Microwave Chemistry

DOI: 10.1002/anie.201100856

Activation and Deactivation of a Chemical Transformation by an Electromagnetic Field: Evidence for Specific Microwave Effects in the Formation of Grignard Reagents**

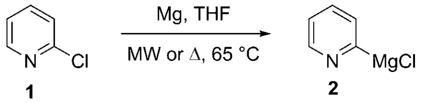
Bernhard Gutmann, Alexander M. Schwan, Benedikt Reichart, Christian Gspan, Ferdinand Hofer, and C. Oliver Kappe*

Despite the large body of published work in the field of microwave-assisted organic synthesis (MAOS),[1–3] there is still considerable controversy on the exact reasons why microwave irradiation is able to enhance or otherwise influence chemical processes.[4] Of particular importance in this context is the question of whether the electromagnetic field—the electric or magnetic field component—can interact with specific substrates in a reaction mixture to generate effects that are not correlated with a macroscopic change in temperature (i.e. "specific" or "nonthermal" microwave effects).[4,5] Although these types of microwave effects have been frequently postulated when the outcome of a chemical transformation performed under microwave conditions was different from the conventionally heated counterpart at the same monitored reaction temperature,[4] recent investigations suggest that in the majority of these cases experimental artifacts connected to erroneous temperature measurements are responsible for the observed phenomena, rather than genuine electromagnetic field effects.[6–8]

Herein we present a unique chemical transformation that under 2.45 GHz microwave irradiation is dramatically influenced by the electromagnetic field, and not by temperature. At the same macroscopically determined reaction temperature, this organometallic process can be either accelerated (relative to the conventionally heated control experiment) in a low-density microwave field or suppressed by applying a high-density field. We also demonstrate that as a result of this exceptional dependence on electric field strength, the same chemical reaction when performed in different microwave instruments can lead to entirely different results.

Our investigations in this area were inspired by a recent report by Hulshof and co-workers on the microwave-assisted insertion of Mg metal into carbon–halogen bonds (Grignard reagent formation).[9] The authors demonstrated that for certain substrates (e.g. 2-halothiophenes) the formation of the corresponding organomagnesium reagents could be significantly accelerated by applying microwave irradiation at constant power utilizing a multimode instrument. The experiments were performed at approximately 65 °C under open vessel reflux conditions using dry THF as solvent in an Ar atmosphere. The interaction between the microwave field and the Mg turnings produced clearly visible electrostatic discharge phenomena between the Mg particles (arcing), causing a distortion of the Mg surface resulting in smaller and thus more reactive spherical Mg particles, as evidenced by scanning electron microscopy (SEM), and possibly also to a removal of the passivating $MgO/Mg(OH)_2$ layer present on the non-activated Mg turnings.[9]

To further enhance these remarkable acceleration effects we decided to reevaluate the formation of Grignard reagents using single-mode microwave reactors, which generally provide substantially higher field densities than multimode instruments.[2] As a suitable model substrate 2-chloropyridine (**1**) was selected as we anticipated that this comparatively nonreactive heteroarene chloride would allow the detection of any rate enhancements comparing conventional and microwave heating techniques in a reliable and reproducible manner (Scheme 1). The following general reaction conditions were chosen: Mg turnings (220 mg, ca. 9 mmol, average particle size 2–3 mm, see Figure S1a in the Supporting Information), anhydrous THF (3.0 mL), and 2-chloropyridine (**1**) (226 mg, 2.0 mmol) were placed in a 10 mL pyrex round-bottom flask fitted with a reflux condenser and a magnetic stir bar under an atmosphere of Ar.



Scheme 1. Model transformation for the investigation of microwave effects.

