Magnetic Nanoparticles

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Inductive Heating for Organic Synthesis by Using Functionalized Magnetic Nanoparticles Inside Microreactors**

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Interest in magnetic nanoparticles[1] has increased considerably lately, with diverse applications as magnetic liquids,[2] in catalysis,[3] in biotechnology and biomedicine,[4] and in magnetic resonance spectroscopy.[5] A principal problem associated with naked metallic nanoparticles is their high chemical reactivity, in particular oxidation by air. This drawback can be overcome by coating the nanoparticles with SiO_2, metal oxides, gold, or carbon. Several applications of these nanoparticles for quasi-homogeneous catalysis have been disclosed. These particles are typically removed after the reaction by exploiting their magnetic properties.[3e,f]

An unexploited and very important feature of magnetic materials is the possibility of heating them in an electromagnetic field. It has been demonstrated that isolated magnetic nanoparticles show magnetic behavior different from that in the bulk. These magnetic nanoparticles when coated with a silica shell can show superparamagnetic behavior.[6,7] The silica coating prevents the magnetic cores from coupling, thereby preserving their superparamagnetic properties. These composites do not have a residual magnetization and their magnetization curves are anhysteretic. However, the susceptibility of a superparamagnetic material is almost as high as that of a ferromagnetic material.

The concept of magnetically induced hyperthermia is based on specific properties of the magnetic nanoparticles upon exposure to a constantly changing magnetic field.[1,8] Surprisingly, this property of magnetic nanoparticles has so far not been applied in chemical synthesis,[9] although organic chemists are constantly testing new technologies such as microwave irradiation, solid-phase synthesis, and new reactor designs in their work with the goal of performing syntheses and workups more efficiently.[10]

Herein we disclose the first application of heating magnetic silica-coated[7] nanoparticles in an electromagnetic field. We demonstrate that these hot particles can be ideally used inside a microfluidic fixed-bed reactor for performing chemical syntheses including catalytic transformations. Thus, besides conventional and microwave heating, magnetic induction in an electromagnetic field is a third way to introduce thermal energy to a reactor.[10]

Superparamagnetic materials like nanoparticles **1** can be heated in medium- or high-frequency fields.[11] As the technical setup for the middle-frequency field (25 kHz) is simpler (see Figure 1 b,c), we investigated the electromagnetic induction of heat in magnetic nanoparticles in this frequency range. In principal, the processes can be operated in a cyclic or a continuous mode. The inductor can accommodate a flowthrough reactor[10,12] (glass; 14 cm length, 9 mm internal diameter), which is filled with superparamagnetic material **1**. The reactor can be operated up to a backup

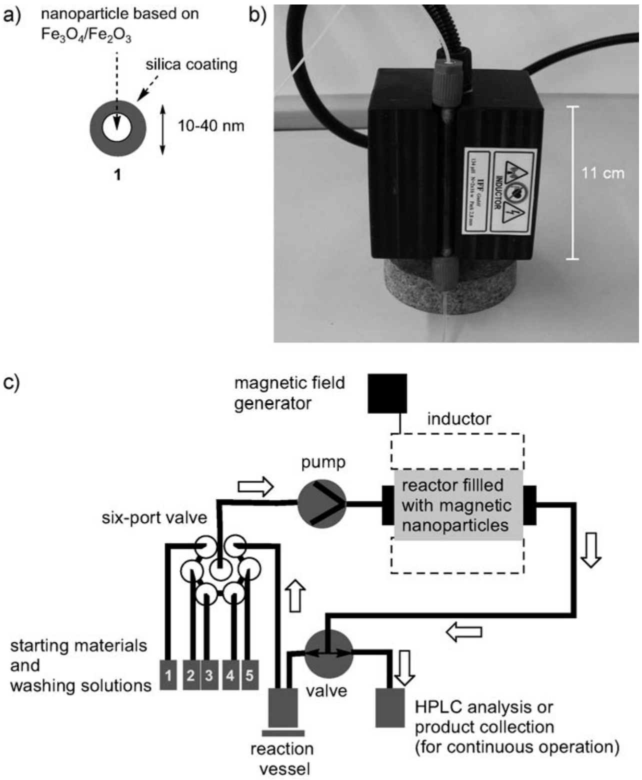

Figure 1. a) Drawing of magnetic nanoparticles **1**[7] (TEM images are shown in the Supporting Information); b) inductor and flow reactor filled with magnetic nanoparticles; c) experimental setup for either cyclic operation or continuous operation.

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pressure of 5 bar. We initially determined the heating profiles of other ferromagnetic materials besides magnetic nanoparticles **1**, such as SiC, iron powder, and Fe_3O_4 (Figure 2). We found that SiC could be heated only under high-frequency conditions (≥ 1000 kHz)[11,13] while iron powder heated up only moderately in a middle-frequency field (MF). The behavior of Fe_3O_4 in the electromagnetic field was similar to that of magnetic nanoparticles **1**. However, as this material is not protected with an inert coating and has reduced mechanical stability, we did not study it further. Additionally, the silica coating on **1** allows for further functionalization (vide supra).

