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Reductive Amination of 5-Hydroxymethylfurfural by the Hydrogenation of Intermediate Imines in the Presence of a Pt/Al_2O_3 Catalyst in a Flow Reactor

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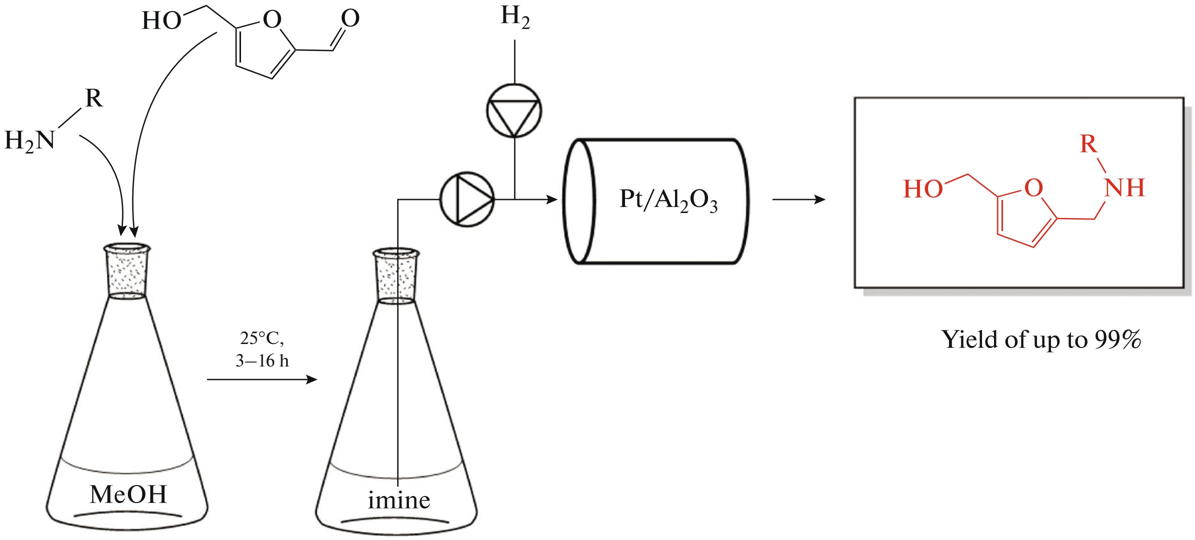
Abstract—The catalytic properties of a platinum catalyst supported on γ-alumina in the hydrogenation of imines formed during the condensation of 5-hydroxymethylfurfural (HMF) with primary amines in methanol have been studied. The reaction has been run in a flow reactor at a hydrogen pressure of 5 bar and a temperature of 15–65ºC. It has been found that the reductive amination of HMF with *n*-hexylamine; aniline; *ortho*-, *meta*-, and *para*-toluidines; and aniline derivatives containing F, Cl, Br, and I substituents at the *para*- or *meta*-positions leads to the formation of N-substituted 5-hydroxymethyl-2-furfuryl amines with high yields (90–99%). At the same time, the reaction of HMF with aromatic amines exhibiting weak nucleophilic properties (*o*-chloroaniline, *p*-aminoacetophenone) provides a target product yield that does not exceed 52%.



Keywords: reductive amination, 5-hydroxymethylfurfural, N-substituted 5-hydroxymethyl-2-furfuryl amines, Pt/Al_2O_3 catalyst, flow reactor, catalytic hydrogenation

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INTRODUCTION

N-substituted 5-hydroxymethyl-2-furfuryl amines are an important class of compounds exhibiting pharmaceutical activity [1–3]. Typically, these amines are synthesized via a reaction of furfuryl alcohol (or furfural) with formaldehyde and primary amines. However, the reaction requires a long-term maintenance of severe conditions (high temperature and pressure), which leads to a low target product yield [4–6]. At the same time, the reductive amination of 5-hydroxymethylfurfural (HMF), which is formed from readily available inedible lignocellulosic biomass, is an attractive method to synthesize aminomethylhydroxymethylfuran (AMHMF) derivatives [2, 3, 7–10].

