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Magnetic Nanoparticle Supports for Asymmetric Catalysts

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The introduction of magnetic nanoparticles (MNPs) had favoured the recovery of the catalysts with techniques for magnetic separation. Moreover, the small size of these functionalized particles becomes a well-designed way to bridge the gap between heterogeneous and homogeneous catalysis. Magnetite can be used as a support for catalytically active metals, decorated with ligands for metal complexes or with organocatalysts, which can be employed in green chemistry and pharmaceutically significant reactions, In particular, asymmetric metal complexes and enantiopure organocatalysts can lead to enantioenriched products and these reactions are summarized in this review.

1. Introduction

The development of green, sustainable, and economical chemical processes is one of the major challenges in chemistry. Besides the traditional need for efficient and selective catalytic reactions that transform raw materials into valuable chemicals, pharmaceuticals and fuels, green chemistry also strives for waste reduction, atomic efficiency, and high rates of catalyst recovery.[1-5]

For long time and even now, in the laboratory scale, chemists generally accept a homogeneous catalyst. In fact, all catalytic sites are accessible because of its solubility in the reaction medium, allowing fine-tuning of the chemo-, regio- and enantioselectivity of the catalyst. When they are used in commercial applications, the difficulty of catalyst separation from the final product creates economic and environmental barriers to broadening their scope. In fact, each separation method has its own limitations of cost, efficiency, or generation of secondary waste.

Nowadays, asymmetric organocatalysis has seen a tremendous rise in popularity.[6-12] The use of purely organic molecules as chiral catalysts offers some attractive benefits: the organic catalysts are generally readily available, and stable, therefore with simple handling and storage, so allowing most reactions to be performed in non-inert reaction conditions such as wet solvent and in air. However, often, the separation and recycling of organocatalysts are problematic due to the difficulty in the recovery of catalysts from the reaction.[4, 13, 14]

Due to these issues, heterogenization of homogeneous catalysts on solid supports has received significant attention.[15, 16] Typical catalyst supports include polymers, carbon, silica, alumina, and other metal oxides that can be separated by conventional separation techniques such as filtration and centrifugation. These heterogeneous supports are high-surface area solids onto which an active component is dispersed or attached, taking care that most of active sites on solid supports are accessible for reaction, thus allowing rates and selectivities comparable to those obtained with homogeneous catalysts. Nevertheless, fewer sites on the surface are available for catalysis; less reactive and selective is the catalytic system. In addition, sometimes the support itself can act as the catalyst of side reactions or, in the asymmetric synthesis, of the background racemic reaction.

In heterogeneous catalysis, covalent anchoring is preferred over simple adsorption as it is robust enough to withstand the reaction conditions and the catalyst can be reused several times. However, also these catalysts have drawbacks. For instance, polymer supported catalysts often have complicated preparation of monomeric ligands and individual fabrication of heterogeneous polymers. Moreover, when catalysts are metal complexes, the ligands can be covalently anchored, but only coordination bonds link the metal ion. Thus, the leaching of the active metal from solid supports because of the breaking of bonds between the metal and the ligand during catalytic reactions is another problem. In fact, in the absence of metal ion, the catalyst is ineffective, while removal of the trace metal contamination from the product remains a challenge, even with the extensive and careful use of the various separation techniques, and this removal is essential, especially in the pharmaceutical industry, which has strict regulations. Furthermore, most of the metal catalysts are traditionally associated with strictly anhydrous conditions, being generally water-unstable, forcing the use of environmentally non-benign solvents. On the other hand, covalently bonded organocatalysts can be never leached during reaction workup.

Magnetic techniques are an inherent part of numerous material treatment operations and they have undergone dramatic developments over the last 30 years.[17] In particular, magnetic nanoparticles (MNPs) have attracted attention as catalyst supports. In fact, owing to their nano nature and high surface

area, supported catalyst acts in a quasi-homogeneous manner, providing a bridge between the homogeneous and heterogeneous phases and combining the advantages of both phases. MNP-supported catalysts have all catalytic sites accessible like homogenous ones, thus allowing low loadings and fine-tuning of the chemo-, regio- and enantioselectivity. Moreover, the magnetic nature of the support avoids the need to separate the catalyst by extraction (homogeneous catalysts) centrifugation or tedious filtration (heterogeneous catalysts) and the chance of covalent binding of the catalysts on the surface of the MNP strongly reduces its dispersion, leading to products with high purity. Thus, MNPs as support for catalyst in organic reactions have many advantages over other techniques, assuming a pivotal role in green and sustainable chemistry, becoming a subject of intense investigation in organic synthesis.[18-23]. In fact, (i) the stability of catalyst linkages allows the use of environmentally more benign solvents than homogeneous catalysis; (ii) simple separation using an external magnet reduces waste and purification steps; (iii) MNPs are non-toxic, highly recyclable, and reusable; (iv) magnetic separation reduces the costs of production.

Discussion on the synthesis, protection, and functionalization of magnetic nano-materials is beyond the scope of this review, but several protocols have been reported in the literature for preparing a wide variety of catalytic magnetic materials and recently reviewed.[24-26] In the catalysis arena, a sustained effort has been made to develop eco-friendly strategies to generate these nanomaterials via pathways that use benign reagents.[27]

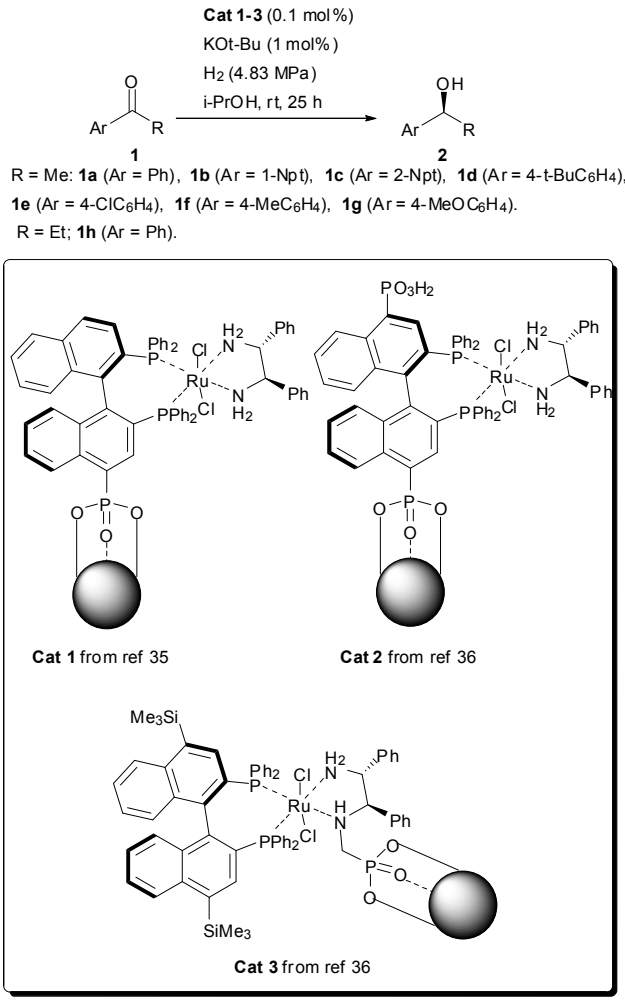
Recently, several reports have shown that many reactions can be conducted by using immobilized MNP catalytic systems,[27-33] with the advantages of the heterogeneous catalysts mentioned above and applicable in asymmetric synthesis, by the use of chiral-ligand-modified or organocatalyst-bonded MNPs as asymmetric catalysts. However, these papers mention asymmetric reaction together many others, so a critical review focused on this topic is still lacking. Only two perspectives in 2009[34] and 2011[35] described the potential application of MNPs in asymmetric catalysis, but, at that time, this research field was young and emerging. This review has the aim to highlight the potential and greenness of these reactions from then to the end of 2014.‡

2. Metal complexes supported on MNPs for asymmetric catalysis

Asymmetric metal complexes supported on MNPs represented a useful tool for the synthesis of enantioenriched products. In most of the reactions decribed in this section, a synergism between the magnetic support and the metal complex is evident. In fact, the modification of the chiral ligand in order to bind it to the magnetic support actes also as stabilizer against leaching minimizing deterioration, preventing sintering and agglomeration, and permitting efficient catalyst recycling. The more this synergism works the more the catalyst can be recycled. However, a rationale for this is not reported.

In the first paper of Lin and co-workers,[36] the catalyst (**Cat 1,** Scheme 1) was anchored to the magnetic core by the help of a phosphonate group. However, authors observed that, in homogeneous phase, enantioselectivity could be greatly enhanced introducing two bulky groups onto the 4,4'-positions of (*R*)-BINAP, thus they introduced the substituents in both positions (**Cat 2**) in order to improve the enantioselectivity.[37] Actually, enantioselectivity increased to 91-98% ee from 71-97% ee with more than 99% of conversion. The catalyst was separated by simple magnetic decantation, recycled, and reused 9 times before observing a decrease of the activity, due to an estimated <2% leaching of ruthenium atoms. Unfortunately, the catalyst cannot be stored because aggregates upon storage owing to the ability of the second phosphonic acid substituent to bind to other MNPs.

To overcome this drawback, **Cat 3** was prepared by linking MNPs through the (*R,R*)-DPEN moiety and inserting (*R*)-4,4'-$(TMS)_2$-BINAP. However, freshly prepared catalyst gave products in comparable enantioselectivity (91-99% ee), but the catalyst did not survive the reaction: conversion decreased to 60% in the second run and there was no conversion at all in the third run. Authors found with targeted experiments that the Ru(II) intermediate for preparation of **Cat 3** was less tolerant of oxidants than the corresponding Ru(II) complex for **Cat 2**, thus much of it is oxidized by Fe(III) on the surface of the MNPs before the formation of the complex with surface-bound DPEN.



