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## Palladium Doping of $\text{In}_2\text{O}_3$ towards a general and selective catalytic hydrogenation of amides to amines and alcohols

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Herein, the first general heterogeneous catalytic protocol for the hydrogenation of primary, secondary and tertiary amides to the corresponding amines and alcohols is described. Advantageously, this catalytic protocol works under additive-free conditions and is compatible with the presence of aromatic rings, which are fully retained in the final products. This hydrogenative C-N bond cleavage methodology is catalyzed by a Pd-doped  $\text{In}_2\text{O}_3$  catalyst prepared by a microwave hydrothermal-assisted method followed by calcination. This catalyst displays highly dispersed  $\text{Pd}^{2+}$  ionic species into the oxide matrix of  $\text{In}_2\text{O}_3$  that have resulted to be essential for its high catalytic performance.

### Introduction

The reduction of carboxylic acid derivatives is a fundamental reaction widely applied to exploratory organic chemistry in research laboratories as well as to industrial scale chemical production.<sup>1</sup> In particular, the reduction of amides yields a vast number of useful bulk platform chemicals and fine-synthesis intermediates for the preparation of dyes, pigments, agrochemicals, pharmaceuticals and other materials.<sup>2</sup> For instance, amine functionalities, which are essential motifs present in many bio-active compounds, are often constructed by initial amide formation followed by reduction.<sup>3</sup> In this context, a promising route for carbon dioxide valorization involving formamides as reaction intermediates is also noteworthy.<sup>4</sup>

Traditionally, amide reduction reactions have been carried out using (over)stoichiometric amounts of classical reagents such as lithium aluminum hydride ( $\text{LiAlH}_4$ ) or boranes ( $\text{B}_2\text{H}_6$ ), which require tedious workup procedures and generate large amounts of waste.<sup>5</sup> Recently emerged non-catalytic protocols using samarium iodide ( $\text{SmI}_2$ )/amine/ $\text{H}_2\text{O}$ ,<sup>6</sup> sodium dispersions with different proton donors,<sup>7</sup> or sodium hydride ( $\text{NaH}$ ) with

zinc halides ( $\text{ZnX}_2$ ; X = Cl, I)<sup>8</sup> have similar limitations. Different catalytic strategies have been developed for the reduction of amides to amines under hydrosilylation,<sup>9</sup> hydroboration<sup>10</sup> and transfer-hydrogenation<sup>11</sup> conditions, which are methodologies with wide applicability for functionalized amides, but they suffer from low atom-efficiency. In this respect, the catalytic hydrogenation of amides represents the most environmentally benign methodology, since water is formed as the only by-product.<sup>12</sup> However, as a result of the low electrophilicity of the carbonyl group, the catalytic reduction of amides with molecular hydrogen is a challenging reaction. In general, the hydrogenation of amides proceeds with the addition of a  $\text{H}_2$  molecule to the carbonyl group to form an intermediate hemiaminal species.<sup>2a, 13</sup> Subsequent elimination of  $\text{H}_2\text{O}$  and hydrogenation of the imine intermediate forms the alkylated amine (deoxygenative reaction; Scheme 1, path A). In contrast, the C-N bond cleavage by collapse of the hemiaminal leads to the formation of the respective alcohol and the deprotected amine products (deaminative reaction; Scheme 1, path B). Both reductive processes are potentially useful because of the importance of the products obtained and, interestingly, the C-N bond cleavage pathway may also be exploited as a selective deprotection methodology in organic synthesis. Moreover, this latter hydrogenative transformation is also relevant to  $\text{H}_2$ -storage systems based on alcohol/amide pairs as liquid organic hydrogen carriers.<sup>14</sup>

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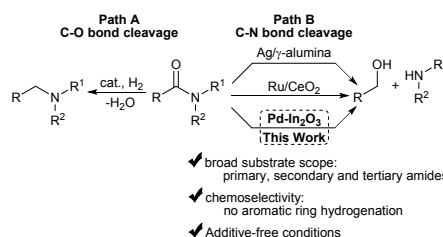
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**Scheme 1** Reaction pathways for the hydrogenation of amides and deaminative hydrogenation over heterogeneous catalysts.

The deoxygenative reaction is a typical route for heterogeneous systems. Early catalysts based on copper-chromium oxides,<sup>15</sup> ReO<sub>3</sub>,<sup>16</sup> Raney catalysts,<sup>17</sup> PtO<sub>2</sub>,<sup>18</sup> and Pd-Re/high surface area graphite (HSAG)<sup>19</sup> catalyzed the hydrogenation of amides to amines under harsh conditions. Mitigation of reaction conditions was accomplished by applying more efficient bimetallic/bifunctional Rh-Re,<sup>20</sup> Ru-Mo,<sup>21</sup> Rh-Mo,<sup>22</sup> Ru-Re,<sup>23</sup> Pt-Re/TiO<sub>2</sub>,<sup>24</sup> Pd-Re/graphite,<sup>25</sup> Rh/MoO<sub>x</sub>-SiO<sub>2</sub>, Ni/LaAlSiO<sub>4</sub>,<sup>26</sup> Pt/Nb<sub>2</sub>O<sub>5</sub>,<sup>27</sup> Pt/MoO<sub>x</sub>-TiO<sub>2</sub><sup>27</sup> and Ir/Mo-mesoporous SiO<sub>2</sub> (KIT-6)<sup>28</sup> catalysts. With this aim, a large screening of bi- and trimetallic systems was also performed, which allowed the identification of a relatively active catalyst based on Pt-Re-In supported on silica (or carbon).<sup>29</sup> Nevertheless, the most significant breakthrough to date has been recently reported, almost at the same time, by the groups led by Kaneda and Shimizu, who applied V-decorated Pt nanoparticles impregnated on hydroxyapatite (HAP)<sup>30</sup> and Re-loaded TiO<sub>2</sub>,<sup>31</sup> respectively, as catalysts for the hydrogenation of amides via C-O bond cleavage (Path A), while inhibiting arene hydrogenation. Since aromatic rings often structurally compose many of the amines used in life science applications, these processes represent important contributions in the synthetic chemist's toolbox, on both an academic and an industrial scale.

