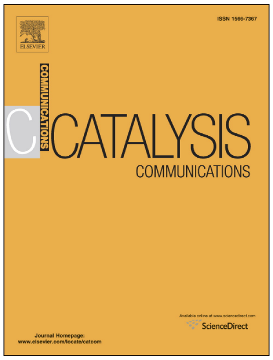

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Synthesis of secondary amines by reductive amination of aldehydes with nitroarenes over supported copper catalysts in a flow reactor

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Abstract

Supported copper catalysts were investigated for the one-pot reductive amination of aldehydes with nitroarenes in a continuous flow reactor. This process is considered advantageous compared to current traditional methods, which present several drawbacks, such as toxicity of reducing or alkylation agent, lack of monoalkylation selectivity and large amounts of waste produced. Various secondary amines were synthesized in good to excellent yields in the reactions of aliphatic aldehydes with nitroarenes using molecular hydrogen as a reducing agent. It was found that the yield of secondary amine depends on the rate of formation of intermediate imine.

Keywords: one-pot reductive amination, aldehyde, nitroarene, supported copper catalyst, continuous flow reactor, molecular hydrogen.

1. Introduction

Secondary amines are important compounds in the chemical industry and are extensively used for the production of pharmaceuticals, agrochemicals and fine chemicals [1]. Traditional methods for their synthesis include reduction of nitroarenes to corresponding anilines [2] and further reaction with alkyl halides, alcohols or carbonyl compounds [3]. However, these processes have significant drawbacks, such as toxicity of reducing or alkylation agents, lack of monoalkylation selectivity and large amounts of waste produced. Hence, there is a continuing interest in cost-effective and environmentally friendly synthesis of secondary amines [4,5].

One-pot reductive amination of aldehydes with nitroarenes over heterogeneous catalysts using molecular hydrogen or other “green” reducing agents is an atom-economical and environmentally attractive method for the synthesis of secondary aromatic amines [6–21]. This process involves three cascade reactions: hydrogenation of nitroarene into primary aromatic amine, reversible condensation of primary amine with aldehyde to imine, and hydrogenation of imine to the desired secondary amine. In general, the reaction is realized in the presence of noble metal-based catalysts, such as Pd [6–11], Pt [11,12] and Au [13–16]. However, the high price and limited availability of these precious metals have spurred interest in heterogeneous catalysis utilizing more earth-abundant metal alternatives.

Recently, reductive amination of aldehydes with nitroaromatic compounds over Fe- and Co-based catalysts has been described [17–22]. The catalysts comprised of Fe_2O_3 particles [17], Co/Co_3O_4 nanocomposites [18], and Co nanoparticles [19–22] embedded in mesoporous nitrogen-doped carbon were found to be active and selective in this reaction. However, the use of expensive organic compounds, such as 1,10-phenanthroline [17,18], 2-methylimidazole [20,22] and phthalocyanine [21,23] for catalyst preparation hinders the application of these materials.

Heterogeneous copper catalysts are attractive for the one-pot synthesis of secondary amines from aldehydes and nitroarenes due to their activity in hydrogenation of nitroarenes (e.g., nitrobenzene [24], nitrotoluenes [24] and chloronitrobenzenes [25, 26]) and reductive amination of carbonyl compounds with anilines [27]. In addition, a range of N,N-dimethylanilines was synthesized with high yields in the reaction of nitroarenes with H_2 and HCHO over skeletal Cu catalyst [28]. However, Cu-based catalysts have not been tested for the synthesis of secondary amines through a reductive amination of carbonyl compounds with nitroarenes.

Generally, the reductive amination of aldehydes with nitroarenes is performed in batch reactors [6-13, 16-22]. Meanwhile, continuous-flow synthesis has emerged in recent years as an attractive alternative to more traditional batch protocols. Potential benefits of flow chemistry include an enhanced safety profile, superior interfacial mass and energy transfer properties, reducing the formation of the side products through a better control over process variables, and shortening the development time from laboratory to final production levels [29,30]. Herein, the behavior of supported copper-based catalysts in the reductive amination of aldehydes with nitroarenes has been studied using a continuous flow reactor and hydrogen as a reducing agent. The facile synthetic procedure and the most common supports, such as silica and γ-alumina, have been used to prepare the Cu-containing supported catalysts.

