

# Towards Magnetic Molecule and Reagent Separation in Organic Synthesis: Development and Use of Covalently Functionalized Nanomagnets

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**Abstract:** Preparative chemistry combines theoretical complexity and arduous practical work in the laboratory. As a result, chemists often spend long hours waiting for products to react, dry, separate, and crystallize or to be analyzed. Partial relief from waiting comes with today's broad access to efficient and elegant synthetic methods. The present contribution addresses the time-consuming work between the actual chemical reaction steps where labor-intensive work is done manually. Even the most skillful chemists admit that reactions typically run on their own while personal time is largely spent on the workup and, most important, on their planning. This article demonstrates how covalently functionalized cobalt nanomagnets can offer an unconventional way to significantly speed up separation of reagents or products in synthesis. Combining concepts from Merrifield chemistry and making use of novel materials preparation methods, reagents or synthetic intermediates can now be covalently attached to nanomagnets. With a size range of 10–50 nm, the tiny metal particles have sufficient specific surface area to attach molecules at a capacity close to presently used Wang resins or Merrifield chemistry. A synthesis can now be run in the presence of the magnetic helping agents and, if necessary, the tagged compounds can be removed from the reaction mixture within seconds. While magnetic molecule separation is still in its infancy, the present review offers insight into the materials origins and first applications.

**Keywords:** Core/shell · Graphene · Merrifield synthesis · Nanoparticle · Solid-phase synthesis

## Introduction

### Magnetic Filtration of Solids

Initiated through the discovery of strong permanent magnets and an improved understanding of magnetism, magnetic filtration rapidly caught and lost the attention of the scientific community in the early 20th century.<sup>[1]</sup> Apart from occasional reports on theoretical reactor design little has hap-

pened since then, and beyond large-scale applications in ore mining and waste recycling, magnetic separation methods have found wide industrial but little academic recognition. This past development reflects two material-related problems: Limited availability of ultrahigh strength magnets, and a lack of filtration agents (particles) of sufficient magnetization. The rapid development of modern nuclear magnetic resonance instruments, however, has heated up research into high-strength magnets and yielded a family of easy to operate, high-strength magnets.

At present, several dozen mainly small companies offer magnetic particles for a broad range of applications ranging from biochemical analysis to magnetic seal fluids for hard disk drive shafts. Magnetic particles as filtration agents have almost exclusively been based on iron or manganese oxides.<sup>[2,3]</sup> Both materials are widely available and would in principle offer an attractive way to develop magnetic separation at a large scale. One may wonder why such iron or manganese oxide particles have not been used yet to link organic molecules to nano-

magnets. Indeed, there have been numerous attempts but a deeper look reveals that covalent attachment of an organic linker to an iron or manganese oxide surface suffers from considerable instability against hydrolysis.<sup>[4,5]</sup> Alternatively, different proposals included addition of a silica or gold<sup>[6]</sup> layer onto a magnetic core and subsequent derivatization of the silica surface using organosilane linkers (e.g. R–Si(OR')<sub>3</sub>). The latter core shell structures are chemically more stable but the required silica layer reduces the already weak magnetization of the metal oxide core to unacceptably weak values.

Diagnostics has required separation of minute quantities of high-molecular weight substances. It is therefore not surprising, that magnetic separation using micrometer-sized beads has originated in clinical medicine and biochemistry.

### Polymer-based Magnetic Microbeads for Diagnostics

The rapidly growing understanding of biochemical processes in the seventies and the availability of low-cost instrumentation

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methods has triggered the introduction of molecular biology concepts into medicinal diagnostics.<sup>[7]</sup> One of the new core technologies has been magnetic separation of analytes from complex biological fluids such as blood or tissue samples. The rapid processing made magnetic separation amenable to automation and can today be found in most clinical laboratories. A look at the current development laboratories of the diagnostic market leaders reveals a high activity towards much broader integration of magnetic separation both in new fields and as a substitute for spin columns, centrifugation or chromatography.

### Why Has it Stopped There?

Chemists talking to their colleagues in biochemistry will find it difficult to justify why they should not use magnetic separation to speed up their syntheses as well. A more detailed discussion, however, reveals some severe barriers separating the current successful applications in biochemistry and potential extension into organic synthesis:

**Nanomolar capacity:** A simple back of the envelope calculation demonstrates that the presently small capacity of micrometer-sized, spherical polymer beads cannot be used in organic synthesis. Tons of beads would be required to handle material on a 1 mol scale.