Alternatively, some elegant homogeneous approaches using Ru,<sup>32</sup> Ir<sup>33</sup> and Mn<sup>34</sup> pincer complexes in combination with specific Brønsted or Lewis acid co-catalysts have also been disclosed for the hydrogenation of amides to the corresponding alkylated amines, which fully retained the aromaticity. In contrast, the use of homogeneous catalysts is usually associated with the preparation of the respective alcohols and amines after C-N bond hydrogenolysis.<sup>35</sup> Although these processes operate under relatively mild conditions, the activity of most of these catalysts relies on metal-ligand cooperation and frequently entails the need for basic additives and synthetically complex ligands. Moreover, homogeneous catalytic systems imply other drawbacks associated with the difficulty involved in catalyst recovery and recycling. Advantageously, the use of heterogeneous catalysts represents a more convenient approach from a practical point of view.

To the best of our knowledge, there are only two examples on the hydrogenation of amides to alcohols and amines mediated by heterogeneous catalysts (Scheme 1). Recently, Milstein *et al.* have demonstrated that it is possible to carry out this C-N bond cleavage reaction by applying a heterogeneous catalytic system based on silver/ $\gamma$ -alumina.<sup>36</sup> However, the scope is mainly limited to secondary amides, showing moderate to low yields for primary and tertiary substrates. Although this heterogeneous catalyst does not promote the hydrogenation of aromatic moieties, it requires an excess of strong bases (such as potassium *tert*-butoxide) to ensure good activity after long reaction times (2-5 days). Shortly after, Tomishige and Tamura *et al.* reported the use of a heterogeneous CeO<sub>2</sub>-supported Ru catalyst for the selective hydrogenation of the C-N bond in primary amides.<sup>37</sup> This reaction has been demonstrated in a

narrow substrate scope, and its use is limited to aliphatic amides, since the unwanted aromatic ring hydrogenation occurs as a major side reaction. Nowadays, there is no heterogeneous catalyst capable of performing the hydrogenation of primary, secondary and tertiary amides in the absence of exogenous additives with concomitant C-N bond cleavage to furnish alcohols and amines containing both aromatic and aliphatic moieties. Hence, the development of more efficient and selective heterogeneous catalysts for amide hydrogenation reactions via C-N bond cleavage under more environmentally benign conditions is currently highly desirable.

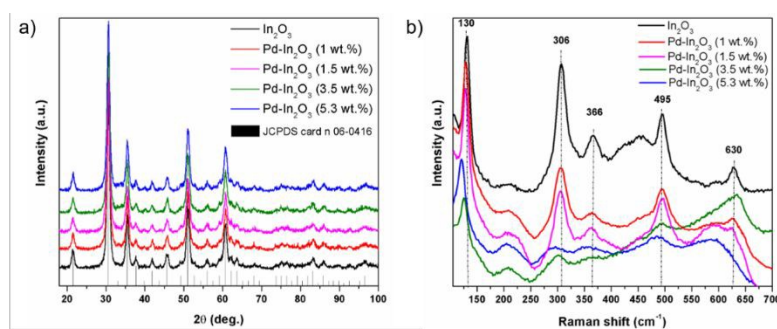
Herein, we describe the preparation of Pd-doped In<sub>2</sub>O<sub>3</sub>-based catalysts by a microwave hydrothermal-assisted method combined with a rapid post-thermal treatment. We demonstrate their performance in the hydrogenation of primary, secondary and tertiary amides to alcohols and amines, establishing the first general and selective heterogeneous catalytic protocol for this reaction that works under additive-free conditions and is compatible with the presence of aromatic ring systems.

## Results and discussion

### Preparation and characterization of catalysts

In<sub>2</sub>O<sub>3</sub>-based materials have emerged as efficient catalytic systems for hydrogenation reactions including the conversion of CO<sub>2</sub> to methanol,<sup>38</sup> to CO (reverse water gas shift)<sup>39</sup> or to C<sub>2</sub>-C<sub>4</sub> hydrocarbons,<sup>40</sup> the conversion of CO into light olefins,<sup>41</sup> and the semihydrogenation of acetylene.<sup>42</sup> In addition, recent density functional theory (DFT) simulations have suggested that In<sub>2</sub>O<sub>3</sub> should also be a promising heterogeneous catalyst for the hydrogenation of acetic acid to ethanol.<sup>43</sup> In general, the experimental and theoretical<sup>44</sup> studies have revealed that oxygen vacancies, commonly formed under hydrogenative conditions,<sup>45</sup> play a crucial role in the adsorption and activation of the reactant molecules as well as in the stabilization of key intermediates during the reaction. Interestingly, the material properties of In<sub>2</sub>O<sub>3</sub> can be modulated by doping with other metals.<sup>46</sup> More specifically, its hydrogenation activity can be enhanced by doping with Pd, which is claimed to facilitate hydrogen splitting and the creation of oxygen vacancies. In addition, the presence of Pd allows the generation of interfacial sites that have been proposed as active sites capable of activating the reactants, thus facilitating the hydrogenation reaction.<sup>42a, 47</sup>

This background led us to hypothesize that Pd-doped In<sub>2</sub>O<sub>3</sub> catalysts should be attractive candidates for the efficient hydrogenation of amides. The low electrophilic carbonyl group of the amide could be activated via Lewis acid-base interaction with the oxygen vacancies (*i.e.* In<sup>III</sup> sites), while the required hydrogen dissociation should be accomplished by neighboring Pd species. Similar cooperative catalysis has been previously reported for homogeneous<sup>3j, 11, 32b-f, 33-34, 35h</sup> as well as heterogeneous catalytic systems.<sup>24a, 27, 30-31</sup>

