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# Polymer- and Dendrimer-Coated Magnetic Nanoparticles as Versatile Supports for Catalysts, Scavengers, and Reagents

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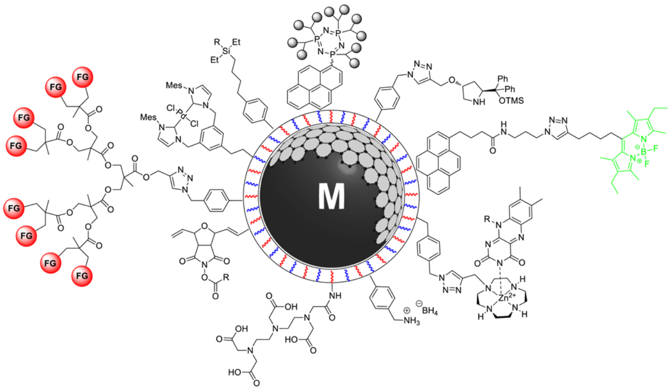
## CONSPECTUS



The work-up of chemical reactions by standard techniques is often time consuming and energy demanding, especially when chemists have to guarantee low levels of metal contamination in the products. Therefore, scientists need new ideas to rapidly purify reaction mixtures that are both economically and environmentally benign. One intriguing approach is to tether functionalities that are required to perform organic reactions to magnetic nanoparticles, for example, catalysts, reagents, scavengers, or chelators. This strategy allows researchers to quickly separate active agents from reaction mixtures by exploiting the magnetic properties of the support. In this Account, we discuss the main attributes of magnetic supports and describe how we can make the different nanomagnets accessible by surface functionalization.

Arguably the most prominent magnetic nanoparticles are superparamagnetic iron oxide nanoparticles (SPIONs) due to their biologically well-accepted constituents, their established size-selective synthesis methods, and their diminished agglomeration (no residual magnetic attraction in the absence of an external magnetic field). However, nanoparticles made of pure metal have a considerably higher magnetization level that is useful in applications where high loadings are needed. A few layers of carbon can efficiently shield such highly reactive metal nanoparticles and, equally important, enable facile covalent functionalization via diazonium chemistry or non-covalent functionalization through $\pi-\pi$ interactions. We highlight carbon-coated cobalt (Co/C) and iron (Fe/C) nanoparticles in this Account and compare them to SPIONs stabilized with surfactants or silica shells.

The graphene-like coating of these nanoparticles offers only low loadings with functional groups via direct surface modification, and the resulting nanomagnets are prone to agglomeration without effective steric stabilization. To overcome these restrictions and to tune the dispersibility of the magnetic supports in different solvents, we can introduce dendrimers and polymers on Co/C and Fe/C platforms by various synthetic strategies. While dendrimers have the advantage of being able to array all functional groups on the surface, polymers need fewer synthetic steps and higher molecular weight analogues are easily accessible.

We present the application of these promising hybrid materials for the extraction of analytes or contaminates from complex aqueous solutions (e.g. waste water treatments or blood analytics), for metal-, organo-, and biocatalysis, and in organic synthesis. In addition, we describe advanced concepts like magnetic protecting groups, a multistep synthesis solely applying magnetic reagents and scavengers, and thermoresponsive self-separating magnetic catalysts. We also discuss the first examples of the use of magnetic scaffolds manipulated by external magnetic fields in flow reactors on the laboratory scale. These hold promise for future applications of magnetic hybrid materials in continuous flow or highly parallelized syntheses with rapid magnetic separation of the applied resins.

## Introduction

In modern organic chemistry with countless reagents and catalysts developed for synthesis, the purification of products often turns out to be the most problematic and tedious step within the whole process. Especially transition-metal catalysts are generally expensive and, more problematic, highly

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toxic. Therefore, sophisticated purification methods have often to be applied to remove these catalysts - particularly in the pharmaceutical industry, where only low limits of heavy metal concentrations are allowed in the final drug molecules.[1] Common purification techniques include column chromatography, liquid–liquid extraction, and filtration. However, all of those have drawbacks, for example, high amounts of solvents needed in order to pump the reaction mixture through packed columns or filters, energy requirements to remove solvents from products, or auxiliary materials, which often cannot be recycled.

Moreover, purification processes of reaction mixtures have to be evaluated by the principles of green and sustainable chemistry established by Anastas and Warner in 1991,[2] emphasizing prevention rather than clean up of chemical waste. Since catalysts and reagents are inevitable for most chemical transformations, one strategy for recovery and recycling is their grafting to insoluble supports, for example, to silica, alumina, ceria, or carbon.[3] However, depending on the nature of the support, the active sites might be buried inside pores or cavities limiting the accessibility for substrates, which results in reduced activity. In addition, rapid filtration from the support can be energy and resource intensive and also difficult from a practical point of view since filters tend to clog.

Within the past few years, magnetic nanoparticles emerged as a new class of semiheterogeneous supports for catalysts.[4–6] The excellent surface-to-volume ratio enables high loading of catalysts accompanied by high catalytic activity, which is usually the prerogative of homogeneous systems. The intrinsic magnetic properties of the support allow for operationally convenient separation (e.g., via magnetic decantation), dispensing with the need for centrifugation or flocculation generally required for the recovery of nonmagnetic nanomaterials.

In this Account, we describe key features of magnetic supports and compare magnetic nanobeads comprising different compositions highlighting carbon-coated metal particles. Furthermore, the surface functionalization of these nanomaterials is discussed aiming at high functional group loading and dispersibility in solvents, being essential for the attachment of ligands, catalysts, scavengers, and reagents and their subsequent application.

