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Tuneable copper catalysed transfer hydrogenation of nitrobenzenes to aniline or azo derivatives

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Abstract. A highly versatile and flexible copper nanoparticle (Cu(0) NPs) catalytic system has been developed for the controlled and selective transfer hydrogenation of nitroarene. Interestingly, the final catalytic product is strongly dependent on the nature of the hydrogen donor source. The yield of nitrobenzene reduction to aniline increased from 20% to an almost quantitative yield over a range of alcohols, diols and aminoalcohols. In glycerol at 130 °C aniline was isolated in 93% yield. In ethanolamine, the reaction was conveniently performed at a lower temperature (55 °C) and gave selectively substituted azobenzene (92% yield). Experimental studies provide support for a reaction pathway in which the Cu(0) NPs catalysed transfer hydrogenation of nitrobenzene to aniline proceeds *via* the condensation route. The high chemoselectivity of both protocols has been proved in experiments on a panel of variously substituted nitroarenes. Enabling technologies, microwave and ultrasound, used both separately and in combination, have successfully increased the reaction rate and reaction yield.

Keywords: copper nanoparticles; azoarene; nitrobenzene; microwave; ultrasound

Introduction

Aromatic amines are key intermediates in the preparation of dyes, pharmaceuticals, pesticides and herbicides, and their interesting redox properties have recently increased the interest in polyaniline conducting polymers.[1] The synthetic methods to produce anilines still involve the classical methods of nitration and the reduction of arenes[2] and there is currently great interest in new synthetic methodologies that can improve the sustainability and applicability of this methodology.[3] A variety of procedures that involve metal catalysts and a number of reducing agents are available for this purpose. The most commonly used reducing agents are Zn, Sn and Fe[4] in acid, while benign methodologies that involve the hydrogenation of nitrobenzene catalysed by non-noble metals are presently seen as possible answer to the growing demand for a new sustainable procedure.[4b,5]

Copper catalysis has gained increasing amounts of attention over the last decade thanks to the significant advantages when compared to other transition metals; indeed, it is readily available, cheaper and can be easily handled, making it highly interesting to industry.[6] Selective and efficient hydrogenation reactions that proceed under sustainable conditions with copper catalysis were identified,[7] and several studies reported copper catalysed nitro reductions to amines.[8] The Cu-catalysed reduction of nitrobenzene generally involves reducing agents such as H_2,[9] $NaBH_4$,[3][10] BH_3,[11] ammonium formate,[12] and hydrazine hydrate,[13] and often makes use of copper nanoparticles (NPs). The catalytic activity of Cu NPs is a rich resource for chemical processes, and a great deal of effort has been devoted to the development of solid-supported Cu NPs and core/shell Cu NPs with the aim of decreasing their sensitivity to oxygen, water and other chemical entities.[6b,14]

The metal catalysed transfer hydrogenation (TH) reaction is a convenient and sustainable alternative to direct hydrogenation by gaseous hydrogen or hydrides.[15] Although Ru,[16] Ir[17] and Rh,[18] are the most popular catalysts, recent trends focused on homogeneous and heterogeneous catalysis using Co,[19] Fe,[20] Ni,[21] and Au[22]. In this frame, Cu catalysed TH reactions involving ketones and aldehydes attracted minor attention,[23] and there is very little literature on the Cu-catalysed TH of nitrobenzene.[24] On the basis of our recent experience Cu could be exploited in TH of nitrobenzene in glycerol to efficiently isolate aniline. [24b]. In accordance with the Haber mechanism,[25] nitrobenzene reduction to aniline follows one of two different pathways (direct route and condensation route, Figure 1). In particular, a study of the time-dependent product distribution for the TH of nitrobenzene can reveal which route the catalytic system is following. The condensation route takes place via the coupling of nitrosobenzene and aniline, forming azoxybenzene as an intermediate, which is subsequently hydrogenated to azoderivative, hydrazino and anilines. This is considered an attractive way to selectively obtain azoxy and azobenzene intermediates. To the best of our knowledge, the selective synthesis of an azo derivative from the Cu-catalysed TH of nitrobenzene has yet to be described.

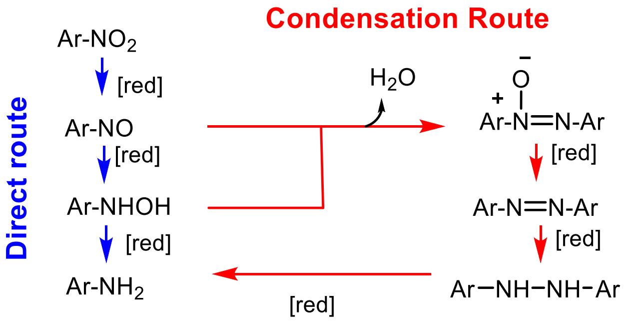


Figure 1. Proposed mechanism of nitrobenzene reduction.[25]

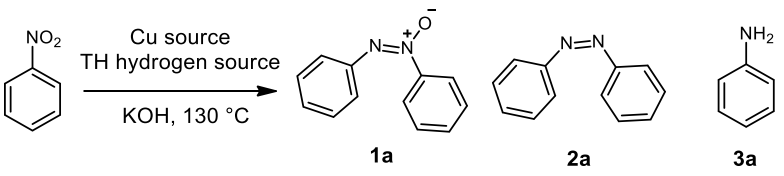
Control of the preferential reduction of nitrobenzene by TH has been successfully achieved by varying the type of metal centre used and the nature of the ligands in homogeneous catalysis. Ir(III) complexes with nitrogen ligands,[26] and solid-supported Au showed good selectivity towards the azo derivative.[27]

Herein, on the basis of the previous successful study on Cu-catalysed TH of nitrobenzene in glycerol,[24b] we have investigated the behaviour of the system by varying the hydrogen source. In the present work, the preferential reduction of nitrobenzene to either aniline or azobenzene has been studied in the presence of a number of different sacrificial hydrogen donor molecules (alcohols, ethers and amines), although mainly primary and secondary alcohols were used. The catalytic activity of Cu(0) NPs has been exploited aiming to optimise a friendly, cheap, straightforward and sustainable procedure. Benign enabling technologies, such as microwave (MW) and ultrasound (US) irradiation, used either separately or in combination (MW/US), have also been investigated as means to maximize reaction rate and increase reaction selectivity.

