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# Gold Catalysis Opens Up a New Route for the Synthesis of Benzimidazoylquinoxaline Derivatives from Biomass-Derived Products (Glycerol)

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*Dedicated to Professor Carmen Najera on her 60th birthday.*

Process intensification by using well-defined solid catalysts able to perform one-pot multistep reactions is one of the open fronts in heterogeneous catalysis. This is even more relevant if new, more efficient synthesis routes are open. Herein, a gold catalyst was used to synthesize benzimidazoylquinoxalines compounds by two efficient and selective novel methods in a multistep one-pot methodology. The first method involved the synthesis of benzimidazoylquinoxaline compounds with the same substituents in both heterocycles through oxidation–cyclization of glycerol with *o*-phenylenediamine derivatives, whereas the second one allowed the synthesis of benzimidazoylquinoxalines compounds with different substituents in each aromatic ring through coupling of *o*-phenylenediamine derivatives with glyceraldehyde in a first stage to produce the benzimidazol compound as an intermediate, followed by an oxidation–cyclization with another *o*-phenylenediamine compound in a second stage. Both stages were performed by using gold nanoparticles supported on nanoparticulated ceria ($Au/CeO_2$) as the catalyst and air as the oxidant, in absence of any homogeneous reagent. A reaction mechanism has been proposed.

## Introduction

The use of renewable resources as replacements for fossil fuels can help to achieve a more sustainable world. In this direction, biomass can be a renewable source of organic carbon to replace fossil fuels and to produce organic chemicals.[1,2]

Oils and fats that do not compete with food will play an even more important role in chemical industry, owing to their competitive cost and worldwide availability. Thus, the production of biodiesel by transesterification of fatty esters with methanol and ethanol has been growing in the last years and co-generates large amounts of glycerol. Because of the oversupply of glycerol, its price has dropped sharply,[3] and the research for new applications of this versatile molecule has been an area of growing interests in the last years. Glycerol is a multifunctionalized compound and a number of conversion processes such as oxidations,[4] transesterifications,[5] etherifications,[6] esterifications,[7] etc. to produce value-added chemicals have been reported. As a consequence, glycerol has been recognized as one of the most important building blocks in the conversion of biomass-derived feedstock to value-added chemicals. Here we present a new synthetic application of glycerol and glycerol derivatives to obtain benzimidazoylquinoxalines through a cascade reaction process catalyzed by gold.

Compounds possessing the benzimidazole moiety exhibit significant activity towards several viruses such as human immunodeficiency virus (HIV), herpes simplex virus (HSV-1), human cytomegalovirus (HCMV), and influenza.[8] Bis-benzimidazole is a DNA minor-grove binding agent possessing antitumor activity.[9] Benzymidazoylquinoxaline compounds have shown properties as a novel class of selective antagonists at human A1 and A3 adenosine receptors.[10] Methods for the synthesis of these heteroarylquinoxalines are limited. An option involves the reaction of the corresponding *o*-phenylenediamine derivative with 3-hydroxyimino-2-butanone and bromine in a one-pot reaction (Scheme 1).[11] Another possibility is to react diamine aromatic compounds with quinoxaline-2-carboxylic acid, but this synthetic route needs to be performed in polyphosphoric acid media at 200 °C.[12] A third route is to react the *o*-phenylenediamine derivative with quinoxaline-2-carbaldehyde with acetic acid in ethanol at reflux temperature. In all three cases the yield of the target product remains very low.[13]

A recent alternative synthetic route for the synthesis of heteroarylquinoxalines with higher yields (72–97 %) involves the reaction between 3-alkanoylquinoxalin-2-ones with 1,2-phenylenediamine derivatives through a novel rearrangement (Scheme 2).[14,15] However the main drawback of this reaction procedure is the difficult synthesis of the alkanoylquinoxalin-2-

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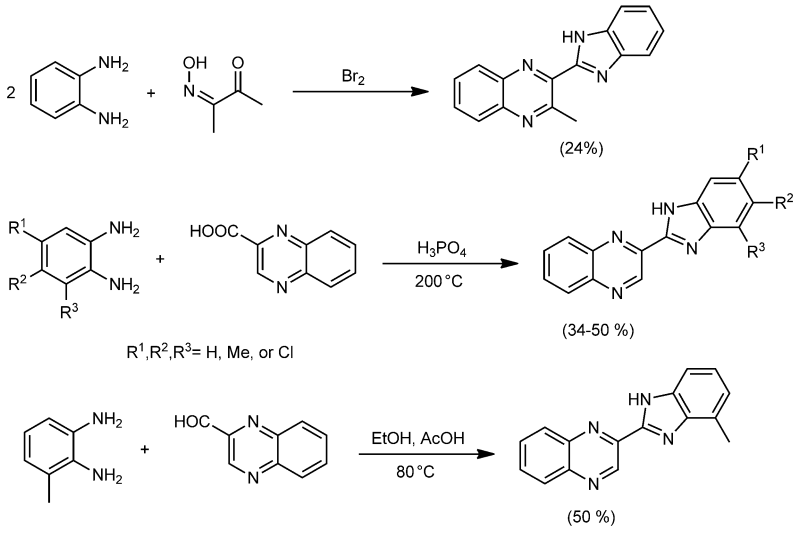
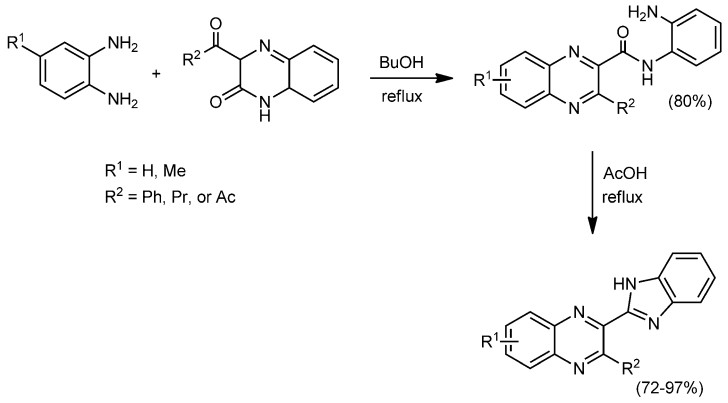



**Scheme 1.** Benzimidazoylquinoxaline synthesis routes according to Refs. [11–13].




**Scheme 2.** Benzimidazoylquinoxaline synthesis through a novel rearrangement in the reactions of 3-alkanoylquinoxalin-2-ones with 1,2-phenylenediamine according to Refs. [14] and [15].

ones reagents,[15] which are obtained in yields of approximately 30%.