## Magnetic Supports: Synthesis and Surface Functionalization

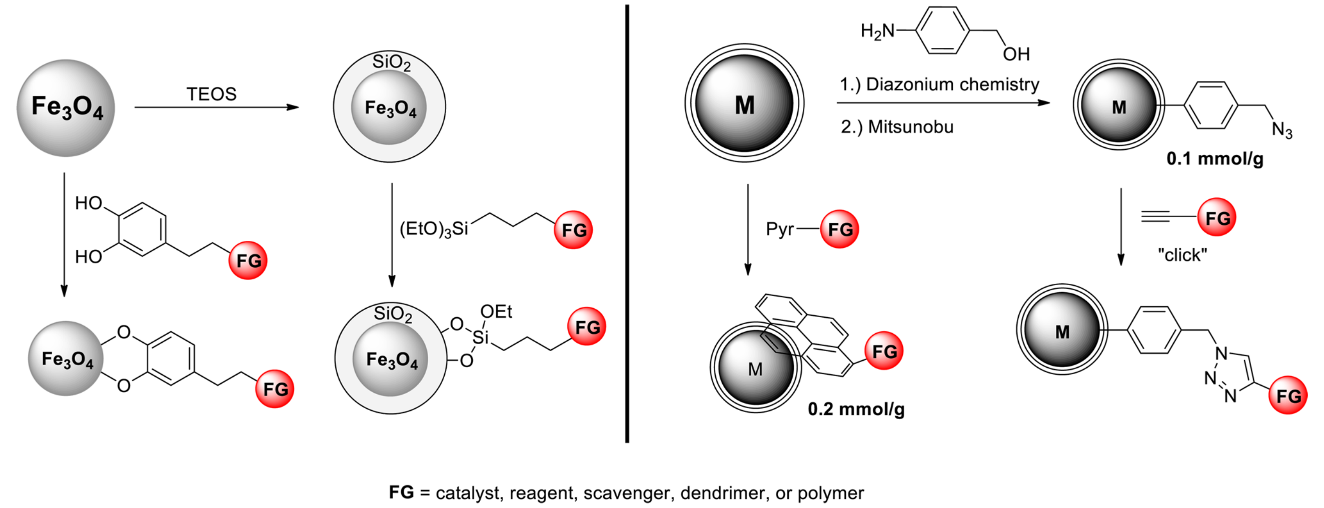
A plethora of magnetic nanoparticles derived from metals (Fe, Co, Ni), alloys (FePt, CoPt), metal oxides (FeO, $Fe_2O_3$, $Fe_3O_4$), or ferrites ($CoFe_2O_4$, $MnFe_2O_4$) with a manifold of characteristics are known. A comprehensive discussion of the synthesis and functionalization of these magnetic nanoparticles is beyond the scope of this Account.[5,7] Instead, we highlight magnetic nanoparticles that are especially suitable as supports for catalysts, scavengers, or reagents.

Desirable properties of an ideal magnetic support should include (i) inexpensive and easily accessible starting materials, (ii) a reproducible and sustainable large-scale synthesis, (iii) a nanosized core with high magnetization and low toxicity, (iv) protection of the core by an impenetrable inert shell for reactions under forcing conditions ($\Delta T$, $H^+$, $OH^-$), and (v) an efficient method to introduce functional groups to the surface.

Magnetic nanoparticles derived from iron oxide, for example, magnetite ($Fe_3O_4$) and maghemite ($\gamma$-$Fe_2O_3$), fulfill most of these requirements, and recent advances in their synthesis give access to size-controlled, monodisperse particles.[8,9] Superparamagnetic iron oxide nanoparticles (SPIONs) show a negligible remanent magnetization and therefore reduced agglomeration.[7] This and their toxicologically uncritical constituents render SPIONs ideal for a broad range of biomedical applications like magnetic drug targeting, magnetic fluid hyperthermia, and magnetic resonance imaging.[10] For the same reasons, SPIONs are also attractive as recyclable supports for catalysts. A protective coating of the surface has to be introduced in order to guarantee their stability under demanding reaction conditions. Long-chain alkyl surfactants, for example, oleic acid or oleylamine, can prevent agglomeration by steric shielding.[9] Phosphonic acid[11] and dopamine[12] derivatives can provide in addition functional groups for the immobilization of catalysts (Scheme 1). A silica shell protects the magnetic core even more efficiently and eliminates unwanted interactions between the core and attached agents. The deposition of silica shells with a thickness between 2 and 100 nm can be achieved via the Stöber method by hydrolyzing a sol–gel precursor such as tetraethoxysilane (TEOS).[13] No additional primer is required due to the strong affinity of iron oxide surfaces to silica, and the silanol groups on the surface allow simple surface functionalization with various silica-modified catalysts (Scheme 1).[14]

Nanoparticles derived from pure metals or metal alloys exceed the saturation magnetization of iron oxides, for example, magnetite ($M_{S,bulk} \leq 92$ emu $g^{-1}$), by far (Co $M_{S,bulk} \leq 163$ emu $g^{-1}$; Fe $M_{S,bulk} \leq 222$ emu $g^{-1}$). However, unprotected metal nanoparticles are highly sensitive to air, which renders them pyrophoric, requiring a strong protective shell

**SCHEME 1.** Common Functionalization Strategies for Magnetite (left) or Carbon-Coated Metal Nanoparticles (right)[a]



**FG** = catalyst, reagent, scavenger, dendrimer, or polymer

[a] M = Co, Fe.