In a number of recent studies, it has been shown that AMHMF derivatives can be obtained by the

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Abbreviations and designations: HMF, 5-hydroxymethylfurfural; AMHMF, aminomethylhydroxymethylfuran derivatives; HRTEM, high-resolution transmission electron microscopy.

reductive amination of HMF using molecular hydrogen in the presence of the dichlorobis(2,9-dimethyl-1,10-phenanthroline)ruthenium(II) complex [7], a Fe–Ni catalyst on a carbon support [8], Pd/C [9], and Pd nanoparticles supported on a composite material based on a porous coordination polymer [10]. In addition, the reductive amination of HMF was implemented using a CO/H_2O reducing system in the presence of an Au/TiO_2 catalyst [2] and stoichiometric amounts of $NaBH_4$ in the absence of a catalyst [3].

The reductive amination of aldehydes (ketones) with primary amines includes the reversible condensation of a carbonyl compound with an amine to form an imine and the reduction of the imine to a secondary amine. Simultaneously, a side reaction—the reduction of the carbonyl group—can occur. Therefore, in the case of a single-stage reductive amination (direct reductive amination), the carbonyl compound is partially reduced to the respective alcohol; therefore, the target product yield decreases [11–13]. This disadvantage can be largely overcome by conducting the synthesis in two stages: through the formation of an imine in the absence of a reducing agent at the first stage and the reduction of the imine with hydrogen at the second stage [14].

An environmentally safe two-stage procedure to synthesize AMHMF derivatives was developed earlier [15]; it included the noncatalytic condensation of HMF (or an acetyl derivative of HMF) with primary amines in methanol at room temperature and the subsequent hydrogenation of the resulting imines in a flow reactor in the presence of a heterogeneous Cu-containing catalyst ($CuAlO_x$) based on the Cu–Al layered double hydroxide. This process does not require the isolation and purification of intermediate imines and provides the formation of various secondary amines with high yields. However, in the case of primary amines containing electron-withdrawing substituents (*o*-chloroaniline, *p*-bromoaniline), the target product yield was low; in the case of using *p*-iodoaniline, imine hydrogenation did not occur at all.

This study is focused on the efficiency of the above approach for the reductive amination of HMF with primary amines of various structures in the presence of Pt and Pd catalysts supported on γ-alumina.

EXPERIMENTAL

Reagents and Materials

Aniline (99.8%), *n*-hexylamine (99%), *o*-toluidine (99%), *m*-toluidine (99%), *p*-toluidine (99%), *o*-chloroaniline (>98%), *m*-chloroaniline (99%), *p*-chloroaniline (98%), *p*-fluoroaniline (98%), *p*-bromoaniline (>99%), *p*-iodoaniline (>99%), *p*-aminoacetophenone (99%)—all purchased from Acros Organics (Belgium)—and HMF (99%, Sigma-Aldrich, United States) were used without further purification. Methanol (99.8%, J.T. Baker, United States) was used as a solvent.

γ-Alumina (specific surface area, 162 m^2/g; pore volume, 0.69 cm^3/g; average pore diameter, 18.6 nm) was prepared by extrusion of a paste consisting of alumina (Puralox TH 100/150, Sasol, Republic of South Africa) and aluminum metahydroxide (Disperal 20, Sasol) in a weight ratio of 30 : 70 and subsequent drying and calcining at 550°C [16]. The prepared granules of the support were carefully crushed and then sieved to separate a working fraction of 0.25–0.50 mm, which was further dedusted by decantation with hot water and then dried at 110°C.

An H_2PdCl_4 solution, which was prepared via the reaction of $PdCl_2$ (high-purity grade, 59.9 wt % Pd, Reakhim, Russia) with HCl (special purity grade, EKOS-1, Russia), K_2PtCl_4 (98%, Sigma-Aldrich), and $NaHCO_3$ (reagent grade, Reakhim), was used to synthesize the catalysts.

