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Bridging the gap in catalysis *via* multidisciplinary approaches

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Emerging strategies in sustainable fine-chemical synthesis: asymmetric catalysis by metal nanoparticles

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The combination of chiral- and nano-technologies is potentially one of the most promising strategies for “green” catalytic conversions aimed at fine-chemical production. This paper reviews the most representative examples and highlights recent achievements in the field of enantioselective processes catalyzed by metal nanoparticles (MNPs), with a view to the potential of the methodology and future perspectives. Applications are described according to the nanocatalyst type used, either liquid-phase suspensions or solid-supported systems. The focus is on the design of the catalysts, their preparation and characterization, applications in catalysis and mechanistic studies.

1. Introduction

The production of fine and speciality chemicals, and particularly of the intermediates for the pharmaceutical and agrochemical market, requires highly selective chemical processes with nearly complete conversions in mild reaction conditions. As a matter of fact, because of the high Turnover Frequencies (TOFs) and enantioselectivities provided, asymmetric synthesis on the industrial scale is largely dominated by homogeneous catalysis, both chemical and enzymatic.¹ On the other hand, the emission of volatile pollutants, the management of wastes, and the costs

associated with the loss of precious catalysts and with the purification procedures may adversely affect the overall economy and environmental impact of homogeneous processes. Indeed, industry has a great preference for heterogeneous catalysts due to the ease of recovery and reuse, the clean separation from the reaction products, and their simpler integration in existing reactor equipment.² Over the last few decades, a wide range of methods have been developed in which the product/catalyst separation has been effectively addressed,³ including nanofiltration and the immobilisation of homogenous catalysts onto insoluble supports.⁴ Despite the great efforts of academia and the progress achieved in this research and technological area, the practical benefits of molecular catalyst immobilization are limited, and examples of the use of heterogenized catalysts in industrial processes are still rare.⁵ The reason is the limited access to and costs of immobilized catalysts, their lower selectivity, the decrease of activity upon reuse and the leaching of (metal) active species in solution.⁶

Metal nanoparticles (MNPs) are very well known for their high chemical activity and for their ability to promote otherwise inaccessible reactions. Coupled with the possibility of being anchored

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field of heterogenized, selective catalysts for sustainable production processes.

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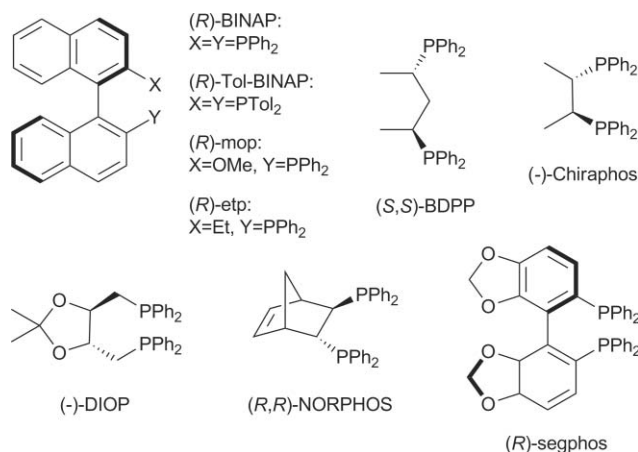
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onto heterogeneous supports and recovered, this justifies the use of MNPs-based materials as catalysts for a large variety of chemical processes in everyday life, including abatement of pollutants, processing of raw materials, synthesis of base organic chemicals, energy production.⁷ Lately, the development of functionalized metal nanoparticles for application in stereo- and asymmetric catalysis has been the subject of increasing interest.⁸

This paper reviews the most representative examples and highlights the recent achievements in the field of enantioselective processes catalyzed by metallic nanoparticles, with a view to the critical factors and the potential of the methodology and to future perspectives. Chirally modified metal surfaces, nanosized metal oxides and nanocrystals,⁹ as well as MNPs as mere support material for other catalytically active species, will not be considered. Irrespective of the process catalyzed, the metal element or the reaction phase (either heterogeneous or quasi-homogeneous), applications will be described according to the type of nanostructured catalytic material, either “unsupported” MNPs, *i.e.* liquid-phase suspensions, or “solid-supported” systems. This choice is motivated by the role played by the chemical-physical environment in determining both the morphology (size, shape) and the performance (activity, lifetime) of MNP-based catalysts. Indeed, nanoparticles are thermodynamically unstable and highly reactive as a result of their large surface area to volume ratio; immobilization into mesoporous (functionalized) solids is one strategy to gain a fine control of their growth and reactivity.¹⁰ Accordingly, catalysts supported onto inorganic (alumina, silica, clays, magnetic nanoparticles) and organic solids (resins, carbon) or stabilized in a liquid phase (*e.g.* colloids) will be described herein. The focus will thereupon be on the design, the synthetic strategies and the characterization of the catalysts, their use in fine-chemicals synthesis and mechanistic studies. A short paragraph outlining the most useful characterization techniques for chiral MNPs is also included.

Adsorption of optically pure ligands on the surface of a metal nanoparticle is the common concept for building chiral-MNP assemblies. Due to their potential dual role in stabilizing and/or functionalizing the metal nanoparticles, chiral ligands are often

referred as stabilizers or modifiers. Examples of chiral ligands employed so far are sketched in Scheme 1.

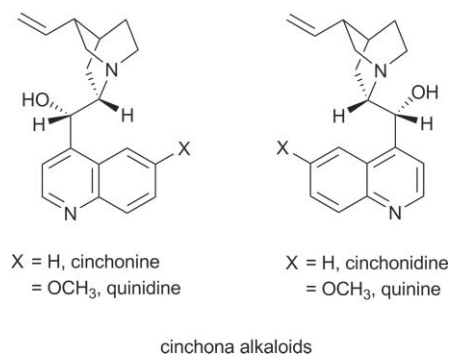
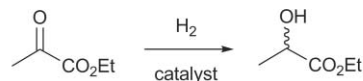


Scheme 1 Sketches of chiral ligands used as MNPs modifiers.

2. MNPs supported on insoluble solids

2.1. Inorganic solids

Alumina. The most explored application of asymmetric catalysis by supported MNPs is, by far, the hydrogenation of α -ketoesters, and particularly ethyl pyruvate, using MNPs modified with cinchona alkaloids (Orito reaction, Scheme 2). Platinum and palladium-based catalysts on alumina, and to a lesser extent on silica and on organic polymers, were mainly used for this purpose, allowing the desired products to be obtained with excellent enantiomeric excesses (*ee*'s) in certain cases (up to 98%). The topic was extensively reviewed in the past (until 2008),¹¹ and a further survey of the topic is thus beyond the scope of the present paper.



Scheme 2 Hydrogenation of ethyl pyruvate (Orito reaction) and sketch of cinchona alkaloids.

