DOI: 10.1002/ejoc.201000628

Inductively Heated Oxides Inside Microreactors – Facile Oxidations under Flow Conditions

Jens Wegner,[a] Sascha Ceylan,[a] Carsten Friese,[b] and Andreas Kirschning*[a]

Keywords: Inductive heating / Microreactors / Oxidation / Metal oxides

Inductively heated iron oxides mixed with solid oxidants like CrO_2 and NiO_2 efficiently oxidize organic substrates under flow conditions in fixed-bed reactors.

Introduction

Recently, we disclosed the first application of ferromagnetic materials like magnetic nanoparticles **1**, coated with a silica shell, as heating media in chemical reactions (Figure 1).[1]

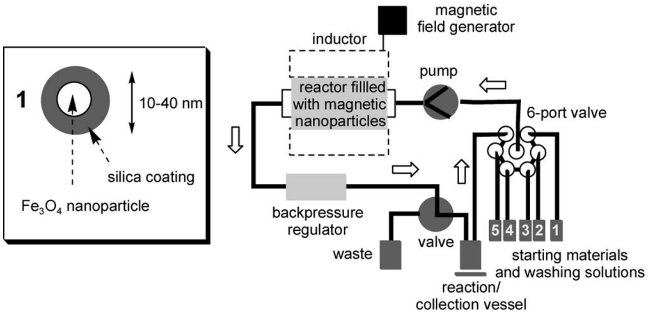


Figure 1. Schematic drawing of magnetic nanoparticles **1** and technical setup.

We showed that inductive heating allows to perform many principle endothermic reactions such as transesterifications, condensations, Pd-catalyzed cross coupling reactions and Wittig olefinations under flow conditions. Although magnetic nanoparticles have gained considerable interest lately due to their magnetic properties, which allow to remove them from a reaction mixture with a magnet,[2] the important property of heating them in an electromagnetic field has been, with the exception of our first communication, unexploited in organic synthesis. The concept of magnetic inductive hyperthermia is based on the fact that loss of magnetic hysteresis creates heat (Néel relaxation), when magnetic nanoparticles are exposed to a constantly changing magnetic field.[2,3] Additionally, a very strong rapidly alternating magnetic field will also induce eddy currents on any conductive material placed in the vicinity of that field. These eddy currents are also able to heat the metal by induction but to a lesser extent than magnetic materials that mainly produce heat through the so called hysteresis effect. 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 thermal activation by electromagnetic fields.

Results and Discussion

Our preliminary results clearly showed that inductive heating of ferromagnetic materials inside flow reactors has great future prospects particularly because the technical setup is much simpler than corresponding microwave devices so that it has the potential of becoming an additional enabling technology for organic synthesis.[4]

In this report we extend our studies on metal oxide mediated oxidations under flow conditions. Several oxides such as CrO_2 (MagTrieve™)[5] and NiO_2 are widely employed solid oxidants in organic chemistry. Commonly, the reduced byproducts are also solids and should not or hardly release metal impurities into solution. Therefore, these metal oxides are well suited for being incorporated into fixed-bed flow reactors. When mixed with inductively heatable materials like nanoparticles **1**[6] an ideal setup for continuous oxidations in micro- or miniflow reactors should be achieved for several reasons: (a) simple setup, (b) only superparamagnetic particles are the initial source for heating, which occurs inside the reactor, (c) metal oxides are heated because of the close proximity to the heating source which guarantees ideal heat exchange, (d) nanoparticles can be superheated (above 500 °C!), and (e) metal leaching is kept to a minimum.[7]

---

[a] Institut für Organische Chemie und Biomolekulares Wirkstoffzentrum (BMWZ), Leibniz Universität Hannover,
Schneiderberg 1b, 30167 Hannover, Germany
Fax: +49-511-762-3011
E-mail: andreas.kirschning@oci.uni-hannover.de
[b] PIT – Plasma Induction Technology,
Lorettostraße 20, 40219 Düsseldorf, Germany

Superparamagnetic materials like nanoparticles **1** can be heated in medium- or high-frequency fields. As the technical setup for the former is simpler than for the latter, we carried out electromagnetic induction of heat in magnetic nanoparticles by applying a medium-frequency field (ca. 25 kHz). The heating profile of these nanoparticles in a medium-frequency field is reported in ref.[1]

