Immobilized Iron Oxide Nanoparticles as Stable and Reusable Catalysts for Hydrazine-Mediated Nitro Reductions in Continuous Flow

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An experimentally easy to perform method for the generation of alumina-supported Fe_3O_4 nanoparticles [(6 ± 1) nm size, 0.67 wt%]and the use of this material in hydrazine-mediated heterogeneously catalyzed reductions of nitroarenes to anilines under batch and continuous-flow conditions is presented. The bench-stable, reusable nano-Fe_3O_4@Al_2O_3 catalyst can selectively reduce functionalized nitroarenes at 1 mol% catalyst loading by using a 20 mol% excess of hydrazine hydrate in an elevated temperature regime (150°C, reaction time 2–6 min in batch). For continuous-flow processing, the catalyst material is packed into dedicated cartridges and used in a commercially available high-temperature/-pressure flow device. In continuous mode, reaction times can be reduced to less than 1 min at 150°C (30 bar back pressure) in a highly intensified process. The nano-Fe_3O_4@Al_2O_3 catalyst demonstrated stable reduction of nitrobenzene (0.5 M in MeOH) for more than 10 h on stream at a productivity of 30 mmol h^{-1} (0.72 mol per day). Importantly, virtually no leaching of the catalytically active material could be observed by inductively coupled plasma MS monitoring.

Introduction

Continuous processing is a long and well-established technique for the synthesis of commodity chemicals on industrial scale. The more recent fusion of continuous processing with microfabrication technology has resulted in an increasing implementation of microreactors for the synthesis of not only commodity chemicals, but also fine chemicals and pharmaceuticals.[1,2] In these devices, in which channel or capillary diameters are typically below 1000 µm, heat and mass transfer can be orders of magnitude higher than classical batch reactors, thereby allowing exquisite control over chemical reactivity. Flow chemistry under these conditions often benefits from extremely fast mixing of reagent streams as well as very accurate reaction time (residence time) and temperature control. This allows chemists to carry out chemical transformations with a level of selectivity that typically is impossible to reproduce in a traditional stirred batch reactor.[3] Furthermore, combustion and explosion hazards are reduced in microreactors and, consequently, unusually harsh process conditions, for example, reactions in the explosive or thermal runaway regime, can be exploited in a safe and controllable manner.[4] Hazardous reagents can be generated on demand, leading to a significantly reduced operator exposure and no need for storage or shipping of such materials.[1,2,4] Because flow reactors can easily operate at higher pressures, low-boiling solvents or even supercritical fluids can be used in a high-temperature regime, resulting in more convenient isolation processes. Therefore, continuous-flow chemistry seems to be an ideal tool for sustainable chemical synthesis.[5]

A key feature of this enabling technology is the straightforward implementation of heterogeneous catalysis in a continuous-flow transformation, since the catalyst can be easily immobilized in a specific region of the flow path.[6] The separation of the reaction mixture from the solid catalyst occurs simultaneously to the desired chemical transformation with the catalytically active material remaining in the flow reactor system. Several different catalyst immobilization techniques, in conjunction with microreactor technology, have been described, including the use of packed-bed catalyst cartridges or the direct immobilization of catalysts inside the channels of microreactors.[6] Owing to the large interfacial areas and the short path required for molecular diffusion in the narrow microchannel space, very efficient liquid/solid (i.e., substrate/catalyst) interactions takes place that are not attainable in normal batch systems.[6] A particularly attractive theme in this context is the use of immobilized nanometer-sized metal catalysts in continuous-flow mode. The nanosize of these catalyst materials leads to a vast surface area to volume ratio and, therefore, to enhanced contact between reactants and catalyst, which may increase the activity dramatically.[7,8] Finely dispersed metal (including metal oxide) nanoparticles (NPs) can be readily supported and stabilized on, for example, porous silica, alumina, zeolites, or a variety of mesoporous materials, and thus, appear to be almost ideal catalysts for packed-bed flow reactors.[9] These often extremely active catalytic systems can be considered as a bridge between homo- and heterogeneous catalysis, combining several of the key advantages of both types of catalysis.[7,8]

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Nanoscale iron-based catalysts, in particular, are of considerable current interest because iron is an abundant, eco-friendly, relatively nontoxic, and inexpensive element, and thus, a very welcome alternative to the use of precious metal catalysts.[10, 11] In this context, we recently demonstrated that colloidal nano-Fe_3O_4 was as a highly reactive catalyst for the selective reduction of aromatic nitro groups to anilines by employing hydrazine as a reducing agent.[12] Functionalized anilines are key intermediates in the synthesis of dyes, pigments, agrochemicals, and pharmaceuticals, and the reduction of aromatic nitro compounds is clearly the most commonly used preparation method.[13, 14] Our new iron-based method, therefore, has the potential to replace traditional precious-metal-based hydrogenation protocols that rely on the use of palladium; platinum; ruthenium; or other expensive, scarce, and toxic transition metals. In our protocol, magnetic nano-Fe_3O_4, was generated in situ from the reaction of an iron salt and $N_2H_4 \cdot H_2O$ in methanol at elevated temperature.[12] The highly reactive colloidal catalyst induced complete and selective reduction of a large array of nitroarenes to the corresponding anilines within 2–8 min at 150 °C by employing only 0.25 mol % of catalyst and a 20 mol % excess of $N_2H_4 \cdot H_2O$, reaching catalyst turnover frequencies (TOFs) of up to 12 000 h^{-1} (Figure 1 A).[12] This method only generates nitrogen gas and water as stoichiometric byproducts, and can be performed in both batch and continuous-flow modes. In the continuous process, the catalyst precursor [Fe(acac)$_3$], $N_2H_4 \cdot H_2O$, and the substrate were dissolved in methanol and pumped through a heated (150 °C) stainless-

steel coil by using a single HPLC pump. After exiting the flow device, the catalyst aggregated, which allowed for easy retrieval of the magnetic material.[12] To simplify the continuous-flow procedure for this industrially relevant reduction process, the development of a stable and robust heterogeneous (i.e., immobilized) version of the nano-Fe_3O_4 catalyst would be highly desirable.

