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### Chemoselective Synthesis of Substituted Imines, Secondary Amines, and β-Amino Carbonyl Compounds from Nitroaromatics through Cascade Reactions on Gold Catalysts

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**Abstract:** Substituted imines,  $\alpha$ , $\beta$ -unsaturated imines, substituted secondary amines, and β-amino carbonyl compounds have been synthesized by means of new cascade reactions with mono- or bifunctional gold-based solid catalysts under mild reaction conditions. The related synthetic route involves the hydrogenation of a nitroaromatic compound in the presence of a second reactant such as an aldehyde,  $\alpha,\beta$ -unsaturated carbonyl compound, or alkyne, which circumvents an ex situ reduction process for producing the aromatic amine. The process is shown to be highly selective towards other competing groups, such as double bonds, carbonyls, halogens, nitriles, or cinnamates, and thereby allows the synthesis

of different substituted nitrogenated compounds. For the preparation of imines, substituted anilines are formed and condensed in situ with aldehydes to provide the final product through two tandem reactions. High chemoselectivity is observed, for instance, when double bonds or halides are present within the reactants. In addition, we show that the Au/TiO<sub>2</sub> system is also able to catalyze the chemoselective hydrogenation of imines, so that secondary amines can be prepared directly through a three-step cascade reaction

**Keywords:** cascade reactions • chemoselectivity • gold • hydrogenation • nitro compounds

by starting from nitroaromatic compounds and aldehydes. On the other hand, Au/TiO<sub>2</sub> can also be used as a bifunctional catalyst to obtain substituted β-amino carbonyl compounds from nitroaromatics and  $\alpha$ . $\beta$ -unsaturated carbonyl compounds. Whereas gold sites promote the in situ formation of anilines, the intrinsic acidity of Ti species on the support surface accelerates the subsequent Michael addition. Finally, two gold-catalyzed reactions, that is, the hydrogenation of nitro groups and a hydroamination, have been coupled to synthesize additional substituted imines from nitroaromatic compounds and alkynes.

#### Introduction

The recent discovery of gold catalysts for the chemoselective reduction of substituted nitroaromatic compounds has introduced new possibilities for the production of aniline derivatives.<sup>[1–5]</sup> By means of rational design, it has been possible to prepare catalysts that preferentially activate the nitro group in the presence of other sensitive functionalities such as double bonds, aldehydes, cyano groups, halides, etc. This interesting property of Au catalysts opens the possibility of planning efficient and clean synthetic routes for the prepara-

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tion of polyfunctional nitrogenated compounds by means of cascade reactions<sup>[6–11]</sup> involving substituted aromatic amines that can now be generated in situ from nitroaromatic compounds. This is of interest for the production of highly demanded chemicals through a process with superior atom efficiency and energy savings.<sup>[12–14]</sup>

We will show here that, by using the appropriate catalyst, it is possible to couple the hydrogenation of nitroaromatic compounds with consecutive reactions between the formed amine and carbonyls, conjugated double bonds, or triple bonds. The proposed approach is ahead of other alternatives when it is taken into account that a) this synthetic route saves an ex situ hydrogenation process to produce the aromatic amine and b) it is highly selective towards very sensitive competing groups. Thanks to the chemoselectivity of the Au/TiO<sub>2</sub> system during the hydrogenation of nitroaromatics, as well as other catalytic properties for the activation of a second functionality, different substituted imines, secondary amines, and substituted  $\beta$ -amino carbonyl com-



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pounds have been successfully synthesized by means of the present approach.