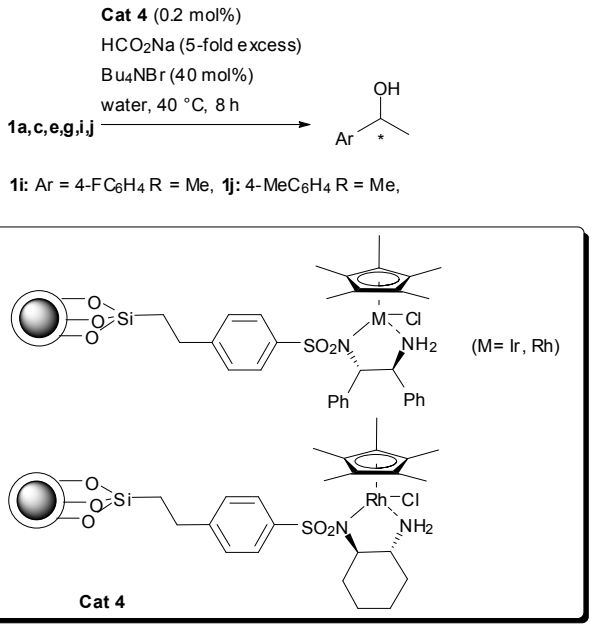
Scheme 1 Asymmetric reduction of aromatic ketones[36,37]

However, in many reactions, the closeness of the catalyst and the MNP surface was demonstrated detrimental to activity and selectivity, thus surface capping methods were introduced. For instance, silanes are frequently used to coat the surface of MNPs

because of the strong affinity of iron oxide towards silica.

Liu and co-workers[38, 39] reported a convenient method for preparing three magnetic catalysts, (Scheme 2), through direct complexation of $[Cp^*IrCl_2]_2$ or $[Cp^*RhCl_2]_2$ with (*S,S*)-TsDPEN and $[Cp^*RhCl_2]_2$ with (*R,R*)-TsDACH modified SiO_2-coated Fe_3O_4 nanoparticles. All synthesized catalysts exhibited excellent catalytic activity (conversion from 98% to almost quantitative) and enantioselectivity (79-88% ee) in the asymmetric transfer hydrogenation of aromatic ketones in water. These properties are comparable to those of their homogeneous counterparts. All catalysts can be quantitatively recovered by using a small magnet and then reused for 10 runs without affecting enantioselectivity, thus showing very low leaching of the metal ion. Moreover, the greeness of the process is enhanced by production of hydrogen by *in situ* decomposition of sodium formate, avoiding the use of dangerous hydrogen gas. [Cp*Ir(*S,S*)-TsDPEN] produced the lowest enantioselectivities. As expected the (*S,S*)-configured catalyst offered, in comparable ee values, the product with opposite configuration with respect to the (*R,R*)-catalyst.

Very recently, the same research group prepared the same Rh-catalyst from hydrophobic phenylene coated Fe_3O_4 nanoparticles.[40] The significant advantages of this phenylene-coated Rh-functionalized MNP with respect to SiO_2-coated are: significant reduction of reaction times (0.5-5 h *vs* 8 h), lower catalyst loading (1 vs 2 mol%), no need of phase transfer catalyst, conversions always almost quantitative and higher ee range (86-96%, *R*-isomer).



Scheme 2 Asymmetric reduction of aromatic ketones[38, 39]

It is worth noting that authors always mentioned (*S,S*)- TsDPEN in all the papers,[38-40] but they represent it as the (*R,R*)-isomer. Thus, configuration depicted in scheme 2 is opposite to that reported by Liu, since I assumed correct the text and not the schemes. On the other hand, I considered correct the match between configuration and chiral HPLC peaks reported in supporting information.

The reduction of ketones to secondary alcohols was also performed with other MNPs, namely $CuFe_2O_4$ (12 wt.% loading amount) supported on mesoporous silica catalyst KIT-6.[41] A simple pre-drying treatment at 100 °C avoid the CuO/Fe_2O_3 phase separation, thus inhibiting the aggregation of $CuFe_2O_4$ nanoparticles and leading to the formation of well-dispersed nanoparticles. These MNPs (2 mol%) with (*S*)-Xyl-Phos ligand (0.5 mol%, Fig. 1 left) catalysed asymmetric reduction of acetophenone to (*S*)-1-phenylethanol in 93% yield with 93% ee after 14 h in air at room temperature with 4 equivalent of polymethylhydrosiloxane as the reductant and *t*-BuONa/*t*-BuOH as the additives.

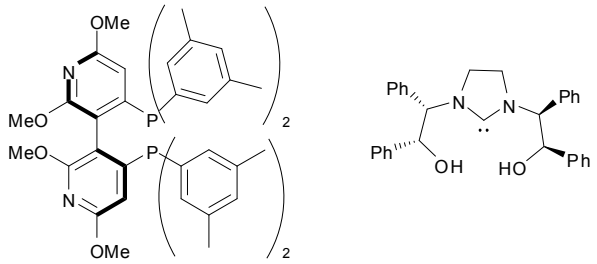


Fig. 1 (*S*)-Xyl-Phos for reduction of aryl ketones (left)[41] and *N*-heterocyclic carbene for asymmetric α-arylation (right)[42]

Later the same authors enlarged the synthetic utility of these MNPs to a wide range of prochiral ketones. The corresponding alcohols **2** were produced in 60-98% yields with 58-97% ee [26 examples, generally (*S*)-**2**].[43] It should be noted that β-chloropropiophenone led to (*R*)-**2**, but authors did not explain this different stereochemical outcome. Cyclohexylarylketones led to the (-)-isomer, but authors did not associate the absolute configuration. It is also worth noting that the enantioselectivity of the reaction under nitrogen was lower than that obtainable in air (86 vs 91% ee for acetophenone). Authors surmised that air could play a role in the formation of the active catalyst precursor in the catalytic cycle. The $CuFe_2O_4$@KIT-6 catalyst was recycled for reuse four times without losing both the activity and selectivity.

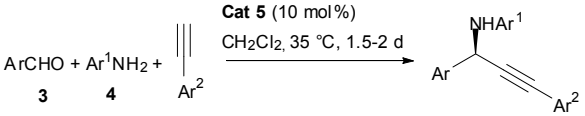
Very recently, a chiral-modified Ni catalyst was supported on reduced graphene oxide and employed for asymmetric hydrogenation of methylacetoacetate. Both enantiomers (98.5% ee) can be produced, modifying the catalyst with the two enantiomeric tartaric acids. [44] The catalyst can be recycled by easy magnetic separation and reused within four consecutive cycles, before observing a significant leaching of tartaric acid, with detriment of enantioselectivity.

Li and co-workers explored the asymmetric three-component aldehyde-alkyne-amine coupling by a magnetite supported copper(I)pybox catalyst. Propargylamines were recovered in 80-94% yield and 84-92% ee (Scheme 3).[45]

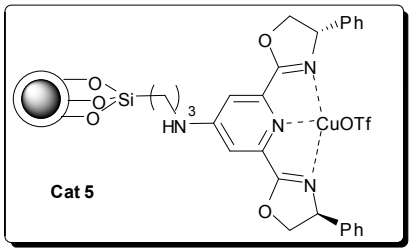
The catalyst was reused in six cycles before leaching of copper ion becomes significant, decreasing activity and enantioselectivity. Unfortunately, the catalyst recovering and storage has to be made under argon to avoid complex decomposition.

The Glorious' group try to develop a combination of Fe_3O_4/Pd and quinine as a chiral heterogeneous Pd catalyst system for the asymmetric α-arylation reaction of tetralone with iodobenzene (Scheme 4).[46] Actually, the (*S*)-product was obtained in 74% yield and 82% ee, but control experiments revealed that the

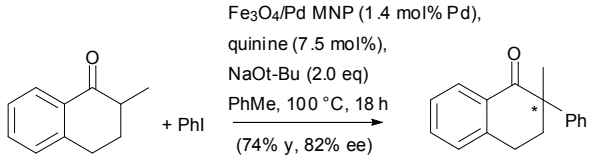
catalytically active species is homogeneous quinine, because the activity of the catalytic system was not affected by the removal of the nanoparticles by filtration during the reaction and the activity of recovered nanoparticles was extremely low. Therefore, this catalyst cannot be counted among MNP-supported ones.



