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Chemicals from Biomass: selective synthesis of N-substituted furfuryl amines by the one-pot direct reductive amination of furanic aldehydes

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ABSTRACT

N-substituted furfuryl amines are an important class of compounds due to their pharmaceutical activities that can be produced by reductive amination of furfuraldehydes derived from biomass. With supported Pd nanoparticles it is possible to obtain high activities and selectivities for the production of secondary amines. CO adsorption monitored by IR show the importance of the Pd crystal size and crystal face on catalyst activity and selectivity. When using Pd on carbon the amount of unsaturated Pd sites is very much enhanced with the corresponding increase in selectivity. The role of carbon deposition on metal terraces on catalytic selectivity is discussed. The optimized catalyst has been successfully applied in the reductive amination of 5-hydroxymethylfurfural with different amines and ammonia as well as in the one-pot reductive amination starting from nitrobenzene instead of aniline, giving the different N-substituted-5-(hydroxymethyl)-2-furfuryl amines with excellent activity and selectivity.

KEYWORDS

HMF, Furfural, C-N bond formation with Pd catalyst, secondary amines, Pd nanoparticles

INTRODUCTION

Research and development of biomass based alternatives for fuels and chemicals has gained significant attention, due to their renewable nature and the environmental problems associated with the use of fossil fuels as feedstock. Raw biomass can be processed into a number of intermediates, called platform molecules,[1] that constitutes valuable starting compounds to obtain biofuels and high value added chemicals.[2] Among them, furfural and 5-hydroxymethyl furfural (HMF), which can be obtained from lignocellulosic biomass by dehydration of hexoses and pentoses respectively, are versatile platform molecules that can be converted in a variety of important chemicals.[3,4]

N-substituted 5-(hydroxymethyl)-2-furfuryl amines, represent an important class of compounds due to their recognized pharmaceutical activities[5,6,7] such as calcium antagonistic activity, cholinergic agent, antimuscarinic agent, and carcinogenesis inhibitors. Moreover with the appropriated amines interesting surfactants can be also obtained.[8]

N-substituted-5-(hydroxymethyl)-2-furfuryl amines are conventionally synthesized through a Mannich-type reaction starting from furfural or furfuryl alcohol, formaldehyde and primary amines[5] (Scheme 1) However, harsh reaction conditions are usually required, that leads to low selectivity to the target compound. Nevertheless, a new sustainable route to access to this type of amines could be envisaged through the reductive amination of HMF.

Reductive amination (RA) of carbonyl compounds (aldehydes and ketones) is one effective method to form C-N bonds, which involves an amine source (ammonia, primary or secondary amines) and a reducing agent. There are two different approaches to perform reductive amination: a) an indirect method (two steps) which involves the formation of an imine intermediate by nucleophilic attack of the amine to the carbonyl group catalyzed by acid sites, followed by the imine reduction using metal hydrides such as, sodium borohydride[9] sodium cyanoborohydride[10] or sodium triacetoxyborohydride[11] (Scheme 2a) and b) a direct method (or one pot procedure) in which the carbonyl compound, amine and a reducing agent (generally molecular hydrogen) are mixed, and the *in situ* formed imine is reduced to the corresponding amine in the presence of a hydrogenating metal catalyst (Scheme 2b).

When the indirect method is used, an excess of the hydride is required and consequently, large amounts of wastes including some toxic wastes can be generated. These problems along with the poor atom economy of this approach, originates that the direct reductive amination of carbonyl compounds using molecular hydrogen was considered as the best strategy to produce amines.[12,13]

A variety of homogeneous and heterogeneous metal catalysts containing Ru, Pd, Pt, Fe or Co have been recently used for the reductive amination of different carbonyl compounds.[12,13,14,15,16,17] However, in spite of the extensive literature concerning the reductive amination of carbonyl compounds, the reductive amination of HMF with primary amines (through both indirect and direct methods) to produce N-substituted 5-(hydroxymethyl)-2-furfuryl amines is really scarce. For instance, N-substituted 5-(hydroxymethyl)-2-furfuryl amines have been prepared by indirect reductive amination of HMF with primary amines through two step process using mainly hydride salts as hydrogen source. Thus, in the patent literature[18] is described the formation of secondary amines starting from HMF and tryptamine with an excess of the expensive sodium cyanoborohydride, while large amounts of toxic waste (NaCN) were generated. More recently, Cukalovic and Stevens[19] reported the synthesis of secondary amines in water or ethanol using $NaBH_4$. In this case, when aromatic amines were used, large reaction time was required. For instance the RA of HMF and 3-methoxyaniline gives the corresponding secondary amine (97% yield) after 51 h reaction.