to exploit them as supports. Depositing silica shells is more difficult due to the lack of OH groups on the metal nanoparticle surface, thus requiring the addition of a primer. Nevertheless, silica shells do not completely block the diffusion of oxygen.[4] Carbon shells offer an alternative due to their superior chemical and thermal stabilities over all aforementioned organic and inorganic coatings.[7,15] The controlled synthesis of carbon-coated metal nanoparticles is, however, challenging and was initially limited to small scale operations (<1 g $h^{-1}$) using arc discharge techniques[16] or chemical vapor deposition (CVD).[17] In 2007, Stark et al.[18] reported a large scale (>30 g $h^{-1}$) synthesis of carbon-coated ferromagnetic cobalt nanoparticles (Co/C) via reducing flame-spray pyrolysis, a process related to flame-aerosol synthesis, which is used in industry on ton-scale for the production of carbon, silica, and titania nanomaterials.[19] The deposition of roughly three carbon layers with a thickness of about 1 nm leads to remarkable stability under acidic, basic, and thermal (up to 190 °C) conditions. However, with a mean particle size of 25 nm, Co/C beads are considerably larger than carbon-coated metal nanoparticles synthesized via CVD.[17] The very high magnetization of 158 emu $g^{-1}$, which is equivalent to that of bulk cobalt, allows for rapid magnetic separation. Iron and iron carbide nanoparticles with similar properties are accessible in an analogous way.[20]

In order to implement functional groups on the surface of the carbon-coated metal nanoparticles, covalent functionalization via diazonium chemistry proved to be effective.[18] We extended this strategy by introducing azide groups, allowing the covalent immobilization of complex acetylene-tagged molecules via Cu(I)-catalyzed "click" reaction (Scheme 1), for example, of TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl) resulting in a robust catalyst for the oxidation of alcohols.[21] Analogously, a Cu(II)-azabis(oxazoline) complex was immobilized and subsequently applied to the kinetic resolution of racemic 1,2-diphenylethane-1,2-diol via asymmetric monobenzoylation.[22] The high magnetization of the carbon-coated nanoparticles made agitation and containment in a reactor by adverse rotating magnets possible, opening the way to a continuous flow setup (Figure 1). Complementary, noncovalent

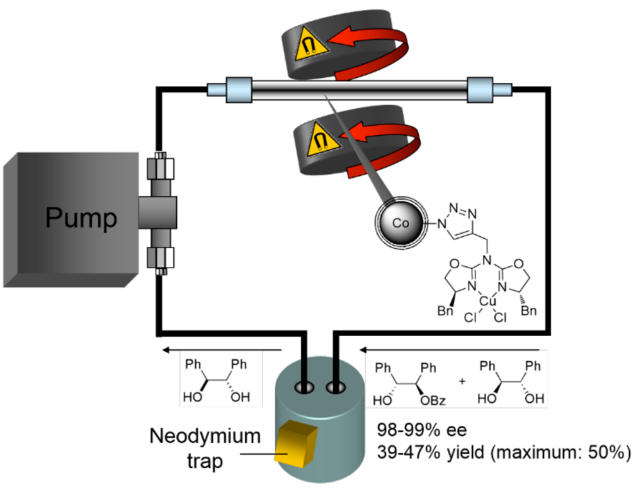


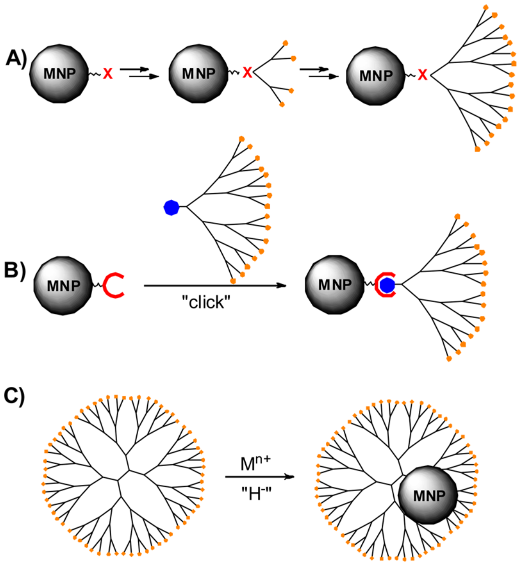
**FIGURE 1.** Cu(II)-azabis(oxazoline) complexes immobilized on magnetic Co/C nanoparticles for continuous-flow kinetic resolutions. Figure adapted with permission from ref 22. Copyright 2006 American Chemical Society.

functionalization via the carbon layer was achieved via $\pi-\pi$ stacking interactions,[23] allowing, for example, the thermally reversible attachment of a pyrene-tagged palladium *N*-heterocyclic carbene (NHC) complex. While in all these examples the catalysts were recovered completely within seconds by magnetic decantation and recycled for several runs, the effective loading with functional molecules was limited to a moderate level of 0.1−0.2 mmol $g^{-1}$. This is sufficient for the immobilization of highly active catalysts but not for the development of magnetic reagents that have to be employed in stoichiometric amounts.

## Dendrimer-Coated Magnetic Nanoparticles

By introduction of a shell of dendrimers or polymers to the surface of the nanoparticles, the loading with functional groups can be considerably increased. Initiated by the pioneering work of Tomalia[24] and Newkome,[25] dendrimers have gained considerable attention as well-defined highly branched structures giving rise to applications in catalysis, sensing, molecular electronics, or nanomedicine.[26] One of the intriguing properties of the starburst dendritic architecture is the high number of functional end groups contrasting linear polymers. There are basically three strategies for decorating solid supports with dendrimers: The divergent synthesis of dendrimers on the surface of the support after introducing a linker, the grafting of presynthesized dendrimers of various generations, and the synthesis of nanoparticles within the boundaries of preformed dendrimers (Scheme 2). While the solution phase synthesis of dendrimers and subsequent grafting might be more easily controlled allowing routine analytics, their generation on the magnetic support can lead to a higher density of functional groups and enables a more convenient work-up after each coupling step.