Catalyst Synthesis Procedure

The $1\%Pt/Al_2O_3$ and $1\%Pd/Al_2O_3$ catalysts were prepared by the hydrolysis of K_2PtCl_4 and H_2PdCl_4, respectively. To this end, a K_2PtCl_4 (or H_2PdCl_4) solution with a required amount of the metal was added dropwise to a vigorously shaken suspension of 2.5 g of γ-Al_2O_3 in an aqueous $NaHCO_3$ solution at a temperature of 90°C (for Pt) and 5°C (for Pd) for 10–15 min to achieve an atomic ratio of Na/Pt = 14 (or Na/Pd = 16). The suspension was further stirred for 15 min and then boiled for 10 min. The completeness of metal deposition was monitored from the reaction of $NaBH_4$ with 0.5–1 mL of the filtered brine. The samples were washed by decantation with hot water and air dried at 80°C overnight. To provide reduction, the sample was placed in a tubular reactor and initially calcined in a nitrogen stream at 100, 120, 150, and 200°C, while holding at each of the temperatures for 10 min, and then heated in a hydrogen stream at 200°C for 30 min. The reactor was cooled and purged with nitrogen; the catalyst was passivated by repeatedly introducing small amounts of air into the nitrogen stream [17].

Investigation Procedures to Determine the Physicochemical Properties of the Catalysts

Chemical analysis to determine the content of platinum and palladium was conducted by atomic absorption spectrometry on an Optima 4300 DV spectrometer (PerkinElmer, United States). The study of the samples by high-resolution transmission electron microscopy (HRTEM) was conducted on a JEM-2010 electron microscope (JEOL, Japan) with a lattice resolution of 0.14 nm at an accelerating voltage of 200 kV. The average particle diameters were calculated from the results of measuring the diameters of at least 250 particles in TEM images recorded at a medium magnification.

Catalytic Testing Procedure

The reaction mixtures formed during the condensation of HMF (0.05 M) with primary amines (0.05 M) in methanol at room temperature for 3–16 h were subjected to hydrogenation in an H-cube Pro flow unit (Thalesnano, Hungary) equipped with reactors made of stainless steel CatCart30 (catalyst bed thickness, 24 mm; inner diameter, 4 mm) [14–17]. Before the onset of the reaction, the catalyst (185 mg) was reduced in a hydrogen stream at a temperature of 70°C for 15 min [17]. After the reduction of the catalyst and the establishment of a required temperature and pressure, the reaction mixture was fed into the reactor. The reaction was run at 15–65°C, a pressure of 5 bar, and flow rates of the reaction mixture and hydrogen of 0.5 and 30 mL/min, respectively. Samples were taken 30–32 min after the feeding of the reaction mixture; the solvent was removed with an air stream; the reaction product composition was determined at a frequency of 500.03 MHz on a Bruker Avance III 500 NMR spectrometer (United States) using deuterochloroform (99.8% D, Aldrich) as a solvent. Chemical shifts were recorded relative to the signal of the solvent (δ = 7.26 ppm for residual chloroform protons). Reaction products were identified using previously published spectra [15]. Examples of ^{1}H nuclear magnetic resonance (NMR) spectra of the final reaction mixtures are shown in the supplementary materials.

RESULTS AND DISCUSSION

The solvent used for the reductive amination of HMF was methanol; it is commonly used in reactions of this class [3, 13–15, 17]. The condensation of HMF with aniline occurs in methanol at room temperature for 3 h with a yield of the respective imine of 98% [15, 17]. The resulting imine **1a** was further reduced with molecular hydrogen in a flow reactor in the presence of Me/Al_2O_3 (Me = Pt, Pd) catalysts containing 1% of the active component. Transmission electron microscopy studies of the 1%Pt/Al_2O_3 sample showed that this catalyst contains nanoparticles with a size of about 1 nm. The average particle size in the 1%Pd/Al_2O_3 sample was 1.9 nm (Fig. 1).

It was found that the hydrogenation of **1a** in the presence of the 1%Pt/Al_2O_3 catalyst at a temperature of 35–45°C and a hydrogen pressure of 5 bar leads to the formation of AMHMF derivative **2a** with a yield of ~98% (Table 1, entries 1, 2). The reaction products contained, in addition to compounds **1a** and **2a**, 2,5-bis((hydroxymethyl)furan (compound **3**). The 1%Pd/Al_2O_3 catalyst showed a slightly lower activity in imine hydrogenation than the activity of 1%Pt/Al_2O_3. For example, in the presence of 1%Pd/Al_2O_3, the yield of **2a** was 94 and 96% at 35 and 45°C, respectively (Table 1, entries 3, 4). Thus, in the presence of the 1%Pt/Al_2O_3 catalyst, the yield of compound **2a** is higher than that in the presence of 1%Pd/Al_2O_3 under identical reaction conditions; therefore, the former sample was subsequently used for the reductive amination of HMF with primary amines of various structures.