Several reports in the literature describe the use of iron-based catalysts in combination with hydrazine as a reducing agent for the preparation of anilines from nitroarenes in batch mode.[15–19] Notably, Beller and co-workers described the selective reduction of nitroarenes with hydrazine by using pyrolyzed carbon-supported Fe(OAc)$_2$–phenanthroline complexes as recyclable catalysts.[18] Excellent selectivities were achieved at 100 °C by using a 1 mol % iron loading and 10 h of reaction time. Another example of an immobilized iron oxide catalyst was recently presented by Chen and co-workers, who used graphene oxide as a support.[19] Their protocol allowed nitro reductions within 18–40 min in excellent yields and selectivities. From an industrial point of view, these catalysts lack the necessary efficiency to be practical on a production scale, because the calculated TOFs range from 5 to 218 h^{-1} and are therefore too low to be of practical use for manufacturing purposes (Figure 1 B).[15–19]

Herein, we present a protocol for the rapid preparation of a highly efficient nano-Fe_3O_4 catalyst immobilized on basic alumina for the continuous reduction of nitroarenes to anilines by using $N_2H_4 \cdot H_2O$ as a hydrogen donor and methanol as the sol-

Previous work

a) Continuous flow: nitro reduction using hydrazine and colloidal iron oxide nanoparticles
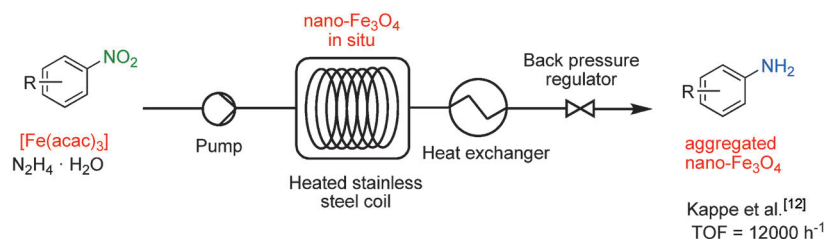
b) Batch: nitro reduction using hydrazine and supported iron oxide nanoparticles
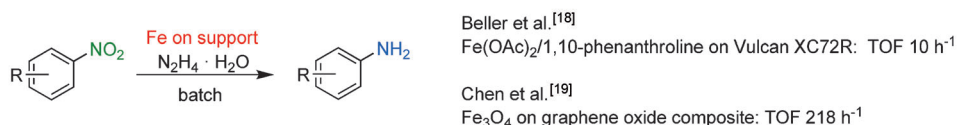
Current work

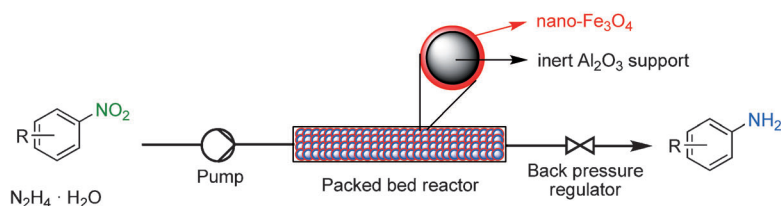c) Continuous nitro reduction using hydrazine and supported iron oxide nanoparticles

Figure 1. Previous and current strategies for the reduction of nitroarenes with iron oxide catalysts and hydrazine. acac = acetylacetonate.

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vent. The shelf-stable, reusable catalyst can be employed as a packed-bed catalyst for continuous processing under high-temperature/-pressure conditions. This heterogeneous system shows excellent performance and TOFs for the production of anilines with residence times in the range of 10–70 s at 150 °C and 30 bar back pressure (Figure 1C). By using carefully optimized reaction conditions, virtually no decrease in catalyst activity was observed for several hours.
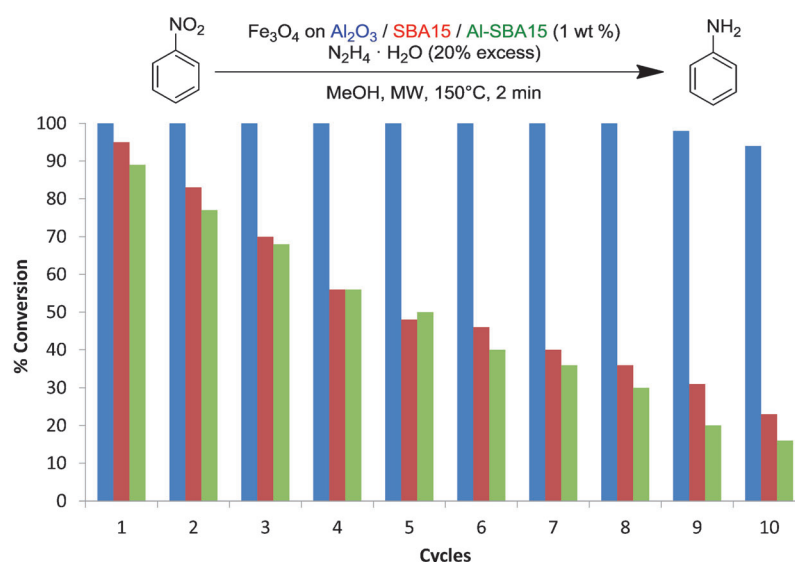

Figure 2. Catalyst recycling for the hydrazine-mediated reduction of nitrobenzene by using Fe_3O_4 NPs on different supports. MW = microwave.

Results and Discussion

Synthesis, evaluation, and characterization of supported Fe_3O_4 NPs

In an initial study, the ability of traditional chromatography-grade silica, mesoporous silica (SBA15), aluminum-substituted mesoporous silica (Al-SBA15), and basic alumina to function as support materials for iron oxide nanocrystals was carefully investigated (see the Experimental Section for specific details of these support materials). As previously reported by our group, treatment of iron salts with $N_2H_4 \cdot H_2O$ at high temperatures (methanol, 150 °C, sealed-vessel microwave irradiation) effectively generates colloidal Fe_3O_4 NPs ((6 ± 2) nm) more or less immediately, which subsequently slowly start to agglomerate upon cooling.[12] We therefore assumed that the colloidal Fe_3O_4 NPs produced in this way could be stabilized and immobilized onto an appropriate support material by simple adding the support to the microwave-assisted NP generation step. Thus, the respective inert material (500 mg), the catalyst precursor [Fe(acac)$_3$] (0.065 mmol), and $N_2H_4 \cdot H_2O$ (1 mmol) were heated in methanol (5 mL) under sealed-vessel microwave conditions to obtain a supported catalyst with a nominal Fe_3O_4 loading of 1 wt% (nominal Fe loading 0.73 wt%). The mixture was irradiated for 10 min at 150 °C ($\approx$16 bar) in a single-mode microwave reactor (Monowave 300, Anton-Paar) by using an optimized heating ramp.[20, 21] This impregnation methodology resulted in a visually uniform material if SBA15, Al-SBA15, or alumina were used as the supports. In contrast, in the case of silica, a non-uniform catalyst/support mixture was obtained. It appears that in this case the Fe_3O_4 NPs simply agglomerated without quantitative fixation on the surface of the inert material. This support material was therefore not considered any further.

With three types of supported Fe_3O_4 catalysts in hand, we moved on to explore the suitability of these materials for the hydrazine-mediated reduction of nitroarenes. The synthesis of aniline from nitrobenzene was chosen as a representative model reaction to evaluate the catalytic efficiency and any po-

tential loss of activity or leaching during catalyst recycling (Figure 2).

