# Hydrazine-mediated Reduction of Nitro and Azide Functionalities Catalyzed by Highly Active and Reusable Magnetic Iron Oxide Nanocrystals

David Cantillo, Mojtaba Mirhosseini Moghaddam, and C. Oliver Kappe*

Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

S Supporting Information

ABSTRACT: Iron oxide (Fe_3O_4) nanocrystals generated *in situ* from an inexpensive and readily available iron source catalyze the reduction of nitroarenes to anilines with unparalleled efficiency. The procedure is chemoselective, avoids the use of precious metals, and can be applied under mild reflux conditions (65 or 80 °C) or using sealed vessel microwave heating in an elevated temperature regime (150 °C). Utilizing microwave conditions, a variety of functionalized anilines have

been prepared in nearly quantitative yields within 2−8 min at 150 °C, in a procedure also successfully applied to the reduction of aliphatic nitro compounds and azides. The iron oxide nanoparticles are generated in a colloidal form, resulting in homogeneous solutions suitable for continuous flow processing. Selected examples of anilines of industrial importance have been prepared in a continuous regime using this protocol.
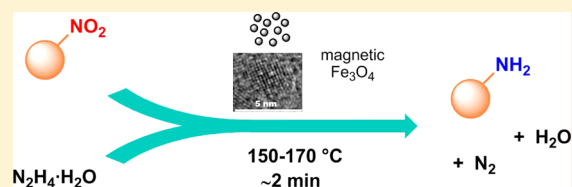
■ INTRODUCTION

The application of metal nanoparticles in catalysis has increased considerably in the past 10 years.[1,2] Colloidal metallic nanoparticles are considered to have properties in between homogeneous and heterogeneous catalysts and present advantages of both systems. The nanosize of these materials leads to an enormous surface area to volume ratio and, therefore, to an enhanced contact between reactants and catalyst, which increases the activity dramatically.[1,2] As metallic nanoparticles are generally insoluble in the reaction mixture, the nanoparticles can easily be separated from the solvent as is typically the case for heterogeneous catalysts. Size, shape and morphology of nanoparticles can be readily controlled, making it possible to tune the activity and selectivity of the catalyst.[1,2]

Iron-based catalysts in particular are becoming very popular in the organic synthesis community, as iron is an abundant, eco-friendly, relatively nontoxic, and inexpensive element.[3] In this context, iron oxide magnetic nanoparticles have turned out to be very attractive in the past few years as readily available and inexpensive nanocatalysts.[4] The magnetic nanoparticles can be easily retrieved from the reaction mixture and reused by simple magnetic separation and, importantly, surface modification of these nanomaterials makes it possible to tailor their reactivity and to design catalysts for specific purposes.[5]

The selective reduction of nitroarenes to anilines is a very important reaction both in industry and academia. Functionalized anilines are relevant intermediates in the synthesis of dyes, pigments, agrochemicals, and pharmaceuticals, and the reduction of aromatic nitro compounds clearly is the most commonly used method of preparation.[6] The traditional noncatalytic process, treating the nitroarene with stoichiometric amounts of Fe metal under acidic conditions (Béchamp

reduction), generates large amounts of waste; thus, catalytic hydrogenation catalyzed by transition metals is now the method of choice for the preparation of anilines.[7] However, selectivity issues in the presence of other reducible functional groups are still a major concern,[8] and therefore carefully screened and selected precious metal catalysts (such as Pd, Pt, or Ru) are usually required.[9] Apart from hydrogen, several other stoichiometric reducing agents have been introduced that allow an efficient reduction of nitroarenes to anilines when used in combination with metal catalysts, including silanes,[10] boranes,[11] $NaBH_4$,[12] ammonium salts,[13] formic acid,[14] or hydrazine.[15] Hydrazine hydrate ($N_2H_4·H_2O$) in particular can be considered as a very suitable reagent for the reduction of nitro groups, as it generates only N_2 as byproduct. Compared to its unstable anhydrous form, hydrazine hydrate is relatively safe and easy to handle. In the past few years, several protocols for the reduction of nitroarenes employing a combination of hydrazine and iron catalysts have been reported,[15a−g] ranging from iron salts and complexes[15a,e] to iron oxides[15c,d,g] and supported catalysts.[15b−f]

Recently, our group has communicated the reduction of nitroarenes with hydrazine catalyzed by iron oxide nanocrystals.[16] The in situ generated colloidal iron oxide particles demonstrated unprecedented efficiency for the reduction of aromatic nitro groups, and high selectivity in the presence of other reducible moieties.[16] Herein, we present the full details of these investigations and an extension to aliphatic nitro compounds and azides. The scope and limitations of these procedures are described ranging from standard reflux
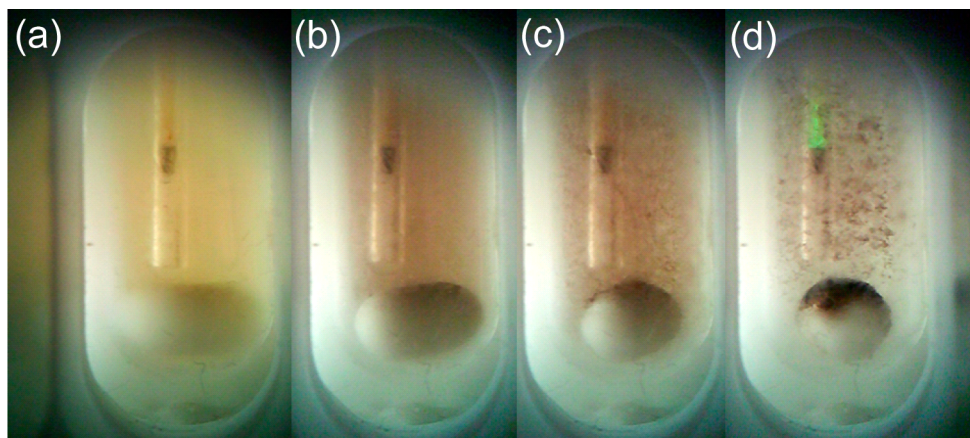
Figure 1. Visual appearance of the formation of the Fe_3O_4 nanoparticles at different stages of microwave processing. Conditions: 2.0 mmol nitrobenzene, 20% excess of $N_2H_4 \cdot H_2O$ (3.6 mmol), 0.25 mol % Fe(acac)$_3$, 1.5 mL MeOH). (a) Reaction mixture at room temperature before heating. (b) At 150 °C, the color turns brown immediately, indicating the formation of the Fe_3O_4 nanocrystals. (c) After ∼5 min at 150 °C, the particles start to aggregate and a dark precipitate can be observed. (d) Upon cooling to 45 °C (∼10 min), the particles form a clearly visible solid precipitate that sticks to the stir bar due to their magnetic properties. Pictures were taken inside the cavity of the microwave instrument with a built-in camera.[21] The glass immersion tube protecting the internal fiber optic temperature probe can be visualized in all the pictures. The dark spot inside the immersion tube is the sensor crystal.

conditions, to highly efficient batch microwave experiments and continuous flow processing. Data on the efficiency, formation and recycling of the colloidal magnetic nanocrystals and mechanistic insights on the reduction process are presented. The application of continuous flow reduction protocols for the scalable preparation of selected anilines of industrial importance is also described.

■ RESULTS AND DISCUSSION

The chemoselective reduction of nitro groups has for many years been a theme of intense research. Due to the importance of anilines as intermediates in organic synthesis, the development of efficient, safe, and environmentally benign protocols for selective nitro group reductions is still highly desirable. Procedures that can be considered as "green" generally involve the use of abundant, cheap and nontoxic catalysts (e.g., iron-based catalysts) and reagents. For example, in 2011 Beller and co-workers have described the selective reduction of nitroarenes with hydrazine using iron-phenanthroline complexes supported on carbon as a recyclable catalyst.[15f] Excellent selectivities were achieved at 100 °C using a 1 mol % Fe loading and a 10 h reaction time.[15f] When Fe-phthalocyanine complexes were chosen as catalysts,[15e] only 0.5 mol % catalyst loading was necessary to accomplish the selective reduction of the nitro group in a number of substrates after 7 h at 120 °C. Commercial iron oxide nanoparticles have also been employed as reusable catalysts,[15d] although in this case a loading of 20 mol % of Fe was necessary.

These reports suggest the Fe/hydrazine system as a promising alternative to precious metal catalysts and hydrogen gas for nitro group reductions. However, from the industrial point of view, the above-described methods lack the necessary efficiency and scalability to be practical on production scale. The calculated turnover frequencies (TOF) range from approximately 5 h^{-1} for the commercial iron oxide nanoparticles[15d] to 10 h^{-1} for the Fe/C catalyst described by Beller and co-workers[15f] to 29 h^{-1} for the Fe/phthalocyanine complexes.[15e] In addition, all of the above-mentioned protocols are batch processes, where the scale-up of an exothermic reaction involving a relatively unstable reagent such as

hydrazine can be considered as inherently hazardous. Therefore, the development of more efficient catalytic systems that are suitable for safe and scalable continuous flow processing is highly desirable.[17,18]

With this background, we have envisaged a novel concept in nanocatalysis applied to the selective reduction of nitroarenes to anilines under continuous flow conditions. The concept relies on the in situ generation of colloidal iron oxide nanocrystals from an inexpensive Fe precursor in a solution containing the nitroarene. Since the nanocrystals are formed in the presence of the substrate, they catalyze the reduction of the nitro group with very high efficiency. Owing to the fact that in the initial phase of the experiment the nanocatalyst remains colloidal continuous flow processing is possible without the usual complications resulting from processing heterogeneous mixtures.[17,18] After completion of the reduction process, the magnetic iron oxide nanoparticles aggregate and the resulting precipitate can be easily separated from the reaction mixture with a magnet.