Results and Discussion

We have recently observed the reduction of nitro benzene to aniline during a study on Cu-mediated Ullman coupling under mechanochemical activation.[28] When the reaction was performed in the presence of 2-amino ethanol, Cu powder, 4-iodonitrobenzene and KOH, the reduction of the nitro moiety was observed together with the desired N-arylation product. We theorised that 2-amino ethanol was acting as a hydrogen source in the presence of the Cu powder because the amount of the reduced aniline side product was minimised when the reaction was performed in the absence of a base. This evidence drove us to support the hypothesis of transfer hydrogenation, as the catalytic performance of the transition metal in the TH reaction is significantly affected by the presence of a base (organic or inorganic).

In a preliminarily phase, a standard reaction between nitrobenzene, Cu powder (2 eq) and KOH was tested with 2-amino ethanol at 130 °C for 5 h (Scheme 1). As described in Table 1, the reaction gave 52% conversion, and 28% of azobenzene and 16% of aniline were detected (Table 1, entry 1). Complete conversion and selectivity towards azobenzene were observed when 5 eq of Cu were used (Table 1, entry 2). The reaction was performed in isopropanol, one of the most commonly employed hydrogen sources, and almost complete conversion was detected in the presence of 2 eq of Cu; conversely, a mixture of azoxy, azobenzene and aniline, 52:17:29 respectively, was observed (Table 1, entry 3). Ethylene glycol and glycerol were also tested, as experience has shown us that alcohol structural features may contribute to the formation of a copper chelating intermediate that can enhance the reaction rate.[28] Gratifyingly, full conversion and selectivity to aniline were observed (Table 1, entry 5, 6). When Cu powder was added in lower amounts (1 eq), nitrobenzene conversion was decreased to 79%, but selectivity to aniline was maintained (Table 1, entry 7).



Scheme 1. Catalytic reduction of nitrobenzene to azoxy-, azobenzene, aniline.

Table 1. Influence of different reducing agents on the reduction of nitrobenzene.[a]

Entry	Copper source	Catalyst (eq or mol%)	Reducing agent	Nitrobenzene unreacted (%)[d]	Azoxy Benzene (**1a**)[d]	Azobenzene (**2a**)[d]	Aniline (**3a**)[d]
1	Cu Powder [b]	2 eq	Ethanolamine	48	8	28	16
2	Cu Powder [b]	5 eq	Ethanolamine	--	18	60	22
3	Cu Powder [b]	2 eq	Isopropanol	2	52	17	29
4	Cu Powder [b]	2 eq	Benzyl alcohol[f]	--		61	28[f]
5	Cu Powder [b]	2 eq	Ethylene glycol	2	0	0	98
6	Cu Powder [b]	2 eq	Glycerol	--	0	0	>99
7	Cu Powder [b]	1 eq	Glycerol	21	0	1	78
8	Cu NPs [c]	10 mol %	Ethanolamine	--	19	53	28
9	Cu NPs [c]	10 mol %	Isopropanol	--	52	24	24
10	Cu NPs [c]	10 mol %	Ethylene glycol	--	0	2	98
11	Cu NPs [c]	5 mol %	Ethylene glycol	--	0	5	95
12	Cu NPs [c]	2.5 mol %	Ethylene glycol	28	3	2	67
13	Cu NPs [c]	10 mol %	Glycerol	--	0	0	>99
14	Cu NPs [c]	5 mol %	Glycerol	--	0	0	>99 (>99) [e]
15	Cu NPs [c]	2.5 mol %	Glycerol	10	0	0	90
16	Copper free	--	Glycerol	75	0	3	22

[a] Reaction conditions: nitrobenzene (1 mmol), KOH (2 mmol), Hydrogen donor (40 mmol), T^a: 130ºC. [b] Reaction time: 5h. [c] Reaction time: 1h. [d] Determined by GC-MS. [e] the reaction was performed with Cu NPs stored under air for six months. [f] the reaction was performed with 20 eq of benzyl alcohol and the aniline % is calculated as the sum of aniline and benzylidenaniline (imine).

A range of different copper sources were also tested in glycerol and ethylene glycol at 130 °C for 5 h. The reaction was performed a number of times using copper wires, copper powder, CuI and Cu (II) salts ($CuCl_2$ and $CuSO_4$).

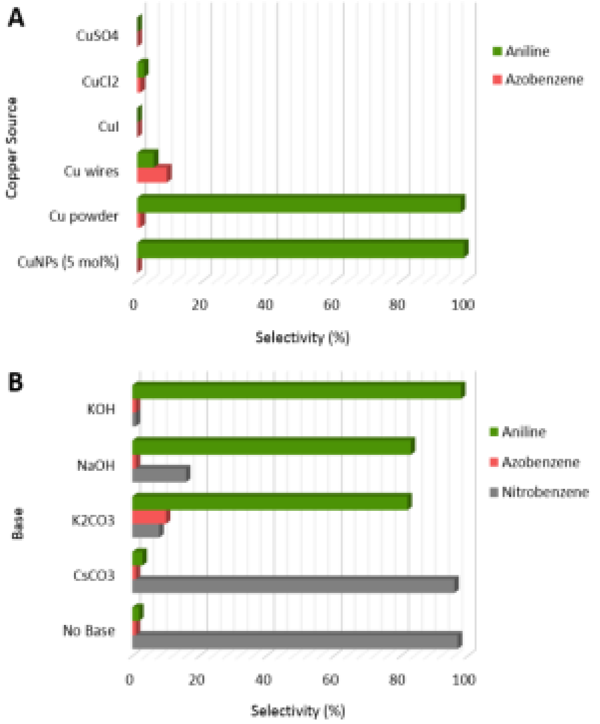


Figure 2. Influence of different copper sources (A) and bases (B) in the nitrobenzene TH. Reaction conditions: nitrobenzene (1 mmol), base (2 mmol), glycerol (40 mmol), Cu source (2 mmol), 130 °C, 5h.