The most recent studies focused on the origin of the rate enhancement commonly observed for the Orito reaction,¹² *i.e.* the fact that the modified (selective) reaction is faster than

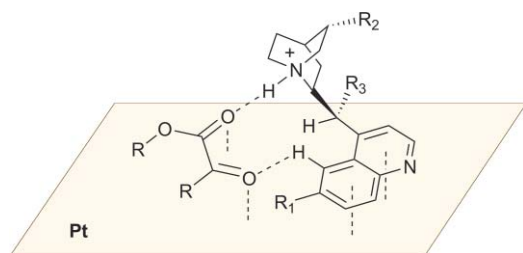


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the unmodified (racemic) one.[†] The commercially available 5% Pt/Al₂O₃ catalysts (Engelhard E4759, mean Pt size 4.5 nm),¹³ was adopted as standard “reference” material. Bartók *et al.* investigated the hydrogenation of various activated ketones by packing the catalyst in a commercial continuous-flow reactor.¹⁴ The enhancement effect was clearly demonstrated using the transient method, namely the serial addition/replacement of the cinchona alkaloid with others that produce the opposite enantiomer, starting with the unmodified catalyst.¹⁵ Continuous sampling allowed the measurement of *ee* and conversion changes. The combination of three factors was suggested to be responsible for the observed rate enhancement: i) the presence of the alkaloid increases the number of active sites (having all the same activity) on the metal surface, and ii) inhibits the deactivation of the Pt catalyst, iii) the alkaloids form effective surface complexes with the substrate.

Further reports by the same group aimed at elucidating the structure of the intermediate between the alkaloids and the substrate, and how this influences the enantioselectivity of the hydrogenation reaction.¹⁶ Based on the commonly accepted 1 : 1 model for the modifier : substrate adduct with a flat adsorption of the quinoline moiety onto the metal surface,¹⁷ reactivity and spectroscopic studies using cinchona alkaloids methylethers suggested a two-point interaction between the modifier and the α -ketoester whose spatial orientation is critical in determining the chiral transfer ability of the modifier (Scheme 3). However, it is worth mentioning that several other models accounting for the origin of induction in cinchona-based catalysts were proposed (see. *e.g.* ref. 11c). Their detailed discussion is out of the scope of this perspective, we thus refer to the specific literature for this purpose.

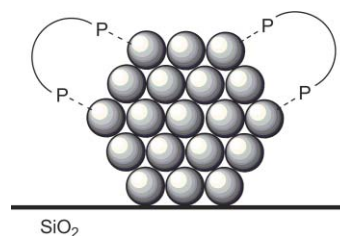


Scheme 3 The proposed structure of the 1 : 1 electrophilic adduct substrate : cinchona alkaloid derivative adsorbed on Pt nanoparticles.

It must be underlined that in Orito-type catalysts, additional portions of cinchona modifier must be usually supplied during the hydrogenation reaction in order to maintain high conversions and *ee*'s.¹⁸ This requirement, which was ascribed to the depletion of the modifier from the metal surface as a consequence of its hydrogenation, may be a serious economical drawback for practical applications if catalyst reuse is pursued.

Silica. One of the earliest examples of silica-supported chiral MNPs was developed by Li *et al.* for the catalytic asymmetric hydroformylation of olefins,¹⁹ and was based on supported rhodium nanoparticles modified with optically pure diphosphino ligands. The catalysts were readily prepared by reacting a slurry

of preformed Rh/SiO₂ particles with variable amounts of ligands in toluene. ³¹P MAS NMR and IR measurements showed that the isolated solid catalysts Ligand-Rh/SiO₂ contain ligands “P-coordinated” to the surface rhodium sites, analogously to what is found in conventional rhodium molecular complexes (Scheme 4). Catalyst activity was dependent on the metal particle size, with optimal conversions in the range 1.5–2.0 nm, at 1.0% wt metal loading. Interestingly, the activity and the enantioselectivity were affected by the ligand/metal molar ratio in the supported catalyst. High *ee*'s and low conversions were observed at L/Rh greater than *ca.* 1, whereas the opposite was obtained at lower ratios. The results for the hydroformylation of styrene catalyzed by (*R*)-BINAP-Rh/SiO₂ are reported in Fig. 1, as example. The trend was justified in terms of ligand occupancy of the rhodium surface sites: the higher the occupancy, the better is the chiral transfer efficiency from the coordinated ligand to the substrate adsorbed on the MNP. On the contrary, a less crowded metal surface results in a lower enantioselection, but in a higher number of accessible metal sites and, ultimately, in an higher activity. These observations suggest that high activities and high enantioselectivities cannot be attained simultaneously using functionalized MNPs, at least in similar phosphine-modified systems. Nevertheless, the fact that the decay of catalyst activity caused by the addition of the ligand is not dramatic in most cases, and that the supported catalysts show activities and selectivities higher than their homogeneous counterparts, makes this approach still worth exploring. Representative data for the hydroformylation of vinyl acetate using modified and unmodified rhodium catalysts are reported in Scheme 5. Recycling of the supported chiral catalyst was possible showing a constant catalytic performance.



Scheme 4 Chirally modified ligand-Rh/SiO₂, rhodium nanoparticles on silica.

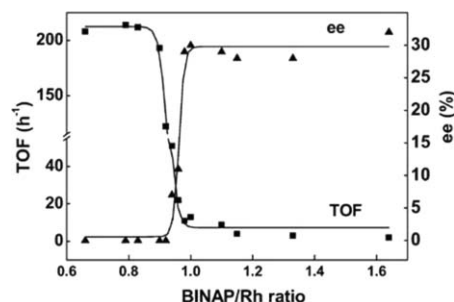
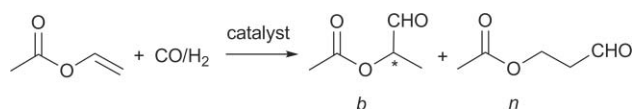


Fig. 1 Influence of the ligand/metal molar ratio on the catalytic performance of (*R*)-BINAP-Rh/SiO₂ in the hydroformylation of styrene. Reprinted from ref. 19 with permission © Elsevier 2006.

The above results are in line with those previously reported for similar hydroformylation systems in which the supported

[†] The phenomenon is also referred as “ligand acceleration” effect, see: M. Garland and H. U. Blaser, *J. Am. Chem. Soc.*, 1990, **112**, 7048.



| catalyst | L/Rh | TOF (h ⁻¹) | b/n | ee (%) |
|--|------|------------------------|-------|--------|
| Rh/SiO ₂ | - | 90 | 98:2 | 0 |
| (<i>R</i>)-BINAP-Rh/SiO ₂ | 1 | 11 | 100:0 | 72 |
| [((<i>R</i>)-BINAP)Rh(COD)]Cl [*] | 1 | 3 | 98:2 | 54 |

^{*} Homogeneous catalyst

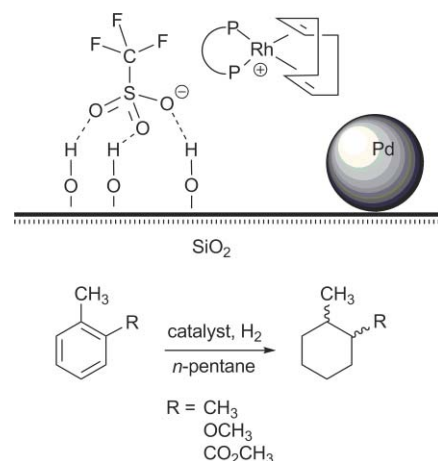
Scheme 5 Hydroformylation of vinyl acetate using (*R*)-BINAP-rhodium catalysts.

catalysts were generated *in situ* by the reaction of preformed 0.71% Rh/SiO₂-Al₂O₃ NPs with (–)-DIOP or (–)-Chiraphos ligands.²⁰ The addition of an excess of modifier to the solid catalyst caused a decrease of the catalytic activity. Very low enantioselectivities were observed, however (max. 9% *ee*). Spectroscopic measurements showed the interaction of the diphosphine with both Rh(I) and Rh(0) heterogeneous sites, although extensive leaching of rhodium in solution cannot rule out the contribution of homogeneous species to the hydroformylation reaction, in that case.