3a Ar = Ph, **3b:** Ar = 4-BrC_6H_4, **3c:** Ar = 4-ClC_6H_4, **3d:** Ar = 4-$CF_3C_6H_4$,
4a: Ar^1 = Ph, **4b:** Ar^1 = 4-BrC_6H_4 Ar^2 = Ph, 4-MeC_6H_4



Scheme 3 Addition of terminal alkynes to imines[45]

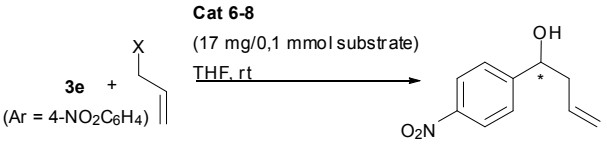


Scheme 4 Attempted enantioselective α-arylation of cyclic ketones[46]

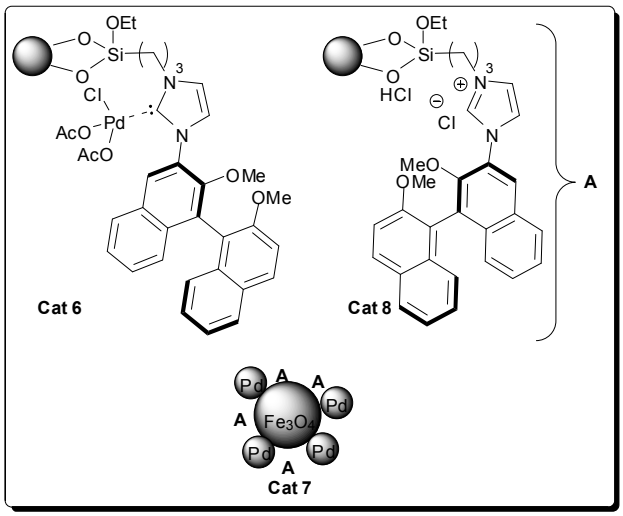
The same research group achieved greater success modifying the surface of Fe_3O_4/Pd MNPs with chiral *N*-heterocyclic carbenes (Fig. 1 right).[42] Although the preparation was identical to that described with quinine (*i.e.* by *in situ* mixing the MNPs with NHCs), this catalyst was heterogeneous in nature. In fact, removal of MNPs during the reaction or poisoning with mercury affected the reactivity. The catalyst can be recycled five times without significant decrease in yield and selectivity (only a negligible leaching of Pd was observed). With 2.5 mol% of NHC ligand loading and under similar conditions to that reported in scheme 4, the α-arylation reaction of methyltetralone and methylindanone with various aryl halides was achieved in 56-91% yields (11 examples) and 33-85% ee. Only optical rotations of products are given in supporting information [(+)-tetralone and (-)-indanone isomers)], but, from reported α_D comparison, the absolute configuration of the products is clearly opposite to that reported for Fe_3O_4/Pd and quinine, therefore the major product of this reaction has (*R*) absolute configuration.

More recently Gloriuos and co-workers prepared three new catalysts, all based on the same axially chiral imidazolium salt immobilized on Fe_3O_4 in different manners (**Cat 6**, **Cat 7** and **Cat 8**, Scheme 5).[47] Each of these catalysts was effective in the enantioselective allylation of 4-nitrobenzaldehyde. Some interesting features were found in this reaction. Firstly, the reaction is restricted to 4-nitrobenzaldehyde, no other aldehyde gave the allylated product. Then, facile recovery of **Cat 6** and **Cat 7** was achieved by using a simple magnetic decantation, whereas, surprisingly, **Cat 8** could not be recovered by magnetic decantation, because the material loses its magnetic properties. **Cat 6** and **Cat 7** can be recycled three times, but a decrease in both activity and selectivity was observed, sharper for **Cat 6**. Surprisingly, with **Cat 7**, the product was obtained with the opposite absolute configuration than the one formed with the other two catalysts, but no explanation is given by authors, except a tilted structure, reproduced in Scheme 5 as **A**, suggesting a different chiral pocket in this catalyst, but the same steric arrangement is present also in **Cat 8**. Finally, **Cat 8** works in the presence of only trimethylallylsilane and a base: DBU (3.0 equiv) giving the best result.

Asymmetric multicomponent catalysts consist of two or more chiral ligands and/or metals in synergistic cooperation, but often the distinct organometallic complexes have intrinsic incompatibility. Immobilization of asymmetric multicomponent catalysts on solid supports may help to keep most multicomponent complexes in their active forms by carefully fixing the chiral ligands and/or metals in proper positions.



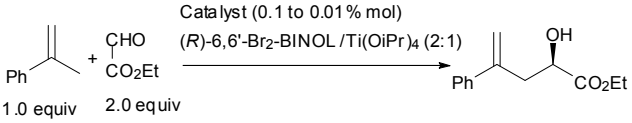
Cat 6 54% y, 43% ee (*R*) X=$SnBu_3$
Cat 7 82% y, 64% ee (*S*) X=$SnBu_3$
Cat 8 68% y, 74% ee (*R*) X=$SiMe_3$



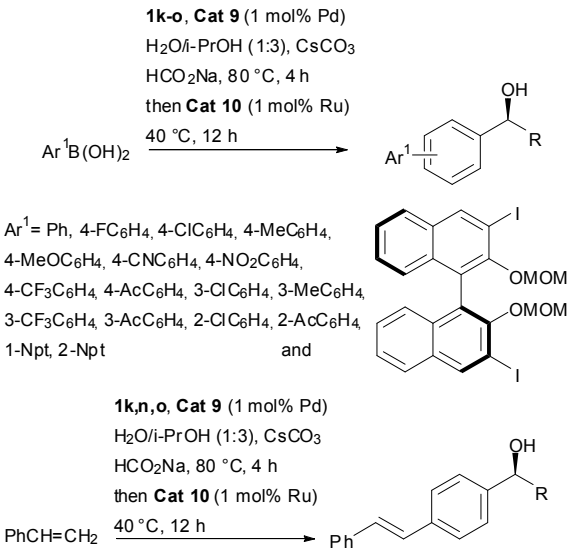
Scheme 5 Fe_3O_4-Supported NHC-based catalysts for enantioselective allylation[47]

Two examples of this strategy are reported with MNPs. The first instance refers to a BINOLate/titanium catalyst, which Yang and co-workers successfully encapsulated in the nano-cages of magnetic mesoporous silica.[48] The enantioselective carbonyl-ene reaction was tested as the model reaction for this catalyst (Scheme 6). The best conditions were obtained with 2:1 molar ratio between BINOL and $Ti(OiPr)_4$ under quasi solvent-free conditions and product was recovered in 95% yield with 92% ee. After the reaction was complete, the solid catalyst was recovered easily from the reaction system through magnet and the separated solid was used for three cycles. However, longer time was needed to obtain higher yield and the enantioselectivity dropped to

86.4%. It is worth noting that this is a new and quite different MNPs with respect to the others described in this review. In fact, the catalyst is neither directly anchored on MNPs nor covalently bound to capped MNPs, but trapped into nano-cages working as nano-reactors.[49]



Scheme 6 Enantioselective carbonyl-ene reaction with BINOLate/titanium catalyst[48]

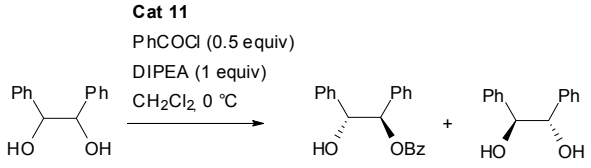


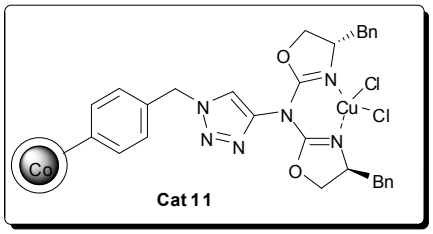
Scheme 7 Double catalysis in multi-component reactions[50]

Another interesting feature of this reaction is that authors consider nanocages as a multicomponent catalyst, although apparently it is not. The fact, that only 2:1 molar ratio between BINOL and $Ti(OiPr)_4$ is effective, suggests that aggregates or oligomeric species existing in the nano-reactor are not able to equilibrate, working as different catalysts. Thus, this nano-reactor is much higher active than the corresponding homogenous catalyst. In fact, in the homogeneous phase, different kinds of species fast equilibrating with each other were found to co-exist during the catalytic process.

The second reported instance refers to the use of an imidazolium-palladium complex linked on silica (**Cat 9**) and ethylene-coated chiral organoruthenium-functionalized magnetic nanoparticles (**Cat 10**). This couple of catalysts allows a cascade Suzuki cross-coupling–asymmetric transfer hydrogenation (Scheme 7).[50] Chiral biaryl alcohols were obtained in >99% conversion with 96-99% ee (*S*-isomer) and 1:1 to 24:1 dr when two asymmetric centres are formed (e.g. (1,1'-biphenyl-n,n'diyl)diethanoles). Upon completion of the reaction, MNP ruthenium catalyst was separated from the reaction mixture using an external magnet, while NCH-silica catalyst is recovered by centrifugation. The catalysts were reused over nine consecutive reactions without affecting yield and selectivity.

Finally, a particular application of MNPs should be mentioned. In all the examples reported above, the use of MNPs is devoted to an easy separation of the catalyst from the reaction mixture. Reiser group surmised that MNPs could be employed as the catalytic bed in a continuous-flow reactor and agitation of the nano-magnets in a rotating external magnetic field might have beneficial influence on the fluid dynamics and surface area within the reactor.[51] Actually, continuous flow chemistry has had positive impact on other chemical processes involving MNPs.[25, 52] Thus, they tested this idea on the kinetic resolution of 1,2-diphenylethane-1,2-diol (Scheme 8), already setup in 2009 by this research group with magnetite@silica tagged with azabis(oxazoline)-copper(II) complexes.[53] Unfortunately, even a flow of 0.2 mL/min was found to leach the supported catalyst, so this catalyst is ineligible for such a continuous-flow apparatus. On the other hand, a carbon coated cobalt nanoparticle tagged with the copper catalyst was efficient in this reaction, owing to its higher ferromagnetism. In fact, the cobalt core facilitates the recycling of the catalyst via magnetic decantation in the batch reactions and enables the continuous-flow reactor. The efficiency of the reaction was 43-49 % yield for the (*R,R*)-mono-benzoylated product with 96-99% ee over 5 cycles in the batch reaction with 1 mol% catalyst loading, and 43% yield with 99% ee in the continuous-flow apparatus at a flow of 0.2 mL/min charged with 5 mol% of catalyst.





