

Recyclable Stereoselective Catalysts

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1. Introduction and Scope

Asymmetric catalysis constitutes one of the most important subjects in chemistry originating thousands of published works every year. But still, the application of such methodologies in chemical industry is rather limited due to the high cost of chiral ligands and noble metals used in such transformations. Additionally, sometimes the final products contain high levels of metal contamination derived from catalyst decomplexation or degradation phenomena, which can become a serious drawback if the metal is toxic for pharmaceutical and food industries. Because of these reasons there are still advantages to using chiral building blocks readily available in nature or by applying resolution of optical isomers.^{1–4}

Stereochemical and chemical efficiencies 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, in some cases, can make the results unpredictable (negative vs novel positive effects).⁵ 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.

Diffusion of molecules inside a matrix adds a delaying contribution to the kinetics equations. In heterogeneous catalysis these phenomena are a sum of two contributions: diffusion of molecules inside the solvent (which is also present in homogeneous catalysis) and diffusion of molecules inside the porous structure of the supporting matrix. Based on this, homogeneous catalysis theoretically has advantages over heterogeneous catalysis. But in heterogeneous catalysis, the catalyst is easily recovered using just filtration or

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Alexandre F. Trindade was born in Lisbon (Portugal) in 1983. He finished his chemistry graduation at the Instituto Superior Técnico (Technical University of Lisbon) in 2006 where he started his Ph.D. in organic chemistry under the supervision of Prof. Dr. Carlos Afonso. His current interests are the development of new methodologies in rhodium catalysis and greener transformations.

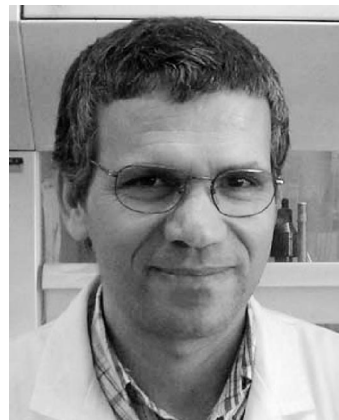


Pedro M. P. Gois was born in Lisbon (Portugal) in 1977. He studied chemistry at the New University of Lisbon from which he also received in 2005 his Ph.D. in organic chemistry under the supervision of Prof. Dr. Carlos Afonso. From May 2005 to May 2008, he worked as a postdoctoral research fellow at the University of Sussex with Prof. Dr. F. Geoffrey N. Cloke, Fellow of the Royal Society, at the University College of London with Prof. Dr. Stephen Caddick, and at the Instituto Superior Técnico (Technical University of Lisbon) with Prof. Dr. Carlos Afonso on the development of novel organic transformations catalyzed by new *N*-heterocyclic carbene rhodium and palladium complexes. From May 2008, he joined the Pharmacy Faculty of the Lisbon University as an assistant research fellow of the medicinal chemistry group (Med.UL - Research Institute for Medicines and Pharmaceutical Sciences). His research encompasses the study of multicomponent reactions, the use of water as a reaction media, the development of new methodologies mediated by metal or organocatalysts and the synthesis of small molecules with potential activity against Alzheimer's and Parkinson's diseases. In 2001, he received a school merit award in chemistry from the Faculty of Sciences and Technology of the New University of Lisbon, and in October 2008, he received an Honor Mention in the Young Research Award of the Deloitte/Technical University of Lisbon.

extraction techniques that are impossible to apply in homogeneous catalysis.

Amorphous and ordered silicas, clays, and highly cross-linked polymers are the standard supports to create a heterogeneous catalyst from a homogeneous catalyst. The principal immobilization mechanisms consist of ligand grafting, metal coordination, microencapsulation, electrostatic interactions, and ion exchange.

It is possible to combine advantages of homogeneous and heterogeneous systems by running reactions with catalysts



Carlos A. M. Afonso graduated from University of Coimbra (1984), and he joined the New University of Lisbon as teaching assistant and received his Ph.D. in 1990 under the supervision of Professor C. D. Maycock where he became assistant professor. He worked for one year as postdoctoral fellow at the Imperial College of Science Technology and Medicine under the supervision of Professor W. B. Motherwell (1990) and one more academic year of sabbatical leave (1997–1998) at the University of Bath, U.K. (Professor J. Williams) and at the University of Toronto (Professor R. Batey). In 2004, he moved to Instituto Superior Técnico of the Technical University of Lisbon as associate professor, and in 2008, he received his *Agregação*. His research focuses on the development of more sustainable methodologies in asymmetric organic transformations and the development and application of new ionic liquids.

that have been chemically linked to soluble macromolecules like oligomeric or low cross-linked soluble polymers, 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.

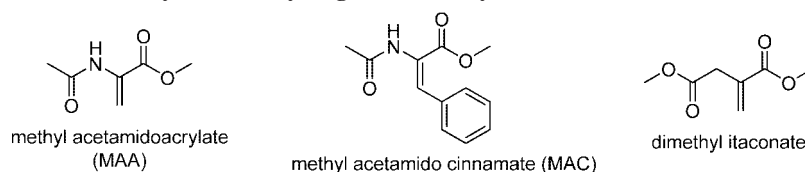
The reutilization of asymmetric catalysts and the reaction media was possible using greener solvents like water, ionic liquids, PEG, perfluorinated solvents, and supercritical CO₂ (scCO₂), which constitute alternatives to volatile organic solvents. Water rises as the cheapest solvent bearing unique characteristics that differ from the others solvents: it is cheaper and the most abundant in nature and proved to have some unexpected beneficial effects in organic transformations.⁶

In recent years, ionic liquids (ILs), which consist of organic cations and appropriate anions (liquid compounds until 100 °C) have received considerable attention due to their potential as alternative recyclable substitutes for volatile chlorinated and nonchlorinated organic solvents as reaction media for chemical processes. They have intrinsically useful properties, such as thermal stability, high ionic conductivity, negligible vapor pressure, and a large electrochemical window.^{7–14}

Perfluoroalkanes present preferential fluorine–fluorine interactions and low interactions with water, protic and polar solvents, hydrocarbons, and common functionalized organic compounds. This property allows the development of efficient separation techniques that could be applied to recycle perfluorinated solvents and catalysts.¹⁵

Supercritical CO₂ is an unconventional solvent, which differs from ordinary solvents due to the gas-like low viscosity, high diffusivity, and liquid-like solubilizing power. Additionally, these properties are readily tunable by changing the operating temperature and pressure. scCO₂ has the added benefits of an environmentally benign nature, being nonflammable, low toxicity, and high availability.¹⁶

The necessity to transfer the asymmetric catalysis methodology to large scale synthesis technology is a crucial goal for synthetic organic scientists worldwide. There are a large

Scheme 1. Main Substrates Used for Asymmetric Hydrogenation Assays

number of contributions toward achieving this goal dispersed in the literature.^{5,17–23} In 2002, Chan and Li tried to combine all these contributions.⁵ During the last five years, several reviews were published in the literature. The majority focus on catalyst immobilization for both chiral and achiral organic transformations, but they do not cover all types of catalyst immobilization processes reported.^{11,24–38} From the reviews that focus only enantioselective catalysis, some cover only one type of transformation or chiral ligand^{39–41} or self-supported heterogeneous catalyst⁴² or solvent-free transformations,⁴³ while Glorius et al. tried to cover several transformations performed with heterogeneous catalysts.⁴⁴

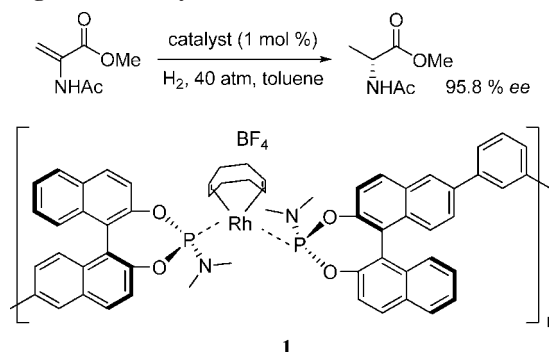
Since 2002, this area of reusable asymmetric catalysts continued to grow surpassing 450 contributions in only 5 years if all types of catalyst immobilization strategies are considered, such as homogeneous and heterogeneous catalysis and unconventional reaction media. This work constitutes an update of the earlier Chan and Li work⁵ covering a larger number of transformations and all types of catalyst recycling methodologies described from 2002 till July 2008.

In the beginning of each section, there is a brief description of the reaction in question or some highlights from the past in that area for the reader to easily perceive the type of development accomplished in each transformation. For the transformations in which considerable diverse efforts were described, the literature was organized to include the following approaches: heterogeneous catalysts, homogeneous catalysts, and alternative reaction media. Within the text, maximum efforts were made to establish comparisons among the homogeneous nonrecyclable protocols with the method for recovery, both in terms of reactivity and enantioselectivity, giving special attention to the recycling process. This recycling process will be analyzed both in terms of executability and efficiency. In terms of efficiency, sometimes the reader can encounter $Y_e(x) = \dots\%$ and $ee_e(x) = \dots\%$. 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:

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

2. Asymmetric Alkene Hydrogenation

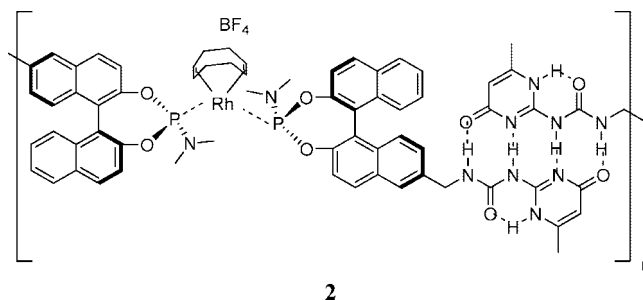
Asymmetric alkene hydrogenation is a powerful tool in organic chemistry to prepare enantiopure compounds with excellent atom economy. The catalysts applied in this transformation are generally based on rhodium(I) and chiral phosphines, which are extremely expensive. Therefore, this transformation attracted considerable attention by chemists interested in obtaining economically sustainable processes. 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 (Scheme 1).

Scheme 2. Hydrogenation Reaction with Self-Supported Heterogeneous Catalyst 1**2.1. Heterogeneous Catalysts**

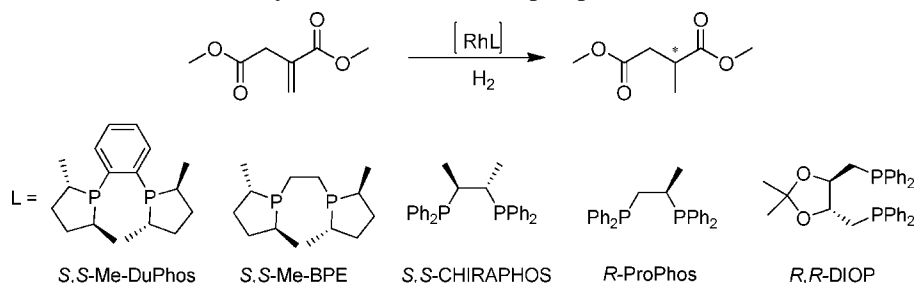
Before 2002, the BINAP ligand was immobilized by grafting to a polystyrene support and copolymerization to form a polyurea polymer. The supported ligands proved to behave similarly to free BINAP.⁵

Ding et al. prepared a self-supported heterogeneous catalyst, **1**, for enamine hydrogenation (10 h, 40 atm, 25 °C) from a Rh complex ($Rh(Cod)_2BF_4$) and a bis-phosphoamidate derived from BINAP (Monophos). Excellent enantioselectivities were obtained with aromatic and alkylic enamines with this heterogeneous catalyst (equivalent to homogeneous ligand, Scheme 2). The catalyst was recycled six times with a minimal 5% enantioselectivity erosion.⁴⁵

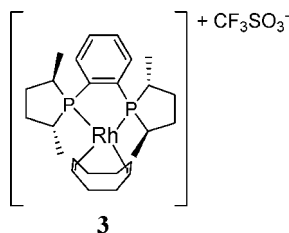
Two years later, Ding et al. prepared a new self-supported polymer based on the same homogeneous catalyst. In this case, the ditopic ligand can self-assemble naturally by hydrogen bonding to a dimeric structure in apolar solvents (instead of being chemically linked). In the presence of rhodium complex, the ligand will assemble into a polymeric structure (catalyst **2**). This polymeric complex proved to be an efficient heterogeneous catalyst for enamine hydrogenation reactions (substrate/catalyst (S/C) = 100, 40 atm H_2 , 91–96% ee). It could be recovered by filtration and reused with minimal ee erosion. The reactivity dropped consecutively during 10 cycles (from 180 to 8 h^{-1}), and this is maybe due to the absence of H_2 during the filtration, which ultimately could lead to catalyst decomposition.⁴⁶



Geresh et al. immobilized the Rh–MeDuPhos catalyst **3** within polyvinyl alcohol cross-linked matrix. This supported catalyst showed low solubility in water and was tested as a

Scheme 3. Hydrogenation Reaction of Dimethyl Itaconate with Rh-Bisphosphines Immobilized in Siliceous Frameworks

heterogeneous catalyst for methyl-2-acetamidoacrylate (MAA) hydrogenation in this solvent. High levels of enantioselectivity were accomplished (up to 97% ee). The catalyst could be recycled twice without negligible enantiomeric excess and yield erosion.⁴⁷

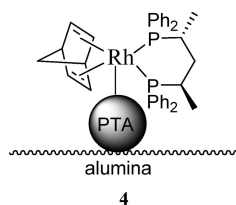


Before 2002, de Rege et al. performed the heterogenization of a chiral rhodium catalyst in MCM-41. This heterogeneous catalyst proved to be as selective as the free catalyst (up to 99% ee) and proved to be recyclable.⁵

Several works have been published based on Augustine's method to perform the immobilization of chiral Rh(I) complexes. In this method, the inorganic support (alumina) bears a phosphotungstic acid (PTA) that coordinates to the homogeneous catalyst to accomplish the immobilization followed by the coordination of the chiral ligand.⁴⁸

The chiral ligands (*R*)-BINAP,⁴⁹ (*R,R*)-MeDuPhos,⁵⁰ and (2*S*,4*S*)-BDPP⁵¹ and carbon-activated^{52,53} supports were studied under this methodology. Generally, the heterogeneous catalysts were found to be less active than their homogeneous partners under batch 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).

Poliakoff et al. conducted dimethyl itaconate asymmetric hydrogenation (see reaction in Scheme 3) under flow conditions using this type of heterogeneous catalyst (immobilization of [Rh(*S,S*-Skewphos)(nbd)]BF₄). The reaction was run under a flow of *sc*CO₂ providing the respective products with enantioselectivities near to conventional batch systems (at 60 °C, 66% conversion and 63% ee). The catalyst **4** worked continuously during 8 h with consistent performance.⁵⁴ Recently this technology was extended to other families of chiral diphosphine ligands.⁵⁵



Hutchings et al. showed that achiral [Rh(cod)₂](BF₄) could be immobilized in mesoporous MCM-41 by ion-exchange,

followed by chiral ligand coordination ((*R,R*)-MeDuPhos). Alternatively, they also immobilized directly the chiral rhodium complex. Both types of heterogeneous catalyst proved to be as efficient as their homogeneous analogues (up to 99% ee) and could be reused 9 times without enantioselectivity erosion in methyl itaconate hydrogenation (S/C = 250, 80 psi H₂).⁵⁶

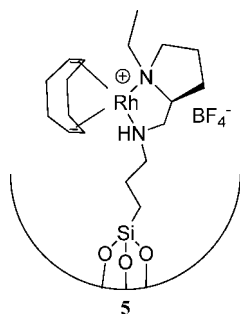
Hoelderich et al. prepared a small library of heterogeneous chiral catalysts by direct immobilization of Rh(*S,S*)-MeDuPhos, Rh(*S,S*)-MeBPE, Rh(*S,S*)-Chiraphos, *R*-Prophos, and (*R,R*)-Diop into several ionic siliceous frameworks (MCM-41, MCM-48, and SBA-15, Scheme 3). These new heterogeneous catalysts were applied in asymmetric hydrogenation reactions of dimethyl itaconate proving to be very reactive (>99% conversion), selective (99%), and enantioselective (up to 98% ee). They could be recovered easily and reused during four consecutive cycles with constant performance, achieving a total TON of 20 000.⁵⁷

Sheldon and Maschmeyer immobilized two asymmetric hydrogenation catalysts, ([Rh(cod)(*R,R*)-MeDuPHOS]BF₄ and [Rh(cod)(*R,R*)-DiPAMP]BF₄), in a new Brønsted acidic aluminosilicate (ALTUD-1) via an ion-exchange protocol. These heterogeneous catalysts were found to have similar behavior compared with the homogeneous catalysts in hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate (S/C = 100, 5 bar H₂), providing the respective products with excellent enantioselectivity (98%). The heterogeneous catalyst bearing the [Rh(cod)(*R,R*)-DiPAMP]BF₄ catalyst was shown to be most stable being reused efficiently during four cycles. The effect of the solvent polarity in rhodium leaching was demonstrated with the most unstable catalyst.⁵⁸

Recently, the same authors screened several anionic supports for electrostatic immobilization of Rh–MonoPhos complex. It was concluded that phosphotungstic acid (PTA) on alumina outperformed the other supports providing excellent levels of enantioselectivity with absence of rhodium leaching (four cycles). The other supports evaluated were Nafion, Nafion–silica composite (SAC-13), and a mesoporous aluminosilicate (ALTUD-1).⁵⁹

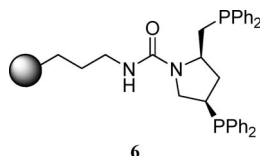
Thomas and co-workers grafted two asymmetric diamine ligands ((*S*)-(–)-2-aminomethyl-1-ethyl pyrrolidine and (1*R*,2*R*)-(+)1,2-diphenylethylenediamine) on siliceous supports with the intent of immobilizing the homogeneous Rh(alkene)₂BF₄ complex. The heterogenization was performed in two types of silica: MCM-41 (concave) and Cabosil (convex). Interestingly, the authors found that the catalyst supported in MCM-41 with concave pores, **5**, slightly enhanced enantioselectivity compared with homogeneous catalyst in asymmetric hydrogenation of (*E*)- α -phenylcinnamic acid and methyl benzoylformate (20 bar H₂, 80–99% conversions, up to 96% ee). The same behavior was not observed in Cabosil due to less hindered

approaches of the reactants to the catalyst. Heterogenized catalyst on MCM-41 proved to be recyclable up to three cycles with minimal ee erosion.⁶⁰

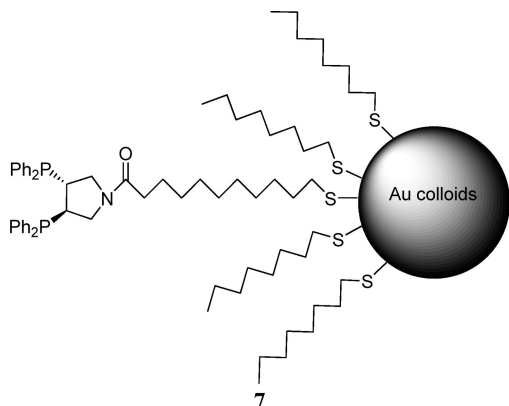


The same authors described an alternative method for immobilization of cation rhodium catalysts. The utilization of a catalyst with trifluoromethanesulfonate anion allowed the immobilization on silica via hydrogen bonding with silanol groups. The immobilization proved to have positive effects on enantioselectivity (up to 94%) in (*E*)- α -phenylcinnamic acid hydrogenation (20 bar H₂) and allowed successful catalyst recycling (once without loss of efficiency).⁶¹

Hayashi and co-workers chose to graft several chiral phosphine ligands to the surface of silica gel using the allylsilane method. Ligand **6** was tested for rhodium-catalyzed hydrogenation of methyl α -acetamido cinnamate proving to be as efficient as the homogeneous ligand (97% yield, 93% ee). When the catalytic system was reused, the reaction became slower, but the enantioselectivity remained unchanged.⁶²

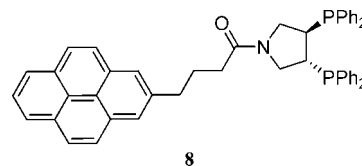


Stöhr and Pfaltz anchored a chiral bisphosphine ligand on the surface of gold nanoparticles. The utilization of long linkers allowed the ligand to be apart from the gold surface, which made it a pseudohomogeneous ligand with heterogeneous properties. The rhodium complex with these ligands (ligand **7**) was tested in asymmetric hydrogenation of methyl α -acetamido cinnamate providing enantioselectivities up to 93%. The catalyst was recovered by filtration and reused three times without loss of enantioselectivity.⁶³

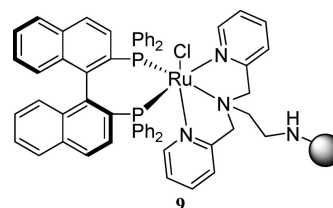


Zhou and co-workers prepared a pyrene-modified Pyrphos ligand with the purpose of immobilizing its rhodium complex inside carbon nanotubes due to π - π stacking interaction.

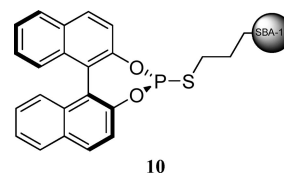
The heterogeneous catalyst **8** was applied on α -dehydroamino esters, hydrogenation proving to be as efficient as that by the unsupported analogue (up to 96% ee, S/C = 100, 10 atm H₂, 20 °C, 2 h). Furthermore, it was recycled eight times with unchanged performance.⁶⁴



Luna et al. grafted a Ru-(BINAP)(dpea) complex on the surface of amorphous AlPO₄ 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 H₂ at 50–70 °C). This heterogeneous catalyst **9** provided the respective products with excellent enantioselectivities (99% ee) during several days and working continuously (up to 10 cycles).⁶⁵



Halligudi et al. prepared a BINOL-derived monodentate phosphorothioate ligand and its iridium complex was covalently anchored to the surface of SBA-15, MCM-41, and MCM-48 (ligand **10**). These heterogeneous catalysts were evaluated in the hydrogenation of dimethyl itaconate, from which the catalyst immobilized on SBA-15 was proven to be the most efficient (ee up to 96%, S/C = 1660, 40 °C, 20 bar H₂, and 20 h). It was found that this catalyst has virtually no degree of leaching, which allowed its recyclability to six cycles without any signs of catalytic activity erosion (total TON = 8300).⁶⁶

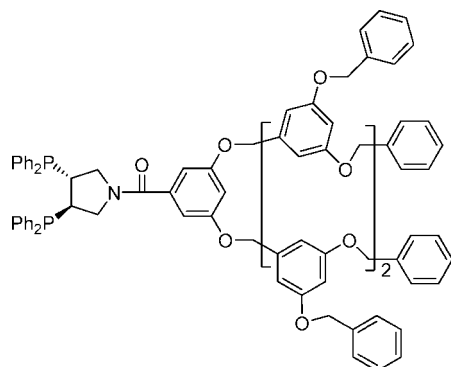


2.2. Homogeneous Catalysts

Prior to 2002, several chiral bisphosphines were immobilized in linear polymeric supports (PEG and polyester polymers) and in dendrimeric structures (Frechet-type dendrimers and others). Generally all types of immobilization had no negative impacts on the enantiomeric results of the hydrogenation reactions, providing the respective alkanes with excellent enantioselectivities (up to 99% ee). Furthermore, some were shown to be highly recyclable (up to 10 cycles).⁵

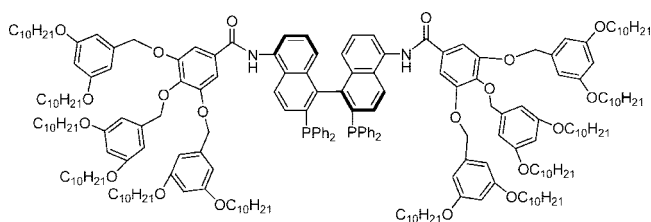
Fan and Chan prepared and tested a chiral dendritic ligand **11** bearing a Pyrphos moiety linked to its core for asymmetric hydrogenation of α -acetamido cinnamic acid. After *in situ* catalyst formation (reaction between Rh(Cod)₂BF₄ and the dendritic ligand **11**), it furnished phenylalanines with excellent ee's (>97% ee vs 99% for unsupported ligand) with all dendritic generations. As the dendrimer generation increases

the catalyst became extremely hindered and therefore less reactive. It was reasoned that the dendritic edges totally microencapsulated the metal center, which should make it more difficult for the reactants and products to move along the dendritic capsule. The catalyst was recovered by filtration and reused with constant ee. However, the conversion decreased considerable upon recycling (run 1 94%, run 3 55%).⁶⁷



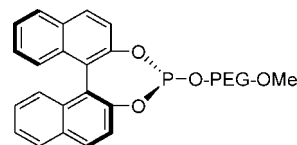
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Fan and Chan developed a new strategy to recover dendritic catalysts based in a two-phase separation (BINAP-derived dendrimer **12**). Hydrogenation reaction of 2-arylacrylic acids were carried on a two-component mixture (hexane/pure ethanol 1:1) at 80 atm H₂ pressure ([RuCl₂(benzene)]₂ S/C = 100) and when total conversion was achieved, a small quantity of water was added (2.5%) to induce phase separation. The catalyst remained in the hexane phase because it contains long aliphatic chains (C₁₀) attached to the dendritic periphery, while products were found in the wet ethanol phase. Furthermore, all dendrimers showed equivalent activity and enantioselectivity compared with the unsupported BINAP (up to 90% ee). When submitted to recycle assays, **12** proved to be very stable, showing no loss of efficiency (over four cycles).⁶⁸



12

Rhodium-catalyzed hydrogenation reaction with monodentate phosphite ligands derived from BINOL tends to afford moderate enantioselectivity (76% ee). The introduction of an alkoxy chain in the ligand proved to have a positive effect on the enantioselectivity since an enhancement to 86% ee was observed. This enhancement was possible by coordination of a hemilabile alkoxy moiety restricting the rotation of the P–Rh bond. Zheng et al. realized that attaching a phosphite ligand to a PEG chain could produce the same effect and also allow reutilization of the expensive catalyst. This polymeric ligand, **13**, enhanced the enantioselectivity up to 96–99% in aromatic enamine hydrogenation (more than its homogeneous analogue). The catalyst was recovered by precipitation and filtration and reused three times with small ee erosion (6%).⁶⁹



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2.3. Alternative Reaction Media

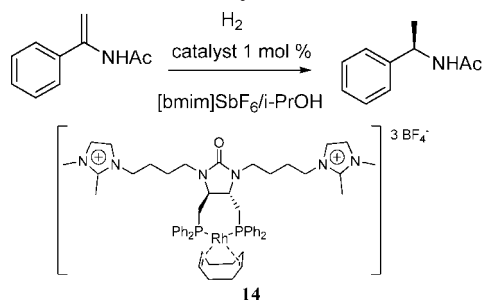
Before 2002, Guernik et al. performed the hydrogenation of methyl α -acetamido cinnamate in the room temperature ionic liquid (IL) [bmim]PF₆ in the presence of Rh–MeDuPHOS with near perfect enantioselectivity. The reutilization of the catalyst in the ionic liquid was demonstrated till the fifth cycle.⁵ Recently, Peters et al. demonstrated the effect of CO₂ in the hydrogenation of methyl α -acetamido cinnamate in [bmim]BF₄ in the presence of Rh–MeDuPHOS. When the partial pressure of CO₂ is increased, the conversion decreases, but the selectivity increases. The recycling of the catalytic system was possible by extracting the products with MTBE.⁷⁰

Task-specific ionic liquids (TSILs) combine two distinct functions, an ionic liquid and a catalyst/ligand. The ionic character allows the catalyst/ligand recovery without leaching because it belongs to the molecular structure of the ionic liquid. Taking advantage of the solubility of ionic liquids in numerous organic solvents, the catalysis has a homogeneous character, and the reaction products could be extracted with low polarity solvents like ethyl ether. In some methodologies where an ionic liquid is used, biphasic conditions are necessary to achieve catalyst recycling, though with some inherent diffusion problems. In the case of TSILs, this issue does not exist since the reaction mixture is homogeneous. Sometimes the attachment of such ionic groups in the catalyst has negative effects on the catalysis.

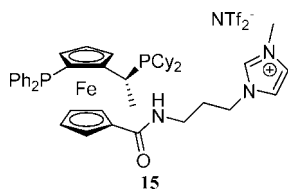
Lee et al. attached two methyl imidazolium units on an asymmetric diphosphine ligand to enhance its solubility in ILs and increase its reutilization capability ((*S,S*)-ILG-BDPMI).⁷¹ Aromatic enamines were hydrogenated using 1 mol % of this new catalyst **14** in [bmim]SbF₆/*i*-PrOH successfully to the respective amine in high enantioselectivity (Scheme 4, S/C = 100, 1 atm H₂, 97% ee). It was found that the catalyst does not leach from the ionic liquid, which could be reused three times with minimal ee erosion (2%) and increasing reaction time (mainly in the last cycle).

It has been recently discovered that in the presence of Rh–(*S,S*)-Me-BDPMI catalyst, hydrogenation of *E* and *Z* isomers of β -acylaminoacrylates could be conducted with the same enantioselectivity, but the conversion was dependent on the solvent polarity. Curiously, the authors found that isomer hydrogenation could be conducted in [bmim]SbF₆/*i*-PrOH with similar conversions (fast rates).⁷² The enantioselectivity was found to be solvent-dependent and slightly lower ee was observed (94% for *Z* isomer and 88% ee for *E* isomer). The Rh–(*S,S*)-Me-BDPMI catalyst was reused at least once, but the conversion readily decreased due to some deactivation. Catalyst **14** was also tested, proving to be slightly more reusable.

Pugin and Blaser showed that the TSIL concept could also be extended to the Josiphos ligand, to which an imidazolium tag was introduced on the lower CP ring. This ligand, **15**, retained Josiphos ligand efficiency providing excellent levels of enantioselectivity for methyl α -acetamidoacrylate (MAA) and methyl α -acetamido cinnamate (MAC) hydrogenation in biphasic methyl *tert*-butyl ether/[bmim]BF₄ (S/C = 200, 1 bar H₂, room temperature, 10 min). It was demonstrated

Scheme 4. Hydrogenation Reaction of Aromatic Enamines in the Presence of TSIL Catalyst


that the TSIL catalyst activity fell more slowly compared with Rh–Josiphos catalyst upon recycling, showing the impact of the ionic tag for catalyst affinity for the IL phase.⁷³



Feng et al. reported the use of wet ILs as biphasic reaction media for MAA and MAC asymmetric hydrogenation.⁷⁴ The mixture of [omim]BF₄/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/isopropanol system (catalyst loading of 0.5 mol %) for all ferrocene-containing catalysts (Scheme 5).

The enantioselectivity enhancement was not caused by the lower H₂ availability in the wet ILs but by characteristic solvation of the components. This biphasic system proved to be very stable, and only at the sixth cycle was an increased reaction time required to achieve complete conversion always with consistently 99% ee. For more apolar substrates like MAC, an organic cosolvent like toluene was added to the wet IL to achieve high enantioselectivity.

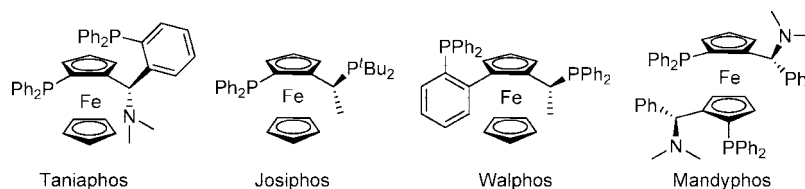
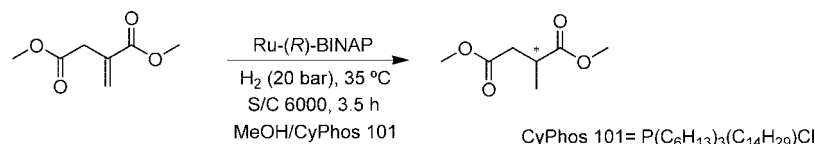
Bakos et al. performed α-acetoamidocinnamic acid asymmetric hydrogenation in a biphasic mixture, [bmim]BF₄/i-PrOH, with Rh(cod)(DIPAMP)BF₄ (0.5 mol %).⁷⁵ Under optimized conditions (55 °C, 5 bar H₂) in 1 h, quantitative conversion was achieved with 91% ee, which corresponds to a value comparable with the literature. The ready solubility of the catalyst in the IL and the products and starting material in the alcoholic phase allowed the catalyst to be recycled. In a third cycle, 10% yield erosion was observed due to some

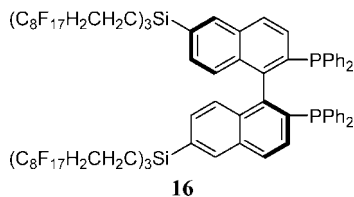
catalyst leaching, while the enantioselectivity remained unchanged. Yuan et al. also used the same biphasic mixture to perform the hydrogenation of dimethyl itaconate in the presence of Rh(*R*)-BINAPS (generated *in situ*, BINAP bearing 3–4 sodium sulfonate moieties) where moderate ee of 64% was achieved. The presence of ionic groups in the ligand was crucial to minimize the ligand and rhodium leaching during the extractions of the recycling experiments.⁷⁶

Livingston et al. performed dimethyl itaconate hydrogenation in a reactor fitted with an organic solvent nanofiltration membrane (OSN Sharmen 122, MWCO = 200 g/mol).⁷⁷ When the reaction was conducted in pure methanol and in the presence of Ru-(*R*)-BINAP catalyst, 82% yield and 75% ee were achieved. After the reaction was completed the mixture was filtered through the OSN membrane allowing catalyst recovery by rejection (99.9% rejection, MW = 794 g/mol). In the further cycles decrease of activity was observed due to catalyst deactivation. When the reaction was carried out with a solvent mixture (methanol/Cyphos 101), it was observed that the IL increased the catalyst stability (being reused up to eight cycles) and enantioselectivity up to 95% ee. Was also found that the introduction of the IL caused a reactivity decrease (20 h was necessary to achieve total conversion instead of 3.5 h, Scheme 6). In later cycles, the reaction became faster, which indicated that the initial low reactivity could be omitted with a catalyst preactivation period in the presence of the IL. Curiously, the yield was depended on IL concentration, increasing when the latter decreased.

Blankermayer and Franciò showed that it was possible to hydrogenate dimethyl itaconate (up to 52% ee) and methyl 2-acetamidoacrylate (up to 69% ee) with chiral induction in the presence of an achiral diphosphine ligand, Rh(Cod)₂BF₄, and triethylamine (as additive) using a chiral ionic liquid as solvent, [proline]NTf₂. The products were removed from the ionic liquid phase by *sc*CO₂ extraction, and the catalytic system was reused twice with 43% yield erosion.⁷⁸

Bannwarth et al. prepared a highly fluorinated BINAP ligand **16** (58% fluorine content) with the purpose of recovering ruthenium hydrogenation catalyst. Instead of using expensive perfluorinated solvents, a fluorinated silica gel (FSG) was tested as noncovalent immobilization agent (500 Å pore size). It was found that if the hydrogenation of dimethyl itaconate was run in a mixture of methanol/α,α,α-trifluorotoluene (1/1), the enantioselectivity obtained reached 93%. At the end of the reaction, the products could be removed with MeOH/water (8/2), leaving the catalytic system retained in the FSG. The recovered catalyst was only reused twice due to catalyst degradation.⁷⁹

Scheme 5. Chiral Biphenyl Phosphine Ligands for Asymmetric Hydrogenation Reaction in [omim]BF₄/Water

Scheme 6. Hydrogenation of Dimethyl Itaconate Using Nanofiltration Technology




Chan et al. showed that poly(ethylene glycol) could be added to methanol to conduct ruthenium- and rhodium-mediated hydrogenation of 2-arylacrylic acids and enamides. 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 to recycle the homogeneous catalysts during nine efficient cycles.⁸⁰

In conclusion, a tendency to reuse the expensive catalysts by heterogeneous methods in detriment to homogeneous methods has been observed, especially when the heterogenization does not involve chiral ligand modification. The introduction of chiral ionic tags on the chiral ligands enhanced the catalyst recyclability in ionic liquids.

3. Asymmetric Ketone Reduction and Hydrogenation

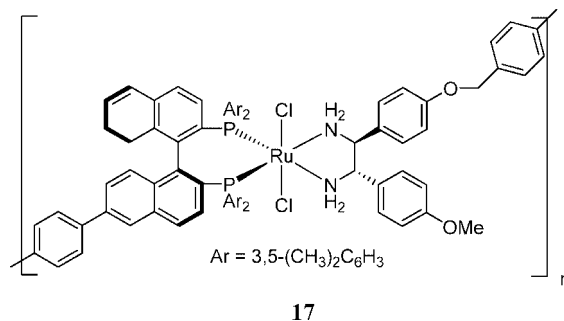
This section deals with catalyst recycling for asymmetric hydrogenations and reductions of ketones (Scheme 7). Unlike the last review,⁵ borane-based catalysts will be described mixed with other immobilization techniques. Several works were reported before 2002 on immobilization of amino alcohols ligands for this borane-mediated transformation using supports like polymers, dendrimers, and inorganic materials. Some of the supported ligands provided excellent levels of chiral induction (up to 98% ee).

3.1. Heterogeneous Catalysts

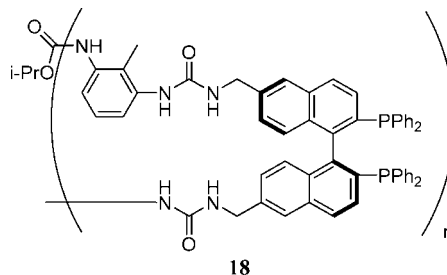
One of the most successful immobilization techniques was carried out by Noyori et al. when they anchored a BINAP derivative to a polystyrene polymer. The ruthenium complex with this ligand and DPEN was used to hydrogenate acetoacetates with 97% ee during 10 consecutive cycles. Polystyrene polymer was also used to immobilize TsDPEN ligand for asymmetric hydrogen transfer reactions providing recoverable ligands that can furnish excellent levels of chiral induction (up to 98% ee).⁵

Ding et al. prepared a self-supported heterogeneous catalyst derived from Noyori's catalyst. The combination of a bisBINAP ligand, Ru complex, and bisDPEN ligand moieties resulted in a pale brown solid **17** insoluble in isopropanol, the solvent of choice for the hydrogenation of aromatic ketones ($S/C = 1000$, 40 atm H_2 , 20 h, 25 °C). This heterogeneous catalyst proved to be superior to a catalyst

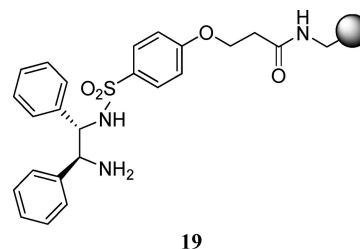
prepared using a bisBIPHEP ligand.^{81,82} After a slight optimization, it was possible to achieve ee's superior to the ones obtained with homogeneous counterpart (>94.5% ee). The heterogeneous character enables the possibility of recycling this catalytic system by simple filtration being successfully recycled six times.



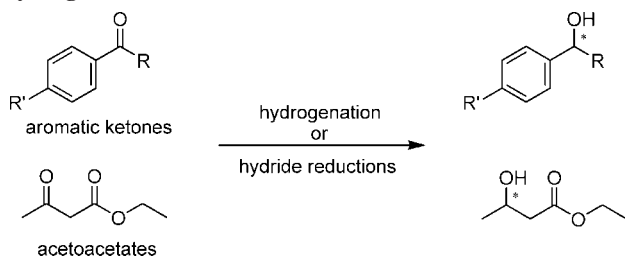
Lemaire et al. immobilized diAm-BINAP in a polymer copolymer using di-isocyanates as the linker. The most rigid copolymer ligand, **18**, was used in ruthenium-mediated hydrogenation of acetoacetates with excellent performance and near perfect selectivity ($S/C = 1000$, 40 atm hydrogen pressure, 50 °C, 16 h, 99% ee). This heterogeneous catalyst (in methanol) was reused three times without any changes in its performance.⁸³



Wang et al. demonstrated that TsDPEN ligand grafted in polystyrene beads (ligand **19**) could be used in ruthenium-mediated hydrogen transfer reactions of 2-cyanoacetophenone. This reaction proceeds to the formation of (*S*)-2-cyano-1-phenyl-1-ethanol with excellent yield and ee ($S/C = 100$, $HCOOH/NEt_3$, 98% yield, 97% ee) comparable with the results obtained with homogeneous catalyst. This system demonstrated a decrease of reactivity upon recycling when it was used to perform the synthesis of an important precursor of fluoxetine.⁸⁴

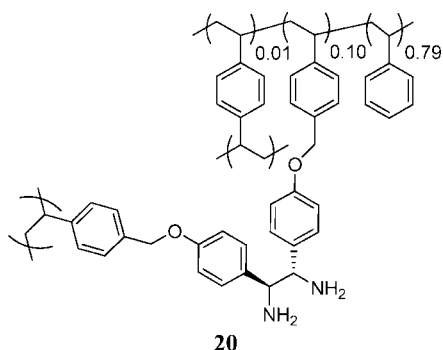


Scheme 7. General Substrates and Methods for Hydrogenation or Reduction of Ketones



Itsuno's group was responsible for interesting contributions in immobilization of DPEN derivatives into polystyrene copolymers. The first catalyst was prepared by joining a Ru complex and BINAP to DPEN ligand supported in polystyrene polymers prepared by grafting a bisphenol derivative of DPEN into a chloromethyl PS resin (ligand **20**). This catalyst was tested in acetophenone hydrogenation providing

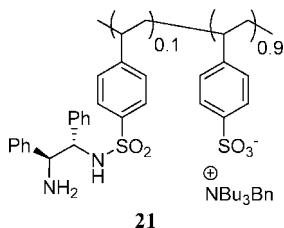
the respective product with 73% ee ($S/C = 200$, 1 MPa H_2) and was reused three times without any decrease on enantioselectivity.^{85,86}



If the DPEN ligand was introduced by copolymerization using a divinylmonomer of DPEN and styrene, the same levels of enantioselectivity and recyclability were obtained since the polymers are chemically equivalent. But the latter was found to be less reactive probably due to some inaccessible DPEN ligands.⁸⁷ Recently, the authors demonstrated that polyacrylate-type polymers are also suitable supports to immobilize DPEN ligand.^{88,89}

Interestingly, when DPEN ligands were immobilized in the same polymeric matrix as a monomer unit the reactivity differences were suppressed. In fact, the catalyst prepared by copolymerization provided identical levels of enantioselectivity compared with the homogeneous catalyst (80% ee), and its recyclability reached 16 efficient cycles.⁹⁰

Following their recent work, Itsuno et al. prepared PS-supported TsDPEN ligand to be used in asymmetric hydrogenation of acetophenone in water by copolymerization. The presence of a styrene derivative monomer bearing a sulfonic group in the polymer structure proved to be crucial for polymer **21** swelling in water, and therefore to its efficiency



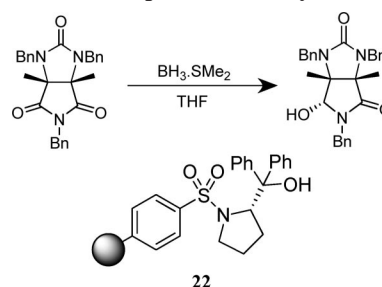
also. The choice of the sulfonic counterion influenced the enantioselectivity of the transformation since tetralkyl ammonium counterion compared with sodium provided higher ee (98%). This heterogeneous catalyst was recycled up to five cycles with the same outcome of enantioselectivity.⁹¹

Chen et al. used a polymer-supported chiral oxazoborolidine **22** for the hydrogenation of meso-cyclic imide with borohydride. This key transformation in the synthesis of D-biotin furnished the desired alcohol in high levels of ee (98.6%, Scheme 8) and proved to be recyclable up to five cycles.⁹²

Cha and Wang prepared a heterogeneous copolymer containing quinine and bisquinine-terephthalic ligands. The complex of this polymeric ligand with $PdCl_2$, was tested for aromatic ketone reduction with sodium borohydride. The optical yield observed never rises above 65% ee, and this system showed efficient recyclability over five cycles.⁹³

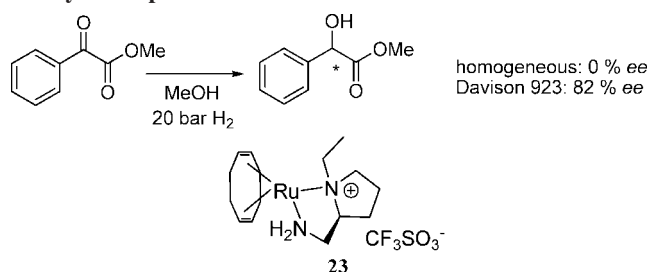
Vinogradov et al. heterogenized the Ru-(S)-BINAP hydrogenation catalyst in a poly(diallyldimethylammonium

Scheme 8. Reduction Step of D-Biotin Synthesis



salt). This heterogeneous catalyst was reused three times in methyl levulinate hydrogenation ($S/C = 200$, 40 atm H_2) affording the respective alcohol with excellent enantioselectivities ($>98\%$ ee).⁹⁴

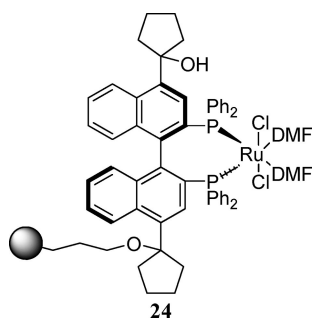
Scheme 9. Hydrogenation Reaction with Chiral Ruthenium Catalyst Incorporated inside Davison 923



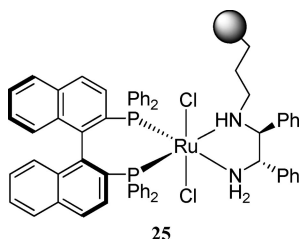
Raja et al. applied Rege method to physically trap several ionic complexes inside desiccant silicas having a narrow pore size distribution (Davison silica type). It was observed that the chiral restriction exerted by the support could induce or improve the enantioselectivity of rhodium- and palladium-mediated α -ketoesters hydrogenation compared with the reaction run in homogeneous media (as an example with catalyst **23**, Scheme 9).⁹⁵ Reutilization details were given in two filed patents.^{96,97}

Lin et al. were interested in preparing hybrid materials containing organic linkers and metal nodes. The catalyst $Ru(4,4'-(PO_3H_2)_2-BINAP)(DPEN)Cl_2$ bearing two phosphonic acid at 4 and 4' positions was synthesized for such purpose. This ruthenium complex was then coordinated to a zirconium salt ($ZrOt-Bu_4$) to prepare the desired structures. With this heterogeneous catalyst in hand, hydrogenation of aromatic ketones was conducted to evaluate its efficiency. Interestingly, this catalyst proved to be much more enantioselective than its homogeneous counterpart achieving excellent enantioselectivities (0.1 mol %, 700 psi of H_2 , 20 h to give up to 99.2% ee). Furthermore, the catalyst was reused seven times. The lost of efficiency observed in the seventh cycle was attributed to some air deactivation.⁹⁸ To efficiently hydrogenate β -ketoesters, $Zr-(4,4'-(PO_3H_2)_2-(BINAP)RuCl_2-(DMF)_2$) and $Zr-(6,6'-(PO_3H_2)_2-(BINAP)RuCl_2-(DMF)_2$) insoluble hybrid materials were prepared using the same methodology. Curiously, in this case the 6,6'-disubstituted one proved to be more enantioselective than the 4,4'-disubstituted one, furnishing ee's up to 95% (1 mol %, 1400 psi H_2 , 20 h). This catalyst was reused efficiently with minimal ee erosion (5%) during five cycles.⁹⁹ Higher levels of enantioselectivity could be obtained (about 5% higher) if this latter complex ($(BINAP)RuCl_2(DMF)_2$) was anchored into well-ordered mesoporous materials (SBA-15, catalyst **24**). Unfortunately, this supported catalyst was less recyclable

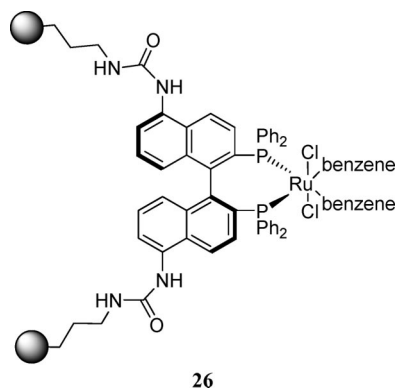
since in the fourth cycle a 10% conversion and enantioselectivity erosion were observed.¹⁰⁰



Kumar and Ghosh grafted DPEN ligand to the surface of several siliceous materials. The catalyst **25** formed with MCM-48 based heterogeneous ligand, BINAP, and ruthenium was tested for the hydrogenation of aromatic ketones (S/C = ~2000, 1.38 MPa H₂, 100 °C) providing the respective products in quantitative conversions with excellent enantioselectivities (up to 98% ee). This system was recycled four times without any erosion of efficiency.¹⁰¹

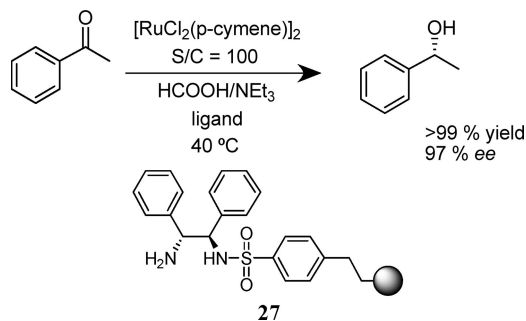


Recently, van Koten and co-workers managed to graft an amino-functionalized BINAP ligand to the surface of silica gel and apply it as ligand for heterogeneous hydrogenations reactions (catalyst **26**). The ruthenium-mediated hydrogenation of acetoacetates was successfully accomplished providing results highly comparable with the ones obtained with unsupported catalyst (40 bar H₂, 50 °C, 100% conversion, > 99% ee). The recycling process could be repeated over four times with no significant loss of efficiency.¹⁰²



Lin et al. coated a ruthenium catalyst [Ru(4-PO₃H₂-BINAP)(DPEN)Cl₂] bearing a phosphoric acid group into magnetite nanoparticles to obtain an easily separable magnetic catalyst for aromatic ketones hydrogenation. This catalyst could be prepared by two methods: thermal decomposition and coprecipitation. The latter provided enhanced chiral induction (0.1 mol %, 700 psi H₂, 20 h, ee about 5% higher on average, up to 98.0%) but was found to be less recyclable (5 vs 14 efficient cycles).¹⁰³

Scheme 10. Hydrogenation Reaction of Acetophenones in the Presence of RuTsDPEN Catalyst Anchored in Silica

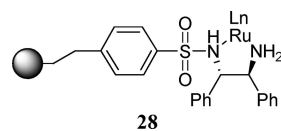


Tu et al. grafted a TsDPEN ligand derivative into several inorganic supports derived from silica gel (ligand **27**). Interestingly, amorphous silica gel behaved consistently better compared with well-ordered supports like MCM-41, SBA-15, or modified silica. Several aromatic ketones were reduced in excellent selectivities and yields, superior or at least equal when compared with unsupported catalyst (Scheme 10). The catalyst presented a great lifetime since it could be reused up to ten cycles without any recharge of ruthenium. The reactivity decrease observed was due to vestigial Ru leaching.¹⁰⁴

Shortly after, the authors showed that the same catalyst can mediate the hydrogenation of aromatic ketones in water in the presence of PTC additives and sodium formate. Curiously, the water induced an acceleration effect on this transformation and the high degree of reusability was conserved.^{105,106}

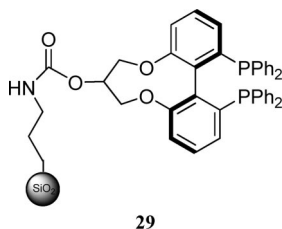
Yang and Li encapsulated an organometallic catalyst inside mesoporous cages before silylation of the cage entrances. This engineered support provides a prison for the catalyst and allows free diffusion of small reactants through the cage entrances. The heterogeneous Ru-TsDPEN/SBA-16-2Ph was prepared by the encapsulation of Ru-TsDPEN in the mesoporous cage of SBA-16 using diphenyldichlorosilane as silylation agent. The heterogeneous system was found to be as selective as the homogeneous one in acetophenone hydrogenation (93% ee), despite being less reactive probably due to diffusion constraints (S/C = 100, HCOONa, Et₄NBr, water). Its reusability reached six efficient cycles.¹⁰⁷

Ying et al. anchored a TsDPEN ligand in several siliceous supports (ligand **28**). The ruthenium complex prepared with such ligands proved to be more stable and reactive and to provide higher levels of enantioselectivity (1 mol %, up to 98% ee), when it was anchored in silica mesocellular foams. Several aromatic ketones were reduced with HCOOH/NEt₃ with high yields and noteworthy enantioselectivities over six cycles (sometimes surpassing homogeneous RuTsDPEN catalyst).¹⁰⁸



Togni and Pugin grafted on the surface of silica gel Grace 332, BIHEP ligands for ruthenium-mediated hydrogenation of methyl phenylglyoxylate (0.01–0.25 mol %, 80 bar H₂ at 40 °C). The addition of HBR (directly or by mixing *in situ* methylsulfonic acid and lithium bromide) was important to achieve excellent levels of enantioselectivity (up to 91%

ee). Interestingly, when **29** was recycled its activity increased gradually till the fourth cycle before decreasing till an eleventh run. The enantioselectivity remained unchanged during seven cycles.¹⁰⁹



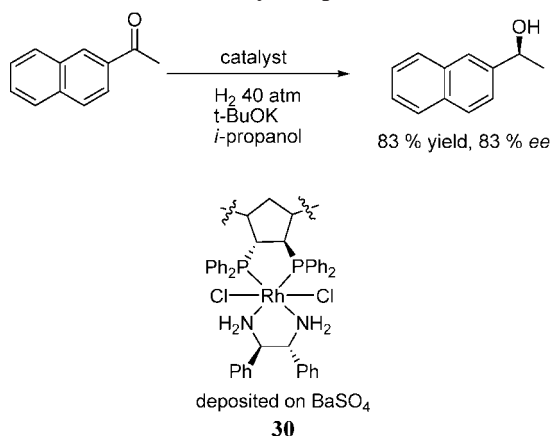
Halligudi et al. immobilized a chiral cyclohexyldiamine based Ru triphenylphosphine complex in mesoporous silica SBA-15 and tested it for asymmetric hydrogenation of aromatic and α,β -unsaturated ketones. It gave enantiomeric excesses comparable with those obtained with the homogeneous system ($S/C = 25640$, 27 atm of H_2 , up to 76% ee). The catalyst was reused twice without any decrease of efficiency.¹¹⁰

Liu et al. immobilized $Ru(PPh_3)_2(Cl)_2((S,S)\text{-DPEN})$ inside the channels of four kinds of mesoporous materials with a method based on a supported ionic liquid system (originally designed to immobilize proline catalyst for aldol reactions). Heterogeneous catalyst supported on silica gel proved to be as efficient as the homogeneous catalyst and consistently recyclable up to five cycles (acetophenone, room temperature, 3 MPa H_2 , 10 h, KOH, >99% conversion, 75–79% ee).¹¹¹

Zhao et al. performed hydrogenation of acetophenone using a ruthenium catalyst adsorbed on alumina in the presence of (*R,R*)-DPEN/triphenyl phosphine. The authors achieved a maximum 60.5% ee and proved that the heterogeneous catalyst can retain its activity during five consecutive cycles.¹¹²

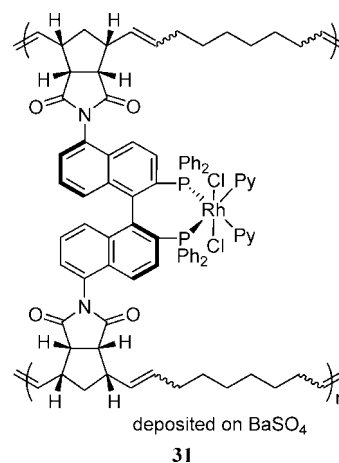
Bergens et al. reported the first polymeric asymmetric catalyst prepared by ring-opening olefin metathesis polymerization (ROMP) of *trans*- $RuCl_2(Py)_2((R,R)\text{-Norphos})$ and cyclooctene. The living ends of the polymer were cross-linked with dicyclopentadiene and the pyridine ligands with chiral DPEN ligand. The deposition of this modified copolymer on $BaSO_4$ afforded the desired heterogeneous catalyst **30**. It was tested in 2-acetonaphthone hydrogenation ($S/C = 500$, 4 atm H_2 , Scheme 11), affording the respective alcohol with 83% yield and 83% ee. This heterogeneous catalyst could be reused up to 10

Scheme 11. Hydrogenation of Aromatic Ketones in the Presence of Chiral Rh Catalyst Deposited in $BaSO_4$



cycles with 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).¹¹³

The enantioselectivity reached 95% ee when the bisphosphine ligand used was exchanged by a BINAP derivative **31**. Furthermore, this catalyst could be reused 25 times without any detrimental effect in the conversion and enantioselectivity using 0.1 mol % of catalyst.¹¹⁴



Kantam et al. reported the application of nanocrystalline copper oxide/BINAP as catalyst for asymmetric hydrosilylation of ketones in the absence of inorganic base. The secondary alcohols can be obtained in very good yields and enantioselectivities after hydrolysis with TBAF (up to 99% ee). This heterogeneous catalyst was reused three times without any yield or enantioselectivity erosion.¹¹⁵

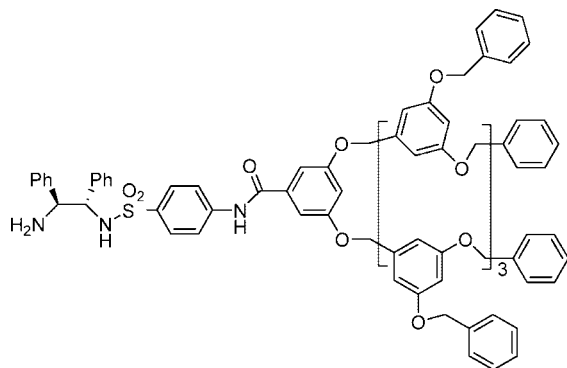
Several co-workers from Jiang's group focus their efforts to prepare several catalysts for the hydrogenation of alkylic ketones.^{116–121} The designed catalysts consisted of several metal salts (palladium and rhodium) complexed to natural biopolymers anchored in inorganic supports. More recently Zhou from the same group designed a chitosan–nickel–iron–nickel complex supported on silical gel to be applied in hydrogenation of aromatic ketones.

3.2. Homogeneous Catalysts

Before 2002, the best results obtained were when TsDPEN ligand was immobilized in polystyrene and PEG polymers providing excellent enantioselectivities (up to 97% ee) in aromatic ketone hydrogen transfer reactions. This ligand was also linked to Frechet-type dendritic structures, ligand **32**, providing the same levels of enantioselectivity. The ruthenium complex with this ligand was reused four times. Recently, Chen and Deng showed that rhodium/ligand **32** catalyst can induce excellent levels of enantioselectivity in aromatic ketone reduction in the presence of sodium formate. The recyclability was also high, achieving six cycles.¹²²

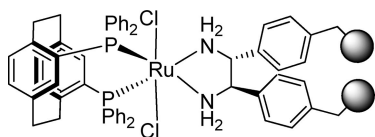
The same efficiency was reported when a PEG-supported BINAP ligand was tested in the ruthenium-mediated hydrogenation of acetoacetates (99% ee). The catalyst was recycled four times and also with consistent efficiency.⁵

Xiao et al. grafted a phenol-derivative of DPEN ligand to a poly(ethylene glycol) polymer to achieve the preparation of a soluble ruthenium catalyst that could be easily recovered by precipitation.¹²³ A catalytic system combining PEG–DPEN, PhanePhos ligand, and a ruthenium complex



32

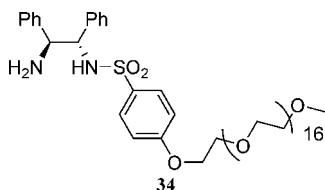
was used to quantitatively hydrogenate several aromatic ketones in very good enantioselectivities (10 bar, 90–97% ee, *S/C* = 2000). The catalyst **33** was successfully recycled three times without any loss of efficiency just by precipitation with diethyl ether.



33

The ligand TsDPEN was also tested with this type of immobilization strategy. In this case, the azeotrope formic acid/triethyl amine was used both as solvent and proton donor instead of hydrogen and no bisphosphine ligand was used (*S/C* = 100).¹²⁴ While the levels of enantioselectivities were only slightly lower (about 5%), the conversion only reached quantitative levels for aromatic ketones containing electron-withdrawing substituents. The catalyst was recovered and recycled, but an appreciable decrease in its activity was detected. For the third cycle, the yield eroded about 43%, while the enantioselectivity decreased about 17%. When the conditions were changed to an aqueous solvent and sodium formate as hydrogen donor, the reactivity increased since generally quantitative conversions were reached for shorter reaction times.¹²⁵ This catalyst proved to be more stable under these new conditions than in formic acid/triethyl amine. This factor was reflected in its highly efficient recyclability (up to 14 cycles).

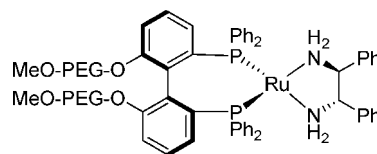
Chan and Li developed a new chiral ligand PEG–BsDPEN for Ru-mediated asymmetric reduction of aromatic ketones with sodium formate in water (*S/C* = 100). Ligand **34** proved to be extremely competitive with the nonpolymeric version providing the respective alcohols with quantitative conversions and with excellent enantioselectivities (89–99% ee). The products were extracted from the reaction media with hexane, and the aqueous phase was reused seven times with only a slight decrease of activity.¹²⁶



34

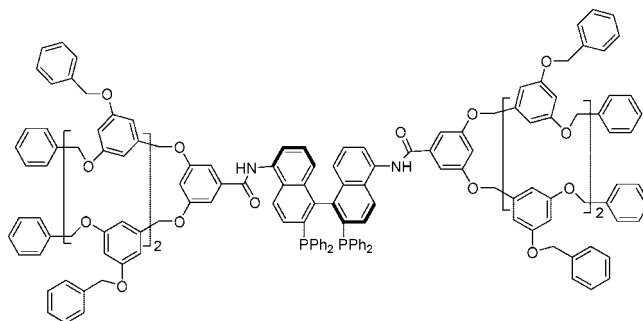
Wang et al. prepared catalyst **35** and tested it in the asymmetric hydrogenation of aromatic ketones. This

polymeric catalyst proved to be at least as efficient as the nonpolymeric analogue, achieving enantioselectivities up to 96.5% using a catalyst loading of 0.1 mol % (25 °C, 20 atm H₂ in 12 h). This catalyst was precipitated upon addition of diethyl ether and reused four times with 6% ee erosion.¹²⁷



35

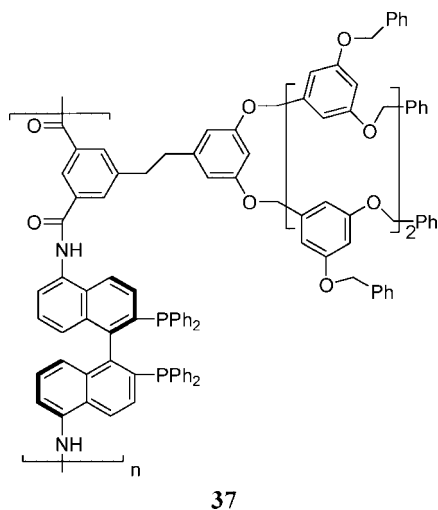
Fan et al. synthesized four dendritic BINAP ligands by condensation of (*R*)-5,5'-diamino-BINAP with Fréchet-type polyether dendrons bearing a carboxyl group at the focal point.¹²⁸ The catalyst prepared with this new ligand, DPEN, and ruthenium was applied in aromatic ketone hydrogenation (*S/C* = 500, 40 atm H₂). Interestingly, it was observed that different generations of the dendrons did not have any influence on the reaction enantioselectivity (75% ee). The third generation complex (e.g., ligand **36**) was found to precipitate quantitatively by addition of methanol to the reaction mixture (isopropanol/toluene) enabling the possibility of its recovery. It was then reused twice efficiently before the conversion fell dramatically in the third cycle (53% erosion).