2. Experimental

2.1 Chemicals

Copper(II) nitrate trihydrate (99 %), nitrobenzene (99%), *o*-chloronitrobenzene (99+%), *p*-chloronitrobenzene (99%), *p*-bromonitrobenzene (99%), *p*-nitroanisole (99+%), *o*-nitrotoluene (99+%), *m*-nitrotoluene (99%), *p*-nitrotoluene (99%), *n*-heptanal (95%), 3-phenylpropionaldehyde (95%), benzaldehyde (98+%), *p*-anisaldehyde (99+%), *p*-chlorobenzaldehyde (98.5+%), *p*-tolualdehyde (99+%), 2-heptanone (98%) and *n*-decane (99+%) from Acros Organics, as well as *n*-dodecanal (95%) from Sigma-Aldrich, were used without additional purification. Toluene (99.5%, ECOS (Russia)), methanol (99.8%, J.T. Baker), tetrahydrofuran (THF, ≥99.9%, Sigma-Aldrich) and isopropanol (≥99.7%, Sigma-Aldrich) were employed as solvents.

The γ-alumina support was prepared by extrusion of a paste obtained by mixing of aluminum oxide (Puralox TH 100/150, Sasol), aluminum hydroxide (Disperal, Sasol) and aqueous solution of nitric acid as described earlier [15]. The silica (KSKG) was supplied from KhromAnalit (Russia).

2.2 Catalyst preparation

Supported copper catalysts were prepared by impregnating the support (grain size of 250–500 μm) with an aqueous solution of copper (II) nitrate followed by drying at 70 °C under vacuum and calcination in air at 300 °C for 3 h. Then the solids were cooled to room temperature, purged in N_2 and then stored in a glass flask before being used.

2.3 Catalyst characterization

The copper content was analyzed by XRF using an ARL instrument. Textural characteristics were determined from nitrogen adsorption-desorption isotherms (77 K) obtained on a Micromeritics ASAP 2400 analyzer. Powder XRD patterns were obtained on a Bruker D8 diffractometer (Cu Kα radiation) equipped with a LynxEye position sensitive detector.

2.4 Catalysts performance

The catalytic activity was investigated under continuous-flow conditions in an H-Cube Pro^{TM} setup (Thalesnano, Hungary) equipped with packed-bed reactors CatCart®30 (length of 30 mm, inner diameter of 4 mm) [15]. Before each catalytic run, the catalyst (0.200 g, CuO/Al_2O_3) was reduced in a mixture of hydrogen with toluene at T=120 °C and P=50 bar for 1 h (flow rates of toluene and H_2: 0.5 and 60 mL min^{-1}, respectively). The inlet was then switched to the flask containing the solution of nitroarene (0.025 M) or nitroarene (0.025 M) and aldehyde (0.0375 M) in toluene. This point in time was chosen as the starting point of the reaction. The catalytic tests were carried out in the 110–125 °C range, 50 bar hydrogen pressure, where liquid and hydrogen feed rates were set to 0.35 and 60 mL min^{-1}, respectively. As a result of special tests, there was no influence of external or internal mass transfer limitations under the conditions used [31]. The performance of a given catalyst was evaluated by analysis of the samples taken 40–45 min after the start of the experiment. Conversion, selectivity and yield were determined by GC (Agilent 6890N instrument with a HP 5-MS capillary column 60m×320μm×0.25μm) and *n*-decane was used as the internal standard. The reaction products were identified by GC–MS (Agilent 7000B Triple Quad System) as well as comparing the GC retention times with the authentic compounds [14].

2.5 Catalyst regeneration

The spent catalyst was washed with a mixture of toluene and isopropanol (1:2 v/v) for 30 min (flow rate of 0.5 mL min^{-1}) and dried in vacuum at 100 °C for 2 h. Afterwards, the catalyst sample was heated in an air oven from room temperature to 330 °C at a heating rate of 5 °C min^{-1} and maintained at this temperature for 2 h [15].

