# Chemicals from Biomass: Chemoselective Reductive Amination of Ethyl Levulinate with Amines

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S *Supporting Information*
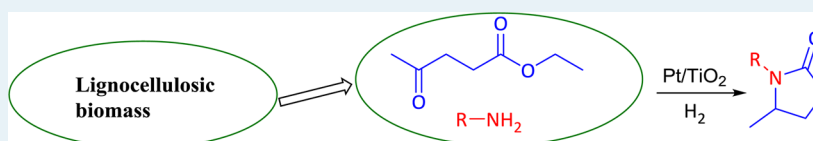
ABSTRACT: N-substituted-5-methyl-2-piyrrolidones have been obtained by reductive amination of ethyl levulinate with amines in the presence of H_2 as reducing agent under solvent-free conditions. The process involves as a first step the formation of an imine intermediate followed by hydrogenation of the imine group and subsequent cyclization into pyrrolidone. Pt/TiO$_2$ with Pt crystal faces decorated with TiOx is a very active and chemoselective catalyst, being possible to achieve high conversion and selectivity to the corresponding N-substituted-5-methyl-2-pyrrolidones even when other groups susceptible of hydrogenation such as vinyl, carbonyl, or cyano groups are present in the amine moiety. A kinetic study showed that the reaction-controlling step is the formation of the imine intermediate. The rate of formation is enhanced by the presence of protonic acid sites generated on the support by hydrogen dissociation on the metal, resulting in a true bifunctional catalyst for the reaction.

KEYWORDS: *chemicals from biomass, ethyl levulinate, reductive amination, Pt/TiO$_2$ catalyst, N-substituted-5-methylpyrrolidones*

■ INTRODUCTION

Biomass is recognized as a renewable source of carbon for the production of fuels[1] and chemicals[2−4] in the search for a more sustainable chemistry. An interesting approach for converting lignocellulosic biomass into fuels and chemicals is through the transformation of platform molecules[5] that keep sufficient functionality to be upgraded into valuable compounds. In this context, levulinic acid (4-oxopentanoic acid, LA) has been identified as a valuable platform molecule which can be easily obtained from lignocellulose biomass by acidic dehydration of carbohydrates.[2,4] Many useful molecules such as gamma-valerolactone (used as liquid fuel, solvent, and food additive), 5-aminolevulinic acid (herbicide and insecticide), levulinic acid esters (intermediates), or N-substituted-5-methyl-2-piyrroli-dones can be produced from levulinic acid.[2] Particularly, 5-methyl-2-pyrrolidones are important compounds widely used in industry as surfactants, intermediates for pharmaceuticals, dispersants in fuel additives compositions, solvents, in the manufacture of agrochemicals, and so forth.[6,7]

N-substituted-5-methyl-2-piyrrolidones can be produced by reductive amination of levulinic acid (LA) or its esters with amines, using molecular hydrogen in the presence of a hydrogenation catalyst. The reductive amination process involves several steps, starting with the formation of an intermediate imine by the nucleophilic attack of the amino group to the ketonic group of LA (or ester). Then, the reductive hydrogenation of imine to amino group has to be performed, followed by the subsequent cyclization by

nucleophilic attack of the amino to the carbonyl group of ester (or acid) to give the corresponding N-substituted-5-methyl-2-pyrrolidone (Scheme 1).

Although the reaction appears to be easy, a variety of consecutive and side reactions such as reduction or aldolization of the ketoester (or ketoacid), condensation of imines with amines to give secondary and tertiary amines, and over reduction of the aromatic ring in the case of amines bearing aromatic groups can also occur, which result in a loss of selectivity. What in practice occurs is that, in general, and depending on the amine involved, the process suffers from a lack of selectivity, and to achieve selectivities above 90% for near total conversion is a challenge.

Although the catalytic hydrogenation is an attractive methodology from an economical and ecological point of view, the number of examples reported in the literature to transform LA (or its esters) into N-substituted-5-methyl-2-piyrrolidones using molecular hydrogen in the presence of heterogeneous catalysts is scarce. In gas phase, the most-studied catalysts involve monometallic systems based on Ni supported on silica gel, Raney nickel,[8] and Pd/Al$_2$O$_3$.[9] In liquid phase, the reductive amination of LA or its esters with amines has been described in several patents[6,10,11] using metals such as Ni, Pd, Pt, Ru, Rh, and Ir supported on carbon or metal oxides such as

Scheme 1. Reaction Pathway in Pyrrolidone Synthesis
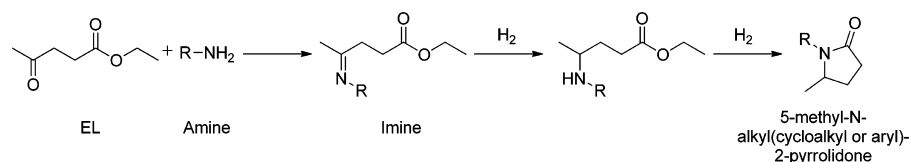
SiO$_2$ and Al$_2$O$_3$. However, hydrogen pressures of 55−69 bar and reaction temperatures of 150−180 °C, as well as organic solvents such as dioxane were used in all the examples reported to achieve N-alkyl(aryl or cyclohexyl)- 5-methyl-2-pyrrolidones. Meanwhile, selectivity, particularly when amines bearing aromatic rings such as for instance aniline or p-toluidine are involved, ranges between 28 and 65%. More recently, Touchy et al.[12] have shown that Pt and MoO$_x$ coloaded on TiO$_2$ (Pt-MoO$_x$/TiO$_2$) is an effective catalyst for the reductive amination of LA with primary amines under solvent-free and mild (100 °C, 3 bar of H$_2$) conditions. The authors showed that the catalyst exhibits high turnover number and a good substrate scope, achieving yields of N-alkyl-5-methyl-2-pyrrolidones between 78 and 96%, though long reaction times (20 h) were required. Moreover, the authors showed that with amines bearing hydrogen-accepting groups such as C−C double and triple bonds, the Pt-MoO$_x$/TiO$_2$ catalyst did not show chemoselectivity and these groups were completely hydrogenated.

In an interesting work, the reductive amination of levulinic acid has been carried out using formic acid as a source of hydrogen, on the basis that the formic acid would be obtained during the transformation of carbohydrates into LA. Then, cyclometalated iridium complexes[13] and dichloro(p-cymene)-ruthenium(II) dimmer with different phosphine ligands (RuCl$_2$/PPh$_3$ complex)[14] were used to perform the reductive amination of LA with amines. Nevertheless, the homogeneous catalytic system presents the difficulty of catalyst recovery and reuse. More recently, Wei et al.[15] have reported an efficient catalyst-free transformation of levulinic acid into pyrrolidones using formic acid and a stoichiometric amount of triethylamine in DMSO as solvent. Although the process is interesting, extracting the product from the DMSO became difficult. Heterogeneous catalysts such as gold nanoparticles deposited on ZrO$_2$ (Au-ZrO$_2$) have also been reported to promote the transformation of LA and ammonia or primary amines into 5-methyl-2-pyrrolidones in the presence of formic acid, because Au on TiO$_2$ was already successfully used to produce pyrrolidone with ammonia and amines.[16] Nevertheless the Au-ZrO$_2$ catalyst described above requires long reaction times to achieve high yields and its reaction scope is rather limited. For instance, when LA, aniline, and formic acid were reacted in water at 130 °C, 88% yield of 5-methyl-N-phenyl-2-pyrrolidone was obtained in 24 h, and no data on catalyst reusability were presented.[17]

In the present work, and given that levulinic acid can be efficiently extracted as alkyl esters by reactive extraction with different alcohols or with olefins from aqueous sulfuric feedstocks,[18] we have studied the synthesis of N-substituted-5-methyl-2-pyrrolidones by reductive amination of levulinate esters using molecular hydrogen as reducing agent and have developed highly active and chemoselective of solid catalysts that are able to work under mild reaction conditions and in absence of solvents. We have found that Pt/TiO$_2$, with Pt crystal faces decorated with TiOx, is an effective and

chemoselective bifunctional catalyst either in batch or in fixed-bed continuous systems for the reductive amination of ethyl levulinate with primary amines giving the corresponding N-substituted-5-methyl-2-pyrrolidones in high conversion and selectivity.