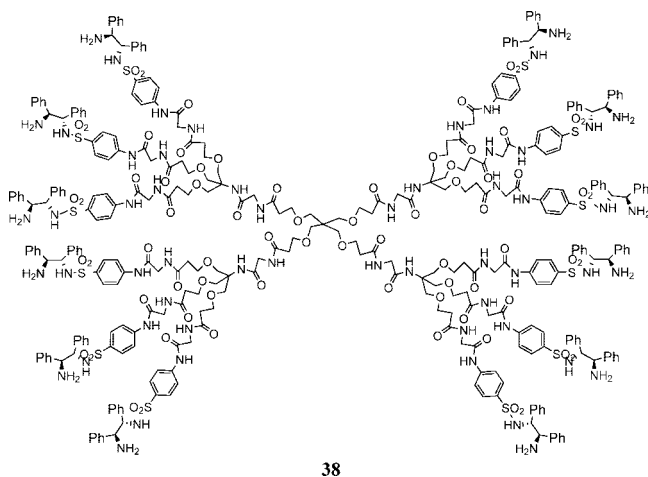
36

As an alternative to this BINAP ligand, Fan et al. prepared a polyurea polymer between diaminoBINAP and a dendron bearing two carboxylic acids at the focal point.¹²⁹ These ligands combined advantages of both polymer and dendrimer macromolecules. In fact, it was not necessary to prepare difficult and tedious higher generation dendrimers to achieve the catalyst precipitation. Catalyst formed with ligand **37** afforded high enantioselectivity for aromatic ketone hydrogenation (*S/C* = 100, 50 atm H₂, up to 92% ee). After each reaction, methanol was added to the reaction vessel promoting the catalyst precipitation. The recovered catalyst could be reused three times with high and consistent enantioselectivity.

Deng et al. anchored the DPEN and TsDPEN ligands on several dendritic structures. The first family of ligands prepared bears the TsDPEN moiety in the periphery of the dendrimer (as in ligand **38**) and was tested for ruthenium-mediated acetophenone reduction (in the presence of triethylamine and formic acid, *S/C* = 100).¹³⁰ This catalyst proved to be as selective as the unsupported one (97.7% ee), but it was difficult to achieve an effective recycling. To overcome this limitation, the authors prepared a hybrid dendrimer, combining a dendron from the previous



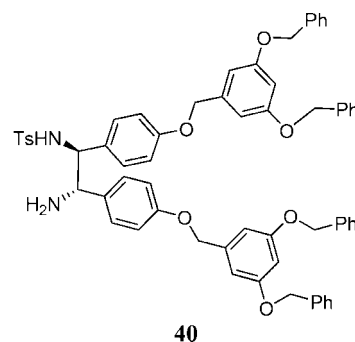
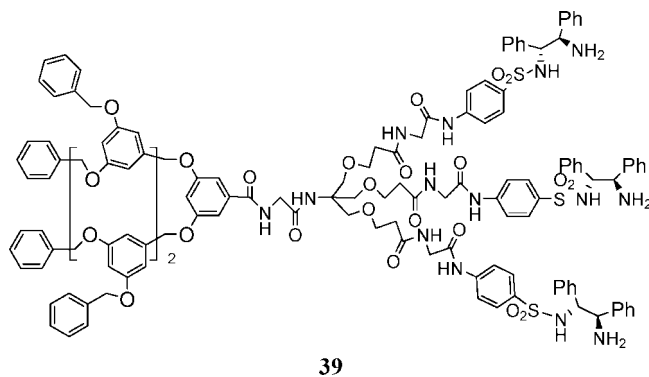
dendrimer (bearing the chiral diamine) with a Frechet-type dendron (as in ligand **39**).¹³¹ The enantioselectivity for acetophenone hydrogenation remained virtually unchanged and recycling was possible (at least twice), but better recyclability was present for a dendritic ligand that bears the TsDPEN moiety in the core (up to five cycles, ligand **32**).



Instead of having the polymer linked to the protecting group of the chiral diamine ligand (in TsDPEN), the dendron can be grown from the phenyl group present in this ligand (ligand **40**). Despite the level of enantioselectivity remaining in the described range, the recycling experiments suffered from consecutive loss of efficiency due to incomplete catalyst recovery (5 cycles, 27% yield erosion).¹³²

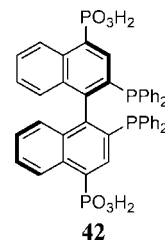
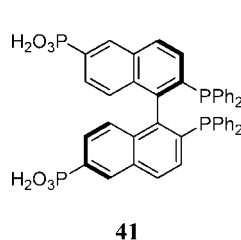
3.3. Alternative Reaction Media

Minghuai et al. prepared a new ionic liquid (IL) containing the *N*-*n*-butylpyridinium cation and the 1-carbadodecaborate anion (BPCB₁₀H₁₂). This new ionic liquid melts at 21 °C and proved to be an excellent reaction media for acetophenone and ethyl formate hydrogenation using a rhodacarborane as catalyst precursor (*[closo-1,3-(η²-3-CH₂=CHCH₂CH₂)-3-H-3-PPh₃-3,1,2-RhC₂B₉H_{10]}*, S/C = 1000, and hydrogen pressure of 12 atm) and BINAP. Quantitative conversion was observed after 8 h with higher ee (>99%) and TOF (>239 h⁻¹) compared with the traditional reaction run in THF. The catalyst and the chiral ligand were recycled in the ionic liquid



by removal of the reaction products under high vacuum and reused up to six cycles without degradation of catalyst activity and selectivity.¹³³

Several groups derivatized BINAP ligand by introducing polar groups to enhance the catalyst (Ru/ligand) affinity with the ionic liquid phase. Lin et al. used two Ru–BINAP precatalysts containing two polar phosphoric acid groups in order to improve their affinity to an IL phase. Hydrogenation of acetoacetates in the presence of this catalyst (1 mol %) under 1500 psi of hydrogen at room temperature were conducted to test the efficiency of these new ligands. However, when the hydrogenation was conducted in pure IL, low ee's were observed. When the solvent used contained an equal quantity of methanol and IL, selectivities above the ones obtained with Ru–BINAP system were obtained with Ru/ligand **42** precatalyst (95–99% ee). The IL propyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl) amide IL (DMPiIm) proved to be the best media for recycling experiments since only in the fifth cycle was some yield erosion detected with unchanged ee.¹³⁴

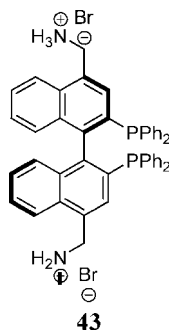


These polar bisphosphonic acid-derived BINAP ligands **41** and **42** were also tested for ruthenium-mediated asymmetric hydrogenation of aromatic ketones in IL under 700 psi of hydrogen (0.1 mol % catalyst loading, in the presence of DPEN ligand). This catalytic system provided ee values up to 98.7% (ligand **42** provided higher ee's). The authors demonstrated that both propyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl) amide IL (DMPiIm) and catalyst

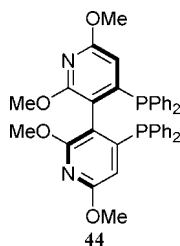
could be recycled and reused efficiently three times for the asymmetric hydrogenation of 1-acetonaphthone in a solvent mixture consisting of DMPIIm/isopropanol.¹³⁵

Alternatively, trimethylsilyl groups were also attached in positions 4 and 4' of BINAP ligand. The catalytic system formed with this new ligand, DPEN, and Ru proved to be only slightly less enantioselective in [bmim]BF₄/MeOH mixture than in pure methanol (>94% ee, 1 mol %, 1400 psi H₂, for acetoacetates). The catalytic system was recycled three times, but both yield and ee dropped consistently (an average 10% efficiency loss in each cycle).¹³⁶

Lemaire et al. linked an ionizable group (ammonium salt) in BINAP ligand to achieve its recycling in ionic liquid media. With a low catalyst loading (0.1 mol %, 50 °C, and 40 bar H₂) acetoacetates were successfully hydrogenated in the presence of Ru–AmBrBINAP **43** catalyst in several ionic liquids. The best IL ([bmim]BF₄) afforded quantitative yields in 15 h with 86% ee, but these results were clearly inferior to those obtained when the same reaction was run in water (95% ee). This is due to some halogenated impurities present in the IL that tend to poison the catalyst. Curiously the enantioselectivity rose to 90% ee in a second cycle.¹³⁷



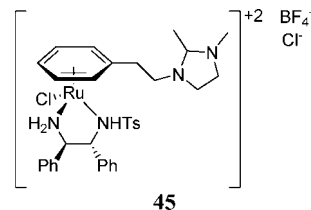
Chan et al. tested the possibility of achieving the recycling of RuP-Phos **44** complex in ionic liquids. First, the authors found that excellent performance of such complex could be obtained using a mixture of IL/MeOH (1/1, 99% conversion with >99% ee for methyl acetoacetate) for hydrogenation of α - and β -ketoesters (1 mol %, 1000 psi H₂). The best recycling experiments were achieved in MeOH/[bmim]PF₆, since after five cycles the yield had only eroded 6% (unchanged ee).¹³⁸



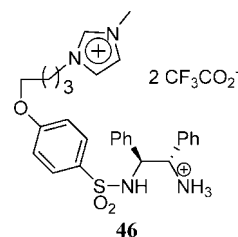
Malhotra et al. demonstrated that stoichiometric LiAlH₄ reduction of aromatic ketones could be carried out in pyridinium-based ionic liquids in the presence of stoichiometric BINOL and 6,6'-Br₂-BINOL. 6,6'-Br₂-BINOL ligand tended to provide only slightly higher levels of chiral induction than BINOL (up to 70% ee). BINOL was recycled three times in [EtPy][BF₄] with minimal ee erosion (4%).¹³⁹

When Geldbach and Pysan linked imidazolium moieties to ruthenium catalysts bearing diamino or amino alcohol ligands, it was observed that the recyclability and catalyst stability was slightly improved compared with a nonionic

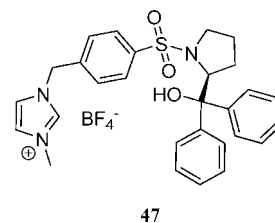
analogue (2-propanol/KOH, S/C = 200). But some degree of leaching still occurred due to catalyst **45** degradation. Curiously, when formic acid/triethylamine was applied as a hydrogen source instead of 2-propanol/KOH, catalyst **45** became less recyclable than the nonionic analogue.¹⁴⁰



Intrigued by the poor results demonstrated by **45** when formic acid/triethylamine azeotrope was used, Ohta et al. decided to synthesize a new TSIL catalyst. In this case, the ionic group (imidazolium) was linked to the asymmetric diamine ligand. Both ionic **46** and neutral catalysts were tested for acetophenone hydrogenation (RuCl₂benzene₂, 1 mol %, 24 h), and both proved to be equally recycled for two cycles. In the fourth cycle, the reaction run with the TSIL ligand presented lower conversion erosion compared with the neutral catalyst (23% vs 36%).¹⁴¹

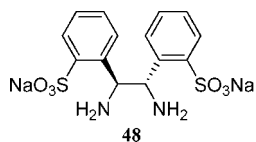


Liang et al. developed a new prolinol-derived sulfonamide catalyst for BH₃ reduction of ketones bearing an ionic imidazolium ring. Reduction of acetophenone was performed in refluxing toluene providing the respective alcohols quantitatively in good enantioselectivities (75% ee, 20 mol % of catalyst). Catalyst **47** proved to be superior to its nonionic analogue providing about 10% enantiomeric excess. Recycling of **47** up to four cycles was possible with 10% enantioselectivity erosion. The recovery protocol involved a series of extractions.¹⁴²

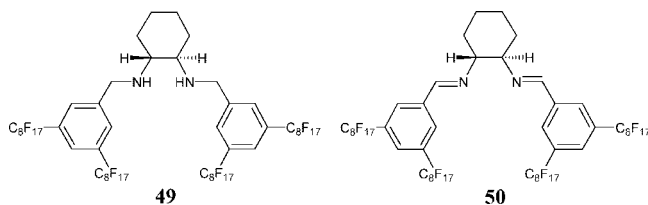


Chen et al. prepared a ruthenium hydrogenation catalyst (TPPTS-Ru) stabilized with tris(3-sulfophenyl)phosphine ligands. This catalyst was found to be extremely reactive for the hydrogenation of acetophenone in [bmim]Ts and in the presence of (1*R*,2*R*)-DPENS **48** (5 Mpa H₂, S/C = 112, 100% conversion, 84.8% ee). The ionic liquid phase containing the catalyst was reused six times with 30% yield erosion.^{143,144}

Maillard et al. prepared a family of ligands derived from salen and tetrahydrosalen ligands, bearing perfluoro alkyl chains. These ligands were applied in acetophenone asymmetric reduction with [Ir(COD)Cl]₂ using isopropanol as the



hydride source (70 °C, 5 mol % catalyst). Ligand **49** provided the highest chiral induction (69–79% ee) when compared with ligand **50** and proved to be stable under liquid–liquid extraction conditions (D-100/isopropanol).¹⁴⁵ Unfortunately when Ir and ligand **49** were reused a significant yield and enantiomeric excess erosion were detected after three recycles.



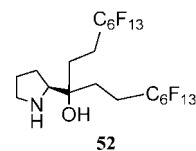
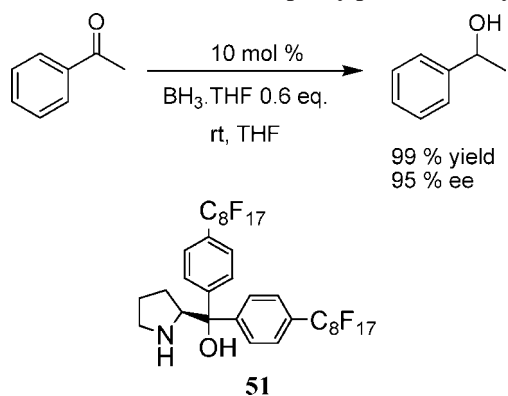
Soós et al. synthesized a prolinol catalyst bearing two perfluoroalkyl chains (ligand **51**). It was coordinated *in situ* to $\text{BH}_3 \cdot \text{THF}$ promoting reduction of aromatic ketones. Using only 10 mol % of catalyst with 0.6 equiv of borane produced quantitative yields with an excellent 95% enantiomeric excess for the acetophenone reduction (Scheme 12). The perfluorinated ligand (rather than oxazaborolidine) was quantitatively recovered with a solid–liquid extraction methodology and reused up to three cycles without any yield and ee erosion.¹⁴⁶

Recently, Yu and Curran showed that the solvent can be exchanged to HFE-7500 (hydrofluoroether) without any negative impact on the reaction efficiency. In this case, dimethylsulfoxide or acetonitrile could be used as extracting solvents to recycle the fluorinated prolinol ligand. With the addition of a fresh amount of borane in each cycle, it was possible to recycle the ligand over eight times.¹⁴⁷

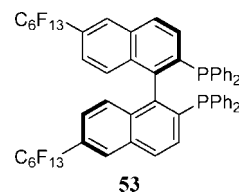
Funabiki et al. prepared a novel prolinol catalyst for borane-mediated reduction of aromatic ketones bearing two perfluoroalkyl chains. Catalyst **52** proved to be less efficient than catalyst **51**, but the recovery protocol is only based on cooling-induced precipitation. Unfortunately, considerable enantioselectivity erosion exists upon recycling.¹⁴⁸

Hope et al. prepared several perfluoroBINAP ligands to be used in the methyl acetoacetate asymmetric hydrogenation with $[\text{RuCl}_2(\text{benzene})_2]$ (S/C = 1000, 50 bar H_2). The authors showed that the introduction of different perfluoroalkyl chains in the BINAP ligand had no negative effect on

Scheme 12. Reduction of Aromatic Ketones with Borane in the Presence of Perfluorinated Diphenylprolinol Catalyst



enantioselectivity of the product (76–80% ee).¹⁴⁹ In the end of the reaction, crude was eluted through a short path of fluoros reverse phase silica gel column using oxygen free solvent to minimize perfluoroBINAP **53** oxidation. The recovered ligand from the chromatography was reused once without any change in the enantiomeric excess output. Curiously, the same result was obtained when nonfluorinated BINAP ligand was submitted to the same treatment.



Water is a greener alternative to organic solvents because it is nontoxic and cheap. The introduction of ionizable groups in the chiral bisphosphine ligands allowed the asymmetric reduction or hydrogenation of ketones to be run in water. At the end of the reaction, the products could be extracted from the aqueous phase leaving the catalytic system behind.⁵

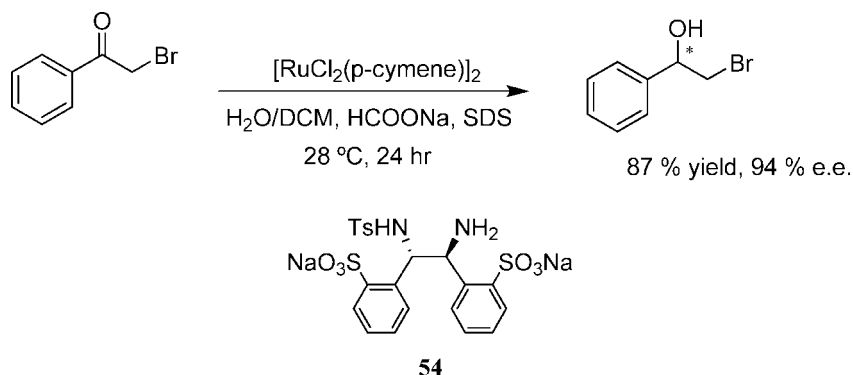
Chun et al. showed that addition of 2 mol % SDS to the reaction mixture enhanced the reactivity ($[\text{RuCl}_2(p\text{-cymene})_2]$, chiral aminoamide, S/C = 100, $\text{HCOOH}/\text{NEt}_3$, up to 95% ee). At the end of the reaction, all organics were extracted while the catalyst remained mainly in the aqueous phase. Unfortunately, in the second cycle, full conversion was not achieved.¹⁵⁰

Zhu and Deng disclosed a biphasic system (water/dichloromethane) that enable the Ru–TsDPEN catalyst recovery and recycle, with aid of a mixture of surfactants (SDS/CTAB, 2/1). This system allowed an increase of activity, chemoselectivity, and enantioselectivity (S/C = 100, up to 99%) in aromatic ketone reduction with sodium formate. The hydrophobic catalyst remained inside the micelles, while the products were found mainly in the dichloromethane phase. The aqueous phase was efficiently reused six times in this transformation.¹⁵¹

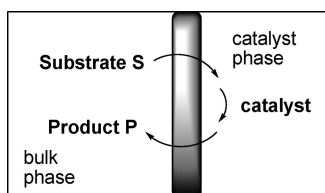
Chan and co-workers showed that a solvent mixture of PEG₄₀₀/water (3/1) was a suitable media to efficiently run reduction of aromatic ketones with sodium formate in the presence of Ru–TsDPEN (S/C = 100). The reaction products were extracted with hexane, and the catalyst could be reused up to 15 cycles with consistent enantioselectivity (95% ee).¹⁵²

Collin and Zouieche showed that $[\text{RuCl}_2(p\text{-cymene})_2]$ in the presence of *N*-phenyl-L-proline amide can promote enantioselective reduction of aromatic ketones in water (with sodium formate). Despite the modest yields (generally below 70%), the system recyclability was demonstrated during a multisubstrate screening (up to seven cycles).¹⁵³

Lemaire et al. applied BINAP ligand **43** and its 4,4'-analogue in 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 to be hydrogenated to the respective alcohol with a 99% enantiomeric excess (both ligands gave identical ee comparable with original homogeneous protocol). At the end

Scheme 13. Reduction of α -Bromo-ketones in Water/Surfactant Media

Scheme 14. Diagram of the Osmosis-Based Reactor

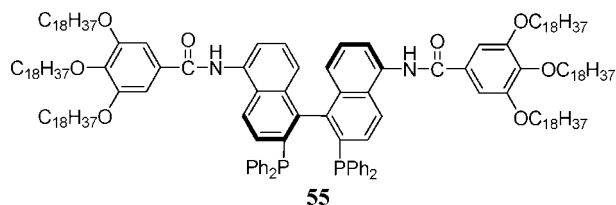


of each cycle, the product was extracted with pentane and the aqueous phase could be reused for at least eight cycles without any decrease of selectivity.¹⁵⁴

Deng et al. developed for the first time a water-soluble chiral TsDPEN bearing two hydrophilic sulfonic groups (ligand **54**). Its ruthenium complex was tested for aromatic ketone reduction with sodium formate providing high enantioselectivity ($S/C = 100$, up to 94% ee, Scheme 13). This water-soluble catalyst could be recycled once with the same enantioselectivity but decreased reactivity. An interesting tolerance for α -bromo-acetone reduction was disclosed.¹⁵⁵

Vankelecom et al. developed a dialysis set up containing a membrane that prevents diffusion of the catalyst from its solution to the reactant phase, while smaller reactants will diffuse by osmosis through both phases (Scheme 14). The choice of solvent increases the catalyst lifetime and prevents membrane swelling (required to minimize the catalyst diffusion). Acetophenone was hydrogenated in the presence of Ru–TsDPEN catalyst with 95% ee. The reactant phase was removed, and a fresh batch was added, opening perspectives of a continuous process. The TON achieved was 370.¹⁵⁶

Fan et al. prepared a BINAP ligand derivative with thermomorphic properties (ligand **55**). The ruthenium complex with this ligand was insoluble in the dioxane/ethanol mixture (1/3) at 0 °C but totally soluble at 60 °C. At 60 °C, the catalyst was tested for acetophenone hydrogenation (H_2 40 atm, 0.5 mol % catalyst loading) providing the same activity as Ru–BINAP complex (up to 98.6% ee). The catalyst insolubility at 0 °C allowed its quantitative recovery and reutilization without any erosion of enantioselectivity, though some loss of reactivity after four cycles was observed.¹⁵⁷



Chan et al. showed that poly(ethylene glycol) could be added to methanol to conduct ruthenium-mediated hydro-

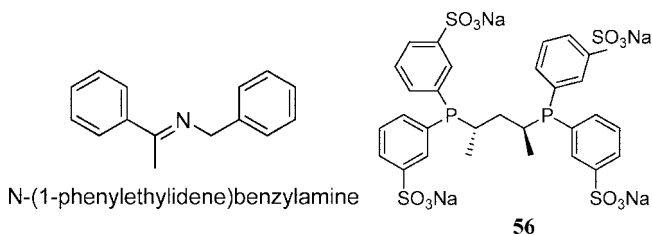
genation of acetoacetates (85.2–99.2% ee) and aromatic ketones (97.4–98.8% ee). This solvent mixture proved to be as efficient as the original solvent used in this transformation providing excellent levels of enantioselectivity. Furthermore, it added the possibility to recycle the homogeneous catalysts employed for five efficient cycles.⁸⁰

Zhang et al. prepared 9-amino(9-deoxy)epiquinine and 9-amino(9-deoxy)epicinchonine to be applied as ligands for iridium- and rhodium-mediated reduction of aromatic ketones in isopropanol. The respective alcohols were obtained in good yields and excellent enantioselectivities (up to 97% ee), and the chiral complex could be quantitatively recovered by extraction with a diluted solution of hydrochloric acid. The recovered catalyst was reused five times with consistent results.¹⁵⁸

This section combines techniques applied in immobilization of catalyst for hydrogenations and hydride reductions of ketones. This reaction has attracted considerable attention during the last 5 years being explored by a many types of techniques, including water-based protocols. However, there are only few contributions using microencapsulation and ion exchange techniques.

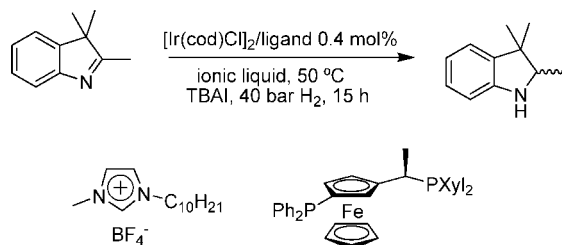
4. Asymmetric Imine Reduction and Hydrogenation

Before 2002, only two works were reported on imine hydrogenation. A hydrosoluble bisphosphine ligand **56** was used to hydrogenate *N*-(1-phenylethylidene)benzylamine in which same levels of enantioselectivity were achieved (63% ee) using this water-soluble ligand compared with the organic-soluble analogue.⁵

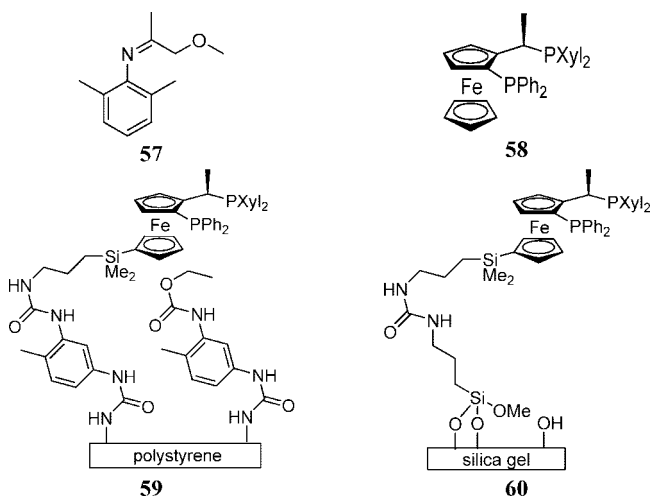


In 2000, Salagre and Fernández showed that the immobilization of the $[Ir(COD)((S,S)\text{-BDPP})]PF_6$ catalyst on montmorillonite and bentonite clays can increase the enantioselectivity in *N*-(1-phenylethylidene)benzylamine hydrogenation reaction (5 atm H_2 and $T = 40$ °C). Curiously, the enantioselectivity also increased upon reutilization.¹⁵⁹

One of the most important herbicides of Syngenta, (*S*)-metolachlor, is produced from a sterically hindered MEA-imine **57** by enantioselective hydrogenation using the Ir-

Scheme 15. Hydrogenation of Trimethyl-indolenine in Ionic Liquid Media

XylylPhos complex **58**. Pugin et al. realized that immobilization of this complex using a functionalized ligand could allow an easy method for catalyst reutilization.¹⁶⁰ The functionalized ligand was attached to silica Grace 332 (catalyst **60**) and aminomethyl-polystyrene resins using a suitable linker (catalyst **59**).

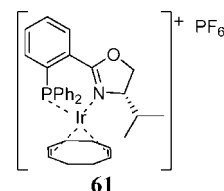


The homogeneous protocol using ligand **58** was found to be very efficient, and the MEA-imine could be reduced at substrate/catalyst ratio as high as 120 000 with TOFs up to 60 000 h^{-1} (80 bar H_2). The enantioselectivity was found to be little affected by the immobilization on silica Grace 332, since a slightly lower ee was observed (78% ee). Unfortunately, the supported catalysts showed much lower reactivity because the TOF did not go over 12 000 h^{-1} (with S/C of 120 000), and it was impossible to reuse the immobilized catalysts. The lower reactivity in the supported catalysts was thought to be due to high local catalyst concentration, which could lead to its deactivation.

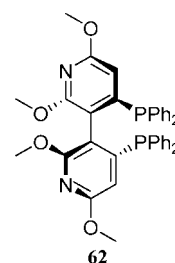
Giernoth and Krumm looked at the scope of application of several room temperature ionic liquids as solvents in the enantioselective trimethyl-indolenine hydrogenation.¹⁶¹ The authors found that applying a preformed catalyst was more beneficial for the reaction success compared with having strictly anaerobic conditions. In fact when $[\text{C}_{10}\text{mim}]\text{BF}_4$ was used, quantitative conversion was achieved with 86% ee (highly comparable with 90% ee obtained in toluene under anaerobic conditions, Scheme 15). The reaction performed in this solvent was conducted at a higher temperature (50 °C) due to the ionic liquid's own viscosity, which allowed the reaction to be faster (15 h).

Leitner et al. performed the *N*-(1-phenylethylidene)aniline hydrogenation in the presence of chiral Ir-oxazolinephosphine catalyst **61** in an ionic liquid/ scCO_2 biphasic mixture.¹⁶² With $[\text{pmim}]\text{PF}_6$ as ionic liquid at 40 °C, 40 atm H_2 , and 0.2 mol % catalyst (formed *in situ*), quantitative conversion was

observed in 22 h with 62% ee. The presence of the ionic liquid improved the catalyst tolerance to molecular oxygen, increasing its lifetime (reused up to seven cycles without efficiency erosion). The scCO_2 was required to drop the ionic liquid density and make the H_2 more available increasing in this way the catalyst activity. The higher affinity of the catalytic system for the ionic liquid phase allowed product extraction using scCO_2 technology without catalyst contamination.

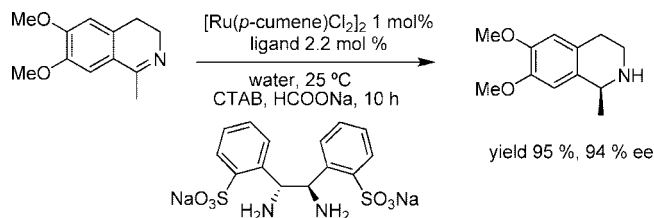


While looking for an air-stable iridium catalyst, Fan and Chan found that a complex with the ligand P-Phos **62** possessed those characteristics.¹⁶³ This catalyst could be prepared *in situ* by joining $[\text{Ir}(\text{cod})\text{Cl}]_2$, (*R*)-P-Phos ligand, and iodide in THF and used to quantitatively hydrogenate quinolines with high enantioselectivities (90–92% ee, 700 psi H_2 , S/C = 200). After this success, the authors made some efforts to develop a protocol where the catalyst could be recycled. The first choices were the immobilization on PEG (MW = 400 Da) and ionic liquids. The catalytic system proved to be much less efficient in those solvents, due to their high polarity. An alternative approach found was the less polar poly(ethylene glycol) dimethyl ether (DMPEG), in which the reaction was carried out with the same levels of efficiency, especially for a biphasic mixture with hexane. After the reaction was completed, the hexane phase could be separated, and the DMPEG phase was reused efficiently after further washings with hexane. The immobilized catalyst was reused seven times without any negative impact on the reaction enantioselectivity. More recently this protocol was extended to other chiral diphosphine ligands.¹⁶⁴

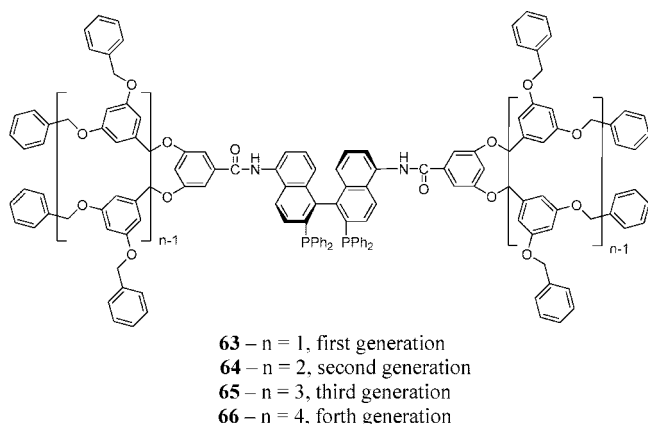


Zhu and Deng showed that Ru-mediated enantioselective reduction of aryl imines could be carried out in aqueous media in the presence of sodium formate.¹⁶⁵ The reaction was run in water with the aid of surfactants in a concentration above the micellar critical concentration, since the formation of micelles was found to enhance the reaction enantioselectivity (CTAB was found to be the most efficient). In this way, a large number of arylimines were quantitatively reduced with excellent enantioselectivity (S/C = 100, generally above 95% ee, Scheme 16).

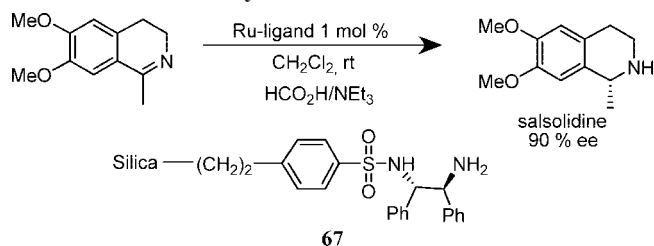
At the end of the reaction, the products were extracted with a diethyl ether/hexane (1/1) mixture leaving the catalyst in the aqueous phase. The catalytic system could be reused over eight consecutive times with consistent 94% ee, though with some yield erosion ($Y_c(8) = 9\%$).

Scheme 16. Reduction of Aromatic Imines in Water/Surfactant Media

Fan et al. tested the dendritic BINAP ligand that they developed in Ir-mediated reduction of quinolines in THF. Second and third generation ligands (ligands **64** and **65**) proved to be more reactive and enantioselective than non-dendritic BINAP (89% vs 71% ee). The presence of iodine as an additive in this reaction proved to be crucial to achieve 43 000 TON and 3450 h⁻¹ TOF (45 atm H₂, S/C = 50 000). The dendritic wedges made the Ir-catalyst more stable and allowed its recovery by precipitation with hexane and reuse with consistent results for at least four runs. Despite the lower activity observed in the fifth cycle, the enantioselectivity did not change.¹⁶⁶



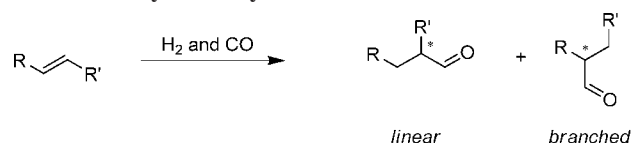
Ying et al. anchored TsDPEN ligand in siliceous meso-cellular foams. The ruthenium catalyst prepared with ligand **67** proved to be the most stable, reactive, and enantioselective (compared with silica gel). Salsolidine, an important precursor of 1-substituted 1,2,3,4-tetrahydro-isoquinoline used for treatment of Parkinson's disease, was reduced with HCOOH/NEt₃ in high yields (95–100%) and consistent 90% ee over six consecutive cycles (Scheme 17).¹⁰⁸

Scheme 17. Reduction of Aromatic Imines in the Presence of Ru–TsDPEN Catalyst Immobilized in Silica

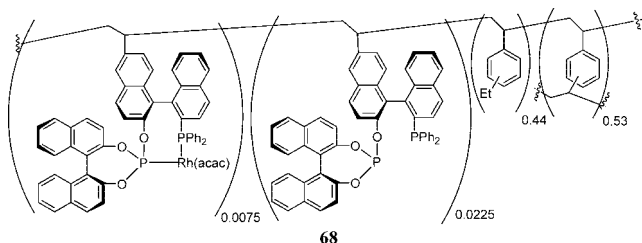
There are several contributions applying homogeneous recoverable catalysts that provided excellent results especially in terms of recyclability. More efforts should be conducted concerning heterogeneous systems.

5. Asymmetric Alkene Hydroformylation

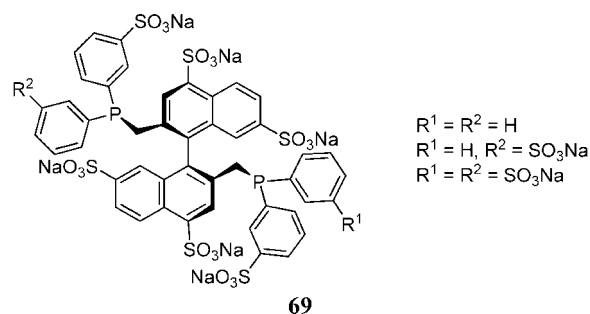
The hydroformylation reaction constitutes one of the most successful organometallic reactions in organic synthesis history. In this transformation an alkene is reacted with molecular hydrogen and carbon monoxide (synthesis gas or syngas) to obtain an aldehyde with high atom economy (Scheme 18). In 1993, Nozaki and co-workers¹⁶⁷ combined an unsymmetrical phosphine–phosphite ligand, (*R,S*)- BI-NAPHOS, and rhodium(I) catalyst to afford chiral aldehydes with excellent enantioselectivities from pro-chiral olefins. Since then, these catalysts, (*R,S*)- BINAPHOS–Rh(I)(acac), became (and still are) the most potent catalysts for asymmetric hydroformylation.

Scheme 18. Hydroformylation Reaction

In the late 1990s, the ligand containing vinyl fragments was synthesized and successfully immobilized on a highly cross-linked polystyrene support and proved to have an excellent performance, without any loss of selectivity (92% ee).⁵ Unfortunately, the immobilized catalyst **68** showed lower catalytic activity than the free catalyst when vinyl acetate was applied (98% vs 54%).

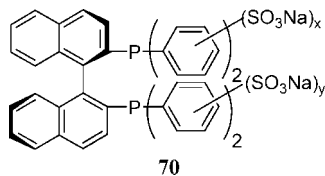


Alternatively, several bisphosphine ligands were derivatized to introduce hydrophilic groups (sulfonic salts) to make them water-soluble, ligand **69**. Several attempts were made, but the enantioselectivity never surpassed 18% ee.



More recently, Yuan et al. observed that a similar bisphosphine ligand **70** bearing the same hydrophilic groups could be reused in vinyl acetate hydroformylation using a toluene/ionic liquid biphasic reaction mixture (ionic liquid used was [bmim]BF₄). The polar groups were essential to retain the complex in the ionic liquid to achieve a successful recovery. In this case, the enantioselectivities observed reached 60% ee, but the conversion was low (<55%).¹⁶⁸

Li et al. immobilized a family of chiral Rh–phosphine ligands in silica to achieve the catalytic system reutilization.



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The authors observed that (*R*)-BINAP ligand induced the highest chiral level for vinyl acetate hydroformylation (72% ee) with 100% selectivity toward the branched isomer, but the conversions were residual (5%). When the phosphine used was the (*S*)-DIOP, an increase in the reactivity (60%) was observed. The catalyst was recovered by centrifugation and reused.¹⁶⁹ More recently, the same authors described a method to prepare Rh nanoparticles stabilized with a phosphine and tetraoctylammonium bromide. Only when triphenylphosphine was applied were conversions of 99% obtained (in the other cases residuals remained).¹⁷⁰

Shibahara and co-workers designed three solvent-free reactors using polymer-supported catalyst **68** fixed on a bed: a vapor-phase batch reactor,¹⁷¹ a continuous vapor-flow column reactor, and a continuous *sc*CO₂-flow column reactor.¹⁷² With the vapor-phase batch reactor, *cis*-2-butene was hydroformylated to (*S*)-2-methylbutanal (syngas 12 atm) in 12 h with a TOF and enantioselectivity of 13 and 79% ee. These results were obtained with liquefied starting materials where the TONs were higher and were comparable to the ones obtained for a homogeneous protocol with unsupported catalyst (TOF of 23 and 82% ee). The rhodium hydride species derived from the catalyst proved to be less stable under this solvent-free vapor phase when compared with the homogeneous protocol, due to changes in the catalyst color.

In order to be used in continuous vapor-flow column reactors, the catalyst was packed 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 aldehyde's strong affinity for the catalyst (9 vs 64).

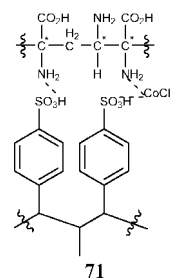
The necessity to obtain a general protocol for hydroformylation of gaseous, liquid, or solid olefins motivated the authors to apply *sc*CO₂ as solvent flow. Styrene was injected portionwise into the column reactor under the flow of syngas and *sc*CO₂, in the following manner: (1) incubation of the catalyst in syngas atmosphere (H₂/CO = 1:1, total 88 or 120 atm) for 15 min, (2) injection of styrene from the injector under the mixed gas flow (total 88 or 120 atm) for 30 min, and (3) sweeping products from the column with higher pressure of *sc*CO₂ flow (120 atm) for 15 min. 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% isaldehyde, 90% conversion, 85% ee, *Y_c*(7) = 11%, and ee_c(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 with a homogeneous procedure.

The major advantage inherent to a heterogeneous apparatus was related to easy catalyst recovery. Adding this advantage to an organic solvent-free protocol offers a greener method for hydroformylation of olefins.

6. Asymmetric Alkene Hydroboration and Hydration

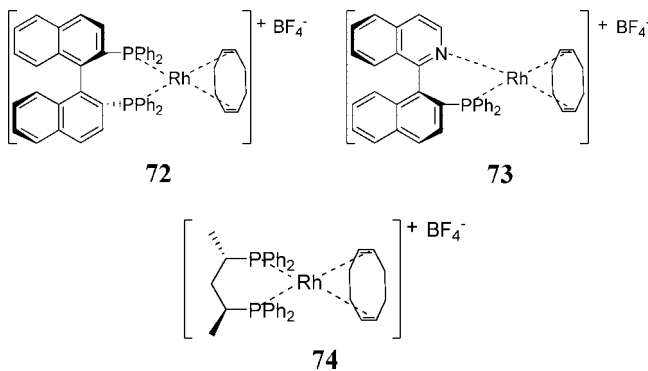
The enantioselective alkene hydroboration reaction catalyzed by extremely expensive Rh–chiral phosphine catalysts constitutes a powerful methodology to functionalize olefins, furnishing a wide range of enantioenriched compounds (alcohols, amines, carboxylic acids, among others). This reaction was not compiled in the previous review.⁵

Zhang et al. prepared a polysulfostyrene–gelatin–cobalt complex (PSS–GE–Co **71**) to catalyze asymmetric hydration of allyl alcohol.¹⁷³ The respective (*S*)-(-)-1,2-propanediol was obtained in 98% yield with 98.9% optical yield under optimal conditions (PSS/GE weight ratio of 4/3, cobalt content of 0.4 mmol/g, 90 °C, and 2 mL of acetic acid for 1 mmol scale). The catalyst was easily recovered by filtration at the end of each run and reused twice without any significant drop of efficiency (*Y_c*(3) = 1% and ee_c(3) = 4%).



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Segarra et al. prepared several heterogeneous asymmetric catalysts for alkene hydroboration by absorbing pure rhodium complexes to smectite clays, montmorillonite K-10 (MK-10) and bentonite (Na⁺-M).¹⁷⁴

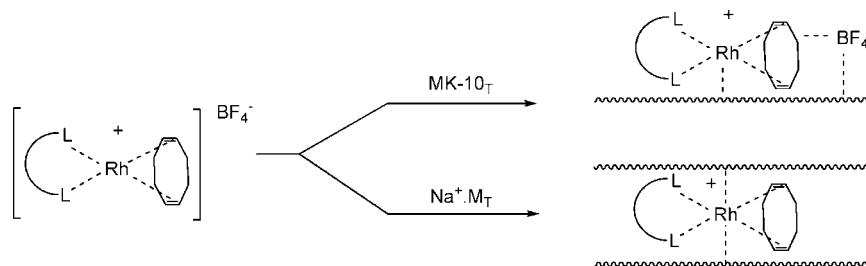


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The mechanism of catalyst immobilization remains unclear, but it was thought to be clearly distinct in these supports. In the case of montmorillonite K-10 (MK-10_T), possible interaction between countercation and counteranion with MK-10_T maybe related to weak electrostatic forces or hydrogen bonding. In the case of bentonite, since the countercation remained in solution, interaction between clay layers and countercation were thought to be responsible by catalyst immobilization (Scheme 19).

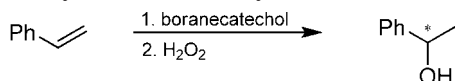
Both supported catalysts were tested for styrene hydroboration using borane–chatecol, but **72**·Na⁺-M_T failed to give the respective asymmetric alcohol with good regio- and enantiocontrol for the first cycle (after oxidative workup, Scheme 20). Curiously in a second cycle the activity increased to moderate levels (94% yield, 63% selectivity, and 35% ee). Meanwhile **72**·MK_T-10 (MK-

Scheme 19. Proposed Immobilization Mechanisms



10 preheated at 100 °C before immobilization) afforded (*R*)-1-phenylethanol in high yield and regioselectivity (96% and 97%, respectively) with moderate 55% ee (values comparable with those obtained with the unsupported catalyst). The catalyst was reused twice without any loss of efficiency.

Scheme 20. Hydroboration of Styrenes



Two less sterically hindered rhodium catalysts, **73** and **74** ($[Rh(cod)(S)-QUINAP]BF_4$ and $[Rh(cod)(S,S)-BDPP]BF_4$, respectively), were also adsorbed into MK_T-10 . While **74**· MK_T-10 failed to give competitive ee values (due to several achiral conformations), **73**· MK_T-10 provided very good enantioselective induction (up to 88% ee) combined with the same efficiency noted for **72**· MK_T-10 . Curiously in the first cycle, modest results were obtained with this catalyst (51% yield, 68% selectivity, and 50% ee), but if the catalyst was submitted to an induction period (by stirring in THF for 2 h), all parameters increased (80% yield, 84% selectivity, and 80% ee). The clay MK_T-10 proved to have preventive actions toward catalyst degradation/oxidation since it could be manipulated in air without any significant loss of efficiency.^{175,176}

Xue et al. used a wool–palladium (II) complex for asymmetric hydration of alkenes.¹⁷⁷ Under optimized conditions (Pd content in wool of 0.1 mmol/g, 1 mol % palladium, 70 °C, N_2 , 24 h, and 0.02 g of oxalic acid), the complex converted 1-octene into the respective *S*-alcohol in 49% yield with 83.2% ee. The catalyst was easily recovered by filtration and reused three times with minimal yield and ee erosion (2%).

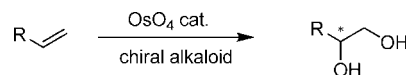
Despite the few reports on immobilized catalysts for alkene hydration/hydroboration, high levels of efficiency were achieved compared with the traditional homogeneous protocols. However, developing systems with better performance is still required.

7. Asymmetric Alkene Dihydroxylation

The osmium-catalyzed asymmetric dihydroxylation (AD) of olefins is a robust methodology to produce a wide range of enantiomerically pure vicinal diols.¹⁷⁸ This transformation became an enantioselective catalysis event when Markó and Sharpless applied *N*-methylmorpholine oxide (NMO) as co-oxidant, allowing osmium tetroxide (OsO_4) and a chiral cinchona alkaloid ligand to be used in catalytic amounts (Scheme 21).¹⁷⁹

Although AD is a very important transformation, it uses expensive reactants (OsO_4 and cinchona alkaloid) and a very toxic and volatile osmium component. A less volatile

Scheme 21. Asymmetric Dihydroxylation Reaction of Alkenes



osmium reactant has been used for AD reactions ($K_2OsO_2(OH)_4$ in place of OsO_4 despite affording diols with lower chemical yield and enantioselectivity. The use of NMO as co-oxidant has the major disadvantage of lowering the enantioselectivity on the diol product if the olefin is not added slowly. On the other hand, if $K_3Fe(CN)_6$ is used as co-oxidant, generally diols are afforded in slightly higher ee's than those obtained with the NMO procedure (with olefin slow addition). Unfortunately in this procedure a large amount of organic salts are used making the reaction mixture too viscous (generally 3 equiv is needed). These issues constitute the main restrictions to the application of AD reactions to a large-scale process. So it became imperative to obtain a simple procedure that would allow the recovery and reuse of the Os ligand with high efficiency and without osmium contamination in the final product. In the past, several methodologies were developed that target this purpose: several groups have investigated the possibility of immobilizing the osmium catalyst by anchoring the ligand to soluble or insoluble polymer matrix or to inorganic solid support (silica) or through microencapsulation or ion exchange techniques.^{5,41}

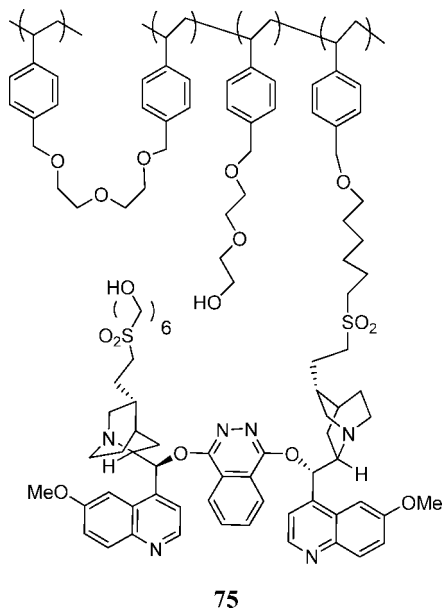
7.1. Heterogeneous Catalysts

Immobilization of cinchona alkaloids on insoluble polymer backbones benefits from a simplified separation by filtration or centrifugation. The methodologies developed were based on copolymerization of a vinyl derivative of a cinchona or bisinchona alkaloids with standard monomers like styrene, divinylbenzene, or acrylonitrile. With this type of catalysts, the AD products were obtained in high yields (above 80%) with excellent ee's (above 90%).⁵

Despite their easy separation, some of these ligands suffer from osmium and ligand leaching problems. In fact, some catalysts have base-sensitive motifs in the spacer unit that are likely to undergo hydrolysis under relatively mild basic conditions, mainly when $K_3Fe(CN)_6$ is used as co-oxidant. In these cases, the supposed heterogeneous catalyst has a soluble ligand species physically trapped in the polymer network, which it is expected would be able to leach appreciably to the solution.

Taking this into consideration, Salvadory et al. developed a method that clears the relationship between the chiral-ligand concentration and enantioselectivity for the AD of two common substrates (styrene and 1-phenylcyclohexene) with UV evaluation of the dissolved ligand and control runs in the filtrate (OsO_4 0.35 mol %, 3 equiv

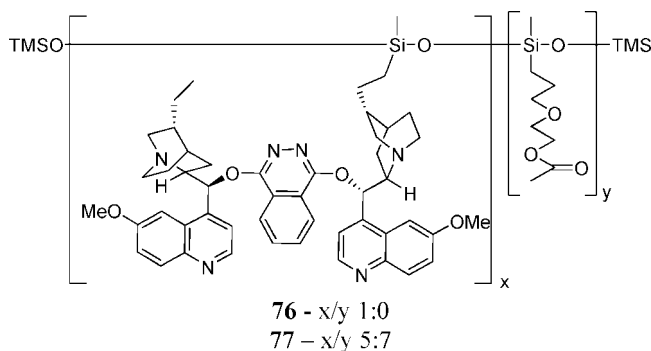
of $\text{K}_3\text{Fe}(\text{CN})_6/\text{K}_2\text{CO}_3$, $0\text{ }^\circ\text{C}$, and $t\text{-BuOH}/\text{H}_2\text{O} = 1:1$). This study showed that for two typical insoluble polymer-bound (IPB) catalysts (grafted on silica or polymeric resins), 4–20% leaching may occur, allowing a homogeneous pathway to occur to some extent. The authors set a 0.5% upper limit to ligand leaching for the IPB derivatives of the phthalazine class, in order to dismiss the possibility of homogeneous catalysis occurring.¹⁸⁰ Salvadori et al. synthesized the supported ligand **75** with a copolymer architecture, which meets the stability requirements to be attested as a truly heterogeneous catalyst (0.3–0.4% leaching).



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 starting material, in the beginning of each new cycle a small amount of OsO_4 (0.35% mol) was added to account losses during the recovery of the ligand. The conversion and optical purity were analyzed at 1.5 h of reaction time. The enantioselectivity fell in the 87–91% range, while the conversion fell in the 72–94% interval during 12 recycles. Interestingly, the conversions under these recycle conditions proved to be comparable to or even higher than those observed in the control experiments (50–71%).

Siegel et al. developed another procedure to immobilize a bis-cinchona alkaloid to a polymer backbone. Following their work with photorefractive polymers, they rationalized that those cinchona alkaloid derivatized polysiloxanes could be an excellent ligand support due to their low solubility under AD conditions. To this matter a modified $(\text{DHQD})_2\text{PHAL}$ ligand was prepared. This ligand can be attached to polysiloxane using standard conditions to provide the monofunctional polymer ligand **76**.¹⁸¹

When ethylene glycol monoallyl ether acetate was used as monomer, a copolymer was obtained granting solubility under AD conditions. When applied to AD reactions, the heterogeneous polymer **76** proved to give comparable or higher yields and ee's than its homogeneous counterpart **77**, despite generally higher reaction times. For example, under the same reactions conditions (OsO_4 1 mol %, ligand 5 mol %, $\text{K}_3\text{Fe}(\text{CN})_6$ 3 equiv, acetone/water 10:1 and $0\text{--}4\text{ }^\circ\text{C}$), *trans*-stilbene was dihydroxylated in 24 h in 98% yield with

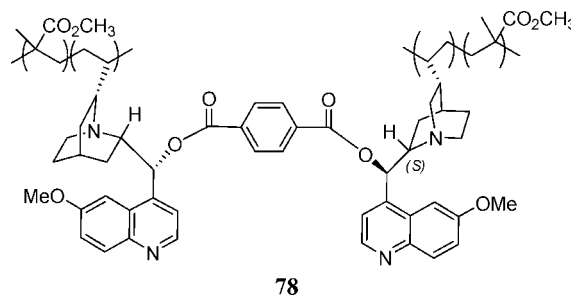


93% ee using the heterogeneous ligand **76**, while when the homogeneous polymer **77** was used, the respective diol was obtained in 21 h in 88% yield and with 83% ee. When NMO was used, the differences between these two ligands were insignificant, and the reaction times lowered to 3 and 2 h, respectively.

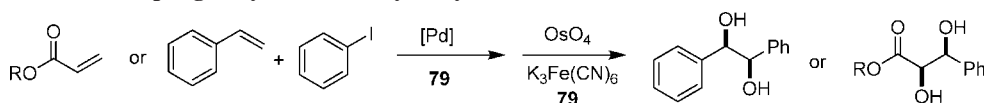
The heterogeneous ligand **76** was easily recovered by a simple filtration and was successfully reused for the AD reaction of *trans*-stilbene ($\text{K}_3\text{Fe}(\text{CN})_6$ as cooxidant) with at least for four runs with no erosion of the excellent activity and selectivity, if it is replenished with a fresh aliquot of catalyst (0.01 equiv of OsO_4 added in each run, $Y_c(4) = 1\%$, $ee_c(4) = 0\%$ with total TON of 367). If no addition is made, a second run only achieves acceptable results after 2 days. The homogeneous catalyst **77** could be recycled as well by precipitation after saturation with water. Unfortunately the recovered ligand did not catalyze a second run if not replenished with fresh OsO_4 (2 weeks is needed to observe formation of some diol from the same substrate using NMO as cooxidant).

Militzer et al. used for the first time chitin as a sole ligand under AD conditions. This biopolymer proved to be very efficient but failed to give enantioenriched diols. An interesting property of chitin relates to its ability to coordinate almost quantitatively all osmium applied on AD. This observation motivated the authors to test several nucleophilic commercial polymers as scavenger polymers for osmium removal.¹⁸²

Cha et al. copolymerized 1,4-bis(9-*O*-quininy)terephthalate monomer in the presence of methacrylate, methylmethacrylate, and acrylonitrile. Once these heterogeneous ligands were tested under dihydroxylation conditions (1 mol % OsO_4 , $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , water/*t*-BuOH 1/1) they showed that the type of copolymer greatly influenced the reaction efficiency. The complex between osmium catalyst and **78** proved to have good recyclability. It maintained a consistent 80% yield for *trans*-stilbene dihydroxylation during six cycles, while the enantioselectivity decreased in the first two reutilizations from 84% to a stable 65% ee.¹⁸³

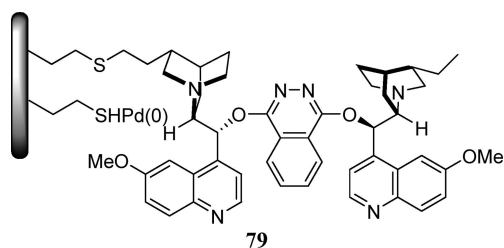


Inorganic solid supports have been used for immobilization of cinchona ligands because they have some advantages over organic polymer-bound matrix. Besides having better me-

Scheme 22. Tandem Heck Coupling—Asymmetric Dihydroxylation Reaction

chanical and thermal properties, they do not need to be carefully designed to perform AD reactions with high efficiency. Before 2002, silica was the preferential inorganic material used for this kind of immobilization. Extraordinarily high yields (up to 97%) and ee's (>99%) were achieved using *trans*-stilbene as starting material; moreover recycling experiments were successful till 6 runs.⁵

More recently, Choudary et al. reported the utilization of catalysts anchored on inorganic supports. They synthesized the bifunctional catalyst **79** for a tandem Heck—asymmetric dihydroxylation procedure. The external surface of silica gel was treated with 3-mercaptopropyl trimethoxysilane to obtain a material with mercaptopropyl ethers. The vinyl alkaloid for asymmetric dihydroxylation could be anchored by reaction with 3-mercaptopropyl moieties in the presence of AIBN in chloroform.¹⁸⁴

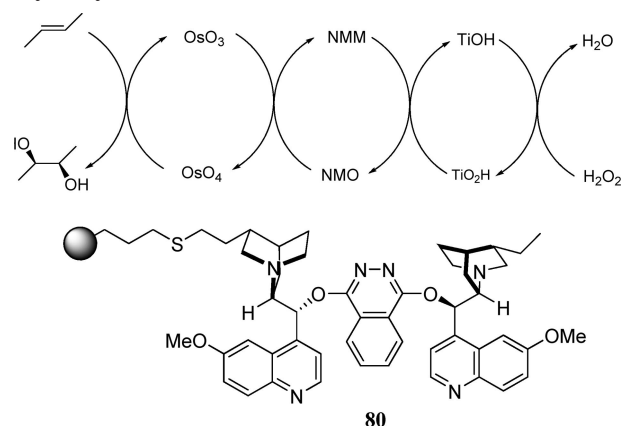


The residual SH groups that did not react with the alkaloid (due to its size), were treated with PdCl₂ in acetone under reflux for 24 h. Finally, the palladium(II) was reduced to elementary metal with hydrazine hydrate in ethanol for 4 h at room temperature to afford **79**. Catalyst **79** was successfully applied in tandem Heck—asymmetric dihydroxylation of aryl iodides and acrylates and styrenes affording diols with comparable or higher chemical yields and enantioselectivity than the ones obtained in the homogeneous procedure (Scheme 22).

The best results were obtained using K₃Fe(CN)₆ as co-oxidant with yields of 90–96% and ee in between 98% and 99% (Os/ligand 1:1, OsO₄ 1 mol %, 12–24 h, 70 °C). When catalyst **79** was reused, it was found that the AD activity dropped (*Y_c*(2) = 29%) due to osmium leaching during the reaction (more OsO₄ was needed to restore first cycle activity) but without changes in the ee. The Et₃N·HI formed in the Heck reaction was found to improve the ee's when NMO was used as co-oxidant (over homogeneous and heterogeneous osmium catalysts), since it accelerates the hydrolysis of osmate ester intermediate. The use of thiol groups for immobilization of palladium reduces the total mass of the bifunctional catalyst, compared with the two heterogeneous catalysts made independently with cinchona alkaloid and Pd.

Bäckvall et al. developed an elegant method for olefin dihydroxylation based on three catalytic cycles.¹⁸⁵ This methodology allows the substitution of expensive stoichiometric NMO by a cheaper terminal oxidant, H₂O₂. The flavin served as an electron transfer mediator (ETM) between the terminal oxidant and NMM, generating NMO *in situ*.

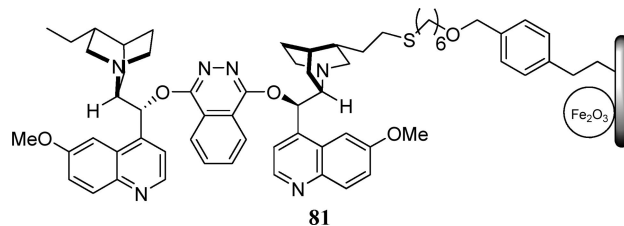
Choudary et al. pointed out that using flavin as ETM constitutes the major limitation of the methodology since it

Scheme 23. Elegant Chain Reaction for Asymmetric Dihydroxylation of Alkenes

cannot be recycled.¹⁸⁶ They substituted flavin by a heterogeneous titanium silicate (TS-1) and anchored the (DHQD)₂PHAL alkaloid ligand to a silica-gel support (SGS, ligand **80**) in order to obtain a recyclable system (Scheme 23).

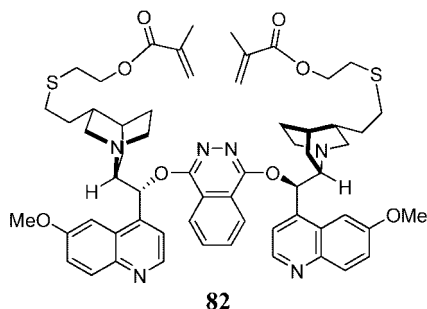
In fact, when the *in situ* generated SGS—(DHQD)₂—PHAL—OsO₄ complex (1 mol %), TS-1 (3.8 mol %), and NMM (5 mol %) were employed in catalytic amounts to the AD reaction of methyl cinnamate in H₂O/*t*-BuOH (3:1), the corresponding diol was afforded in excellent yield (94%) and enantioselectivity (98% ee). This method proved to be very efficient for these kind of olefins (cinnamates) yielding diols with higher enantiomeric excess (>98%) than those reported previously (<98%). The cornerstone to obtain these high enantiomeric excess is related to the slow addition of the terminal oxidant and the olefin (1:1 ligand/osmium tetroxide, 1 mol % of osmium, 12 h at rt). This system could be recycled at least for three cycles with replenishment of 30% of osmium in the beginning of each cycle with low yield (*Y_c*(3) = 2%) and enantioselectivity erosion (ee_c(3) = 2%) providing a total TON of 277.

Lee et al. prepared mesoporous silica foam with ordered mesoporous walls containing magnetic nanoparticles (γ-Fe₂O₃) and (DHQ)₂PHAL ligand grafted in the pore surface (ligand **81**).¹⁸⁷ This ligand was tested for AD reaction using K₃Fe(CN)₆ as co-oxidant (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 end of each reaction to maintain a high level of conversion.



Choudary et al. anchored for the first time (QN)₂PHAL in MCM-41 and used it for the heterogeneous asymmetric dihydroxylation of olefins to afford diols with good to excellent enantiomeric excesses in the presence of NMO, K₃Fe(CN)₆, or oxygen as co-oxidants.¹⁸⁸ However, it was reused once with considerable yield erosion.

Park et al. copolymerized the vinyl alkaloid ligand **82** in the presence of styrene and divinylbenzene. Osmium tetroxide was also encapsulated in the polymer by osmylation of untreated alkene bonds. This catalyst was submitted to dihydroxylation of several olefins with excellent results (quantitative yields, up to 99% ee). It was also reused four times with 18% yield erosion (and increased reaction time) due to osmium leaching.¹⁸⁹



Using catalysts where OsO₄ was heterogenized offers another efficient approach to recycle the catalytic system. The most notable advantage of this methodology is related with the ability to retain all toxic osmium content, without product contamination. In general, all heterogenized osmium provides an osmium font that is not toxic and volatile as OsO₄. Before 2002, there were only two groups that worked in this approach. Kobayashi and co-workers developed several catalysts based on osmium encapsulation within polymer microcapsules.^{5,190} In the initial work, the authors tried to use simple polystyrene as support (PS-MC-OsO₄), but it was found that the yields and selectivities in dihydroxylation reactions as well as recovery of the catalyst were not satisfactory. Furthermore, styrene dissolved such a polymeric support. Poly(acrylonitrile-*co*-butadiene-*co*-styrene) microencapsulated OsO₄ (ABS-MC-OsO₄) and phenoxyethoxystyrene-*co*-styrene microencapsulated OsO₄ (PEM-MC-OsO₄) appeared to solve those limitations.

Choudary et al. used an ion-exchange method to immobilize osmium. Layered double hydroxide (LDH) consisting of alternating cationic M(II)_{1-x}(OH)₂^{x+1} (*x* = 0–1) and anionic A^{m-}·*z*H₂O was chosen as ion exchanger. Both methods afforded diols in excellent yields and with enantioselectivities up to 99%. Choudary et al. also quaternized the surface of Merrifield resin with a tertiary amine to achieve osmium tetroxide immobilization. Aromatic olefins were reacted with excellent 96% ee, but in the third cycle, only 10% conversion was obtained due to osmium leaching.

