Chiral Organometallic Catalysts in Confined Nanospaces: Significantly Enhanced Enantioselectivity and Stability

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This microreview presents some selected representative examples which demonstrate that significant improvement in the catalytic performance (increase in catalytic activity, stability and chemo- and enantioselectivity) of organometallic chiral catalysts as well as their recycling ability can be achieved by heterogenizing them in the confined spaces of porous or layered support materials. The positive effects of immobilization on the catalytic efficiencies are discussed in terms of the confinement effect and site-isolation effect, etc., with the aim of understanding the extent to which such effects lead to positive changes in the catalytic properties.

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Introduction

For economic, environmental and social reasons, the trend towards the application of optically pure compounds is undoubtedly increasing. Among the various methods which can be used to selectively produce single enantiomer, asymmetric catalysis is the most attractive method from the atom-economic point of view.[1,2] Over the last thirty years, numerous catalytic reactions allowing the enantioselective formation of C–H, C–C, C–O, C–N and other bonds have been discovered. A number of homogeneous organometallic chiral catalysts have gained wide acceptance in terms of their efficiency and selectivity, and some of them are even

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used on an industrial scale.[3–5] However, in spite of the huge amount of work devoted to this subject in both the academic and industrial fields, the contribution of asymmetric catalysis to the overall production of chiral chemicals is much lower than originally expected. One of the major drawbacks of homogeneous catalysis is the need to separate the relatively expensive chiral catalysts from the reaction mixture at the end of the process. The possible contamination of the product with metal catalysts also severely restricts their use in industry. In order to overcome these drawbacks, a great deal of effort has been made to develop effective heterogenized catalyst systems, mainly, by immobilizing homogeneous chiral catalyst on solid supports by: (i) covalent bonding, (ii) adsorption or ion-pair formation, (iii) encapsulation, or (iv) entrapment, etc.[6–8] In any case of heterogenization method, the support materials need to be thermally, chemically, and mechanically stable during the reaction process. Moreover, the structure of the support needs to be such that the active sites are well dispersed on its surface and easily accessible. Generally, this requires the support to have a reasonably high surface area (typically $>100 \text{ m}^2\text{g}^{-1}$) and an appropriate pore size (i.e. >20 Å), in order to allow for the easy diffusion of the reactants to the active sites.[9] Thus, inorganic supports[10] such as mesoporous silica and clay, have been extensively used for the immobilization of catalysts because of their large surface area, chemical and physical stability, and tunable pore or layer structure. One obvious benefit of supported catalysts is the easy separation of the relatively expensive chiral catalysts from the reaction mixture at the end of the process. In addition, catalysts immobilized on porous or layered materials have sometimes been found to exhibit much better catalytic performances than their homogeneous analogues due to geometrical constraints imposed by the pores or layers.[11–13]

The instability of homogeneous catalysts is often due to the formation of inactive multinuclear species. However, the colocalization of the catalytic sites can easily be prevented by immobilizing the catalysts in confined spaces, i.e., by the site-isolation of the catalytic sites,[14–16] consequently increasing the stability and turnover numbers of the catalyst. In this respect, mesoporous-type materials appear to be more attractive, due to their regular structures and tunable pore diameters. In addition to this enhanced stability, increased activity and selectivity were also observed upon immobilization in the confined space, due to the confinement effect originating from the weak interactions (hydrogen bond, van der Waals force, adsorption, etc.) between catalyst/substrate and pore surfaces. The polar or acidic pore surface can participate in the catalysis cooperatively, e.g., by stabilizing a charged transition state and thereby increasing the reaction rate.[17–19] In addition, because this weak interactions between catalyst/substrate and pore surfaces is about the same level as the energy difference between the two transition states corresponding to the (R) product and the (S) product, the enantioselectivity can also be very sensitively (positively or negatively) altered.[11] Enantioselectivity can be, thus, increased or decreased, or even reversed. Therefore, the enantioselectivity could be improved by careful tuning the confinement effect based on the molecular designing of the pore/surface and the immobilized catalysts according to the requirements of chiral reactions.[11–13] In this microreview, some selected examples will be given which can nicely demonstrate that a significant improvement in the stereoselectivity of the organometallic catalyst may be achieved by heterogenizing it into the confined nanospaces of porous or layered materials. Also, the effects positively influencing the catalytic efficiencies of the supported catalysts are discussed in terms of the confinement effect and site-isolation effect, etc., with the aim of understanding how such effects lead to positive changes in the catalytic properties.

