Functionalized nanoparticles as catalysts for enantioselective processes

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Received 24th February 2009, Accepted 30th March 2009
First published as an Advance Article on the web 28th April 2009
DOI: 10.1039/b903921j

Functionalized nanoparticles find increasing application as catalysts for enantioselective transformations. In this account the different strategies followed for the preparation of chirally modified nanoparticles and their application in asymmetric catalysis are reviewed.

Introduction

The fast development experienced by nanotechnology in recent times has provided chemists with a huge variety of functional nanoparticles (NP). The application of these nanometre sized particles in catalysis has attracted considerable attention, since the very high specific surface of these materials, with some tenths of their constituent atoms in the outer shell, should lead to catalytic activities approaching those of homogeneous, molecular systems.[1] Moreover, the development of highly efficient methods for the separation of nanoparticles such as centrifugation, precipitation–flocculation, nanofiltration, or magnetic decantation (when magnetic nanoparticles are used), makes nanoparticles highly desirable over homogeneous catalysts from an environmental point of view.

Several reports have appeared on the use of nanoparticles as catalysts in organic synthesis for the formation of carbon–carbon,[2] carbon–nitrogen,[3] carbon–sulfur,[4] and carbon–oxygen bonds,[5] as well as in oxidation,[1a] and reduction[6–7] processes. Except for the asymmetric hydrogenation of pyruvates,[7] most of the catalytic applications of nanoparticles reported so far are confined to non-asymmetric types of reaction regardless of the huge progress experienced by asymmetric catalysis. In this review we will present work involving well defined functional nanoparticles in catalytic asymmetric processes other than hydrogenation of carbon–carbon double bonds.

In the catalytic enantioselective application of nanoparticles two general approaches can be followed depending on the role exerted by the metal from which the nanoparticle is made and the location of the chiral ligand with respect to the particle (Fig. 1). This fact has been used as a basis for the organisation of this review.

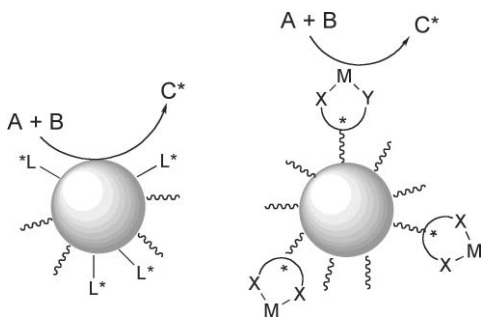

Fig. 1 Modes of functionalization of nanoparticles.

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Miquel A. Pericàs

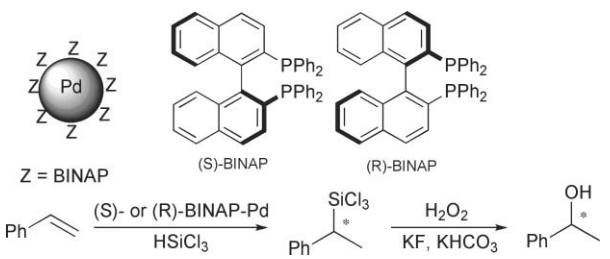
Miquel A. Pericàs studied Chemical Engineering at the Institut Químic de Sarrià and Chemistry at the Universitat de Barcelona, and obtained his doctorate in 1979 under the guidance of Fèlix Serratosa at the Universitat de Barcelona. After post-doctoral studies at the Spanish research council (CSIC) with Prof. Francesc Camps, he joined the Universitat de Barcelona in 1980. Since 1991 he has been a full professor of Organic Chemistry at that institution. In June 2000, he was appointed as director of the Institute of Chemical Research of Catalonia (ICIQ). His major research interest is focused on asymmetric catalysis with supported systems.

Nanoparticles as catalytic materials

This approach involves the use of systems where the nanoparticle constituent metal is also responsible for the planned catalytic activity, and the ligand is coordinatively bonded to the metal surface through some of the chelating atoms present in its structure (Fig. 1). In this case, the catalytic process takes place on the surface of the nanoparticle, and the achievement of enantiocontrol depends on how the ligands/capping agents are able to transmit their influence to substrate molecules coordinated to the particle in their vicinity. Functional nanoparticles operating according to this scheme are analogous to asymmetric heterogeneous catalysts, except that they can form stable suspensions.

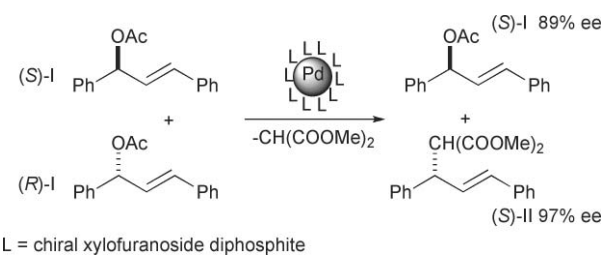
Use of chiral nanopalladium catalysts

Hydrosilylation of olefin. Fujihara and Tamura first reported a facile synthesis of chiral palladium nanoparticles stabilized by BINAP ligands.[8] When these chiral palladium nanoparticles were employed in the hydrosilylation of styrene, phenylethanol was obtained in very high yield and in excellent optical purity (Scheme 1).[8] It is worth noting that the same reaction did not take place when a molecular chiral palladium catalyst was used. This clearly established the impact that functional nanoparticles might have in asymmetric catalysis.