Colloidal Fe_3O_4 Generation for the Reduction of Nitroarenes. Formation of iron oxide (Fe_3O_4) nanocrystals by treatment of iron salts with hydrazine is a well-established method.[19,20] Our initial experiments were performed in a small-scale microwave batch heating device equipped with a built-in camera (Monowave 300, Anton-Paar),[21] thus online monitoring of particle formation and aggregation during the irradiation process was possible (Figure 1). In a typical reaction mixture hydrazine hydrate and the nitroarene were added to a solution of the iron precursor, that is, Fe(acac)$_3$, in methanol (Figure 1a). The solution was then heated at 150 °C in a sealed microwave vessel and when the mixture reached the desired temperature the formation of the dark particles could be visually observed (Figure 1b). As expected, after a few minutes, the colloidal, nonstabilized, nanoparticles started to aggregate and separated from the solution (Figures 1c and d). The magnetic particles could then be isolated and characterized by X-ray powder diffraction (XRD) and high-resolution transmission electron microscopy (HRTEM).[16] XRD patterns identified the magnetic solid as single-phase cubic Fe_3O_4, while HRTEM micrographs revealed the colloidal nanocrystals

to have a size of 6 ± 2 nm.[16] Although the images shown in Figure 1 reflect the situation when a nitroarene substrate was present in the reaction mixture, nearly identical results were obtained when the experiment was repeated in the absence of a substrate, demonstrating the ease with which Fe_3O_4 nanoparticles are generated from Fe salts and hydrazine at elevated temperatures (see below).[19,20]

We next investigated the efficiency of the in situ generated Fe_3O_4 nanocrystals under reflux conditions using nitrobenzene as model substrate. In our first attempt, 0.5 mol % $Fe(acac)_3$ were added to the reaction mixture consisting of a ~1 M solution of nitrobenzene in methanol and 20% excess of hydrazine hydrate. Gratifyingly, the substrate was reduced to aniline in approximately 6 h (Figure 2) using only a small
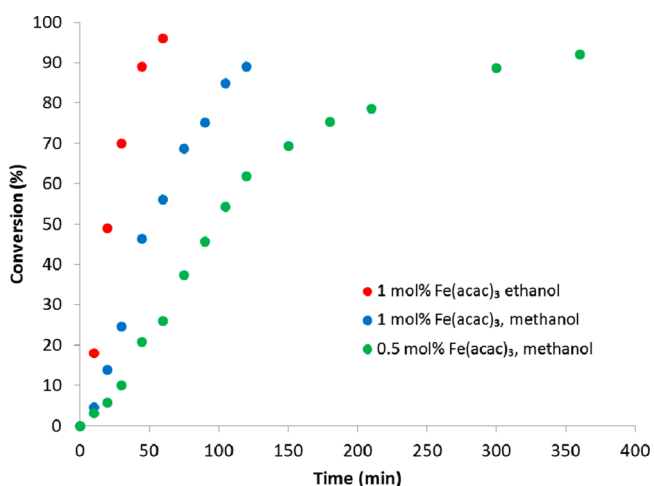

Figure 2. Reduction of nitrobenzene with hydrazine mediated by Fe_3O_4 nanoparticles generated in situ from $Fe(acac)_3$ in refluxing methanol (65 °C) or ethanol (80 °C).

excess (20%) of the reducing reagent. The reaction outcome could be easily improved by slightly increasing the catalyst loading to 1 mol % $Fe(acac)_3$. When the reaction temperature was increased (refluxing ethanol instead of methanol) full conversion of the substrate could be achieved after 1 h (Figure 2). Further increase of the catalyst loading to 3 mol % resulted in full conversion to aniline in 20−30 min. It should be noted that 3 mol % of $Fe(acac)_3$ correspond to 1 mol % of Fe_3O_4, which is the active species for the reduction process. The required stoichiometry of hydrazine is 1.5 equiv per nitro group to be reduced (see below), so a 20% excess corresponds to an effective hydrazine to substrate ratio of 1.8 equiv.

In the following step, the chemoselectivity of this protocol in the presence of other reducible groups was explored. To provide preliminary information about the functional group tolerance and reactivity of the catalytic system we tested 5 examples including halogen, amine, and amide functionalities (Table 1). In all cases excellent conversions and selectivities were obtained, with no dehalogenation (entry 2), amide reduction/hydrolysis, or other side-products observed, after reaction times ranging from 10 to 60 min. Importantly, the protocol demonstrated complete selectivity for the nitro reduction in 4-chloro-2′-nitrobiphenyl (Table 1, entry 5), a key intermediate in the preparation of the commercial fungicide Boscalid (see Scheme 3).[22]

Intermediates and Reaction Mechanism. The mechanism of the catalyzed reduction of nitroarenes to anilines is
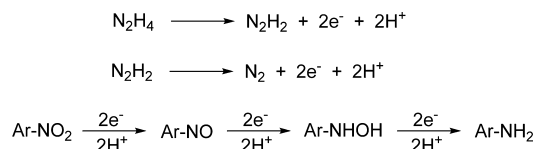
Table 1. Reduction of Nitroarenes with Hydrazine Hydrate Mediated by in situ Generated Fe_3O_4 Nanocrystals under Reflux Conditions[a]

Entry	Substrate	T [min]	Conv.[b] [%]	Yield[c] [%]
1		30	>99	90
2		10	>99	89
3		60	>99	88
4		20	>99	92
5		60	92	84

[a]Conditions: 2 mmol of nitroarene, 20% excess of $N_2H_4·H_2O$ (3.6 mmol), 1.5 mL ethanol, 3 mol % $Fe(acac)_3$, reflux. [b]Determined by GC-MS. [c]Isolated yields (see Experimental Section for details).

known to follow a three-step redox mechanism, each of them being a two-electron reduction (Scheme 1).[23] In the first step

Scheme 1. Accepted Mechanism for the Reduction of Nitroarenes

$$N_2H_4 \longrightarrow N_2H_2 + 2e^- + 2H^+$$

$$N_2H_2 \longrightarrow N_2 + 2e^- + 2H^+$$

$$Ar\text{-}NO_2 \xrightarrow[2H^+]{2e^-} Ar\text{-}NO \xrightarrow[2H^+]{2e^-} Ar\text{-}NHOH \xrightarrow[2H^+]{2e^-} Ar\text{-}NH_2$$

the nitroarene is reduced to the corresponding nitroso derivative. The second intermediate corresponds to the hydroxylamine species, which is subsequently reduced to the aniline. In cases where hydrazine is used as reagent it is the oxidation of hydrazine that provides the electrons necessary for the reduction. This oxidation takes place via a diimide intermediate (Scheme 1), and a total of 4 electrons are generated after the complete oxidation to N_2 gas. Since 6 electrons are required for the reduction of NO_2 to NH_2, 1.5 equivalents of hydrazine are necessary for a stoichiometric reaction as mentioned above. When the reaction is catalyzed by iron species, in particular iron oxides, it has been shown that the hydrazine generates Fe^{2+} from Fe^{3+}, which presumably is subsequently responsible for the electron transfer necessary for the reduction.[24] Formation of aromatic nitroso and hydroxylamine intermediates during the preparation of anilines is a matter of significant concern. The generation of hydroxylamine derivatives is particularly problematic, as many hydroxylamines are known carcinogens[25] and often thermally unstable causing explosions.[26] Accumulation of high amounts of hydroxylamines during the catalytic hydrogenation of nitroarenes is often observed in the presence of platinum catalysts.[27] Hydroxyl-

amines have also been detected in the carbon catalyzed preparation of anilines.[28]

When the reduction of nitrobenzene catalyzed by the Fe_3O_4 nanocrystals was performed under the conditions described in Figure 2 no traces of nitrosobenzene or phenylhydroxylamine were detected during the reaction (GC-MS). However, problems of hydroxylamine accumulation are more frequently encountered when electron withdrawing substituents (e.g., sulfonamides, halogens) are attached to the aromatic ring.[29] A suitable model reaction representative of this scenario is the reduction of 2-chloronitrobenzene and 4-chloronitrobenzene.[29a−c] Gratifyingly, monitoring the reduction of these two model substrates at 80 °C (Figure 3) by GC-MS revealed no
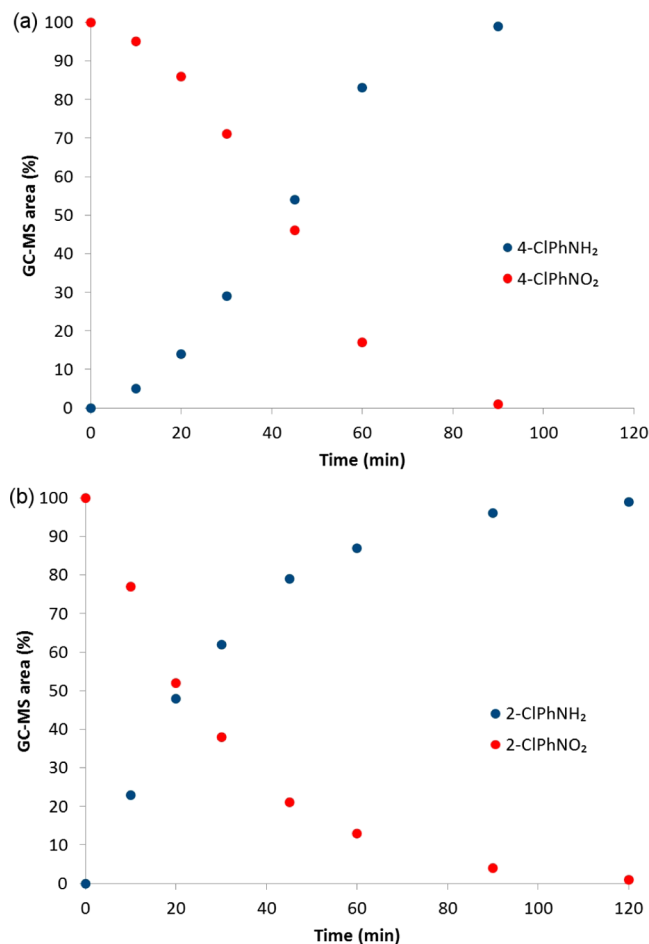

Figure 3. GC-MS monitoring of the hydrazine-mediated reduction of 4-chloro- and 2-chloronitrobezene at 80 °C. During the reduction process, no accumulation or traces of nitroso- or hydroxylamine intermediates could be observed. Conditions: 2 mmol of nitroarene, 20% excess of $N_2H_4 \cdot H_2O$ (3.6 mmol), 1.5 mL methanol, 0.5 mol % $Fe(acac)_3$.

traces of intermediates during the reaction, and only substrate and the corresponding aniline could be detected. Presumably, the nitroso and hydroxylamine species react very rapidly with hydrazine at the conditions necessary for the initial reduction of the nitro group. To verify this, solutions (0.5 M) of pure nitrosobenzene and phenylhydroxylamine in methanol were treated with hydrazine hydrate in the absence of a metal catalyst. In both cases nearly spontaneous formation of aniline was observed (GC-MS) even at room temperature, with vigorous gas release and the occurrence of an exotherm for

nitrosobenzene in agreement with literature reports.[30] Trace amounts of azobenzene, denoted by an orange coloration observed in the reaction mixtures, were likely also formed although the quantities were not sufficient for GC-MS detection.

