Green chemistry by nano-catalysis

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Nano-materials are important in many diverse areas, from basic research to various applications in electronics, biochemical sensors, catalysis and energy. They have emerged as sustainable alternatives to conventional materials, as robust high surface area heterogeneous catalysts and catalyst supports. The nano-sized particles increase the exposed surface area of the active component of the catalyst, thereby enhancing the contact between reactants and catalyst dramatically and mimicking the homogeneous catalysts. This review focuses on the use of nano-catalysis for green chemistry development including the strategy of using microwave heating with nano-catalysis in benign aqueous reaction media which offers an extraordinary synergistic effect with greater potential than these three components in isolation. To illustrate the proof-of-concept of this "green and sustainable" approach, representative examples are discussed in this article.

Introduction

Catalysis lies at the heart of countless chemical protocols, from academic research laboratories to the chemical industry. A variety of products, such as medicines, fine chemicals, polymers, fibers, fuels, paints, lubricants, and a myriad of other value-added products essential to humans, would not be feasible in the absence of catalysts. These active compounds arbitrate the mechanism by which chemical transformations take place thus enabling the commercially viable creation of desired materials. Manufacturing protocols can be made more economic, green, and sustainable by the design and vigilant use of catalysts.

Why do we need nano-catalysis?

A homogeneous catalyst, where the catalyst is in the same phase as the reactants, is generally accepted by chemists.[1] One attractive property is that all catalytic sites are accessible because the catalyst is generally a soluble metal complex. Furthermore, it is possible to tune the chemo-, regio- and enantioselectivity of the catalyst. Homogeneous catalysts have a number of other advantages such as high selectivities, better yield, and easy

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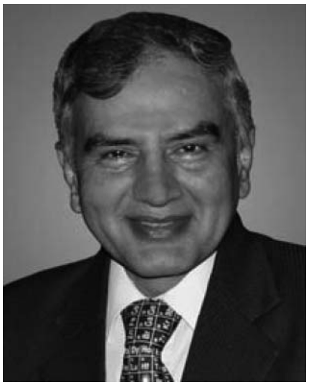
Vivek Polshettiwar

Dr Vivek Polshettiwar was born in Mangli, India in 1979. He obtained his Ph.D. (2005) under the supervision of Prof. M. P. Kaushik from Jiwaji University and DRDE, Gwalior. He investigated nano-structured silica-catalysis, with Prof. J. J. E. Moreau and Prof. P. Hesemann in 2006 during his postdoctoral research at ENSCM, Montpellier (France). Then he moved to the U. S. Environmental Protection Agency (2007-2009) to research nano-catalysis and MW-assisted new synthetic methods for green chemistry with Prof. R. S. Varma. Currently, he is working as senior research scientist at KAUST catalysis center directed by Prof. J. M. Basset. His research interests are in the area of advanced nano-materials for perfect catalysis. He has over 50 publications including various review articles and book chapters.



Rajender S. Varma

Prof. Rajender S. Varma was born in India (Ph.D., Delhi University 1976). After post-doctoral research at Robert Robinson Laboratories, Liverpool, UK, he was a faculty member at Baylor College of Medicine and Sam Houston State University prior to joining the US Environmental Protection Agency in 1999. He has over 35 years of research experience in management of multi-disciplinary programs that include nanomaterials and development of environmentally friendlier alternatives for synthetic methods using microwaves, and ultrasound etc. He has published over 300 scientific papers and has been awarded 6 US Patents.

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optimization of catalytic systems by modification of ligand and metals. They are widely used in a number of commercial applications, but the difficulty of catalyst separation from the final product creates economic and environmental barriers to broadening their scope. Despite their advantages and their wide use in a number of applications, many homogeneous catalytic systems have not been commercialized because of the difficulty encountered in separating the catalyst from the final reaction product. Removal of trace amounts of catalyst from the end product is essential since metal contamination is highly regulated, especially by the pharmaceutical industry. Even with the extensive and careful use of various techniques such as distillation, chromatography, or extraction, removal of trace amounts of catalyst remains a challenge.

To overcome the separation problems in homogeneous catalysis, chemists and engineers have investigated a wide range of strategies and the use of heterogeneous catalyst systems appears to be the best logical solution.[2] The majority of the novel heterogenized catalysts are based on silica supports, primarily because silica displays some advantageous properties, such as excellent stability (chemical and thermal), good accessibility, porosity, and the fact that organic groups can be robustly anchored to the surface to provide catalytic centers.[3] The common structural feature of these materials is the entrapment or anchoring of the dopant (catalytic) molecule in the pores of silica, a phenomenon which imparts unique chemical and physical properties to resulting hybrid silica. Anchoring can be achieved by covalent binding of the molecules or by simple adsorption; however covalent anchoring is robust enough to withstand the harsh reaction conditions and the catalyst can be reused several times. A vast majority of the industrial heterogeneous catalysts are high-surface area solids onto which an active component is dispersed or attached.

Although attempts have been made to make all active sites on solid supports accessible for reaction, allowing rates and selectivities comparable to those obtained with homogeneous catalysts, only sites on the surface are available for catalysis, which decreases the overall reactivity of the catalyst system. Another problem is the leaching of active molecule/complex from solid supports because of breaking of bonds between metal and ligand during catalytic reactions, which again necessitates separation of trace metals from final product. Consequently, new catalyst systems that allow for rapid, selective chemical transformations with excellent product yield coupled with the ease of catalyst separation and recovery are highly desired for "greening" chemical manufacturing processes (Fig. 1).

What is nano-catalysis?

Nanoparticles have emerged as sustainable alternatives to conventional materials, as robust, high surface area heterogeneous catalysts[4] and catalyst supports.[5] The nano-sized particles increase the exposed surface area of the active component of the catalyst, thereby enhancing the contact between reactants and catalyst dramatically and mimicking the homogeneous catalysts. However, their insolubility in reaction solvents renders them easily separable from the reaction mixture like heterogeneous catalysts, which in turn makes the product isolation stage effortless. Also, the activity and selectivity of nano-catalyst can be manipulated by tailoring chemical and physical properties like size, shape, composition and morphology (Fig. 2).

