Dong, M. M., Zhang, C., Liu, S. X. (2007). Covalently anchored chiral Mn(III) salen-containing ionic species on mesoporous materials as effective catalysts for asymmetric epoxidation of unfunctionalized olefins. *J. Catal.*, *249*, 102–110.

[122] Lou, L. L., Yu, K., Ding, F., Zhou, W., Peng, X. J., Liu, S. X. (2006). An effective approach for the immobilization of chiral Mn(III) salen complexes through a supported ionic liquid phase. *Tetrahedron Lett.*, *47*, 6513–6516.

[123] Bhattacharjee, S., Dines, T. J., Anderson, J. A. (2004). Synthesis and application of layered double hydroxide-hosted catalysts for stereoselective epoxidation using molecular oxygen or air. *J. Catal.*, *225*, 398–407.

[124] Bhattacharjee, S., Anderson, J. A. (2006). Novel chiral sulphonato-salen-manganese (III)-pillared hydrotalcite catalysts for the asymmetric epoxidation of styrenes and cyclic alkenes. *Adv. Synth. Catal.*, *348*, 151–158.

[125] (a) Kureshy, R. I., Khan, N. U. H., Abdi, S. H. R., Ahmad, I., Singh, S., Jasra, R. V. (2004). Dicationic chiral Mn(III) salen complex exchanged in the interlayers of

montmorillonite clay: a heterogeneous enantioselective catalyst for epoxidation of nonfunctionalized alkenes. *J. Catal.*, *221*, 234–240; (b) Kureshy, R. I., Khan, N. H., Abdi, S. H. R., Ahmad, I., Singh, S., Jasra, R. V. (2003). Immobilization of dicationic Mn(III) salen in the interlayers of montmorillonite clay for enantioselective epoxidation of nonfunctionalized alkenes. *Catal. Lett.*, *91*, 207–210.

[126] Choudary, B. M., Ramani, T., Maheswaran, H., Prashant, L., Ranganath, K. V. S., Kumar, K. V. (2006). Catalytic asymmetric epoxidation of unfunctionalised olefins using silica, LDH and resin-supported sulfonato-Mn(salen) complex. *Adv. Synth. Catal.*, *348*, 493–498.

[127] Beigi, M., Haag, R., Liese, A. (2008). Continuous application of polyglycerol-supported salen in a membrane reactor: asymmetric epoxidation of 6-cyano-2,2-dimethylchromene. *Adv. Synth. Catal.*, *350*, 919–925.

[128] Sellner, H., Karjalainen, J. K., Seebach, D. (2001). Preparation of dendritic and non-dendritic styryl-substituted salens for cross-linking suspension copolymerization with styrene and multiple use of the corresponding Mn and Cr complexes in enantioselective epoxidations and hetero-Diels-Alder reactions. *Chem. Eur. J.*, *7*, 2873–2887.

[129] Kureshy, R. I., Khan, N. U. H., Abdi, S. H. R., Singh, S., Ahmad, I., Jasra, R. V., Vyas, A. P. (2004). Enantioselective epoxidation of nonfunctionalized alkenes catalyzed by recyclable new homochiral dimeric Mn(III) salen complexes. *J. Catal.*, *224*, 229–235.

[130] Kureshy, R. I., Singh, S., Khan, N. U. H., Abdi, S. H. R., Ahmed, I., Bhatt, A., Jasra, R. V. (2006). Environment friendly protocol for enantioselective epoxidation of non-functionalized alkenes catalyzed by recyclable homochiral dimeric Mn(III) salen complexes with hydrogen peroxide and UHP adduct as oxidants. *Catal. Lett.*, *107*, 127–130.

[131] Smith, K., Liu, S. F., El-Hiti, G. A. (2004). Use of ionic liquids as solvents for epoxidation reactions catalysed by a chiral Katsuki-type salen complex: enhanced reactivity and recovery of catalyst. *Catal. Lett.*, *98*, 95–101.

[132] (a) Yang, H. Q., Zhang, L., Su, W. G., Yang, Q. H., Li, C. (2007). Asymmetric ring-opening of epoxides on chiral Co(Salen) catalyst synthesized in SBA-16 through the ship in a bottle strategy. *J. Catal.*, *248*, 204–212; (b) Yang, H. Q., Zhang, L., Zhong, L., Yang, Q. H., Li, C. (2007). Enhanced cooperative activation effect in the hydrolytic kinetic resolution of epoxides on (Co[salen]) catalysts confined in nanocages. *Angew. Chem. Int. Ed.*, *46*, 6861–6865.

