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Yeast supported gold nanoparticles: an efficient catalyst for the synthesis of commercially important aryl amines†

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Candida parapsilosis ATCC 7330 supported gold nanoparticles (CpGNP), prepared by a simple and green method can selectively reduce nitroarenes and substituted nitroarenes with different functional groups like halides (–F, –Cl, –Br), olefins, esters and nitriles using sodium borohydride. The product aryl amines which are useful for the preparation of pharmaceuticals, polymers and agrochemicals were obtained in good yields (up to >95%) using CpGNP catalyst under mild conditions. The catalyst showed high recyclability (≥10 cycles) and is a robust free flowing powder, stored and used after eight months without any loss in catalytic activity.

Introduction

Improved efficiency and environmental acceptability requirements of organic synthetic processes have given a huge impetus to the development of heterogeneous catalysts[1] especially those based on bio-supported metal nanoparticles.[2] Bio-inspired methods require relatively milder conditions and the use of microorganisms like bacteria, fungi, actinomycetes, algae for the synthesis of metal nanoparticles.[3] Unlike metal oxide and other catalytic supports, microbes produce supported metal nanoparticles in one-pot, and are renewable.[4] Besides, microbes are also used as supports for pre-synthesized metal nanoparticles. The use of bio-supported metal nanoparticles as sustainable catalysts meets the design principles of 'green' nanoscience.[5]

Among the supported metal nanoparticles, palladium based supported nanocatalysts are widely reported in the field of heterogeneous catalysis and the catalytic performance of bio-supported palladium nanoparticles has been well documented for various commercially important organic reactions like hydrogenation.[6] The leaching of toxic metals like palladium[7] from the supporting matrix of the catalyst is a critical problem with their acceptable limit of <5 ppm in the preparation of pharmaceuticals.[8] Gold nanoparticles are a sustainable catalyst[9] as gold is non-toxic and environment friendly as compared to transition metals such as Pd, Rh, Ru being used.[10] Supported gold nanoparticles are efficient heterogeneous catalysts for the organic synthesis of compounds like aryl amines through hydrogenation/reduction of nitroaromatic compounds. The final reduced products, aryl amines, are precursors in the synthesis of biopharmaceuticals and intermediates such as amides, imines, azo compounds, isocyanates and diazonium salts which form the building blocks of various nitrogen-containing biologically active compounds *viz.*, agrochemicals, dyes, and polymers.[11] So far, catalytic reduction of nitroarenes using gold nanoparticles with different supporting matrices namely magnesium oxide,[12] rutile/TiO_2,[13] SiO_2 coated branched polyethylenimine[14] and chitosan grafted graphene oxide[15] are prepared[16] *via* impregnation, co-precipitation and ion-exchange methods. However, these methodologies involves multiple steps and a number of unit operations,[17] energy expensive techniques[18] and volatile organic solvents.[19] Thus there is a constant effort required to develop green methods[20] for the selective reduction of nitro aromatic compounds.

Microbially synthesized bio-supported gold nanoparticles reported so far for the catalytic reduction of 4-nitrophenol to 4-aminophenol do not report the isolated yields and therefore their commercial viability is difficult to evaluate.[21] Recently, we reported the preparation of yeast supported gold nanoparticles using the resting cells of the *Candida parapsilosis* ATCC 7330.[22] In our constant efforts to develop green methods, this is the first report for the synthesis of aryl amines from nitroaromatic compounds using these bio-supported gold nanoparticles (abbreviated as CpGNP) as catalyst and sodium borohydride as the hydride source. Chemoselective reduction of nitroarenes which have more than one reducible group is of utmost

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importance and the nature of the solid support also contributes towards activity and selectivity.[23] This study demonstrates the chemoselectivity of the developed CpGNP catalyst for the reduction of nitroarenes in the presence of sensitive reducible groups like keto, aldehyde, nitriles, esters and olefins. A few challenging nitroarenes which are reduced using the catalyst and are reported here for the first time, extended the scope of the developed catalyst. The reusable efficiency and shelf life of the CpGNP make it a desirable catalyst.

Experimental

Chemicals and reagents

Nitroarenes were purchased from Aldrich, Alfa Aesar, Rankem, Spectrochem and SRL chemicals and used without further purification. Sodium borohydride was procured from Merck. Synthesis of 4-(4-nitrophenyl)but-3-en-2-one was carried out using the reported[24] procedure. Preparation of sodium 4-nitrobenzoate from 4-nitrobenzoic acid was carried out using the known[25] procedure.

