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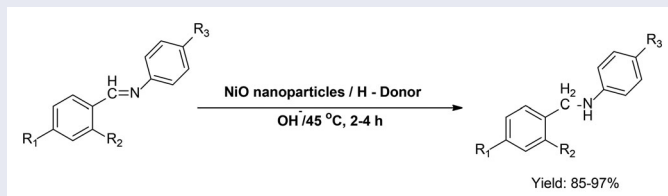
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ABSTRACT

An innovative and simple approach for the reduction of aldimines to the corresponding secondary amines was described using biosynthesized nickel oxide nanoparticles as heterogeneous catalyst and ammonium formate as the hydrogen donor. This catalytic transfer hydrogenation method was highly efficient and helps to synthesize amines with remarkable yields and without any coarse environment.

GRAPHICAL ABSTRACT



ARTICLE HISTORY

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Nickel oxide; heterogeneous catalyst; imines; reduction

Introduction

Since the value of amines in the pharmaceutical and natural products industry is high, researchers are interested in the efficient synthesis of secondary amines. Though numerous pathways are available for the synthesis of secondary amines, still research is going on to improve the reaction scheme to get a simplified procedure.^[1-6]

Among the techniques reported, reduction of C=N bond of imine is a promising route for the synthesis of secondary amines. Reducing agents like lithium aluminum hydride,^[6] sodium borohydride,^[7,8] NH₃/Ra-Ni,^[9] Zn dust/ammonium formate,^[10] NaBH₄/Ra-Ni^[11] etc. have been used to reduce the C=N of imines. But most of these reactions are cost-intensive, toxic and sensitive to environmental conditions. Chemo-selectivity of the reaction is also a major issue which has to be solved.^[12]

In the recent years, reduction of imines using nanoparticles as catalyst is gaining more interest due to its simple procedure and eco-friendly reaction conditions. Several attempts have been done to develop a new protocol using nanoparticles as catalyst to reduce the imines using catalytic transfer hydrogenation method.

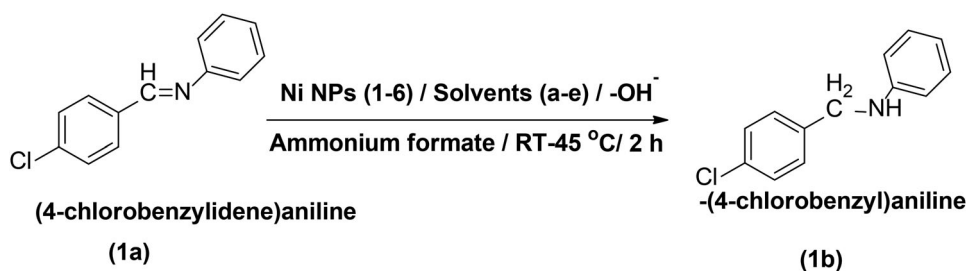
Nanoporous gold was used as catalyst for the reduction of aldimines in the coexistence of aldehydes.^[13] Silver nanoparticles supported on alumina was used for the reduction of imines to primary and secondary amines.^[14] Asymmetric reduction of

ketimine was demonstrated using functionalized gold nanoparticles as homogeneous catalyst.^[15] All these reaction protocols can't be used for large scale synthesis due to the usage of noble metals for the synthesis of nanoparticles. Some of these have a lack to explain the catalyst recyclability and failed to demonstrate the stability of the catalyst. Nano NiLa₂O₄ spinel was used as the heterogeneous catalyst for the selective reduction of imines using NaBH₄ as reducing agent.^[16] This report demonstrated an extended procedure which required much attention and care to proceed the reaction.

Recently, we have reported the reduction of aromatic aldehydes using the metal oxide nanoparticles which are biosynthesized from the immature fruit of *Cocos nucifera* as catalyst.^[17] We found that biosynthesized nanoparticles showed better activity than the chemically synthesized nanoparticles. In our effort to explore the catalytic property of biosynthesized nanoparticles, herein we report the reduction of imines using nickel oxide nanoparticles as heterogeneous catalyst, prepared from the immature coconut fruit extract as the biomaterial. To the best of our knowledge, this is the first report to use biosynthesized metal oxide nanoparticles as catalyst for the catalytic transfer hydrogenation of imines to secondary amines.

Experimental section

The fresh immature coconut fruit which was fallen from the coconut tree was collected from Palayamkottai area,



Scheme 1. NiO NPs catalyzed reduction of imine 1a.

