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One pot synthesis of cyclohexanone oxime from nitrobenzene using a bifunctional catalyst†

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Cyclohexanone oxime is formed from nitrobenzene with 97% yield in a one-pot reaction catalysed by palladium and gold nanoparticles on carbon. The reaction is carried out under hydrogen at 60 °C and the overall transformation involves a multi-step catalysed mechanism from which intermediates and catalytically active species have been identified.

Cyclohexanone oxime is the key intermediate in the production of nylon **6** fibers and resins, and its worldwide market is one of the largest among chemical products.[1] Its manufacturing is typically carried out using a three-step procedure: (a) synthesis of cyclohexane by metal-catalysed hydrogenation of benzene;[2] (b) synthesis of cyclohexanone by oxidation of cyclohexane at low conversions per pass ($<8\%$)[3–5] or by hydrogenation of phenol;[6–9] and (c) formation of cyclohexanone oxime from cyclohexanone and external hydroxylamine or hydroxylamine formed *in situ* with aqueous NH_3 and H_2O_2.[5,10–12]

The modern chemical industry demands the intensification of chemical processes in order to save chemicals, energy and waste treatments[13–15] and, to our knowledge, only one example has applied the concept of one-pot reaction for some steps during the synthesis of cyclohexanone oxime,[16] from phenol to ε-caprolactam.

Fig. 1 shows the long-sought hydrogenation of nitrobenzene to cyclohexanone oxime, a paradigmatic example of process intensification since nitrobenzene is a multi-ton primary product of benzene with all the atoms needed to form the cyclohexanone oxime structure. Then, it will be much interesting from a fundamental, as well as from an applied point of view, to find a catalytic process able to directly convert nitrobenzene into cyclohexanone oxime.

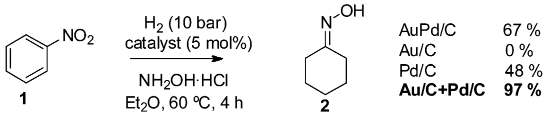

Fig. 1 Hydrogenation of nitrobenzene to cyclohexanone oxime under static pressure catalysed by Au and/or Pd/C catalysts. The yield with Au/C + Pd/C is reproduced with semi-continuous dynamic pressure (see ESI† for details).

Here we show that cyclohexanone oxime is formed in high yields from nitrobenzene in a one-pot reaction using palladium and gold nanoparticles supported on carbon as catalysts under a hydrogen atmosphere. An in-depth study of the mechanism will show the role of both metal catalysts in each step of the reaction sequence.

Fig. 1 shows that when nitrobenzene **1** was reacted with hydrogen in the presence of catalytic amounts of AuPd/C (5 mol%) and hydroxylamine hydrochloride, cyclohexanone oxime **2** was obtained in a remarkable 67% yield.

If Au/C is used alone at the same catalytic loading, cyclohexanone oxime **2** is not obtained. On the other hand, if Pd/C is used alone it is possible to obtain the oxime but the yield is below 50%. Other metals such as ruthenium, iron and rhodium were also ineffective in catalysing the formation of cyclohexanone oxime **2** (Table S1, ESI†). The AuPd/C catalyst was characterized by Electron Dispersive X-Ray (EDX) spectroscopy coupled to High-Resolution Transmission Electron Microscopy (HR-TEM, Fig. S1A, ESI†). It can be observed that the catalyst is composed of well-dispersed small (<3 nm) palladium nanoparticles, gold being separated and grouped into ∼20 nm particles. Mapping of AuPd/C showed no clear interaction between both metals (Fig. S1B and C, ESI†) and, since the nanoparticles of each metal were independent in the AuPd/C catalyst, we compared the catalytic activity of a physical mixture of Au/C and Pd/C, *i.e.*, supported gold and supported palladium on separated carbon particles, and the yield of cyclohexanone oxime **2** increased to 97% (see Fig. 1, the reaction can also be carried out at the gram scale with high yields of isolated oxime). TEM images of the reference catalyst, with palladium and gold placed in different particles, showed a particle size similar to that of AuPd/C for each metal (>5 nm for gold and <3 nm for palladium in