Therefore, there is a clear incentive to develop catalytic processes able to produce the benzimidazoylquinoxalines by more sustainable methods, with high activity and selectivity whereas minimizing the number of reaction steps. Following our ongoing program for searching new environmentally friendly methods for synthesizing fine chemicals,[2,16,17] we report here a novel straightforward synthetic method of benzimidazoylquinoxaline derivatives through oxidative coupling of glycerol or glyceraldehyde with *o*-phenylenediamine derivatives in the presence of an $Au/CeO_2$ catalyst.

## Results and Discussion

### Synthesis of benzimidazoylquinoxalines by oxidative coupling of glycerol with *o*-phenylenediamine derivatives

In earlier work we have performed the oxidative coupling of alcohols with *o*-phenylenediamine derivatives to form benzimidazole or quinoxaline compounds by using gold in the form of nanoparticles as a catalyst, in the absence of base and under mild reaction conditions.[18,19] Catalyst optimization studies showed that Au nanoparticles supported on nanosized $CeO_2$ ($Au/CeO_2$) were the most active and selective catalysts to obtain quinoxalines. The influence of the support on the rate of the alcohol oxidation by gold has been ascribed to changes produced on the crystallite shape as well as to the participation of the support in the catalytic cycle.[20] It has been reported that in the case of $CeO_2$, its surface saturation by $O_2$ is achieved at relatively low partial pressure of $O_2$, owing to the excellent capacity of $CeO_2$ to act as an oxygen pump caused by the presence of surface oxygen vacancies that arise from the nanometer size of ceria.[21]

We assumed that by using this catalyst it could be possible to obtain benzimidazoylquinoxalines through the oxidative coupling of triol derivatives with *o*-phenylenediamine compounds. Thus, the reaction between 1,2-phenylenediamine (**1a**) and glycerol (**2**) was performed with and without $Au/CeO_2$ as a catalyst in diglyme as a solvent at 140 °C. As we have shown previously,[18] this solvent was able to dissolve completely both reactants (polyols and 1,2-phenylenediamine derivatives) and products and al-

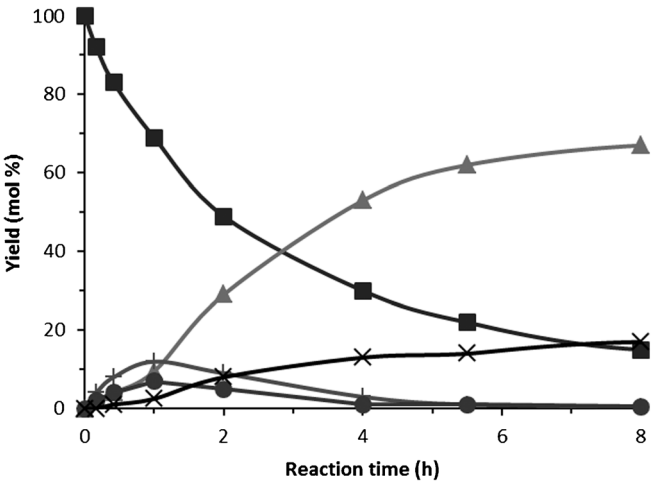
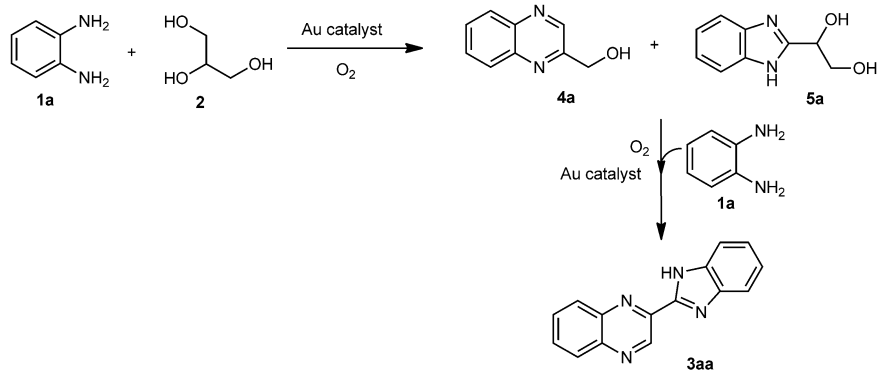