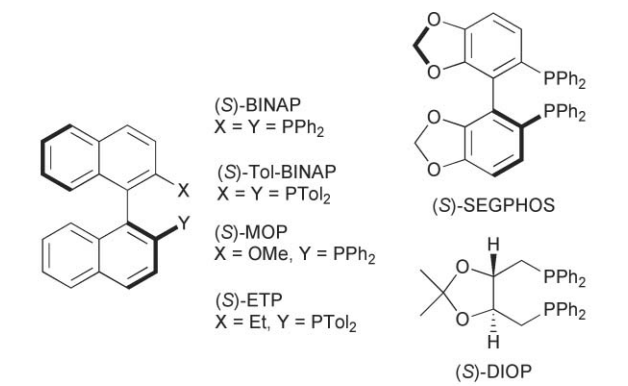
Scheme 1 Application of chirally modified Pd nanoparticles in the asymmetric hydrosilylation of styrene.

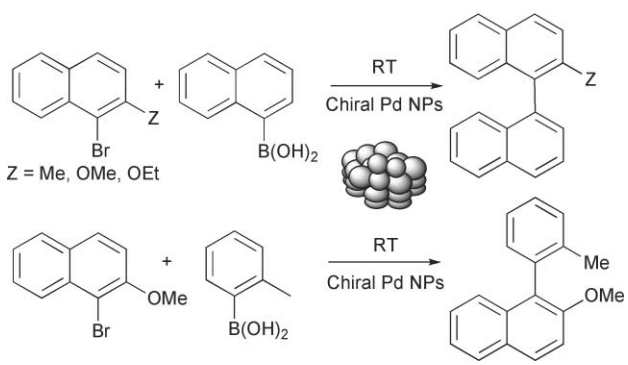
Allylic alkylation. While molecular palladium-based catalysts have been extensively used in asymmetric allylic alkylation reactions in the presence of different chiral modifiers,[9] the application of NPs has fewer literature precedents. In 2004 Gómez, Philippot, Chaudret and co-workers reported the first use of a chirally modified nanopalladium catalyst in the highly enantioselective (97% ee) allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate (Scheme 2).[10a] The nanopalladium catalyst and the corresponding molecular palladium species exhibited a very different reactivity behaviour. While the use of the former led to incomplete reactions, associated with a very high level of kinetic resolution (89% ee in the remaining substrate), almost full conversion but no kinetic resolution was observed when the molecular palladium catalyst was used. The authors could demonstrate that the different behaviour of the colloidal and the molecular catalysts has its origin in the relative rates of alkylation of the two enantiomers of the substrate. While the kinetic preference for the *R*-substrate was only greater by a factor of 2 with the molecular system, the *R*-substrate reacted 12 to 20 times faster when the colloidal catalyst was used. Later on, the same group reported a detailed study of the same reaction involving palladium nanoparticles and different chiral diphosphite ligands derived from carbohydrates.[10b] It was shown that the colloidal system was much more sensitive to the adjustment between the metal, the ligand and the substrate than the corresponding molecular catalysts. In any case, the high enantiospecificity depicted by the chirally modified palladium nanoparticles is still awaiting a definitive explanation.



Scheme 2 Chiral Pd nanoparticle catalyzed asymmetric allylic alkylation and kinetic resolution of allylic acetate.

Suzuki–Miyaura coupling. Very recently Fujihara *et al.* have reported[11] another interesting application of palladium nanoparticles (NP) in the asymmetric Suzuki–Miyaura coupling reaction. These authors prepared palladium nanoparticles stabilized by several phosphine ligands and found out that palladium nanoparticles stabilized by (*S*)-BINAP are the catalysts of choice for enantioselective Suzuki–Miyaura coupling reactions (Scheme 3). Interestingly, the product obtained using the palladium nanoparticles stabilized by (*S*)-BINAP was of higher enantiomeric purity than the one prepared with the molecular system consisting of $PdCl_2$ and (*S*)-BINAP.





Scheme 3 Asymmetric Suzuki–Miyaura coupling catalyzed by chiral Pd nanoparticles.

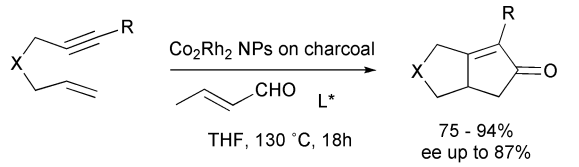
In any case, it is important to note that the nature (colloidal or molecular) of the real catalyst when palladium nanoparticles are used to catalyze cross-coupling reactions is not exempt from debate. Doubts on this issue are fed by the fact that, according to the commonly admitted mechanism, enantioselective cross-coupling reactions require at least three coordination sites at a square-planar palladium centre, and it is hardly conceivable that a single surface atom could fulfil these requirements. While strong arguments in favour of the colloidal nature of the catalyst were provided in the 2004 report on allylic alkylation by Gómez, Philippot, Chaudret, and co-workers,[10a] a recent study by Dieguez, Gómez, van Leeuwen and co-workers[10c] reached an opposite conclusion. These authors prepared palladium nanoparticles stabilized by sugar-based phosphite-oxazolines and used them as catalysts in asymmetric allylic alkylation and Heck reactions. Results obtained with a continuous-flow membrane reactor (CFMR) and supported by TEM, poisoning and kinetic measurements showed that monometallic, molecular species originating by leaching could account for the observed catalytic activity.[10d] In particular, the CFMR experiments strongly indicated that leached molecular palladium species containing oxazolinylphosphite ligands were the actual catalysts.

Use of chiral nanoruthenium catalysts

Transfer hydrogenation. In an effort to understand the difference between the catalytic activity of the metal nanoparticles and the molecular catalysts, Gómez, Philippot, Chaudret and co-workers studied the asymmetric reduction of ketones and dimethyl itaconate in the presence of ruthenium nanoparticles stabilized by different chiral amino alcohols, mono-oxazolines and bis-oxazolines.[12] These authors found that the presence of a phenolic moiety in the chiral modifier completely poisoned the molecular catalyst in the transfer hydrogenation of acetophenone by forming a π–bonded phenoxo complex, whereas the catalyst derived from the ruthenium nanoparticles remained active. Moreover, ligands with multiple binding sites such as N, S and a π-system were found to be better promoters of a nanoruthenium catalyst than of molecular ruthenium species. The only shortcoming of this nanoruthenium system, however, was its lower asymmetric induction compared with the corresponding molecular systems.