**SCHEME 2.** Synthesis of Dendrimer-Coated Magnetic Nanoparticles via Step-Wise Divergent Synthesis (A), Grafting of Complete Dendrons (B), or Synthesis of Magnetic Nanoparticles (MNP) inside Globular Dendrimers (C)

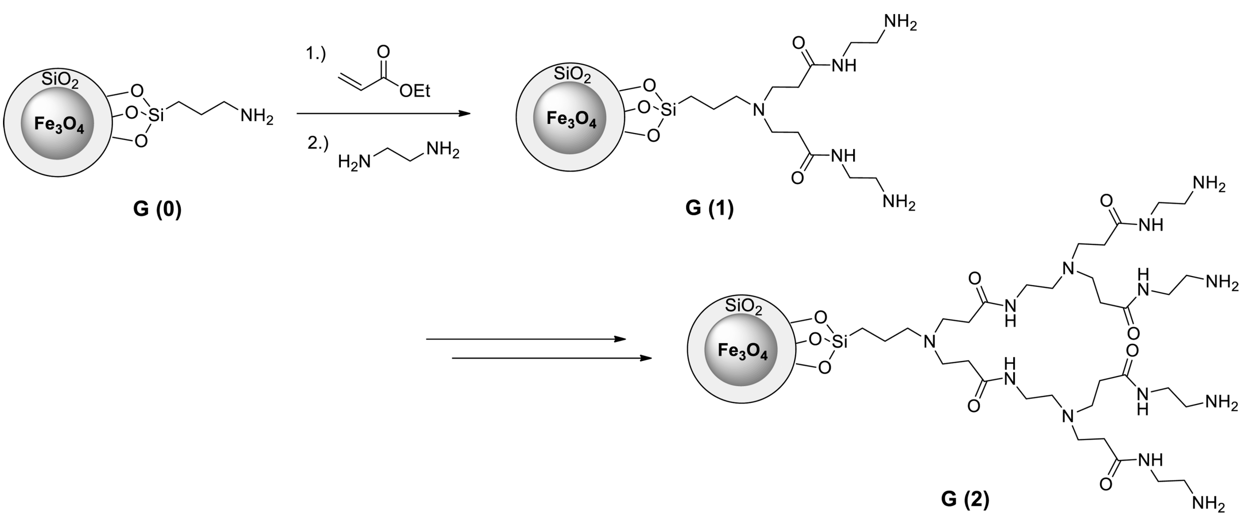


Dendrimers are often introduced onto magnetic nanobeads to improve the dispersion of the latter in organic solvents and to multiply functional groups on the surface. Alper and co-workers grew poly(amidoamine) (PAMAM) dendrimers on the surface of silica-coated magnetite nanoparticles.[27] Magnetic core−shell particles with an approximate size of 60 nm were functionalized with (3-aminopropyl)triethoxysilane (APTMS) to provide an amino group as a starting point. PAMAM dendrons up to generation three were then generated by Michael-type addition of methyl acrylate followed by subsequent amide formation with ethylenediamine (Scheme 3). Long reaction times of up to 5 days and reduced yields in the coupling steps might limit the applicability of this method. Nevertheless, supported Rh complexes could be formed, and the resulting magnetic catalysts were applied in hydroformylations of styrenes giving rise to excellent selectivities and reactivities for five runs. Recently, microwave heating was applied to improve the synthesis of PAMAM dendrimers on the surface of silica coated magnetite beads. Upon immobilization of bovine serum albumin (BSA), the chiral hybrid particles were successfully used for the direct separation of amino acids.[28]

Magnetite nanoparticles were also directly functionalized with APTMS[29] for the surface-initiated PAMAM synthesis, omitting the extended silica shell. Invertase was subsequently attached via glutaraldehyde linkers leading to a 2.5 times higher loading compared with analogous particles lacking the dendrimer shell. Moreover, the shelf stability of the enzyme was improved upon immobilization. In another application, PAMAM coated magnetite particles proved their high adsorption capacities of heavy metals in the reversible extraction of Zn(II) from aqueous solutions.[30] pH induced desorption was triggered by washing with diluted HCl allowing for 10 consecutive cycles at full efficiency.

Entire fourth generation PAMAM dendrimers were grafted on the surface of magnetite beads preactivated with cyano moieties. Again, glutaraldehyde linkers were used to immobilize an antibody, and the hybrid material was applied as a magnetic-controlled potentiometric immunosensor.[31] In another study, PAMAM dendrons of various generations comprising a thiol group at the focal point were grafted on maleimide-functionalized magnetite beads.[32] However, a reduced degree of immobilization was observed

**SCHEME 3.** Growing PAMAM Dendrimers on the Surface of Silica-Coated Magnetite Beads[a]

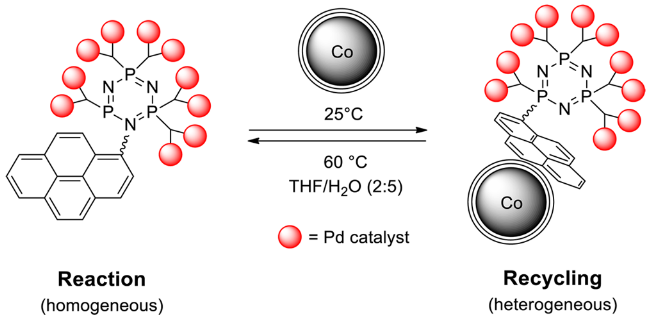


[a]Scheme adapted from ref 27.

for G3–G6 dendrons compared with analogous materials synthesized by the divergent approach. The magnetic hybrid material was applied for the recovery of $\lambda$-DNA with modest success. A significant improvement (96% of DNA recovered) was achieved by integrating phospholipid bilayers between the magnetic beads and the dendrimers, increasing the flexibility of the support. While PAMAM dendrimers are most commonly used, other dendrimers also were efficiently immobilized on magnetic nanoparticles. Fujita and co-workers reported the dihydroxylation of olefins by magnetite beads modified with osmate(VI) quaternary ammonium salts.[33] The grafting of ether-based dendrimers reduced the leaching of the osmium catalyst to a large extent (positive dendritic effect).