Scheme 8 Kinetic resolution of 1,2-diphenylethane-1,2-diol[51]

3. Organocatalysts supported on MNPs

Asymmetric organocatalysis has seen a tremendous rise in popularity because the use of purely organic molecules as chiral catalysts fills a gap between metal- and enzyme-catalysis complementing these approaches to asymmetric catalysis. Chiral organocatalysts do not need strictly anhydrous or inert conditions as metal catalyzed asymmetric transformations and the catalyst cannot leach.[54]

Amino acids and their derivatives are typical organocatalysts for asymmetric syntheses. Surprisingly, the majority of amino acid functionalized MNP did not meet this issue or information was not given if the reactions were enantioselective or not (more likely). We report in this section the most recent applications in asymmetric synthesis and only some representative instances of non-asymmetric use.

There is a tentative study concerning the immobilization onto magnetic nanoparticles of three useful classes of chiral organocatalyst (Figure 2).[55] In this study, Connon and co-workers found that nanoparticles cannot be *a priori* considered inert in all catalytic processes and the structure of the immobilized catalyst plays a pivotal role in the success of the reaction to be catalyzed.

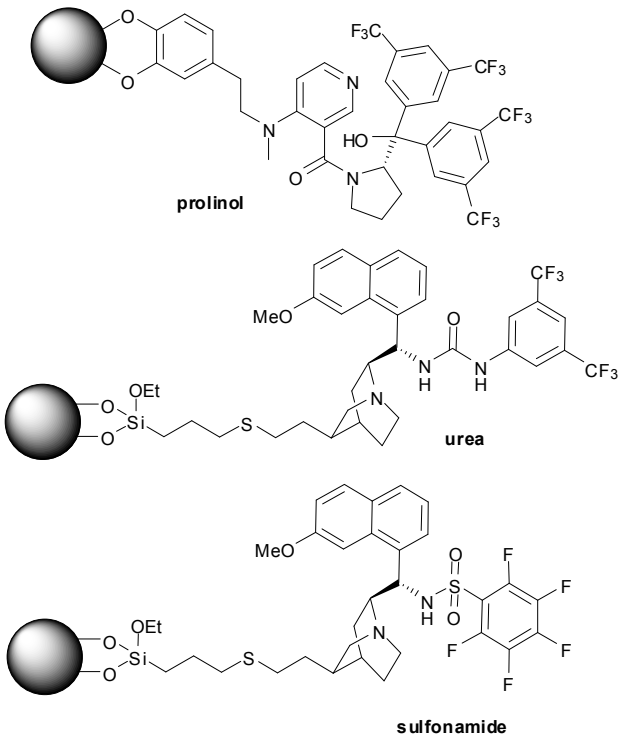


Fig.2 Chiral organocatalysts supported on magnetic nanoparticles studied by Connon's group[55]

In fact, the chiral prolinol derivative gave a highly active heterogeneous catalyst, capable of promoting the kinetic resolution of *sec*-alcohols for 32 cycles without significant loss of yield and selectivity (run 1: 72% y, 99% ee; run 32: 64% y, 93% ee). In sharp contrast, urea catalyst demonstrated a marked drop in catalyst efficacy after immobilization and the catalyst was efficient only for 3 cycles in the Michael addition of malonate to nitrostyrene. Authors found evidence that the origin of the poor selectivity results from background catalysis by the particles themselves, while the instability was ascribed to a design limitation rather than mishandling during experimentation. The sulfonamide catalyst showed intermediate features. In fact, the catalyst promoted the asymmetric addition of alcohols to *meso*-anhydrides for 20 cycles without significant loss of yield and selectivity (run 1: 100% y, 80% ee; run 20: 97% y, 77% ee), but enantiomeric excess using the immobilized catalyst is consistently lower (ca. 80% vs 97% ee) than that obtained using the corresponding homogeneous catalyst. Again, MNPs catalyzed background reaction.

3.1. Asymmetric syntheses

Jørgensen–Hayashi catalysts [(*S*)-α,α-diarylprolinoltrimethylsilyl ethers] are one of the most powerful classes of organocatalysts. This catalyst can be fixed on MNPs via either the phenyl or the pyrrolidine moiety. The Michael addition of several aldehydes to nitroalkenes was performed with Jørgensen–Hayashi catalyst linked to silica coated MNPs by the phenyl moiety (Scheme 9, **JHC 1**).[56] Products were recovered in 53-96% yields with 3:1 to >99:1 dr and 75-90% ee [(***2R,3S)*-7**].

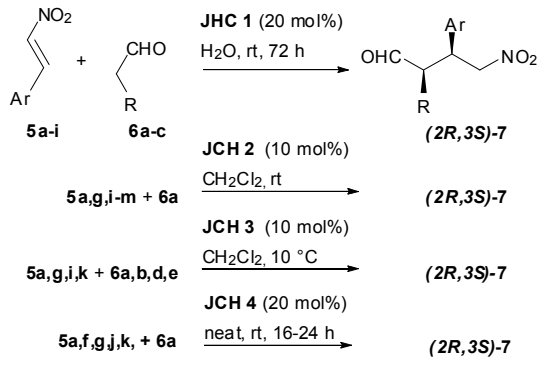
In another approach, Pericàs and co-workers prepared compounds **(*2R,3S)*-7** in 70-89% yields with 3:1 to 8:1 dr and 75-97% ee (Scheme 9, **JHC 2**).[57] The most relevant features with respect to Wang's procedure are the anchoring of the catalyst with the pyrrolidine moiety to the uncoated MNPs, the well-defined nanoparticles size, and lesser amounts (10 mol% versus 20 mol%, respectively). In both reactions, recycling via magnetic separation was possible for four times without significant loss of selectivity but with decrease of product yield (from 80 to 42% and from 89 to 57%, respectively). Pericàs believed that the drop was caused by hydrolytic loss of the silyl group attached to the catalytic moiety and, although not reported, the same explanation could be given for the Wang's procedure.

Other features of the Pericàs reaction should be outlined. All substrates need different reaction times. Higher product yields and enantioselectivity were observed with toluene as the solvent, but the rate of the reaction was very slow, use of water as a solvent did not improve the reactions, because of the poor dispersion of these MNPs in it. Michael addition of acetaldehyde to nitrostyrene gave rise to a racemic mixture of products.

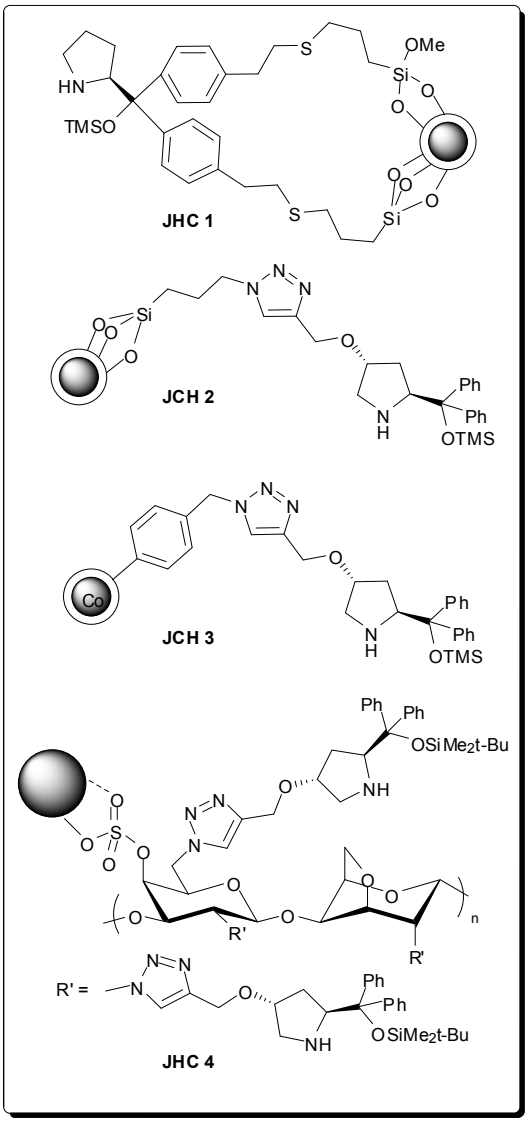
Also carbon-coated cobalt MNPs were used as supports for a Jørgensen–Hayashi-type catalyst (Scheme 9, **JHC 3**).[58] Reaction conditions are very similar to those used by Pericàs (only lower temperature 10 °C vs rt) and **(*2R,3S)*-7** were recovered in 96-99% yields (except for heptanal in which product yield was only 42%), with 3.5:1 to 11.5:1 dr and 93-99% ee. Thus, this reaction appears the most performing reaction among the three. Once again, the yield dropped from 99% to 34% already in the fourth recycling run.

Finally, a diphenylprolinolsilyl ether linked to a κ-carrageenan coated MNP was found to promote the reaction, giving rise to **(*2R,3S*)-7** in 57-83% yields, with 2:3 to 9:1 dr and 86-93% ee (Scheme 9, **JHC 4**).[59] Authors noted a synergistic effect between the MNPs and κ-carrageenan, since both simple MNP and a κ-carrageenan were unable to give the reaction. Moreover, although κ-carrageenan coated MNP provides a chiral environment for the reaction, no enantioselectivity was observed when JHC is not grafted. No information is given about how many cycles the

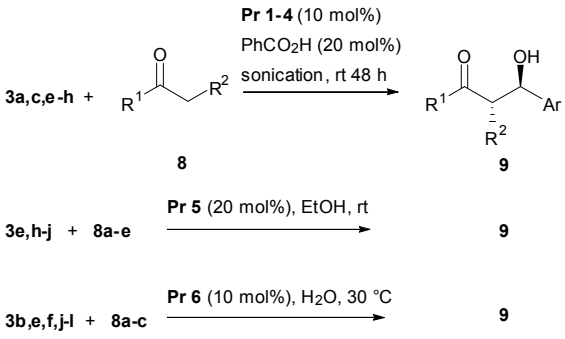
catalyst can do before losing selectivity.