The hydrazine-mediated reactions were carried out on a 2 mmol scale in methanol by using a 20 mol% stoichiometric excess of $N_2H_4 \cdot H_2O$ (3.6 mmol)[22] and 500 mg of the respective supported catalyst, which theoretically corresponded to 1 mol% Fe_3O_4 catalyst loading, assuming a nominal Fe_3O_4 loading of 1 wt% (0.065 mmol of the iron precursor, [Fe(acac)$_3$], corresponds to 0.022 mmol Fe_3O_4). The individual reaction mixtures were heated to 150 °C by using controlled microwave irradiation for 2 min. Due to the exothermic nature of these hydrazine-based nitro reductions at high-temperature, the so-called "simultaneous cooling" technique was used.[23] By applying this procedure, the reaction mixture was cooled with compressed air during microwave heating to avoid the occurrence of exotherms; this resulted in reproducible heating profiles and safe processing of the microwave experiments.[24]

The catalyst support screening showed quantitative conversion of the nitroarene when alumina was used as the support material, as determined by GC flame ionization detection (FID) analysis. Mesoporous silica and its alumina-substituted analogue resulted in conversions of around 90%. To determine a possible loss of activity or leaching of the catalytically active species from the support, ten cycles were carried out with each catalyst support. For this purpose, the solid material was retrieved after each reaction by filtration and washed several times with methanol before adding a fresh solution of nitrobenzene and $N_2H_4 \cdot H_2O$ in methanol. As clearly demonstrated by the results given in Table 1, standard chromatography-grade basic alumina was far superior as a support material compared with SBA15 and Al-SBA15.[25] Quantitative conversions were obtained for eight cycles when utilizing the same recycled catalyst material; very minor losses of activity were observed for the

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Table 1. Reduction of nitroarenes with $N_2H_4 \cdot H_2O$ catalyzed by nano-$Fe_3O_4@Al_2O_3$ by using batch microwave heating conditions.[a]

$$Ar\!-\!NO_2 \xrightarrow[\text{MW, 150°C}]{\substack{\text{nano-}Fe_3O_4@Al_2O_3 \\ N_2H_4 \cdot H_2O\ (20\%\ \text{excess})}} Ar\!-\!NH_2$$

Entry	Substrate	t [min]	Solvent	Conversion (selectivity)[b] [%]
1	C_6H_5	2	MeOH	> 99 (> 99)
2	$2\text{-Cl}\!-\!C_6H_4$	4	MeOH	> 99 (> 99)
3	$3,4\text{-(Cl)}_2\!-\!C_6H_3$	3	MeOH	> 99 (> 99)
4	6-quinolinyl	3	DMF	> 99 (> 99)
5	4-(pyridin-4-ylmethyl)	3	MeCN/DMF (20:1)	> 99 (> 99)
6	$4\text{-MeO}\!-\!C_6H_4$	6	MeCN/DMF (20:1)	> 99 (> 99)
7	$2,5\text{-(EtO)}_2\!-\!C_6H_3$	6	MeOH	> 99 (> 99)
8	$3\text{-(CO}_2\text{Me)}\!-\!C_6H_4$	3	CH_3CN	> 99 (> 99)
9	$3\text{-NC}\!-\!C_6H_4$	2	CH_3CN/DMF (20:1)	> 99 (> 99)
10	$4\text{-NH}_2\!-\!C_6H_4$	6	MeOH/DMF (20:1)	> 99 (> 99)
11	$4\text{-F}\!-\!C_6H_4$	2	MeOH	95 (> 99)

[a] Conditions: $ArNO_2$ (1 mmol), $N_2H_4 \cdot H_2O$ (1.8 mmol), solvent (2 mL), nano-$Fe_3O_4@Al_2O_3$ (500 mg; 0.93 wt % Fe_3O_4), single-mode microwave heating at 150 °C with simultaneous cooling (Monowave 300). [b] Determined as GC-FID peak area percent.

ninth and tenth cycles. Alumina was already applied successfully as a support for Fe_2O_3 nanocrystals for the production of olefins from synthesis gas (H_2/CO),[26] but, to the best of our knowledge, immobilization of magnetite (Fe_3O_4) on this support has not yet been reported. In contrast to alumina, SBA15 and Al-SBA15 showed an unsatisfactory recycling behavior. After five cycles, the conversion of the nitroarene was already reduced to less than 50 %. This was presumably a result of leaching of the catalytically active species from the support during the reaction, leading to homogenous iron oxide colloids, which were removed by the applied washing procedure. Although SBA15 and Al-SBA15 have previously been successfully used as supports for iron oxide NPs,[27] it appears that under our reaction conditions the metal particles are either not properly immobilized or leach during the reduction process.

Aluminum oxide appears to be an appropriate material for this experimentally very simple immobilization technique and analysis of the iron oxide supported on alumina (nano-$Fe_3O_4@Al_2O_3$) by TEM indeed showed finely dispersed and homogeneously distributed NPs on the alumina surface (Figure 3). The average particle size was determined as (6 ± 1) nm and was therefore in good agreement with previous observations of unsupported (colloidal) Fe_3O_4 NPs, which were synthesized by a similar method $((6 \pm 2)$ nm).[12] Analysis of the iron content of the supported material by inductively coupled plasma mass spectrometry (ICPMS) showed an iron loading of (0.67 ± 2) wt % (corresponding to 0.93 wt % of Fe_3O_4), which was in good agreement with the theoretical value (73 wt % Fe/1 wt % Fe_3O_4). Further ICPMS screening on possible catalytically active transition-metal impurities showed no significant amounts of other metal species (for details, see the Experimental Section).

Bench stability of nano-$Fe_3O_4@Al_2O_3$

The efficient and reusable nano-$Fe_3O_4@Al_2O_3$ system was further analyzed by a simple set of experiments related to its sen-
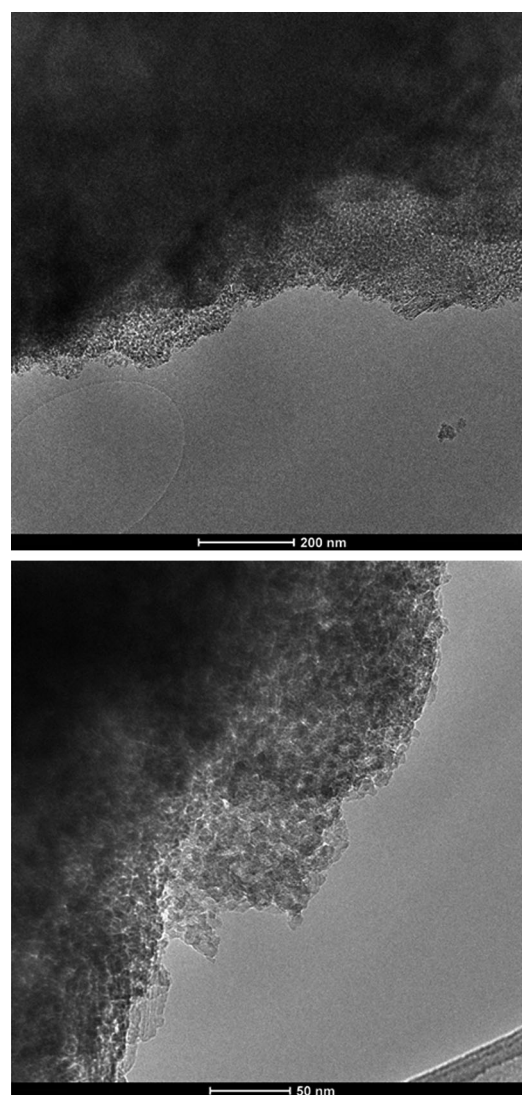

Figure 3. TEM images of the nano-$Fe_3O_4@Al_2O_3$ particles at different degrees of magnification. The active catalyst is largely dispersed and homogeneously distributed over the alumina surface. The average Fe_3O_4 particle size is about (6 ± 1) nm. For an XRD characterization of the nano-Fe_3O_4 particles without support, see Ref. [12].

sitivity to air and humidity over a longer time period to determine a possible change in the catalytic activity. Therefore, the alumina-supported catalyst (5 g) was prepared and stored in an open flask. During a period of 10 weeks, samples of nano-$Fe_3O_4@Al_2O_3$ (500 mg) were removed every 7 days and applied for the batch reduction of nitrobenzene. Conditions were similar to the support evaluation experiments described above. Gratifyingly, the activity of the catalytic system was very stable during the whole period, showing only a slight decrease in activity after the first 5 weeks, then stagnating at 95 % conversion (Figure 4).