Use of heterobimetallic Co/Rh nanoparticles

Pauson–Khand type reactions. Park and Chung prepared Co/Rh heterobimetallic nanoparticles by thermal decomposition of several cobalt–rhodium carbonyl clusters and immobilized them on charcoal.[13] The immobilized nanoparticles with a Co_2Rh_2 stoichiometry behaved as a highly effective catalyst for intra- and intermolecular Pauson–Khand-type reactions in the presence of an aldehyde as a source of carbon monoxide. When the intramolecular reactions were carried out in the presence of chiral diphosphines (BINAP, Tol-BINAP, NORPHOS, DIOP, and BDPP), ee values up to 87% were observed (Scheme 4). Interestingly, the catalytic system could be easily separated by filtration and reused at least five times in the presence of chiral diphosphines without loss of catalytic activity and enantioselectivity. Poisoning experiments show that addition of Hg(0) completely inhibits further catalysis, which strongly supports that the reaction takes place at the nanoparticles surface.

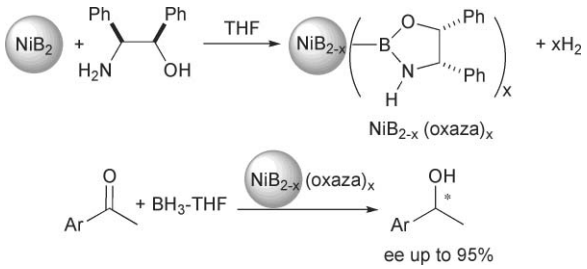


X: O, TsN, $(MeOOC)_2C$, $(EtOOC)_2C$
R: Me, Bu, Ph
L*: (*R*)-BINAP, (*R*)-Tol-BINAP, (*R*)-DIOP, (*R*)-NORPHOS, (*S,S*)-BDPP

Scheme 4 Bimetallic Co–Rh nanoparticle catalyzed asymmetric Pauson–Khand reaction.

Use of chiral nickel boride catalysts

Enantioselective borane reduction of ketones. Court *et al.* reported an elegant method of borane reduction of ketones in the presence of nickel boride nanoparticles modified with a chiral amino alcohol (Scheme 5).[14a,b] A variety of ketones were reduced with very high enantioselectivity. The main advantages of this protocol lie in the easy synthesis of the catalyst, its ready separation from the reaction medium and its high reusability. Later on the same group reported the use of chiral phosphinamide functionalized nickel boride for the same reaction with moderate enantioselectivity.[14c]

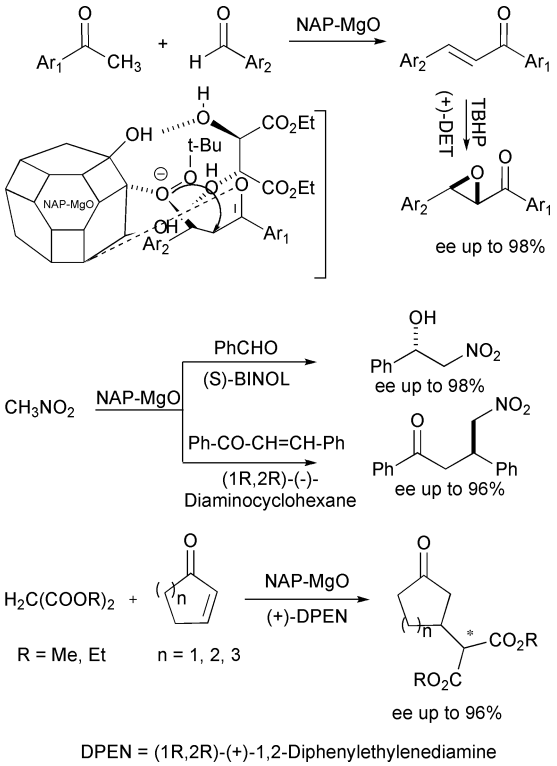


Scheme 5 Asymmetric hydrogenation of ketones using functional nickel boride nanoparticles.

Use of nanocrystalline magnesium oxide catalysts in asymmetric catalysis

C–C bond forming reactions. In 2004 Choudary *et al.* showed that aerogel prepared nanocrystalline magnesium oxide (NAP-MgO) can be very effectively utilized for the Claisen–Schmidt condensation (CSC) followed by asymmetric epoxidation in the presence of (+)-diethyl tartrate (DET) (Scheme 6).[15a] As the CSC and epoxidation of deactivated olefins are usually catalyzed by bases, these authors reasoned that the -OH and O^{2-} moieties on the surface of the NAP-MgO crystals are responsible for promoting these reactions. Indeed, these authors demonstrated that surface silylated NAP-MgO was far less reactive. After establishing the role of the surface -OH groups in catalyzing the reaction, they further showed that surface -OH groups were also necessary for the asymmetric induction as the surface silylated NAP-MgO gave rise to racemic epoxides.

The same research group further extended the application of NAP-MgO to the asymmetric Henry and Michael reactions

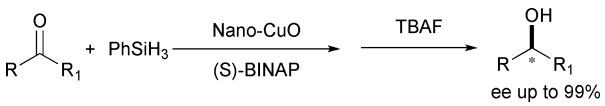


Scheme 6 Application of nanocrystalline MgO in different asymmetric C–C bond forming reactions.