■ RESULTS AND DISCUSSION

Noble metals such as Pt, Pd, Rh are largely used as hydrogenation catalyst.[19] When Au/TiO$_2$ was used for hydrogenation reactions with hydrogen, their activity was generally lower, which can be due to the relatively lower activity of gold for hydrogen activation. This was, in fact, the case for hydrogenation of nitrobenzene and substituted nitrobenzenes.[20] In that particular case, the rate of nitrobenzene hydrogenation on Au/TiO$_2$ was highly enhanced when 100 ppm of Pt were added to the catalyst, being the role of the platinum to increase the rate of hydrogen dissociation.[16] On the other hand, when gold was fully substituted by Pt, then the rate of hydrogenation of nitrobenzene derivatives was much higher but the chemoselectivity was strongly reduced, unless very highly dispersed Pt or Pt decorated with TiOx were used.[21,22] Taking this into account and the observation that supported gold was active and selective for the preparation of pyrrolidone by hydrogenation of succinic and levulinic acid with NH$_3$ or amines, but under high pressures of hydrogen and temperature, we aimed to develop an optimized Pt catalyst to perform the synthesis of N-substituted-5-methyl-2-pyrrolidones at high conversions under mild reaction conditions. Thus, when the reductive amination of ethyl levulinate (EL) and aniline was carried out on a Pt/TiO$_2$ catalyst calcined at 450 °C, one can deduce from the shape of the curves (see Figure 1) that the corresponding imine is a primary and unstable product, whereas the 5-methyl-N-phenyl-2-pyrrolydone appears as a secondary and stable product.

From the yields to the products given in Figure 1, it can be deduced that when the imine is formed, it rapidly reacts to give the aminoester and the final 5-methyl-N-phenyl-2-pyrrolidone (see Scheme 1). In fact, the cyclization of the aminoester to give the pyrrolidone (step 3 in Scheme 1) is so fast that the former intermediate product is not detected. From the above results, it appears that the controlling step for the global reaction can be the formation of imine. To validate that hypothesis, the two steps of the reaction (i.e., imine formation and imine hydrogenation) were studied separately. First, the reaction between ethyl levulinate and the amine (aniline) was performed in the presence of Pt/TiO$_2$ calcined at 450 °C in the presence of H$_2$, but the reaction was carried out in the presence of nitrogen instead of hydrogen to avoid the subsequent hydrogenation of the imine (Figure 2). In this case, the initial reaction rate (step 1, Scheme 1) is 0.09 mmol h^{-1}. On the other hand, when the imine formed in step 1 was independently hydrogenated with Pt/TiO$_2$ catalyst calcined at 450 °C in H$_2$, the rate of the reaction was 0. 59 mmol h^{-1} (Figure 3). These results allow us to conclude that, indeed, the controlling step in the multistep process given in Scheme 1 is the first one (i.e., the
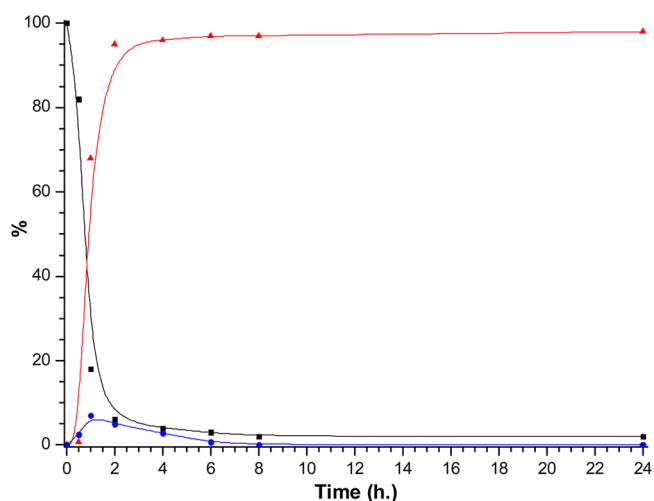
Figure 1. Reductive amination of EL with aniline using Pt/TiO$_{2D}$ (100 mg, 0.05 mol % Pt) as catalyst, 10 bar hydrogen at 120 °C without solvent. [■] aniline conversion; [red ▲] 5-methyl-2-pyrrolidone yield; [blue ●] imine yield.
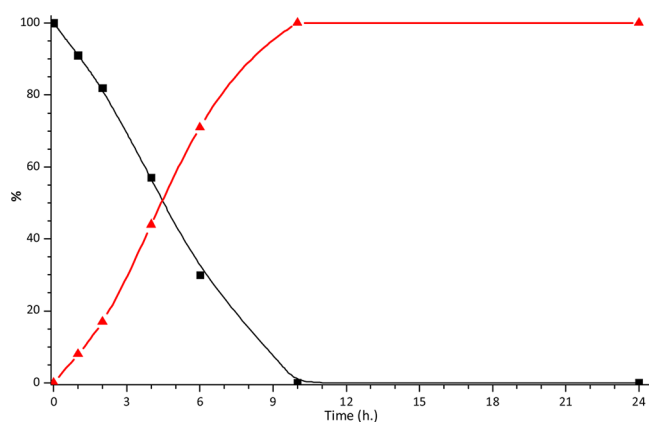

Figure 2. Catalytic activity of 0.2 wt %Pt/TiO$_{2D}$ for the formation of imine between EL and aniline at 120 °C in absence of hydrogen and solvent. [■] EL conversion; [red ▲] imine yield.
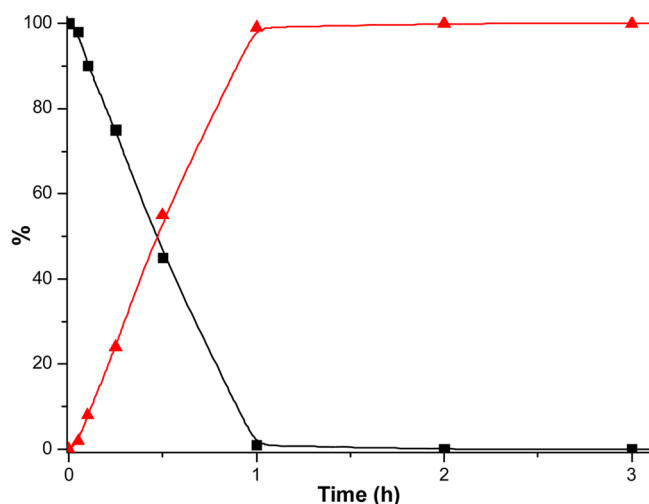

Figure 3. Catalytic activity of 0.2 wt %Pt/TiO$_{2D}$ for the hydrogenation of imine at 120 °C in the absence of solvent. [■] imine conversion; [red ▲] pyrrolidone yield.

formation of the imine). However, if the results are further analyzed, it could be expected that the reaction rate for the global process should be the same than the rate of the slowest step i.e., 0.09 mmol h^{-1} that corresponds to the formation of the imine. In spite of that, the global rate of the reaction calculated from Figure 1 was 0.39 mmol h^{-1}. This is clearly larger than the 0.09 mmol h^{-1} obtained for the formation of the imine in nitrogen atmosphere and lower than the 0.59 mmol h^{-1} for hydrogenation of the imine. To find answers to this puzzling situation, we considered that (a) the first step (i.e., imine formation) is a reaction that does not require the presence of a catalyst to occur, but nevertheless, the rate can be enhanced in the presence of an acid catalyst and (b) the reaction for independently studying the imine formation, and which resulted in an initial reaction rate of 0.09 mmol h^{-1}, was not performed exactly under the same conditions than the global reaction. Indeed, the global reaction was performed under hydrogen, while when the first step was studied separately, it was carried out under nitrogen, to avoid subsequent hydrogenation.