Scope and limitations in batch

With the highly active and stable supported nano-Fe_3O_4 catalyst in hand, we moved on to evaluate the synthetic applicability and functional group tolerance of the system on a series of
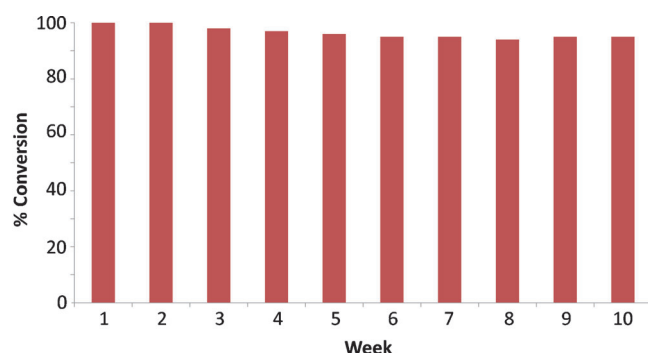
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Figure 4. Shelf stability of nano-Fe_3O_4@Al_2O_3 over a period of ten weeks.

nitroarenes. Special emphasis was placed on the homogeneity of the reaction mixture (except for the nano-Fe_3O_4@Al_2O_3) to later translate the batch microwave conditions to a flow protocol by following the well-established "microwave-to-flow paradigm".[28] We therefore carried out several microwave batch experiments with 1 mmol of the respective nitroarene in the presence of 1.8 equivalents of $N_2H_4 \cdot H_2O$ (20 mol% excess) and 500 mg of nano-Fe_3O_4@Al_2O_3 (0.93 wt% of Fe_3O_4 loading, corresponding to 2 mol%) for an initial screening of the reaction conditions (Table 1). In some cases (Table 1, entries 4–6 and 8–10), the solvent system had to be changed to fully dissolve the substrate and/or the resulting amine product. Excellent selectivities were reached with high to full conversion within reaction times of 2–6 min under the conditions discussed above (GC-FID). Importantly, we observed neither dehalogenation of chloro- or fluoro-substituted nitroarenes (Table 1, entries 2, 3, and 11) nor other possible side reactions for cyano, amino, ether, ester, or even heterocyclic moieties. Evidently, the hydrazine-based reduction protocol will lead to the formation of hydrazone derivatives when ketone or aldehyde functionalities are present in the starting material. Thus, other protocols with alternative reducing agents, such as silanes,[29] siloxanes,[30] or even molecular hydrogen,[31] in combination with an iron catalyst could be used in such cases. The presence of unsaturated carbon–carbon bonds will also be troublesome, because diimide can be readily generated by hydrazine oxidation with air, which would subsequently reduce olefinic double bonds in the substrate or product.[32]

Continuous-flow reactor

Continuous-flow reactions were performed in an X-Cube flow reactor (ThalesNano; Figure 5 A),[33] which allowed catalyzed reac-

tions to be performed heterogeneously by using CatCart cartridges (ThalesNano; Figure 5 B) at temperatures and pressures of up to 200 °C and 150 bar.[34] The cartridges (70×4 mm with a total inner volume of 0.88 mL) were packed with approximately 920 mg of nano-Fe_3O_4@Al_2O_3 (Figure 5 C) and placed in the dedicated heating zones. Determination of the dead volume of a representative packed cartridge produced a value of around 600 μL. During a standard flow experiment, the reaction mixture was pumped by a built-in HPLC pump (allowing flow rates from 0.1 to 3 mL min^{-1}) through the heated catalyst cartridge and collected after passing through the pressure-regulating unit before analysis or isolation of the desired amine species.

A significant benefit from this continuous-flow-type processing is that the exothermicity of the nitro group reduction can be appropriately controlled owing to the high surface-to-volume ratio inside the packed-bed reactor and the resulting efficient heat transfer.[1,2,6] In batch mode, this phenomenon has to be controlled by "simultaneous cooling" (see above), even at small scales, and thus, scaling up in such traditional environments is troublesome.

Process intensification in continuous flow

A continuous-flow protocol for rapid nitroarene to aniline reductions is clearly of potential industrial importance because several relevant molecules, such as the fungicide Boscalid,[34d] the muscle relaxant Tizanidine,[35] or the antibiotic Linezolid,[36] have nitroarene reductions as intermediate steps in their production. Thus, an immobilized, inexpensive, iron oxide based catalyst inside a packed-bed reactor enables a synthetic procedure with a minimum of workup steps because catalyst separa-
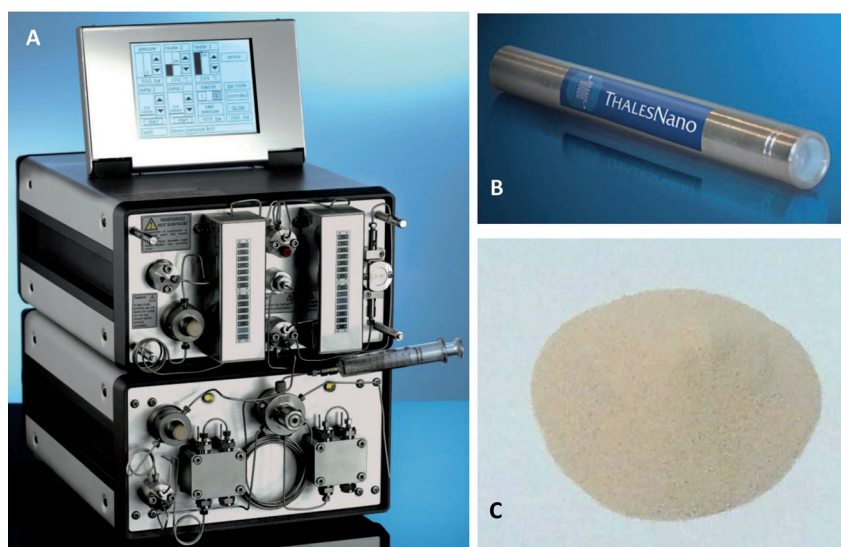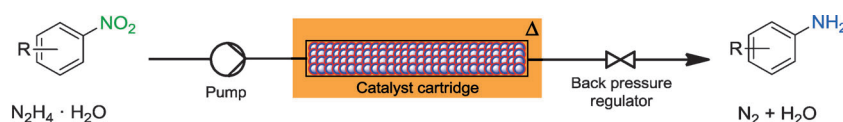

Figure 5. Schematic illustration of the continuous-flow setup performed in the X-Cube flow reactor (A) by using an exchangeable catalyst cartridge (CatCart) system (B) containing nano-Fe_3O_4@Al_2O_3 (≈920 mg; 0.67 wt% Fe/ 0.93 wt% Fe_3O_4; C).