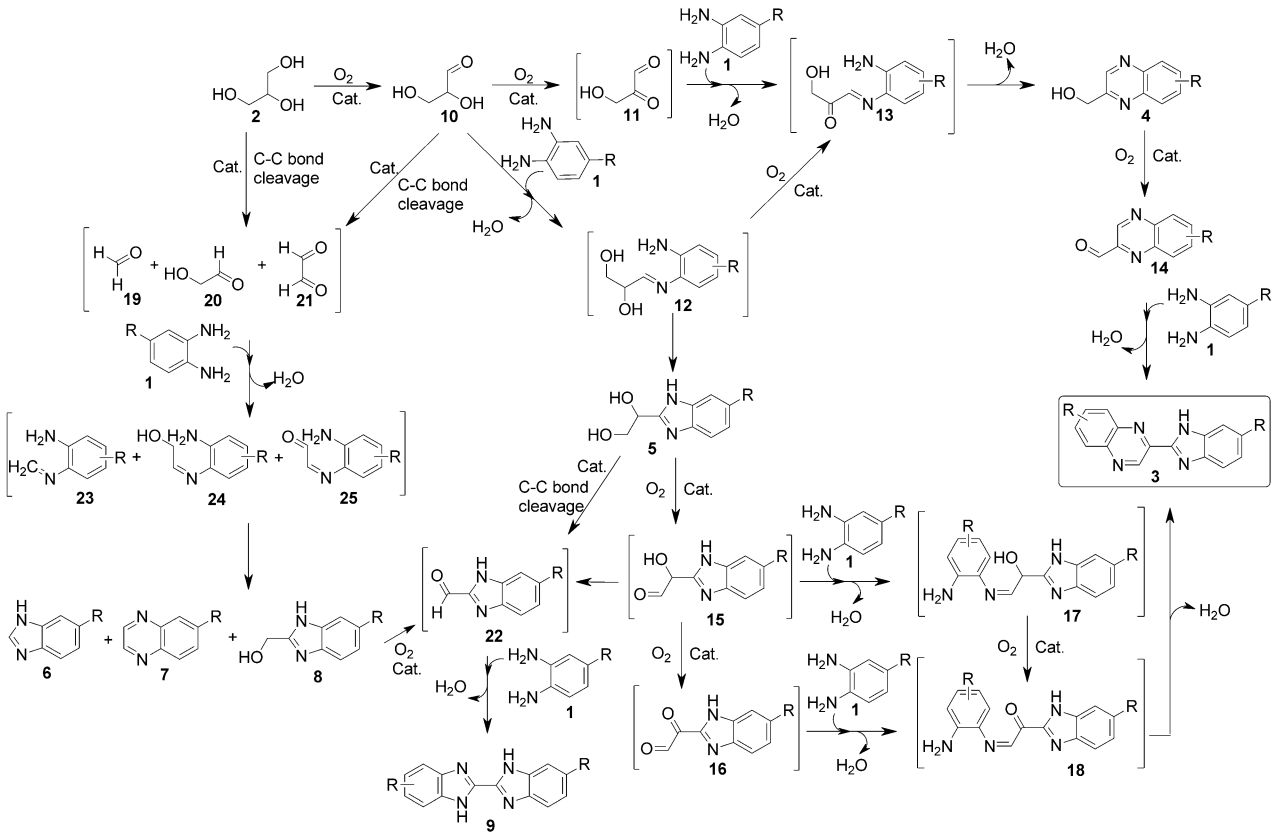

**Figure 1.** Kinetic plots of the different compounds detected in the oxidation–cyclization reaction of **2** with **1a** using $Au/CeO_2$: **1a** (■), **3aa** (▲), **4a** (+), **5a** (●), **6a**+**7a**+**8a**+**9aa** (**X**). Reaction conditions: **1a** (1.2 mmol), **2** (0.5 mmol), diglyme (1.5 mL), $Au/CeO_2$ (2.33 wt%), **2**/Au molar ratio = 100, at 140 °C.

lowed us to work at temperature of 140 °C. No reaction was observed in the absence of a catalyst. However, in the presence of $Au/CeO_2$, the reaction kinetics given in Figure 1 clearly revealed the formation of benzimidazoylquinoxaline (**3 aa**) as the main product, with a yield of 79% after 8 h reaction time. However, at the beginning of the reaction, the quinoxalin-2-ylmethanol (**4 a**), formed by oxidative coupling between glycerol and *o*-phenylenediamine, and the 1-(1*H*-benzo-[*d*]imidazol-2-yl)ethane-1,2-diol (**5 a**), which could be produced through the oxidation of one of the primary alcohol groups of glycerol and subsequent coupling with *o*-phenylenediamines, were the predominant products (Scheme 3). Both compounds (**4 a** and **5 a**) exhibited a primary and unstable character and after one hour of reaction, the concentrations of both intermediates began to decrease, which was caused by their conversion into 2-(1*H*-benzo[*d*]imidazol-2-yl)quinoxaline (**3 aa**), produced through oxidation–cyclization of **4 a** and **5 a** with another *o*-phenylenediamine molecule (see Figure 1). Other byproducts such as 1*H*-benzo[*d*]imidazole (**6 a**), quinoxaline (**7 a**), (1*H*-benzo[*d*]imidazole-2-yl)methanol (**8 a**) and 1*H*,1′*H*-2,2′-bibenzo[*d*]-imidazole (**9 aa**) were also detected in the reaction media (see the Supporting Information, Scheme S1).

Taking into account the kinetic behavior of the different compounds presented in Figure 1, a reaction network is presented in Scheme 4 in which glycerol **2** is firstly oxidized to glyceraldehyde **10** and subsequently to the dicarbonyl compound **11** (nondetectable by GC). Both compounds can condensate with the diamine **1** to produce the imine intermediates **12** and **13**, with **12** converted into product **13** by fast oxidation of the remaining hydroxyl group. Later, product **13** follows a condensation reaction to yield

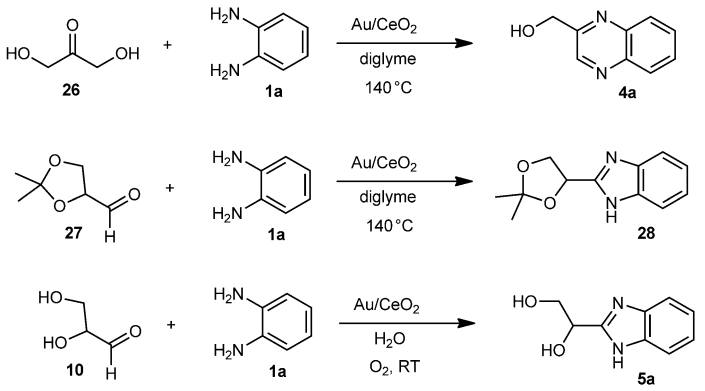



**Scheme 3.** Reaction pathway for the benzimidazoylquinoxaline synthesis with glycerol.




**Scheme 4.** Proposed benzimidazoyquinoxalines (**3**) synthesis mechanism starting from 1,2-phenylenediamine derivatives and glycerol.

hydroxymethylquinoxaline intermediate **4**, which can be further oxidized to 2-carbaldehydequinoxaline **14**, which couples with another diamine molecule **1** to reach the benzimidazoylquinoxaline derivative **3**. Moreover, the imine intermediate **12** can give the dihydroxybenzimidazole intermediate **5**, which through a subsequent oxidative coupling with the diamine **1** produces the benzimidazoylquinoxaline derivative **3**. On the other hand, the formation of the byproducts detected could be explained by the oxidative cleavage of glycerol (**2**), glyceraldehyde (**10**), the dihydroxybenzimidazole intermediate **5**, and the α-hydroxycarbonylbenzimidazole intermediate **15** into different carbonyl compounds such as **19**, **20**, **21**, and **22** followed by the coupling with diamine **1** to produce the byproducts **6**, **7**, **8**, and **9** through cyclization in minor amounts.