In a recent work, the catalytic asymmetric hydrogenation of ethyl pyruvate by (–)-cinchonidine/Pt/SiO₂ nanoparticles was performed in a continuous flow reactor.²¹ The catalyst was prepared by the silica impregnation method using a colloidal Pt dispersion containing the alkaloid (see section 3).²² The procedure allowed for a careful control of the supported metal particle size, as a result of the stabilizing effect of the modifier. Increasing amounts of modifier inhibited the growth of the metallic aggregates, thus providing particles of smaller dimensions. This influenced directly the catalyst performance since both activity and enantioselectivity increased with decreasing Pt particle size (up to 72% conversion and 60% *ee* at 1% Pt loading and 1.6 nm size). Exactly the opposite result was reported by the same authors when the modifier was added *in situ* to the catalytic system, using a batch reactor:²³ larger particles provided higher yields and selectivities (max. 33% *ee*).

It is worth mentioning a completely different approach to asymmetric catalysis by silica-supported MNPs and based on the synergic effect showed by hybrid Rh-molecular catalysts/Pd-nanoparticles systems in the hydrogenation reaction of arenes (see Scheme 6). This approach was inspired by recent work in which SiO₂-tethered catalysts combining cationic diphosphine rhodium complexes [(P–P)Rh(COD)]CF₃SO₃ (anchored by SHB technique through a triflate anion, COD = 1,5-cyclooctadiene) and Pd(0)-NPs were four times more active than the monometallic Pd-NPs system in the hydrogenation of benzene.²⁴ It was suggested that the combined action of the two metals is such that the role of palladium is mandatory for the conversion of benzene to cyclohexa-1,3-diene, while the hydrogenation of the latter requires the rhodium complex to be fast and irreversible. Preliminary results for the hydrogenation of di-substituted arenes using (–)-Chiraphos and (–)-DIOP ligands and ordered mesoporous silicas showed that the chiral transfer was effective, despite the low selectivity.²⁵

Clays. Examples are limited to the earlier use of Pt NPs onto montmorillonite, hectorite and bentonite in the Orito

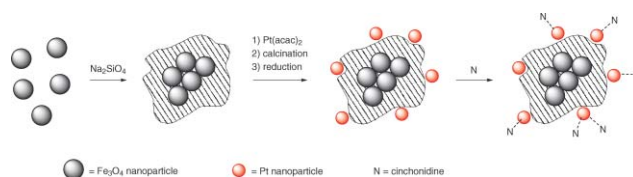


Scheme 6 Nanoparticle/molecular catalyst hybrid systems.

reaction.^{26,27} The supported catalysts were prepared by successive cation exchange using cinchona alkaloid hydrochlorides and Pt(II) precursors, followed by reduction. The location and the size of the metal particles were affected by the sequence of the reduction and the ion-exchange steps. Placement of the MNPs with respect of the clay layers significantly affected the catalysts performance, whereas the contribution of particle size was less important.

Magnetic nanoparticles. The recent introduction of magnetic nanoparticles in the area of catalysis represented a breakthrough for their potential use in catalyst separation and reuse, since the application of an external magnetic field allows the effective and easy recovery of these particles from the reaction solution.²⁸ In most applications however, and particularly in asymmetric catalysis, magnetic nanoparticles were used as support to tether chiral ligands (organocatalysis),²⁹ or to immobilize homogeneous catalysts,³⁰ so that the catalytically active species was not the metal particle.

To the best of our knowledge, the only example of chiral MNP catalysts on magnetic nanoparticles was recently reported by Baiker,³¹ and involves the silica-mediated immobilization of Pt NPs modified with cinchonidine (size 5 nm), using preformed magnetite particles (mean size 10 nm) (Scheme 7).[‡] The system was described as “a dispersion of larger agglomerates of magnetic Fe₃O₄ nanoparticles in a silica matrix”. The chiral catalyst was prepared *in situ* into a batch reactor, and used in the hydrogenation of activated ketones. Both activities and *ee*'s (80%) were satisfactory and, in any case, comparable with those of the “standard”



Scheme 7 Reaction scheme for the preparation of chirally modified Pt/SiO₂/Fe₃O₄ nanoparticles (ref. 31).

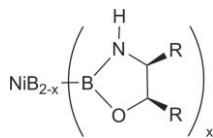
[‡] Nanosized, mixed copper–iron oxides was reported to catalyze the asymmetric hydrosilylation of ketones, see: M. L. Kantam, J. Yadav, S. Laha, P. Srinivas, B. Sreedhar and F. Figueras, *J. Org. Chem.*, 2009, **74**, 4608.

Pt/Al₂O₃ catalyst in the same reaction conditions (E4759, see above). Recycling of the catalyst was possible with only a slight *ee* decrease, a 10% conversion drop and negligible Pt and Fe leaching after eight cycles. An interesting feature of this synthetic approach is the absence of self-aggregation of the catalyst particles due to their superparamagnetic properties, thus providing stable suspensions.

Others. Occasional use of other inorganic support materials was limited to titania and nickel boride.

In the former case, cinchonine-modified Pd NPs (either from deposition–reduction or wet impregnation method) were used to catalyze the *in situ* asymmetric hydrogenation of the enamides C=C bond.³² The reaction selectivity was mainly sensitive to both particle size and to the extent of their coverage by the modifier, passing through a maximum (*ee* 30%) at *ca.* 2.5 nm diameter and at a modifier/Pd ratio of *ca.* 10. The nature of the support played a minor role, as demonstrated by the comparable *ee*'s provided by similar Pd/TiO₂ and Pd/Al₂O₃ systems.

Nickel boride nanoparticles bearing chiral β-aminoalcohol (or phosphinamide) moieties were employed in the catalytic borane reduction of ketones (Scheme 8).³³ The role of nickel particles was only to heterogenize the soluble oxazaborolidines catalysts, however.



Scheme 8 Nickel borides modified with chiral aminoalcohols.

2.2. Organic solids

Polystyrenes and functionalized resins. Few recent examples are known in which MNPs supported on polymeric organic matrices were used as catalysts for the Orito reaction (see Scheme 2).

Platinum NPs stabilized with cinchonidine were incorporated into hypercrosslinked polystyrene (HPS) for this purpose.³⁴ Use of HPS was prompted by its large surface area, the ability to swell in several solvents and its gel structure, consisting of a narrow distribution of nanopores, which allows a controlled growth of small metal particles with a limited size distribution (Fig. 2).³⁵ Thus, 2 nm chiral Pt particles were obtained by impregnation of the polymer with hexachloroplatinic acid, followed by sodium borohydride reduction and treatment with the cinchona alkaloid. Interestingly, the isolated cinchonidine/Pt/HPS catalyst thus prepared showed better selectivity (*ee* 75%) and reusability (TOF *ca.* 720 h^{−1} constant over five recycles) compared to the conventional Pt/Al₂O₃ catalyst and to the analogous *in situ* system. The result was explained in terms of a better stabilization of the metal nanoparticles within the small pores of HPS and with its higher mechanical resistance compared to Al₂O₃, and by the fact that the modifier is not leached from the MNP surface during the hydrogenation reaction. The catalyst performance showed no significant dependence from both modifier concentration and metal loading, whereas use of hydrazine as reducing agent afforded less efficient catalysts.