Selected Examples

Asymmetric Hydrogenation

Several striking examples of the positive control effected by nanopores have been provided by the research group of Thomas and Johnson.[20–24] The Pd catalyst **1** supported on the mesoporous channels of MCM-41 affected the hydrogenation of ethyl 1,4,5,6-tetrahydronicotinate (**3**) to afford nipecotic acid ethyl ester (**4**) in 17% *ee*, whereas the use of the soluble version **2** resulted in a racemic mixture (Scheme 1). This enhanced chiral induction was explained in terms of the confinement effect of the ordered mesopore of MCM-41, which confine the substrate and ligand of the catalysts.[21]
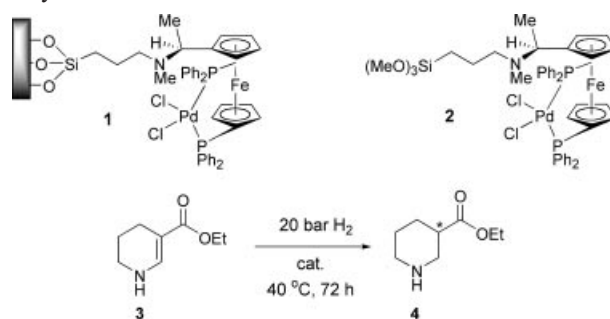
Using homogeneous catalyst **2**: racemic, TON = 98
Using heterogeneous catalyst **1**: 17% *ee*, TON = 291

Scheme 1.

The same research group[23] incorporated (*S*)-2-aminomethyl-1-ethylpyrrolidine (AEP) or (1*R*,2*R*)-1,2-diphenylethylenediamine (DED) into the concave surface of MCM-41 (pore diameter 30 Å) and to the convex surface of nonporous silica (Carbosil). Catalytic reactions were carried out using heterogeneous Rh and Pd catalysts for the asymmetric hydrogenation of (*E*)-α-phenylcinnamic acid and methyl benzoyl formate. Compared to the corresponding homogeneous catalyst or silica-supported catalyst, a significant enhancement of the *ee* value was observed for the MCM-41-supported catalyst (with the concave surface). For example, surprisingly, the Rh(COD)- and Pd(allyl)
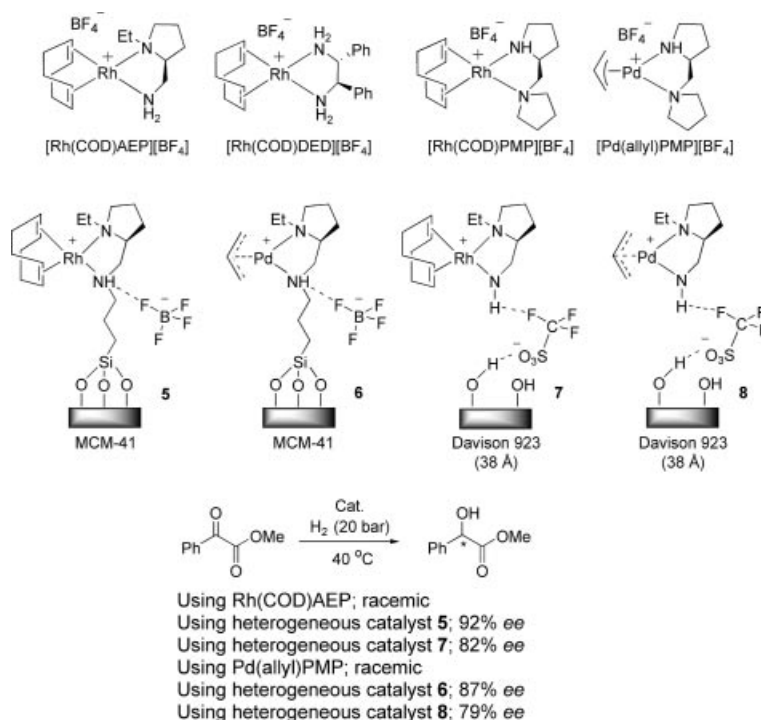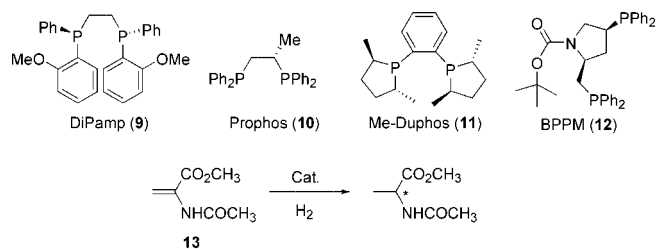
Scheme 2.

complex of AEP anchored on MCM-41, **5** and **6**, gave 92 and 87% *ee*, respectively, in the hydrogenation of methyl benzoyl formate, while the homogeneous catalysts gave a racemic product (Scheme 2). This increase in the *ee* values was attributed to the restricted access of the reactant to the active site generated by the concavity of the pore. Soon after, the same group[24] also anchored [Rh(COD)(*S*)-PMP][CF$_3$SO$_3$], [Pd(allyl)(*S*)-1-(2-PMP)] [CF$_3$SO$_3$], [Rh(COD)(*S*)-AEP] [CF$_3$SO$_3$] and [Rh(COD) (1*R*,2*R*)-DED][CF$_3$SO$_3$] noncovalently through N–H···F hydrogen bonding with the triflate ion, CF$_3$SO$_3^-$ to the inner surface of a set of silicas with narrowed pore-size distributions (38, 60, and 250 Å). The catalytic performances of the heterogeneous catalysts were tested in the asymmetric hydrogenation of methyl benzoyl formate to produce methyl mandelate. The supported catalysts generally exhibited remarkably higher *ee* values than their homogeneous counterparts. Notably, the heterogeneous catalysts **7** and **8** gave up to 82 and 79% *ee*, respectively, while their two homogeneous counterparts, [Rh(COD)AEP]$^+$ and [Rh(COD)DED]$^+$, did not display any significant *ee* (Scheme 2). The increase of the *ee* values of the supported catalysts was observed in a manner that logically reflects the declining influence of spatial constraint in proceeding from the 38-Å- to the 60-Å- to the 250-Å-pore-diameter silica. A similar enhancement of enantioselectivity in the hydrogenation of (*E*)-α-phenylcinnamic acid affording 2,3-diphenylpropanoic acid was also observed by heterogenizing [Rh(COD)(*S*)-AEP][CF$_3$SO$_3$] and [Rh(COD)(1*R*,2*R*)-DED][CF$_3$SO$_3$] noncovalently through H bonding of the triflate ion, CF$_3$SO$_3^-$ to the silanol groups of inner surface of MCM-41.[25]