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Table 2. Continuous-flow optimization for the reduction of nitrobenzene by using $N_2H_4 \cdot H_2O$ and nano-Fe_3O_4@Al_2O_3.[a]

$$Ar-NO_2 \xrightarrow[\text{continuous flow}]{\substack{\text{nano-Fe}_3\text{O}_4@\text{Al}_2\text{O}_3 \\ N_2H_4 \cdot H_2O \text{ (20\% excess)}}} Ar-NH_2$$

Entry	Conc. PhNO$_2$ [mol L^{-1}]	Flow rate [mL min^{-1}]	T [°C]	Conversion[b] [%]
1	0.2	0.5	150	> 99
2	0.5	0.5	150	> 99
3	1	0.5	150	> 99
4	1	1	150	> 99 (99)[c]
5	1	2	150	> 99
6	1	3	150	> 99
7[d]	1	1	150	5
8	1	3	120	36
9	1	3	100	4

[a] Reactions were carried out on a 0.2–1 mmol nitroarene scale in MeOH (1 mL) by using a 20 mol% excess of $N_2H_4 \cdot H_2O$, and nano-Fe_3O_4@Al_2O_3 ($\approx$ 920 mg) as the catalyst (0. 67 wt% Fe/0.93 wt% Fe_3O_4) in a catalyst cartridge. [b] Determined as GC-FID peak area percent. [c] Yield of product isolated is given in parentheses. [d] Cartridge filled with untreated Al_2O_3 for a catalyst-free control experiment.

Table 3. Reduction of nitroarenes with $N_2H_4 \cdot H_2O$ catalyzed by nano-Fe_3O_4@Al_2O_3 in continuous flow.[a]

$$Ar-NO_2 \xrightarrow[\text{continuous flow, MeOH, 150°C, 30 bar}]{\substack{\text{nano-Fe}_3\text{O}_4@\text{Al}_2\text{O}_3 \\ N_2H_4 \cdot H_2O \text{ (20\% excess)}}} Ar-NH_2$$

Entry	Ar	Flow rate [mL min^{-1}]	Conversion[c] [%]	Yield[d] [%]
1[b]	2-Cl-C$_6$H$_4$	1	> 99	99
2	3,4-(Cl)$_2$-C$_6$H$_3$	1	> 99	97
3	4-(pyridin-4-ylmethyl)	1	> 99	98
4	4-MeO-C$_6$H$_4$	0.5	97	92
5	2,5-(EtO)$_2$-C$_6$H$_3$	0.5	98	95
6	3-(CO$_2$Me)-C$_6$H$_4$	0.5	> 99	98
7	3-NC-C$_6$H$_4$	1	> 99	97
8	4-NH$_2$-C$_6$H$_4$	1	> 99	98
9	4-F-C$_6$H$_4$	1	95	90

[a] Reactions were carried out by using 0.1 M solutions of $ArNO_2$ in MeOH with 20 mol% excess of $N_2H_4 \cdot H_2O$, with nano-Fe_3O_4@Al_2O_3 ($\approx$ 920 mg; 0. 67 wt% Fe/0.93 wt% Fe_3O_4) in a catalyst cartridge at 150 °C and 30 bar back pressure. [b] A 1 M solution of the substrate in MeOH was used. [c] Determined as GC-FID peak area percent. [d] Yield of product isolated.

tion is avoided. Furthermore, the protocol benefits from the fact that only nitrogen and water are produced as waste, resulting in evaporation as the, in principal, only necessary purification step. We therefore turned our attention to intensifying the reduction process in a continuous-flow regime. Thus, solutions of nitrobenzene and $N_2H_4 \cdot H_2O$ (20 mol% excess) in methanol were pumped through the heated catalyst cartridge at different conditions and analyzed by GC-FID (Table 2). Initial investigations were carried out by using different substrate concentrations at a 0.5 mL min^{-1} flow rate at 150 °C and 30 bar back pressure (Table 2, entries 1–3). Gratifyingly, even at a concentration of 1M, aniline was formed quantitatively. Subsequently, the flow rate was increased to higher values and gave full conversion of the starting material in every case (Table 2, entries 4–6). Because the dead volume of the heated cartridge is in the range of 600 μL, a flow rate of 1 or 2 mL min^{-1} corresponds to a residence time of about 35 and 20 s, respectively. Even at the maximum flow rate of the flow instrument, 3 mL min^{-1} (corresponding to $\approx$ 10 s residence time), we could not detect any decrease in the substrate consumption. As proof of principle, the product of the experiment obtained by using a 1 mL min^{-1} flow rate was isolated by filtering the reaction mixture through a plug of silica to remove unreacted hydrazine. After careful evaporation of the solvent, quantitative amounts of analytically pure aniline were obtained. Because the X-cube continuous-flow reactor is essentially made out of stainless steel, a blank experiment with a cartridge filled with untreated Al_2O_3 was additionally carried out to exclude any catalytic effects by the reactor itself (5% conversion; Table 2, entry 7). Further attempts to reduce the reaction temperature resulted in a significant decrease in conversion (Table 2, entries 8 and 9).

Scope and limitations in continuous flow

To test the applicability of the continuous-flow procedure on more sophisticated substrates, we moved on to carry out several nitroarene reductions under the intensified conditions (Table 3). As already pointed out during experiments in batch mode, the main limitation of the above-described procedure is the low solubility of either the substrate or the respective amine in pure methanol. The only example of using a concentration of 1 M was 1-chloro-2-nitrobenzene, which underwent quantitative conversion at a flow rate of 1 mL min^{-1} at 150 °C and 30 bar back pressure by using a 20 mol% excess of $N_2H_4 \cdot H_2O$. In cases in which batch experiments could be carried out successfully by using other solvents or solvent combinations (Table 1, entries 4–6 and 8–10), the flow approach showed some drawbacks because these solvents did not allow the use of a catalyst cartridge for extended time periods. In particular, a significant decrease in conversion was observed when DMF was used as the solvent during the continuous processing. Because this is presumably due to catalyst leaching or inactivation (e.g., passivation) of the catalytically active Fe_3O_4 nanocrystals, we decided to perform all further flow experimentation with pure methanol as the solvent. Thus, a significantly lower substrate concentration (0.1 M) was employed to avoid possible clogging of the flow apparatus. Despite this limitation, most reactions gave excellent conversions, while maintaining the high selectivity observed in the batch experiments described above. As expected from the microwave batch experiments, in which 1-methoxy-4-nitrobenzene (Table 1, entry 6) and 1,3-diethoxy-5-nitrobenzene (Table 1, entry 5) had to be reacted for longer times (6 min), continuous processing also needed a slight re-optimization by lowering the flow rate to 0.5 mL min^{-1}, resulting in a theoretical residence time of about 70 s (Table 3, entries 4 and 5). In addition, 3-nitrobenzoate was also less active, but again reducing the throughput resulted in quantitative conversion to the desired aniline derivative (Table 3, entry 6). Surprisingly, in the case of 4-nitroaniline (Table 3, entry 8), the parameters did not require any readjustment, although earlier studies on theses substrate suggested a low reaction rate (Table 1, entry 10).