Synthesis and characterization of CpGNP catalyst

Bio-supported gold nanoparticles (CpGNP) was prepared as follows: cell suspension (50 g L^{-1}) of resting cells of *Candida parapsilosis* ATCC 7330 (24 h culture age) was treated with 1 mM gold(III) chloride and the reaction flasks were kept for incubation at 37 °C, 200 rpm for 72 h. After the incubation period, CpGNP was collected as a pellet by centrifugation (12 800 × *g*, 15 min) and washed with MilliQ water and the same process was repeated once.[22] Powder X-ray diffraction studies of CpGNP catalyst and control yeast cells was recorded using the Bruker Discover D8 diffractometer at room temperature in 2θ (30° to 100°) using Cu (Kα) radiation (λ/Å = 1.5406). Fourier transform-Infra red spectroscopy of CpGNP and control yeast cells was recorded using the Eco-ATR Bruker ALPHA spectrometer in the range of 600–4000 cm^{-1} with a resolution of 4 cm^{-1}. X-ray Photoelectron Spectroscopy analysis was performed using aKratos Ultra-2 spectrometer (SHIMADZU Axis Supra) with monochromatic Al Kα radiation source (14 keV). The binding energy values of the elements were corrected in accordance to values of the standard carbon element and XPS spectra were plotted. Induced coupled plasma-Optical emission spectrometry (PerkinElmer Optima 5300 DV) was employed to estimate the concentration of gold species in CpGNP after acid digestion using aqua regia. Prior to this analysis, a standard curve was plotted based on the optical emission recorded for known concentrations of gold at λ/nm (267.595). Transmission electron microscopy (Philips CM12) – 120 kV was performed to examine the morphology of the CpGNP catalyst. Sample preparation involves coating a drop of the CpGNP catalyst dispersed in MilliQ water on copper grids and allowed to air dry.

Typical procedure for the catalytic reduction of nitroarenes

In the present study, nitrobenzene was tested as the model substrate for catalytic reduction using CpGNP. To the catalyst, CpGNP (20 mg) (0.24 mol% Au) suspended in 3 mL of distilled water in a round-bottomed flask, nitrobenzene (0.5 mmol) was added with continuous stirring. $NaBH_4$ (2 mmol) was slowly added to the cooled reaction mixture (~0–4 °C). After five minutes, the ice bath was removed and the reaction mixture was allowed to stir at room temperature. The reaction was monitored by thin layer chromatography and ninhydrin staining. Once the reaction was completed, the product was extracted thrice with ethyl acetate (5 mL) and the organic layer was dried over anhydrous sodium sulfate and further concentrated. The conversion of nitroarenes to amine products was monitored using High performance liquid chromatography (HPLC) and confirmed using Gas chromatography-Mass spectrometry (GC-MS) analysis. For initial optimization studies, the same sequence of experiments was performed with different ratios of catalyst to the sodium borohydride (see ESI†). Similar procedures were followed for the reusability and storage stability studies. Unless otherwise mentioned, the reaction conditions were identical for all the substrates tested.

Catalyst leaching, reusability and storage stability studies

The leaching of the CpGNP catalyst was studied by suspending the catalyst in water and allowed to stir for 4 h. Later, the catalyst was separated by filtration and the filtrate solution was used for the reduction of nitrobenzene in the presence of $NaBH_4$ under optimized conditions. CpGNP reusability was monitored for the reduction of nitrobenzene to aniline. After every cycle, the catalyst was removed from the water layer by filtration. Catalyst was washed twice with MilliQ water and then subjected to next catalytic reaction and the process continues for up to 10 cycles. The collected aqueous layer was extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated using rotary evaporator. The as-prepared CpGNP catalyst was lyophilized (10^{-3} bar pressure and −50 °C) for 16 h and the freeze-dried catalyst was stored at 2–8 °C. The shelf life of the catalyst was studied by monitoring the catalytic reduction of nitrobenzene using lyophilized CpGNP stored at 2–8 °C for up to 8 months.

Analytical methods

^{1}H NMR spectroscopy was recorded in $CDCl_3$ or DMSO-d_6 (Cambridge Isotope Laboratories, Inc, USA) at room temperature using Bruker AVANCE III 500 MHz (AV 500) multi-nuclei solution NMR Spectrometer, TMS as internal reference, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad, app = apparent), coupling constants (*J*; Hz), and assignment. ^{13}C and Dept-135 NMR spectrum was also recorded. Chemical shifts are in ppm. High performance liquid chromatography (Jasco PU-1580 liquid chromatography) was performed to determine the conversion of the products formed using reverse-phase C18 column with a photodiode array detector. Acetonitrile and water mixture in the ratio of 85 : 15 was used as mobile phase with a flow rate of 0.5 mL min^{-1}.

Gas Chromatography was recorded using SHIMADZU GCMS QP 2010 Ultra equipped with Omega wax 320 capillary column (30 m × 0.32 mm i.d × 0.25 μm film thickness) and EI detector.