In our initial studies we chose CrO_2 and NiO_2 (nickel peroxide) as representative oxides. Commonly, superparamagnetic nanoparticles **1** were mixed with the oxidant inside a flow reactor made of glass and encased with an inductor. The dimensions of the reactor are 14 cm length and 8.5 mm internal diameter. The inner volume (for the fluid) of this fixed-bed reactor was determined to be about 4 mL. In cases when a higher temperature than the boiling point of the solvent was needed a tailor-made PEEK (polyetherether ketone) reactor with the same inner dimensions and equipped with an inline back-pressure regulator was applied (see Figure 2, right). Principally, the processes can be operated in a circular or a continuous mode.[8] However, we optimized several reaction parameters to achieve full conversion in one pass: (a) the concentration of reactants/product for avoiding solubility problems, (b) the flow rates in order to achieve full conversion in one pass, and (c) induction parameters for heating the superparamagnetic fixed bed without degradation of reactants or products. This allows to carry out oxidations in a continuous fashion until the oxidant is exhausted.[9] It must be noted that temperature determination of individual nanoparticles is a very difficult task. As described in ref.[1], we used an IR-pyrometer for measuring the surface temperature of the fixed bed inside the glass reactor.[10] We found that heating of the solutions proceeds very rapidly once they have entered the reactor. The desired temperature was commonly reached within the first cm of the reactor.[11]

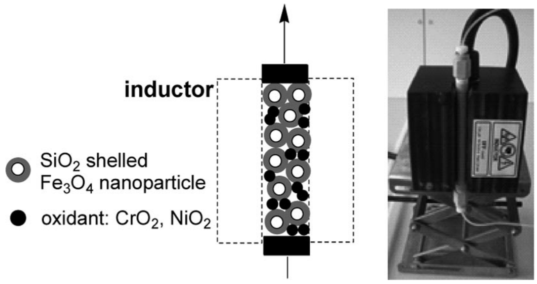
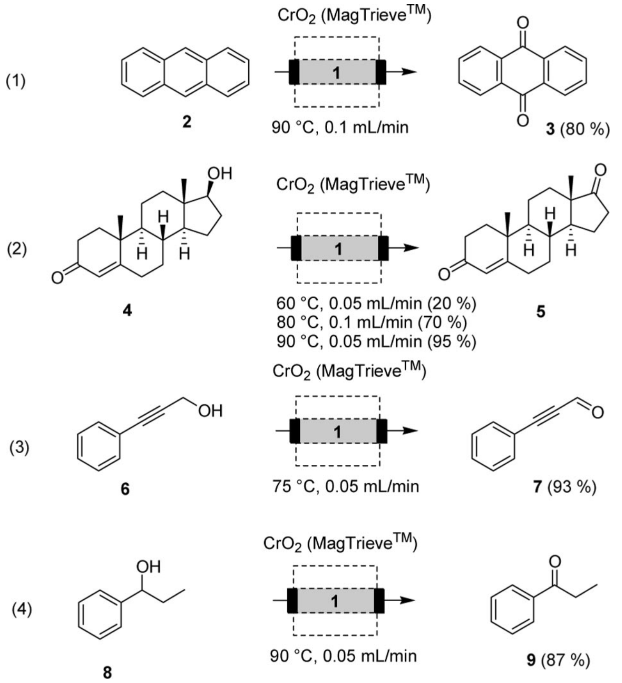


Figure 2. Flow reactor filled with magnetic nanoparticles and solid oxidant (left) and PEEK reactor encased with an inductor (right).

First, we oxidized different alcohols such as the propargylic alcohol **6** and the benzyl alcohol **8** to the corresponding aldehyde **7** and ketone **9**, respectively, using CrO_2 as solid oxidant (Scheme 1). It was also possible to readily oxidize the steroidal alcohol **4** or to directly transform weakly activated C–H bonds as is shown for the oxidation of anthracene (**2**) to anthraquinone (**3**). The reactions were carried out in glass reactors with an inductive frequency of 25 kHz. The substrates were commonly dissolved in toluene (0.15 M). The influence of the flow rate and temperature induced by the inductive field on the efficiency of the process is exemplified for Equation (2) in Scheme 1. At a flow rate of 0.05 mL/min at 60 °C only 20 % of transformation was encountered after one pass, whereas at 90 °C full conversion occurred. If the flow rate is increased to 0.1 mL/min, 70 % conversion was reached at 80 °C.