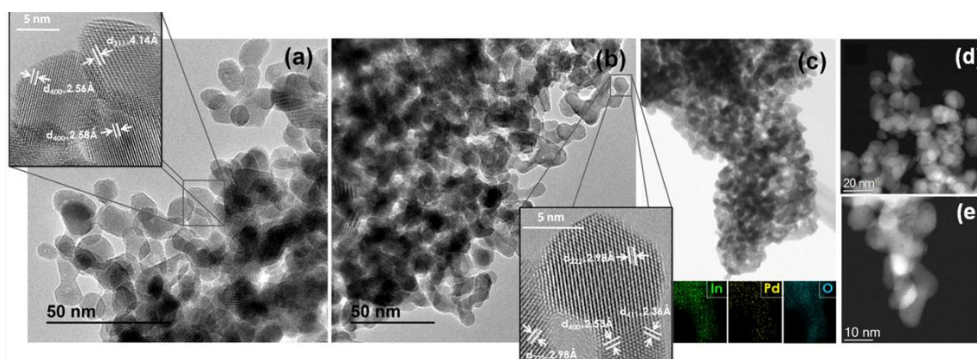


**Figure 1** (a) X-ray diffraction patterns of  $\text{In}_2\text{O}_3$  and Pd-doped  $\text{In}_2\text{O}_3$  catalysts. The vertical lines below the XRD patterns indicate the expected reflection positions of body-centered cubic (bcc)- $\text{In}_2\text{O}_3$  (b) Raman spectra of  $\text{In}_2\text{O}_3$  and Pd-doped  $\text{In}_2\text{O}_3$  catalysts.

Based on this premise, we attempted to prepare an active Pd-doped  $\text{In}_2\text{O}_3$  catalyst for the hydrogenation of amides by a microwave hydrothermal-assisted method,<sup>48</sup> which is a well-established technique for the preparation of metal oxide precursors with a homogeneous distribution and control over their morphology,<sup>46c, 49</sup> combined with a calcination treatment. To this end, aqueous solutions of In(III) acetate and variable amounts of Pd(II) chloride were adjusted to pH 12 and reacted in an autoclave under microwave heating at 140 °C. The final Pd-doped  $\text{In}_2\text{O}_3$  materials were obtained by subsequent calcination at 400 °C for 2 min (see the Experimental Section for details of the preparation). The Pd content of the prepared materials was 1, 1.5, 3.5 and 5.3 wt.%, as determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis. In addition, for the sake of comparison the pure  $\text{In}_2\text{O}_3$  material was also synthesized using the same preparation methodology.

Figure 1a shows the X-ray diffraction (XRD) patterns of the pure  $\text{In}_2\text{O}_3$  and Pd-doped  $\text{In}_2\text{O}_3$  materials after the annealing treatment. All observed diffraction peaks were indexed to the crystalline body-centered cubic (bcc)- $\text{In}_2\text{O}_3$  structure (JCPDS card n° 06-0416). No additional diffraction peaks associated with the presence of secondary phases were detected in the Pd-doped  $\text{In}_2\text{O}_3$  materials, indicating that the synthetic methodology used allows for the insertion of  $\text{Pd}^{2+}$  ions into the  $\text{In}_2\text{O}_3$  matrix without the formation of other Pd species. This insertion influences the long-range periodicity of the materials and also implies a decrease in their crystal size compared to pure  $\text{In}_2\text{O}_3$  (Table S1 in the ESI).

The substitution process of  $\text{In}^{3+}$  by  $\text{Pd}^{2+}$  should also entail local distortions in the oxide lattice, which can be detected by Raman-scattering measurements. The Raman spectra for the prepared  $\text{In}_2\text{O}_3$  and Pd-doped  $\text{In}_2\text{O}_3$  materials ranging from 105 to 700  $\text{cm}^{-1}$  are depicted in Figure 1b. All of them display the characteristic bands of the vibration modes of the (bcc)- $\text{In}_2\text{O}_3$  structure, which fully agree with the values reported in the literature.<sup>50</sup> Signals at 130, 306 and 366  $\text{cm}^{-1}$  are related to the vibration of the O-In-O bending angle of the  $\text{InO}_6$  octahedron units, as building blocks of the  $\text{In}_2\text{O}_3$  lattice, while the peaks at 495 and 630  $\text{cm}^{-1}$  are assigned to the stretching of the In-O bond of these  $\text{InO}_6$  octahedrons. Interestingly, the peak located at 306  $\text{cm}^{-1}$  is known to be correlated to the oxygen vacancies/defects within the lattice of  $\text{In}_2\text{O}_3$ .<sup>51</sup> A decrease in the crystallite size and the presence of local distortions, both associated to the existence of oxygen vacancies in a higher extent, produce the broadening of this Raman peak.<sup>52</sup> As shown in Figure 1b (and Table S1 in the ESI), in the Pd-doped  $\text{In}_2\text{O}_3$  materials this Raman mode is broader with the increase of the Pd content, thus denoting a higher density of oxygen defects in these materials. Moreover, the creation of oxygen vacancies also provokes the weakness of the In-O bonds, which is reflected in the redshift of this Raman peak for the Pd-doped  $\text{In}_2\text{O}_3$  materials.<sup>53</sup> It should be noted that no additional Raman modes, including those of Pd(II) oxide,<sup>54</sup> are observed for the Pd-doped  $\text{In}_2\text{O}_3$  materials, thus denoting the absence of any impurity phase, in good agreement with the XRD analysis.



**Figure 2** TEM micrographs of (a)  $\text{In}_2\text{O}_3$  and (b) Pd- $\text{In}_2\text{O}_3$  (5.3 wt.%) catalysts. HRTEM images are depicted in the inset. (c) STEM image and EDX elemental mapping of In, Pd and O for catalyst Pd- $\text{In}_2\text{O}_3$  (5.3 wt.%). Low- (d) and high- (e) magnification images for the  $\text{C}_5$ -corrected HAADF-STEM analysis of catalyst Pd- $\text{In}_2\text{O}_3$  (5.3 wt.%).

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Figure 2 depicts the images obtained by transmission electron microscopy (TEM). The pure  $\text{In}_2\text{O}_3$  and  $\text{Pd-In}_2\text{O}_3$  (5.3 wt.%) materials exhibit nanostructures with a homogeneous size distribution, which vary from 5 up to 20 nm, and rounded shaped morphology (Figure 2a-b). High-resolution TEM analysis confirms the high crystallinity of the materials being possible to visualize some of the planes associated with the (bcc)- $\text{In}_2\text{O}_3$  structure (insets of Figure 2a-b). However, no Pd nanoparticles were detected in the  $\text{Pd-In}_2\text{O}_3$  (5.3 wt.%) material even by spherical aberration ( $C_s$ )-corrected HAADF-STEM analysis (Figure 2d-e). In contrast, a uniform distribution of Pd can clearly be inferred by energy-dispersed X-ray (EDX) elemental mapping (Figure 2c), thus suggesting that Pd is atomically distributed along the structure of  $\text{In}_2\text{O}_3$ .