While the indirect reductive amination of furanic aldehydes leads in general to good yields of the corresponding secondary amines, the direct reductive amination using molecular hydrogen in the presence of homogeneous or heterogeneous catalysts can be a non selective process. In fact with furanic aldehydes, besides the possible hydrogenation of the carbonyl group, other competitive reactions such as the reduction of the furanic ring as well as the ring opening reaction can take place, and the selectivity to the secondary amine strongly depends on the nature of the catalyst and reaction conditions. For instance Villard et al.[20] used Ni Raney (20 wt%) in the reductive amination of HMF with alanine sodium salt under hydrogen pressure (5 bar), and low yield (38% after 48h) of the corresponding secondary amine was obtained. Similar results were also reported by Kirchekker et al.[21] for the same process. Better results were reported by Chieffi et al.[22] for the reductive amination of HMF with different amines using carbonized filter paper supported FeNi alloy as catalyst in a continuous fixed bed reactor (WHSV= $24h^{-1}$) under 10 bar of hydrogen and temperatures between 100 and 125 ^{o}C. High HMF conversions (>99%) were achieved, however the selectivity to the secondary amine did not surpass 78 %.

Much more efficient procedure for the synthesis N-substituted-5-(hydroxymethyl)-2-furfuryl amines by RA of HMF and primary amines has been recently reported by Xu et al.[16] using a homogeneous Ru^{II} complex catalyst ($Ru(DMP)_2Cl_2$). For instance, when reacted aniline with HMF under the optimized reaction conditions (11 bar of hydrogen pressure at 60 ^{o}C), 93% yield of the secondary amine was achieved after 6 h reaction. However, the main disadvantages of this homogeneous catalytic system, besides the difficulty associated to catalyst recuperation and reuse, is that the structure of the amine strongly influences the activity because the amine can interact with the transition metal catalyst to form inactive complexes. More recently, Zhu et al.[23] reported the reductive amination of HMF with different primary and secondary amines using rutile titania supported gold assisted by CO/H_2O as catalytic system. They obtained high yields of the corresponding aminofurans, however high pressure of CO (20-40 bar) were required.

The lack of an efficient and sustainable process to produce N-substituted-5-(hydroxymethyl)-2-furfuryl amines, prompted us to study the possibility to develop an active, selective and robust heterogeneous catalytic system based on supported metal nanoparticles to carry out the direct reductive amination of HMF with amines, using hydrogen as reducing agent. In this work, we will show that by properly selecting the catalyst support as well as the size of the supported metal nanoparticles, it is possible to prepare highly active, selective and stable catalyst for the reductive amination of HMF and other derivatives. We will also show that the catalyst is chemoselective for performing the one pot reductive amination starting from the primary nitroderivates instead of starting from the more elaborated amines.

Experimental Section

Materials

All the reagents used were of analytical grade, purchased from Sigma Aldrich or ABCR and used without any purification unless otherwise specified.

General Reaction Procedure

Catalytic experiments were performed under H_2 atmosphere in a 2 mL reinforced glass-made reactor. To a solution of HMF (1 mmol), amine (1 mmol) and dodecane as internal standard (0.2 mmol) in 1 ml trifluorotoluene (TFT) was added the Pd catalyst. After sealing the reactor, air was purged by flushing twice with 5 bar of nitrogen. Then, the mixture of substrates and catalyst were heated to the desired temperature, and then it was pressurized with H_2 (3 bar) (this was taken as t=0). The resulting mixture was kept under stirring for the time indicated. To avoid the control by external diffusion the reaction was carried under different stirring speed (600, 1000, 1400 rpm). It was found that working at stirring speeds between 1000 and 1400 rpm there is not influence on the initial reaction rates. Thus, all the experiments were carried out at 1000 rpm. During the experiment, the pressure was kept constant, and aliquots (~20 µL) were taken from the reactor at different reaction times. The products were analyzed on Agilent GC-7980A gas chromatograph equipped with a capillary column HP-5 (30 m × 0.25 µm × 0.25 mm) and FID detector. The identification of the products was performed by using a GC-MS spectrometer.

Reductive amination of HMF with ammonia

The reductive amination of HMF with ammonia was performed in a stainless steel high-pressure reactor. HMF (0.5 mmol), 5mL of a solution of NH_3 in methanol (2.0 M, Aldrich)(10 mmol NH_3) and 1 %Pd/C (25mg, S/C=212) were introduced into the reactor, purged with N_2 and H_2 and finally, pressurized at 14 bar of H_2 and heated at 110 ºC under stirring (1000rpm).

Preparation and characterization of the catalysts

Pd/Al_2O_3 and Pd/C with different metal loading were prepared by incipient wetness impregnation of the support with the appropriate amount of a solution of $Pd(acac)_2$ in water free toluene. The mixture was dried at 120°C, and then the catalyst was reduced with a stream of H_2 at 250 °C for 3 h.

Pd/Al_2O_3 with 1 wt % Pd loading (1%Pd/Al_2O_3) was a commercial sample from Sigma Aldrich.

The amount of palladium on the catalysts was measured by ICP-AES analysis. The metal crystallite size was determined by transmission electron spectroscopy (TEM) using a JEM 1010 transmission electron microscopy operated at 100 kV.

IR spectra were recorded with a Nexus 8700 FTIR spectrometer using a DTGS detector and acquiring at 4 cm^{-1} resolution. An IR cell allowing in situ treatments in controlled atmospheres and temperatures was connected to a vacuum system with gas dosing facility. For imine adsorption desorption study, the catalysts (Al_2O_3 and 1%Pd/Al_2O_3) were impregnated “ex situ” with the corresponding imine in a CH_2Cl_2 solution at room temperature during 4 h. After impregnation, the samples were dried under vacuum and pressed into selfsupported wafers for IR studies. IR Spectra were acquired under dynamic vacuum at 10^{-5} mbar and at desorption temperatures of 50 and 150 ºC.