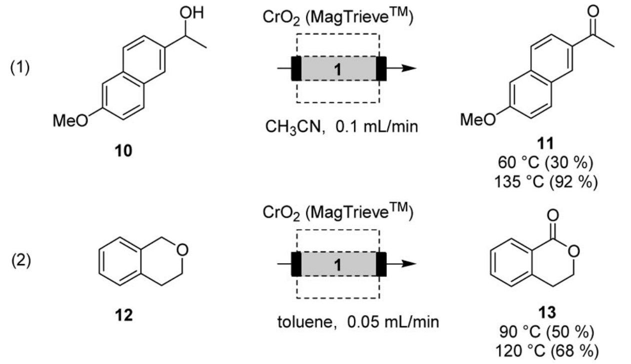
Scheme 1. Continuous (single pass; full conversion) CrO_2-promoted flow oxidation with inductive heating (isolated yields); yields and conditions for batch reactions: **3**: toluene, 90 °C, 7 h, 46 %; **5**: toluene, 90 °C, 22 h, 95 %; **7**: toluene, 90 °C, 7 h, 62 %; **9**: toluene, 90 °C, 7 h, 95 %.

All these reactions were carried out in glass reactors that cannot be operated at backpressure drops above 40 psi. In order to circumvent these limitations, we employed our PEEK reactor that is solvent-resistant and able to withstand backpressures well above 100 psi at higher temperatures (up to 250 °C). These reactors can be operated when substrates like benzyl alcohol **10** or benzyl ether **12** could only rapidly (single pass under flow conditions) be oxidized at higher temperature, typically well above the boiling point of the solvent. Both reactions were performed in 0.15 M solutions at 100 psi back pressure (Scheme 2).

Noteworthy, when the reaction mixtures were inductively heated in the presence of the oxidant MagTrieve™ above 150 °C in toluene, we observed some oxidation of the solvent and formation of benzoic acid (ca. 0.04 % with respect to toluene). For the oxidation of alcohol **10** to ketone **11** acetonitrile had to be used as solvent because of solubility problems.

At this point it needs to be stressed that despite the fact that CrO_2 is paramagnetic and can be removed with a magnet, it cannot be heated in an inductive field because it does not have conductive properties.

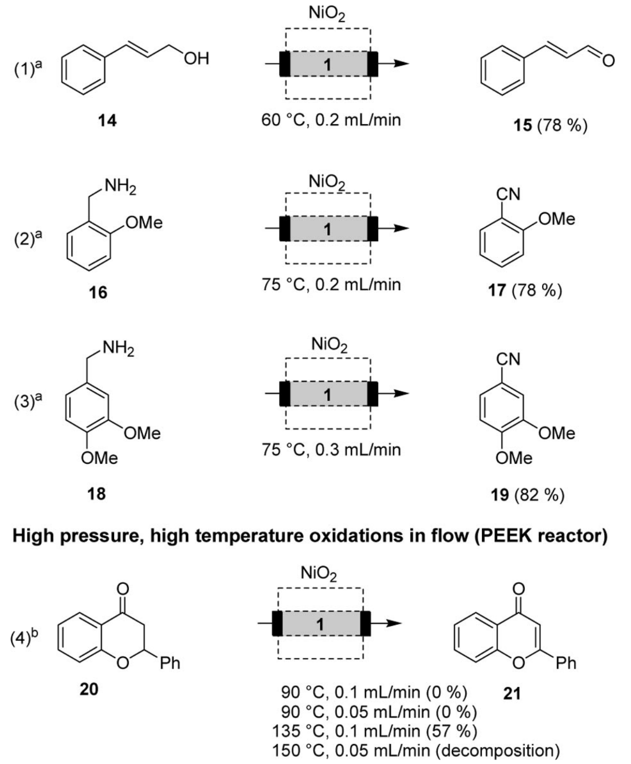
Compared to the same reactions conducted in a flask, the workup is highly simplified. In principle it is possible to