## Catalytic Results

Initial hydrogenation experiments were performed in toluene at 160 °C, under a pressure of 60 bar of  $\text{H}_2$  and using benzanilide (**1**) as a model substrate. Under these conditions, catalyst  $\text{Pd-In}_2\text{O}_3$  (5.3 wt.%) afforded aniline (**2**) and benzyl alcohol (**3**) in 98 and 92 % yields, respectively, with only traces (2 % yield) of *N*-benzylaniline (**4**) as a by-product (Figure 3b and Table 1, entry 1). Importantly, no ring-hydrogenated products were detected. Evaluation of Pd-doped  $\text{In}_2\text{O}_3$  catalysts with different Pd content showed that the initial reaction rate for the hydrogenation of **1** increases linearly with the Pd loading, while almost no reaction took place using pure  $\text{In}_2\text{O}_3$  as a catalyst (Figure 3a and Figures S1-S2 in the ESI). These results demonstrate that the Pd site density plays a crucial role not only in the generation of oxygen vacancies in a higher extent (according to the Raman characterization), but also in the hydrogen activation, which is essential for the hydrogenation of **1** to be achieved.

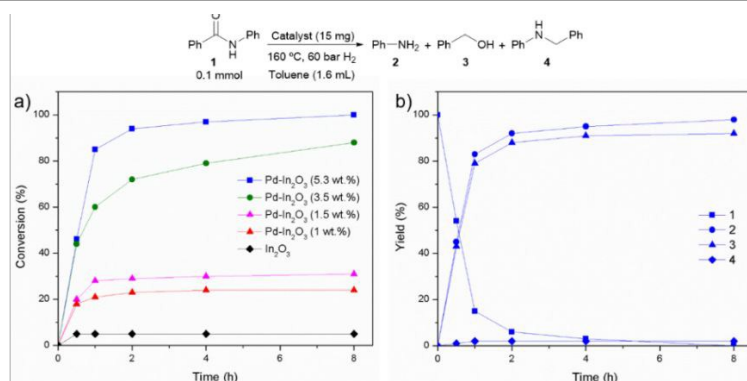
This hydrogenative reaction proceeds with high selectivity towards the formation of products **2** and **3** in moderate to good yields depending on the hydrogen pressure used (Table 1, entries 2 and 3). Temperature also affects the hydrogenation outcome since lower

activity was achieved at 130 °C (Table 1, entry 4). The screening of different solvents was carried out at this temperature (130 °C) in order to observe their possible positive effect on the reaction. However, while ether-based solvents, such as THF and 1,4-dioxane, provided considerably lower conversions, almost no reaction took place in the presence of alcohols, probably as a result of the partial or full blockage of the existing oxygen vacancies,<sup>45</sup> thus preventing the substrate-catalyst interaction (Table 1, entries 5-9). Indeed, similar results to toluene were afforded by using non-oxygenated solvents (Table 1, entries 10-11). Nevertheless, toluene remained the best of those tested, and therefore it was the solvent of choice for further catalytic studies.

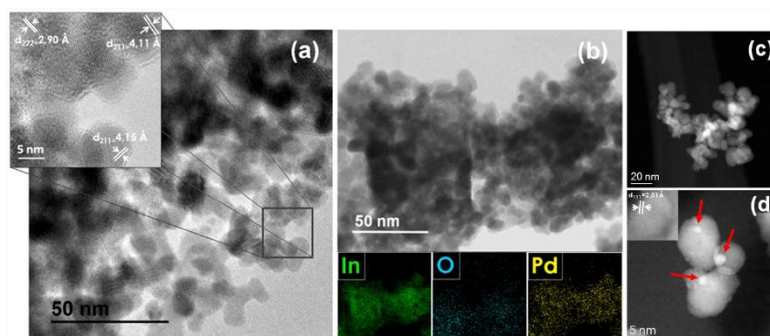
**Table 1** Hydrogenation of benzanilide (**1**) catalyzed by  $\text{Pd-In}_2\text{O}_3$  (5.3 wt.%)<sup>a</sup>

| Entry           | Solvent          | Conversion <sup>b</sup> [%] | Yield <sup>b,c</sup> [%] |          |          |
|-----------------|------------------|-----------------------------|--------------------------|----------|----------|
|                 |                  |                             | <b>2</b>                 | <b>3</b> | <b>4</b> |
| 1               | Toluene          | >99                         | 98 (90)                  | 92 (84)  | 2        |
| 2 <sup>d</sup>  | Toluene          | 82                          | 81                       | 76       | 1        |
| 3 <sup>e</sup>  | Toluene          | 62                          | 56                       | 52       | 1        |
| 4 <sup>f</sup>  | Toluene          | 66                          | 64                       | 62       | 2        |
| 5 <sup>f</sup>  | THF              | 18                          | 18                       | 16       | -        |
| 6 <sup>f</sup>  | 1,4-dioxane      | 20                          | 17                       | 16       | -        |
| 7 <sup>f</sup>  | MeOH             | 2                           | 2                        | 1        | -        |
| 8 <sup>f</sup>  | EtOH             | 2                           | 2                        | 2        | -        |
| 9 <sup>f</sup>  | <i>i</i> -PrOH   | 12                          | 11                       | 10       | -        |
| 10 <sup>f</sup> | Me-Cyclohexane   | 59                          | 55                       | 51       | 4        |
| 11 <sup>f</sup> | <i>n</i> -hexane | 58                          | 55                       | 52       | 3        |

<sup>a</sup> Reaction conditions: **1** (0.1 mmol), catalyst (15 mg), solvent (1.6 mL), 60 bar  $\text{H}_2$ , 160 °C, 15 h. <sup>b</sup> Determined by GC using *n*-hexadecane as an internal standard. <sup>c</sup> Yield of isolated product starting from 5 mmol of **1** shown in parentheses. <sup>d</sup> 30 bar  $\text{H}_2$ . <sup>e</sup> 15 bar  $\text{H}_2$ . <sup>f</sup> 130 °C.

