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Safe and Selective Nitro Group Reductions Catalyzed by Sustainable and Recyclable Fe/ppm Pd Nanoparticles in Water at Room Temperature

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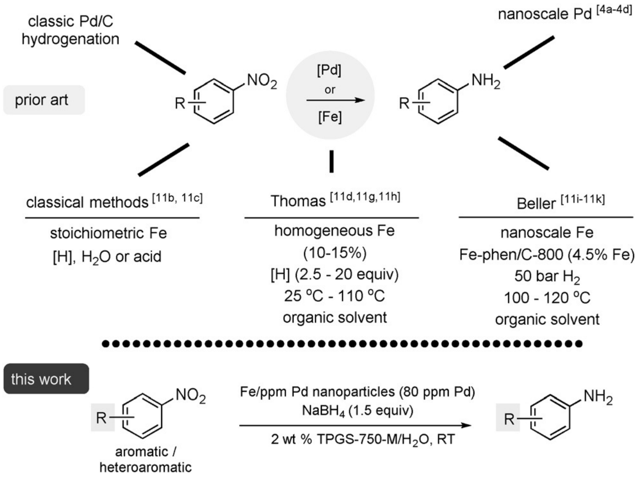
Abstract: *As a result of a unique synergy between ligand-free Fe/ppm Pd nanoparticles and PEG-containing designer surfactants, a facile and selective reduction of nitro-containing aromatics and heteroaromatics can be effected in water at room temperature in the presence of* $NaBH_4$*. This new nanotechnology involves low catalyst loadings, is highly chemoselective, and tolerates a wide variety of functional groups. The process, which includes recycling of the entire aqueous medium, offers a general, environmentally responsible, and notably safe approach to highly valued reductions of nitro-containing compounds.*

Aromatic and heteroaromatic amines represent a class of indispensible intermediates in the course of preparing fine chemicals, biochemicals, and pharmaceuticals.[1] While numerous synthetic pathways to generate such species exist, perhaps the most prominent among them relies on hydrogenation of nitro-containing compounds[2] and catalytic C–N bond-forming processes.[3] Hydrogenations typically depend upon well-developed precious-metal-catalyzed reductions (e.g., Pd,[4] Au,[5] Ru,[6] and alloys).[7] Alternatively, earth-abundant metal-mediated reductions have also been described using Zn,[8] Co,[9] Ni,[10] and Fe.[11]

Palladium-catalyzed hydrogenation of a nitro group is among the most widely used methods. Development of highly active and reusable palladium catalysts remains an active area of research for that transformation.[4a] Nonetheless, the levels of palladium involved may lead to contamination of the product, and various reaction parameters associated with its use (e.g., the solvent, etc.) may raise environmental concerns. Alternative, environmentally benign catalysts based on iron, in particular, make an ideal choice for hydrogenations of a nitro group. Early work in this area focused on stoichiometric iron-mediated reductions of nitro compounds under aqueous acidic conditions (Scheme 1).[11b,e] Subsequent reports by Thomas and co-workers, and others[11d,g,h] focused on homogeneous conditions, although high catalyst loadings, excess reducing agent, and limited substrate scope characterize these protocols. More recently, Beller and co-workers have presented a number of very efficient, heterogeneous nanoscale iron-oxide-based net reductions under reaction conditions which involve either H_2 at 50 bar, $N_2H_4{\cdot}H_2O$, or $HCOOH/Et_3N$ as the hydrogen source.[11i–k] Energy-intensive conditions (800 °C) may represent an impediment to reagent preparation, while the need for elevated reaction temperatures may place limitations on potential applications to otherwise highly functionalized, sensitive molecules. Reaction rates can also be a major factor, especially with processes at scale where time in the kettle must be minimized for effective use of a company's assets.



Scheme 1. Strategies towards reductions of nitro groups.

From an environmental perspective, use of either palladium or iron catalysis, to date, involves use of organic solvents. Water-miscible reaction media, such as commonly used THF, can lead to large volumes of organic waste, and even larger amounts of waste water streams. Thus, an opportunity remains for new technology which takes these important issues into consideration, thus providing a solution that offers: simple reagent formation, broad substrate scope, low catalyst loadings, short reaction times, high efficiency, ambient temperature conditions, reaction medium recyclability, and the elimination of organic solvents. Herein we describe a new reagent and procedure which accomplishes all of these goals and results in a safe reduction protocol.