### **Results and Discussion**

Synthesis of substituted imines and secondary amines from nitroaromatic compounds and aldehydes: Imines are important organic intermediates in the synthesis of secondary amines<sup>[15–18]</sup> and propargylamines,<sup>[19–22]</sup> with applications for fine chemicals, pharmacy, and agrochemistry.<sup>[23–33]</sup> The most frequent routes to prepare imines include the condensation of amines with carbonyl compounds<sup>[34,35]</sup> (Scheme 1 a) or the



Scheme 1. Most frequent reaction routes for the synthesis of imines.

direct oxidation of secondary

amines<sup>[36-38]</sup> (Scheme 1b). In the

case of aryl imines, aniline and

aryl-substituted amines, which

are produced by the hydrogenation of nitrobenzene and nitrobenzene derivatives, respective-

ly, are generally used as starting reactants. Whereas the hydrogenation of nitrobenzene to aniline can be easily carried out

with  $H_2$  to provide quantitative yields of the desired product, the complexity of the process notably increases in the case of

nitroaromatic compounds substituted with double bonds, carbonyls, nitriles, or halogens. It would be of interest to se-

lectively hydrogenate nitroaromatic compounds in the presence of a second molecule containing a carbonyl group, in order to synthesize the corresponding imine through a cascade-type reaction, as shown in



Scheme 2. One-pot synthesis of substituted aromatic imines by using Au/ TiO<sub>2</sub> catalysts.

ported by coupling nitrobenzenes and aldehydes with Fe(0) powder,<sup>[39]</sup> this process requires the presence of a strong inorganic acid (HCl), and the global selectivity notably falls down if olefinic groups are present.

In order to initially prove if the synthetic route given in Scheme 2 could be catalyzed by gold-based materials, we have first treated nitrobenzene with benzaldehyde. The results show that, at 4 bar of H<sub>2</sub> and 120 °C, *N*-benzylideneaniline can be obtained with 93% selectivity at 94% conversion after 2 hours of reaction by using Au/TiO<sub>2</sub> as the catalyst (Table 1, entry 1). The high yield of desired product ob-

Table 1. Catalytic results during the synthesis of different substituted imines from nitroaromatics and aldehydes by using Au/TiO<sub>2</sub> catalysts (see Table S1 in the Supporting Information for the corresponding feeding compositions).

Entry	Product	Т [°С]	P <sub>H2</sub> [bar]	% Au <sup>[a]</sup>	<i>t</i> [h]	Conversion [%] <sup>[b]</sup>	Selectivit
1		120	4	0.24	2	94	93
2		120	8	0.25	6	91	93
3		120	8	0.25	9	92	91
4		120	4	0.22	2	96	90
5	4 BrN	130	12	0.97	7	91	87

[a] Mol Au/mol nitroaromatic×100. [b] Based on aniline after complete exhaustion (>95%) of the nitroaromatic. [c] Loss of selectivity due to further hydrogenation of the imine group to the corresponding secondary amine.

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Scheme 2. Although a similar

approach has been recently re-

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tained shows that both the carbonyl group of benzaldehyde and the C=N group of the product imine remain unaffected during the reduction of nitrobenzene. Interestingly, this result is much better in terms of conversion and selectivity than those recently reported through the oxidation of *N*phenylbenzylamine,<sup>[36,37]</sup> in which, besides requiring at least 2 independent reaction steps, only 18% of the desired imine is obtained. On the contrary, with the procedure presented here, nitrobenzene is directly used as the starting reactant and undergoes a hydrogenation process to form aniline, which condenses in situ with the aldehyde to provide the final imine through a cascade reaction.

The benefits of this catalytic process are more evident when other easily reducible groups are present in the nitroaromatic compound or in the aldehyde. For instance, high chemoselectivity is observed when double bonds or halide functional groups are included within the reactants (Table 1). In fact, the selective reduction of the nitro groups is practically independent of the position of the substitutions within the reactants, as can be inferred by comparing the yields of imines when a vinyl group is bonded to the aromatic ring of nitrobenzene (3-vinylnitrobenzene as a reactant: Table 1, entry 2) or to the aromatic ring of benzaldehyde (3vinylbenzaldehyde as a reactant: Table 1, entry 3). In both cases, the imines are obtained with selectivity over 90% and at conversion levels above 90%, whereas the hydrogenation of the carbonyl, the C=C, and the C=N groups are avoided.