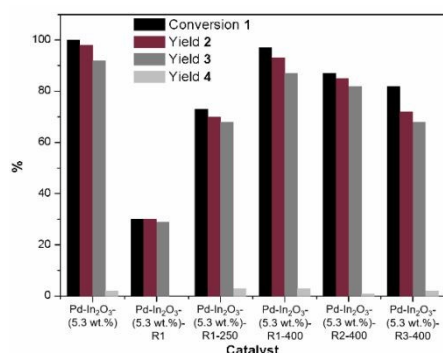


**Figure 3** (a) Benzanilide (**1**) conversion over  $\text{In}_2\text{O}_3$  and Pd-doped  $\text{In}_2\text{O}_3$  catalysts versus reaction time. (b) Yield-time for the hydrogenation of **1** in the presence of catalyst  $\text{Pd-In}_2\text{O}_3$  (5.3 wt.%).



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**Figure 4** (a) TEM micrographs of catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1. HRTEM images is depicted in the inset. (b) STEM image and EDX elemental mapping of In, O and Pd for catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1. Low- (c) and high- (d) magnification images for the Cs-corrected HAADF-STEM analysis of catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%). The red arrows point the generated Pd nanoparticles, and the lattice fringes shown in the inset.



**Figure 5** a) Catalyst recycling experiments for the hydrogenation of benzanilide (**1**). Reaction conditions: **1** (0.2 mmol), catalyst (30 mg), toluene (3.2 mL), 60 bar H<sub>2</sub>, 160 °C, 15 h.

Characterization of the recovered catalyst (Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1) by XRD after the hydrogenation reaction of the model substrate under the established reaction conditions (see Table 1, entry 1) demonstrated the preservation of the cubic (bcc)-structure In<sub>2</sub>O<sub>3</sub> phase (Figure S3 in the ESI). Catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1 also preserves its high crystallinity with a homogenous dispersion of Pd species as revealed by HRTEM and EDX elemental mapping (Figure 4a-b). However, a thorough analysis by Cs-corrected HAADF-STEM denoted the formation of few and isolated Pd nanoparticles (below 5 nm) with an interlayer d-spacing of 2.31 Å associated to the {111} plane of Pd(0), denoting that some desorption of Pd species from the In<sub>2</sub>O<sub>3</sub> backbone is taking place during catalysis (Figure 4c-d). It should be noted that ICP-AES analysis of the reaction filtrate after catalyst separation confirmed that the content of Pd and In in solution was below the detection limit, which suggests that, after desorption, the Pd species agglomerate to form the metal nanoparticles.

In a second run, the recovered catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1 achieved low conversion of benzanilide (30%) towards the formation of aniline and benzyl alcohol. Nevertheless, to our delight its catalytic activity could be efficiently recovered by a rapid (2 min) annealing treatment at 400 °C (see the ESI for further details), which made possible the use of the catalyst for successive recycles with no significant loss of activity (Figure 5).

To shed light on the catalyst deactivation/activation process, and therefore on the species involved during catalysis, X-ray

photoelectron spectroscopy (XPS) studies of the fresh (Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)), used (Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1) and reactivated (Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1-400) catalysts were performed. As shown in Figure 6a, the In 3d core level spectrum of catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) displays two peaks with electron-binding energy values of 443.4 and 451.0 eV, which are associated with the characteristic spin-orbit split 3d<sub>5/2</sub> and 3d<sub>3/2</sub>, respectively, and denote the presence of In(III) species. The Pd 3d spectrum also evidences a doublet peak, namely, the 3d<sub>5/2</sub> and the 3d<sub>3/2</sub> peaks located at 336.1 and 341.5 eV, respectively (Figure 6e). These peaks with a separation of 5.4 eV and an area ratio of 1.7 (63.1 and 36.9 %, respectively) are associated with the presence of Pd(II). Interestingly, since other separated Pd(II)-containing phases were not detected by XRD and Raman analysis (Figure 1), these results also ratify the insertion of Pd into the In<sub>2</sub>O<sub>3</sub> matrix. In contrast, while the XPS spectrum of the used catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1 only shows in the In 3d region the characteristic doublet peak with the same separated spin-orbit components of 7.6 eV associated with In(III), the Pd core level spectrum displays four peaks after deconvolution and fitting (Figure 6b and 6f, respectively). Two peaks are located at practically the same binding energies (336.6 and 342.1 eV), with the same area ratio (28.1 and 17.4 %, respectively) and peak separation (5.5 eV) as those observed for the fresh catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%). In addition, a new doublet peak attributed to Pd(0) at 334.6 and 340.0 eV, with an area ratio of 1.6 (33.7 and 20.9%, respectively) and peak separation of 5.4 eV is also present (Figure 6f). These results confirm the integrity of In(III) and the partial reduction of Pd(II) to Pd(0) species under reaction conditions, respectively. It should be noted that the absence of diffraction peaks associated with the presence of metallic Pd(0) in the XRD pattern of the used catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1 (Figure S3 in the ESI) indicates that these species are highly dispersed on the In<sub>2</sub>O<sub>3</sub> structure, as revealed by EDX elemental mapping, and in a minor degree, forming agglomerated metallic nanoparticles (see Figure 4d).