(Scheme 6).[15b,c] The specific role of surface -OH groups was also highlighted in these cases. Later on, they also reported direct asymmetric aldol reactions using NAP-MgO as the catalyst in combination with enantiopure 1,2-diaminocyclohexane as a chiral ligand.[15d] In each case, the NAP-MgO was shown to be reusable with consistent activities.

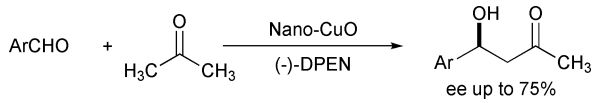
Use of nanocrystalline copper oxide catalysts

Hydrosilylation of ketones. Kantam and co-workers reported a highly efficient protocol for the asymmetric hydrosilylation of ketones using copper oxide (CuO) nanoparticles in the presence of (*S*)-BINAP (Scheme 7).[16a] According to expectations, it was found that CuO nanoparticles with high specific surface area behaved as better catalysts than low surface area CuO in terms of yield and asymmetric induction. The reusability of the CuO nanoparticles is an important advantage of this approach.



Scheme 7 Asymmetric hydrosilylation of ketones in the presence of CuO nanoparticles.

Aldol reaction. Kantam *et al.* have also reported a direct asymmetric aldol reaction in the presence of CuO nanoparticles and (1*S*,2S)-(−)-1,2-diphenylethylenediamine (DPEN) as the chiral ligand (Scheme 8).[16b] The copper oxide nanoparticles were used for up to four cycles with consistent activities.



Scheme 8 Asymmetric aldol reaction catalyzed by CuO nanoparticles.

Nanoparticles as structuring elements

In this alternative approach, the nanoparticles act as the structuring element for an assembly of ligands, which are bonded to the particle through an additional function, different from the chelating functional groups defining the catalytic centre. In these cases, the catalytic activity arises from a metal different from the one constituting the nanoparticle. The main advantages expected from this approach range from increased catalytic activity due to the accumulation of active centres on the nanoparticle periphery to the possibility of enhanced enantiocontrol due to the close similarity with purely homogeneous processes, or to the ease of separation and recycling of the catalyst through the application of a magnetic field whenever the nanoparticles possess a magnetic core.

Functional gold nanoparticle in asymmetric catalysis

The functionalization of gold nanoparticles is normally based on the strong interaction established between gold surfaces and thiol groups. According to this principle, ligands to be supported on gold nanoparticles are modified to include additional thiol group(s). Best results are normally obtained when the thiol-modified ligands are diluted on the nanoparticle surface among non-functional thiols acting as mere nanoparticle stabilizers. In this situation, an additional issue on the availability of the thiol-modified ligand to the substrate molecule and to reagents appears. To ensure the efficient exposure of the catalytic sites to the reagents, the thiol-modified ligands normally incorporate spacers so that the chain connecting the ligand with the nanoparticle is longer than that of the non-functional thiol merely acting as a stabilizer (Fig. 2).

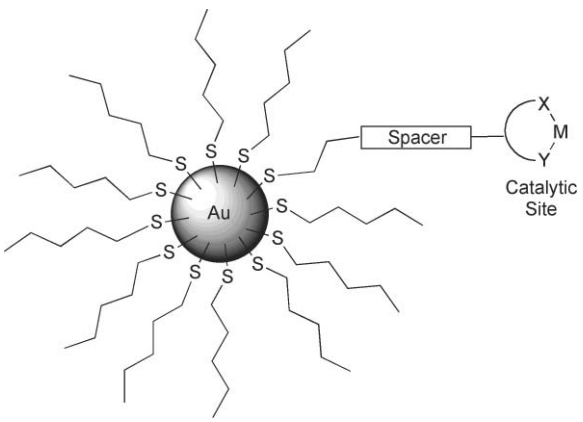


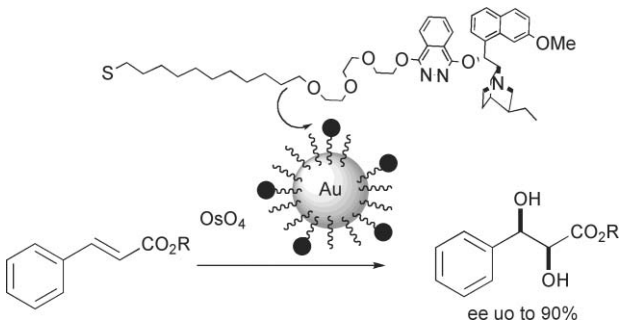
Fig. 2 Schematic representation of a thiol-functionalized ligand anchored on a thiol-stabilized gold nanoparticle.

One of the relevant issues in catalytic processes mediated by functional nanoparticles is that of catalyst separation and recycling. Functional gold nanoparticles stabilized by alkanethiol self-assembled monolayers (SAMs) exhibit in many cases an

agglomeration behaviour that is highly responsive to solvent polarity. In this manner, it is possible to shift from the optimal situation in catalysis (maximal dispersion) to the optimal situation for catalyst separation (maximal agglomeration) by the simple addition of an appropriate solvent to the reaction mixture.

Catalytic asymmetric dihydroxylation

In an early attempt, Mrksich *et al.* reported the synthesis of gold nanoparticles protected with a mixture of alkanethiolate and an alkanethiolate-functionalized dihydroquinidine ligand (3:1 ratio) through a ligand exchange approach and used them in the asymmetric Sharpless dihydroxylation of *trans*-olefins containing an aryl substituent (Scheme 9).[17] Yields comparable to those obtained with monomeric ligands were recorded while enantioselectivities (84–90% ee) were slightly lower when using the gold nanoparticle supported ligand. The ligand-functionalized colloids were easily separated by gel permeation chromatography and could be reused once with only a modest decrease in enantioselectivity. As pointed out by these authors, the interest of these particles stems from two important features. First, as the structure of the chemisorbed monolayer of alkanethiolates is reasonably well-ordered, it is possible to control the density and environments of functional molecules present on the nanoparticle surface. Second, the preparation of the modified colloids is straightforward and allows wide flexibility in tailoring both the size and the chemical functionality of the particles.