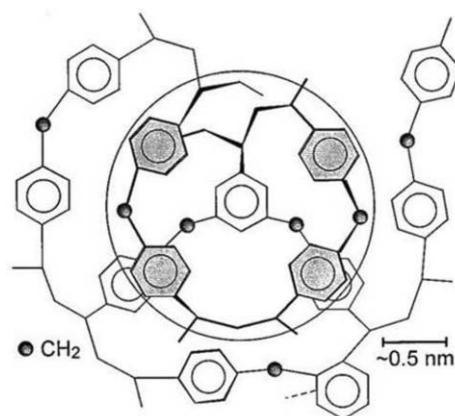
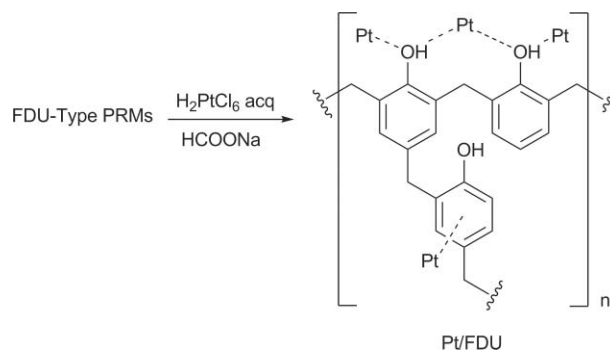


Fig. 2 Sketch of hypercrosslinked polystyrene structure. Reprinted from ref. 35a with permission © American Chemical Society 1999.

Another promising class of organic polymers for the immobilization of MNPs are the FDU-type periodic mesoporous resols (PMRs), due to their ordered porous structure, uniform pore size and large surface area.³⁶ Impregnation of FDU-PMRs with H₂PtCl₆, followed by conventional reduction, afforded uniformly dispersed Pt nanoparticles of 3 nm size (Scheme 9).³⁷ When cinchonidine was added *in situ* to the system, the material catalyzed the hydrogenation of ethyl pyruvate in good conversions and moderate *ee*'s (up to 62% in acetic acid). Use of the benign water solvent was also possible with higher reaction rates (TOF *ca.* 3900 h^{−1}). The catalysts could be recycled with pretty constant activity and selectivity, provided that the chiral modifier is regularly added to the feed.



Scheme 9 Sketch of Pd nanoparticles on FDU-PMRs.

Carbon and carbon nanotubes. To date, only a few examples are known in which carbonaceous materials (charcoals, carbon, graphite, carbon nanotubes) were used to support chiral MNPs catalysts.

In an early report, Blaser described the hydrogenation of ethyl nicotinate to ethyl nipecotate catalyzed by 10,11-dihydrocinchonidine-modified Pd, Rh and Ir commercial catalysts on carbon or graphite.³⁸ The highest *ee*'s (19%) were obtained at relatively low conversions (12% after 25 h) using Pd/C in DMF.

Single-Walled Carbon Nanotubes were used as support for (–)-cinchonidine-modified Pt nanoparticles and the catalyst applied in the asymmetric hydrogenation of ethyl pyruvate, albeit with low *ee*'s.³⁹

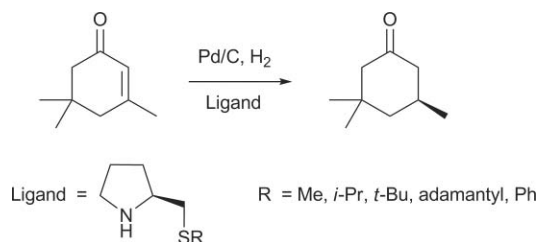
Table 1 Immobilized Co_2Rh_2 -catalyzed asymmetric Pauson–Khand reaction^a

| Substrate | | Ligand | Yield (%) | ee (%) |
|-------------------------------------|-----------------|---------------|-----------------|-----------------|
| X | R | | | |
| O | Ph | (R)-BINAP | 93 | 79 |
| O | Ph | (R)-Tol-BINAP | 91 | 73 |
| O | Ph | (R)-DIOP | 90 | 34 |
| O | Ph | (R,R)-NORPHOS | 83 | — |
| O | Ph | (S,S)-BDPP | 91 ^b | 84 ^b |
| | | | 90 ^c | 85 ^c |
| | | | 89 ^d | 80 ^d |
| | | | 93 ^e | 83 ^e |
| O | Bu | (S,S)-BDPP | 75 | 62 |
| O | CH ₃ | (S,S)-BDPP | 85 | 80 |
| (MeO ₂ C) ₂ C | Ph | (S,S)-BDPP | 89 | 64 |
| (EtO ₂ C) ₂ C | Ph | (S,S)-BDPP | 94 | 51 |

^a Catalyst: Co_2Rh_2 immobilized on charcoal (total metal = 12.2 mg), ligand 0.11 mmol; ^b first cycle; ^c second cycle; ^d third cycle; ^e fourth cycle

A more sophisticated system based on Co/Rh heterobimetallic nanoparticles (2 nm) obtained from the cobalt-rhodium carbonyl clusters $\text{Co}_2\text{Rh}_2(\text{CO})_{12}$ and $\text{Co}_3\text{Rh}(\text{CO})_{12}$, and immobilized on charcoal, was investigated by Park *et al.*⁴⁰ The NPs were modified using chiral diphosphines and applied in the Pauson–Khand reaction (see Table 1). Yields ranging from 75 to 94% and *ee*'s up to 85% were obtained with no loss of activity compared to the unmodified system. The catalysts could be recycled with overall metal leaching below 4 ppm after four cycles. Mercury poisoning experiments provided clear evidences of the true heterogeneity of the Co/Rh catalyst.

Recently, commercial Pd/C nanoparticles modified with chiral amino-sulfide ligands were tested in the *in situ* asymmetric catalytic hydrogenation of isophorone (Scheme 10).⁴¹ The choice of the ligand was motivated by the presence of nitrogen and a sulfide functionalities able to interact with the substrate and with the metal, respectively. The heterogeneous catalysts showed up to 20% *ee*, which was improved by increasing the modifier concentration and the hindrance of the alkyl substituent on the ligand. This latter effect was attributed to the better ligand dispersion as separate molecules on the Pd surface facilitated by bulky ligands, which leads to more effective asymmetric induction as compared to the closer ligand package caused by smaller substituents.

**Scheme 10** Ligands used in the asymmetric hydrogenation of isophorone.

3. MNPs liquid-phase suspensions

Colloids

The first definition of a colloid was introduced in 1861 by Graham to indicate an even dispersion of a solid or liquid phase into another.⁴² He postulated that the dispersed phase consists of suspended particles whose size is in the range 1 nm – 1 μm , with no-crystalline state and a slow tendency to deposition. The dispersions of inorganic particles, and particularly of metal nanoparticles, are of great interest for diverse technological applications, such as photochemistry, nanoelectronics, optics, and above all catalysis, because of the large portion of active atoms at the interface. The advancements obtained in the field allow the preparation of monodispersed liquid-phase metal colloids with a careful control of particle size and shape. The principal shortcoming of colloidal MNPs is the tendency to aggregate with a consequent loss of activity. The use of stabilizing agents able to induce repulsive forces opposed to the van der Waals interactions is thus required. Four main stabilization methods are used:⁴³

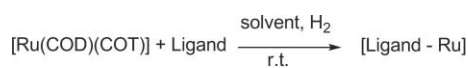
- 1) electrostatic, by ionic agents such as halides, carboxylates and polyoxoanions,
- 2) steric, by bulky macromolecules such as block polymers,⁴⁴ polymers,⁴⁵ and dendrimers,
- 3) electrosteric, by ionic surfactants or polyelectrolytes,
- 4) stabilization by ligands and solvents.