The scientific challenge is the synthesis of specific-size and shape nano-catalysts to allow facile movement of materials in the reacting phase and control over morphology of nanostructures to tailor their physical and chemical properties. However, the rapid advancement of nano-technology made possible the

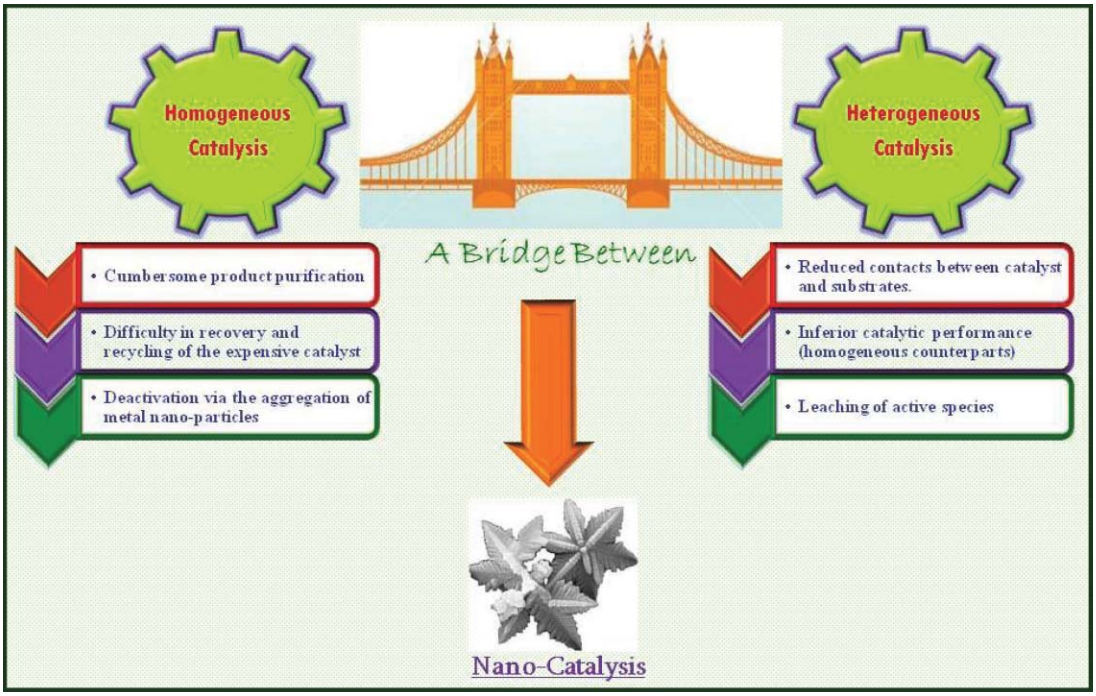

Fig. 1 Why do we need nano-catalysis?

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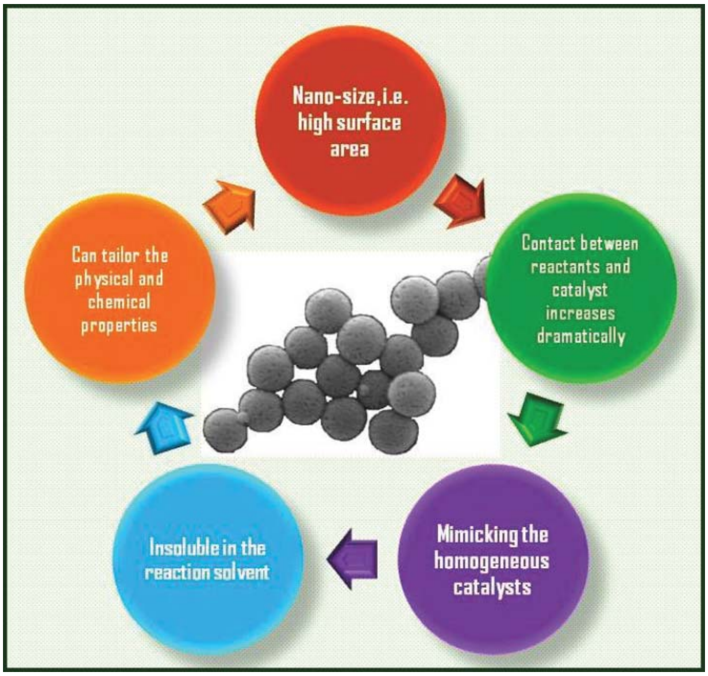

Fig. 2 What is nano-catalysis?

preparation of a variety of nanoparticles with controlled size, shape, morphology and composition.[6]

Greener approaches to nanomaterials

The development of solution-based controlled synthesis of nanomaterials *via* a bottoms-up approach has made this possible without difficulty[7] wherein benign entities such as vitamin B_1,[7d] B_2,[7e] vitamin C,[7f] tea polyphenols,[7g] simple sugars[7h] and polyethylene glycol[7i] (PEG) can generate nanoparticles; they can be cross-linked to form nanocomposites with cellulose[7j] or polyvinyl alcohol (PVA).[7k]

The control over size and morphology of nanostructures to tailor the physical and chemical properties has become a fundamental issue in nano-science including toxicological aspects.[7l,7m] Recently, we designed a convenient method for the synthesis of metal oxides with 3D nanostructures.[7b,7c] These materials were readily prepared from inexpensive starting materials in water without using any reducing or capping reagent. This economical and environmental sustainable synthetic concept could ultimately enable the fine-tuning of material responses to magnetic, electrical, optical, and mechanical stimuli. Five well-defined morphologies, including octahedron, sphere, triangular rod, pine, and hexagonal snowflake with particles in the size range of 100-500 nm were obtained (Fig. 3). Nano-ferrites were then functionalized and coated with Pd metal, which catalyzed various C–C coupling and hydrogenation reactions with high yields. In addition, the effortless recovery and increased efficiency, combined with the inherent stability of this catalyst, rendered the method sustainable.[7b,7c] Because of these unique morphologies, synthesized nano-materials will have significant applications in biomedical science and catalysis.

To render the protocol greener, we have used vitamin B_1 for a one-step synthesis of palladium (Pd) nanobelts, nanoplates and nanotrees without using any special capping agents at room temperature (Fig. 4).[7d] Depending upon the Pd concentration, Pd nanoparticles crystallized in various shapes and sizes. At lower Pd concentration, a plate-like shape was obtained. The Pd plates were grown on a single Pd nano-rod backbone mimicking leaf-like structures. However, with an increase in Pd

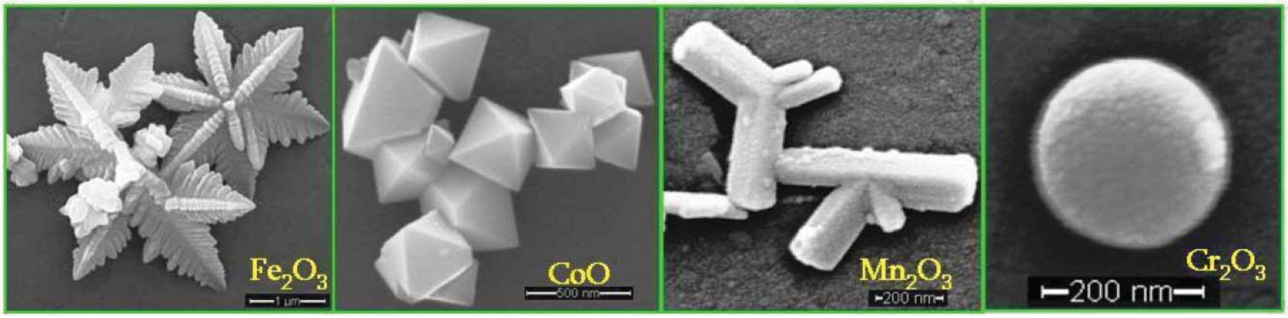

Fig. 3 Metal oxides with well-defined morphologies.