Recently, Kobayashi et al. used a phenoxyethoxymethyl-polystyrene-microencapsulated OsO₄ catalyst (PEM-MC) for AD of styrene in aqueous media without any success, since the alkaloid ligand had low solubility in water.¹⁹¹ To overcome this problem, the authors added surfactants to the reaction, where it afforded the respective diols in higher yields (up to 80%) and ee (up to 74%). Zwitterionic surfactants tended to coordinate osmium promoting its leaching into the aqueous media (e.g., CH₃(CH₂)₁₁N(CH₃)₂[(CH₂)SO₃]), while nonionic additives like Triton

Table 1. Asymmetric Dihydroxylation Reaction of Styrene with OsO₄ Microencapsulated in Phenoxyethoxymethyl-Polystyrene

run	yield (%)	TON	ee (%)	leaching of Os (%)
1	86	17.2	74	not detected
2	82	16.4	76	not detected
3	83	16.6	75	not detected

Table 2. Asymmetric Dihydroxylation Reaction of Styrene with OsO₄ Microencapsulated in Polystyrene-1% Divinylbenzene

run	yield (%)	TON	ee (%)	leaching of Os (%)
1	81	16.2	78	not detected
2	84	16.8	76	not detected
3	78	15.6	77	not detected
4	86	17.2	74	not detected
5	85	17.0	72	not detected

X-405 showed limited leaching of osmium. When the reaction with Triton X-405 was quenched with aqueous H₂SO₄ (2 N), no leaching was detected (Table 1).

The PEM-MC OsO₄ catalyst could be easily recovered at the end of the reaction upon filtration allowing its reuse. This catalyst could be recycled and reused for at least three cycles with low yield erosion (~3%) and without ee erosion in a total TON of 50 (Table 1). The ligand is not easily recovered like in the water/acetone solvent system. Both poly(acrylonitrile-*co*-butadiene-*co*-styrene) microencapsulated OsO₄ (ABS-MC-OsO₄) and phenoxyethoxystyrene-*co*-styrene microencapsulated OsO₄ (PEM-MC-OsO₄) were found to be soluble in some organic solvents, which could increase the osmium leaching. To overcome this limitation, Kobayashi et al. prepared a DVB cross-linked polymer using suspension polymerization. After impregnation of the resin with OsO₄, an Os energy-dispersive X-ray (EDX) map showed that capsules as small as 10–20 nm were filled with osmium. This cross-linked catalyst proved to be insoluble in several solvents providing a simple method for its recycling. When submitted to AD conditions with styrene, it afforded the respective diol in high yields and ee's (Table 2); furthermore it was reused in five consecutive cycles with the same level of activity and negligible ee erosion (ee_c(5) = 7.7%) with a total TON of 75.¹⁹²

For the AD reaction of 1-phenyl-1-cyclohexene, the yield and ee's were improved using PSresin-MC Os (yield 94% and ee's of 82%) compared with those obtained using PEM-MC OsO₄ as the catalyst (yield 82% and ee's of 26%).

These resins allowed complete retention of OsO₄, which was its major advantage when compared with other methodologies, but it failed to recycle the whole catalytic system (alkaloid ligand). Furthermore it requires higher loads of Os (5 mol %) than a homogeneous system and affords diols in lower yields and enantioselectivities.

Following their work on ion-exchange techniques with double layered hydroxides, Choudary et al. designed a bifunctional catalyst composed of OsO₄⁻–WO₄⁻ for one-pot synthesis of chiral diols via N-oxidation-asymmetric dihydroxylation reaction. This heterogeneous catalyst was

Table 3. Asymmetric Dihydroxylation Reaction with Heterogenized OsO₄

Olefin	K ₂ OsO ₄ ·2H ₂ O-Na ₂ WO ₄ ·2H ₂ O		LDH-OsW	
	Yield (%)	ee (%)	Yield (%)	ee (%)
	92	95	92	96
	93	92	95	93
	92	94	93	96
	87	92	90	93
	91	90	89	91
	85	99	93	99
	82	99	89	99
	91	99	92	99

found to be more active under AD conditions than its homogeneous analogue, providing diols with comparable or even higher yields and ee's (NMM, Table 3). Furthermore, it provided the advantage of easy separation from organic products and uses lower amounts of the chiral alkaloid ligand ((DHQD)₂PHAL as well.¹⁹³

This methodology offers diols with higher yields and ee's than the Kobayashi PSresin-MC Os system. In addition, this system was easily recycled and reused at least for five cycles with minimal loss of activity and enantioselectivity ($Y_e(5) = 2\%$, $ee_e(5) = 0\%$).

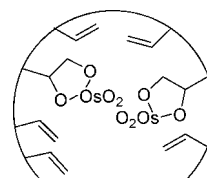
Motivated by these results the authors conceived and developed a trifunctional catalyst based on PdCl₄[−]–OsO₄[−]–WO₄[−] for tandem Heck coupling–N-oxidation–asymmetric dihydroxylation reactions, using the same ion exchange technology. A mixture of iodobenzene, styrene, and NEt₃ in the presence of 1 mol % LDH–PdOsW was stirred without solvent at 70 °C for 8 h. Then, the heating was stopped and a mixture of (DHQD)₂PHAL (1 mol %) and NMM in *t*-BuOH/H₂O (5:1) was added. Subsequently hydrogen peroxide was slowly added over 12 h to afford the desired diol 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 by this way the number of unit operations needed in the process. The success of this kind of catalyst motivated the filing of several patents protecting this technology.^{194–196}

Choudary et al. applied their resins with covalently bonded quaternary ammonium salts with immobilized osmium tetroxide to asymmetrically dihydroxylate aliphatic olefins. This osmium–resin catalyst proved to be very efficient, since it afforded diols with high yields and ee's (Table 4).¹⁹⁷

This study showed that one of the most successful ligands in AD, (DHQD)₂PHAL, gave lower ee's when used instead of (DHQD)₂AQN. As a matter of fact when the amount of ligand was increased by 3-fold in relation to the osmium content, no great change was observed in the enantioselectivity of the diol. This solid catalyst was easily recovered by filtration and could be reused (after replenishment of the chiral ligand) for at least five runs without change in the activity ($Y_e(5) = 2.3\%$) and enantioselectivity ($ee_e(5) = 2.5\%$). Like Choudary's LDH–PdOsW catalyst, this resin was also protected by patents.¹⁹⁸

Table 4. Asymmetric Dihydroxylation of Aliphatic Alkenes with Heterogenized OsO₄

olefin	Yield (%)	ee (%)	Diol config.
	85	82	<i>R,R</i>
	83	80	<i>R,R</i>
	80	74	<i>R,R</i>
	80	70	<i>R,R</i>
	85	84	<i>R,R</i>
	90	75	<i>S,S</i>

Scheme 24. Graphical Scheme of Osmylated Amberlist XAD-4 and XAD-7

Searching for a more efficient heterogeneous catalytic system for AD reactions, Song et al. immobilized osmium on nonionic porous resins such as Amberlist XAD-4 (polystyrene-based resin) and XAD-7 (polyacrylate-based resin) bearing residual vinyl groups by osmylation (Scheme 24).¹⁹⁹

In fact, the resulting osmylated resins proved to be very air-stable, nonvolatile, and much easier to handle than OsO₄. AD reactions ((DHQ)₂PHAL (1 mol %), Amberlite XAD-4·OsO₄ (1 mol %) or Amberlite XAD-7·OsO₄ (1 mol %), K₃Fe(CN)₆/K₂CO₃ (3 equiv), CH₃SO₂NH₂ (1 equiv), *t*-BuOH/H₂O) with mono-, di-, or tri-substituted olefins and cinnamates afforded the respective diols in excellent yield (88–97%) and ee's (88–99%) for both resins. The most fascinating result was observed when styrene was dihydroxylated with XAD-4·OsO₄ yielding the respective diol in 92% with an ee of 95% in 30 min! When the osmium content was reduced to 0.1 mol % (approaching homogeneous AD conditions), the reaction became slower (5–6 h) but retained the overall activity and enantioselectivity. This result constitutes a major step forward in the heterogeneous AD methodology. This catalytic system was easily recycled by simple filtration and could be reused for at least five cycles (with addition of further ligand and XAD-4·OsO₄ (1 mol %)) with low yield erosion ($Y_e(5) = 5\%$) but with some increase in reaction time (from 2 to 24 h for fifth cycle). When the recycle experiments were performed under pseudohomogenous conditions (XAD-7·OsO₄ 0.2 mol %) at the third cycle a major drop in the activity was observed ($Y_e(3) = 25\%$), but the total TON observed reached 1325 (accounting with the less efficient third run).

More recently, Song et al. improved the efficiency of these later protocols by using the same type of resin bearing not only residual vinyl groups but also quaternary ammonium moieties.²⁰⁰ In fact, this resin became more efficient, suffering from less osmium leaching providing faster reactions. Therefore, it could be reused five times with the same outcome. The ligand was also recycled by acid/base extractions.

Janda et al. conceived that osmium tetroxide could be immobilized in an ionic polymer by means of electrostatic forces. For this purpose, ionic polymers were prepared by the reaction of poly(4-vinylpyridine/styrene) with distinct pyridine content (10, 20, 30, and 50 pyridines per styrene unit) by

Table 5. Asymmetric Dihydroxylation Reaction Catalyzed by OsO₄ Immobilized in Quaternized Poly(4-vinylpyridine/styrene) Polymers

olefin	yield (%)	ee (%)
styrene	97	88
4-methoxystyrene	88	99
<i>trans</i> -stilbene	96	98
<i>trans</i> -4-stilbene carboxaldehyde	99	97
methyl- <i>trans</i> -cinnamate	89	99

quaternization with tri(ethylene glycol) monomesylate monomethyl ether (MsO-PEG₃-OMe). The mesilate anion was substituted by BF₄[−] by treatment with NH₄BF₄. Then osmium could be immobilized in this polymeric matrix by shaking a suspension of OsO₄ with an ionic polymer solution in water/acetonitrile (0.19 mmol of osmium per gram of catalyst).²⁰¹

With the most efficient resin ([³⁰P/S-PEG₃][BF₄][OsO₄]) under AD conditions (olefins (1 mmol), catalyst (2 mol %), (DHQD)₂PHAL (3 mol %), NMO (1.5 mmol) and 6–24 h at room temperature), typical olefins were dihydroxylated to the respective diol in high yields and ee's (Table 5).

This resin could be easily recovered by filtration and successfully reused at least four times for AD reaction with *trans*-stilbene-4-carboxaldehyde (additional ligand was needed) with high conversion (99%) and high enantioselectivity (96%) in a total TON of 247. It should be noted that the activity dropped consecutively during several runs due to osmium leaching. This had a major consequence on the increase of reaction time to achieve full conversion in consecutive cycles. In fact, in the filtrates of several cycles, the authors found small amounts of osmium (~4%).






Another interesting alternative for heterogeneous AD with heterogenized osmium tetroxide was developed by Miao et al.²⁰² They prepared a wool–osmium tetroxide complex by slowly heating a solution of OsO₄ in *t*-BuOH with well-washed wool till the temperature reached 60 °C (24 h and under N₂ atmosphere). When this natural biopolymer complex was tested for AD of allylamine (wool–OsO₄ 1 mol %, K₃Fe(CN)₆ (3 equiv), K₂CO₃ (3 equiv), *t*-BuOH/H₂O 1.1), it afforded the respective diol in 80.2% yield with 83.7% ee. It should be noted that no chiral alkaloid ligand was used. This catalyst could be reused for three runs without activity lost (*Y*_c(3) = 0.2%) and with stable ee's (ee_c(3) = 1.9%) for a total TON of 240.

Caps et al. reported the heterogenization of Os₃(CO)₁₂ on the internal surface of Al-MCM-41 using simple chemical vapor deposition.²⁰³ This catalyst was used to dihydroxylate *trans*-stilbene in good yields (64–80%) with enantioselectivity up to 90%, without using any chiral ligand. However, in a second cycle, it experienced some deactivation.

Venkateswarlu et al. microencapsulated osmium tetroxide inside a polysulfone polymer.²⁰⁴ This catalyst was successfully tested in AD reaction of aromatic and aliphatic olefins in excellent yields and ee's (>89% ee) with a fast protocol (30 min). The resin could be recovered by filtration and reused up to five cycles with only 8% yield erosion (and constant enantioselectivity).

Dehury and Hariharakrishnan heterogenized osmium tetroxide in chlorapatite by anion exchange. The heterogenization did not prove to be selectively detrimental since several aromatic and electron-poor olefins were oxidized to the respective diols with high enantioselectivity (>90%) in good to excellent yields (71–96%). Furthermore, both osmium salts and chiral alkaloid ligand ((DHQD)₂PHAL) could be recovered and reused four times with efficiency.²⁰⁵

Table 6. Asymmetric dihydroxylation reaction with QN-AQN ligand anchored to PEG

Olefin	T (°C)	t (h)	Yield (%)	ee (%)
	0	19	89	91
	0	24	90	93
	0	24	92	95
	0	17	92	80
	rt	24	80	92

7.2. Homogeneous Catalysts

One of the major advantages of soluble polymer-bound catalyst resides in the absence of diffusion problems of the reactants, which traditionally characterizes heterogeneous systems. This issue is experimentally observed by the increase of the reaction time for the heterogeneous systems.

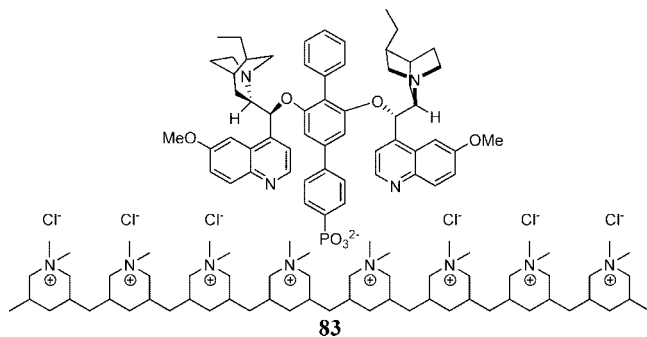
Before 2002, homogeneous systems using soluble polymer catalysts were based on chemical immobilization of cinchona alkaloids to a poly(ethylene glycol) chain (PEG) with distinct spacers.⁵ One of the best results was obtained by Bolm and Gerlach using a DHQD ligand attached to MeO-PEG via an aryl spacer (linked to PYR segment). They successfully dihydroxylated several vinylic and aliphatic olefins in high yields and high ee's, 95–99% and 87–90% ee, respectively. This system was reused six times without a detrimental change to its enantioselectivity (ee_c(6) = 2%).

This section should account for all the cases where the alkaloid ligand was covalently bound to a polymer chain (as before 2002) and where it is attached to the polymer matrix by physical interactions.

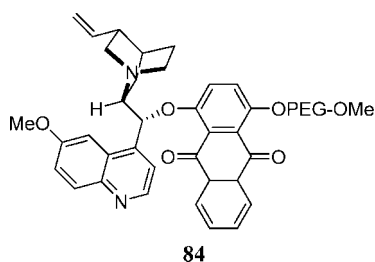
Chandrasekhar et al. used PEG (MW 400) as unique solvent under AD conditions (OsO₄ 0.5 mol %, (DHQD)₂PHAL 2 mol %, and NMO 1.3 equiv). They obtained the respective diol from *trans*-stilbene in only 2 h with an excellent yield (95%) and ee (94%). The product was removed with ether in an extraction procedure, after which the PEG phase could be reused five times without any significant decrease in activity (*Y*_c(5) = 4.2%) and enantioselectivity (ee_c(5) = 4.2%) in a total TON of 922. Additional (DHQD)₂PHAL was added in the beginning of each recycle preventing a drop of 30% of the ee during five cycles.²⁰⁶

Zhang et al. tried to perform AD reactions in the same conditions using the same PEG as sole solvent and a zwitterionic ligand **87**; they failed to obtain competitive ee's. To improve the enantioselectivity (to equal levels), olefins were added slowly during 10 h, and the reaction was performed using PEG as a cosolvent in an acetone–water (10:1) mixture. For this procedure, both osmium and ligand were successfully reused for five cycles with minimal loss of activity (*Y*_c(5) = 11%) and enantioselectivity (ee_c(5) = 7.3%) with a total TON of 830.²⁰⁷

Another interesting approach for immobilization of the chiral alkaloid ligand was developed by Miltizer et al.. They rationalized that once they attached an ionizable functional group at (DHQD)₂PHAL, it could be anchored by means of electrostatic forces to a polyelectrolyte matrix.¹⁸² Unfortunately when this ligand **83** was applied to AD reactions, using NaOCl as co-oxidant, with slight variations of pH (basic), it afforded the respective diol with low enantioselectivity. Perhaps the presence of such long-chained ionic polymers interferes with the enantioselection step in the dihydroxylation cycle probably by strong dipolar interactions.

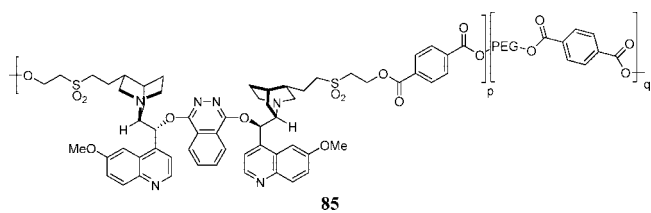


More recently Zhang et al. synthesized a novel polymer-bound alkaloid ligand QN-AQN-OPEG-OMe **84** and successfully applied it to AD on several olefins giving diols with high yields and higher ee's than the corresponding system in which the free ligand was used, (QN)₂AQN (catalyst 10 mol %, K₂OsO₂(OH)₄ 0.4 mol %, K₃Fe(CN)₆ and K₂CO₃ 3 equiv, *t*-BuOH/H₂O 1:1, Table 6).²⁰⁸



Under AD conditions (*t*-BuOH/water 1:1), the catalyst was totally soluble, and when the reaction was finished, the catalyst could be extracted with dichloromethane and then precipitated with ethyl ether (97% recovery). Despite the addition of 40% of the initial amount of K₂OsO₂(OH)₄ in the beginning of each recycle, the catalytic system was successfully recycled in asymmetric dihydroxylation of 4-chlorostyrene for five runs with no reduction of activity or enantioselectivity (*Y*_c(5) = 1% and ee_c(5) = 1% providing a total TON of 1162).

Zhang et al. reported the immobilization of cinchona alkaloids in PEG-4000 (MW = 4000) instead of PEG-OMe. The ligand **85** was recovered always in good yields (95%) and reused four times without changes in the activity (high yields up to 87%, up to 99% ee).²⁰⁹



7.3. Alternative Reaction Media

In the last four years, another method for recycling the catalytic system of AD reactions has emerged. This method is based on greater affinity of the alkaloid–OsO₄ complex for the room temperature ionic liquids (RTILs) phase. This affinity allows the extraction of the AD product with low osmium contamination using solvents immiscible with the RTIL phase. The leach of osmium occurs always when the complex has some solubility in the solvent used for extraction.

Table 7. Comparative Dihydroxylation Reactions Run in Different Reaction Media

Olefin	Ligand	<i>t</i> -BuOH/H ₂ O		RTIL/H ₂ O		RTIL/ <i>t</i> -BuOH/H ₂ O	
		Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)
	PHAL	88	97	87	62	86	94
	PYR	91	93	86	75	90	89
	PHAL	83	92	80	66	85	84
	PYR	95	77	77	71	97	80
	PHAL	92	90	71	90	88	89
	PYR	93	94	96	90	96	91
	PHAL	91	87	47	92	53	87
	PYR	63	90	66	86	57	83
	PHAL	89	96	87	98	92	99
	PYR	94	87	81	96	79	77
	PHAL	94	94	69	87	96	92
	PYR	79	75	52	63	92	96

Afonso et al. 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/H₂O system and a monophasic RTIL/H₂O/*t*-BuOH system, using two different ligands ((DHQD)₂PHAL and (DHQD)₂PYR). With [bmim]PF₆, both systems gave similar or even higher results compared with the traditional *t*-BuOH/H₂O system (K₂OsO₂(OH)₄ (0.5 mol %), (DHQD)₂PYR/PHAL (1 mol %), K₃Fe(CN)₆ (3 equiv), solvent, room temperature during 24 h, Table 7).²¹⁰

Once again the use of K₂OsO₂(OH)₄ as oxidant proved to be less efficient, affording diols with lower chemical yield and ee's than OsO₄. But the authors believe that this decrease was well compensated by using a less toxic oxidant.

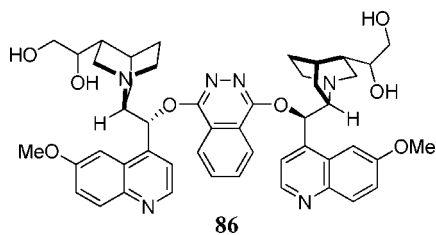
Both systems could be easily recycled as the products were extracted with diethyl ether. The biphasic system was efficiently reused for nine runs without loss of activity and enantioselectivity (*Y*_c(9) = 10%, ee_c(9) = 4%, and total TON = 1334), while the monophasic system proved to be a little more robust since it was successfully recycled 10 times (*Y*_c(10) = 12.5%, ee_c(10) = 9%, and total TON = 1720) affording higher yields. In all assays, the osmium content on the extracted phase was analyzed being on average under 4% from its initial amount (0.5 mol %). After a more intensive study, all reaction parameters were evaluated (e.g., solvent system, co-oxidant, and extraction solvent), and the authors concluded the following:

For a biphasic system, the best solvent is a mixture of [bmim]PF₆ and H₂O (1:2); using NMO as a co-oxidant provides higher yields and ee's compared with K₃Fe(CN)₆ with a contamination level under 2%.

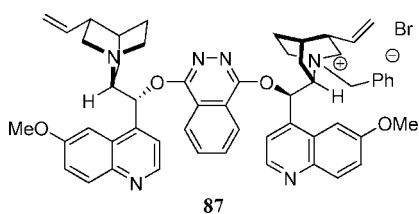
For a monophasic system, the best solvent is a mixture of [bmim]PF₆, H₂O, and *t*-BuOH (1:1:2); K₃Fe(CN)₆ proved to be more advantageous than NMO despite having a higher contamination level (~4%). In general for both systems, the optimum reaction temperature occurs between 25 and 40 °C.²¹¹

Using (DHQ)₂PHAL as ligand and [bmim]PF₆ as RTIL, Song et al. obtained similar results as those reported by Afonso et al. But in this case, the solvent system used was acetone/H₂O, 10:1, in which the RTIL is dissolved. When Song et al. submitted their system to recycling assays, they found out that a large amount of osmium was partitioned to the ether phase. To solve this problem, they realized that using an alkaloid with higher polarity would decrease osmium leaching. So they used (QN)₂PHAL as ligand (5 equiv in relation to OsO₄), which was dihydroxylated during the reaction to a more polar ligand **86**.²¹²

This catalytic system (NMO 1.5 equiv, OsO₄ 1 mol %, ligand 5 mol %, olefin slow addition for 12 h) could be



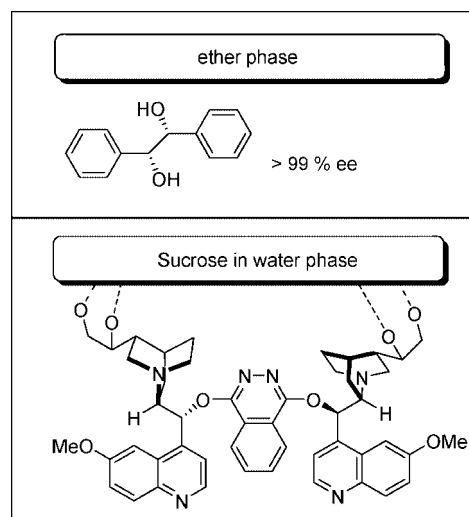
reused at least for three runs with high efficiency for *trans*-stilbene dihydroxylation (92% yield, 98–94% ee, $Y_c(3) = 1\%$, and $ee_c(3) = 4\%$). When OsO_4 content was reduced from 1 to 0.1 mol %, the system became less effective but still could be used for three runs in a total TON of 2370 (in the third run, the diol was only obtained with 58% yield). Improvements to this system were published recently by Song and Park using $(\text{QD})_2\text{PHAL}$ allyl bromide salt, where the recyclability reached five efficient cycles (with 0.1 mol % of OsO_4 in *t*-BuOH/water).²¹³ The same results were observed by Sheldon et al. when they studied the effect of the chiral alkaloid ligand on the catalytic system recyclability.²¹⁴ Like Song, Zhang et al. prepared and used a quaternary salt of the alkaloid ligand **87** to minimize osmium contamination to 2 mol % of total osmium tetroxide.²⁰⁷ This catalytic system was recycled four times with 12% erosion of yield and enantioselectivity (86%, 95% ee). The quaternization of the tertiary amine was not detrimental for the enantioselectivity.



This system was clearly improved in terms of recyclability when osmium leaching was stopped by using also a tetraalkylammonium TentaGel resin (also in ionic liquid phase). Up to 10 cycles of reutilization were conducted in which only 15% of efficiency was lost.²¹⁵

Afonso et al. explored an interesting property of RTILs to minimize osmium contamination in their procedures.²¹⁶ It is known that RTILs are not soluble in supercritical carbon dioxide ($sc\text{CO}_2$), but the last is very soluble in RTILs. This property allows $sc\text{CO}_2$ to be used as extraction solvent, and in addition, RTIL could be used as sole solvent for AD reactions. The extraction was realized using 120 cm³ of $sc\text{CO}_2$ at 100 bar (CO_2 pressure) in a 0.5 mmol scale. By this new procedure, the catalytic system could be recycled eight times with osmium contamination under 0.6%. Unfortunately, the erosion of yields and ee's was higher than when using diethyl ether as extraction solvent. It is known that the solvent power of $sc\text{CO}_2$ varies with its density (the solvent power follows the density of $sc\text{CO}_2$) and could be improved by changing operating pressure. For example, the diol product from AD reaction on methyl *trans*-cinnamate is more polar than 1,2-hexanediol; therefore higher extraction pressure was required.²¹⁷ With $[\text{C}_8\text{mim}]\text{PF}_6$ as unique solvent, methyl *trans*-cinnamate was dihydroxylated for six cycles using MNO as co-oxidant (run 1, 91% yield and 77% ee; run 6, 85% yield and 84% ee). At the end of each cycle, the products of AD reactions were extracted with $sc\text{CO}_2$ at 125 bar.

Scheme 25. Catalytic System Recycling Mechanism

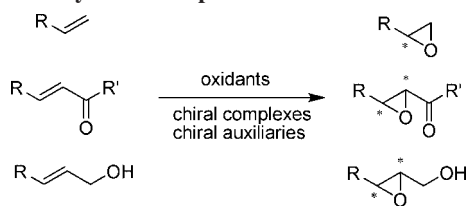


As mentioned, in this procedure the RTIL was the unique solvent used; besides the easy recovery of the products by the described method, the authors observed another interesting advantage. If the olefins were added at once to the RTIL phase, a second phase was initially observed due to low solubility of the starting material in the RTIL. This second phase disappeared slowly during the reaction acting as a slow addition protocol affording diols with high optical purity (above 90%) using NMO as co-oxidant.

Song et al. developed a simple method to achieve both ligand $(\text{QN})_2\text{PHAL}$ and osmium tetroxide recycle without aid of any solid or polymeric support nor with the use of alternative reaction media like ionic liquids or perfluorophases.²¹⁸ In a simple and traditional homogeneous protocol, sucrose was added to the reaction media prior to the AD reaction. At the end, the AD product could be extracted solely to an ether phase, while the ligand and osmium were retained in the water phase. This retention was due to hydrogen bonding between the ligand and the sucrose (Scheme 25). It should be remembered that the applied ligand also undergoes AD becoming 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.²¹⁹ At the end of the reaction, osmium tetroxide was mainly in the organic phase (as neutral OsO_4) due to the large excess of co-oxidant employed. Addition of a low-weight olefin-like ethyl vinyl ether brings back the reduced species (OsO_4^{2-}) to the aqueous phase, which will be retained when all co-oxidant 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.

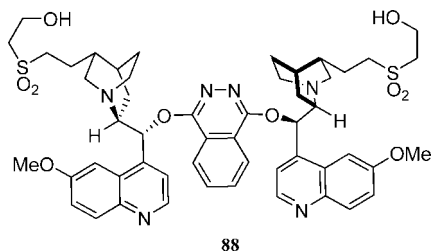
Ferreira and Crespo showed that nanofiltration can be used to achieve the recycling of the asymmetric dihydroxylation catalytic system in acetone/water solvent system. A total TON of 334 over six consecutive cycles was obtained in 1-hexene dihydroxylation ($\text{K}_2\text{OsO}_2(\text{OH})_4$ 0.8 mol %, $(\text{DHQD})_2\text{PHAL}$ 3.5 mol %, 71% ee).²²⁰ Recently, the authors tested the nanofiltration technology in this reaction using a water/surfactant as reaction media, in the absence of organic solvents.²²¹

Scheme 26. Asymmetric Epoxidation Reaction**7.4. Asymmetric Alkene Aminohydroxylation**

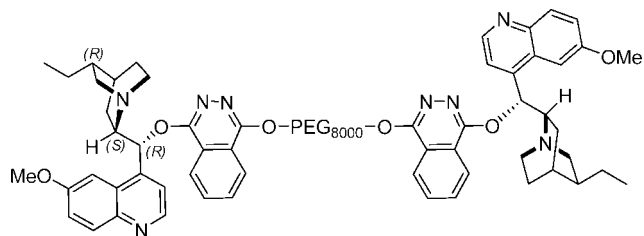
Song et al. applied their osmylated resins, XAD-4 (Scheme 24), in asymmetric aminohydroxylation (AA) of olefins (4 mol % catalyst, 5 mol % ligand, AcNHBr, and LiOH). Excellent enantioselectivities (>99% ee) were achieved for *trans*-cinnamates in quantitative yields. Both resin and ligand were recycled up to three cycles with unchanged enantioselectivity and 22% yield decrease.²²²

In parallel, Choudary et al. also applied their LDH-supported osmium tetroxide in an asymmetric aminohydroxylation reaction, but lower yields (<55%) and ee's (<78% ee) were observed. Recycle assays immediately showed a decrease in activity.²²³

Zhang et al. prepared the monomeric alkaloid ligand [QN(SO₂CH₂CH₂OH)₂]₂PYDZ, **88**, and showed that it could be recovered quantitatively (together with half-quantity of osmium catalyst) after addition of PEG to the reaction mixture (asymmetric aminohydroxylation of isopropyl *trans*-cinnamate). This method was used to recycle the catalytic system up to six cycles (96% ee, 20% yield erosion).²²⁴

**88**

Xu and Lin developed a methodology to prepare a family of new PEG-bound bicinchona alkaloid ligands. This new family was evaluated on cinnamic ester aminohydroxylation in order to understand the ideal polymer length. The ligand that had the biggest polymeric chain (PEG₈₀₀₀, ligand **89**) behaved better in terms of efficiency (90% yield, 99% ee) and allowed the capture of osmium during the recycling procedure (precipitation upon addition of ethyl ether). Despite decreasing reactivity in each run the recyclability achieved five cycles.²²⁵

**89**

In the past years, some of the methods for AD reactions already afforded diols with excellent yields and enantiopurity. In this way, AD studies became more focused on method optimization, where both osmium and ligand can be ef-

ficiently recovered and reused. That is measured not only in terms of a large number of successful recycles but also in lowering the loading of the catalyst systems. In contrast, less extended approaches have been reported for the parent AA reaction.

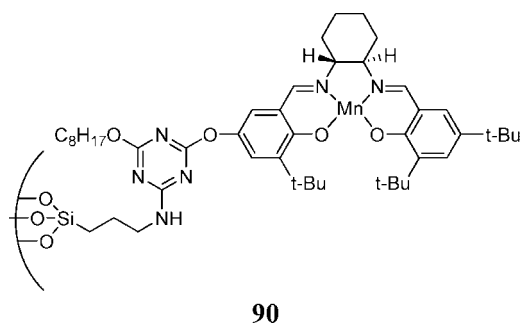
8. Asymmetric Alkene Epoxidation

The asymmetric epoxidation reaction constitutes a powerful tool to functionalize a large range of olefins (Scheme 26). Several efforts were made to substitute the traditional oxidizing agents with greener options such as molecular oxygen or hydrogen peroxide. Along with Sharpless,²²⁶ Jacobsen,²²⁷ Juliá-Colonna^{228,229} systems and other Lewis acid-based BINOL catalysts³⁹ have a crucial role in this synthetic methodology.

8.1. Heterogeneous Catalysts

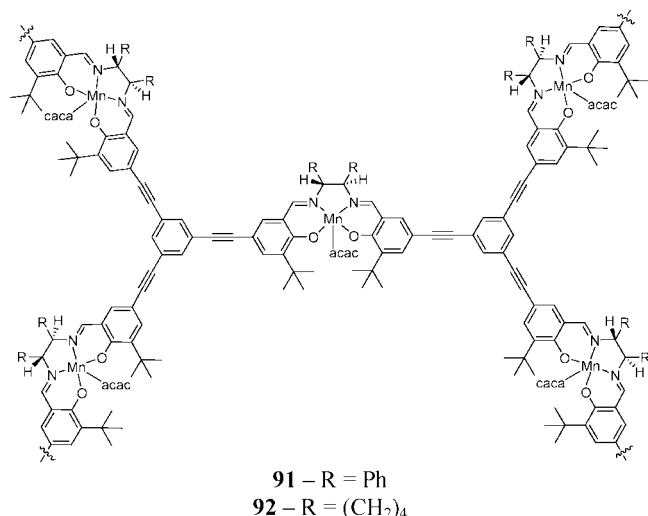
Before 2002, several works were reported for Mn–salen immobilization on insoluble polymers. Grafted catalysts tended to function better than copolymerized vinyl–Mn–salen catalysts providing enantioselectivities competitive with original Mn–salen catalyst. In the previous review, the immobilization of chiral Mn–salen catalyst was performed using two strategies: immobilization inside zeolites and immobilization on the surface of silica. Using the first methodology, the best ee value obtained was 88% for β -methylstyrene epoxidation. In the latter methodology, catalyst **90** provided good results in terms of enantioselectivities (up to 82% ee) and recyclability.⁵

Gothelf et al. synthesized a new type of highly cross-linked polymer having locally ordered domains by condensation of a rigid trialdehyde with chiral ethylene diamine.²³⁰ Manganese complexation to the ligands completed the synthesis of polymer containing Mn–salen complexes. Epoxidation of

**90**

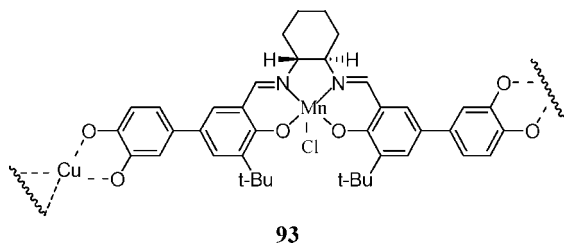
cis-2-methylstyrene with *m*-CPBA (2 equiv) and NMO (5 equiv) in dichloromethane at 0 °C was chosen to test the efficiency of the prepared catalyst (0.5 mol % loading).

Catalyst **91**, R = Ph, proved to be the most reactive (73% conversion), stereoselective (*cis/trans* ratio = 12), and enantioselective (57% ee for *cis* isomer). The homogeneous complex has more tendency to furnish the *trans* isomer (*cis/trans* ratio = 0.46) with higher ee (93%). When both catalysts were reused a nonlinear variation behavior was observed for all parameters (conversion, selectivity, and ee). From the first to the second cycle, a decrease was observed for all parameters, but in the subsequent cycles all parameters increased (in some cases above the first run values).



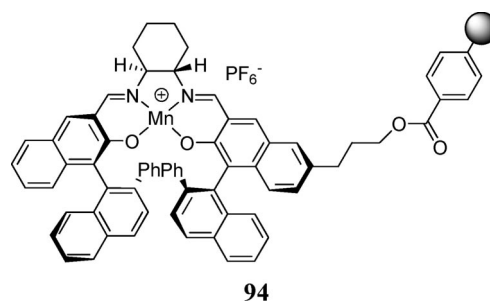
Hupp et al. synthesized a microporous metal–organic framework in the shape of a paddle-wheel from a dipyrilid–Mn–salen complex, zinc ions, and a second ligand (biphenyldicarboxylate) with a molecular formula $\text{Zn}_2(\text{bpdc})_2 \cdot \text{L} \cdot 10\text{DMF} \cdot 8\text{H}_2\text{O}$.²³¹ This catalyst proved to be very stable providing an easy method for Mn–salen recovery and recycling since it is insoluble. The 1,1-dimethyl-2*H*-chromene was epoxidized with yield (71%) and enantioselectivity (82% ee) comparable to the homogeneous analogue and was reused twice with minimal yield erosion (constant ee). The reaction occurs mainly inside the framework channels offering some degree of size selectivity.

Nguyen and Hupp prepared a coordination polymer by reaction of a [bis(catechol)salen]Mn(III) complex with several di- and trivalent metal ions (Cu, Mn, Cd, Mg, Cr, Zn, Fe, and Ni). The polymer prepared with copper was found to be insoluble in several organic solvents and proved to be a good heterogeneous catalyst to perform the asymmetric epoxidation of 2,2-dimethyl-2*H*-chromene with 2-(tert-butylsulfonyl)iodosylbenzene (79% yield, 76% ee). The catalyst **93** could be reused during 10 cycles with minimal yield erosion (10%) and constant enantioselectivity.²³²

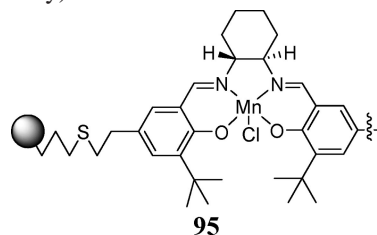


Smith et al. grafted a Katsuki-type catalyst on a functionalized polystyrene polymer via an ester linkage.²³³ Immobilization did not affect the enantioselectivity of 1,2-dihydronaphthalene epoxidation (94% ee) but the reactivity decreased considerably. While reactions with homogeneous catalyst were finished after 7.5 h, the polymeric catalyst **94** never furnished yields above 70% in less than 48 h. The recycling protocol was not easy due to some extent of polymer loss due to technical difficulties requiring reactant recalculations on going from run to run. Gladly it gave consistent enantioselectivity during six cycles. In 2004, the authors performed the asymmetric epoxidation of dihydronaphthalene in the presence of original Mn–Katsuki-type salen catalyst in ionic liquid media ([bmim]PF₆, 2.5 mol %,

93% ee). The ionic liquid phase bearing the catalyst was reused eight times ($Y_e(9) = 25\%$, $ee_e(9) = 13\%$).²³⁴

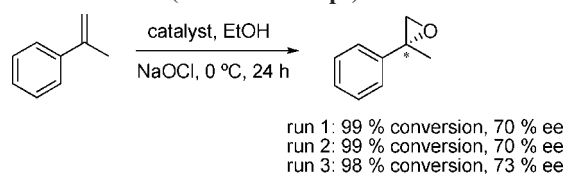


Heckel and Seebach immobilized Mn–salen complex in a pore-controlled glass silica gel support, and its efficiency was tested for styrene epoxidation (20 mol %) with *m*-CPBA/NMO in dichloromethane in 30 min at -20°C .²³⁵ Catalyst **95** proved to be virtually as efficient as the Jacobsen catalyst, furnishing the respective epoxide in 95% yield with 74% ee. The catalyst could be recovered by filtration and reused up to five cycles with some yield and ee erosion (31% and 6%, respectively).



Li et al. grafted phenolic groups on the mesoporous surface of siliceous MCM-41 heterogeneous support.^{236,237} The chiral Mn–salen complex was then anchored into this 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). When the reactions were run with EtOH as solvent and NaOCl as oxidant at 0°C , quantitative conversions (99%) were accomplished (Scheme 27).

Scheme 27. Recycling of Mn–Salen Catalyst Anchored in Modified MCM-41 (Phenolic Groups)

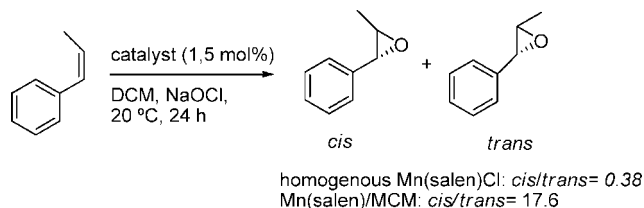


Interestingly, alkenes that do not fit inside the cavities (like 1-phenylcyclohexene) were not epoxidized; a proof that all Mn–salen complexes were strongly anchored and behaved like a heterogeneous catalyst. The catalyst was reused three times without any loss of activity and enantioselectivity.

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).^{238,239} Once again those groups were used to axially coordinate Mn–salen complexes like the phenoxy groups previously reported. Despite all epoxidation reactions of α -methylstyrene furnishing lower yields, under heterogeneous conditions the enantioselectivity remained higher than those observed in the homogeneous protocol (homogeneous catalyst gave

55% ee, supported Mn–salen–MCM-41 and Mn–salen–silica catalysts gave 78% and 76% ee, respectively). When 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 a homogeneous environment to small-sized pores, the *cis*/*trans* ratio changed from 0.38 to 17.6 (Scheme 28). 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.

Scheme 28. “Pore Effect” in the Selectivity of *cis*- β -Methylstyrene Epoxidation

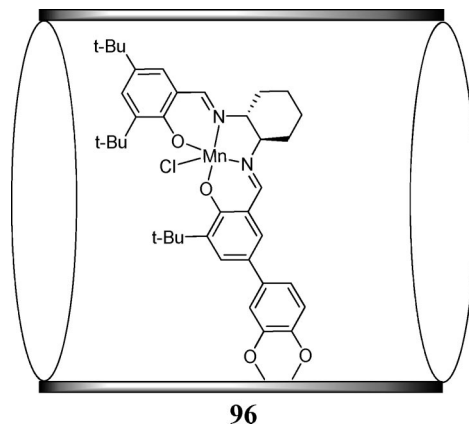


The sulfonic and phenoxy groups were also prepared in the surface of highly cross-linked polystyrene resins.²⁴⁰ These new catalysts proved to be easier to handle than the silica-based ones, providing the same results.

The authors disclosed that the presence of a phenol ligand axially coordinated to homogeneous Mn–salen did not improve the reaction enantioselectivity and that the catalysts immobilized inside nanopores tended to give higher enantioselectivities than those anchored on the external surface.²⁴¹ A possible explanation was related to the unique spatial environment constituted by the axial bulkiness and rigidity of the ligand and by the reaction taking place inside a confined space (in the nanopore). It was also reasoned that the inversion on the *cis*- β -methylstyrene epoxidation selectivity was due to affected rotation motions necessary to achieve the *trans* transition state caused by the lack of space inside the nanopore. Kureshy et al. used MCM-41 silica functionalized with *N*-oxide groups to covalently anchor Mn–salen. The authors also observed an increase in enantioselectivities compared with the homogeneous catalysts for the epoxidation of several aromatic alkenes. Curiously they were able to successfully oxidate bulkier alkenes, like chromenes. Since no signs of metal leaching were observed and the MCM-41 matrix was not able to catalyze the transformation, this clearly indicated that the anchored Mn–salen complexes are accessible for bulky alkenes.²⁴²

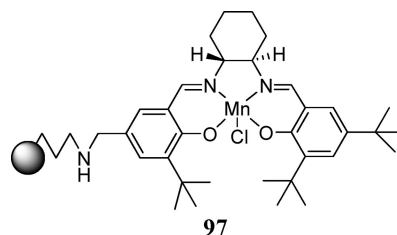
Hupp et al. immobilized a Mn–salen catalyst in a mesoporous anodic aluminum oxide membrane containing well-ordered, densely packed, and nanoscale pores that allow easy access to the catalyst by the substrates.²⁴³ This was achieved by preparing a catechol-substituted salen ligand that strongly adsorbed in the surface of Al_2O_3 . Catalyst **96** proved to be as efficient as its unsupported analogue, providing the 2,2-dimethyl-2*H*-chromene oxide in 79% yield with 81% ee (100% selectivity). Moreover the catalytic membrane can be recovered and reused after a simple cleaning procedure. It was reused three times experiencing some yield (35%) and enantioselectivity (15%) erosion due to manganese leaching.

The catalytic membrane was incorporated in a membrane reactor but lower conversions were observed so far, compared with batch protocol.



Choudary et al. performed asymmetric epoxidations using $\text{Mn}(\text{acac})_3$ as catalyst, stabilized in a nanocrystalline magnesium oxide (NAP-MgO) in the presence of chiral 1,2-diaminocyclohexane.²⁴⁴ As an example, styrene was epoxidized in 24 h to form styrene oxide in 70% yield and 42% ee. Reutilization of such catalyst was possible up to a third cycle with 18% yield erosion due to manganese leaching events.

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.²⁴⁵

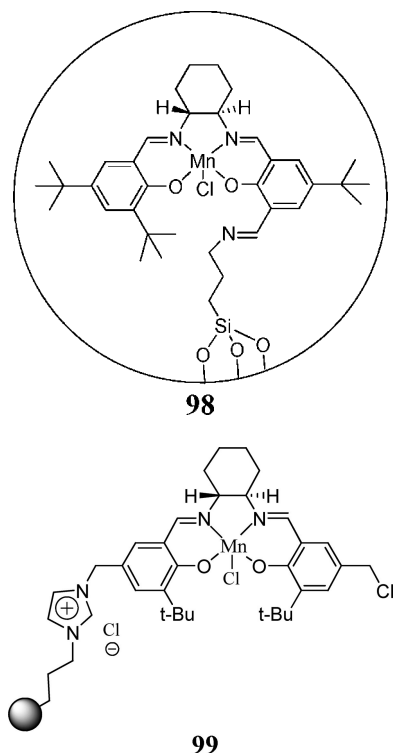


Both heterogeneous catalysts **97** proved to be nearly as efficient as the unsupported analogue where quantitative yields were achieved with good to excellent levels of enantioselectivities (5 mol %, up to 94% ee). Furthermore they were successfully recycled with minimal yield erosion and consistent ee up to four cycles. In the case of styrene derivatives, the heterogenized catalyst provided the respective epoxides with higher enantioselectivity.²⁴⁶ 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, nevertheless with a penalty on the epoxide enantioselectivity.²⁴⁷

Liu et al. anchored a Mn(III)–salen complex in MCM-48 and tested it in unfunctionalized olefin asymmetric epoxidation in the presence of *m*-CPBA/NMO. The enantioselectivity and reactivity of the immobilized catalyst **98** sometimes surpassed those obtained with the homogeneous complex, and it could be recycled up to three cycles.²⁴⁸

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 **99** was recycled five times with success.²⁴⁹

Liu et al. immobilized the Mn(III)–salen complexes in MCM-48 modified with imidazolium-based ionic liquid units treated with [bmim]PF₆. This heterogeneous catalyst was tested in asymmetric epoxidation of unfunctionalized



olefins, where it was found to be stable and recyclable (three cycles) and exhibited comparable activity and considerably higher enantioselectivities than those obtained by the homogeneous counterparts (e.g., >99%, 92% ee for α -methylstyrene).²⁵⁰

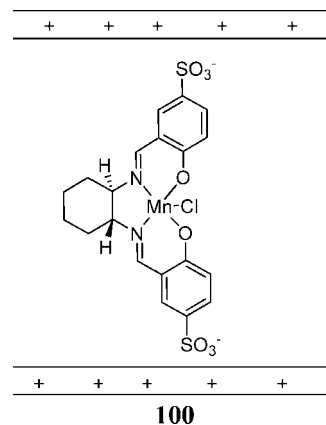
The Freire group performed the coordination of hydroxyl groups present in activated carbon to the axial position of chiral Mn(III)–salen complex and its application in asymmetric epoxidation. The heterogeneous catalyst lost its efficiency upon recycling.^{251,252}

Before 2002, Fraile et al. immobilized the homogeneous Mn–salen catalyst in several clays. Despite revealing the same activity, the heterogeneous catalysts provided lower values of enantioselectivity.⁵

Freire and Pires encapsulated a chiral Mn(III)–salen catalyst into three types of aluminium-pillared clays, but it was found that these supports affected dramatically the reaction enantioselectivity.²⁵³

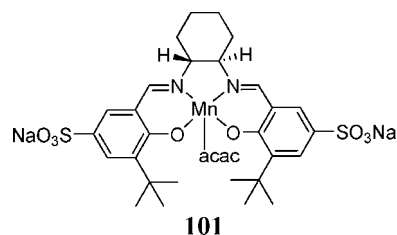
Anderson et al. prepared a hydrotalcite-like material, $\text{ZnAl}[\text{C}_6\text{H}_5\text{CO}_2^-]$, by coprecipitation of a solution of zinc and aluminum nitrates with an aqueous solution of NaOH and benzoic acid.²⁵⁴ Ion exchange of benzoate anion with a bisulfonic derivative of Mn(III)–salen complex completed the immobilization of an epoxidation catalyst inside the layered double hydroxides (LDH) host. The heterogeneous catalyst **100** was tested for (–)-limonene epoxidation (in the presence of pivaldehyde as co-oxidant and *N*-methylimidazole) where 100% conversion with 91% selectivity and 54% diastereomeric ratio were achieved. Aerobic epoxidation

(oxygen pressure of 150 psi) was chosen since it constitutes a greener alternative to other hazardous oxidants. The catalyst could be recovered and reused twice without any efficiency loss. Later it was shown that this LDH–[Mn(Cl)salen] catalyst showed slightly higher conversion, selectivity and diastereomeric excess for *R*-(+)-limonene and (–)- α -pinene epoxidation under atmospheric pressure of air and oxygen.²⁵⁵



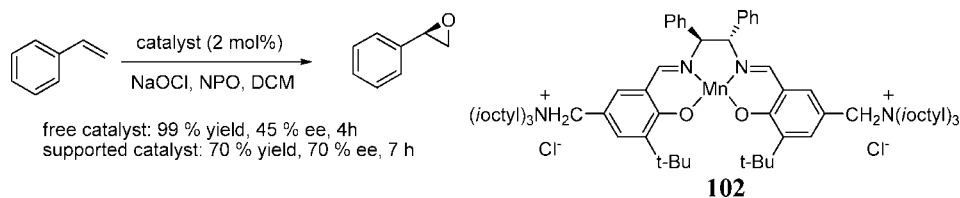
When tested for benchmark epoxidation reactions (with styrene or α -methylstyrene), **100** was readily shown to be inferior to other catalysts in terms of enantioselectivity. The highest enantiomeric excess observed was 68% ee for 1-methylcyclohexene epoxidation.²⁵⁶ The main advantages of this protocol were related to using less dangerous oxidants (dioxxygen or air) at room temperature instead of low temperatures required in Jacobsen's system and utilization of nonchlorinated solvents.

Choudary et al. immobilized a Mn–salen complex containing the two sulfonic ionic (catalyst **101**) groups attached to silica, LDH, and a cationic resin.²⁵⁷ Catalyst immobilization on silica through hydrogen bonding suffers from catalyst leaching, which results in great drops in activity and enantioselectivity in two reutilizations. Immobilization on LDH and cationic resin proved to have beneficial effects on catalyst recycling in terms of enantioselectivity (which remains unchanged up to five cycles). Generally all tested olefins were quantitatively epoxidized after 10 min. 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).



Kureshy et al. immobilized dicationic salen complexes (dialkyl ammonium salts, catalyst **102**) inside the interstitial

Scheme 29. Enantioselectivity Enhancement inside Montmorillonite Clays (Epoxidation)

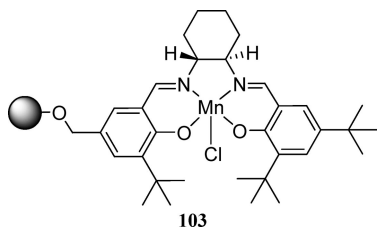


space of montmorillonite clay layers (AlSiO_x).^{258,259} The immobilization enhanced the enantioselectivity of the styrene epoxidation reaction compared with the unsupported catalyst, but the lower yields and higher reaction times are accounted due to slow diffusion rates inside the layers (Scheme 29). In this case and in clear contrast to Li et al. MCM-41 catalysts, heavy alkenes could be epoxidized since the double layers are flexible. Reutilization of such catalyst was possible up to four cycles without efficiency erosion but with increasing reaction times.

8.2. Homogeneous Catalysts

Before 2002, several works were reported for Mn–salen immobilization on insoluble polymers. Grafted catalysts tended to work better than copolymerized vinyl–Mn–salen catalysts providing enantioselectivities competitive with original Mn–salen catalyst. The same good results were also observed using soluble supported Mn–salen catalysts (PEG, non-cross-linked polystyrene, or dendrimers).⁵

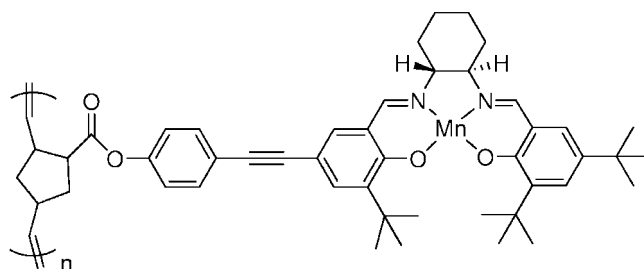
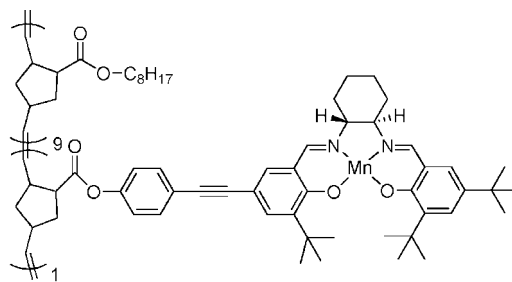
Liese et al. reported the application of a chiral Mn(III)–salen complex covalently anchored to a hyperbranched polyglycerol polymer as an efficient recyclable catalyst for asymmetric epoxidation of chromenes (96% conversion, 96% ee; competitive with Jacobsen catalyst). First, the authors demonstrated the catalyst stability during four consecutive batch epoxidations (total TON = 80). At the end of each reaction, the polymer was precipitated and reused. Subsequently, epoxidation of 6-cyano-2,2-dimethylchromene using catalyst **103** was carried out in a continuously operated chemical membrane reactor for 20 residence times, and steady conversions up to 70%, as well as steady enantiomeric excesses up to 92%, were achieved (total TON = 240).²⁶⁰



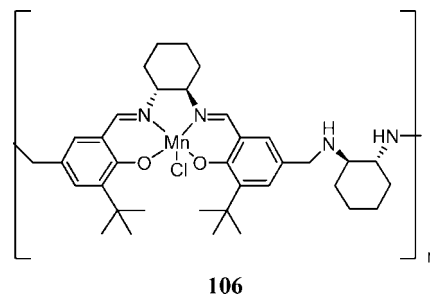
Recently, Liese et al. showed that the hyperbranched polyglycerol structure could be used as support for Co-mediated resolution of racemic epoxides. The dendritic structure of this polymeric support allowed the possibility that two nearby cobalt units could cooperate providing a catalyst with enhanced catalytic ability compared with the respective nonimmobilized catalyst (possible bimetallic mechanism).²⁶¹

Holbach and Weck polymerized and copolymerized (functionalized norbornene) a salen ligand bearing a norbornene group by metathesis ring-opening polymerization.²⁶² Polymeric catalysts proved to be as effective as nonsupported analogues in the epoxidation of styrene, *cis*- β -methylstyrene and 1,2-dihydronaphthalene. Unfortunately, the catalyst could not be reused due to chemical and physical property degradation during its recovery.

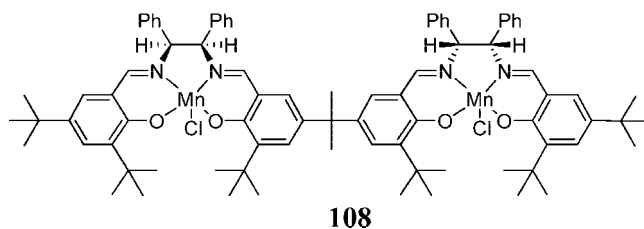
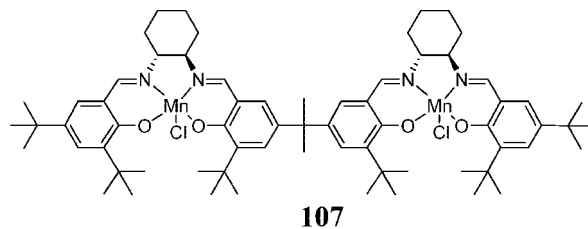
Yu et al. prepared a polymer containing a Mn(III)–salen complex and tested it in unfunctionalized olefin asymmetric epoxidations, in the presence of *m*-CPBA/NMO. The enantioselectivity and reactivity observed with catalyst **106** was in the range of those obtained with the homogeneous Mn(III)–salen complex for styrene epoxidation, reaching 98% yield and 47% ee. The polymeric catalyst was recovered by solvent precipitation and was reused efficiently twice.²⁶³



Kureshy et al. showed that dimeric Mn(III)–salen complexes **107** and **108** are able to catalyze the epoxidation of

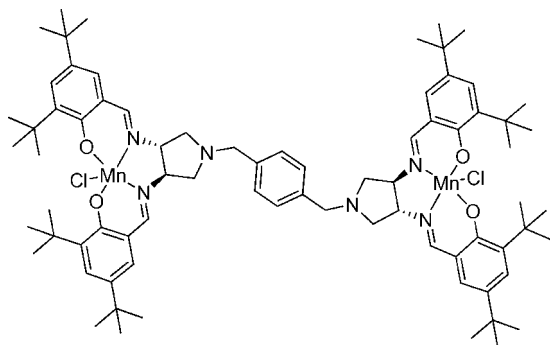


several alkenes (in the presence of a 4-PhPy-oxide and NaOCl) with the same efficiency described for Jacobsen's catalysts; however the first was recoverable by precipitation. It was shown that their reusability can achieve five cycles without any efficiency erosion.²⁶⁴ Later, the authors described a greener protocol where NaOCl was substituted by urea–hydrogen peroxide.²⁶⁵



Recently, Wang and Sun tested a dimeric pyrrolidine-based Mn(III)–salen catalyst for epoxidation of styrene and chromenes. The two salen units being covalently attached from a spacer linked to the chiral diamine did not affect the

catalyst efficiency (**109** was superior to equivalent homogeneous monomeric catalysts). The recovery protocol was also based on precipitation with addition of hexane, but when reused, its activity readily dropped.²⁶⁶

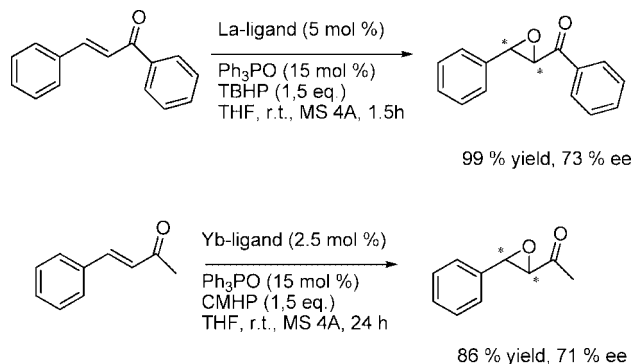
**109**

8.3. Other Epoxidation Catalysts

This section will focus on the catalyst recycling for epoxidation reactions of α,β -unsaturated alkenes and other miscellaneous catalysts. Pu et al. reported before 2002 the epoxidation of α,β -unsaturated ketones in the presence of a polymeric BINOL ligand, *t*-BuOOH, and diethylzinc with enantioselectivities of 81% ee.⁵ Catalysts applied in Juliá–Colonna epoxidation tend to be gel- or paste-like, which makes them difficult to handle. To circumvent this problem, poly(amino acid)s supported on organic polymers through covalent bonds or inorganic materials through simple physical absorption have been explored.^{267–272}

Sasai et al. reported the use of polymeric BINOL **110** as ligand to catalyze Yb-promoted epoxidation of benzalacetone and La-promoted epoxidation of chalcone.²⁷³ The optimal conditions for benzalacetone epoxidations with *tert*-butylhydroperoxide required the presence of 15 mol % triphenylphosphine oxide to afford the respective epoxide in 86% yield with 71% ee. In the case of chalcone, additional phosphine oxide was added during the catalyst preparation to achieve 99% yield of epoxide with 73% ee (Scheme 30). The ligands proved to be less efficient than their homogeneous counterparts. The ligands were recovered by centrifugation and were reused once, furnishing epoxides with decreased enantioselectivity (about 9–18% lower).

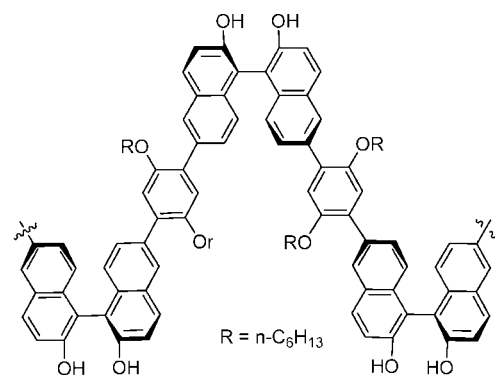
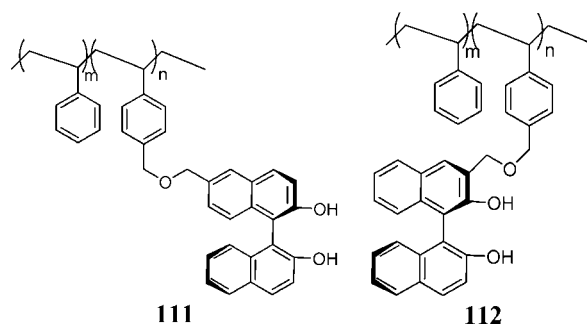
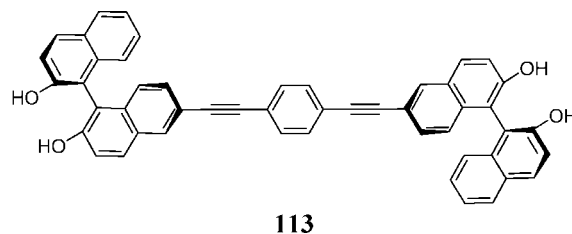
Scheme 30. Asymmetric Epoxidation of Chalcones and Benzalacetone in the Presence of Lanthanides



The heterogenization of BINOL ligands on polystyrene (copolymerization, ligands **111** and **112**) allowed further improvement on the enantioselectivities in the chalcone and benzalacetone epoxidation (98% ee and 88% ee, respec-

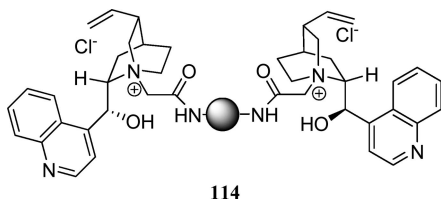
tively).²⁷⁴ These latter catalysts (heterogeneous ligand and metal) were reused twice with consistent enantioselectivity (but 30% yield erosion).

Ding et al. prepared a heterogeneous La-BINOL catalyst based on self-supported polymerization between the multi-topic ligand **113** and a lanthanum source.²⁷⁵ The heterogeneous self-supported catalyst was applied in chalcone epoxidation with cumene hydroperoxide in the presence of triphenylphosphine to afford the respective epoxide in quantitative yields and 98% ee. Not only did this heterogeneous catalyst prove to be as efficient as its homogeneous version (also when extended to other enones), but the reaction was complete in a shorter period of time (30 min vs 18–24 h from the previous protocols). The recovered catalyst could be reused up to six cycles with some yield erosion (16%) and nearly unchanged enantioselectivity.

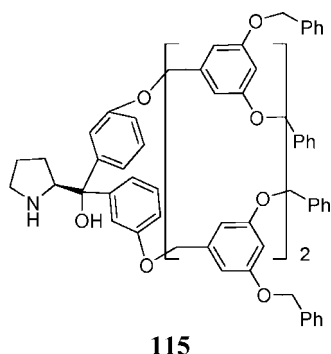
**110****111****112****113**

Wang et al. prepared a phase transfer catalyst based on cinchona alkaloid derivatives supported on a PEG chain (MW = 2000).²⁷⁶ This polymer-supported catalyst **114** was tested in the enantioselective epoxidation of chalcone furnishing the respective epoxide in 90% yield with 86% ee. Despite its recyclability (three efficient cycles), it failed to give good results in terms of enantioselectivity when the scope was extended to other chalcones.

