


 Cite this: *RSC Adv.*, 2020, 10, 32296

 Received 30th July 2020
 Accepted 19th August 2020

DOI: 10.1039/d0ra06937j

rsc.li/rsc-advances

One-pot reductive amination of carbonyl compounds with nitro compounds over a Ni/NiO composite†

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Easily prepared Ni/NiO acts as a heterogeneous catalyst for the one-pot reductive amination of carbonyl compounds with nitroarenes to afford secondary amines with H₂ as a hydride source. This catalytic system does not require a special technique to avoid air-exposure, in contrast to the common heterogeneous Ni catalysts.

Amines are among the most important organic compounds for the chemical, materials, pharmaceutical and agrochemical industries.¹ In particular, aromatic and heteroaromatic amines occupy a privileged position in medicinal chemistry,^{1,2} as exemplified in top-selling drugs such as atorvastatin, hydrochlorothiazide, furosemide and acetaminophen.³ The general methods to prepare aryl and heteroaryl amines are the reductive amination of carbonyl compounds,⁴ direct alkylation of amines with alkyl halides,⁵ Buchwald–Hartwig amination⁶ and Ullman-type C–N bond formation.⁷ These amination systems utilize aniline derivatives which are usually prepared in advance by hydrogenation of nitroarenes.⁸ Direct amine synthesis using nitroarenes is attractive because it eliminates the hydrogenation step, which saves time, energy and cost. Among the amination reactions, reductive amination has been actively investigated due to its high atom economy and ease of industrial application (Scheme 1);⁹ however, reductive amination has frequently been accompanied by unwanted side products due to the reduction of carbonyl compounds to alcohols and/or over-alkylation of product amines. One-pot reductive amination with nitro compounds has been achieved by precious metal catalysis.¹⁰ Recently, precious metal alloy nanoparticles were demonstrated to exhibit high catalytic performance for one-pot reductive amination with nitro compounds, even under mild reaction conditions.¹¹ In the context of economic efficiency and a ubiquitous element strategy, the replacement of precious metals with earth-abundant metals has gained much attention. Although some catalytic systems based on Fe,¹² Cu,¹³ Co¹⁴ and

Mo¹⁵ have been reported using H₂ as a reductant, severe reaction conditions are typically required (Table S1, ESI†). It is noteworthy that the nitrogen-doped carbon supported cobalt catalysts were reported to be active for one-pot reductive amination using nitroarenes using formic acid or CO/H₂O as a reductant though high temperature was required (Table S2, ESI†).¹⁶

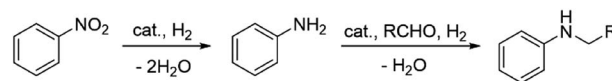
To develop active catalysts for one-pot reductive amination using nitro compounds, we have focused on nickel catalysts, which are known as active catalysts for many transformation reactions.^{17,18} The active species is typically metallic nickel, which is easily oxidized in air and becomes covered with NiO.¹⁹ Therefore, special techniques to avoid air-exposure (*i.e.*, pre-reduction in the reaction vessel, glovebox) are required to achieve high catalytic performance for liquid phase reactions. Herein we report an easily prepared Ni/NiO composite as a heterogeneous catalyst for one-pot reductive amination using nitro compounds. This Ni catalyst can be handled under an air atmosphere, even though the supposedly active species, metallic nickel, is oxidized by air-exposure.

Ni/NiO was prepared by the partial reduction of NiO with H₂ in the temperature range from 200 to 500 °C (Ni/NiO-X: X = reduction temperature). X-ray diffraction (XRD) patterns of the prepared Ni catalysts after exposure to air are summarized in Fig. 1(A). When NiO is treated in H₂ at 200 °C, the dominant phase produced is still nickel oxide. Metallic nickel was formed by reduction at ≥250 °C, which is consistent with the H₂-

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra06937j



- High atom economy
- Use of readily available nitroarenes
- Skipping separation and purification of aniline derivatives

Scheme 1 One-pot reductive amination using nitroarenes.