[133] Kawthekar, R. B., Lee, Y. H., Kim, G. J. (2009). Asymmetric catalysis by chiral salen complexes immobilized on mesoporous materials having modified pore channel system by dimethylcarbonate. *J. Porous Mater.*, *16*, 367–378.

[134] Goyal, P., Zheng, X., Weck, M. (2008). Enhanced cooperativity in hydrolytic kinetic resolution of epoxides using poly(styrene) resin-supported dendronized Co-(salen) catalysts. *Adv. Synth. Catal.*, *350*, 1816–1822.

[135] Belser, T., Jacobsen, E. N. (2008). Cooperative catalysis in the hydrolytic kinetic resolution of epoxides by chiral [(salen)Co(III)] complexes immobilized on gold colloids. *Adv. Synth. Catal.*, *350*, 967–971.

[136] Gill, C. S., Venkatasubbaiah, K., Phan, N. T. S., Weck, M., Jones, C. W. (2008). Enhanced cooperativity through design: pendant Co(III)-salen polymer brush

catalysts for the hydrolytic kinetic resolution of epichlorohydrin (salen-bis(salicylidene)ethylenediamine dianion. *Chem. Eur. J.*, *14*, 7306–7313.

[137] Gill, C. S., Long, W., Jones, C. W. (2009). Magnetic nanoparticle polymer brush catalysts: alternative hybrid organic/inorganic structures to obtain high, local catalyst loadings for use in organic transformations. *Catal. Lett.*, *131*, 425–431.

[138] Kwon, M. A., Kim, G. J. (2003). Synthesis of polymeric salen complexes and application in the enantioselective hydrolytic kinetic resolution of epoxides as catalysts. *Catal. Today*, *87*, 145–151.

[139] Lee, K. Y., Kawthekar, R. B., Kim, G. J. (2007). Synthesis of chiral intermediates catalyzed by new chiral polymeric (salen) cobalt complexes bearing Lewis acidic metal halides. *Bull. Korean Chem. Soc.*, *28*, 1553–1561.

[140] Song, Y. M., Yao, X. Q., Chen, H. L., Bai, C. M., Hu, X. Q., Zheng, Z. (2002). Highly enantioselective resolution of terminal epoxides using polymeric catalysts. *Tetrahedron Lett.*, *43*, 6625–6627.

[141] Rossbach, B. M., Leopold, K., Weberskirch, R. (2006). Self-assembled nanoreactors as highly active catalysts in the hydrolytic kinetic resolution (HKR) of epoxides in water. *Angew. Chem. Int. Ed.*, *45*, 1309–1312.

[142] (a) Song, C. E., Oh, C. R., Roh, E. J., Choo, D. J. (2000). Cr(salen) catalysed asymmetric ring opening reactions of epoxides in room temperature ionic liquids. *Chem. Commun.*, 1743–1744; (b) Oh, C. R., Choo, D. J., Shim, W. H., Lee, D. H., Roh, E. J., Lee, S., Song, C. E. (2003). Chiral Co(III) (salen)-catalysed hydrolytic kinetic resolution of racemic epoxides in ionic liquids. *Chem. Commun.*, 1100–1101.

[143] Kureshy, R. I., Prathap, K. J., Agrawal, S., Kumar, M., Khan, N. U. H., Abdi, S. H. R., Bajaj, H. C. (2009). Highly efficient recyclable Co-III-salen complexes in the catalyzed asymmetric aminolytic kinetic resolution of aryloxy/terminal epoxides for the simultaneous production of *N*-protected 1,2-amino alcohols and the corresponding epoxides in high optical purity. *Eur. J. Org. Chem.*, 2863–2871.

[144] Baleizao, C., Gigante, B., Das, D., Alvaro, M., Garcia, H., Corma, A. (2003). Synthesis and catalytic activity of a chiral periodic mesoporous organosilica (ChiMO). *Chem. Commun.*, 1860–1861.