The above examples provided by the research group of Thomas and Johnson strongly suggest that the conventional heterogenization approach, i.e., heterogenizing those catalysts designed for homogeneous processes, may not necessarily be the best solution for the development of efficient heterogenized chiral catalyst systems when it comes to immobilizing catalysts in the confined spaces of porous or layered support materials. Moreover, the above-mentioned results also suggest that the heterogenization of catalysts in confined spaces may provide a new paradigm for the development of highly efficient chiral catalysts.

Other Examples

Augustine et al.[26] immobilized various Rh complexes of well-known chiral bis(phosphane) ligands, such as DiPamp (**9**), Prophos (**10**), Me-DuPhos (**11**), and BPPM (**12**) onto heteropolyacid-modified inorganic supports, e.g., montmorillonite K, alumina. Somewhat surprisingly, both reaction rates and enantioselectivities significantly increased upon subsequent reuse of the recovered immobilized catalysts. After 9th reuse, DiPamp-rhodium supported on a PTA-alumina gave rise to a 97% *ee* vs. 76% *ee* for the homogeneous complex during the hydrogenation of methyl 2-acetamidoacrylate (**13**) (Scheme 3). Rege et al. also observed that the noncovalent immobilization of [(*R*,*R*)-Me-(DuPHOS)Rh(COD)]OTf afforded by interaction of triflate counterion with surface silanol groups of MCM-41 resulted in 99% *ee* in the hydrogenation of **13**, compared to 87% *ee* with the homogeneous Rh complex of **11** (Scheme 3).[27]

DiPamp (9)   Prophos (10)   Me-Duphos (11)   BPPM (12)

13

Using homogeneous catalyst **9**; 76% *ee*, TOF(min^{-1}) = 0.25
Using PTA-alumina supported **9**; 97% *ee*, TOF(min^{-1}) = 1.29
Using homogeneous catalyst **11**; 87% *ee* (in hexane)
Using MCM-41 supported **11**; 99% *ee* (in hexane)

Scheme 3.

Corma et al.[28–31] immobilized a number of proline derivatives on silica and modified USY zeolite (pore diameter 12–30 Å) (e.g. **15a** and **15b** in Scheme 4), and used them for the hydrogenation of various (*Z*)-*N*-acylcinnamic acid derivatives such as **16a** and **16b**. For all of the substrates tested using these catalysts, the enantioselectivity was higher with the zeolite-supported complex **15a** than with either the silica-supported **15b** or unsupported complex **14**, suggesting that the steric constraints of the support play an important role, especially in the case of zeolite where the reaction must take place in the confined spaces of the supermicropores. This is the first example in which the steric constraints of support (in this case, zeolite) was found to have positive effect on enantioselectivity.[28,29]
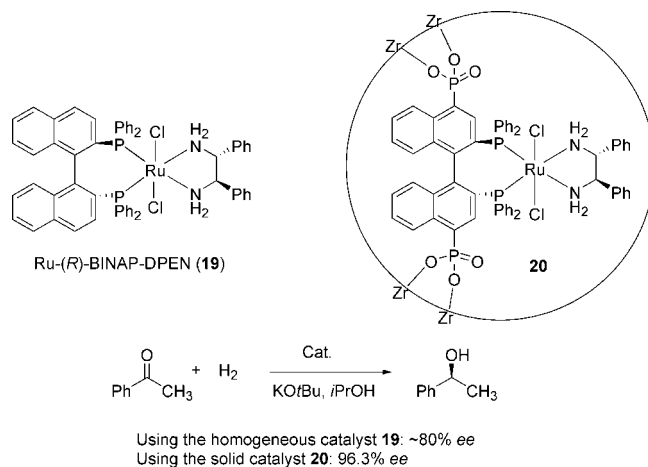
Pérez et al. also reported that the enantioselectivity of the supported complex was significantly increased compared with that obtained with the homogeneous one.[32] (*S*)-MAB-Ru anchored onto MCM-41 (**19**-Ru) catalyze the asymmetric hydrogenation of itaconic acid and α-acetamidocinnamic acid to yield the (*R*) product with 100% yield and 97% *ee*, while the homogeneous one, (*S*)-MAB-Ru (**18**-Ru), gave only moderate *ee* values (80 and 69.8%, respectively) (Scheme 5). The authors hypothesized that the interaction of the ligands with the pendant hydroxy groups present on the pores of MCM-41 may increase the rigidity of the overall catalytic structure. This, in turn, would restrict the rotation of the transition state and favor formation of nearly pure stereoisomers. In addition, the reaction