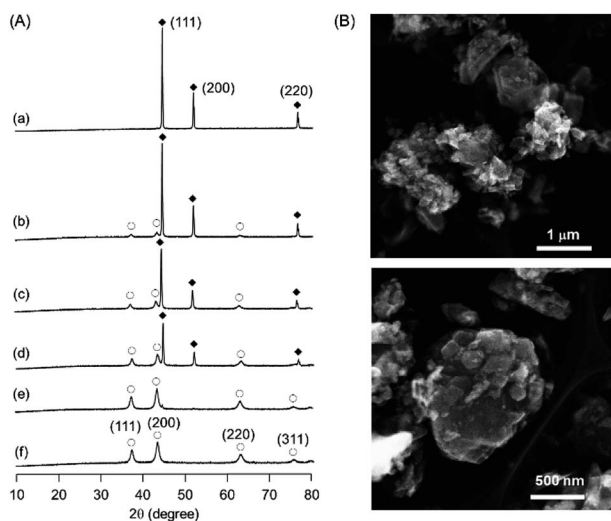


Fig. 1 (A) XRD patterns for Ni/NiO-X; (a) Ni/NiO-500, (b) Ni/NiO-400, (c) Ni/NiO-350, (d) Ni/NiO-300, (e) Ni/NiO-250, and (f) Ni/NiO-200 (◆: Ni, ○: NiO), and (B) SEM images of Ni/NiO-300.

temperature programmed reduction (H_2 -TPR) profile of NiO in which the H_2 consumption peak begins to increase at around 250 °C.²⁰ The ratio of Ni to NiO, determined by Rietveld analysis, increased with increasing reduction temperature and no peaks attributed to metallic nickel were evident for Ni/NiO-500 (Table 1). The Brunauer-Emmett-Teller (BET) specific surface area of Ni/NiO was decreased by the reduction treatment with H_2 (Table 1). The decrease of the specific surface areas is due to the aggregation of Ni particles during reduction, as evidenced by scanning electron microscopy (SEM) images of Ni/NiO-X (Fig. S3, ESI[†]) and crystallite diameter estimated from (111) diffraction lines using Scherrer's equation (Table S3, ESI[†]). Fig. 1(C) shows an SEM image of Ni/NiO-300, where the particle size was estimated to be 0.5–3 μm , and the layered structure of NiO was maintained after the reduction treatment (see also Fig. S4, ESI[†]).

The one-pot reductive amination of benzaldehyde (**2a**) with nitrobenzene (**1a**) was evaluated with the prepared Ni catalyst using molecular hydrogen as the reductant (Table 2). In addition to the desired secondary amine **3aa**, aniline, benzyl alcohol

Table 1 Specific surface areas and weight ratios of Ni to NiO

Entry	Catalyst	Specific surface area ^a ($\text{m}^2 \text{g}^{-1}$)	Weight ratio ^b (%)	
			Ni	NiO
1	Ni/NiO-200	82	—	100
2	Ni/NiO-250	78	2	98
3	Ni/NiO-300	41	43	57
4	Ni/NiO-350	25	66	34
5	Ni/NiO-400	10	85	15
6	Ni/NiO-500	<5	100	—

^a Specific surface areas were obtained from BET measurements.

^b Weight ratios were obtained by Rietveld analysis.