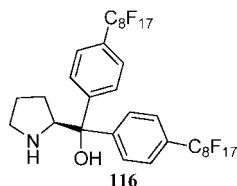
Zhao et al. tested a dendritic catalyst for enantioselective epoxidation of enones bearing a chiral pyrrolidinylmethanol moiety in the core.²⁷⁷ Under optimized conditions chalcone was epoxidized in 84% yield and 74% ee (CCl₄, TBHP, room temperature, MS 4 Å, and 144 h). This method proved to be



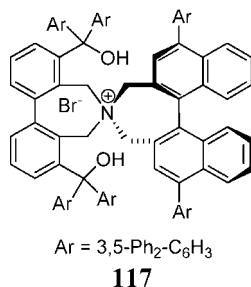
more general than the previous ones due to more consistent results on the epoxidation of other chalcones (60–93% yield with ee's above 73% ee, generally). The dendritic catalyst **115** was recovered by precipitation and was reused four times without any loss of efficiency.



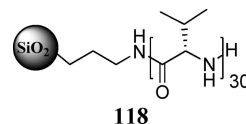
Recently a perfluorinated diphenylprolinol derivative was applied in asymmetric epoxidation of chalcones. Zhu et al. tested a family of catalysts from which **116** provided the best results (30 mol %, 31–67%, 75–84% ee, CCl₄, TBHP, room temperature). The catalyst **116** was recovered due to its low solubility in methanol and reused three times without any performance degradation.²⁷⁸



Maruoka et al. reported the application of a new improved chiral *N*-spiro quaternary ammonium salt **117** as a phase transfer catalyst in the epoxidation of aromatic and aliphatic enones with excellent enantioselectivities (>86% ee).²⁷⁹ The PTC catalyst was recovered by column chromatography and reused four times without loss of efficiency.

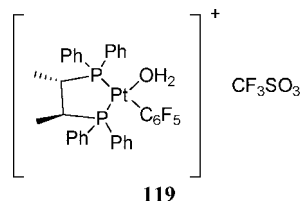


Recently, Tang et al. heterogenized a poly(L-leucine) peptide in silica gel and tested this catalyst in asymmetric epoxidation of chalcone (10 mol %) in the presence of sodium percarbonate, producing excellent yields (91%) and ee (up to 97% ee). The catalyst **118** was recycled five times without any erosion of efficiency.²⁸⁰



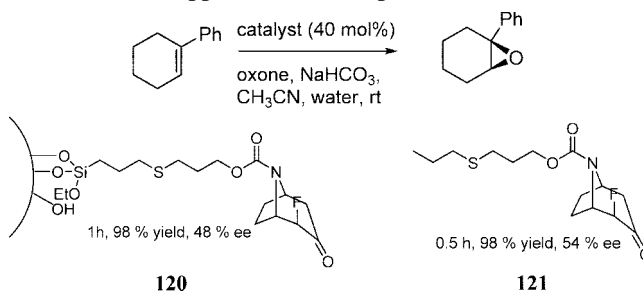
Han et al. prepared a new chiral biopolymer complex, silica-supported casein–Co complex.²⁸¹ This complex was found to successfully epoxidize allyl alcohol under aerobic conditions (1 atm O₂, 70 °C, 0.2 mmol/g Co content, and 2,4-dihydroxybenzaldehyde as reductant) with 70% yield in 91% ee. The recovered catalyst was reused twice with minimal drops of activity (*Y*_c(3) = 1% and ee_c(3) = 2%).

Strukul et al. demonstrated that terminal alkyl-substituted alkenes could be epoxidized in water in the presence of a platinum catalyst, **119**, and hydrogen peroxide. The presence of Triton-X100 was crucial to solubilize the catalyst in water to promote any catalysis. Furthermore, a considerable enhancement of enantioselectivity was observed when the reaction was conducted under these conditions compared with that in organic solvents (58% vs 82% ee; yield ~55%).²⁸² Under optimized reaction conditions, recycling experiments were not possible.



Sartori et al. immobilized an enantioenriched fluorotroponone ligand (78% ee) for organic epoxidation (with oxone) in siliceous supports (amorphous silica KG-60 and mesoporous MCM-41).²⁸³ It was found that sulfide groups in the spacer react with oxone; therefore the catalyst had to be preoxidized before being tested in the epoxidation reactions. The pretreated catalyst **120** had a similar performance to the homogeneous analog **121** (Scheme 31) and could be reused twice without yield and ee erosion, for both siliceous-supported catalysts. The protocol scope was successfully extended to other alkenes with only a slight drop in ee.

Scheme 31. Organocatalytic Asymmetric Epoxidation Reaction with Supported Fluorotroponone



Clearly, Jacobsen-type catalysts were heterogenized in several types of supports behaving generally better than homogeneous catalysts, being much more explored. Unambiguous experimental evidence was discovered for the “pore effect” in catalysis, where enantioselectivity enhancements were disclosed.

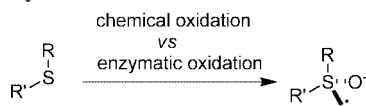
One of the main problems dealing with Mn–salen complexes is the tendency for some degree of manganese leaching from the supported catalyst to occur. This phenomenon limits some of the procedures described herein in terms

of catalyst recyclability. In the case of other types of epoxidation catalysts, more efforts should be made in order to increase the recyclability.

9. Asymmetric Sulfide Oxidation

Several methodologies have been applied for the oxidation of the sulfide moiety to chiral sulfoxides (Scheme 32). Peroxidase-type enzymes offer an interesting alternative to metal-catalyzed technology, but the high catalyst cost constitutes a major drawback. Despite its importance, to our knowledge, this reaction was not been the subject of any review on the specific context of catalyst reuse.⁵

Scheme 32. Asymmetric Sulfide Oxidation to Sulfoxides

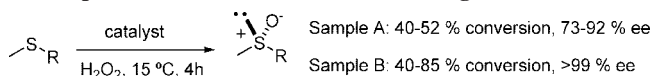


Enzyme-Catalyzed Sulfide Oxidation. Kostić and Kadenikova studied the effect of microperoxidase-11 (MP-11) immobilization on the reactivity and enantioselectivity of phenyl methyl sulfide oxidation to the respective sulfoxide.²⁸⁴ The enzyme was encapsulated on sol-gel silica glass and physisorbed, chemisorbed, and covalently attached to silica gel.

Interestingly the free enzyme behaved poorly in terms of methylphenyl sulfoxide formation (15%) when compared with its immobilized partners (55–95% yield). Regarding the enantioselectivity, none of the immobilized catalysts surpassed the 36% ee observed when using the free enzyme as catalyst. The increase in the reactivity upon immobilization was proven to be related to the existence of monomeric MP-11 under the immobilized conditions, since in solution MP-11 tends to aggregate reducing its effectiveness. The lower ee's observed for the immobilized ligands are explained by the interactions between the support and MP-11 that could alter the catalyst conformation. Only a few of the immobilized catalysts were reused once with some efficiency (MP-11 chemisorbed, physisorbed, and covalently bonded on silica gel). According to the authors, this lack of efficiency was due to catalyst leaching during the recovery protocol.

Leaching problems due to desorption events could be an important issue when working with adsorbed catalysts. Therefore, Strukul et al. immobilized chloroperoxidase (CPO) in a microporous silica gel cage to prevent leaching events and catalyst deactivation with hydrogen peroxide (Scheme 33). Two distinct samples were prepared.²⁸⁵ 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 33. Asymmetric Sulfide Oxidation in the Presence of Chloroperoxidase Immobilized in Silica Cages



R = Ph, 4-MeC₆H₄, 4-ClC₆H₄ and 2-pyridil

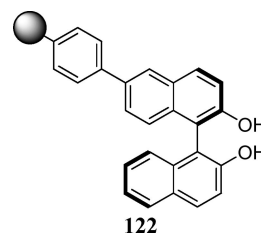
In terms of reactivity, sample B reacted faster despite not always giving higher conversions. Sample A failed to be reused in a second cycle (dramatic drops in reactivity and enantioselectivity were detected), while sample B was efficiently applied in four consecutive cycles affording chiral sulfoxides in >99% ee with only 6% yield erosion.

As mentioned before CPO denaturation promoted by hydrogen peroxide with the known low solubility of organic compounds in water constitutes the most important drawback of CPO utilization in industrial applications. To overcome this limitation, Spreti et al. reported the utilization of poly(ethylene glycol) polymers on CPO-catalyzed asymmetric sulfide oxidation.²⁸⁶ The addition of poly(ethylene glycol) 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% enantiomeric excess (in the case of thioanisole oxidation). Unfortunately, the chemical yield dropped about 15% on each recycle.

Metal-Catalyzed Sulfide Oxidation. Chaudhuri et al. developed two different methodologies to achieve the immobilization of bisoxazolidine (Box) ligands and applied them in sulfide oxidation to sulfimide.²⁸⁷ In the first strategy, phenyl- and *tert*-butyl-substituted Box ligands and Cu(acac)₂ were microencapsulated in a polystyrene polymer with a copper content of 0.38 mmol/g. The other methodology involved the catalyst immobilization in the ionic liquid phase ([bmim]BF₄). Both methodologies provided sulfimides in identical yields (in a range of 72–86% yield, from aromatic sulfides), but the reaction run in IL proceeded faster due to its homogeneous character. Interestingly phenyl-substituted Box behaved in distinct fashions. This ligand, when immobilized in IL, afforded sulfimides with higher enantioselectivities (50% ee). *tert*-Butyl-substituted Box failed to give competitive chiral induction. The reaction product could be extracted from the ionic liquid phase with the aid of ethyl acetate/hexane, 1/4. Furthermore, the catalyst was recovered and reused several times with consistent reactivity and enantioselectivity.

Kantam et al. tested a recoverable Cu(AcO)₂-poly(vinylpyrrolidone) catalyst in asymmetric sulfimidation of several thioethers in the presence of PhI=NTs and chiral *t*-BuBox ligand (2,3 mol %). Several sulfimides were obtained in very good yields (78–96%), but the enantiomeric excesses varied from 5% to 68% ee. The catalytic system was shown to retain its reactivity after three cycles, but the enantiomeric excess readily decreased due to ligand leaching.²⁸⁸

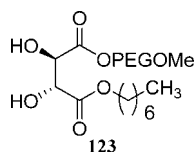
Hodge and Zhang disclosed a straightforward method to immobilize a BINOL unit in polystyrene beads via a Suzuki coupling. Such heterogeneous ligands were coordinated to titanium tetrakisopropoxide and tested in oxidation of prochiral thioethers (10 mol % titanium loading, ee up to 91%). The authors observed that retreatment of polymeric BINOL **122** with titanium complex allowed four runs with consistent enantioselectivities.²⁸⁹



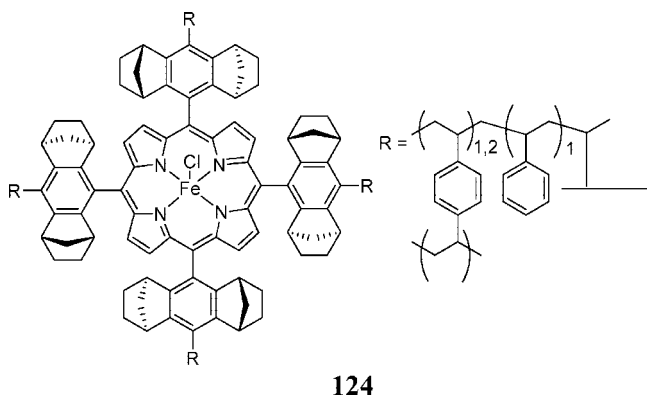
122

Guo and Wang used tartarate ligands linked to PEGOME polymers in titanium-promoted sulfide oxidation to sulfoxides. From a large family, ligand **123** afforded sulfoxides

with higher levels of enantioselectivity for a larger number of sulfides (50 mol % catalyst, 62–91% yields, up to 99% ee). This soluble ligand was recycled three times with consistent results.²⁹⁰



Ferrand et al. reported the preparation of optically active Frechet-type polymers bearing chiral iron porphyrins (catalyst **124**) and their application in asymmetric heterogeneous sulfide oxidation.²⁹¹



The main disadvantage of the homogeneous protocol was related to the low yields obtained (43% for thioanisole), which were improved upon immobilization on polymeric supports (up to 89%). The reaction enantioselectivity was always comparable to or even higher than the one obtained with the homogeneous catalyst (68% ee). The supported catalyst **124** was easily recovered by filtration and reused up to 15 cycles with 33% yield and 15% ee erosion.

Kantam et al. tested the possibility of using their osmium tetroxide immobilized catalysts on LDH layers in thioanisole oxidation reaction.²⁹² The reactions were conducted in the presence of (DHQD)₂PHAL, but the enantioselectivity never surpassed 28% ee. The catalytic system was reused three times with 20% loss of efficiency.

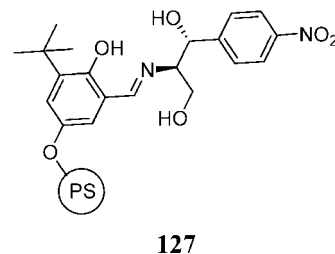
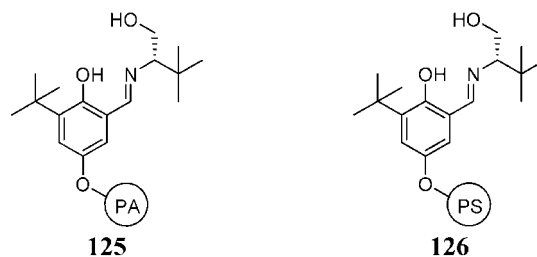
Barbarini et al. prepared several imine-alcohol ligands anchored in polymeric polystyrene and polyacrylate for VO(acac)₂-mediated oxidation of sulfide (**125–127**).²⁹³ Generally, polystyrene-based catalysts performed better affording higher yields and enantioselectivity than polyacrylate based ones in thioanisole oxidation with hydrogen peroxide. Comparable yields were observed between supported and homogeneous catalysts (51–72% yield), while the enantioselectivity was always lower (8–50% ee). The best supported catalyst was reused three times with minimal yield and ee erosion (7%).

So far, titanium-promoted sulfide oxidations have proven to be more recyclable than enzymatic procedures. Both methods can provide near perfect enantioselectivities, which make the chemical process noteworthy.

10. Kinetic Resolution of Racemic Epoxides

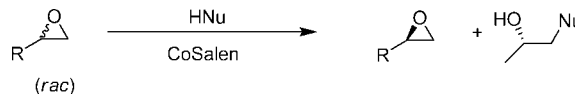
Lighter epoxides can be easily separated from the kinetic resolution catalyst due to a high vapor pressure difference (Scheme 34). Both monomeric^{294,295} and dimeric²⁹⁶ Jacobsen

PA – polyacrylate; PS – polystyrene



catalysts could be recovered and reused without any decrease of efficiency using this procedure. The catalyst loading applied in these procedures is about 0.2–0.5 mol %. Obviously, this protocol is rather limited since other heavier epoxides cannot be removed by distillation or if so could follow some degree of degradation. So the development of alternatives with mild protocols is required.

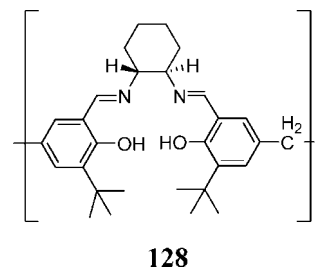
Scheme 34. Kinetic Resolution of Racemic Epoxides



10.1. Heterogeneous Catalysts

Allen et al. reported before 2002 the application of a Co–salen catalyst linked to a polystyrene polymer. This supported heterogeneous catalyst was tested in racemic epichlorohydrin resolution for five consecutive cycles with the same efficiency (50% conversion, 92% ee diol, and >99% ee epoxide).⁵

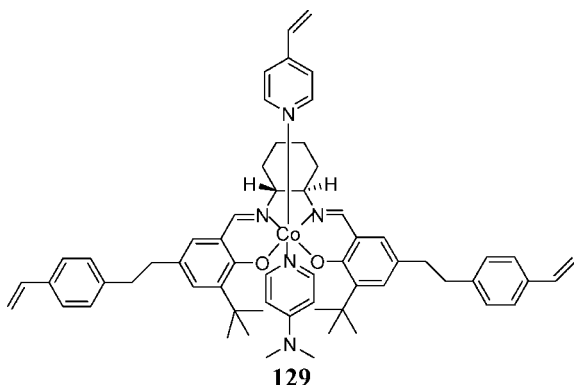
Kim et al. tested a family of polymeric (linear and cross-linked) salen ligands for Co(II)-mediated kinetic resolution of terminal epoxides containing two distinct anions (tetrafluoroborate and hexafluorophosphate).²⁹⁷ With 0.5 mol % Co/salen **128**, racemic epoxides were resolved with excellent enantioselectivity (>99% ee for both diol and epoxide).



Interestingly the application of such anions improved the catalyst recycling ability, which was not observed for polymeric Co–salen having acetate as the anion. 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 efficiency and enantioselectivity of polymeric Co(III) –salen catalysts.²⁹⁸

Borovik et al. prepared a polymeric catalyst with high local order using a tris-styryl– Co –salen complex **129** as cross-linker and tested it for kinetic resolution of terminal epoxides (3.6 mol % catalyst).²⁹⁹ As the cross-linking degree increased from 5% to 50%, the catalyst became more efficient in terms of reactivity due to metal center approximation. Unfortunately, low epoxide enantioselectivity was observed (<42% ee), while the diol enantioselectivity did not surpass 86%. The use of DMAP in the synthesis sequence proved to be detrimental in the first recycle since inefficient removal was accomplished during washing protocols, blocking the substrate coordination to cobalt.

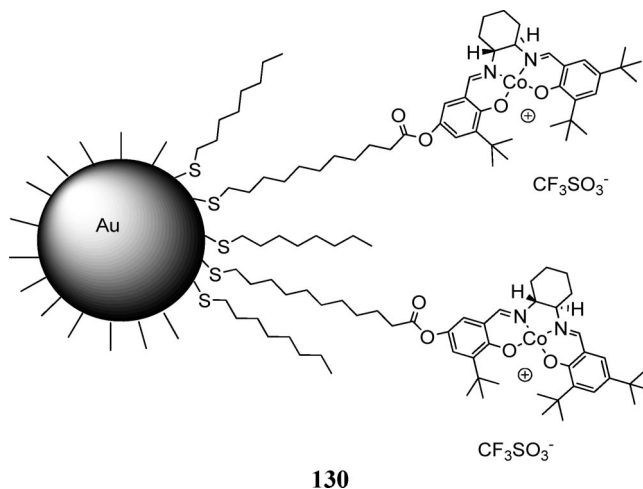


Choi and Kim immobilized Co(III) –salen complexes in a ZSM-5/Anodisc membrane and applied it as catalyst for hydrolytic kinetic resolution of terminal epoxides with water. The catalyst $[\text{Co(III)}\text{--salen}]\text{PF}_6$ was immobilized in the Anodisc membrane, which was in contact with water and protected from the organic phase by the ZSM-5 layer, which forbids its diffusion. Since the catalyst was also insoluble in water, it remained immobilized. The products diffused from the organic phase to the Anodisc layer. The unreacted epoxide returned to the organic phase, while the diol passed to the aqueous phase. Enantioselectivities up to 98% were achieved in this way for several distinct epoxides (epichlorohydrin, styrene oxide, and 1,2-epoxybutane) in 60–100 h.³⁰⁰

Jacobsen et al. prepared gold colloids coated with a monolayer of *n*-octanethiolates and thiolates with chiral Co(III) –salen catalyst and tested it as catalyst for the hydrolytic kinetic resolution of hexene-1-oxide. Due to cooperative effects, the catalyst **130** exhibits a significant acceleration relative to the homogeneous system (>99.9% ee epoxide, 0.01 mol % catalyst). Recovery of immobilized catalyst was possible by simple filtration, and after catalyst reoxidation, it was reused seven times without any loss of activity and enantioselectivity.³⁰¹

Yang and Li demonstrated for the first time that cooperative activation effects (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 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).^{302,303}

Jacobs et al. physically adsorbed a Cr –salen complex in dry silica gel (20 μmol catalyst/g of silica) and tested it for hydrolytic kinetic resolution of terminal epoxides with



TMSN_3 (1.25 wt % catalyst).³⁰⁴ The solid catalyst was removed upon sedimentation/filtration procedure and was reused up to 10 cycles efficiently in the resolution of 1,2-epoxyhexane. With this procedure, the unreacted epoxide achieved high enantioselectivities (85–93% ee). In the latest recycles, it was necessary to use a Soxhlet apparatus to achieve catalyst recovery on a useful time scale, because the small sized particles had a low sedimentation rate. Attempts to desorb the catalyst from the crushed silica to be reabsorbed in a fresh support turned out to be less competitive. If a dimeric Cr(III) –salen complex was impregnated in silica, a lower degree of leaching was observed, allowing two more efficient recycles.^{305,306}

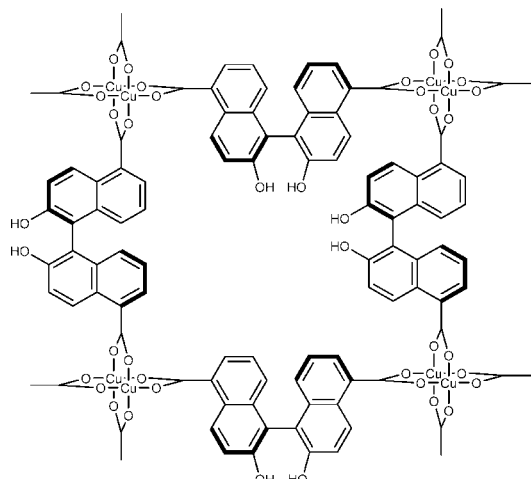
Alternatively, the Cr(III) –salen complex was coordinated to amino-functionalized silica.³⁰⁷ Although, noncoordinating solvents could be used, some degree of metal leaching by decomplexation (up to 1% per cycle) was always observed. This catalyst resolved meso-epoxides (cyclohexane oxide) with TMSN_3 providing excellent conversions and moderate enantioselectivities (3 mol % of catalyst, 65–77% ee).

Tanaka et al. prepared a novel chiral metal–organic framework from $\text{Cu}(\text{NO}_3)_2$ and chiral 2,2′-dihydroxy-1,1′-binaphthalene-5,5′-dicarboxylic acid. The heterogeneous catalyst **131** was applied in dynamic kinetic resolution of racemic cyclohexene oxide with anilines (BINOL itself does not catalyze this reaction under the same conditions). The authors found that this reaction can be run under solvent-free conditions (51% yield, 51% ee for the product). After each reaction, the catalyst could be filtered and reused without any appreciable loss of reactivity and enantioselectivity.³⁰⁸

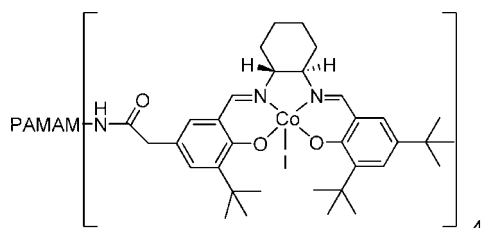
10.2. Homogeneous Catalysts

Breinbauer and Jacobsen reported before 2002 the application of Co –salen catalyst supported in polyamidoamine (PAMAM) dendrimers. This catalyst, **132**, proved to be very efficient (the first generation dendrimer) in epoxyhexane resolution where the respective diol was obtained in 43% yield and >99% ee.⁵

Song et al. showed that kinetic resolution 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%).³⁰⁹ Hydrolytic kinetic resolution of more reactive epoxides like epichlorohydrin featured a different behavior with the formation of a unique phase. The free terminal amine from the catalyst **133** probably reacted with the epoxide, improving its solubility in water allowing an easier



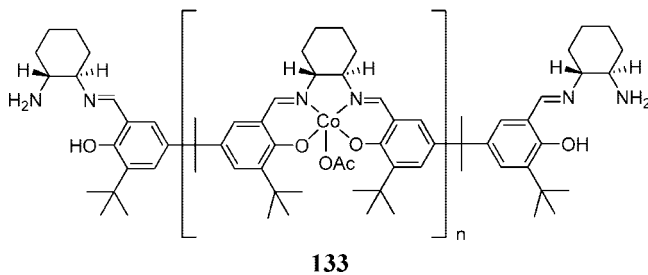
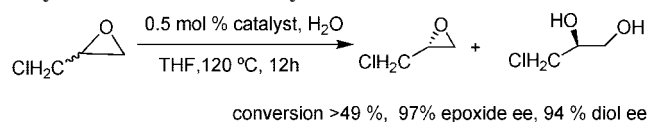
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132

method to achieve catalyst recovery. The recovered polymer catalyst **133** showed good activity and selectivity (Scheme 35).

Scheme 35. Racemic Epichlorohydrin Resolution with Polymeric Co–Salen Catalyst

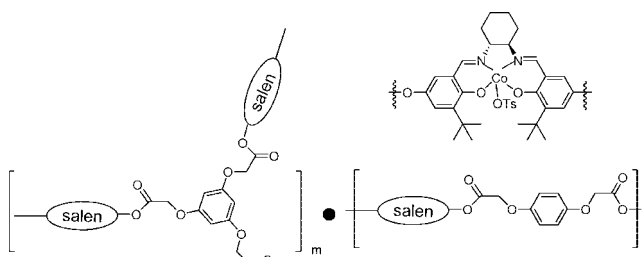


133

Kureshy et al. tested the same type of polymeric salen complex with chromium coordinated instead of cobalt with chloride as the counteranion.³¹⁰ The supported catalyst was tested for hydrolytic resolution of styryl epoxides with anilines affording the respective amino alcohol in enantioselectivities up to 87% ee (100% upon recrystallization), while the remaining epoxide had 80% ee. In this case, precipitation with hexane was required to achieve catalyst recovery, after which catalyst was reused up to five cycles with 10% yield erosion and consistent enantioselectivities. Recently, the authors observed that a dimeric catalyst provides better results in terms of both reactivity and enantioselectivity. The recyclability was also improved, since no yield erosion was detected.³¹¹

Following the excellent results observed with oligomeric Jacobsen's catalyst, Zheng et al. developed a family of

polymeric Co–salen catalysts produced with di- and trialdehydes (cross-linkers) and chiral amine.³¹² Combination of several di- and trialdehyde ratios furnished polymeric supported catalysts with several cross-linking degrees, which were expected to achieve the same levels of cooperativity of two nearby cobalt atoms observed with oligomeric Jacobsen's catalyst. These new catalysts were tested in racemic epichlorohydrin kinetic resolution with water (0.02% catalyst loading).



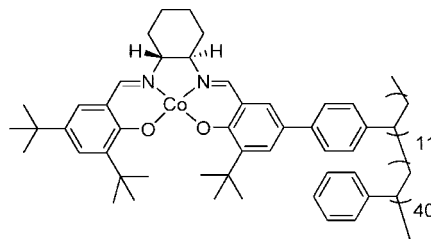
134 – Tri/Di = 0/100

135 – Tri/Di = 0.5/100–50/100

136 – Tri/Di = 100/0

Oligomeric catalysts **134** were less reactive than highly cross-linked ones (more time to achieve ~50% conversion), though the first tended to give higher enantioselectivities (up to 98% ee for the epoxide and 97% ee for diol). Fully cross-linked catalyst **136** was found to be less reactive due to inaccessible catalyst sites. These results reflect that the effect of cooperativity between two nearby cobalt atoms is dependent on Co concentration and polymer rigidity. No recycling data was given.

Jones and Weck prepared a family of Co–salen complexes immobilized in polystyrene polymers by radical self-polymerization of vinyl–salen derivatives and copolymerization with styrene.³¹³ These catalysts were tested in racemic epichlorohydrin kinetic resolution with water (0.5% of catalyst loading). The reaction was run under solvent-free conditions since the polymers were soluble in the epoxide.

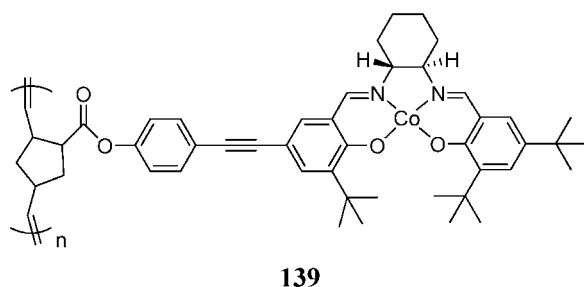
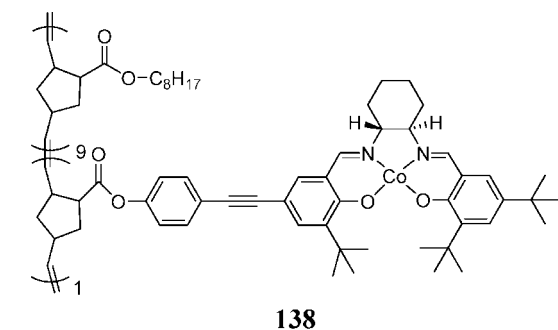


137

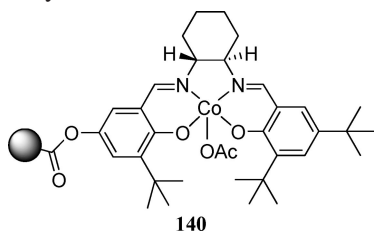
The catalyst that produced better results was copolymer **137**, with lower salen content, providing higher reactivity (54% conversion) and excellent enantioselectivity (from 81% to >99% ee). This observation can be explained by increasing substrate mobility within the polymer chains that allowed intramolecular cooperation between nearby cobalt units. The polymeric catalyst could be recovered by precipitation from diethylether and was reused three times with only a slight decrease in reactivity (time needed increased from 1 to 2 h) but with consistent conversion and enantioselectivity.

Holbach and Weck polymerized and copolymerized a salen ligand bearing a norbornene group by metathesis ring-opening polymerization.²⁶² The homopolymeric catalyst **139** proved

to be as effective as the unsupported analogue for the racemic epichlorohydrin kinetic resolution, while highly diluted copolymer **138** proved to be less efficient. Unfortunately, the catalyst lost its properties when precipitated with diethyl ether and became much less soluble and less reactive. Surprisingly, if the organic phase was removed by distillation the recovered catalyst was found to be more efficiently recycled.



Weberskirch et al. built a self-assembled nanoreactor to perform hydrolytic kinetic resolution of aromatic epoxides in pure water. The Co(III)–salen complex was anchored to an amphiphilic copolymer that formed micellar structures in water. The local high concentration of catalyst and the reasonably low concentration of water inside the micellar reactor allowed resolution of several types of aromatic epoxides with excellent enantioselectivities (up to ~51% conversion, 99% ee of epoxide, 96% ee of diol). The polymeric catalyst **140** 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.³¹⁴



Lu and co-workers showed that it is possible to resolve a mixture of racemic epoxides by epoxide/CO₂ coupling in the presence of chiral Co(III)–salen and quaternary ammonium halide salts under solvent-free conditions. The respective cyclic carbonate was obtained in 50–51% yield (total conversion) with enantioselectivities up to 70% in which the catalyst was reused efficiently only once.³¹⁵

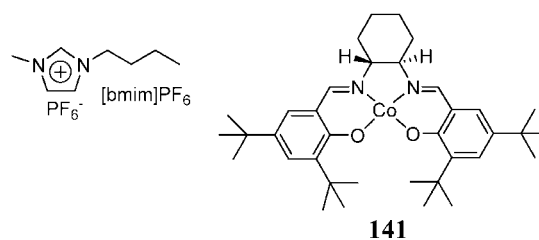
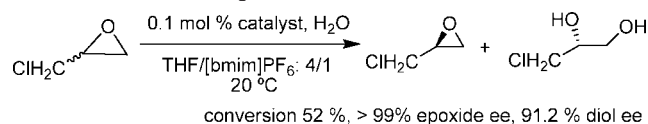
10.3. Alternative Reaction Media

Song et al. performed the hydrolytic kinetic resolution of racemic epoxides with water in the presence of Jacobsen

catalyst (Co–salen **141**) in a mixture of ionic liquid and tetrahydrofuran ([bmim]PF₆/THF, 1/4).³¹⁶ The kinetic resolution of epichlorohydrins in water was achieved with excellent enantioselectivities (>99% ee for the epoxide and 92% ee for the diol with 0.1 mol % catalyst, Scheme 36). 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. It was also found that cobalt(II) inactive species could be used as the catalyst precursor since some degree of Co oxidation occurs in the ionic phase without addition of acetic acid (the usual activating agent of organic media reactions). 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).

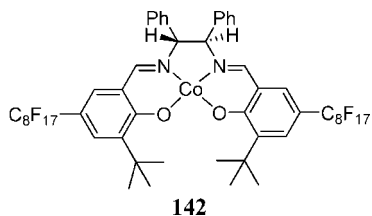
Pozzi et al. substituted both *tert*-butyl groups at 5 and 5' positions in Jacobsen's catalyst by perfluoroalkyl chains to achieve catalyst recycling by standard perfluorous extraction techniques.³¹⁷ The authors tested this catalyst, **142**, for the hydrolytic kinetic resolution of racemic 1-hexene oxide with water in the absence of solvent, since the catalyst was soluble in the epoxide. This system afforded the respective resolution with 46% conversion in 6 h with ee of 99% for diol and ee of 91.2% for epoxide (S/C = 500).

Scheme 36. Racemic Epichlorohydrin Resolution with Co–Salen in Ionic Liquids

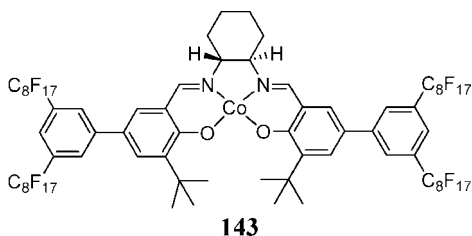


Catalyst **142** was recovered by means of product fractional distillation, and it was reused up to four cycles without efficiency erosion. To avoid a distillation process, standard perfluoro techniques were tested also. Liquid–liquid extraction at room temperature with a perfluorinated solvent afforded the best results (50% conversion, 99% diol ee in the second cycle) with the lowest Co leaching (about 16%). Solid-phase extraction allowed full catalyst retention, but only 50% was recovered from the solid phase. The physical immobilization on perfluorosilica particles could allow running the resolution in the presence of a heterogeneous catalyst, but no activity was detected. It should be mentioned that after catalyst oxidative activation with perfluorononanoic acid, it became more reactive and more soluble in perfluoro solvents.

Then the authors prepared a highly fluorinated Co–salen complex in order to improve the catalyst solubility in perfluorosolvents and diminish the epoxide reaction mixture.³¹⁸ Indeed, catalyst **143** (after activation with C₈F₁₇COOH) provided the desired characteristics and could be applied in biphasic fluorine catalysis using perfluorooctane as the cosolvent of the racemic epoxide. It gave clean



reactions (with 1-hexene oxide) without detectable traces of byproduct, affording highly selective kinetic resolutions (>99% ee for both diol and epoxide) over reasonable reaction times (2–24 h) even at low catalyst loadings (0.2 mol %). At the end of each reaction, the catalyst was precipitated with acetonitrile, filtered off, and reactivated for further reuse. Sadly a drop of activity was observed in a second run, while the diol enantioselectivity remained unchanged. The heavily fluorinated catalyst was less efficient upon recycling than the lightly fluorinated one previously described. The reason for activity loss remains uncertain.



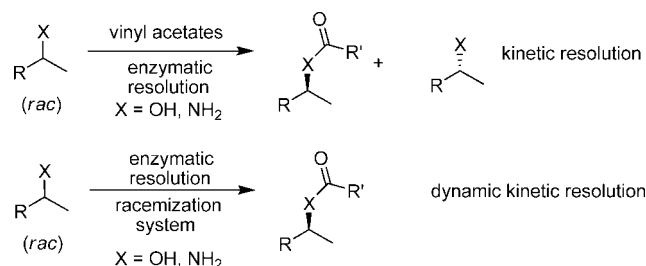
As Jacobsen-type catalysts were developed for asymmetric epoxidation, several examples and techniques arose for hydrolytic kinetic resolution of racemic epoxides. Homogeneous protocols tended to afford equivalent results compared with traditional protocols or heterogeneous or macromolecule-supported catalysts; one should be aware of mechanistic evidence (synergistic effects by near metal units) in its design 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) amount of catalyst loading compared with traditional homogeneous reactions. This is outstanding since 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 reactivities.

11. Kinetic Racemic Resolution of Alcohols and Amines

The kinetic resolution of racemic alcohols is a straightforward protocol to sometimes circumvent impossible enantiomer separation.³¹⁹ The acetylating enzymes that recognize preferentially one isomer transforming it into the respective acetate allows an easier separation protocol by polarity differences. This kinetic alcohol resolution has one limitation: 50% is the maximum yield. In this way, dynamic kinetic resolution allows total conversion of a racemic mixture in only one optical isomer using the resolving catalyst and a new catalyst that will racemize the remaining alcohol (Scheme 37). Both catalysts used to achieve such a state are extremely expensive, and therefore it is highly desirable that recycling protocols should be developed. This reaction was not reviewed in the previous review.⁵

Enzyme-Catalyzed Resolution. Bäckvall et al. envisaged the possibility to perform the reutilization of the catalytic

Scheme 37. Kinetic Resolution vs Dynamic Kinetic Resolution of Alcohols and Amines



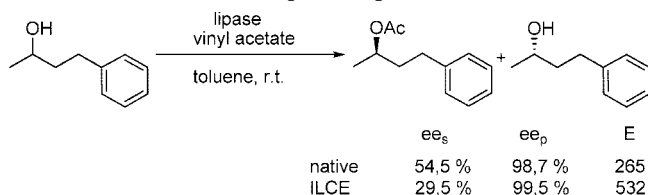
system used in alcohol dynamic kinetic resolution (DKR).³²⁰ *Candida antarctica* lipase B was recovered by filtration and recycled more than three times in kinetic resolution (KR) of β -hydroxynitriles (providing enantioselectivities up to >99% and 50% conversion). The racemization ruthenium catalyst (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 needs several purification 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 with [PPMIM]PF₆ (PPMIM = 1-(3'-phenyl-propyl)-3-methylimidazolium), which becomes liquid above 53 °C. The catalyst preparation protocol was very simple. The powdered enzyme was added to the liquid [PPMIM]PF₆ and stirred till a uniform heterogeneous solution was formed, after which the solution was cooled 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 (2-fold enhancement, Scheme 38).³²¹

The authors observed that fresh ILCE showed reduced activity in the first cycle due to some diffusion difficulties, which were relieved in the second cycle when the particle size 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 (*Candida antarctica* lipase B) in an ionic liquid, which acted as a stationary phase and a racemic mixture could be flowed through the biocatalyst using *sc*CO₂ as the mobile phase.³²² More polar ionic liquid-like [emim]NTf₂ tended to gave higher selectivities (86.3% vs 84.8%) and half-life time (24 vs 22 cycles) when compared with the less polar [bmim]NTf₂. The (*R*)-1-phenyl ethyl propionate was always obtained with conversions higher than 35% and 99.9% ee's. The use of IL as the stationary phase provided a protective effect for the biocatalyst; therefore higher life times are observed (about 2-fold) compared with enzyme adsorbed on celite.

Matsuda et al. applied the same flow methodology reported by Iborra et al.,³²² but did not use ionic liquid to immobilize *Candida antarctica* Novozym 435.³²³ The kinetic resolution of racemic 1-phenylethanol was conducted with this technology for more than 3 days operation under supercritical conditions (12.9–13 MPa of CO₂ 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

Scheme 38. Kinetic Resolution of Secondary Alcohols with IL-Coated *Pseudomonas cepacia* Lipase


using 1.73 g of the immobilized enzyme. This new flow system proved to be much more efficient than the batch protocol.

Reetz et al. reported an efficient method for the resolution of racemic secondary alcohol coupled with enantiomer separation.³²⁴ Novozym SP 435 was used to perform 1-phenylethanol racemic resolution in ionic liquid media ([bmim]NTf₂) with vinyl laureate as the acyl donor. The use of vinyl laureate allowed the formation of a low vapor pressure (*R*)-ester that could be retained in the ionic liquid together with the enzyme, while unreacted (*S*)-alcohol was recovered in several cryotrap by flowing *sc*CO₂ through the ionic liquid (66% yield, >99.9% ee). The ester was removed from the ionic phase by employing higher CO₂ pressure when all alcohol was recovered (89% yield, >99.9% ee). Since the recovered enzyme displayed the same activity for at least nine cycles, a continuous flow apparatus was tested and exhibited an enhancement on the separation yields. The major drawback in this system is the time required to execute all the processes (112 h), which lead to the recovery of a few grams (~15 g).

Reetz and Wiesenhofer performed the kinetic resolution of racemic 1-phenylethanol also in the presence of *Candida antarctica* lipase B using the biphasic system PEG₁₅₀₀/*sc*CO₂.³²⁵ In a batch reaction, an ideal conversion of 50.4% was obtained, affording (*R*)-(1-phenylethyl) acetate in 98.1% ee and (*S*)-1-phenylethanol with 99.7% ee. The enzyme was retained in the PEG phase, while both products could be extracted with *sc*CO₂ (55 °C/140 bar). The recovered enzyme could be reused up to 11 cycles with minimal loss of efficiency (<4%). The authors also found that correct tuning of CO₂ pressure allowed selective isolation of (*R*)-ester product from the (*S*)-1-phenylethanol (73% selectivity).

Zong et al. tested an immobilized Novozym-435 at [bmim]PF₆ in enantioselective resolution of racemic 1-trimethylsilylethanol with vinyl acetate. A remarkable enhancement in the initial rate and the enantioselectivity of the acylation was observed by using ILs as the reaction media compared with the organic solvents. Quantitative conversions were achieved (50.7%) providing unreacted alcohol in 97% ee. The enzyme was recycled four times without a substantial lost in activity and enantioselectivity.³²⁶

Itoh et al. showed that [bdmim]BF₄ was a suitable reaction media to perform the enzymatic resolution of 5-phenyl-1-penten-3-ol and methyl mandelate with Novozym 345. The products and acetaldehyde could be efficiently separated from the ionic liquid phase and enzyme allowing its reuse up to ten cycles.³²⁷ In 2006, the authors described the application of several types of imidazolium-type ionic liquids derived from poly(oxyethylene glycol)alkyl sulfate as additive or coating material for lipase (*Burkholderia cepacia* lipase and *Candida rugosa* lipase). It was disclosed that this material accelerated the enzymatic resolution by 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.³²⁸

Afonso et al. performed kinetic resolution of a racemic precursor of indinavir with vinylacetate in the presence of CALB in Aliquat 336 dicyanamide (Scheme 39). The biocatalyst was filtered, and the products were removed from the ionic liquid by sublimation allowing both medium and biocatalyst reutilization.³²⁹

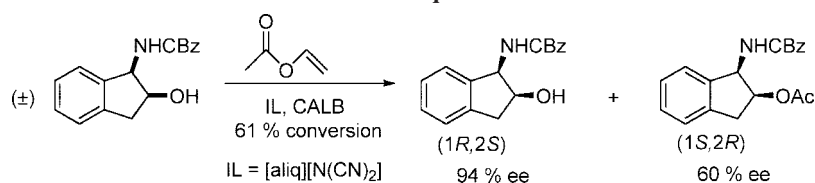
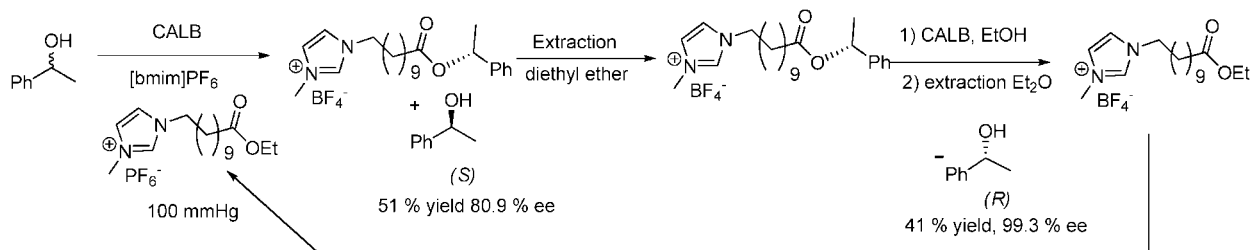
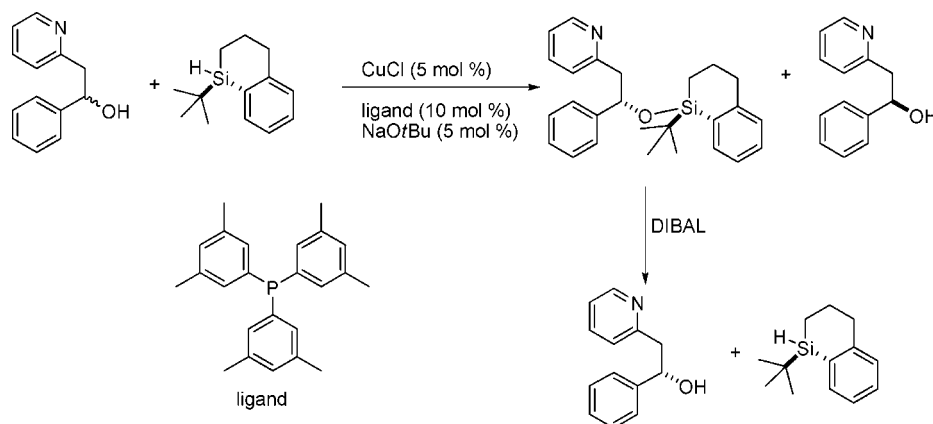
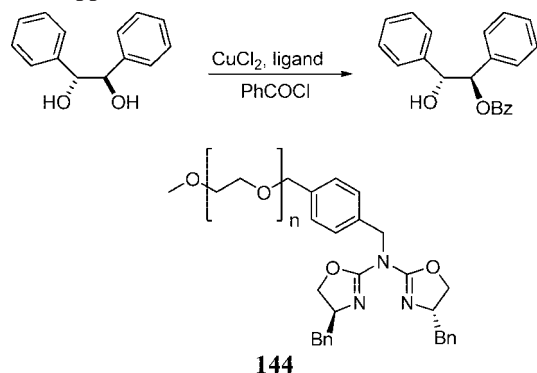
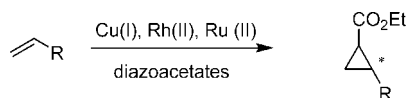
The same group developed a new method to achieve the separation of both enantiomers of secondary alcohol racemic mixtures without application of laborious chromatographic separations. The separation was accomplished by using an ionic acylating agent that remains in the ionic liquid medium ([bmim]PF₆) while the unreacted *S*-enantiomer was removed by extraction. 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 40).³³⁰

Park and Kim prepared a palladium nanoparticle entrapped in aluminum hydroxide and found that they could catalyze the racemization of secondary amines. In combination with Novozym-435, they achieved the kinetic resolution of achiral benzylic amines in toluene at 70 °C using ethyl acetate or ethyl methoxyacetate as acyl donor (1 mol % catalyst loading and 15 mg/mmol of enzyme). Aliphatic amines required 100 °C, higher catalyst loading (12 mol % and 120 mg/mmol of enzyme), and 1 atm of hydrogen gas to achieve the same quantitative yields with 98–99% ee. The aliphatic enzyme was tested in recycling experiments under more aggressive conditions. Nine consecutive cycles were achieved with 9% yield erosion and 7% enantioselectivity erosion.³³¹

De Vos et al. immobilized a palladium catalyst in alkaline-earth supports and found that also this catalyst could 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 heterogeneous catalytic system was reused twice without efficiency erosion. The support for the palladium catalyst proved to have an important role in controlling the byproduct formation.³³² Recently, the authors discovered that microwave irradiation could be used to accelerate the racemization rate without affecting the catalytic activity of Novozym 435.³³³

Meanwhile, de Vos and co-workers discovered that Raney Ni catalyst can be used to replace palladium as the racemization agent. This new catalyst generally presented higher racemization activity and selectivity than Raney Co, and it is able to racemize aliphatic primary amines with higher selectivity. In the case of aliphatic amines, racemization and enzymatic resolution could be combined in one pot, resulting in an efficient DKR. But for benzylic amines, physical separation of the racemization from the resolution reaction between two vessels was required to obtain an efficient DKR.³³⁴

Transition-Metal-Catalyzed Resolution of Alcohols and Amines. Rendler et al. developed a new strategy for transition metal kinetic resolution of secondary alcohols based on copper(I) dehydrogenative silicon–oxygen coupling of racemic alcohols with chiral organosilanes (Scheme 41).³³⁵ The presence of a donor residue (pyridine) in the alcohol was required to achieve 50% conversion (20 °C for 20 h) in

Scheme 39. Kinetic Resolution of Indinavir Precursor in Ionic Liquid**Scheme 40. Protocol for Separation of Secondary Alcohol Enantiomers without Using Any Chromatography Separation****Scheme 41. Chemical Kinetic Resolution of Alcohols with a Recyclable Silane****Scheme 42. Disymmetrization of 1,2-Diols with Copper and Polymer-Supported AzaBox****Scheme 43. Benchmark Reaction Applied for Asymmetric Cyclopropanation Reactions**

92:8 dr due to a more rigid conformational binding to the copper center.

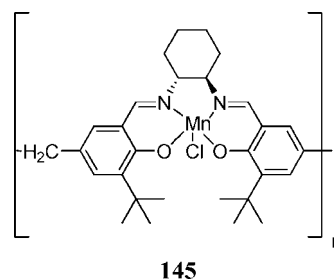
Despite the ingenious idea behind the protocol, the main disadvantage of this method was related to the necessity of several polarity dependent separations to recover the chiral organosilane compound.

Gissibl et al. reported the immobilization of azaBox ligand on PEG ($M_w = 5000$) via N-alkylation and its application

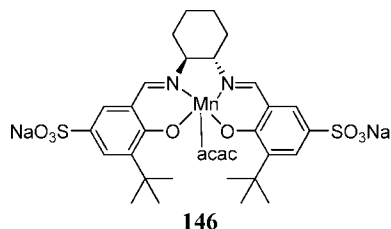
in kinetic resolution of racemic 1,2-diols (copper-catalyzed benzylation, Scheme 42).³³⁶

The supported ligand provided the formation of the product in 41% yield with >99% ee, while the homogeneous counterpart was more efficient in terms of activity furnishing 49% yield. The azaBox ligand **144** could be recovered in high yields (>95%) and reused up to five cycles without efficiency variations. Recently this ligand was also immobilized in a dendritic structure.³³⁷

Kureshy et al. used a chiral Mn(II)–salen polymer to resolve a mixture of racemic secondary alcohols by oxidation in the presence of $\text{PhI}(\text{OAc})_2$ and KBr (dichloromethane/water 1:2). The complex selectively oxidized one enantiomer to the respective ketone furnishing enantiopure unreacted alcohol (>99%). The catalyst **145** could be recovered by precipitation with hexanes and reused in subsequent experiments. Its activity slowly decreased over five runs ($Y_c(5) = 18\%$), while the alcohol was always isolated with high enantioselectivity (95–96% ee).^{338,339}



Kantam et al. immobilized a sulfonate derivative of Mn–salen catalyst **146** in a resin bearing tetraalkyl ammonium groups. This heterogeneous catalyst was also tested in the oxidative resolution of racemic secondary alcohols in the presence of $\text{PhI}(\text{OAc})_2$ and KBr (1 mol %), providing conversions of 60% with a large range of ee's (18–96%). The catalyst was recovered by filtration and reused efficiently during four cycles.³⁴⁰



As can be seen, some efficient recycling methodologies already exist for kinetic resolution of racemic alcohols based on both metal and enzyme catalysts, but the dynamic kinetic resolution remains a challenge (mainly for alcohols).

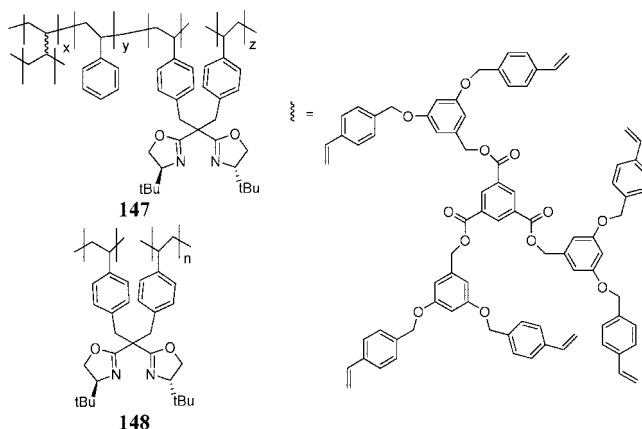
12. Asymmetric Alkene Cyclopropanation

The discovery that rhodium and ruthenium catalysts could be used to form controlled metallocarbenes derived from diazo compound decomposition brought new perspectives to asymmetric cyclopropanation (Scheme 43). In the earlier review, no example of such chemistry was reported where the main attention was still focused on copper-catalyzed cyclopropanations. Heterogeneous copper catalysts were prepared containing Box ligands doubly linked at this bridge carbon. Inorganic supports and insoluble polymers were the first choices, but the observed enantioselectivities were rather low. When an aza-Box ligand was anchored to PEG chains (by only one of the substitutes at the bridge carbon) competitive and recyclable catalysts were born. The enantioselectivity observed for these catalysts rose to 90% ee, and they could be used for nine consecutive cycles.⁵

12.1. Heterogeneous Catalysts

Mayoral et al. prepared two Box ligands bearing two styryl moieties linked at the bridge carbon atom to be polymerized and copolymerized it with styrene (and cross-linker) in the presence of AIBN (ligands **147** and **148**, the latter was first described in 2000).^{341–343} 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 unsupported ligand (37/63 *trans/cis* selectivity, 78%/72% ee (*trans/cis*)).

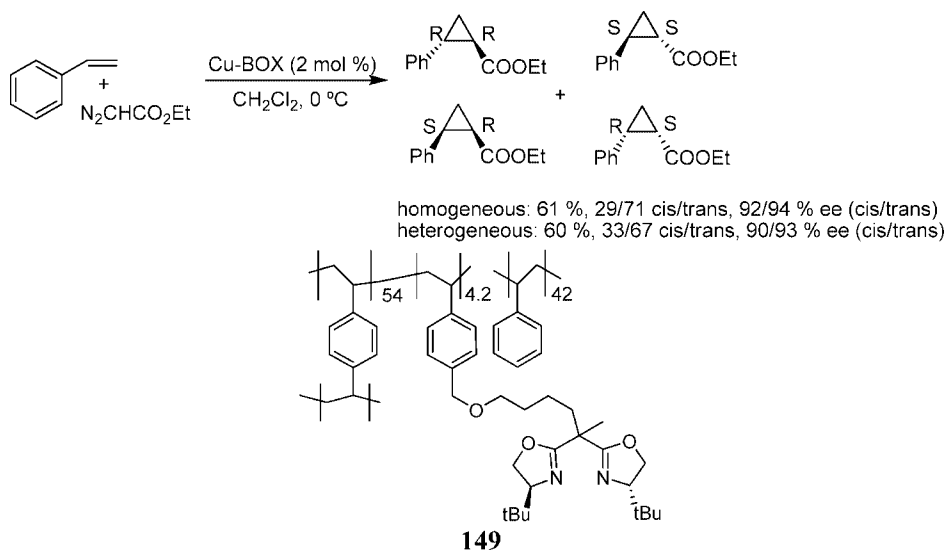
It is known that a Box bearing two methyl groups attached at the C-bridge atom provide cyclopropanes with higher enantioselectivities compared with Box ligands bearing benzyl groups. Salvadori et al. successfully achieved the immobilization of such ligands in polystyrene using a flexible linker that separated the ligand from the polymer backbone (Scheme 44).³⁴⁴ Not only did the immobilization have a minor effect on the enantioselectivity of the reaction, but the polymeric catalyst (Cu/Box **149**) could be recycled five times without any efficiency erosion.



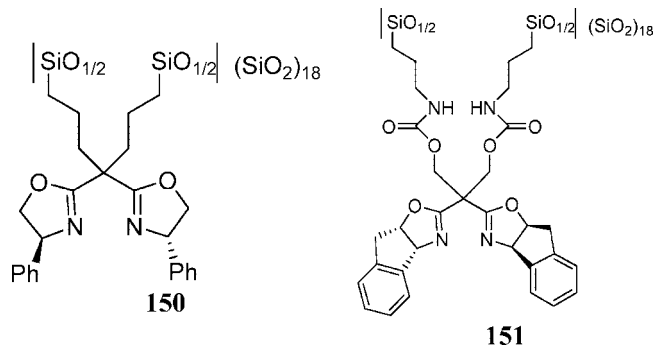
Recently, this catalyst was also immobilized in an insoluble matrix of poly(dimethylsiloxane) providing the same results as described previously.³⁴⁵

Mayoral et al. grafted Box-type ligands on the surface of silica gel.³⁴⁶ Both IndaBox and Ph-Box were immobilized

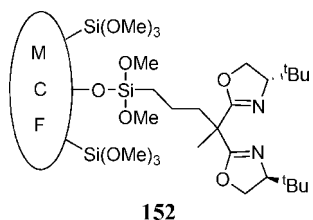
Scheme 44. Benchmark Cyclopropanation Reaction Promoted by Copper/Polymer-Supported AzaBox Complex



in this hybrid organic–inorganic support and were tested in the cyclopropanation benchmark reaction. While IndaBox–silica ligand **151** failed to give competitive results, the ligand **150** proved to be only slightly less efficient than its homogeneous analogue (64/36 *trans/cis*, 53/45% ee *trans/cis*). The latter could be reused once with minimal loss of efficiency. In both cases, the cyclopropanes were isolated in ~33% yield.

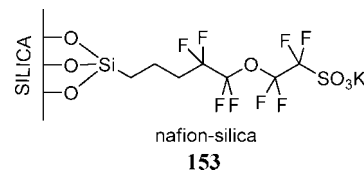


Alternatively, Ying et al. grafted a chiral Box ligand to the surface of siliceous mesocellular foams using only one silanized linker.³⁴⁷ The siliceous mesocellular foams (MCFs) are stable mesoporous silica with interconnected pores, high mechanical strength, chemical robustness, and thermal stability. The ability to control their ultralarge pore size and 3D pore structure during the preparation of this type of inorganic support make them well suited for fixating bulky complexes and for catalyzing reactions involving large substrates (higher diffusion rates than traditional silicas). It was necessary to protect free silanol groups with trimethylsilane in order to achieve excellent enantioselectivities. The heterogeneous ligand **152** was applied in styrene cyclopropanation providing cyclopropanes in 80% yield with excellent enantiomeric excesses (65/35 *trans/cis*, 95/92% ee *trans/cis*, superior to the homogeneous counterpart). The catalyst loading could be decreased to 0.2 mol % without compromising the reaction outcome. The Cu/ligand **152** was reused 12 consecutive reactions without losing activity or enantioselectivity. Once again, monotethered Box ligands proved to be more selective than bis-tethered ones.³⁴⁸



Reiser and Mayoral scoped Cu-Box and Cu-azaBox catalyst immobilization by electrostatic interactions with laponite (clay) and nafion–silica **153**.^{349–352} The theoretical studies enforced the idea that copper is more strongly coordinated to azaBox ligands than to Box ligands. This could explain the poor results in terms of enantioselectivity observed with Cu-Box immobilized complexes, due to minor coordination strength and interference of the ionic support. When the catalyst Cu-*t*-Bu-azaBox was immobilized in nafion–silica, it proved to be as efficient as its homogeneous analogue, furnishing moderate enantioselectivities (16–90% ee). In addition it could be reused once without any efficiency loss.

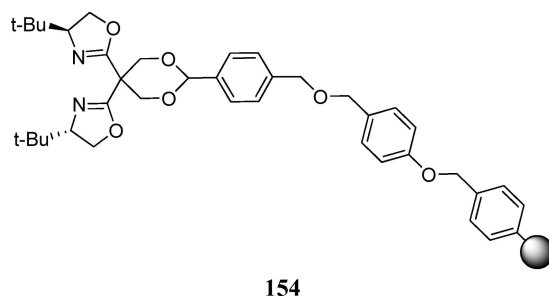
Mayoral et al. prepared a supported ionic liquid film on laponite containing a Cu-Box complex. This heterogeneous



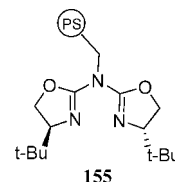
catalyst was tested in benchmark styrene cyclopropanation reaction with diethyl diazoacetate with moderate success. Interestingly, the reaction proceeded with a different *trans/cis* ratio for this catalyst when compared with the same reaction run in ionic liquid media. It was disclosed that the thickness of the film had a crucial influence on the selectivity.³⁵³ Recently, the Cu-Box complex immobilized in laponite clay was tested for C–H insertion of carbenoid compounds to tetrahydrofuran. The immobilization of the catalyst allowed enantioselectivity increase for the resulting products (up to 88% ee).³⁵⁴

Iglesias and Sanchez immobilized a chiral diamine ligand on zeolites achieving a recyclability of four cycles in the benchmark cyclopropanation reaction.³⁵⁵

Knight and Belcher grafted a *t*-butyl-Box ligand to a Wang-type resin using a linker containing a 1,3-dioxane ring.³⁵⁶ This supported ligand **154** proved to be about 30% less enantioselective (furnishing 65% ee) than its unsupported partner in the benchmark cyclopropanation reaction.



Mayoral et al. prepared several polymer-bound aza-Box ligands **155** by grafting and copolymerization to be tested for Cu(I)-catalyzed cyclopropanations of styrene with ethyl diazoacetate.³⁵⁷ The supported ligands derived from grafting proved to have a large number of catalytically active centers accessible to substrate molecules providing enhanced catalysts. The respective cyclopropanes were isolated with enantioselectivities comparable to or even higher than those provided by homogeneous and unsupported catalysts for several olefins (as example, for styrene: 94%, 1 mol % catalyst, up to 99% ee). The catalyst could be recycled up to five cycles for reactive alkenes. When less reactive substrates were used, the catalyst became inefficient and was readily poisoned by the reaction byproducts.³⁵²

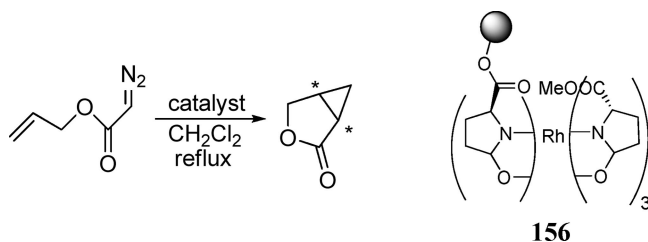


Doyle et al. grafted a methyl 2-oxa-pyrrolidine-(5*S*)-carboxylate moiety into two commercially available polymeric supports: NovaSyn TentaGel and Merrifield resins.³⁵⁸ Both polymeric carboxyamides were coordinated to rhodium(II) complex and tested as catalysts in intramolecular

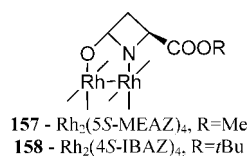
Table 8. Recycling Performance of Two Chiral Rhodium(II) Catalysts Applying the Scavenger Argopore–Wang Resin

Rh ₂ (S-TBSP) ₄				Rh ₂ (S-biTISP) ₂			
cycle	time (min)	yield (%)	ee (%)	cycle	time (min)	yield (%)	ee (%)
1	10	92	82	1	18	91	85
2	17	91	78	2	23	91	86
3	14	89	73	3	26	90	87
4	14	89	70	4	36	90	87
				10	60	87	88
				15	92	89	88

cyclopropanation of allyl diazoacetate (1 mol % catalyst, Scheme 45).