From the comparison between glycerol and ethylene glycol we were not able to demonstrate any appreciable differences (Figure 2 shows results in glycerol, see Supporting Information, Figure S3 for comparison between both hydrogen sources). As shown in Figure 2A, the Cu powder gave complete conversion and selectivity towards aniline. Cu salts gave very low conversion, nevertheless when the reaction was performed overnight, CuI in ethylene glycol gave the best results of all the copper salts; conversion was 58% and partial selectivity toward the azo derivative was observed (See Supporting Information, Figure S4).

The successful reaction with glycerol and Cu powder was repeated using different bases, and KOH gave the highest conversion (Figure 2B). The reaction was selective to the aniline in all the experiments.

In order to prove the transfer hydrogenation mechanism and the expected hydrogen borrowing cycle involving alcohol dehydrogenation as well as nitro hydrogenation, benzyl alcohol was selected as hydrogen donor. The reaction was carried out using 20 eq of benzyl alcohol with the aim to monitor the reaction outcome by GC-MS and to detect the benzaldehyde. As described in Table 1 (entry 4) the reaction gave complete conversion with 3% aniline, 25% benzylidenaniline and 61% azobenzene. By GC-MS we could also detect benzaldehyde. Based on the fact that the benzaldehyde obtained from the oxidation step reacted in situ with the reduced aniline to obtain the corresponding imine, we could prove the transfer hydrogenation mechanism.

Because of the high surface area, Cu(0) NPs were then prepared in glycerol as well as in ethylene glycol in order to decrease the catalyst amount and improve the catalytic activity. Based on our previous experience, NPs were generated from the reduction of Cu(SO$_4$).[24b] Copper sulfate was either dispersed in water:glycerol (5:1) or water:ethylene glycol (5:1) and NaBH$_4$ was added after the formation of a white blue precipitate (Cu(OH)$_2$) caused by the addition of an NaOH solution.

As will be discussed in the following paragraphs, the Cu(0) NPs prepared with glycerol displayed comparable catalytic activity as those with ethylene glycol as capping agent. However, the amount of catalyst can be significantly lowered when the reaction is carried out in the presence of glycerol as the solvent. Therefore, a detailed characterization of glycerol-capped Cu NPs was performed and representative TEM and HR-TEM images with the corresponding particle size distribution are shown in Figure 3A, B, D and C respectively. Most of the NPs have diameter between 8 and 12 nm, and average particle size of 9.7 ± 3.5 nm. Due to their low size, the unsupported Cu NPs tend to form agglomerates. As recently reported for this system,[24b] a core-shell morphology, with a crystalline Cu^0 core and an amorphous glycerol shell was observed (Figure 3D). Moreover, the Cu NPs did not coalesce upon prolonged exposure under the electronic beam of the instrument, pointing out a stabilising effect of the glycerol layer. The diffraction fringes related to the presence of the (111) plane of metallic Cu in the cubic phase (JCPDS file number 00-001-1241) were observed by HR-TEM analysis (panel E of Figure 3) along with the fringes related to the (200) plane of the same crystalline phase (not shown).

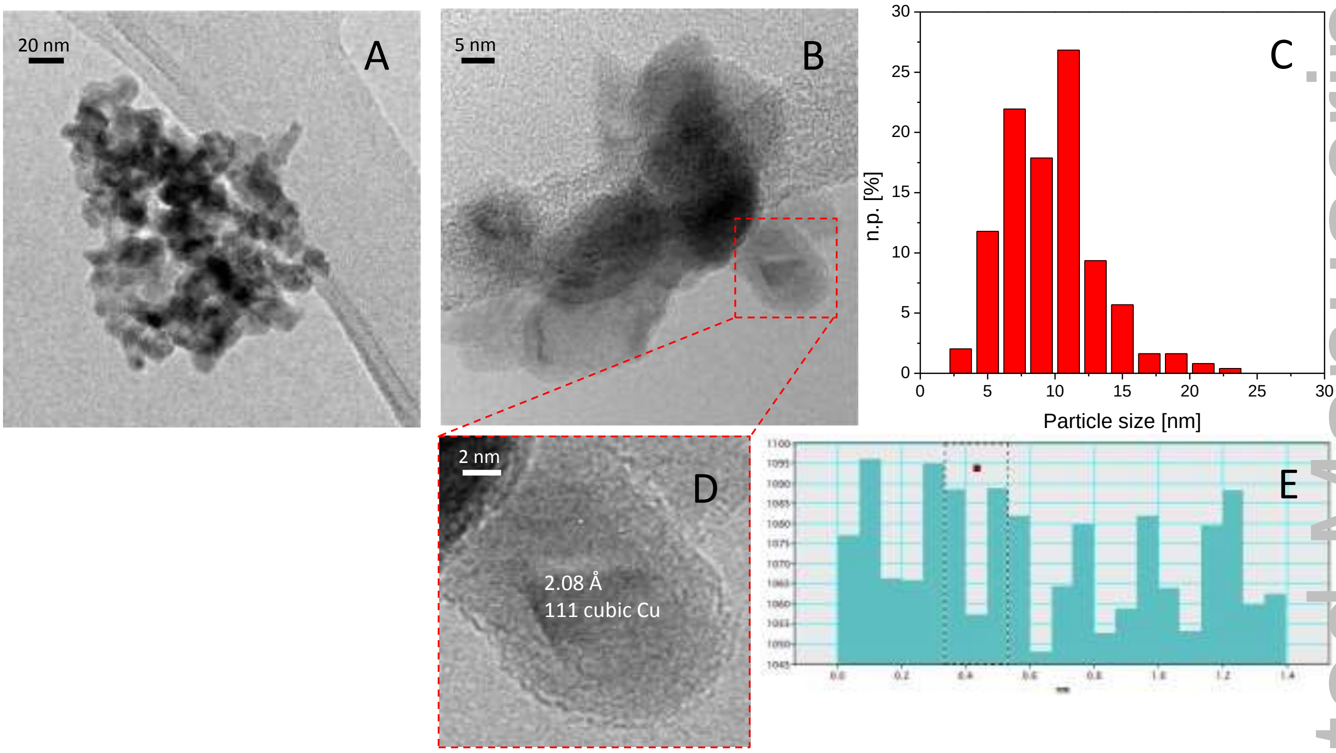


Figure 3. a) TEM, b) HR-TEM images and c) Cu particle size distributions of the Cu NPs catalyst prepared with glycerol as capping agent. d) detail of b) and e) measure of the spacing between the diffraction fringes observed in the zone highlighted by the red dashed square in b). Instrumental magnification: 50000× and 300000×, respectively. n.p.[%]= number of counted particles of diameter d$_i$.