Although we have little doubt that this reduction process follows the accepted three-step mechanism (Scheme 1),[23] since none of the intermediates could be detected during the reduction process, we decided to provide experimental evidence of the transient intermediacy of both the nitroso and hydroxylamine species. As indicated in the work of Larsen et al.,[28] during the reduction of 2,2′-dinitrobiphenyl 1 (Scheme 2)

Scheme 2. Plausible Side Product Formation during the Reduction of 2,2′-Dinitrobiphenyl 1
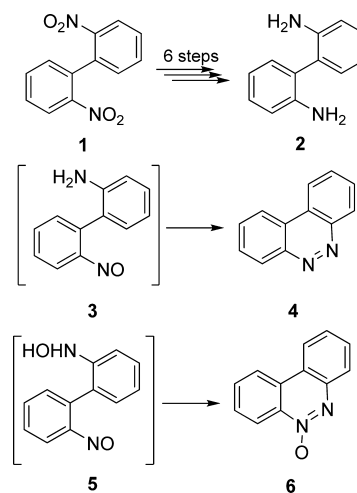
partially reduced nitroso (3) and hydroxylamine species (5) are formed which rapidly undergo cyclization as depicted in Scheme 2, providing benzo[c]cinnoline 4 and the corresponding N-oxide 6, respectively. Therefore, a solution of 2,2′-dinitrobiphenyl 1 (2 mmol), 2.4 equiv (7.2 mmol) of hydrazine hydrate, and 0.25 mol % $Fe(acac)_3$ in ethanol (1.5 mL) was heated at 120 °C for 15 min (at 80 °C the reaction was very slow). GC-MS analysis of the crude reaction mixture (Figure 4a) revealed the formation of the expected final product 2,2′-diaminobiphenyl 2, together with the partially reduced 2-amino-2′-nitrobiphenyl and, notably, approximately 4% of benzocinnoline 4. Further enhancement of the reduction efficiency by increasing the catalyst loading to 0.5 mol % $Fe(acac)_3$ efficiently suppressed the formation of byproducts and furnished dianiline 2 with excellent selectivity (Figure 4b). Finally, in a deliberate attempt to decrease the selectivity and favor the formation of side-products, the reaction mixture was rapidly heated in a microwave vial to 180 °C. Intense gas formation and coloration of the mixture was observed and, gratifyingly, significant amounts of 4 and of the N-oxide 6 were observed by GC-MS analysis, demonstrating the transient formation of the intermediates 3 and 5 under our experimental conditions (Scheme 2).

Process Intensification under Microwave Conditions. The protocol described above is clearly of potential industrial importance owing to the low cost of the reagents, and the fact that only nitrogen and water are produced as waste. However, reaction times are too long to be of use in an industrial process, in particular for an envisaged continuous flow process. We therefore turned our attention into intensifying the reduction
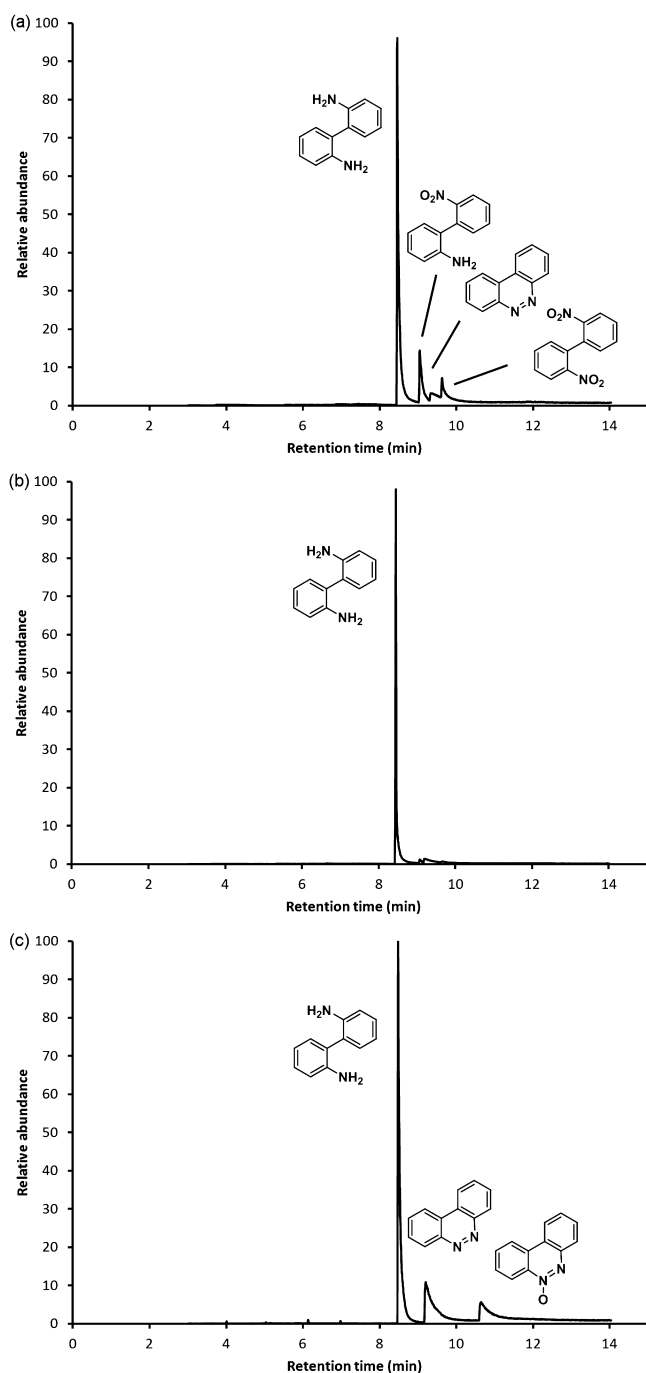
Figure 4. GC-MS analyses of the crude reaction mixtures obtained for the reduction of 2,2′-dinitrobiphenyl with hydrazine hydrate: (a) at 120 °C for 15 min with 0.25 mol % Fe(acac)$_3$, (b) at 120 °C for 15 min with 0.5 mol % Fe(acac)$_3$, and (c) at 180 °C for 1 min with 0.25 mol % Fe(acac)$_3$.

min (hold time at 150 °C, in addition to a ∼30 s ramp time to 150 °C and a ∼2 min cooling period, cf. Figure 7 below) with a catalyst loading of only 0.25 mol % Fe(acac)$_3$ using a 20% excess of hydrazine hydrate. Under these optimized conditions full conversion of nitrobenzene to aniline was achieved, and no traces of substrate, intermediates, or side-products were detected by GC-MS. The calculated TOF of 12000 h^{-1} under these conditions is remarkable compared to the efficiency achieved with other Fe/hydrazine protocols[15d−f] which ranged from 5 to 29 h^{-1} (see above). Notably, this efficiency is attained with only 20% excess hydrazine hydrate, while the previously described protocols typically employed 4−6 equivalents of reducing agent,[15d−f] thereby significantly simplifying product workup and improving the greenness of the process.

Different iron sources for the reduction of nitrobenzene with hydrazine were also evaluated under the optimized conditions (150 °C, 2 min, 20% excess N$_2$H$_4$·H$_2$O). The results (Table 2) revealed that all tested iron salts catalyze the reduction with the same efficiency, as all are capable of producing Fe$_3$O$_4$ nanocrystals when treated with hydrazine at elevated temperatures. In contrast, commercially available Fe$_3$O$_4$ powder (Table 2, entry 5) showed poor performance, providing a conversion of only 2% even when the catalyst loading was increased to 1 mol %. Utilizing commercially available 50 nm sized Fe$_3$O$_4$ nanoparticles, the conversion increased to 10% (Table 2, entry 6). As expected, in the absence of iron species or hydrazine (Table 2, entries 8 and 9), no significant reduction of the nitro group was observed.

The effect of different solvents on the reaction outcome was also investigated (Table 3). Alcohols (methanol, ethanol, and 2-propanol) performed very efficiently with full conversion in all three cases. For acetonitrile and water the efficiency of the reduction significantly decreased and 89% and 25% conversion were obtained, respectively. Water is arguably the most convenient solvent for any chemical process owing to its inherent safety and nontoxicity. Therefore we decided to further explore the suitability of high-temperature water for this procedure.[31] Importantly, increasing the reaction temperature to 180 °C, full conversion of the substrate was observed after 10 min. When this protocol was applied to the reduction of 4-chloronitrobenzene full conversion was also obtained with complete selectivity (no dehalogenation or other side reactions were observed, data not shown).

To exclude any direct effect of the electromagnetic field on the reduction process (for example, via selective heating of the magnetic Fe$_3$O$_4$ nanocatalyst) a control experiment was performed using a ceramic reaction vial made out of strongly microwave absorbing silicon carbide (SiC), which efficiently shields the content of the vial from the electromagnetic field thereby simulating conventional autoclave conditions.[32] Using the optimal conditions described above (Table 3, entry 1) the reaction was heated in the microwave reactor at 150 °C for 2 min (hold time). As expected, identical results were obtained using the SiC and Pyrex vials, confirming that reaction enhancement under microwave conditions in these reduction processes is due to a purely bulk thermal phenomenon.[33]

Catalyst Recovery and Recycling. A key feature of magnetic nanoparticles is the possibility of a simple recovery from the reaction mixture utilizing magnetic separation.[5] The colloidal nanocrystals generated in the above-described protocols slowly aggregate forming a magnetic black precipitate within 3−10 min, which can be easily separated from the solution with a standard magnet (Figure 6). ICP-MS analysis of

process and to the subsequent translation of this procedure to continuous flow conditions. A set of microwave batch experiments was performed in an elevated temperature regime to optimize reaction temperature and time, as well as catalyst loading (Figure 5). Thus, solutions containing 2 mmol of nitrobenzene, 3.6 mmol of N$_2$H$_4$·H$_2$O (20% excess), and Fe(acac)$_3$ in methanol (1.5 mL) were placed in a sealed microwave vessel and irradiated in a Monowave 300 single-mode microwave reactor. At a temperature of 150 °C (13 bar internal pressure), the reaction time could be reduced to only 2
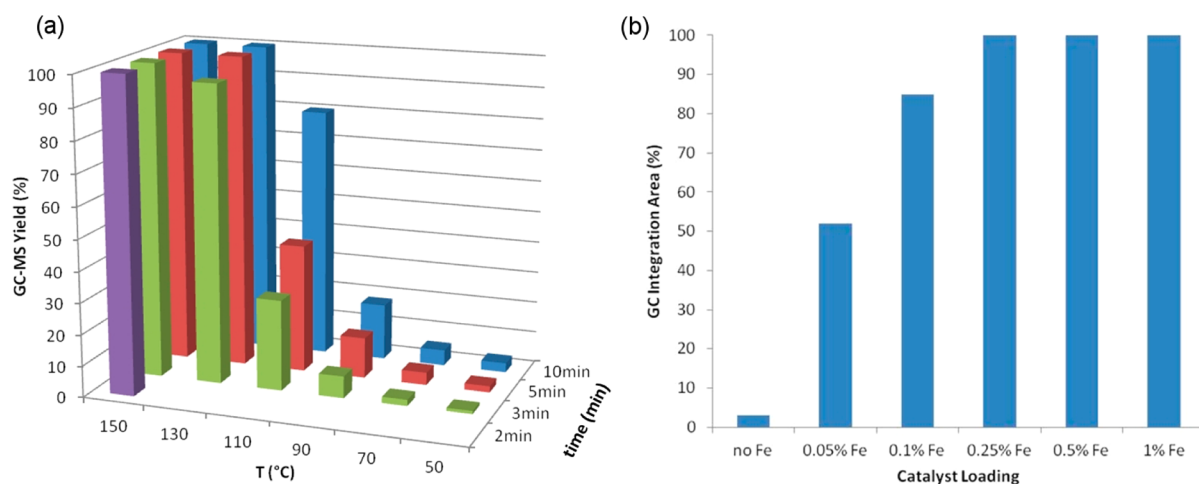
Figure 5. Optimization studies for the batch microwave reduction of nitrobenzene with hydrazine catalyzed by in situ generated Fe_3O_4 nanocrystals. (a) Temperature/hold time optimization, keeping the catalyst loading constant (0.25 mol % Fe(acac)$_3$. (b) Effect of the catalyst loading, at constant temperature and time (150 °C, 2 min). Conditions: 2.0 mmol PhNO$_2$, 3.6 mmol N$_2$H$_4$·H$_2$O, 1.5 mL of methanol, single-mode microwave heating with simultaneous cooling (Monowave 300).