Conventional ligands such as thiols,⁴⁶ amines,⁴⁷ diphosphines, oxazolines, carbohydrates or weakly coordinating solvents such as THF, thioethers or alcohols can be used to stabilize colloidal solutions for long periods of time.⁴⁸

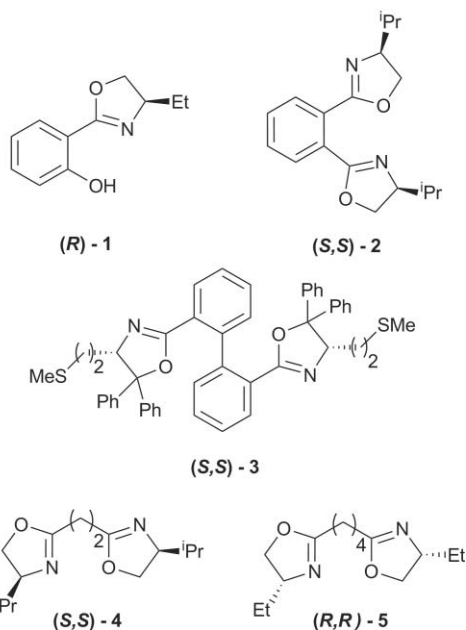
Among the synthetic approaches for the preparation of colloidal chiral MNPs, the most used one is the decomposition of an appropriate metal precursor solution by a reducing agent (H_2 , carbon monoxide, alcohols, hydrazine, (boro)hydrides, citrate) in the presence of an optically pure ligand.⁴⁹

Chiral ruthenium colloids were prepared by the reaction of $[\text{Ru}(\text{COD})(\text{COT})]$ ($\text{COT} = 1,3,5$ cyclooctatriene) with hydrogen, in the presence of small amounts (0.2 equivalents) of the enantiopure *N*-donor ligands sketched in Scheme 11.⁵⁰ Change of the ligand provided colloidal MNPs with a different size and dispersion. The hydroxyoxazoline **1** and the bis(oxazolines) **2**, **3** gave well-dispersed, small metal particles (2.7 and 1.6 nm, respectively), whereas use of the methylene-bridged derivatives **4**, **5** resulted in the formation of larger super-structures (bowls). The colloids were tested in the catalytic hydrogen transfer reaction of acetophenone, and in the hydrogenation of *ortho*-, *para*-methylanisole and dimethylitaconate (Scheme 12). Moderate to good activities were observed in any case (up to 87 and 100% conversion for anisoles and dimethylitaconate, respectively), in some instances better than the corresponding molecular catalyst (*i.e.* acetophenone, 98% yield), but with very low selectivities (max. *ee* 10%). The low enantiodiscrimination was attributed to a fluxional behaviour of the chiral ligands on the surface of the metal nanoparticles. The addition of an excess of ligand caused a decrease of the activity without any effect on selectivity in all reactions. No direct correlation of catalyst performance with metal particle dimension was highlighted.

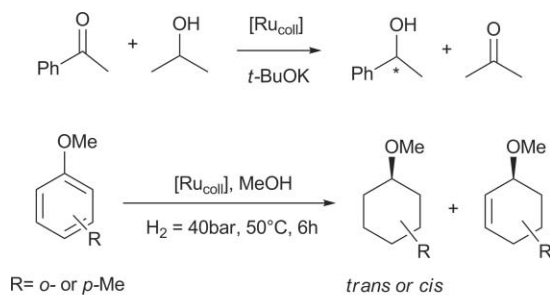
The ligands in Scheme 11 were also used to prepare chiral platinum colloids by reacting $\text{Pt}_2(\text{dba})_3$ with 0.5 equivalents of ligand



Reaction condition: solvent: THF or THF/MeOH,
 $P_{\text{H}_2} = 3$ bar, molar ratio Ligand/Ru = 0.2



Scheme 11 Synthesis of Ru colloids stabilized by chiral N-donor ligands.



Scheme 12 Hydrogen transfer reaction to acetophenone, hydrogenation of methylanisole and dimethylitaconate catalyzed by chiral Ru colloids.

and carbon monoxide in toluene (dba = dibenzylidene acetone).⁵¹ As shown by HRTEM analysis, the Pt nanoparticles organized into elegant supramolecular aggregates (disks, dendrites, wires, arborescences, depending on the ligand) in that case. Preliminary studies on the hydrogenation of ethyl pyruvate catalyzed by these colloids were unsatisfactory, however.

DIOP-modified Pt-nanoparticles (2 nm) were obtained by the same synthetic approach as above, using H_2 and one equivalent of ligand.⁵² Despite a high activity, the colloid showed a very poor chiral induction in the hydrogenation of ethyl pyruvate (80% yield, 4.4% ee). A model accounting for the transfer of chirality to the substrate was proposed, similar to that suggested for cinchonidine-stabilized Pt nanoparticles (see section 2.1).

The high interest for enantioselective C–C coupling reactions (e.g. Suzuki, Heck) prompted chemists to develop appropriate

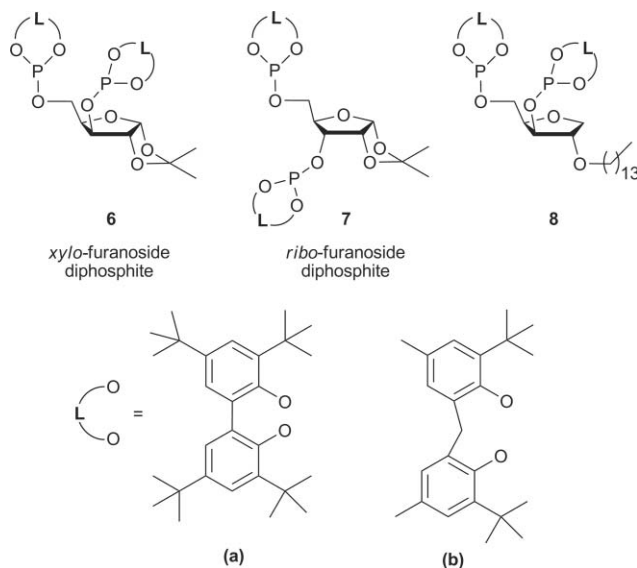
Table 2 Catalytic allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate using Pd NPs

| Pd col. | Free ligand added (Pd/Ligand) | Time/h | Yield (%) | ee (%) |
|-----------------------|-------------------------------|--------|-----------|--------|
| 6a | 1/0 | 168 | 0 | — |
| 6a | 1/0.2 | 168 | 59 | 97 |
| 6a | 1/1.05 | 168 | 61 | 97 |
| 7a | 1/0 | 168 | 0 | — |
| 7a | 1/1.05 | 48 | 100 | 11 |
| 7a^a | 1/1.05 | 24 | 100 | 89 |

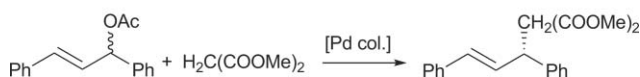
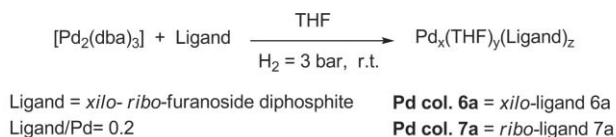
^a Free *xilo*-ligand added.

metal colloidal catalysts. A number of systems stabilized by “chiral pool” ligands were exploited for this purpose, particularly based on carbohydrate moieties.