Scheme 2. High-pressure, high-temperature oxidations (single pass) in flow with PEEK reactor; yields and conditions for batch reactions: **11**: CH_3CN, 90 °C, 7 h, 57%; **13**: toluene, 90 °C, 7 h, 51%.

remove the oxidants by a magnet or by filtration from the batch reaction mixture, which requires a significant amount of solvent for complete removal of all nanoparticles. In the case of our fixed-bed flow system a clear solution left the reactor with very low metal contaminations[7] allowing for isolation of the product by direct removal of the solvent under reduced pressure.

In order to broaden this experimental concept, we extended these studies to nickel peroxide as solid oxidant inside our inductively heated flow reactors (Scheme 3). Thus, allyl alcohol **14** was oxidized to the corresponding aldehyde **15** under flow conditions. Importantly, we were also able to transform benzylamines **16** and **18** into nitriles **17** and **19**, respectively.



Scheme 3. Continuous [single pass; full conversion except for Entry 4 (a,b)] nickel peroxide promoted flow oxidations with inductive heating (isolated yields). (a) Substrates in toluene (0.15 M), inductive frequency 25 kHz, glass reactor. (b) PEEK reactor: **20** dissolved in toluene (0.125 M), 100 psi backpressure. (c) Yields and conditions for batch reactions: **15**: toluene, 90 °C, 2 h, 72%; **17**: toluene, 90 °C, 6 h, 72%; **19**: toluene, 90 °C, 4 h, 70%; **21**: toluene, 90 °C, 24 h, 42%.

In general we observed that, except for substrates **8** and **12**, oxidations in the flow mode gave similar or higher yields compared to batch experiments. The major practical advantage of conducting these oxidations in the flow mode lies in the better time/yield ratio. Whereas many reactions had to be conducted for more than 22 h to achieve full conversion in the flask, the same reaction took 2–7 h operation time (which correlates with a residence time of 40–80 min) under flow conditions [Scheme 1, Equation (2); Scheme 3, Equation (4)]. Additionally, workup for products collected from flow syntheses was highly simplified.

Conclusions

We disclose the first applications of inductive heating inside flow reactors by employing mixtures of superparamagnetic nanoparticles and solid oxides as fixed-bed materials. This fixed bed shows very good oxidizing properties and can be utilized to reach full conversion in a single pass. In selected cases, the flow reactor was operated under high-pressure/high-temperature conditions by using PEEK reactors. In essence, besides conventional and microwave-initiated heating, exposition of magnetic nanoparticles to an electromagnetic field is a third and new principal way for introducing thermal energy into a reactor.[4] This heating concept can particularly well be applied in micro- and mini-reactor setups and has potential to be employed in an industrial context.

Experimental Section

General Information: ^1H NMR spectra were recorded at 400 MHz with a Bruker AVS-400 spectrometer. ^{13}C NMR spectra were recorded at 100 MHz with a Bruker AVS-400 spectrometer. Mass spectra (EI) were obtained at 70 eV with a type VG Autospec apparatus (Micromass) or with a type LCT (ESI) (Micromass). GC–MS analyses were performed with an HP 5890 GC equipped with an HP 5972 MS. Analytical thin-layer chromatography was performed by using precoated silica gel 60 F_{254} plates (Merck, Darmstadt), and the spots were visualized with UV light at 254 nm or by staining with H_2SO_4/4-methoxybenzaldehyde in ethanol. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh). The inductor was constructed by IFF GmbH (Ismaning). Pumps were obtained from CHELONA GmbH (Potsdam). All reagents were purchased from Aldrich, Acros or ABCR. Superparamagnetic nanoparticles **1** were prepared according to ref.[12] Toluene, acetonitrile and MagTrieve™ were used as received. NiO_2 was prepared according to ref.[13] Leaching analytics of metal species (iron, nickel and chromium) were performed by using a SPECTRO ARCOS inductively coupled plasma-optical emission spectrometer (ICP-OES, Spectro Analytical Instruments GmbH, Germany) and calculated on an average of all conducted reactions. All products are known and were identified by comparison with the data reported in the literature (see ref.[14]). For all oxidations 1 g of oxidant was inserted into the reactor (CrO_2 or NiO_2). The precise loading is difficult to estimate because mainly the surface of the oxidant reacts. Commonly, a large excess of oxidant is employed as reported in literature examples.[9] All reactions were performed on a 0.5–1.0 mmolar scale.