Para- and *meta*-toluidines, in common with aniline, react with HMF to form compounds **2b** and **2c** with a yield of 98–99% (Table 1, entries 5, 6). The imine formation rate in the condensation of HMF with *o*-toluidine is significantly lower than that in the reaction with aniline; this fact is attributed to steric hindrances imposed by the methyl group at the *ortho*-position [14, 15, 17]. Therefore, to provide the formation of an AMHMF derivative with a high yield, the condensation of HMF with *o*-toluidine was run for 16 h. The hydrogenation of the formed imine **1d** in the presence of the 1%Pt/Al_2O_3 catalyst resulted in the formation of compounds **2d** with a yield of 95–96% (Table 1, entries 7, 8).

The introduction of electron-withdrawing substituents (F, Cl, Br, I, $C(O)CH_3$) at the *para*-position of aniline decreases the yield of compounds **2** (Table 1, entries 9–16) because the respective aromatic amines exhibit weaker nucleophilic properties than those of aniline; this factor leads to a lower imine yield at the first stage [14]. Owing to different inductive and mesomeric effects of the substituents, the nucleophilicity decreases in the following order: *p*-fluoroaniline > *p*-chloroaniline > *p*-bromoaniline ~ *p*-iodoaniline ≫ *p*-aminoacetophenone. The target product yield decreases in the same order: F (**2e**, 96%) ~ Cl (**2f**, 96%) > Br (**2g**, 90%) ~ I (**2h**, 90%) ≫ $C(O)CH_3$ (**2i**, 44%).

In the reaction of HMF with *p*-bromoaniline, the formation of compound **2a**, in addition to products **1g** and **2g**, was recorded; however, the amount of **2a** did not exceed 2–3% (Table 1, entries 11, 12); this fact indicates a low rate of the hydrodebromination reaction under the experimental conditions. In the case of *p*-iodoaniline, the yield of the **2h** target product at 35°C was 79% (Table 1, entry 13); in this case, the presence of a significant amount of the hydrodehalogenation product (~10%) was detected. A decrease in the reaction temperature to 25 and 15°C provided a significant slow down of the hydrogenation of the C–I bond and the formation of **2h** with a yield of 86 and 90%, respectively (Table 1, entries 14, 15).

The position of the electron-withdrawing substituent in the aromatic amine has a significant effect on the occurrence of the reaction (Table 1, entries 10, 17, 18). The yield of AMHMF derivatives in the reaction of HMF with chloraniline isomers decreases in the following order: *p*-chloroaniline (**2f**, 96%) > *m*-chloroaniline (**2j**, 94%) ≫ *o*-chloroaniline (**2k**, 52%); this fact is attributed to a decrease in the nucleophilic properties of amines in this order [15, 17]. Thus, the