Catalyst stability in continuous flow

One of the most important features of immobilized catalysts in continuous applications is, apart from the activity of the catalyst, the ability to be used over several hours or even days. We therefore placed special emphasis on monitoring the nano-$Fe_3O_4@Al_2O_3$-catalyzed reduction of nitrobenzene over a prolonged time period. Initially, an investigation on the influence of the liquid flow rate and the substrate concentration was carried out (Figure 6A). Each experiment was performed with a fresh catalyst cartridge. Iron leaching was determined by ICPMS analysis of the processed reaction mixture after solvent removal. In addition, the conversion was measured during the respective experiments by separately collecting a small amount of the reaction mixture (≈ 200 µL), which was immediately analyzed by GC. At the maximum possible flow rate (3 mL min^{-1}), a dramatic decline in the substrate consumption was observed after a total processing time of 30 min by using a nitrobenzene concentration of 1 M. Determination of the iron content in the processed reaction mixture resulted in a value of 88 µg of iron. By assuming a total iron content of about 6.2 mg in the nano-$Fe_3O_4@Al_2O_3$ cartridge (≈ 920 mg with 0.67 wt% Fe loading), the rationalization for the significant drop in conversion is likely to be a result of mechanical deactivation.[37] Furthermore, oversaturation of the catalytically active species or a deactivating mechanism could be a possible explanation for the observed decrease in conversion, although the stable reaction during the first 30 min is inconsistent with such phenomena. Therefore, the molarity of the reaction mixture and the liquid flow rate were reduced to 0.5 M and 2 mL min^{-1}, respectively. The modified conditions resulted in a stable reaction for about 1 h until a similar activity loss was observed. Again, analysis of the iron content in the processed

reaction mixture (73 µg) suggested that the reduced conversions were not directly related to iron leaching from the catalytic support. Gratifyingly, further reduction of the liquid flow rate to 1 mL min^{-1} gave stable conversions over a time period of 300 min, which indicated that the problems observed above were indeed caused by mechanical stress. We thus extended this experiment and were pleased to find that the activity of the nano-$Fe_3O_4@Al_2O_3$ system under these conditions (0.5 M substrate concentration in methanol, 1 mL min^{-1} flow rate) did not change, even after 10 h of processing (Figure 6B). This corresponds to a productivity of 30 mmol h^{-1} (720 mmol per day) for the continuous reduction of nitrobenzene. ICPMS analysis of the crude product mixture processed for 10 h resulted in a rather insignificant amount of iron (15 µg) leached from the reactor. A control experiment of pumping the reaction mixture under exactly the same conditions for 10 h through a cartridge filled with untreated alumina showed similar results (18 µg); this indicated that the small amount of detected iron was likely to be derived from the stainless-steel-based continuous-flow reactor itself.

Because the use of other solvents or solvent mixtures resulted in decreased activity during previous experiments (see above), another continuous experiment was carried out by using acetonitrile as the reaction medium (Figure 6B). Surprisingly, the drop in conversion was not as sudden as in the experiments with methanol at higher flow rates and molarities. The conversion pattern of this stability study showed a linear decrease, resulting in 82% after 10 h. Only 4 µg of iron washed out from the continuous-flow apparatus; this was comparable with the values obtained by using methanol. Due to the obtained linear decrease in conversion, the catalyst seems to slowly lose its activity, presumably as a result of poisoning or deactivation mechanisms not caused by mechanical stress.[37]
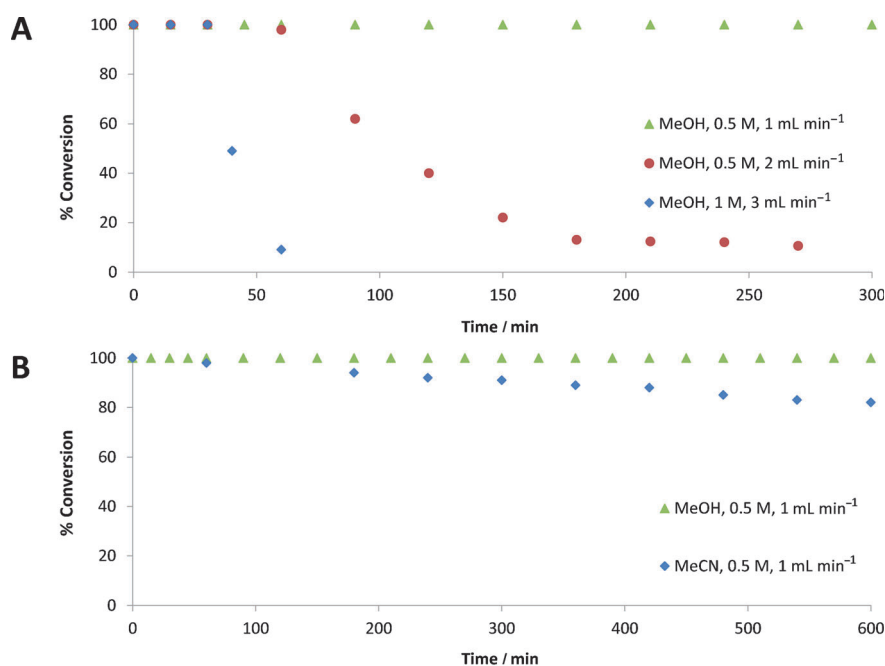
Conclusions

An extremely rapid and experimentally easy to perform method for the generation of alumina-supported Fe_3O_4 NPs and their use in heterogeneously catalyzed nitroarene to aniline reductions in batch and continuous-flow mode was studied. The immobilized metal NPs could be easily prepared by a simple impregnation method on basic Al_2O_3 by using [Fe(acac)$_3$] as an iron precursor and $N_2H_4 \cdot H_2O$ in methanol at high temperatures. Analysis of the material showed finely dispersed and homogeneously distributed Fe_3O_4 NPs on the surface of the immobilization matrix. Batch experiments for the $N_2H_4 \cdot H_2O$-mediated transformation of nitroarenes to their

Figure 6. Long run studies for the continuous reduction of nitrobenzene at different concentrations and flow rates (A) and a comparison of MeOH and MeCN as solvents (B).

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corresponding anilines catalyzed by nano-Fe$_3$O$_4$@Al$_2$O$_3$ exhibited excellent yields and high selectivities in only 2–6 min under single-mode microwave irradiation at 150 °C. Furthermore it was shown that the bench-stable, supported nano-Fe$_3$O$_4$ catalyst could be conveniently recycled by a simple filtration step. However, because batch experiments required simultaneous cooling from the outside to control the exotherm in these reactions, batch scaleup was likely to be impractical and potentially hazardous. This limitation could be avoided by translating batch conditions to a continuous-flow format by packing the supported iron oxide nanocrystals in a heatable and pressure-stable catalyst cartridge, resulting in a simple and scalable reduction process. Reaction times could be decreased to less than 1 min in most cases by pumping a mixture of the respective nitroarene and N$_2$H$_4$·H$_2$O in methanol through the packed bed reactor at 150 °C and 30 bar back pressure, resulting in a more or less workup-free procedure. Careful optimization of all relevant process parameters resulted in a stable reaction for more than 10 h at a productivity rate of 30 mmol h^{-1}. Analysis of the processed reaction mixture showed virtually no leaching of the active material.