Table 2. Efficiency of Several Fe Species for Activating the Reduction of Nitrobenzene with Hydrazine Hydrate[a]

entry	Fe species	conv.[b] (%)
1	Fe(acac)$_3$	>99
2	FeCl$_2$.4H$_2$O	>99
3	FeCl$_3$.6H$_2$O	>99
4	Fe(OAc)$_2$	>99
5	Fe$_3$O$_4$ (magnetite powder)[c,d]	2
6	Fe$_3$O$_4$ (50 nm size)[c]	10
7	Fe(0) (4.6−5.2 μm size)[c,d]	2
8	No catalyst	2
9	Fe(acac)$_3$ [No hydrazine]	0

[a]Conditions: 2.0 mmol PhNO$_2$, 3.6 mmol N$_2$H$_4$·H$_2$O, 1.5 mL of methanol, 0.25 mol % total Fe. Single-mode microwave heating at 150 °C for 2 min (hold time) with simultaneous cooling (Monowave 300). [b]Obtained by GC-MS analyses. [c]Commercially available from Sigma-Aldrich. [d]1 mol % total Fe.

Table 3. Effect of the Solvent Utilized during the Reduction Reaction[a]

solvent	conv.[b] (%)
MeOH	>99
EtOH	>99
2-propanol	>99
MeCN	89
H$_2$O	25
H$_2$O[c]	>99

[a]Conditions: 2.0 mmol PhNO$_2$, 3.6 mmol N$_2$H$_4$·H$_2$O, 1.5 mL of the corresponding solvent, 0.25 mol % Fe(acac)$_3$. Single-mode microwave heating at 150 °C for 2 min (hold time) with simultaneous cooling (Monowave 300). [b]Obtained by GC-MS analyses. [c]180 °C, 10 min.

the supernatant layer revealed that with this rather crude separation method ∼95% of the total Fe contained in the sample was recovered. Washing of the precipitate with methanol and addition of a fresh reaction mixture containing nitrobenzene and hydrazine hydrate in standard concentrations allowed an evaluation of the reusability of the nanocatalyst. We were able to reduce nitrobenzene to aniline without a decrease in efficiency 3 times before the conversion started a gradual

Figure 6. Retrieval of the magnetic Fe$_3$O$_4$ nanocrystals from a reaction mixture using an externally applied magnet.

decrease, likely due to the continuing loss of iron (ca. 5% according to ICP-MS) during the magnetic retrieval.

Interestingly, independently prepared Fe$_3$O$_4$ nanocrystals following the general Fe precursor/hydrazine microwave heating protocol[19,20] could be isolated, dried, and stored for several weeks retaining their catalytic efficiency. In a typical preparative procedure (see Experimental Section for further details), Fe$_3$O$_4$ nanocrystals were generated by heating a solution of Fe(acac)$_3$ and excess hydrazine hydrate (without substrate) in methanol in the microwave reactor at 150 °C for 1 min. Retrieval of the particles after keeping the reaction mixture for 20−30 min at room temperature was carried out by magnetic separation or centrifugation. The particles were then washed several times with methanol. Drying overnight in an oven at 70 °C provided a black, magnetic powder. Addition of this solid (corresponding to 0.25 mol % Fe loading) to a methanol solution containing nitrobenzene and hydrazine followed by sonication for 15 min returned the Fe$_3$O$_4$ particles into a colloidal form. Processing under standard reaction conditions (Table 3, entry 1) allowed reduction of nitro-benzene in ∼80% conversion. Importantly, the same activity was obtained with catalyst material that was stored for several

Table 4. Reduction of Nitroarenes with Hydrazine Hydrate Catalyzed by in-situ Generated Fe_3O_4 Nanocrystals under Microwave Irradiation[a]

$$Ar-NO_2 \xrightarrow[\text{MW, 150 °C, 2-8 min}]{\overset{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O (20\% excess)}}{\text{0.25 mol\% Fe(acac)}_3}} Ar-NH_2$$

| entry	Ar	t (min)	yield[b] (%)	entry	Ar	t (min)	yield[b] (%)
1	C_6H_5	2	99	12	3-NC-C_6H_4	2	99
2	4−Cl-C_6H_4	2	99	13	4-(NHAc)-C_6H_4	4	99
3	2−Cl-C_6H_4	4	97	14	4-NH_2−C_6H_4	6	99
4	3,4-$(Cl)_2$-C_6H_3	2	99	15	2-NH_2−C_6H_4	8	98
5	4−Br-C_6H_4	2	99	16	4-Me-C_6H_4	2	99
6	4−I-C_6H_4	2	98	17	6-quinolinyl	2	99
7	2-HO-C_6H_4	8	99	18	5-indolyl	8	97
8	2-Cl-5-OH-C_6H_3	4	99	19	4-(pyridin-4-ylmethyl)	4	99
9	4-MeO-C_6H_4	6	99	20	2-(4−Cl-C_6H_4)-C_6H_4	4	98
10	2,5-$(EtO)_2$-C_6H_3	6	99	21	2-NH_2-5−Cl-C_6H_3	8	98
11	3-(CO_2Me)-C_6H_4	6	95	22	3-F-4-(morpholinyl)-C_6H_4[c]	2	96

[a]Conditions: 2.0 mmol $ArNO_2$, 3.6 mmol $N_2H_4\cdot H_2O$, 1.5 mL of MeOH, 0.25 mol % $Fe(acac)_3$. Single-mode microwave heating at 150 °C with simultaneous cooling (Monowave 300). [b]Isolated yield. [c]3 mol % $Fe(acac)_3$ was used.

weeks. Notably, the activity of these particles is significantly higher than the activity of commercially available 50 nm sized Fe_3O_4 nanoparticles (cf. Table 2, entry 6).

Scope and Limitations. The in situ generated Fe_3O_4 nanocrystals displayed very high efficiency for the reduction of nitrobenzene to aniline, reaching full conversion within 2 min and a catalyst loading of only 0.25 mol % $Fe(acac)_3$ at 150 °C. To demonstrate the applicability and functional group tolerance of the system under these conditions a series of nitroarenes was transformed into the corresponding anilines following this general protocol (Table 4), significantly extending the preliminary substrate scope described under reflux conditions (Table 1). In all studied cases full conversion of the substrate was achieved within very short reaction time (2−8 min) with excellent selectivities. For chloro-, bromo- or iodo-substituted nitroarenes (Table 4, entries 2−6) no dehalogenation was observed by GC-MS monitoring of the crude reaction mixture and excellent isolated product yields were obtained after heating the reaction mixture for 2−4 min. Substrates containing alcohol-, ether-, ester-, amide-, cyano- and amino groups, in addition to heterocyclic moieties, were also successfully reduced using this protocol. Since only a small excess of reducing agent is employed (20%) and the side products of the hydrazine-mediated reduction are water and nitrogen, workup involved simple filtration through a plug of silica gel and evaporation of the solvent yielding the pure anilines.

It should be pointed out that hydrazine-mediated protocols cannot be used, in agreement with previous reports,[15] for substrates that contain aldehyde or ketone functionalities, since these carbonyl derivatives readily react with hydrazine at room temperature to the corresponding hydrazones. For these substrate types alternative reducing reagents such as silanes or siloxanes in combination with an Fe catalyst can be used.[10] A similar limitation exists for nitroarenes containing olefinic double bonds owing to the fact that diimide is generated as intermediate during the oxidation of hydrazine (Scheme 1), which is known to rapidly reduce olefinic double bonds.[34]
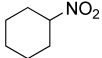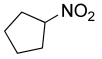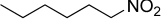
Notably, we were able to apply this intensified procedure to several important nitroarene to aniline reductions of industrial relevance (Scheme 3, Table 4, entries 20−22). Examples include the reduction of 4-chloro-2′-nitrobiphenyl **7** (a key

Scheme 3. Selected Reductions of Nitroarenes of Industrial Relevance
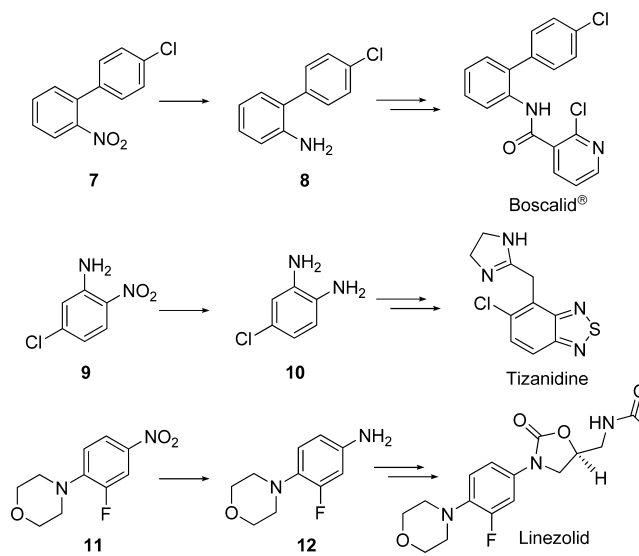
intermediate in the preparation of the fungicide Boscalid),[22] 2-amino-4-chloro-nitrobenzene **9** (an intermediate in the synthesis of the muscle relaxant Tizanidine),[35] and 3-fluoro-4-morpholinylnitrobenzene **11** (an intermediate in the preparation of the antibiotic Linezolid).[36] Both 4-chloro-2′-nitrobiphenyl **7** and 2-amino-4-chloro-nitrobenzene **9** could be efficiently and selectively reduced using the general conditions and the desired anilines were isolated with excellent yields (Table 4). In the case of the more challenging 3-fluoro-4-morpholinylnitrobenzene **11** the amount of iron catalyst was increased to 3 mol % in order to shorten the reaction time and thus avoid the formation of undesired side products.