For IR-CO studies, the sample was activated in situ in H_2 flow (10 ml/min) at 250 ºC and for 2 h, followed by evacuation at 300 ºC for 40 min and cooling down to 25 ºC. CO was dosed from 0.1 mbar to 9 mbar at 25 ºC. Spectra were acquired at each dosing.

DRIFTS CO adsorption studies were performed with a Bruker Vertex 70 spectrometer using a MCT detector and acquiring at 4 cm^{-1} resolution. A commercial Praying Mantis High temperature reaction cell form Harrick Scientific products has been used. The catalysts (~10 mg) were reduced in situ with H_2 flow (10ml/min) at 200 ºC for 1h, followed by cooling down in helium flow (10 ml/min) to 25 ºC. At 25 ºC the gas was switched to 4 % CO/He (10 ml/min) and IR spectra were acquired after ~30 min gas flow.

RESULTS AND DISCUSSION

For this study, firstly we selected the reductive amination of HMF with aniline as the model reaction (Scheme 3). The reaction was carried out at 100 ^{o}C, under 3 bar H_2 pressure using trifluorotoluene (TFT) as a solvent. In this reaction, the aniline acts as a nucleophile that attacks the carbonyl group of the HMF forming imine **1** as an intermediate, which is subsequently hydrogenated to the corresponding secondary amine N-phenyl-5-(hydroxymethyl)-2-furfuryl amine (**2**).

Since Pd is a metal widely used in the C-N bond formation reactions[24] two catalysts based on Pd nanoparticles (1 wt %) supported on Al_2O_3 and on activated carbon with similar Pd crystal size were prepared (TEM images and particle size distribution are presented in Tables S1 and S2). The catalysts were screened under the same reaction conditions and the results showed in Table 1. In both cases it was observed that the intermediate imine **1** was formed very fast, in such way that when introducing the H_2 in the reactor (see experimental section) a complete conversion of HMF into **1** already occurred. Additionally, a blank experiment, in absence of catalyst, showed that the imine **1** was the only product observed, being its formation very fast under our reaction conditions, indicating that the synthesis of intermediate imine does not require the presence of catalyst.

As can be seen in Table 1, 1%Pd/Al_2O_3 and 1%Pd/C catalysts performed well the reductive amination of HMF, with good selectivity to the amine **2**. However, Pd/C catalyst was able to hydrogenate the imine **1** with total selectivity to the amine **2**, while with Pd/Al_2O_3 the amine **2a** coming from the further hydrogenation of the furan ring was detected as by-product. In Figures S1 and S2 the evolution of reactant and products with time is presented.

Other interesting furfuryl amine derivatives can be achieved following the same protocol through the reductive amination of furfural (Scheme 4). Then, we checked the two catalysts under the same reaction conditions using furfural and aniline as reagents. It was found that the reactions performed very fast under these conditions, and consequently the amount of catalyst was decreased to one half (Table 2).

As can be observed in Table 2, in the case of Pd/C catalyst the hydrogenation of the imine **3** into the secondary amine **4** takes place with total selectivity. However, with Pd/Al_2O_3 the selectivity to the secondary amine **4** is lower than in the case of HMF, as consequence of the competitive hydrogenation of the furanic ring which produces the amine **4a** in higher yield. Figures S3 and S4 show the reaction kinetics. Moreover, an additional experiment using lower amount of Pd/Al_2O_3 catalyst showed that, as expected, the rate of hydrogenation decreases, but the selectivity to the desired secondary amine **4** was not improved (see entry 3, Table 2, and Figure S5)

To explain the lower selectivity found with 1%Pd/Al_2O_3 catalyst for the reductive amination of furfural with respect to HMF (Table 1 and 2), we considered first the influence that the presence of the hydroxymethyl group in the HMF may have on adsorption and reactivity. Then, the adsorption modes of the intermediate imines **1** and **3** on the 1%Pd/Al_2O_3 sample was investigated by IR spectroscopy. The IR spectra of both reactants adsorbed on the 1%Pd/Al_2O_3 sample and desorbed at 50 ºC and 150 ºC are displayed Figure S6. By performing desorption IR studies at different temperatures it is possible to determine the interaction of the molecule with the catalyst surface, which could help to understand the different catalytic performance.