Experimental Section

General

All solvents and substrates were obtained from standard commercial vendors and were used without any further purification. [Fe(acac)$_3$] (99.9 + % metal basis), aluminum oxide (activated, basic Brockmann I, standard grade, ca. 150 mesh), and high-purity silica (pore size 60 Å, 60–100 mesh) were purchased from Sigma–Aldrich. SBA15, and Al-SBA15 were obtained from the University of Cordona, Spain, with specifications described in ref. [38]. Microwave experiments were carried out by using a Monowave 300 (Anton Paar) single-mode microwave reactor fitted with a built-in camera and equipped with a fiber optic (ruby) thermometer for internal online temperature monitoring.[21] GC-FID analysis was performed on a Trace-GC (ThermoFisher) with a flame ionization detector equipped with a HP5 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 4 min. The detector gas for flame ionization was H$_2$ and compressed air (5.0 quality). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz instrument by using [D$_6$]DMSO or CDCl$_3$ as the solvent. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane (TMS) as an internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. The HRTEM images were collected by using a Tecnai G220-Twin microscope working at an accelerating voltage of 200 kV. For TEM analysis, the particles were dispersed in water, one drop was placed on a lacey carbon-coated Cu grid (Agar Scientific, 300 mesh), and dried at room temperature for 48 h. ICPMS analyses were performed in an Agilent 7500ce inductively coupled plasma mass spectrometer. All synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy analysis and identified by data reported in literature.

Catalyst preparation

A sample of the support (500 mg; basic alumina, high purity silica, SBA15 or Al-SBA15, [Fe(acac)$_3$] (23 mg, 0.065 mmol; to achieve ca.

1 wt % nominal loading), N$_2$H$_4$·H$_2$O (50 μL, 1 mmol), and MeOH (5 mL) were transferred to a 30 mL Pyrex microwave vessel equipped with a stirrer bar. The vessel was subsequently sealed with a Teflon septum and heated to 150 °C by microwave irradiation at a 3 min ramp time and a hold time of 10 min. After cooling, the resulting supported NPs were centrifuged at 3000*g* for 10 min to separate unsupported Fe$_3$O$_4$ particles, filtered off, and thoroughly washed with methanol. The prepared Fe$_3$O$_4$ NPs supported on basic alumina had an iron content of about 0.673 wt % (0.926 wt % of Fe$_3$O$_4$), as determined by ICPMS. Additional ICPMS analysis demonstrated that the amount of other catalytically active metal species, apart from Ni (0.61 ppm), Cu (1.69 ppm), and Mn (1.77 ppm), were below 0.01 ppm.

General procedure for the reduction of nitroarenes by using batch microwave heating

The respective nitroarene (2.0 mmol), N$_2$H$_4$·H$_2$O (0.175 mL, 3.6 mmol, 1.8 equiv), supported catalyst (500 mg), and MeOH (5 mL) were placed into a 30 mL microwave process vial equipped with a magnetic stirrer bar. The vial was capped with a Teflon septum and heated at 150 °C for the specified time in "as-fast-as-possible" mode. To avoid exotherms/overheating, the reaction vessel was simultaneously cooled with a flow of compressed air (6 bar).[24] After completion, the mixture was cooled to 55 °C by compressed air. The solvent was evaporated under reduced pressure and the crude mixture was dissolved in ethyl acetate and then filtered through a plug of silica gel (10 g) to obtain the pure amine after careful evaporation of the solvent.

Catalyst stability and recycling

A sample of nano-Fe$_3$O$_4$@Al$_2$O$_3$ (5 g) was prepared as described above (10 batches at 500 mg each) and stored at room temperature in an open vessel. Samples (500 mg) of this catalyst were used for the reduction of the nitrobenzene as described above. The experiment was repeated over ten weeks (one reduction each week) to check the stability of the catalyst. For recycling experiments (Table 1), reduction of nitrobenzene to aniline by using supported Fe$_3$O$_4$ NPs was carried out by utilizing nitrobenzene (2 mmol, 205 μL), N$_2$H$_4$·H$_2$O (3.6 mmol, 175 μL), Fe$_3$O$_4$ NPs (1 wt %) supported on basic alumina, SBA15, or Al-SBA15. Methanol (5 mL) was added to a 30 mL microwave vessel and heated up to 150 °C in as-fast-as-possible mode and held at this temperature for 3 min and then cooled to 50 °C by using compressed air. Afterwards, the catalyst was recycled by filtration through filter paper and the fresh substrate, N$_2$H$_4$·H$_2$O, and methanol were added before further processing.

Description of the continuous-flow reactor

The ThalesNano X-cube reactor[33] (see Figure 3 A) contained two main parts: 1) the built-in dual HPLC pump system for delivery of the substrates with 0.1–3 mL min^{-1} flow rates; and 2) the reactor box, which consisted of two heating units that could be heated up to 200 °C to encapsulate so-called CatCart systems packed with nano-Fe$_3$O$_4$@Al$_2$O$_3$. Additionally, the whole system could be pressurized up to 150 bar by using a back pressure regulator.

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Dead volume determination of a packed CatCart cartridge

The sealing and filter unit of a representative cartridge was carefully removed at one end. Afterwards, the nano-$Fe_3O_4@Al_2O_3$ material from the cartridge was filled in a preweighed volumetric flask (2 mL). After weighing, MeOH was added to result in an overall volume of 2 mL. The mass of the added solvent was determined to calculate the volume of nano-$Fe_3O_4@Al_2O_3$ (≈ 270 μL). This resulted in a dead volume of about 600 μL because the total volume of a CatCart cartridge was 880 μL.

Representative procedure for the reduction of nitroarenes under continuous-flow conditions (Table 3)

For a typical experiment, a 0.1 M solution (3 mL) of the respective nitroarene in methanol containing $N_2H_4 \cdot H_2O$ (1.8 equiv) was pumped through a fresh catalyst cartridge (CatCart, filled with ≈ 920 mg of nano-$Fe_3O_4@Al_2O_3$) at 150 °C at a flow rate of 0.5–1 mL min^{-1}. After passing a back-pressure regulator (30 bar), the reaction mixture was collected and the solvent was removed carefully under reduced pressure. The crude mixture was dissolved in ethyl acetate and filtered through a plug of silica gel (10 g). Unless otherwise noted, the pure amine was isolated after careful evaporation of the solvent.

Aniline (Table 3, entry 1): From a solution of 1 M nitrobenzene in MeOH with a flow rate of 1 mL min^{-1}. Yield: 277 mg (99%); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.24$–7.12 (m, 2H), 6.83–6.75 (m, 1H), 6.71 (ddd, $J = 4.3$, 3.2, 1.7 Hz, 2H), 3.66 ppm (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 146.3$, 129.1, 118.4, 114.8 ppm.