Given the high efficiency of this procedure in reducing nitroarenes to the corresponding anilines, we decided to additionally evaluate the reduction of aliphatic nitro compounds and azides. Aliphatic nitro compounds revealed a significantly lower reactivity toward reduction than their aromatic counterparts. Indeed, when 0.25 mol % $Fe(acac)_3$ were added as catalyst the process required long reaction times and side reactions of the amine product with unreacted

Table 5. Reduction of Aliphatic Nitro Compounds with Hydrazine Hydrate Mediated by in-situ Generated Fe₃O₄ Nanocrystals[a]

| Entry	Substrate	T [min]	Conv.[b] [%]	Yield[c] [%]
1	cyclohexyl-NO₂	2	>99	99
2	cyclopentyl-NO₂	2	>99	96
3	pentyl-NO₂	2	>99	97
4	tert-butyl-NO₂	2	>99	99

[a]Conditions: 2 mmol of substrate, 20% excess of $N_2H_4\cdot H_2O$ (3.6 mmol), 1.5 mL methanol, 3 mol % $Fe(acac)_3$. Single-mode microwave heating at 150 °C with simultaneous cooling (Monowave 300). [b]Calculated by GC-MS. [c]Isolated yield as hydrochloride salt.

hydrazine were observed. By simply increasing the catalyst loading to 3 mol %, all evaluated reactions (Table 5) could be shortened to 2 min, with full conversion and excellent selectivities for all cases. Since some of the prepared amines have relatively low boiling points all products were isolated as hydrochloride salts. Therefore, the crude reaction mixtures were filtered through a plug of silica gel to remove the iron particles and the excess of hydrazine, diluted with ethyl acetate, and extracted with 1 M HCl. The aqueous phase was evaporated under reduced pressure yielding the amine hydrochlorides in excellent yields (Table 5).

The reduction of aromatic azides is an alternative method toward the preparation of anilines when the nitroarene precursors are not readily accessible. The azide precursors can be synthesized from aryl halides by treatment with sodium azide[37] and then reduced to the desired aniline. While palladium-catalyzed reductions of azides with hydrazine have been reported,[38,39] iron-catalyzed azide reductions mediated by hydrazine to the best of our knowledge are not known in the literature. Applying the same conditions used for the reduction of nitroarenes, a number of aryl azides containing electron donating and electron withdrawing groups were satisfactorily reduced to the corresponding anilines in very short reaction times (3−5 min) (Table 6). Reduction of an aliphatic azide (entry 5) proved to be more difficult, similar to the situation found for the nitro analogs, and an increase of the catalyst loading to 1 mol % was necessary to accomplish the transformation within 3 min. The byproduct of the reduction of azides with hydrazine is only nitrogen, and therefore the workup simply required filtration through a plug of silica and evaporation of the solvent under reduced pressure, furnishing the pure amines in excellent yields (Table 6).

Continuous Flow Reduction of Nitroarenes. A significant disadvantage of the above-described experiments from the industrial point of view is the exothermicity of the hydrazine-based high-temperature reductions, which limits the possibility for a safe scale-up in batch format. Indeed, all microwave experiments performed at 150 °C were carried out using the so-called "simultaneous cooling" technique[40] to avoid the pronounced exotherms obtained when the samples were irradiated without compressed air cooling. Figure 7a shows the temperature, pressure and power profiles for the reduction of 2 mmol of nitrobenzene under sealed vessel microwave conditions in the absence of simultaneous cooling. Even though the magnetron output power is reduced to zero, the internal reaction temperature measured by the fiber-optic probe

Table 6. Reduction of Azides with Hydrazine Hydrate Mediated by in-situ Generated Fe₃O₄ Nanocrystals[a]

Entry	Substrate	t [min]	Conv.[b] [%]	Yield[c] [%]
1	phenyl-N₃	3	>99	99
2	4-methylphenyl-N₃	3	>99	97
3	4-chlorophenyl-N₃ (Cl)	3	>99	99
4	4-methoxyphenyl-N₃ (MeO)	5	>99	98
5	benzyl-N₃ [d]	3	>99	99

[a]Conditions: 2 mmol of substrate, 3.6 mmol of $N_2H_4\cdot H_2O$, 1.5 mL methanol, 0.25% $Fe(acac)_3$. Single-mode microwave heating at 150 °C with simultaneous cooling (Monowave 300). [b]Calculated by GC-MS. [c]Isolated yields. [d]1 mol % $Fe(acac)_3$.

still increases with an overshoot of ~25 °C, leading to an internal reaction pressure of 27 bar. By simultaneously cooling (Figure 7b) the reaction mixture from the outside with compressed air, the overshoot is controlled and the reaction temperature can be maintained at the desired set temperature of 150 °C for the duration of the experiment.

Although in a small scale microwave batch experiment the considerably exothermic reduction process can be appropriately controlled, this would clearly not be the case on larger scale and therefore presents an important limitation in the context of industrial manufacturing. Therefore we turned our attention to the translation of the high-temperature batch microwave protocols toward scalable continuous flow processes following the "microwave-to-flow" paradigm.[41] Heat transfer is extremely efficient in a capillary microreactor due to the high surface-to-volume ratio and exothermic reactions can typically be controlled with relative ease.[17,18] The application of in situ generated Fe₃O₄ nanocrystals appears to be ideally suited for a continuous flow application. As the nanocrystals are initially colloidal, the reaction mixture stays homogeneous for a few minutes and can be pumped through the reactor without risk of clogging the microchannels.[42]
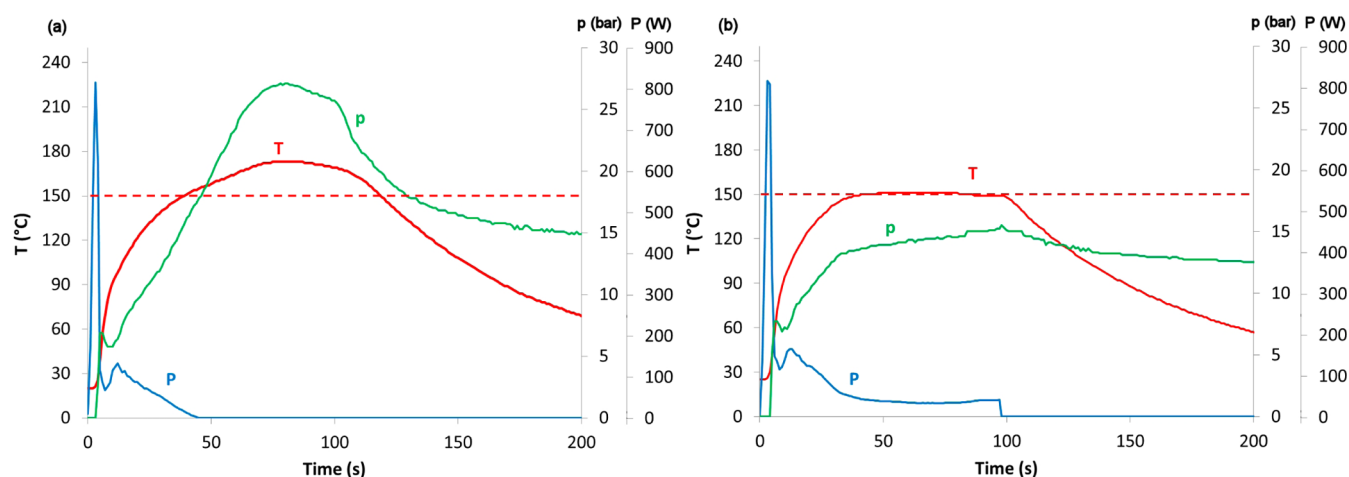
Figure 7. Internal reaction temperature (T), pressure (p) and power (P) profiles for the reduction of nitrobenzene with hydrazine under microwave irradiation (for reaction conditions, see Table 2, entry 1), set target temperature 150 °C. (a) Without simultaneous cooling; (b) with simultaneous cooling by compressed air.

All our experiments were carried out in a FlowSyn reactor from Uniqsis Ltd.[43] equipped with two HPLC pumps, each allowing flow rates up to 10 mL min^{-1} (20 mL min^{-1} in total), a stainless steel coil reactor of 25 m length and 1.0 mm internal diameter (20 mL internal volume) heated on an aluminum heating block, a heat exchanger with water cooling, and a 34 bar backpressure regulator (Figure 8). The initial continuous flow
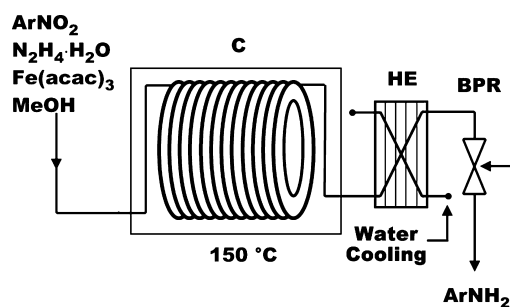

Figure 8. Schematic diagram for the continuous flow nitroarene reduction performed in a FlowSyn reactor from Uniqsis Ltd. C, Stainless steel coil reactor (20 mL internal volume, 1.0 mm i.d.); HE, heat-exchanger; BPR, back pressure regulator (34 bar).

experiments were carried out using nitrobenzene as model substrate. A ~1 M solution of nitrobenzene in methanol containing hydrazine hydrate (20 mol % excess) and 0.25 mol % Fe(acac)$_3$ was pumped through the reactor preheated at 150 °C with a flow rate of 4.0 mL min^{-1}. GC-MS analysis of the crude reaction mixture collected at the output line after a residence time of approximately 1.8 min revealed full conversion of the substrate to aniline. The residence time was lower than expected from the flow rates and reactor volume due to the evolution of N$_2$ gas during the reaction, which generates additional pressure and transports the reaction mixture at a different flow rate than the nominal flow rate stated by the HPLC pumps. Therefore, residence times had to be experimentally determined (see Experimental Section for details). Notably, the Fe$_3$O$_4$ nanocrystals started to aggregate only 5−10 min after the reaction was completed. Further increase of the flow rate to 6 mL min^{-1} (1.6 min residence time) did not lead to a decrease in the conversion. Applying this flow rate 0.1 mol of nitrobenzene could be reduced to

aniline within 15 min. Evaporation of the solvent and filtration through a plug of silica gel produced 8.9 g (96%) of pure aniline. It should be noted that when the iron precursor was not added to the reaction mixture, very poor conversions (<3%) were achieved, thus ruling out any activity of the stainless steel coil.

We then focused on a more difficult example such as the reduction of 2-chloronitrobenzene. Our goal was to find optimal continuous flow conditions for an ortho-halogen substituted nitroarene substrate, mimicking conditions that could later be applied to the industrially relevant 4′-chloro-2-nitrobiphenyl (**7**) (see Scheme 3). In this case, a concentration of ~0.5 M for the substrate was selected to ensure complete solubility of both the substrate and product. In a set of optimizing experiments, the flow rate and coil temperature were successively increased to 12 mL min^{-1} and 170 °C, respectively (residence time 1.3 min). Under these conditions, no dehalogenation was observed by GC-MS monitoring, and the substrate was fully converted to the desired aniline. Pumping a solution of 0.1 mol of 2-chloronitrobenzene in MeOH (200 mL) through the coil for approximately 15 min 12.1 g (95%) of 2-chloroaniline were obtained after workup.