Table 1. Reduction of imine 1a using various Nickel catalysts.

S. No.	Catalyst	Hydrogen donor	Yield (%)
1	NiCl ₂ salt	Ammonium formate	–
2	NiO NPs synthesized from <i>Cocos nucifera</i>	Ammonium formate	94
3	NiO NPs synthesized from from <i>Cocos nucifera</i>	EtOH	–
4	Ni-Cys NPs	Ammonium formate	69
5	NiO NPs synthesized by chemical method	Ammonium formate	78
6	No catalyst	Ammonium formate	–
7	NiO NPs synthesized from <i>Cocos nucifera</i>	–	–

Reaction conditions: imine (0.14 mmol), catalyst (1 mg), EtOH (2 ml), hydrogen donor (0.13 mmol), NaOH (0.05 mmol), pH = 8, Time (2 h).

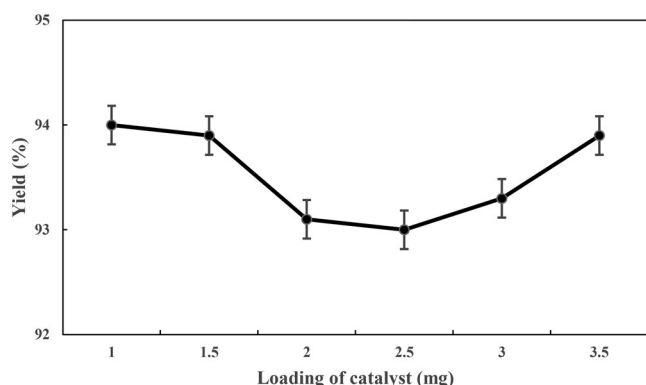


Figure 1. Yield of the reduction of imine 1a with various amounts of catalyst (biosynthesized NiO nanoparticles) loading.

Tirunelveli, Tamil Nadu, India. Nickel chloride hexahydrate (NiCl₂·6H₂O), 4-Chlorobenzaldehyde (C₇H₅ClO) and Sodium hydroxide (NaOH) were purchased from SRL chemicals. Ammonium formate (HCOONH₄) was purchased from Loba chemicals. 4-Methoxybenzaldehyde (C₈H₈O₂) and 4-Nitroaniline (C₆H₆N₂O₂) were purchased from SD Fine chemicals. Aniline (C₆H₅NH₂) and 4-Chloroaniline (C₆H₄ClN) were purchased from Nice chemicals, India. 4-Methylbenzaldehyde (C₈H₈O) was purchased from Alfa Aesar. 2-Hydroxybenzaldehyde (C₇H₆O₂) was purchased from Avra chemicals, India. All the reagents used were of AR Grade. All aqueous solutions were made up of double distilled water.

Synthesis of NiO nanoparticles

Nickel Oxide nanoparticles with size 51 nm were prepared from the aqueous immature fruit extract of *Cocos nucifera* plant and characterized as reported by us.^[17]

Table 2. Reduction of imine 1a in different solvents.

Entry No.	Solvents	Yield (%)
a	Ethanol	94
b	Tetrahydrofuran	–
c	Methanol	75
d	Dichloromethane	–
e	Water + ethanol (1:1 ratio)	59
f	Acetonitrile	–

Reaction conditions: imine (0.14 mmol), Biosynthesized NiO nanoparticles (1 mg), solvent (2 ml), ammonium formate (0.13 mmol), NaOH (0.05 mmol) dissolved in 2 ml water, Temp. 45 °C, Time (2 h).

Synthesis of imines

Imine substrates were synthesized based on the two reported literatures (A and B)^[18,19] and the products were recrystallized from organic solvents and the formation of imines were confirmed by FT-IR, ¹H and ¹³C NMR studies.

Method A: 1:1.2 molar ratio of aromatic aldehyde and amine were dissolved in ethanol and stirred at room temperature to form the product.

Method B: 1:1.2 molar ratio of aldehyde and amine were mixed and treated under microwave irradiation [MW power level 40% (~150–180 °C) for 5–20 min].