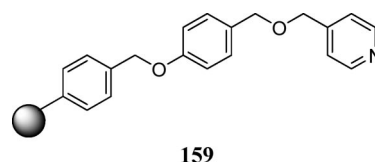
Scheme 45. Intramolecular Cyclopropanation Reaction Promoted by Polymer-Supported Rhodium Methyl 2-Oxa-pyrrolidine-(5S)-carboxylate

When the reaction was conducted with the unsupported catalyst, the bicyclic lactone was obtained with 95% ee (75% yield). With the heterogenized catalyst **156** in Merrifield resin, it was possible to obtain comparable results during nine cycles (92% ee, ~75% yield). The catalyst supported on TentaGel gave slightly lower enantioselectivities and was reused during seven cycles. The extremely active catalysts **157** and **158** were also grafted to NovaSyn TentaGel and Merrifield resins by the same methodology.³⁵⁹



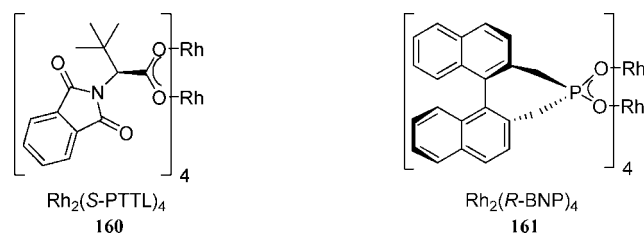
This approach to recover the asymmetric catalysts could be problematic because any ligand modification could negatively modify the catalyst chiral environment. Davies and Nagashima³⁶⁰ rationalized that the catalyst recovery could be done using a scavenger-type polymeric support, **159**

(Argopore–Wang) containing one pyridine terminal residue, able to coordinate the dirhodium catalyst (at the vacant axial position).



Two chiral rhodium(II) catalysts, Rh₂(S-TBSP)₄ and Rh₂(S-biTISP)₂, were immobilized in such a support and tested in asymmetric styrene cyclopropanation with diethyl diazoacetate (0.5 mol %). Both catalysts were found to be active, but the latter provided a longer lifetime (15 cycles) with consistent results (Table 8).

The immobilization mechanism remains unclear, but empirical evidence³⁶¹ suggests that it could be due to a combination of pyridine coordination and an encapsulation effect within the polystyrene matrix. More recently, this immobilization methodology was extended to other asymmetric dirhodium catalysts (like Rh₂(S-PTTL)₄ and Rh₂(R-BNP)₄).³⁶² Both catalysts, **160** and **161**, were used for asymmetric cyclopropanation and for asymmetric C–H bond intramolecular diazo insertion. Their recyclability was demonstrated for three consecutive cycles.



The same methodology was successfully extended to Rh₂(DOSP)₄, which was tested for asymmetric intermolecular C–H insertion reactions.³⁶³

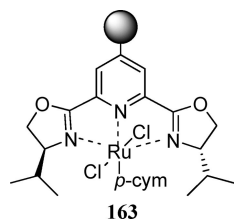
Úbeda et al. immobilized several dirhodium dicarboxylate complexes bearing two ortho-metalated phosphine ligands in a polystyrene support. The immobilization was accomplished by exchanging the two carboxylate ligands from the homogeneous catalyst with the carboxylic acid groups present in the polystyrene polymer. This heterogeneous complex **162** was tested as catalyst for asymmetric cyclopropanation reaction between styrene and ethyldiazoacetate (0.01 mmol per 100 mg of polymer, Table 9).

Table 9. Benchmark Cyclopropanation Reaction Catalyzed by Polystyrene-Supported Rhodium Complex

cycle	yield (%)	cis/trans	ee, % (1S,2R)	ee, % (1S,2S)
1	94	41:59	52	61
2	94	42:58	52	62
3	93	42:58	51	63
4	91	43:57	52	63
5	89	41:59	52	65
6	89	42:58	52	65
7	89	43:57	51	65
8	84	43:57	45	65
9	62	42:58	43	61

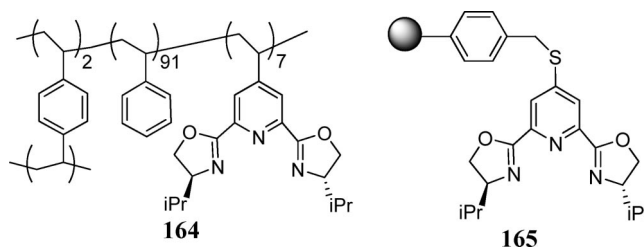
This catalyst afforded higher yields and ee's than its homogeneous counterpart (up to 67% yields). The catalyst was efficiently recycled up to eight cycles.³⁶⁴ Recently another methodology to recycle this type of catalyst was explored. The aromatic phosphine ligands had styryl groups that were copolymerized in the presence of divinyl benzene. This family retained the good recyclability observed for catalyst **162**.³⁶⁵

Mayoral et al. immobilized PyBox ligand to a polystyrene polymer by copolymerization. The polymeric ligand was then impregnated with $[\text{RuCl}_2(p\text{-cymene})]_2$ affording the respective polymeric catalyst **163** with a ruthenium content of 0.27 mmol/g.³⁶⁶



This catalyst proved to be active for the cyclopropanation of styrene with ethyl diazoacetate (3 mol % ruthenium). The respective cyclopropanes were isolated with high *trans* selectivity (85:15 *trans/cis*), in which the major diastereomer was obtained in 85% ee's with ~30% yields. This lack of reactivity could be explained by the presence of several inaccessible catalyst sites inside the polymer chains. Furthermore, higher levels of enantioselectivities are achieved in the homogeneous protocol due to application of large excess of ligand (~4 equiv). As a heterogeneous catalyst, it was easily recovered at the end of each cycle by filtration. Unfortunately, in the third consecutive cycle, both activity and enantioselectivity dropped about 50%. Recently, the authors prepared a monolithic polystyrene resin bearing the Ru-PyBox to be used under continuous flow conditions.³⁶⁷ Grafting PyBox ligands to the surface of silica constitutes an alternative method of immobilization, but it provided inferior catalysts.³⁶⁸ The polymeric ligand **164** with a lower cross-linking degree provided an efficient catalyst (52–70% yields, *trans/cis* selectivity of 90/10 and enantioselectivities around 85–91% for the *trans*-cyclopropanes).³⁶⁹ The cata-

lytic system was reused consistently during four cycles; however the recovery protocol required inert conditions.



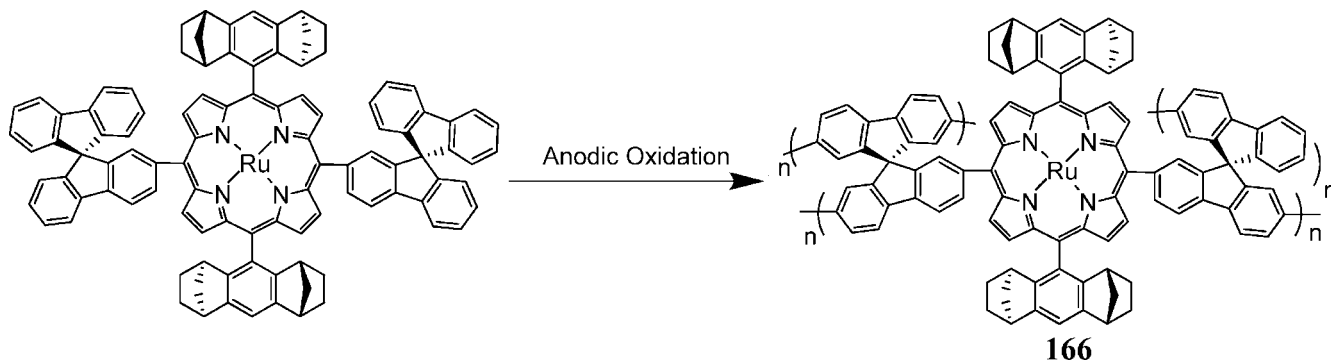
The same ligand was also grafted in Merrifield resins but proved to be slightly less efficient than polymerized analogues (ligand **165**, 36–47% yields, *trans/cis* selectivity of 88/12 and enantioselectivities around 77–83% for the *trans*-cyclopropanes).

Reversible microencapsulation was also studied as a method to achieve catalytic system recycling.³⁷⁰ Both polystyrene and Ru-PyBox were soluble in dichloromethane (solvent used in the cyclopropanation reaction), but when hexane was added, the polymers tended to microencapsulate the catalyst, precipitating together. The grafted catalyst leads to slightly lower yields than the microencapsulated one and afforded comparable enantioselectivity (46–63% yields, *trans/cis* selectivity of 88/12 and enantioselectivities around 75–85% for the *trans*-cyclopropanes). Although polymerization is the best method for the immobilization of the Ru-PyBox system (with low cross-linking degree), microencapsulation is a competitive alternative since no ligand modification is required.

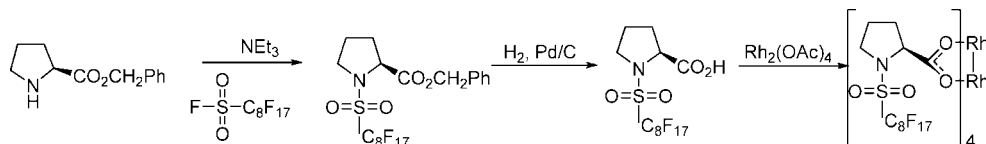
Simonneaux et al. prepared optically active electropolymers bearing chiral metalloporphyrins by anodic oxidation polymerization (Scheme 46).³⁷¹

The polyporphyrin **166** was coordinated to ruthenium and tested as catalyst in asymmetric styrene cyclopropanation, affording the respective products in excellent yield (80–90%) but with moderate enantioselectivities (<53% ee). The chiral polymer catalyst was simply recovered by filtration and reused six times with minimal erosion of activity and enantioselectivity.

Scheme 46. Anodic Polymerization of Ru-Porphyrin



Scheme 47. Preparation of Perfluorinated Dirhodium(II)-tetraprolinate Catalyst



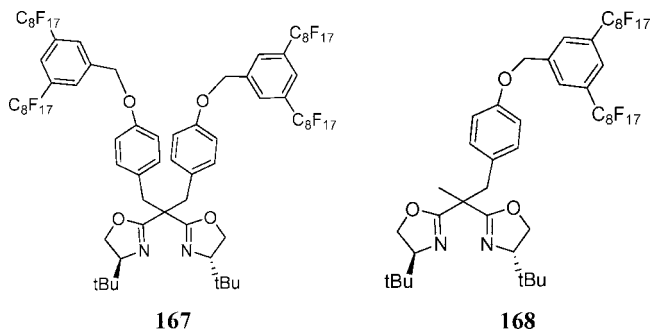
12.2. Alternative Reaction Media

Mayoral and co-workers used room temperature ionic liquids as solvent to achieve catalyst immobilization and recycling in the asymmetric cyclopropanation reactions.³⁷² Since the cyclopropanes derived from styrene have low polarity compared with Cu-Box catalyst, solvents like hexane can be used to extract the reaction product from [bmim]OTf phase without catalyst leaching. It is known that chlorine and water tend to coordinate to Cu(I) promoting nonchiral pathways. This is why in general copper(I) triflates are used as precatalyst rather than copper(I) chloride (72% vs 24% yield and 94% vs 2% ee's of *trans* product).

Interestingly, when overdried [emim][OTf] with P₂O₅ as solvent prepared from direct alkylation on alkyltriflates was used, it was possible to use CuCl to obtain cyclopropanes with high ee's (75–85% for *trans* and 72–79% for *cis*, 1 mol %) despite copper triflate providing higher yields (72% vs 32–51%). The application of overdried RTIL's constitutes a disadvantage since they generally are very hygroscopic and can accumulate water during the recycling protocols. Davies et al. showed that the presence of 5% of halide impurities on the RTIL phase was more than enough to completely deactivate the catalyst.³⁷³

Mayoral et al. showed that the Cu-*t*-BuBox catalyst could be reused four times in the styrene cyclopropanation reaction with drops of 17% in activity and 27% in enantioselectivity due to ligand extraction to hexane phases from the [emim][OTf] phase.³⁷² This problem could be solved using an azaBox ligand that will coordinate more efficiently to Cu(I). Despite the isolated yield observed with azaBox ligand being about 7% lower during each cycle (40–35% for aza-Box and 40–55% for Box), the Cu-aza-Box complex proved to be more stable than the Cu-Box complex. The enantioselectivity of *trans* product remained at 90% ee during more cycles (eight cycles).³⁷⁴

Benaglia and co-workers conceived of and synthesized two new Box ligands for asymmetric cyclopropanation.³⁷⁵ These new ligands have the peculiarity of bearing one (ligand **167**) or two (ligand **168**) perfluoroalkyl chains attached to the bridged carbon. The fluorine contents of F-Box **167** and **168** were calculated to be 55.5% and 49.2%, respectively.



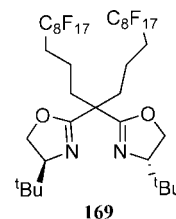
The ligand **168** was soluble in several nonfluorinated solvents, while ligand **167** had more affinity for the perfluoro-octane phase due to its higher fluorine content. These ligands were coordinated to copper(I) and tested in the benchmark cyclopropanation reaction (styrene cyclopropanation with diazoacetate).

The F-Box ligand **168** performed better in terms of enantioselectivity than F-Box ligand **167** (78% vs 60%, respectively). The level of enantioselectivity achieved is

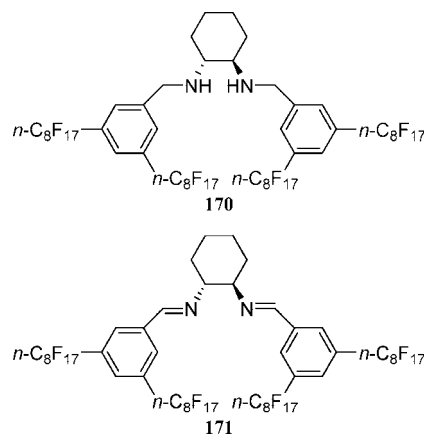
about 20% lower when compared with the best result reported in the literature with the traditional method. This difference in enantioselectivity was probably due to some steric hindrance and electronic repulsion between the perfluorotails, which will alter the Box coordination angle.

The F-Box **168** ligand was recovered by filtration through a short-length silica path, while F-Box ligand **167** was more easily recovered by performing a dichloromethane/perfluorooctane extraction. Both recovered ligands presented some levels of contamination, which had negative effects upon recycling, lowering both their yield (from 68% to 60%) and enantioselectivity (from 78% to 66% ee).

Sinou et al. alkylated the same ligand with two less sterically hindered perfluoro chains obtaining a ligand with 54.4% fluorine content.³⁷⁶ Despite the lower yields obtained (<63%), the enantioselectivity observed was higher (83% ee). Ligand **169** proved to be more stable providing consistent ee's during five cycles (while the activity eroded 30%).

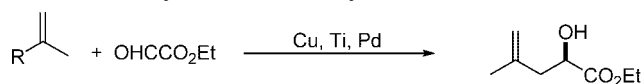


O'Hagan et al. prepared C₂-symmetric fluorinated diamines **170** and diimines **171**, ligands that were used in Cu(I)-promoted cyclopropanation reaction of styrene under biphasic conditions (perfluorooctane/dichloromethane).³⁷⁷ Despite the promising results (yield = 77%, *trans/cis* = 67:33 and 62% ee *trans* isomer), the ligand presented signs of degradation when recycled.



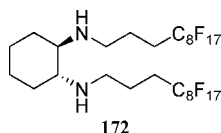
Biffis et al. chose McKervy's dirhodium(II)-tetraprolinates to synthesize perfluoroalkyl analogues that could be recycled (Scheme 47).

This catalyst was more easily synthesized than perfluoro-Box ligands described previously with an overall yield of 66% (<26% overall yield for F-Box ligands). This complex has a fluorine content of 50% and showed good affinity for perfluorinated phases like perfluoromethylcyclohexane (PFMC). In this case, styrene was rapidly cyclopropanated with phenyl diazoacetate (4 h for rhodium prolinates vs 22 h for copper-Box ligands), affording the respective *E* cyclopropane in high yield (87% reaction carried out in dichloromethane or 79% when carried out

Scheme 48. Asymmetric Carbonyl–Ene Reaction

directly in perfluoromethylcyclohexane, PFMC). The reaction carried out in the perfluorinated phase provided cyclopropanes with higher levels of enantioselectivities (62% vs 48% ee). In both protocols, the catalyst and the nonperfluorinated compounds were separated by liquid–liquid extraction. The recovered catalyst was reused twice without yield and enantioselectivity erosion.³⁷⁸

Pozzi et al. described the application of chiral (1*R*,2*R*)-diaminocyclohexane ligand **172** with perfluorous tails for Cu(I)-promoted cyclopropanation of styrene with ethyl diazoacetate. The corresponding cyclopropanes could be obtained in 75% yield, 67/33 *trans/cis*, 44–45% ee for *trans* and *cis*. The ligand lost a part of its efficiency when reused. This ligand was also tested in the palladium-promoted allylic substitutions and aromatic ketone reduction.³⁷⁹



CuBox catalysts immobilized in insoluble polymeric supports offer less limitations than those immobilized on siliceous materials, where precapping could be necessary. However, grafting a Box ligand to MCF provided a catalyst competitive with the catalyst immobilized in PEG. Perfluoroligands or immobilization of catalyst on ionic liquid suffered from lack of competitive recycle protocols. Rh-catalyzed cyclopropanation proved to be extremely competitive with the first catalyst family. In this case, it was possible to achieve high recyclability without ligand modification using a scavenger type polymer.

13. Asymmetric Carbonyl–Ene Reaction

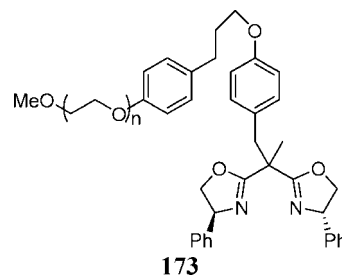
The carbonyl–ene coupling mediated by titanium or copper catalyst allows the formation of a new C–C bond with a high level of enantioselectivity (Scheme 48). Generally, the copper catalyst applied in this transformation is Cu(II)-bisoxazoline, which is prepared with an expensive ligand. Apart from this, high catalyst loadings are normally required to achieve good results (1–20 mol %). Titanium-based catalysts applied in this chemistry use BINOL-type

Table 10. Recycling Assays on Asymmetric Carbonyl–Ene Reaction Catalyzed by Anchored Cu-Box Complexes in Gold Nanoparticles

recycle	yield (%)	ee (%)
0	99	86
1	94	84
2	90	85
3	87	84
4	80	84

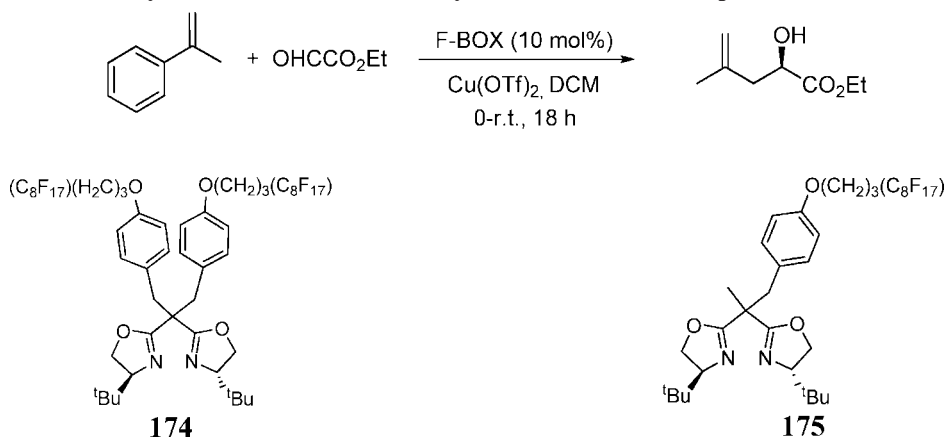
ligands, which are rather expensive as well. Therefore it is necessary to achieve reutilization of such catalysts to boost their industrial application.

Before 2002, one work of Cozzi and co-workers had been reviewed.⁵ In that method, a PEG-immobilized Ph-Box **173** was used to perform the benchmark carbonyl–ene reaction between α -methylstyrene and glyoxylate, affording the respective product in 96% yield with 95% ee (10 mol % catalyst). The supported catalyst was precipitated with diethyl ether and reused twice with marginal loss of efficiency.

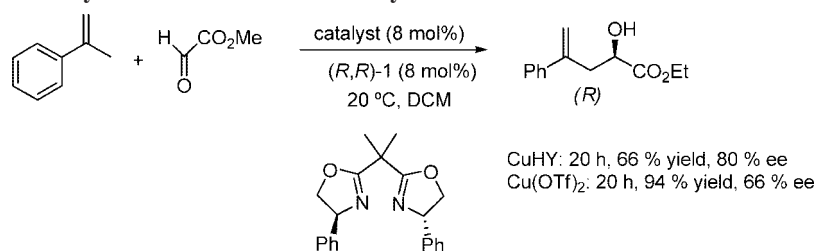


Copper-Catalyzed Reactions. Benaglia et al. prepared two new perfluorinated bisoxazolines ligands, which were characterized by their low fluorine content (Box **174** with 46.2% and Box **175** with 38.1%), light fluorous ligands.³⁸⁰ These new ligands were tested in the Cu-promoted carbonyl–ene reaction between α -methylstyrene and ethyl glyoxalate (Scheme 49). Catalyst Cu/**175** (*C*₁-symmetric) behaved better in terms of enantioselectivity (65% yield, 74% ee, not far from the 89% ee obtained by Evans et al.) than *C*₂-symmetric catalyst Cu/**174** (73% yield, 7% ee).

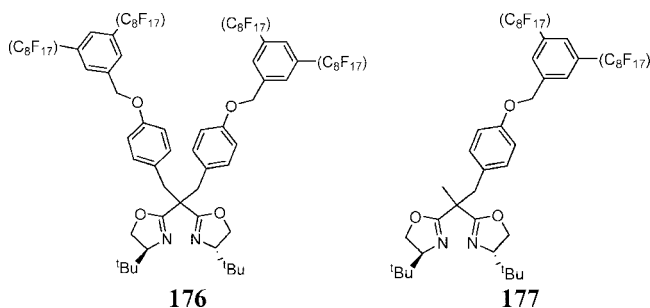
The authors rationalized that this selectivity difference was due to the proximity of the two highly fluorinated tails, which could be responsible for some electronic and steric hindrance that will alter the original bite angle of the Box ligand. This behavior had been already observed by Benaglia et al., when the authors tested two Box ligands with heavier fluorine content for the same transformation

Scheme 49. Asymmetric Carbonyl–Ene Reaction Promoted by Cu–PerfluoroBox Complexes

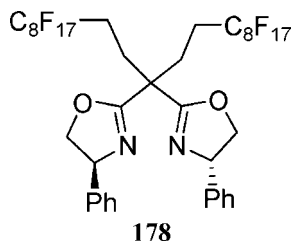
Scheme 50. Asymmetric Carbonyl–Ene Reaction Promoted by Cu-Box Immobilized in Zeolite-Y Matrix



(ligands **176** and **177**). The best light fluorinated ligand **175** could only be efficiently recovered with the aid of a short silica-gel column (fluorous solid-phase extraction) and was reused in a second cycle with 4% erosion in the yield and ee (run 1, 65% yield in 74% ee; run 2, 62% yield in 71% ee).³⁷⁵



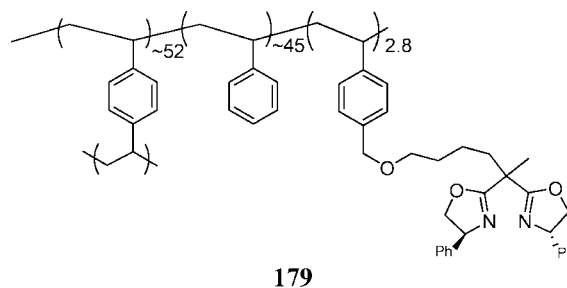
Sinou et al. prepared the perfluorinated ligand **178** and tested its recyclability in the same transformation. The respective alcohol derived from α -methylstyrene and ethyl glyoxalate was obtained in 78% yield with 87% ee. The catalyst was reused efficiently at least five times with the aid of fluorous reverse phase silica gel.³⁸¹



Salvadori et al. copolymerized a styryl-substituted bis(oxazoline) **179** in the presence of styrene and divinylbenzene to obtain an insoluble polymeric catalyst for the carbonyl–ene coupling reaction of α -methylstyrene and ethyl glyoxalate.³⁸² With 10 mol % catalyst loading, similar yields and enantioselectivities were observed (96% yield with 90% ee, in 6 h) compared with those from the homogeneous analogue and the Evans protocol (99% yield with 89% ee). According to the authors, the heterogeneous properties were responsible for the slower reactions rates and the lower yields observed when with different alkenes were tested (65–83% vs 87–92%). In the recycling assays, consistent 90% enantiomeric excesses were obtained during five cycles. However, the reaction time required to achieve high conversions increased gradually in each cycle (~95% in 18 h).

Recently, this ligand was also immobilized in an insoluble matrix of poly(dimethylsiloxane) providing the same results. The copper complex was also tested with excellent results for the Mukaiyama aldol reaction.³⁴⁵

Kanemasa et al. attached a new linker to the bridge Box carbon atom, an alkyl thiol chain. This new spacer allowed

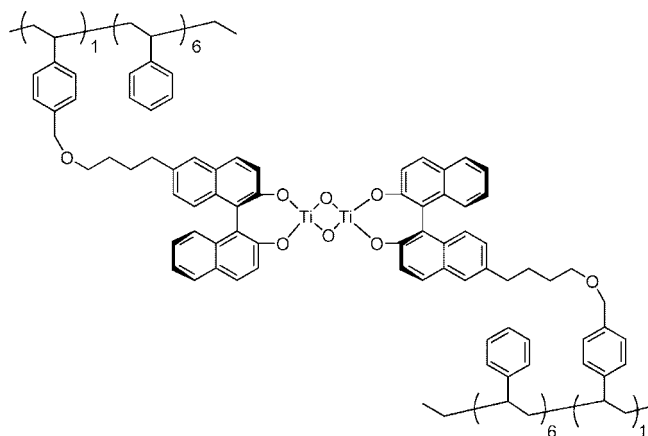


the immobilization of the Box ligand in the periphery of gold nanoparticles. These nanoparticles acted as a homogeneous catalyst but aggregated when the reaction was diluted with hexane (reaction carried out in dichloromethane) allowing a method for catalyst recovery (reaction of Scheme 49, 10 mol %, room temperature, 5 h, Table 10). The recovery protocol is rather complex, which could constitute an important drawback.³⁸³

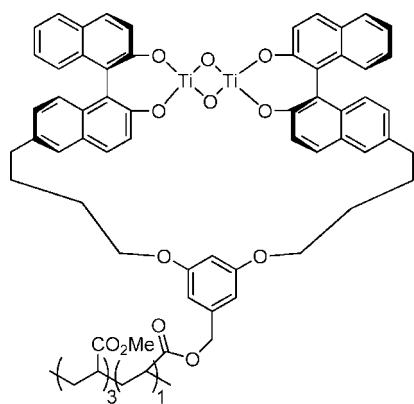
Hutchings et al. immobilized Cu-Ph-Box catalyst within a zeolite-Y matrix by electrostatic cation retention. The heterogeneous catalyst behaved well in terms of activity and enantioselectivity. In some cases, higher ee's were observed with the supported catalyst compared with the unsupported one despite its lower reactivity (Scheme 50). The catalyst was also applied in imine–ene reaction broadening the methodology scope. The recovered catalyst did not suffer from copper or ligand leaching, but efficient washings were required to achieve a reusability of four cycles without any loss of efficiency. The major drawback of the protocol was related to the long reaction times required to achieve yields in a range of 65–71%.³⁸⁴

Titanium(IV)-Promoted Reactions. Yamada et al. synthesized an insoluble polymeric catalyst similar to Nakai's catalyst. Inorganic titanium species were added to non-cross-linked copolymers bearing BINOL ligands, which self-assembled to a cross-linked heterogeneous catalyst, **180**. The prepared catalysts were not found to be active under Nakai conditions (DCM, –30 °C, 3 h, 93% yield with 98% ee). At room temperature and in diethyl ether, moderate 68% yield was achieved with 84% ee (5 mol % catalyst loading) for the same reaction described above. When the loading was increased to 20 mol %, the isolated yield increased to 85% (with 88% ee). The catalyst could be recovered by filtration and reused up to four cycles with some yield (10%) and ee (7%) erosion.³⁸⁵

Sasai et al. reported the immobilization of a μ -oxodititanium bisBINOL complex for asymmetric catalysis. Immobilization was achieved by copolymerization of a vinyl-bisBINOLS ligand with methyl methacrylate (ligand/acrylate, 1/3) in the presence of AIBN. After treatment with Ti(O-*i*-Pr)₄, the heterogeneous catalyst **181** was tested in the benchmark carbonyl–ene reaction furnishing quantitative yields with 96% ee. The recovered catalyst was reused twice with 25% yield erosion and consistent enantioselectivity.³⁸⁶

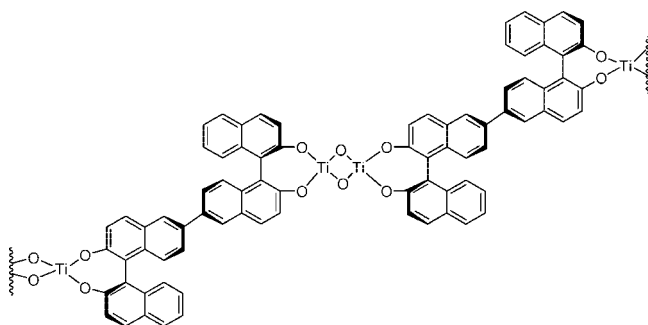


180



181

Sasai et al. reported the first example of a chiral self-assembled structure, formed through 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 **182** was simply prepared by treating (*R,R*)-bis(BINOL) with $\text{Ti}(\text{O}-i\text{-Pr})_4$ and water in toluene at room temperature (stirred for 24 h) to obtain a red solid.³⁸⁷

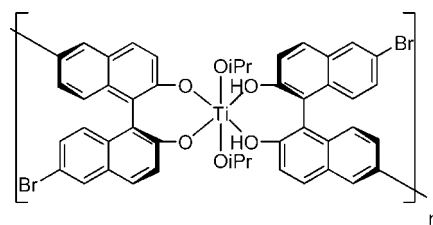


182

This insoluble polymeric catalyst was tested for benchmark carbonyl–ene reaction affording the respective product in 98 h in 88% yield with 88% ee. While the enantioselectivity remained unchanged for more four cycles, the reactivity suffered a considerable decrease (reaction time increased to 147 h to afford only 66% in the fifth cycle).

Wang et al. showed that the enantioselectivity could be increased to 95% ee using only 1 mol % catalyst, 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, **183**, that provided quantitative yields with 97% enantiomeric excess. This new catalyst was also reused four times, but in this case both yield (19%) and enantioselectivity (27%) decreased.³⁸⁸



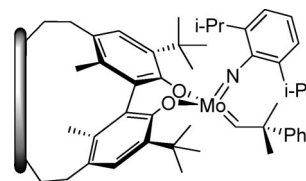
183

Palladium-Promoted Reactions. Shen et al. demonstrated that chiral Pd(II)/BINAP complexes can catalyze the asymmetric glyoxylate–ene reaction between α -methyl styrene and ethyl glyoxylate in $[\text{bmim}]\text{PF}_6$. The respective product could be obtained in quantitative yields with 70% ee. The catalytic system and ionic liquid was reused four times without any loss of efficiency.³⁸⁹

The carbonyl–ene coupling has attracted less attention than olefin cyclopropanation. Titanium-based catalysts sometimes suffer from considerable loss of reactivity upon recycling probably due to catalyst deactivation or metal leaching. Taking into consideration their potential, more developments should be performed. Copper-based catalysts present generally higher recyclability since some of them are the same as those applied in cyclopropanation.

14. Asymmetric Alkene Metathesis

Hoveyda and Schrock synthesized in 2002 the first chiral molybdenum-based polymer-supported catalyst **184** for asymmetric olefin metathesis. The supported catalyst proved to be as effective as the unsupported analogue in asymmetric ring-opening or cross metathesis (AROM/CM), though when it was tested in reactions involving asymmetric ring-closing metathesis (ARCM), it failed to give competitive results in terms of both yield and enantioselectivity.³⁹⁰



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Molybdenum-Based Catalysts. Two years later, the same group prepared several polymeric catalysts for AROM/CM and ARCM reactions. These seven new catalysts were divided in three main categories. In the first, the catalysts possess a bisphenol-moiety linked to a polystyrene backbone (copolymerization), which included the catalyst reported in 2002. The heterogeneous catalysts from this family differed in the nitrenoid and carbenoid ligands (Scheme 51).³⁹¹

Catalyst **185** was mainly applied for ARCM reactions, providing good to excellent activities and enantioselectivities (inferior to its free partner), while catalyst **186** proved to have a similar performance compared with the free catalyst under AROM/CM and AROM/ARCM conditions. The catalyst **186** suffers from high metal leaching (18–38%), in clear contrast to **185** (1%). The degree of

Scheme 51. Asymmetric Metathesis Reactions with Molybdenum Catalysts Immobilized in PS Resins

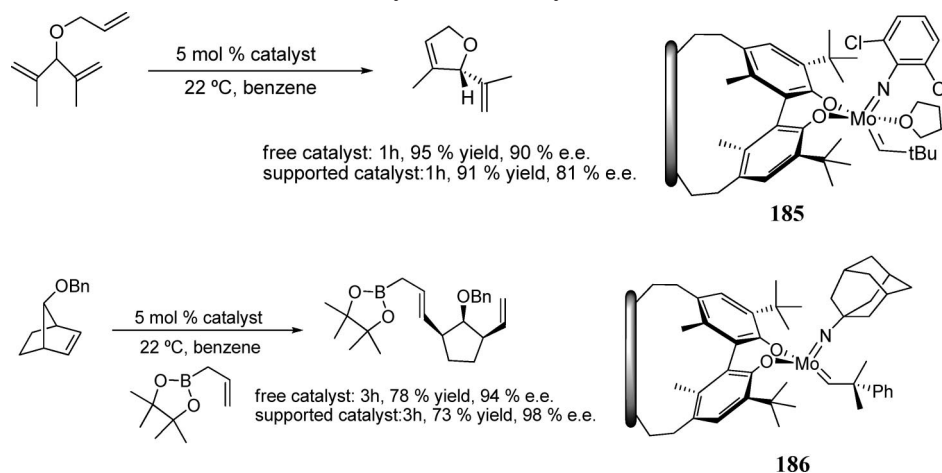


Table 11. Asymmetric Metathesis Reactions with Molybdenum Catalyst Immobilized in PS Resins

187

Substrate	Product	Mol (%): Temp. (°C)	Free catalyst Time (h); Yield (%); ee (%)	Supported catalyst Time (h); Yield (%); ee (%)
		5; 60	3; 86; >98	3; 86; >98
		5; 50	6; 87; 91	6; 85; 65
		5; 22	0.3; 89; 94	0.3; 62; 84
		5; 22	2; 83; 91	2; 89; 86

leaching detected for catalyst **185** was 5% less than that for catalyst **184**.

In the second family, the molybdenum complex was immobilized to the polystyrene backbone bearing a bisnaphthol moiety instead of bisphenol. Considering this family, only catalyst **187** proved to be as effective as the free catalyst under ARCM/AROM and ARCM conditions (Table 11).

The third class rose up due to a drawback from polystyrene-supported catalysts. The catalysts from the previous families were prepared by coordinating the molybdenum complex to the polymer-supported diol ligand. Consequently, reactions involving any manipulation of the supported chiral ligand cannot be rigorously monitored, and the intermediates cannot be analyzed and purified. To overcome this problem, the authors conceived three new catalysts where the molybdenum complex was prepared just before the polymerization process (Scheme 52).

These new catalysts were characterized by possessing the biphenol moiety and carbene ligand attached to a polynorbornene polymer with 8% cross-linking prepared by ROMP (ring opening metathesis polymerization). As the polymer degree of cross-linking decreased, the reaction efficiency increased toward the free catalyst level. In this category, the authors found that the polymeric catalyst could provide identical or even superior yields and enantioselectivities when compared with the free catalyst under the same ARCM conditions (Scheme 53).

Unfortunately, polynorbornene supports suffer from oligomeric release under the reactions conditions, which will contaminate the final products. Both catalysts from the first and second categories failed the recycling assays due to dramatic drops in activity under a few recycle events.

One year before, Buchmeiser et al. reported the synthesis of a supported chiral Mo complex **191**, identical to the catalyst **188**, and tested it in ARCM reactions, providing similar results to catalyst **188**. This catalyst was submitted to recycle assays, where drops of 50% in activity were observed in the second cycle (enantiomeric excesses remained unchanged).³⁹²

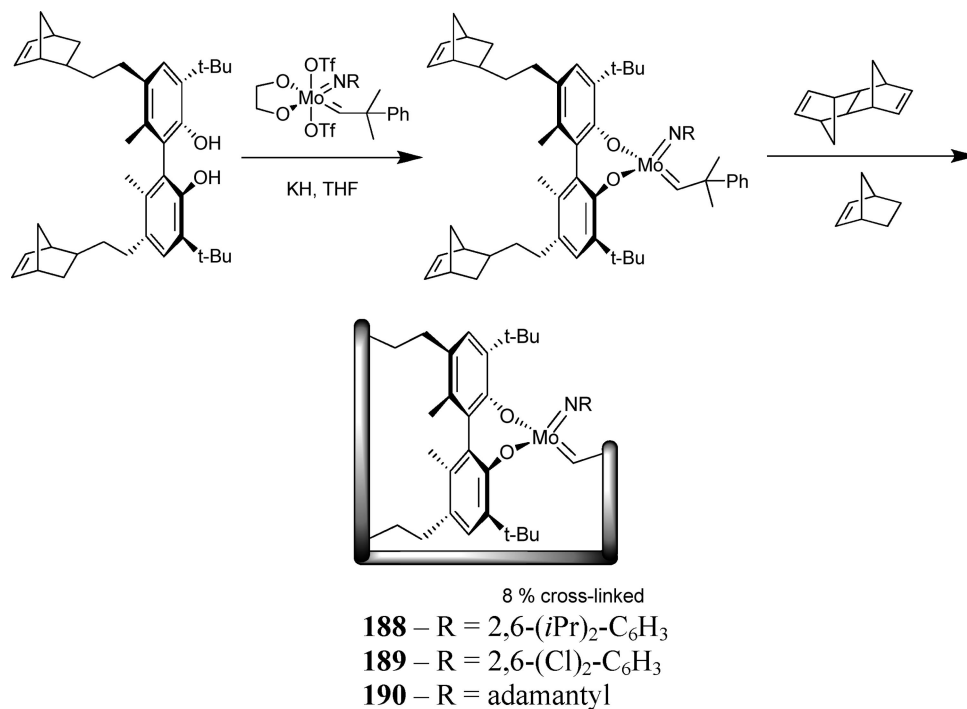
Buchmeiser et al. immobilized Schrock chiral olefin metathesis catalyst on Ag-perfluoroalkylsulfonate-modified PS and PS-DVB materials via arylimido ligand for the first time. The catalyst **192** was applied in ARCM reactions providing values of enantioselectivity close to those of the corresponding homogeneous catalyst (up to 95% ee). Despite heterogeneous catalyst being easily recovered, no data related to recycle experiments were given.³⁹³

Ruthenium-Based Catalysts. There is an interesting complementarity between ruthenium-based and molybdenum-based catalysts in metathesis reactions in terms of substrate reactivity and functional group tolerance. As an example, with a Mo-based catalyst some substrates tend to undergo competitive oligomerization which does not happen when Ru-based catalyst is applied.

Inspired by the ruthenium Grubbs catalyst, Hoveyda et al. designed, synthesized and tested an asymmetric version for asymmetric ring-opening metathesis (catalyst **193**, Table 12).

Catalyst **193** was an effective and practical chiral catalyst for enantioselective metathesis reactions (up to 98% ee), in particular in AROM/CM using aliphatic olefins such as 1-heptene and vinylcyclohexane. The authors found that this catalyst is air stable and can be recovered by silica gel

Scheme 52. Methodology for Molybdenum Metathesis Catalysts Immobilization by ROMP



Scheme 53. Asymmetric Metathesis Reactions with Molybdenum Catalyst Immobilized in Polynorbornene Polymer

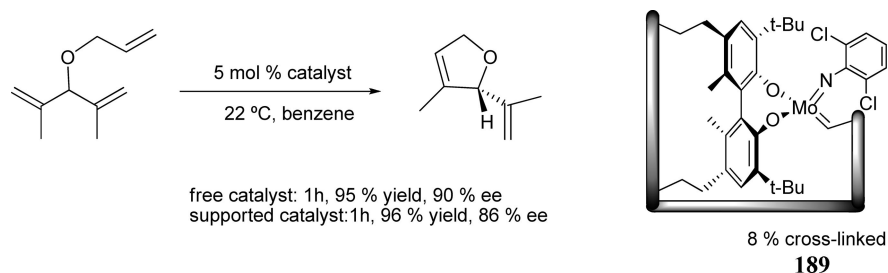
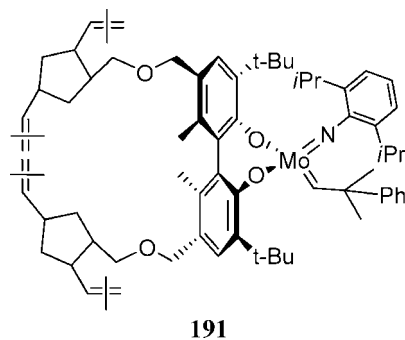
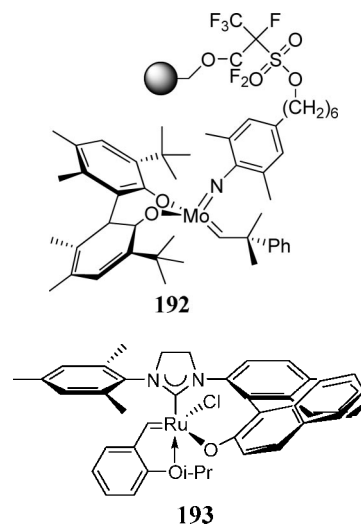


Table 12. -Asymmetric Metathesis Reactions with Recoverable Ruthenium Catalyst

R	temp (°C); time (h)	conv (%); yield (%)	recov. catal. (%)	<i>trans/cis</i>	ee (%)
Ph	50; 1.0	<98; 71	96	>98:2	80
<i>n</i> -C ₅ H ₁₁	50; 1.5	<98; 57	92	>98:2	>98
Cy	50; 1.0	<98; 60	88	>98:2	>98

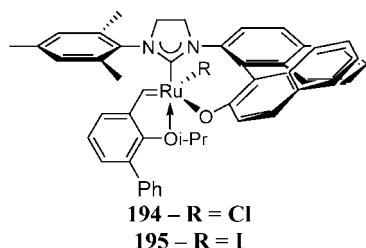


chromatography. It was reused once without any loss of performance.



Hoveyda and co-workers developed a catalyst family based on the catalyst **193** with slight structural changes. Curiously it was found that catalysts that performed 100 times faster than catalyst **193** were inefficiently recovered (catalyst **194**, <50%).³⁹⁴

Motivated by recent findings of Grubbs et al.,³⁹⁵ Hoveyda et al. decided to synthesize an iodide derivative of the first asymmetric Grubbs-type catalyst **195** by heating **194** (70 °C) with NaI in THF.³⁹⁶ As expected by the authors, this new



catalyst **195** generally afforded AROM/CM reactions with 2,6-disubstituted 3-hydroxypyrans in higher levels of enantioselectivity but with a 10-fold decrease in the reactivity. As a result a small percentage of catalyst **195** was recovered. Meanwhile, in this case catalyst **194** could be more efficiently recovered (by chromatography) and recycled up to five cycles with 10% yield erosion and without any decrease in enantioselectivity (Table 13).

The catalyst reusability and air stability makes catalyst **194** a noteworthy catalyst. However, the recovery protocol should be easier. A recent patent application was filed by the authors.³⁹⁷ In the case of molybdenum-based catalyst other methods for immobilization should be tested in order to minimize metal leaching.

15. Asymmetric Aldol-Type Reactions

The aldol reaction is an important transformation to obtain new carbon–carbon bonds generally with formation of stereocenters. There exist two main types of catalysis for aldol reaction: organocatalysis and Lewis acid catalysis. The first three subsections focus on several methodologies to recycle organocatalysts, while the last one will focus contributions to recycle Lewis acid catalysts. This section will also describe examples of aldol-type reactions like Mukaiyama-aldol, nitro-aldol, Mannich, and nitro-Mannich.

Cozzi et al. reported before 2002 the immobilization of proline on PEG (MW = 5000 Da) to catalyze aldol reactions between acetone and several aldehydes (as an example of this, with 4-nitrobenzaldehyde 77% ee was achieved). The catalyst was reused twice with similar efficiency.⁵

15.1. Heterogeneous Catalysts (Proline)

Fernández-Mayoralas et al. used several mesoporous and lamellar siliceous materials (MCM-41, silica, ITQ-2, and ITQ-6) with different topologies to heterogenize (by grafting) a proline derivative.³⁹⁸ The organic catalyst **196** was tested for hydroxyacetone aldol addition (20% of catalyst) to isobutyraldehyde and benzaldehyde (24 h in DMSO). From the results, MCM-41 proved to be the best support, affording the highest yield (45–55% with >99% ee) along with reutilization, twice with low yield erosion (~10%).

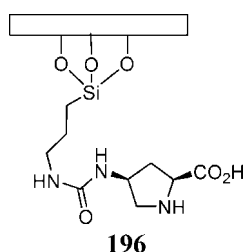
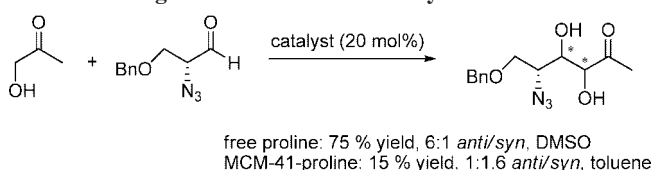


Table 13. Asymmetric Metathesis Reactions with Recoverable Ruthenium Catalyst

cycle	time (h); yield (%)	<i>E/Z</i>	ee (%)	recov. catal. (%)
1	1; 80	>98:2	94	90
2	1; 75	>98:2	93	85
3	1; 78	>98:2	94	88
4	1.5; 78	>98:2	94	80
5	1.5; 72	>98:2	94	67

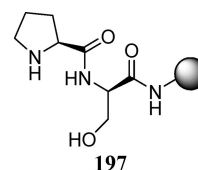
Scheme 54. Selectivity Differences for Asymmetric Aldol Reaction Using MCM-41–Proline Catalyst



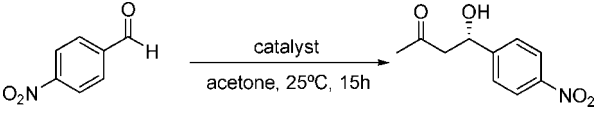
Interestingly, the reactions with supported catalysts could be run in a less polar solvent like toluene with almost unchanged yield (maximum yield variation of 15%). The diastereomeric ratio (*anti/syn* selectivity) did not follow the same behavior. When aliphatic aldehydes were used, no significant change could be detected, and when more polar aldehydes were used, total dr inversion was observed on going from free proline to supported proline in toluene (Scheme 54).

This inversion of dr was found to be related to some interactions between the reactants and the free silanol groups on the surface of the support, probably because they could provide new transition states for the transformation. High time exposure of polar aldehydes with free silanols will make the transformation less selective. Under microwave conditions, the reaction could be completed in shorter reactions times improving the selectivity (up to 90% yield). Recently, this heterogenized catalyst was tested with other types of ketones and showed that its efficiency is extremely dependent on the solvent nature.³⁹⁹

One of the major disadvantages of proline immobilization via grafting is related to some degree of enantioselectivity loss. In many protocols described, proline was covalently attached to a support through its carboxylate group, which is responsible for the high ee's observed in the DMSO system. The discovery by Gong and Wu that hydroxyprolinamides restore the activity by synergistic effect of an additional H-bond group donor (OH) with the proline amide granted a solution for proline-supported catalysts. Davis et al., motivated by this latter discovery, immobilized proline by grafting it into a TentaGel resin (PEG-PS).⁴⁰⁰ The proline in this supported catalyst **197** was separated from the polymer chain by a suitable spacer that has a near hydroxyl group (like Wu and Gong catalyst).



Dipeptides and tripeptides were chosen to act as spacer. Dipeptides containing Pro-Ser/Thr showed enhanced enan-

Table 14. Recycling Assays for Aldol Reaction with Proline Immobilized in a Polyelectrolyte Resin


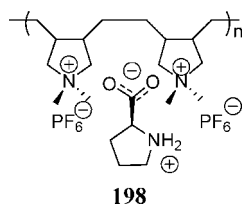
run	yield (%)	ee (%)
1	98	70
2	97	68
3	95	71
4	94	72
5	97	70
6	97	69

tioselectivity compared with the unspaced catalyst (30% vs 82% ee) in the 4-nitrobenzaldehyde aldol reaction with acetone (13 mol % of catalyst, -25°C and 41 h). A dipeptide spacer provides better results than a tripeptide spacer.

Almost simultaneously, Kudo et al. reported the application of proline tripeptides (D-Pro-Tyr-Phe) immobilized in PEG-PS aminated resins for aldol reactions in a triphasic solvent media (water/acetone/THF, 1/1/1).⁴⁰¹ Interestingly, this tripeptide behaved better than those reported by Davis et al. in terms of reactivity (quantitative yields, 71% ee). Furthermore, the catalyst could be recycled four times without any loss of efficacy. Recently, the same authors achieved a one-pot sequential acidic deacetalization and basic enantioselective aldol reaction between acetone and 4-nitrobenzaldehyde dimethyl acetal in the presence of Amberlyst. The recyclability of this system reached six cycles without erosion of efficiency.⁴⁰²

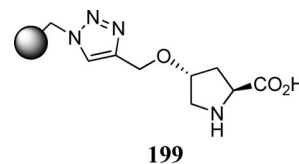
Zhang et al. applied (4*S*)-phenoxy-(*S*)-proline as an asymmetric catalyst for aldol addition of acetone to 2-nitrobenzaldehyde.⁴⁰³ Using only 10 mol % of catalyst, the authors generated the respective 1,3-hydroxyacetone in 90.2% yield and 83.4% ee in 16 h in the presence of β -cyclodextrin. The existence of the hydrophobic phenol moiety on the catalyst allowed the formation of a host–guest complex with the β -cyclodextrin. The heterogeneous character of such complex allowed catalyst separation by filtration and consequent reuse up to four cycles with 10% yield erosion and constant enantioselectivity.

Zlotin et al. reported the first example of proline immobilization in the polyelectrolyte (*S*)-proline/poly(diallyldimethylammonium) hexafluorophosphate and its application for aldol reactions.⁴⁰⁴ Aromatic benzaldehydes were reacted with acetone in the presence of catalyst **198** to afford the respective aldol product in good yields and ee's, comparable with those on the protocol with DMSO. The advantage of this system relies on its reutilization. The recovered catalyst (by filtration) could be reused up to six cycles with unchanged efficiency (Table 14).



Pericàs et al. anchored an organocatalyst for aldol reactions in water via a 1,3-dipolar cycloaddition between a Merrifield resin functionalized with an azide and an alkyne-substituted 4-hydroxyproline. Catalyst **199** promoted the aldol reaction

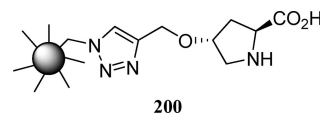
between cyclohexanone and benzaldehyde, but the reactivity was low and extended reaction times (18–144 h) were generally required to achieve quantitative conversions but with excellent chiral induction (*anti/syn* of 95:5, e_{anti} of 95%). The presence of catalytically amounts of DiMePEG₂₀₀₀ improved the reactivity of the system probably due to easier diffusion of the reactants, decreasing the reaction time and improving the isolated yields. Interestingly, the heterogeneous catalyst proved to be extremely recyclable without loss of efficiency.⁴⁰⁵



Recently, the same authors tested their Merrifield-supported 4-hydroxyproline in α -aminoxylation of aldehydes and ketones in chloroform with appreciable success. Excellent levels of enantioselectivities (>96% ee) and good yields were obtained for both aldehydes and ketones. Once again the resin was reused three times without loss of efficiency.⁴⁰⁶

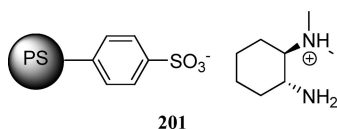
Gruttadauria et al. anchored the 4-hydroxyproline in a polystyrene resin to achieve its recycling in aldol reactions. The authors observed that water was the solvent of choice for aldol reactions between cyclohexanone and aromatic aldehydes. High isolated yields (up to 98%), *anti/syn* selectivity (96/4), and enantioselectivity (up to 98%) were achieved. Recycling investigations have shown that this material can be reused without loss of efficiency for at least five cycles.^{407,408} These good results were recently corroborated by Tao et al. using another type of linker that connects the proline moiety to the polystyrene.⁴⁰⁹

Portnoy et al. grafted proline-functionalized dendrons to a heterogeneous polystyrene support via dipolar cycloaddition (an example of this is catalyst **200**). A family of catalysts was evaluated in asymmetric aldol reaction between acetone and benzaldehydes (30 mol % catalyst). It was discovered that the dendron generation (spacer length) played an important role in this transformation. With a third generation catalyst, it was possible to achieve an enantioselectivity of 71%, but the yield was very low (35% yield). Some attempts were made to recycle these catalysts, but their activity rapidly decreased in a second cycle probably due to catalyst decomposition (but with consistent enantioselectivity).⁴¹⁰



Recently, Luo and Cheng described a new strategy to immobilize pyrrolidine-type organocatalysts. The authors constructed a library by combining a PS resin bearing sulfonic acid groups with several chiral amines to achieve immobilization by acid–base interactions. The support played a role as catalyst anchor and as modulator for activity and stereoselectivity. These heterogeneous organocatalysts were successfully applied in aldol and Michael addition reactions. Cyclic ketones and acetone were reacted with several benzaldehydes in the presence of 10 mol % of catalyst **201** providing the respective products

with excellent enantioselectivities and *anti/syn* ratio (up to 91:9 *anti/syn*, 97% ee for cyclohexanone, 83% ee for acetone). The catalyst retained most of its activity up to four cycles.⁴¹¹



15.2. Homogeneous Catalysts (Proline)

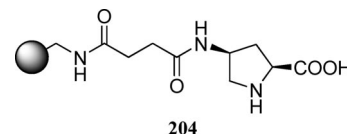
Benaglia et al. immobilized (2*S*,4*R*)-4-hydroxyproline on PEG₅₀₀₀ monomethylether for asymmetric aldol reactions.⁴¹² Two catalysts (**202** and **203**) with different inherent proline loading were prepared and showed good performance, highly comparable to those reported for the proline/DMSO protocol (Scheme 55). Catalyst **202** could be recovered in high yields (up to 80%) by diethyl ether precipitation and reused three times with constant enantioselectivity but falling reactivity (about 5% per cycle). Furthermore, the last could be efficiently applied in aldol reactions using other aldehydes or hydroxyacetone with good efficiency.

Tao et al. chose linear polystyrene to immobilize proline catalyst for asymmetric aldol reactions between benzaldehydes and cyclic ketones in wet DMF. Catalyst **204** behaved much better in terms of chiral discrimination (up to 96:4 dr and 96% ee) than in terms of activity (modest to good yields) probably due to the low catalyst loading applied (5 mol %). Reutilization was conducted after catalyst precipitation from the reaction mixture (four recycles with 10% overall efficiency loss).⁴¹³

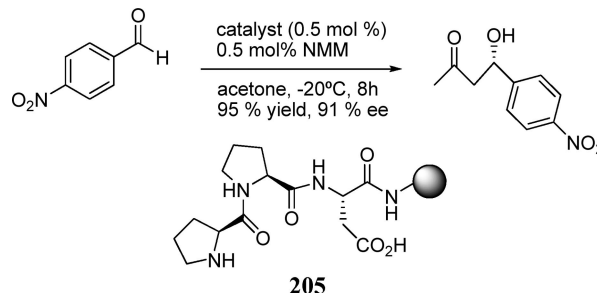
The recent discovery of a proline containing tripeptide (H-Pro-Pro-Asp-NH₂) that promotes higher induction levels than proline motivated further studies to improve its solubility in order to enhance its catalytic performance.⁴¹⁴ Wennemers et al. covalently attached such tripeptide to TentaGel resins and to PEG polymer chains.⁴¹⁵ PEG-supported tripeptide showed great solubility in several organic solvents and when tested for acetone aldol addition to 4-nitrobenzaldehyde showed the desired enhanced activity. As an example, using 0.5 mol % of catalyst the supported tripeptide reacted in 8 h at -20 °C to give 95% yield with 91% ee (Scheme 56), while the free tripeptide needed 24 h to achieve quantitative yield (98%) and the same level of enantioselectivity using 5 mol %.

TentaGel-supported tripeptide also proved to be as efficient as the unsupported tripeptide (93% vs 99% yield with equal ee) with recycling ability. Although enantioselectivity remained high during six consecutive cycles, its activity started to decrease after the second cycle.

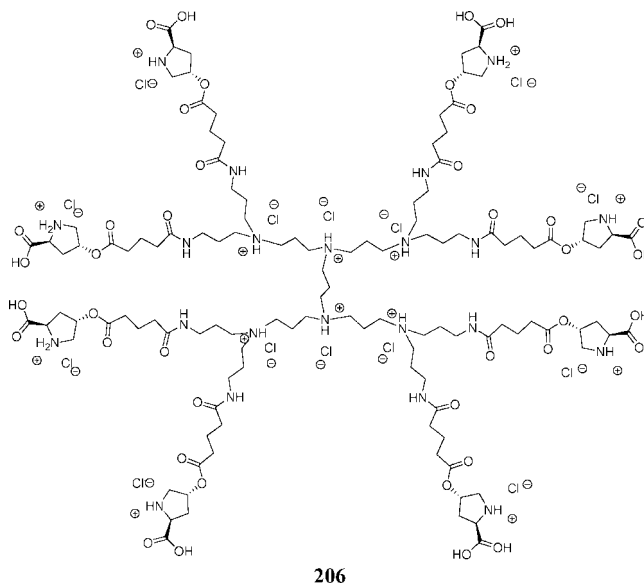
Kokotos et al. reported the immobilization of 4-hydroxy-(*S*)-prolines in diaminobutane poly(propyleneimine) dendrimers containing a glutamate spacer and its application in



Scheme 56. Asymmetric Aldol Reaction Using PEG-Supported Peptidic Catalyst

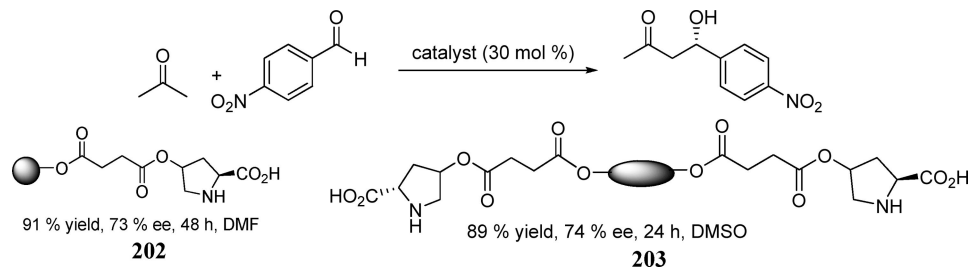


aldol reactions.⁴¹⁶ The second generation dendrimer **206** proved to be the most efficient among other generation catalysts, affording the respective aldol product between acetone and 4-nitrobenzaldehyde in 61% yield with 65% ee (which was somewhat inferior to the DMSO protocol, 68% yield with 76% ee).

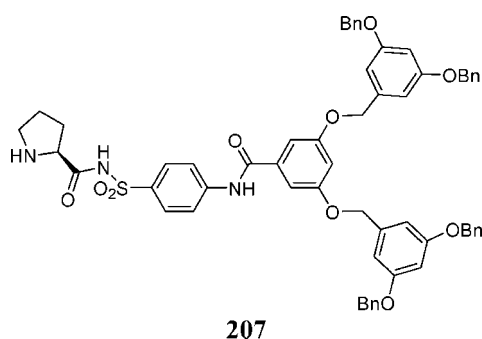


Envisioning an alternative, Zhao and Wang grafted a proline molecule to the core of a Frechet-type dendrimer. This new dendritic catalyst proved to be much more efficient than the previous providing the respective aldol product between acetone and 4-nitrobenzaldehyde in 72% yield and 87% ee. The catalyst also catalyzed the reaction of benzaldehydes with cyclic ketones providing almost enantiomeri-

Scheme 55. Asymmetric Aldol Reaction Using PEG-Supported Proline Catalysts



cally pure alcohols. It was possible to recover the catalyst by precipitation almost quantitatively. Catalyst **207** retained its catalytic activity during at least five cycles.⁴¹⁷



Luo and Cheng prepared a highly efficient hybrid organocatalyst for aldol reactions from chiral amines and polyoxometalate acids (Scheme 57). The catalyst **208** was soluble in the reaction solvent (acetone) and provided the respective alcohols with excellent yields (up to 99%) and excellent enantioselectivity (90–99% ee). The catalyst was precipitated by addition of diethyl ether and was reused four times with minimal yield erosion (10%) and consistent ee.⁴¹⁸

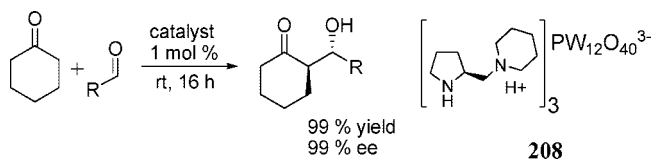
15.3. Alternative Reaction Media (Proline)

Loh and Toma reported simultaneously the use of an ionic liquid media for proline-catalyzed aldol reactions. Loh et al. evaluated the scope of using several imidazolium-based room temperature ionic liquids (RTILs) as solvent and verified that all tested solvents gave comparable or even higher enantioselectivities than traditional DMSO system.⁴¹⁹ However, the elimination product/aldol product ratio varied from 12:75 to 55:45 by changing the ionic phase. The [bmim]PF₆ ionic liquid proved to be the best solvent affording the aldol product of acetone and benzaldehyde (30 mol % proline) in 25 h in 58% isolated yield (75% conversion to aldol product) with 71% ee (Scheme 58).

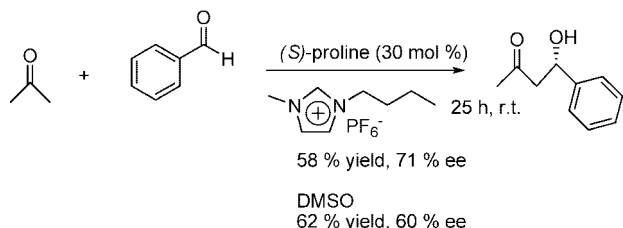
Since [bmim]PF₆ and proline have low solubility in the extracting organic solvent (diethyl ether), the catalytic system could be recycled up to four cycles with low erosion of yield and ee (<10%).