Table 2 Catalyst screening^a

Entry	Catalyst	Conv. of 1a (%)	Yield of 3aa (%)	Yield of 4aa (%)
1	Ni/NiO-200	24	—	—
2	Ni/NiO-250	22	—	4
3	Ni/NiO-300	>99	77	5
4 ^b	Ni/NiO-300	>99	92	—
5 ^c	Ni/NiO-300	>99	89	—
6	Ni/NiO-350	>99	62	2
7	Ni/NiO-400	82	9	30
8	Ni/NiO-500	16	—	6
9	Ni/Nb ₂ O ₅	>99	12	51
10	Ni/TiO ₂	36	—	27
11	Ni/SiO ₂	>99	73	17
12	Ni/ZrO ₂	>99	25	33
13 ^d	RANEY® Ni ^e	>99	—	22
14	NiO	23	—	—
15	Ni(OH) ₂	20	—	—

^a Reaction conditions: catalyst (0.05 g), **1a** (1 mmol), **2a** (1 mmol), toluene (5 mL), H_2 (1 MPa), 80 °C, 20 h. Conversion and yield were determined by GC analysis. ^b 1.2 mmol of **2a** and 1 mL of toluene were used. ^c Run at 0.5 MPa H_2 pressure for 50 h. ^d Methanol was used as a solvent. ^e Generated by the treatment of RANEY® alloy with NaOH.

and imine intermediate **4aa** were observed in the reaction mixture by gas chromatography (GC) analysis. The catalytic activity of the Ni/NiO catalyst was strongly affected by the reduction temperature during catalyst preparation with Ni/NiO-300 showing the highest activity (entry 2). The lack of activity for Ni/NiO-200 can be rationalized by insufficient reduction, as evident from the XRD pattern (entry 1). In addition, a low yield of **3aa** was obtained with the catalysts prepared by reduction at elevated temperatures (entries 6–8). The lower activities of Ni/NiO-350, -400 and -500 were probably due to smaller amounts of active sites due to the reduction of the surface area and/or the aggregation of metallic Ni particles (Tables 1 and S3[†]). For comparison of Ni/NiO with simple supported Ni catalysts, one-pot reductive amination was conducted over Ni catalysts supported on simple metal oxides of Nb₂O₅, TiO₂, SiO₂ and ZrO₂ (entries 9–12). Ni/SiO₂ exhibited comparable activity to Ni/NiO (entry 9); however, significant leaching (3.9%) of the Ni species was observed in the reaction mixture, as opposed to that with Ni/NiO-300 (0.1%). Although RANEY® Ni is known to be active for reductive amination,²¹ **3aa** was obtained only in 22% yield under the present reaction conditions (entry 13). No desired product was observed using unreduced NiO and Ni(OH)₂²² (entries 14 and 15). In the case of the reactions with low material balances such as Ni/NiO-400, Ni/Nb₂O₅ and Ni/ZrO₂, we observed benzyl alcohol as a main byproduct, suggesting that the hydrogenation of aldehydes is the competitive side reaction. Because of the high selectivity of Ni/NiO-300, NiO

support can contribute to suppress the hydrogenation of aldehyde. Further optimization was then conducted (Table S2, ESI†). The yield of **3aa** was finally increased to 92% under higher concentration conditions using 1.5 equivalents of **2a** (entry 4). Reductive amination proceeded even under lower hydrogen pressure (0.5 MPa), although a longer reaction time was required (entry 5). The lower loading of Ni/NiO (15 mg) was accomplished by prolonging the reaction time, affording **3aa** in 90% yield (entry 10, Table S4†).

The reusability of Ni/NiO-300 was examined next. The used Ni/NiO-300 could be recovered from the reaction mixture by simple filtration, washing with methanol, and drying at 90 °C. The XRD patterns and the ratio of Ni to NiO were not changed during one-pot reductive amination (Fig. S2, ESI†). The SEM images of the recovered catalyst indicates that morphological changes were negligible (Fig. S6, ESI†). The recovered Ni/NiO catalyst was reactivated by pre-treatment (150 °C, 1 h under H₂ flow), by which the catalytic activity was maintained at a high level without obvious decline, even after the 3rd reuse (Fig. 2(A)).