The catalytic ability of freshly prepared Cu(0) NPs was tested in the TH of nitrobenzene. An initial screening was carried out with 10 mol % of catalyst and 2 eq of KOH in glycerol at 130 °C for 1h (see Table 1, entry 13). The amount of catalyst and the hydrogen source were varied, while both conversion and selectivity were analysed using GC-MS. The NPs that were capped with glycerol and ethylene glycol showed comparable properties.

Differences in selectivity were observed when using different hydrogen sources: secondary alcohol, an amino-alcohol, a diol and glycerol (Table 1, entries 8-15). With ethanolamine (Table 1, entry 8), the reaction proceeded smoothly toward the aniline and showed a certain selectivity to azobenzene. Ethylene glycol and glycerol were highly selective to aniline (Table 1, entries 10-15) and selectivity towards the azoxybenzene was observed in the presence of isopropanol (Table 1, entry 9). An attempt to reduce the amount of catalyst to 2.5 mol% in glycerol and ethylene glycol was followed and good conversions were obtained but still some nitrobenzene was recovered unreacted (Table 1, entries 12, 15). Glycerol was demonstrated to perform better than ethylene glycol. It can be proposed that the amorphous glycerol shell can favor the catalyst dispersion in the glycerol reaction solvent, resulting in an enhancement of the active metallic surface area. We could observe that not only freshly prepared catalyst was active, but also the Cu NPs saved aside for six months (Table 1, entry 14). Due to the well-known instability of Cu(0) NPs toward oxidation, XRD measurements were carried out on the Cu NPs after six months storage under air atmosphere to evaluate their stability and catalytic activity. The analysis evidenced that the Cu NPs are mainly made up by metallic copper in the cubic phase, showing only a minor amount of Cu_2O. Indeed, along with the reflections related to the 111, 200, 220, 311 and 222 planes of the Cu(0) phase, two additional and broad peaks with significant lower intensity were observed at 36.84° and 61.73° (see Supporting Information, Figure S2). These peaks have been assigned respectively to the 111 and 220 planes of Cu_2O in the cubic phase. The presence of a copper oxide phase is reasonably due to air exposition. In addition, the position of these peaks is slightly shifted toward high angles with respect to the reference peaks (signalled at 36.65° and 61.34°, respectively), but above all the relative intensity (I [%]) of the two peaks is significantly different with respect to those reported, i.e. 100% and 18% instead of 100% and 44%, respectively. These features suggest some preferential orientation of the copper oxide phase and support the idea for a Cu_2O layer covering a metallic Cu(0) core formed upon air exposition. XRD analysis therefore confirmed a good stability of Cu NPs over months conferred upon the Cu(0) by the capping glycerol. It can be reasonably proposed that Cu NPs catalytic activity is maintained because the Cu(I) external layer is promptly converted to Cu(0) by glycerol, explaining in that manner the comparable results obtained in the TH of nitrobenzene even after passing six months from their synthesis (Table 1, entry 14).

In order to investigate the influence of the hydrogen donor on reaction selectivity, the reaction was repeated using a set of 7 different sacrificial hydrogen sources at three temperatures (130 °C, 80 °C and 55 °C). The reaction was monitored after 1 h at 130 °C, after 2 h at 80 °C and after 20 h at 55 °C and interesting trends were observed (Table 2). Isopropanol, 3-amino-1-propanol and ethylendiamine were the most selective to azoxybenzene when the temperature was decreased to 80 °C (Table 2, entries 2-4). Unexpectedly, the reaction conversion was insignificant in glycerol and ethylene glycol at 80 °C, while selectivity to aniline was confirmed (Table 2, entries 6-7). The high viscosity of these two polyalcohols prevents the homogeneous magnetic stirring when decreasing the reaction temperature to 55 °C, thereby invalidating the nitrobenzene reduction. Surprisingly, the reaction reached full conversion in ethanolamine at 55 °C and showed high selectivity to the azobenzene.

Despite the fact that sodium hydroxide-catalysed TH has been successfully reported in isopropanol in the absence of a catalyst,[30] only 25% conversion was observed (22% selectivity to aniline, Table 1, entry 16) when the reaction was performed with KOH in glycerol at 130 °C for 1h.

Table 2. Influence of different reducing agents at different temperatures on the reduction of nitrobenzene. [a]

Entry	Reducing agent	T (ºC)	Conversion (%)[b]	Azoxy Benzene (**1a**) (%)[b]	Azobenzene (**2a**) (%)[b]	Aniline (**3a**) (%)[b]
1	Ethanolamine	130 [c]	>99	19	53	28
		80 [d]	>99	32	61	7
		55 [e]	>99	10	88	2
2	Ethylendiamine	130 [c]	>99	30	47	23
		80 [d]	88	65	3	20
		55 [e]	68	42	6	20
3	3-amino-1-propanol	130 [c]	79	63	8	8
		80 [d]	>99	80	4	16
		55 [e]	>99	43	23	34
4	2-propanol	130 [c]	>99	52	24	24
		80 [d]	82	62	2	18
		55 [e]	16	6	0	10
5	1,4-butanodiol	130 [c]	89	48	21	20
		80 [d]	11	4	0	7
		55 [e]	3	1	0	2
6	Ethylene glycol	130 [c]	>99	0	2	98
		80 [d]	0	0	0	0
		55 [e]	0	0	0	0
7	Glycerol	130 [c]	>99	0	0	>99
		80 [d]	20	0	0	20
		55 [e]	0	0	0	0

[a)] Reaction conditions: nitrobenzene (1 mmol), KOH (2 mmol), reducing agent (40 mmol), Cu NPs (5 mol%), oil bath. [b)] Determined by GC-MS. [c)] Reaction time: 1h. [d)] Reaction time: 2h. [e)] Reaction time: 20h.