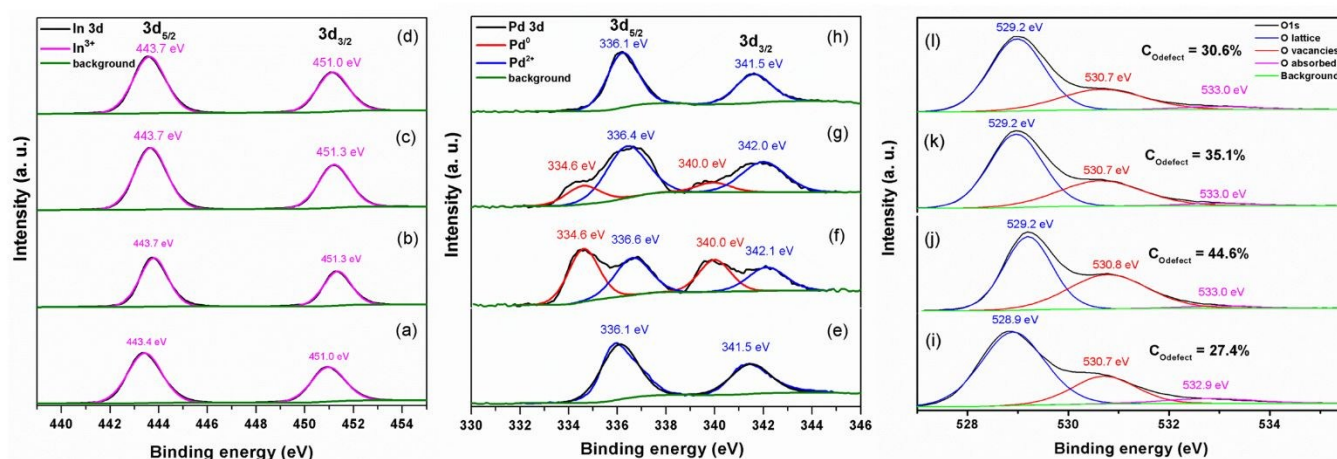
Under the annealing process at 400 °C, through which the catalyst recovers its catalytic activity, the Pd(0) species are completely oxidized to Pd(II), as confirmed in the Pd 3d core level spectrum of catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) -R1-400 (Figure 6h) by the presence of only two peaks at the same binding energies (336.1 and 341.5 eV), same peak separation (5.4 eV) and area ratio (1.7) as those observed for the fresh catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%). These results suggest that the reduction of Pd(II) to Pd(0) species might be the main reason for catalyst deactivation. Therefore, to obtain further

confirmation on this assumption, the used catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1 was annealed at 250 °C to obtain a partially oxidized catalyst (Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1-250). As shown in Figure 6g, the intensity of the peaks associated with Pd(0) in the XPS spectrum for the Pd 3d region of this catalyst is considerably lower than for the used one Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1 (Figure 6f). Consequently, an enhanced catalytic activity was obtained in the presence of catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1-250, which achieved good conversion of benzanilide (73%) with excellent selectivity towards the hydrogenative C–N bond cleavage affording aniline and benzyl alcohol in 70 and 68% yields, respectively (Figure 5). Nonetheless, its catalytic activity is still lower than that of the fully oxidized catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1-400, thus demonstrating that the catalytic performance of these Pd-In<sub>2</sub>O<sub>3</sub> catalysts is diminished when the relative content of Pd(0) is increased with respect to Pd(II) species in the In<sub>2</sub>O<sub>3</sub> surface.

The O 1s core level spectrum of the fresh catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) shows three peaks after deconvolution at 528.9, 530.7 and 532.9 eV, which can be ascribed to the lattice oxygen of In<sub>2</sub>O<sub>3</sub>, to oxygen defects (i.e. oxygen vacancies, in good agreement with the Raman characterization) and to adsorbed oxygen (O<sub>2</sub>, O<sup>•</sup>, OH<sup>•</sup>, etc), respectively (Figure 6i). After the catalytic reaction, an increase of the relative oxygen vacancies concentration (C<sub>Odefect</sub>) is observed in the used catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1, thus revealing that the reduction of the Pd species from Pd(II) to Pd(0) also implies the creation of an excess of oxygen vacancies in the oxide surface as a way to compensate the charge difference (Figure 6j). In line with the previously observed re-oxidation process, catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1-250 displays a decreased C<sub>Odefect</sub> compared to that of the used catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1 (Figure 6k and 6j, respectively), while the catalyst obtained under the treatment at 400 °C (Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1-400) presents almost the same defect density than the fresh catalyst (Figure 6l and 6i, respectively), which also evidences the successful recovery of the catalyst surface after the first activation process. However, in view of the slight progressive

decrease of the catalytic activity observed with successive runs (Figure 5 and Scheme S1 in the ESI), no total recovery of the original catalyst surface seems to be taking place after consecutive deactivation/activation processes, likely as result of the desorption of Pd species from the In<sub>2</sub>O<sub>3</sub> surface in a higher extent.

The general applicability of the catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) was investigated by testing a broad range of primary, secondary and tertiary amides, including both aromatic as well as aliphatic moieties. The investigation of the substrate scope was performed at 160 °C, 60 bar of H<sub>2</sub> pressure and using toluene as the solvent for a standard reaction time of 15 h, while higher catalyst loadings were used to improve the conversion of the less reactive substrates (Table 2). Firstly, substituted benzanilides were hydrogenated, affording the corresponding anilines and benzyl alcohols derivatives in good to excellent yields (Table 2, entries 1–4). Benzanilides functionalized at the *N*-aryl group seem to be hydrogenated more easily than their benzoyl-substituted counterparts. The hydrogenation reaction could be efficiently accomplished in the presence of electron-donating groups, such as methoxy- or methyl-, as well as for fluoro-substituted benzanilides. For instance, 4-fluoro-*N*-phenylbenzamide was successfully hydrogenated, and aniline and 4-fluorobenzyl alcohol were afforded in 85 and 72 % yields, respectively (Table 2, entry 4). However, the hydrogenation of benzanilides containing other electron-withdrawing functional groups, such as 4-chloro-*N*-phenylbenzamide, was reluctant (see Scheme S1 in the ESI), thus revealing that the electronic properties of the substituents have an important impact on the catalytic performance of the catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%). The hydrogenation ability of this catalyst is not limited to *N*-aryl-substituted benzamides. Indeed, *N,N*-dimethylbenzamide was smoothly hydrogenated resulting in 95 % yield of benzyl alcohol (Table 2, entry 5), and interestingly the hydrogenation of the most challenging primary benzamide could also be achieved in moderate conversion and high selectivity (Table 2, entry 6).

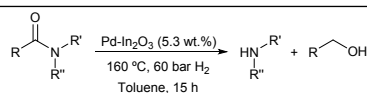


**Figure 6** In 3d, Pd 3d and O 1s XPS spectra of (a, e, i) catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%), (b, f, j) Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1, (c, g, k) Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1-250, (d, h, l) Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%)–R1-400, respectively. C<sub>Odefect</sub> values were calculated according to ref. 47d.