Taking these results into account, we decided to apply the methodology for coupling aniline (generated in situ from nitrobenzene) with an  $\alpha$ , $\beta$ -unsaturated aldehyde to produce  $\alpha$ , $\beta$ -unsaturated imines through a cascade-type reaction (Scheme 3). As confirmation of the feasibility of this route, good yields of the desired product were obtained by using Au/TiO<sub>2</sub> as the catalyst (Table 1, entry 4).



Scheme 3. One-pot synthesis of  $\alpha_{\beta}$ -unsaturated aromatic imines by using Au/TiO<sub>2</sub> catalysts.

It should be considered that the selectivity of formation of the imine may change depending on the electron-withdrawing or electron-donating character of the groups attached to the aromatic rings. Indeed, an increase in the rate of hydrolysis of the resultant imine can be expected when electron-withdrawing groups are present in the nitroaromatic compound used as the initial reactant. In order to quantify this potential drawback, we treated 4-bromonitrobenzene with benzaldehyde. However, 87% selectivity at 91% conversion of the intermediate aniline (complete exhaustion of the nitroaromatic starting material) was still achieved in this case, which indicates that only a small fraction of the corresponding imine is hydrolyzed by water (Table 1, entry 5). In fact, the decrease in selectivity observed with these substrates is related to partial hydrogenation of the C=N bond, which leads to formation of the corresponding secondary amine. Nevertheless, global selectivity is still high (87%), and no dehalogenation of the bromide group is observed.

Finally, we have considered the possibility of using the proposed synthetic route for preparing substituted secondary amines, after taking into account the fact that gold is able to catalyze the enantioselective hydrogenation of imines.<sup>[17]</sup> Therefore, if the C=N group could be chemoselectively reduced to C–NH after complete exhaustion of the nitroaromatic compound, secondary amines could be prepared by starting from nitroaromatics and aldehydes through a three-step cascade reaction. During this process, several consecutive and parallel reactions can compete with the desired transformation, as shown in Scheme 4 for a representative case.



Scheme 4. Example of the one-pot synthesis of substituted secondary amines from nitrobenzenes and aldehydes.

To check this, we have studied the reaction between nitrobenzene and 3-vinylbenzaldehyde. It has been found that, if the reaction is continued after complete exhaustion of the nitroaromatic compound, the imine group can also be chemoselectively hydrogenated by the Au/TiO<sub>2</sub> catalyst without reducing the vinyl group; this leads to the preferential formation of N-(3-vinylbenzyl)aniline (**6**) with 90% selectivity. The results displayed in Figure 1 show that the kinetic behavior of gold during this process allows the selective production of either the substituted imine by stopping the hydrogenation just before complete exhaustion of the nitroaromatic compound or, on the contrary, the substituted secondary amine if the reduction reaction is allowed to proceed further.

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Figure 1. Distribution of products as a function of the conversion level during the three-component reaction between nitrobenzene, 3-vinylbenzaldehyde, and H<sub>2</sub> with the Au/TiO<sub>2</sub> catalyst ( $\bullet$  3;  $\Box$  6; × 12;  $\diamond$  13; see Scheme 4). Reaction conditions: 120 °C, 8 bar H<sub>2</sub>, 0.0025 mol Au/mol nitrobenzene. Feeding composition: 83 mol % toluene, 8 mol % nitrobenzene, 8 mol % 3-vinylbenzaldehyde, 1 mol % *o*-xylene.

One-pot synthesis of substituted  $\beta$ -amino carbonyl compounds from nitroaromatics and  $\alpha$ , $\beta$ -unsaturated ketones with a bifunctional catalyst: For several decades, the Michael addition reaction between amines and  $\alpha$ , $\beta$ -unsaturated ketones (see the example in Scheme 5) has been used as an



Scheme 5. Synthesis of  $\beta$ -amino carbonyl compounds through Michael addition reactions between amines and ketones.