The kinetics of nitrobenzene reduction were studied in order to obtain more information about the reaction mechanism. The product distribution of our catalytic system was obtained by monitoring the reaction in a time dependent manner. Reactions performed in glycerol at 130 °C and in ethanolamine at 55 °C gave the best results. As shown in Figure 4A, the yield of aniline in glycerol steadily increased with time, while the concentration of nitrobenzene decreased. The concentrations of the intermediate products azoxybenzene and azobenzene were found to be particularly low. After 30 min, conversion to aniline was almost complete and only aniline could be detected after 1h. It was found that nitrobenzene was first reduced to azoxybenzene and then to azobenzene in the presence of ethanolamine at 55 °C (Figure 4B). Aniline was detected in traces (<5%). Azobenzene was detected at 96% purity after 25 h at 55 °C.

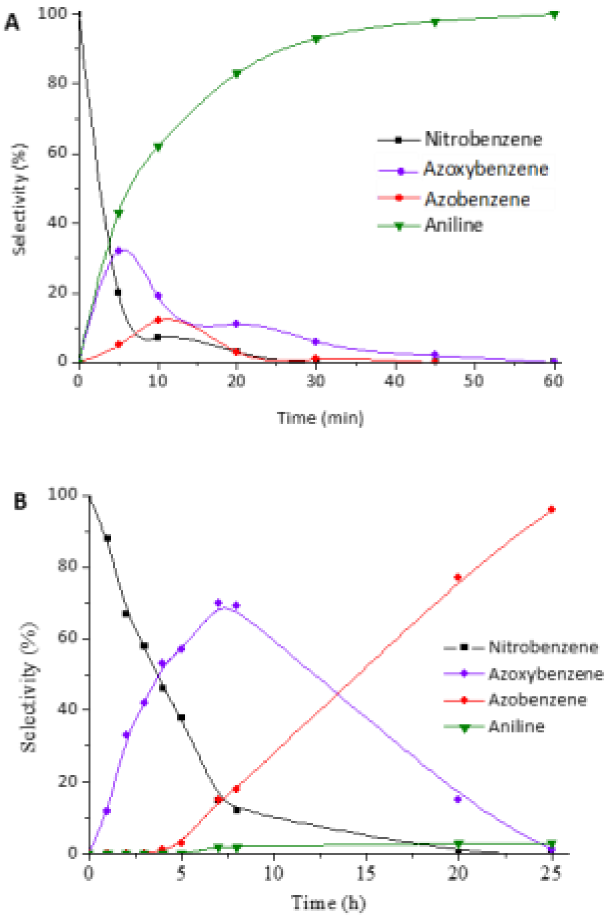


Figure 4. TH kinetics of nitrobenzene (A) Glycerol, T: 130 °C and (B) Ethanolamine, T: 55 °C. Reaction conditions: nitrobenzene (1 mmol), KOH (2 mmol), solvent (40 mmol), Cu NPs (5 mol%). Determined by GC-MS.

Non-conventional, non-contact energy sources have been used in this work. The effects of dielectric heating and US irradiation have been explored with the aim of enhancing reaction rate and maximising catalyst dispersion of nitrobenzene TH in ethanolamine and glycerol. As shown in Figure 5, all the reactions were carried out in parallel under the following conditions: i) under stirring and conventional heating (oil bath at 130 °C); ii) under microwave (MW) irradiation (Milestone MicroSynth, Program: 2 min P_{max}= 400W heat as fast as possible to 130 °C, and then P: 80W); iii) under US irradiation (Ultrasonic horn F(kHz):20.3, P(W):30); iv) under combined MW/US irradiation. Conversion to aniline and azobenzene were monitored by GC-MS. As shown in Figure 5, both of the kinetic profiles (Figures 5A and 5B) of the reactions revealed that nitrobenzene was always converted into aniline or azobenzene, respectively, without the significant formation of side products. The reaction rate of the hydrogenation was highly dependent on the technique used and was greatly accelerated by the MW and US irradiation combination as already demonstrate for nitro reduction in glycerol to aniline.[24b] In fact, glycerol is an optimal solvent for catalysis purposes because of its high polarity and because it remains in the liquid state over a large temperature range (from 17.8 to 290 °C). Moreover, it has low vapour pressure, long relaxation time and high acoustic impedance, making it an optimal solvent for reactions performed under MW and US irradiation conditions. The reduction of nitrobenzene to aniline in glycerol at 130 °C led to reaction completion in approximately 1 h under conventional conditions, whereas either US and MW irradiations increased reaction rate (see Figure 5A). In fact, under US irradiation, disaggregation of Cu(0)NP agglomerates is promoted, resulting in enhanced active surface area and full conversion to aniline after 45 min. Indeed, as already demonstrated in a previous study [24b], US can dramatically improve particle dispersion and favour mechanical depassivation. Therefore, when the particle-size distribution was measured before and after US treatment with a laser diffractometer, a great decrease in the average size was confirmed. Moreover, MW showed a high impact on speeding up the reaction rate and after 15 min only aniline can be detected. The beneficial influence of US provided further enhancement of MW promoted reaction rate, and after only 10 min full selective conversion to aniline is evidenced. Gratifyingly, when the reaction was performed under US/MW irradiation the catalyst amount could be reduced to 2.5 mol% without evidencing any differences in reaction outcome (see Figure 5A). This trend was confirmed in the reduction of nitrobenzene to azobenzene in ethanolamine at 55 °C. The combination of the non-conventional techniques gave the desired product in a notably shorter reaction time. Whereas under conventional heating the reduction reaction required 25 hours to reach completion, the MW and US irradiation combination achieved completion in 1 hour.