2-Chloroaniline (Table 3, entry 2): From a solution of 1 M 1-chloro-2-nitrobenzene in MeOH at a flow rate of 1 mL min^{-1}. Yield: 379 mg (99%); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.27$ (dd, $J = 7.8$, 1.2 Hz, 1H), 7.09 (td, $J = 8.0$, 1.4 Hz, 1H), 6.78 (dd, $J = 8.0$, 1.5 Hz, 1H), 6.71 (ddd, $J = 7.9$, 7.4, 1.5 Hz, 1H), 4.06 ppm (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 142.9$, 129.4, 127.6, 119.3, 119.0, 115.9 ppm.

3,4-Dichloroaniline (Table 3, entry 3): From a solution of 0.1 M 1,2-dichloro-4-nitrobenzene in MeOH at a flow rate of 1 mL min^{-1}. Yield: 47 mg (97%); ^{1}H NMR (300 MHz, DMSO): $\delta = 7.18$ (d, $J = 8.7$ Hz, 1H), 6.74 (d, $J = 2.3$ Hz, 1H), 6.52 (dd, $J = 8.7$, 2.4 Hz, 1H), 5.54 ppm (s, 2H); ^{13}C NMR (75 MHz, DMSO): $\delta = 149.6$, 131.3, 130.9, 116.4, 114.9, 114.5 ppm.

4-(Pyridin-4-ylmethyl)aniline (Table 3, entry 4): From a solution of 0.1 M 4-(4-nitrobenzyl) pyridine in MeOH at a flow rate of 1 mL min^{-1}. Yield: 54 mg (98%); ^{1}H NMR (300 MHz, DMSO): $\delta = 8.42$ (dd, $J = 4.5$, 1.5 Hz, 1H), 7.18 (d, $J = 5.8$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.50 (d, $J = 8.3$ Hz, 1H), 4.94 (s, 1H), 3.75 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 151.1$, 149.8, 144.9, 130.0, 128.4, 124.0, 115.2, 40.6 ppm.

4-Methoxyaniline (Table 3, entry 5): From a solution of 0.1 M 1-methoxy-4-nitrobenzene in MeOH at a flow rate of 0.5 mL min^{-1}. Yield: 35 mg (92%) after column chromatography; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 6.86$–6.73 (m, 2H), 6.71–6.62 (m, 2H), 3.77 (s, 3H), 3.42 ppm (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 152.5$, 139.8, 116.5, 114.8, 55.5 ppm.

2,5-Diethoxyaniline (Table 3, entry 6): From a solution of 0.1 M 1,3-diethoxy-5-nitrobenzene in MeOH at a flow rate of 0.5 mL min^{-1}. Yield: 52 mg (95%); ^{1}H NMR (300 MHz, DMSO): $\delta = 6.62$ (t, $J = 13.4$ Hz, 1H), 6.26 (t, $J = 11.7$ Hz, 1H), 6.02 (dd, $J = 8.6$, 2.7 Hz, 1H), 4.69 (s, 2H), 3.87 (dq, $J = 13.8$, 6.9 Hz, 4H), 1.28 ppm (dt, $J = 9.6$, 7.0 Hz, 6H); ^{13}C NMR (75 MHz, DMSO): $\delta = 153.9$, 140.0, 139.3, 113.6, 101.5, 101.2, 64.6, 63.3, 15.4, 15.3 ppm.

Methyl 3-aminobenzoate (Table 3, entry 7): From a solution of 0.1 M methyl 3-nitrobenzoate in MeOH at a flow rate of 0.5 mL min^{-1}. Yield: 44.5 mg (98%); ^{1}H NMR (300 MHz, DMSO): $\delta = 7.22$–7.04 (m, $J = 13.1$, 7.6, 1.6 Hz, 3H), 6.93–6.39 (m, 1H), 5.37 (s, 2H), 3.80 ppm (s, 3H); ^{13}C NMR (75 MHz, DMSO): $\delta = 167.2$, 149.4, 130.8, 129.3, 118.8, 116.6, 114.3, 52.2 ppm.

3-Aminobenzonitrile (Table 3, entry 8): From a solution of 0.1 M 3-nitrobenzonitrile in MeOH at a flow rate of 1 mL min^{-1}. Yield: 34.5 mg (97%); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.36$–7.15 (m, 1H), 7.09–6.98 (m, 1H), 6.94–6.81 (m, 2H), 3.81 ppm (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 146.7$, 130.1, 121.9, 119.3, 119.2, 117.3, 112.6 ppm.

1,4-Diaminobenzene (Table 3, entry 9): From a solution of 0.1 M 4-nitroaniline in MeOH at a flow rate of 1 mL min^{-1}. Yield: 32 mg (98%); ^{1}H NMR (300 MHz, DMSO): $\delta = 6.35$ (s, 4H), 4.18 ppm (s, 4H); ^{13}C NMR (75 MHz, DMSO): $\delta = 139.4$, 115.7 ppm.

4-Fluoroaniline (Table 3, entry 10): From a solution of 0.1 M 4-fluoro-4-nitrobenzene in MeOH at a flow rate of 1 mL min^{-1}. Yield: 30 mg (90%) after column chromatography; ^{1}H NMR (300 MHz, DMSO): $\delta = 6.89$–6.76 (m, 1H), 6.59–6.49 (m, 1H), 4.93 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO): $\delta = 156.3$, 153.0, 145.61,145.63, 115.7, 115.4, 115.1, 115.0 ppm.

Long-term stability and leaching study in continuous flow (Figure 6)

Solutions of nitrobenzene in MeOH or MeCN (0.5–1 M) containing $N_2H_4 \cdot H_2O$ (1.8 equiv) were passed through the continuous reactor equipped with a fresh catalyst cartridge (CatCart, filled with ≈ 920 mg of nano-$Fe_3O_4@Al_2O_3$) for 1–10 h with a 1–3 mL min^{-1} flow rate at 150 °C and 30 bar back pressure. Every 60 min, the conversion was determined by GC-FID. For ICPMS determination of iron leaching, an aliquot (50 mL) of the collected solution was evaporated carefully and analyzed after dissolving the solid residue in HNO$_3$ (1 mL).

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FULL PAPERS

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Immobilized Iron Oxide Nanoparticles as Stable and Reusable Catalysts for Hydrazine-Mediated Nitro Reductions in Continuous Flow
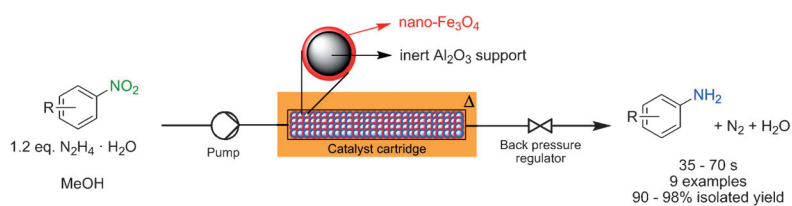
Support it! A simple and convenient experimental procedure for the effective immobilization of Fe_3O_4 nanocrystals on alumina is presented. This supported catalyst shows excellent behavior for reduction of nitroarenes to anilines in continuous-flow formats over a prolonged time period at high productivity rates without leaching of the catalyst.

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