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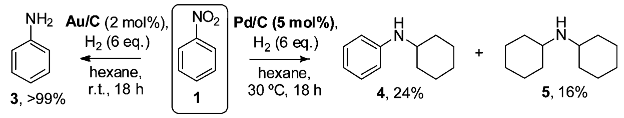


Fig. 2 Role of Au/C and Pd/C in the hydrogenation of nitrobenzene **1**.

Au/C and Pd/C, respectively, Fig. S2 and S3, ESI†). These results reflect that Au and Pd are involved in different steps of the catalytic cycle and the absence of any of the two metals somehow hampers the formation of cyclohexanone oxime **2**. If desired, the amount of noble metals can be decreased below 1 mol% provided longer reaction times are set (Table S2, ESI†).

At this point, and in order to find the reaction network and the role of each metal component, the single metal Au/C and Pd/C catalysts were studied independently in the different reaction steps. First, when nitrobenzene **1** was reacted in the presence of Au/C but in the absence of hydroxylamine hydrochloride, the only product obtained was aniline **3** (Fig. 2). However, the same reaction but in the presence of Pd/C gave, surprisingly, cyclohexylaniline **4** and dicyclohexylamine **5** as the main products. It seems to be then plausible that Au/C is unable to reduce nitrobenzene **1** further than aniline **3**, while the Pd/C-catalysed formation of the secondary amines **4** and **5** is in some way connected with the synthesis of cyclohexanone oxime **2**.

Fig. 3 shows kinetics for the hydrogenation of nitrobenzene **1** using the Pd/C catalyst, in where each point corresponds to an independent batch reaction. Aniline **3** is formed as a primary and unstable product that, by partial hydrogenation, gives cyclohexylaniline **4** as a secondary product that, by further hydrogenation, produces dicyclohexylamine **5** as a tertiary product. No intermediate diazo products were detected.[17–19] The reaction sequence was confirmed by reacting cyclohexylaniline **4** at 60 °C in the presence of Pd/C. In this case, dicyclohexylamine **5** was obtained with very high selectivity, as a primary product.

It is interesting to note that cyclohexanamine **6** was not observed among the reaction products. Since the hydrogenation of the primary product aniline **3** to cyclohexanamine **6** is very plausible, the latter must be rapidly consumed during the process, and a possible way would be the corresponding condensation with **3** to form cyclohexylaniline **4**. To check this hypothesis, aniline **3** and cyclohexanamine **6** were reacted under the above reaction conditions in the presence of Pd/C and a combined 55% yield of the coupled products **4** and **5** was observed. This result strongly suggests that Pd/C catalyses the formation of **4** and **5** from nitrobenzene **1** in the presence of H_2 by *in situ* condensation of aniline **3** and cyclohexanamine **6**. We then postulate a hydrogen-borrowing mechanism to explain the formation of cyclohexylaniline **4**, as shown in Fig. 4. Thus, dehydrogenation of **6** would give cyclohexanimine **7** that couples with remaining aniline **3** to give cyclohexylaniline **4**, after ammonia release. The hydrogen borrowing mechanism is consistent with the kinetic experiments in Fig. 3 since aniline **3** is smoothly consumed while the coupled products are formed, and production of cyclohexylaniline **4** stops when no aniline **3** remains in the reaction media.

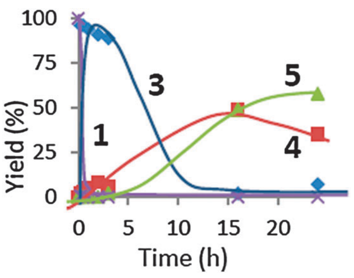


Fig. 3 Plot-time yield for the hydrogenation of nitrobenzene **1** using the Pd/C catalyst at 60 °C. Each kinetic point belongs to an independent reaction.