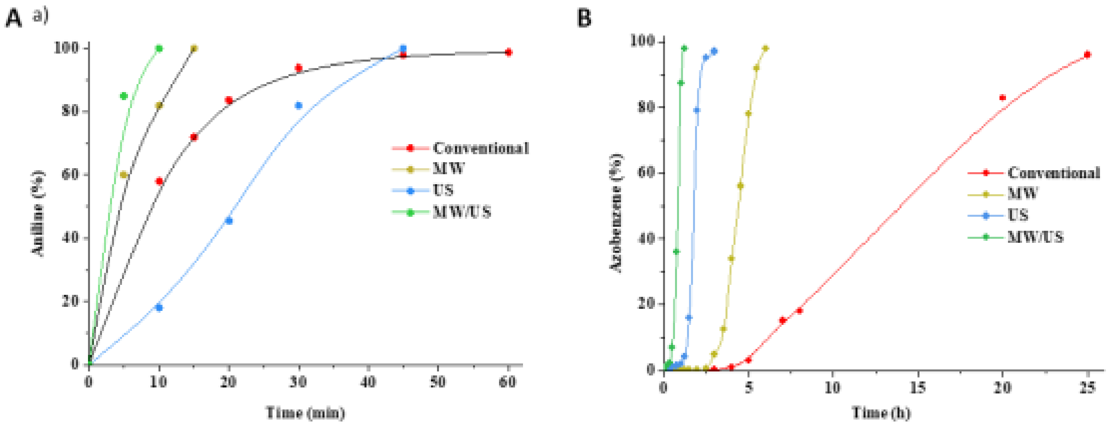
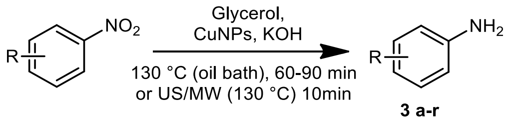
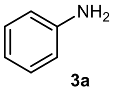
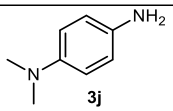
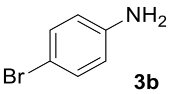
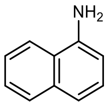
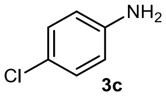
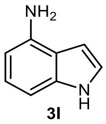
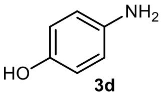
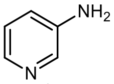
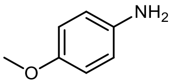
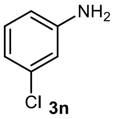
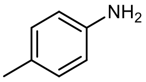
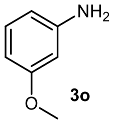
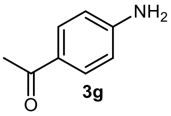
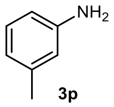
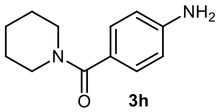
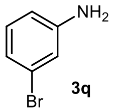


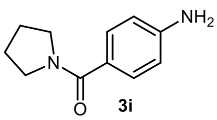
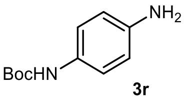
Figure 5. TH kinetic data of nitrobenzene catalysed by Cu NPs. (A) Glycerol, T: 130 °C and (B) Ethanolamine, T: 55 °C. Reaction conditions: nitrobenzene (1mmol), solvent (40 mmol), KOH (2 mmol), Cu NPs (5 mol%, [a)] when the reaction was performed under US/MW irradiation the catalyst was used in 2.5 mol %). Determined by GC-MS.

Table 3. Scope of the TH of aromatic nitro benzene derivatives to anilines as catalysed by Cu NPs in glycerol. [a]



3 a-r

Entry	Product	Yield[%][b] (%)[c]	Entry	Product	Yield [%][b] (%)[c]
1	 3a	85 (93)	10	 3j	90 (94)
2	 3b	85 (87)	11	 3k	85 (92)
3	 3c	85 (92)	12	 3l	86 (88)
4	 3d	80 (88)	13	 3m	80 (87)
5	 3e	84 (92)	14	 3n	87 (93)
6	 3f	88 (96)	15	 3o	90 (94)
7	 3g	82 (90)	16	 3p	88 (92)
8	 3h	85 (89)	17	 3q	86 (89)

9	 **3i**	86 (88)	18	 **3r**	87 (88)

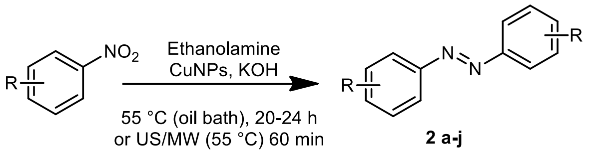
a) Reaction conditions: nitroarene (3mmol), glycerol (20 mL), KOH (6 mmol), Cu NPs (5 mol%, when the reaction was performed under US/MW irradiation the catalyst was used in 2.5 mol %), T:130ºC. b) Isolated yield. Reaction performed under conventional stirring in oil bath at 130 °C 60-90 min c) Isolated yield for reaction performed under combined US (20.3 kHz, 30 Wcm^{-2}) and MW (2.45 GHz, 80 W) irradiation, 130 °C, 10 min.

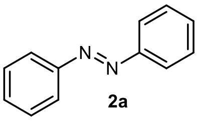
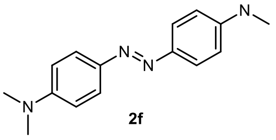
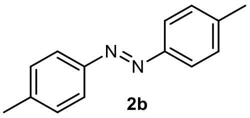
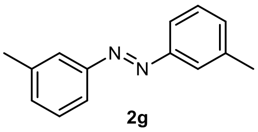
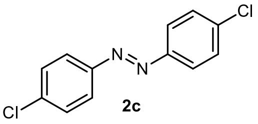
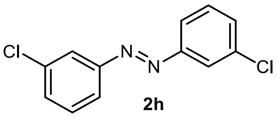
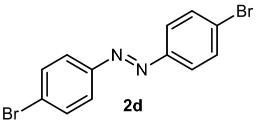
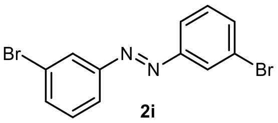
The scope of these reactions was explored by reducing a number of nitroarenes with different functional groups (Tables 3 and 4). The reactions were performed either conventionally or under non-conventional conditions.

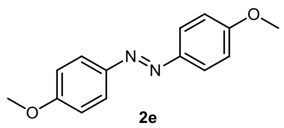
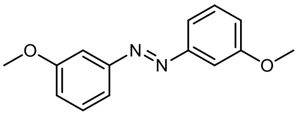
Excellent results were obtained for the full reduction of nitrobenzene derivatives in glycerol, and a 91% average yield was achieved over a series of 18 substrates. Interestingly, the reaction showed excellent chemoselectivity when performed in the presence of a carbonyl moiety (Table 3, entry 7) and amido derivatives (Table 3, entries 8 and 9). The reaction yield was not affected by the presence of a phenolic moiety (Table 3, entry 4). No Ullmann nucleophilic aromatic substitution products were detected when the reaction was performed in the presence of halo nitro benzenes (Table 3, entries 2, 3, 14, 17); only traces of reduced dehydrogenated aniline were found. The *t*Boc protecting group was observed to be stable under the optimised reduction conditions (Table 3, entry 18).