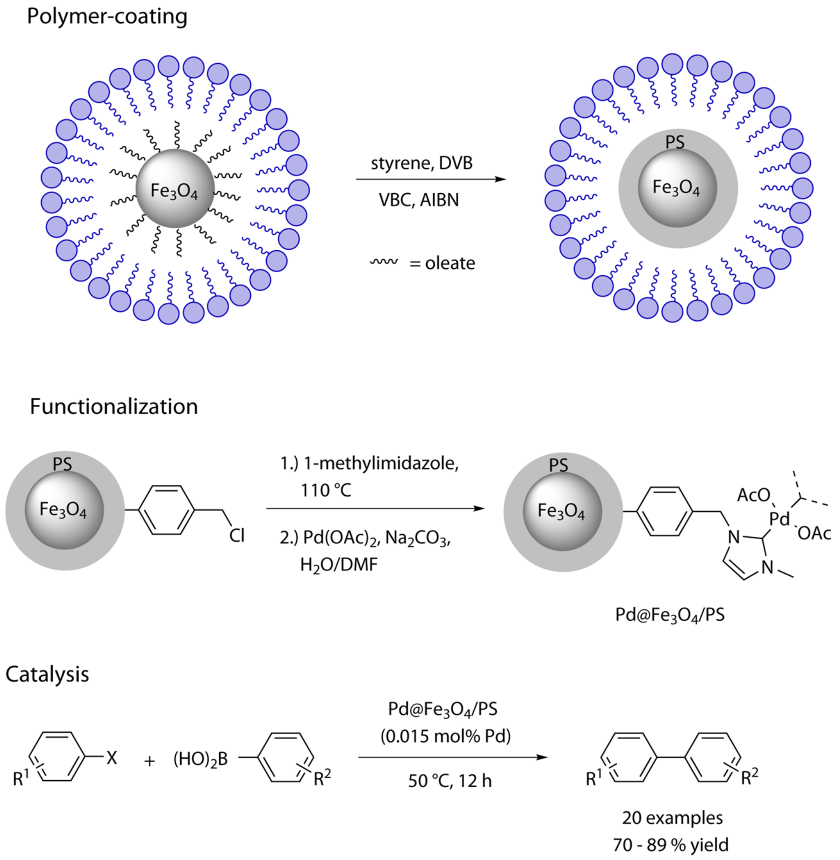
The grafting approach was also exploited by us to functionalize Co/C nanobeads with polyester dendrons.[34] First, azide moieties were introduced covalently followed by "click" reaction with dendrons bearing alkynes at the focal point and either hydroxy or ammonium groups at the periphery. The loading with functional groups was increased by a factor of 3 through the dendron shell, and the stability of particle dispersions in water improved considerably. Next to the covalently grafted dendrons, an orthogonal and reversible noncovalent functionalization with pyrene-tagged boradiazaindacene (BODIPY) fluorescent dye was possible through $\pi-\pi$ stacking on the carbon surface. Fluorescence quenching, a problem typical for dyes on $sp^2$-hybridized carbon materials, for example, CNTs, was not observed. Majoral and co-workers subsequently exploited $\pi-\pi$ interactions for a thermally triggered catch and release system of catalyst-loaded dendrimers (Scheme 4).[31] Phosphorus dendrimers with a pyrene-tagged phosphazene core and phosphine end groups were applied for Pd-catalyzed Suzuki–Miyaura cross-coupling reactions. Efficient recovery of the catalyst system was achieved by cooling to room temperature, inducing the noncovalent attachment of the pyrene-tagged complexes to the surface of the Co/C beads, and subsequent magnetic decantation. Upon heating at the reaction temperature (60 °C), the catalyst was desorbed again, and the system was reused for up to 12 iterative runs without significant loss of activity.

**SCHEME 4.** A Thermally Triggered Catalyst Catch and Release System.[36]



A completely different approach is based on the synthesis of metal nanoparticles within the core area of globular dendrimers. The variation of the dendrimer generation allows size-tuning of incorporated metal nanoparticles and therefore their properties as demonstrated for the synthesis of G6 PAMAM dendrimer-encapsulated Ni nanoparticles containing <150 Ni atoms, showing diameters of 1.5 nm but a rather low magnetic saturation of <4 emu/g.[35]

**SCHEME 5.** Synthesis of Polymer-Coated Iron Oxide Nanoparticles via Emulsion Polymerization, Subsequent Functionalization with Pd-NHC Complexes, and the Application in Suzuki Couplings[a]



[a] AIBN = azobisisobutyronitrile. Scheme adapted from ref 39.

Despite the dendrimer protective layers, the Ni nanoparticles were found to be prone to oxidation when exposed to air, so far restricting their application in catalysis.