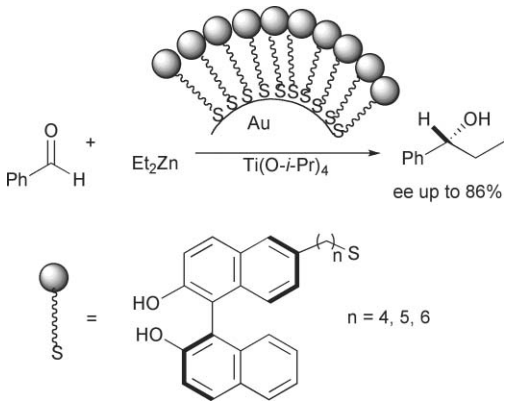
Scheme 9 Gold nanoparticles in the asymmetric dihydroxylation of olefins.

Catalytic asymmetric alkylation of aldehydes

In 2003 Sasai *et al.* reported a practical synthesis of a gold nanoparticle-supported 1,1′-bi-2-naphthol (BINOL) and efficiently employed this nanostructured ligand for the asymmetric alkylation of aldehydes with diethylzinc (Scheme 10).[18] The asymmetric induction exerted by the supported ligand depends on the length of the spacer connecting the BINOL moiety with the nanoparticle, and in the optimal case led to results almost comparable with those obtained with BINOL itself. Very interestingly, these gold-supported ligands were stable to the acidic work up of the alkylation reaction and could be reused without deterioration of their properties.

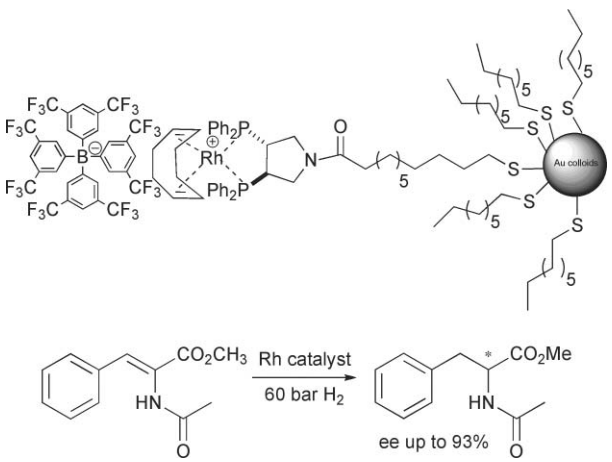
Asymmetric hydrogenation

In 2005, Pfaltz and co-workers reported the rhodium catalyzed asymmetric hydrogenation of methyl α-acetamidocinnamate



Scheme 10 Functional gold nanoparticles in asymmetric alkylation.

mediated by functional gold nanoparticles (Scheme 11).[19] In this study, *ca.* 3 nm gold nanoparticles stabilized by a self-assembled octanethiolate monolayer were submitted to ligand exchange with a thiol-functionalized Rh(COD)(PYRPHOS) catalyst, and the resulting gold nanoparticles modified with chiral ligands were tested as hydrogenation catalysts. With methyl α-acetamidocinnamate as the substrate, the functional gold NPs led to the same enantioselectivity as the molecular homogeneous catalytic system; *i.e.*, [Rh(COD)(PYRPHOS)]BArF.



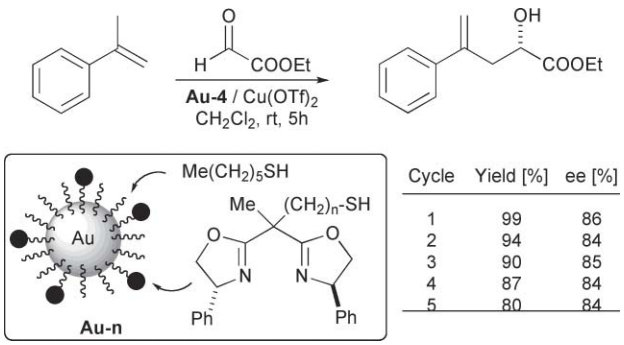
Scheme 11 Functional gold nanoparticle immobilized Rh catalyzed hydrogenation reaction.

The nanocatalysts could be easily separated by filtration and used for three consecutive runs without losses in enantioselectivity. Catalytic activity, in turn, importantly decreased in recycled catalyst samples. To understand the structure and dynamics of mixed thiol monolayers, such as those present on these gold nanoparticles, STM studies of analogous SAMs on Au(111) were performed. The STM images showed that the catalyst-bearing thiolates are distributed statistically on the nanoparticle surface and that the ordered structure of the n-octanethiolate SAM can be retained during incorporation of the catalyst-bearing thiols using the place-exchange methodology.

Asymmetric ene reaction

Kanemasa *et al.* reported another interesting application of gold nanoparticles in asymmetric catalysis by supporting bisoxazoline

(BOX) type ligands on their surface.[20] They prepared by ligand exchange gold nanoparticle-supported BOX ligands containing thiol-terminated spacers of different length (4, 6, 8, and 10 carbons) and applied them to the asymmetric ene type reaction between 2-phenylpropene and ethyl glyoxylate in the presence of $Cu(OTf)_2$ (Scheme 12). While all four ligands depicted essentially identical enantioselectivities approaching that of the homogeneous Ph-BOX/$Cu(OTf)_2$ system, the nanoparticles containing the BOX ligand attached to the gold nanoparticles through the shortest 4 carbon spacer showed the best activity profile during recycling. The authors attributed this behaviour to the fact that this particular ligand presented the polar Cu-BOX moiety buried in an array of neighbouring hexanethiolate ligands, and that this led to an optimal dispersion of the nanoparticles in the reaction media. However, since the differences in catalytic activity increase as the recycling proceeds, the existence of more important leaching levels in the nanoparticles where the functional BOX fragments emerge from the hexanethiol SAM can probably not be excluded. The catalyst was separated by precipitation and reused for five cycles with a moderate decrease in its activity, but with the same enantioselectivity.