Toma et al. also studied the effect of the same ionic liquid ([bmim]PF₆) in aldol reactions.⁴²⁰ They obtained comparable values (yield and ee's) as those in Loh's work (and DMSO

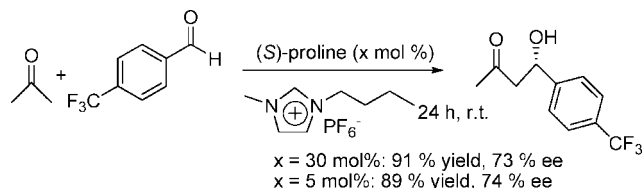
Scheme 57. Asymmetric Aldol Reaction Using Pyrrolidine Catalyst Immobilized in Polyoxometalate Acids



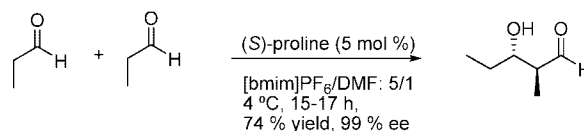
Scheme 58. Asymmetric Aldol Reaction with Proline in Ionic Liquids



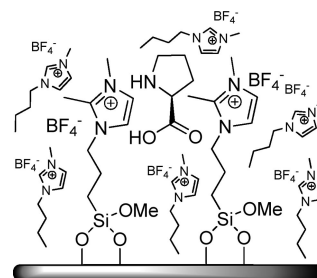
Scheme 59. Asymmetric Aldol Reaction with Proline in Ionic Liquids



Scheme 60. Asymmetric Cross-Aldol Reaction between Aldehydes with Proline in Ionic Liquids



Scheme 61. Silica Gel Modified and Treated with Ionic Liquids for Proline Immobilization for Aldol Reactions



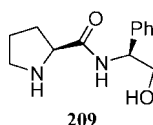
system) for acetone condensation with benzaldehyde (30 mol % of proline). However the authors expanded the methodology scope to other benzaldehydes, which reacted in good yields (60–94%) and ee's (63–82% ee). Interestingly, comparable results were obtained when proline loading was decreased from 30 to 5 mol % (Scheme 59). Loh et al. had observed a similar result that lowering the catalyst loading to 20 mol % resulted in an increase of reaction time and decrease of efficiency.

Two years later Córdova reported the first cross-aldol reaction between aldehydes in an ionic liquid phase.⁴²¹ Using a mixture of [bmim]PF₆/DMF: 5/1 with a lower proline loading (5 mol %) allowed the formation of β -hydroxy aldehydes in good yields (69–76%) and excellent enantioselectivity (>99% ee, Scheme 60). As previously discussed, the proline is not extracted from the ionic phase allowing its recycling up to four times without any efficiency erosion. The methodology was applied to natural polyketide synthesis with sequential cross-aldol couplings.

More recently, Guo and Huang simultaneously reported the application of [bmim]BF₄ as solvent in α -aminoxylation of aldehydes and ketones in the presence of 20% of proline.^{422,423} Guo et al. proved that this protocol was comparable or even superior to the original protocol using chloroform as solvent (up to 99% ee), besides allowing the catalyst reutilization. Huang et al. obtained better results in their recycling experiments on α -aminoxylation of both propanal and cyclohexanone, achieving six cycles with consistent enantioselectivity and with a small decrease in the reactivity (eroded 10%).

Gong et al. reported the utilization of L-prolinamide to catalyze the asymmetric direct aldol reaction between acetone and aromatic or aliphatic aldehydes in [bmim]BF₄.^{424,425} A wide scope of aldehydes were reacted with acetone in the presence of 20 mol % of (S,S,S)-pyrrolidine-2-carboxylic acid

(2'-hydroxyl-1',2'-diphenyl-ethyl)-amine, **209**, affording their aldol products in good yields (46–82%, higher than in acetone) with 91% to >99% ee's for aromatic aldehydes and 99% ee's for aliphatic aldehydes (higher than in acetone). The catalyst was also able to be recycled (by permanence in the ionic phase) and reused in the reaction of 4-CF₃C₆H₅COH with acetone up to four cycles with constant ee, though with considerable decrease in the reaction yield after the third cycle (50%).

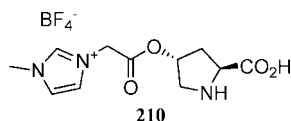


The next work is described in this section because the reaction occurs in a liquid ionic layer, despite the heterogeneous nature of the support.

Gruttadauria et al. covalently attached an ionic liquid moiety to the surface of silica gel. This monolayer was treated with more ionic liquid before being used to immobilize proline for aldol reactions. This ionic layer covering the silica gel particles acted as the reaction media, and it is readily recovered upon filtration (Scheme 61).^{425,426} With this protocol, 4-nitrobenzaldehyde was reacted with acetone in excellent selectivity to afford the respective aldol product in 85% yield and 66% ee (higher than in DMSO) and showed great consistency upon recycling up to four cycles where no efficiency erosion (30 mol % L-proline) was shown. From the fourth cycle, the enantioselectivity started to drop, while the isolated yield remained high (till cycle 9). Consistent regeneration of the support by recharging with fresh proline allowed the system to be recyclable up to 13 cycles. Recently, this methodology was extended to other linkers and to H-Pro-Pro-Asp-NH₂ organocatalyst. This last catalyst provided higher levels of enantioselectivity (up to 86% ee) but was less recyclable.⁴²⁷

Luo and Cheng reported the application of a functionalized ionic liquid in the aldol reaction of acetone and cyclopentanone with aromatic aldehydes (20 mol % catalyst). This ionic liquid bearing a chiral pyrrolidine proved to be easily recyclable up to six cycles with an increase of the reaction time by almost 2-fold (2 to 17 h). When cyclopentenone was tested the dr observed generally decreased from 4.8:1 to 2.1:1. The enantioselectivity of the minor diastereomer was superior to the one observed for the major diastereomer (~30% vs 10%).⁴²⁸

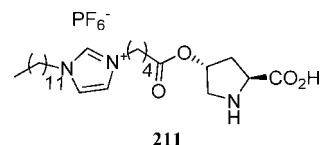
Chan et al. showed that the same catalyst could be attached to an ionic liquid functionality, which increased further the reactivity and enantioselectivity compared with proline/DMSO system (up to 87% ee). The catalyst **210** was extremely efficient under neat conditions and showed good recyclability (four cycles). The catalyst was recovered due to its insolubility in dichloromethane.⁴²⁹



More recently, Lombardo et al. tested two catalysts bearing ionic tags (imidazolium ring and quaternary ammonium) in asymmetric aldol reactions between cyclic and acyclic ketones and aromatic aldehydes in [bmim]NTf₂. The authors were able to reduce the amount of catalyst used to 5 mol %

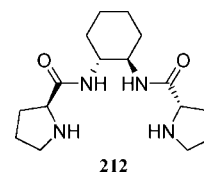
and still obtained superior results to those afforded using the original proline/DMSO system. However, this catalyst loading made the recycling protocol more difficult and limited reuse to two efficient cycles.⁴³⁰

Zlotin et al. immobilized the same catalyst using an ionic liquid with a pronounced amphiphilic character. Catalyst **211** was applied for the direct aldol reaction between cyclic ketones with benzaldehydes in water achieving excellent *anti/syn* and enantioselectivities (97:3, 99% ee for cyclopentanone). The good recyclability of **211**/water was demonstrated till a fifth cycle.⁴³¹



Luo and Cheng prepared a family of functionalized ionic liquids incorporated with chiral pyrrolidine and tested them as reusable organocatalysts for direct aldol reactions. The absence of the carboxylic acid functionality made these catalysts inefficient in terms of chiral induction (<10% ee) for direct aldol between acetone and benzaldehydes. The enantioselectivities increased to 30% when cyclic ketones were used. Despite this limitation, the catalyst showed good recyclability (up to six cycles).⁴²⁸

Kucherenko et al. developed a new highly active and recoverable (three cycles) catalytic system based on bis(prolinamide)cyclohexane **212**/[bmim][BF₄] for asymmetric aldol reactions between several alkyl ketones and nitrobenzaldehyde. The respective 3-hydroxyketones were prepared in moderate to good yields in the presence of a 3-fold excess of ketone with good enantioselectivities (6–70% ee).⁴³²



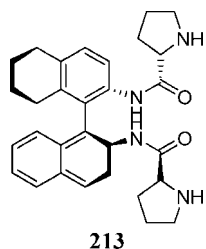
Han et al. tested the biorenewable ionic liquid [choline][proline] as catalyst in the aldol reaction between several ketones and benzaldehydes in water. In general, the reaction provided the respective product in yields comparable with those reported in the literature, but the enantioselectivity never rose above 10%. The ionic character of the catalyst allowed its retention in the water phase, while the products were extracted with ethyl acetate (five cycles).⁴³³

Xu and co-workers disclosed that a catalytical amount of an imidazolium ionic liquid bearing a camphorsulfonic anion can speed-up proline-catalyzed aldol reactions. Unfortunately, no data for catalytic system recycling is provided.⁴³⁴

Chandrasekhar et al. reported the utilization of low-weight poly(ethylene glycol), PEG MW = 400 Da, as reaction media for aldol reactions between acetone and several aldehydes.^{435,436} Not only had the system proved to be as efficient as DMSO, but also it was shown to have excellent consistency upon recycling. The immobilized proline (10 mol %) was retained in the PEG phase and was reused to add acetone to 4-nitrobenzaldehyde up to 10 cycles with constant enantioselectivity (67%) and some yield erosion (10%).

Nájera et al. reported the application of the BINAM-bisprolinamide **213** as recoverable catalysts in the direct aldol condensation reaction of 4-nitrobenzaldehyde with acetone

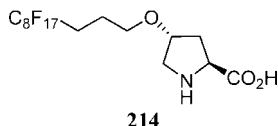
in a mixture of DMF/water 1/1. The catalyst was recovered by acid/base extraction protocols and was reused twice with 18% yield erosion (from quantitative) and constant 79% ee.⁴³⁷ Recently the authors demonstrated that the catalyst retains its efficiency under solvent-free conditions and it was also possible to reduce the quantity of ketone applied to 2 equiv.⁴³⁸



213

Benaglia et al. proved that BINAM–monoprolinamide could be used to catalyze aldol reaction between acetone and benzaldehyde “on water” with excellent chiral induction in the presence of stearic acid (dr up to 99% and ee up to 95%). Unfortunately, the recovered organocatalyst lost about 40% of its activity, though the chiral induction remained unchanged.⁴³⁹

Fache and Piva functionalized 4-hydroxy-L-proline with a perfluoroalkyl chain (catalyst **214**) and was applied as an organocatalyst in the aldol reaction of 4-nitrobenzaldehyde with acetone in a perfluorous-phase (benzenetrifluoride).⁴⁴⁰ The aldol product was isolated in 72% yield with 73% ee in one day. Despite the low reaction rate the result was highly comparable to the one obtained with proline in DMSO (68% yield with 76% ee).



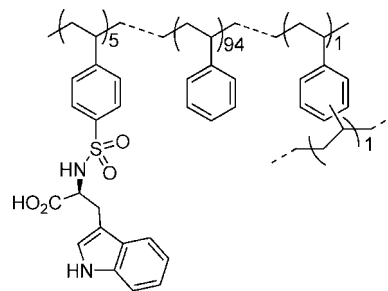
214

The immobilization of proline became one of the most explored targets to achieve recycling assays. In a few years, several alternative solvents and supported catalysts have been explored with excellent results. Ionic liquid based protocols described in this section have an advantage compared with supported catalysts, due to the required catalyst synthesis on the latter.

15.4. Lewis Acid Catalysts

Orlandi et al. before 2002 used a polymerized PS-based bisoxazoline ligand to catalyze (with Cu(OTf)₂) the Mukaiyama-aldol reaction between a silylketene and methylglyoxalate. This catalyst besides offering high enantioselectivity (91% ee) was reused seven times with consistent enantioselectivity.

Itsumo et al. prepared a polymer-supported (*S*)-tryptophan by copolymerization of styrene, divinylbenzene, and a chiral *N*-sulfonylated α -amino acid monomer derived from (*S*)-tryptophan. This ligand, **215**, was coordinated to 3,5-bis(trifluoromethyl)phenyl boron dichloride and used as an asymmetric catalyst for the Mukaiyama aldol reaction. The polymeric catalyst proved to be only slightly less enantioselective than the homogeneous one achieving good to excellent yields with enantioselectivities up to 95% ee for Mukaiyama aldol reaction between benzaldehydes and silylenol ethers. The recyclability of the polymer was demonstrated in a second run.⁴⁴¹



215

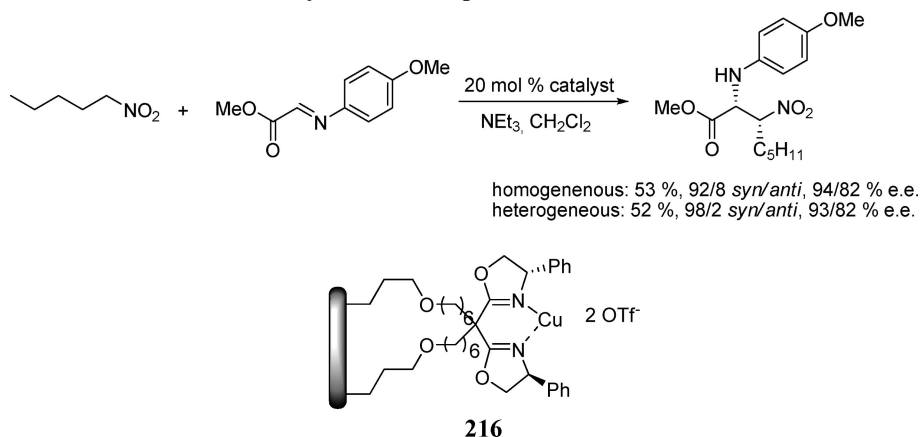
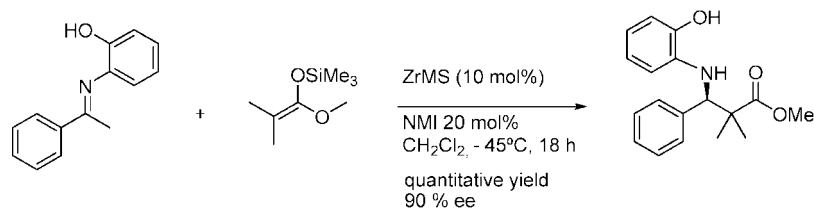
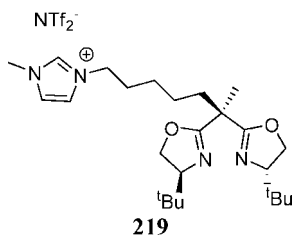
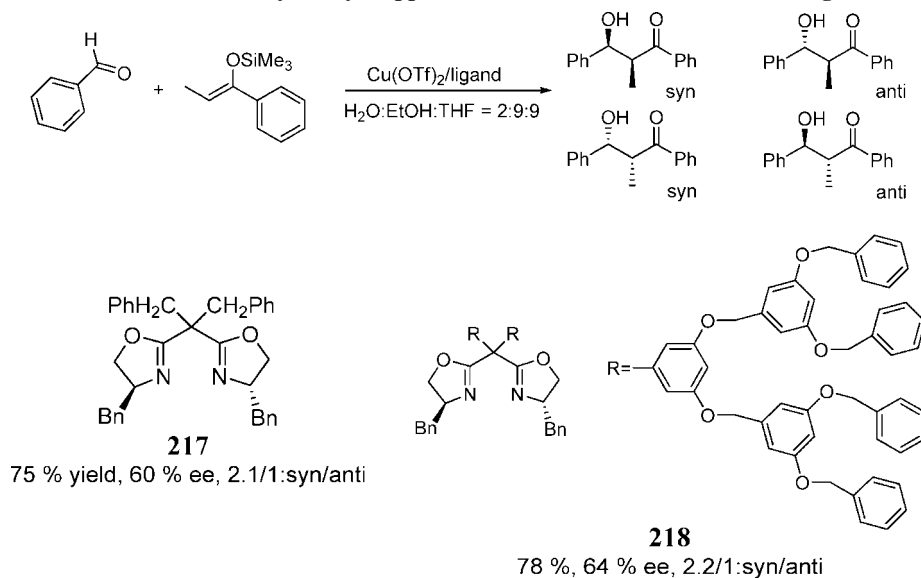
Kim and Hyeon immobilized a chiral bisoxazolidine ligand on mesoporous silica SBA-15 and examined its performance on the asymmetric copper-promoted nitro-Mannich reaction (Scheme 62). The catalyst heterogenization had a positive impact on the reaction enantioselectivity surpassing the homogeneous catalyst. However, the reaction became slower, 3 days being necessary to achieve comparative yields that are obtained in 1 day using the homogeneous Cu-Box catalyst. The catalyst **216** was easily recovered and reused five times without loss of reactivity. However, the enantioselectivity and diastereoselectivity decreased gradually on each cycle.⁴⁴²

Kobayashi et al. synthesized a chiral zirconium catalyst immobilized in molecular sieves powder.^{443,444} It was prepared from Zr(OTf)₄, (*R*)-6,6'-bis(pentafluoroethyl)-1,1'-bi-2-naphthol, *N*-methylimidazole (NMI), and powdered MS 5 Å in benzene at 80 °C for 2 h. After solvent removal under reduced pressure at 50 °C for 1 h, a chiral zirconium catalyst with powdered molecular sieves was formed. Such catalyst was tested in a Mannich-type reaction of an aromatic imine with ketene silyl acetal, furnishing quantitative yields with 90% ee of the respective product in 18 h (Scheme 63). The methodology was successfully expanded to other imines and ketene silyl acetal combinations with comparable or even higher yield and ee. The Lewis acid catalyst showed great stability if stored under air, and its heterogeneous character allows an easy recovery, and it could be reused twice without any loss of efficiency (despite some leaching detected in all cycles, ~5%).

Fan et al. prepared a dendronized chiral Box for copper-catalyzed Mukaiyama-aldol reactions in aqueous media (water/ethanol/THF = 2:9:9).⁴⁴⁵ Dibenzyl-substituted chiral Box was doubly alkylated with four-generation dendrons at the C-bridge atom, and those new catalysts were tested with standard Mukaiyama-aldol reaction. Second-generation dendrimer proved more efficient than zero-generation dendrimer (equivalent to unsupported catalyst) affording 1,3-dihydroxyketone with 78% yield in 64% ee and 2.2/1 syn/anti selectivity (Scheme 64).

This supported catalyst could be recovered quantitatively by precipitation and was reused without copper recharge with falling activity.

Doherty and Hardacre demonstrated the positive impact that the [emim]NTf₂ exerted on the Mukaiyama-aldol reaction between methyl pyruvate and 1-methoxy-1-trimethylsilyloxypropene. When this transformation was run in IL media at room temperature, catalyzed by Cu(II)-*t*-BuBox, it was possible to obtain the respective product in 90% ee (at –78 °C in dichloromethane an ee of 86% was observed). The catalytic activity of this system was retained over three cycles if an ionic tag was present on the Box ligand (ligand **219**).

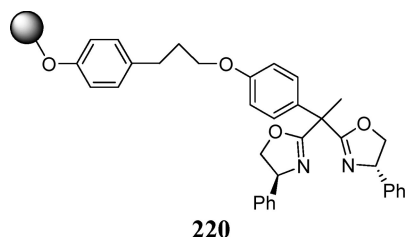
Scheme 62. Nitro-Mannich Reaction Promoted by Cu-Box Complex Anchored to SBA-15**Scheme 63. Mannich-type Reaction Catalyzed by heterogeneous Zr-BINOL-MS Catalyst****Scheme 64. Mukaiyama-Aldol Reaction Catalyzed by Copper in the Presence of Dendritic Box Ligand**

The authors also studied the possibility of recycling the catalyst by electrostatic interaction with silica. They found that it was necessary to treat the silica with the ionic liquid to achieve excellent levels of enantioselectivities for this reaction (up to 91% ee with ligand **219**). Silica modified with imidazolium units and treated with ionic liquid was also prepared and studied in this transformation. It was found that it provided slightly higher enantioselectivities (up to 96% ee) but two fewer recycles than unmodified silica (eight

cycles vs six cycles). This result is in contradiction with Gruttadauria's findings for proline-catalyzed aldol reactions. Probably the silica gel support is not totally inert under Mukaiyama-aldol reaction conditions.⁴⁴⁶

Benaglia et al. reported PEG-immobilized Box application to Mukaiyama-aldol reactions in water (20 mol %).⁴⁴⁷ The Cu-Box catalyst **220** did not suffer from enantioselectivity lowering upon immobilization since slightly higher ee's were observed (55–62% ee using benzyl-substituted Box) compared with other protocols in water (53% ee using isopropyl-substituted Box). Unfortunately, lower chemical yield (13–26% vs 88% yield) was obtained due to low aldehyde solubility in water since no surfactant was used. Extraction of the Mukaiyama-aldol condensation product from water with an organic solvent in which PEG–Cu-Box is not soluble allowed catalyst recovery up to 85% yield. The recovered

catalyst was pretreated before being reused twice with low yield and ee erosion (5% and 10%, respectively).

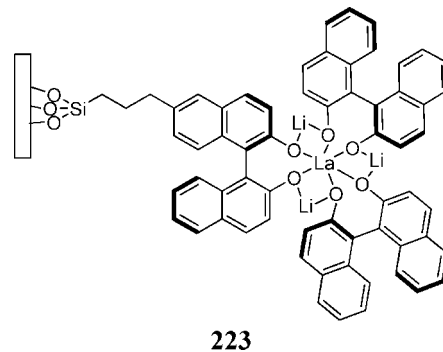


Benaglia et al. prepared two new fluorinated Box ligands, which were characterized by their low fluorine content (for Box **221** 46.2% and for Box **222** 38.1%), light fluorosyl ligands.³⁸⁰ These new two ligands were tested for Cu(II)-promoted Mukaiyama-aldol reaction between silylketene and ethylglyoxalate (Scheme 65). Catalyst Cu/**222**, C_1 -symmetric, behaved better in terms of enantioselectivity (85% ee, not far from the 92% ee obtained by Evans) than C_2 -symmetric catalyst Cu/**221** (7% ee). The recovered ligand **222** was reused once with minimal efficiency erosion.

Abdi et al. chemically attached a chiral lanthanum–lithium–BINOL ligand to the surface of silica and on the inside of micropores in MCM-41.⁴⁴⁸ The heterogeneous catalyst was tested for nitroaldol between nitromethane and several alkylic aldehydes (3.3 mol %, THF, -42°C). This supported catalyst **223** proved to be slightly less efficient than the unsupported analogue affording the respective aldol products in up to 86% yield and in 84% ee. The catalyst immobilized on MCM-41 tended to afford higher enantioselectivities due to the pore effect. This latter catalyst was reused 3 times with minimal yield and ee erosion.

Choudary and Kantam tested their catalyst developed for conjugated additions (nanocrystalline magnesium oxide) in direct asymmetric aldol reaction between acetone and aromatic aldehydes in the presence of chiral 1,2-diaminocyclohexane. The respective aldol products were obtained in good yields and with moderate enantioselectivities, but the catalyst could be reused up to four cycles with consistent outcome.⁴⁴⁹ Recently, the authors also applied a nanocrystalline copper oxide to this reaction and obtained the same results.⁴⁵⁰

Choudary et al. used commercially available magnesium oxide crystals containing Lewis acidic sites (Mg^{2+}), Lewis basic sites (O^{2-} and O^-) and isolated Brønsted hydroxyls (NAP–MgO). This catalyst was tested in the nitroaldol reaction between nitromethane and several benzaldehydes in the presence of (*S*)-BINOL (-78°C , THF). The respective



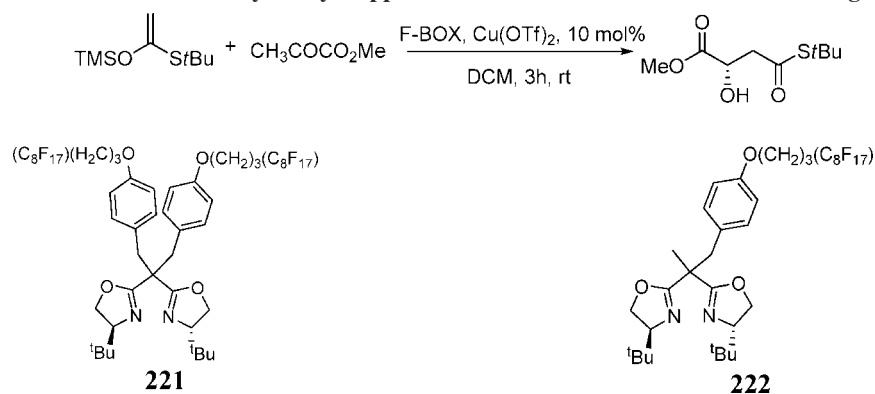
1,2-nitroalcohols were obtained in excellent yields (up to 95%) and good to excellent enantioselectivities (60–98% ee).⁴⁵¹

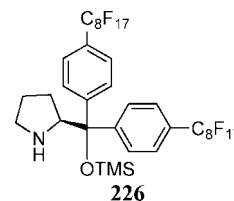
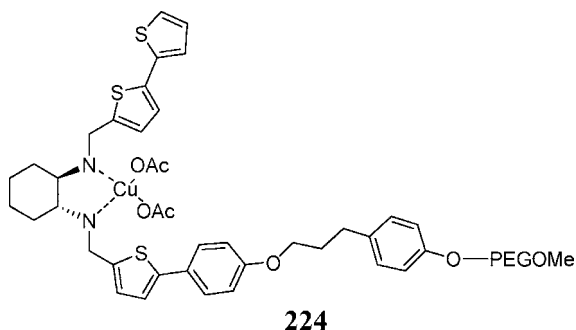
The application of this heterogeneous catalyst was also demonstrated in the preparation of chiral epoxides via a two-step Claisen–Schmidt condensation and asymmetric epoxidation reaction. The epoxidation step with NAP–MgO showed comparable ee's with an absolute configuration similar to that observed in the homogeneous system using dibutylmagnesium, diethyl tartarate, and *tert*-butylhydroperoxide (up to 98% ee).⁴⁵²

Bandini and Umani-Ronchi tethered a chiral diamino-bithiophene derivative to MeO-PEG_{5000} to achieve the recycling of the Cu(II) complex in the nitromethane addition to aldehydes. The traditional reaction was run in dry ethanol, but the supported catalyst **224** was not totally soluble in this solvent. Therefore a large excess (40 equiv) of nitromethane was necessary to solubilize the catalyst, and in this way, the authors achieved quantitative conversions with 89% ee. The catalyst could be retrieved by evaporation of volatile compounds and washings with diethyl ether. The recovered catalyst was reused up to five cycles without recharge of copper salt with consistent enantioselectivity (84–87% ee) and only moderate decreasing conversions.⁴⁵³

The application of proline and proline-type catalysts in organocatalysis boosted its study as a potential recoverable catalyst. Heterogenized proline and application of ionic liquids as catalysts or solvent media are the most explored recycling techniques for aldol reactions. Both produced good results in terms of recyclability, but the latter also proved to enhance the organocatalyst performance. Several Lewis acid catalyzed aldol reactions during the last years were explored broadening the number of contributions. Primarily, the protocols are heterogeneous-based.

Scheme 65. Mukaiyama-Aldol Reaction Catalyzed by Copper in the Presence of Perfluorinated-Box Ligand

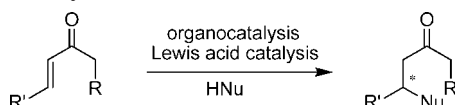




16. Asymmetric Michael Additions

The asymmetric Michael addition reaction (Scheme 66) is an important transformation to obtain new carbon–carbon bonds generally with formation of new stereocenters. There exist two main types of catalysis for this transformation: organocatalysis and Lewis acid catalysis. This section first will discuss several methodologies to recycle organocatalysts and then will focus on contributions to recycle Lewis acid catalysts.

Scheme 66. Asymmetric Michael Additions



Recyclable Organocatalysts. Prior to 2002, Alvarez et al. immobilized quinine and quinidine alkaloids in Merrifield resins with several spacers. The best catalyst provided 85% yield with 87% ee for cyclic acetoacetate addition to methylvinylketone.⁵

Wang et al. designed and prepared a fluoros (*S*)-pyrrolidine sulfonamide **225** to catalyze the asymmetric 1,4-addition of cyclic ketones to nitroolefins in water.⁴⁵⁴ The presence of a C₄-fluorous tail made the catalyst hydrophobic, forcing some degree of aggregation with the substrates in the aqueous phase, enhancing in this way the reactivity (compared with lighter fluoros catalysts). In fact, cyclohexanone was reacted with *trans*- β -nitrostyrene over 9 h to afford the respective product in 95% yield with 90% ee and 27:1 dr (10 mol %). The light-fluorous catalyst was almost quantitatively recovered (>90%) using a fluoros solid-phase extraction technique and was reused up to six cycles with consistent enantioselectivity though with some yield erosion (22%, Table 15).

Almost simultaneously, the same authors tested a fluoros (*S*)-diphenylpyrrolidinemethanol silyl ether **226** as a catalyst in the asymmetric 1,4-addition of aldehydes to nitroolefins.⁴⁵⁵ In this case, the reaction was performed in a fluoros solvent (CF₃Ph), using 20 mol % loading, affording the desired

product in high yields (>82%) and excellent ee (>97%). The light-fluorous catalyst was also recovered by the same technique and reused in six consecutive runs with unchanged outcome (Table 16).

Proline also catalyzes the asymmetric 1,4-additions of cyclohexanone to nitroolefins, but a lower level of enantioselectivity was observed (50% ee in MeOH). Salunkhe et al. used ionic liquids, such as [moemim]OMs, to replace methanol as the reaction solvent, improving the reaction enantioselectivity (73% ee in the presence of 40 mol % of proline).⁴⁵⁶ Unfortunately not all ketones showed the same behavior as observed when using cyclohexanone (low yields and ee's for other acyclic ketones). The catalyst solubility in the ionic phase allowed its reutilization up to three cycles with constant yield (75%) though with a considerable drop in selectivity (65% erosion).

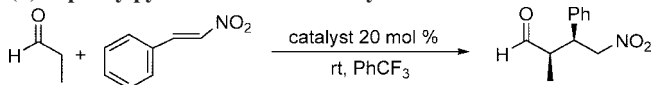
Benaglia et al. tested their proline-immobilized catalyst **202** described in the aldol section for the iminium-promoted addition of nitro-alkenes to cyclohexenone and enamine-catalyzed addition of ketones to 2-nitrostyrene.⁴⁵⁷ In the case of enamine-type catalysis, the supported catalyst did not give comparable yields and ee's (60% and 35% ee) to those with the unsupported proline catalyst (79% and 57% ee). Iminium catalysis was tested under Yamaguchi conditions (81% yield and 59% ee's) using sodium proline as the catalyst, and also in this case a lower efficiency was observed (65% yield and 42% ee). The recycling experiments on iminium-type catalysis were the most robust, affording consistent yields and only 25% erosion of ee's after four cycles.

Wang and co-workers anchored a chiral pyrrolidine containing a near imidazolium unit to a Merrifield resin and tested it as catalyst for asymmetric addition of cyclic and acyclic ketones to nitrostyrenes. With 10 mol % **227**, it was possible to run this reaction under solvent-free conditions, generally achieving quantitative yields, enantioselectivities above 90%, and near-perfect >99:1 diastereomeric ratios after 24 h. This heterogeneous catalyst was recycled seven times with only 10% erosion of activity.⁴⁵⁸

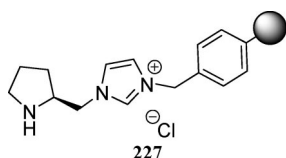
Zhao et al. anchored a 4-aminoproline organocatalyst to PEG using two sulfonamide–succinate linkers. The catalyst **228** furnished higher levels of chiral induction in 1,4-addition of cyclohexanone to nitrostyrene than free proline. Several substrates were tested with this catalyst, providing the

Table 15. Recycling Assays for Asymmetric Michael Additions Catalyzed by Fluorous (*S*)-Pyrrolidine Sulfonamide

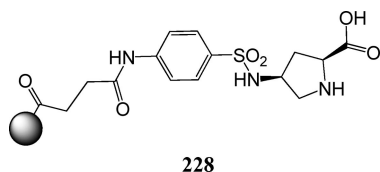
cycle	time (h)	yield (%)	ee (%)	dr
1	6	92	90	34:1
2	9	95	90	33:1
3	10	90	90	33:1
4	14	95	89	36:1
5	24	85	89	22:1
6	50	70	89	11:1

Table 16. Asymmetric Michael Addition Catalyzed by Fluorous (S)-Diphenylpyrrolidinemethanol Silyl Ether


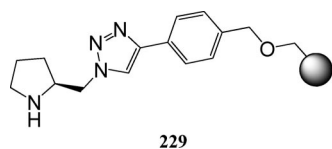
cycle	time (h)	yield (%)	ee (%)	dr
1	4	89	>99	21:1
2	5	86	>99	24:1
3	10	90	>99	23:1
4	20	90	>99	24:1
5	23	89	>99	23:1
6	36	86	>99	28:1



products in good yields (24–94%) with excellent diastereoselectivities (>98/2) and moderate enantioselectivities (5–86%). The recovered catalyst obtained by precipitation was reused several times, but in the second cycle, a considerable decrease in the conversion (30%) was observed. However, the enantioselectivity remained constant (60% ee).⁴⁵⁹



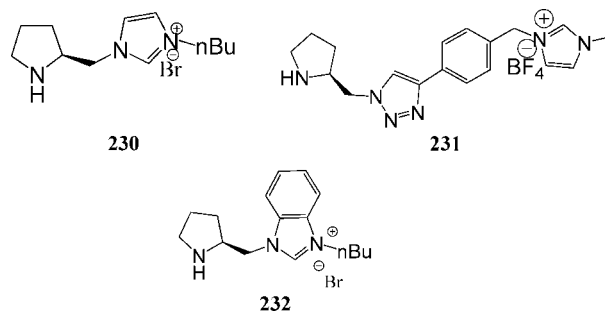
Independently, Wang and Pericàs and their co-workers immobilized a pyrrolidine derivative of proline in a polystyrene resin bearing alkyne groups via 1,3-dipolar cycloaddition for asymmetric Michael addition reactions.^{460,461} The organocatalyst **229** provided very good results for cyclohexanone 1,4-addition to several nitrostyrenes, when the reaction was run in water and in the presence of an additive (DiMePEG 10 mol %, catalyst 10 mol %, quantitative conversions, *syn/anti* 95:5, and ee's up to 99%). The catalyst was recycled three times without yield and selectivity erosion. When the reactions were run using ketone as solvent, the recyclability achieved 10 cycles.



Luo and Cheng prepared a family of ionic pyrrolidines and used them as organocatalysts for asymmetric Michael addition of ketones to nitrostyrenes (TSIL, catalyst **230**). The reaction between nitrostyrene and cyclohexanone was performed under solvent-free conditions in the presence of 15 mol % catalyst and 5 mol % trifluoroacetic acid. The products were obtained in excellent yields (up to 100%), selectivities (*syn/anti*, 99:1), and enantioselectivities (up to 99%). At the end of the reaction, the catalyst was recovered by precipitation (addition of diethyl ether) and was reused three times slowly losing its reactivity (increased reaction time). The ionic liquid moiety not only acts as a phase tag to facilitate catalyst recycling but also can function as an efficient chiral

inductor group to ensure high selectivity (by electronic interference with nitro group).

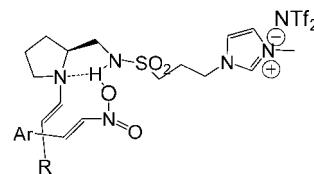
Identical results were obtained by Liang et al. who linked the ionic tag via 1,3-cycloaddition between an azidopyrrolidine and ionic tags bearing an alkyne (catalyst **231**).^{462,463}



The same authors described that an identical catalyst (catalyst **232**) can be applied efficiently in the desymmetrization of 4-substituted cyclohexanones in Michael addition reactions, providing products (with three asymmetric centers) in good diastereoselectivities (up to 8.1:1).⁴⁶⁴ Xu et al. showed that this type of catalyst forms a host–guest complex in PEG-800, which provided a protocol with higher recyclability, up to seven cycles.⁴⁶⁵

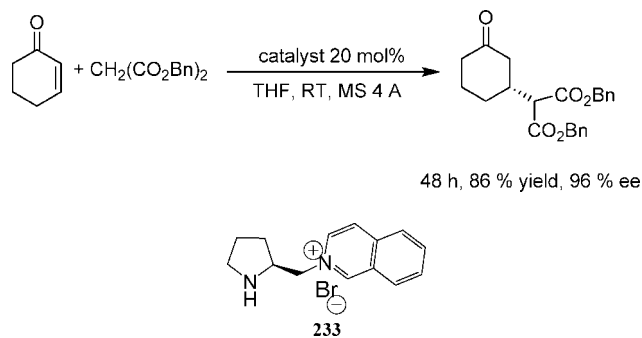
Headley and co-workers attached the same functionalities together using a 3-chloro-propane-1-sulfonyl chloride as the linker. This organocatalyst was tested in Michael addition reactions of aldehydes with nitrostyrenes providing the respective products in moderate yields (up to 64%), good enantioselectivities (up to 82% ee), and high diastereoselectivities (*syn/anti* ratio up to 97:3). The authors rationalized that the high levels of selectivity were due to a hydrogen bond formed between the nitrostyrene and sulfonamide rather than the presence of the ionic group (Scheme 67). The catalyst was efficiently recycled twice.⁴⁶⁶ It was possible to increase the reaction yields maintaining the same levels of enantioselectivity when the reaction was conducted in methanol and using a catalyst bearing an ionic liquid with a shorter alkyl chain (only one methylene between imidazolium ring and sulfoxide).⁴⁶⁷

Scheme 67. Mechanistic Rationalization for the High Levels of Selectivity

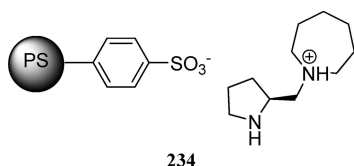


Xu et al. prepared a family of pyrrolidine–pyridinium-based organocatalysts for asymmetric Michael addition of cyclohexanone to nitrostyrenes in ionic liquids ([bmim]BF₄). The best catalyst, **233**, provided the respective products in excellent yields, selectivities, and enantioselectivities and proved to be recyclable (together with the ionic liquid phase) four times (quantitative yields, up to >99% ee, and >90:10 *syn/anti* selectivity).⁴⁶⁸ Headley et al. explored the pyrrolidine-based chiral pyridinium ionic liquids under neat conditions obtaining the same results.⁴⁶⁹

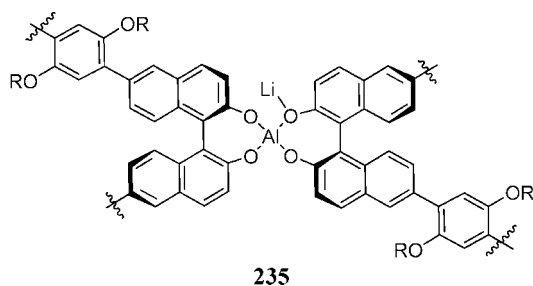
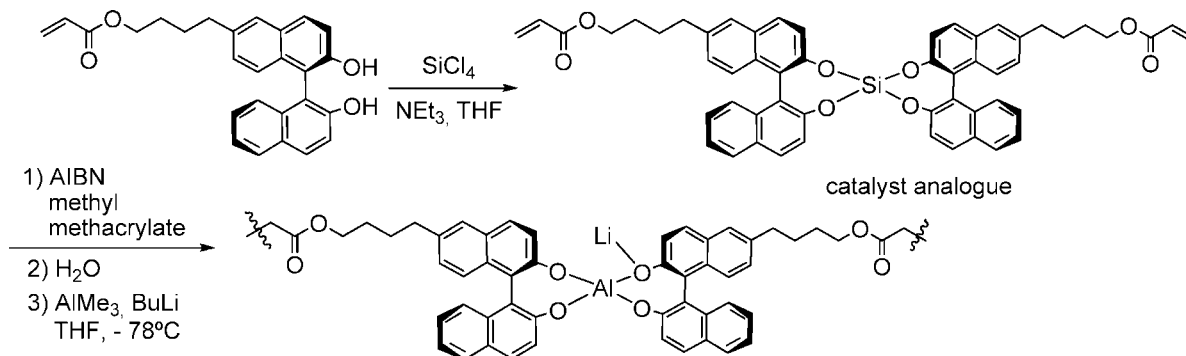
Recently, Luo and Cheng described a new strategy to immobilize pyrrolidine-type organocatalysts. The authors constructed a library by combining a PS resin bearing sulfonic acid groups with several chiral amines to achieve

Scheme 68. Asymmetric Michael Addition Catalyzed by Insoluble Self-Assembled Catalyst

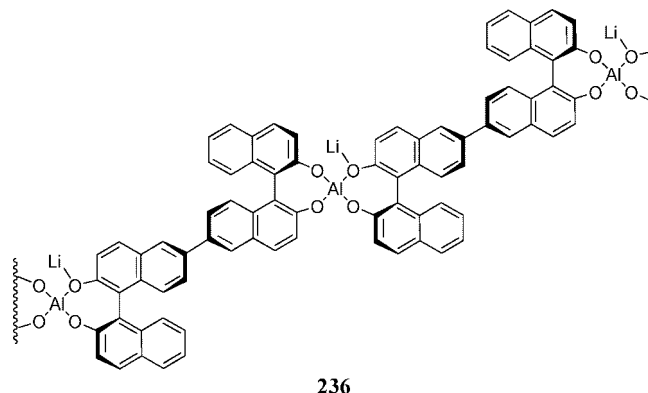
the immobilization by acid–base interactions. The support played a role as catalyst anchor and as modulator for activity and stereoselectivity. These heterogeneous organocatalysts were successfully applied in aldol and Michael addition reactions. Cyclic ketones and acetone were reacted with several nitroolefins in the presence of 10 mol % catalyst **234** providing the respective products with excellent enantioselectivities and *anti/syn* ratio (up to 94:6 *anti/syn*, 87% ee for cyclohexanone). The catalyst retained most of its activity up to six cycles.⁴¹¹



Recyclable Metal-Based Catalysts. Before 2002, Arai et al. prepared a poly-ALB compound, **235**, and successfully applied it in the asymmetric 1,4-addition of malonates to cyclohexenone in 78% yield and 93% ee. This catalyst was reused four times with 35% yield and 20% ee erosion.⁵

**Scheme 69. Preparation of Polymeric ALB Catalyst via the Catalyst Analogue Concept**

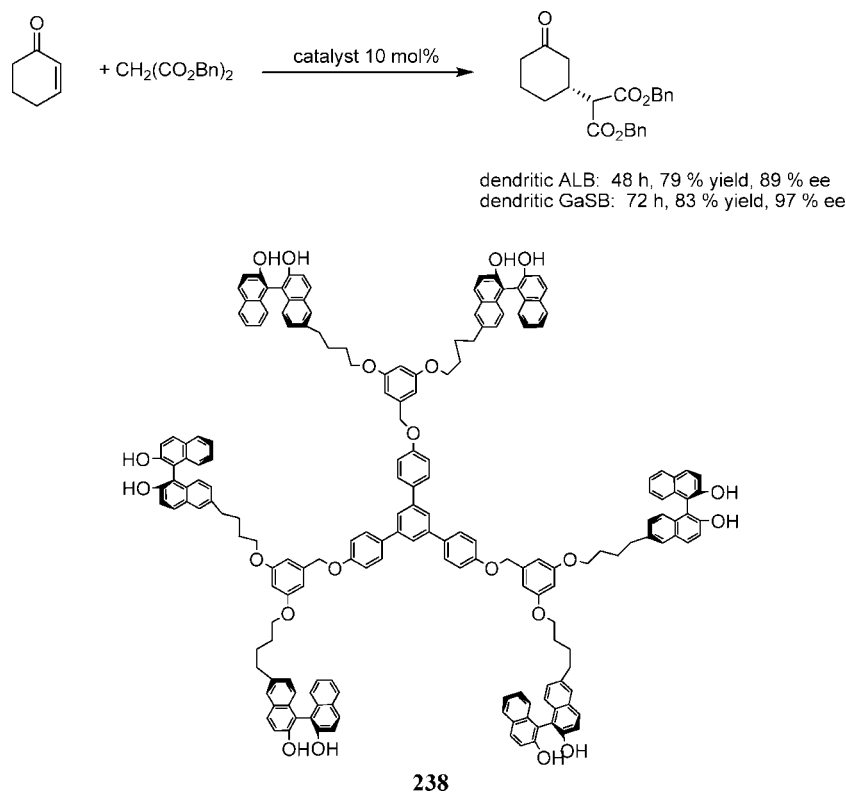
Takizawa et al. reported the first example of a chiral self-assembled structure, formed through self-assembly of chiral multidentate ligands with a metal that acted as an asymmetric catalyst for Michael additions in high enantioselectivity.³⁸⁷ Catalyst **236** was simply prepared by treating (*R,R*)-bis-(BINOL) with LiAlH₄ and BuLi in THF at 0 °C to obtain a white solid compound.



This insoluble polymeric catalyst was tested in enantioselective Michael addition of benzyl malonates to cyclohexenone and showed a similar performance (Scheme 68) to the homogeneous monomer ALB (Al–Li–bis(binaphthoxide), 12 h, quantitative yield, 97% ee).

At the end of the reaction, the supernatant solution was removed with the aid of a syringe and the catalyst could be reused. In the fourth cycle, significant erosion on the activity (~30%) and enantioselectivity (~20%) was observed.

Sasai et al. developed a new synthetic methodology to prepare cross-linked polymers for multicomponent asymmetric catalysis based on the concept of catalyst analogue (Scheme 69).⁴⁷⁰ The Si-tethered BINOL complex is more stable than the structurally identical ALB complex, which allowed its application as template during the polymerization to provide the correct cross-linking degree to the polymer, being later hydrolyzed to furnish the free ligand. The ligand was then treated with AlMe₃ and BuLi to provide the polymeric ALB-type catalyst. When the catalyst **237** was applied, the enantioselectivity obtained was 91% ee, while if no catalyst analogue was used to act as a template only 21% ee was observed (10 mol %). In the case of ALB complexes, the requirement of coordination of two BINOLs to the same titanium metal to achieve high levels of enantioselectivity was clearly favored by the construction

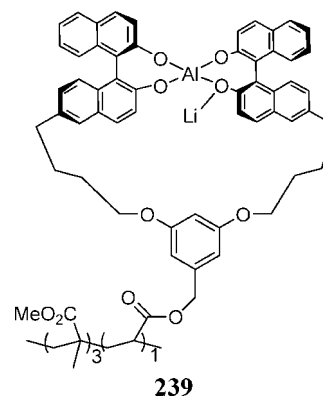
Scheme 70. Asymmetric Michael Addition Catalyzed by Dendritic ALB and GaSB Catalysts

of a polymer using the catalyst analogue. In the absence of catalyst analogue, random polymerization occurred, and the existence of two BINOL units near for coordination was not guaranteed. Unfortunately no recycle experiment was reported.

Suitable dendrimers with BINOL ligands in the periphery offer another strategy to form ordered ALB complexes (ligand **238**). Sasai et al. prepared a dendrimer with such characteristics and showed that it catalyzed the same transformation in high levels of enantioselectivities (>91% ee) but in low yields (<63%).⁴⁷¹ The addition of sodium *tert*-butoxide allowed an increase in the reaction yield to 79% (with slight ee decrease to 89%). The same transformation was also catalyzed by a complex formed by Ga–Na in 83% yield with 97% ee (Scheme 70).

Sekiguti et al. reported the immobilization of a multi-component asymmetric catalyst (Al–Li–bisBINOL) by copolymerization of a vinylbisBINOLS ligand with methyl methacrylate (ligand/acrylate 1:3) in the presence of AIBN.³⁸⁶ Subsequent treatment with AlMe₃ and BuLi afforded a suitable homogeneous catalyst **239** for 1,4-

additions of benzyl malonates to cyclohexenone in high yields (91%) and high ee's (93%). The recyclability of this catalyst was demonstrated for carbonyl–ene coupling.



Weck et al. tested an AlCl(salen) immobilized in a poly(norbornene) polymeric matrix with a relatively flex-

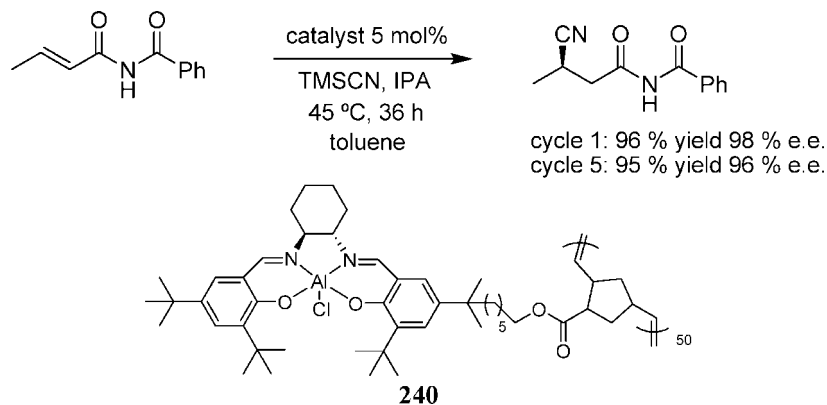
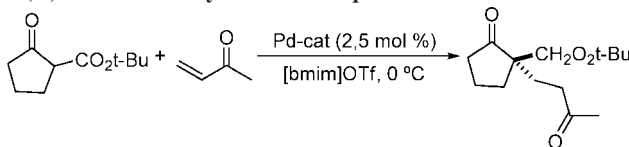
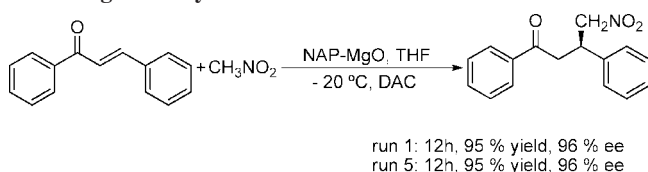
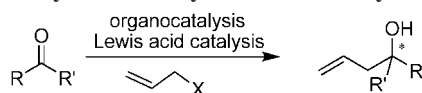
Scheme 71. Asymmetric Michael Addition Catalyzed by AlCl(Salen) Anchored to Polynorbornene Resin

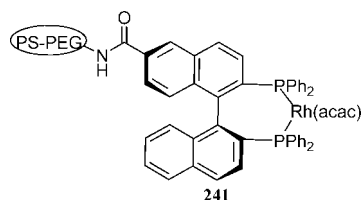
Table 17. Asymmetric Michael Addition Catalyzed by Pd(II)–BINAP Catalyst in Ionic Liquids


cycle	time (h)	yield (%)	ee (%)
1	8	98	83
2	8	98	84
3	8	92	83
4	8	91	84
5	15	94	84

Scheme 72. Asymmetric Michael Addition Catalyzed by NAP–MgO Catalyst**Scheme 73. Asymmetric Allylation of Carbonyl Compounds**

ible linker in the asymmetric addition of cyanide to α,β -unsaturated imides (Scheme 71). The homogeneous polymeric catalyst **240** could be used in a 5 mol % loading providing the respective products in quantitative yields and excellent enantioselectivities (up to 99% ee). After precipitation, it could be reused four times without any decrease in efficiency. Kinetic studies indicated that the activity of the polymeric catalyst is significantly higher than that of the unsupported analogue suggesting an enhancement effect of the bimetallic pathway due to catalytic site proximity.⁴⁷²

Hayashi et al. reported BINOL ligand immobilization (via grafting) to a PEG–PS resin.⁴⁷³ The amphiphilic character of the support allowed the 1,4-addition of phenylboronic acids to cyclopentanones catalyzed by $\text{Rh}(\text{acac})_2(\text{C}_2\text{H}_4)_2$ to be carried out in water. Since the catalyst **241** was insoluble, it could be easily recovered by filtration and reused up to five runs with unchanged enantioselectivity (3 mol %, 94% ee). Sometimes some loss of activity was observed probably due to catalyst air sensitivity. Excellent levels of enantioselectivity were maintained (>91% ee) in the reaction of several cyclic enones.



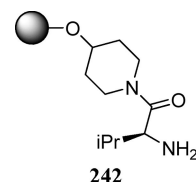
Choudary et al. used commercially available magnesium oxide crystals containing Lewis acidic sites (Mg^{2+}), Lewis basic sites (O^{2-} and O^-) and isolated Brønsted hydroxyls (NAP–MgO).^{451,474} This inorganic material was used in the asymmetric Michael additions of nitromethanes to chalcones in the presence of (1*R*,2*R*)-(–)-diaminocyclohexane (DAC) as a chiral auxiliary. Acidic Lewis sites promoted the

electrophilic activation of chalcone carbonyls, while the basic Lewis site tends to activate nitroalkane by deprotonation. The Brønsted hydroxyls groups formed hydrogen bonds with DAC and with the nitro group directing an asymmetric Michael addition in excellent yields (95%) and enantioselectivities (96% ee, Scheme 72).

The NAP–MgO catalyst was reused after heating at 250 °C for 1 h under nitrogen atmosphere. The reactivated catalyst was reused five times and showed consistent yields and ee's for asymmetric Michael additions.

Sodeoka et al. used an ionic liquid phase to enable Pd(II)–BINAP complex immobilization.⁴⁷⁵ Using [hmim]BF₄ as solvent, cyclic acetoacetates were added to methyl vinyl ketone (5 mol %, –20 °C in 15 h) affording the respective product in 97% yield with 88% ee. In a traditional protocol, where THF is used instead of the ionic liquid, yields and enantioselectivities up to 92% were observed, but the reaction was somewhat slower. Efforts to achieve catalyst recycling using this IL ended in the formation of black palladium resulting from catalyst degradation. When [hmim]BF₄ was replaced by [bmim]OTf (8 h at 0 °C), slightly lower enantioselectivity (83% ee) resulted, but catalyst recycling was accomplished (without formation of black palladium) over five cycles with minimal erosions (Table 17).

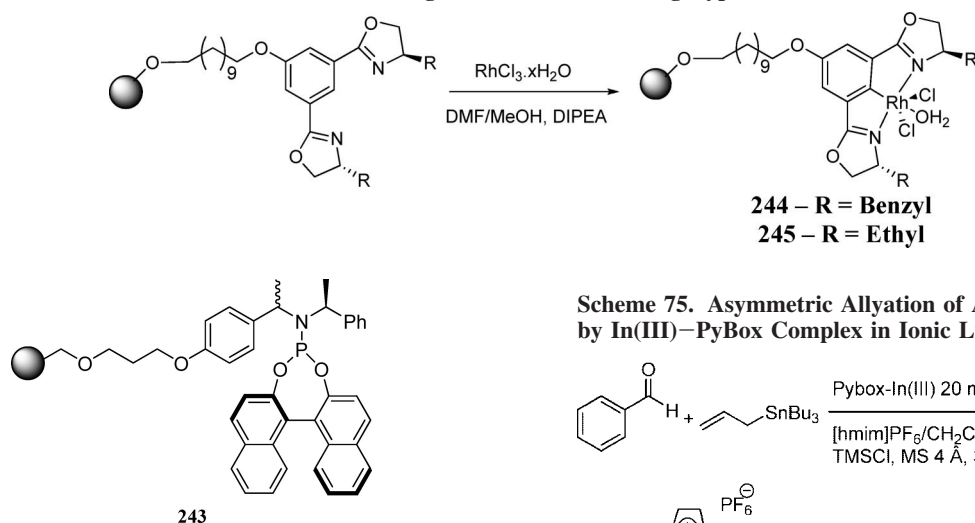
Christoffers et al. grafted a L-valinamide to a poly(ethylene glycol) chain providing a soluble supported chiral auxiliary **242** that promotes the enantioselective addition of cyclic acetoacetates to methyl vinyl ketone in the presence of $\text{Cu}(\text{OAc})_2$.⁴⁷⁶ Excellent levels of enantioselectivities were achieved (97% ee) even in the second cycle (90% ee).



Kaneda et al. heterogenized La^{3+} species and (*R,R*)-tartaric acid on fluoroapatite.⁴⁷⁷ This supported catalyst was successfully tested in the addition of cyclic acetoacetates to methyl vinyl ketone in toluene, affording the respective product in 97% yield and 60% ee. Due to its heterogeneous character, the catalyst was reused during three cycles without any readdition of organic ligand.

Salvadori et al. prepared a chiral phosphoramidite ligand **243**, anchored to Merrifield resin and tested it in the copper-mediated diethylzinc conjugated addition to cyclohexenone. The heterogeneous catalyst based on ligand **243** proved to be less reactive, requiring 24 times more time to achieve complete conversion compared with the homogeneous protocol, and the enantioselectivities observed were 20% lower (74% vs 95% ee). For the recycling assays, it was necessary to add copper in the beginning of each cycle due to some leaching problems. In a second cycle, the enantioselectivity increased to 84% ee, but in the two subsequent cycles, it fell to 65% ee.⁴⁷⁸

As can be seen, proline and pyrrolidine-type catalyst surpassed the alkaloid based methods. The protocols with perfluoro-organocatalysts are very efficient, but the discovery that the presence of ionic tags on the catalyst can provide positive effects on the reaction selectivity has attracted considerable attention. Metal-based catalysts were also considerably studied, which resulted in the appearance of a new concept, the catalyst analogue. However, more efforts

Scheme 74. Coordination of Rhodium to Phe-Box Ligand Anchored to Wang-Type Resin

should be made in this area to obtain more desirable recyclable protocols.

17. Asymmetric Allylation of Carbonyl Compounds

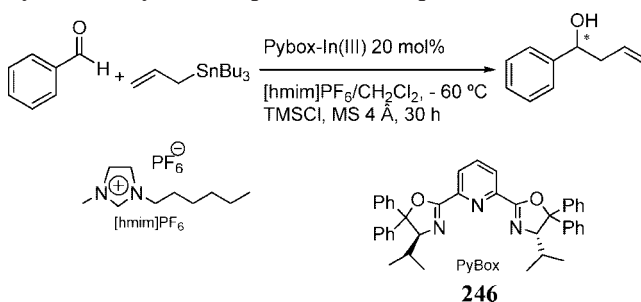
The asymmetric allylation of carbonyl compounds (Scheme 73) is one of the most efficient asymmetric C–C bond forming reactions. In addition, enantiomerically enriched homoallyl alcohols are important intermediates in synthesis, which can be converted to a wide variety of synthetically useful compounds. Several methodologies have been developed using rhodium, titanium, or indium catalysts, as well as organic catalysts. Some of these catalysts bear expensive building blocks that are more economically applied if reused.

Before 2002, two important works in this area were reported: Yoshida et al. used a dendritic Ti–BINOL complex to perform this transformation with high enantioselectivity (up to 92% ee). The utilization of polymer-supported chiral *N*-sulfonamide alcohols was also accomplished but provided lower levels of enantioselectivity.⁵

Portnoy's group has been responsible for introducing a new methodology for stepwise synthesis of Box and PyBox heterogeneous ligands via solid-phase chemistry.⁴⁷⁹ Weissberg and Portnoy extended the scope of such methodology to Rh–PheBox catalyst immobilization.⁴⁸⁰ PheBOX ligands were first prepared by anchoring to Wang-type resins, and catalyst formation was completed by direct ligand metalation with RhCl₃ (Scheme 74).

This new catalyst family was tested in benzaldehyde enantioselective allylation with allyltributyltin to afford homoallylic alcohols (3 mol %). Rather surprisingly, the well-known catalyst **244** provided low asymmetric induction (<9% ee) since in solution its unsupported analogue was the most selective (61% ee).⁴⁸¹ In this work, catalyst **245** provided the higher enantiomeric excess (48% ee). Despite the low levels of chiral induction, high yields were obtained in all reactions (73–83%), which do not suffer from great loss of activity (about 4% erosion) upon one recycle.

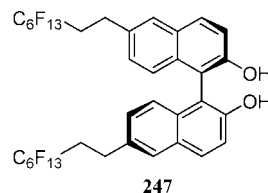
The same chemistry has been evaluated by Lu et al. In this case, In(III)–PyBox was used as catalyst, and its reutilization was achieved using a mixture of [hmim]PF₆/dichloromethane as reaction media (the reactions proceeded at –60 °C, Scheme 75).⁴⁸²

Scheme 75. Asymmetric Allylation of Aldehydes Catalyzed by In(III)–PyBox Complex in Ionic Liquids

By use of a heavily substituted PyBox ligand, **246**, homoallylic alcohol was isolated in 72% yield with 88% ee. This result was not far from those obtained when the reaction was run only in dichloromethane where 81% yield and 92% ee were obtained.⁴⁸³ Evaporation of dichloromethane and product extraction with hexane showed that In(III)–PyBox was retained in the ionic liquid phase, and further reuse up to four cycles with consistent yield and slightly decreasing ee (ee_4 = 12%) was achieved. Other aliphatic and conjugated aldehydes were also reacted furnishing good yields and high ee (up to 94% ee).

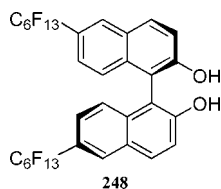
The same methodology was also applied in the asymmetric allyltributylstannane addition to ketones.⁴⁸⁴ The authors observed that the ionic media provided conditions to achieve slightly higher yield (58–82%) and asymmetric inductions (55–93% ee) for the range of ketones tested (aryl, vinyl, and alkyl ketones). The In(III)–PyBox catalyst was also retained in the ionic media and recycled up to four cycles with some enantioselectivity erosion (about 14%). The reactivity remained nearly unchanged (Y_4 = 4%).

Yin et al. reported the application of perfluoro-BINOL ligand **247** for Ti(IV)-mediated addition (10 mol % catalyst) of allyltributylstannane to benzaldehyde.⁴⁸⁵ This protocol only afforded good results (85% yield, 90% ee) when the reaction was carried out under biphasic fluoruous conditions (FC-72/hexane), but it proved to be limited to substrates with strong electron-withdrawing groups, and the ligand was recovered by liquid/liquid extraction and purified by column chromatography.

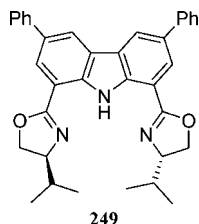


Stuart et al. applied ligand **248** in this transformation obtaining the respective allylic alcohols with comparable yield and slight lower enantioselectivity (75% ee). The perfluorinated

ligand was recovered using fluororous reverse phase silica gel and reused three times with 10% overall efficiency erosion.⁴⁸⁶



Nakada et al. described the application of Cr(III)–ligand **249** in asymmetric Nozaki–Hiyama allylation of benzaldehydes with allyl bromide. The catalyst was recycled once maintaining its high efficiency (up to 90% yield, 92–94% ee).⁴⁸⁷



Allyltrichloride silanes are a viable alternative to tin-allylating agents.⁴⁸⁸ Allyltrichloride silanes react with aldehydes in the presence of a chiral organocatalyst (phosphoramides) to form the desired homoallyl alcohol. It was known that a reaction that occurs via two phosphoramides coordinated with the organosilane grants higher reactivity and enantioselectivity than the one-phosphoramidate pathway. In this way, Oyama et al. expected that phosphoramides immobilization in a polymer would create a high local concentration and also allow asymmetric catalyst reutilization.⁴⁸⁹ So, two styryl-substituted phosphoramides were self-polymerized and copolymerized with styrene in the presence of AIBN (80 °C, 24 h) and tested for enantioselective benzaldehyde allylation (Scheme 76).

As expected both homopolymers derived from monomers **250** and **251** behaved better in terms of activity (62% and 84% yield with homopolymer **250** and **251**, respectively) than the respective unsupported analogues **252** and **253**, respectively. In the case of homopolymer **251** higher yield and comparable ee (63% ee) were observed when compared with the most effective monodentate phosphoramidate catalyst **254** (36% yield and 60% ee). Introduction of styrene monomers to obtain copolymers did not provide any improvement.

These are the first examples of catalyst immobilization for aldehyde allylation reactions. As can be seen, PyBOX ligand tends to afford higher levels of enantioselectivities compared with PheBOX ligands, but both methodologies still have an important drawback of general use or formation of toxic organotin compounds. The organosilane allylating agents constitute a greener alternative to such compounds, making further development of new highly effective phosphoramidate organocatalysts imperative.

18. Asymmetric Dialkylzinc Addition to Aldehydes

The asymmetric dialkylzinc addition to aldehydes (Scheme 77) is an important transformation that creates new carbon–carbon bonds. The reaction can be conducted by direct dialkylzinc addition to aldehydes promoted by chiral amino alcohols. Alternatively, it is possible to conduct titanium-promoted dialkylzinc addition to aldehydes in the presence of BINOL-type ligands and chiral amino alcohols.