yield remained at 100% while the enantioselectivity decreased only slightly, from 97 to 94%, after three runs.
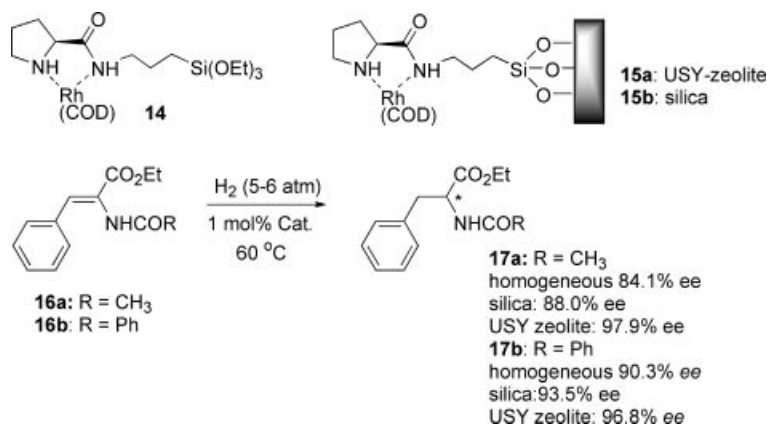

(S)-MAP (18)   (S)-MAP-MCM-41 (19)
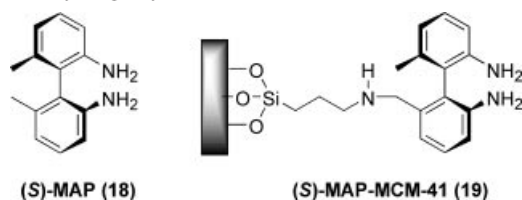
Scheme 5.

In an effort to rationally design functional hybrid solids based on organic linkers and metal nodes, Hu et al.[33] designed and synthesized novel chiral porous zirconium phosphonates containing Ru-BINAP-DPEN moieties **20**. The synthesized chiral porous hybrid solid catalyzed the asymmetric hydrogenation of unfunctionalized aromatic ketones with remarkably higher activity and enantioselectivity (up to 99.2% *ee*) than the parent homogeneous counterpart Ru-BINAP-DPEN system **19**. For example, acetophenone was hydrogenated to 1-phenylethanol with complete conversion and 96.3% *ee* in 2-propanol with 0.1 mol% loading of the solid catalyst **20**. This level of enantioselectivity is significantly higher than that observed for the parent homogeneous catalyst **19** which typically gives ca. 80% *ee* for the

Ru-(*R*)-BINAP-DPEN (**19**)   20

Using the homogeneous catalyst **19**: ~80% *ee*
Using the solid catalyst **20**: 96.3% *ee*

Scheme 6.

14   15a: USY-zeolite
15b: silica

16a: R = CH$_3$
16b: R = Ph

H$_2$ (5-6 atm)
1 mol% Cat.
60 °C

17a: R = CH$_3$
homogeneous 84.1% ee
silica: 88.0% ee
USY zeolite: 97.9% ee
17b: R = Ph
homogeneous 90.3% ee
silica:93.5% ee
USY zeolite: 96.8% ee

Scheme 4.

same reaction (Scheme 6). A similar method has also been used to synthesize other chiral, porous hybrid ruthenium solids.[34] In the heterogeneous asymmetric hydrogenation of β-keto esters, an *ee* value of up to 95% was achieved.

Asymmetric Oxidation

An extremely exciting example was very recently provided by Caps et al.,[35] which demonstrates that the heterogenization of catalysts in confined spaces can be used not only to improve the stereoselectivity but also to generate a new chiral species in situ from achiral catalyst precursors. The heterogenization of the achiral cluster, $Os_3(CO)_{12}$, on the internal space of MCM-41 using simple chemical vapor deposition (CVD) gave a superior enantioselectivity towards the (*S,S*) configuration of the 1,2-diphenyl-1,2-ethanediol in the dihydroxylation of *trans*-stilbene using *N*-methylmorpholine *N*-oxide (NMO) as an oxidant without adding any chiral ligand. This surprising effect was even more pronounced when surface Al sites were introduced into the silicate [90% *ee* for (*S,S*)-isomer] (Scheme 7). This 90% *ee* towards the (*S,S*) configuration is much higher than that reported using a homogeneous OsO_4/NMO/acetone/water system containing a chiral ligand (78%).[36] One possible reason for this chiral induction might be the "spontaneous symmetry breaking"[37–39] of achiral $Os_3(CO)_{12}$ during CVD on the MCM-41 or related surfaces, resulting in a new surface-chiral catalytic species. However, unfortunately, many attempts by us to reproduce this highly interesting result have been failed yet.
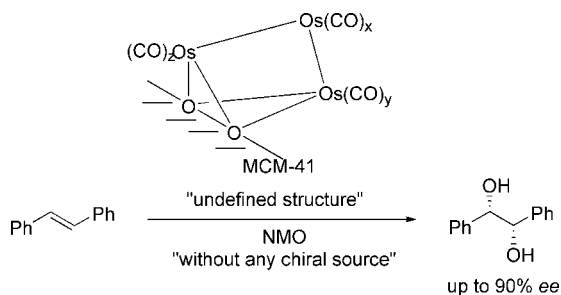
Scheme 7.