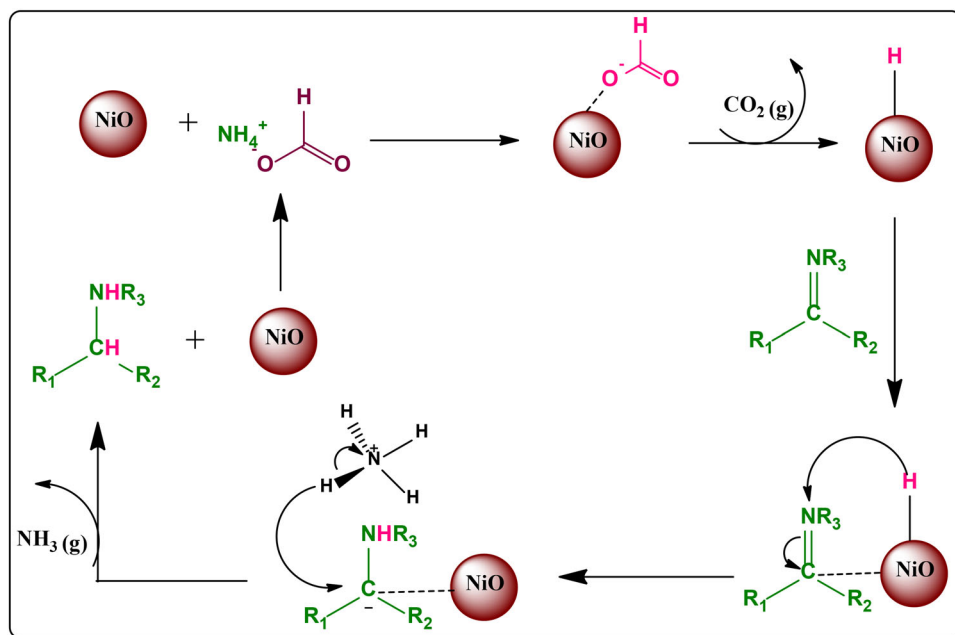
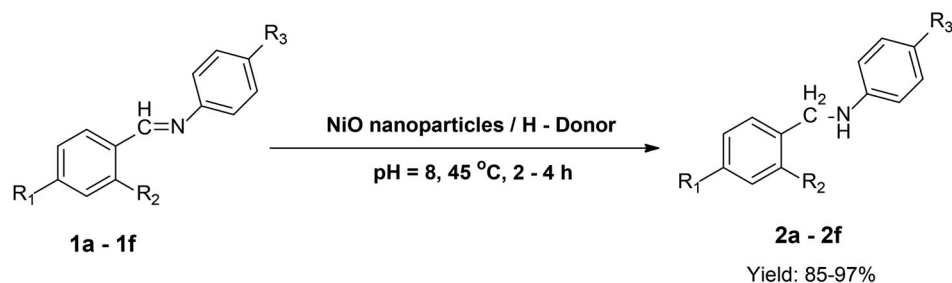
Catalytic activity of NiO NPs on the reduction of aromatic imines

Imine 1a (30 mg, 0.14 mmol), biosynthesized NiO nanoparticles (1 mg) and ammonium formate (0.13 mmol), ethanol (2 ml) were mixed and stirred in a magnetic stirrer. NaOH (0.05 mmol) in 2 ml of water was added to the reaction mixture to maintain the pH at 8 and heated to about 45 °C. Completion of the reaction was confirmed by checking TLC. Then, the catalyst was removed through centrifugation and the organic layer was evaporated. The crude product was extracted with ethyl acetate and dried using anhydrous sodium sulfate. All the products were purified using column chromatography.

Table 3. Reduction of imine **1a** at different temperatures.

S. No.	Temperature (°C)	Yield (%)
i	Room temperature	56
ii	35	61
iii	40	69.3
iv	45	94
v	50	93.8
vi	55	93.5
vii	60	94

Reaction conditions: imine (0.14 mmol), Biosynthesized NiO nanoparticles (1 mg), Ethanol (2 ml), ammonium formate (0.13 mmol), NaOH (0.05 mmol), pH = 8, Time (2 h).

**Scheme 2.** Proposed mechanism for the reduction of aldimines.

Characterization

FT-IR spectra of the products were recorded at room temperature on IR affinity (FT-IR spectrophotometer, Shimadzu, ANJA College, Sivakasi, Tamil Nadu, India) ranging from 4000 to 400 cm^{-1} . Proton and carbon NMR was recorded at 400 MHz (Bruker) at VIT University, Vellore and Avance III HD Nanobay 400 MHz FT-NMR spectrometer at Gandhigram rural institute, Dindigul, Tamil Nadu, India. Mass spectrometer was recorded using the instrument Q-TOF at Pondicherry University, Puducherry, India.