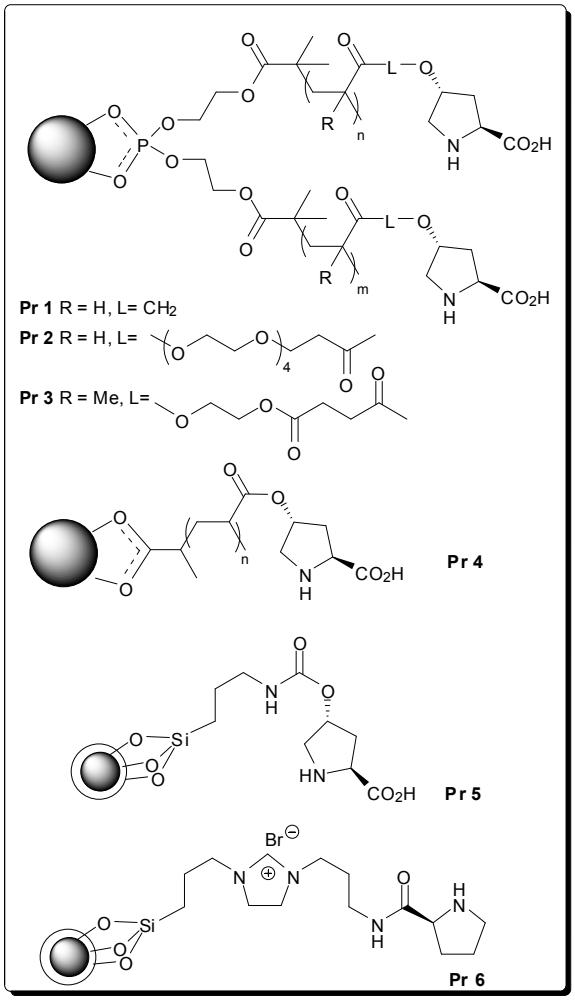
5a: Ar = Ph, **5b:** Ar = 2-$NO_2C_6H_4$, **5c:** Ar = 2-ClC_6H_4, **5d:** Ar = 2-BrC_6H_4, **5e:** Ar = 3-MeC_6H_4, **5f:** Ar = 4-ClC_6H_4, **5g:** Ar = 4-$MeOC_6H_4$, **5h:** Ar = 1-Npt, **5i:** Ar = 2-furyl, **5j:** Ar = 4-MeC_6H_4, **5k:** Ar = 4-BrC_6H_4, **5l:** Ar = 2-$MeOC_6H_4$, **5m:** Ar = 2,3-$(OCH_2O)C_6H_3$.
6a: R = Me, **6b:** R = Pr, **6c:** R = CH_2=$CH(CH_2)_7$, **6d:** R = Et, **6e:** R = n-C_5H_{11}



Scheme 9 Asymmetric Michael additions from ref [56-59]



3f: Ar = 4-$MeOC_6H_4$, **3g:** Ar = 4-FC_6H_4, **3h:** Ar = 3-$NO_2C_6H_4$, **3i:** Ar = 4-CNC_6H_4, **3j:** Ar = 2-$NO_2C_6H_4$, **3k;** Ar = 2-ClC_6H_4, **3l;** Ar = 2-Npt
8a: R^1 = Me, R^2=H, **8b:** R^1-R^2 = $(CH_2)_4$, **8c:** R^1-R^2 =$(CH_2)_3$, **8d:** R^1-R^2 = $(CH_2)_5$, **8e:** R^1-R^2 = $(CH_2)_6$



Scheme 10 Proline functionalized MNPs for asymmetric aldol reactions from ref [61-63]

(*S*)-Proline itself was conjugated with MNPs as asymmetric catalyst especially for aldol reaction. For instance, proline-based MNPs were obtained by absorption of (*S*)-proline on MNPs trapped into a cross-linked polymer from bis-vinylimidazolium salts. The resulting material (30 mol% (*S*)-proline) catalysed the reaction of acetone with 4-nitrobenzaldehyde at room temperature

for 3.5 h affording the aldol product in 90% yield and 69% ee (*R*-isomer).[60] The reuse of the supported proline was investigated and, in the fourth cycle, a decrease in yield was observed, probably due to leaching of proline.

Better results can be obtained by linking proline to the MNP both from the 4-ring position and from the carboxylic moiety. Some acrylate and methacrylate monomers containing the (*2S,4R*)-4-hydoxyproline moiety were submitted to polymerization reactions in the presence of MNP covered with acrylic acid or a methacryloyl-containing phosphate (Scheme 10).[61]

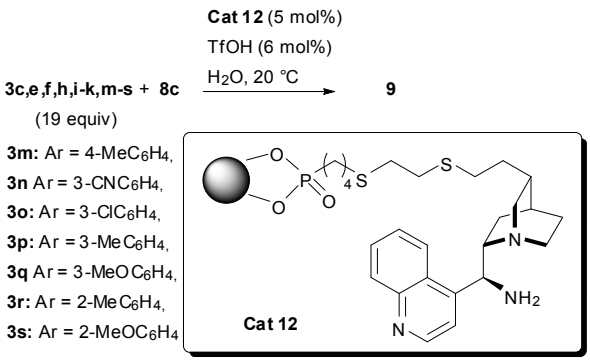
These catalysts efficiently catalysed the asymmetric aldol reactions of aryl aldehydes with ketones used also as the solvent (10 mol% loading, 66-94% yield, 88-99 % ee), but with low diastereoselectivity (1.2:1 to 3.5:1). However, this is the most efficient aldol reaction catalysed by MNPs-proline reported until now in the literature (compare yields and ee with the following reactions). Sonication and addition of benzoic acid (but not other acids) were crucial in order to achieve good results. However, authors did not explain if the benzoic acid has specific interactions with the aromatic aldehydes and/or the organic shell of the nanoparticles. The catalyst can easily be separated by magnetic decantation, recycled, and reapplied in further aldol reactions up to 10 times.

4-Hydroxyproline was also attached to silica coated MNPs by a triethoxysilylpropanecarbamate (Scheme 10, **Pr 5**).[62] Aldehydes carrying strong electron withdrawing groups such as nitro or cyano group were good substrates for the aldol reaction, but steric effects on the aldehyde decrease enantioselectivity and the increase of the carbon numbers onto the cyclic ketone drops the yields. (24-96% yields, 6-99% ee). It should be noted that diastereoselectivity does not follow a clear trend and sometimes ***anti*-9** is the major stereoisomer, other times the ***syn*-9** prevails. Moreover, the efficiency of this reaction was not as good as in cases of the polymer coated MNP mentioned above,[61] even when 20 mol% catalyst was used instead of 10 mol%.

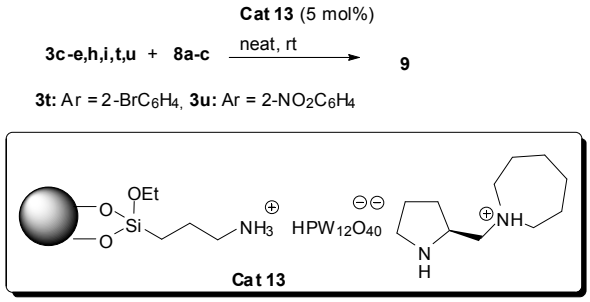
(*S*)-Proline was also linked to silica coated MNP via the carboxyl group by an amide bond (Scheme 10, **Pr 6**).[63] In analogy with Grattadauria's reaction[60] a ionic liquid is used to disperse proline on the MNPs, but here the aminoacid is grafted to the nanoparticle and leaching of proline is avoided. Products **9** were obtained in 30-96% yields, 45-85% ee. Once more, the lowest yields and enantioselectivities were observed with sterically hindered aldehydes. With cyclohexanone, ***anti*-9** is recovered in 3:1 to 99:1 dr, whereas the only instance with cyclopentanone gave ***syn*-9** in 2:1 dr. The advantage of this catalyst resides in its efficiency in bulk water as the solvent. Finally, recycling for five runs revealed that the yield slightly diminished from initially 92% to 89% while the ee remained constant.

The synthesis of proline catalysts linked to MNP via the carboxyl group requires protection of proline nitrogen: for instance, Boc-proline was employed in the preparation of **Pr 6**. Guénin and co-workers bound Boc and Fmoc protected proline to MNPs. (4-Amino-1-hydroxybutylidene)bisphosphonic acid was able to provide phosphoric groups to graft γ-Fe_2O_3 and an NH_2 moiety to link proline derivatives through peptide formation.[64] Fmoc deprotection led to the desired products, conversely from Boc deprotection. Moreover, the use of Fmoc protection allowed quantifying the number of grafted proline onto the MNPs by UV measurement. However, authors postpone the evaluation of the catalytic efficiency of this new nano-organocatalyst toward enantioselective reactions to a further publication, which is not appeared yet in the literature.

Besides proline derivatives, also a magnetically recoverable 9-amino-9-deoxy-epicinchonidine organocatalyst was tested in the aldol condensation reaction. The catalyst was prepared using phosphonic acid as the anchor point (Scheme 11).[65] Only cyclohexanone was used as the ketone partner, but, differently from examples reported above, the reaction worked also with aromatic aldehydes with strong electron-donating substituents, although in lower yields and selectivity (electron-withdrawing substituents: 86-100% yields, *anti/syn* 4.5:1 to 49:1, 93-98% ee; electron-donating substituents: 36-97% yields, *anti/syn* 4.5:1 to 24:1, 75-97% ee). Selectivity depends on arm chain length (the optimum was four, see Scheme 11) and preparation method (co-precipitation afforded better performance than coated MNPs). The enantiomers of **9** can be obtained in comparable yields and selectivity by the use of the pseudo enantiomer of the cinchona derivative. Furthermore, these MNPs-supported organocatalysts can be quantitatively recovered and reused six times without detriment of catalytic performance.