**Low strength:** The saturation magnetization determines the rate of particle collection in a magnetic field and is an inherent physical property of the applied materials. Presently used iron oxide is rather weak. In some cases metallic iron has been applied, but protecting it against oxidation or iron ion leaching requires thick polymer or silica coatings, thus killing the overall magnetization properties.

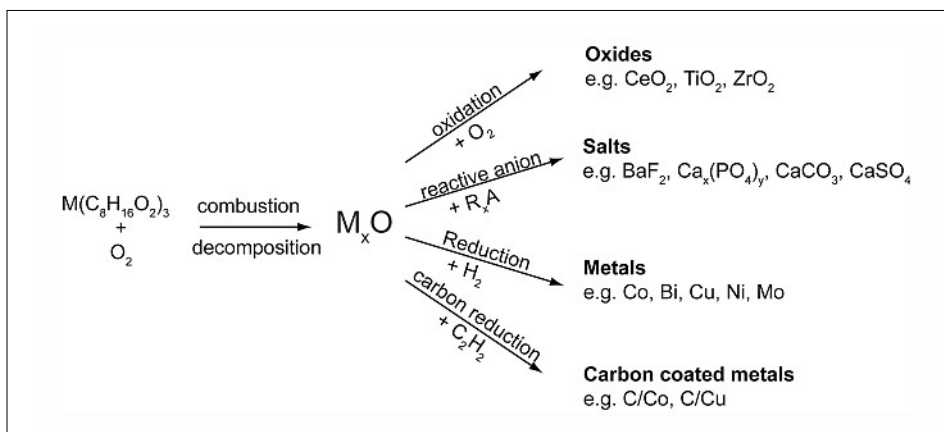
**Chemical and thermal stability:** Organic synthesis varies from cryogenic to rather high temperatures and uses aggressive solvents that can swell or dissolve polymer-based materials.

The following sections shall demonstrate how materials engineering can circumvent the above problems and offer a high-temperature stable, strongly magnetic material with a capacity close to presently used Merrifield supports.<sup>[8]</sup> However, we have to make a small excursion into nanomaterials synthesis first:

### From Oxides to Complex Salts and Metal Nanoparticles

#### Almost a Bit of Alchemy: Chemistry in Flames (Scheme 1)

In spite of the often cited novelty of nanomaterials, three large-scale commodities have been around for half a century.<sup>[9]</sup> Pigmentary titania (white pigment), aero-



Scheme 1. Moving from traditional flame synthesis in air (top entry) to running simultaneous chemical reaction with additional anion delivering precursors ( $R_A$ ) allows the preparation of most inorganic, temperature-stable, complex salts. As an example, addition of tributyl phosphate to a flame reactor combusting calcium carboxylates gives access to nanoparticles of calcium phosphate. Applying reducing conditions during combustion opens a low cost route to specific metal and alloy nanoparticles. An optional coating of carbon can be applied through the addition of acetylene.

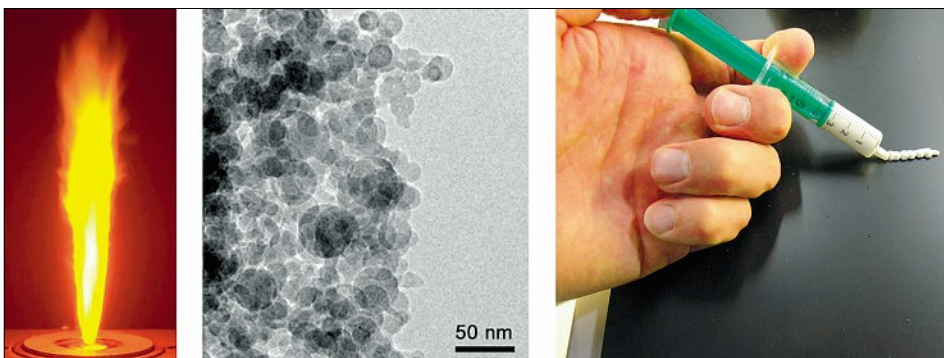


Fig. 1. The combination of anion and cation delivering precursors in flame synthesis (left) allowed extension of classical oxides ( $\text{SiO}_2$ ,  $\text{TiO}_2$ ) to complex inorganic materials such as amorphous tricalcium phosphate (middle). The tiny particles can easily be suspended in buffer and can serve as an injectable bone cement (left). The small size allows a strongly improved reactivity (hardening within minutes) compared to currently used micron-sized materials that take hours to days to solidify.