**Scheme 5.** Possible synthetic routes to yield the intermediate quinoxaline (**4a**) or benzimidazoles (**28**, **5a**).

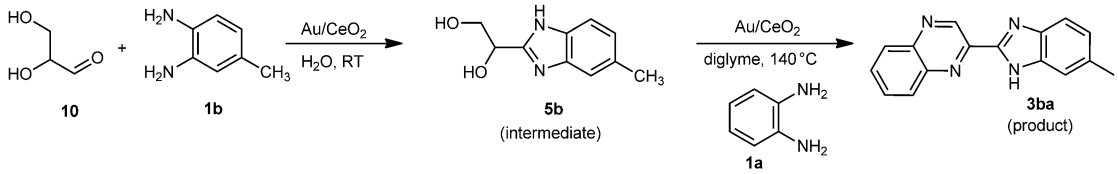
### Scope of the reaction

The influence of different substituents at position 4 of 1,2-phenylenediamine **1a** (i.e., 4-methylbenzene-1,2-diamine **1b**, 4-chlorobenzene-1,2-diamine **1c**, 4-nitrobenzene-1,2-diamine **1d**, 3,4-diaminobenzonitrile **1e**, 4-methoxybenzene-1,2-diamine **1f**, naphthalene-2,3-diamine **1g**), on the performance for the oxidation–cyclization process of glycerol (**2**), was studied in the presence of $Au/CeO_2$. As can be seen in Table 1, good yields to benzimidazoylquinoxaline derivatives were obtained, which were almost always better than those described in the literature (compare entries 1–7 with 8–11). However, if electron-withdrawing substituents such as nitro, chloride, or nitrile groups were present, the yields of quinoxaline derivatives were slightly lower with respect to those of 1,2-phenylenediamine or with respect to phenylenediamine molecules with electron-donating substituents. The same trend has been described in the literature for the reaction between α-hydroxycarbonyl compounds and 1,2-phenylenediamine derivatives.[18,22]

### Synthesis of benzimidazoylquinoxalines with different substituents in heteroaromatic moieties

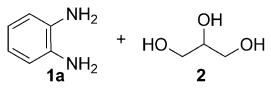
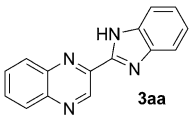
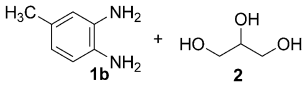
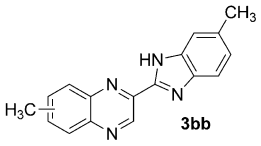
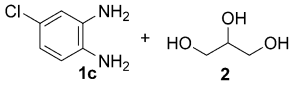
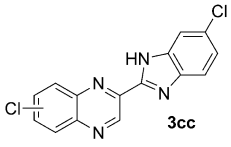
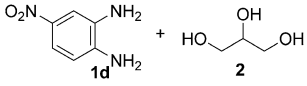
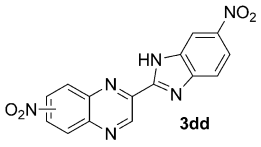
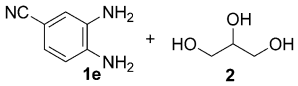
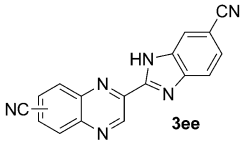
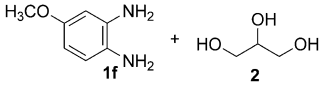
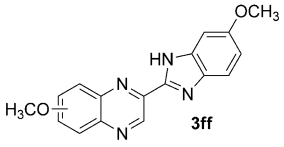
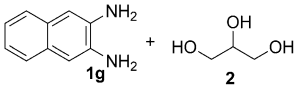
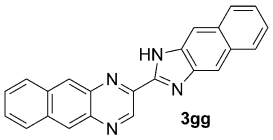
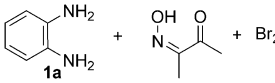
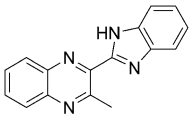
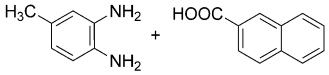
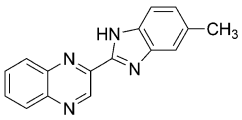
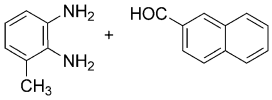
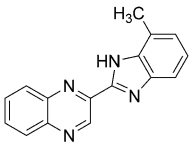
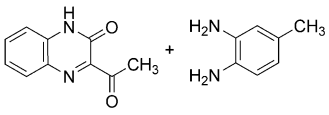
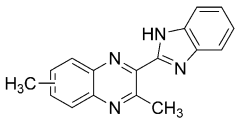
The results presented here demonstrated that our approach based on the one-pot oxidative coupling of glycerol with 1,2-phenylenediamines was a straightforward synthetic method which gave benzimidazoylquinoxaline derivatives in much higher yields than the conventional synthetic methods reported up to now. However, using this approach, owing to the rapid oxidative coupling of the intermediate **4** and **5** with the 1,2-phenylenediamine derivative, it was only possible to obtain regioisomers of the correspondent benzimidazoylquinoxaline derivatives with the same substituents on the quinoxaline and on the benzimidazole aromatic rings. Then, in order to expand the synthetic scope, other alternative routes that allow combining different substituents in both heteroaromatic moieties have been studied. The different strategies studied involved, as first step, the synthesis of diverse intermediates such as those showed in Scheme 5, which could be oxidatively coupled with differently substituted 1,2-phenylenediamine in a second step. The synthesis of these intermediates (**4a**, **28**, and **5**) was performed by oxidative coupling of dihydroxyacetone (**26**), solketylaldehyde (**27**), and glyceraldehyde (**10**) with *o*-phenylenediamine, respectively, using $Au/CeO_2$ as a catalyst. After optimization of the reaction conditions with the different substrates, the results presented in Table 2 revealed that only the reaction between glyceraldehyde and 1,2-phenylenediamine (route III) in the presence of $Au/CeO_2$, oxygen pressure, and at room temperature, produced the benzimidazole intermediate **5** with high selectivity at complete conversion. Therefore, the synthesis of the benzimidazole intermediate from glyceraldehyde and 1,2-phenylenediamine derivative was chosen as the optimum first step of the reaction.

