

In Situ Generated Iron Oxide Nanocrystals as Efficient and Selective Catalysts for the Reduction of Nitroarenes using a Continuous Flow Method**

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Functionalized anilines are industrially important intermediates in the preparation of pharmaceuticals, agrochemicals, dyes, and pigments. The most commonly used method for the synthesis of anilines is the reduction of aromatic nitro compounds.^[1] While traditional non-catalytic reduction processes (that is using Fe/HCl) generate large amounts of undesirable waste; catalytic hydrogenation using heterogeneous transition-metal catalysts is a well-established technique and often the method of choice for the reduction of nitroarenes to anilines.^[2,3] However, selectivity problems in the presence of other common functional groups can occur,^[4] often requiring the use of carefully selected and expensive precious metal catalysts (for example, Pd, Pt, or Ru).^[3] Therefore, significant efforts have been made to develop more efficient and sustainable methods to achieve the selective reduction of nitroarenes to anilines. Apart from the use of hydrogen, several other stoichiometric reducing agents such as ammonium salts,^[5] silanes,^[6] boranes,^[7] sodium borohydride,^[8] formic acid,^[9] and hydrazine,^[10] have been used in combination with a number of different metal catalysts.^[5–10] Hydrazine, specifically the less hazardous hydrazine hydrate (N₂H₄·H₂O), is a particularly good reagent because it generates only N₂ as a side product and is comparatively safe to handle.

In the past few years, interest in the use of iron-based catalysts in organic synthesis has increased dramatically.^[11] Iron is an abundant, eco-friendly, relatively nontoxic, and inexpensive element, and thus the development of catalysts based on this metal is highly desirable. Several Fe-catalyzed procedures for the hydrazine-mediated reduction of nitroarenes have been reported.^[10a–g] In the general context of nanocatalysis, magnetic nanomaterials, in particular iron oxide nanoparticles, have become very attractive as inex-

pensive nanocatalysts that can be easily separated and recovered after the reaction.^[12,13] Nanosized materials feature unique properties as catalysts: the high surface-to-volume ratio of nanoparticles compared to a bulk material generally results in an extremely high catalytic activity and often improved selectivity.^[12]

Herein, we present a novel method in nanocatalysis applied to the selective reduction of nitroarenes to anilines in a continuous-flow format. In a solution containing the nitroarene, Fe₃O₄ nanocrystals were generated in situ from an inexpensive Fe precursor using hydrazine hydrate as the reducing agent at elevated temperatures. Upon formation, the highly reactive nanocrystals then selectively catalyze the reduction of the nitro group with hydrazine with unparalleled efficiency. Importantly, the originally colloidal nanocatalyst remains in solution during the time required for nitro group reduction. The Fe₃O₄ nanocrystals subsequently start to aggregate forming a precipitate that is easily removable using a simple magnet. This unique process combines the benefits of homogeneous and heterogeneous nanocatalysts, and is particularly valuable for continuous manufacturing applications because the initial homogeneous reaction mixture can be easily processed in a safe and scalable way using continuous-flow technology.

First, we evaluated the generation of iron oxide (that is, magnetite, Fe₃O₄) nanoparticles by treatment of various Fe precursors with hydrazine hydrate, essentially following known procedures.^[14] All experiments were performed using small-scale microwave batch heating at elevated temperatures, thus rapidly generating the desired nanoparticles, ensuring short reaction times for the nitroarene reductions, and a high throughput for use in the continuous-flow method. A typical reaction mixture (see Table 1) consisted of a solution of tris(acetylacetonato)iron(III) (Fe(acac)₃), nitrobenzene, and hydrazine in methanol at 150 °C in a sealed vessel with microwave irradiation, the formation of solid magnetic particles during the irradiation process could be readily observed after a few minutes with the aid of a built-in camera (see Supporting Information, Figure S1). The magnetic particles could be unambiguously identified as single-phase cubic Fe₃O₄ by their X-ray powder diffraction (XRD) patterns (Figure S2), while high-resolution transmission electron microscopy (HRTEM) micrographs obtained from a sample of stabilized colloidal Fe₃O₄ nanocrystals revealed the size of the crystals to be 6 ± 2 nm (Figure S3).