Stable Pd colloids (4 nm) were isolated in the solid state after conventional reduction of $\text{Pd}_2(\text{dba})_3$ with H_2 in THF in the presence of 0.2 eq. of the *xilo*- or *ribo*-furanoside diphosphite ligands sketched in Scheme 13,⁵³ and tested in enantioselective allylic alkylations (Scheme 14).⁵⁴ The work demonstrated the considerable influence of minor structural changes of the chiral ligand on MNP catalyst efficiency. Indeed, none of the isolated colloids was catalytically active, unless additional portions of free ligand were added to the reaction mixture (Table 2). In the case of the *xilo*-modifier, 0.2 eq. of free ligand sufficed to give a 59% conversion and 97% ee, while larger ligand amounts did not affect neither the conversion nor the selectivity. Complete conversion,



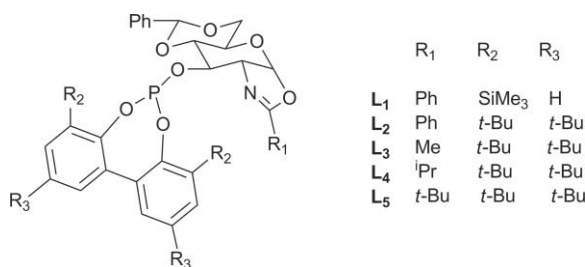
Scheme 13 Chiral *xilo*- and *ribo*-diphosphite ligands.



Scheme 14 Synthesis of diphosphite-stabilized Pd colloids and allylic alkylation reaction.

but low enantioselectivity (*ee* 11%) was observed using the *ribo*-derivative after shorter reaction times. Interestingly, the cross system containing Pd coll. **7a** and the free *xylo*-ligand provided complete conversion and high selectivity (*ee* 89%) after 24 h, thus suggesting the possible contribution of molecular catalysts species to the reaction.

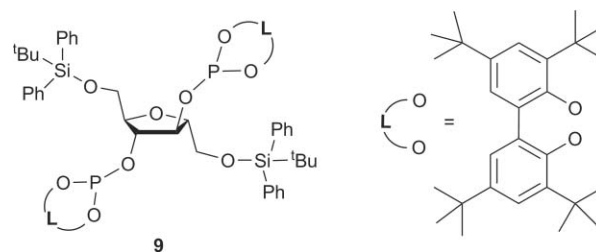
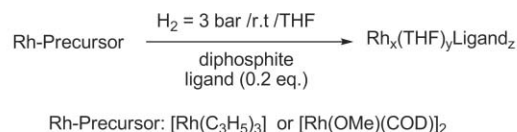
Use of parent sugar-based oxazolines-phosphite ligands (Scheme 15) gave similar results:⁵⁵ the addition of 5–10% of free-ligand raised the activity and the enantioselectivity up to 60% and 71% *ee*, respectively, while the use of more hindered ligands (e.g. ligand **L**₅) caused an increase of the yield (100%), but a decrease of the enantioselectivity (20% *ee*). This latter system was carefully investigated by using a continuous-flow membrane reactor (CFMR), TEM, poisoning and kinetic measurements. The experiments unequivocally proved that monometallic, molecular palladium species leached from the nanoparticles, and containing the ligands, were the actual catalysts and that all conversions could be justified by the amount of palladium leached in solution, as measured by ICP-AES (Inductively Coupled Plasma Atomic Emission Spectroscopy).



Scheme 15 Oxazolinyl-phosphite ligands.

Ruthenium colloids stabilized by the carbohydrate ligands reported in Scheme 13 were synthesized by decomposition of [Ru(COD)(COT)] with H₂ in THF in the presence of the ligand, and applied in the catalytic hydrogenation of arenes.⁵⁶ The size of the Ru nanoparticles was dependent on the substituent on the C(2) carbohydrate atom, being 4.0, 2.9 and 1.8 nm for ligands **6a**, **6b** and **8b**, respectively. This had a direct consequence on the catalyst activity, as shown by the hydrogenation reaction of 3- and 2-methylanisole in pentane, for which the **8b**-stabilized catalyst (100% yield at *P* = 10 bar) was much more active than the **6a**- and **6b**-derivatives (39% and 100% yield at *P* = 40 bar, respectively). The complete inactivity of these systems in THF or CH₃CN was explained by the competitive adsorption between the substrate and the solvent at the metal surface. Unfortunately, a poor enantioselectivity (less than 6% *ee*) was observed only in the hydrogenation of 2-methylanisole.⁵⁷

The catalytic asymmetric hydroformylation of styrene was performed using rhodium colloids obtained by H₂ reduction of Rh precursors in THF in the presence of 0.2 equivalents of the chiral ligands **6a** or **9** (Scheme 16).⁵⁸ The [Rh(η³-C₃H₅)₃] complex provided well formed, 2–3 nm size nanoparticles, whereas [Rh(μ-OMe)(COD)]₂ gave sponge-like superstructures (50 nm). Compared to the corresponding molecular catalysts in the same reaction conditions, the activity of the colloids was invariably lower, although a slightly higher enantioselectivity was observed (max. 45% *ee*). Again, the addition of free ligand to the colloid



Scheme 16 Synthesis of rhodium nanoparticles from chiral diphosphite ligands.

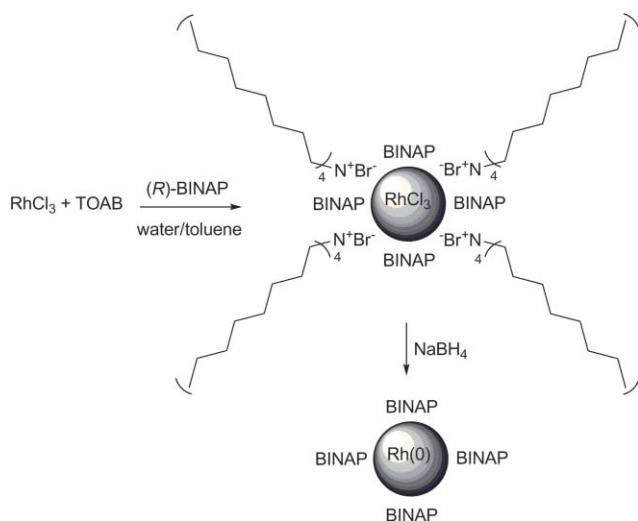
caused a slight decrease in the conversion, but an increase in the regio and enantioselectivity.