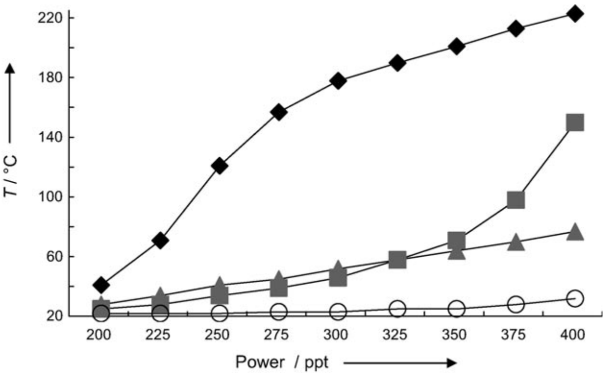
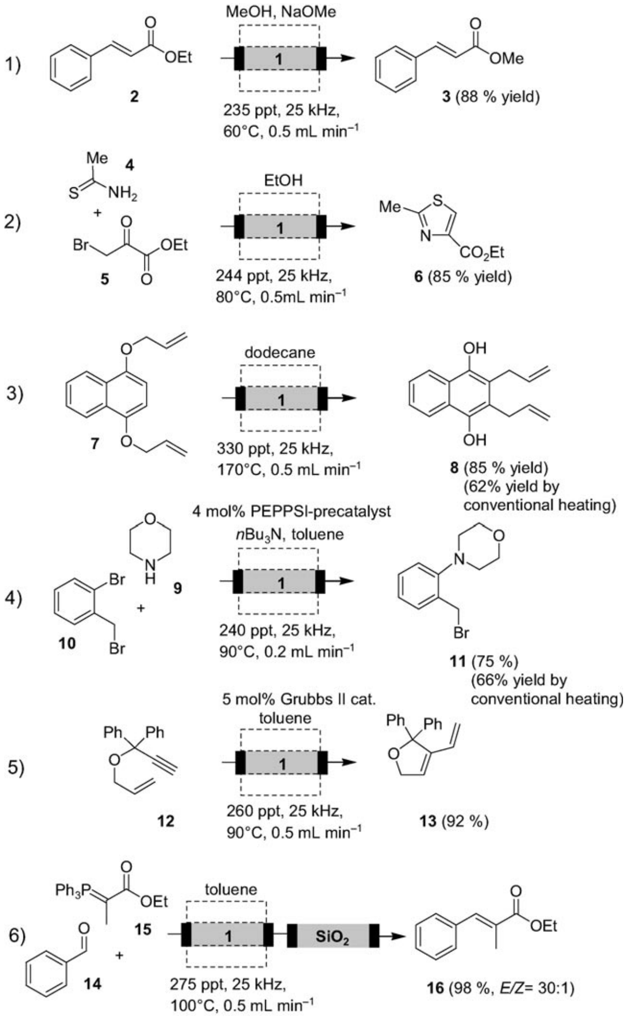


Figure 2. Heating profile of different materials in an electromagnetic field. Applied power output refers to the percentage of the power provided by the magnetic field that is being transferred into the magnetic material to be heated. 1000 parts per thousand (ppt)[13] is therefore the maximum; ◆: nanoparticle **1**, ■: Fe_3O_4, ▲: Fe powder, ○: SiC

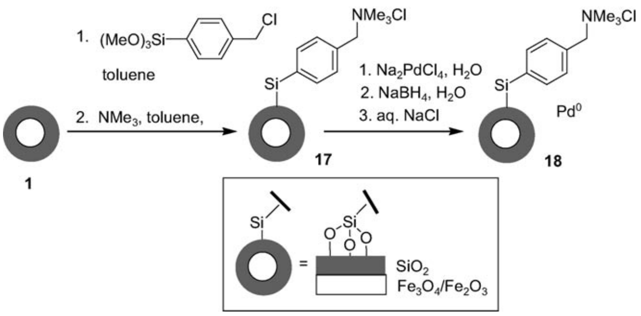
By exploiting the unique properties of our superparamagnetic nanoparticles we performed several transformations under continuous-flow conditions: the transesterification of **2** (Reaction 1 in Scheme 1), condensation to form thiazole **6** (Reaction 2), and Claisen rearrangements of **7** (Reaction 3) using magnetic nanoparticles **1** as a packed bed inside the flow reactor. Furthermore, we performed catalytic transformations such as the Buchwald–Hartwig amination of aryl bromide **11** (Reaction 4) and enyne metathesis to yield dihydrofuran **13** (Reaction 5). A simplified purification procedure was demonstrated also for the Wittig reaction of benzaldehyde (**14**) and ylide **15** (Reaction 6). In this case an additional packed-bed reactor filled with silica was implemented behind the first reactor, and the ethyl ester **16** was obtained in quantitative yield after simple removal of the solvent. Finally, the Claisen rearrangement and the Hartwig–Buchwald amination were repeated under identical conditions with the same reactor except that the reactor was heated in an oil bath. The yields of isolated product after one run were reduced because complete conversion could not be achieved. This observation can be rationalized by the fact that the inductively induced heat is generated inside the reactor directly where the reaction takes place.