Results and discussion

Biosynthesized NiO nanoparticles from the aqueous extract of immature fruit of *Cocos nucifera* was used for the

reduction of aromatic imines to study its catalytic activity using ammonium formate as the hydrogen donor at basic pH. At trial, we have synthesized (*E*)-*N*-(4-chlorobenzylidene)aniline (**1a**) and tried to reduce the C=N bond of the imine using biosynthesized NiO NPs as catalyst and ammonium formate as the hydrogen donor. Encouraged by getting 71% yield of the secondary amine **1b** from the trial experiment [Reaction condition^[17]: Imine **1a** (0.14 mmol), EtOH (2 ml), catalyst (1 mg), ammonium formate (0.3 mmol), NaOH (0.15 mmol), Temp 60 °C, pH =10], we further proceeded the reaction to fine tune the reaction conditions. For this purpose, (*E*)-*N*-(4-chlorobenzylidene)aniline (**1a**) was taken as the ideal compound to improve the reaction parameters (Scheme 1). When the pH of the reaction mixture was maintained at 8 by reducing the amount of sodium hydroxide (0.05 mmol) and ammonium formate

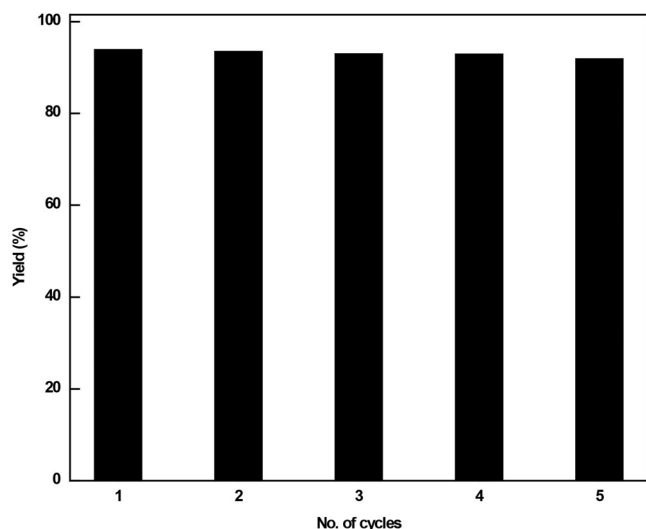


Figure 2. Recycling of the NiO nanoparticles catalyst.

(0.13 mmol), the yield of the product **1b** was improved to 94%.

Further, catalyst screening experiments were conducted under similar reaction conditions to prove the better catalytic proficiency of the biosynthesized NiO nanoparticles (Table 1). All the reactions were monitored by TLC for the product confirmation. Attractively, biosynthesized NiO nanoparticles from the immature fruit of *Cocos nucifera* (entry 2) was capable of reducing maximum amount of reactant to give the promising yield (94%) of amine (**1b**) whereas chemically synthesized NiO nanoparticles^[20] (entry 5) gave only 78% yield which proved that the biomolecules that acted as the stabilizing agents on the surface of NiO nanoparticles have the influence to increase the yield of the reaction.

The reaction didn't proceed in the absence of the catalyst (entry 6) and in the absence of hydrogen donor (entry 7). Reduction catalyzed by Cys capped Ni nanoparticles^[21] (entry 4) gave 69% conversion. When the metal precursor salt (Nickel chloride) was used for the hydrogenation of Schiff bases, no product formation was recorded.

Having obtained the good yield of the reduction of imine using biosynthesized NiO nanoparticles, the effect of varying the amount of catalyst on the reduction was examined. It was found that increasing the amount of catalyst loading didn't increase the yield of the reaction (Figure 1).

Further, the reaction was optimized by using various solvents (Table 2). All the reactions were carried out using 2 ml of the chosen solvent and 2 ml of water in which NaOH was dissolved. The reaction moved smoothly to a maximum with ethanol as solvent (entry a) (94%) whereas no product formation was observed using solvents such as tetrahydrofuran, dichloromethane and acetonitrile. Methanol as solvent gave the amine in 75% yield and water and ethanol mixture (1:1) gave the product in moderate yield (59%).