[145] Baleizao, C., Gigante, B., Garcia, H., Corma, A. (2004). Chiral vanadyl salen complex anchored on supports as recoverable catalysts for the enantioselective cyanosilylation of aldehydes. Comparison among silica, single wall carbon nanotube, activated carbon and imidazolium ion as support. *Tetrahedron*, *60*, 10461–10468.

[146] Baleizao, C., Gigante, B., Garcia, H., Corma, A. (2002). Ionic liquids as green solvents for the asymmetric synthesis of cyanohydrins catalysed by VO(salen) complexes. *Green Chem.*, *4*, 272–274.

[147] Baleizao, C., Gigante, B., Garcia, H., Corma, A. (2003). Chiral vanadyl Schiff base complex anchored on silicas as solid enantioselective catalysts for formation of cyanohydrins: optimization of the asymmetric induction by support modification. *J. Catal.*, *215*, 199–207.

[148] Huang, W., Song, Y. M., Bai, C. M., Cao, G. Y., Zheng, Z. (2004). Asymmetric addition of KCN and Ac_2O to aldehydes catalyzed by recyclable polymeric salen-Ti(IV) complexes. *Tetrahedron Lett.*, *45*, 4763–4767.

[149] (a) Khan, N. U. H., Agrawal, S., Kureshy, R. I., Abdi, S. H. R., Mayani, V. J., Jasra, R. V. (2006). Asymmetric addition of trimethylsilyl cyanide to aldehydes promoted by chiral polymeric vanadium(V) salen complex as an efficient and recyclable catalyst. *Tetrahedron Asymmetry*, *17*, 2659–2666; (b) Khan, N. U. H., Agrawal, S., Kureshy, R. I., Abdi, S. H. R., Mayani, V. J., Jasra, R. V. (2007). Easily recyclable polymeric V(V) salen complex for the enantioselective *O*-acetyl cyanation of aldehydes. *J. Mol. Catal. A Chem.*, *264*, 140–145.

[150] Khan, N. U. H., Agrawal, S., Kureshy, R. I., Abdi, S. H. R., Mayani, V. J., Jasra, R. V. (2006). Asymmetric synthesis of *O*-acetylcyanohydrins by reaction of aldehydes with NaCN/KCN catalyzed by recyclable chiral dimeric titanium(IV)/vanadium(V) salen complexes. *Eur. J. Org. Chem.*, 3175–3180.

[151] Anyanwu, U. K., Venkataraman, D. (2005). Soxhlet-dialysis: a method to recover soluble polymer supported catalysts. *Green Chem.*, *7*, 424–425.

[152] Mellah, M., Ansel, B., Patureau, F., Voituriez, A., Schulz, E. (2007). Electropolymerized Cr-salen complexes for the heterogeneous asymmetric hetero Diels-Alder reaction. *J. Mol. Catal. A Chem.*, *272*, 20–25.

[153] Zulauf, A., Mellah, M., Schulz, E. (2009). New chiral thiophene–salen chromium complexes for the asymmetric Henry reaction. *J. Org. Chem.*, *74*, 2242–2245.

[154] Zulauf, A., Mellah, M., Guillot, R., Schulz, E. (2008). Chromium-thiophene-salen-based polymers for heterogeneous asymmetric hetero-Diels-Alder reactions. *Eur. J. Org. Chem.*, 2118–2129.

[155] Heckel, A., Seebach, D. (2002). Enantioselective heterogeneous epoxidation and hetero-Diels-Alder reaction with Mn- and Cr-salen complexes immobilized on silica gel by radical grafting. *Helv. Chim. Acta.*, *85*, 913–926.

[156] Madhavan, N., Weck, M. (2008). Highly active polymer-supported (salen)Al catalysts for the enantioselective addition of cyanide to alpha,beta-unsaturated imides. *Adv. Synth. Catal.*, *350*, 419–425.

[157] (a) Kureshy, R. I., Ahmad, I., Pathak, K., Khan, N. U. H., Abdi, S. H. R., Prathap, J. K., Jasra, R. V. (2007). Easily recyclable chiral polymeric Mn(III) salen complexes for oxidative kinetic resolution of racemic secondary alcohols. *Chirality*, *19*, 352–357; (b) Pathak, K., Ahmad, I., Abdi, S. H. R., Kureshy, R. I., Khan, N. U. H., Jasra, R. V. (2007). Oxidative kinetic resolution of racemic secondary alcohols catalyzed by recyclable chiral dimeric Mn(III) salen catalysts. *J. Mol. Catal. A Chem.*, *274*, 120–126.