**Table 2** Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) catalyzed hydrogenation of amides to amines and alcohols<sup>a</sup>

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| Entry             | Amide | Conv. [%] <sup>b</sup> | Yield [%]            |                        | Entry             | Amide | Conv. [%] <sup>b</sup> | Yield [%]                          |                        |
|-------------------|-------|------------------------|----------------------|------------------------|-------------------|-------|------------------------|------------------------------------|------------------------|
|                   |       |                        | Amine <sup>b,c</sup> | Alcohol <sup>b,c</sup> |                   |       |                        | Amine <sup>b,c</sup>               | Alcohol <sup>b,c</sup> |
| 1                 |       | >99                    | >99 (90)             | 89 (82)                | 12 <sup>d,n</sup> |       | >99                    | 97 (85)                            | 88                     |
| 2 <sup>d,e</sup>  |       | >99                    | 95 (87)              | 86 (73)                | 13 <sup>l,o</sup> |       | >99                    | 95 (88)                            | 86                     |
| 3 <sup>f,g</sup>  |       | >99                    | 97 (90)              | 90 (79)                | 14 <sup>h,p</sup> |       | >99                    | 98 (90)                            | 90                     |
| 4 <sup>f,h</sup>  |       | >99                    | 85                   | 71                     | 15 <sup>d,q</sup> |       | >99                    | 87 (79)                            | 76                     |
| 5 <sup>i</sup>    |       | >99                    | n.d.                 | 95 (85)                | 16 <sup>r</sup>   |       | >99                    | 93 (84)                            | 83                     |
| 6 <sup>i</sup>    |       | 70                     | n.d.                 | 62 (51)                | 17 <sup>s</sup>   |       | 84                     | 83 (72)                            | 75                     |
| 7                 |       | >99                    | >99 (91)             | 91                     | 18                |       | >99                    | 36 <sup>t</sup><br>64 <sup>v</sup> | -                      |
| 8                 |       | >99                    | >99 (93)             | 93                     | 19                |       | >99                    | 67 <sup>t</sup><br>33 <sup>v</sup> | -                      |
| 9                 |       | >99                    | >99 (95)             | 91                     | 20                |       | >99                    | >99                                | 90                     |
| 10 <sup>d,k</sup> |       | >99                    | 97 (88)              | 86                     | 21 <sup>w</sup>   |       | >99                    | n.d.                               | 89                     |
| 11 <sup>l,m</sup> |       | >99                    | 98 (88)              | 88                     | 22 <sup>w</sup>   |       | >99                    | n.d.                               | 85 (76)                |

<sup>a</sup> Reaction conditions: amide (0.1 mmol), catalyst (15 mg), toluene (1.6 mL), 60 bar H<sub>2</sub>, 160 °C, 15 h. <sup>b</sup> Determined by GC using *n*-hexadecane as an internal standard. <sup>c</sup> Yield of isolated product starting from 0.5 mmol of amide shown in parentheses. <sup>d</sup> Catalyst (30 mg). <sup>e</sup> *N*-(4-methoxybenzyl)aniline (4 %) and 1-methoxy-4-methylbenzene (3 %) as by-products. <sup>f</sup> Catalyst (40 mg). <sup>g</sup> *N*-(3-methylbenzyl)aniline (3 %) as a by-product. <sup>h</sup> *N*-(4-fluorobenzyl)aniline (14 %) and benzyl alcohol (10 %) as by-products. <sup>i</sup> Catalyst (20 mg). <sup>j</sup> Catalyst (60 mg). <sup>k</sup> *N*-ethylaniline (2 %) as a by-product. <sup>l</sup> Catalyst (35 mg). <sup>m</sup> *N*-ethyl-2-methylaniline (2 %) as a by-product. <sup>n</sup> *N*-ethyl-3-methylaniline (2 %) as a by-product. <sup>o</sup> *N*-ethyl-4-methylaniline (4 %) as a by-product. <sup>p</sup> *N*-ethyl-2-methoxyaniline (2 %) as a by-product. <sup>q</sup> *N*-ethyl-4-methoxyaniline (12 %) as a by-product. <sup>r</sup> *N*-ethyl-4-fluoroaniline (6 %) as a by-product. <sup>s</sup> *N*-ethylpyridin-2-amine (<1 %) as a by-product. <sup>t</sup> Yield of aniline. <sup>v</sup> Yield of *N*-methylaniline. <sup>w</sup> Catalyst (50 mg).

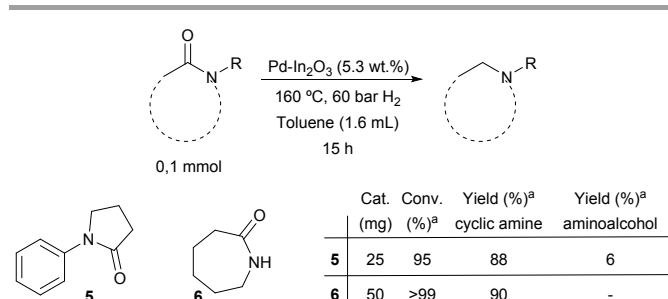
Next, a family of secondary and tertiary acetanilides were tested. *N*-methyl-*N*-phenylacetamide, *N*-acetyl-1,2,3,4-tetrahydroquinoline and the more sterically hindered *N,N*-diphenylacetamide, underwent hydrogenation to the corresponding secondary amines in quantitative yields (Table 2, entries 7-9). Acetanilide and its functionalized derivatives were also fully converted with excellent selectivity for C-N bond cleavage in the presence of an increased catalyst loading (Table 2, entries 10-16). Importantly, catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) is also compatible with the presence of potentially reducing pyridine rings, which are typically present in important bioactive amides (Table 2, entry 17). Overall, these results demonstrate that this hydrogenative heterogeneous catalytic protocol that makes use of catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%) offers an environmentally benign alternative to the stoichiometric methods traditionally used to liberate aromatic amines protected as acetamides.<sup>55</sup> A mixture of the methylated and the primary aniline

was obtained by using *N*-phenylformamide and *N,N'*-diphenylurea as reactants (Table 2, entries 18-19). Moreover, aliphatic amides were also suitable substrates to accomplish the C-N bond cleavage efficiently. Morpholine was afforded in a quantitative yield by hydrogenation of 4-acetylmorpholine (Table 2, entry 20), and alkyl and branched primary amides, such as butyramide and cyclohexanecarboxamide, were hydrogenated to give the corresponding aliphatic alcohols in 90 and 85 % yields, respectively (Table 2, entries 21-22).