important tool for preparative organic synthesis. The obtained β-amino carbonyl functionalities are ubiquitous motifs in natural products such as alkaloids and polyketides,[40-43] as well as important intermediates for the synthesis of amino alcohols, diamines, and β-amino acid derivatives or β-lactams,<sup>[44-51]</sup> many of which are used, among other pharmaceutical applications, as powerful antibiotics. Michael reactions are facilitated by protic acid, protic base, or Lewis acid catalysts<sup>[40,48,52-57]</sup> and can proceed through Markovnikov or anti-Markovnikov additions, which lead to either branched or linear compounds, respectively. Together with high levels of regioselectivity, high chemoselectivity with regard to other sensitive functional groups is desired. However, this may become problematic if strong acids/bases or harsh reaction conditions are used, due to the generation of different undesired byproducts.<sup>[57-61]</sup> Consequently, other procedures, based on transition-metal catalysts in solution, have been recently proposed.[62-69]

In the present paper, we consider the possibility of using Au/TiO<sub>2</sub> as a heterogeneous catalyst to develop a new catalytic route for synthesizing  $\beta$ -amino carbonyl compounds through a simple, green, and efficient cascade reaction starting directly from nitroaromatics and conjugated ketones (see Scheme 6).



Scheme 6. One-pot synthesis of the  $\beta$ -amino carbonyl compound from nitrobenzene and 1-buten-3-one by using the Au/TiO<sub>2</sub> catalyst.

To do this, we have first checked the possibility of using  $TiO_2$  to catalyze the Michael addition between aromatic amines and  $\alpha$ , $\beta$ -unsaturated ketones. When the uncatalyzed reaction between aniline and 1-buten-3-one is carried out at 80 °C, and the conversion of the reactants was followed with time, nucleophilic addition of the amine group to the conjugated double bond occurs, but at a low rate (Figure 2). On



Figure 2. Catalytic results during the Michael addition of 1-buten-3-one to aniline in the presence ( $\bullet$ ) and absence ( $\Box$ ) of TiO<sub>2</sub>. Reaction conditions: 80 °C, air atmosphere, 50 mg TiO<sub>2</sub>/mL feeding. Feeding composition: 86 mol% toluene, 5 mol% aniline, 8 mol% 1-buten-3-one, 1 mol% *o*-xylene.

the contrary, the reaction occurs approximately 20 times faster in the presence of  $TiO_2$ , to provide almost quantitative yields of the desired product. This result opens up the possibility of performing a cascade reaction by starting from nitrobenzene and 1-buten-3-one with an Au/TiO<sub>2</sub> catalyst. The gold would initially produce the chemoselective hydrogenation of the nitro group to an amine, then the mild acidity of  $TiO_2$  would promote the addition of the conjugated double bond to the amine group.

Indeed, under  $H_2$  pressure, the corresponding  $\beta$ -amino ketone is produced in excellent yields after one hour of reaction (Table 2, entry 1). The practical absence of products

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plex case in which two gold-cat-

alyzed reactions are carried out

in a one-pot process. It has

been reported that gold can ac-

tivate the coupling of triple bonds with amines, which leads to the formation of the corre-

sponding imines.<sup>[20,21]</sup> The per-

formance of this reaction through a cascade-type reaction, by starting from a nitroar-

omatic compound, is a real

challenge because the catalyst has to reduce chemoselectively

the nitro group without hydrogenating the triple bond, while

it also has to activate the triplebond function for the subsequent amine-alkyne coupling

The results with nitrobenzene

and phenylacetylene as sub-

(see Scheme 7).

Table 2. Catalytic results during the synthesis of substituted  $\beta$ -amino carbonyl compounds from nitroaromatics and 1-buten-3-one by using Au/TiO<sub>2</sub> catalysts (see the Supporting Information for the corresponding feeding compositions).