Initial reference experiments were performed using conventional heating in a preheated oil bath. As the formation of Grignard reagents by direct insertion of Mg metal into carbon–halogen bonds is notoriously difficult to control and

---

[*] B. Gutmann, A. M. Schwan, B. Reichart, Prof. Dr. C. O. Kappe
Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University Graz
Heinrichstrasse 28, 8010 Graz (Austria)
Fax: (+43) 0316-380-9840
E-mail: oliver.kappe@uni-graz.at
Homepage: http://www.maos.net
C. Gspan, Prof. Dr. F. Hofer
Institute for Electron Microscopy and Fine Structure Research
Graz University of Technology
Steyrergasse 17, 8010 Graz (Austria)

[**] This work was supported by a grant from the Christian Doppler Research Society (CDG). We thank D. I. Heimo Kotzian for performing electromagnetic field simulations.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201100856.

to reproduce,[10] all sets of experiments described herein were performed at least five times to ensure statistical relevance. Not entirely unexpectedly, the obtained conversion data for the formation of Grignard reagent **2** using conventional heating (THF reflux, 65 °C) showed significant variability; initiation started between 25 and 45 min (Figure S2a in the Supporting Information). In a subsequent set of experiments the exact same transformation was performed in a single-mode microwave reactor (CEM Discover) in open-vessel mode.[2] Similar to the results reported by Hulshof and co-workers, a significant rate acceleration of the initiation step was observed (5–15 min) using either 200 W or 300 W of constant microwave power (these experiments are discussed in detail in the Supporting Information; see Figures S2–S4). In some respects, these accelerations are related to the activation of Mg metal and the initiation of the formation of Grignard reagents under sonochemical conditions.[10]

In an attempt to further enhance this transformation and to probe the influence of a higher electric field strength on the initiation step, we subsequently performed experiments in a single-mode microwave reactor with 850 W installed maximum magnetron output power (Anton Paar Monowave 300).[8] Apart from the higher nominal magnetron power, the specific design of the single-mode cavity in this instrument generates a significantly higher electric field strength and thus power density than other single-mode microwave reactors.[11] Since this instrument only allows sealed vessel microwave processing in cylindrical tubes, temperature controlled runs at 65 °C monitored by an internal fiber-optic probe were carried out to mimic the open vessel experiments executed at constant power and reflux conditions described above. The Grignard reagent formation (Scheme 1) was initially performed by applying a set temperature of 65 °C using the standard "as-fast-as-possible" heating option on the Monowave 300.[8] This heating algorithm attempts to reach the set temperature as rapidly as possible (ca. 30 s) and thus comparatively high initial microwave power levels are applied. Violent electrostatic discharges were observed by using a built-in camera, in particular during the initial 25 s heating phase of the experiment in which nominal magnetron output power levels of up to 150 W were reached. The arcing was particularly intense when the reaction vial was concurrently cooled with compressed air during microwave irradiation. This so-called "simultaneous cooling" technique allows higher levels of microwave power to be administered to the reaction mixture, thereby potentially enhancing any effects that are dependent on the electric field strength.[12] In our case, when using simultaneous cooling a maximum power level of 240 W was observed (Figure 1 a), leading to very intense arcing during the initial phase of the experiment.

To our surprise, monitoring of the reaction mixture by HPLC–UV revealed that under these high power density conditions virtually no conversion was observed. Even after 60 min of irradiation at 65 °C in all of the six attempts the reaction mixture consisted mainly of unreacted 2-chloropyridine starting material (**1**), and only very small amounts of pyridine quenching product (0–5 %) were detected.

In contrast, when a heating ramp of 2 min was programmed on the Monowave 300 instrument, which rises the reaction temperature only gradually to the target value of 65 °C, the applied magnetron power was drastically reduced and never rises above 16 W (Figure 1 b). Under these conditions, the occurrence of electrostatic discharges is minimized, as clearly seen by the built-in camera, and for all runs full conversion of the 2-chloropyridine starting material (**1**) was observed within 60 min.