Helium was used as carrier gas at flow rate of 1.49 mL min^{-1}. The column temperature was 50 °C for 2 min, increased to 210 °C at 4 °C min^{-1} and kept for 18 min in split mode with 2 : 1 split ratio. In mass spectrometry, temperature of the ion source and interface was 220 °C and 250 °C respectively with *m*/*z* detection in the range of 45–900 (scan mode). High resolution mass spectra (HRMS) were recorded using the Thermo Scientific-Orbitrap Elite with Electrospray ionization. Thin layer chromatography analysis was performed using Kieselgel 60 F254 aluminum sheets (Merck 1.05554) with UV light and ninhydrin used as staining agent for detection of amines.

Results and discussion

Synthesis and characterization of CpGNP catalyst

Recently, we reported the synthesis of gold nanoparticles using the resting cells of the yeast *Candida parapsilosis* ATCC 7330.[22] The gold nanoparticles thus formed are found to be supported within the yeast cell. These bio-supported gold nanoparticles is hereinafter abbreviated as CpGNP. Fourier Transform-Infrared Spectroscopy analysis was performed on CpGNP and yeast biomass (control sample) and the shift in frequency was indexed based on the earlier literature.[26] FT-IR signature band of N–H stretching of the bonded amines at 3270 cm^{-1} (for yeast cells) was shifted to 3275 cm^{-1} for CpGNP. On the other hand, a band at 1542 cm^{-1} was downshifted to 1538 cm^{-1} which is a characteristic of amide II *i.e.*, interactions between C═O stretching and N–H deformation coupling. Interaction of gold with the C═O symmetric stretching of the COO^- showed band shift from 1400 cm^{-1} to 1375 cm^{-1}. Relatively, about 4 nm downshift in the FT-IR band assigned to the hydroxyl groups of the saccharide molecules (1043 cm^{-1}) was observed for the CpGNP. Collectively, a frequency shift in the signature bands corresponding to amines, amides, carboxyl groups and hydroxyl groups was observed in metallized yeast as compared to the control yeast cells (Fig. S1, ESI†). Powder X-ray diffraction studies of the as-prepared CpGNP as shown in Fig. S2(b) (ESI†), indicated the presence of crystalline gold nanoparticles (ICDD card no. 00-04-0784), but with very low intensity. XRD studies showed that the control-yeast cells (Fig. S2(a), ESI†) are amorphous in nature. The poor intensity of XRD peaks observed with as-prepared CpGNP may be due to the fact that gold nanoparticles (<30 nm dia.) were found associated with yeast cells (2.5 to 4 μm dia.) which is in agreement with literature ref. 27 X-ray Photoelectron Spectroscopy (XPS) analysis of lyophilized CpGNP showed the presence of orbital peaks of elements such as P_{2p}, C_{1s}, N_{1s}, O_{1s} and Au_{4f} which is supported with reported[28] binding energy values (Fig. S3, ESI†). Wide scan XPS spectra of Au_{4f} showed the presence of gold nanoparticles on the yeast cell surface with two characteristic peaks of metallic gold assigned to $4f_{7/2}$ and $4f_{5/2}$ at 83.1 eV and 86.8 eV respectively (Fig. S4, ESI†), with Au (4f) peak spin–orbit splitting of 3.7 eV. Quantitative estimation of gold was found to be 1.06 (±0.06) ppm per mg dry weight of CpGNP determined using induced coupled plasma-optical emission spectrometry (ICP-OES).

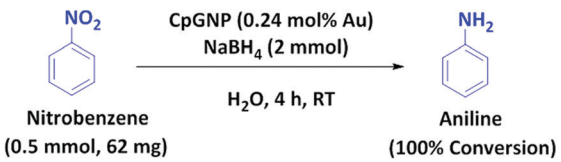
CpGNP mediated catalytic reduction of nitrobenzene

In the present study, catalytic performance of yeast supported gold nanoparticles (CpGNP) for the reduction of nitroaromatic compounds using sodium borohydride as a hydride source was optimized. The complete reduction of nitrobenzene to aniline using CpGNP (0.24 mol% Au) catalyst (Scheme 1 and Fig. S5 and S6, ESI†) in aqueous medium occurred in four hours in the presence of 2.0 mmol $NaBH_4$. Scale up (8 fold) reaction showed completion of the reaction with an isolated yield of 90% aniline under optimized reaction conditions.