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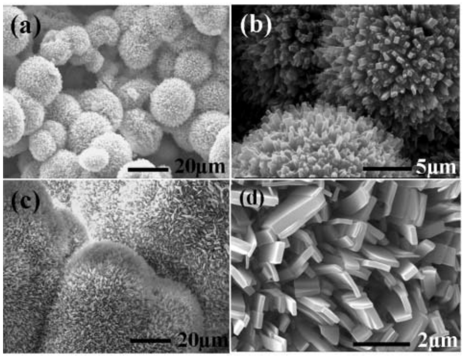


Fig. 4 SEM images of Pd-nanoparticles.

concentration, formation of tree-like structures was observed. Upon a further increase in concentration, Pd-nanoplates become thicker by vertically aligning themselves to form a ball-like shape. Interestingly, this protocol can be extended to prepare other noble nanomaterials such as gold (Au) and platinum (Pt).

Catalytic applications of nanomaterials

Somorjai *et al.* synthesized a Pt metal core coated with a mesoporous silica nano-catalyst.[8] The porous silica coating not only encaged the Pt cores up to an elevated temperature of 750 °C in air but also allowed direct access of the catalytically active Pt. This excellent nano-catalyst system (Pt-Core: Silica-Shell) demonstrated outstanding activity (due to an increase in the contact of nano-Pt with reactants), which enabled their usage in high temperature catalytic reactions such as ethylene hydrogenation and CO oxidation (due to thermal stability of catalyst).

It is not only the size of catalyst particles that has a significant effect on catalysis; their shape and morphology are also important. Xie and co-workers recently demonstrated that Co_3O_4 in the form of nano-rods allowed preferential exposure of catalytically active sites and increased its catalytic activity considerably for oxidation of CO at very low temperature.[9] They found the catalyst was stable even in feed gases containing large amounts of H_2O and CO_2. In addition to reactivity and stability of the catalyst, selectivity was also influenced by controlling the shape of the catalytic nano-particles. Lee *et al.* achieved selective isomerization of *trans* olefins to their less thermodynamically favorable *cis* isomers by using (111) facets of the Pt-metal.[10]

Dendrimer-encapsulated bimetallic nanoparticles showed excellent activity as catalysts for various reactions.[11] Recently Chandler and co-workers prepared a Pt/SiO_2 catalyst by using 4-hydroxyl terminated polyamidoamine dendrimer encapsulated nanoparticles as a precursor. Pt nanoparticles were prepared and stabilized in polyamidoamine dendrimers, which were then deposited onto silica with a high surface area. After thermal activation and treatment with hydrogen (Fig. 5), materials were found to be active catalysts for oxidation and hydrogenation reactions.[12]

Chandler and co-workers also prepared Pt[13] and Au[14] supported on a titania catalyst using a similar procedure. Pt/TiO_2 was found to be active for CO oxidation and toluene hydrogenation reactions; however, it was observed that catalyst activity decreased (in the case of toluene hydrogenation) with harsh reduction treatments.

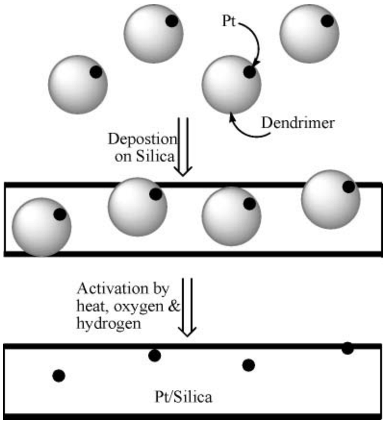
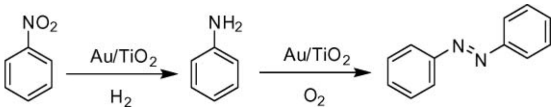


Fig. 5 Synthesis of Pt/silica catalyst.

Gold nanoparticles were used by Corma for chemo-selective hydrogenation of nitro compounds;[15a] no accumulation of hydroxylamines and their potential exothermic decomposition was observed. The same group used Au nanoparticles supported on titania and ceria for aerobic oxidation of aromatic aniline to aromatic azo compounds with excellent yields and mild reaction conditions.[15b] Notably, Au/TiO_2 catalyzes both reduction of aromatic nitro compounds as well as oxidation of aromatic amine in a one-pot process (Scheme 1).



Scheme 1 Au/TiO_2 catalyzed one-pot synthesis of azobenzene.

Gold nano-catalysts were also used by Hutchings' group for the oxidation of primary alcohols,[16a] hydrocarbons[16b] and carbon monoxide[16c] which are important processes for the synthesis of chemical intermediates in the manufacture of high-tonnage commodities, high-value fine chemicals, agrochemicals and pharmaceuticals.

Basset, Candy and their team recently reported monodispersed and highly accessible Pt nanoparticles in channels of silica pores. These materials were prepared by the control growth of silica around a colloidal solution of Pt nanoparticles with the help of a stabilizing agent (*n*-octylsilane).[17a] This was achieved by directing the nanoparticles to enter in the hydrophobic core of the surfactant micelles without disturbing the surfactant micelles. This group had previously used a similar strategy for the synthesis of monodispersed ruthenium (Ru) nano-particles (2-3 nm) deploying *n*-octylsilane as a stabilizing agent (Fig. 6).[17b]

Neiderer and co-workers also prepared a metal-silica-catalyst by incorporation of surfactant stabilized metal (Pd, Ir, Rh) nanoparticles in the pores of silica.[18] After calcinations, three different silica catalysts, [Pd]*x*-MCM-41, [Ir]*x*-MCM-41 and [Rh]*x*-MCM-41 were obtained and found to be highly active and selective for the hydrogenation of a variety of cyclic olefins.

Rothenberg *et al.* synthesized mono-dispersed Ni–Pd (core-shell) bi-metallic nano-clusters using combined electrochemical and 'wet chemical' techniques.[19] These materials were then tested

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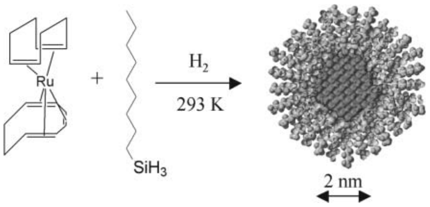
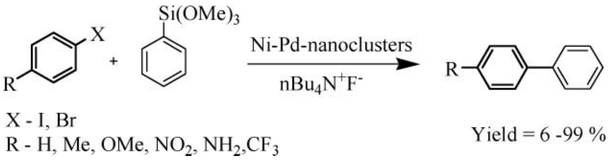


Fig. 6 Fabrication of monodispersed Ru nanoparticles.

as a catalyst for the Hiyama reaction and good product yield was obtained with a variety of aromatic halides (Scheme 2). Importantly, a negligible amount of homocoupling product was observed.