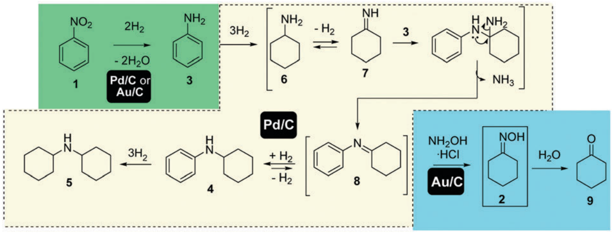
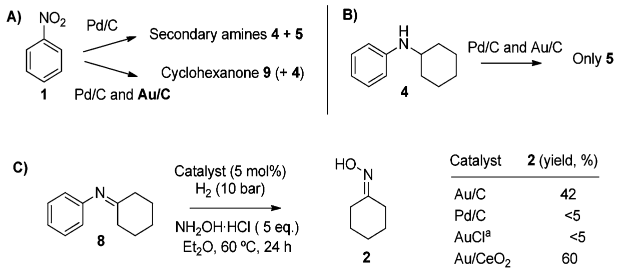


Fig. 4 Proposed mechanism for the Au/C and Pd/C-catalysed hydrogenation of nitrobenzene **1** to cyclohexanone oxime **2**, cyclohexylaniline **4** and dicyclohexylamine **5**.

Fig. 5A shows that, if Au/C is added to the reaction in the presence of Pd/C, the formation of secondary amines is nearly suppressed and cyclohexanone **9**, the necessary precursor of cyclohexanone oxime **2**, is formed, together with small amounts of cyclohexylaniline **4**.

Since dicyclohexylamine **5** is not detected when Au/C is added and cyclohexanone oxime **2** is formed, it seems to be reasonable to associate the role of the gold catalyst with a reaction with cyclohexylaniline **4**. However, cyclohexanone **9** was not formed when **4** was reacted in the presence of the Au/C catalyst, even if Pd/C is present (Fig. 5B). Following the hydrogen-borrowing mechanism in Fig. 4, it sounds plausible that cyclohexylaniline **4** could be in equilibrium with the corresponding imine **8** and, since the latter is reluctant to further amine condensation,[20–22] there is an opportunity for further hydrolysis to give cyclohexanone **9**. To check this, the intermediate *N*-cyclohexylideneaniline **8** was synthesized[23] and tested under reaction conditions using the Au/C catalyst (Fig. 5C). The result shows that cyclohexanone **9** was obtained in significant yields. In contrast, Pd/C catalyses the



Catalyst	2 (yield, %)
Au/C	42
Pd/C	<5
AuCl[a]	<5
Au/CeO_2	60

Fig. 5 (A) Synthetic switch to cyclohexanone **9** by Au/C. (B) Failed formation of **9** from cyclohexylaniline **4**. (C) Hydrolysis of *N*-cyclohexylideneaniline **8** under hydrogenating conditions using different catalysts. Yields are corrected after blank experiments. [a] Similar results obtained for $PdCl_2$, soluble palladium nanoparticles and gold nanoparticles.

hydrolysis to a much lesser extent, after correction with the blank experiment. These results strongly suggest that gold catalyses the hydrolysis of *N*-cyclohexylideneaniline **8** formed from **4**. The possible hydrolysis of cyclohexanimine **7** must not be excluded.