The efficiency of the Fe₃O₄ nanocrystals generated in situ for the reduction of nitroarenes was first studied using nitrobenzene as model substrate (Figures S4, S5). Experi-

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Table 1: Synthesis of anilines by reduction of nitroarenes with hydrazine hydrate using Fe_3O_4 nanocrystals generated in situ as a catalyst.^[a]

$\text{R}-\text{C}_6\text{H}_4-\text{NO}_2 \xrightarrow[\text{microwaves, 150 } ^\circ\text{C, 2-8 min}]{\text{Fe(acac)}_3 \text{ (0.25 mol\%)} \\ \text{20 mol\% excess N}_2\text{H}_4\cdot\text{H}_2\text{O} \\ \text{MeOH (ca. 1 M)}} \text{R}-\text{C}_6\text{H}_4-\text{NH}_2$							
Entry	Substrate	<i>t</i> [min] ^[b]	Yield [%]	Entry	Substrate	<i>t</i> [min] ^[b]	Yield [%]
1		2	99	11		6	95
2		2	99	12		2	99
3		4	97	13		4	99
4		2	99	14		6	99
5		2	99	15		8	98
6		2	98	16		2	99
7		8	99	17		2	99
8		4	99	18		8	97
9		6	99	19		4	99
10		6	99	20		4	98

[a] Conditions: 2.0 mmol nitroarene, 3.6 mmol $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (20% stoichiometric excess), 1.5 mL MeOH, 0.25 mol% Fe(acac)_3 . Single-mode microwave heating at 150 °C (see Supporting Information for details). [b] Reaction times refer to the hold times at 150 °C (ramp time approximately 30 s, cooling time approximately 2 min).

ments with different catalyst loadings (Figure S4) revealed that full conversion could be achieved with just 0.25 mol % of Fe(acac)_3 and only 20% stoichiometric excess of hydrazine hydrate within two minutes of microwave heating at 150 °C (approximately 15 bar) using methanol as the solvent (Table 1, entry 1). In the absence of the Fe catalyst, the yield of the reduction reaction was very poor (2%), similar to an experiment where no reducing agent ($\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$) was added to the reaction mixture. The reaction efficiency is apparently independent of the Fe precursor, as long as the precursor is soluble in the reaction mixture. Reactions using Fe(acac)_3 , $\text{FeCl}_2\cdot 4\text{H}_2\text{O}$, $\text{FeCl}_3\cdot 6\text{H}_2\text{O}$, and Fe(OAc)_2 all gave full conversion of the substrate into aniline within two minutes (Table S1). Notably, commercially available Fe_3O_4 and Fe^0 powder did not show any activity under these reaction

conditions even when 1 mol% catalyst loading was used (Table S1). In contrast, the recycled agglomerated Fe_3O_4 nanoparticles (Figure S1) could be reused several times before a decrease in activity was observed (Figure S8).

These optimized conditions were then applied to a selection of 20 substituted nitroarenes containing additional reducible groups to test the chemoselectivity of the Fe_3O_4 nanocatalytic system (Table 1).^[15] In all cases studied herein, full conversion of the substrates with excellent selectivity for the desired anilines was achieved with very short reaction times (2–8 min). Despite the relatively high reaction temperature, in the case of chloro-, bromo-, or iodo-substituted nitroarenes (Table 1, entries 2–6) no dehalogenation was observed by GC–MS monitoring of the crude reaction mixture and nearly quantitative yields were obtained after two to four minutes reaction time. This procedure also selectively reduced other functionalized nitroarenes, including derivatives containing alcohol, ether, ester, amide, and amino groups, in addition to heterocyclic moieties (Table 1). Notably, 3-cyano-substituted nitrobenzene was also selectively reduced (Table 1, entry 12), a reaction of considerable importance in organic synthesis. In addition, 4-chloro-2'-nitrobiphenyl, a key intermediate in the synthesis of the marketed fungicide Boscalid,^[16] could be efficiently and selectively reduced within four minutes (Table 1, entry 20), providing

an excellent yield of the isolated aniline product.