From the first consideration (i.e., possible acid catalysis for imine formation), we can not expect TiO$_2$ to behave like a strong solid acid catalyst for this reaction, and indeed, the rate of formation of the imine under N$_2$ in the presence or absence of the Pt/TiO$_2$ was 0.09 and 0.004 mmol h^{-1}, respectively, indicating that the acidity of TiO$_2$ is still limited. However, it is clear from the kinetic results that when the reaction was carried out in the presence of hydrogen, the rate of the imine formation was strongly increased. A positive effect of H$_2$ was observed by Santoro et al.,[23] who indicate that it may drag the reaction by withdrawing the imine by hydrogenation. Although this could be a possible explanation, an increase in the acidity of the Pt/TiO$_2$ catalyst in the presence of hydrogen could also contribute to the increase in the rate of imine formation. In fact, the formation of protonic acid sites from hydrogen dissociation on metal-supported catalyst has precedents.[24] Hattori and Shishido showed that hydrogen can be dissociatively adsorbed on metallic sites (Pt) to form hydrogen atoms, which migrate by spillover to Lewis acid sites of the support. There hydrogen atoms can release one electron to became a proton that may be stabilized on the oxygen atom near to the Lewis acid center of the support generating protonic acid sites that can be active for acid-catalyzed reactions. This can certainly occur in our case, considering the semiconductor characteristics of the support. In fact, IR spectra clearly show the formation of new acid sites on the Pt/TiO$_2$ catalyst in the presence of H$_2$ (see Figure S1).

Then, confirming our above explanation, two additional experiments were carried out. In a first series of experiments, the reductive amination of EL with aniline was carried out in the presence of TiO$_2$ with no Pt and hydrogen, and only 10% of imine was detected after 12 h of reaction time. In a second set of experiments, a reaction typically catalyzed by acid sites such as the acetalization of carbonyl compounds (i.e., cyclohexanone with ethanol) was carried out at 120 °C using Pt/TiO$_2$ as catalysts in the presence and in absence of hydrogen. In the absence of hydrogen, we did not observe the formation of the diethyl acetal of cyclohexanone. However, in the presence of hydrogen, 70% of diethylacetal together with 30% of cyclohexanol was formed after 12 h, indicating that the acid-catalyzed reaction only occurs on Pt/TiO$_2$ when hydrogen was present.

The results given above support the hypothesis that protonic acid sites can be formed on the surface of Pt/TiO$_2$ by hydrogen

Table 1. Reductive Amination of EL with Different Amine-Bearing Reducible Groups

Entry	Catalyst	Amines	t (h)	Conv.%[a]	Select.%[b]	Yield.%[b]
1	0.2Pt/TiO$_{2D}$	H$_2$C=CH—C$_6$H$_4$—NH$_2$	2	90	94	85
2	0.2Pt/TiO$_{2ND}$	H$_2$C=CH—C$_6$H$_4$—NH$_2$	2	46	60[c]	28
3	0.2Pt/ZrO$_2$	H$_2$C=CH—C$_6$H$_4$—NH$_2$	2	56	37[d]	21
4	0.2Pt/TiO$_{2D}$	NC—C$_6$H$_4$—NH$_2$	2	91	90	82
5	0.2Pt/TiO$_{2D}$	H$_3$COC—C$_6$H$_4$—NH$_2$	2	90	90	81

Reaction conditions: ethyl levulinate (2 mmol), amine (2 mmol), hydrogen (P = 10 bar) 100 mg of catalyst (0.05 mol %), at 120 °C, 2 h. [a]EL conversion. [b]Selectivity and yield of pyrrolidone. [c]10% of the pyrrolidone hydrogenated at C=C was detected. [d]26% of the pyrrolidone hydrogenated at C=C was detected.

dissociation on Pt and spillover, and the acid sites formed can catalyze the formation of imine. In other words, in this case, we have a bifunctional catalyst.

Nature of the Pt Sites for Chemoselective Reductive Amination. After finding that Pt/TiO$_2$ was an active catalyst for the conversion of EL and aniline into *N*-phenyl-5-methyl-2-pyrrolidone, and in our search for a chemoselective catalyst to prepare N-substituted-5-methyl-2-pyrrolidones, the reductive amination was performed with a vinyl aniline and EL. Results in Table 1 (entries 2 and 3) show that when the reductive amination of EL with *p*-vinylaniline was performed on a Pt/TiO$_2$ catalyst calcined at 250 °C in the presence of H$_2$ (0.2% Pt/TiO$_{2ND}$) or with 0.2%Pt/TZrO$_2$, the chemoselectivity was relatively lower, in which the vinyl group was also hydrogenated, resulting in the formation of the *N*-(4-ethylphenyl)-5-methyl-2-pyrrolidone (see Scheme 2). This result would be in

Scheme 2. Reductive Amination of EL with 4-Vinylaniline in the Presence of 0.2%Pt/TiO$_{2ND}$
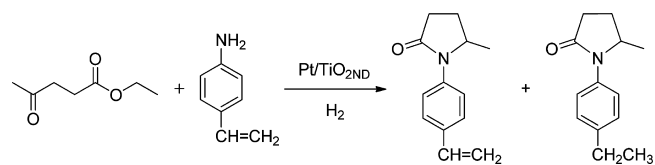
line with our previous observation that Pt/TiO$_2$ was not a chemoselective catalyst for hydrogenation of substituted nitrobenzenes unless the surface of the Pt was decorated with TiO$_2$ by calcining the Pt/TiO$_2$ at 450 °C in the presence of hydrogen.[21] Following that, the Pt/TiO$_2$ was calcined at 450 °C (0.2%Pt/TiO$_{2D}$), and the results given in Table 1 clearly show that the resultant catalyst is not only more active but also more chemoselective when the reductive amination was performed with *p*-vinylaniline (see Table 1, entry 1). As could be expected,

preferential hydrogenation of the imine intermediate also occurred when the aromatic ring substituents included a carbonyl group or a nitrile group. Because the intrinsic rate for imine hydrogenation is higher than the rate for hydrogenation of the vinyl group in the decorated catalyst, although the opposite occurs in the non decorated catalyst, we could assume, in first approximation, that there is a preferential adsorption of the imine versus the double bond on the catalytic site, which is responsible for the high activity and selectivity exhibited by 0.2%Pt/TiO$_{2D}$ catalyst. To test this hypothesis, a set of catalytic experiments combined with an "in situ" IR spectroscopy study were designed. In a model of reactants, the imine of the ethyl levulinate with butyl amine (ethyl 4-(butylimino)pentanoate) and styrene first separately and then as a mixture were hydrogenated in the presence of 0.2%Pt/TiO$_{2D}$ and 0.2%Pt/TiO$_{2ND}$. The results of TOFs for each case are presented in Table 2. As shown in the table, the hydrogenation of the C=C of styrene is highly favored on the 0.2%Pt/TiO$_{2ND}$ compared with 0.2%Pt/TiO$_{2D}$, whereas the rate of hydrogenation of the imine (TOF) is superior on 0.2%Pt/TiO$_{2D}$ than on 0.2%Pt/TiO$_{2ND}$. Moreover, the TOF for imine hydrogenation is practically maintained for each catalyst when the imine is hydrogenated alone or in the presence of styrene. However, the hydrogenation of styrene is strongly inhibited when the imine is present on 0.2%Pt/TiO$_{2ND}$, and particularly, on 0.2%Pt/TiO$_{2D}$. These results suggest that hydrogenation of C=C group does not compete with the hydrogenation of the imine group on the Pt sites in 0.2%Pt/TiO$_{2D}$, due to a possible preferential adsorption of the imine with respect to the vinyl group.