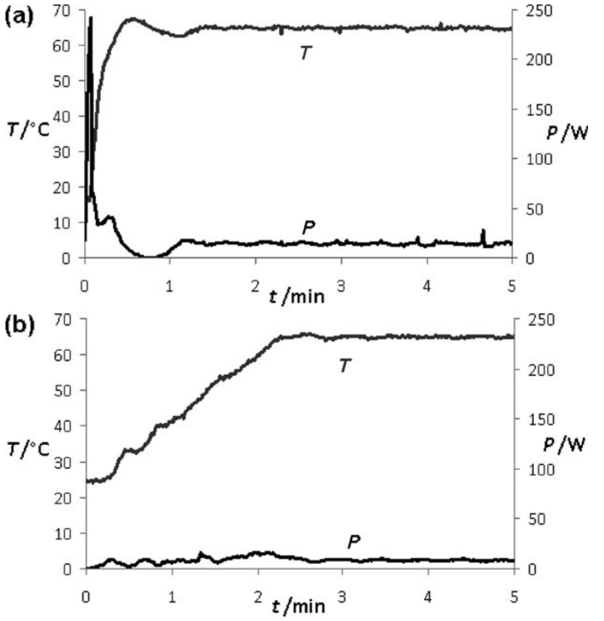


Figure 1. Temperature (*T*) and power (*P*) profiles for the microwave-assisted conversion of 2-chloropyridine (**1**) to Grignard reagent **2** (Scheme 1) in temperature-control mode. Monowave 300 reactor, 65 °C set temperature, internal fiber-optic temperature control, simultaneous cooling, magnetic stirring (600 rpm). Data are shown using "as-fast-as-possible" (a), and "ramp" modes (b). For clarity, only the first 5 min of the experiment is shown. A simulation of the corresponding electric field strength and volume power distribution at 16 and 240 W microwave power is shown in Figures S5 and S6 in the Supporting Information.

Evidently, both the acceleration and retardation of the Grignard reagent formation from 2-chloropyridine (**1**) and Mg metal is somehow connected to arcing phenomena resulting from exposure of electrically conductive Mg turnings to a microwave field. Remarkably, using comparatively low electric field strengths the reaction is accelerated, while applying high electric field strength conditions the same transformation experiencing an identical 65 °C macroscopic bulk temperature is almost completely retarded. Since we hypothesized that both phenomena are associated to an activation/deactivation effect of the Mg surface, the electrostatic discharges occurring between Mg turnings in THF were studied in more detail. For this purpose, the microwave irradiation experiments described above were repeated in the absence of the 2-chloropyridine substrate (**1**); Mg turnings with THF alone were irradiated in various microwave instruments.

Arcing phenomena in metal–solvent systems under microwave irradiation have been studied in detail by Whittaker and Mingos and are critically dependent on many factors including, for example, metal particle size and morphology, solvent ionization energy and dielectric loss tangent, and the applied electric field strength.[13] With the CEM Discover system under open vessel THF reflux conditions as described above, light arcing between individual Mg turnings could be observed at an applied constant magnetron power of 200 W. After 5 min of irradiation at 65 °C applying constant 200 W magnetron power, slight discoloration and the formation of small amounts of a fine dispersion of gray particles/powder was observed, not unlike the results described by Hulshof and co-workers using a multimode microwave system (see Figure S7a).[9]

To perform valid comparative studies of arcing results achieved in individual single-mode microwave reactors, experiments under sealed vessel conditions were subsequently carried out in the Discover system. A stirred Mg/THF mixture exposed to 300 W of constant microwave power in a 10 mL sealed pyrex vial reached a temperature of 65 °C, corresponding to the boiling point of THF, within 17 s. After this comparatively short irradiation period, the Mg turnings appeared essentially unchanged (Figure 2 a). Only by extending the irradiation time to 20 min in a temperature controlled run (65 °C) were small amounts of a dispersion of gray particles/powder formed as a result of mild arcing, similar to the results obtained under open-vessel conditions (Figure S7b).