To our pleasant surprise, the hydrogenation of the cyclic amides 1-phenyl-2-pyrrolidinone and  $\epsilon$ -caprolactam renders the corresponding cyclic amines in excellent yields (Scheme 2). Results shown in Table 2 and the detection of 2-(phenylamino)ethan-1-ol as an intermediate during the course of the hydrogenation of 1-phenyl-2-pyrrolidinone suggest that the reaction mechanism for the



formation of cyclic amines also proceeds through a hydrogenative C-N bond cleavage to form, firstly, the corresponding aminoalcohols, followed by cyclization, that is likely driven by the ring stabilization energy. Indeed, the reaction of 6-amino-1-hexanol under otherwise the same conditions as those used for the hydrogenation of  $\epsilon$ -caprolactam achieved the cyclic hexamethyleneimine in good yield (see Scheme S2 in the ESI).



**Scheme 2** Hydrogenation of cyclic amides with catalyst Pd-In<sub>2</sub>O<sub>3</sub> (5.3 wt.%). <sup>a</sup> Determined by GC using *n*-hexadecane as an internal standard

## Conclusions

In summary, we have prepared a series of Pd-doped In<sub>2</sub>O<sub>3</sub>-based materials by a microwave hydrothermal-assisted method combined with a calcination treatment. Their structural and morphological characterization reveals the formation of the body-centered cubic (bcc)-In<sub>2</sub>O<sub>3</sub> structure and the successful insertion of Pd(II) cationic species inside the oxide matrix of In<sub>2</sub>O<sub>3</sub>. The resulting materials are efficient catalysts for the selective hydrogenation of amides to the corresponding alcohols and amines. Their catalytic performance relies on the degree of the Pd-doping and, more specifically, on the relative content of Pd<sup>2+</sup> cationic species, which are mainly vanished during the reaction and can be easily recovered by a rapid annealing treatment.

Application of a prepared highly active Pd-doped In<sub>2</sub>O<sub>3</sub> catalyst allows for the development of the first general heterogeneous catalytic protocol for the hydrogenative C-N bond cleavage of a wide range of amides. Structurally different primary, secondary and tertiary amides, including both aromatic and aliphatic ones, are efficiently hydrogenated to produce alcohols and amines in good to excellent yields. Notably, cyclic amides give access to the corresponding cyclic amines. Compared to the previously reported heterogeneous catalytic systems for this reaction, the Pd-doped In<sub>2</sub>O<sub>3</sub> catalyst presented herein has the important advantages of working under additive-free conditions and without promoting de-aromatization during the hydrogenation reactions. Therefore, this superior catalyst could find increasing applications on both the academia and the industrial scale for the production of alcohols and amines, as well as in organic synthetic deprotection methodologies.

## Experimental details

### Synthesis of Pd-doped In<sub>2</sub>O<sub>3</sub> catalysts

Catalyst preparation was performed by a microwave hydrothermal-assisted method followed by a rapid calcination process. Variable amounts of PdCl<sub>2</sub>, previously dispersed in 1.5

mL of HNO<sub>3</sub> at 160 °C for 30 min, were added to a solution of In(CH<sub>3</sub>CO<sub>2</sub>)<sub>3</sub> in 40 mL of distilled H<sub>2</sub>O under vigorous stirring. Then, the pH was adjusted to 12.0 by adding drop by drop an aqueous KOH solution (3 M). This mixture was transferred to an autoclave, sealed and heated at 140 °C under static conditions for 8 min with a heating rate of 5 °C/min in a microwave-hydrothermal equipment. After cooling down to reaction temperature, the precipitate powder was separated by decantation, washed with distilled water, ethanol, and dispersed again in this organic solvent to be dried under slow evaporation at 60 °C. The final aggregate solid was finely ground and annealed at 400 °C for 2 min in a conventional oven (5 °C/min) to obtain In<sub>2</sub>O<sub>3</sub>-based materials with different degree of palladium doping (0, 1, 1.5, 3.5 or 5.3 wt.%) depending on the amount of In(CH<sub>3</sub>CO<sub>2</sub>)<sub>3</sub> (0.5468, 0.5379, 0.5324, 0.5182 or 0.5042) and PdCl<sub>2</sub> (0, 3.3, 9.9, 19.7 or 29 mg, respectively) used.

### General procedure for the hydrogenation of amides

An 8 mL vial containing a stirring bar was charged with the amide substrate (0.1 mmol), the catalyst (15 mg), *n*-hexadecane (25  $\mu$ L) as an internal standard, and toluene (1.6 mL). The vial was then sealed with a septum cap perforated with an extremely fine syringe needle, and placed on an alloy plate inside a 300 mL stainless steel autoclave vessel. The autoclave was tightly closed and pressurized with hydrogen, firstly purging three times with 30 bar, and then at 60 bar. After reaction time, the autoclave was allowed to cool down to room temperature and carefully depressurized. The reaction mixture was diluted with ethyl acetate and an aliquot was taken to be analyzed by GC. To determine the isolated yields, no internal standard was added and the general procedure was scaled up by a factor of five. After reaction completion and dilution with ethyl acetate, the catalyst was separated off by filtration and the solvent was removed under reduced pressure. The final products were purified by column chromatography (silica; *n*-hexane/ethyl acetate mixture = 10:1  $\rightarrow$  5:1).

### Conflicts of interest

There are no conflicts to declare.

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## Graphical Abstract

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The first general heterogeneous hydrogenation of amides to amines and alcohols is performed under additive-free conditions and without products de-aromatization applying a Pd-doped  $\text{In}_2\text{O}_3$  catalyst.