In our previous work,[12] it was found that commercial sources of $FeCl_3$ naturally contain varying levels of palladium. $FeCl_3$ containing trace amounts of palladium, or $FeCl_3$ doped

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with 320 ppm $Pd(OAc)_2$, when processed into nanoparticles (NPs) readily catalyze Suzuki–Miyaura cross-couplings in water under very mild reaction conditions.[12,13] Key to this discovery was the use of aqueous nanomicelles composed of our designer surfactant TPGS-750-M. These nanoparticles serve as reaction solvent, and by virtue of the MPEG contained therein, aggregate around the Fe/ppm Pd NPs, thereby delivering a substrate to the catalyst. Their content, aside from greater than 320 ppm palladium, includes an equal amount of ligand (SPhos), which was crucial in supporting catalyst activity. However, they are inactive towards reductions of nitro groups.

By modifying the composition of these Fe/ppm Pd NPs, new NPs can be quickly generated by an even simpler protocol. Reduction of commercially available $FeCl_3$ (e.g., Sigma–Aldrich, 97 %), doped with only 80 ppm (0.008 mol %) $Pd(OAc)_2$,[14] with MeMgCl (1 equiv) in THF at room temperature, followed by quenching with wet pentanes and then triturating with (additional) pentanes affords the desired NPs. A ligand is not required for either NP activity or stability, however, THF as a solvent is crucial for optimal activity. No reaction is observed with the corresponding NPs prepared from $FeCl_3$ in the absence of $Pd(OAc)_2$. The nanoparticles can be either made in situ and used directly, or isolated and stored for at least a month at ambient temperatures. They are well dispersed in water, forming about 3 nm spherical particles (Figure 1, left). These Fe/ppm Pd nanoparticles were found to contain THF (Figure 1, right), albeit in bound form, as was evident from peak broadening in the C–H stretching vibration at 3000–3500 cm^{-1} (see the Supporting Information). Analysis by XPS indicates that the content of iron is about 8.6 %.

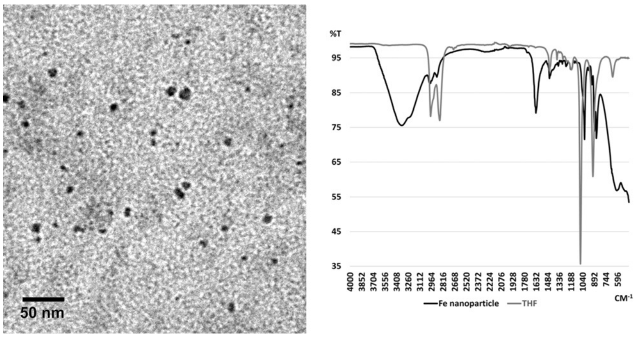

Figure 1. TEM analyses and IR spectra of THF-bound Fe/ppm Pd nanoparticles (NPs).

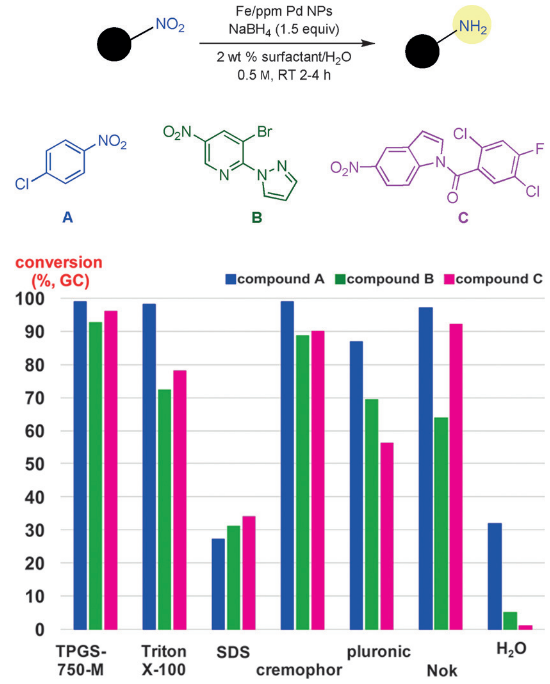

Figure 2. Influence of the surfactant on nitro group reductions of A, B, and C.