A time-course analysis was then conducted under the optimized conditions (Fig. 2(B)). Aniline was generated by the hydrogenation of nitrobenzene, and imine **4aa** was then gradually formed through the dehydrative coupling of **2a** with aniline. Hydrogenation of **4aa** subsequently afforded the secondary amine **3aa**. To determine which step is key for the one-pot reductive amination, each step was examined using Ni/NiO-300 and Ni/SiO₂, respectively. Imine formation step proceeded smoothly even without catalyst (Table S5, ESI†). For the hydrogenation of **1a**, Ni/NiO and Ni/SiO₂ gave the comparable results (Table S6, ESI†). For the imine hydrogenation step, we observed the higher activity of Ni/NiO than Ni/SiO₂ (Fig. 3 and Table S7†). With these results, the high hydrogenating ability of

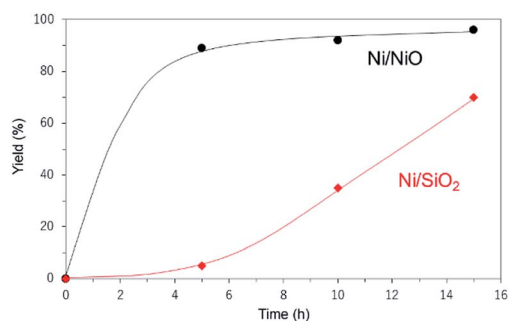


Fig. 3 Hydrogenation of **4aa** over Ni/NiO and Ni/SiO₂. Reaction conditions: catalyst (0.05 g), **4aa** (1 mmol), toluene (1 mL), H₂ (1 MPa), 80 °C.

Ni/NiO for imine hydrogenation is the key for the high activity on one-pot reductive amination.

Ni/NiO-300 could be applied to the one-pot reductive amination of other substrates (Table 3). A number of functional

Table 3 Substrate scope^a

$\text{R-NO}_2 + \text{O=C-R}' \xrightarrow[\text{80 } ^\circ\text{C, 20 h}]{\text{Ni/NiO-300, H}_2 \text{ (1 MPa), toluene}} \text{R-NH-CH}_2\text{-R}'$			
Entry	1	2	Isolated yield of 3 (%)
1 ^b		2a	93
2 ^c		2a	74
3		2a	88
4		2a	82
5 ^c	1a		62
6 ^{b,c}	1a		94
7 ^b	1a		98
8 ^d	1a		75
9 ^d	1a		21 ^e

^a Reaction conditions: Ni/NiO-300 (0.05 g), **1a** (1 mmol), **2a** (1.2 mmol), toluene (1 mL), H₂ (1 MPa), 80 °C, 20 h. ^b Run at 100 °C. ^c Run for 40 h. ^d Run at 120 °C for 96 h. ^e NMR yield.

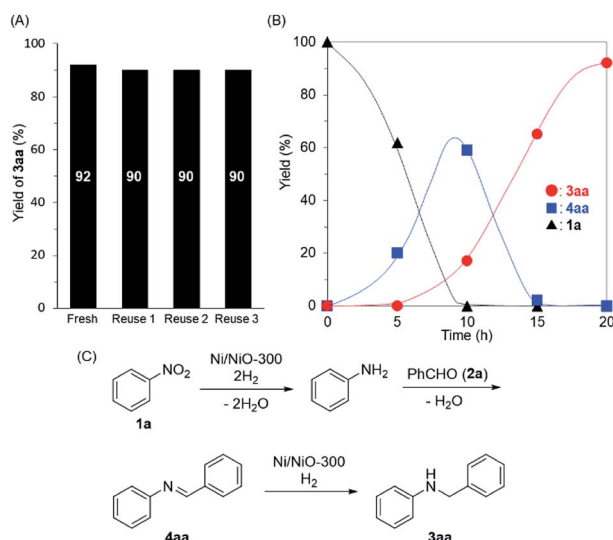


Fig. 2 (A) Reuse experiments. Reaction conditions: Ni/NiO-300 (0.05 g), **1a**, (1 mmol), **2a**, (1.2 mmol), toluene (1 mL), H₂ (1 MPa), 80 °C, 20 h. (B) Time course of the one-pot reductive amination over Ni/NiO-300. Reaction conditions: Ni/NiO-300 (0.05 g), **1a** (1 mmol), **2a** (1.2 mmol), toluene (1 mL), H₂ (1 MPa), 80 °C. (C) Reaction pathway for one-pot reductive amination over Ni/NiO-300.