[a] Mol Au/mol nitroaromatic  $\times$  100. [b] Based on aniline after complete exhaustion (>95%) of the nitroaromatic. [c] Loss of selectivity mainly due to the Michael addition of a second 1-buten-3-one molecule onto the desired  $\beta$ -amino carbonyl compounds.

derived from reduction of the  $\alpha$ , $\beta$ -unsaturated ketone indicates that the chemoselectivity of the Au/TiO<sub>2</sub> catalyst for the hydrogenation of nitroaromatic compounds is retained when the double bond and the carbonyl function are conjugated. In this situation, the slight decrease in selectivity at high conversion levels is due to the addition of a second 1butene-3-one molecule onto the obtained keto amine. On the other hand, the short reaction times required to perform the whole cascade process indicate effective cooperative behavior between the Au nanoparticles and the TiO<sub>2</sub> support to achieve the selective hydrogenation of the nitro group and the consecutive Michael addition reaction, respectively.

Finally, to expand the variety of polyfunctional  $\beta$ -amino carbonyl compounds that can be obtained through this method, we have carried out analogous experiments with different substituted nitroaromatic compounds, and the results are summarized in entries 2 and 3 of Table 2. The selected reactants include sensitive functional groups such as ethyl cinnamates or nitriles, which are very commonly used for the synthesis of pharmaceuticals, fragrances, or biocides.<sup>[70-72]</sup> In all cases, high yields of the corresponding keto amines are obtained with Au/TiO<sub>2</sub>, a result indicating that the proposed methodology is chemoselective with different substituted nitrobenzenes.

In conclusion, we have shown that the use of gold-based bifunctional catalysts can open a new preparative route that allows the chemoselective synthesis of substituted imines, as well as the synthesis of the corresponding amines, and  $\beta$ -amino carbonyl compounds, by starting directly from substituted nitroaromatics, through a cascade-type reaction.

Synthesis of substituted imines involving nitroaromatic compounds and alkynes: We have also considered a more com $\begin{array}{c} \stackrel{NO_2}{\underset{R^1}{\longrightarrow}} + \underset{R^2}{\underset{R^2}{\longrightarrow}} \stackrel{H_2}{\underset{Au/TiO_2}{\longrightarrow}} \left[ \begin{array}{c} \stackrel{NH_2}{\underset{R^1}{\longrightarrow}} + \underset{R^2}{\underset{R^2}{\longrightarrow}} \right] \\ & \downarrow Au/TiO_2 \\ & \downarrow$ 

Scheme 7. One-pot synthesis of substituted imines from nitrobenzenes and alkynes by using Au/TiO<sub>2</sub> catalysts.

strates (Table 3, entry 1) show that this synthetic route is feasible with the Au/TiO<sub>2</sub> catalyst and that it allows the corresponding imine to be obtained without producing other byproducts such as styrene, ethylbenzene, or *N*-(1-phenylethyl)aniline (the hydrogenated imine). However, this reaction is particularly complex due to other possible additional side transformations, such as the hydrolysis of the imine to provide aniline and acetophenone.<sup>[73]</sup> In contrast to the results with imines coming from anilines and benzaldehydes, the presence of a methyl group adjacent to the nitrogen atom has a strong effect on the reactivity of the N=C bond and favors the attack of nucleophiles such as water (see Scheme 8).

As a consequence, the conversion decreases and so does the selectivity, owing to the formation of acetophenone by hydrolysis of the imine. Indeed, evidence for the formation

Table 3. Catalytic results during the synthesis of substituted imines from nitroaromatics and alkynes by using  $Au/TiO_2$  catalysts (see the Supporting Information for the corresponding feeding compositions).