sol-made silica and carbon black (tire soot) are made by flame processes at several megatonnes per year. Production of these materials started in the forties. In principle, it would appear attractive to extend these apparently useful flame processes to other materials.<sup>[10]</sup> Flame-made oxides have been explored for applications in heterogeneous catalysis,<sup>[11–17]</sup> sensors,<sup>[18,19]</sup> lasing materials,<sup>[20]</sup> computer chip manufacturing and numerous other industrial sectors. Earlier this decade, the aerosol community gained access to most oxide materials, but few inorganics have become accessible. Studying the chemical problems of preparing complex inorganic materials in flame reactors, we have successfully extended the range of accessible products from oxides to most inorganic salts.<sup>[21,22]</sup> As a result, a number of everyday materials have become available in the form of nanoparticles: nano-limestone,<sup>[23]</sup> nano-gypsum,<sup>[24]</sup> nano-salt<sup>[21]</sup> and nano-Portland cements<sup>[25]</sup> have populated the nano-zoo next to nano-tricalcium phosphate<sup>[22,26]</sup> (Fig. 1) and nano-glasses.<sup>[27]</sup>

The latter two have been incorporated in a number of biomedical materials<sup>[26,28–31]</sup> and first *in vivo* tests demonstrated successful application as biomaterials.<sup>[32]</sup> A different, preclinical study has most recently demonstrated the advantageous re-mineralization properties of nanobioglass for damaged dentin (tooth repair).<sup>[33]</sup>

Inorganic chemistry goes well beyond complex salts and oxides. Yet the availability of metals in the form of nanoparticles has been largely restricted to noble metals with few examples accessible at an industrially important scale.

### Flame Synthesis of Metals

Chemistry in flames does not have to stop at dealing with anion/cation combinations. Most recently, we have modified flame reactors to operate under reducing (oxygen starved) conditions.<sup>[34]</sup> This can in principle be done rather straightforwardly by running a flame reactor inside a glove box and the construction of a sufficiently

powerful gas regeneration unit. Since this setup basically simulates typical metal ore reduction processes in refining, reducing flame synthesis can give access to metal nanoparticles.<sup>[18,34,35]</sup>

This shift from oxygen-rich to oxygen-deficient flames now offers low-cost access to bulk nano-metals as they can be prepared from the corresponding metal nanoparticles by consolidation. We most recently demonstrated this by the preparation of three-dimensional bulk nanocrystalline metals<sup>[36]</sup> and metal/ceramic composites.<sup>[37]</sup> The nanocrystalline, pure cobalt exhibits a Vickers hardness of typical tungsten containing alloys confirming the theoretically predicted significant improvements in material properties when shifting to nanomaterials. With the availability of alloys such as Ni/Mo-based superalloys, reducing flame synthesis has become a raw material supplier to modern metallurgy.<sup>[38]</sup>

### In situ Graphene Coating of Metal Nanoparticles

Carbon deposition on metal surfaces has probably been one of the most unwellcome topics in heterogeneous catalysis as it routinely kills catalytic activity.<sup>[39]</sup> In contrast, carbon nanotubes are grown on metal nanoparticles using the same chemical activity of certain transition metals.<sup>[40]</sup> Here carbonization is most welcomed. Appropriate flame reactor design has allowed carbon deposition to be fine-tuned when preparing metal nanoparticles by reducing flame synthesis.<sup>[18]</sup> In principle, the degree and rate of carbon deposition depends on temperature, gas composition and the

metal surface.<sup>[38]</sup> Controlled temperature profiles in the exit stream of flame reactors and additional feeding of hydrogen, carbon mono- or dioxide, methane or even acetylene provides an option to *in situ* coat metals with a carbon layer. The properties of such core/shell metal/carbon materials can yield unexpected bulk properties and we could most recently demonstrate the suitability of 1 nm carbon-coated copper particles for temperature or pressure sensing.<sup>[18]</sup> A complex tunneling mechanism enables sensitivities comparable to currently commercially used, optimized spinels.<sup>[19]</sup> Water-based dispersions or inks of such carbon-coated copper nanoparticles have recently provided access to highly sensitive humidity sensor coatings (Fig. 2).<sup>[41]</sup>

Exchanging the copper core by cobalt allows the preparation of carbon-coated nanomagnets with extremely low coercivity and a high saturation magnetization (Fig. 3).<sup>[42]</sup>