To develop a new one-pot approach to produce benzimidazoylquinoxalines differently substituted in the aromatic rings, we performed in a first step the oxidative coupling between glyceraldehyde (**10**) and 4-methylbenzene-1,2-diamine (**1b**) in the presence of $Au/CeO_2$ with pure oxygen (3 bar), at room temperature, and with water as a solvent. Once complete conversion of glyceraldehyde was achieved, a solution of 1,2-phenylenediamine (**1a)** in diglyme was added and the temperature raised up to 140 °C, during which the water was removed




**Scheme 6.** New one-pot two-step process to produce benzimidazoylquinoxalines starting from glyceraldehyde (**10**).

**Table 1.** Synthesis of benzimidazoylquinoxaline derivatives starting from diamine and glycerol using $Au/CeO_2$ as the catalyst.[a]

| Entry | Reactants | Product | Sel. to **3**[b] [mol%] | Yield[b] [mol%] |
|---|---|---|---|---|
| 1 |  **1a** + **2** |  **3aa** | 81 | 79 |
| 2 |  **1b** + **2** |  **3bb** | 82 | 80[c] |
| 3 |  **1c** + **2** |  **3cc** | 78 | 75[c] |
| 4 |  **1d** + **2** |  **3dd** | 76 | 71[c] |
| 5 |  **1e** + **2** |  **3ee** | 76 | 72[c] |
| 6 |  **1f** + **2** |  **3ff** | 81 | 75[c] |
| 7 |  **1g** + **2** |  **3gg** | 83 | 77 |
| 8 |  **1a** + + $Br_2$ |  | | 24[d] |
| 9 |  |  | | 50[e] |
| 10 |  |  | | 50[f] |
| 11 |  |  | | 72[c,g] |

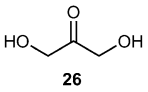
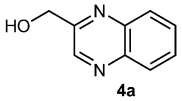
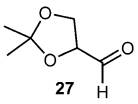
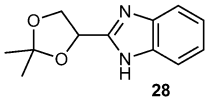
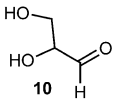
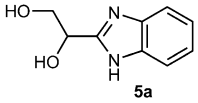
[a] Reaction conditions: diamine (1.2 mmol), **2** (0.5 mmol), diglyme (1.5 mL), $Au/CeO_2$ (2.33 wt%), **2**/Au molar ratio = 100, at 140 °C, 24 h; [b] Selectivity to **3** at 90% conversion. Yield values were determined from Equations (1) and (3); [c] A mixture of regioisomers was obtained. [d] Yield from reaction reported in Ref. [11], [e] Ref. [12], [f] Ref. [13], and [g] Ref. [15].

by a Dean Stark system (Scheme 6). In this second step, the main product observed at short times was the desired product **3ba** (Figure 2), formed by oxidation of the hydroxyl groups of **5b** and subsequent cyclization with *o*-phenylenediamine (**1a**). However, also in this case, byproducts coming from the oxidative cleavage of the intermediate 1-(5-methyl-1*H*-benzo[*d*]imidazol-2-yl)ethane-1,2-diol (**5b**), such as 6-methyl-1*H*-benzo[*d*]imidazole (**6b**), 1*H*-benzo[*d*]imidazole (**6a**), quinoxaline (**7a**), (1*H*-benzo[*d*]imidazol-2-yl)methanol (**8a**) and 6-methyl-1*H*,1′*H*-2,2′-bibenzo[*d*]imidazole (**9ba**) were formed (Scheme S2). From the kinetic behavior of the different products obtained in the second stage (see Figure 2), it can be seen that all of them were stable products that were formed from the oxidation–cyclization reaction of 1-(5-methyl-1*H*-benzo[*d*]imidazol-2-yl)ethane-1,2-diol (**5b**) or from the oxidation–cyclization reaction of the byproducts obtained through oxidative cleavage of **5b**. From the kinetic behavior of these reactions, a reaction network is presented in Scheme 7, in which glyceraldehyde **10** is firstly cyclized to the benzimidazoyl intermediate **5** in the first stage, and subsequently **5** is oxidatively coupled with other diamine **1** to produce the benzimidazoylquinoxaline derivative **3**.

### Scope of the reaction

To study the scope of the reaction, different 4-substituted 1,2-phenylenediamines (1,2-phenylenediamine (**1a**), 4-methylbenzene-1,2-diamine (**1b**), 4-chlorobenzene-1,2-diamine (**1c**), 4-nitrobenzene-1,2-diamine (**1d**), 3,4-diaminobenzonitrile (**1e**), 4-methoxybenzene-1,2-diamine (**1f**), and naphthalene-2,3-diamine (**1g**)) were used in the first and second step of the reaction in the presence of $Au/CeO_2$ as the catalyst. As can be seen in Table 3, very good yields of benzimidazoylquinoxaline derivatives were obtained in all cases. This is even more remarkable if we consider that this synthetic route allowed us to synthesize benzimidazoylquinoxaline derivatives with different substituents in each aromatic ring. Furthermore, if *o*-phenylenediamine with substituents was used in the first stage of this synthetic route, only one regioisomer of the target product was obtained, unlike what occurred for the synthetic route starting from glycerol described above or the synthetic routes

**Table 2.** Synthesis of different intermediates in the synthesis of benzimidazoylquinoxaline derivatives.[a]

| Synthetic route | Reactant | Product | Sel. to product[b] [mol%] |
|---|---|---|---|
| I |  **26** |  **4a** | 62 |
| II |  **27** |  **28** | 82 |
| III |  **10** |  **5a** | 95 |

[a] Reaction conditions route I and II: **1a** (0.5 mmol), reactant (0.5 mmol), diglyme (1.5 mL), $Au/CeO_2$ (2.33 wt%), reactant/Au molar ratio = 100, and 140 °C. Reaction conditions route III: **1a** (0.5 mmol), reactant (0.5 mmol), $H_2O$ (2.0 mL), $Au/CeO_2$ (2.33 wt%), reactant/Au mol ratio = 100, $PO_2$ = 3 bar, room temperature, 4 h; [b] Selectivity values to product at complete conversion were determined from the equation: Sel. (%) = (mol product)$_t$/[(mol **1**)$_0$ − (mol **1**)$_t$] × 100.