In the case of the Pd/Al_2O_3 sample, at 50 ^{o}C, the imine **1** interacts with the catalyst surface through the -OH group (IR band at 1186 cm^{-1}), the furan group (IR bands at 1590 and 1485 cm^{-1})[25] and the aromatic group (IR bands at 1603 and 1500 cm^{-1})[26] (spectra a). After desorption at 150 ^{o}C (spectra b), it is possible to see that the interaction strength of the -OH and the furan group with the catalyst surface is weaker than that of the aromatic ring. This can be deduced from the prevalence of the IR bands at 1603 and 1500 cm^{-1}, ascribed to the aromatic ring, while the intensity of the other IR bands decrease (spectra b). However, a different scenario can be observed in the adsorption of the imine **3**. In this case, the molecule interacts with the catalyst surface by the aromatic ring (IR band at 1603 and 1500cm^{-1}) and by the furan ring (IR bands at 1590 and 1568 cm^{-1} and 1491 and 1485 cm^{-1}) (spectra c). When increasing the temperature to 150ºC, the interaction of the furan ring with the catalyst surface is stronger than the interaction of the aromatic ring (spectra d). In fact, the bands at 1603 and 1500 cm^{-1} decrease in intensity, while those of the furan ring, specifically the bands at 1568 and 1491 cm^{-1}, remains. Interestingly, these two last IR bands have not been observed in the adsorption of the imine **1**, and could correspond to a different adsorption mode of the furan ring of imine **3** with the catalyst. As reference, the adsorption of both imines on the pure Al_2O_3 have been also studied (Figure S7). Based on Figure S7 the IR bands at 1590 and 1480 cm^{-1} are ascribed to the interaction of the furan ring with Lewis acid sites of the Al_2O_3 support. The other IR bands at 1568 and 1491 cm^{-1} observed on the 1%Pd/Al_2O_3 sample with the imine **3**, may correspond to an interaction of the furan ring with the Pd metal surface sites. The presence of Pd (111) sites (titrated by IR of CO adsorption as displayed in Figure S8), may favour an interaction of the aromatic furan ring with the Pd sites boosted by a π-electron back donation of the Pd metal sites to the aromatic furan ring and a flat surface extension.

From these results, we can conclude that the interaction mode of the furan ring with the surface is strongly influenced by the presence of the hydroxymethyl group. Thus, the presence of the hydroxymethyl group in the imine **1** promotes a weak interaction of the furan ring with the Al_2O_3 support, being less susceptible to hydrogenation. In opposite, in the absence of the hydroxymethyl group, the furan ring interacts with the surface and preferentially with the Pd

(111) surface, being this interaction strong and, accordingly, more susceptible to be hydrogenated.

These results explain the higher selectivity observed for the reductive amination of HMF compared to that of furfural using the 1%Pd/Al_2O_3 catalyst. Moreover, the presence of 111 faces in the Pd metal particle seems to be detrimental for catalyst selectivity providing a suitable interaction of the furan ring being thus more susceptible for hydrogenation.

It is known that by changing the metal crystallite size, one can modify the proportion of non‒exposed to exposed metal atoms, (that can be reflected on total conversion). This implies that the relative ratio of less saturated Pd atoms (placed at the crystal corners) versus the more saturated Pd atoms (placed on 111 and 100 crystal faces) will be also changed, in such way that this ratio will be higher when smaller is the crystal size. Then, as the electronic properties of those more unsaturated Pd atoms should be different, and bearing also in mind geometric factors of interaction of the substrate with the catalyst surface, the activity and selectivity of the catalyst can be adjusted by changing the crystal size of the Pd nanoparticles**.** In order to check the influence of crystal size of Pd nanoparticles on the selectivity we have modified the metal crystallite size by changing the amount of Pd on the support. Thus, we prepared two additional Pd/Al_2O_3 samples with average Pd crystal size of 4.5 and 1.9 nm instead of the 2.5 nm in the 1%Pd/Al_2O_3 catalyst. The particle size distribution of the Pd nanoparticles was determined by Transmission Electron Microscopy (TEM). As can be observed in the histograms (Table S1), the average size of Pd nanoparticles and the distribution range increases when increasing the percentage of metal on the support.

These samples were tested in the reductive amination of HMF and furfural with aniline (Tables 1 and 2 respectively). As can be observed, in the case of HMF similar selectivities were achieved in all cases (kinetic plots are displayed in Figures S9 and S10). However, in the case of furfural, (Table 2, and Figures S11 and S12) where the furan ring interacts with the Pd (111) surface, an increase of the selectivity was observed when decreasing the crystal size (i.e. when increasing the relative ratio between less saturated Pd atoms to the more saturated Pd atoms placed in terraces). Then, by decreasing the crystallite size in the Pd/Al_2O_3 catalyst from 4.5 to 1.9 nm, the selectivity to the secondary amine **4** could be increased from 75 % up to 94%.

Effect of metal crystal size on the catalytic activity of Pd/C catalysts for reductive amination of HMF

It was shown above that 1%Pd/C sample, with an average crystal size of 2.7 nm is an active catalyst giving total selectivity to the secondary amines **2** and **4** in the reductive amination of HMF and furfural respectively. Then, to study the effect of the metal crystal size of Pd/C samples on the catalytic activity and selectivity the amount of Pd on the support was modified. Thus, Pd/C samples containing between 0.2 to 10 wt % of Pd on activated carbon were prepared. In Table S2 are showed the TEM images and the histograms of nanoparticles distribution range.

When these samples were tested in the reductive amination of HMF it was observed that all samples give total selectivity to the secondary amine **2** while the catalytic activity, as measured by initial reaction rate (conversion below 15 % divided by time), increases when decreasing the particle crystal size of Pd, achieving maximum activity for the catalysts with particle sizes around 2.7 nm (Table 3). However, further decrease of the metal crystal size does not improve the catalytic activity.