Product	Т [°С]	$P_{\rm H_2}$ [bar]	% Au <sup>[a]</sup>	<i>t</i> [h]	Conversion [%] <sup>[b]</sup>	Selectivity [%] <sup>[c]</sup>
	120	2	0.50	9	55	55
	120	5	0.50	4.8	50	83
	120	5	0.50	9	62	83
	Product N 10 N N 10 N 10 N N 10 N N N N N N N N	Product $T$ [°C] 10 10 10 10 10 10 10 120 120	Product $T = P_{H_2}$ [°C] [bar] 120 2 10 10 120 5 10 MeO N 120 5 11	Product $T = P_{H_2} = \% \operatorname{Au}^{[a]}$ [°C] [bar] % Au <sup>[a]</sup> [bar] % Au <sup>[</sup>	Product       T $P_{H_2}$ % Au <sup>[a]</sup> t         [°C]       [bar]       % Au <sup>[a]</sup> t         [N]       120       2       0.50       9         10       120       5       0.50       4.8         10       120       5       0.50       9         10       120       5       0.50       9         11       120       5       0.50       9	ProductT [°C] $P_{H_2}$ [bar]% Au <sup>[a]</sup> [h]t (% [%] <sup>[b]</sup> (°C][bar]12020.509551012050.504.8501012050.504.8501012050.50962

[a] Mol Au/mol nitroaromatic  $\times 100$ . [b] Based on aniline after complete exhaustion (>95%) of the nitroaromatic. [c] Loss of selectivity due to formation of acetophenone by hydrolysis of the imines with water. [d] Au/TiO<sub>2</sub> catalyst doped with Na.



Scheme 8. Hydrolysis of imines in the presence of Lewis acids.

of acetophenone from this type of imines has been found, in the presence of the Au/TiO<sub>2</sub> catalyst, even when low concentrations of water are present.<sup>[73]</sup> This hydrolysis reaction can be completely avoided in most cases by simply drying the reactants, the solvent, and the catalyst before the reaction. However, when the synthetic route in Scheme 7 is considered, water is formed as a byproduct during the nitroaromatic hydrogenation, which makes it much more difficult to stabilize the N=C group. In this situation, only 55 % conversion of aniline (after complete exhaustion of nitrobenzene) is obtained, and only 55 % remains as the desired imine, with acetophenone being the main byproduct, together with small amounts of the hydrogenated imine.

Removal of the water formed during the reaction is not an easy task under our reaction conditions, so we thought about modifying the catalyst to avoid the hydrolysis reaction. Thus, considering that hydrolysis reactions are usually catalyzed by acids or bases,<sup>[35]</sup> we have attempted to reduce the rate of hydrolysis by decreasing the acidity of the Au/ TiO<sub>2</sub> system. To do that, the surface of the TiO<sub>2</sub> has been doped with a controlled amount of sodium acetate (see the Experimental Section), and the resultant sample was tested in the reaction between nitrobenzene and phenylacetylene under H<sub>2</sub> pressure. A significant increase of the selectivity for the imine was observed, from an imine/ketone ratio of  $\approx 1$  with the undoped Au/TiO<sub>2</sub> sample to  $\approx 5$  for the sodium-containing Au/TiO<sub>2</sub> catalyst (Table 3, entry 2). Consequently, selectivity for the desired imine was increased up

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to 83%. Improved selectivities were also observed with other substituted nitrobenzenes (for example, 4-nitroanisole). This unprecedented cascade-type reaction represents a powerful synthetic route for the preparation of substituted imines that combines the exceptional properties of gold for activating nitro groups and triple bonds, which allows the design of new alternative routes for the synthesis of substituted imines and related derivatives.

#### Conclusion

Gold catalysts have been applied to design cascade-type reactions for the synthesis of different nitrogen-based compounds. Firstly, substituted imines have been successfully prepared from nitroaromatic compounds and aldehydes, with results showing that the method is efficient even for synthesizing  $\alpha,\beta$ -unsaturated imines. In addition, unknown properties of gold to reduce selectively the imine group in the presence of sensitive functional groups such as double bonds have been discovered, which opens up the possibility of easily preparing substituted secondary aromatic amines through a cascade-type reaction. We have also shown that the Au/TiO<sub>2</sub> system can operate as a bifunctional catalyst for preparing substituted  $\beta$ amino carbonyl compounds from nitroaromatics and  $\alpha,\beta$ -unsaturated carbonyls. In this matter, while the gold sites promote the in situ formation of anilines by hydrogenation of the nitroaromatic, the intrinsic acidity of the Ti species on the support surface accelerates the subsequent Michael addition of the conjugated double bond. Finally, the gold-catalyzed reaction between amines and alkynes to prepare imines has been performed in a one-pot reaction by starting directly from nitrobenzenes. The Au/TiO<sub>2</sub> catalyst is shown to be able to activate simultaneously the nitro group (hydrogenation) and the triple bond (coupling reaction) without losing selectivity due to the generation of other hydrogenation byproducts. Moreover, we have found an appropriate method to avoid other undesired side reactions, such as the hydrolysis of the formed imine to acetophenone, by controlling the surface acidity of the support.