[158] Kantam, M. L., Ramani, T., Chakrapani, L., Choudary, B. M. (2007). Oxidative kinetic resolution of racemic secondary alcohols catalyzed by resin supported sulfonato-Mn(salen) complex in water. *J. Mol. Catal. A Chem.*, *274*, 11–15.

[159] Hanefeld, U., Gardossi, L., Magner, E. (2009). Understanding enzyme immobilisation. *Chem. Soc. Rev.*, *38*, 453–468.

[160] Ghanem, A., Aboul-Enein, H. Y. (2005). Application of lipases in kinetic resolution of racemates. *Chirality*, *17*, 1–15.

[161] Allen, J. V., Williams, J. M. J. (1996). Dynamic kinetic resolution with enzyme and palladium combinations. *Tetrahedron Lett.*, *37*, 1859–1862.

[162] Pamies, O., Bäckvall, J. E. (2002). Efficient lipase-catalyzed kinetic resolution of and dynamic kinetic resolution of beta-hydroxy nitriles. Correction of absolute configuration and transformation to chiral beta-hydroxy acids and gamma-amino alcohols. *Adv. Synth. Catal.*, *344*, 947–952.

[163] Lee, J. K., Kim, M. J. (2002). Ionic liquid-coated enzyme for biocatalysis in organic solvent. *J. Org. Chem.*, *67*, 6845–6847.

[164] Lozano, P., de Diego, T., Carrie, D., Vaultier, M., Iborra, J. L. (2002). Continuous green biocatalytic processes using ionic liquids and supercritical carbon dioxide. *Chem. Commun.*, 692–693.

[165] Matsuda, T., Watanabe, K., Harada, T., Nakamura, K., Arita, Y., Misumi, Y., Ichikawa, S., Ikariya, T. (2004). High-efficiency and minimum-waste continuous kinetic resolution of racemic alcohols by using lipase in supercritical carbon dioxide. *Chem. Commun.*, 2286–2287.

[166] Itoh, T., Nishimura, Y., Ouchi, N., Hayase, S. (2003). 1-Butyl-2,3-dimethylimidazolium tetrafluoroborate: the most desirable ionic liquid solvent for recycling use of enzyme in lipase-catalyzed transesterification using vinyl acetate as acyl donor. *J. Mol. Catal. B Enzymol.*, *26*, 41–45.

[167] Itoh, T., Matsushita, Y., Abe, Y., Han, S. H., Wada, S., Hayase, S., Kawatsura, M., Takai, S., Morimoto, M., Hirose, Y. (2006). Increased enantioselectivity and remarkable acceleration of lipase-catalyzed transesterification by using an imidazolium PEG-alkyl sulfate ionic liquid. *Chem. Eur. J.*, *12*, 9228–9237.

[168] Lourenco, N. M. T., Afonso, C. A. M. (2007). One-pot enzymatic resolution and separation of sec-alcohols based on ionic acylating agents. *Angew. Chem. Int. Ed.*, *46*, 8178–8181.

[169] Monteiro, C. M., Lourenco, N. M. T., Afonso, C. A. M. (2010). Separation of secondary alcohols via enzymatic kinetic resolution using fatty esters as reusable acylating agents. *Tetrahedron Asymmetry*, *21*, 952–956.

[170] Parvulescu, A. N., Jacobs, P. A., De Vos, D. E. (2007). Palladium catalysts on alkaline-earth supports for racemization and dynamic kinetic resolution of benzylic amines. *Chem. Eur. J.*, *13*, 2034–2043.

[171] Parvulescu, A. N., Van der Eycken, E., Jacobs, P. A., De Vos, D. E. (2008). Microwave-promoted racemization and dynamic kinetic resolution of chiral amines over Pd on alkaline earth supports and lipases. *J. Catal.*, *255*, 206–212.

[172] Parvulescu, A. N., Jacobs, P. A., De Vos, D. E. (2008). Heterogeneous Raney nickel and cobalt catalysts for racemization and dynamic kinetic resolution of amines. *Adv. Synth. Catal.*, *350*, 113–121.