groups, such as ether, ester, chloro and bromo groups proved to be compatible with this catalytic system. The reaction was not sensitive to the steric environment of the nitro group, but was sensitive to that of the formyl group (entries 4 and 8). Electron-donating groups retarded the imine hydrogenation step and thus required higher reaction temperatures (entries 1 and 5). On the other hand, longer reaction times were necessary for the electron-withdrawing group on nitrobenzene derivatives due to the weak nucleophilicity of the aniline intermediates (entry 2). Indeed, imine formation is delayed by electron-withdrawing group on aniline derivative (Table S5†). The electron-withdrawing group on the benzaldehyde derivative retarded reductive amination, although it could facilitate both imine formation and imine hydrogenation (entry 6). Aliphatic aldehyde was also applicable though the yield was low due to the decomposition of aldehyde (entry 9).

The surface of metallic Ni is easily oxidized in air; therefore, the surface states of Ni/NiO-300 were analysed by X-ray photoelectron spectroscopy (XPS) and the results are shown in Fig. 3. In the Ni 2p region of the spectrum for Ni/NiO-300, the main $2p_{3/2}$ peak is observed at 856.1 eV, which is assignable to $\text{Ni}(\text{OH})_2$.²³ The catalyst was exposed to ambient conditions; therefore, hydroxylation of the surface was inevitable.²⁴ Similarly, NiO and RANEY® Ni were also covered with $\text{Ni}(\text{OH})_2$ after exposure to ambient conditions (Fig. 4). Considering the lack of activity for NiO and the low activity of RANEY® Ni for one-pot reductive amination (Table 1, entries 13 and 14), the boundary region among Ni, NiO and $\text{Ni}(\text{OH})_2$ is considered to be crucial for high catalytic performance. The lack of a metallic Ni peak (852.6 eV)²⁵ in the XPS spectrum suggests that Ni^{2+} species covers the catalyst surface. This is the reason why Ni/NiO can be handled under an air atmosphere, in contrast to common heterogeneous Ni catalysts.

In summary, Ni/NiO acts as a catalyst for one-pot reductive amination with nitro compounds to afford the secondary amines. No special technique (pre-reduction in the reaction vessel or glovebox) is required in the reaction setup. The reaction could proceed under milder conditions than those reported for typical catalytic systems. Ni/NiO could be reused without any significant loss of activity. This catalytic system could be applied to a variety of substrates that bear functional groups.

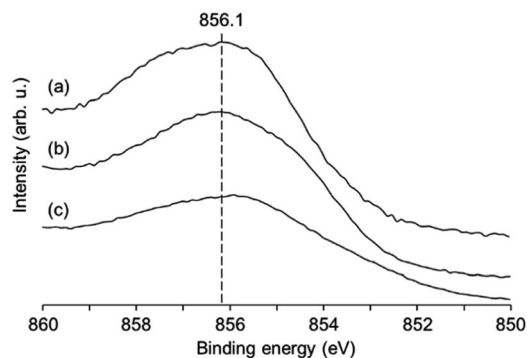


Fig. 4 Ni 2p XPS spectra for (a) Ni/NiO-300, (b) NiO, and (c) RANEY® Ni after exposure to ambient conditions.

Mechanistic studies suggested that $\text{Ni}(\text{OH})_2$ on metallic nickel can exhibit catalytic activity toward the present one-pot reductive amination. These results provide new insights into the development of heterogeneous Ni catalysts.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by the Advanced Low Carbon Technology Research and Development Program (ALCA) of the Japan Science and Technology Agency (JST) (JPMJAL1205). A part of this work was supported by the Nagoya University microstructural characterization platform as a program of the “Nanotechnology Platform” of the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT).

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