To further check that hypothesis, the competitive adsorption of the imine formed from EL and butylamine, and styrene was followed by "in situ" IR spectroscopy. Thus, an equimolar mixture of imine and styrene adsorbed on 0.2%Pt/TiO$_{2D}$ catalyst (Figure 4) gave IR bands at 1600 and 1580 cm^{-1} associated with the ν(C=N) stretching frequency of the imine

Table 2. Results of TOF for the Hydrogenation of Styrene, Ethyl 4-(Butylimino)pentanoate, and a Mixture of Them Using 0.2% Pt/TiO$_{2D}$ and 0.2%Pt/TiO$_{2ND}$ Catalyst

| | TOF (h^{-1})[a] | | | |
| | | | imine + styrene mixture | |
	styrene hydrogenation	imine hydrogenation	styrene hydrogenation	imine hydrogenation
0.2 wt %Pt/TiO$_{2D}$	357	632	0	578
0.2 wt %Pt/TiO$_{2ND}$	5265	187	19	174

Reaction conditions: imine (1 mmol), styrene (1 mmol), hydrogen (P = 10 bar) 50 mg of catalyst (0.05 mol %), at 120 °C. [a]Calculated as mol of product/mol Pt × h^{-1}.
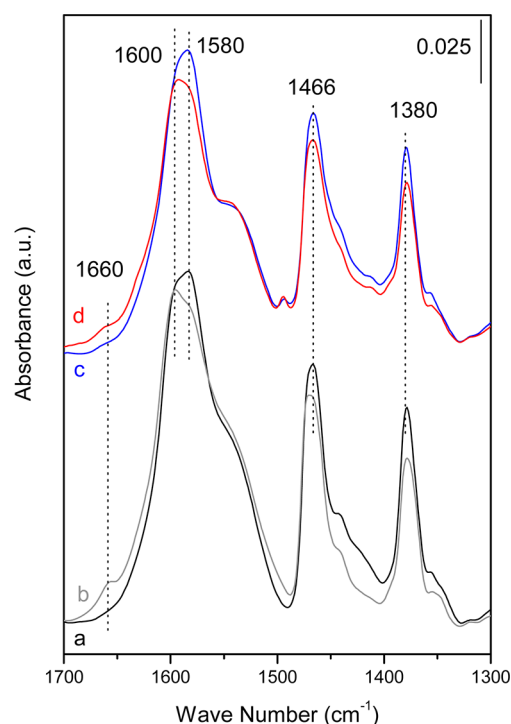

Figure 4. IR spectra of 3 mbar ethyl-4-(butylimino)pentanoate adsorption at 25 °C (a) followed by 3 mbar styrene coadsorption on the 0.2 wt %Pt/TiO$_{2D}$ catalyst at 25 °C (b) 120 °C (c), and subsequent addition of 30 mbar H$_2$ at 120 °C (d). All spectra were recorded after 30 min of equilibrium time.

and the IR band at 1660 cm^{-1} that can be associated with the C=C stretching frequency in styrene. In other words, both the imine and styrene can adsorb but the intensity of the band at 1660 cm^{-1} associated with styrene is much lower than the intensity of the bands associated with the imine at either 25 or 120 °C (Figure 4, spectra b and c, respectively). Furthermore, at 120 °C, when H$_2$ was introduced (Figure 4, spectra d), the IR bands associated with the imine (i.e., 1600, 1580, 1466, and 1380 cm^{-1} decrease), whereas the IR band at 1660 cm^{-1} associated with the C=C group in the styrene remains practically the same. These results confirm that the preferential adsorption of the imine group on the active Pt sites versus the C=C bond and can explain the high chemoselectivity observed on the 0.2%Pt/TiO$_{2D}$ sample.

Effect of Crystal Size of Metal on the Catalytic Activity. Since the controlling step is the imine formation and, as was discussed above, hydrogen dissociation and spillover is required to form the Bronsted acid sites on the support, metal dispersion should have an impact on the rate of reaction. Thus, we have modified the metal crystallite size by changing the amount of Pt on the support.

Transmission electron microscopy (TEM) was applied to determine the particle size distribution of the platinum nanoparticles. The images revealed that the sizes of the platinum nanoparticles increased by increasing the percentage of platinum from 0.2 to 5%. The particle distributions presented in Figure 5 were achieved by treatment of the images using Image software. As observed in the histograms, the average size of metal nanoparticles and the distribution range increases when increasing the percentage of platinum on the support. Moreover the IR spectrum of adsorbed CO (Figure 6) on samples with larger Pt crystal size (5%Pt/TiO$_{2D}$, 1%Pt/TiO$_{2D}$) showed mainly bands in the 2100−2086 cm^{-1} region, which correspond to CO molecules adsorbed on Pt (111) terraces (sites with coordination number 9). The IR bands in the 2077−2071 cm^{-1} are related to CO molecules adsorbed on Pt(100) sites (Pt sites with coordination number of 8), which are clearly observed when the crystal size is decreased from 6 to 7 nm to 4−5 nm (1%Pt/TiO$_{2D}$ sample). Finally, IR bands at lower frequencies (2059 and 2040−2020 cm^{-1}) are associated with the presence of Pt sites of low surface coordination, like steps and corners,[25] mainly present on the sample of the lowest crystal size (0.2%Pt/TiO$_{2D}$).

When these samples were tested in the reductive amination of EL, with aniline it was observed that the 0.2%Pt/TiO$_{2D}$ sample, with smaller particle size (i.e., higher proportion of Pt sites within low surface coordination) gave the highest activity and selectivity to 5-methyl-N-phenyl-2-pyrrolidone (see Table 3), indicating that a high proportion of the imine adsorption sites occur at defects of Pt nanoparticles, which have to increase when decreasing the crystal size. In fact, the IR spectra of imine adsorption on Pt/TiO$_2$ samples of different sizes shows a stronger interaction on the sample of lowest crystal size (0.2% Pt/TiO$_{2D}$) versus the sample of bigger crystal size (5%Pt/TiO$_{2D}$) (Figure.S2a), whereas an opposite trend is observed when styrene has been adsorbed on the same samples. In this case, a higher interaction is observed on the sample of biggest crystal size (5%Pt/TiO$_{2D}$), whereas a lower interaction is observed on the smallest one (0.2%Pt/TiO$_{2D}$) (Figure S2b). These results suggest that the presence of higher proportion of Pt sites with low surface coordination in the small crystal size samples (0.2%Pt/TiO$_{2D}$) are expected to be the chemoselective active sites for hydrogenation of the imine versus hydrogenation of the C=C bond. In fact, the reductive amination of ethyl levulinate with p-vinylaniline (Table S1) showed 94% selectivity to the respective pyrrolidone on the small crystal size sample, whereas 95% selectivity to C=C bond hydrogenation was observed on the bigger crystal size sample.