The activation of imine **8** requires an acid resistant to hydrogenation. However, many Lewis metal cations, able to catalyse the hydrolysis of **8**, will be rapidly reduced under the strong hydrogenating conditions of the reaction. Brönsted acids are of course reluctant to hydrogenation, but independent experiments with acetic, sulfuric and *p*-toluenesulfonic acid, besides HCl, showed low amounts of cyclohexanone **9** (Table S3, ESI†). In contrast, it appears that gold nanoparticles possess certain Lewis acidity even under hydrogenating conditions and, for instance, it has been reported that gold-supported nanoparticles are able to activate imines towards hydroalkynylation.[24] However, the formation of the imine on supported-Pd sites makes occurrence of the Lewis activation of the imine in Au-supported sites difficult since both sites are separated. Thus, study on whether one of the catalysts for the oxime formation, palladium or gold, may have free movement in the reaction or, in other words, be soluble, was performed. For this, we carried out the formation of oxime from **8** with catalytic amounts of palladium(II) chloride, gold(I) chloride, soluble palladium nanoparticles, and gold nanoparticles (see Fig. 5C) but none of them improved the formation of oxime from **8**.[25–27] However, the reaction occurred to a good extent when we used a sample of Au/CeO$_2$ containing leachable sub-nanometric gold clusters.[26] Soluble sub-nanometric gold clusters have recently shown extremely high catalytic activities for hydration reactions[28] and since gold nanoparticles were not active, the catalytic activity of Au/CeO$_2$ suggests that gold clusters might be involved in the hydrolysis of **8** to cyclohexanone **9**. X-ray Photoelectron Spectroscopy (XPS) of the Au/C catalyst confirmed the presence of ∼10% cationic gold species on the solid, as in the case of Au/CeO$_2$ (Fig. S4, ESI†). To confirm the presence of gold clusters in solution during reaction, fluorescence measurements of the reaction mixture after filtration of the Au/C and Pd/C solids were carried out. According to the jellium theory, these clusters should present clear fluorescence bands in the visible region and, in addition, the corresponding wavelength emission would enable the estimation of the cluster size.[28] Since it is known that the other chromophores in the reaction medium such as nitrobenzene, protonated anilines and cyclohexanone oxime do not have fluorescence bands, which was confirmed by blank experiments, we must accept that the emission bands shown in Fig. 6A belong to small gold clusters within a wavelength range expected for 3 atoms. Ultraviolet-visible (UV-Vis) spectroscopy showed the complete absence of the plasmon band and thus of gold nanoparticles in solution (∼550 nm, Fig. 6B).

Dynamic Light Scattering (DLS) combined with zeta-potential measurements (Fig. S5, ESI†) revealed that these sub-nanometric particles present in solution are positively-charged. From all the above results one may suggest that sub-nanometric gold clusters leached into solution are responsible for the last catalysed step of the transformation of nitrobenzene **1** to cyclohexanone oxime **2**, namely the hydrolysis of imine **8**.

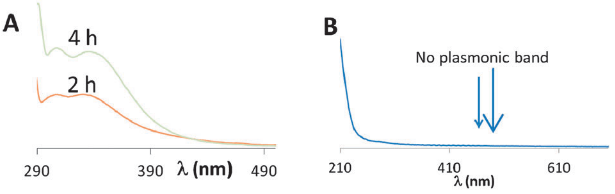


Fig. 6 (A) Fluorescence measurements of the reaction mixture for the formation of cyclohexanone oxime **2** under Au/C and Pd/C-catalysed conditions. (B) Corresponding UV-Vis spectrum at 2 h.

In summary, we have described here the synthesis of cyclohexanone oxime from nitrobenzene with Pd and Au on carbon in a multi-step cascade reaction that involves: (1) hydrogenation of **1** to aniline **3**; (2) further hydrogenation of **3** to cyclohexanamine **6**; (3) coupling of **3** and **6** by the hydrogen-borrowing mechanism to form amine **4**; (4) formation and hydrolysis of the imine **8** to generate cyclohexanone **9** and aniline **3** that is recycled for the coupling; and (5) formation of oxime **2**. The cascade reaction can potentially be extended since the production of hydroxylamine hydrochloride is based on the Pd/C-catalysed hydrogenation of ammonium nitrate and the latter is produced from nitric acid and ammonia (Fig. S6, ESI†), all these chemicals being used in the process reported here.

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