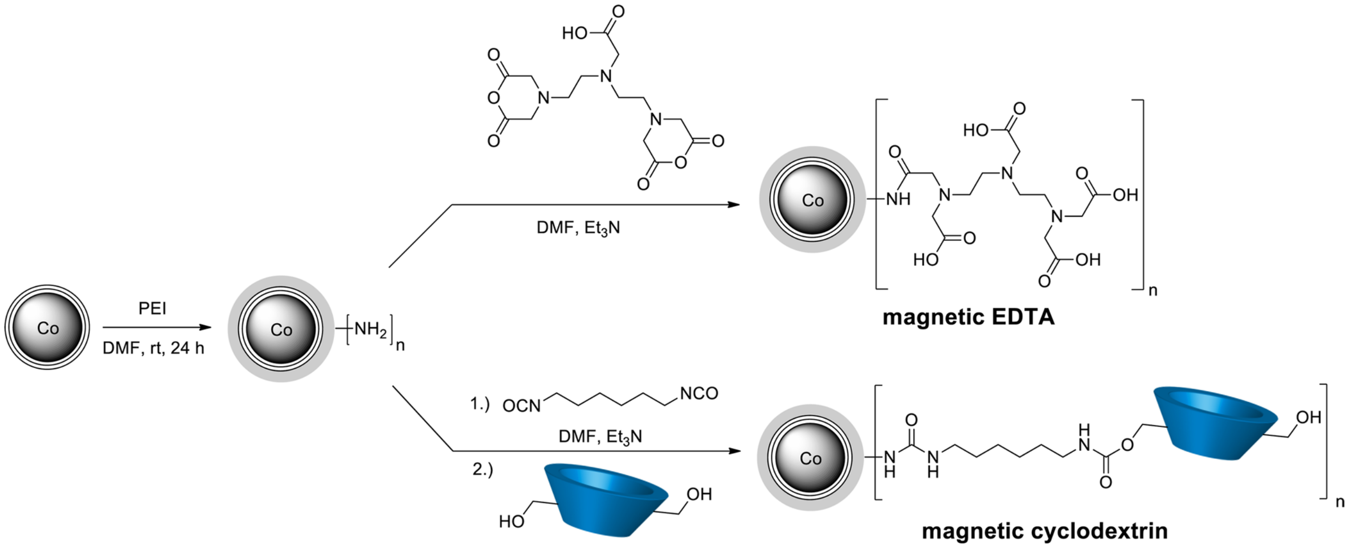
## Polymer-Functionalized Magnetic Nanoparticles

While dendrimers can efficiently multiply functional groups on the surface of magnetic nanoparticles, polymers offer other advantages: They usually require less synthetic effort to arrive at high molecular weight analogues, which expedites dispersion stabilities of the particles due to increased steric repulsion. However, polymer-coatings deal with an inherent limitation: within dense polymer diffusion, and as a consequence thereof, access to active sites can be hampered. While this is also the case for less common dendrimers with intradendritic active sites, typically they are constructed to display well exposed active sites on their surface. At higher generations, however, steric crowding might also limit the accessibility to active sites in such cases (negative dendritic effect).

The synthesis of magnetic colloids in polymer matrices and the self-assembly of polymer layers onto magnetic nanoparticles have been known for decades and have been extensively reviewed.[37,38] Less explored are methods to generate stable polymer–nanoparticle interactions that can withstand conditions applied for typical organic reactions (e.g., elevated temperatures).

Emulsion polymerization was examined by Gao and coworkers as an effective route to core/shell polymer-coated iron oxide nanoparticles.[39] $\gamma$-$Fe_2O_3$ nanocrystals coated with a layer of oleate were trapped in micelles by vigorously stirring with an amphiphilic surfactant in an aqueous medium (Scheme 5). 4-Vinylbenzene chloride (VBC) and 1,4-divinylbenzene (DVB) were embedded into the hydrophobic micellar cores and polymerized upon addition of a radical initiator forming very thin (~2 nm) polymer shells around the magnetic nanoparticles. *N*-Heterocyclic carbenes were subsequently introduced followed by the formation of Pd-complexes, which were subsequently applied in Suzuki–Miyaura reactions requiring very low catalyst loadings (0.015 mol %).

**SCHEME 6.** Physisorption of PEI on Co/C Nanobeads for the Synthesis of Magnetic Extractors[a]



[a]Scheme adapted from refs 43 and 46.

One straightforward method to covalently link poly(acrylic acid) to the surface of as-prepared magnetite nanoparticles was reported by Chen.[40] Carbodiimide activation of acid groups within the polymer was used to form ester linkages with hydroxyl groups present on the surface of the iron oxide beads. The resulting hybrid beads showed a high ion exchange capacity and were used for the reversible extraction of lysozyme. Another recent study demonstrated the successful grafting of poly(ethylene imine) (PEI) on citrate-capped magnetite beads via amide bonds.[41] Pd nanoparticles were synthesized inside the PEI shell by impregnation with a Pd(II) precursor and subsequent reduction to Pd(0). The amine groups within the PEI effectively stabilized the Pd nanoparticles for more than 10 consecutive runs of ligand-free Suzuki–Miyaura couplings.

Surface-initiated atom transfer radical polymerization (ATRP) is another efficient method to control the molecular weight of surface-bound polymer brushes and therefore the thickness of the polymer shell. The growth of poly(2-hydroxyethyl methacrylate) on $Fe_3O_4$/Si beads and the subsequent immobilization of $Ni^{2+}$-nitrilotriacetate ($Ni^{2+}$-NTA) allowed the selective extraction of histidine-tagged proteins.[42] However, additional stabilizing layers, for example, silica shells, as well as extended polymers, gradually diminish the magnetization levels of the hybrid materials. For example, the $Ni^{2+}$-NTA functionalized particles exhibited a saturation magnetization of less than 2.5 emu $g^{-1}$ requiring strong magnets for acceptable recovery times. Therefore, the highest potential for the polymer-encapsulated SPIONs might be found in biomedical applications due to reduced agglomeration,[10] while magnetic resins featuring stronger magnetic metal cores have more potential as recyclable tools for organic chemistry.