A significant enhancement of the enantioselectivity as a result of the confinement effect was also observed in the epoxidation of α-methylstyrene with hypochlorite.[40] Jacobsen's Mn(salen) complex encapsulated in the spacious supercages of MCM-22 (**22**) showed significantly better enantioselectivity than the homogeneous catalyst **21** under the same conditions, i.e., 91.3% *ee* vs. 51% *ee* (Scheme 8). Moreover, the encapsulated complex was three times more active than the homogeneous counterpart **21**, which is also attributed to site-isolation, i.e., to the suppressed formation of dimeric and other oligomeric Mn oxo complexes due to geometric constraints.
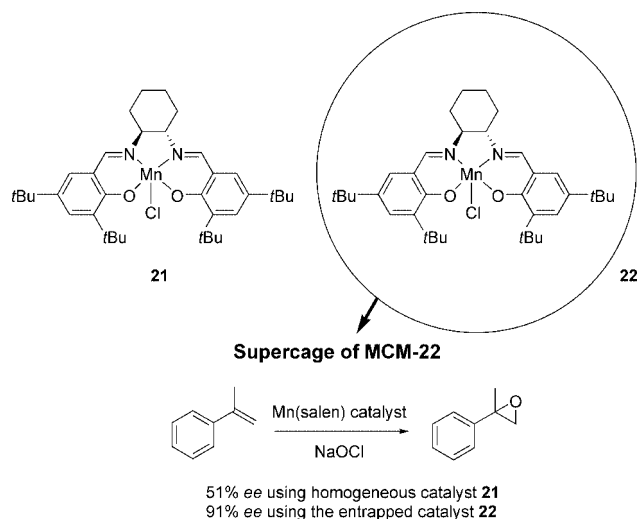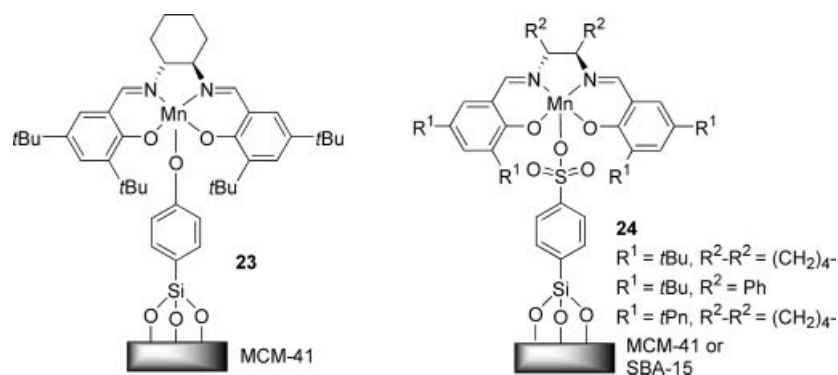

Scheme 8.

Li et al. also observed that the immobilization of the chiral Mn(salen) complex through the complexation of manganese by the oxygen atoms of the phenoxyl groups grafted on the surface of MCM-41 leads to a markedly higher *ee* value than that observed for the free complex in the asymmetric epoxidation of simple olefins.[41] For example, in the epoxidation of α-methylstyrene in CH_2Cl_2 with NaOCl as the oxidant, the enantiomeric excess is notably increased from 56% for the homogeneous catalyst to 72% for the heterogeneous Mn(salen)/MCM-41 catalyst (**23**). Soon after, the same group also reported that chiral manganese(salen) catalysts axially immobilized in nanopores by Ph sulfonic groups (**24**) also resulted in remarkably higher *ee* values (up to 95%) for the asymmetric epoxidation of unfunctionalized olefins (Scheme 9).[42,43]

Similar results were observed with other salen-M complexes anchored on porous supports.[44–46] Kim et al.[44] reported that, for the asymmetric epoxidation of α-methylstyrene, the *ee* value increased from 51% to 59% after the immobilization of Mn(salen) on the siliceous MCM-41 by multi-step grafting. Kureshy et al.[45] also reported that montmorillonite clay supported dicationic Mn(salen) exhibited similar or even higher *ee* values for the epoxidation of 2,2-dimethyl-6-nitrochromene, indene, and styrene than the corresponding homogeneous catalysts. It has also been reported that, for the enantioselective epoxidation of β-methylstyrene, the *ee* value increased from 54% to 73% after the immobilization of Cr(salen) through axial NH_2 complexation.[46]