[173] Trevisan, V., Signoretto, M., Colonna, S., Pironti, V., Strukul, G. (2004). Microencapsulated chloroperoxidase as a recyclable catalyst for the enantioselective oxidation of sulfides with hydrogen peroxide. *Angew. Chem. Int. Ed.*, *43*, 4097–4099.

[174] Spreti, N., Germani, R., Incani, A., Savelli, G. (2004). Stabilization of chloroperoxidase by polyethylene glycols in aqueous media: kinetic studies and synthetic applications. *Biotechnol. Prog.*, *20*, 96–101.

[175] Wang, W., Xu, Y., Wang, D. I. C., Li, Z. (2009). Recyclable nanobiocatalyst for enantioselective sulfoxidation: facile fabrication and high performance of chloroperoxidase-coated magnetic nanoparticles with ion oxide core and polymer shell. *J. Am. Chem. Soc.*, *131*, 12892–12893.

[176] Gladiali, S., Alberico, E. (2006). Asymmetric transfer hydrogenation: chiral ligands and applications. *Chem. Soc. Rev.*, *35*, 226–236.

[177] (a) Li, Y. Z., Li, Z. M., Li, F., Wang, Q. R., Tao, F. G. (2005). Preparation of polymer-supported Ru-TsDPEN catalysts and use for enantioselective synthesis of (*S*)-

fluoxetine. *Org. Biomol. Chem.*, *3*, 2513–2518; (b) Arakawa, Y., Chiba, A., Haraguchi, N., Itsuno, S. (2008). Asymmetric transfer hydrogenation of aromatic ketones in water using a polymer-supported chiral catalyst containing a hydrophilic pendant group. *Adv. Synth. Catal.*, *350*, 2295–2304.

[178] Arakawa, Y., Haraguchi, N., Itsuno, S. (2006). Design of novel polymer-supported chiral catalyst for asymmetric transfer hydrogenation in water. *Tetrahedron Lett.*, *47*, 3239–3243.

[179] Liu, P. N., Gu, P. M., Wang, F., Tu, Y. Q. (2004). Efficient heterogeneous asymmetric transfer hydrogenation of ketones using highly recyclable and accessible silica-immobilized Ru-TsDPEN catalysts. *Org. Lett.*, *6*, 169–172.

[180] Yang, H. Q., Li, J., Yang, J., Liu, Z. M., Yang, Q. H., Li, C. (2007). Asymmetric reactions on chiral catalysts entrapped within a mesoporous cage. *Chem. Commun.*, 1086–1088.

[181] Huang, X. H., Ying, J. Y. (2007). Asymmetric transfer hydrogenation over Ru-TsDPEN catalysts supported on siliceous mesocellular foam. *Chem. Commun.*, 1825–1827.

[182] Li, J., Zhang, Y., Han, D., Gao, Q., Li, C. (2009). Asymmetric transfer hydrogenation using recoverable ruthenium catalyst immobilized into magnetic mesoporous silica. *J. Mol. Catal. A Chem.*, *298*, 31–35.

[183] (a) Liu, P. N., Deng, J. G., Tu, Y. Q., Wang, S. H. (2004). Highly efficient and recyclable heterogeneous asymmetric transfer hydrogenation of ketones in water. *Chem. Commun.*, 2070–2071; (b) Liu, P. N., Gu, P. M., Deng, J. G., Tu, Y. Q., Ma, Y. P. (2005). Efficient heterogeneous asymmetric transfer hydrogenation catalyzed by recyclable silica-supported ruthenium complexes. *Eur. J. Org. Chem.*, 3221–3227.

[184] Jiang, L., Wu, T. F., Chen, Y. C., Zhu, J., Deng, J. G. (2006). Asymmetric transfer hydrogenation catalysed by hydrophobic dendritic DACH-rhodium complex in water. *Org. Biomol. Chem.*, *4*, 3319–3324.

[185] Chen, Y. C., Wu, T. F., Deng, J. G., Liu, H., Cui, X., Zhu, J., Jiang, Y. Z., Choi, M. C. K., Chan, A. S. C. (2002). Multiple dendritic catalysts for asymmetric transfer hydrogenation. *J. Org. Chem.*, *67*, 5301–5306.

[186] Chen, Y. C., Wu, T. F., Jiang, L., Deng, J. G., Liu, H., Zhu, J., Jiang, Y. Z. (2005). Synthesis of dendritic catalysts and application in asymmetric transfer hydrogenation. *J. Org. Chem.*, *70*, 1006–1010.