Moreover, the Pt-TiO$_2$ interphase and therefore a higher hydrogen spillover and potential formation of a higher acidity can occur for the sample with a higher Pt dispersion. To check that, the acetalization of cyclohexanone with ethanol was
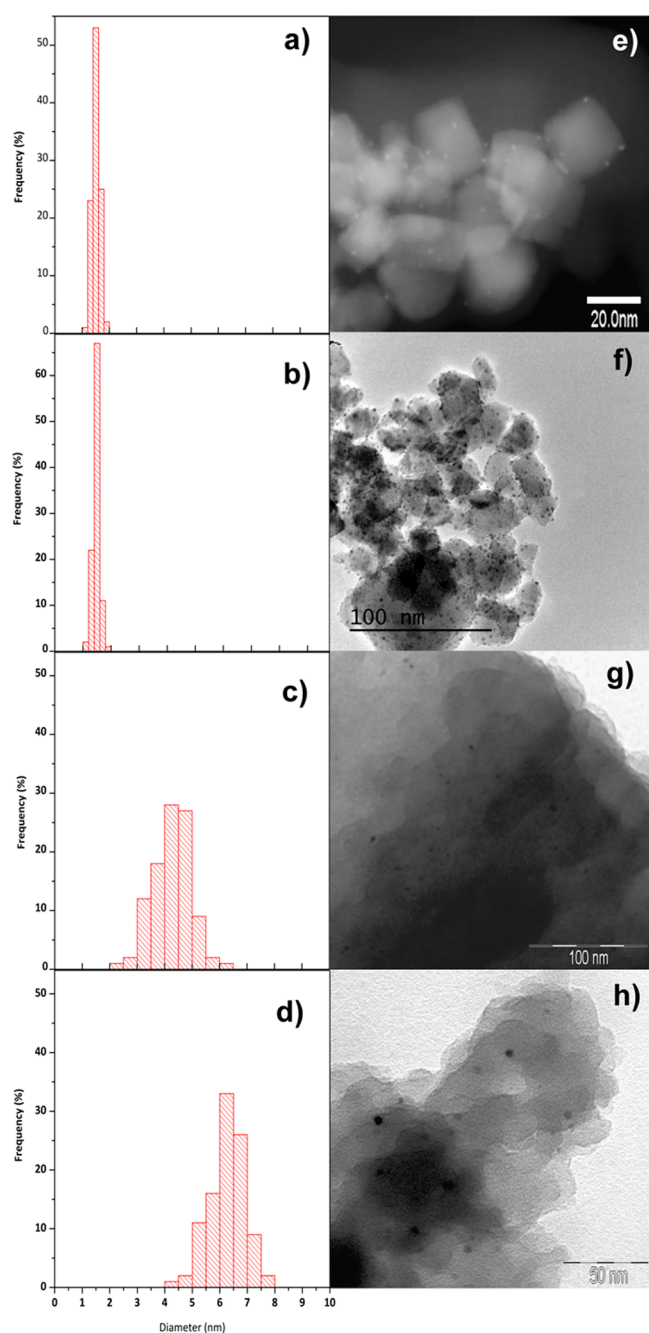
Figure 5. Particle size distribution (PSD) of Pt obtained from TEM images for Pt/TiO$_2$ samples. Corresponding diameter histograms: (a) 0.2%Pt/TiO$_{2D}$, (b) 0.2%Pt/TiO$_{2\ ND}$, (c) 1%Pt/TiO$_{2D}$, and (d) 5%Pt/TiO$_{2D}$; corresponding TEM images (e−h).

Figure 6. IR spectroscopy of CO adsorbed onto Pt/TiO$_{2D}$ (spectra were normalized on the Pt-content for the materials). (A) 5% Pt/TiO$_2$, (B) 1% Pt/TiO$_2$, (C) 0.2% Pt/TiO$_2$.

carried out in hydrogen on the Pt/TiO$_2$ with different Pt dispersion after being treated at 450 °C in hydrogen. The results in Table 4 show an increase in activity (TOF) when metal dispersion increases.

Scope of the Reductive Amination. The scope of the reaction was studied by performing the reductive amination of ethyl levulinate with different aryl, alkyl, and cycloalkyl amines with 0.2%Pt/TiO$_{2D}$ as catalyst and 2000 substrate/catalyst molar ratio. In Table 5 can be seen that aromatic amines with electron-withdrawing groups (entries 11−13) are more reactive than aromatic amines with electron-donating substituents (entries 4−10), which required longer reaction times in order
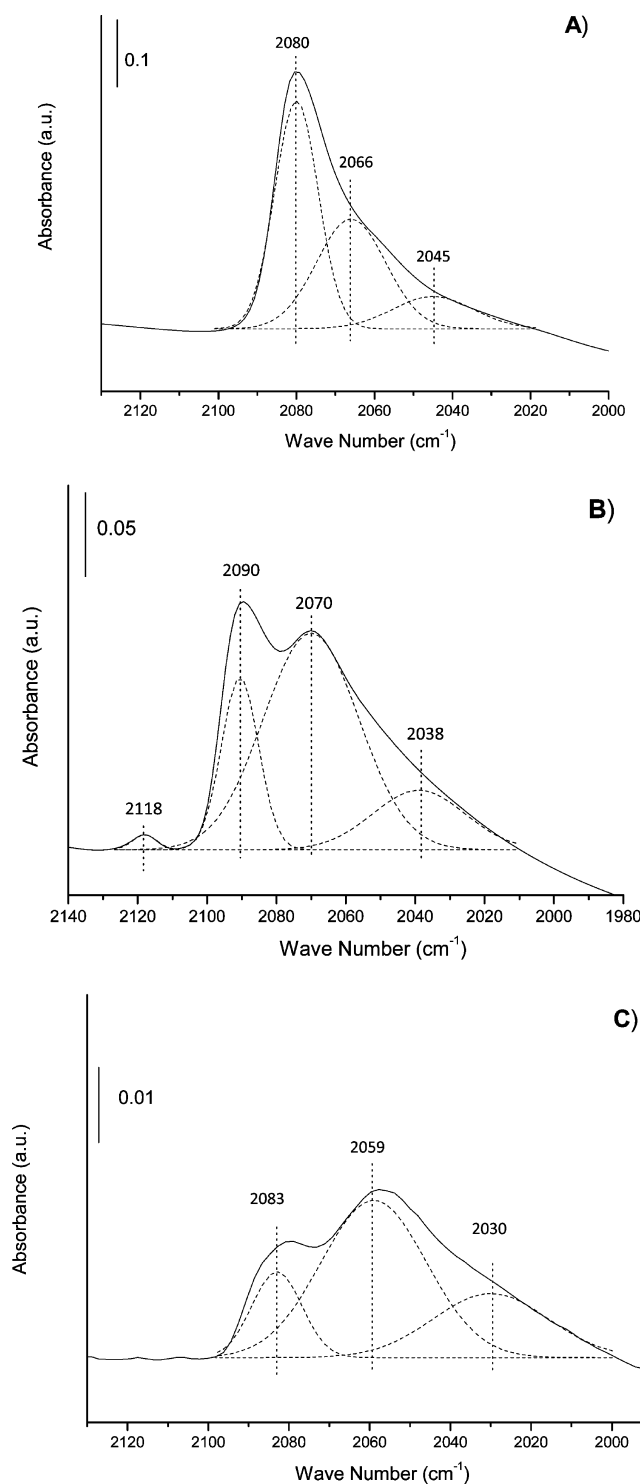
to reach good yields (92−98%). Moreover, when a substituent at the 2-position of aniline is present, a strong decrease in selectivity to 5-methyl-2-pyrrolidone is observed. In these cases, the fact that EL conversion was very high, while the yield of pyrrolidones was low, could be due to steric hindrance for the adsorption of the imine intermediate and subsequent hydrogenation (Table 5, entries 4−6). In fact, the imine intermediate was the main product detected in the reaction media, whereas

Table 3. Catalytic Activity of Different Pt/TiO$_2$ with Different Pt Loading in the Reductive Amination of EL with Aniline

Pt content (wt %)	conv. (%)	yield (%)	TOF (h^{-1})[a]
5	14	9	194
1	42	29	295
0.2	98	97	733

Reaction conditions: EL (2 mmol) and aniline (2 mmol), catalysts (0.05 mol %), hydrogen (10 bar), 6 h, at 120 °C. [a]Calculated as mol of product/mol Pt × h^{-1}

Table 4. Initial Reaction Rates of Acetalization of Cyclohexanone with Ethanol Using Pt/TiO$_2$ Samples with Different Metal Dispersion

catalyst	r_0 (mmol h^{-1})[a]	TOF (h^{-1})[b]
0.2 wt %Pt/TiO$_{2D}$	0.35	682
1 wt %Pt/TiO$_{2D}$	0.20	390
5 wt %Pt/TiO$_{2D}$	0.15	292

Reaction conditions: cyclohexanone (1 mmol); ethanol (1 mL); 0.05 mol % Pt, 10 bar H$_2$ at 120 °C. [a]Initial reaction rate of formation of the acetal. [b]Calculated as mol of product/mol Pt × h^{-1}

no other byproducts were detected. In general, good conversions and selectivities were achieved in the case of alkyl amines and hydroxyamines (entries 17−21), and in the case of cycloalkyl amines, the conversion and selectivity strongly depends on the size of the cycloalkyl ring. This result can be related with the existence of steric hindrance for the imine formation and subsequent hydrogenation.