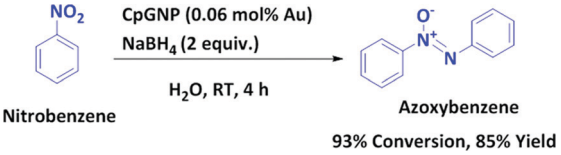
Metal nanoparticles mediate the hydride transfer reduction of nitroarenes using the electron relay effect.[29] Metal nanoparticles involve two different pathways in the reduction of nitroarenes to aryl amines *viz.*, (i) direct pathway involve intermediates like nitrosobenzene and phenyl hydroxyl amine and (ii) indirect pathway involve azoxybenzene, azobenzene and diazobenzene as reaction intermediates.[30] In order to investigate the pathway, the reaction mixture of CpGNP mediated reduction of nitrobenzene before completion was subjected to GCMS analysis. Detection of (*Z*)-1,2-diphenyldiazene oxide(azoxybenzene) and (*E*)-1,2-diphenyldiazene(azobenzene) (Fig. S7–S9, ESI†) confirmed that this reaction proceeds through indirect (condensation) pathway (Scheme S1, ESI†). The intermediate (*Z*)-1,2-diphenyldiazene oxide was isolated and characterized. Maximum conversion of up to 93% (*Z*)-1,2-diphenyldiazene oxide (85% yield) was achieved using CpGNP (0.06 mol% Au) and $NaBH_4$ (1 mmol, 2 equiv.) within a reaction time of 4 h (Scheme 2 and Table S2, ESI†). This is the first report to elucidate the mechanistic route in the reduction of nitroarenes to aryl amines using bio-supported metal nanoparticles as catalyst. A similar mechanism is reported for the hydrogenation of nitroarenes using gold nanoparticles/CeO_2 as a supported catalyst.[31]

Reduction of substituted nitroarenes using CpGNP catalyst

Catalytic performance of CpGNP catalyst for the reduction of substituted nitroarenes (Table 1) was investigated. Nitroarenes with electron donating groups such as -OH, -NH_2 were



Scheme 1 Schematic of the reduction of nitrobenzene to aniline using CpGNP/$NaBH_4$.



Scheme 2 Reduction of nitrobenzene to (*Z*)-1,2-diphenyldiazene oxide(azoxybenzene) using CpGNP/$NaBH_4$.

completely reduced (Table 1, entries 2–7) to their corresponding anilines within 4 h but 4-methyl nitrobenzene (Table 1, entry 8), required 8 equiv. of $NaBH_4$ and 6 h for the reaction to complete.

The reduction of substituted nitroarenes containing electron withdrawing groups namely –CHO, –COOR, –CN, $–NO_2$, –COOH showed that the reduction of *-o*, *-m*, *-p* nitro-substituted benzaldehydes to their corresponding aminobenzyl alcohols proceeds with good yields (Table 1, entries 9–11). CpGNP mediated reduction of 2-nitrobenzyl alcohol also yields 2-aminobenzyl alcohol in good quantitative yield (Table 1, entry 12). CpGNP/$NaBH_4$ catalyzes the reduction of a series of nitroacetophenones *i.e.*, *-o*, *-m*, *-p* nitro-substituted acetophenone to their corresponding 1-(amino phenyl)ethanol (Table 1, entries 13–15) with good yields. This catalyst reduced nitro group along with keto and aldehdyde carbonyl groups (Table 1, entries 9–11; 13–15; 32). The reduction of carbonyl groups in the absence of nitro groups was faster with borohydride alone (without CpGNP) as compared to CpGNP/$NaBH_4$.

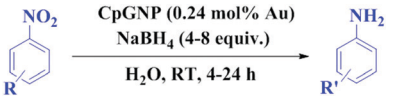
Dinitrobenzenes took about 24 h to yield ≥70% benzenediamine and 20–25% nitroanilines using CpGNP/$NaBH_4$ (Table 2, entries 16–18). This prompted us to re-look at the reaction time in the reduction of dinitrobenzene. At 4 h, 1, 2-dinitrobenzene, showed the formation of benzene-1,2-diamine (53%) and 2-nitroaniline (24%) while the reduction of 1, 3-dinitrobenzene showed the formation of benzene-1, 3-diamine (44%) and 3-nitroaniline (25%) (Table 2). At 4 h, reduction of 1,4-dinitrobenzene gave 4-nitroaniline (81%) as the major product with only traces (2%) of benzene-1, 4-diamine (Table 2). The present methodology can be used to selectively synthesize 4-nitroanilines from 1,4-dinitrobenzene in lesser reaction time.

Table 2 Conversion profile for the reduction of dinitrobenzenes (DNBs) at 4 h

	Products	
Substrates (DNBs)	Nitroaniline (%)	Benzenediamine (%)
1,2-Dinitrobenzene	24 ± 2	53 ± 4
1,3-Dinitrobenzene	25 ± 3	44 ± 1
1,4-Dinitrobenzene	81 ± 3	2 ± 1

Note: Remaining were the unreduced substrate.