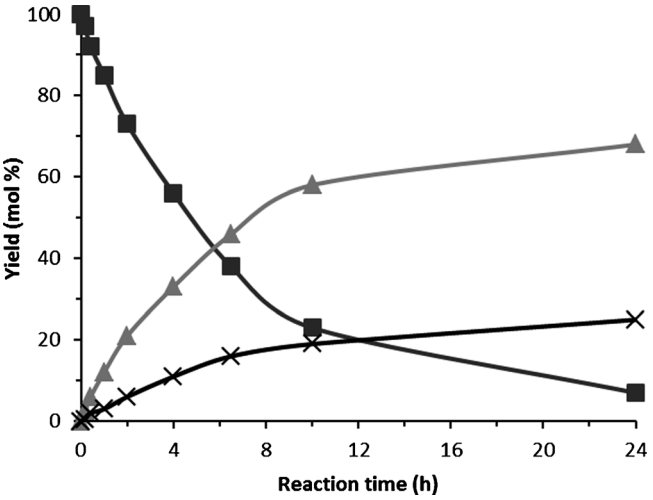
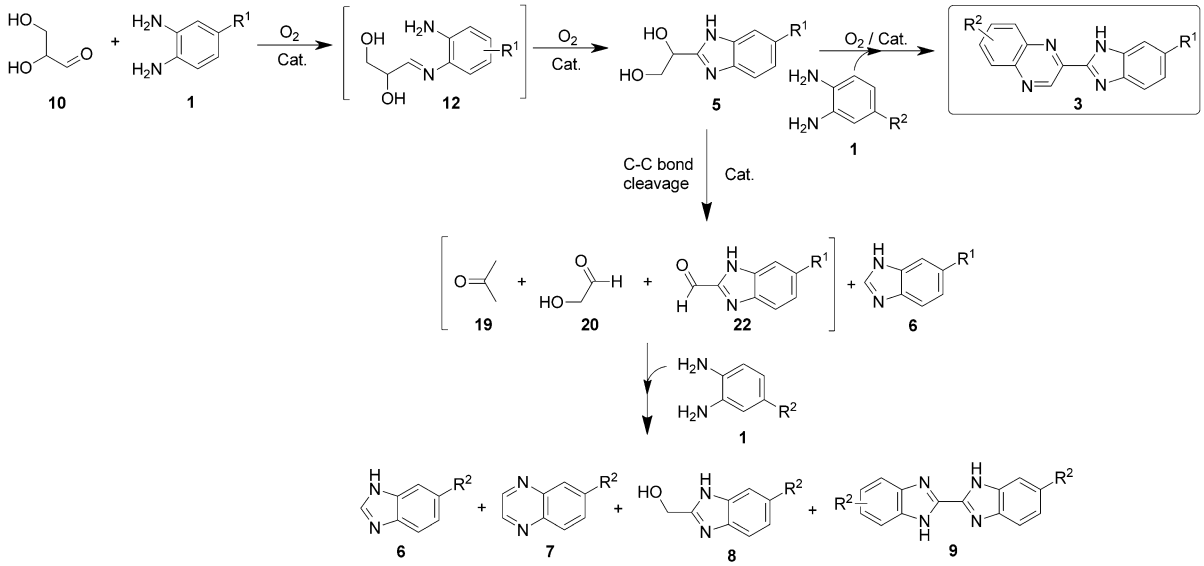



**Figure 2.** Kinetics plots of the different compounds detected in the second stage of the benzimidazoylquinoxaline synthesis starting from glyceraldehyde (**10**) and using $Au/CeO_2$. **5b** (■), **3ba** (▲), **6b** + **6a** + **7a** + **8a** + **9ba** (**X**). Stage 1: diamine **1b** first step (0.5 mmol), **10** (0.5 mmol), $H_2O$ (2.0 mL), $Au/CeO_2$ (2.33 wt%), **10**/Au mol ratio = 100, $PO_2$ = 3 bar, room temperature, 4 h. Stage 2: diamine **1a** step 2 (0.6 mmol) and diglyme (1.5 mL) were added to the reaction mixture, provided with a Dean Stark system, at atmospheric pressure and 140 °C.

starting from 3-hydroxyimino-2-butanone[11] or alkanoylquinoxalin-2-ones (see Scheme 2 and 4).[14,15] Entries 1–6 reveal the influence on the selectivity to **3** of the substituent of the diamine used in the second stage, which was responsible for the substituent present in the quinoxaline ring of the benzimidazoylquinoxaline product. Entries 7–12 reveal the influence of the diamine substituent in the first stage, which was responsible for the substituent present in the benzimidazole group. The results demonstrate that there were no significant differences in selectivity if the substituent was changed in the diamine of the second stage as occurs in the case of the oxidative coupling with glycerol. However, if the substituent was changed in the diamine of the first stage, more important differences in selectivity were observed. If electron-donating substituents were present in intermediate **5** (see Scheme 7), the selectivity to **3** decreased considerably (entries 7, 11, and 12; however, the $H_3CO$ group in entry 11 is not really electron-donating). These results show that electron-donating substituents favored the competitive oxidative cleavage of the diol **5**, which is in good agreement with the results reported in the literature for the reaction between diols and 1,2-phenylenediamine derivatives.[23]




**Scheme 7.** Proposed benzimidazoylquinoxalines (**3**) synthesis mechanism from 1,2-phenylenediamine derivatives (**1**) and glyceraldehyde (**10**).

### Stability and reusability of $Au/CeO_2$ catalyst

Catalyst recyclability was checked by performing successive reuses of the catalyst under the same reaction conditions as for benzimidazoylquinoxaline (**3aa**) synthesis by oxidative coupling of glycerol with *o*-phenylenediamine (**1a**). For the reuse, the recovered catalyst was used in a subsequent run as described in the Experimental Section. According to our previous results for the synthesis of quinoxalines,[18] no leached gold species were detected in the reaction media, whereas the gold content in the used catalyst, as measured by X-ray fluorescence, remained the same after each run. Nevertheless, some catalyst deactivation was observed (Figure 3). This catalyst deactivation should be mainly associated to deposition of organic material on the catalyst surface. Therefore, to burn off the organic deposits, the $Au/CeO_2$ catalyst was pretreated before each reuse with oxygen flow at 250 °C during 2 h. This pretreatment allowed us to regenerate a large fraction of the initial activity, as can be seen in Figure 4, whereby the selectivity to benzimidazoylquinoxaline (**3aa**) was maintained.