For comparison purposes in Table 5 (entries 3, 9, and 24), we have included the results reported in patent literature when using 5% Pt/C as catalyst.[10] It can be observed that using a clear excess of hydrogen, a limited selectivity, particularly for the formation of 5-methyl-N-aryl-2-pyrrolidones can be achieved, which is due to overhydrogenation of the aromatic ring.[10] Then, as far as we know, the results presented in this work on the reductive amination of ethyl levulinate using molecular hydrogen and Pt/TiO$_{2D}$ under mild reaction conditions are the best currently reported.

Stability and Reusability of the 0.2%Pt/TiO$_{2D}$ Catalyst. To demonstrate that the catalytic process involves a heterogeneous metallic Pt species, an additional experiment was carried out where the reductive amination of EL with octylamine in the presence of 0.2%Pt/TiO$_{2D}$ was stopped after 60 min. At this point, the catalyst was filtered off and the reaction was continued for an additional 6 h, but no further conversion was detected (Figure 7), indicating that the catalyst is stable and that active Pt species are not leached into the reaction media, which is in good agreement with the results of ICP analysis.

In order to test the reusability of the catalyst, after being used in the reaction, the catalyst was removed by filtering and washed thoroughly with methanol before each consecutive reuse (see experimental section). As can be observed in Figure 8, the conversion and selectivity slightly decreased when the catalyst was subjected to five consecutive cycles. Thus, a decrease <16% of conversion and <6% in selectivity was observed after five cycles, with an accumulated TON (mol of pyrrolidone formed/mol Pt) of 8540 mol mol^{-1}. The slight

Table 5. Reductive Amination of EL with Different Amines Using 0.2%Pt/TiO$_{2D}$ Catalyst

entry	amine	t (h)	EL conv. (%)[a]	pyrrolidone select. (%)	pyrrolidone yield (%)
1	aniline	6	98	95	93
2[a]	aniline	18	100	100	100
3[b]	aniline	4	58	28	16
4	2-methylaniline	6	96	42	40
5	2-ethylaniline	6	92	28	26
6	2-isopropylaniline	6	92	40	37
7	4-ethylaniline	6	93	97	90
8	4-methylaniline	6	98	91	90
9[b]	4-methylaniline	6	78.1	63.9	50
10	4-methoxyaniline	6	91	99	90
11	4-cloroaniline	2	95	91	87
12	4-cyanoaniline	2	91	90	82
13	4-acetylaniline	2	90	90	81
14	4-vinylaniline	2	90	94	85
15	phenylmethylamine	2	99	91	90
16	2-phenylethylamine	2	97	97	94
17	butylamine	6	88	94	83
18	hexylamine	2	75	98	62
19	octylamine	2	98	100	98
20	2-hydroxyethylamine	6	96	95	92
21	3-hydroxypropylamine	2	98	92	90
22	cyclopentylamine	6	61	80	49
23	cyclohexylamine	2	94	97	91
24[b]	cyclohexylamine	4	92	86.6	79
25	cycloheptylamine	2	53	67	35

Reaction conditions: EL (2 mmol), amine (2 mmol), hydrogen (P = 10 bar), 100 mg of 0.2%Pt/TiO$_{2D}$ catalyst (0.05 mol %), S/C = 2000, at 120 °C without solvent. [a]5 bar at 150 °C; [b]Results reported in ref 10. Reaction conditions: EL/amine/dioxane (wt %) = 0.30:0.25:0.50 g, 50 mg of commercial 5%Pt/C (ESCAT-248), S/C = 0.15, 150 °C, hydrogen (55−69 bar).
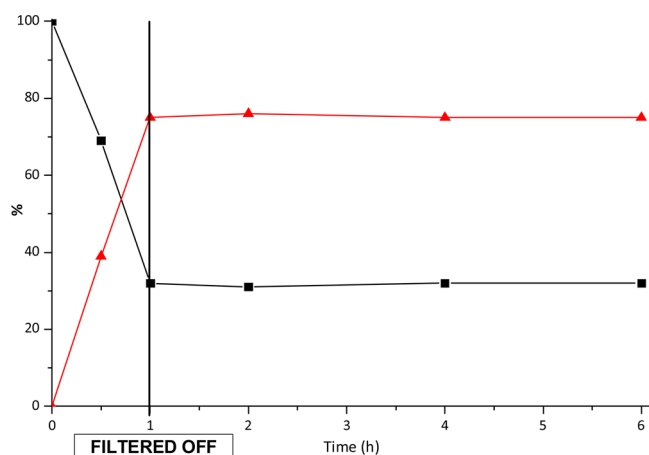
Figure 7. Reductive amination of EL with octylamine using 0.2 wt % Pt/TiO$_{2D}$ (100 mg, 0.05 mol % Pt) as catalyst, 10 bar hydrogen at 120 °C without solvent. The catalyst was filtered off at 1 h. [■] aniline conversion; [red ▲] pyrrolidone yield.
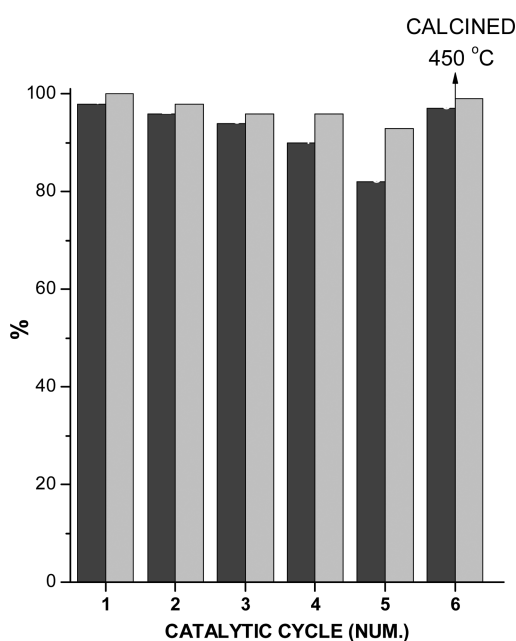

Figure 8. Reuses of 0.2%wtPt/TiO$_{2D}$ catalyst in the reductive amination of EL with octylamine. Reaction conditions: ethyl levulinate (2 mmol), amine (2 mmol), hydrogen (P$_0$ = 10 bar), 100 mg of 0.2% wtPt/TiO$_{2D}$ catalyst (0.05 mol %), S/C = 2000, at 120 °C, without solvent, 6 h. [■] EL conversion; [gray-colored □] pyrrolidone selectivity.

decrease in activity cannot be attributed to Pt leaching during the recycle process because the total amount of platinum (0.2%) was maintained at least during the five consecutive cycles as detected by ICP-AES. The observed effect could be attributed to adsorption of organic compounds on the surface of the catalyst. Indeed, when the catalyst was calcined at 450 °C, the catalytic activity was restored.

Synthesis of Pyrrolidones in a Fixed-Bed Continuous-Flow Reactor. After the study of the one-pot selective reductive amination of biomass-derived ethyl levulinate with primary amines to obtain pyrrolidones in a batch reactor, we thought to explore the possibility of carrying out the process in

a fixed-bed continuous reactor, which may offer industrial advantages when processing larger volumes.