Scheme 11 Cinchona modified MNPs for aldol condensation[65]



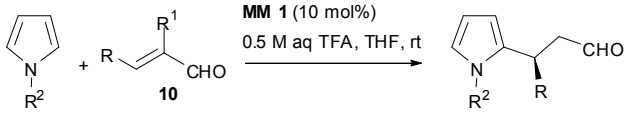
Scheme 12 MNPs supported polyoxometalates and chiral amines via non-covalent interaction[66]

Finally, a quite different approach has to be mentioned. Polyoxometalates can functionalize MNPs by non-covalent interactions and, furthermore, act as a catalyst support for chiral amines (Scheme 12).[66] **Cat 13** was tested in aldol reactions and the desired products were recovered in 72-97% yields, *anti/syn* ratios from 3:1 to 15.7:1 and 87-99% ee. The reaction is more efficient with cyclic ketones, than with acetone. It should be

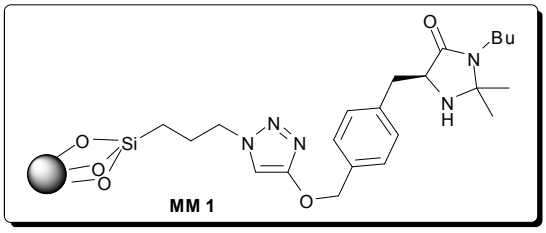
outlined that this non-covalently assembled catalyst showed excellent reusability, being maintained yield and enantioselectivity even after 11 cycles.

All papers, describing reactions reported in schemes 10-12, pictured products **9** with the absolute configuration showed in scheme 10 top line, even when *R,S* descriptors are not used in the text or in the supporting information.

Other classical organocatalysts are the so-called MacMillan type catalysts that are asymmetric imidazolin-4-one compounds based on amino acids. A MNP-immobilized first generation MacMillan type catalyst was used in asymmetric Friedel-Crafts alkylation of *N*-substituted pyrroles with α,β-unsaturated aldehydes.[67] Products were recovered in 13-98% yields with 65-91% ee (*S*-isomer, Scheme 13). Authors prepared and applied the same catalyst immobilized on polystyrene. Comparing these two catalysts, the polystyrene based catalyst led to higher yields and enantioselectivities in shorter times in all cases, but led to decreased yields after the third cycle. The one based on magnetic nanoparticles is easier separated and active until the fifth recycling. Moreover, both heterogeneous catalysts require shorter reaction times and milder conditions compared with the homogeneous catalyst.



R^1 = H, **10a** (R = Me), **10b** (R = Pr), **10c** (R = Ph), **10d** (R = 4-$NO_2C_6H_4$)
10e (R = 4-$MeOC_6H_4$), **10f** (R = 4-ClC_6H_4), **10g** (R = 2-$NO_2C_6H_4$)
R^2 = Me, Bn



Scheme 13 MacMillan organocatalyst for Friedel-Crafts reactions.[67]

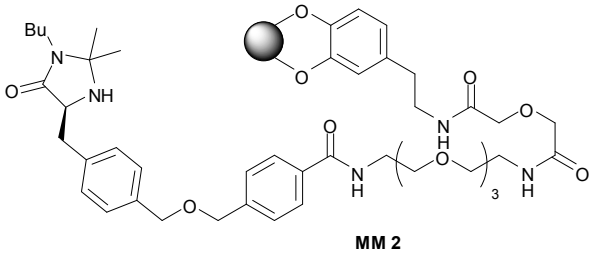
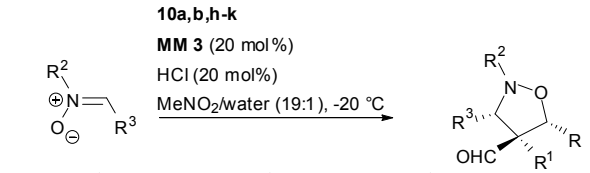


Fig. 3 MacMillan organocatalyst for Diels-Alder reaction from ref [68]

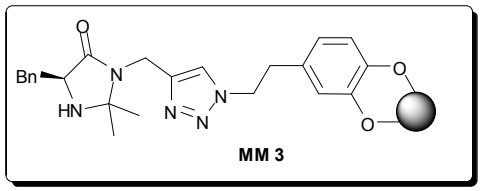
The MacMillan catalyst found large application the Diels‑Alder reaction and therefore examples of MNPs supported imidazolinones cannot be missing in the literature.

Benaglia's group prepared a supported MacMillan catalyst (Figure 3)[68] and tested it (10 mol%) exclusively in the Diels-Alder cycloaddition of cyclopentadiene (5-fold excess) with (*E*)-cinnamaldehyde. The reaction was not diastereoselective, because *exo/endo* ratio is always near 1:1, and eventually with *exo*-isomer prevalence. Reaction yield increases with temperature (from 51% at 0 °C to 83% at 25 °C), but enantioselectivity decreases from 93% to 81% ee for *exo*- and from 79 to 75% ee for the *endo*-isomer. The absolute configuration of the major isomer is not reported. In the third run, the catalytic system showed a diminished chemical efficiency, which falls down in the following runs. This number of recycles was lower than other supported systems, very likely for aggregation of the MNPs.

Dash and co-workers set-up a general and effective cycloaddition of *N*-methyl- and *N*-benzylnitrones to α,β-unsaturated aldehydes to afford isoxazolidines in 62-96% yields, 4:1 to 13:1 *endo: exo*, 82-95% ee (*3R,4S,5R*-isomer, Scheme 14).[69] It should be mentioned that sterically crowded aldehydes did not react, and that catalyst is achieved quantitatively by magnetic separation and it was successfully reused for four times without appreciable loss of activity. It should also be noted that **MM 3** is grafted through N-3 instead through the phenyl ring of the benzyl substituent as in **MM 1** and **MM 2**.



10h: R = R^1 = H; **10i:** R = Bn, R^1 = H; **10j:** R = H, R^1 = Me;
10k: R = Et, R^1 = Me



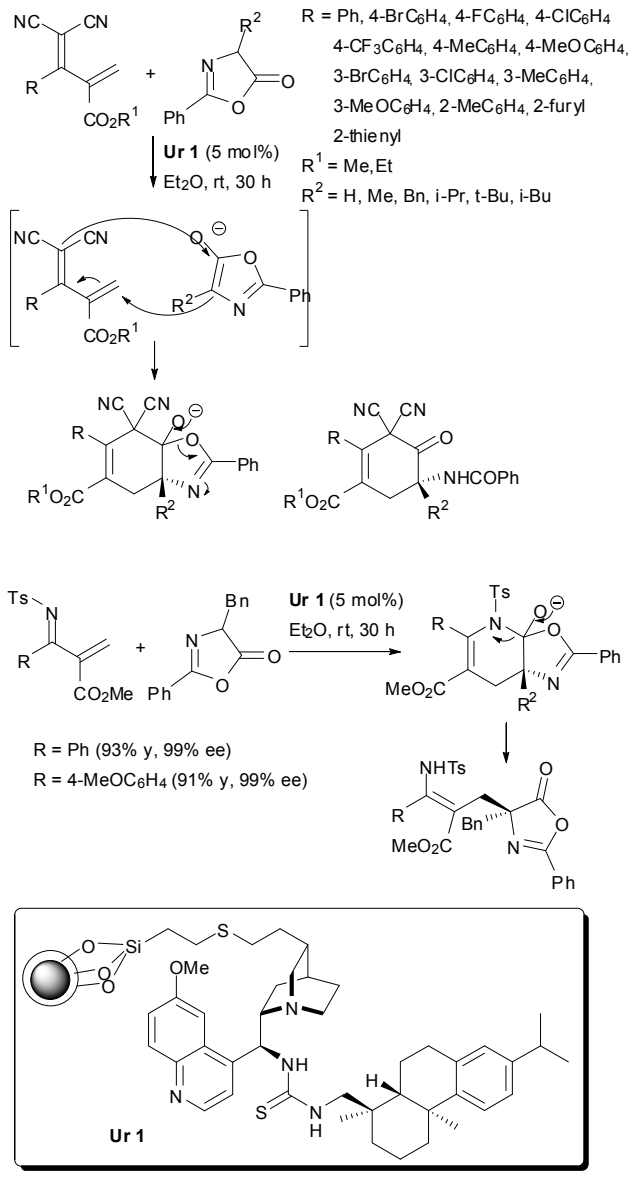
Scheme 14 MacMillan organocatalyst for Diels-Alder reaction from ref [69]

Urea derivatives are another class of typical organocatalysts and they are linked to MNPs, too. For instance, cinchonine-derived thioureas MNPs were applied to inverse electron-demanding Diels-Alder reactions (Scheme 15, top). Cyclohexene cycloadducts were obtained in 92-99% yields and 90->99% ee (*R*), and the catalyst can be reused up to 10 runs.[70] Under the same experimental conditions, *N*-tosyl-2-methylenebut-3-enoates afforded (*S,E*)-γ,δ-unsaturated α-amino acid precursors (Scheme 15, bottom).[70]

Chiral β-amino acid precursors can be obtained by using MNPs supported bifunctional rosin-derived tertiary amino thiourea catalysts.[71] Both enantiomers can be prepared by modifying the configuration of the cyclohexyldiamine moiety of the catalyst (Scheme 16). Except for aliphatic substrates, the reaction affords *R* adducts in 80-92% yield with 90-96% ee and *S* adducts in 81-90% yields with 90–96% ee. Moreover, the catalyst is particularly robust and can be recycled up to 15 times with no loss of yield and enantioselectivity. Decarboxylation to β-amino acid can be performed without affecting the asymmetric centre.