Application of these conditions (170 °C, 12 mL min^{-1}) to the preparation of 2-amino-4′-chlorobiphenyl **8** (Scheme 3) resulted in only 94% conversion, therefore the flow rate was slightly reduced to 10 mL min^{-1} to yield full conversion to the desired aniline (residence time 1.5 min). In a scale-out approach, a solution containing 40 mmol of the substrate dissolved in 80 mL of methanol was passed through the reactor in a 7−8 min run. Full conversion and complete selectivity was obtained in a completely chemoselective reaction, and workup provided 7.9 g (97%) of pure 2-amino-4′-chlorobiphenyl. This protocol results in a productivity of >60 g/h of the pure aniline product.

The selective reduction of the nitro group in 2-amino-5-chloronitrobenzene (**9**) also drew our attention. The resulting 1,2-diamino-5-chlorobenzene is a key intermediate during the manufacture of Tizanidine (Scheme 3), a drug used as muscular relaxant and marketed by several pharmaceutical companies.[35] Batch experiments (Table 4, entry 21) revealed the reduction of this substrate to be more difficult, and 8 min reaction time were necessary to achieve full conversion at 150 °C. Moreover, the

substrate is not well soluble in methanol, and 1 M solutions could not be prepared. Homogeneously diluted samples (~0.5 M) suitable for continuous flow processing were therefore prepared and processed under microwave batch conditions in a preliminary screening exercise. Gratifyingly, the reaction time could be reduced to 2 min in batch when the sample was heated at 180 °C (internal pressure 25 bar) and even at this relatively high temperature, no side products were observed by GC-MS monitoring. Applying continuous flow conditions, the coil was consequently preheated at 180 °C, and a ~0.5 M solution of 2-amino-5-chloronitrobenzene containing the reducing agent and the iron precursor was pumped through the reactor with a flow rate of 8 mL min^{-1} (residence time 1.8 min). Full conversion of the substrate and complete selectivity was achieved, and in a scale-out experiment 5.6 g (98% yield) of the target aniline were produced running the reactor for 10 min. It is worth noting that at these high temperatures and flow rates an appropriate heat exchanger with external water cooling system is essential to avoid the output line from reaching temperatures above the boiling point of the solvent (65 °C).[43]

The most challenging transformation we tackled was the continuous flow preparation of 3-fluoro-4-morpholinylaniline, an intermediate in the synthesis of Linezolid, a potent oxazolidinone-based antibiotic manufactured by Pfizer (Scheme 3).[36] Batch microwave experiments revealed the formation of several side products under the standard conditions (0.25 mol % Fe(acac)$_3$, 150 °C), and a catalyst loading of 3 mol % Fe(acac)$_3$ was necessary to shorten the reaction time and to avoid side reactions (Table 4, entry 22). Moreover, 3-fluoro-4-morpholinylnitrobenzene is poorly soluble in methanol and other tested alcohols at room temperature and therefore a reoptimization under more diluted conditions was required. Homogeneous solutions suitable for flow processing were obtained by diluting the samples to ~0.25 M and preheating the solutions to ~40 °C before pumping them through the hot coil. An optimal set of conditions was then carefully investigated in batch format (Table 7). When a reaction mixture containing 1.5 mol % Fe(acac)$_3$ was heated at 170 °C for 1.5 min full conversion of the substrate with an excellent selectivity (99%) was achieved. Translating these conditions into a continuous flow format, a 40 °C preheated solution containing the substrate (~0.25M), hydrazine hydrate and 1.5 mol % Fe(acac)$_3$ was passed through the hot coil (170 °C) with
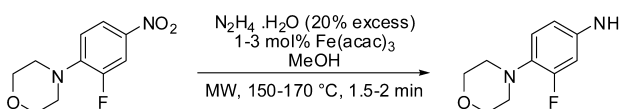
a flow rate of 10 mL min^{-1} (residence time 1.5 min). GC-MS monitoring of the product collected from the output line revealed full conversion of the substrate and only traces (<1%) of side products were observed. Workup of the crude reaction mixture yielded 95% of pure 3-fluoro-4-morpholinylaniline, which corresponds to a productivity in continuous format of ~30 g/h.

It should be pointed out that, as described above for the analogous batch experiments, the Fe$_3$O$_4$ nanocrystals can also be retrieved and recycled from continuous flow processes.[42] When the pure isolated nanoparticles (the procedure for isolation of the nanoparticles is described above) were added to a solution of nitrobenzene and hydrazine hydrate in methanol, and the mixture was sonicated for 15 min, the magnetic nanocrystals returned to their original colloidal state, and the mixture was therefore suitable for continuous flow processing. When the solution containing 0.08 mol % Fe$_3$O$_4$ (corresponding to 0.24 mol % Fe in the form of Fe(acac)$_3$) was pumped through the hot coil (150 °C, 6 mL min^{-1}) a 75% conversion was achieved. The same decrease in catalytic activity for the recycled particles was also observed in the batch experiments described above. However, full conversion of nitrobenzene to aniline could be achieved when 0.17 mol % of recycled Fe$_3$O$_4$ were used as catalyst, corresponding to 0.50 mol % Fe(acac)$_3$. Although Fe(acac)$_3$ is a nontoxic, cheap, stable, and easy to handle reagent, the alternative use of purified isolated magnetic Fe$_3$O$_4$ nanocrystals may also be of interest, in particular due to the fact that the aggregated nanoparticles are shelf stable for many weeks and by applying sonication technology can be readily transformed to a catalytically highly active colloidal material within a few minutes.

■ CONCLUSIONS

In summary, an efficient and chemoselective procedure for the reduction of nitroarenes with hydrazine hydrate based on the in situ generation of highly active Fe$_3$O$_4$ nanocrystals is described. This protocol, that eliminates the use of a precious metal catalyst and of hydrogen gas, is suitable for the preparation of anilines under both reflux conditions (65−80 °C) and using sealed vessel microwave technology. Excellent yields and selectivities were obtained under microwave conditions at 150 °C in reaction times of 2−8 min. Mechanistic insights on this Fe$_3$O$_4$-catalyzed reduction revealed that, although the reaction follows the traditional 3-step pathway, hazardous nitroso or hydroxylamine intermediates do not accumulate in the reaction mixture in detectable amounts. The initial colloidal state of the catalyst leads to fully homogeneous reaction mixtures suitable for continuous flow processing, and therefore to the possibility of an efficient, safe, and scalable preparation of anilines. In this context, three anilines of industrial importance, 2′-amino-4-chlorobiphenyl, 1,2-diamino-5-chlorobenzene, and 3-fluoro-4-morpholinylaniline, have been prepared in a continuous regime with excellent yields. The hydrazine/iron oxide nanocrystal method presented herein can also be used for the reduction of more challenging aliphatic nitro compounds and, importantly, efficiently reduces aromatic azides to their corresponding anilines. Owing to the magnetic properties of the Fe$_3$O$_4$ nanocrystals, the catalyst can be easily retrieved from the crude reaction mixture and reused, isolated and stored for several weeks.

Table 7. Batch Optimization Study for the Reduction of 3-Fluoro-4-morpholinylnitrobenzene with Hydrazine Hydrate Catalyzed by in-situ Generated Fe$_3$O$_4$ Nanocrystals[a]

substrate concentration (M)	Fe(acac)$_3$ (mol %)	t (min)	T (°C)	conv.[b] (%)	selectivity (%)[b]
1[c]	3	2	150	>99	>99
0.25	1	2	160	77	94
0.25	1.5	2	160	>99	97
0.25	1	2	170	99	96
0.25	1.5	1.5	170	99	99

[a]Conditions: 2 mmol of nitroarene **11**, 20% excess of N$_2$H$_4$·H$_2$O (3.6 mmol), 1.5 mL methanol. Single-mode microwave heating at 150−170 °C with simultaneous cooling (Monowave 300). [b]Determined by GC-MS. [c]Sample not homogeneous.

■ EXPERIMENTAL SECTION

General Experimental Details. ^{1}H NMR spectra were recorded on a 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. GC-MS monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m × 0.250 mm × 0.025 μm). After 1 min at 50 °C the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL min^{-1} in constant-flow mode. All solvents and hydrazine hydrate (reagent grade, 98%) were obtained from standard commercial vendors and were used without any further purification. Fe(acac)$_3$ 99.9+% metal basis purchased from Sigma-Aldrich was employed. 4-Chloro-2′-nitrobiphenyl **7** and 3-fluoro-4-morpholinylnitrobenzene **11** were prepared according to reported procedures.[19,44] All other chemicals were obtained from standard commercial vendors.

All compounds synthesized herein are known in the literature. Proof of purity and identity was obtained by ^{1}H NMR, ^{13}C NMR and MS spectroscopy.

General Procedure for Reduction of Nitroarenes Using Reflux Conditions (Table 1). To a solution of 2.0 mmol of substrate in ethanol (1.5 mL) were added 3.6 mmol (1.2 equiv, 0.175 mL) of N$_2$H$_4$·H$_2$O, and 3 mol % Fe(acac)$_3$. The mixture was placed into a 10 mL round-bottom flask and heated at reflux for the desired time (Table 1). When the nitroarene was consumed the reaction mixture was cooled to room temperature. Then, the solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (hexane/ethyl acetate). Careful solvent evaporation yielded the pure aniline.

Aniline (Table 1, entry 1): (167 mg, 90%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (t, J = 9.0 Hz, 2H), 6.80 (t, J = 9.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 3.64 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.3, 129.3, 118.5, 115.1; MS-EI: m/z 93 (100%), 66 (40%).

4-Chloroaniline (Table 1, entry 2): (226 mg, 89%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.11 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 9.0 Hz, 2H), 3.58 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 144.9, 129.1, 123.1, 116.2; MS-EI: m/z 129 (30%), 127 (100%), 100 (12%), 92 (16%), 65 (24%).

1,4-Diaminobenzene (Table 1, entry 3): (190 mg, 88%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.36 (s, 4H), 4.18 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 139.3, 115.8; MS-EI: m/z 108 (100%), 107 (30%), 80 (40%).

4-Acetamidoaniline (Table 1, entry 4): (276 mg, 92%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.19 (d, J = 8.7 Hz, 2H), 6.48 (d, J = 8.7 Hz, 2H), 4.82 (s, 2H),, 1.95 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 145.0, 129.0, 121.2, 114.2, 24.1. MS-EI: m/z 150 (55%), 108 (100%), 107 (40%), 80 (30%).

4-Chloro-2′-aminobiphenyl (Table 1, entry 5): (342 mg, 84%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.49 − 7.39 (m, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 6.86 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 3.67 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.4, 137.9, 133.1, 130.4, 130.3, 129.0, 128.8, 126.3, 118.7, 115.7. MS-EI: m/z 205 (30%), 203 (100%), 168 (50%), 167 (80%), 84 (30%).