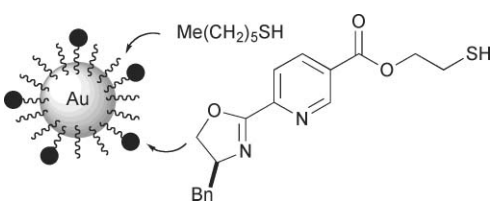


Cycle	Yield [%]	ee [%]
1	99	86
2	94	84
3	90	85
4	87	84
5	80	84

Scheme 12 Functional gold nanoparticle catalyzed asymmetric ene reaction.

Asymmetric allylic alkylation

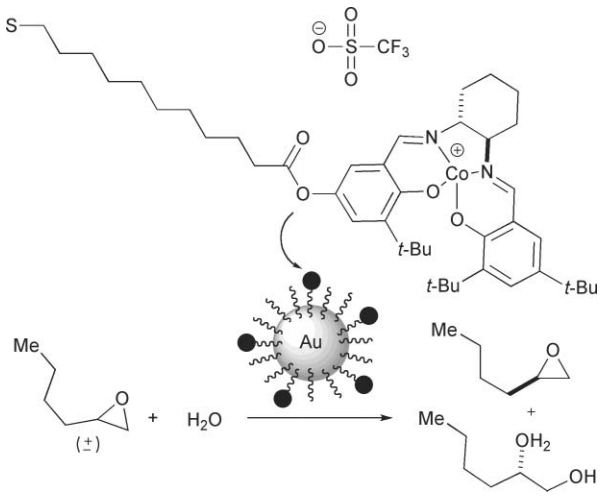
In 2006 Koskinen and Oila[21] reported the preparation of gold nanoparticles functionalized with a thiol-modified PyOX ligand (Scheme 13) and showed that the corresponding π-allylpalladium complexes were able to catalyze the allylic alkylation of 1,3-diphenylallyl acetate with dimethyl malonate under the standard conditions. Although the enantioselectivity depicted by the functional nanoparticles was not high, the gold supported ligand was found to be superior to a similar ligand immobilized onto a polymer, and only slightly inferior to a soluble derivative of the PyOX ligand.



Scheme 13 Gold NP supported PyOX.

Hydrolytic kinetic resolution of epoxides

In 2008 Belser and Jacobsen reported a highly efficient hydrolytic kinetic resolution of epoxides by chiral[(salen)Co(III)] complexes immobilized on gold nanoparticles (Scheme 14).[22] The nanoparticle-supported catalyst showed significantly higher reactivity than the homogeneous ones, while showing similarly high k_{rel} (selectivity factor) values. This turned out to be the first example of cooperative reactivity in gold nanoparticle functionalized catalysts. The catalyst maintained its high reactivity as well as excellent enantioselectivity for up to six recycles; from this point, its activity decreased significantly. It could be established that this decrease in activity was due to reduction of the Co(III) centre, and not to leaching. Thus, oxidation of the catalyst restored its initial activity.



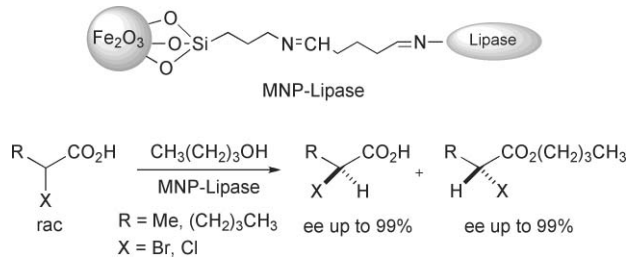
Scheme 14 Hydrolytic kinetic resolution of epoxides with functionalized gold nanoparticles.

Functional magnetic nanoparticles in asymmetric catalysis

The use of functional magnetic nanoparticles for enantioselective catalytic applications is attracting increasing interest. Given the manifold applications of these materials, there are many reliable procedures for their production and stabilization. In fact, the same methodologies that have been developed for supporting active fragments on magnetic nanoparticles for many different applications can also be used to support a catalytic ligand. The opportunity of controlling the motion of these species by application of a magnetic field is translated, in catalytic applications, into the opportunity for catalyst separation and recycling by magnetic decantation. Until now, most applications in this field have been based on readily available iron oxide nanocolloids. Other magnetic nanomaterials, such as ε-cobalt, have recently demonstrated their suitability for the same purposes.