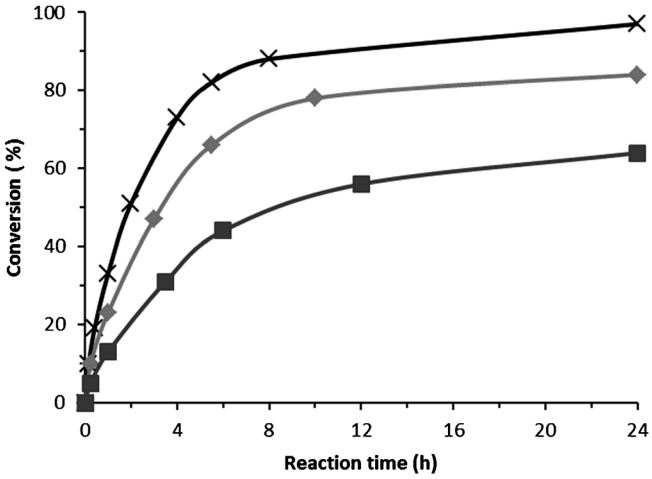



**Figure 3.** Conversion kinetic plots of the oxidation–cyclization of glycerol with *o*-phenylenediamine to **3aa** under successive reuses of $Au/CeO_2$: 1st use (**X**), 2nd use (◆), 3rd use (■). Reaction conditions: **1a** (1.2 mmol), **2** (0.5 mmol), diglyme (1.5 mL), $Au/CeO_2$ (2.33 wt%), **2**/Au mol ratio = 100, at 140 °C.

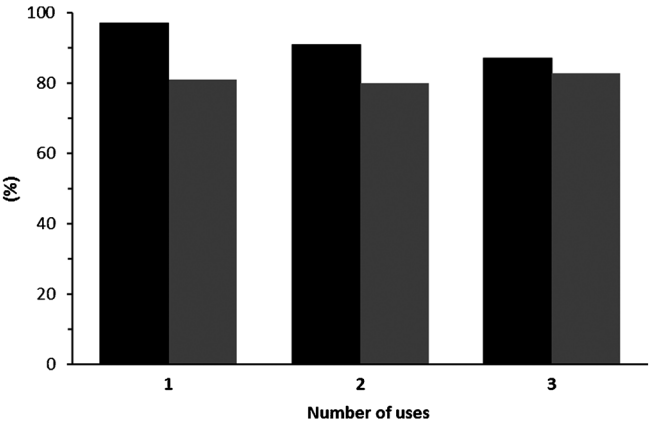



**Figure 4.** Conversion of **1a** (■) and selectivity to **3aa** (■) with successive reuses of $Au/CeO_2$ as a catalyst in the oxidation–cyclization reaction of **2** with **1a**, and with previous treatment of the catalyst under oxygen flow at 250 °C during 2 h. Reaction conditions: **1a** (1.2 mmol), **2** (0.5 mmol), diglyme (1.5 mL), $Au/CeO_2$ (2.33 wt%), **1a**/Au molar ratio = 100, at 140 °C.

## Conclusions

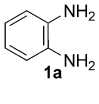
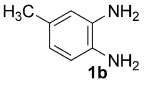
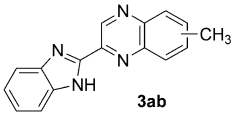
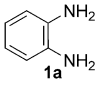
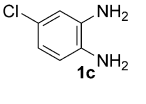
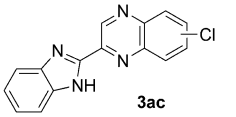
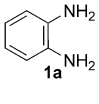
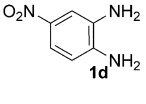
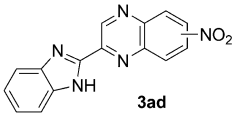
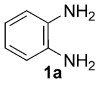
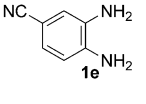
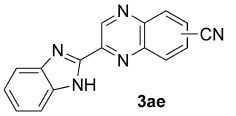
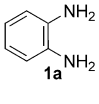
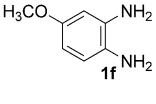
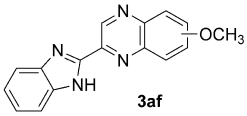
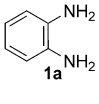
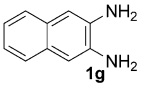
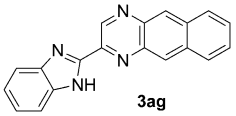
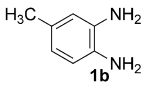
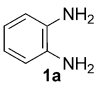
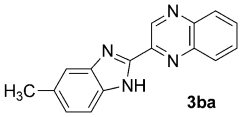
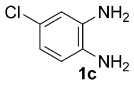
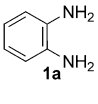
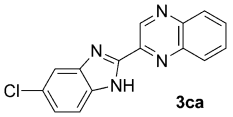
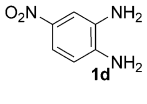
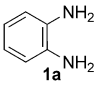
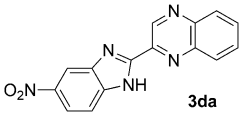
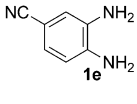
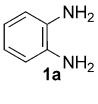
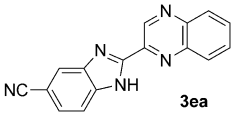
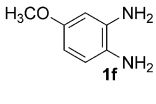
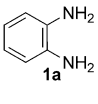
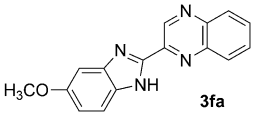
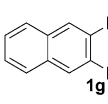
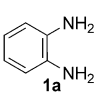
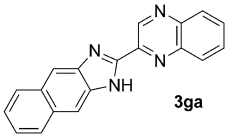
$Au/CeO_2$ was an excellent catalyst for the synthesis of benzimidazoylquinoxaline derivatives through the one-pot oxidative coupling of glycerol with 1,2-phenylenediamine derivatives, or from glyceraldehyde in a two-steps reaction. The last process involved a cyclocondensation with 1,2-phenylenediamine derivative to form the benzimidazole intermediate **5**, followed by oxidative coupling with a different 1,2-phenylenediamine derivative, which allowed us to perform the synthesis of benzimidazoylquinoxaline derivatives with different substituents in each aromatic ring. Both approaches were performed under base-free conditions, at mild temperature and by using air as the oxidant. The reaction network has been established for both syntheses. Oxidative cleavage was a competitive reaction responsible for the formation of byproducts. Moreover, the influence of the substituent in position 4 of the diamine compound was studied, and it was demonstrated that this substituent had a high importance on the selectivity as it was present in the intermediate **5**. Electron-withdrawing substituents improved the selectivity to the benzimidazoylquinoxaline compound. $Au/CeO_2$ could be easily recovered and reused with a small loss of activity whereby maintaining high selectivities towards 2-(1*H*-benzo[*d*]imidazol-2-yl)quinoxaline.