The presence of a surfactant is crucial for the observed reactivity. That is, it provides both the hydrophobic inner core for substrate binding, as well as substrate delivery based on the MPEG present in each molecule. Screening of surfactants using three different substrates identified TPGS-750-M (2 wt %) as the preferred amphiphile in water (Figure 2). Ionic surfactants such as SDS proved to be less effective. The background reaction in water led to low levels of conversion even under prolonged reaction times (see the Supporting Information).

Further screening focused on the stoichiometric source of hydrogen. Inexpensive sodium borohydride was quickly identified as the reagent of choice (see the Supporting Information). The loading of $NaBH_4$ in the range of 1.0–3.0 equivalents is sufficient, as the dihydrogen released has far greater dissolution in organic media relative to water,[15] hence, higher concentrations of H_2 should be present inside the nanomicelles compared to the surrounding aqueous medium.

Following optimization, several substrates were treated with Fe/ppm Pd NPs to assess the generality and scope of this technology (Table 1). Several nitroarenes with substituents such as chloro, bromo, cyano, ester, and methylmercapto showed good tolerance based on yields of the isolated and desired amino derivatives. Remarkably, 4-nitrobenzoic acid was successfully reduced (product **4**), and is a highly challenging example of such a reduction in the presence of a free carboxylic acid. By contrast, competitive side reactions led to a decrease in yield in the case of 1-iodo-4-nitrobenzene (product **7**). The reduction is also amenable to nitroarenes bearing other valuable substituents (CF_3, F, CN, OH, etc.). Sterically demanding substrates, such as those leading to products **9** and **17**, required prolonged reaction times relative to the more typical 2–6 hours. Sites of unsaturation were also well tolerated (e.g., CN, RCOR′, C≡C, C=C). Several heterocycles containing nitro residues, likewise, proved to be amenable (products **11**, **15**, **19**, **20**, **22**–**25**). Aliphatic nitro compounds were briefly examined, for example, ethyl 2-nitropropanoate and 1, 2-dimethoxy-4-(2-nitroethyl)benzene. These could also be smoothly converted into the correspond-

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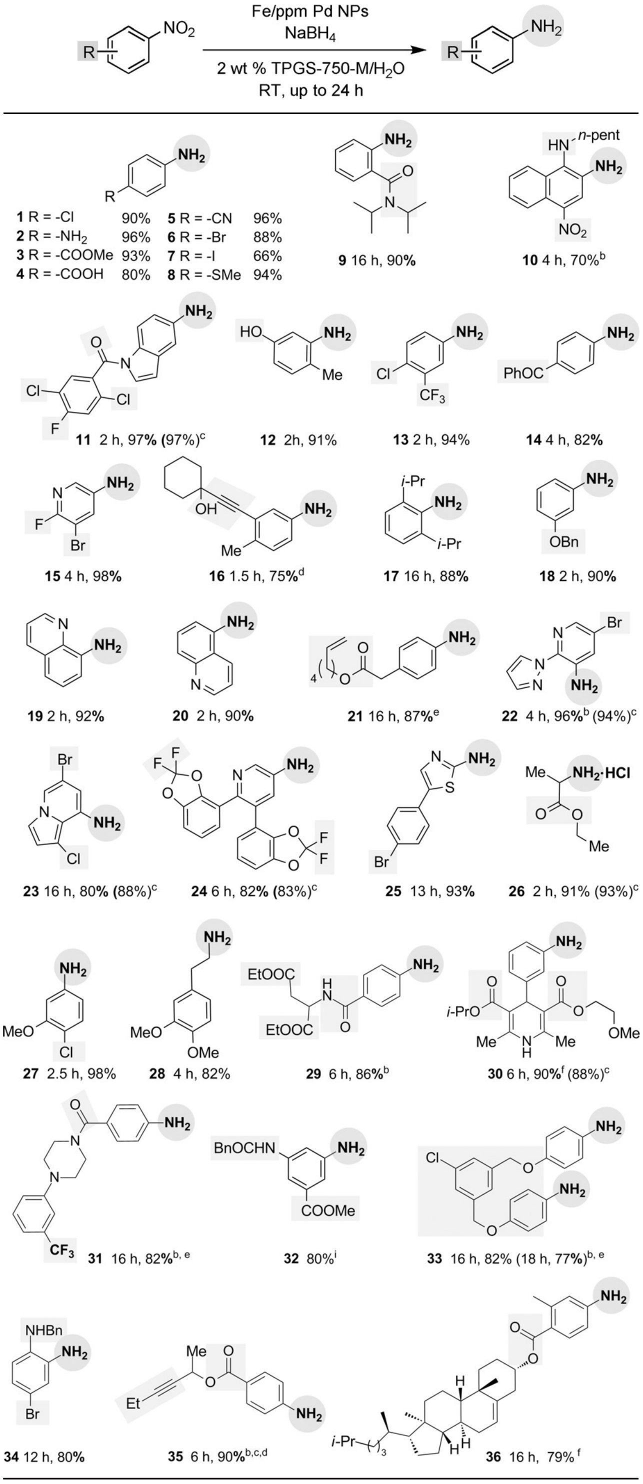
Table 1: Representative reductions of nitro-group-containing educts.[a,b]