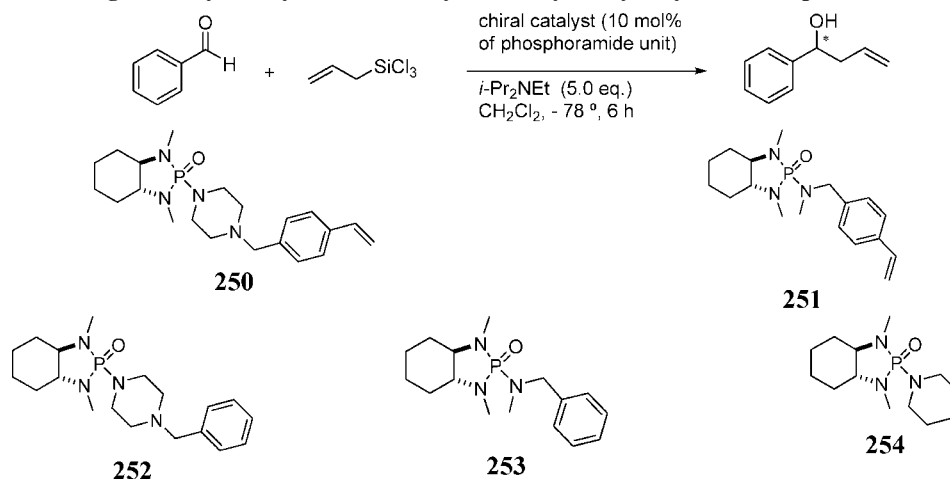
18.1. Heterogeneous Catalysts

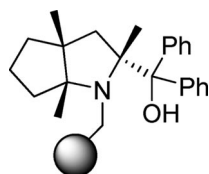
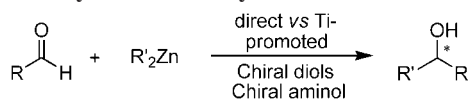
Before 2002, the three main types of chiral ligands for this transformation (amino alcohols, BINOL, and TADDOL) were immobilized in both soluble and insoluble polymers with considerable success. Several polymeric ligands provided high levels of enantioselectivity (up to 98% ee) and proved to be recyclable. Ephedrine ligand was anchored to siliceous supports to achieve its recyclability. The immobilization provided ligands that proved to be as enantioselective as ephedrine itself (up to 64% ee), while anchoring a diphenylprolinol derivative failed to give competitive enantioselectivity.⁵

Martens and his co-workers immobilized a chiral amino alcohol by two different strategies in polystyrene polymers by grafting or copolymerization.^{490,491} The grafted ligand **255** was soluble under the reaction conditions and proved to be as efficient as its unsupported partner in the direct addition of ethylzinc to benzaldehyde. (*R*)-1-Phenylpropanol was isolated in 83% yield with 89% ee (24 h, 25 °C and 10% mol ligand), but when reused, both yield and ee dropped about 9%.

In the second strategy, the amino alcohol was immobilized by copolymerization with styrene and divinylbenzene affording the polymeric ligand **256**. Due to its high degree of cross-linking, the ligand acts as a heterogeneous catalyst once

Scheme 76. Asymmetric Organocatalytic Allylation of Aldehydes Catalyzed by Polymeric Phosphoramides



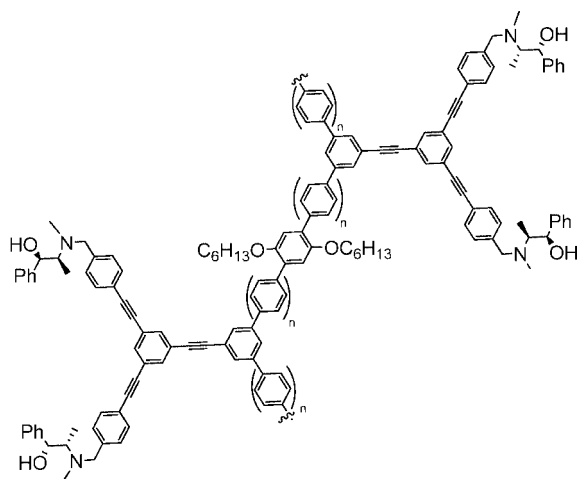
Scheme 77. Asymmetric Dialkylzinc Addition to Aldehydes

255 - grafted
256 - polymerized

in the presence of diethylzinc. The appropriate polymerization conditions provided a monolith with the desired morphology and properties, which could be applied as 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 h. 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 applications because the need for catalyst separation is suppressed and the products can be easily isolated just by removing the solvent, increasing the overall efficiency.

Hu et al. used (1*R*,2*S*)-ephedrine-bearing dendronized polymers with poly(phenylene) backbones to be applied for direct asymmetric addition of diethylzinc to benzaldehyde.⁴⁹² With only 5 mol % ligand, both prepared polymers (**257** and **258**) afforded the (*R*)-1-phenylpropanol in 73–75% ee. The recovered catalyst (by filtration) was reused once without any drop of activity.



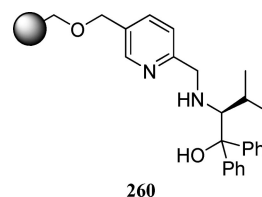
257 - *n* = 0
258 - *n* = 1

Pericàs et al. reported in 2003 the synthesis of (*R*)-2-piperidino-1,1,2-triphenylethanol covalently bonded to polystyrene polymeric support.⁴⁹³ Despite its enormous effi-

ciency, the price paid for its efficiency was still high, since the preparation of the ready-to-anchor ligand involved up to five steps from commercial precursors. More recently, Castellnou et al.⁴⁹⁴ reported a simplified procedure (in two steps) for such supported-ligand synthesis (Scheme 78).

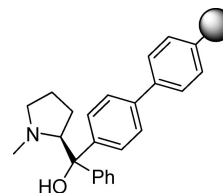
The supported catalyst **259** was tested in the direct diethylzinc addition to benzaldehydes where 94–95% ee was obtained in high yield using only 2 mol % catalytic resin at 0 °C after 4 h. The catalyst could be recovered and was used to prepare 1-phenylpropanol in five consecutive batches under standard conditions (resin 4 mol %, toluene, 0 °C) with the same catalyst sample. The reactions were completed in all cases in 6 h, with the resulting alcohol having constant enantiomeric purity (95% ee). Recently such a 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 unprecedentedly short residence times (less than 3 min).⁴⁹⁵

Recently, Gros et al. described the application of a pyridine-based tridentate chiral ligand in enantioselective direct addition of diethylzinc to benzaldehydes supported on Merrifield resin. This heterogeneous ligand, **260**, provided the respective phenylpropanols with excellent levels of enantioselectivities (up to 93% ee) and proved to be fully recyclable during five cycles.⁴⁹⁶



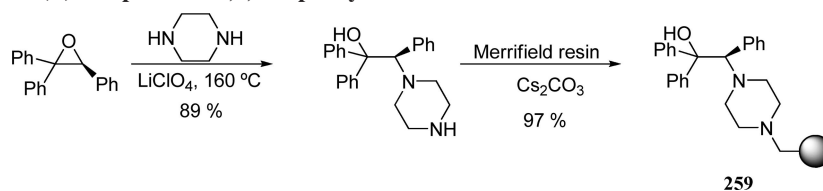
260

Hodge et al. applied a diphenylprolinol grafted in polystyrene beads as catalyst for alkylzinc addition to benzaldehydes. High levels of catalyst loading were required to obtain levels of enantioselectivities comparable with the homogeneous system (78–94% ee). The polystyrene-based catalyst **261** was recycled efficiently nine times.⁴⁹⁷



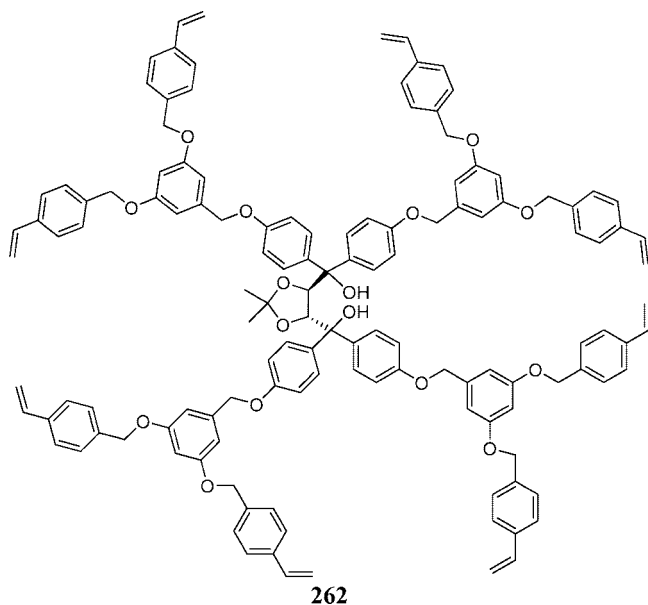
261

Seebach et al. synthesized a family of TADDOL-supported polystyrene ligands for titanium-promoted diethylzinc addition to aldehydes.⁴⁹⁸ The polymers were obtained by radical copolymerization of suitable dendritic cross-linkers (containing TADDOL ligand in the center) in styrene and divinylbenzene mixtures. A detailed study of this family showed

Scheme 78. Preparation of (*R*)-2-Piperidino-1,1,2-triphenylethanol Anchored in Merrifield Resin

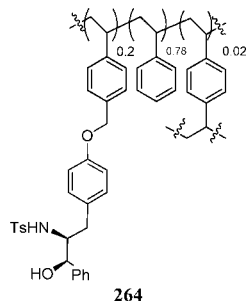
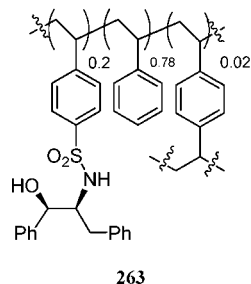
259

that the best dendritic cross-linker was ligand **262** when present in a content of 0.1 mmol/g.

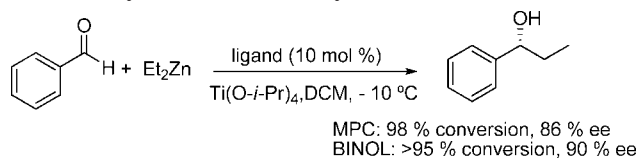


These kinds of dendritic cross-linkers have the advantage of creating a less hindered catalytic center. In fact, the supported ligand performance was impressive. It was observed that (*S*)-1-phenylpropanol was formed in a constant reaction rate through 20 consecutive cycles with consistent enantioselectivity. In fact, this system proved to be almost as efficient as the unsupported TADDOL (99% for TADDOL vs 98:2 er for polymeric ligand **262**). The swelling ability of this catalyst during the 20 recycles remains unchanged, which can explain the excellent performance. In fact, the heterogeneous polymeric ligand **262** performed faster than the homogeneous counterpart, which is quite rare (20 mol % ligand). Altava et al. prepared several polymeric monoliths bearing the TADDOL ligand that showed good performance in titanium-promoted diethylzinc addition to benzaldehyde working under flow conditions.⁴⁹⁹

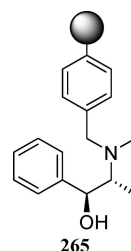
Gau et al. copolymerized a styrene-substituted N-sulfonylated amino alcohol with styrene and divinylbenzene to achieve its recycling. The complex formed with this ligand, **263**, and titanium was tested in diethylzinc addition to aldehydes. It was disclosed that when 20% of ligand was in the heterogeneous polymer, it resulted in excellent levels of enantioselectivity and activity (up to 95% ee). The ligand, recovered by filtration, was reused several times with small erosion of enantioselectivity in each cycle (about 3%).⁵⁰⁰ Recently, the authors described ligand **264**, which is more reactive and more reusable than **263** (nine efficient recycles).⁵⁰¹



Scheme 79. Asymmetric Dialkylzinc Addition to Aldehydes Promoted by MPC-Based Catalyst



El-Shehawy prepared several norephedrine derivatives immobilized in polystyrene resins by copolymerization. Such heterogeneous ligands were tested in enantioselective diethylzinc addition to the exocyclic C=N bond of some 1,2,4-*N*-triazinylarylimines in the presence of TIPSCl as activator. The enantioselectivities of the addition products obtained with copolymer chiral ligand (up to 91% ee) were comparable with those obtained in the homogeneous unsupported protocol (up to 92% ee). The polymer **265** was reused once efficiently.⁵⁰²



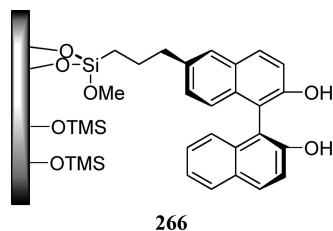
Moreau et al. used a trialkoxylated camphorsulfonamide for synthesis of functional organosilicas as a highly ordered material using template-directed hydrolysis–polycondensation with tetraethylorthosilicate (TEOS). This heterogeneous ligand was tested in titanium-promoted addition of diethylzinc to benzaldehyde. The presence of uncapped free silanol groups made this catalyst less enantioselective than the unsupported analogues.⁵⁰³

Ma et al. immobilized the chiral (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol on the layered frame of zirconium phosphate to obtain a chiral heterogeneous ligands for diethylzinc addition to aldehydes. Despite the modest levels of enantioselectivity achieved (<52% ee), the ligand proved to be easily recyclable (up to 10 cycles).^{504,505}

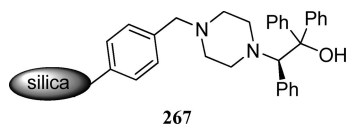
Sasai and his co-workers immobilized a sulfide derivative (*R*)-BINOL ligand by anchoring it to the surface of a gold cluster forming a monolayer-protected gold cluster (MPC).^{506,507} The distance between the BINOL and the cluster influenced the enantiomeric route of titanium-mediated addition of diethylzinc to benzaldehydes. The spacer length should provide the necessary distance to make the ligand readily available for titanium coordination (pseudohomogeneous reaction). The optimum spacer length disclosed five carbon atoms since it proved to be as efficient as free BINOL (Scheme 79). Unfortunately in a second cycle, the ee decreased 18% although the conversion suffered from a smaller decrease.

An organosilane-substituted (*S*)-BINOL was anchored in the surface of siliceous materials, MCM-41, MCF, and SBA-15 by Abdi et al.^{508,509} These heterogeneous catalysts were applied to Ti(IV)-mediated diethylzinc addition to aldehydes where MCF readily proved to be the most efficient support. In the preliminary results, low enantioselectivities were observed and was caused by free-silanol groups present in the support, which interact with titanium. When those groups

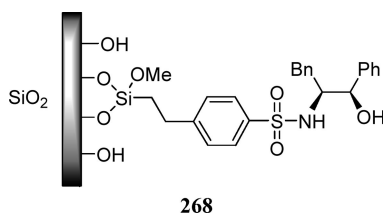
were protected with tetramethylsilane, enantioselectivities increased to 94% ee (comparable with free BINOL). The ligand **266** was recovered by simple filtration and reused up to four efficient cycles with some yield (27%) and enantioselectivity (9%) erosion before regeneration.



Mayoral et al. immobilized a readily available chiral amino alcohol ligand ((*R*)-1,1,2-triphenyl-2-(piperazin-1-yl)ethanol) on silica by sol–gel synthesis and grafting. Both ligands were tested in the direct diethylzinc addition to benzaldehyde, but only **267**, prepared by grafting, provided good enantiomeric excesses (77% ee). The recovered solid was reused, though with a considerable loss of activity (49% yield erosion) with nearly unchanged enantioselectivity (6% erosion). The addition of butyl lithium to the reaction proved to be crucial to achieve these results.⁵¹⁰



Xu et al. immobilized N-sulfonylated amino alcohols in amorphous silica to be used in titanium-mediated ethylzinc addition to aldehydes. In the first tests, the requirement to pretreat the free silanols with titanium isopropoxide to achieve any reaction (98% yield, 80% ee, substrate benzaldehyde) was disclosed. The catalyst **268** showed an impressive recycling ability, since was reused nine times without any significant decrease of reactivity and enantioselectivity.⁵¹¹



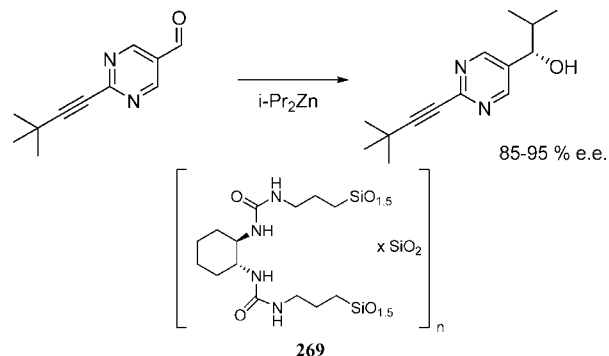
Soai et al. reported the use of chiral organic–inorganic hybrid material (silesquioxane), derived from silylated *trans*-1,2-diaminocyclohexane, as chiral initiator in asymmetric autocatalysis (Scheme 80). The heterogeneous initiator **269** could be reused several times without any decrease of efficiency.⁵¹²

18.2. Homogeneous Catalysts

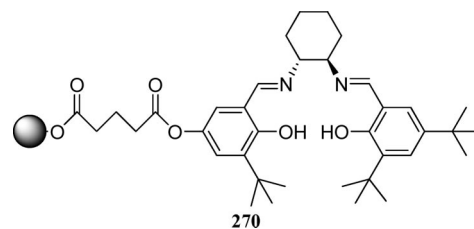
Before 2002, the three main types of chiral ligands for this transformation (amino alcohols, BINOL, and TADDOL) were immobilized in both soluble and insoluble polymers with considerable success. Several polymeric ligands provided high levels of enantioselectivities (up to 98% ee) and proved to be recyclable.⁵

Venkataraman and Anyanwu covalently anchored salen ligands at the end of monomethoxy–PEG chain polymers

Scheme 80. Autocatalytic Asymmetric Dialkylzinc Addition to Aldehydes Promoted by a Chiral Organic–Inorganic Hybrid Material

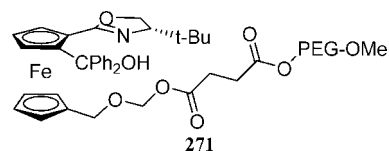


(MeO–PEG, average MW = 5000 Da) and prepared a family of three supported ligands.⁵¹³ When salen ligand was directly coupled to the MeO–PEG (without any spacer) the catalytic system showed poor selectivity (66:34 er), probably because the PEG support was affecting the catalyst microenvironment. This idea gained special importance when supported salen ligand **270** showed better selectivity (91:9 er). The same behavior improvement was observed with the unsupported analogs of **270** bearing the spacer, indicating that immobilization on the polymer had no effect on the selectivity. This parameter, in this case, was mainly controlled by the spacer nature.



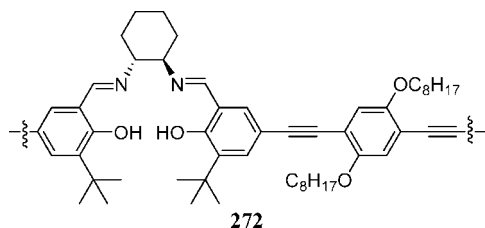
Furthermore, ligand **270** proved to be as selective as the unsupported salen ligand, despite being less reactive. The supported ligand could be recovered quantitatively by precipitation from ethyl ether and reused five times without any significant loss in selectivity or reactivity.

Bolm et al. prepared two new chiral polymer-supported ferrocenyl oxazolidines for enantioselective alkyl transfer to aldehydes (PEG and trityl resin). The catalyst immobilized in PEG was the only one to give comparable values of chiral induction compared with the unsupported analogue (catalyst **271**). It was also shown that it could be recycled four times without any yield and enantioselectivity erosion.⁵¹⁴

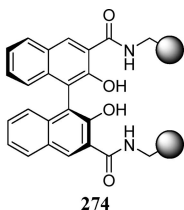
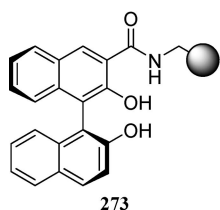


Punniyamurthy et al. prepared a polymeric salen ligand **272** and tested it in direct diethylzinc addition to benzaldehydes. The respective alcohol was obtained in good yields (74%) and good enantioselectivities (70% ee). The ligand was successfully reused once.⁵¹⁵

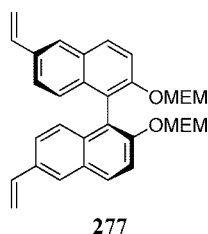
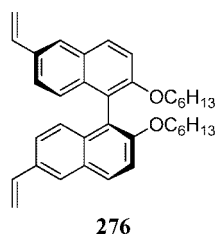
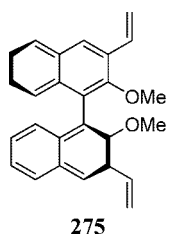
In the case of reactions promoted by titanium, Chan et al.⁵¹⁶ synthesized two polymer-supported BINOLs, **273** and **274**, by coupling an aminomethyl polystyrene resin with (*S*)-



2,20-dihydroxy-1,10-bis(phenyl)-3-carboxylic acid and (*S*)-2,20-dihydroxy-1,10-bis(phenyl)-3,30-dicarboxylic acid. Both **273** and **274** provided better performance than their unsupported analogues for titanium-promoted diethylzinc addition to arylaldehydes (20 mol % ligand). The higher conformational rigidity of polymer **274** resulted in significant improvement of enantioselectivity (from about 60% to 90%). The reutilization of these ligands was demonstrated in an alkene hydrogenation reaction.

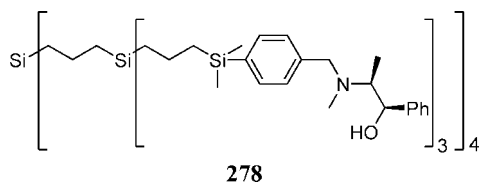


Moreau et al.⁵¹⁷ studied a distinct methodology to immobilize BINOL ligands by copolymerization of vinyl-substituted BINOL monomers (cross-linkers) with styrene.

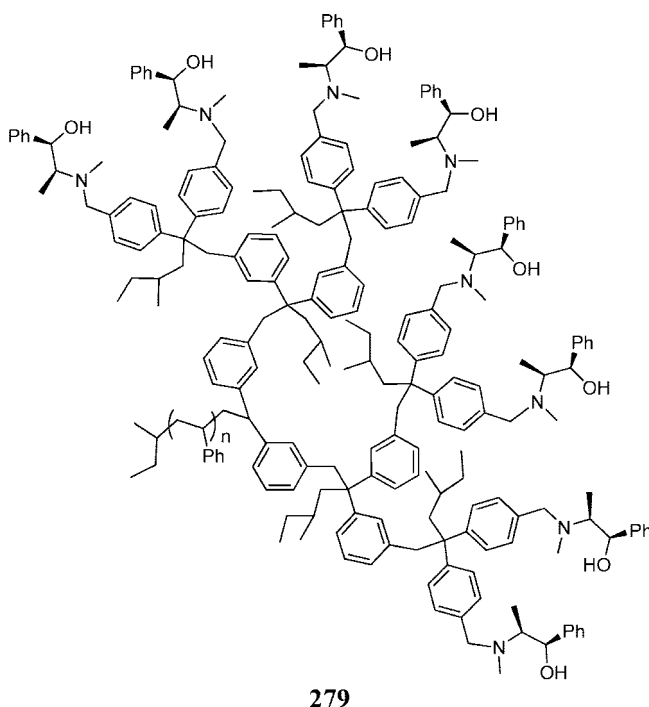


Polymers derived from monomer **275** behaved poorly in terms of enantioselectivity like polymers with a great degree of cross-linking probably due to difficult access or steric hindrance to the BINOL moiety (10 mol % ligand). Low degree of cross-linking in polymers derived from **276** and **277** monomers showed comparable efficiency (conversions >99% and 73–78% ee's) to unsupported BINOL (conversion >99% and 80% ee).

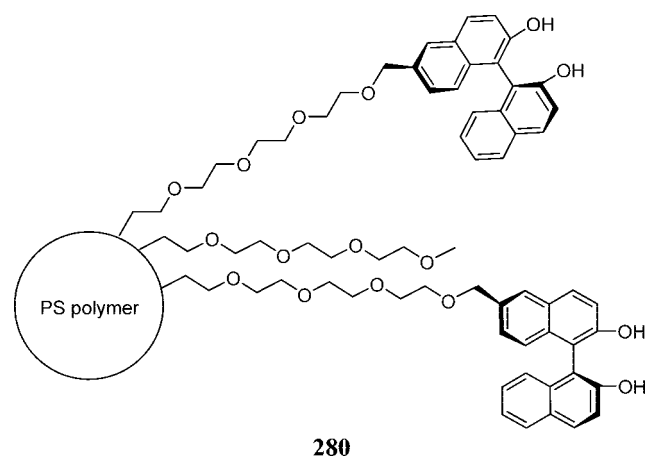
Soai et al. synthesized a hyperbranched dendrimer with a flexible carbosilane core and chiral ephedrine ligands in the periphery. These dendrimeric catalysts were successfully applied in the direct dialkylzinc addition to aromatic aldehydes providing the respective products in moderate to good yields with very good levels of enantioselectivity (74–93% ee). Catalyst **278** was reused once efficiently.⁵¹⁸ This dendritic ligand was also studied in the reaction of diethylzinc with *N*-(diphenylphosphoryl)imines.⁵¹⁹



Recently, El-Shehawey et al. were able to improve the enantiomeric induction using chiral ephedrine ligands chemically anchored to soluble or insoluble supports (88–94% ee). The authors prepared a chiral dendrimer bearing ephedrine ligands on the periphery and a styrene moiety in the core that was polymerized to form a linear and soluble polystyrene chain. This macromolecule, **279**, could be precipitated and reused without considerable efficiency erosion.⁵²⁰



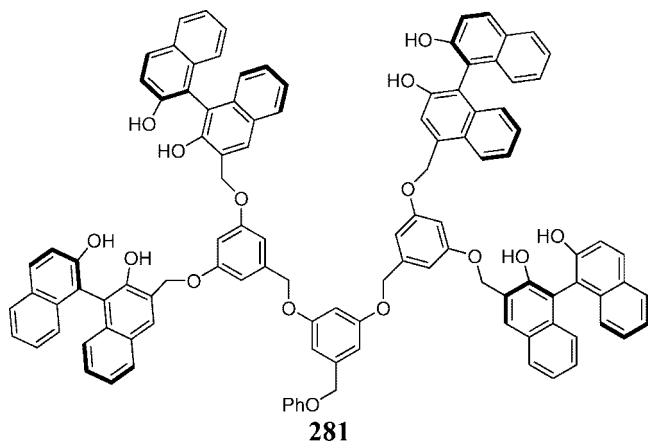
Sasai et al. prepared micellar nanoparticles via polymerization of amphiphilic units containing a styrene moiety in water. The asymmetric ligand BINOL derivative prepared could be grafted before or after polymerization. This nanoligand, **280**, was tested in titanium-promoted diethylzinc addition to aldehydes. The homogeneous micellar ligand proved to be less efficient than free BINOL (yield 60% vs > 99%; ee 81% vs 89%) and suffered from a considerable drop of enantioselectivity upon just one recycle.^{507,521}



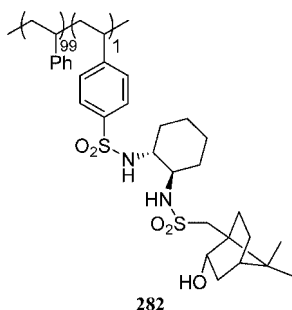
Wang et al. grafted a chiral amino alcohol ligand derived from proline onto two polymeric supports (PS and PEG). Only the soluble ligand (in PEG) furnished competitive

results compared with unsupported ligand in diethylzinc addition to aldehyde reactions, but it failed in the recycling assays.⁵²²

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, sometimes surpassing the free BINOL based system (up to 89% ee). Ligand **281** could be recovered by precipitation with methanol addition and reused twice without yield and enantioselectivity erosion.⁵²³



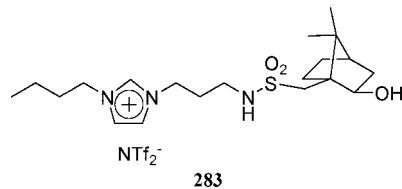
Ramón and Yus applied the polymer-supported *trans*-1-phenylsulfonylamino-2-isoborneolsulfonylaminocyclohexane ligand **282** in titanium-promoted phenyl addition of acetophenones. The respective tertiary alcohols were obtained in quantitative yields and very good enantioselectivities (up to 90% ee). However, the system proved to suffer from considerable loss of efficiency upon recycling.⁵²⁴



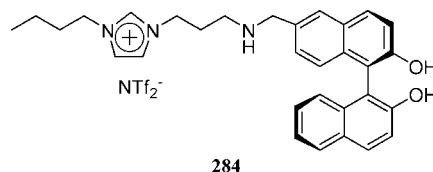
18.3. Alternative Reaction Media

Moreau et al. immobilized two types of ligands for titanium-promoted ethylzinc addition to benzaldehyde in an ionic liquid: camphorsulfonamides⁵²⁵ and BINOL derivatives.⁵²⁶ In the first case, a family of camphorsulfonamide-like ligands was prepared. They afforded the respective alcohol in quantitative conversions (25 °C, 18 h). The ligand **283** showed the highest consistency in terms of enantioselectivity; in addition it could be reused for four consecutive cycles affording (*S*)-1-phenylpropanol with a constant 64–65% ee.

The BINOL-derived ligand was immobilized in a similar fashion by coupling with an ionic liquid moiety. The immobilized ligand **284** proved to be as effective as the BINOL itself, affording (*S*)-1-phenylpropanol with 82% ee, and its recovery was achieved by filtration after several

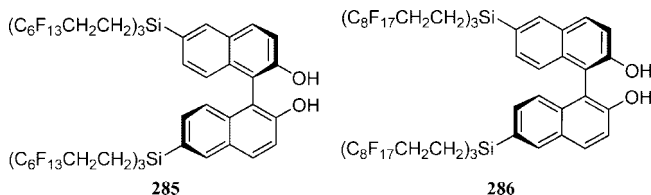


extraction protocols. It was reused three times with constant enantioselectivity (81–82% ee).



The application of fluorinated BINOL-type ligand **285** in this reaction was reported before 2002. It provided higher enantioselectivity (82% ee) and higher recyclability. Other perfluorinated amino alcohol ligands were also tested providing the same levels of efficiency.^{5,527}

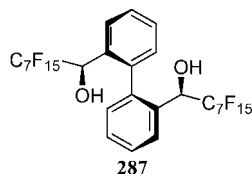
Curran et al. reported, in a previous work, the ligand **285** with a fluorine content of 61.2% that provided results comparable to the original system (81–89% yield and 80–83% ee vs 97% yield and 85% ee) in titanium-promoted diethylzinc addition to aldehydes using a biphasic solvent system of toluene/hexane/FC-72. However, it was known that ligand **285** had a slight affinity for the extracting organic solvent probably due to its fluorine content (61.2%). Later, the same authors designed and synthesized a new perfluorinated BINOL ligand, **286**, with a higher fluorine content (64.1%).^{528,529}



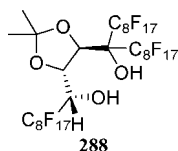
The ligand **286** had high affinity toward the perfluorinated phase in detriment to organic phase (hexane), but the activity and enantioselectivity were somehow slightly inferior when compared with ligand **285**. Clearly, ligand **285** provided the best results, and its reutilization problems were 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 **285** was recovered using FC-72 and was reused up to four cycles without any efficiency loss.

Kumadaki et al.^{530–532} reported the synthesis of new axially dissymmetric ligand with perfluoroalkyl groups, (*Ra*)-2,2'-bis[(*R*)-1-hydroxy-1*H*-perfluorooctyl]biphenyl. The ligand **287** was tested for titanium-promoted diethylzinc addition to aldehydes and proved to be superior to shorter length perfluoroalkyl analogues previously reported and to free BINOL, affording the respective alcohol in 96% yield with 97% ee (5 mol %). Due to its high fluorine content, the perfluoroligand was extracted to an FC-72 phase and reused seven times without any sign of efficiency drop. More recently, this ligand was used in the addition of methyl group to aldehydes.⁵³³

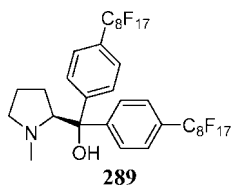
Ando and co-workers synthesized a perfluorinated TAD-DOL-like ligand for asymmetric titanium-promoted dimeth-



ylzinc additions to aromatic aldehydes. The ligand **288** proved to be an efficient promoter for this transformation providing excellent levels of enantioselectivity (up to 98% ee). Taking advantage of the low solubility of the ligand in cold toluene made it possible to recover and reuse it. During the five recycles, the enantioselectivity slightly decreased. The reason for such behavior remains unclear because no signs of epimerization were observed for the recovered ligand.⁵³⁴



Kim et al. described a method for the modification of pyrrolidinylmethanol derivatives in direct asymmetric addition of diethylzinc to aldehydes.⁵³⁵ The optimal reaction conditions were found to be at 40 °C, under biphasic conditions, affording the desired product in 92% ee. Curiously, the perfluorinated derivative provided an unusual enantioselectivity behavior upon temperature variation.



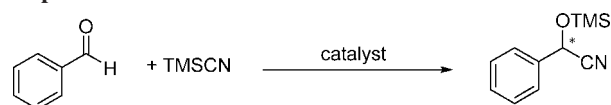
The ligand was recovered by lowering the temperature to 0 °C, where a phase separation occurred and in this way allowed an effective separation (FC-72/hexane). Interestingly, the partition coefficient observed for ligand **289** at 0 °C was only 2.3. So, it was reasoned by the authors that stable **289**·Li·Et₂Zn forced the ligand to stay in the FC-72 phase. This protocol allows **289** to have a long lifetime (about 9 runs) affording (*S*)-1-phenylpropanol with high ee's (run 1 92% ee vs run 9 82% ee, ee_c(9) = 11%).

For this reaction, perfluoro and heterogenized ligands were the main methodologies explored. Silica and insoluble polymer-supported catalysts proved to be extremely efficient and recyclable being used as solid phase in continuous flow studies. Diphenylprolinol-type ligands have now proven to be efficient and recoverable catalysts.

19. Asymmetric Cyanosilylation of Carbonyl Compounds

The cyanosilylation reaction is a straightforward method to prepare cyanohydrins, which are used as precursors for the preparation of a wide range of pharmaceuticals, agrochemicals, and insecticides (Scheme 81). Two of the most important methodologies so far developed are those based on chiral vanadyl salen (VOsalen) complexes and chiral titanium salen (Ti(IV)salen) complexes. Excellent levels of enantioselectivities were achieved in cyanosilylations of

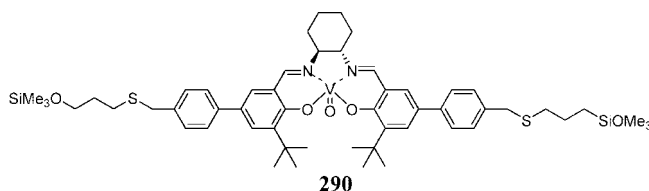
Scheme 81. Asymmetric Cyanosilylation of Carbonyl Compounds



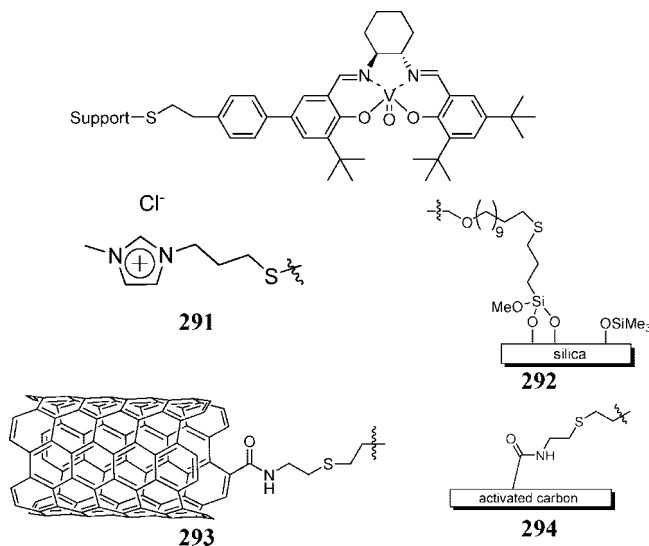
aromatic aldehydes, such as benzaldehyde (94% ee with VOsalen and 88% ee with Ti(IV)salen catalyst).⁵³⁶

There are obvious advantages to developing new methods that allow efficient catalyst reutilization. Seebach et al. reported cyano addition to pivaldehyde in the presence of 20 mol % dendritic Ti–BINOL complex with 72% ee. The catalyst was recycled four times with increasing enantioselectivity (to 83% ee).⁵

Corma and collaborators were responsible for a very interesting study comparing different protocols to achieved VOsalen catalyst reutilization. In 2003, the authors prepared a disilylated salen precursor **290** to be grafted into the walls of a structured inorganic mesoporous material by a postsynthesis treatment.⁵³⁷ These solids are called periodic mesoporous organosilicas (PMOs). The resultant material (0.25 mmol % to benzaldehyde) shows a high TON (320) for the room temperature silylcyanation with TMSCN (3 equiv) of benzaldehyde with an enantiomeric excess of 30%. The result is still far from the 94% ee achieved with the unsupported homogeneous catalyst.



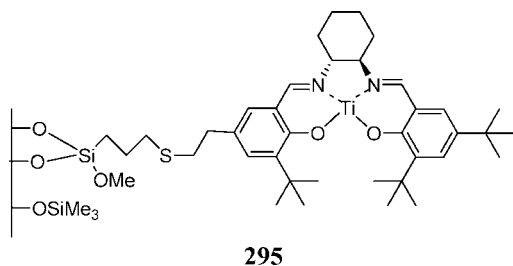
One year later, the same catalyst (VOsalen) was immobilized by five distinct methods: by grafting in single wall nanotubes (catalyst **293**), in activated carbon (catalyst **294**), in silica (catalyst **292**), by covalent bonding to an ionic moiety (catalyst **291**), and finally by retention in an ionic liquid phase ([beim]PF₆ and [emim]PF₆).⁵³⁸



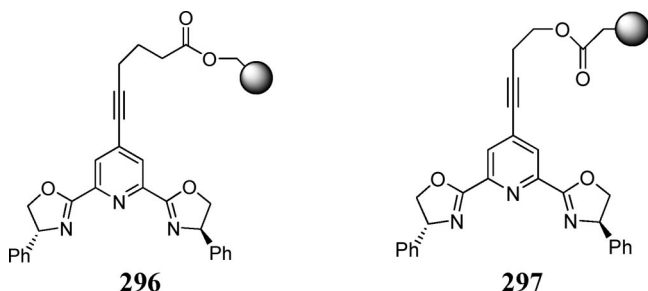
Generally all catalysts exhibit moderate to high reactivities (67–88% conversions, 0.24–1 mol % catalyst), but catalysts **293**, **294**, and **291** performed poorly in terms of enantiomeric excesses (48–66% ee). Catalyst **292** and the VOsalen

catalyst in the ionic liquid phase ([emim]PF₆ or [beim]PF₆) afforded higher enantioselectivities (85% and 89% ee, respectively).⁵³⁹ In the case of catalysts **293** and **294**, the low enantioselectivity observed could be due to achiral interference of the solid support. When VOsalen catalyst was covalently attached to an ionic moiety, some negative effects on the reaction enantioselectivity were observed, as previously reported.⁵⁴⁰ The two catalysts with the best performance were submitted to recycling experiments. Heterogeneous catalyst **292** was tested in three consecutive cycles providing the same enantioselectivity ($Y_c(3) = 4\%$, further reuse up to five cycles showed great drops on both conversion and ee),⁵⁴¹ while the homogeneous VOsalen catalyst immobilized in IL presented a higher recyclability ($Y_c(5) = 2\%$).⁵³⁹

Kim et al. prepared a family of chiral Ti(IV)salen complexes immobilized on ordered mesoporous silica (MCM-41). The immobilization was performed according to two different methods: direct condensation of a Ti(IV)salen silanol derivative and multigrafting of salicylaldehyde derivatives and diaminocyclohexane on 3-mercaptopropyl-functionalized MCM-41. Both methods provided catalysts that behaved poorly in terms of conversion (<50%, 10 mol % catalyst **295**), but the latter furnished levels of enantioselectivities comparable with the homogeneous partners (up to 93%).⁵⁴²



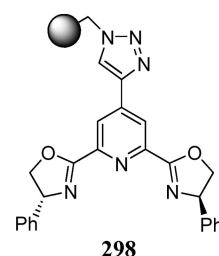
In 2003, Moberg and co-workers immobilized Ph-PyBox ligand to TentaGel resin using two different spacers. This was accomplished by connecting a 4-bromo-substituted Ph-PyBox ligand to a spacer bearing a terminal alkyne (via Sonogashira coupling). This spacer contained an alcohol or a carboxylic acid functionality, which was reacted with the suitable resin to establish an ester linkage.⁵⁴³



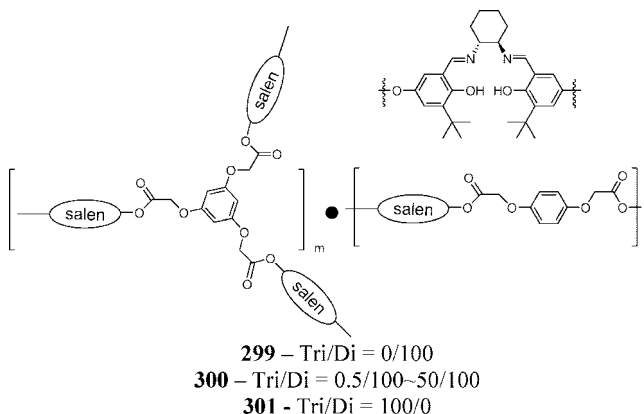
Both heterogeneous Ph-PyBox ligands **296** and **297** (20 mol %) were tested in the catalytic asymmetric silylcyanation of benzaldehyde in the presence of 10 mol % YbCl₃. The respective cyanohydrins were prepared within 30 min with 88–89% conversion. The supported catalysts retained the reactivity level of the homogeneous catalyst, while the enantiomeric excesses obtained were slightly lower than the homogeneous analogue (80–81% ee for heterogeneous catalyst vs 89% ee for homogeneous analogue). The authors justified this decrease in the enantioselectivity as a result of

the ligand immobilization. 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.

More recently, Moberg and Levacher anchored an alkyne-Ph-PyBox ligand into a polystyrene-supported resin bearing an azide group via a cycloaddition reaction. Ligand **298** was tested in cyanosilylation of aromatic aldehydes promoted by lanthanides (ytterbium and lutetium). High conversions (68–87%) and high enantioselectivities (67–78% ee) were obtained for this reaction in four consecutive cycles (10 mol % catalyst, acetonitrile/dichloromethane 3:2).⁵⁴⁴

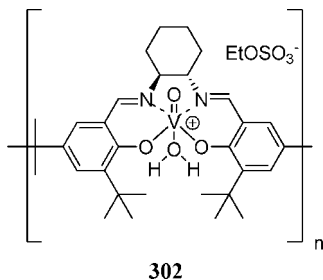


Zheng et al. prepared a polymeric Ti(IV)salen catalyst for the synthesis of *O*-acetylcyanohydrins from KCN, Ac₂O, and aldehydes. The polymeric catalysts were prepared by copolymerization of di- or tribenzaldehydes with a chiral diamine to obtain supported catalysts with several degrees of cross-linking.⁵⁴⁵

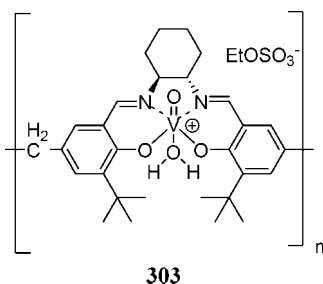


The optimal cross-linking degree was placed between 0.5/100 and 2/100 (tri/di), where 91% conversion with 89% ee were obtained (–20 °C and 4 h, highly comparable with the homogeneous analogue). With increase of the cross-linking degree, it became more difficult for the catalyst to form oxo bridges between two near metal centers, which resulted in lower levels of enantioselectivity. However, the respective catalysts became more stable and therefore more reusable. The polymeric ligand with a cross-linking ratio of 25/100 was reused six times with minimal conversion (run 1 99%, $C_e(7) = 4\%$) and ee erosion (run 1 80% ee, $ee_c(7) = 7\%$) if the reactions were prolonged to 16 h.

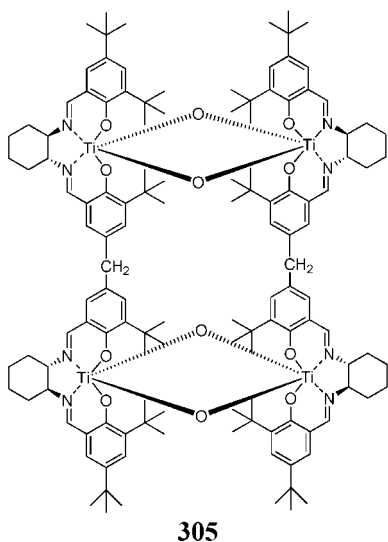
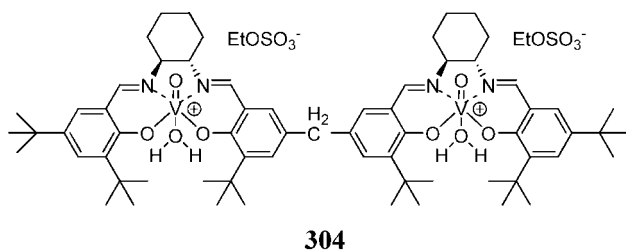
The polymeric linear VOsalen catalyst **302** was prepared and tested in this transformation, proving to be superior to the linear polymeric Ti(IV)salen catalysts (2 mol %, –20 °C, 90% yield and ee). Unfortunately, it was not possible to reuse it.⁵⁴⁶



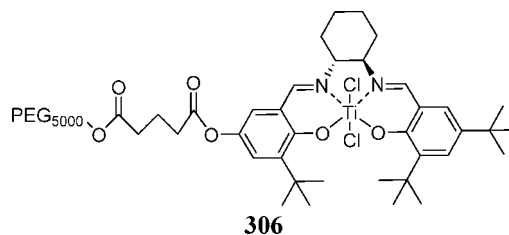
Khan et al. prepared a new polymeric VOsalen catalyst identical to Zheng's catalyst. This new catalyst, **303**, proved to be as reactive as Zheng's catalyst but provided higher levels of enantioselectivity (1 mol %, room temperature, 97% yield and 94% ee). Furthermore, it tends to precipitate in apolar solvents, allowing its reutilization (up to four efficient cycles).^{547,548}



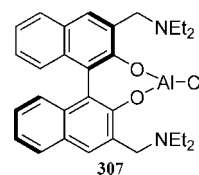
Khan et al. tested two dimeric VOsalen and Ti(IV)salen catalysts under identical conditions. Both catalysts showed improved efficiency, where conversions up to 99% with enantioselectivities up to 96% were obtained for several benzaldehydes. Furthermore, catalysts **304** and **305** were recovered by precipitation (with hexane) and reused up to four cycles with consistent enantioselectivity.⁵⁴⁹



It is known that strategies based on catalyst immobilization in soluble macromolecules require precipitation techniques to achieve catalyst 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. Venkataraman and Anyanwu showed that a PEG-supported titanium–salen complex **306** could be recovered and reused for silylcyanation of benzaldehyde (0.1 mol % of catalyst) at least five times without any loss of activity (conversions always above 95%) and enantioselectivity (run 1 = 86%, run 5 = 85%, ee(5) = 1%).⁵⁵⁰ These results are comparable with those obtained with the unsupported catalyst analogue. The recovery process involved a Soxhlet-dialysis protocol, where the Soxhlet chamber was refilled with fresh dichloromethane every 20 min. After 38 h about 98% of cyanohydrins are separated from the PEG-supported titanium–salen complex.



Saá et al. prepared the chloride aluminum–BINOLAM catalyst **307** for silylcyanation of benzaldehydes. With this catalyst in the presence of triphosphine oxide and molecular sieves, it was possible to achieve conversions and enantioselectivities above 99%. Enantiomerically pure (*S*)-BINOLAM was almost quantitatively recovered by acid–base extraction and purification and was reused without any loss of efficiency.⁵⁵¹

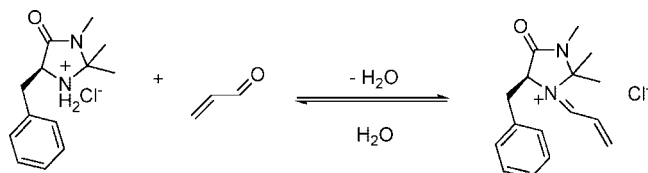


The method for heterogenization of Ti(IV)salen catalysts should allow the formation of Ti oxo bridges between two near units. This is the reason polymeric supports behaved better than inorganic supports. On the other hand, VOsalen catalysts maintained most of their activity when immobilized in silica and homopolymers. It should be interesting to see the performance of those catalysts when incorporated or grafted in polystyrene-type resins. Lanthanide-based catalysts should also be further studied in order to decrease the degree of metal leaching.

20. Asymmetric Cycloadditions

Organocatalysts. Before 2002, boranes were coordinated in polymers containing BINOL, amino acid, or tartaric acid moieties to be used as catalysts in Diels–Alder reactions between cyclopentadiene and methacrolein.⁵ The best supported catalyst provided excellent performance with high selectivity toward the exo isomer (selectivity >99% with 88% ee). This catalyst was constructed by loading a polymeric BINOL with B(OMe)₃ in the presence of 4 Å MS.

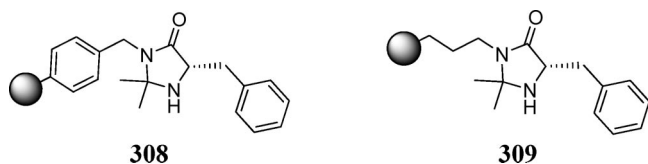
Since its first report, chiral imidazolidinones developed by MacMillan et al.⁵⁵² quickly demonstrated their enormous

Scheme 82. Iminium Catalysis Promoted by MacMillan-type Catalysts

potential to induce formation of new asymmetric centers at a high level of enantioselectivity on iminium- and enamide-based catalysis.⁵⁵³ Among several successful examples of reactions catalyzed by this organocatalyst family, Diels–Alder cycloadditions figure among the most important methodologies scoped (iminium catalysis, Scheme 82).

Despite some of the organocatalysts proving to be easily prepared from enantiopure amino acids in good yields, others do not follow that characteristic. So it was not surprising that some attempts to immobilize and recover such catalysts started to appear.

Pihko et al. reported the first heterogeneous immobilization of a MacMillan-type catalyst.⁵⁵⁴ The supported catalysts, in silica and JandaGel resins, were prepared by solid-phase synthesis (three steps). JandaGel-supported catalyst **308** (20 mol %) was found to be more suitable for reactions with low polarity transition states (when cyclopentadiene was applied as diene) affording good yields (60–73%) with high enantioselectivities (83–99% ee), sometimes even surpassing the homogeneous catalyst. This system was recovered by filtration and reused once with slight yield and ee decrease (5–10%, with 10 mol % catalyst loading). Silica-supported catalyst **309** (20 mol %) was found to be more appropriate for Diels–Alder reaction of 1,3-cyclohexadiene/2-methylbutadiene with acrolein affording high yields (79–83%) and 90% ee.



Interestingly cycloaddition between cyclopentadiene and acrolein in the presence of 3.3 mol % silica-supported catalyst **309** was more efficient than the same reaction run in the presence of 20 mol % JandaGel-supported catalyst **308**. Unfortunately, the same behavior was not observed with the other aldehydes tested.

Benaglia et al. used tyrosine instead of phenylalanine to prepare a functionalized version of MacMillan's catalyst.⁵⁵⁵ The hydroxyl group was used to graft that organocatalyst to

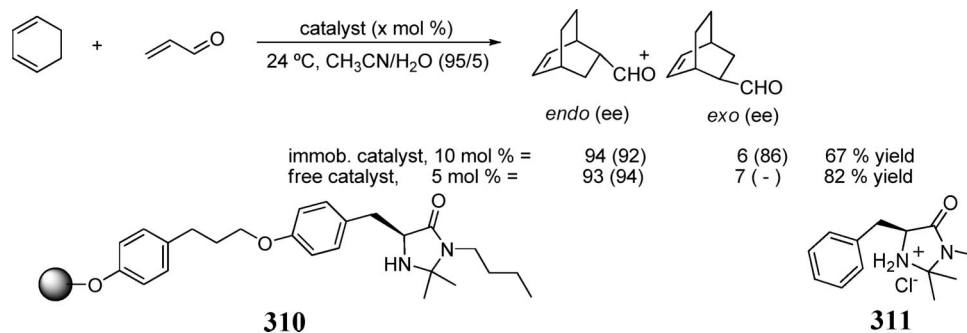
poly(ethylene glycol) chains (MW > 2000 Da) achieving a practical method for its immobilization. Acrolein and 1,3-cyclohexadiene were reacted with 10 mol % supported catalyst **310**/TFA mixture in 40 h to furnish the Diels–Alder adduct in 67% yield, 94:6 *endo:exo* selectivity, and 92% ee for the major isomer (Scheme 83). These results were inferior to those obtained by MacMillan et al. working under similar conditions with 5 mol % (*S*)-5-benzyl-2,3,3-trimethylimidazolidin-4-one hydrochloride **311** as the catalyst (82% yield, 93:7 *endo:exo* selectivity, and 94% ee of the major isomer).

Catalyst **310** could be recovered by precipitation from diethyl ether in 70–80% yield. Some degree of degradation accounts for the considerable decrease in the yield during five cycles (from 67% to 38%). This PEG–OMe-supported catalyst was also applied in 1,3-dipolar cycloadditions of phenylnitrones with acrolein with identical performance. For this type of cycloaddition, HBF₄ proved to be best the acidic additive.⁵⁵⁶

Ying et al. anchored a MacMillan-type catalyst in novel siliceous mesocellular foams by two different strategies. In the first one, allyl silanes bearing the organocatalyst were reacted with the siliceous material and sequentially capped with hexamethyldisilazane (catalyst **312**). In a second approach, a mixture of styrene, divinylbenzene, and a styrene derivative of the organocatalyst were copolymerized inside the siliceous support. The polymer coated the well ordered walls of the structure (catalyst **313**). When both catalysts were tested in the Diels–Alder reaction of cinnamaldehyde with cyclopentadiene, they proved to be as reactive as the unsupported organocatalyst (5 mol %, quantitative yields). Unfortunately the process was about 10% less enantioselective than the original protocol (93% vs 83% ee). The PS-coated catalyst **313** was the only one that retained the same outcome in a second cycle.⁵⁵⁷

Kim et al. performed the cycloaddition of acrolein with 1,3-cyclohexadiene catalyzed by the MacMillan catalyst (**311**) in ionic liquid media. Due to the catalyst ionic character, (*S*)-5-benzyl-2,3,3-trimethylimidazolidin-4-one hydrochloride (5 mol %) was found to be soluble in a wide range of ionic liquids. However, the reaction only occurred in high yield (85%) and enantioselectivity (93% ee, Scheme 84) on a hygroscopic IL (like [bmim]PF₆). The authors rationalized that the residual water in the IL helped the reaction turn over. The cycloaddition reaction occurred faster in [bmim]PF₆ than in acetonitrile and displayed comparable efficiency, and the catalyst could be recycled three times with 20–25% loss of efficiency (both yield and ee).⁵⁵⁸

Zhang et al. prepared a MacMillan-type catalyst bearing a perfluorinated tail to achieve its recycling using fluororous solid-phase extractions. The catalyst **314** was tested in Diels–Alder reaction between cyclohexadiene and acrolein

Scheme 83. Asymmetric Cycloaddition Reactions Promoted by MacMillan-type Catalysts Immobilized in PEG

Scheme 84. Asymmetric Cycloaddition Reactions Promoted by MacMillan-type Catalyst in Ionic Liquids

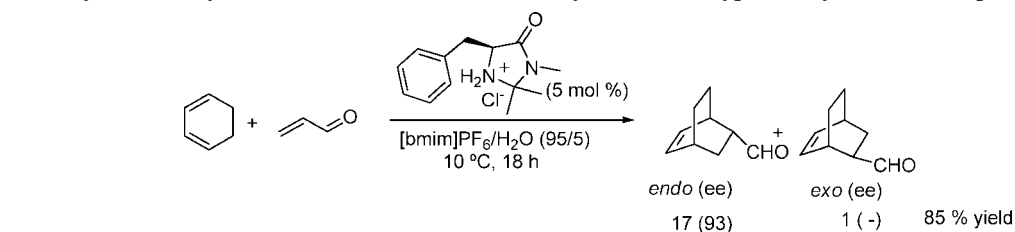
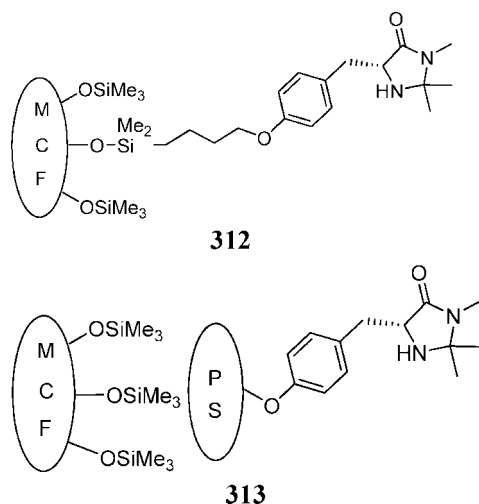
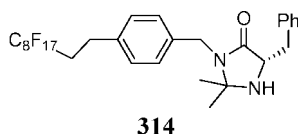


Table 18. Recycling Assays for Asymmetric Cycloaddition Reactions Promoted by Polymeric Crsalen Catalyst

recycling	<i>t</i> (h)	yield (%)	ee (%)
1st cycle	23	74	62
2nd cycle	24	77	62
3rd cycle	22	71	64
4th cycle	23	60	66
5th cycle	24	55	63
6th cycle	22	56	63
7th cycle	23	17	63



and proven to be superior to the original catalyst (93.4:6.6 *endo/exo* selectivity, 93.4% ee *endo*). The catalyst was recovered by retention in a fluorous silica phase, while the products were eluted with acetonitrile/water (65/35). The recovered catalyst (84%) was used in a second cycle with similar efficiency.⁵⁵⁹



The Corey group reported several works since 2002 using a family of chiral oxazaborolidinium salts (catalyst **315** and **316**) to catalyze cycloadditions of electron-withdrawing dienophiles (acrylates). The catalysts were recovered by silica-gel column chromatography, which is not a practical method for catalyst recovery.^{560–564}

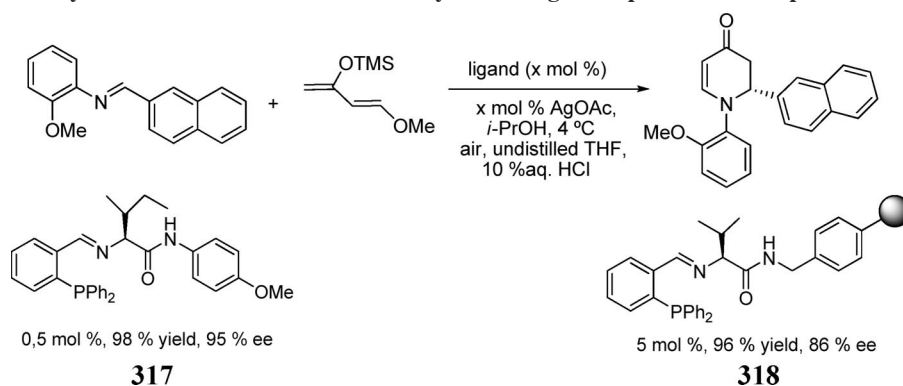
Lewis Acid Catalysts. Metal-based asymmetric catalysts act as Lewis acids activating the dienophile in cycloaddition reactions. The main strategies earlier developed relied on direct ligand linkage with the recoverable support, where

several Lewis acids could be coordinated. The most consistent catalysts built contained the BINOL moiety (grafted or copolymerized) and an aluminum or titanium metal center. These systems furnished the desired products with excellent enantioselectivities (above 90% ee).⁵

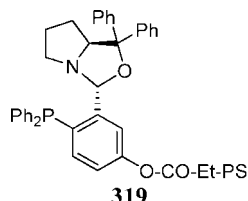
Hoveyda et al. immobilized a chiral phosphininime ligand in a Wang resin to achieve its recovery and recycling.⁵⁶⁵ This ligand **318** was applied in a Danishefsky diene and arylimine cycloaddition reaction catalyzed by Ag(I)/ligand in air with undistilled THF as the solvent. With 5 mol % catalyst, 96% yield and 86% ee were obtained, and ligand reutilization achieved five cycles. Under the same conditions, the unsupported protocol (ligand **317**) furnishes the respective arylenamine with 98% yield and 95% ee (Scheme 85).

Nakano et al. also grafted this type of ligand to several polystyrene-based resins and tested them in palladium-catalyzed Diels–Alder reactions. The authors found that the support had a significant influence in the reaction efficiency, where the PS–Et–COOH support provided the best results. Cyclopentadiene was reacted with acryloyl-1,3-oxazolidin-2-one in the presence of 20 mol % palladium (II)/ligand **319** complex, with 79% yield, 93:7 *endo/exo* selectivity, and 92%

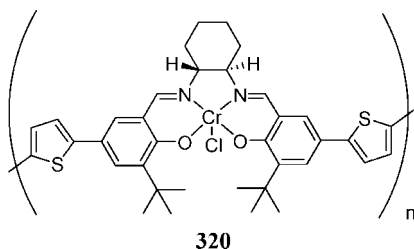
Scheme 85. Asymmetric Cycloaddition Reactions Promoted by Chiral Ag–Phosphininime Complex Immobilized in Wang Resin



ee. The heterogeneous catalyst was reused twice with 30% yield and enantioselectivity erosion.⁵⁶⁶



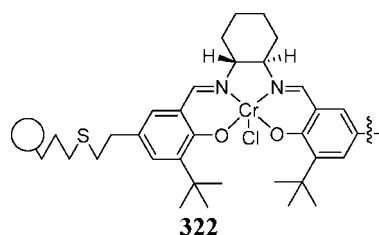
Schulz and co-workers applied a distinct immobilization technique to recycle Crsalen catalyst. The authors prepared a bis-thiophene–Crsalen complex and induced electropolymerization of this monomer. The resulting polymer **320** was then addressed for the same transformation (4 mol % catalyst). The hetero-Diels–Alder reaction between Danishefsky's diene and heptanal in THF during 24 h at room temperature was conducted to study this heterogeneous polymeric catalyst recyclability (Table 18). The catalyst immobilization proved to be a bit detrimental for the reaction enantioselectivity since it decreased 10%.⁵⁶⁷ The authors showed that despite some yield fluctuation this system was very robust, achieving a recyclability of 20 cycles.⁵⁶⁸



Ding and Meng synthesized a new type of dendritic 2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN)-derived Schiff-base ligand and applied it to titanium-catalyzed hetero-Diels–Alder reaction of Danishefsky's diene with aldehydes. The first generation dendrimeric ligand **321** was found to give higher enantioselectivity than the homogeneous unsupported ligand. A large number of aldehydes were reacted with this catalyst (10 mol %, Scheme 86), affording the respective adduct in quantitative yields and with high ee (>90%). The catalyst was quantitatively recovered by

precipitation/filtration and reused without further titanium and additive ((*S*)-naproxen) recharge up to four cycles with minimal yield (10%) and ee (2%) erosion.⁵⁶⁹

Heckel and Seebach immobilized Crsalen complex in a pore-controlled glass silica gel support, and its efficiency (2 mol %) was tested in hetero-Diels–Alder reaction of Danishefsky's diene with caproaldehyde (HOCC₅H₁₁) in *tert*-butylmethylether over 24 h at room temperature.²³⁵ The supported catalyst **322** 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, whereas the conversion showed some fluctuations (91–55%), the enantioselectivity increased with the number of runs up to a certain level (~84%).