Resolution of racemic carboxylates

In a pioneer development, Gao and co-workers reported the kinetic resolution of racemic carboxylates catalyzed by a magnetic nanoparticle-supported lipase from *Candida rugosa* (Scheme 15).[23] Following what has become an almost universal approach for the functionalization of nanoparticles made of iron oxides, highly

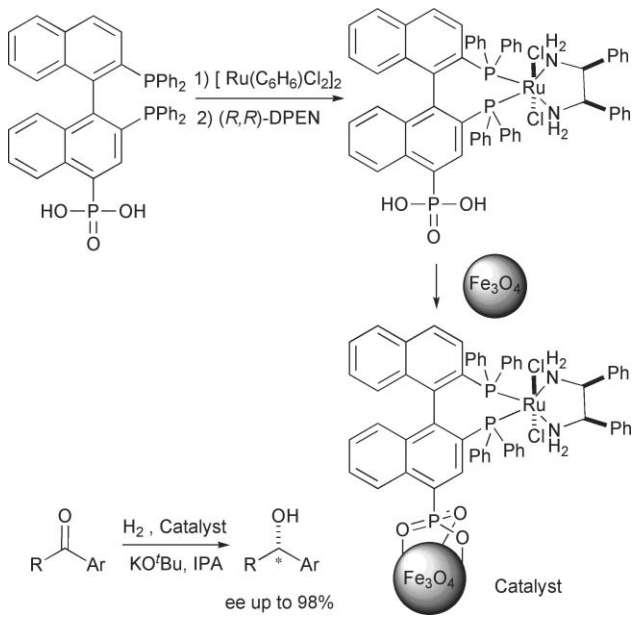


Scheme 15 Kinetic resolution of carboxylates using magnetic NP immobilized lipase.

crystalline 11 nm maghemite nanocrystals were first functionalized with 3-aminopropyltriethoxysilane. Then, glutaraldehyde was used as a linker to tether the lipase to the surface of the magnetic nanoparticles leading to an iron oxide–lipase assembly (MNP-Lipase). The MNP-Lipase biocatalyst exhibited high stereoselectivity in the kinetic resolution of racemic carboxylates and improved long-term stability over its parent free enzyme, allowing the supported enzyme to be repeatedly used for a series of chiral resolution reactions. Immobilization of the lipase onto the magnetic nanoparticle has the advantages of facile recovery and excellent stability of the expensive enzyme catalyst over several cycles.

Reduction of ketones

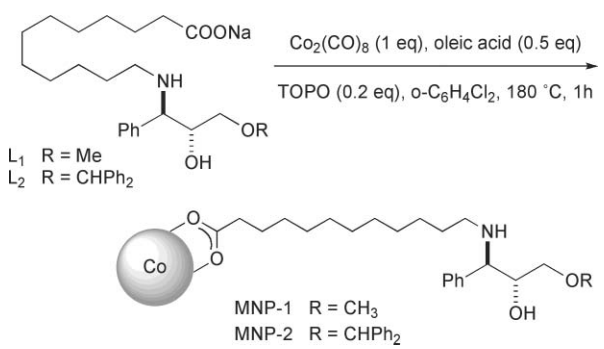
In 2005, Lin *et al.* successfully attached a phosphonic acid substituted BINAP-ruthenium complex onto magnetite (Fe_3O_4) nanoparticles prepared either by thermal decomposition (8.9 nm mean diameter) or by co-precipitation (6.6 nm mean diameter) and used the supported catalyst in the hydrogenation of aromatic ketones (Scheme 16).[24] When the catalysts involving either nanoparticle size were tested in the hydrogenation of a broad family of ketone substrates, the slightly larger magnetite particles prepared by thermal decomposition led to the



Scheme 16 Asymmetric reduction of ketones catalyzed by magnetic nanoparticle immobilized Ru-catalyst.

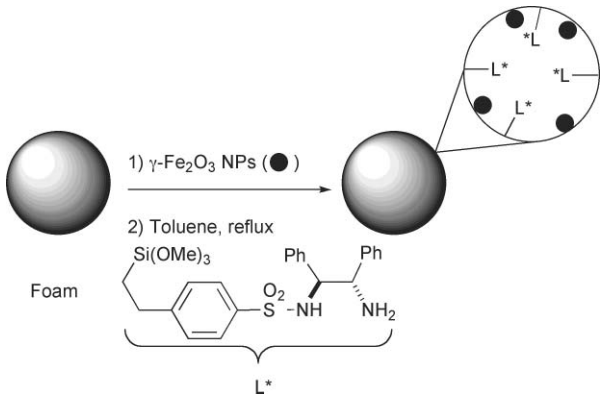
corresponding secondary alcohols with enantioselectivities higher than those recorded with the homogeneous Noyori's catalyst, Ru(BINAP)(DPEN)Cl_2. Interestingly, when the catalyst involving the smaller particles prepared by co-precipitation was recovered by magnetic decantation and reused, no decrease in catalytic activity or in enantioselectivity was observed over 14 consecutive runs. Most likely, the three-point binding provided by the phosphonic acid group plays a fundamental role in preventing leaching of the catalytic species into solution, thus contributing to the preservation of the catalytic activity. This study nicely illustrates the tremendous potential of magnetic nanoparticles in asymmetric catalysis.

Very recently, Pericàs and co-workers have reported the first application of magnetic ε-cobalt nanoparticles in asymmetric catalysis. Cobalt NPs are usually stabilized by long chain carboxylic acids (such as oleic acid). When the preparation of the particles is performed in the presence of modular, enantiopure amino alcohol ligands modified with long chain carboxylic acids, they are also incorporated at the surface (Scheme 17).[25] These nanoparticles have been then used as magnetically decantable ligands in the Ru-catalyzed asymmetric transfer hydrogenation of alkyl aryl ketones with interesting results. In contrast with what was observed with the free ligands $\mathbf{L_1}$ and $\mathbf{L_2}$, it was found that the Co NPs decorated with the less bulky ligand (**MNP-1**) induced the highest enantioselectivity in the reactions. Even more importantly, it was found that the enantioselectivities recorded with the functional nanoparticles **MNP-1**, are generally higher than those observed with structurally related, monomeric amino alcohols.[26] This fact confirms the advantages derived from supporting the ligand on nanosized particles for this particular application. The main drawback associated with this approach is the poor reusability. Thus, a significant decrease in catalytic activity was detected upon magnetic recovery and reuse appears to be subject to leaching of the carboxylate ligands. The differences in stability between nanoparticle–ligand assemblies involving three-point (Scheme 16) and two-point binding become evident from these examples.