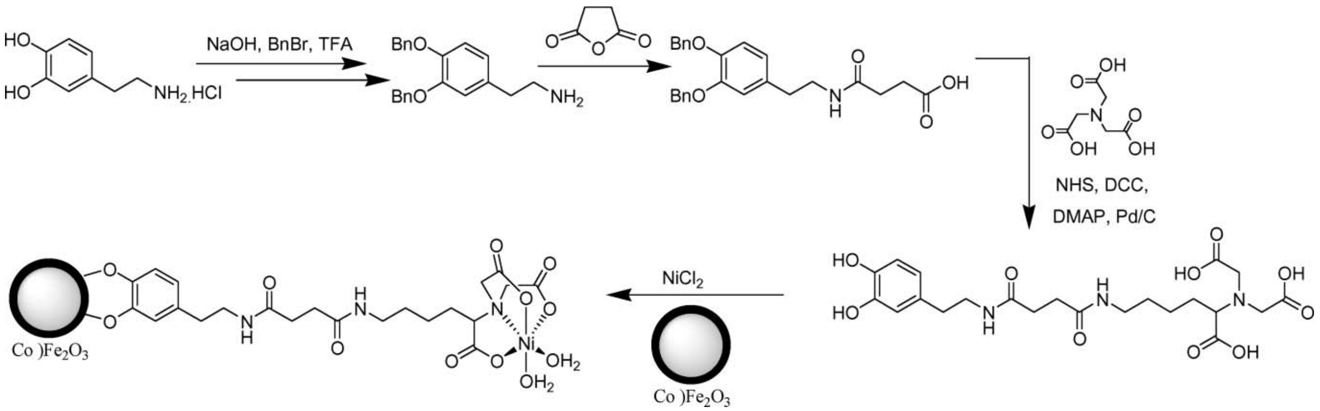
Scheme 2 Hiyama coupling reaction.

On similar lines, Dumesic's group screened more than 130 Pt and Pd bimetallic catalysts for hydrogen production by aqueous-phase reforming of ethylene glycol solutions using a high-throughput reactor.[20] They found bimetallic PtNi, PtCo, PtFe and PdFe systems considerably more active with higher turnover frequencies for hydrogen production than monometallic Pt and Pd catalysts. The rationale advanced is that alloying Pt with Ni, Co or Fe improves the activity by lowering the d-band center, which decreases the heats of CO and hydrogen adsorption, which in turn increases the fraction of the surface available for reaction with ethylene glycol.

A large percentage of known hydrogenation catalysts are based on precious metals such as palladium, rhodium, and ruthenium, because of their high activity and wide applicability. However, due to the higher cost and toxicity of these regularly used metals, there is a need to develop less expensive and easily available non-precious metal catalysts for such protocols. In this regard, de Vries and his co-workers developed an inexpensive and benign iron-based hydrogenation catalyst. They prepared iron nanoparticles by reduction of $FeCl_3$ using EtMgCl and successfully used them as a catalyst for hydrogenation of a variety of alkenes and alkynes.[21]

Visible light-driven hydrogen production by water splitting is one of the smart approaches to convert solar energy into a fuel and an important area in photosynthesis. Nano-catalysis can be used to achieve this objective. Recently, MoS_2 nanoparticles with sizes less than 10 nm were used as an efficient catalyst for hydrogen evolution from a transition metal complex containing molecular systems in visible light.[22] Authors observed that MoS_2 nanoparticles catalyzed the reduction of protons more efficiently than the conventional MoS_2/Al_2O_3 catalyst. This work clearly demonstrated the advantage of using nano-catalysts over conventional catalysts.

Recently, magnetic nanoparticles have emerged as viable alternatives to conventional materials, as robust, readily available, high surface area heterogeneous catalyst supports.[23] Post-synthetic surface modification of magnetic nanoparticles imparts desirable chemical functionality and enables the generation of catalytic sites on the surfaces of the resulting nano-catalyst. Their insoluble and paramagnetic natures enable trouble-free separation of these nano-catalysts from the reaction mixture using an external magnet, which eliminates the necessity of catalyst filtration. Successful application of these nanomaterials is highly dependent on their stability during the reaction as well as their particle size. These novel nano-catalysts bridge the gap between homogeneous and heterogeneous catalysis, thus preserving the desirable attributes of both systems. Applications require chosen molecules/ligands to be immobilized on the surfaces of the nanoparticles. In 2004, Xu and his coworkers developed a simple and efficient functionalization protocol for ferrites using dopamine as an anchor (Scheme 3)[24] essentially due to two reasons: i) dopamine changes the un-coordinated Fe surface sites back to a bulk-like lattice structure with an octahedral geometry for oxygen-coordinated iron and this resulted in its tight binding with iron oxide;[25] ii) as per Langmuir isotherms, desorption of dopamine molecules from metal oxides was less favorable than its absorption,[26] thus minimizing its chances of leaching from the surfaces. These functionalized materials with Ni-complex (Scheme 3) displayed high specificity for protein separation and excellent stability to heating and high salt concentrations. This concept was then explored further, for the development of other metal-catalysts[7b,7c,27] including a



Scheme 3 Dopamine functionalization of ferrites.

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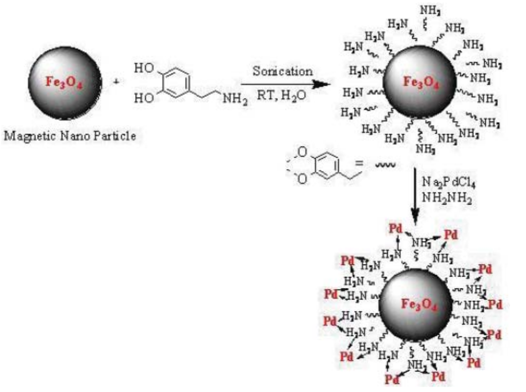
nano-ferrite-supported Pd catalyst from inexpensive starting materials in water (Scheme 4).[5e,5g] This material catalyzed the oxidation of alcohols and olefins with high turn over numbers and excellent selectivity. The catalyst was able to be magnetically separated, which eliminated the requirement of its filtration, which was an additional sustainable attribute of this oxidation protocol.



Scheme 4 Dopamine functionalized nano-ferrite Pd catalyst.