Gratifyingly, excellent results were also obtained in ethanolamine at 55 °C, and the Cu-catalysed TH of nitrobenzene derivatives afforded the azo derivative in an 85% average yield over a series of 10 different substrates. The product of N-arylation was only isolated as the main side product when the reaction was performed starting from bromo nitrobenzenes (Table 4, Entries 4 and 9). When the reaction was performed conventionally, the longer reaction time (25 h *versus* 1 h under MW/US irradiation) gave a slightly decreased reaction yield.

Table 4. Scope of the hydride-free reduction of aromatic nitro compounds to azo compounds as catalysed by Cu NPs. [a]



Entry	Product	Yield[%] [b] (%) [c]	Entry	Product	Yield[%] [b] (%) [c]
1	 **2a**	86 (92)	6	 **2f**	80 (86)
2	 **2b**	84 (90)	7	 **2g**	85 (88)
3	 **2c**	72 (83)	8	 **2h**	79 (82)
4	 **2d**	68 (72)	9	 **2i**	70 (77)

5	 **2e**	87 (91)	10	 **2j**	82 (86)

[a] Reaction conditions: nitroarene (3mmol), Ethanolamine (20 mL), KOH (6 mmol), Cu NPs (5 mol%), T:55ºC. [b] Isolated yield. Reaction performed under conventional stirring in oil bath at 55 ºC, 25 h. [c] Isolated yield. Reaction performed under combined US (20.3 kHz, 15 Wcm^{-2}) and MW (2.45 GHz, 15 W) irradiation (MW/US), 55 °C 1 h. Compound purity proved by ^{1}H-NMR and ^{13}C-NMR (see Supporting Info).

Conclusion

In summary, it has been demonstrated that Cu(0) NPs act as an efficient catalyst for the transfer hydrogenation of aromatic nitro compounds to amino compounds and azo compounds. A convenient and highly efficient protocol for the reduction of a range of structurally diverse nitroarenes has been developed. Mechanistic studies and a series of controlled experiments into the TH of nitrobenzene using different hydrogen sources has revealed that this catalytic system preferentially follows the condensation route, while product distribution analysis demonstrated that it is possible to selectively obtain an aniline or azobenzene product by varying the hydrogen donor.

Glycerol is a sustainable solvent, widely available and rich in functionalities, and has, as such, been successfully exploited as a “sacrificial” hydrogen source for the copper-catalysed transfer hydrogenation of nitroarenes to anilines. Ethanolamine has proven itself to be the best hydrogen donor for the synthesis of azobenzene from nitrobenzene under mild conditions. Two enabling technologies, MW and US, have been used either alone or in combination to provide a notable increase in reaction rate.

Experimental Section

All chemicals were purchased from Sigma-Aldrich (Milan, Italy) and used without further purification. Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates (Milan, Italy), which were visualized by UV inspection and/or by heating after a spraying with 0,5% ninhydrin in ethanol or phosphomolybdic acid. Reactions were carried out in conventional oil bath and in a combined system MW/US (Figure S1, Supporting Information). This device has been designed in our laboratory by inserting a sonic horn made of pirex inside a RotoShynth (Milestone) microwave chamber. NMR spectra (300 or 600 MHz and 75 or 125 MHz for 1H and 13C, respectively) were recorded. Chemical shifts were calibrated to the residual proton and carbon resonances of the solvent; DMSO-d6 (δH = 2.54, δC = 39.5), $CDCl_3$ (δH = 7.26, δC = 77.16), D_2O (δH = 4.79). Chemical shifts (δ) are given in ppm, and coupling constants (J) in Hz. GC-MS analyses were performed in a GC Agilent 6890 (Agilent Technologies, Santa Clara, CA, USA) that was fitted with a mass detector Agilent Network 5973, using a 30 m capillary column, i.d. of 0.25 mm and film thickness 0.25 μm. GC conditions were: injection split 1:10, injector temperature 250 °C, detector temperature 280 °C. Gas carrier: helium (1.2 mL/min), temperature program: from 50 °C (5 min) to 100 °C (1 min) at 10 °C/min, to 230 °C (1 min) at 20 °C/min, to 300 °C (5 min) at 20 °C/min.

General procedure for Cu(0) NPs preparation and characterization

Copper (II) sulphate is dissolved in a H_2O:glycerol (5:1) solution (0.01 M) and NaOH (2M) is dropwised until reaching pH=11. After having a well stirred deep blue solution, 0.5 M $NaBH_4$ in water is added into the flask. Initially, the solution gradually turns colourless and afterwards it becomes burgundy, confirming the formation of copper colloids. The Cu NPs are recovered on a Büchner funnel with a sintered glass disc washing with water and methanol.

High resolution transmission electron microscopy (HR-TEM) analyses were carried out employing a side entry Jeol JEM 3010 (300 kV) microscope equipped with a LaB_6 filament and fitted with X-ray EDS analysis by a Link ISIS 200 detector. The Cu NPs were deposited on a copper grid coated with a porous carbon film. The digital micrographs were acquired by an Ultrascan 1000 camera and the images were processed by Gatan digital micrograph. Histogram of the Cu particle size distribution was built by considering more than 250 nanoparticles and the mean particle diameter (d_m) was calculated as:

$$d_m = \Sigma d_i n_i / \Sigma n_i$$

where n_i is the number of particles of diameter d_i.