[187] Li, X. G., Chen, W. P., Hems, W., King, F., Xiao, J. L. (2004). Asymmetric transfer hydrogenation of ketones with a polymer-supported chiral diamine. *Tetrahedron Lett.*, *45*, 951–953.

[188] Li, X. G., Wu, X. F., Chen, W. P., Hancock, F. E., King, F., Xiao, J. L. (2004). Asymmetric transfer hydrogenation in water with a supported Noyori-Ikariya. *Catal. Org. Lett.*, *6*, 3321–3324.

[189] Liu, J. T., Zhou, Y. G., Wu, Y. N., Li, X. S., Chan, A. S. C. (2008). Asymmetric transfer hydrogenation of ketones with a polyethylene glycol bound Ru catalyst in water. *Tetrahedron Asymmetry*, *19*, 832–837.

[190] Geldbach, T. J., Dyson, P. J. (2004). A versatile ruthenium precursor for biphasic catalysis and its application in ionic liquid biphasic transfer hydrogenation: conventional versus task-specific catalysts. *J. Am. Chem. Soc.*, *126*, 8114–8115.

[191] Kawasaki, I., Tsunoda, K., Tsuji, T., Yamaguchi, T., Shibuta, H., Uchida, N., Yamashita, M., Ohta, S. (2005). A recyclable catalyst for asymmetric transfer hydrogenation with a formic acid-triethylamine mixture in ionic liquid. *Chem. Commun.*, 2134–2136.

[192] Zhou, Z., Sun, Y. (2009). Water-soluble chiral aminosulfonamides as ligands for ruthenium(II)-catalyzed asymmetric transfer hydrogenation. *Catal. Commun.*, *10*, 1685–1688.

[193] Ma, Y. P., Liu, H., Chen, L., Cui, X., Zhu, J., Deng, J. E. (2003). Asymmetric transfer hydrogenation of prochiral ketones in aqueous media with new water-soluble chiral vicinal diamine as ligand. *Org. Lett.*, *5*, 2103–2106.

[194] Wang, F., Liu, H., Cun, L. F., Zhu, J., Deng, J. G., Jiang, Y. Z. (2005). Asymmetric transfer hydrogenation of ketones catalyzed by hydrophobic metal-amido complexes in aqueous micelles and vesicles. *J. Org. Chem.*, *70*, 9424–9429.

[195] Zhou, H. F., Fan, Q. H., Huang, Y. Y., Wu, L., He, Y. M., Tang, W. J., Gu, L. Q., Chan, A. S. C. (2007). Mixture of poly(ethylene glycol) and water as environmentally friendly media for efficient enantioselective transfer hydrogenation and catalyst recycling. *J. Mol. Catal. A Chem.*, *275*, 47–53.

[196] Wu, J. S., Wang, F., Ma, Y. P., Cui, X. C., Cun, L. F., Zhu, J., Deng, J. G., Yu, B. L. (2006). Asymmetric transfer hydrogenation of imines and iminiums catalyzed by a water-soluble catalyst in water. *Chem. Commun.*, 1766–1768.

[197] Sandee, A. J., Petra, M. G. I., Reek, J. N. H., Kamer, P. C. J., van Leeuwen, P. W. N. M. (2001). Solid-phase synthesis of homogeneous ruthenium catalysts on silica for the continuous asymmetric transfer hydrogenation reaction. *Chem. Eur. J.*, 1202–1208.

[198] Felder, M., Giffels, G., Wandrey, C. (1997). A polymer-enlarged homogeneously soluble oxazaborolidine catalyst for the asymmetric reduction of ketones by borane. *Tetrahedron Asymmetry*, *8*, 1975–1977.

[199] Giffels, G., Beliczey, J., Felder, M., Kragl, U. (1998). Polymer enlarged oxazaborolidines in a membrane reactor: enhancing effectivity by retention of the homogeneous catalyst. *Tetrahedron Asymmetry*, *9*, 691–696.

[200] Dalicsek, Z., Pollreisz, F., Gomory, A., Soós, T. (2005). Recoverable fluorous CBS methodology for asymmetric reduction of ketones. *Org. Lett.*, *7*, 3243–3246.