Lin *et al.* designed a magnetite nanoparticle-supported chiral catalyst by Ru-complex formation with BINAP followed by functionalization on the ferrite surfaces (Scheme 5). The as-synthesized material catalyzed the asymmetric hydrogenation of aromatic ketones under heterogeneous conditions with high activity and enantioselectivity. The catalyst could be recovered by using an external magnet and was used up to 14 times without any change in activity.[5a]

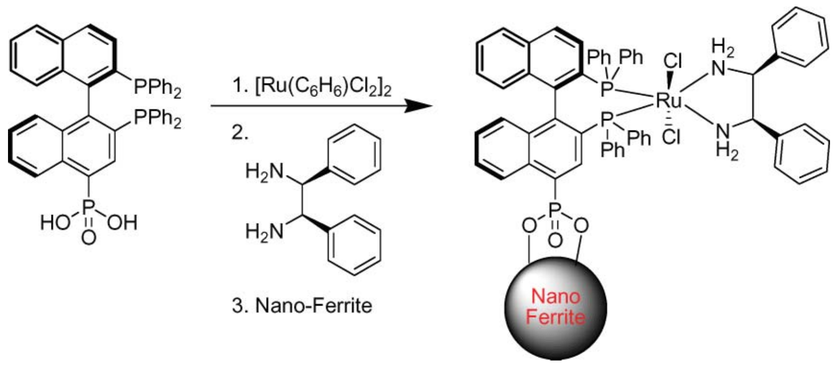
The aforementioned concept of magnetically separable catalysts was also explored by Jones *et al.* for a one-pot multistep reaction. They used a polymer resin-based acid catalyst and magnetic ferrite-based base catalyst, for conversion of 1-(dimethoxymethyl)benzene to 2-benzylidenemalononitrile in a two-step single pot reaction (Scheme 6). After completion of the reaction, the resin-based catalyst was removed by decantation and the ferrite-based catalyst was removed by an external magnet, essentially in pure form.[5b]

Alper and his co-workers developed the method to homogenize these magnetically separable heterogeneous catalysts by growing polyaminoamido dendrons on silica-coated nanoferrites up to three generations, followed by phosphination.[5c] The material was then complexed with rhodium and used as a catalyst for a hydroformylation reaction (Scheme 7). The ensuing catalyst was found to be stable and more soluble in organic solvent and catalyzed the reaction with excellent reactivity and selectivity.

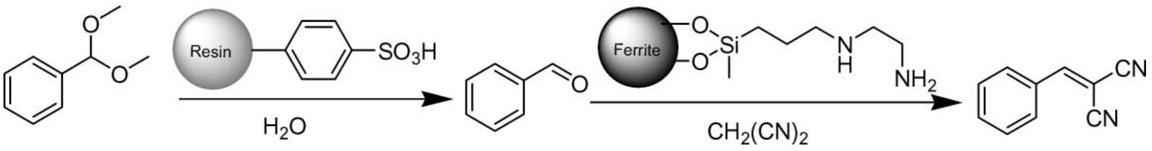
Similarly, Kitamura and co-workers prepared a deallylation catalyst by immobilization of [CpRu(η^3-C_3H_5)(2-pyridinecarboxylato]PF_6 on silica-coated nano-ferrite particles.[28] The obtained materials showed high saturation magnetization and levels of dispersibility with weak coercive forces. The catalyst was highly active for deallylation reactions (Scheme 8) and no extra additives were needed to complete the reaction. Only volatile allyl ethers were the co-products of the reaction. The catalyst was removed using an external magnet and reused, making the protocol economical.

Beller used this magnetically separable nano-ferrite as a support for the development of Ru–Fe_3O_4 catalyst[5f] and successfully demonstrated its catalytic prowess for the synthesis of a variety of sulfonamides with excellent yield (Scheme 9). Further, it was observed that only one equivalent of alcohol was needed to complete the reaction and the catalyst could be used several times, making the protocol green and sustainable.

Connon prepared the magnetic nanoparticle-supported 4-*N*,*N*-dimethylaminopyridine analogue and successfully used it as a heterogeneous catalyst for a range of useful synthetic transformations with excellent activity and recyclability (Scheme 10). The ease of recovery, as well as superb stability of the catalyst system, made it easily recyclable using an external magnet. The catalyst was used up to 30 times without any noticeable loss in



Scheme 5 Synthesis of nanoparticle-supported chiral Ru-catalyst.



Scheme 6 Synthesis of magnetically separable acid catalyst.

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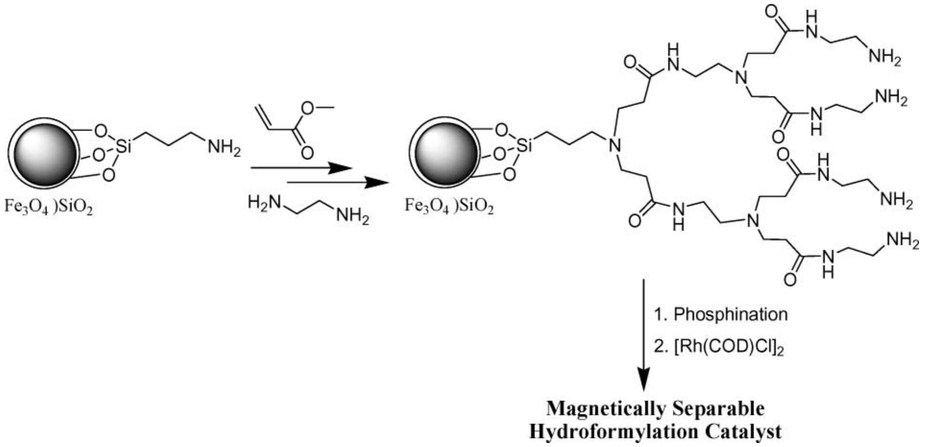
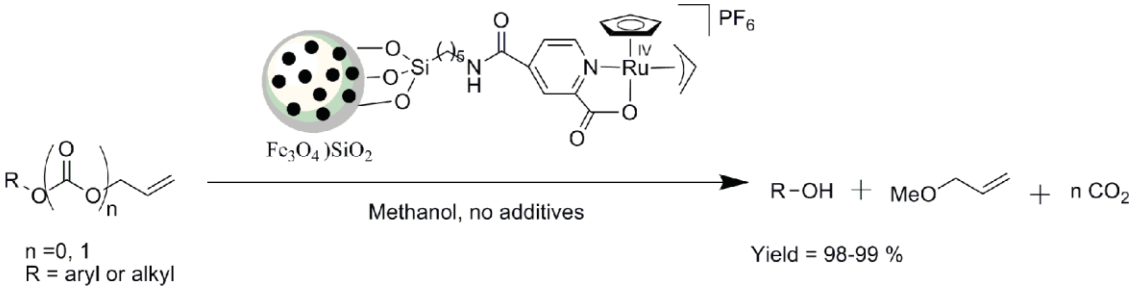
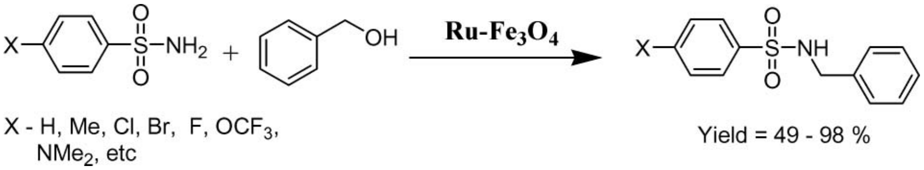


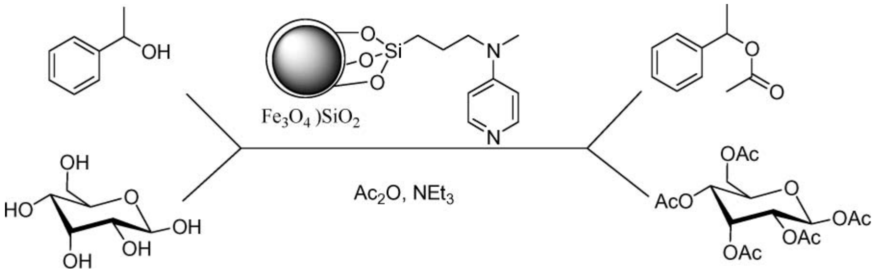
Scheme 7 Synthesis of magnetically separable hydroformylation catalyst.