It should be noted, that the excellent chemoselectivity observed for the Fe_3O_4 nanocatalyst generated in situ for the reduction of aromatic nitro groups with hydrazine is similar to that previously reported for some other Fe-based/hydrazine reducing systems.^[10a–g] However, the overall catalytic efficiency of the current process in terms of catalyst turn-over number (TON), turn-over frequency (TOF), and required hydrazine stoichiometry is far superior to all previously reported selective Fe-based nitro group reductions.^[10a–g,17] Owing to the small amounts of Fe_3O_4 catalyst (0.25 mol %) and reducing agent (20% stoichiometric excess) required in our procedure, and since no additional additives are required, the purification of the crude products is very simple and resulted in excellent yields (95–99%) for the pure anilines in

all 20 cases. Simple filtration or separation of the Fe_3O_4 particles with a magnet followed by filtration through a plug of silica gel to remove the small amounts of hydrazine or water gave the aniline products in excellent yields and purities. Removal of the agglomerated Fe_3O_4 particles with a magnet (Figure S1) recovered approximately 95 % of the total Fe from the sample, according to ICP-MS measurements.

The methods described above are superior in many ways to most other selective nitro group reduction methods, and could be of significant industrial importance owing to the low cost of the reagents, the high process efficiency, and the fact that only nitrogen and water are produced as waste. However, a significant disadvantage is the exothermicity of the hydrazine-based reduction, limiting the possibility for a safe scale-up in batch format (see Figure S6). Therefore we turned our attention to the translation of the small-scale batch microwave method towards a scalable continuous-flow process.^[18] Owing to the high surface-to-volume ratio in a capillary microreactor, heat transfer is extremely efficient and exothermic reactions can typically be controlled with relative ease.^[19,20] Because the catalytic Fe_3O_4 nanocrystals generated in situ are initially formed as colloids, the reaction mixture remains homogeneous for a few minutes and is therefore ideally suited for continuous-flow processing. No precipitation occurs that could potentially block the reactor coil or backpressure regulator. Similar to the microwave batch experiments, initial trials were carried out using nitrobenzene as a substrate. When an approximately 1 M solution of nitrobenzene in methanol, containing 0.25 mol % $\text{Fe}(\text{acac})_3$ precursor and hydrazine hydrate (20 % molar excess) was pumped at 4.0 mL min^{-1} through a 20 mL (1.0 mm i.d.) stainless-steel coil preheated to 150°C (Uniqsis FlowSyn reactor, Figure S7),^[21] the crude reaction mixture collected at the output line after a residence time of approximately 1.8 min revealed full conversion to aniline (GC-MS). Notably, in the absence of the $\text{Fe}(\text{acac})_3$ precursor, an extremely poor conversion (2–3 %) was achieved, ruling out any catalytic activity of the stainless steel coil itself. The flow rate could be further increased to 6 mL min^{-1} maintaining the temperature at 150°C (1.6 minutes residence time), without a decrease in the observed conversion. Using these conditions, 0.1 mol of nitrobenzene were reduced in a continuous-flow regime operating the reactor for approximately 15 minutes. No remaining traces of the substrate were detected in the collected crude reaction mixture (GC-MS). Evaporation of the solvent under reduced pressure and filtration through a plug of silica gel produced 8.9 g (96 %) of pure aniline, which represents a productivity of 30 g h^{-1} .

A more challenging and interesting example from an industrial viewpoint is the reduction of 4-chloro-2'-nitrobiphenyl (Table 1, entry 20). The preparation of 4-chloro-2'-aminobiphenyl by reduction of the corresponding nitro compound is a key step in the production of Boscalid, an important fungicide produced on a scale of 1000 tons/year.^[16] Increasing the coil temperature to 170°C , we could selectively and fully reduce 4-chloro-2'-nitrobiphenyl using a flow rate of 10 mL min^{-1} (measured residence time of 1.5 minutes). Again, no dehalogenation was observed in this apparently

completely chemoselective reaction. 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 seven to eight minute run. Full conversion and complete selectivity was obtained, and the work-up provided 7.9 g (97 %) of pure 4-chloro-2'-aminobiphenyl. This method results in the productivity of a single coil of more than 60 g h^{-1} of the pure aniline product (see Table S3).

In conclusion, we have developed an environmentally benign, safe, scalable, and extremely efficient method for the selective reduction of nitroarenes to anilines, which eliminates the use of a precious-metal catalyst and of hydrogen gas. Instead, our method relies on the use of hydrazine hydrate as a reducing reagent, combined with the rapid generation in situ of colloidal Fe_3O_4 nanocrystals with high catalytic activity, which after the reduction process agglomerate and can be removed using a simple magnet. The use of 0.25 mol % of an inexpensive Fe source and processing times of only a few minutes makes this method extremely valuable both on a laboratory scale, but also on an industrial scale, by applying continuous-flow processing.

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