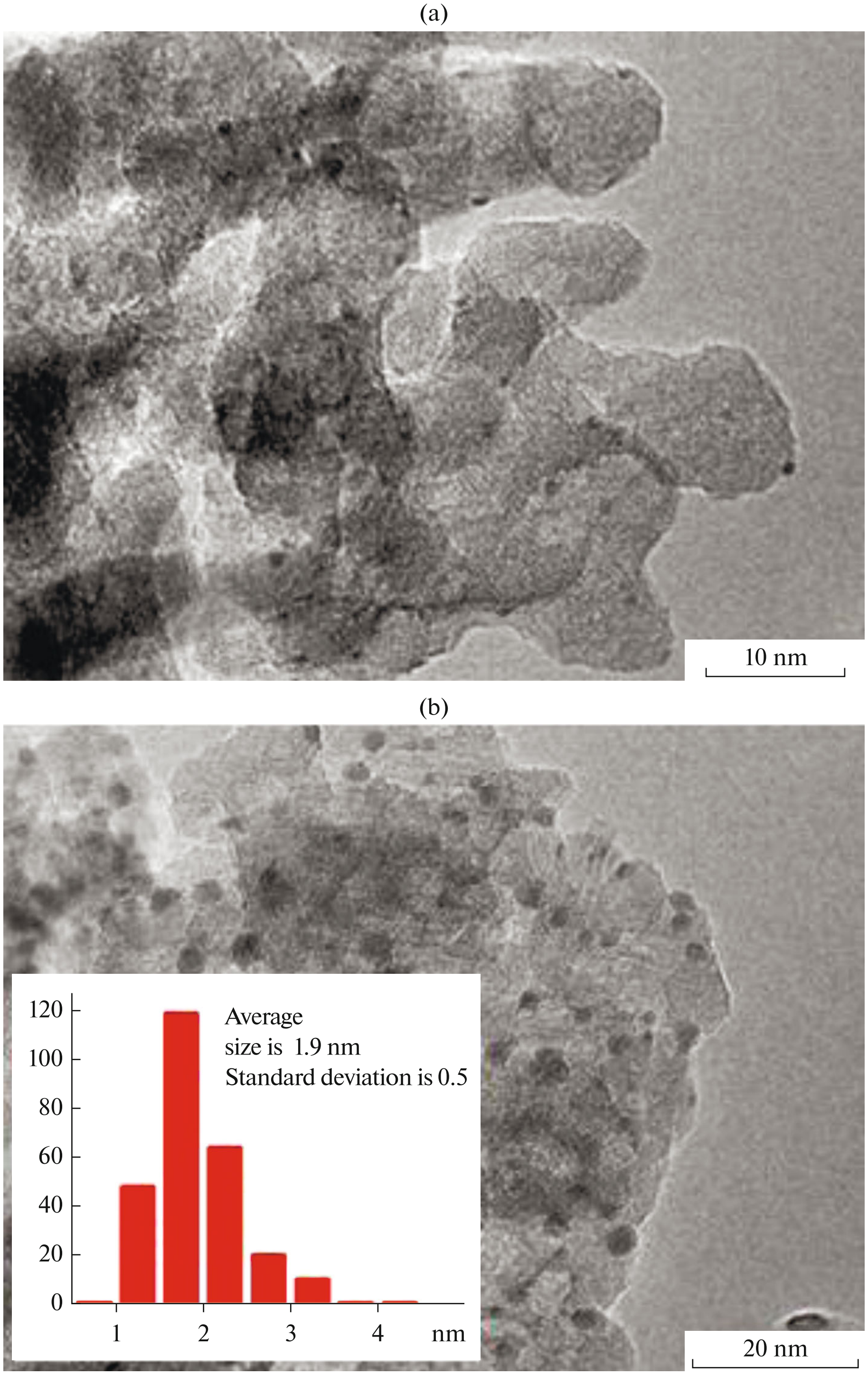
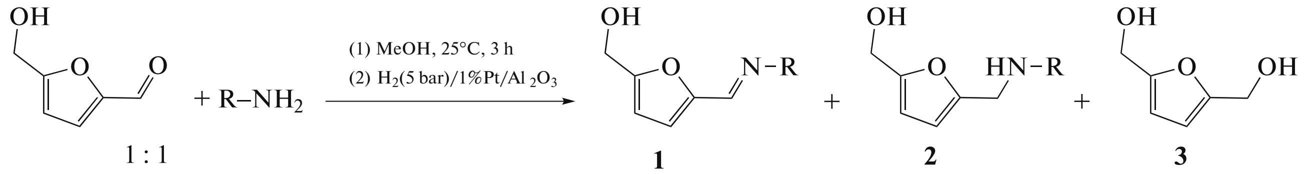


Fig. 1. Transmission electron microscopy images of (a) the 1%Pt/Al_2O_3 and (b) 1%Pd/Al_2O_3 catalysts.

yield of AMHMF derivatives is apparently determined by the imine yield at the first stage: an increase in the yield of the intermediate imine leads to an increase in the yield of the respective target product **2** [14].

In addition, the use of *n*-hexylamine as a reactant leads to the formation of compound **2l** with a yield of up to 99% (Table 1, entries 19, 20), which is considerably higher than the yield of this AMHMF derivative in the presence of a $CuAlO_x$ catalyst [15]. Analysis of the time dependence of the yield of target product **2l** at a temperature of 65°C showed that it remained unchanged (99%) for 3 h. Thus, the 1%Pt/Al_2O_3 catalyst shows a fairly high stability during the reaction.