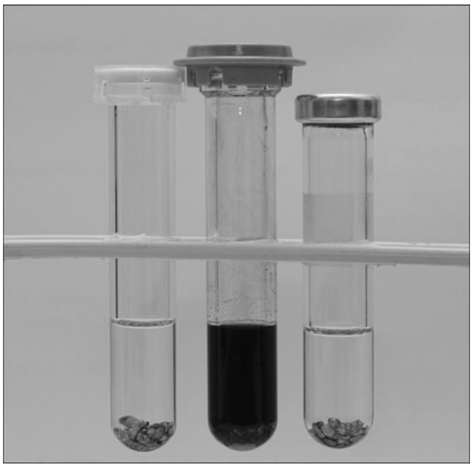


Figure 2. Effect of constant power microwave irradiation (300 W) on stirred Mg turnings in THF (maximum temperature 65 °C) using three single-mode microwave reactors with different field strengths: a) CEM Discover; b) Anton Paar Monowave 300; c) Biotage Initiator EXP 2.5. See main text for discussion.

In stark contrast, using the Monowave 300 for the same constant power sealed vessel experiment applying 300 W nominal magnetron output power for just 8 s (maximum reached temperature again 65 °C) produced violent electrical arcing, which was accompanied by the formation of substantial amounts of carbonaceous material resulting from the decomposition of THF solvent (Figure 2 b).[13,14] Visual inspection of the Mg turnings after microwave irradiation clearly revealed that the morphology of the Mg metal surface had undergone significant changes and that the originally shiny Mg surface was now covered with dark material, presumably resulting from THF decomposition (see below).

To establish if the extreme arcing phenomena seen in the Monowave 300 instrument could also be reproduced in a different single-mode microwave reactor of similar design, the same set of Mg/THF irradiation experiments was repeated in a Biotage Initiator 2.5 instrument, which provides 400 W of maximum magnetron output power.[2] Remarkably, under comparable conditions (300 W constant power, 20 s, 65 °C maximum temperature), no arcing was experienced at all and the Mg turnings recovered after microwave irradiation were therefore very similar in appearance to untreated samples (Figure 2 c). Even applying 400 W of constant magnetron power for 2 min (reaching 200 °C) did not lead to any visible changes on the Mg particles or to the formation of carbonaceous material as a result of arcing.

To obtain preparative amounts of the carbonaceous material described above for analytical purposes, an experiment involving several heating and cooling cycles in the Monowave 300 reactor was designed, which allowed higher power levels to be administered for prolonged time periods. Intense arcing during irradiation was maintained over a period of 4 × 50 s by performing four heating/cooling cycles at a set temperature of 120 °C (see Figure S8). Extreme arcing was clearly audible and visible on the built-in camera (Figure 3) and led to around 30 mg of black amorphous material, which could easily be separated by sedimentation techniques from the heavier Mg particles.

Figure 3. Real-time images of electrostatic discharge (arcing) between stirred Mg turnings in THF in a high field density microwave reactor (Monowave 300). Clearly visible is the stir bar at the bottom of the vial.

The remaining THF solution and a toluene extract of the carbonaceous material was analyzed by GC–(EI)MS analysis, which revealed the presence of trace amounts of a range of (poly)aromatic hydrocarbons, including, for example, naphthalene, pyrene, fluoranthene, and 4-*H*-cyclopenta-[*def*]phenantrene (Figure S9). Because of the apparent solvent disintegration in these experiments, the pressure in the sealed microwave vial increased to around 17 bar, presumably as a result of low molecular weight solvent decomposition products (Figure S8).

Careful analysis of the irradiated Mg turnings themselves (and of somewhat smaller Mg particles formed during the arcing process) by scanning electron microscopy (SEM) in combination with energy-dispersive x-ray spectrometry (EDXS) confirmed our assumption that the Mg turnings, while clearly showing the impact of violent electrostatic discharges, were covered with a layer of the carbonaceous material formed during solvent decomposition (Figures S10 and S11 in the Supporting Information). Examination of the fine black carbonaceous powder by X-ray diffraction (XRD) analysis revealed the occurrence of small Mg metal particles in addition to finely distributed MgO nanoparticles (Figure S12 in the Supporting Information). TEM investigations (Figure 4) demonstrated that the MgO nanoparticles had diameters ranging from 2 to 20 nm (black particles in Figure 4a) and were covered by partly graphitized carbon (Figure 4b) to form MgO/carbon core/shell nanostructures.[14] An electron energy loss spectrum (EELS) was recorded from the specimen region shown in Figure 4a highlighting the typical near-edge fine structures for the C-K edge (π* and σ* peaks of graphite) and also for the Mg- and O-K edges (Figure S13).[15] These findings were confirmed by an electron diffraction investigation (Figure S14). Apparently, microwave arcing under these extreme conditions will produce a plasma environment with temperatures $>1100\,^{\circ}C$,[13] leading in the particular case discussed herein to the carbonization of the THF solvent and to the formation of MgO nanoparticles, the oxygen presumably being derived from the THF molecule.