### Covalent Functionalization of Nanomagnets

While biochemical methods have routinely relied on non-covalent bonding (*e.g.* ELISA assays) and magnetic separation of proteins,<sup>[7]</sup> the normally weak adsorption of molecules on a carrier requires covalent bonding to keep reactants or linkers in place. Merrifield solid-state synthesis routinely relies on covalently attached linkers to a polymer support resin.<sup>[8]</sup> Transfer of this most successful linker concept to magnetic separation for organic synthesis therefore requires reliable attachment of such linkers to the surface of a nanomag-

net. This can be done through the covalent functionalization of mechanically trapped metal particles in their carbon coating. Realizing that the here reported carbon coatings were physically similar to carbon nanotube (CNT) walls, we tested the transfer of most successful CNT derivatization developed by Bahr and Tour to metal nanomagnets.<sup>[43]</sup> Recent experiments have demonstrated that a broad range of derivatization reagents based on diazonium chemistry succeed on these nanoparticles carbon coatings as well.<sup>[42]</sup>

### Linking Molecules to Metallic Nanomagnets

The possibility to link chloro-, bromo-, nitro-, and other functionalized *para*-substituted phenyl units to C/Co nanoparticles provides a starting point to the organic chemists' creativity to derivatize the nanomagnets into magnetic protection agents, magnetic homogeneous noble metal catalyst ligands or magnetic chelating reagents for metal removal and extraction (Scheme 2).<sup>[42]</sup> In principle, solid-phase-bound magnetic reagent supports can now be used in classical laboratory glass wear and processing equipment as typical suspensions of magnetically attached products.

### Technical Robustness

Both laboratory scale and production environments demand technical robustness if a reagent shall repeatedly find broader use. The harsh conditions during

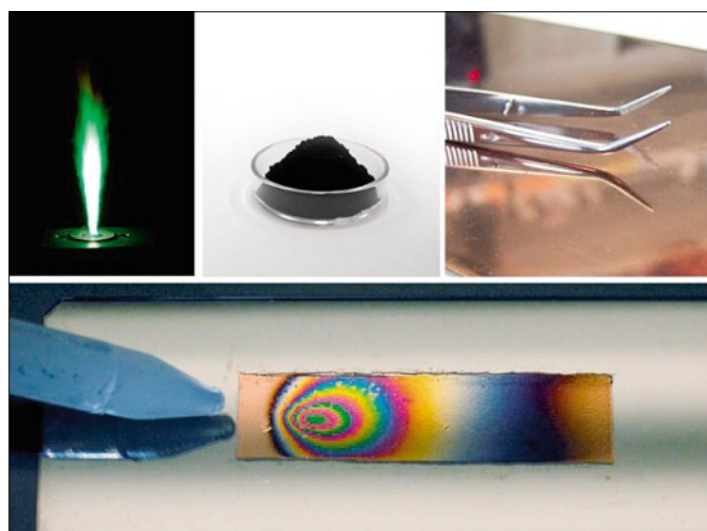


Fig. 2. Copper nanoparticles manufactured by reducing flame synthesis (left) at 30 g copper per hour. Using a 1 nm carbon coating, copper nanoparticles are rendered air-stable (middle). The particles can be used to paint metallic surfaces (top, right) with high reflectivity. Using porous, surfactant-loaded copper films (bottom) allows use as humidity or solvent vapor sensors. As a demonstration, ethanol vapor is fed through the plastic tube on a sensor surface. This optical read-out does not require any electronics and makes such films attractive to high volume, low cost applications in packaging.

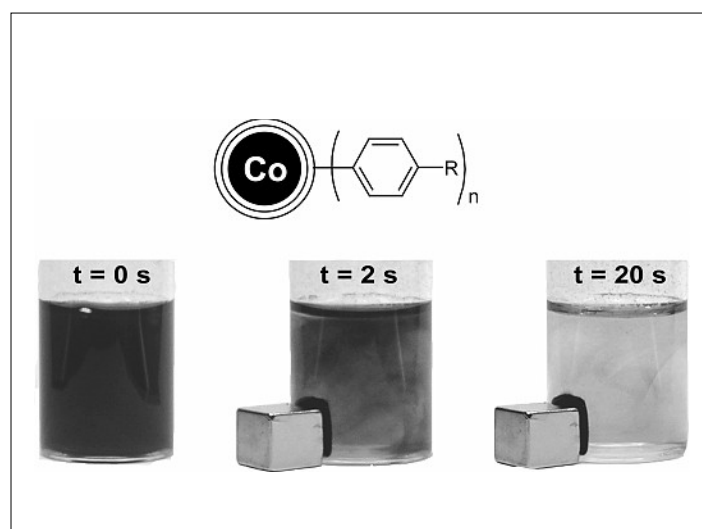
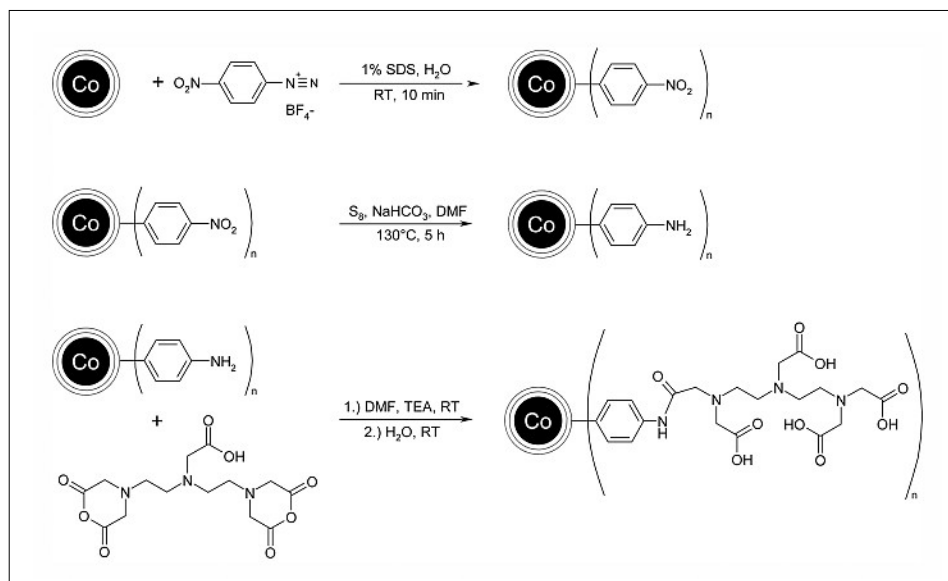