Scheme 8 Magnetically separable deallylation catalyst.



Scheme 9 Magnetically separable Ru catalyst for synthesis of sulfonamides.



Scheme 10 Magnetically separable 4-*N*,*N*-dimethylaminopyridine as a catalyst.

activity.[5d] Similarly, they prepared a chiral version of this catalyst and it was successfully used for an enantioselective acylation reaction.[29]

Microwave-assisted nano-catalysis in an aqueous medium

Conventional processes of chemical synthesis are orders of magnitude too slow to satisfy the current demand for the generation of new compounds. Although the fields of combinatorial and automated chemistry have emerged to meet this burgeoning demand, most of these techniques generate considerable quantities of chemical waste. Chemists have been under growing pressure to develop new methods, which should be rapid and environmentally benign. One of the alternatives is the use of nano-catalysis in conjunction with non-conventional microwave (MW) heating technology. The efficiency of MW flash-heating has resulted in dramatic reductions in reaction times, reduced from days to minutes, which is potentially important in process chemistry for the expedient generation of fine chemicals and nanomaterials.[30]

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In the last few years, MW-assisted chemistry has blossomed into a mature and useful technique for a variety of applications. Although MW-assisted reactions in conventional solvents have developed rapidly, the center of attention has now shifted to the environmentally benign processes,[31] which use nano-catalysts and greener solvents such as water. Naturally abundant water is a good alternative because of its non-toxic, non-corrosive, and non-flammable nature, which will reduce the reliance of chemists on ecologically hazardous solvents.[32] Further, water can be contained because of its relatively lower vapor pressure as compared to organic solvents, thus rendering it a sustainable alternative. Interestingly, the combination of MW and aqueous medium showed excellent benefits such as shorter reaction times, homogeneous heating, and enhanced yields and selectivity.[33] In addition to these microwave "thermal effects" and "non-thermal effects",[34] there are some additional advantages of using microwaves for nano-catalyzed aqueous protocols.

1. Selectivity towards water. Microwave heating depends on composition and structure of molecules (*i.e.* their dielectric properties) and this property can facilitate selective heating. Microwaves initiate rapid intense heating of polar molecules such as water while non-polar molecules do not absorb the radiation and are not heated. Loupy and Varma,[30a] Strauss[30c,35] and Larhed[36] demonstrated that this selective heating can be exploited to develop a high yield rapid microwave protocol using a two phase (polar: non-polar) solvent system. The advantageous use of water in the MW-assisted processes, especially without the use of phase-transfer catalysts,[30a] has been well demonstrated.[33]

2. Selectivity towards catalyst. Selective heating can be exploited in heterogeneous catalysis protocols. This was demonstrated in MW-assisted rapid molybdenum-catalyzed allylic reactions by Larhead and his co-workers,[37] and in the case of oxidation of alcohol using Magtrieve™ by Bogdal *et al.*[38] They established that the polar catalyst absorbed extra energy and heated at a higher temperature than the overall reaction temperature, thus making the process more energy efficient.

3. Nano-catalysts as susceptors. Susceptors are materials that efficiently absorb MW irradiation and transfer the generated thermal energy to molecules in the vicinity that are weak MW absorbers. Although transmission of the energy occurs through conventional mechanisms, MW heating is more rapid than conventional heating. Pioneers in the field of MW chemistry, Kappe[39] and Leadbeater[40] used silicon carbide and ionic liquid, respectively, as susceptors and established that addition of these materials in the reaction mixture enhanced its overall capacity to absorb MW and significantly reduced the required MW energy. However, the addition of these materials as susceptors in the reaction mixture added to the overall cost of the protocol. Ideally, if nano-materials can play a dual role of catalyst and susceptor, then all the related advantages can be enjoyed without need of any additional material as a susceptor.

4. Stability of nano-catalyst. Since MW-assisted reactions are rapid, the residence time of nano-catalysts at this high temperature is minimum. Catalytic processes with short reaction times safeguard the catalyst from deactivation and decomposition, consequently increasing the overall efficiency of the catalyst and the entire protocol.

Thus, it appears that this approach of fusing MW technique with nano-catalysis and benign water (as a reaction medium) can offer an extraordinary synergistic effect with greater potential than these three individual components in isolation. To illustrate the "proof-of-concept" of this "green and sustainable" approach, two representative protocols have been reviewed in this article.

Ruthenium hydroxide nano-catalyst for MW-assisted hydration of nitriles in water

Amides, an important class of compounds in the chemical and pharmaceutical industries, have been generally prepared by the hydration of nitriles, catalyzed by strong acids and bases. This strategy produced several by-products including carboxylic acids. Because of the use of strong reagents/catalyst and harsh conditions, sensitive functional groups on nitrile molecules could not be kept intact, consequently decreasing the selectivity of the reaction protocol. Several heterogeneous catalyst systems were developed to overcome the drawbacks of homogeneous processes. However, turnover numbers of these protocols were still small and reusability of the catalyst was a challenge. A recently developed hydration method in pure water was a good attempt in terms of reaction conditions and product yield,[41] but it used expensive ruthenium complexes as catalysts and needed traditional work-up using toxic organic solvents for isolation of the product.

This hydration protocol was successfully achieved in a green and sustainable way by using a ruthenium hydroxide nano-catalyst under aqueous MW conditions.[42] Nano-Ru(OH)$_x$ was prepared in two steps: 1) magnetic nanoparticles were functionalized by post-synthetic functionalization[7b,7c] *via* sonication of nano-ferrites with dopamine in an aqueous medium, and 2) ruthenium (Ru) chloride was added, followed by hydrolysis using sodium hydroxide solution (Fig. 7).