#### **Experimental Section**

**Catalysts preparation**: The gold catalyst used in the present work consists of 1.5 wt% gold on  $\text{TiO}_2$ , which can be supplied by the World Gold Council (reference catalysts Type A) or, otherwise, could be prepared by depositing the gold on  $\text{TiO}_2$  (P25 Degussa) from an aqueous solution of HAuCl<sub>4</sub>. The deposition–precipitation procedure is done under stirring at 70 °C and with a pH value of 7, with NaOH used to maintain this pH

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value for 2 h. Under these conditions, 80% of efficiency in the deposition of gold is expected. The catalyst is then recovered from the solution by filtering, washed with deionized water, and dried at 100°C overnight. Finally, the powder is calcined at 400°C in an air flow for 4 h. By using this procedure, gold nanoparticles that present an average diameter of 3.5 nm are deposited on the  $TiO_2$ , as determined by TEM (see Figure S1 in the Supporting Information).

The acid-free Au/TiO<sub>2</sub> catalyst was prepared by impregnating the 1.5 wt% Au/TiO<sub>2</sub> sample with 6000 ppm Na (sodium acetate as the precursor). As an example, to prepare 10 g of the material doped with 6000 ppm Na, 20 mL of an aqueous solution containing 214.1 mg of CH<sub>3</sub>COONa were used. After homogenization of the resulting gel, the material was dried at 100 °C for 6 h before the catalytic tests.

Reaction procedure: Catalytic reactions were performed in a reinforced glass reactor (2 mL capacity) equipped with a manometer and a capillary tube for either pressurizing the reactor with gas or extracting liquid samples (luer-lock valve). In a typical experiment, a mixture of reactants and solvent (1 mL) is introduced inside the reactor, together with a catalytic amount of the 1.5 wt % Au/TiO2 catalyst. For the reactions presented in Table 1 and Table 2, o-xylene was used as the internal standard, while 1,3,5-trimethylbenzene was used for the examples in Table 3. After sealing of the reactor, the air contained inside must be purged by flushing 3 times with hydrogen (10 bar). The reaction mixture is then magnetically stirred (1000 rpm), heated in a silicone oil bath up to the selected temperature, and pressurized with H<sub>2</sub> gas at the set-point value (the starting point of the reaction). The temperature, H<sub>2</sub> pressure, and stirring rate were maintained constant until the end of the experiment. During the reaction, different aliquots ( $\approx$  30 µL) are taken at different times and analyzed by gas chromatography. After exhaustion of the nitroaromatic compound (95-98% conversion), the reactor is depressurized and left at the same temperature and stirring rate until completion of the cascade process. The conversion and selectivity levels were determined from the GC results after correction of the chromatographic areas with the corresponding detection factors, by using o-xylene or 1,3,5-trimethylbenzene as the internal standard. Finally, the catalyst was filtered and the organic solution was concentrated under vacuum. The crude product was purified by column chromatography on silica gel, with a mixture of hexane:ethyl acetate (99:1) as the eluent.

**Analysis of products**: Reaction byproducts were identified by mass spectroscopy (GC/MS); the main reaction product was also identified by NMR spectroscopy. GC/MS analyses were performed on an Agilent 5973N spectrometer equipped with the same column and under the same conditions as the gas chromatograph. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> with tetramethylsilane as the internal standard at 25°C on a Bruker Avance 300. (NMR spectra of the reaction products can be found in the Supporting Information).

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