Arguably the easiest way to introduce a polymer shell to the surface of carbon-coated metal nanoparticles is the noncovalent grafting by stirring with an appropriate polymer solution. Stark and co-workers adsorbed PEI onto Fe/C nanomagnets and demonstrated the stability of this coating by several washing steps with acetate buffer (pH 3.5),[43] owing to the high energy needed to simultaneously disrupt all binding interactions between the first layer of the high molecular weight polymer and the carbon surface. The amino groups within the immobilized PEI were used as linkers to tether an ethylenediaminetetraacetic acid (EDTA)-like ligand to the polymer-coated supports (Scheme 6). The magnetic EDTA analogue was subsequently applied for the rapid removal of heavy metals from contaminated water[43] and blood[44] efficiently recycling the metal chelators after each extraction. This method was later transferred to the pilot scale level, allowing continuous magnetic extractions and subsequent filtration at 1 $m^3$ $h^{-1}$, circumventing pressure drops common with conventional large-scale solid phase extraction systems.[45] Also, an efficient removal of organic contaminants was achieved by covalently linking $\beta$-cyclodextrin to the PEI coated nanoparticles (Scheme 6).[46] The trapped molecules were completely released by filling the cyclodextrin cavity with microbiologically well accepted benzyl alcohol, and experiments at ultralow concentrations

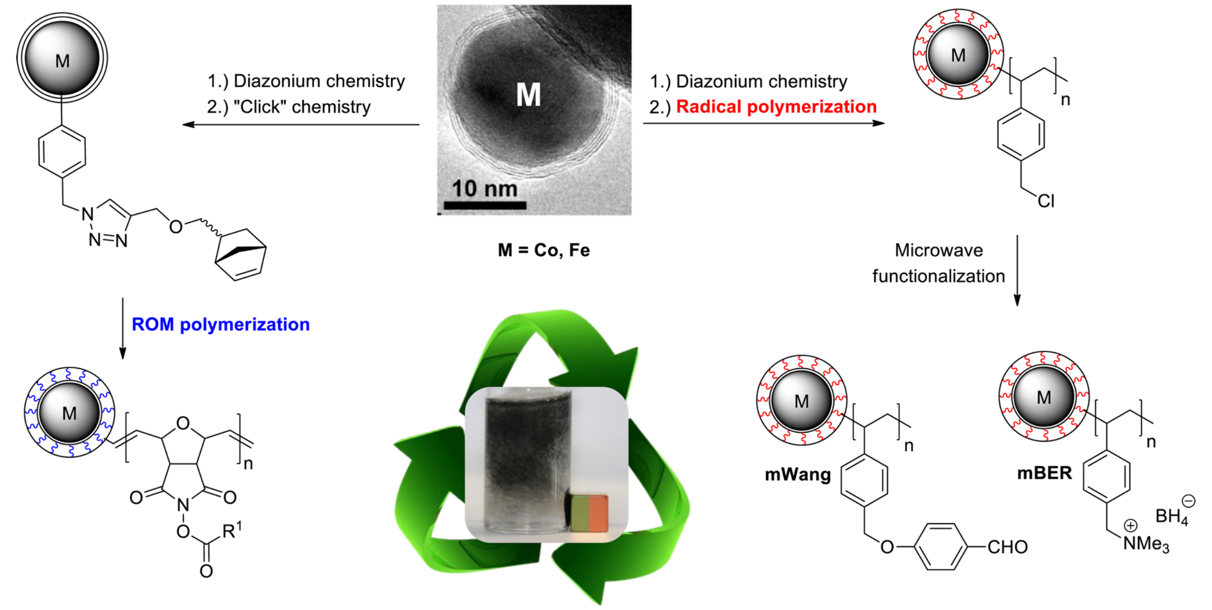


**FIGURE 2.** Preparation of polymer-coated magnetic nanoparticles via ROMP or free radical polymerization leading to highly magnetic as well as high loading reagents and scavengers.

of 160 ppb showed the potential of this hybrid system as enrichment tool for trace analysis.

One versatile strategy to generate functionalized polymers covalently bound to carbon-coated magnetic nanobeads was developed by introducing norbornene tags on their surface (Figure 3).[47] After activation with Grubbs second generation catalyst, surface-initiated ring-opening metathesis polymerization (ROMP) with norbornene-modified triphenylphosphine was carried out followed by complexation with $Pd(OAc)_2$. The saturation magnetization of the resulting magnetic hybrid material (34 emu $g^{-1}$) was consistent with the mass percentage of cobalt in the sample, and the magnetic catalyst was applied in iterative Suzuki–Miyaura reactions without loss of activity or material. Hanson and co-workers applied the Co/C nanoparticles preactivated with metathesis catalyst in the purification of intermolecular[48] and intramolecular[49] Mitsunobu reactions. Rapid sequestration of excess and depleted norbornene-tagged reagents was achieved by surface-initiated ROM polymerization on the magnetic supports. Simple magnetic decantation completely removed the reagents together with the magnetic beads giving rise to pure products. However, it was not possible to recycle the magnetic auxiliaries due to irreversibly bound polymer. Recently, we extended this methodology to the synthesis of high loading and recyclable magnetic acylation reagents.[50] Active esters derived from *N*-hydroxysuccinimide (NHS) were polymerized via surface-initiated ROMP on Co/C and Fe/C nanobeads (Figure 2). A high loading of up to 2.6 mmol $g^{-1}$ was achieved, which is 25-times higher than for nanoparticles lacking the polymer layer. The NHS ROMP gel was successfully applied for the acylation of primary and secondary amines. After isolation of the products in excellent yields and purities, the magnetic resin was readily reacylated by various acid chlorides, anhydrides, and carboxylic acids.