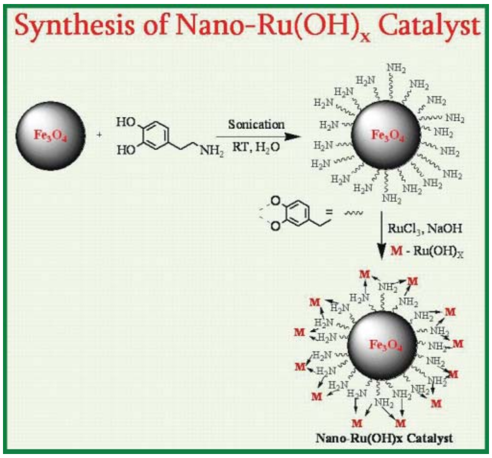

Fig. 7 Magnetically separable nano-Ru(OH)$_x$ catalyst.

The nano-Ru(OH)$_x$ catalyst showed high activity for hydration of a range of activated, inactivated, and heterocyclic nitriles in water medium. The rates of the reactions were not influenced by the nature of the substituents on benzonitrile molecules. The hydration of nitrile with the same substituents at the *m*- or *p*-position proceeded with similar rates, without

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any difference in reactivity. Neither an electronic effect nor the position of the substituents influenced the reaction rate, which proved the high catalytic activity. This protocol showed excellent chemoselectivity; during the hydration of the benzonitrile-containing dioxole ring, the reaction proceeded only at the cyano- group to afford the corresponding amide, while keeping the ring untouched (Fig. 8). Consequently, this protocol can be very useful in the total synthesis of drug molecules, where it is required that a nitrile group be selectively hydrated to amide without affecting other sensitive functional groups. The use of aqueous MW chemistry expedited the rate of the reaction, due to the efficiency of the interaction of microwaves with the polar nano-catalyst. Because of the relatively high dielectric constant of water molecules, the reaction mixture was rapidly heated to precise temperatures under MW irradiation conditions.

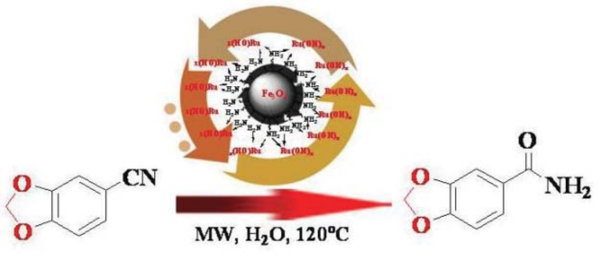

Fig. 8 Hydration of nitrile using nano-$Ru(OH)_x$ catalyst.

After completion of reaction and as the stirring was stopped, the reaction mixture turned clear and catalyst was deposited on the magnetic bar because of the paramagnetic nature of the nano-$Ru(OH)_x$. The catalyst was easily removed using an external magnet, thus avoiding a filtration step. After separation of catalyst, the clear reaction mixture was cooled slowly and crystals of benzamides with acceptable purity were precipitated. The entire procedure was carried out in pure aqueous medium and no organic solvents were used during the reaction or in the work-up steps (Fig. 9).

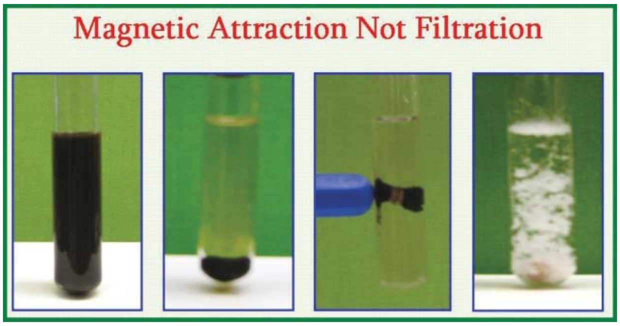

Fig. 9 Product isolation without filtration.

Metal leaching has been an important criterion for selecting a heterogeneous catalyst because metal contamination is highly regulated by chemical industries.[43] This aqueous MW protocol for hydration of nitriles catalyzed by nano-$Ru(OH)_x$ was tested for metal leaching using a 'hot filtration' test. Metal analyses were performed before and after the reaction and on the final product by ICP-AES analysis (Fig. 10). All tests confirmed no detectable Ru leaching. This clearly showed the advantage of post-synthetic functionalization of nano-materials, *i.e.* creating an active surface with well-defined amine-binding sites, acting as pseudo-ligands by non-covalent binding with $Ru(OH)_x$ through metal–ligand interactions. This in turn minimized deterioration and leaching of supported nanocatalysts. The most important criteria in choosing a catalyst are its recovery and reusability. In this protocol, the reaction proceeded with a high turnover number (because of the use of nano-catalyst) and at high turnover frequencies (because of the use of MWs). The catalyst was successfully used several times and left no remnants of metal in the end product.

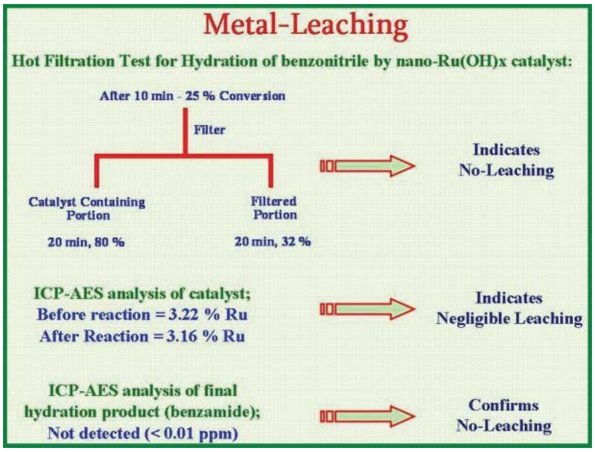

Fig. 10 Metal-leaching studies.

Glutathione-based nano-organocatalyst for MW-assisted synthesis of heterocycles in water

Heterocyclic molecules have a tremendous ability to selectively influence the activity of biological systems. The outstanding nature of heterocyclic nuclei to act as biomimetics and pharmacophores has extensively contributed to their unique value as traditional key elements of numerous drugs.[44] In both lead identification and optimization processes, there is an acute need for the preparation of new heterocycle-based active molecules in a benign fashion. Synthetic protocols can be made more economic, green, and sustainable by designing novel catalysts which do not damage human health and the environment. In this regard, organocatalysis has become a very noteworthy area of research and this metal-free approach has attracted global interest. Although a wide range of reactions has been successfully developed using this strategy, most of these transformations were generally conducted in organic solvents. In a recently developed aqueous protocol, it was observed that the addition of water often accelerated the organocatalyst-mediated reaction, making the overall protocol efficient and green.[45] However, most of these reports use small amounts of water as a reaction medium and excessive amounts of hazardous organic solvents during the work-up, which unfortunately defeated the core intention of reducing the environmental burden of organic contaminants.[46]

These drawbacks were successfully circumvented in a green and sustainable manner using a glutathione-based nano-organocatalyst under aqueous MW conditions.[47] Glutathione is a tripeptide consisting of glutamic acid, cysteine, and glycine units and is a ubiquitous antioxidant present in human