Table 1 CpGNP mediated transfer hydrogenation of functionalized nitroarenes



Entry	R	R′	Substrate : $NaBH_4$ (equiv.)	Reaction time (h)	% conversion (% selectivity)[a]	Yields (%)[b]
1.	–H	–H	1 : 4	4	100	>95
2.	2-OH	2-OH	1 : 4	4	100	>95
3.	3-OH	3-OH	1 : 4	4	100	>95
4.	4-OH	4-OH	1 : 4	4	100	>95
5.	2-NH_2	2-NH_2	1 : 4	3	100	>95
6	3-NH_2	3-NH_2	1 : 4	24	14	—
7.	4-NH_2	4-NH_2	1 : 4	3	100	>95
8.	4-CH_3	4-CH_3	1 : 8	6	100	>95
9.	2-CHO	2-CH_2OH	1 : 4	4	100	>95
10.	3-CHO	3-CH_2OH	1 : 4	4	100	>95
11.	4-CHO	4-CH_2OH	1 : 4	4	100	>95
12.	2-CH_2OH	2-CH_2OH	1 : 4	4	100	>95
13.	2-$COCH_3$	2-$CHOHCH_3$	1 : 4	5	100	>95
14.	3-$COCH_3$	3-$CHOHCH_3$	1 : 4	5	100	>95
15.	4-$COCH_3$	4-$CHOHCH_3$	1 : 4	5	92	70[c]
16.	2-NO_2	2-NH_2	1 : 4	24	100 (73/27)	50/24[c]
17.	3-NO_2	3-NH_2	1 : 4	24	100 (71/29)	46/22[c]
18.	4-NO_2	4-NH_2	1 : 4	24	100 (78/22)	53/21[c]
19.	4-COOH	4-COOH	1 : 4	24	39	—
20.	3,4-F	3,4-F	1 : 4	4	100 (>99)	>95
21.	2-Cl	2-Cl	1 : 4	5	100 (>99)	>95
22.	4-Cl	4-Cl	1 : 4	5	100 (>99)	>95
23.	4-Br	4-Br	1 : 8	6	45 (>99)	35[c]
24.	4-I	—	1 : 8	6	100	>95
25.	4-(CH=CH-COOEt)	4-(CH=CH-COOEt)	1 : 4	8	33 (>99)	—
26.	4-COOEt	4-COOEt	1 : 4	5	100 (>99)	>95
27.	3-CN	3-CN	1 : 4	6	100 (>99)	>95
28.	4-CN	4-CN	1 : 4	6	100 (>99)	>95
29.	2-CN, 4-Cl	2-CN, 4-Cl	1 : 8	24	71 (>99)	63[c]
30.	2-CN, 5-CF_3	2-CN, 5-CF_3	1 : 4	6	100 (>99)	>95
31.	4-(SO_2NH_2)	4-(SO_2NH_2)	1 : 4	8	100 (>99)	>95
32.	2-(CH=CH-CHO)	2-(CH=CH-CH_2OH)	1 : 4	6	60	54[c]
33.	4-(CH=CH-CH_2OH)	4-(CH=CH-CH_2OH)	1 : 4	4	100 (>99)	>95
34.	3-(CH=CH_2)	3-(CH=CH_2)	1 : 8	6	100 (>99)	>95

[a] Conversions are calculated based on HPLC. [b] Yield after work up. [c] Yield obtained after column chromatography.

Similarly, a prolonged reaction time of 24 h was required for the formation of ~39% of 4-aminobenzoic acid from 4-nitrobenzoic acid using CpGNP/$NaBH_4$. Under similar conditions, reduction of sodium 4-nitrobenzoate gave ~63% of 4-aminobenzoate which was confirmed by TLC and HPLC analysis (Fig. S10, ESI†).

Reduction of halo-substituted nitroarenes by CpGNP catalyst

A range of halogenated nitroarenes was subjected to reduction using CpGNP/$NaBH_4$ (Table 1, entries 20–24). Reduction of 3,4-difluoronitrobenzene to obtain 3,4-difluoroaniline (>95% yield), an important building block for the synthesis of compounds of biological interest, was achieved using supported gold catalyst (CpGNP) at ambient conditions for the first time (Table 1, entry 20). Recent studies showed that high temperature is required for the preparation of 3,4-difluoroaniline.[32] More importantly, CpGNP catalyst does not affect the chlorine group during the reduction of *-o* and *-p* substituted chloronitrobenzenes and as a result, the respective chloroanilines were formed. Sobjerg *et al.* reported the quantitative reduction of 4-chloronitrobenzene to 4-chloroaniline using bio-supported palladium at 70 °C and ethanol.[6c] Unlike metal catalysts such as Pt[33] and Pd,[34] reductive dechlorination was not observed with CpGNP/$NaBH_4$.