Quantification of the relative amount of the different Pd sites, i.e. Pd in 111 and 100 and unsaturated centres, can be achieved by IR spectroscopy using CO as probe molecule. However, due to the impossibility to obtain auto-consistent pellets of the Pd/C catalysts, the IR of the adsorbed CO was performed by DRIFTS.

In Figure 1 are presented the DRIFTS spectra of CO adsorbed on the different samples. The spectra show that in all cases absorption bands at 2041 y 1939 cm^{-1} corresponding to unsaturated Pd species are clearly observed. While CO adsorbed on Pd (111) terraces (2100-2090 cm^{-1} band) is not observed, even in the case of the sample with higher Pd crystal size (12.4 nm). These results appear to indicate that during the activation process the deposition of carbonaceous particles of the support on the metal nanoparticles, particularly on terraces take place.[27,28] Moreover, the deposition of carbonaceous species on the metal could be the reason of the lower activity observed for the sample with the lowest crystal size (1.8 nm). Although the DRIFTS technique does not allow the quantification of the relative amount of unsaturated Pd sites on the catalysts, it does allow us to conclude that the unsaturated Pd atoms are the active sites in the Pd/C samples. In order to check if the intrinsic activity of these unsaturated Pd sites was dependent of the Pd crystal size, we calculated activation energy (Ea) for the samples with 1.8, 2.7 and 12.4 nm crystal size by performing the reaction at 100, 80 and 60 ^{o}C. Ea values of 28.7±2.8, 30.0±1.6 and 31.4±2.2 KJ/mol were found respectively, indicating that the intrinsic activity of the unsaturated Pd sites is the same independently of the Pd crystal size. Therefore the increase in catalytic activity when decreasing the metal particle size can be attributed to the presence of a greater number of accessible unsaturated centres. Then, we have to expect that the TOF values considering the mmol of accessible Pd sites in surface should be similar for all samples independently of the Pd crystal size. However, when the TOF values were calculated by considering the mmol of Pd on the surface (estimated from the size of nanoparticles measured by TEM) we can see (Table 3) that the TOF values are not similar but increase with the crystal size. These results are in good agreement with the presence of deposits of carbon on the Pd nanoparticles that decrease the number of potential Pd active sites. In fact, we have performed the CO chemisorption on the 10 %Pd/C sample (12.4 nm crystal size) an the results indicate that the number of Pd sites on surface is lower (2.85 10^{-8} mole) than that expected (3.69 10^{-7} mole) from the Pd particle size measured by TEM.

On the other hand, when reductive hydrogenation of furfural (more susceptible for the hydrogenation of the furan ring) was performed with 5%Pd/C sample (with 7.9 nm crystal size), 100 % selectivity (at 100 % conversion) to the corresponding secondary amine **4** was obtained (See Figure S13). Therefore the high selectivity observed in Pd/C samples in the reductive amination of HMF and furfural can be explained by the absence of Pd 111 crystal facets in these samples as consequence of the deposition of carbonaceous species on the Pd crystals.

Recovery and Reuse of Pd/C catalyst

Following the steps of sustainable chemistry, an important aspect for the practical use of any heterogeneous catalyst, is their stability and possibility to recycle.

The reusability of Pd/C catalyst was investigated in the reaction of HMF with aniline under a hydrogen pressure of 3 bar and at 100 ^{o}C. After reaction, the catalyst was separated by filtration, and washed three times with ethanol. Then, the washed catalyst was dried in an oven at 100 °C for 5 h and reused in a second cycle. As can be seen in Figure S14, Pd/C catalyst could be recycled at least up to three consecutive cycles without significant loss of activity.

To test if the catalytic process involves possible Pd leached into the solution, an additional experiment was carried out where the reductive amination of HMF with aniline with 1%Pd/C was stopped after 10 min. At this point, the catalyst was filtered off in hot and the reaction was continued for 2 h, but no further conversion was detected indicating that Pd leaching does not take place during the reaction (see Figure S15). Moreover, this was confirmed by the inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis of the used catalyst that showed that the original amount of Pd on the catalyst was retained after the third run.

Scope of the reaction

The general applicability of the Pd/C catalyst was evaluated by performing the reductive amination of HMF with various aromatic and aliphatic amines under optimal conditions. As show in Table 4 a variety of substituted anilines were reacted to give the corresponding secondary amines in excellent yields at reasonable time. These results contrast with the low activities showed by aromatic amines in the two steps reductive amination of carbonyl compounds reported by Cukalovic et al.[19] using $NaBH_4$.