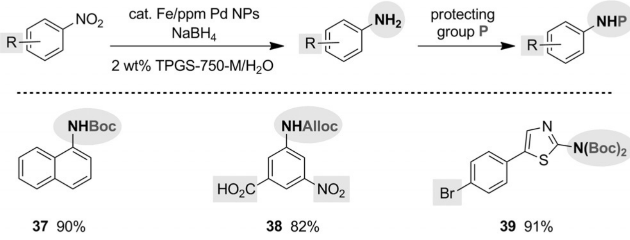


[a] Unless otherwise noted, reaction conditions were as follows: nitro compound (0.5 mmol, 1 equiv), Fe/ppm Pd nanoparticles (6 mg), $NaBH_4$ (0.75–3.0 mmol, 1.5–3.0 equiv), 2 wt% TPGS-750-M/H_2O (1 mL). Yields are those of the isolated products. [b] Iron nanoparticles (12 mg, 3.6%). [c] Using standardized Fe/ppm Pd (80 ppm) nanoparticles. [d] $NaBH_4$ (0.55 mmol, 1.1 equiv). [e] $NaBH_4$ (1.5 mmol, 3 equiv). [f] Iron nanoparticles (12 mg), $NaBH_4$ (1.5 mmol, 3 equiv), additional 0.1 mL THF. Bn = benzyl.

ing amines in satisfactory yields (see the Supporting Information).

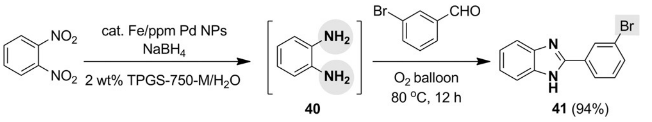
Several products reflecting potential interest from the pharmaceutical perspective, that is, reductions of nitro-containing species which may lead to either bioactive or drug-like fragments, using low levels of metal-based reagents, are also illustrated in Table 1 (**29**–**32**, **35**, **36**). For example, a multistep synthesis of an intermediate en route to a potential measles virus inhibitor[16] (**32**) was prepared by a four-step synthesis, starting with a dinitro-substituted benzoic acid ester. Importantly, the residual palladium content in several of the amino-containing products (e.g., **23**, **30**) was below 1 ppm in all cases.

The opportunity to effect tandem reactions based on formation of amines, given the widespread applicability of nanomicelles composed of TPGS-750-M in water, is illustrated in Scheme 2. Thus, a newly formed aniline could smoothly be converted into its corresponding carbamate derivative, including derivatization with standard protecting groups such as Boc (**37**) Alloc (**38**), and the bis-proteced amine **39**, all in a one-pot process.



Scheme 2. Nitro group reduction/amine protection in situ. Alloc = allyloxycarbonyl, Boc = *tert*-butoxyccarbonyl.