Using a completely different synthetic approach, palladium and platinum nanoparticles were prepared by electron beam evaporation of the metals followed by co-condensation with methylethylketone vapours, in the presence of a stabilising agent (the commercial KD1 or KD2 polymers).⁵⁹ Well-dispersed NPs in the size range 2.3–2.8 nm and 2.7–3.8 nm (TEM), for Pt and Pd respectively, were obtained which, upon *in situ* treatment with cinchona alkaloids, were tested as catalysts in the Orito reaction (Scheme 2). The systems provided hydrogenation results comparable with those of standard Pd or Pt supported catalysts (see section 2.1). Complete conversion, but low enantioselectivity (*ee* 36%), was obtained with colloidal Pt/cinchonine in acetone/water, although higher than standard catalyst.

Other cinchona-modified platinum colloids were obtained by formate reduction of PtCl₄ in the presence of water soluble dihydrocinchonidine hydroformate (DHCinH⁺HCO₂⁻),⁶⁰ or by addition of the alkaloid to preformed polyvinylpyrrolidone (PVP)-stabilized Pt nanoparticles.⁶¹ In the former case, the isolated colloid was used as a catalyst for the asymmetric hydrogenation of ethylpyruvate after addition of further DHC in to an acetic acid/methanol solution of the reactants. A constant *ee* of about 76% was achieved, irrespective of a decrease in alkaloid content which led to a reduced activity. This fact was attributed to the reduction of the accessible surface area because of the agglomeration of the colloid at low modifier concentration. PVP–Pt colloidal clusters were highly effective and displayed enantioselectivity up to 97.6% *ee* in the hydrogenation of alkylpyruvates.

It must be noted that several chiral MNP-based catalysts were prepared by a modification the well-know, biphasic method of Brust and Walker.⁶²

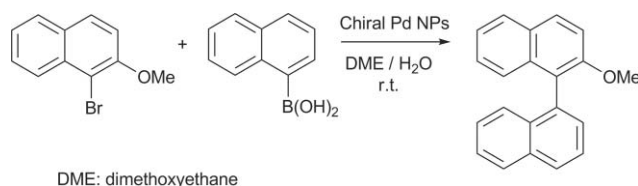
Thus, following their previous work on silica-supported NPs (section 2.1, ref. 19), Li *et al.* synthesized Rh nanoparticles of small and narrowly distributed size (1.5–2.0 nm), by a *one-pot* NaBH₄ reduction of RhCl₃ in the presence of tetraoctylammonium bromide (TOAB) and (*R*)-BINAP (Scheme 17).⁶³ The role of the alkyl bromide is to act as a phase-transfer agent, whereas the chiral modifier adsorbed on the metal surface stabilizes the NPs after reduction. The method is indeed extremely convenient, as very stable NPs are obtained which can be handled and characterized as a conventional chemical compound,



Scheme 17 Surfactant-mediated synthesis of chiral Rh nanoparticles.

isolated in the solid state and re-dispersed in non-polar organic solvents. The nanostructured material performed similarly to the corresponding silica-supported system (section 2.1) in the catalytic hydroformylation reaction of styrene and vinyl acetate, both for activity and selectivity. Interestingly, the chiral rhodium nanoparticles prepared by this route could be immobilized on silica by adsorption. No particular advantages in terms of catalytic performance were observed, however.

Similarly, Pd nanoparticles stabilized by the diphosphines $(S)\text{-BINAP}$, $(S)\text{-Tol-BINAP}$, $(S)\text{-segphos}$, $(S)\text{-DIOP}$ and by the monophosphines $(S)\text{-mop}$ and $(S)\text{-etp}$ (Scheme 1) were synthesized using the same method as above, by the reduction of K_2PdCl_4 with NaBH_4 in the presence of TOAB.⁶⁴ The composition of the chiral NPs was estimated on the basis of TEM and thermogravimetric analysis,⁶⁵ showing that the diameter of all NPs was in the range 1.2–1.7 nm and that the average formula for $(S)\text{-BINAP}$ and $(S)\text{-Tol-BINAP}$ derivatives, for example, was $\text{Pd}_{103}(\text{BINAP})_{86}$ and $\text{Pd}_{46}(\text{Tol-BINAP})_{44}$, respectively. Despite the similar size, the MNPs performed very differently as catalysts for the Suzuki–Miyaura coupling reaction between 1-bromo-2-methoxynaphthalene and naphthalen-1-yl boronic acid, depending on the ligand (Scheme 18). Particularly, both activity and selectivity decreased in the order $\text{BINAP} > \text{Tol-BINAP} > \text{segphos} > \text{etp} \geq \text{mop} > \text{DIOP}$. Although no clear explanation for this behaviour was given, the dihedral angle of the ligands seems to play a role. The same Pd-based and the parent Au catalysts (from the reduction of HAuCl_4) were successfully employed in the catalytic hydrosilylation of styrene with *ee*'s up to 95%.⁶⁶



Scheme 18 Suzuki–Miyaura cross-coupling reaction catalyzed by chiral Pd NPs.

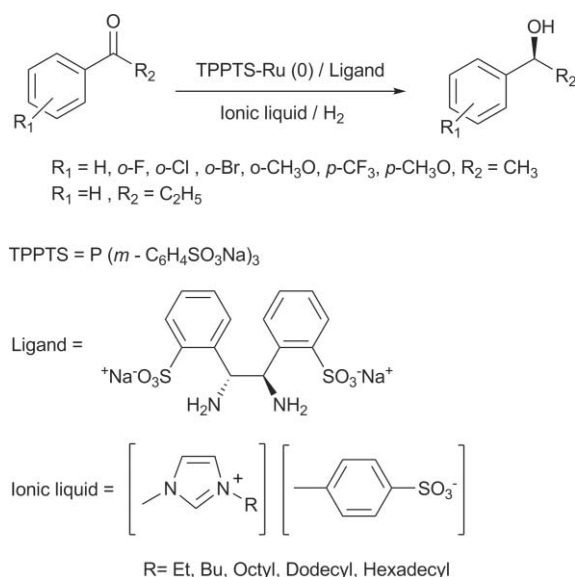
Micelles

MNPs-based catalysts can be effectively stabilized into micellar solutions; the preparation and use of these systems were extensively examined in the past.⁶⁷ The methodology has been extended to enantioselective catalysis,⁶⁸ however, to the best of our knowledge, the only likely example in the field and in which the MNPs do not act only as support, was recently described by Roucoux.⁶⁹ Thus, modified cinchonidine platinum nanoparticles (2.5 nm) were obtained by the reduction of H_2PtCl_4 with H_2 in water and in the presence of the alkaloid and the surfactant *N,N*-dimethyl-*N*-cetyl-*N*-(2 hydroxyethyl)ammonium chloride salt (HEA16Cl). The as-prepared aqueous suspension was employed in the catalytic hydrogenation of ethyl pyruvate showing enantioselectivities up to 55% *ee*. The optimal catalytic performance was observed for a cinchonidine/ $\text{Pt}(0)$ molar ratio of *ca.* 2. The surfactant-protected NPs could be reused over three cycles with no appreciable decrease of selectivity.