We started our study using Pt/TiO$_{2D}$ as catalyst with different platinum content (0.2%, 1%, and 5%) in the reductive amination of EL with aniline, and the results are displayed in Figure 9. As expected, higher selectivity to 5-methyl-N-phenyl-
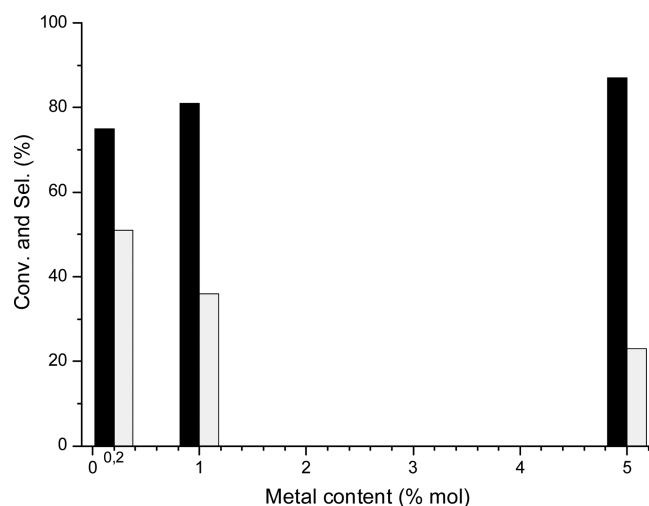

Figure 9. Reductive amination of EL with aniline in a fixed-bed reactor using Pt/TiO$_{2D}$ with different metal content. Reaction conditions: equimolar ratio of EL/aniline, at feed rate of 0.5 mL h^{-1}, together with a hydrogen flow of 10 mL min^{-1}, pressure hydrogen (P = 10 bar), 1500 mg Pt/TiO$_2$ catalyst, at 120 °C, after 10 h. [■] EL conversion; [gray-colored □] pyrrolidone yield.

2-pyrrolidone was achieved using 0.2%Pt/TiO$_{2D}$ after 4.5 h time on stream. Thus, the study of the influence of different parameters such as temperature, hydrogen pressure, and contact time (τ) in the fixed-bed reactor on the catalytic activity was optimized using 0.2%Pt/TiO$_{2D}$ as catalyst. For instance, in Figure 10 is presented the study of the influence of the contact time (τ) on the yield of 5-methyl-N-phenyl-2-pyrrolidone.

Under optimized reaction parameters (i.e., 150 °C), 5 bar of hydrogen, and contact time (τ)= 4.5 h, ethyl levulinate conversion and 5-methyl-N-phenyl-2-pyrrolidone selectivity of 85 and 90%, respectively, that remain constant during 10 h on stream were obtained (see Figure 10).

■ CONCLUSIONS

We have successfully performed the reductive amination of ethyl levulinate with amines, yielding the corresponding N-substituted-5-methyl-2-pyrrolidones using H$_2$ as reducing agent in the presence of Pt/TiO$_2$ as catalyst under solvent-free conditions. The process involves as a first step the formation of an imine intermediate followed by hydrogenation of the imine group and subsequent cyclization into pyrrolidone. The Pt/TiO$_2$ increases their catalytic activity and chemoselectivity when the Pt crystal faces are decorated with TiOx, and it is possible to achieve high conversion and selectivity to the corresponding N-substituted-5-methyl-2-pyrrolidones even when other groups susceptible of hydrogenation are present in the amine moiety. A series of reactivity studies showed that the reaction-controlling step is the formation of the imine intermediate, and the rate of formation is increased by the presence of protonic acid sites generated by spillover on the
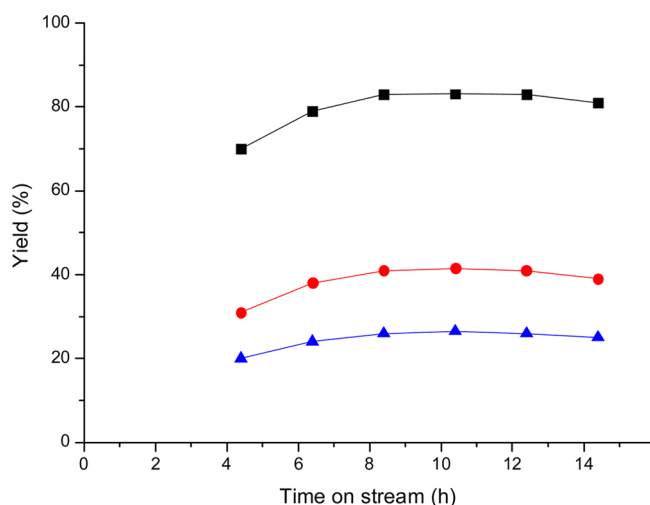
Figure 10. Plot-time yield of reductive amination of EL with aniline in a fixed-bed reactor. Reaction conditions: equimolar ratio EL/aniline, with a hydrogen flow of 10 mL min^{-1}, pressure hydrogen (P = 5 bar), 1500 mg 0.2 wt %Pt/TiO$_{2D}$ catalyst, at 150 °C without solvent. Rate of feed: [■] 0.5 mL h^{-1}, contact time of 4.50 h, WHSV = 0.223 h^{-1}; [red ●] 1.0 mL h^{-1} contact time of 2.25 h, WHSV = 0.444 h^{-1} and [blue ▲] 1.5 mL h^{-1} contact time of 1.50 h, WHSV = 0.667 h^{-1}.

TiO$_2$ support of hydrogen dissociated on the metal. The study of the influence of the metal crystal size on the catalytic activity and selectivity showed that the sample with the lowest crystal size presents the highest activity and selectivity to 2-pyrrolidone. This finding was attributed to the presence of their higher concentration of Pt sites of low surface coordination, which are responsible for the preferential adsorption of the imine intermediate. The optimized catalyst can be regenerated and reused up to five consecutive cycles, showing a slight loss of activity. However, the initial activity could be completely restored after calcinations of the catalyst at 450 °C. The Pt/TiO$_{2D}$ can be used to produce a variety of 2-pyrrolidones with excellent yields. Finally, it is presented that the preparation of N-substituted-5-methyl-2-pyrrolidones starting from ethyl levulinate and amines can be carried out successfully in a continuous fixed-bed reactor.

■ EXPERIMENTAL SECTION

Catalysts Preparation. Pt/TiO$_2$ catalysts were prepared by using H$_2$PtCl$_6$ hexahydrate as Pt source according to the method reported in ref 26. Typically, 0.2%Pt/TiO$_{2D}$ catalyst was prepared by a modified deposition−precipitation (DP) method by mixing TiO$_2$ powders (5 g) with an appropriate amount of an aqueous solution of hexachloroplatinic acid. The mixture was stirred overnight at room temperature under inert atmosphere, and then the catalyst was dried at 100 °C in a forced air oven for 5 h, followed by reduction with a stream of H$_2$ at 450 °C for 3 h. The 0.2%Pt/TiO$_{2ND}$ sample was reduced with a stream of H$_2$ at 250 °C for 3 h. The concentration of platinum was 0.2% Pt by weight (ICP-AES analysis).

Pt/ZrO$_2$ catalyst were prepared by a modified deposition−precipitation (DP) method by mixing ZrO$_2$ powders (5 g) with appropriate amounts of aqueous solutions of tetrachloroplatinic acid (10 mL). After overnight stirring at room temperature under inert atmosphere, the catalyst was dried at 100 °C in a forced-air oven for 5 h, followed by reduction with a stream of H$_2$ at 450 °C for 3 h. The concentration of platinum (0.2%) was measured by ICP-AES analysis.

Catalysts Characterization. Transmission electron microscopy (TEM) images for supported platinum catalysts were taken with a JEOL 2100 electron microscope operating at 200 kV. Before being transferred into the TEM chamber, the samples dispersed with dichloromethane were deposited onto a carbon-coated copper grid and then quickly moved into the vacuum evaporator. The size distribution of the metal nanoclusters was determined by measuring about 200 random particles on the images.

Additionally, to reveal subtle details of the surface composition of the Pt nanoparticles in the catalysts, nano-analysis by STEM-EELS have been performed.

The Pt loading of the catalysts was measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES) using a Varian 715-ES spectrometer.