General procedure for Cu(0) NPs catalysed TH of nitrobenzenes to aniline derivatives

Synthesis under conventional heating and stirring

The nitroarene (3 mmol), KOH (6 mmol) and Cu(0)NPs (5 mol%) were dissolved in 20 mL of glycerol. The reaction was carried out under magnetic stirring in an oil bath at 130 °C for 60 – 90 min. The crude product was analysed by GC-MS. The reaction mixture was cooled down to room temperature and filtered to remove Cu NPs. 30 mL of water were added and extracted with ethyl acetate (2x30 mL). To the organic phase, aqueous HCl (0.01M) was added and after extraction the aqueous phase was basified with NaOH (0.01 M), extracted with ethyl acetate (3x30 mL) and dried (Na_2SO_4). After removal of the solvent the desired product was characterized without any further purification. Products were analysed using GC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

Synthesis under MW irradiation

The nitroarene (3 mmol), KOH (6 mmol) and Cu(0)NPs (5 mol%) were dissolved in 20 mL of glycerol. The reaction was carried out under MW irradiation (Milestone MicroSynth) at 130 °C (maximum power 400 W) for 15 min. The reaction mixture was then cooled down to room temperature and filtered to remove Cu NPs. The crude product was analysed by GC-MS. 30 mL of water were added and extracted with ethyl acetate (2x30 mL). To the organic phase, aqueous HCl (0.01M) was added and after extraction the aqueous phase was basified with NaOH (0.01 M), extracted with ethyl acetate (3x30 mL) and dried (Na_2SO_4). After removal of the solvent, the desired products were characterized without any further purification. Product identity and purity was obtained by GC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

Synthesis under US irradiation

The nitroarene (3 mmol), KOH (6 mmol) and Cu(0)NPs (5mol%) were dissolved in 20 mL of glycerol. The reaction mixture was sonicated by using a Pyrex horn (20.3 kHz, 30 W) for 45 min. The reaction mixture was then cooled down to room temperature and the catalyst was filtered. The crude product was analysed by GC-MS. 30 mL of water were added and extracted with ethyl acetate (2x30 mL). To the organic phase, aqueous HCl (0.01M) was added and after extraction the aqueous phase was basified with NaOH (0.01 M), extracted with ethyl acetate (3x30 mL) and dried (Na_2SO_4). After removal of the solvent the desired products were characterized without any further purification. Product identity and purity was obtained by GC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

Synthesis under MW and US combined irradiation

Combined US (20.3 kHz, 30 Wcm^{-2}) and MW (2.45 GHz, 80 W) irradiation was carried out in an oven (Milestone MicroSynth) equipped with a Pyrex horn inserted. The reaction mixture with the nitroarene (3 mmol), KOH (6 mmol), Cu(0)NPs (2.5 mol%) and 20 mL of glycerol was irradiated with the combined system for 10 min. The crude was then cooled down to room temperature and the catalyst was filtered. The crude product was analyzed by GC-MS. 30 mL of water were added and extracted with ethyl acetate (2x30 mL). To the organic phase, aqueous HCl (0.01M) was added and after extraction the aqueous phase was basified with NaOH (0.01 M), extracted with ethyl acetate (3x30 mL) and dried (Na_2SO_4). After removal of the solvent, the desired products were characterized without any further purification. Product identity and purity was obtained by GC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

General procedure for Cu(0) NPs catalysed TH of nitro benzenes to azobenzene derivatives

Synthesis under conventional heating and stirring

The nitroarene (3 mmol), KOH (6 mmol) and Cu(0)NPs (5 mol%) were dissolved in 20 mL of ethanolamine. The reaction was carried out under magnetic stirring in an oil bath at 50-60 °C for 20-24 h. The mixture was then cool down to room temperature and the catalyst was filtered. 30 mL of water was added, extracted with CH_2Cl_2 (2x30 mL) and dried with Na_2SO_4. The desired product was purified by chromatography on silica gel (petroleum ether: ethyl acetate) and analysed using GC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

Synthesis under MW irradiation

The nitroarene (3 mmol), KOH (6 mmol) and Cu(0)NPs (5 mol%) were dissolved in 20 mL of ethanolamine. The reaction was carried out under MW irradiation (Milestone MicroSynth) at 50-60 °C (maximum power 200 W) for 6 hours and a half. The reaction mixture was then cooled down to room temperature and the catalyst was filtered. 30 mL of water was added, extracted with CH_2Cl_2 (2x30 mL) and dried with Na_2SO_4. The desired product was purified by chromatography on silica gel (petroleum ether: ethyl acetate) and analysed using GC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

Synthesis under US irradiation

The nitroarene (3 mmol), KOH (6 mmol) and Cu(0)NPs (5 mol%) were dissolved in 20 mL of ethanolamine. The reaction mixture was sonicated by using a Pyrex horn (20.3 kHz, 20 W) for 3 h. The reaction mixture was then cooled down to room temperature and the catalyst was filtered. 30 mL of water were added, extracted with CH_2Cl_2 (2x30 mL) and dried with Na_2SO_4. The desired product was purified by chromatography on silica gel (petroleum ether: ethyl acetate) and analysed using GC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

Synthesis under MW and US combined irradiation

Combined US (20.3 kHz, 15 Wcm^{-2}) and MW (2.45 GHz, 15 W) irradiation was carried out in an oven (Microsynth-Milestone) equipped with a Pyrex horn inserted. The reaction mixture with the nitroarene (3 mmol), KOH (6 mmol), Cu(0)NPs (5 mol%) and 20 mL of ethanolamine was irradiated with combined MW/US for 1 h. The crude was then cooled down to room temperature and the catalyst was filtered. 30 mL of water were added, extracted with CH_2Cl_2 (2x30 mL) and dried with Na_2SO_4. The desired product was purified by chromatography on silica gel (petroleum ether: ethyl acetate) and analysed using GC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy.

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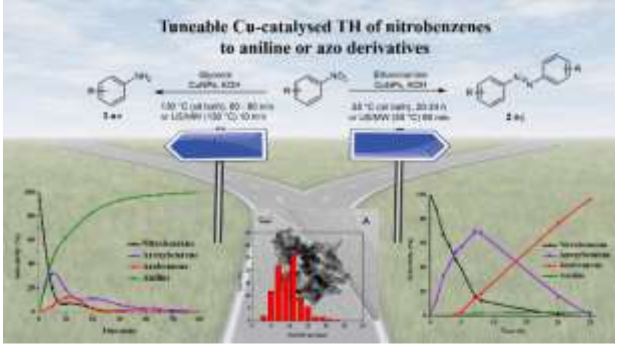

Tuneable copper catalysed transfer hydrogenation of nitrobenzenes to aniline or azo derivatives

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