[201] (a) Burguete, M. I., Garcia-Verdugo, E., Vicent, M. J., Luis, S. V., Pennemann, H., von Keyserling, N. G., Martens, J. (2002). New supported beta-amino alcohols as efficient catalysts for the enantioselective addition of diethylzinc to benzaldehyde under flow conditions. *Org. Lett.*, *4*, 3947–3950; (b) Luis, S. V., Altava, B., Burguete, M. I., Collado, M., Escorihuela, J., Garcia-Verdugo, E., Vicent, M. J., Martens, J. (2003). Preparation and optimization of polymer-supported and amino alcohol based enantioselective reagents and catalysts. *Ind. Eng. Chem. Res.*, *42*, 5977–5982.

[202] Castellnou, D., Sola, L., Jimeno, C., Fraile, J. M., Mayoral, J. A., Riera, A., Pericàs, M. A. (2005). Polystyrene-supported (*R*)-2-piperazino-1,1,2-triphenylethanol: a readily available supported ligand with unparalleled catalytic activity and enantioselectivity. *J. Org. Chem.*, *70*, 433–438.

[203] Pericàs, M. A., Castellnou, D., Rodriguez, I., Riera, A., Sola, L. (2003). Tail-tied ligands: an immobilized analogue of (*R*)-2-piperidino-1,1,2-triphenylethanol with intact high catalytic activity and enantioselectivity. *Adv. Synth. Catal.*, *345*, 1305–1313.

[204] Pericas, M. A., Herrerias, C. I., Sola, L. (2008). Fast and enantioselective production of 1-aryl-1-propanols through a single pass, continuous flow process. *Adv. Synth. Catal.*, *350*, 927–932.

[205] Kelsen, V., Pierrat, P., Gros, P. C. (2007). Enantioselective ethylation of aldehydes using a regenerable polymer-supported *N*-picolylvalinol tridentate ligand. *Tetrahedron.*, *63*, 10693–10697.

[206] Kell, R. J., Hodge, P., Nisar, M., Watson, D. (2002). Towards more chemically robust polymer-supported chiral catalysts for the reactions of aldehydes with dialkylzincs. *Bioorg. Med. Chem. Lett.*, *12*, 1803–1807.

[207] Hui, X. P., Chen, C. A., Wu, K. H., Gau, H. M. (2007). Polystyrene-supported *N*-sulfonylated amino alcohols and their applications to titanium(IV) complexes catalyzed enantioselective diethylzinc additions to aldehydes. *Chirality.*, *19*, 10–15.

[208] Chen, C. A., Wu, K. H., Gau, H. M. (2008). Synthesis and application of polymer-supported *N*-sulfonylated aminoalcohols as enantioselective catalysts. *Polymer.*, *49*, 1512–1519.

[209] Huang, L. N., Hui, X. P., Xu, P. F. (2006). Asymmetric addition of diethylzinc to benzaldehyde catalyzed by silica-immobilized titanium(IV) complexes of *N*-sulfonylated amino alcohols. *J. Mol. Catal. A Chem.*, *258*, 216–220.

[210] Forrat, V. J., Ramon, D. J., Yus, M. (2006). Polymer supported trans-1-phenylsulfonylamino-2-isoborneolsulfonylaminocyclohexane ligand for the titanium catalyzed organozinc addition to ketones. *Tetrahedron Asymmetry*, *17*, 2054–2058.

[211] Sato, I., Kodaka, R., Hosoi, K., Soai, K. (2002). Highly enantioselective addition of dialkylzincs to aldehydes using dendritic chiral catalysts with flexible carbosilane backbones. *Tetrahedron Asymmetry*, *13*, 805–808.

[212] El-Shehawy, A. A., Sugiyama, K., Hirao, A. (2008). Application of well-defined chain-end-functionalized polystyrenes with dendritic chiral ephedrine moieties as reagents for highly catalytic enantioselective addition of dialkylzines to aldehydes. *Tetrahedron Asymmetry*, *19*, 425–434.

[213] Park, J. K., Lee, H. G., Bolm, C., Kim, B. M. (2005). Asymmetric diethyl- and diphenylzinc additions to aldehydes by using a fluorine-containing chiral amino alcohol: a striking temperature effect on the enantioselectivity, a minimal amino alcohol loading, and an efficient recycling of the amino alcohol. *Chem. Eur. J.*, *11*, 945–950.