The infrared spectra (IR) were measured with a Bruker "Vertex 70" spectrophotometer, at 4 cm^{-1} resolution and using a DTGS detector. An IR cell allowing in situ treatments in controlled atmospheres and temperatures from −176 to 500 °C has been used and connected to a vacuum system with gas dosing facility. The samples were pressed into self-supporting pellets of 10 mg/cm^2 and activated in situ in the IR cell. For activation, the samples were heated at 250 °C for 2 h in an hydrogen flow (15 mL/min), followed by 1 h outgassing at the same temperature under 10^{-6} mbar dynamic vacuum conditions. For the IR experiments of CO adsorption, the catalysts, after activation, were cooled to −176 °C under dynamic vacuum conditions followed by CO dosing at increasing pressure (0.1−1.5 mbar). IR spectra were recorded after each dosage. For the mechanistic IR studies, the catalysts, after activation, were cooled to 25 °C under dynamic vacuum conditions. Ethyl-4-(butylimino)pentanoate (3 mbar) was coadsorbed with 3 mbar of styrene. IR spectra were recorded in the presence of both reactants after 30 min, collecting spectra at 25 °C and after increasing temperature to 120 °C. At that temperature, 15 mbar H$_2$ wasadded, and the IR spectra were recorded after 30 min of reaction time. Preliminary IR experiments, in which the order of addition of both reactants into the IR cell has been inverted, show no influence on the final IR spectrum. Origin software was used for spectra decovolution.

General Procedure for the Production of Pyrrolidones by Reductive Amination of Levulinic Acid Derivates with Amines. Catalytic experiments were performed under H$_2$ atmosphere in a 2 mL glass-made reactor. For each reaction, a mixture of EL (2 mmol), primary amine (2 mmol), supported metal catalysts (metal 0.05 mol %), and dodecane (0.2 mmol) as internal standard, were charged into the reactor. After sealing the reactor, air was purged by flushing twice with 10 bar of hydrogen. Then, the mixture of substrates and catalyst were heated to the desired temperature in less than 2 min, and it was pressurized with H$_2$ at the selected set point.

During the experiment, the pressure was kept constant, and the stirring rate was fixed at 1000 rpm. Aliquots (∼20 μL) were taken from the reactor at different reaction times. The product composition was 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.

Recovery and Reuse of Pt/TiO$_{2D}$. First, 100 mg of fresh 0.2%Pt/TiO$_{2D}$ catalyst was used in a mixture containing EL (2 mmol), amine (2 mmol) in a 2 mL pressure reactor. The reaction was performed according to the protocol described

previously. After the reaction, the catalyst was recovered, filtered, washed three times with methanol, dried under vacuum at room temperature, and reused in a consecutive run.

Reductive Amination Reaction in a Continuous Fixed-Bed Reactor. The reductive amination reaction of EL and aniline with 0.2%Pt/TiO$_{2D}$ in a continuous fixed-bed reactor was performed under hydrogen pressure in a tubular stainless-steel reactor (400 mm long, 4.25 mm inner diameter). In a typical experiment, Pt/TiO$_{2D}$ (1.5 g) was pelletized and sieved to a particle size of 0.20−0.40 mm, diluted with silicon carbide and placed in the fixed-bed reactor. After that, an equimolar mixture of EL and aniline was fed by using a syringe pump perfusion at a rate of 0.5 mL h^{-1} (which corresponds to a weight hourly space velocity (WHSV) of 0.223 h^{-1} or a contact time of 4.50 h) along with a hydrogen flow of 10 mL min^{-1} at 5 bar pressure. The reaction temperature, measured by using a thermocouple in direct contact with the catalytic bed, was maintained during the reaction at the selected point. The reaction products were analyzed by gas chromatography (GC) and GC−MS using dodecane as an external standard.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01113.

Supplemental IR spectra and data for the reductive amination of ethyl levulinate with 4-vinyl aniline on Pt/TiO$_2$ samples of different crystal sizes (PDF)

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Notes
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■ REFERENCES

(1) (a) Huber, G. W.; Iborra, S.; Huber, G. W. *Chem. Rev.* **2006**, *106*, 4044−4098. (b) Vispute, T. P.; Zhang, H.; Sanna, A.; Xiao, R.; Huber, G. W. *Science* **2010**, *330*, 1222−1227. (c) Climent, M. J.; Corma, A.; Iborra, S. *Green Chem.* **2014**, *16*, 516−547.

(2) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411−2502.

(3) Climent, M. J.; Corma, A.; Iborra, S. *Green Chem.* **2011**, *13* (3), 520−540.

(4) Gallezot, P. *Chem. Soc. Rev.* **2012**, *41*, 1538−1558.

(5) (a) Werpy, T.; Petersen, G. R. *Top Value Added Chemicals from Biomass*, Volume I. Results of Screening for Potential Candidates from Sugars and Synthesis Gas; U.S. Department of Energy; U.S. Government Printing Office: Washington, DC, 2004. (b) Bozell, J. J.; Petersen, G. R. *Green Chem.* **2010**, *12*, 539−554.

(6) Manzer, L. E. US 6743819B1, 2004.

(7) Manzer, L. E. US 247443A1, 2006.

(8) (a) Shilling, W. L. US Patent 32355562, 1966. (b) Croock, L. R.; Jansen, B. A.; Spencer, K. E.; Watson, D. H. GB Patent 1036694, 1996.

(9) van der Stoel, R. E.; Bosma, M. A. R.; Janssen, P. H. J.; van de Moesdijk, C. G. M. US 4560760, 1985.

(10) Manzer, L. E. US 7129362, 2006.

(11) Manzer, L. E. US 0247444, 2006.

(12) Touchy, A. S.; Siddiki, S. M. A. H.; Kon, K.; Shimizu, K. *ACS Catal.* **2014**, *4*, 3045−3050.

(13) Wei, Y.; Wang, C.; Jiang, X.; Xue, D.; Li, J.; Xiao, J. *Chem. Commun.* **2013**, *49*, 5408−5410.

(14) Huang, Y. B.; Dai, J.-J.; Deng, X.-J.; Qu, Y.-C.; Guo, Q.-X.; Fu, Y. *ChemSusChem* **2011**, *4*, 1578−1581.

(15) Wei, Y.; Wang, C.; Jiang, X.; Xue, D.; Liu, Z. T.; Xiao, J. *Green Chem.* **2014**, *16*, 1093−1096.

(16) Budroni, G.; Corma, A. *J. Catal.* **2008**, *257*, 403−408.

(17) Du, X.-L.; He, L.; Zhao, S.; Liu, Y.-M.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7815−7819.

(18) (a) Gurbuz, E. I.; Alonso, D. M.; Bond, J. Q.; Dumesic, J. A. *ChemSusChem* **2011**, *4*, 357−361. (b) Peng, L.; Lin, L.; Li, H.; Yang, Q. *Appl. Energy* **2011**, *88*, 4590−4596. (c) Ayoub, P. M.; Lange, J. P. WO 2008/142127, 2008. (d) Fagan, P. J.; Manzer, L. O. US US7153996 2006.

(19) (a) Bond, G. C. *Chemistry & Industry* **1967**, 2018−2025. (b) Kacer, P.; Cerveny, L. *Appl. Catal., A* **2002**, *229*, 193−216.

(20) Corma, A.; Concepcion, P.; Serna, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7266−7269.

(21) Corma, A.; Serna, P.; Calvino, J. J. *J. Am. Chem. Soc.* **2008**, *130*, 8748−8753.

(22) (a) Climent, M. J.; Corma, A.; Iborra, S.; Santos, L. *Chem. - Eur. J.* **2009**, *15*, 8834−8841. (b) Climent, M. J.; Corma, A.; Iborra, S.; Marti, L. *ACS Catal.* **2015**, *5*, 157−166.

(23) Santoro, F.; Psaro, R.; Ravasio, N.; Zaccheria, F. *ChemCatChem* **2012**, *4*, 1249−1254.

(24) Hattori, H.; Shishido, T. *Catal. Surv. Jpn.* **1997**, *1*, 205−213.

(25) (a) Jin, T.; Zhou, Y.; Mains, G. J.; White, J. M. *J. Phys. Chem.* **1987**, *91*, 5931. (b) Raskó, J. *J. Catal.* **2003**, *217*, 478. (c) Boccuzzi, F.; Chiorino, A.; Guglielminotti, E. *Surf. Sci.* **1996**, *368*, 264−269.

(26) Serna, P.; Lopez-Haro, M.; Calvino, J. J.; Corma, A. *J. Catal.* **2009**, *263*, 328−324.