3. Results and Discussion

3.1 Catalyst preparation and characterization

Supported CuO/Al_2O_3 and CuO/SiO_2 samples containing approximately 5 wt.% Cu were prepared by the incipient wetness impregnation of γ-alumina and silica grains with an aqueous solution of copper (II) nitrate with a subsequent drying at 70 °C under vacuum and calcination in air at 300 °C for 3 h. The copper content and textural characteristics of the catalysts are presented in Table 1. It was found that the CuO phase of these materials can be reduced to supported metallic copper by a mixture of hydrogen with toluene at 120 °C and 50 bar in a flow reactor. The characteristic peaks of metallic copper can be seen in the XRD pattern of pre-reduced catalysts that confirms the reduction of CuO phase to supported metallic copper under the conditions used (Fig. 1 and Electronic Supplementary Information, ESI). The optimal pre-reduction time is 60 min (see ESI).

3.2 Catalytic performance

The catalytic performance of the pre-reduced Cu/Al_2O_3 and Cu/SiO_2 solids have been evaluated for the liquid-phase hydrogenation of nitroarenes to anilines, which is the first stage of one-pot synthesis of secondary amines. The Cu/Al_2O_3 catalyst is shown to provide a highly selective hydrogenation of nitroarenes containing –Cl, –Br and –OCH_3 group to the corresponding anilines (Table 2, entries 3–10). Hydrogenation of nitroarenes containing –Cl and –Br substituents occurs more slowly than in the case of nitrobenzene and *p*-nitroanisole. Moreover, the use of methanol instead of toluene results in a significant increase in the hydrogenation rate (Table 2, entries 5 and 7). The Cu/SiO_2 catalyst exhibits a much lower activity than Cu/Al_2O_3 (Table 2, entries 11 and 12), and this could be attributed to the faster adsorption of *o*-chloronitrobenzene through the nitro group on γ-alumina than on silica [32,33].

Encouraged by the good activity of Cu/Al_2O_3 catalyst for the nitroarene hydrogenation, this catalyst was tested in one-pot reductive amination of aldehydes with nitroarenes in the presence of molecular hydrogen. Since aldehyde could produce the corresponding alcohol in a side reaction [14,15], the reaction was carried out at a 1.5-fold excess of aldehyde. As shown in Table 3, various secondary amines could be obtained over the Cu/Al_2O_3 catalyst with a yield up to 97% using toluene as a solvent. Aliphatic aldehydes (*n*-heptanal, 3-phenylpropionaldehyde and *n*-dodecanal) give higher yields of secondary amine in the reaction with *p*-nitrotoluene as compared with benzaldehyde derivatives (Table 3, entries 3, and 6–15). This result can be explained by the faster interaction between *p*-toluidine formed in the course of the reaction and aliphatic aldehydes, due to the stronger electrophilic properties of the latter [14]. The utilization of ketone (2-heptanone) instead of aldehydes led to the formation of secondary amines in negligible yields, which is connected with the much weaker electrophilic properties of ketones.

The effect of the substituent's nature and its position in nitroaromatic compound on the reductive amination of aldehydes was investigated using the reactions between *n*-heptanal and various nitrobenzenes. It was shown that the introduction of electron-donating substituents ($–CH_3$, $–OCH_3$) in the *para*-position of the nitrobenzene improved the yield of secondary amines (Table 3, entries 1, 3 and 16). At the same time, in the case of nitroarenes with electron-withdrawing substituent (–Cl, –Br), the reduction in the yield of the desired products was observed under the same reaction conditions (Table 3, entries 17 and 18). The observed effect of substituents with the electron-donating or electron-withdrawing properties can be explained by their impact on the nucleophilic properties of the intermediate primary aromatic amines [15]. The position of the substituent in nitroarene structure also has a strong influence on the reaction. Therefore, the yield of secondary amine in the reaction of *n*-heptanal and *o*-nitrotoluene is much lower than with *p*-nitrotoluene and *m*-nitrotoluene (Table 3, entries 3, 19 and 20). It is explained by the weaker nucleophilic properties of *o*-toluidine formed during the reaction due to the steric hindrance effect created by a methyl group in *ortho*-position that leads to a decrease of the imine formation rate through the reaction with aldehyde [15]. Thus, the yield of secondary amine is determined by the rate of imine formation. At the same time, the complete conversion of nitroarenes and low yields of imines (Table 3) indicate a fast hydrogenation of nitroarenes and imines in most of the experiments.