Mechanistic and Kinetic Investigations. To obtain the kinetic data presented in Figures 2 and 3, solutions containing the corresponding nitroarene (2 mmol), hydrazine hydrate (20% excess, 3.6 mmol), and the stated amount of Fe(acac)$_3$ (0.5 mol % or 1 mol %, Figures 2 and 3) in methanol or ethanol were heated under reflux conditions. Monitoring of the reaction progress was performed by GC-MS analysis of the reaction mixture after given intervals of time. Samples suitable for GC-MS analysis were prepared by diluting ~1 μL of the reaction mixture in 1 mL of acetonitrile. Conversions were calculated by integration of the peak areas.

General Procedure for Reduction of Nitroarenes Using Microwave Heating (Table 4). Into a 10 mL microwave process vial equipped with a magnetic stir bar were placed 2.0 mmol of the nitroarene, 1.5 mL of methanol, 3.6 mmol (1.2 equiv, 0.175 mL) of N$_2$H$_4$·H$_2$O, and 0.25 mol % Fe(acac)$_3$ (unless otherwise stated, see

Table 4). The vial was capped with a Teflon septum and irradiated in a Monowave 300 single-mode microwave reactor (Anton Paar GmbH, Graz, Austria) fitted with a built-in camera and equipped with a fiber-optic (ruby) thermometer for internal online temperature monitoring at 150 °C for the specified time. In order to prevent the occurrence of exotherms/overheating, the reaction vessel was concurrently cooled with compressed air (6 bar). After the reaction time elapsed, the mixture was cooled to 45 °C by compressed air. The solvent was evaporated under reduced pressure and the crude mixture, dissolved in ethyl acetate, was filtered through a plug of silica gel (10 g) to provide the pure aniline products after careful solvent evaporation.

In order to evaluate the effect of the microwave electromagnetic field, two identical reaction mixtures containing nitrobenzene as substrate were prepared following the general procedure and placed into 10 mL microwave vials made out of Pyrex and SiC with exactly the same geometry. The vials were then capped with a Teflon septum and heated at 150 °C for 2 min (see General Procedure). GC-MS analyses of the crude mixtures obtained from both vials revealed exactly the same conversion and purity profile.

The characterization data for anilines shown in Table 4 are given in ref 16.

General Procedure for Reduction of Aliphatic Nitro Compounds Using Microwave Heating (Table 5). To a solution of 2.0 mmol of substrate in methanol (1.5 mL) were added 3.6 mmol (1.2 equiv, 0.175 mL) of N$_2$H$_4$·H$_2$O, and 3 mol % Fe(acac)$_3$. The mixture was placed into a 10 mL microwave process vial equipped with a magnetic stir bar, capped with a Teflon septum and irradiated in a Monowave 300 single-mode microwave reactor (Anton Paar GmbH, Graz, Austria) fitted with a built-in camera and equipped with a fiber-optic (ruby) thermometer for internal online temperature monitoring at 150 °C for the specified time. In order to prevent the occurrence of exotherms/overheating, the reaction vessel was concurrently cooled with compressed air (6 bar). After the reaction time elapsed, the mixture was cooled to 45 °C by compressed air. The crude reaction mixture was then filtered through a plug of silica gel, diluted with ethyl acetate (10 mL) and extracted with HCl 1 M (3 × 5 mL). The combined aqueous fractions were evaporated under reduced pressure yielding the corresponding pure amine hydrochloride as white solids.

Cyclohexylamine Hydrochloride (Table 5, entry 1): (267 mg, 99%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.15−2.95 (m, 1H), 1.95−1.7 (m, 2H), 1.75−1.60 (m, 2H), 1.57−1.45 (m, 1H), 1.32−0.95 (m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 50.3, 30.3, 24.2, 23.8.

Cyclopentylamine Hydrochloride (Table 5, entry 2): (233 mg, 96%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.47 (m, 1H), 1.89−1.80 (m, 2H), 1.56−1.41 (m, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 52.0, 30.5, 23.4.

n-Hexylamine Hydrochloride (Table 5, entry 3): (267 mg, 97%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.86 (t, J 7.5 Hz, 2H), 1.58−1.48 (m, 2H), 1.29−1.15 (m, 6H), 0.77−0.72 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 39.5, 30.4, 26.6, 25.2, 21.7, 13.2.

2-Methyl-2-propylamine Hydrochloride (Table 5, entry 4): (216 mg, 99%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.32 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 51.9, 26.6.

General Procedure for Reduction of Azides Using Microwave Heating (Table 6). Reduction of azides was carried out following the general procedure for the reduction of nitroarenes using microwave heating (see above). Azides were purchased from Sigma-Aldrich as 0.5 M *tert*-butyl methylether solutions. The solvent was gently evaporated under reduced pressure to obtain the pure azides which were then used as substrate.

Aniline (Table 6, entry 1): (184 mg, 99%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (t, J = 9.0 Hz, 2H), 6.80 (t, J = 9.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 3.64 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.3, 129.3, 118.5, 115.1; MS-EI: m/z 93 (100%), 66 (40%).

4-Aminotoluene (Table 6, entry 2): (210 mg, 97%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.00 (d, J = 7.9 Hz, 2H), 6.64 (d, J = 8.3 Hz, 2H), 3.55 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.8, 129.7, 127.8, 115.2, 20.4; MS-EI: m/z 107 (62%), 105 (100%), 77 (15%).

4-Chloroaniline (Table 6, entry 3): (254 mg, 99%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.11 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 9.0 Hz, 2H), 3.58 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 144.9, 129.1, 123.1, 116.2; MS-EI: m/z 129 (30%), 127 (100%), 100 (12%), 92 (16%), 65 (24%).

4-Methoxyaniline (Table 6, entry 4): (243 mg, 98%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.77 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 3.76 (s, 3H), 3.41 (s, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.7, 139.9, 116.4, 114.8, 55.7; MS-EI: m/z 123 (72%), 108 (100%), 80 (43%).

Benzylamine (Table 6, entry 5): (212 mg, 99%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38−7.25 (m, 5H), 3.87 (s, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.5, 128.5, 127.1, 126.8, 46.5; MS-EI: m/z 107 (50%), 106 (100%), 79 (35%), 77 (25%).

Preparation and Isolation of Fe$_3$O$_4$ Nanoparticles. A solution of Fe(acac)$_3$ 0.02 mmol (7.1 mg) and hydrazine hydrate (2 mmol) in methanol (1.5 mL) was placed into a 10 mL microwave vial and heated at 150 °C for 1 min. The resulting mixture was cooled at room temperature and after 20−30 min the black precipitate was retrieved with magnetic separation or centrifugation (5000 rpm, 5 min). The solid was washed three times with fresh methanol and dried overnight in a drying oven at 70 °C. The obtained Fe$_3$O$_4$ nanocrystals were characterized by means of X-ray powder diffraction (XRD) and high-resolution transmission electron microscopy (HRTEM).[16]

Representative Procedure for the Reduction of Nitroarenes Using Continuous Flow Conditions. Flow experiments were performed using a Uniqsis FlowSyn[43] reactor equipped with a 20 mL stainless steel coil and a 34 bar backpressure regulator. After the desired reaction parameters were achieved, a mixture containing methanol (2 mL), the substrate (2 mmol), hydrazine hydrate (3.6 mmol), and Fe(acac)$_3$ (0.25 mol %) was pumped through the system. Due to the generation of N$_2$ gas during the reaction, careful control of the residence time is necessary because the extra pressure generated will transport the reaction mixture at a different flow rate than the nominal flow rate stated by the HPLC pumps. The residence time was estimated by observing the total residence time in the reactor (visual inspection, the reaction mixture is dark after the processing) and taking into account the volume of the "cold" zones of the reactor (pumps, tubing, etc) and the flow rate. The crude reaction mixture was collected at the reaction outlet and purified as described above for the microwave chemistry experiments.

4-Chloro-2′-aminobiphenyl (8): (7.9 g, 97% yield, in a 40 mmol scale reaction) for characterization data, see above.

4-Chloro-1,2-diaminobenzene (10): (5.6 g, 98%, in a 40 mmol scale reaction); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.50 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 6.34 (dd, J = 2.4, 8.2 Hz, 1H), 4.63 (sa, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 137.1, 134.3, 120.8, 116.5, 115.4, 113.7. MS-EI: m/z 144 (30%), 142 (100%), 141 (22%), 114 (22%), 80 (25%)

3-Fluoro-4-morpholinylaniline (12): (3.7 g, 95%, a 20 mmol scale reaction); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (t, J = 8.6 Hz, 1H), 6.37−6.29 (m, 2H), 4.99 (s, 2H), 3.68 (t, J = 4.6 Hz, 4H), 2.80 (t, J = 4.6 Hz, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.4, 155.2, 146.0, 145.9, 129.6, 129.4, 121.0, 120.9, 110.0, 102.5, 102.2, 66.9, 52.1, 52.0. MS-EI: m/z 196 (60%), 138 (100%), 136.9 (50%).

ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR spectra of all prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: oliver.kappe@uni-graz.at.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) *Nanoparticles and Catalysis*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

(2) For general reviews see: (a) Polshettiwar, V.; Varma, R. S. *Green Chem.* **2010**, *12*, 743−754. (b) Astruc, D.; Lu, F.; Ruiz Aranzaes, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7852−7872. (c) Kalidindi, S. B.; Jagirdar, B. R. *ChemSusChem* **2012**, *5*, 65−75. (d) Zahmakiran, M.; Ozkar, S. *Nanoscale* **2011**, *3*, 3462−3481. (e) Wang, D. S.; Xie, T.; Li, Y. D. *Nano Res.* **2009**, *2*, 30−46. (f) Schlogl, R.; Abd Hamid, S. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 1628−1637.

(3) Plietker, B. *Iron Catalysis in Organic Chemistry*; Wiley-VCH: Wienheim, Germany, 2008.

(4) For some recent examples of iron oxide nanocatalysts see: (a) Luque, R.; Baruwati, B.; Varma, R. S. *Green Chem.* **2010**, *12*, 1540−1543. (b) Zeng, T.; Chen, W.-W.; Cirtiu, C. M.; Moores, A.; Song, G.; Li, C.-J. *Green Chem.* **2010**, *12*, 570−573. (c) Koukabi, N.; Kolvari, E.; Khazaei, A.; Zolfigol, M. A.; Shirmardi-Shaghasemi, B.; Khavasi, H. R. *Chem. Commun.* **2011**, *47*, 9230−9233. (d) Yang, C.; Wu, J.; Hou, Y. *Chem. Commun.* **2011**, *47*, 5130−5141.

(5) For recent reviews on magnetic nanocatalysts see: (a) Shylesh, S.; Schünemann, V.; Thiel, W. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 3428−3459. (b) Polshettiwar, V.; Luque, R.; Fihri, A.; Zhu, H.; Bouhrara, M.; Basset, J.-M. *Chem. Rev.* **2011**, *111*, 3036−3075. (c) Nasir, R. B.; Varma, R. S. *Chem. Commun.* **2013**, *49*, 752−770.