Another good example of the confinement effect in heterogenized catalysts on porous supports was provided by Corma et al. The use of Mo^{VI} complexes of chiral ligands derived from (2*S*,4*R*)-4-hydroxyproline, heterogenized onto a modified USY zeolite by covalent bonding,[47] in the epoxidation of geraniol and nerol with TBHP as the oxygen source resulted in much higher enantioselectivities (47% *ee* for geraniol and 64% *ee* for nerol) than those (up to 27.6% *ee* for geraniol and up to 10.4% *ee* for nerol) obtained with the homogeneous counterpart **25**. This enhanced enantio-
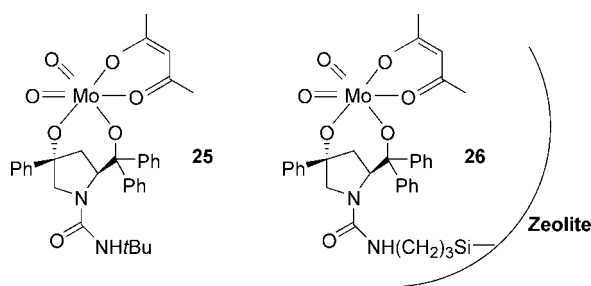
Scheme 9.

selectivity can also be ascribed to the additional steric constraints imposed by the zeolite pores. The lifetime of the heterogenized catalyst was also examined by the repeated use of the catalyst **26** which showed similar rates and yields of epoxide, even after five runs (Scheme 10). The enhanced stability of the heterogenized complex was ascribed to the stronger coordination of the dihydroxy ligand to Mo than

that of the acetylacetonate or hydroxy group present on the substrate, *tert*-butyl alcohol or hydroperoxide. The site-isolated catalyst molecules on the mesopores could also avoid being deactivated by dimerization and oligomerization of the Mo species.

Asymmetric C–X and C–C Bond-Forming Reactions

A good example of the confinement effect dramatically improving the performance of chiral catalysts for C–X bond-forming reactions was described by Thomas et al.[48] In the case of the allylic amination of cinnamyl acetate, catalyst **29**, immobilized on the inner walls of mesoporous MCM-41, exhibited superior catalytic properties than catalyst **28** anchored on Carbosil (a nonporous, high-area silica) and than homogeneous catalyst **27**. The MCM-41-immobilized catalyst **29** showed a degree of regioselectivity for the desirable branched product (51%) and extremely high enantioselectivity (>99% ee), whereas the Carbosil-immo-

Scheme 10.

| Catalyst	Conversion (%)	Straight chain (%)	Branched (%)	%ee
27	76	>99	-	-
28	98	98	2	43
29	>99	49	51	>99
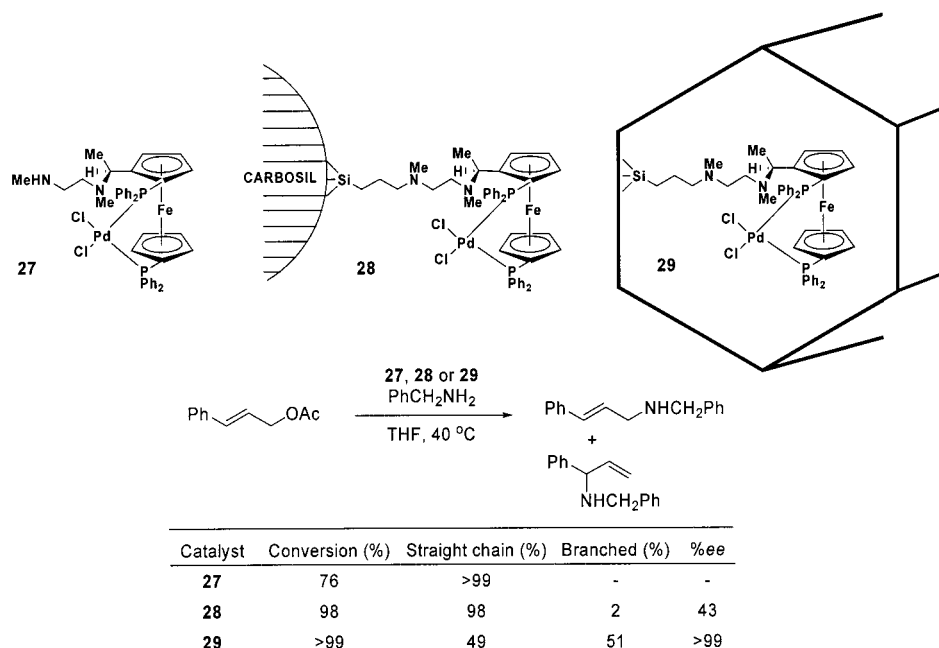
Scheme 11.

bilized catalysts **28** afforded the branched product in only 2% yield and with 43% *ee*. In the case of the homogeneous catalyst **27**, the reaction produced solely the straight chain product (Scheme 11). Although the regioselectivity of **29** is still not very high, the careful design of active centers and the control of pore size of supports will probably lead to more unexpected selectivities.