Additionally, as a result of the silica coating, the surface of the magnetic nanoparticles can be functionalized.[14] We found that palladium particles obtained by reductive precipitation of ammonium-bound tetrachloropalladate salts gave nanoparticles **18** which showed good catalytic activity under flow conditions. The preparation of **18** is briefly depicted in Scheme 2 and is based on our earlier studies.[15]

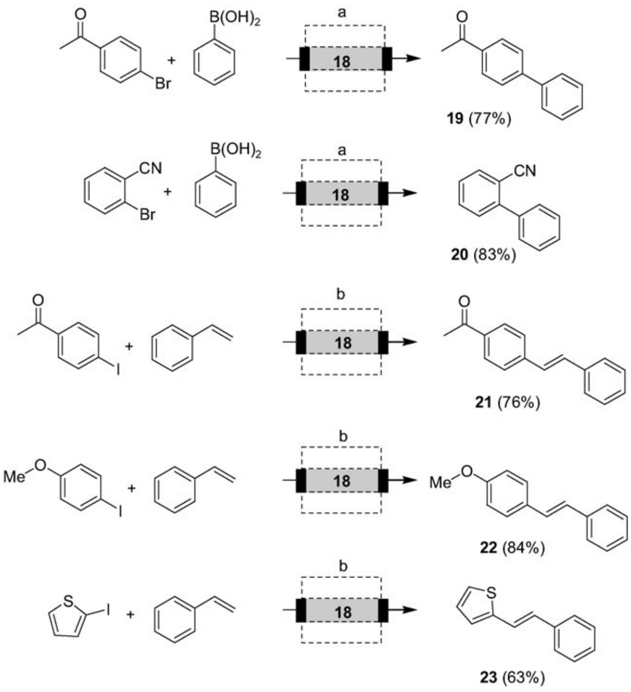


Scheme 1. Continuous-flow syntheses with inductive heating (conventional heating). Complete transformation in one run; 0.5–2 mmol scale (see the Supporting Information); yields of isolated products.[16]

We employed these particles in various Pd-catalyzed cross-coupling reactions (Scheme 3). In these reactions only



Scheme 2. Preparation of magnetic nanoparticles functionalized with Pd^0.



Scheme 3. Suzuki–Miyaura and Heck coupling reactions under flow conditions (cyclic operation) with inductive heating of **18** (1 mmol scale; yields of isolated products). Conditions: a) 1.5 equiv phenyl boronic acid, 1 equiv aryl bromide, 2.4 equiv CsF, 2.8 mol% **18**, DMF/H_2O, 1 h, flow rate: 2 mL min^{-1}, inductor: 750 ppt,[17] 25 kHz (100 °C); b) 1 equiv aryl iodide, 3 equiv styrene, 3 equiv nBu$_3$N, 2.8 mol% **18**, DMF, 1 h, flow rate: 2 mL min^{-1}, inductor: 325 ppt, 25 kHz (120 °C).[16]

little leaching of palladium was found (ICP-MS analytic indicated 34 ppm for Suzuki–Miyaura reactions and 100 ppm for Heck reactions), and the catalyst could be reused more than three times without a decrease in activity.

In conclusion, we have disclosed the first application of magnetic nanoparticles as heatable media in an electromagnetic field for chemical synthesis. We have demonstrated that these materials can ideally be used in continuous-flow processes. In addition, we have shown that the silica coating used to protect the nanoparticles based on Fe_3O_4/Fe_2O_3 can be further modified with catalytically active palladium. Our experimental setup is much simpler than that for heating a flowthrough reactor by microwave irradiation. It must be noted that not only nanoparticles based on Fe_3O_4/Fe_2O_3 can be heated efficiently in electromagnetic fields but principally also those based on Co and Ni, and other materials (e.g. transition metals and lanthanides and combinations such as alloys).[18] Thus, this inductive heating technique has great potential both in laboratory and industrial processes. Current work is dedicated to the development of new reactors that can withstand higher temperatures and pressures so that reactions can be accelerated further.

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[11] With conductive materials, about 80% of the heating effect occurs on the surface. Small or thin parts generally heat more quickly than large thick parts, especially if the larger parts need to be heated all the way through. Therefore, magnetic nanoparticles are ideally suited for being heated through electromagnetic fields.

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[13] The temperature was measured under steady-state conditions using an IR pyrometer. This instrument determines the overall temperature of the reactor interior but fails to measure the temperature of the nanoparticles. Other methods for measuring the fluid temperature like thermocouples positioned inside the reactor were not suitable because the sensor interacts with the electromagnetic field.

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[16] The temperature achieved by inductive heating is dependent on several factors such as reactor diameter, inductor design, and the nature of the nanoparticles used. Therefore, the ppt value has to be recalibrated for every inductor/reactor system. This situation is comparable with the use of microwave heating devices, where, for example, the choice of solvent has a crucial impact on the heat generated.

[17] The ppt value is significantly higher than in the other cases. Here, a first-generation inductor was employed.

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