(6) (a) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, *37*, 121−136. (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(7) (a) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, 2001. (b) Arnold, H.; Döbert, F.; Gaube, J. In *Handbook of Heterogeneous Catalysis*; Wiley-Interscience: New York, 2008; pp 3266−3284.

(8) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035−2052.

(9) (a) Corma, A.; Serna, P. *Science* **2006**, *313*, 332−334. (b) He, L.; Wang, L.-C.; Sun, H.; Ni, J.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2009**, *48*, 9538−9541. (c) Li, M.; Hu, L.; Cao, X.; Hong, H.; Lu, J.; Gu, H. *Chem.—Eur. J.* **2011**, *17*, 2763−2768. (d) Wu, H.; Zhuo, L.; He, Q.; Liao, X.; Shi, B. *Appl. Catal., A* **2009**, *366*, 44−56. (e) Amali, A. J.; Rana, R. K. *Green Chem.* **2009**, *11*, 1781−1786. (f) Li, J.; Shi, X.; Bi, Y.; Wei, J.; Chen, Z. *ACS Catal.* **2011**, *1*, 657−664.

(10) (a) Junge, K.; Wendt, B.; Shaikh, N.; Beller, M. *Chem. Commun.* **2010**, *46*, 1769−1771. (b) Pehlivan, L.; Métay, E.; Laval, S.; Dayoub, W.; Demonchaux, P.; Mignani, G.; Lemaire, M. *Tetrahedron Lett.* **2010**, *51*, 1939−1941.

(11) Bae, J. W.; Cho, Y. J.; Lee, S. H.; Yoon, C. O. M.; Yoon, C. M. *Chem. Commun.* **2000**, 1857−1858.

(12) Lin, X.; Wu, M.; Wu, D.; Kuga, S.; Endoe, T.; Huang, Y. *Green Chem.* **2011**, *13*, 283−287.

(13) Berthold, H.; Schotten, T.; Hönig, H. *Synthesis* **2002**, 1607−1610.

(14) (a) Wienhöfer, G.; Sorribes, I.; Boddien, A.; Westerhaus, F.; Junge, K.; Junge, H.; Llusar, R.; Beller, M. *J. Am. Chem. Soc.* **2011**, *133*, 12875−12879. (b) Sorribes, I.; Wienhöfer, G.; Vicent, C.; Junge, K.; Llusar, R.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 7794−7798.

(15) (a) Vass, A.; Dudas, J.; Toth, J.; Varma, R. S. *Tetrahedron Lett.* **2001**, *42*, 5347−5349. (b) Kumarraja, M.; Pitchumani, K. *Appl. Catal. A: Gen.* **2004**, *265*, 135−139. (c) Shi, Q.; Lu, R.; Jin, K.; Zhang, Z.; Zhao, D. *Green Chem.* **2006**, *8*, 868−870. (d) Kim, S.; Kim, E.; Kim, B. M. *Chem. Asian J.* **2011**, *6*, 1921−1925. (e) Sharma, U.; Verma, P. K.; Kumar, N.; Kumar, V.; Bala, M.; Singh, B. *Chem.—Eur. J.* **2011**, *17*, 5903−5907. (f) Jagadeesh, R. V.; Wienhöfer, G.; Westerhaus, F. A.; Surkus, A.-E.; Pohl, M.-M.; Junge, H.; Junge, K.; Beller, M. *Chem. Commun.* **2011**, *47*, 10972−10974. (g) Shi, Q.; Lu, R.; Lu, L.; Fu, X.;

Zhao, D. *Adv. Synth. Catal.* **2007**, *349*, 1877−1881. (h) Luo, P.; Xu, K.; Zhang, R.; Huang, L.; Wang, J.; Xing, W.; Huang, J. *Catal. Sci. Technol.* **2012**, *2*, 301−304.

(16) Cantillo, D.; Baghbanzadeh, M.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2012**, *51*, 10190−10193.

(17) For recent books on continuous flow/microreactor chemistry, see: (a) Wiles, C.; Watts, P. *Micro Reaction Technology in Organic Synthesis*; CRC Press: Boca Raton, FL, 2011. (b) *Handbook of Micro Reactors*; Hessel, V., Schouten, J. C., Renken, A., Wang, Y., Yoshida, J.-i., Eds.; Wiley-VCH: Weinheim, 2009. (c) *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2008.

(18) For recent reviews on continuous flow/microreactor chemistry, see: (a) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17−57. (b) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38−54. (c) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7502−7519.

(19) (a) Lu, J.; Jiao, X.; Chen, D.; Li, W. *J. Phys. Chem. C* **2009**, *113*, 4012−4017. (b) Guardia, P.; Labarta, A.; Batlle, X. *J. Phys. Chem C* **2011**, *115*, 390−395. (c) Druzhinina, T. S.; Herzer, N.; Hoeppener, S.; Schubert, U. S. *ChemPhysChem* **2011**, *12*, 781−784. (d) Wiogo, H.; Lim, M.; Munroe, P.; Arnal, R. *Cryst. Grown Des.* **2011**, *11*, 1689−1696. (e) Iida, H.; Nakanishi, T.; Takada, H.; Osaka, T. *Electrochim. Acta* **2006**, *52*, 292−296.

(20) For microwave assisted Fe_3O_4 preparations, see: (a) Wang, W.-W.; Zhu, Y.-J.; Ruan, M.-L. *J. Nanopart. Res.* **2007**, *9*, 419−426. (b) Osborne, E. A.; Atkins, T. M.; Gilbert, D. A.; Kauzlarich, S. M.; Liu, K.; Louie, A. Y. *Nanotechnology* **2012**, *23*, 215602. (c) Jia, J.; Yu, J. C.; Zhu, X.-M.; Chan, K. M.; Wang, Y.-X. J. *J. Colloid Interface Sci.* **2012**, *379*, 1−7.

(21) Hayden, S.; Damm, M.; Kappe, C. O. *Macromol. Chem. Phys.* **2013**, *214*, 423−434.

(22) Glasnov, T. N.; Kappe, C. O. *Adv. Synth. Catal.* **2010**, *352*, 3089−3097 and references therein.

(23) (a) Haber, F. Z. *Elektrochem. Angew. Phys. Chem.* **1898**, *22*, 506−514. (b) Dyson, R. M.; Hazenkamp, M.; Kaufmann, K.; Maeder, M.; Studer, M.; Zilian, A. *J. Chemometrics* **2000**, *14*, 737−750.

(24) (a) Benz, M.; Van der Kraan, A. M.; Prins, R. *Appl. Catal., A* **1998**, *172*, 149−157. (b) Kumbhar, P. S.; Sanchez-Valente, J.; Millet, J. M. M.; Figueras, F. *J. Catal.* **2000**, *191*, 467−473. (c) Kumarraja, M.; Pitchumani, K. *Appl. Catal., A* **2004**, *265*, 135−139.

(25) Miller, J. A. *Cancer Res.* **1970**, *3*, 559−576.

(26) (a) *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Urben, P. G., Ed.; Accademic Press: Oxford, 2007. (b) Tong, W. R.; Seagrave, R. L.; Wiederhorn, R. *AIChE Loss Prev.* **1977**, *11*, 71−75.

(27) Siegrist, U.; Baumeister, P.; Blaser, H.-U.; Studer, M. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Deker Inc: New York, 1998; pp 207−219.

(28) Larsen, J. W.; Freund, M.; Kim, K. Y.; Sidovar, M.; Stuart, J. L. *Carbon* **2000**, *38*, 655−661.

(29) (a) Studer, M.; Neto, S.; Blaser, H.-U. *Top. Catal.* **2000**, *13*, 205−212. (b) Menga, X.; Chengb, H.; Fujitaa, S.-i.; Haob, Y.; Shangb, Y.; Yu, Y.; Cai, S.; Zhao, F.; Arai, M. *J. Catal.* **2010**, *269*, 131−139. (c) Cárdenas-Lizana, F.; Gómez-Quero, S.; Keane, M. A. *Appl. Catal., A* **2008**, *334*, 199−206. (d) Baumeister, P.; Blaser, H.-U.; Studer, M. *Catal. Lett.* **1997**, *49*, 219−222.

(30) Minato, H.; Jujisawa, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1054−1058.

(31) For a review on high-temperature microwave chemistry in water, see: Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563−2591.

(32) (a) Obermayer, D.; Gutmann, B.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321−8324. (b) Gutmann, B.; Obermayer, D.; Reichart, B.; Prekodravac, B.; Irfan, M.; Kremsner, J. M.; Kappe, C. O. *Chem.—Eur. J.* **2010**, *16*, 12182−12194. (c) Kappe, C. O. *Acc. Chem. Res.* **2013**, DOI: 10.1021/ar300318c.

(33) For a recent discussion on microwave effects, see: Kappe, C. O.; Pieber, B.; Dallinger, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 1088−1094.

(34) Lamani, M.; Ravikumara, G. S.; Prabhu, K. R. *Adv. Synth. Catal.* **2012**, *354*, 1437−1442.

(35) Coward, D. M. *Neurology* **1994**, *44*, S6−S11.

(36) Moellering, R. C. *Ann. Intern. Med.* **2003**, *138*, 135−142.

(37) (a) Andersen, J.; Madsen, U.; Björkling, F.; Liang, X. *Synlett* **2005**, *14*, 2209−2213. (b) Kopach, M. E.; Murray, M. M.; Braden, T. M.; Kobierski, M. E.; Williams, O. L. *Org. Process. Res. Dev.* **2009**, *13*, 152−160.

(38) Malik, A. A.; Preston, S. B.; Archibald, T. G.; Cohen, M. P.; Baum, K. *Synthesis* **1989**, *6*, 450−451.

(39) For an uncatalyzed version providing low selectivity, see: Paterson, T. M.; Smalley, R. K.; Suschitzky, H. *Tetrahedron Lett.* **1977**, *45*, 3973−3976.

(40) (a) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417−1424. For a recent review of examples of microwave chemistry using the simultaneous cooling technique, see: (b) O'Brien, M.; Denton, R.; Ley, S. V. *Synthesis* **2011**, *42*, 1157−1192.

(41) Glasnov, T. N.; Kappe, C. O. *Chem.—Eur. J.* **2011**, *17*, 11956−11968.

(42) For the continuous flow synthesis of Fe_3O_4 nanocrystals, see: Simmons, M.; Wiles, C.; Rocher, V.; Francesconi, M. G.; Watts, P. *J. Flow Chem.* **2013**, *3*, 7−10 and references cited therein.

(43) For a detailed description of the Uniqsis FlowSyn set-up, see: Gutmann, B.; Roduit, J.-P.; Roberge, D.; Kappe, C. O. *J. Flow Chem.* **2012**, *2*, 8−19.

(44) Chen, L.; Wang, J.-W.; Hai, L.; Wang, G.-M.; Wu, Y. *Synth. Commun.* **2010**, *40*, 789−798.