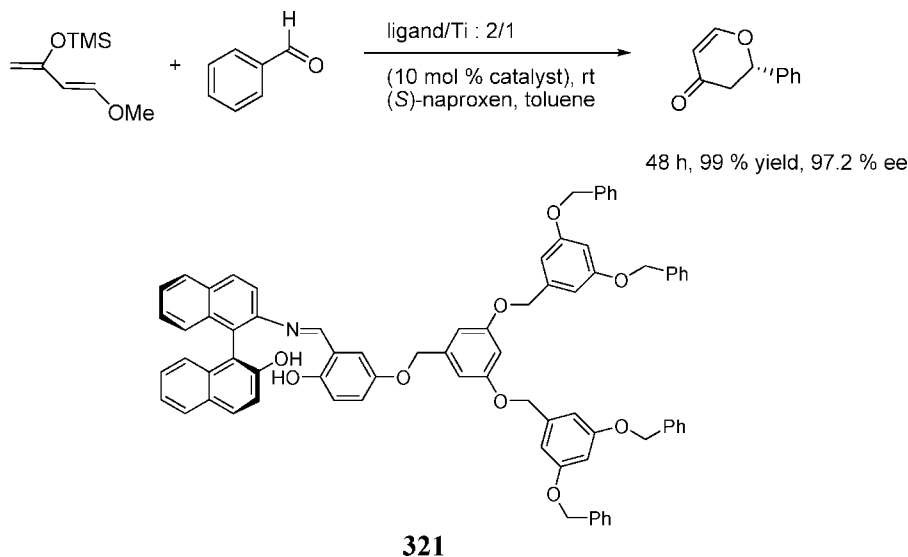


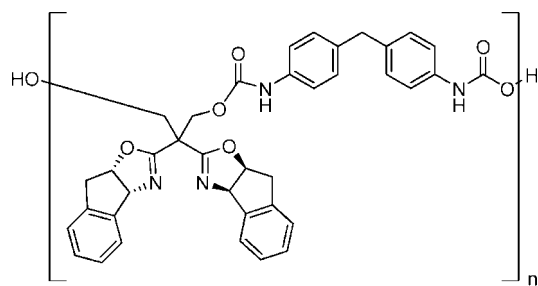
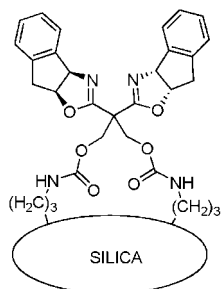
Lemaire et al. heterogenized an IndaBox ligand by grafting it onto a silica surface and by copolymerization with methylene diphenyl isocyanate (MDI). Both catalysts were tested in Cu(II)-promoted cycloaddition of 3-acryloyl-2-oxazolidinone with cyclopentadiene (Cu(OTf)₂ 8 mol %, dry dichloromethane, –78 to 0 °C). The polymer **323** gave 100% conversion with 89% *endo* selectivity in 51% ee and was successfully recycled twice. On the other hand, silica-supported catalyst **324** gave higher ee (79%) even at higher temperature but failed to provide consistent results upon recycling.⁵⁷⁰

Capping off the free silanol groups on the support proved to be highly desirable since it was shown to have a linear impact on increasing the enantioselectivity.⁵⁷¹ The same methodology for immobilization on silica was extended to Cu-Box ligands by the Iwasawa group.⁵⁷²

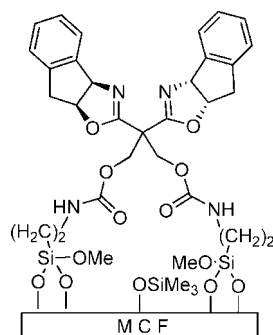
Lancaster et al. immobilized Box ligands onto mesocellular foam (MCF).⁵⁷³ This silica support has high surface area (814 m² g^{–1}) containing ultralarge pores of 25 nm, which

Scheme 86. Asymmetric Cycloaddition Reactions Promoted by Dendritic Ti–NOBIN Catalyst



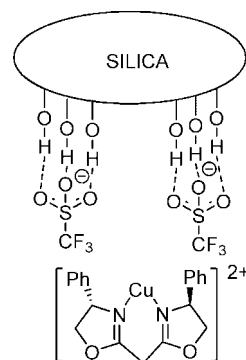
**323****324**

were interconnected by windows of 11 nm. The IndaBox ligand was grafted to the surface of this siliceous material followed by free silanol capping with organosilanes. The existence of free silanols proved to have detrimental effects on the enantioselectivity of Cu(II)-catalyzed cycloaddition of 3-cryloyl-2-oxazolidinone with cyclopentadiene (70% ee vs 47% ee). Upon immobilization, a slight decrease of enantioselectivity was observed (about 10%), but the reaction with immobilized catalyst was always faster. At $-78\text{ }^{\circ}\text{C}$, the immobilized catalyst **325** gave quantitative conversion in 8 h with 96% *endo* selectivity in 88% ee. This feature could be explained by the pore structure, which would prevent any steric issues associated with the immobilization of bulky ligands and minimize any diffusion limitation of large substrates. The catalyst was reused at least four times without any observable efficiency loss.

**325**

O'Leary et al. immobilized Cu((*S,S*)-phenyl-Box)(OTf)₂ catalyst to amorphous silica via hydrogen bonds. The catalyst was tested in a Diels–Alder reaction between *N*-acryloyloxazolidinone and cyclopentadiene and proved to be more enantioselective than the nonimmobilized counterpart (33% vs 20% ee). Its reusability was tested, and the authors verified that the catalyst complex could be reused at least once without any activity loss.⁵⁷⁴

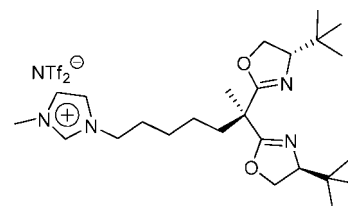
Curiously the supported catalyst **326** provided the opposite optical isomer compared with the traditional homogeneous

**326**

catalyst. The immobilization greatly alters the catalyst active site conformation in this case.

Wang et al. extended the same strategy to several others catalytic systems (phenyl- and *tert*-butyl- substituted Box ligands combined with three different metal centers, Mg, Zn, and Cu) and found out that the best system requires Cu-*t*-BuBox as catalyst and toluene as the solvent.⁵⁷⁵ High enantioselectivity (>90% ee) and moderate reusability (up to three recycles) were observed under such conditions in the same transformation. Experimental and theoretical studies showed that the inversion of the absolute configuration upon immobilization of the Cu(II)-PhBox catalyst was triggered by the anion dissociation (triflate anion) from the Cu(II) onto the surface of the support.

Doherty and co-workers observed an accelerating effect in the Diels–Alder reaction between *N*-acryloyloxazolidinone and cyclopentadiene in the presence of Cu-*t*-BuBox when conducted in [emim]NTf₂ compared with organic solvents. This enhancement of reactivity was also useful to achieve good results in more challenging substrates. The authors attached an imidazolium ring in one of the bridge carbon substituents to achieve catalyst recycle (ligand **327**). This slight modification was not detrimental for the reaction efficiency and allowed the catalytic system to be reused nine times without yield or enantioselectivity erosion (leaching degree below 0.03%).⁵⁷⁶

**327**

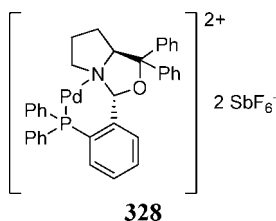
Kim et al. observed that the same transformation catalyzed by Cu-IndaBox ligand can have its enantioselectivity enhanced to 94% ee if [bmim]SbF₆ is used instead of dichloromethane (8 mol % catalyst, 3 $^{\circ}\text{C}$, 10 min). Furthermore, the authors showed that the catalytic system and ionic liquid could be recycle 16 times with residual enantioselectivity erosion (88–92% yields, 10 min).⁵⁷⁷

Doherty et al. found that when platinum complexes with BINAP ligands catalyze the cycloaddition reaction between cyclopentadiene and acrylalyl-*N*-oxazolidinone in an IL phase ([emim]NTf₂), the enantioselectivity and reactivity of the catalytic system was increased (100% conversion, 92% ee) compared with reactions run in dichloromethane.⁵⁷⁸ It was reasoned that the ionic liquid exerted some kind of stabilization of a reaction intermediary that was responsible for such

improvement. Furthermore, product extraction with diethyl ether allowed the catalyst to be recycled up to three cycles with minimal yield and ee erosion.

Loh et al. performed the cycloaddition of acroleins with butadienes and cyclopentadiene in [hmim]PF₆ in the presence of (*S*)-BINOL–In(III) and allyltributyl stannane. This system performed better in terms of yields (78–92%) in the ionic liquid media than in dichloromethane and furnished excellent enantioselectivities (up to 98% ee). Furthermore, the catalytic system remained in the ionic liquid while the products were extracted allowing its recycle. In the seventh cycle, the yield eroded 5% while the enantioselectivity fell 12%.⁵⁷⁹

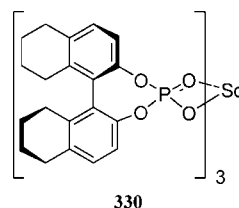
Nakano et al. tested the cycloaddition of cyclopentadiene and acryloyl-1,3-oxazolidin-2-one in several ionic liquids in the presence of a cationic Pd-phosphinooxazolidine catalyst **328**. The [bmim]BF₄ proved to be an excellent media for this transformation, furnishing at room temperature the same levels of conversion and chiral induction obtained in dichloromethane at –50 °C (89% yield, 96:4 *endo/exo*, and 96% ee). In the first recycle experiment (at room temperature), an enantioselectivity decrease of 11% was observed in the third cycle. The authors optimized these experiments, performing the reaction at –40 °C in a mixture of IL/dichloromethane (1:2, due to ionic liquid viscosity). At the end of the reaction, the dichloromethane was removed under pressure, and the products were extracted with diethyl ether. With these optimizations, eight efficient recycles were achieved.⁵⁸⁰



Chollet et al. reported the application of a charge transfer complex in Cu(II)-promoted cycloaddition of 3-acryloyl-2-oxazolidinone with cyclopentadiene.⁵⁸¹ The charge transfer complex forms when an electron-poor molecule gets in contact with an electron-rich molecule. The attachment of an electron-rich moiety to IndaBox ligand allowed catalyst

immobilization. The charge transfer complex **329** was successfully employed affording quantitative conversion, 93% de, and 84% ee, values which are comparable to those obtained with the unsupported catalysts (Scheme 87). The catalytic system was recovered by precipitation with pentane and filtration. 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 dropped from 44 h (run 1) to 0.5 h (run 11).

Furuno et al. reported the use of new rare earth catalysts with chiral BINAP-type phosphorates.⁵⁸² The new catalysts showed enhanced solubility in dichloromethane (without aid of any additive) and were tested in hetero-Diels–Alder reaction of Danishefsky's diene with aromatic aldehydes. Heavy lanthanides such as Yb and Er tended to afford higher ee's (up to 98%) than lighter ones (up to 91%). The catalyst **330** proved to be the most robust combination showing 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%) and ee (6%) erosion.



Carmona et al. reported the use of rhodium aquo compounds in asymmetric 1,3-dipolar cycloaddition between methacrolein and aryl nitrones ($[\eta^5\text{-C}_5\text{Me}_5]\text{Rh}((R)\text{-Prophos})(\text{H}_2\text{O})](\text{SbF}_6)_2$) affording the respective adducts in quantitative yield (5 mol %), 63:37 *endo/exo* selectivity in 90%/75% ee (*endo/exo*).⁵⁸³ Due to the catalyst's inherent solubility in water, it could be recovered and reused up to five cycles with constant enantioselectivity and dropping yield ($Y_c(5) = 25\%$).

Valerga et al. demonstrated that a TpRu complex with a chiral phosphinoamine ligand can be efficiently used as a Lewis acid catalyst for enantioselective solvent-free Diels–Alder reactions and 1,3-dipolar cycloadditions. With this catalyst, methacrolein was reacted with cyclopentadiene, and the

Scheme 87. Asymmetric Cycloaddition Reactions Promoted by Cu-Box Complex Immobilized in a Charge Transfer Complex

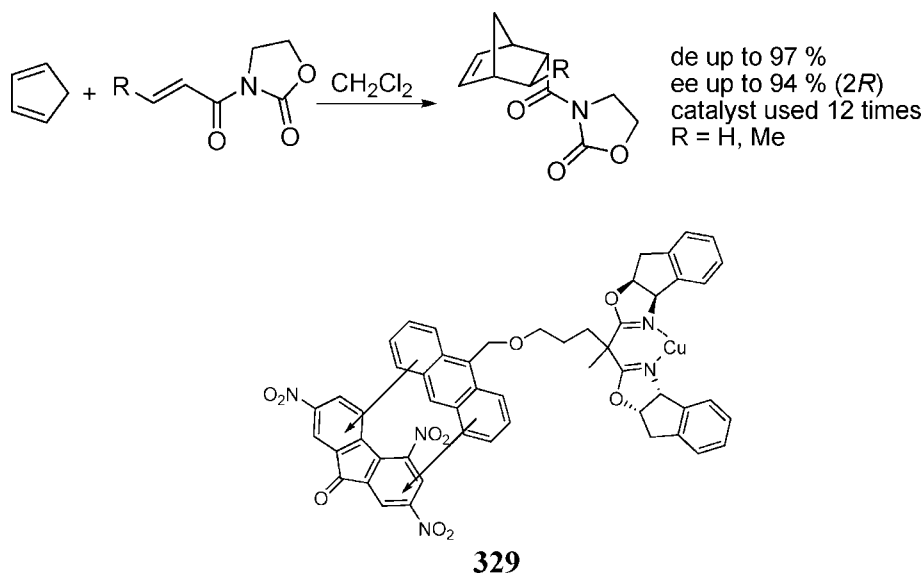
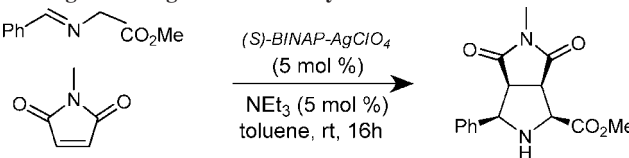


Table 19. Asymmetric Cycloaddition Reactions Promoted by Heterogeneous Ag–BINAP Catalyst


cycle	catalyst (mmol)	% recovered	yield (%)	ee _{endo} (%)
1	0.060	95	91	>99
2	0.057	93	89	>99
3	0.053	92	91	>99
4	0.047	90	90	99
5	0.042	90	88	98

product was obtained in moderate enantiomeric excess (36–70%). The catalyst was recovered at the end of the reaction by filtration.⁵⁸⁴

Nájera and Sansano discovered that (*S*)-BINAP–AgClO₄ complex was insoluble in toluene, and it promotes the 1,3-dipolar cycloaddition reaction between azomethine ylides and maleimides (Table 19). 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.⁵⁸⁵

From the literature reviewed in this section, it can be said that in general recyclable metal-based Lewis acid catalysts were more efficiently reused than immobilized organocatalysts, perhaps due to higher chemical stability. Furthermore, it was shown that a large scope of Lewis acids could be recycled in this reaction. There are some contributions where high levels of recyclability were obtained (more than five cycles); however there are still a large number of examples where loss of efficiency becomes a limitation. Since only a few protocols discuss the degree of metal leaching present in their studies, it is difficult at this stage to understand whether that low recyclability is due to metal leaching or catalyst degradation.

21. Asymmetric Iminic Glycine Ester Alkylation

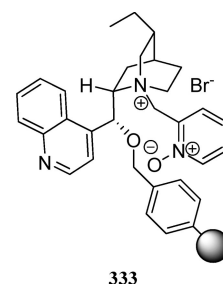
Cinchona derivative alkaloid salts have been elegantly applied as phase transfer catalysts. Due to their economic value, it is highly desirable to combine two phase catalysis with catalyst reutilization. In the past, the application of

O-supported polymeric cinchonidinium **331** was reported achieving ee's up to 94% in enantioselective alkylation reaction of N-protected glycine esters.⁵⁸⁶

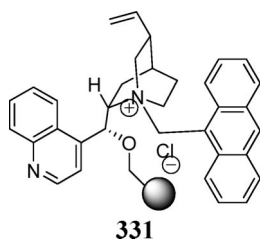
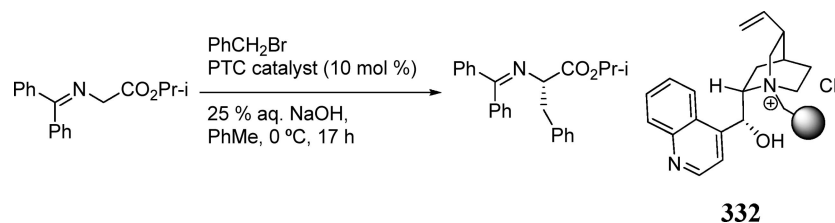
Nájera et al. prepared several insoluble chiral polymeric ammonium salts by N-quaternization of a family of cinchona-related alkaloids with different types of commercially available polystyrene resins (Merrifield resin and polystyrene grafted to polypropylene resin).⁵⁸⁷ All these polymers were tested as insoluble phase transfer catalysts (PTC) in the triphase enantioselective alkylation reaction of N-protected glycine esters with benzyl bromide using an aqueous base (Scheme 88).

Generally, all catalysts were found to be effective, but the chiral induction was disappointingly low (<40% ee). Merrifield-supported cinchonidinium salt **332** was the exception, affording the desired product in high yields and enantioselectivities up to 90% ee. When this catalyst was tested with other alkylating agents, generally inferior enantioselectivities were observed, except when benzylbromide was used.⁵⁸⁸ All polymers were recovered by filtration after the alkylation reaction and reused up to three cycles without any loss of activity.

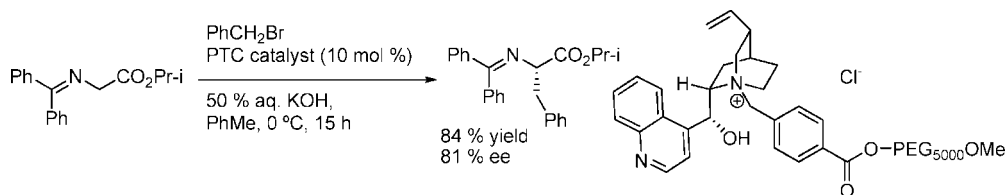
Park and Jew prepared a family of hydrocinchonidine-derived ammonium salts supported on Merrifield resin. The authors found that the presence of functionality with the ability to form hydrogen bonds in the quaternization group can enhance the enantioselectivity of the alkylation of glycine enamines. This was proposed to be due to the formation of a more rigid transition state. Several electrophiles were tested providing generally amino acids with excellent enantioselectivities (76–96% ee) in good yields. The polymeric phase-transfer catalyst **333** could be recycled four times without efficiency erosion.⁵⁸⁹

**333**

Cahard et al. quaternized four diastereomeric alkaloids with soluble PEG chain polymers to obtain immobilized phase-transfer catalyst **334**.⁵⁹⁰ Among quinine (33% ee (*S*)-enantiomer), quinidine (13% ee (*R*)-enantiomer), cinchonine (53% ee (*R*)-enantiomer), and cinchonidine (81% ee (*S*)-enantiomer), only the latter performed well in terms of enantioselectivity (Scheme 89). It is interesting to see that these four quasi-enantiomeric PTC catalysts sometimes offer rather different results. Merrifield-supported catalysts described previously afforded higher yields and enantioselectivities.

**331****Scheme 88. Asymmetric Iminic Glycine Ester Alkylation Promoted by Polymer-Supported Alkaloids****332**

Scheme 89. Asymmetric Iminic Glycine Ester Alkylation Promoted by Polymer-Supported Alkaloids

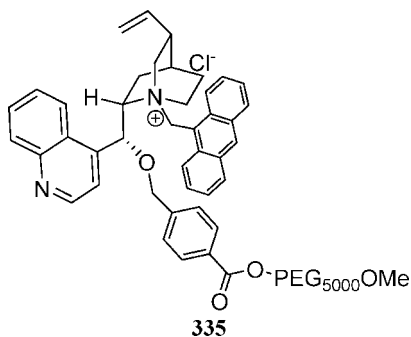


334

tivities than PEG-supported catalysts. The recovered catalyst was reused once, but the enantioselectivity decreased, probably due to some catalyst degradation.

When the benzyl bromide was replaced by other alkylating agents, the observed ee did not surpass 34%, which constitutes a drawback since those agents usually afforded higher ee than benzyl bromide. Kim and Huh immobilized the same cinchonidine catalyst to PEG₅₀₀₀ by quaternization substituting the ester functionality by ether and protecting the free alcohol. This phase transfer catalyst showed similar efficiency compared with Cahard's polymeric alkaloids but showed higher efficiency in a second cycle (1st cycle 83% yield and 73% ee; second cycle 69% yield and 70% ee).⁵⁹¹

In an attempt to improve the asymmetric induction, Cahard et al. attached the PEG chain to the alcohol via an ether or ester linkage, leaving the quinuclidine moiety free to be quaternized with bulky 9-(chloromethyl)-anthracene, **335**. Sadly the chiral induction was lower than the selectivity described when N-linked-PEG catalyst was used (<62% ee, rather low compared with 94% ee obtained by Corey et al.⁵⁹²).

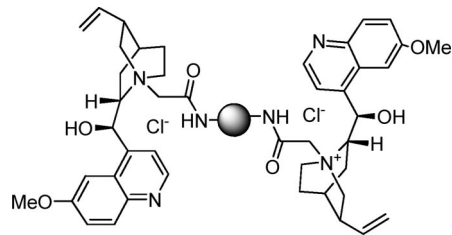


335

Benaglia et al. showed that substitution of PEG polymers of MW = 5000 Da by lighter polymers (PEG₂₀₀₀) in catalyst **335** allowed some improvement in the enantioselectivity to 64%. The authors justify that PEG exerted some influence in the steric course of the reaction. PEG increased the polarity of the organic phase enhancing the solubility of the inorganic cation leading to competing nonstereoselective alkylation.⁵⁹³

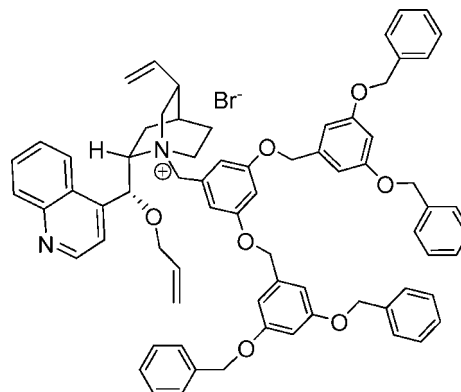
Wang et al. prepared a dimeric chiral PTC with two cinchona salts linked by a long PEG₂₀₀₀ chain. Catalyst **336** was stable under basic aqueous media and promoted the alkylation of glycine Schiff bases in high enantioselectivity (up to 97%) and high yields (up to 98%).⁵⁹⁴ The PTC was recovered by precipitation with diethyl ether after extraction from the aqueous phase with dichloromethane. The catalyst was reused twice with low yield erosion (5%) and consistent enantioselectivity.

Nájera et al. anchored a family of PTCs derived from cinchonidine at the core of soluble dendritic structures.⁵⁹⁵ The dendritic catalysts were tested for protected glycine alkylation and generally undergo the reaction with high yields (76–94%), but only the second generation catalyst **337**



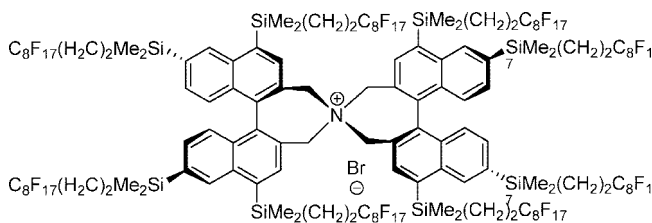
336

afforded high enantioselectivity (76% ee). Due to their high molecular weight, the dendritic structures could be recovered by dialysis membrane processes and reused. An increase of the reaction time was related to the drop of activity in the subsequent cycles, while the ee fell 25% after three cycles. Higher generation catalysts proved to be more stable under recovery conditions, giving more consistent results despite low performance.

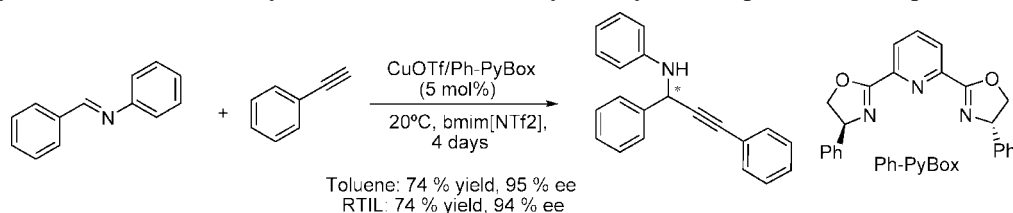
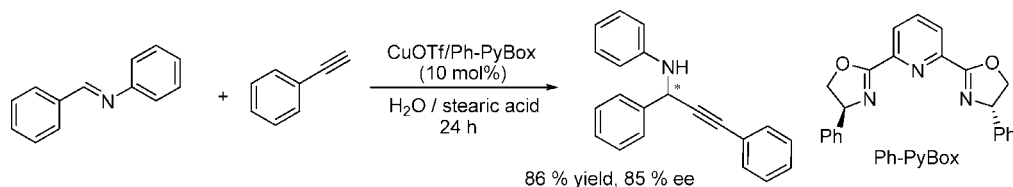


337

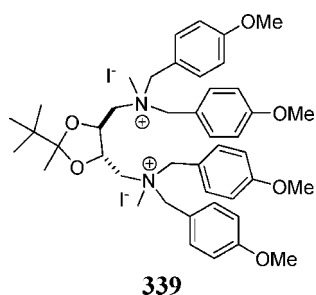
Maruoka et al. developed for the first time a perfluorous phase transfer catalyst derived from binaphthyl-modified *N*-spiro-type catalysts.⁵⁹⁶ The new catalyst **338** (3 mol %) was tested in the alkylation of protected glycine esters in a biphasic system (50% aq KOH/toluene 1:3). The respective products were obtained in 82% yield and 90% ee after 96 h at 0 °C for a range of alkylating agents (comparable to traditional nonfluorinated catalysts⁵⁹⁷). The catalyst was extracted to the FC-72 phase and reused twice with negligible yield and ee erosion (1–2%).



338

Scheme 90. Asymmetric Addition of Alkynes to Imines Promoted by Cu–PyBox Complex in Ionic Liquids**Scheme 91. Asymmetric Addition of Alkynes to Imines Promoted by Cu–PyBox Complex in Water/Stearic Acid Medium**

Ditetraalkyl ammonium salts derived from tartaric acid were applied by Shibasaki et al. in asymmetric phase transfer alkylation of N-protected glycine esters with benzyl bromide.⁵⁹⁸ Catalyst **339** (10 mol %) was the homogeneous promoter that can achieve higher yields and ee (90% yield and 70% ee) and can be recovered by precipitation and decantation upon diethyl ether and water addition to the reaction mixture. These catalysts were very useful and their recycling ability has been recently applied in the total synthesis of aeruginosin 298-A.⁵⁹⁹



In this section, the inherent difficulty to prepare supported chiral PTC alkaloid-based catalysts without compromising the reaction enantioselectivity was elucidated. One of the main limitations was related to altering the inorganic base solubility on the organic phase that will promote some achiral alkylations. It could be interesting to study whether such modifications applied to Maruoka's catalysts produce better results.

22. Asymmetric Addition of Alkynes to Imines

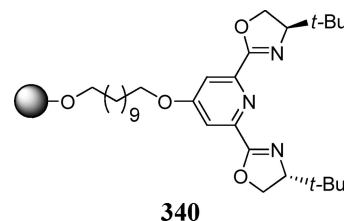
Alkyne addition to imines catalyzed by Cu(I)–PyBox complexes provided an important class of enantioenriched propargyl amines that have been used for the synthesis of various amino derivatives, including biologically active compounds. The development of methodologies to achieve product separation from the expensive catalyst was therefore important. In this reaction, sources of Cu(I) that are air-unstable were applied, constituting a clear limitation for traditional recovery protocols. The utilization of solvents in which dioxygen has low solubility combined with a recycling ability could be the solution for this problem. This reaction was not reviewed in the previous work.⁵

Afonso et al. studied the possibility of using room temperature ionic liquids (RTILs) as the solvent media for Cu(I)-promoted phenylacetylene addition to *N*-benzylideneaniline. They observed that the substitution of toluene by

[bmim]NTf₂ as solvent (in the presence of CuOTf and Ph-PyBox) had no effect on the isolated yield and enantiomeric excess of the amine product (Scheme 90).⁶⁰⁰ It should be noted that using only 5 mol % catalyst/ligand afforded similar results to a reaction run in toluene using 10 mol %.

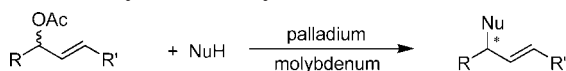
Since the catalytic system was not soluble in hexane, this solvent was used to extract the nonorganometallic products from the ionic liquid phase, achieving the desired recycle protocol (six cycles). However, hexane was not polar enough to fully extract the reaction product from the ionic liquid, while diethyl ether was able to accomplish such task. Unfortunately, 25% of catalyst was also extracted to the ether phase.

Weissberg et al. developed a new methodology for preparing heterogeneous bis(oxazolines) ligands based on solid-phase synthesis.⁴⁷⁹ Recently, this methodology was extended for the synthesis of PyBox-supported ligands supported on Wang resin.⁶⁰¹



After incubation of ligand **340** with a solution of CuOTf in dichloromethane, a light brown polymer was obtained. The heterogeneous catalyst was used for the first time to catalyze phenylacetylene addition to *N*-benzylideneaniline (10 mol % catalyst, 40 °C, 24 h), where a 63% yield with 83% ee was achieved. In a second cycle, the recovered catalyst showed signs of metal oxidation, which resulted in a decreased yield (20%, with constant enantioselectivity). When the solvent was switched to THF, higher yield was obtained (80%) but the enantioselectivity of the product fell to 54% ee in the first cycle. Addition of ascorbic acid to reduce Cu(II) to active Cu(I) enhanced the reutilization (run 1 80% yield; runs 2 and 3 78% yield), but the products are isolated in near racemic form (<5% ee).

Li et al. developed a protocol to execute Cu(I)-catalyzed addition of alkynes to aromatic imines in water with reduced reaction time (24 h) in the presence of a surfactant (stearic acid) and chiral Ph–PyBox ligand (Scheme 91). The respective amines were obtained in good yields (up to 89%) and enantioselectivities rounding 35–97% ee. Furthermore, the products were extracted with hexane at the end of the

Scheme 92. Asymmetric Allylic Substitution

reaction leaving the catalytic system behind in the aqueous phase. This protocol was efficiently applied during five cycles.⁶⁰² Under certain conditions, the hydrolysis of PyBox ligands in the presence of Lewis acids ($\text{Ce}(\text{OTf})_4$) or in acidic conditions has been observed.⁶⁰³ No signs of decomposition were reported on this example.

Alternatively, O'Leary and co-workers immobilized a Cu(I) – and Cu(II) – Ph –PyBox triflate complex on silica due to electrostatic interactions. Both heterogeneous complexes were tested in asymmetric addition of phenylacetylene addition to *N*-benzylidene-aniline (2.8 mol % copper), proving to behave similarly compared with the homogeneous catalyst (quantitative yield, up to 80% ee). The catalyst reusability was studied during three cycles.⁶⁰⁴

In these first results, comparable values of reactivity and enantioselectivity were obtained with the respective to unsupported and homogeneous protocols, but still there are some flaws in the reutilization process that need to be improved. The ionic liquid based protocol provided similar enantioselectivity to that observed in original homogeneous protocol, but the recycling processes were limited due to leaching problems.

23. Asymmetric Allylic Substitution

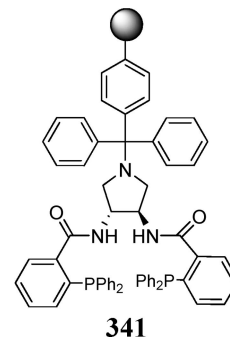
The asymmetric allylic substitution reaction (Scheme 92) constitutes an important tool to build chiral building blocks for several compounds with economical interest. This reaction is traditionally performed using palladium and molybdenum catalysts in the presence of expensive chiral mono- and bidentate phosphines.

23.1. Heterogeneous Catalysts

In 2002, two approaches were disclosed that demonstrate well the state-of-art of this reaction. In the first one, Hallman et al. used a phenyl-substituted Box linked at the bridge carbon atom to an ArgoGel resin. Despite this catalyst (ligand + palladium) being found troublesome in the recycling assays, it afforded constant high enantioselectivities (94–95% ee). In the second approach, Uozumi et al. reported the application of TentaGel-supported aminophosphine ligands in asymmetric allyl alkylation with enantioselectivity up to 98%.⁵

Song et al. reported the immobilization of Trost-type bisphosphane ligands in two polymeric resins, Merrifield and JandaJel, and its application on desymmetrization reaction of *cis*-1,4-bis-(benzoyloxy)cyclopent-2-ene with dimethyl malonate in the presence of elemental palladium (Scheme 93).⁶⁰⁵ The ligand immobilized in JandaJel resin (ligand **341**) proved to be much more reactive (quantitative yields in shorter times) than its homogeneous analogue furnishing the same levels of enantioselectivity (96% ee). The same was not observed with the catalyst supported in the Merrifield resin due to its inferior swelling ability. The Pd /ligand **341** was reused four times with some efficiency erosion.

Almost simultaneously, Trost et al. reported the immobilization of their ligand (bisphosphane **342**) to an ArgoGel resin.⁶⁰⁶ In this case, the reaction chosen to test the supported catalyst efficiency was the intramolecular desymmetrization of *cis*-1,4-bis(urethane)cyclopent-2-ene (2.5 mol % Pd , Scheme 94). The supported system was less efficient than its unsupported

Scheme 93. Asymmetric Allylic Substitution Promoted by Palladium and Trost-type Bisphosphane Ligands Immobilized in Polymeric Resins

analogue (78% yield with 90% ee vs 97% yield with 99% ee, $n = 2$). A consistent behavior was observed when the catalyst was recycled during four cycles, with minimal yield erosion (about 5%).

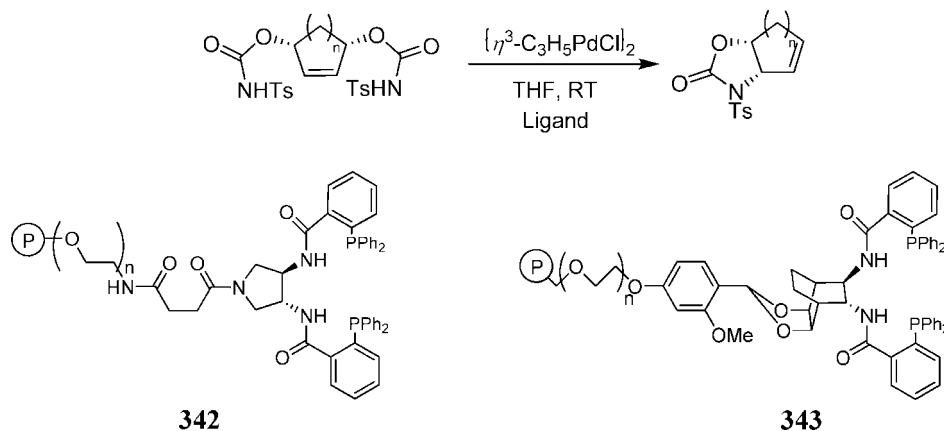
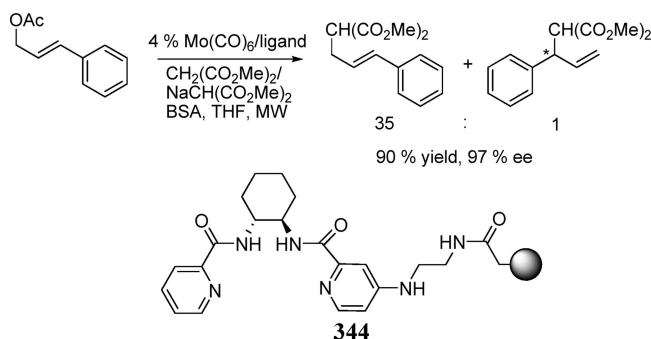
The more rigid ligand **343** was also prepared but proved to be less efficient than bisphosphane **342** (81% yield with 73% ee, $n = 1$). The reutilization of the supported catalyst **343** was possible up to seven cycles with almost unchanged enantioselectivity, however with decreased activity ($Y_c(7) = 18\%$).

Moberg et al. reported the immobilization of a bis-pyridylamide ligand to TentaGel resin via grafting.⁶⁰⁷ This new supported ligand **344** was tested in molybdenum-based asymmetric allyl alkylations with enhanced efficiency when compared with the best homogeneous analogue. Despite the reaction being somewhat slower due to the heterogeneous character of the catalyst, the same level of conversion and enantioselectivity were found (90% yield with 97% ee) with greater branched-to-linear product selectivity (35:1 vs 19:1, Scheme 95). Curiously the attachment of a -OMe group in the *para* position of one of the pyridine rings enhanced that selectivity up to 98:1. The ligand could be reused seven times without changes in the reaction outcome.

Uozumi and co-workers covalently attached a phosphinamine ligand to an amphiphilic resin (PS-PEG).⁶⁰⁸ The supported ligand **345** was tested in the asymmetric allylic amination of cycloalkenyl carboxylates under heterogeneous conditions in water. Good to excellent yields and excellent enantioselectivities (up to 98% ee) were obtained for a wide range of substrates (10 mol %, Scheme 96). The easily recoverable catalyst was reused twice with the same efficiency. More recently, this methodology was applied equally to asymmetric allyl etherification.⁶⁰⁹

This supported ligand was also tested in palladium catalyzed asymmetric allylic alkylation during a three step protocol to prepare cyclopentanes via enantioselective alkylation, propargylation, and cycloisomerization of 1,6-enynes in water (Scheme 97).⁶¹⁰

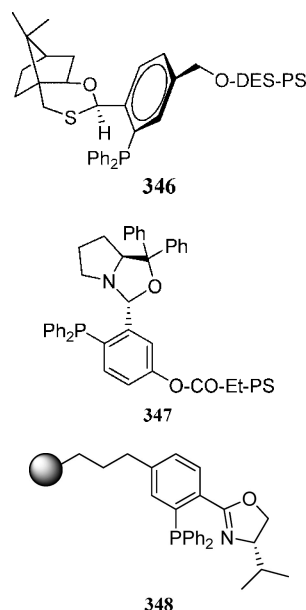
Nakano et al. grafted a chiral phosphinoxathiane ligand to several polystyrene-based resins and tested them in palladium-catalyzed allylic alkylation and amination of allyl acetates. The authors found that the support had a significant influence on the reaction efficiency, where the diethylsilyl-chloride polystyrene support provided the best results. As an example, ligand **346** promoted quantitative benzylamine condensation with allylic acetate in 99% ee. The heteroge-

Scheme 94. Intramolecular Desymmetrization of *cis*-1,4-Bis(urethane)cyclopent-2-ene Catalyzed by Palladium/Bisphosphane Complex Anchored in ArgoGel Resin**Scheme 95. Asymmetric Allylic Substitution Catalyzed by Molybdenum/Bis-pyridylamide Complex Anchored in TentaGel Resin**

neous Pd–ligand complex was reused twice with 30% and 20% yield and enantioselectivity erosion, respectively.⁶¹¹

Better results for alkylation of allylic acetate were obtained when a chiral phosphonioxazolidine ligand **347** was heterogenized using the same strategy. In this case, the best support was PS–Et–COOH, with which the respective product was obtained in 99% yield and 99% ee. Unfortunately, if no palladium was added for the subsequent run, 57% yield and 33% enantioselectivity erosion were detected.⁵⁶⁶

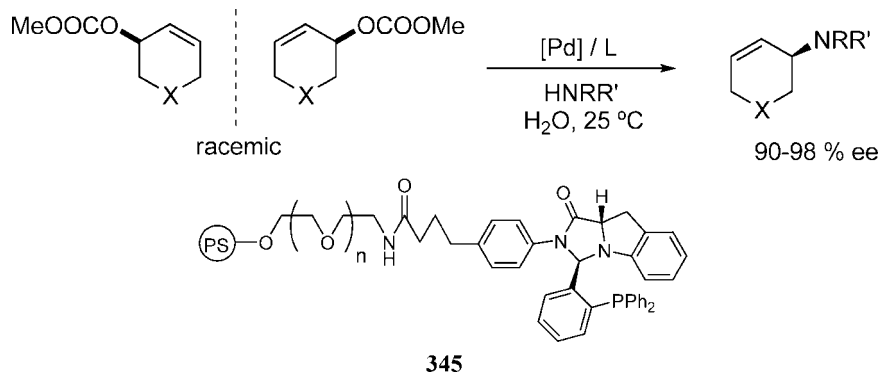
Hayashi and co-workers chose to graft several chiral phosphine ligands to the surface of silica gel using the allylsilane method. Ligand **348** was tested in palladium-promoted allyl acetate substitution with NaCH(COOMe)₂, proving to be slightly less enantioselective than the homogeneous ligand (98% vs 81% ee). Interestingly, when the catalytic system was reused for the third run, an enantioselectivity of 90% was observed.⁶²

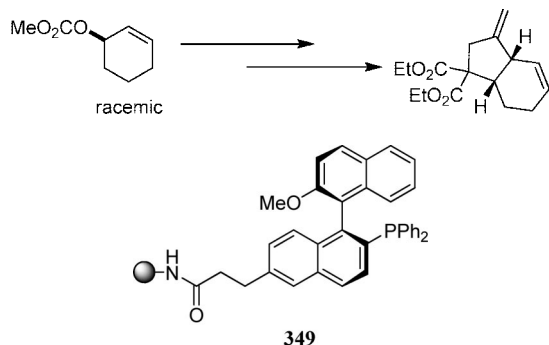


Uozumi et al. reported the application of MOP ligand anchored to PS–PEG resin (ligand **349**) in palladium-catalyzed allylic reduction of allylic acetates. The respective products were obtained in very good yields (up to 82%) and ee's up to 80% during seven cycles.⁶¹²

23.2. Homogeneous Catalysts

Ding et al. prepared a new type of C₂-symmetric bisphosphine ligand bearing a cyclobutane backbone and tested it in the palladium-promoted allylic alkylation and amination reaction.⁶¹³ Due to the excellent results obtained with those

Scheme 96. Desymmetrization of Cycloalkenyl Carboxylates with Palladium/Phosphinamine Anchored in PS–PEG Resin

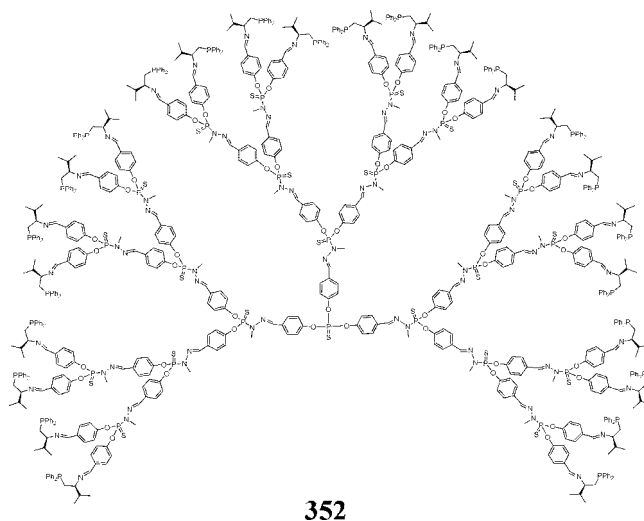
Scheme 97. Palladium-Catalyzed Asymmetric Allylic Alkylation during a Three Step Protocol To Prepare Cyclopentanes


new ligands, considerable efforts were made to link them to soluble poly(ethylene glycol) polymers to accomplish their recovery at the end of each reaction. In fact, one of those polymer-supported ligands (ligand **351**) was found to be more enantioselective than its unsupported partner (ligand **350**) (Scheme 98).

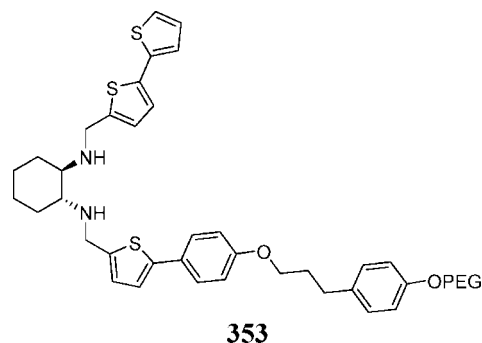
The supported catalyst was quantitatively recovered by filtration and reused three times in allylic alkylation and eight times in allylic amination reaction, though with some yield (11–18%) and ee (6–8%) erosion.

Caminade et al. reported the application of a dendritic ligand bearing iminophosphine ligands in the periphery in the benchmark asymmetric allyl alkylation reaction ((*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with malonates, 2.5 mol % Pd).⁶¹⁴ The third generation dendrimer ligand **352** provided quantitative yields with high enantioselectivity (90%) and could be reused twice with some efficiency loss (8% erosion on both yield and ee).

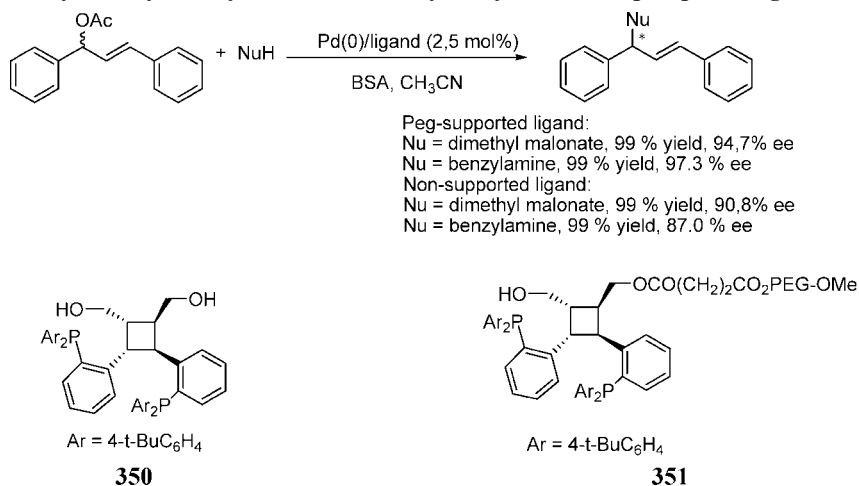
Bandini and Benaglia grafted a chiral *C*₁-symmetric diamino-oligothiophene ligand in a soluble polymeric support. This ligand, **353**, was coordinated *in situ* with palladium(II) species and tested in asymmetric allyl alkylation reactions of malonates and allyl carbonates in the presence of Cs₂CO₃. When the reaction was conducted in THF, the catalyst was insoluble and proved to be as efficient as the homogeneous unsupported catalyst (up to 98% yield, 99% ee). When the reaction was run in dichloromethane, the yield and ee decreased slightly, but this solvent allowed an easier method for catalyst recovery by precipitation. Unfortunately, the catalytic system was less efficient in a second cycle. If the reaction mixture was passed through Celite, only the

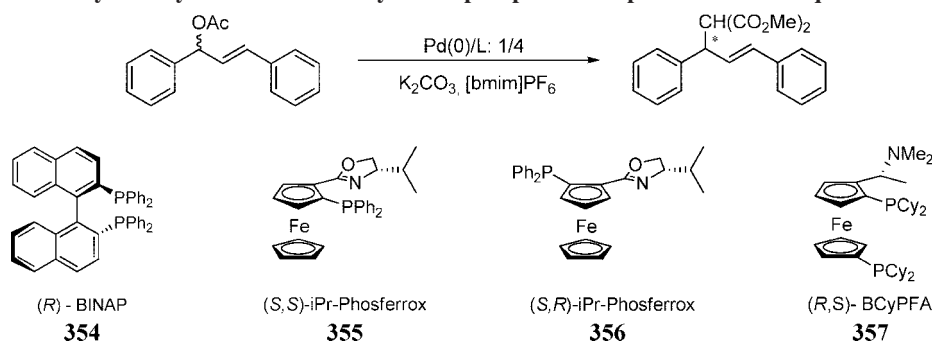


ligand was recovered. The batches were refilled with palladium to improve the recyclability allowing up to three cycles with minimal ee erosion.⁶¹⁵


23.3. Alternative Reaction Media

Toma et al. envisioned the possibility of using 3-butyl-1-methylimidazolium hexafluorophosphate ([bmim]PF₆) as the reaction media and an opportunity to achieve Pd(0)/ligand recycle.⁶¹⁶ Several ferrocenylphosphine ligands such as (*R*)-BINAP **354**, ((*S,S*)-*i*-Pr-Phosferrox **355**, (*S,R*)-*i*-Pr-Phosferrox **356**, and (*R,S*)-BCyPFA **357** were tested in the asymmetric allylic substitution of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate (Scheme 99). Generally it was difficult to find a combination of ligand and base (potassium carbonate and bis(trimethylsilyl)aceta-

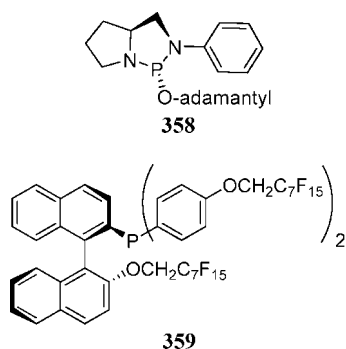
Scheme 98. Palladium-Catalyzed Allylic Alkylation Promoted by C₂-Symmetric Bisphosphine Ligand Immobilized in PEG


Scheme 99. Asymmetric Allylic Alkylation Promoted by Pd/Bisphosphine Complexes in Ionic Liquids

midate/potassium acetate) that could furnish both high yield and enantioselectivity. Furthermore, due to the low quantity of ionic liquid applied, it was not possible to prevent some catalyst loss during the workup, which implied some decrease in the activity upon recycling. Under optimized conditions (2 mol % $\text{Pd}_2(\text{dba})_3$, 15 h, 40 °C, potassium carbonate), ligands (*S,S*)-iPr-Phosferrox or (*S,R*)-iPr-Phosferrox afforded the respective allyl substitution product in 86% yield with 90% ee.

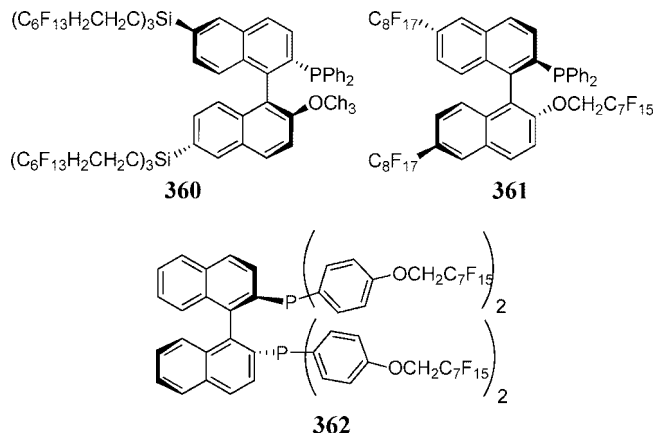
Lyubimov et al. reported the first application of an ionic liquid as solvent in an allylic amination reaction (Scheme 100).⁶¹⁷ In the reaction between (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with dipropylamine in the presence of a Pd(0) catalyst/asymmetric diamidophosphite ligand **358** in 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim]BF₄) a quantitative transformation resulted in 48 h with 84% ee (4 mol % Pd). Any attempt to recycle the catalyst failed.

Before 2002, Cavazzini et al. prepared a chiral “light fluoruous” phosphine ligand (ligand **359**) and carried out the Pd-complex-catalyzed allylic alkylation with malonates with excellent enantioselectivities (44–99% ee). Due to its low F-content, it could not be fully extracted to the *n*-perfluorooctane phase. Further variations on this type of ligand did not improve the previous results.



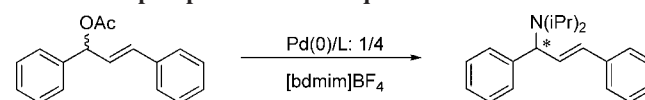
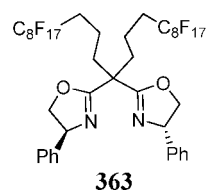
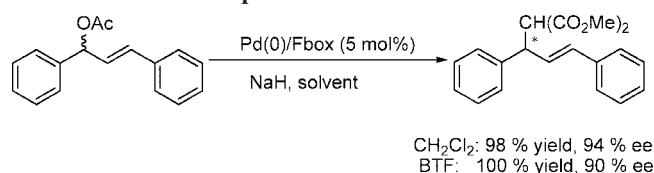
Sinou et al. prepared two new fluorinated MOP-derived ligands containing perfluoroalkyl chains in the positions 6 and 6' (ligand **360** and **361**).⁶¹⁸ Both ligands were tested in the palladium-mediated asymmetric allylic alkylation reaction of racemic (*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with malonates and both proved to be rather ineffective in inducing high levels of asymmetry (<37% ee).

One year later Pozzi and Sinou presented another perfluoroligand, in this case based on BINAP (ligand **362**), for asymmetric allylic alkylation reactions. Unfortunately, this ligand was not as efficient as its MOP analogue (presented earlier in the introduction section) since it did not afford enantiomeric excesses higher than 37%.⁶¹⁹



With the development of chiral Perfluoro-Box ligands for cyclopropanation reactions, carbonyl–ene among others reactions, their application was somehow expected in asymmetric allylic substitutions. Sinou et al. tested two of those catalysts in allylic alkylation reaction of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with malonates in excellent results.⁶²⁰ Both reactions run in dichloromethane and in benzenetrifluoride (BTF) afforded quantitative yields of product with excellent levels of enantioselectivity (90–94% ee, ligand **363**, Scheme 101).

An early attempt to recover the catalyst was made by performing a liquid/liquid extraction (FC-12/CH₂Cl₂), but this resulted in the formation of black palladium. Another

Scheme 100. Asymmetric Allylic Amination Promoted by Pd/Diamidophosphite in Ionic Liquids**Scheme 101. Asymmetric Allylic Alkylation Promoted by Pd/PerfluoroBox Complex**

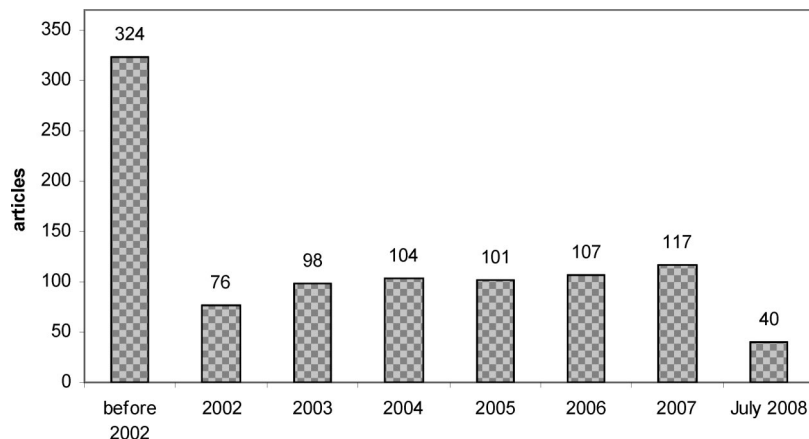
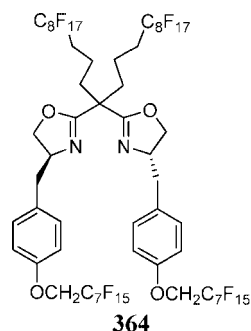


Figure 1. Annual evolution of publications under the theme of recyclable stereoselective catalysts.

approach was based on the solvent evaporation with removal of 70% of catalyst by redissolving in FC-72. The recovered catalyst was reused furnishing the same level of chiral induction. These ligands were also applied in allylic oxidation of electron-rich alkenes.

More recently another perfluorinated Box ligand was tested by the same authors in the same reaction. This new ligand **364** has more perfluorinated tails, which allowed its extraction from acetonitrile to FC-72 and therefore its reutilization (one time without efficiency erosion) with excellent levels of enantiomeric excess (92% ee).⁶²¹

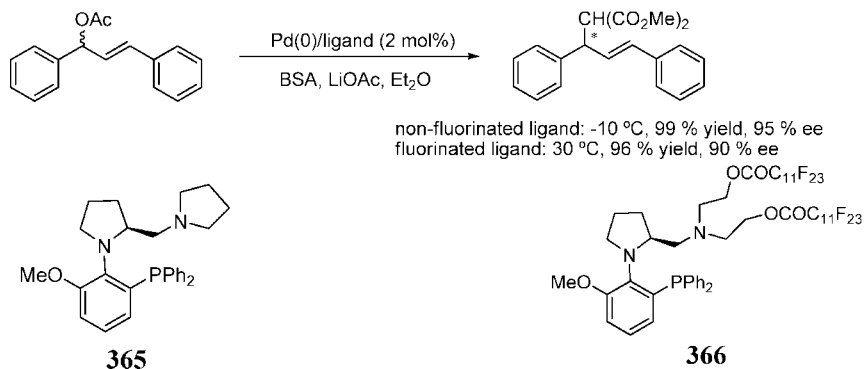
Mino et al. attached two perfluoroalkyl chains on diaminophosphine ligand to achieve its recycle together with the palladium catalyst (Scheme 102).⁶²² The Pd/perfluoro ligand **366** complex was tested in the allylic alkylation reaction of racemic (*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with malonate, proving that it retained some of the qualities of the parent nonfluorinated ligand **365**. The



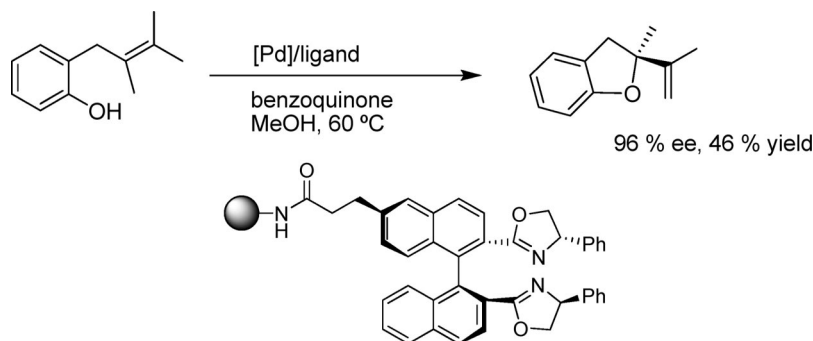
reaction became slower requiring higher temperature (30 °C) to achieve quantitative conversion with 90% ee.

With 5 mol % catalyst loading, it was possible to recycle both ligand and palladium efficiently up to six cycles with nearly unchanged outcome. At the end of each reaction, the solvent was removed under low pressure. Redissolution of the product in hexane and supernatant removal with a

Scheme 102. Asymmetric Allylic Alkylation Promoted by Pd/Perfluoro Diaminophosphine Complex



Scheme 103. Wacker-type Cyclization Promoted by Pd/PEG-Supported Boxax Complex



syringe finished the recovery protocol. The development of ligands with higher F-content clearly improved the recycling efficiency.

The main strategies for catalyst recycling explored in the literature are ionic liquids, perfluoruous techniques, and polymer-supported ligands (mainly heterogeneous). In several cases, the recyclability of the catalyst was quite low due to palladium leaching.

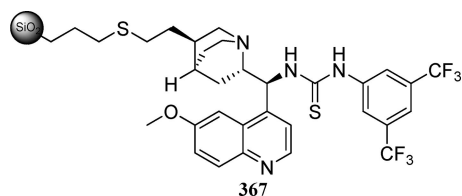
24. Miscellaneous Reactions

In this section, important contributions will be discussed that could not be considered in the previous categories.

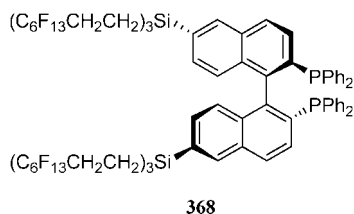
Chung et al. showed that a nanoparticle cluster of cobalt–rhodium carbonyls could be efficiently applied in chiral Pauson–Khand reaction in the presence of (*S,S*)-2,4-bis(diphenylphosphine) pentane. The respective cyclopentenones were obtained consecutively during five cycles in quantitative yields with unchanged 84% ee (1 atm CO at 130 °C).⁶²³

Uozumi et al. prepared 6'-substituted Boxax ligands to be anchored in several soluble and insoluble supports. PEG-supported Boxax ligands were used in Pd-mediated Wacker-type cyclization providing good levels of chiral induction though poor reactivity (Scheme 103).^{624,625}

He et al. described the application of a novel 9-thiourea epiquinine supported on mesoporous silica that exhibits a high enantioselectivity (up to 99.2%) in Friedel–Crafts reaction of imines with indoles. This chiral ligand **367** was reused three times with 20% yield erosion and stable enantioselectivity.⁶²⁶

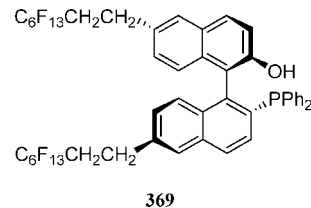


Nakamura et al. disclosed that fluoruous BINAP ligand **368** provided higher levels of enantioselectivity than BINAP in palladium-promoted asymmetric Heck reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate (up to 93% ee). Recycling experiments failed due to ligand oxidation in FC-72 phase.⁶²⁷



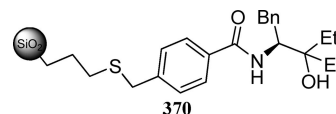
Shi and co-workers observed the same oxidative degradation of chiral phosphine ligand **369** chains tested in aza-Morita–Baylis–Hillman reaction. This chiral Lewis base provided excellent levels of enantioselectivity for the reaction of methylvinyl ketone with aromatic imines (up to 95% ee).⁶²⁸

Abdi et al. employed a new polymeric Zn(salen) complex in the enantioselective phenylacetylene addition to aldehydes and ketones to produce corresponding chiral secondary propargylic alcohols with yields up to 96% and enantioselectivity up to 72% and tertiary propargylic

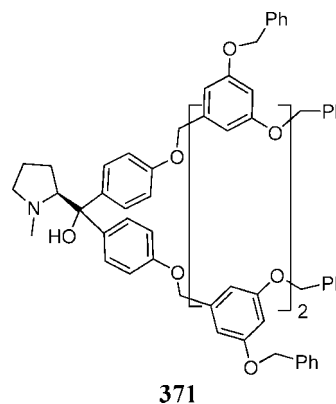


alcohols with yields up to 79% and enantioselectivity up to 68% at room temperature, with the added advantage of reuse four times with retention of enantioselectivity.⁶²⁹

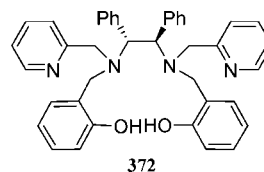
Xu and Hui obtained slightly superior enantioselectivities for titanium-promoted phenylacetylene addition to aldehydes (up to 81% ee) with the chiral β -hydroxylamide grafted on the surface of amorphous silica. After ligand **370** is restored it could be reused five times with 10% yield erosion and consistent enantioselectivity.⁶³⁰



Zhao and Zhu prepared a new dendritic chiral pyrrolidinylmethanol derivative and showed that it is an efficient chiral ligand for asymmetric catalytic aryl transfer to aldehydes with the $\text{PhB(OH)}_2/\text{ZnEt}_2$. The respective diaryl methanols were obtained with excellent enantioselectivities (up to 98% ee), and the chiral ligand **371** was recycled four times without efficiency erosion.⁶³¹



Zhu et al. prepared a new chiral ligand **372** for ytterbium catalyzed Biginelli reaction that proved to furnish azaheterocycles with excellent levels of enantioselectivity (up to >99% ee). The catalyst could be recovered by pH-controlled extractions and reused efficiently several cycles.⁶³²



Nishiyama et al. showed that Rh–PheBox complex could be recovered after silica gel chromatography and reused once with some selectivity decrease in asymmetric reductive aldol reactions between benzaldehydes and acrylates.⁶³³

25. Conclusions

Since the previous review published in 2002,⁵ 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, ionic liquids, perfluorinated solvents and catalysts, supercritical CO₂, and membrane separation technology. This area has been established as one of the “hottest” areas in organic chemistry with consistently 100 contributions every year (Figure 1). 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 the most recent asymmetric transformations based on different organocatalysts.

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.

26. Acknowledgments

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