Fig. 3. A dispersion of magnetically tagged molecules (left) is separated from a reaction solution (or model waste water) by the application of a permanent magnet (cube). After about twenty seconds, most of the particles have already moved to the container's wall (>99% clearance). It can be expected that magnetic protection groups, ligands for homogeneous catalysts and antibodies for protein capture will strongly contribute to saving time in separation processes.



Scheme 2. Reaction sequence for the derivatization of carbon-coated cobalt nanomagnets using a diazonium salt (top). Subsequent reduction and coupling to diethylene triamine penta acetic acid yields magnetic metal chelators for heavy metal extraction and recovery from waste water. This 'magnetic DTPA' can clean highly diluted heavy metal solutions within minutes.

organic synthesis require resistance to solvent swelling and dissolution. This apparently simple requirement prohibits use of polystyrene-based magnetic composites in most solvents. In contrast, the graphene coating and metal core geometry resists most chemical treatment conditions. The thermal stability of most polymers applicable to magnetic composites is restricted to below 100 °C. Carbon-coated metals have shown astonishingly high protection against oxidation up to 200 °C.

### Strings and Pitfalls

Nanomaterials are prone to agglomeration. Their Brownian motion makes particle–particle collisions a very rapid process and unless specific precautions are taken, nanoparticle dispersions precipitate within seconds to minutes, depending on surface charge.<sup>[44]</sup> The examples presented here of metal/water or metal/solvent dispersions are no exception to this problem. As a result, particles must be surface modified to prohibit agglomeration in the absence of a magnetic field. This surface modification can interfere with the need to attach specific molecules or reagents. Here, carefully chosen combinations of surface coatings may be used, or, in other cases, the synthetic chemist may choose to ignore agglomeration and stir the dispersions mechanically. In most cases, this will be sufficient to keep the material afloat even if partially agglomerated.

A second point of improvement is the particle's capacity for binding. At present, the use of 10–30 nm sized particles physically limits the specific surface area to a few ten square meters. Slightly smaller particles will significantly improve the ca-

capacity of the material, ideally up to about 1 millimol per gram. This is in the range of presently used solid supports such as Wang resins and offers a technically useable solution. An alternative way to further increase capacity would be the use of dendrimer-like ligands or short functionalized polymer chains.

### Outlook

#### What Can We Expect from Magnetic Separation in Chemistry?

A look back at the development in biochemistry and diagnostics shows that high-throughput experimentation strongly depended on automation. Reagent pumping and product separation largely determine whether a given range of processes can be done automatically and at low volumes. Magnetic separation has today become the key separation method in standard biochemical and diagnostic protocols even though simple centrifugation would work well in most cases. Such mechanical processes, however, are prone to failure and have constantly lost ground in favor of magnetic microbead technology. We believe that a similar development will take place in organic chemistry and the presently highly labor-intensive preparatory work in the laboratory will greatly profit from rapid product separation and reagent handling. Productivity and attractiveness of the daily life of the synthetic organic chemist will profit from a shift in workload to a larger portion of time dedicated to thinking about a synthesis rather than mechanically working on it.

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