Radical polymerization is an alternative approach to synthesize polymer shells around carbon-coated nanoparticles, thus deaggregating the formerly densely packed ferromagnetic nanoparticles (Figure 3). Stark et al.[15] reported the surface-initiated grafting polymerization of 4-chloromethylstyrene onto vinyl-functionalized Co/C scaffolds. Optimization of the reaction conditions resulted in a nearly complete incorporation of the monomer into the hybrid material leading to high loadings of up to 3 mmol $g^{-1}$ at magnetization levels ($M_S$ = 33 emu $g^{-1}$) typical for lower loading (<1.1 mmol $g^{-1}$) magnetite materials. The functionalization with a trialkylsilane reagent allowed application as "magnetic silyl protecting group" for various primary and secondary alcohols. In this case, the exceptional durability of the scaffold was a prerequisite to withstand the harsh acidic cleavage conditions applied in the recycling process. Also, magnetic amine (mAmine), borohydride exchange (mBER), and Wang aldehyde (mWang) resins were conveniently prepared from the magnetic poly(benzyl chloride) resin by rapid microwave functionalization exploiting the strong microwave absorbing properties of the metal cores

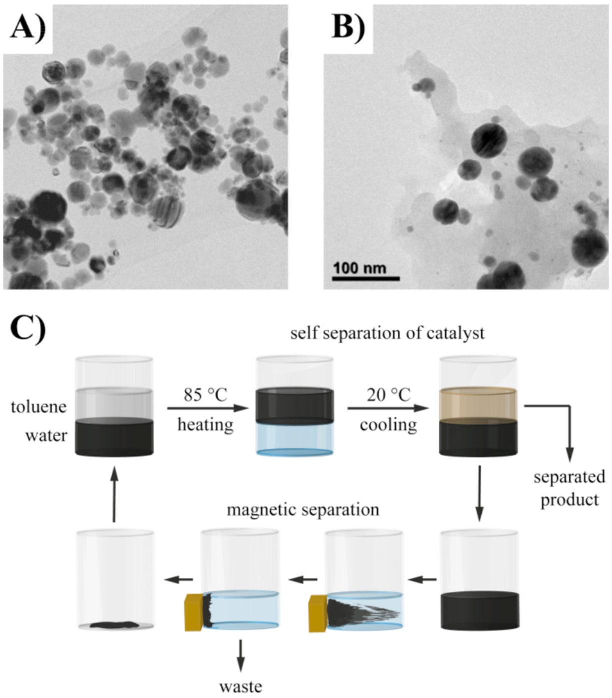


**FIGURE 3.** Transmission electron micrographs (TEM) of non-functionalized Fe/C (A) and particles with covalently attached polystyrene (B). Panel C shows the concept of a self-separating magnetic catalyst. Panels A and B were reproduced with permission from ref 52. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA. Panel C adapted from ref 53.

(Figure 2).[51] A small library of (thio)ureas was prepared in a multistep sequence exclusively applying these high loading magnetic scavengers and reagents. Excellent purities of the products were obtained with convenient magnetic decantation as the sole purification step, and the magnetic resins were efficiently regenerated.

Apart from the preparation of high loading reagents and scavengers, polystyrene-coated Co/C and Fe/C nanoparticles also proved to be suitable for the immobilization of a Jørgensen–Hayashi organocatalyst[54] or palladium NHC complexes.[55] Likewise, the extraction of organic compounds and heavy metals particularly benefits from high magnetizations (rapid separations) as well as high loadings of immobilized chelators (low material input). This was demonstrated with the covalent immobilization of zinc(II)–cyclen complexes on polystyrene-coated Fe/C beads that allowed the rapid quantitative extraction and release of riboflavin (vitamin $B_2$) from a vitamin tablet in six consecutive extractions.[52] A similar concept was used by Stark et al. for the pH-dependent reversible extraction of As(IV) using polystyrene-coated nanoparticles functionalized with *N*-methyl-D-glucamine (NMDG) as chelating ligand in a moving bed reactor system.[56]

The properties of polymer-coated magnetic nanoparticles can be tuned not only by late-stage functionalization but also by using different monomers. For example, amphiphilic *N*-isopropylacrylamide (NIPAM) was polymerized on vinyl-tagged Co/C nanoparticles.[53] The incorporation of *N*-acryloxysuccinimide monomers allowed the tethering of Pd-phosphine complexes. The novel "smart" material was applied for Suzuki–Miyaura cross-coupling reactions in a biphasic toluene–water mixture (Figure 3C). At elevated temperatures, the thermoresponsive part of the polymer collapses, and the particles translocate into the organic phase where the reaction takes place. Upon cooling to room temperature, the catalyst returns to the aqueous phase resulting in a self-separating catalyst, which can be completely removed by applying an external magnet.

## Conclusion and Perspectives

Current synthetic advances facilitated the preparation of well-defined superparamagnetic iron oxide nanoparticles and the large-scale production of ferromagnetic carbon-coated metal nanoparticles. Both types of nanomaterial have specific benefits, such as diminished agglomeration for SPIONs and high stabilities and magnetization levels for Co/C and Fe/C nanoparticles. The introduction of dendrimers and polymers to the surface of the nanomagnets boosts the loading capacity with functional groups considerably, either by ligation with presynthesized dendrimers or polymers or by surface-initiated synthesis. While the ligation allows for the attachment of well-defined and possibly commercial material, the synthesis on the particles enables a denser functionalization and an easy tuning of the properties. The resulting core–shell hybrid materials were extensively used as recyclable platforms for organic chemistry, for example, in the extraction of analytes or contaminants, as supports for metal- and organocatalysts, and in the preparation of magnetic scavengers and reagents. All these applications have in common that a high loading magnetic hybrid material was used that allowed for convenient magnetic separation and, whenever possible, recycling for further runs. It has also been shown that a full multistep synthesis can be performed exclusively by applying magnetic reagents and scavengers.

Further work is required to bring these multifunctional materials closer to industrial applications: synthetic methods have to be pushed to the multikilogram scale at reasonable costs, the particle size and size distributions need to be fully controlled, and state of the art polymerization techniques have to be applied in order to yield site isolated particles with a well-defined shell. First examples of continuous-flow synthesis using catalysts and reagents immobilized on highly magnetic supports that are contained in the system exclusively by external magnets need further exploration. Furthermore, the automation of recycling by magnetic decantation has to be investigated in detail in order to establish magnetic nanoparticles as useful supports for highly parallelized as well as high throughput syntheses.

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## BIOGRAPHICAL INFORMATION

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