Typical Procedure for CrO$_2$ Oxidations: See Scheme 2, Equation (1). A PEEK reactor was filled with a mixture of nanoparticles **1** and MagTrieve^{TM} (2:1 wt.-%) and incased with the inductor. The reactor (void volume: 4 mL) was connected to a pump and on the opposite side to a back-pressure device (100 psi), which led to the collection vial. The flow device was flushed with acetonitrile, and the temperature was adjusted to 135 °C. Once the temperature of the flow (flow rate 0.1 mL/min) had reached constancy, a solution of alcohol **10** in acetonitrile (0.15 M) was pumped through the system (residence time ca. 40 min). The reaction mixture was collected, and, after removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silica gel) to yield ketone **11** in 92% yield.

Typical Procedure for NiO$_2$ Oxidations: The procedure is identical to the CrO$_2$ oxidation with the exception that NiO$_2$ was used instead of CrO$_2$.

Acknowledgments

This work was supported by the Fonds der Chemischen Industrie. We thank Henkel KGaA (Düsseldorf, Germany), Evonik Industries AG (Essen, Germany) and IFF GmbH (München, Germany) for financial or technical support. We thank Prof. T. Scheper and co-workers (Institute of Technical Chemistry, Leibniz University of Hannover) for designing and constructing PEEK reactors. ICP-OES analyses for measuring the degree of leaching by T. Klande (member of the group of Prof. C. Vogt, Institute of Inorganic and Analytical Chemistry, Leibniz University of Hannover) is gratefully acknowledged.

---

[1] S. Ceylan, C. Friese, C. Lammel, K. Mazac, A. Kirschning, *Angew. Chem.* **2008**, *120*, 9083–9086; *Angew. Chem. Int. Ed.* **2008**, *47*, 8950–8953.

[2] a) A.-H. Lu, E. L. Salabas, F. Schüth, *Angew. Chem.* **2007**, *119*, 1242–1266; *Angew. Chem. Int. Ed.* **2007**, *46*, 1222–1244; b) Y.-W. Jun, J. S. Choi, J. Cheon, *Chem. Commun.* **2007**, 1203–1214; c) X. K. Zhang, Y. F. Li, J. Q. Xiao, E. D. Wetzel, *J. Appl. Phys.* **2003**, *93*, 7124–7126.

[3] R. Hiergeist, W. Andrä, N. Buske, R. Hergt, I. Hilger, U. Richter, W. J. Kaiser, *J. Magn. Magn. Mater.* **1999**, *201*, 420–422.

[4] Enabling technologies include techniques such as nonconventional heating, solid-phase assistance and new reactor designs. They allow carrying out syntheses faster and performing workup more efficiently. We first reviewed and defined enabling technologies for organic synthesis in: A. Kirschning, W. Solodenko, K. Mennecke, *Chem. Eur. J.* **2006**, *12*, 5972–5990.

[5] M. Lukasiewcz, D. Bogdal, J. Pielichowski, *Adv. Synth. Catal.* **2003**, *345*, 1260–1272.

[6] Besides magnetic nanoparticles **1**, we also determined the heating profiles of other ferromagnetic materials such as Fe powder and Fe$_3$O$_4$ but found that MagSilica^{TM} **1** had the best heating properties (for details see ref.[1]).

[7] For all reactions described, leaching values were determined for Fe, Cr and Ni, respectively, by using ICP-OES analysis: Average values for Fe: 4.15 ppm; Cr: 1.75 ppm; Ni: 0.15 ppm.