Also in the Si–H insertion reactions of dimethylphenylsilane with methylphenyldiazoacetate, a significant improvement in enantioselectivity was observed by immobilizing the chiral dirhodium complexes on Aerosil 200.[49,50] This immobilized catalyst, SiO_2–$(CH_2)_2COO$–$Rh_2[(4S)$-BNOX$]_3$ (**31**), showed a more than 10-fold increase in enantioselectivity (up to 28% *ee*), while the homogeneous analogue $Rh_2[(4R)$-BNOX$]_4$ (**30**) gave nearly racemic product (Scheme 12). In contrast to the catalysts immobilized on Aerosil 200 having an average pore size of 50 nm, none of the catalysts immobilized inside the pores of MCM-41 showed any activity. It is possible that there is not enough space inside the pores of MCM-41 for the reaction to take place. This result is reasonable, considering that the average pore diameter (19 Å) of MCM-41 is only slightly larger than the catalyst size (between 19 and 13 Å). A transition state requiring a space-demanding conformation of the catalyst might, therefore, be impossible under these circumstances.

Sanchez and co-workers[51] anchored the Ni complex of the L-proline amide **32b** on USY zeolites or silica by covalent bonding. Although the use of the insoluble catalysts **33** and **34** caused the conjugate addition of $ZnEt_2$ to the enones **35** to take place more slowly, the *ee* values of the resulting saturated ketones **36** were much higher for the zeolite-supported Ni complex **33** (91 and 95% *ee*, for R = Ph and Me, respectively) than its homogeneous counterpart **32a** (77 and 75% *ee*, for R = Ph and Me, respectively) or the silica-supported analogue **34** (34% *ee*, R = Ph) (Scheme 13). The steric constraint imposed by the zeolite pore was thought to contribute to the enhanced enantioselectivities that were observed. Sanchez et al. also attached

a series of chiral amines covalently to modified USY zeolite and MCM-41 zeolite supports, and evaluated the ability of the obtained chiral base catalysts confined in porous hosts to improve stereoselectivity in conjugate additions of nucleophiles to enones.[52] It was found that the reaction rate was enhanced, and the catalysts showed higher selectivity than the free amines.
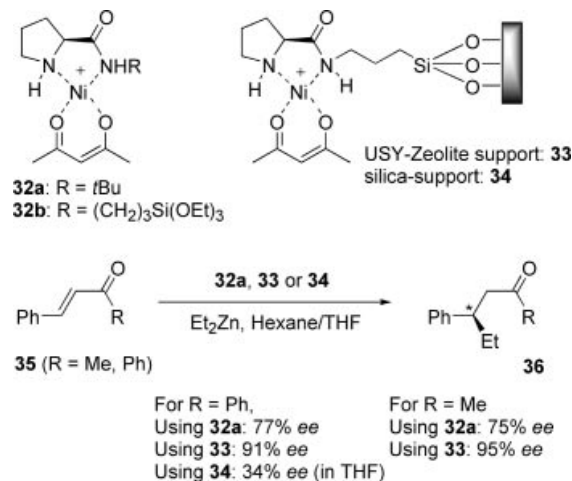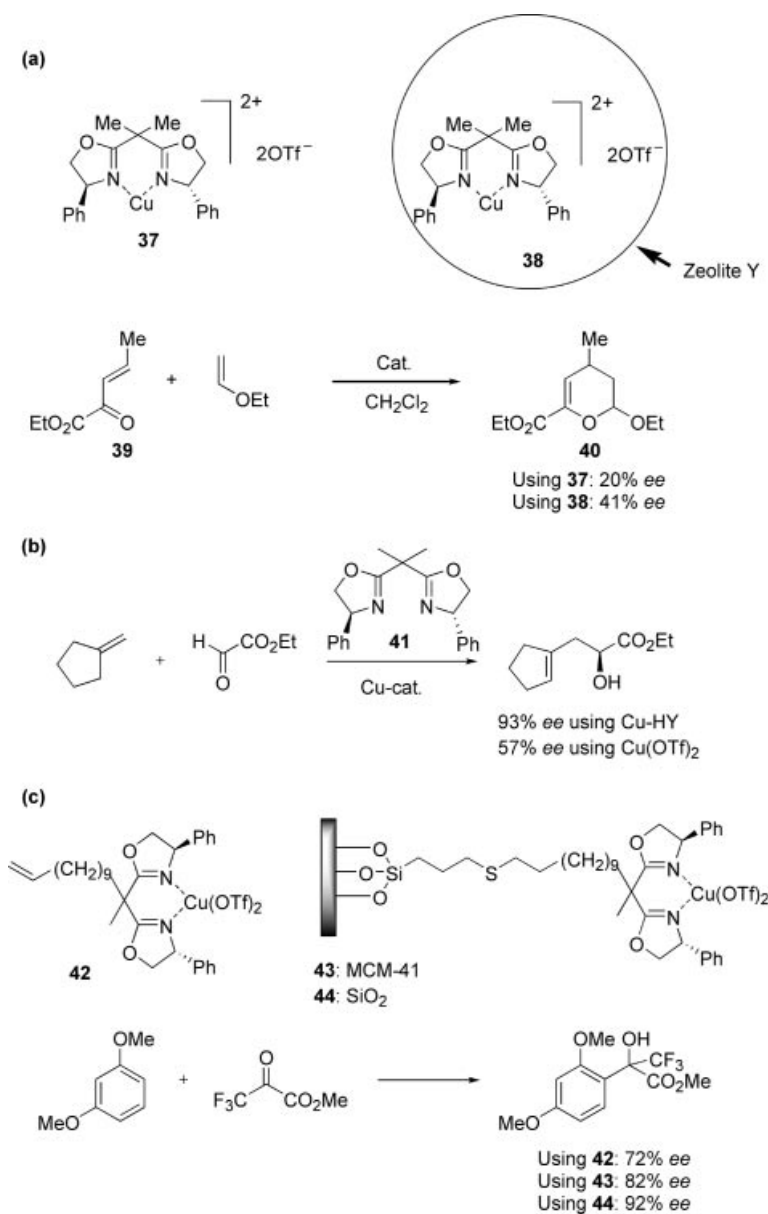