Table 1. Two-stage reductive amination of HMF with primary amines in the presence of the 1%Pt/Al_2O_3 catalyst



No.	*R*	*T*, °C	**2**	Conversion, %	Yield, %			
					1	**2**	**3**	others
1	Ph	35	**2a**	100	1	98	1	–*
2	Ph	45	**2a**	100	<1	>98	1	–*
3**	Ph	35	**2a**	98	5.5	94	<0.5	–*
4**	Ph	45	**2a**	99	2	96	1	–*
5	*p*-$CH_3C_6H_4$	45	**2b**	100	<0.5	99	<1	–*
6	*m*-$CH_3C_6H_4$	45	**2c**	100	1	98	1	–*
7***	*o*-$CH_3C_6H_4$	45	**2d**	>99.5	1.5	95	2	1
8***	*o*-$CH_3C_6H_4$	55	**2d**	100	<1	96	2	1
9	*p*-FC_6H_4	55	**2e**	100	1	96	3	–*
10	*p*-ClC_6H_4	55	**2f**	100	2	96	2	–*
11	*p*-BrC_6H_4	45	**2g**	99	5.5	88	3	2.5****
12	*p*-BrC_6H_4	55	**2g**	100	3	90	4	3****
13	*p*-IC_6H_4	35	**2h**	>99.5	3	79	8	10****
14	*p*-IC_6H_4	25	**2h**	99.5	4	86	4	5****
15	*p*-IC_6H_4	15	**2h**	99	6	90	2	1****
16***	*p*-$CH_3C(O)C_6H_4$	55	**2i**	69	12	44	11	2
17***	*m*-ClC_6H_4	55	**2j**	100	3	94	3	–*
18***	*o*-ClC_6H_4	55	**2k**	73	6	52	13	2
19	*n*-Hexyl	55	**2l**	>99.5	2	98	0	<0.5
20	*n*-Hexyl	65	**2l**	100	<1	99	0	0.5

* Not detected.

** The catalyst is 1%Pd/Al_2O_3.

*** The duration of the first stage is 16 h.

**** Hydrodehalogenation products.

Reaction conditions for the hydrogenation stage: flow reactor; [HMF] + [imine] = 0.05 M; catalyst loading, 185 mg; methanol; H_2, 5 bar; and flow rates of the reaction mixture and hydrogen, 0.5 and 30 mL/min, respectively. Reaction product composition was determined by ^1H NMR spectroscopy in $CDCl_3$.

CONCLUSIONS

In this study, a set of AMHMF derivatives has been synthesized via the two-stage reductive amination of HMF with primary amines. The imines formed during the noncatalytic condensation of HMF with amines in methanol at room temperature have been reduced with molecular hydrogen in a flow reactor in the presence of 1%Pt/Al_2O_3 and 1%Pd/Al_2O_3 supported catalysts; 1%Pt/Al_2O_3 has exhibited a higher activity in the hydrogenation of the C=N bond.

Various N-substituted 5-(hydroxymethyl)-2-furfuryl amines have been synthesized in the presence of the 1%Pt/Al_2O_3 catalyst. It has been found that the two-stage reductive amination of HMF with *n*-hexylamine; aniline; *ortho*-, *meta*-, and *para*-toluidines; and aniline derivatives containing F, Cl, Br, and I substituents at the *para*- or *meta*-position leads to the formation of the target product with a high yield (90–99%). In the reaction of HMF with aromatic amines exhibiting weak nucleophilic properties (*o*-chloroaniline, *p*-aminoacetophenone), the AMHMF derivative yield does not exceed 52%. Unlike the $CuAlO_x$ mixed oxide, the 1%Pt/Al_2O_3 catalyst provides a high yield of N-substituted 5-(hydroxymethyl)-2-furfuryl amines in the reaction of HMF with *p*-bromoaniline and *p*-iodaniline. In addition, the reductive amination of HMF with *o*-toluidone and *n*-hexylamine occurs with a target product yield of 96 and 99%, which is significantly higher than the previously obtained values in the case of using $CuAlO_x$ as the catalyst.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

SUPPLEMENTARY INFORMATION

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