[214] (a) Pathak, K., Bhatt, A. P., Abdi, S. H. R., Kureshy, R. I., Khan, N. H., Ahmad, I., Jasra, R. V. (2006). Enantioselective addition of diethylzinc to aldehydes using immobilized chiral BINOL-Ti complex on ordered mesoporous silicas. *Tetrahedron Asymmetry*, *17*, 1506–1513; (b) Pathak, K., Ahmad, I., Abdi, S. H. R., Kureshy, R. I., Khan, N. U. H., Jasra, R. V. (2008). The synthesis of silica-supported chiral BINOL: application in Ti-catalyzed asymmetric addition of diethylzinc to aldehydes. *J. Mol. Catal. A Chem.*, *280*, 106–114.

[215] Yin, L., Li, R., Wang, F. S., Wang, H. L., Zheng, Y. F., Wang, C. F., Ma, J. T. (2007). The synthesis of dendritic BINOL ligands and their applications in the asymmetric addition of diethylzinc to benzaldehyde. *Tetrahedron Asymmetry*, *18*, 1383–1389.

[216] Gadenne, B., Hesemann, P., Moreau, J. J. E. (2005). Easily recoverable BINOL ligand with ionic tag for asymmetric catalysis. *Tetrahedron Asymmetry*, *16*, 2001–2006.

[217] (a) Nakamura, Y., Takeuchi, S., Okumura, K., Ohgo, Y., Curran, D. P. (2002). Recyclable fluorous chiral ligands and catalysts: asymmetric addition of diethylzinc to aromatic aldehydes catalyzed by fluorous BINOL-Ti complexes. *Tetrahedron.*, *58*, 3963–3969; (b) Nakamura, Y., Takeuchi, S., Ohgo, Y. (2003). Enantioselective carbon-carbon bond forming reactions using fluorous chiral catalysts. *J. Fluorine Chem.*, *120*, 121–129.

[218] Takizawa, S., Somei, H., Jayaprakash, D., Sasai, H. (2003). Metal-bridged polymers as insoluble multicomponent asymmetric catalysts with high enantiocontrol: an approach for the immobilization of catalysts without using any support. *Angew. Chem. Int. Ed.*, *42*, 5711–5714.

[219] Wang, X. S., Wang, X. W., Guo, H. C., Wang, Z., Ding, K. L. (2005). Self-supported heterogeneous titanium catalysts for enantioselective carbonyl-ene and sulfoxidation reactions. *Chem. Eur. J.*, *11*, 4078–4088.

[220] Fu, F., Teo, Y. C., Loh, T. P. (2006). Catalytic enantioselective Diels-Alder reaction in ionic liquid via a recyclable chiral In(III) complex. *Org. Lett.*, *8*, 5999–6001.

[221] Fawcett, J., Hope, E. G., Stuart, A. M., West, A. J. (2005). Recycling of a perfluoroalkylated BINOL ligand using fluorous solid-phase extraction. *Green Chem.*, *7*, 316–320.

[222] Choudary, B. M., Ranganath, K. V. S., Pal, U., Kantam, M. L., Sreedhar, B. (2005). Nanocrystalline MgO for asymmetric Henry and Michael reactions. *J. Am. Chem. Soc.*, *127*, 13167–13171.

[223] Choudary, B. M., Kantam, M. L., Ranganath, K. V. S., Mahendar, K., Sreedhar, B. (2004). Bifunctional nanocrystalline MgO for chiral epoxy ketones via Claisen-Schmidt condensation-asymmetric epoxidation reactions. *J. Am. Chem. Soc.*, *126*, 3396–3397.

[224] Yuan, X. Y., Li, H. Y., Hodge, P., Kilner, M., Tastard, C. Y., Zhang, Z. P. (2006). An easy synthesis of robust polymer-supported chiral 1,1′-bi-(2-naphthol)s (BINOLs): application to the catalysis of the oxidation of prochiral thioethers to chiral sulfoxides. *Tetrahedron Asymmetry*, *17*, 2401–2407.

[225] Sahoo, S., Kumar, P., Lefebvre, F., Halligudi, S. B. (2009). Synthesis of chiral sulfoxides by enantioselective sulfide oxidation and subsequent oxidative kinetic resolution using immobilized Ti-binol complex. *J. Catal.*, *262*, 111–118.