The influence of solvent, hydrogen pressure and pre-reduction duration on the course of the reaction was also studied. The utilization of methanol as a solvent led to a significant decrease in the yield of secondary amines (Table 3, entries 1 and 2), probably due to the higher hydrogenation rate of aldehydes in methanol than in toluene [14]. At the same time, no reaction was observed when THF or isopropanol was used as a solvent. These results can be explained by the fast deactivation of the catalyst during the pre-reduction procedure caused by the hydrogenation of solvent molecules over Cu/Al_2O_3 with the subsequent formation of carbonaceous deposits. Moreover, it was found that a decrease in both the hydrogen pressure (from 50 to 40 bar) and pre-reduction duration (from 60 min to 30 min) leads to a visible reduction in the yield of secondary amines (Table 3, entries 3–5).

In previous studies, we found that 2.5 wt% Au/Al_2O_3 catalyst with a mean gold particle size of 3.4 nm provides the one-pot reductive amination of aldehydes with nitroarenes in a flow reactor [14,15]. The secondary amines were synthesized with a yield up to 99% at 80–100 °C and $P(H_2)$=50 bar. To compare the catalytic performance of supported copper and gold catalysts, the space time yield (STY) of 5.3 wt% Cu/Al_2O_3 and 2.5 wt% Au/Al_2O_3 catalysts were calculated. The STY is defined as the mass of the secondary amine (g) produced during 1 h per mass of metal (g) in the catalyst [34]. As shown in Table 4, STY of the secondary amines for the Cu/Al_2O_3 catalyst was only 3.3–4.1 times lower than those for the Au/Al_2O_3 catalyst.

The evolution of the reaction products over the Cu/Al_2O_3 catalyst in the course of the reductive amination of *n*-heptanal with *p*-nitrotoluene showed a slight deactivation of the catalyst with time-on-stream (Fig. 2), which can be explained by the formation of carbonaceous deposits on the catalyst surface [14,15,35]. The activity of the spent Cu/Al_2O_3 catalyst could be recovered after washing with a mixture of toluene/isopropanol (1:2 v/v) followed by oxidative treatment in air at 330 °C for 2 h (Fig. 3). Importantly, no leaching of Cu from the Cu/Al_2O_3 catalyst or deterioration of its textural structure was detected after reaction and regeneration (Table 1).

4. Conclusions

In summary, inexpensive and easily prepared $Cu/\gamma\text{-}Al_2O_3$ catalyst provided chemoselective hydrogenation of nitroarenes to anilines and one-pot reductive amination of aldehydes with nitroarenes in a continuous flow reactor. Various secondary amines were synthesized in 82–97% yields by one-pot reaction of aliphatic aldehydes with nitroarenes using molecular hydrogen as a reducing agent. The yield of secondary amine is determined by the rate of imine formation.

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Table 1

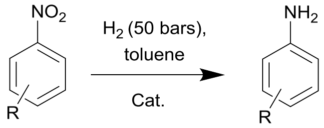
Textural characteristics of supports and supported CuO catalysts.

	Cu Content (wt%)	BET surface area (m^2 g^{-1})	Total pore volume (cm^3 g^{-1})	Mean pore diameter (nm)
γ-Al_2O_3	–	179	0.61	13.7
SiO_2	–	300	0.81	10.6
CuO/Al_2O_3	5.3	169	0.59	13.8
CuO/SiO_2	5.4	260	0.74	11.0
Regenerated CuO/Al_2O_3[a]	5.1	160	0.56	13.6

[a] The catalyst after two cycles (~4 h on-stream) of the reductive amination of *n*-heptanal (0.0375 M) with *p*-nitrotoluene (0.025 M) at 115 °C and 50 bar.

Table 2

Catalytic performance of supported copper catalysts in a flow reactor for the liquid-phase hydrogenation of nitroarenes to anilines.[a]



Entry	Catalyst	R	T (°C)	Conversion (%)	Selectivity (%)
1	Cu/Al_2O_3	H	115	99	99.7
2	Cu/Al_2O_3	H	125	100	100
3	Cu/Al_2O_3	*o*-Cl	115	72	95
4	Cu/Al_2O_3	*o*-Cl	125	99	98
5	Cu/Al_2O_3	*p*-Cl	115	76	100
6	Cu/Al_2O_3	*p*-Cl	125	100	99.5
7[b]	Cu/Al_2O_3	*p*-Cl	115	100	100
8	Cu/Al_2O_3	*p*-Br	125	96	99
9	Cu/Al_2O_3	*p*-OCH_3	115	99	99.8
10	Cu/Al_2O_3	*p*-OCH_3	120	100	99.7
11[c]	Cu/SiO_2	*o*-Cl	115	16	100
12[c]	Cu/SiO_2	*o*-Cl	125	27	100