Ionic liquids

Ionic liquids have attracted great attention as an alternative to conventional organic solvents because of their very low vapour pressure and the possibility to tune their properties (polarity, hydrophobicity, solvent miscibility). Consequently, they found significant applications in catalysis, particularly in homogeneous biphasic catalysis and in catalysts recycling *via* catalysts immobilization. More recently, functionalized ionic liquids-stabilized MNPs showing high catalytic activity and low metal leaching were described.⁷⁰

TPPTS-stabilized Ru nanoparticles modified with the water soluble chiral ligand $(1R,2R)\text{-1,2-diphenyl-1,2-ethylene-diamine}$ disulfonate sodium salt were used as catalysts for the enantioselective hydrogenation of aromatic ketones in ionic liquids (Scheme 19).⁷¹ Both conversion and selectivity were dependent from the solubility of the catalyst in the ionic liquid. Thus, the addition of small amounts of water increased the yield and the *ee*



Scheme 19 TPPTS-stabilized Ru chiral NP and hydrogenation of ketones in ionic liquids.

up to 100% and 85.1%, respectively; whereas use of less hydrophilic ionic liquids, *i.e.* with longer alkyl chains, caused a decrease in both parameters. The reaction products could be easily separated from the catalyst immobilized in the ionic liquid by simple extraction with *n*-hexane, and the catalyst reused up to seven times with only a slight loss of selectivity and conversion. Although similar enantioselectivity were obtained in the homogeneous phase using $\text{RuCl}_2(\text{TPPTS})$, the NP-based catalyst in the ionic liquid was more active under the same experimental conditions.

4. Characterization techniques

The characterization of chirally modified MNPs can be performed using various instrumental techniques depending on the parameter or structural element to be determined. The most important features relevant to chiral MNPs are:

- 1) MNPs structure, including size distribution, morphology (crystal structure, aspect ratio, class of symmetry, surface structure, exposed planes, *etc.*),
- 2) nature and arrangement of the adsorbed chiral modifier (interacting group, distribution over the particles, occurrence of superstructures, energy of interaction, *etc.*).

Each parameter needs a peculiar care in the choice of the proper characterization “tool” while sensitivity, selectivity, and resolution of the technique must be considered at the same time. Quite obviously, a single technique can not fit all the requirements. Hence, detailed studies should be performed by using a pool of complementary techniques, comparing the information obtained and, if necessary, by performing modelling studies to confirm and/or support the hypothesis derived from experimental evidences. While several techniques are commonly employed for the analysis of MNP-based systems (and above all those based on a microscopy method, *i.e.* Scanning Tunnelling Microscopy, Atomic Force Microscopy, Transmission Electron Microscopy, and X-ray Absorption Spectroscopy),⁷² those directly related to the presence of a chiral modifier on a MNPs surface are more limited in number and use.⁷³

DRIFTS (Diffuse Reflectance Infra-Red Fourier Transform Spectroscopy) was used to determine the orientation of a ligand with respect of a metal surface, as in the case of the DIOP-modified Pt colloids previously discussed (see section 3, ref. 52). The chiroptical techniques, *e.g.* Circular Dichroism (CD) and Vibrational Circular Dichroism (VCD),^{74,75} were extensively employed in the characterization of gold nanoparticles functionalized with the enantiopure chiral thiols L-glutathione,⁷⁶ penicillamine,⁷⁷ *N*-isobutyl-cysteine,^{78,79} 1,1'-binaphthyl-2,2'-dithiol,⁸⁰ or with phosphines, such as BINAP.⁸¹

Few examples of the use of techniques for the direct optical activity measurement of chiral surfaces and micro-sized crystals, such as High-Accuracy Universal Polarimetry,⁸² Reflection-Absorption Infrared Spectroscopy,⁸³ Second-Harmonic Generation⁸⁴ and Near-field Scanning Optical Microscopy,⁸⁵ were reported as a consequence of their low sensitivity and the required sample amount.

The NMR techniques, and particularly the High-Resolution Magic-Angle Spinning (HRMAS), are extremely useful in the determination of the binding status of the chiral modifier adsorbed on the metal surface. Successful examples were reported for ³¹P NMR on chiral phosphine-functionalized Pd NPs,⁸⁶ and for

¹³C, ²⁹Si, and ³¹P MAS NMR experiments on rhodium, gold and superparamagnetic iron oxides nanoparticles modified with organic ligands (see, *e.g.* section 2.1, ref. 19).⁸⁷

The use of surface science techniques (*e.g.* Electron Energy Loss Spectroscopy, X-ray Photoelectron Spectroscopy, Low Energy Electron Diffraction) was recently reviewed by Raval, highlighting that these methods can be applied to almost every kind of chiral surface ranging from 0-D (chiral single molecule adsorbed on surface) to 2-D systems (chiral self assembled monolayers).⁸⁸

The main applications of modelling studies, including those on chiral surfaces, particularly density functional theory (DFT) and force fields, were summarized in two recent reviews.⁸⁹ DFT calculations were applied to the study of the reaction pathways in the hydrogenation of (*R*)-1-hydroxy-1-phenyl-2-propanone over $\text{Pt}/\text{Al}_2\text{O}_3$, in the presence of cinchonidine modifier.⁹⁰

5. Conclusions

The examples illustrated in the previous sections clearly show the potential of MNP-based chiral catalysts in asymmetric synthesis. Their major advantage is to combine the easy handling of immobilized ligands with the activity typical of soluble systems.

When supported onto solid insoluble materials, MNPs can be effectively separated from the reaction products, recovered and reused. Compared with heterogenized enantioselective molecular catalysts, they are more easily accessible and reactive, often with a minor loss of activity upon recycling. Adaptation for the use in flow reactors is also straightforward.

When colloidal suspensions are used, quasi-homogeneous conditions are met, and the catalysts behave similarly to homogeneous-phase ones.⁹¹ Moreover, methods were developed allowing for the preparation of very stable MNPs that can be quantitatively isolated in the solid-state and re-dispersed in a liquid phase.

Noticeably, MNPs are ideally suited to operate in “green” processes, *e.g.* in aqueous media and/or in mild reaction conditions.

However, with a few notable exceptions, in practice the cinchona alkaloids-based hydrogenations and some C–C couplings reactions, the main drawback of ligand-stabilized chiral MNPs is that the enantioselectivities provided are generally poor, and not comparable with those granted by the corresponding molecular catalyst. In most of these systems, the mechanism for the transfer of chirality to the substrate is far from understood, but the experimental evidences demonstrate that several, often subtle, factors may influence the efficiency of asymmetric induction.

For *in situ* prepared catalysts, *i.e.* when an excess of chiral ligand is added to the reaction mixture containing the MNPs, continuous feed of the modifier is usually required to maintain high *ee*'s, which makes catalyst reuse not economically convenient nor environmentally acceptable.

When preformed chiral MNPs are used, and particularly if solid-supported, the performance of the catalyst, both for activity and selectivity, is mainly determined by the particle size, and by the degree of their coverage by the ligand. As a general rule, smaller particles correspond to more selective (and more active) catalysts. On the other hand, the change in the modifier/metal ratio has two opposite effects: more crowded metal surfaces show higher selectivity but, invariably, a lower activity.

It must be finally underlined that the efficiency of solid-supported, heterogeneous MNPs-based catalysts is definitely determined by both the (*meso*) porosity and the functionalization (if any) of the support, as a consequence of the inhibition of particle growth and reduced particle aggregation. However, the participation of homogeneous species (potentially featured by high enantioselectivity) cannot be ruled out in most applications.

The conclusions summarized above suggest that new, alternative synthetic approaches to chirally modified metal nanoparticles are strongly awaited, aimed at the preparation of catalytic systems showing improved asymmetric induction.

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