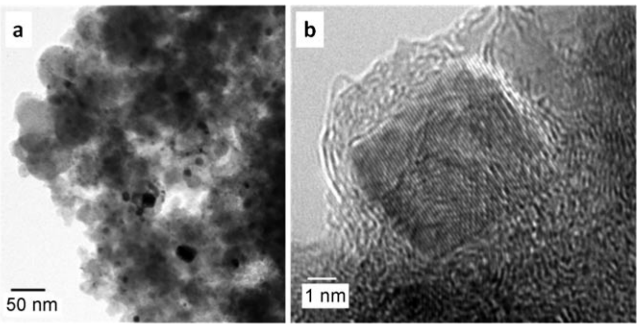


Figure 4. Transmission electron microscopy (TEM) investigation of the fine black carbonaceous powder formed by high field density microwave irradiation of Mg turnings. a) Dark MgO particles are embedded in carbon; b) high resolution TEM image showing a MgO cube with the [100] lattice fringes which is covered by partly graphitized carbon (for further characterization data, see Figures S12–S14 in the Supporting Information).

The results presented herein demonstrate for the first time that the outcome of a chemical reaction can be influenced both in a positive (activation) or negative (deactivation) way by electric field strength using microwave irradiation. For the formation of organomagnesium (Grignard) reagent **2** from 2-chloropyridine and Mg metal in THF at reflux temperature (Scheme 1), microwave irradiation using low field density conditions will lead to an apparent acceleration of the insertion of Mg metal into the carbon–chlorine bond by reducing the initiation period. This result can be rationalized by a "cleansing effect" on the Mg surface or to the formation of more reactive spherical Mg particles as a result of mild electrostatic discharges between individual Mg turnings ("activation").[9] In contrast, exposure of the same reaction mixture to high field density conditions results in more intense electrostatic discharges resulting in the creation of carbonaceous material by solvent decomposition. This disintegration of the THF solvent into carbonaceous material produces a passivating layer of graphitized core/shell MgO/carbon nanoparticles covering the Mg metal, effectively preventing access of the organohalogen reagent to the Mg metal surface and thus shutting down the formation of the organomagnesium (Grignard) reagent. Both pathways are probably best categorized as examples of "specific" microwave effects as the macroscopic reaction temperature in both cases relative to the conventionally heated experiment is the same (Figure S15), and clearly both the activation and deactivation seen under microwave irradiation cannot be duplicated by conventional conductive heat-transfer methods.[5,16] Of general importance to the field of microwave chemistry, the data presented herein for the first time provide clear evidence that the exact same reaction when carried out in different commercially available microwave instruments can lead to entirely different results, even at the same macroscopically determined reaction temperature.

Received: February 2, 2011

Keywords: electromagnetic fields · Grignard reaction · microwave chemistry · nanoparticles

---

[1] For recent books, see: a) *Microwave Heating as a Tool for Sustainable Chemistry* (Ed.: N. E. Leadbeater), CRC, Boca Raton, **2011**; b) *Aqueous Microwave-Assisted Chemistry* (Eds.: V. Polshettiwar, R. S. Varma), Royal Society of Chemistry, Cambridge, **2010**; c) *Microwaves in Organic Synthesis*, 2nd ed. (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2006**; d) *Microwave Methods in Organic Synthesis* (Eds.: M. Larhed, K. Olofsson), Springer, Berlin, **2006**; e) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, **2005**.