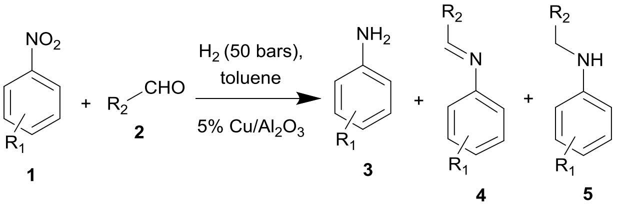
[a] Reaction conditions: nitroarene (0.025 mol L^{-1}), catalyst (200 mg, CuO/Al_2O_3), toluene, 50 bar H_2, pre-reduction time 60 min, reaction time 40–45 min. Conversion and selectivity were determined by GC analysis.

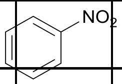
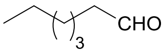
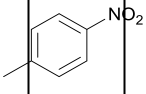
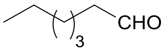
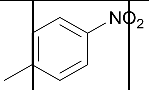
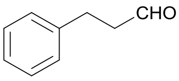
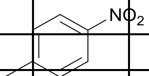
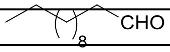
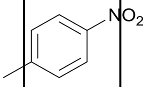
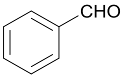
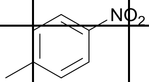
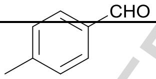
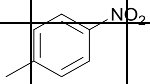
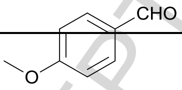
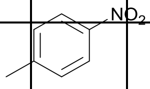
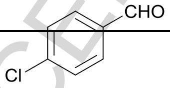
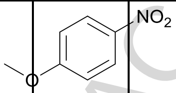
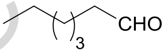
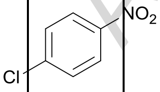
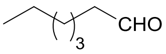
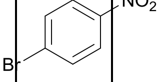
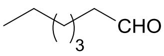
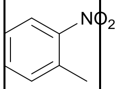
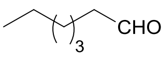
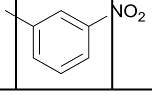
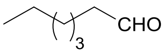
[b] in methanol.

[c] Catalyst loading: 156 mg (CuO/SiO_2).

Table 3

Reductive amination of aldehydes with nitroarenes over the Cu/Al_2O_3 catalyst.[a]



Entry	1	2	T	Conversion	Conversion	Yield (%)[b]		
			(°C)	of **1** (%)	of **2** (%)	**3**	**4**	**5**
1			115	100	100	18	0	82
2[c]			115	100	100	41	0	59
3			115	100	100	9	0	91
4[d]			115	100	99	16	1	83
5[e]			115	100	94	16	2	82
6			105	100	100	16	0	84
7			110	100	100	14	0	86
8			115	100	100	15	0	85
9			125	100	82	12	1	87
10			110	100	95	33	6	61
11			115	100	100	32	1	67
12			120	100	100	32	1	67
13			115	100	100	36	1	63
14			115	100	100	40	0	60
15			125	80	62	16	42	22
16			125	100	100	3	0	97
17			125	74	47	30	33	11
18			125	71	53	42	19	10
19			115	100	100	51	0	49
20			115	100	100	15	0	85

[a] Reaction conditions: **1** (0.025 mol L^{-1}), **2** (0.0375 mol L^{-1}), catalyst (200 mg, CuO/Al_2O_3), toluene, 50 bar H_2, pre-reduction time 60 min, reaction time 40–45 min.

[b] The product yields were calculated based on the nitro-compounds using GC.

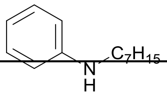
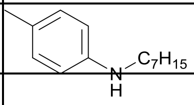
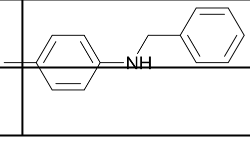
[c] in methanol.

[d] $P(H_2)$=40 bar.

[e] Pre-reduction time: 30 min.