Reduction of 4-bromonitrobenzene yielded 4-bromoaniline (46%) and the remaining was the starting material. On the contrary, deiodination was observed in case of 4-iodonitrobenzene, which resulted in aniline as final product (Table 1, entry 24). Within 8 h, only 33% of amine ester was formed as a result of CpGNP/$NaBH_4$ mediated reduction of ethyl-3-(4-nitrophenyl) acrylate (nitroaromatic ester) (Table 1, entry 25) which could be due to poor substrate solubility.

Till date, there is no report on the reduction of ethyl 4-nitrobenzoate to ethyl 4-aminobenzoate (local anesthetic) using supported gold nanoparticles catalyst. Ethyl 4-aminobenzoate (benzocaine) was obtained in high yield (95%) using CpGNP mediated reduction of ethyl 4-nitrobenzoate under mild conditions (Table 1, entry 26). Previous reports indicated the synthesis of benzocaine in low yield, employing harsh reaction conditions[35] with more equivalents of hydride[36] source.

Chemoselectivity of CpGNP catalyst

CpGNP catalyzed the reduction of *m-* or *p*-substituted nitrobenzonitrile to their corresponding aminobenzonitriles (Table 1, entries 27 and 28) with good yields, which are the building blocks of hormone analogues[37] and fluorescent[38] markers. Unlike supported catalyst such as magnetic carbon nanotubes-supported Pt(II)[39] and Pd-metal-loaded silicon semiconductor,[40] CpGNP selectively reduce the nitro group leaving the nitrile group intact. Wang *et al.* showed that gold nanoparticles/TiO_2 require 100 °C, 10 bar and toluene for the reduction of 3-nitrobenzonitrile to 3-aminobenzonitrile with 95% conversion (~98% selectivity) in 6.5 h.[41]

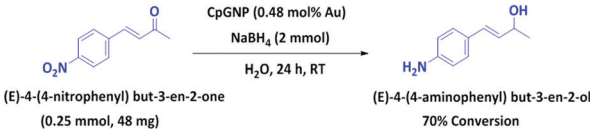
4-Chloro-2-aminobenzonitrile and its derivatives are important nitrogen-containing aromatic compounds useful in the preparation of anti-bacterial agents.[42] CpGNP selectively reduced 4-chloro-2-nitrobenzonitrile to 4-chloro-2-aminobenzonitrile (71% conversion) with 61% yield. Besides few metal catalysts which are already known,[43] the use of a gold catalyst (CpGNP) for the reduction of 4-chloro-2-nitrobenzonitrile to 4-chloro-2-aminobenzonitrile is reported here for the first time. Synthesis of 2-amino-4-(trifluoromethyl)benzonitrile, a positional isomer of the anti-cancer drug, 4-amino-2-(trifluoromethyl)benzonitrile was achieved in good yields (>95%) using CpGNP/$NaBH_4$ for the first time. A separate study reported the reduction of 2-nitro-4-(trifluoromethyl)benzonitrile to 2-amino-4-(trifluoromethyl)benzonitrile (78%) and 2-amino-4-(trifluoromethyl)benzamide (20%) using Pd catalyst.[44]

Evidently, CpGNP catalyzes the reduction of nitro group to amine without affecting nitrile and $-CF_3$ groups. Synthesis of 4-aminobenzene sulfonamide, an aryl amine core structure of an anti-HIV drug was obtained with good yields (>95%) (Table 1, entry 31) using CpGNP/$NaBH_4$ under mild conditions. A similar reduction is reported but which utilizes 50 bar hydrogen, a temperature of 120 °C, tetrahydrofuran as solvent and a reaction time of 18 h.[45]

Chemoselectivity of CpGNP catalyst in the reduction of 2-nitrocinnamaldehyde, resulted in the formation of 2-aminocinnamyl alcohol (60%) (Table 1, entry 32) and quinolone (40%) (Fig. S11, ESI†). In this case, cyclization of the reduced product leads to quinolone[46] formation. Within 4 h, CpGNP/$NaBH_4$ catalyzes the reduction of 4-nitrocinnamyl alcohol to yield aminocinnamyl alcohol (>95%) (Table 1, entry 33). This is the first report with gold supported catalysts (CpGNP) whereas previous reports[47] showed the use of metals such as indium, osmium and samarium as catalysts.

Synthesis of 3-aminostyrene and its derivatives are useful in polymer synthesis.[48] For the substrate 1-nitro-3-vinyl benzene, CpGNP requires 8 equiv. of $NaBH_4$ to produce 3-aminostyrene in good yields within 6 h (Table 1, entry 34). Creamer *et al.* reported that bio-Pd nanocatalyst reduced 3-nitrostyrene to 1-ethyl-3-nitrobenzene (74%) and 1-ethyl-3-aminobenzene (7%).[6a] Unlike few reported metal nanoparticles catalysts,[49] CpGNP selectively reduces the nitro group leaving the double bond intact.