Finally, chiral resolution of racemic mixtures should be mentioned, although it is not properly an asymmetric catalysis. In particular, *S*-isomers of the aromatic amino acids were selectively adsorbed onto β-cyclodextrin modified MNPs leaving in the

solution the *R*-isomer in 97%, 77%, 60% ee, (tryptophan, phenylalanine and tyrosine, respectively).[72] The absorbed *S*-isomer can be released with *trans*-4-methyl-[4'-(3-trimethyl-amoniumpropyloxy)phenyl]azobenzene. Finally, photo-irradiation switches *trans*-azobenzene into the bulkier *cis*-isomer, which is released thus restoring the starting cyclodextrin. Authors surmised host-guest recognition as the responsible of the enantiomer separation.



Scheme 15 Cyclohexenes by Diels-Alder reaction catalysed by MNPs[70]

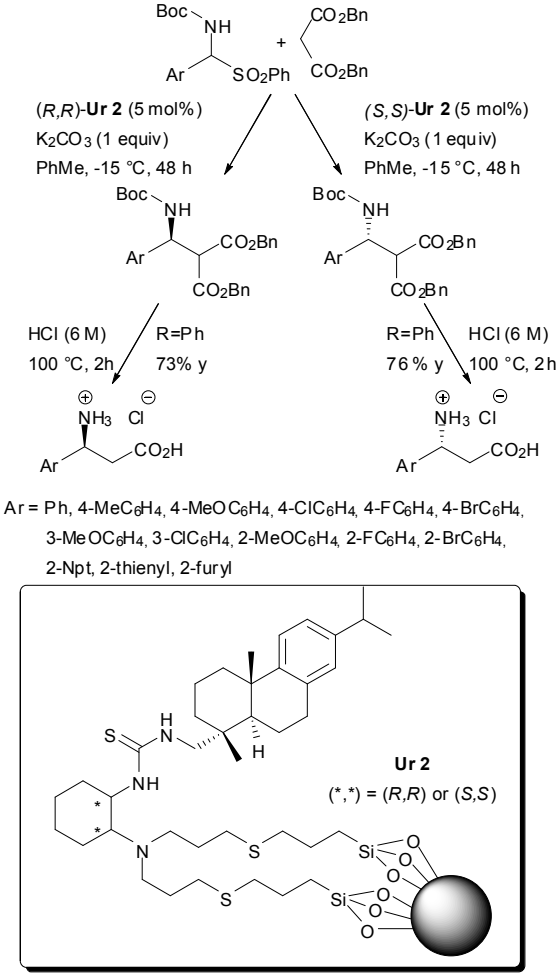
Uddin's group obtained similar results with silica and carboxymethyl-β-cyclodextrin coated MNPs.[73] *S*-Amino acids were adsorbed from phosphate buffer solutions in 94%, 73% and 58% ee (tryptophan, phenylalanine and tyrosine, respectively). Selectivity was explained in terms of preferential hydrogen bond formation between amino group and secondary hydroxyl group of carboxymethyl-β-cyclodextrin in the *S* enantiomer with respect the *R* one. Details on release of the adsorbed enantiomer are not given.

Finally, a capillary stationary phase coated with 3-(aminopropyl)triethoxysilane MNPs was applied in enantio-separation in capillary electrophoresis of ofloxacin and propranolol. More than 80 replicated analyses were tolerated and several parameters were tested. Further details are difficult to be obtained because only the abstract of the paper is in English.[74]

3.2. Non-asymmetric syntheses

Some enantiopure organocatalysts were also employed in reaction leading to symmetric molecules or without enantio-enrichment of the products. However, they are worth of mention in this review.

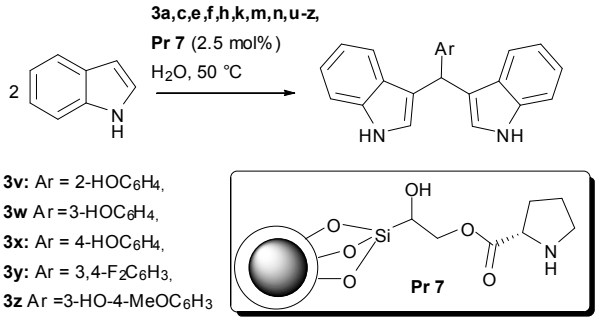
A (*S*)-proline-MNP was evaluated in the condensation reaction between indole and aldehydes (Scheme 17).[75] Unfortunately, under these reaction conditions two subsequent Friedel-Crafts reactions occur and only achiral bis(indol-3-yl)methanes were recovered in 80-95% yields.



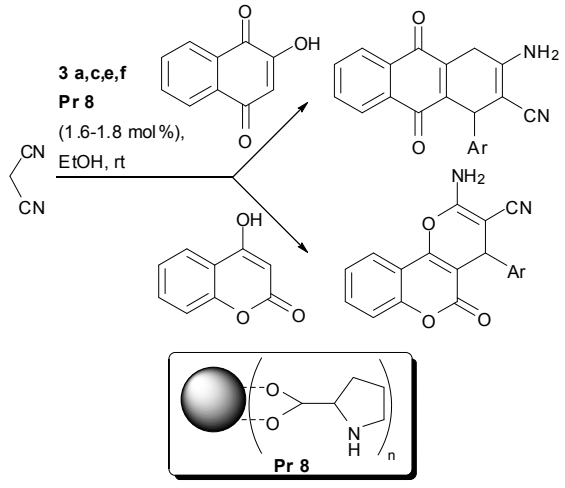
Scheme 16 β-Amino acid precursors by Mannich reaction catalysed by MNPs[71]

Furthermore, proline (paper did not report if chiral or racemic) linked to MNPs without any supplemental linker is capable of catalysing chromene derivative formation in 78-94% yields (Scheme 18).[76] However, also chromenes are achiral molecules. The catalyst can be recycled four times without significant loss in

activity. It should be noted that proline is truly grafted to MNPs, very likely with the carboxylic group. In fact, removing the catalyst using a magnet after 30 min from the beginning of reaction resulted in a stop of the reaction, clearly confirming that the active species is not proline floating in the solvent (compare for a similar behaviour reactions reported in refs 46 and 42).



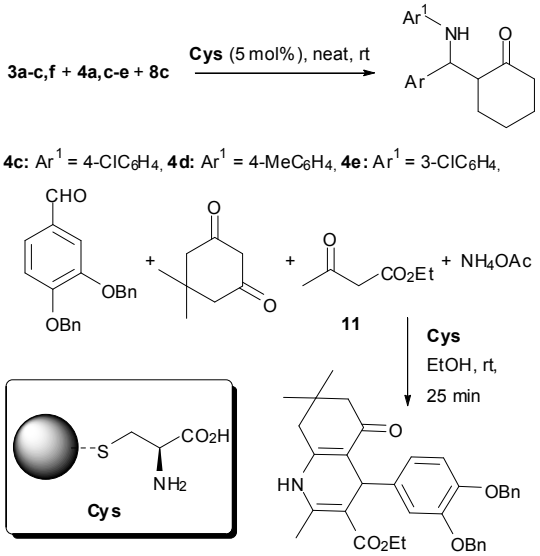
Scheme 17 Proline-modified MNPs for the synthesis of bis(indolyl)methanes[75]



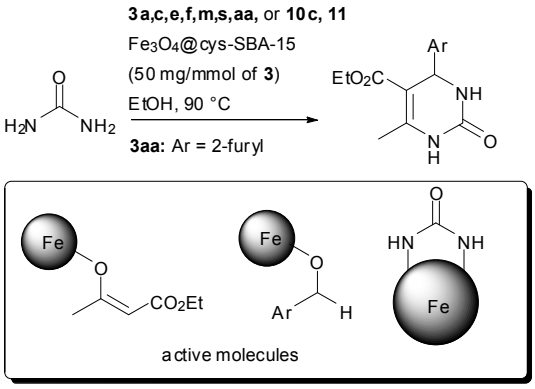
Scheme 18 Proline MNPs for the synthesis of chromenes[76]

Also (*S*)-cysteine can be directly grafted to MNPs, very likely by the SH group and used in the Mannich reaction. Products were obtained in 89-93% yields, but in only 1:1 to 1.6:1 *anti* diastereoselectivities (Scheme 19).[77] It should be noted that in solution diastereoselectivity is higher and opposite in ethanol and water (*syn/anti* 2.3:1 and 1:5.7, respectively), but yields are lower (55% and 75%). Nothing was mentioned about eventual enantioselectivity regardless the fact that a chiral catalyst was used. The catalyst was recycled and used in nine consecutive cycles. Finally the same catalyst was applied in the multicomponent synthesis between 3,4-diphenoxy benzaldehyde, ammonium acetate, ethyl acetoacetate and 5,5-dimethyl-cyclohexane-1,3-dione affording a hydroquinoline carboxylates in 88% yield.

Bhaumik and co-workers attached cysteine to SBA-15. The resulting mesoporous material was mixed with magnetic nanoparticles in order to incorporate them into the pores, then this catalyst was applied in the Biginelli condensation leading to achiral dihydropyrimidones in 78-85% yields (Scheme 20).[78] The catalyst can be reused seven times without loss of activity.