To study the influence of the electronic and steric effects of the aniline on the reductive amination, amines bearing electron-donating groups (*ortho*-CH_3, *para*-CH_3, OCH_3) (entries 2-4, Table 4) and electron-withdrawing groups (Cl, CN, $COCH_3$) (entries 5-7, Table 4) were selected. As can be seen in Table 4 when the reactions were carried out with aniline derivatives with electron-donating groups such as p-CH_3 and OCH_3 (entry 2-3) excellent yields 98-99% of the corresponding secondary amines were obtained in short reaction time (1h). Only a moderate yield (76%) was obtained in the case of *ortho*-methylaniline due to steric effects, as it is clearly illustrated by the different reactivity of *ortho* and *para* methylaniline (entries 2 and 3, Table 4). Anilines with electron-withdrawing groups were also transformed into the corresponding secondary amine in good yields (86-96 %) (entries 5-7, Table 4) but longer reaction time (3 h) was required. It should be noted that, in the case of 4-chloroaniline, the presence of dehalogenation products was not observed, nor the reduction of substituents susceptible to be reduced (entries 6 and 7). It is interesting to note that these yields are considerably superior to those reported by Xu et al.[16] using $Ru(DMP)_2Cl_2$ in homogeneous media under 11 bar of hydrogen. The authors reported 66 % yield of the secondary amine when using 4-acetylaniline, while the reductive amination does not take place at all with 4-cyanoaniline probably due to their interaction as a ligand with the catalyst. Excellent yield and selectivity to the secondary amine was also obtained using aliphatic amines such as 2-phenylethanamine and octylamine (entries 8 and 9, Table 4). Finally, the reductive amination of HMF with NH_3 was also performed (see experimental section). When the reaction was carried out in the presence of NH_3, excellent yield and selectivity to the corresponding amine ((5-aminomethyl-furan-2-yl)-methanol was obtained (Table 4, entry 10), although higher H_2 pressure (14 bar) was required. The only byproduct observed was the secondary amine, difurfurylamine, while the formation of tertiary amines was not detected.

One-Pot reaction

Finally, we tested the possibility to obtain the furfuryl amine derivatives starting from nitrocompounds instead of amines through a one pot reaction. To do that, nitrobenzene and HMF were reacted in the presence of 1%Pd/C catalyst (Figure S16). Under these conditions, reduction of HMF was not observed and 100 % HMF conversion with 100 % selectivity to amine **2** was achieved within 6h reaction time. As can be seen in Figure S17, the imine intermediate was detected as traces in the reaction media indicating that the reduction of nitrobenzene should be the controlling step of reaction. In fact, we did an additional experiment of hydrogenation of nitrobenzene with 1%Pd/C catalyst that showed that the initial reaction rate was of 0.8 $mmolh^{-1}$ which is 4 times lower than the rate of imine hydrogenation (3.2 $mmolh^{-1}$).

CONCLUSIONS

Reductive amination of HMF with amines to obtain N-substituted-5-(hydroxymethyl)-2-furfuryl amines has been performed with excellent activity and selectivity using Pd nanoparticles supported on activated carbon. Pd/C catalysts give total selectivity to the corresponding amine, while Pd supported on Al_2O_3 showed lower selectivity as consequence of the further hydrogenation of the furan ring, particularly in the reductive amination of furfural. This behavior was attributed to the presence of Pd 111 crystal facets in the Pd nanoparticles of the Pd/Al_2O_3 catalysts, as evidenced the IR of adsorbed CO, providing a suitable interaction of the furan ring being thus more susceptible for hydrogenation. However in the case of the Pd/C samples, only unsaturated Pd sites were detected due to deposition of carbonaceous species on the terraces. The study of the influence of the Pd crystal size of the Pd/C samples on the catalytic activity showed that the intrinsic activity of the Pd unsaturated sites was similar independently of the crystal size indicating that the differences in activity are due to the different amount of accessible active sites in each sample. The optimum Pd/C catalyst, with 1 wt % Pd loading and crystal size around 2.7 nm resulted a stable and recyclable catalyst and was successfully applied in the reductive amination of HMF with different amines and with ammonia as well as in the one-pot reaction starting from nitrobenzene, giving the different N-substituted-5-(hydroxymethyl)-2-furfuryl amines with excellent activity and selectivity.

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In SI are included kinetic curves, IR spectra of adsorption of imines and CO, Figures of the recycle of the catalyst and leaching test, Tables with average particle size distribution and TEM images.