Table 4

Space time yield (STY) of secondary amines for the Cu/Al_2O_3 and Au/Al_2O_3 catalysts.[a]

Entry	Catalyst	Product	T, °C	STY, g g-metal^{-1} h^{-1}
1	5.3% Cu/Al_2O_3		115	7.8
2	2.5% Au/Al_2O_3		80	26.9 [14]
3	5.3% Cu/Al_2O_3		115	9.2
4	2.5% Au/Al_2O_3		80	30.4 [14]
5	5.3% Cu/Al_2O_3		115	6.5
6	2.5% Au/Al_2O_3		80	26.9 [14]

[a] Reaction conditions: nitroarene (0.025 mol L^{-1}), aldehyde (0.0375 mol L^{-1}), toluene, 50 bar H_2.

Figure captions

Fig. 1. Powder XRD patterns of CuO/Al_2O_3 and pre-reduced Cu/Al_2O_3 catalysts.

Fig. 2. Evolution of product yields with time-on-stream for the reductive amination of *n*-heptanal (0.0375 M) with *p*-nitrotoluene (0.025 M) at 115 °C and 50 bar over the Cu/Al_2O_3 catalyst.

Fig. 3. The time dependence of secondary amine yield in the reaction between *p*-nitrotoluene (0.025 M) and *n*-heptanal (0.0375 M) over the as-prepared and regenerated Cu/Al_2O_3 catalysts at 115 °C and 50 bar.

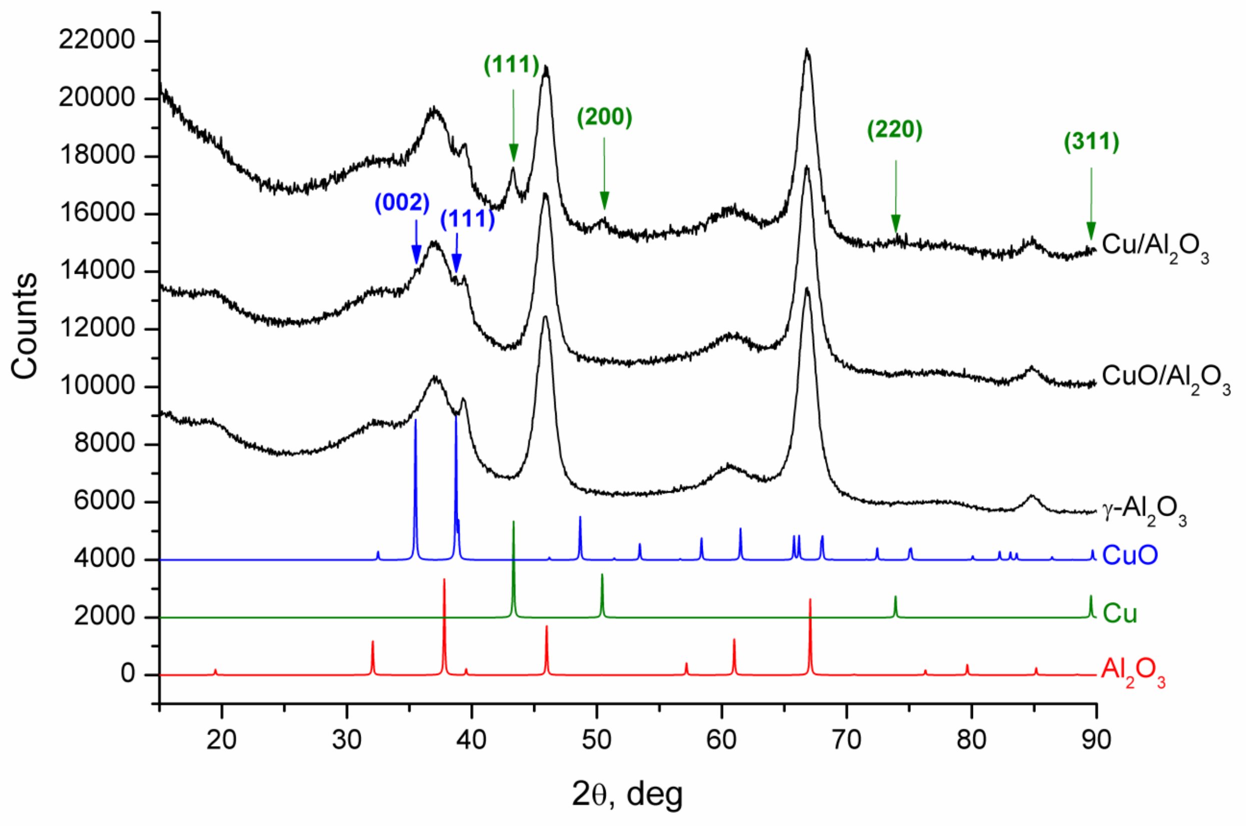

Counts
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
20
30
40
50
60
70
80
90
2θ, deg
(111)
(200)
(220)
(311)
(002)
(111)
Cu/Al2O3
CuO/Al2O3
γ-Al2O3
CuO
Cu
Al2O3