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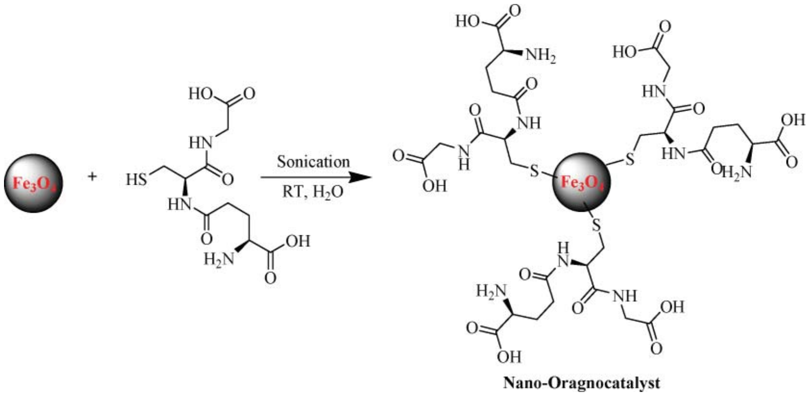


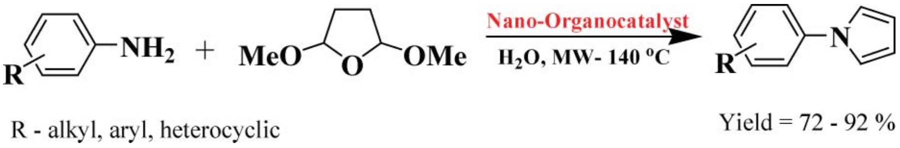
Fig. 11 Nano-ferrite functionalization using glutathione.

and plant cells. Besides the thiol group, each molecule also contains amine and carboxylate functionalities that provide coupling possibilities for further cross-linking to other molecules. The use of glutathione (over other amino acids) as an active catalytic moiety is preferred due to its benign nature as well as the presence of the highly active thiol group, which can be used for attachment to a solid support (ferrites). The catalyst was prepared by sono-chemical covalent anchoring of glutathione molecules *via* coupling of its thiol group with the free hydroxyl groups of ferrite surfaces (Fig. 11).

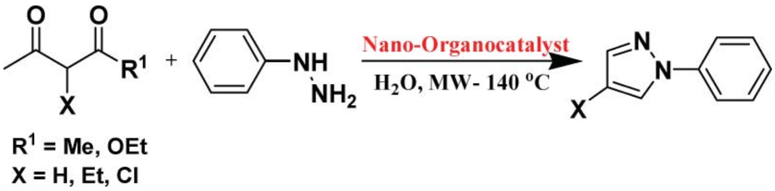
This glutathione-based nano-organocatalyst was efficiently used for the synthesis of a series of pyrrole heterocycles by Paal–Knorr reaction under aqueous MW conditions. It showed excellent catalytic activity and several amines reacted with tetrahydro-2,5-dimethoxyfuran to produce the respective pyrrole derivatives in good yields (Scheme 11).[47] Both aliphatic and aromatic amines reacted smoothly, proving the high activity of the nano-organocatalyst. This protocol was also suitable for acid hydrazides and substituted amines (which were selectively converted to pyrroles while keeping other reactive functional groups intact). Interestingly, in the case of diamines, mono- and di-pyrrole derivatives were synthesized just by changing the mole ratio and reaction time. It is worth mentioning that this aqueous reaction protocol proceeded well without any phase-transfer catalyst, which can be explained on the basis of selective absorption of microwaves by substrates, polar nano-organocatalyst, and the aqueous medium.

In addition to pyrrole, pyrazole-based molecules have been an important drug target in medicinal chemistry in both lead identification and optimization processes. Using the above developed strategy, various hydrazines and hydrazides reacted efficiently with 1,3-diketones and afforded the desired pyrazoles in good yields (Scheme 12).[47] All these reactions proceeded efficiently in an aqueous medium and were completed in less than 20 min under MW irradiation conditions.

Separation of the catalyst and final product from the reaction mixture is one of the most vital aspects of synthetic protocols. Catalyst recovery, which is generally performed by filtration, is relatively inefficient. Another technique, extractive isolation of products, also requires excessive amounts of organic solvents. However, in the aforementioned protocols, within a few seconds after stirring was stopped, catalyst was deposited on the magnetic bar and then easily removed using an external magnet, leaving the clear reaction mixture. In most of the experiments, after completion of the reactions, the phase separation of the desired product from the aqueous medium occurred which facilitated the isolation of synthesized heterocycles by simple decantation, without using any volatile organic solvents during the reaction or during product work-up (Fig. 12).[47]



Scheme 11 Paal–Knorr reactions using nano-organocatalyst.



Scheme 12 Pyrazole synthesis using nano-organocatalyst.

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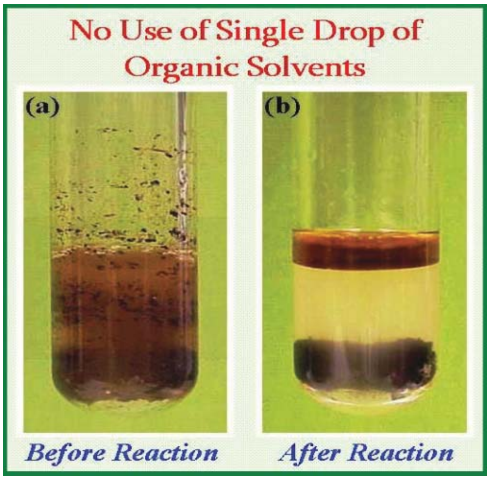

Fig. 12 Paal–Knorr reaction in pure aqueous medium.

Conclusions

Catalysts that enhance reactions rates and product yield, with good selectivity and stability are of great technological importance. Most catalysts consist of highly dispersed metal nanoparticles supported on porous silica, alumina, zeolites, mesoporous materials and other oxides and also in many cases non-supported metal nano-clusters. Nano-catalysts mimic homogeneous (high surface area, easily accessible) as well as heterogeneous (stable, easy to handle, easy to isolate) catalyst systems. Nano-catalyst systems encompassing a paramagnetic core allow rapid and selective chemical transformations with excellent product yield coupled with the ease of catalyst separation and recovery.

Nanomaterials-catalyzed transformations in an aqueous reaction medium are one of the ideal solutions for the development of green and sustainable protocols. However, execution of many organic reactions in water is not simple due to the inherent limitation of solubility of non-polar reactants in polar aqueous media, which can be overcome by using MW irradiation conditions. Thus, the *fusion* of a benign water medium, non-conventional MW heating, and nano-catalyst seems to be the preeminent way to develop the next generation of highly efficient processes.

Despite this well-recognized demand of nano-catalysis, knowledge of the prevailing mechanisms at such small scales is empirical and fairly sparse. A detailed study of the mechanistic aspect of these catalytic processes to develop a scientific basis is needed which will help to tune and tailor the new catalyst system.[48] The true potential of this concept in various processes has not been fully explored yet, and further progress is expected in the future.

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