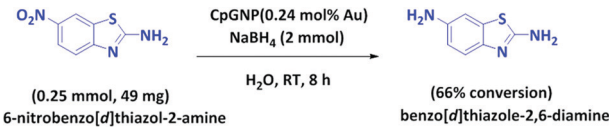
Uniconazole derivatives function as agrochemical bioregulators and are composed of an aryl amine core structure like 4-(4-aminophenyl)but-3-en-2-ol.[50] CpGNP catalyze the reduction of 4-(4-nitrophenyl)but-3-en-2-one to give 4-(4-aminophenyl)but-3-en-2-ol in a single step which is reported here for the first time. A ratio of 1 : 4 nitroarene to $NaBH_4$, and CpGNP (0.24 mol% Au) showed the formation of 4-(4-aminophenyl)but-3-en-2-ol (~45%) which was confirmed by High Resolution Mass Spectrometry (Fig. S12, ESI†) and Nuclear Magnetic Resonance Spectroscopy (Fig. S13 and S14, ESI†). Under these conditions, doubling $NaBH_4$ (8 equiv.) showed a conversion of ~48% whereas doubling the catalyst *i.e.*, 0.48 mol% Au increased the conversion up to ~70% (Scheme 3 and Fig. S15, ESI†). Control experiments show that $NaBH_4$ non-selectively reduces the keto group of 4-(4-nitrophenyl)but-3-en-2-one and as a result, 4-(4-nitrophenyl)but-3-en-2-ol is formed whereas the starting material remains intact in reactions with either CpGNP or yeast cells alone (Fig. S16, ESI†).



Scheme 3 Synthesis of 4-(4-aminophenyl)but-3-en-2-ol from its nitro precursor, 4-(4-nitrophenyl)but-3-en-2-one using CpGNP/$NaBH_4$.

$CpGNP/NaBH_4$ catalyzes the reduction of a nitro-substituted heterocyclic compound, 2-amino-6-nitrobenzothiazole, to obtain the desired product benzothiazole-2, 6-diamine (66%) for the first time, which is an important scaffold in medicinal chemistry[51] (Scheme 4 and Fig. S17, ESI†). A methodology reported by Ramnauth *et al.* involves the use of $SnCl_2$ and ethanol to obtain benzothiazole-2,6-diamine (50% yield).[52]

Unlike conventional supported gold nanoparticles catalyst[53] prepared by chemical methods, the sustainable yeast supported gold nanoparticles (CpGNP) reported here catalyzes the quantitative reduction of a wide range of substituted nitroarenes to their respective aryl amines using less equivalents of $NaBH_4$ (4–8 equiv.) under mild conditions. Also, the recent methodologies developed for the synthesis of aryl amines which reportedly use toxic metal catalysts,[54] organic solvents,[55] high temperature[56] and inert conditions.[31] Collectively, the present study delivers a benign methodology to produce a variety of industrially important aryl amines (Fig. 1) from nitroarenes with good selectivity using bio-supported Au NPs catalyst prepared from readily available renewable resource *i.e.*, the yeast, *Candida parapsilosis* ATCC 7330 and this work was recently patented.[57]



Scheme 4 $CpGNP/NaBH_4$ mediated reduction of 6-nitrobenzo[*d*]thiazol-2-amine under mild conditions.

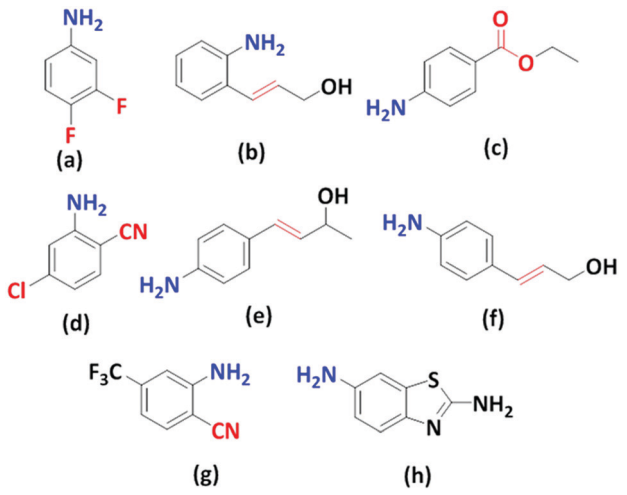


Fig. 1 Reduced compounds (a–h) obtained using bio-supported gold nanoparticles catalyst for the first time. CpGNP reduces the nitro group in the presence of olefins, nitriles, halogenated nitrobenzenes and esters (as highlighted in red).