[8] Selected reviews on chemically functionalized flow-through systems: a) G. Jas, A. Kirschning, *Chem. Eur. J.* **2003**, *9*, 5708–5723; b) A. Kirschning, G. Jas, *Top. Curr. Chem.* **2004**, *242*, 209–239; c) I. R. Baxendale, S. V. Ley in *New Avenues to Efficient Chemical Synthesis: Emerging Technologies* (Eds.: P. H. Seeberger, T. Blume), Springer, Berlin, Heidelberg, **2007**, pp. 151–185; d) I. R. Baxendale, J. J. Hayward, S. Lanners, S. V. Ley, C. D. Smith in *Microreactors in Organic Synthesis and Catalysis* (Eds.: T. Wirth), Wiley-VCH, Weinheim, **2008**, chapter 4.2, pp. 84–122; e) B. Ahmed-Omed, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733–740; f) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. MacQuade, *Chem. Rev.* **2007**, *107*, 2300–2318; g) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151–163; h) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450–7459; i) X. Y. Mak, P. Laurino, P. H. Seeberger, *Beilstein J. Org. Chem.* **2009**, *5*, 19; j) S. Ceylan, A. Kirschning in *Recoverable and Recyclable Catalysts* (Ed.: M. Benaglia), John Wiley & Sons Ltd., Chichester, **2009**, chapter 13, pp. 379–411.

[9] When two identical fixed-bed reactors are employed in a parallel setup, the flow can be switched to the second reactor once the oxidant inside the first flow reactor is exhausted. This reactor can then be reactivated; see also: R. Lee, D. Donald, *Tetrahedron Lett.* **1997**, *38*, 3857–3860 for MagTrieve^{TM}; K. Nakagawa, R. Konaka, T. Nakata, *J. Org. Chem.* **1962**, *27*, 1597–1601 for NiO$_2$. In an integrated flow system the LC-online determination can be used to determine, when the oxidant is exhausted, and the reactor has to be exchanged.

[10] Before the flow system was used, the setup was calibrated with respect to electric power and the induced temperature in different solvents at different flow rates (see ref.[1]).

[11] It has to be noted that the stream of reactants is rapidly heated within the first cm of the reactor until the solution reaches the desired temperature. After that first zone dispersion is kept to a minimum. Furthermore, the design of the inductor allowed maximum homogeneity of the magnetic field inside the flow reactor, which guarantees homogeneous heating conditions all through the reactor.

[12] a) M. Kröll, M. Pridöhl, G. Zimmermann, *Mater. Res. Soc. Symp. Proc.* **2004**, *788*, L4.3.1–L4.3.6; b) M. R. Zachariah, M. I. Aquino, R. D. Shull, B. E. Steel, *Nanostruct. Mater.* **1995**, *5*, 383–392; c) S. H. Ehrman, S. K. Friedlander, M. R. Zachariah, *J. Mater. Res.* **1999**, *14*, 4551–4561.

[13] K. Nakagawa, R. Konaka, T. Nakata, *J. Org. Chem.* **1962**, *27*, 1597–1601.

[14] a) Androst-4-ene-3,17-dione (**5**), see: M. L. Almeida, P. Kocovsky, J.-E. Bäckvall, *J. Org. Chem.* **1996**, *61*, 6587–6590; b) 3-phenylpropiolaldehyde (**7**), see: M. Noro, T. Masuda, A. S. Ichimura, N. Koga, H. Iwamura, *J. Am. Chem. Soc.* **1994**, *116*, 6179; c) 3-phenylpropenal (**15**), see: A. Gangloff, T. M. Judge, H. Paul, *J. Org. Chem.* **1990**, *4*, 3679–3682; d) 2-methoxybenzonitrile (**17**), see: R. K. Arvela, N. E. Leadbeater, *J. Org. Chem.* **2003**, *68*, 9122–9125; e) 3,4-dimethoxybenzonitrile (**19**), see: S. Murahashi, T. Naota, N. J. Nakajima, *J. Org. Chem.* **1986**, *51*, 898–901; f) 2-phenylchromen-4-one (**21**), see: S. Cui, X. Lin, Y. Wang, *Org. Lett.* **2006**, *8*, 3315–3318.

Received: May 4, 2010
Published Online: July 13, 2010