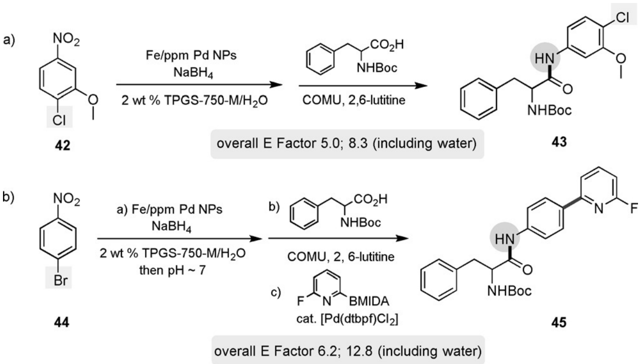
A nitro group reduction can also serve as the precursor step to other useful secondary reactions. For example, benzene-1,2-diamine **40** is produced from 1,2-dinitrobenzene, which can be converted, by oxidative cyclization in situ, into the benzimidazole **41** in excellent overall yield. (Scheme 3).



Scheme 3. One-pot nitro group reduction/oxidative cyclization.

Another major feature associated with this protocol is the opportunity to recycle the aqueous reaction mixture. Once a reduction is complete, in-flask extraction with minimum amounts of a single organic solvent (e.g., EtOAc) allows for isolation and purification of the desired product. Adjustment of the pH to 7 with concentrated HCl, along with addition of fresh $NaBH_4$, leads to an active catalyst ready for reintroduction of a nitroarene (see the Supporting Information).

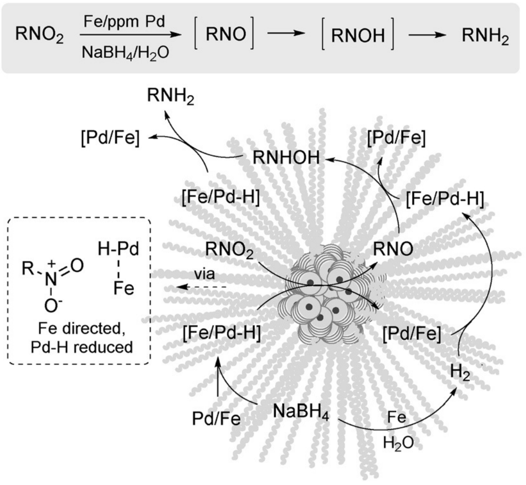
Two multistep, one-pot sequences, each involving a nitro group reduction, are shown in Scheme 4, thus highlighting the



Scheme 4. Sequential one-pot reactions and associated E Factors.

dramatic reduction of organic waste using micellar catalysis. The overall E Factors,[17] based on utilization of organic solvents (for extraction) are only 5–6, or 8–13 if water is included. These values are quite low relative to existing literature procedures, as well as those characteristic of the fine chemicals (5–25) and pharmaceutical areas (25–100).[18] Both reactions (Scheme 4a,b) involve a subsequent amidation step, likewise, done in water.[19] The three-step sequence beginning with 1-bromo-4-nitrobenzene **44** leads to the complex biaryl **45** in good overall yield and, again, with relatively little organic waste.

Mechanistically, such nitro group reductions may follow along classical lines, involving a palladium hydride species. Initial release of H_2 from $NaBH_4$ upon contact with water, should populate inside the nanomicelles, thus leading to palladium hydride on the surface of these iron NPs (Scheme 5). The interaction with nanomicelles housing the nitro-group-containing substrate is likely given the precedent associated with palladium-catalyzed Lindlar reductions using the same source of hydrogen.[20] Sequential nitro reduction should proceed, therefore, via intermediate nitroso and hydroxylamines. It is assumed at this stage that the source of hydrogen forming the amine derives from the reductant, and not water.[20] However, the potential interaction between palladium and iron remains unclear, as without the iron NPs, 80 ppm palladium is insufficient to effect reduction to any degree. Based on the observed chemoselectivity and functional-group compatibility, the iron NP lattice may be crucial in dispersing the ppm level of palladium present, thus leading to highly active and efficient nanoparticles and avoiding high aggregation states potentially formed during NP preparation.



Scheme 5. Proposed mechanism for nitro group reductions in water.

In summary, a robust technology has been developed and allows chemoselective, general, and efficient reductions of nitro compounds in water at ambient temperatures. The interaction of mixed metal nanoparticles containing iron and ppm levels of palladium matched to surfactant-based nanomicelles accounts for the exceptionally mild reaction profile, unmatched by current literature procedures. Moreover, the soon to be commercially available reagent, Fe/ppm Pd NPs,[21] offers unique opportunities for multicomponent reactions run in a single-pot operation, while the aqueous medium can recycled, thus leading overall to environmentally responsible chemistry.

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