Scheme 13.

Chiral bis(oxazoline)copper complexes are known to be highly effective enantioselective, homogeneous catalysts for many C–C and C–X bond -forming reactions, such as Diels–Alder, aldol, Michael, ene, amination and aziridination reactions. It has also been reported that chiral bis-(oxazoline)copper complexes constrained within the confined spaces of porous materials exhibited substantially higher enantioselectivity than the homogeneous catalyst.[53–56] For example, Wan et al. immobilized the Ph-substituted bis(oxazoline)copper(II) complex in zeolite Y for the hetero-Diels–Alder reaction of (ethyl *E*)-pentenoate (**39**) with ethyl vinyl ether, affording the dihydropyran **40** (Scheme 14).[53] The enantioselectivity (41%) of the solid catalyst **38** was significantly higher than that obtained with
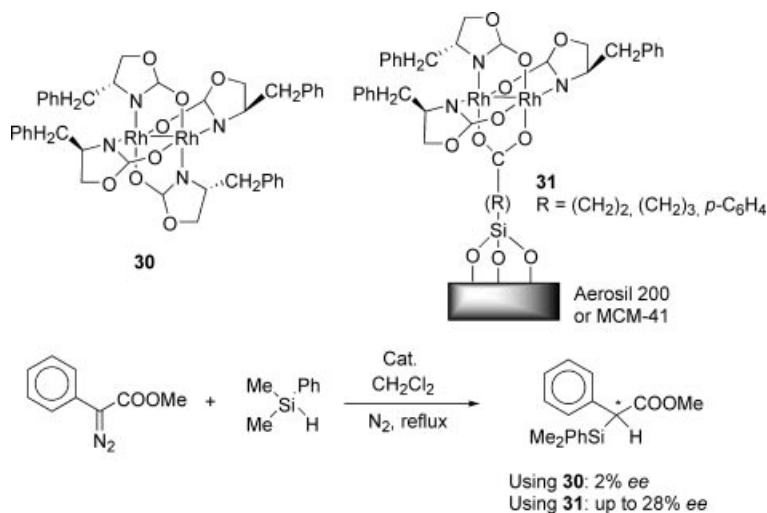
Scheme 12.

Scheme 14. Selected examples of chiral bis(oxazoline)copper complexes constrained within confined spaces and their use in catalytic reactions.

the homogeneous catalyst **37** (20% *ee*) (Scheme 14a). Very interestingly, the configuration of the (2*S*,4*R*) product obtained from the heterogeneous reaction is opposite to the (2*R*,4*S*) product obtained from the homogeneous reaction. As described in the introduction section, this reversed enantioselectivity could also be attributed to the confinement effect of the porous supports.

The heterogeneous catalyst obtained by impregnating Cu[II] ion in zeolite Y and subsequent modification with the bisoxazoline ligand **41**[54] also exhibited the superior enantioselectivity (93% *ee*) compared to the homogeneous catalyst (57% *ee*) for the reaction of methylenecyclopentane with ethyl glyoxylate (Scheme 14, b). The same authors observed a similar enhancement of the *ee* value in the aziridination reaction which result from the confinement effect of the zeolite pores.[55]

Corma et al. covalently anchored the chiral bis(oxazoline)copper(II) onto silica and MCM-41 and tested its catalytic ability in the Friedel–Crafts hydroxyalkylation of 1,3-dimethoxybenzene with 3,3,3-trifluoropyruvate.[56] The activity and enantioselectivity of the two heterogeneous catalysts were higher than those of the homogeneous analogue (Scheme 14, c).

Conclusions

This microreview presents some selected representative examples which demonstrate that not only facile catalyst recycling but also a significant improvement in the catalytic performances (activity, stability and enantioselectivity) of the organometallic chiral catalysts can be achieved by hetero-

genizing them in the confined spaces of porous or layered support materials. Surprisingly, in some cases, even non-enantioselective catalysts showed significant asymmetric induction when they were anchored into confined nanospaces.[21,23,24,35,48] These results suggest that the conventional approaches, i.e. (i) designing chiral catalysts for homogeneous conditions and (ii) heterogenizing those catalysts well-designed for homogeneous processes, may not necessarily be the best solution for the development of efficient chiral catalyst systems. In conclusion, the heterogenization of catalysts in confined spaces will provide a new paradigm for the development of a highly efficient chiral catalyst in future.

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