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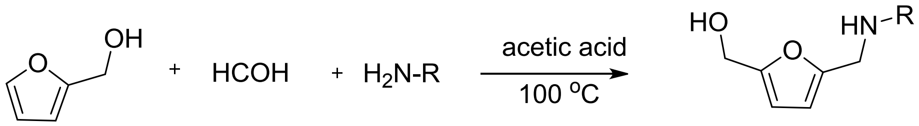
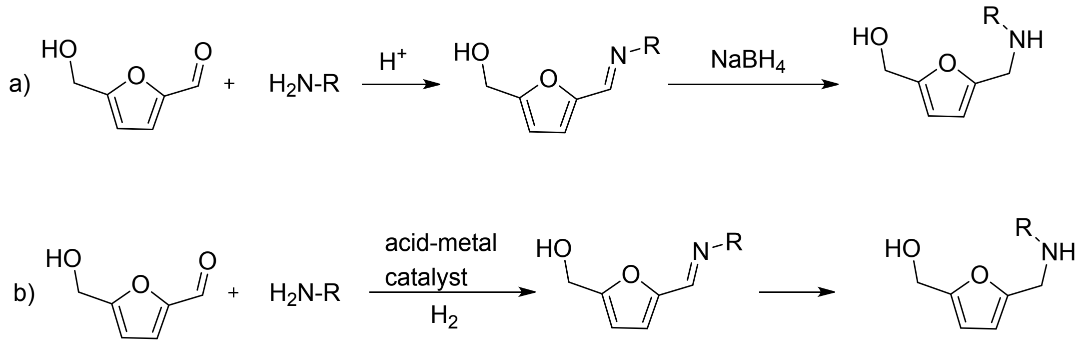
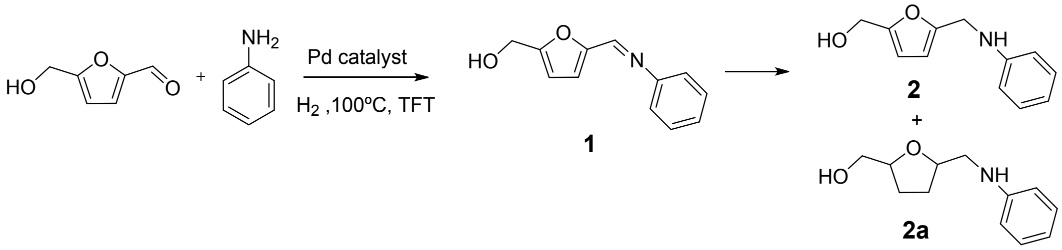


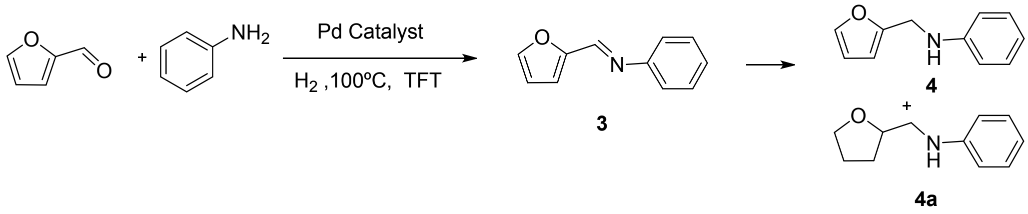
Scheme 1. Mannich-type reaction for the synthesis of N-substituted-5-(hydroxymethyl)-2-furfuryl amines



Scheme 2. Indirect (a) and direct method (b) of reductive amination of HMF with primary amines



Scheme 3. Direct reductive amination of HMF with aniline



Scheme 4. Reductive amination of furfural with aniline

Table 1. Results of reductive amination of HMF with aniline (AN) over different Pd catalysts.[a]

catalysts	r^o	Pd crystal size (nm)	time (h)	conversion imine **1**(%)	yield **2a** (%)	yield **2** (%)	selectivity **2** (%)
1%Pd/C	3.2	2.7	1	100	0	100	100
1%Pd/Al_2O_3	1.9	2.5	1	100	5	95	95
5%Pd/Al_2O_3	0.9	4.5	1	100	6	94	94
0.2%Pd/Al_2O_3	2.1	1.9	2	100	3	97	97

[a] Reaction conditions: HMF (1 mmol), AN (1 mmol), 3 bar H_2, substrate/catalyst molar ratio = 212, 1 mL TFT. r^o: initial reaction rate of appearance of amine **2** (mol h^{-1}) 10^3

Table 2. Results of the reductive amination of furfural with aniline over different Pd catalysts.[a]

entry	catalyst	r°	time (h)	conv. Imine **3** (%)	yield **4a** (%)	yield **4** (%)	selectivity **4** (%)
1	1%Pd/C	2.3	4	100	0	100	100
2	1%Pd/Al_2O_3	4.0	1	100	20	80	80
3[b]	1%Pd/Al_2O_3	3.0	1	100	19	81	81
4	5% Pd/Al_2O_3	2.8	1	100	25	75	75
5	0.2%Pd/Al_2O_3	1.4	2	100	8	92	92

[a] Reaction conditions : Furfural (1 mmol), AN (1 mmol), 3 bar H_2, substrate/catalyst molar ratio = 424, 1 mL TFT. r°: initial reaction rate of appearance of amine **4** (mol h^{-1}) 10^3. [b] Reaction was performed using a substrate/catalyst molar ratio = 848

Table 3. Catalytic activity of Pd/C with different particle size distribution in the reductive amination of HMF with aniline.[a]

Entry	Pd loading (wt %)	Pd crystal size (nm)	r^{o}	time (h)	Conv. Imine **1** (%)	yield **2** (%)	selec **2** (%)	TOF (h-1)[b]	TOF (h-1)[c]
1	0.2	1.8	0.6	5	100	100	100	236	127
2	1	2.7	3.2	1	100	100	100	1888	678
3	5	7.9	1.7	6	98	98	100	2761	360
4	10	12.4	1.6	6	97	97	100	4604	339

[a] Reaction conditions: HMF (1 mmol), AN (1 mmol), 3 bar H_2, susbtrate/catalyst molar ratio= 212, 1 mL TFT. r^{o} : initial reaction rate of appearance of amine **2** (mol h^{-1}) 10^3. [b] Defined as initial reaction rate divided by mmol of Pd in surface (calculated from the size of nanoparticles measured by TEM). [c] Defined as initial reaction rate divided by mmol of bulk Pd