Scheme 17 Preparation of functional ε-cobalt nanoparticles for asymmetric transfer hydrogenation of ketones.

Quite recently, magnetic γ-Fe_2O_3 nanoparticles trapped inside a siliceous mesocellular foam have been used to impart magnetic mobility to Ru-TsDPEN (TsDPEN =*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) complexes grafted on the siliceous matrix (Scheme 18) and this material has been used as a catalyst for the transfer hydrogenation of imines and ketones. Very high yields and enantioselectivities were noticed for at least nine consecutive

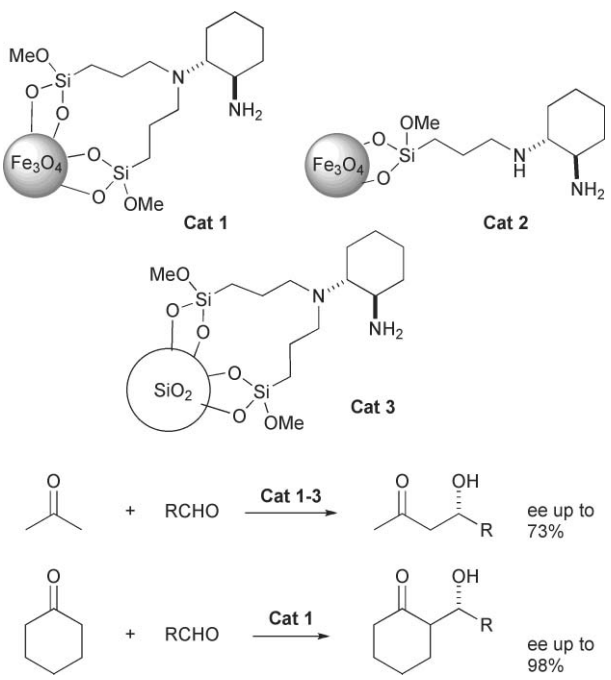


Scheme 18 Functionalization of a siliceous mesocellular foam for Ru-mediated asymmetric transfer hydrogenation.

uses of the catalyst, thus demonstrating the robustness of this approach.[27]

Aldol reaction

Late in 2008 Luo *et al.* reported an asymmetric aldol reaction catalyzed by magnetic nanoparticle supported primary amine catalysts (Scheme 19).[28] These authors have prepared several chiral amine catalysts supported on magnetic nanoparticles and silica. It was observed that the tertiary–primary amine catalyst supported on magnetic NPs (**Cat 1**) was better than the secondary–primary amine catalyst on the same support (**Cat 2**). The same tertiary–primary diamine catalyst supported on chromatographic silica (**Cat 3**) showed less activity than **Cat 1**, thus highlighting the effect of the nanometric size of the particles. The optimal catalyst (**Cat 1**) was recycled for 11 times with consistent activity and enantioselectivity. Another very interesting asymmetric aldol



Scheme 19 Chiral amines supported on magnetic nanoparticles for asymmetric, amine-catalyzed aldol reactions.

reaction was reported by Liu *et al.* using an oligopeptide supported on magnetic NPs through an ionic liquid spacer.[29]

Summary and outlook

The present literature survey illustrates the potential of functional nanoparticles in asymmetric catalysis. This field, now growing fast, still presents many areas to be explored and, overall, it holds the promise of providing the chemical community with highly active, fully recoverable and reusable catalytic systems leading to enantioselectivities similar to or even better than those depicted by comparable homogeneous systems.

As shown in this review, two completely different approaches can be followed for the development of catalytically active nanoparticles, each with its own advantages and shortcomings.

The approach where the structural material of the nanoparticles is also the catalytic material, benefits from the ready availability of the catalytically active nanoparticle–ligand assembly, but suffers from a still poor understanding of the mechanism that allows the transmission of chiral information from ligand to substrate molecules. Within this approach, the potential of magnetic decantation offered by magnetic nanoparticles remains completely unexplored when enantioselective processes are considered.

The alternative approach, where nanoparticles are simply used as structuring elements for the assembly of dendritic arrangements of ligands suffers from a higher synthetic complexity but, in turn, offers many different opportunities for control and fine-tuning.

When the structural material of the nanoparticles is considered, much effort has been put into gold, for the existence of an almost generally valid approach to the self assembly of monolayers around the particles and for readily controllable, solvent dependent dispersion/agglomeration behaviour, or on magnetic materials (mostly iron oxides) in view of magnetic decantation. Many other materials are thus still awaiting evaluation for this purpose.

With respect to the strategy for anchoring the ligand on the nanoparticle, it seems clear that either covalent grafting (via alkoxysilanes) or multipoint ionic binding are important to prevent leaching and, thus, deterioration of activity. The development of new supporting strategies characterized by robustness and flexibility will open in the near future important opportunities in this field.

The promise of high catalytic activity with functional nanoparticles due to a high concentration of active sites in the periphery of the nanoparticle plus ligand assembly, as happens with dendrimers (dendrimer effects)[30] still awaits definitive confirmation. Aspects such as functional dilution (*i. e.*; the molar ratio between ligand and stabilizing agent molecules), chain length ratio between the ligand and stabilising agent molecules, and agglomeration control still require a substantial and systematic research effort.

Finally, enantioselectivity strongly depends on ligand design. In the available examples, whenever the ligand molecules to be supported on nanoparticles have been modified in such a way that neither the linker nor the nanoparticle bulk perturbs the catalytically active site, enantioselectivities comparable to those recorded in the homogeneous phase have been achieved.

Work along the lines outlined here will lead with high probability to a new generation of highly active and enantioselective, fully

recyclable catalysts for metal-catalyzed and organo-catalyzed reactions.

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