Scheme 19 Cysteine MNPs for the Mannich reaction[77]



Scheme 20 MNPs dispersed on cysteine-modified SBA-15 for Biginelli reaction[78]

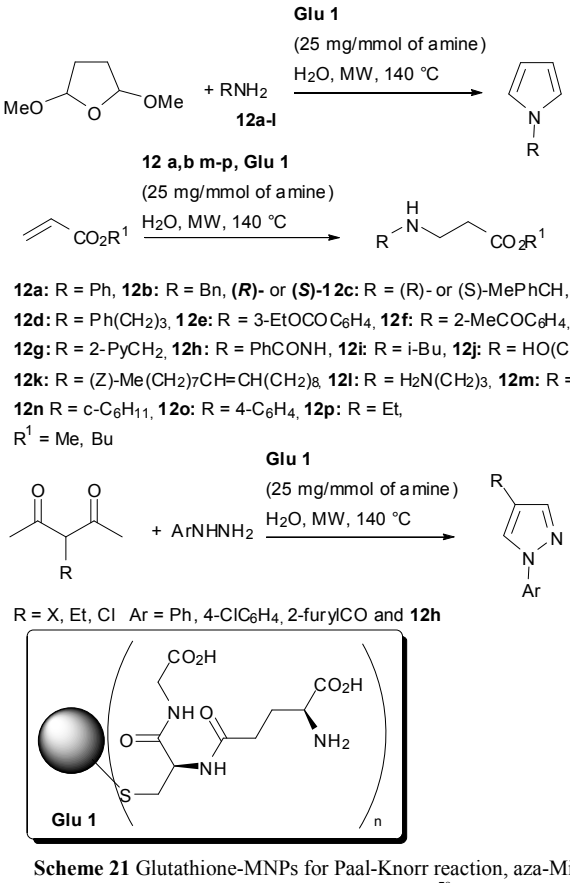
It is worth noting the comparison of how this catalyst and that reported above by Yang work.[48] There the catalyst is cysteine and the magnetic nanoparticle is the support, here the active catalytic sites are the electron deficient surface Fe atoms of MNPs. These sites co-ordinate the carbonyl groups of the aldehyde, the 1,3-dicabonyl compound and the *N*-donor atoms of the urea. In fact, cysteine-modified SBA-15 and SBA-15 itself are unable to give the reaction. Thus, even if chiral molecules could be produced, the mechanism precludes their enantio-enrichment. In conclusion, why authors selected cys-SBA-15 instead of simple SBA-15 as a mesoporous material for incorporation of magnetite is unclear, because the cysteine role is obscure.

4. Enzymes supported on MNPs

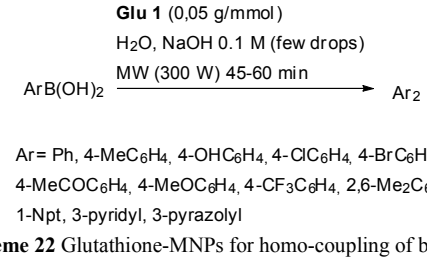
In the time range covered by this review, a series of papers were published wherein enzymes were linked to MNPs in order to manage them as heterogeneous catalysts. In fact, enzyme separation from product after reaction and efficient recovery and reuse of costly enzymes especially in industrial (large-scale) processes is a serious problem.

Considering the fact that these catalysts are chiral, it is surprising that asymmetric reactions were not included.

In particular, glutathione-magnetite conjugates with metal-S bonds were checked in various reactions. For instance, the Paal-Knorr synthesis of a variety of 1-substituted pyrroles (72-92% yields), the aza-Michael reaction (90-92% yields), and the pyrazole synthesis (78-96% yields) were carried out in water under microwave conditions (Scheme 21).[79] It should be noted that for diamines both mono and dipyrroles can be obtained by changing molar ratio and reaction temperature and that the Paal-Knorr reaction of acid hydrazides is efficient, whereas amides and hydrazines are unreactive under these reaction conditions. Recycling tests revealed that the catalyst could be used in five runs.



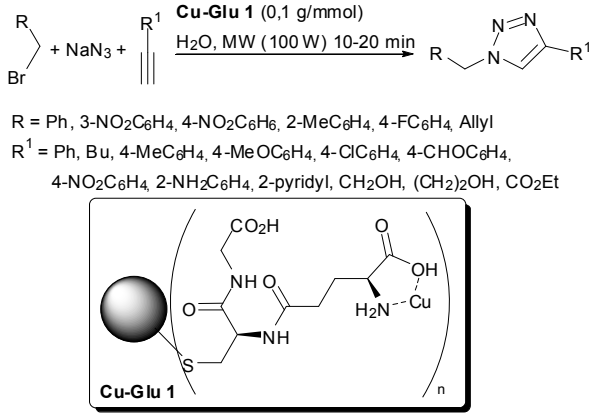
Scheme 21 Glutathione-MNPs for Paal-Knorr reaction, aza-Michael addition, and pyrazole synthesis[79]



Scheme 22 Glutathione-MNPs for homo-coupling of boronic acids[80]

Interestingly, the catalyst also catalysed homo coupling of aryl boronic acid derivatives. Thus, the same research group investigated this reaction in detail.[80] Glutathione coating was found essential for good selectivity, very likely for its basicity, but addition of large amounts of NaOH to the reaction mixture was detrimental, removing glutathione from MNP. In addition, microwave irradiation increases conversion. Under the optimum reaction conditions, diaryls were recovered in 59-94% yields (Scheme 22). The catalyst was also found to preserve over 90% of its initial activity after 4 cycles.

The synthesis of 1,2,3-triazoles by Huisgen 1,3-dipolar cycloadditions was carried out in aqueous media, by using **Cu-Glu 1**, a copper complex of **Glu 1**, under MW irradiation. Simple MNP or **Glu 1** as well as Fe_3O_4-Cu gave worse results in terms of yield or 1,4- vs 1,5-selectivity. Reactions between benzyl azide and various alkynes as well as multicomponent reactions between benzyl bromides, sodium azide, and alkynes afforded only the corresponding 1,4-adducts in 80-99 % yields (Scheme 23).[81] It should be noted that, to avoid reaction of free amine group with bromide, the reaction of 2-aminophenylacetylene needs some modification of the reaction procedure: it has to be added after formation of the azide. Catalyst can be reused three times without decrease of yield and Cu leaching was not detected in all the reactions.



Scheme 23 Glutathione-MNPs for Huisgen 1,3-dipolar cycloadditions[81]

Other enzymes were immobilized on MNPs and tested in simple organic reactions. They are mentioned here without comments as additional information, because out of the topic of this review. *Candida rugosa* lipase was immobilized on MNPs by dopamine or 3,4-dihydroxyhydrocinnamic acid linkers and used in 10 cycles for the hydrolysis of olive oil.[82].

Three different sizes of magnetic nanoparticles with glucose oxidase covalently bound by 3-(aminopropyl)triethoxysilane and, glutaraldehyde were prepared, but retained only 15-23% of the native enzyme activity.[83] The two larger MNPs lose 20% of activity and the smallest about 96% activity after ten cycles.

β-Glucosidase, α-chymotrypsin, and lipase B were covalently immobilized on the magnetic cobalt MNPs, the activity and stability after immobilization remained unaltered from millilitre to litre scale in three typical reaction of these enzymes.[84]

5. Conclusion

Catalysts supported on MNPs have rapidly developed in the last few years, for many reasons: (i) they work under quasi-homogeneous conditions with good performances; (ii) reactions works well under mild conditions often in water; (iii) the catalysts can be easily separated by magnetic decantation and reused many

times. Thus, they are tool for green chemistry and probably for industrial application. In fact, these reactions are run out in environmentally benign solvents, have good atom economy, produce low waste and environmental pollution.

However, there are still few examples of asymmetric catalysis, although in particular chiral organocatalysts are worth to get recycled. In these systems, the enantioselectivities are comparable to those in the corresponding homogeneous catalytic systems, but sometimes showed different selectivities, indicating that chiral MNP catalysts should be considered as distinct active species than only "immobilized catalysts".

Moreover, there is a high need for more focused studies on the chiral arrangement of the various catalysts, because none of the researches reported in this review hypothesizes any chiral transition state for the reactions in order to explain the observed stereochemistry. Such studies could give explanation of the different behaviour in different substrates as reported in reactions described, for instance, in refs 43, 47 and 62.

In the future, there are intriguing opportunities for the development of novel hybrid inorganic/organic multifunctional nano-catalytic systems, which could enable multistep transformations in one-pot reactions with magnetically retrievable and re-usable catalysts. There is also a great potential for biopharmaceutical applications of new magnetically immobilised enzymatic catalysts

6. Abbreviations

BINAP	2,2'-bis(Diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	$PhCH_2$
Boc	t-Butoxycarbonyl
Bz	PhCO
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7- ene
DIPEA	*N,N*-Diisopropylethylamine
Fmoc	Fluorenylmethyloxycarbonyl
MNP	Magnetic nanoparticle
NHC	*N*-heterocyclic carbene
Npt	Naphthyl
Py	Pyridyl
Pybox	2,6-bis(oxazoline)pyridine
Tf	Trifluoromethanesulfonyl
TsDACH	N-(p-toluenesulfonyl)-1,2-diaminocyclohexane
TsDPEN	N-(p-toluenesulfonyl)-1,2-diphenylethylenediamine
Xyl-P-Phos	(2,2',6,6'-tetramethoxy-4,4'-bis[di(3,5-dimethylphenyl)phosphino]-3,3'-bipyridine

7. Notes and References

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‡ **Note added in proof:** During the reviewing process a contribution on the same topic appeared in the literature R. B. Nasir Baig, M. N. Nadagouda and R. S. Varma, *Coord. Chem. Rev.*, **2015**, *287*, 137-156

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