Leaching, reusability and storage stability

Reduction of nitrobenzene by CpGNP filtrate did not show any traces of aniline under the optimized conditions (Fig. S18, ESI†) while the pellet (CpGNP) gave the final reduced product, aniline. Reusability studies showed that conversion as high as 96% of aniline was observed even after 10^{th} cycle (Fig. 2) and the results were comparable to other gold supported[15,53a] catalysts. ICP-OES analysis showed that only trace amounts of gold (0.251 ppm, 1.2%) were present in the reaction supernatants after 10^{th} catalytic cycle.

Cellular integrity of yeast support in CpGNP is crucial because the gold nanoparticles were found associated with them. Loss of membrane integrity in yeast support could lead to leaching of gold nanoparticles from CpGNP, which is undesirable from viewpoint of heterogeneous catalysis. Transmission electron microscopic (TEM) analysis of the recovered catalyst (after 10^{th} catalytic cycle) showed the presence of intact yeast cells *i.e.*, bio-support (Fig. 3). These microscopic observations substantiate that yeast cells with gold nanoparticles produced (CpGNP) *in situ* act as an excellent support matrix in sustainable catalysis. Attempts to separate gold nanoparticles from CpGNP showed that these nanoparticles are bound strongly to the cellular matrix thus confirming the heterogeneity of the bio-supported gold nanoparticles prepared using yeast *Candida parapsilosis* ATCC 7330 (Table S3, ESI†). CpGNP suspension subjected to ultrasonication showed well dispersed gold nanoparticles of size <30 nm in TEM micrographs (Fig. S19, ESI†) whereas the same sample showed the particle hydrodynamic diameter of 2648 nm. This result indicated that the gold nanoparticles are strongly interacted with yeast cells in CpGNP. The dispersity of the gold nanoparticles in CpGNP even after subjecting to harsh extraction procedure (like ultrasonication) highlights their stability in reaction conditions for multiple catalytic cycles.

Visual inspection of the lyophilized powder of CpGNP shows the presence of pink coloration which is due to gold

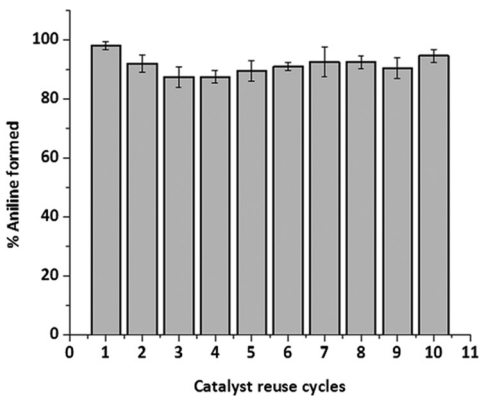


Fig. 2 Catalyst reusability studies for the reduction of nitrobenzene to aniline.

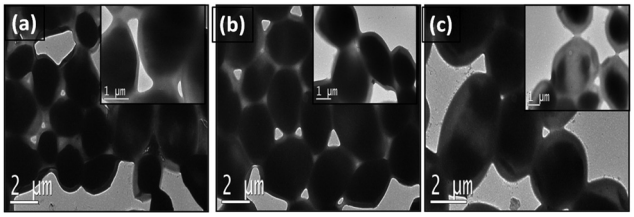


Fig. 3 Transmission electron microscopic study of the yeast support in CpGNP catalyst (a) in as-prepared catalyst, (b) after one catalytic run and (c) after 10 catalytic cycles. Inset shows enlarged images of the bionanocatalyst.

nanoparticles in it (Fig. S20, ESI†). Freeze-dried CpGNP catalyst showed complete reduction of nitrobenzene to aniline (Fig. S21, ESI†) without loss in catalytic activity even after storage for up to eight months at 2–8 °C (Fig. S22, ESI†).

Conclusions

The present study demonstrates an efficient and sustainable method for the synthesis of aryl amines using *Candida parapsilosis* ATCC 7330 supported gold nanoparticles (CpGNP) and its use as a novel heterogeneous catalyst with $NaBH_4$ as a reducing agent in aqueous medium at ambient temperature. Preparation of industrially important aryl amines is demonstrated by the developed catalytic system for the reduction of $-NO_2$ group in the presence of halides (-F, -Cl, -Br), nitriles, esters, olefins and amides. Importantly, reduction of eight nitroarenes to their respective aryl amines using bio-supported gold nanoparticles catalyst are reported here for the first time and one of the aryl amine synthesized, 4-(4-aminophenyl)but-3-en-2-ol is a novel compound, a building block of agrochemical regulator. The heterogeneity, recyclability and storage stability of the CpGNP catalyst emphasizes its suitability and robustness towards the selective reduction of nitroarenes to aryl amines.

Author contributions

SK and PNP contributed to the conception, design, data analysis, and interpretation of the experimental data. SK carried out the experiments and wrote the manuscript. AC supervised the findings of this work. All the authors discussed the results and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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