Figure 1

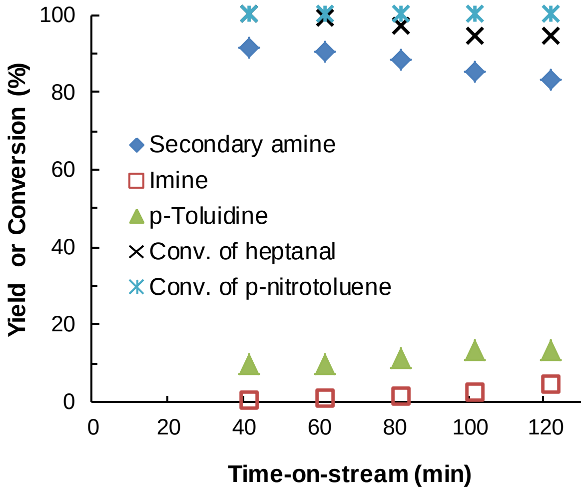

Yield or Conversion (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
Time-on-stream (min)
◆ Secondary amine
□ Imine
▲ p-Toluidine
× Conv. of heptanal
✳ Conv. of p-nitrotoluene

Figure 2

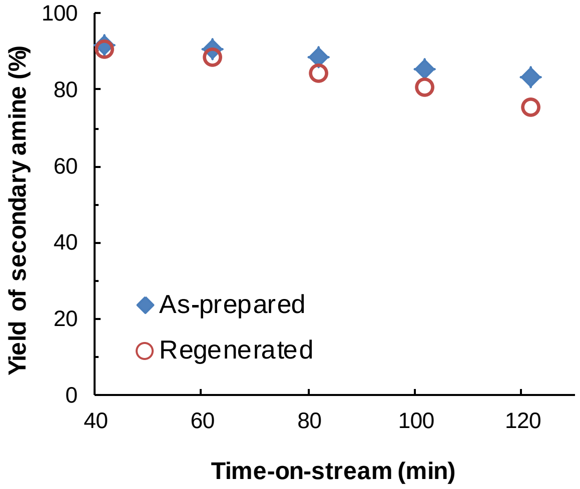
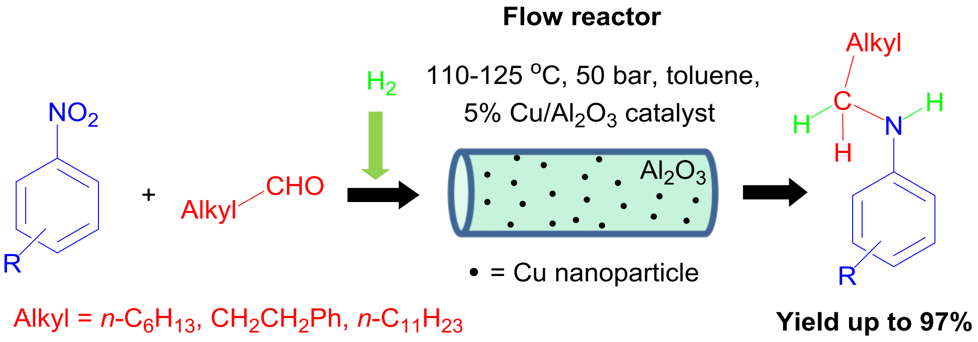

Yield of secondary amine (%)
100
80
60
40
20
0
40
60
80
100
120
Time-on-stream (min)
◆ As-prepared
○ Regenerated

Figure 3



Graphical abstract

Highlights

- Cu/Al_2O_3 catalyst is effective for reductive amination of aldehydes with nitroarenes
- Various secondary amines were obtained in a high yield under flow conditions
- The yield of secondary amine is determined by the rate of imine formation