Table 4. Results of direct reductive amination of HMF with primary amines in the presence of 1%Pd/C as catalyst[a]

Entry	primary amine	time (h)	conversion imine (%)	yield amine (%)	selec. amine (%)

1	Aniline	1	100	100	100
2	2-Methylaniline	3	76	76	100
3	4-Methylaniline	1	98	98	100
4	4-Methoxyaniline	1	99	99	100
5	4-Chloroaniline	3	89	89	100
6	4-Cyanoaniline	3	96	96	100
7	4-Acetyl aniline	3	86	86	100
8	2-Phenylethylamine	1	99	99	100
9	Octylamine	1	100	100	100
10[b]	NH_3	2	100	94	94[c]

[a]Reaction conditions: HMF (1 mmol), amine (1 mmol), 3 bar H_2, 50 mg 1%Pd/C, substrate/catalyst molar ratio= 212, 1 mL TFT. [b] NH_3 (10 mmol) (5 mL of NH_3 2.0 M in methanol), 14 bar H_2, [c] 6 % of the difurfurylamine was the only byproduct detected

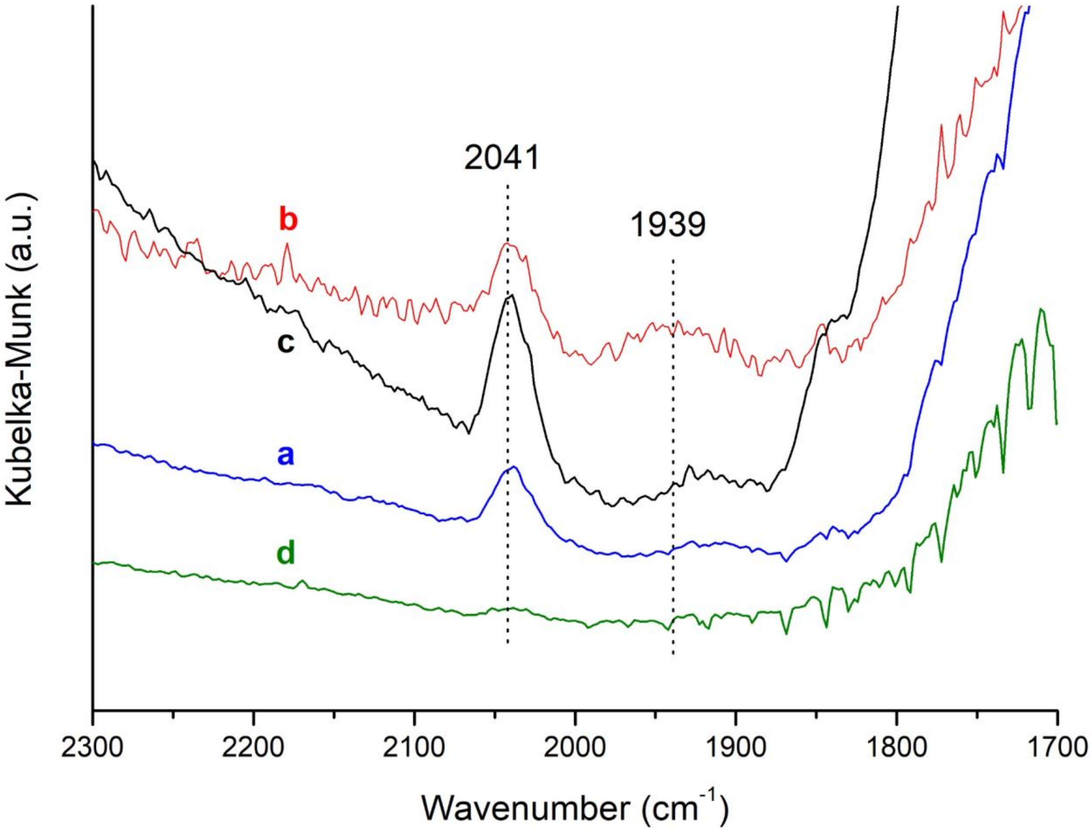


Figure 1. DRIFT spectra of CO adsorbed on a) 10%Pd/C b) 5%Pd/C, c) 1%Pd/C and d) 0.2%Pd/C.

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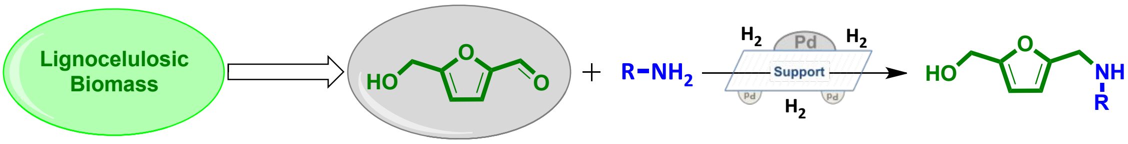

Furanic aldehydes from biomass are easily converted into N-substituted furfuryl amines using supported Pd nanoparticles as heterogeneous catalysts