The effect of temperature on the course of reduction was analyzed. At room temperature, 56% of the reduced product **1b** (Table 3 entry 1) was obtained and the yield of the reaction was increased gradually with the increase in

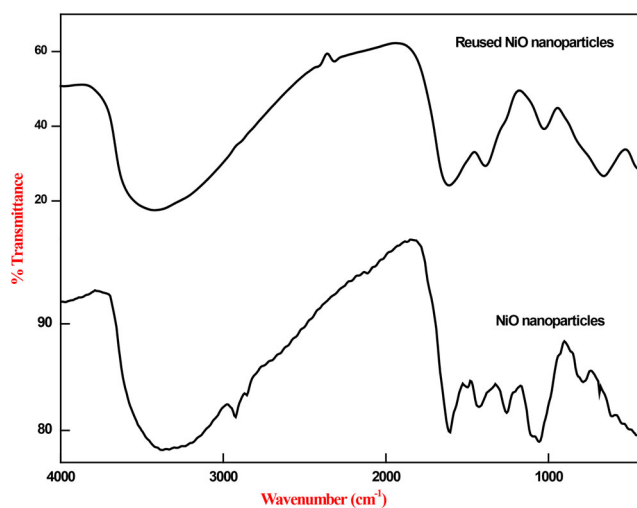


Figure 3. FT-IR spectra of (a) biosynthesized NiO nanoparticles and (b) reused NiO nanoparticles.

Table 4. Reduction of imines 1a-1f using biosynthesized NiO nanoparticles as catalyst.

S. No.	Reactant	Product	Time (h)	Yield (%)
1.	R ₁ =Cl, R ₂ =H, R ₃ =H (1a)	1b	2	94
2.	R ₁ =H, R ₂ =OH, R ₃ =NO ₂ (2a)	2b	4	97
3.	R ₁ =OCH ₃ , R ₂ =H, R ₃ =H (3a)	3b	2	85
4.	R ₁ =CH ₃ , R ₂ =H, R ₃ =H (4a)	4b	2	89
5.	R ₁ =H, R ₂ =OH, R ₃ =Cl (5a)	5b	4	95
6.	R ₁ =NO ₂ , R ₂ =H, R ₃ =Cl (6a)	6b	2	92

Reaction conditions: imine (30 mg), catalyst (1 mg), ammonium formate (0.13 mmol), NaOH (0.05 mmol), Temp. 45 °C.

temperature. After 45 °C, further increase in temperature didn't affect the yield of the reaction (Table 3).

Finally, the reduction of imine **1a** was optimized at 45 °C using ammonium formate as the hydrogen donor and biosynthesized NiO nanoparticles as catalyst and the reaction was done at mild basic conditions (pH = 8) within 2 h, with 94% of yield. The following mechanism was proposed for the reduction of imines (Scheme. 2).

Firstly, hydrogen atom from the hydrogen donor (ammonium formate) co-ordinately bound on the surface of the catalyst to form a complex^[22] which was then reacted with the reactant to supply hydrogen to the C=N of the imine followed by the transfer of hydrogen from ammonium ion to the reactant, thereby forming the product amine. The catalyst was regenerated at final.

Catalyst reusability is an important key tool for analyzing the efficiency of a catalyst. After completion of the reaction, the catalyst was filtered off, washed repeatedly with ethyl acetate, dried and used for further cycles. Even after five cycles of the reaction, the catalyst showed greater activity to reduce imines (>92% yield) (Figure 2). FT-IR spectra of the biosynthesized NiO NPs and the reused NiO NPs catalyst after five cycles were compared. Figure 3 indicates that there is no remarkable change in the IR spectrum of the reused catalyst from the fresh catalyst, thus proved the stability of the catalyst.

Having done the optimization studies, the reduction of various aromatic imines was carried out using biosynthesized NiO nanoparticles as catalyst (Table 4). Imines having

electron withdrawing ($-\text{Cl}$ and $-\text{NO}_2$) and electron donating ($-\text{CH}_3$, $-\text{OCH}_3$ and $-\text{OH}$) groups in their side chains didn't interfere the course of the reaction. The reduction was complete within 2–4 h and the yield of the reaction was in the range of 85–97%.

Conclusion

In summary, an easy and cost-effective protocol was demonstrated for the catalytic transfer hydrogenation of Schiff bases using biosynthesized nickel oxide nanoparticles as heterogeneous catalyst. The influence of various reaction parameters such as catalyst, temperature, solvent and the catalyst loading on the reduction of imines was examined. The results implied that the biosynthesized NiO nanoparticles reduced imines with minimum amount (1 mg) of the catalyst loading and good reusability of the catalyst was demonstrated.

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