[2] C. O. Kappe, D. Dallinger, S. S. Murphree, *Practical Microwave Synthesis for Organic Chemists—Strategies, Instruments, and Protocols*, Wiley-VCH, Weinheim, **2009**.

[3] For recent reviews, see: a) S. Caddick, R. Fitzmaurice, *Tetrahedron* **2009**, *65*, 3325; b) C. O. Kappe, D. Dallinger, *Mol. Diversity* **2009**, *13*, 71, and references therein.

[4] a) L. Perreux, A. Loupy, *Tetrahedron* **2001**, *57*, 9199; b) A. De La Hoz, A. Diaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, *34*, 164; c) see also Ref. [1c].

[5] For a definition and examples of thermal, specific, and nonthermal microwave effects in organic chemistry, see: C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250. Specific microwave effects are defined as *"modifications of chemical transformations in a microwave field that cannot be achieved or duplicated by conventional heating, but essentially are still thermal effects."*

[6] J. R. Schmink, N. E. Leadbeater, *Org. Biomol. Chem.* **2009**, *7*, 3842.

[7] a) M. Hosseini, N. Stiasni, V. Barbieri, C. O. Kappe, *J. Org. Chem.* **2007**, *72*, 1417; b) M. A. Herrero, J. M. Kremsner, C. O. Kappe, *J. Org. Chem.* **2008**, *73*, 36; c) B. Bacsa, K. Horváti, S. Bösze, F. Andreae, C. O. Kappe, *J. Org. Chem.* **2008**, *73*, 7532.

[8] a) D. Obermayer, B. Gutmann, C. O. Kappe, *Angew. Chem.* **2009**, *121*, 8471; *Angew. Chem. Int. Ed.* **2009**, *48*, 8321; b) B. Gutmann, D. Obermayer, B. Reichart, B. Prekodravac, M. Irfan, J. M. Kremsner, C. O. Kappe, *Chem. Eur. J.* **2010**, *16*, 12182.

[9] B. H. P. van de Kruijs, M. H. C. L. Dressen, J. Meuldijk, J. A. J. M. Vekemansa, L. A. Hulshof, *Org. Biomol. Chem.* **2010**, *8*, 1688.

[10] a) *Grignard Reagents. New Developments* (Ed.: H. G. Riche, Jr.), Wiley, Chichester, **2000**; b) *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**; c) Y. H. Lai, *Synthesis* **1981**, 585.

[11] a) J. Robinson, S. Kingman, D. Irvine, P. Licence, A. Smith, G. Dimitrakis, D. Obermayer, C. O. Kappe, *Phys. Chem. Chem. Phys.* **2010**, *12*, 4750; b) H. Kotzian, K.-J. Pendl, J. Zach, R. Zentner (Anton Paar GmbH), Eur. Pat. Appl. EP 2,244,529A1, **2010**; c) see also Figures S5 and S6 in the Supporting Information.

[12] a) B. L. Hayes, M. J. Collins, Jr., World Patent WO 04002617, **2004**; b) B. L. Hayes, *Aldrichimica Acta* **2004**, *37*, 66. See also Ref. [7a].

[13] a) A. G. Whittaker, D. M. P. Mingos, *J. Chem. Soc. Dalton Trans.* **2000**, 1521; b) A. G. Whittaker, D. M. P. Mingos, *J. Chem. Soc. Dalton Trans.* **2002**, 3967.

[14] Y.-L. Hsin, C.-F. Lin, Y.-C. Liang, K. C. Hwang, J.-C. Horng, J. A. Ho, C.-C. Lin, J. R Hwu, *Adv. Funct. Mater.* **2008**, *18*, 2048.

[15] V. J. Keast, A. J. Scott, R. Brydson, D. B. Williams, J. Bruley, *J. Microsc.* **2001**, *203*, 135.

[16] Arcing phenomena may also play a role in other microwave-assisted protocols involving metal powders; see Figure S16 for details.