## Experimental Section

### Preparation of supported gold nanoparticles on nanoparticulated ceria

$Au/CeO_2$ was prepared by gold deposition on cerium oxide nanoparticles with a BET surface area of 180 $m^2 g^{-1}$, by using the following procedure. A solution of $HAuCl_4 \cdot 3H_2O$ (360 mg) in deionized water (160 mL) was brought to pH 10 by addition of a solution of 0.2 M NaOH. Once the pH value was stable, the solution was added to a second solution containing colloidal $CeO_2$ (4.01 g) in $H_2O$ (50 mL). After adjusting again the pH with 0.2 M NaOH, the slurry was left under vigorous stirring at RT for 18 h. The $Au/CeO_2$ solid was then filtered and exhaustively washed with distilled water until no traces of chlorides were detected by the $AgNO_3$ test. The catalyst was dried at RT under vacuum. After this, the supported gold nanoparticles were reduced with 1-phenylethanol (10 mL), at 160 °C, during 2 h under constant agitation. The total Au content of the final catalyst was 2.33 wt% as determined by chemical analysis using X-ray fluorescence, comparing the response of the $Au/CeO_2$ with standards. With this procedure, gold nanoparticles with an average size of 3-4 nm supported on $CeO_2$ were obtained as measured by high-angle annular dark field scanning transmission electron microscopy (HAADF-STEM).

**Table 3.** Synthesis of benzimidazoylquinoxaline derivatives starting from diamine and glyceraldehyde using $Au/CeO_2$ as the catalyst.[a]

| Entry | Diamine step 1 | Diamine step 2 | Product | Sel. to **3**[b] [mol%] | Yield [mol%] |
|---|---|---|---|---|---|
| 1 |  **1a** |  **1b** |  **3ab** | 79 | 77[c] |
| 2 |  **1a** |  **1c** |  **3ac** | 76 | 74[c] |
| 3 |  **1a** |  **1d** |  **3ad** | 75 | 72[c] |
| 4 |  **1a** |  **1e** |  **3ae** | 72 | 68[c] |
| 5 |  **1a** |  **1f** |  **3af** | 77 | 72[c] |
| 6 |  **1a** |  **1g** |  **3ag** | 79 | 75 |
| 7 |  **1b** |  **1a** |  **3ba** | 73 | 68 |
| 8 |  **1c** |  **1a** |  **3ca** | 79 | 76 |
| 9 |  **1d** |  **1a** |  **3da** | 82 | 79 |
| 10 |  **1e** |  **1a** |  **3ea** | 78 | 74 |
| 11 |  **1f** |  **1a** |  **3fa** | 66 | 63 |
| 12 |  **1g** |  **1a** |  **3ga** | 69 | 65 |

[a] Reaction conditions: Stage 1: diamine first step (0.5 mmol), **10** (0.5 mmol), $H_2O$ (1.5 mL), $Au/CeO_2$ (2.33 wt%), **10**/Au mol ratio = 100, $PO_2$ = 3 bar, room temperature, 4 h. Stage 2: diamine second step (0.6 mmol) and diglyme (1.5 mL) were added to the reaction mixture, provided with a Dean Stark system, atmospheric pressure and 140 °C; [b] Selectivity to **3** at 90% conversion and yield values were determined from Equations (4) and (6); [c] A mixture of regioisomers was obtained.

### Reagents

All reagents were purchased from Sigma Aldrich except 4-methoxybenzene-1,2-diamine, which was synthesized from 4-methoxy-2-nitroaniline by hydrogenation of the nitro group over $Au/CeO_2$ following Ref. [16]

### Catalyst regeneration and reuse

For catalyst reuse, the catalyst was collected after the reaction by vacuum filtration and then it was repeatedly washed. First, it was washed with ethyl acetate under stirring in ultrasounds to remove organic compounds, and subsequently it was washed with NaOH (0.2 mol $L^{-1}$) to remove any acid byproducts that may poison the gold nanoparticles. Then water was used to remove traces of NaOH on the catalyst, and at last the catalyst was washed with diethyl ether again. Finally, the catalyst was dried overnight, after which it was ready for reuse.

### Reaction procedure

Synthesis of benzimidazoylquinoxaline derivatives with the same substituents in each aromatic ring: A generic experiment was as follows. In a two-neck round-bottom flask of 10 mL placed in a silicone bath that contained a magnetic stirrer, a temperature controller, 1,2-phenylenediamine derivative (**1**, 1.2 mmol), glycerol (**2**, 0.5 mmol), diethylene glycol (1.5 mL), and dimethyl ether (diglyme) as a solvent. Subsequently the reaction mixture was heated at 140 °C, under atmospheric pressure and an amount of 42 mg of $Au/CeO_2$ (2.33 wt%) catalyst was added. The yield of the correspondent benzimidazoylquinoxaline derivative (**3**), the conversion of **1**, and the selectivity into the desired product **3** were calculated according to Equations (1–3).

$$\text{Yield}\ (\%) = \frac{n3_t}{n2_0} \times 100 \quad (1)$$

$$\text{Conv.}\ (\%) = \frac{n1_0 - n1_t}{2 \times n2_0} \times 100 \quad (2)$$

$$\text{Sel.}\ (\%) = \frac{\text{Yield}}{\text{Conv.}} = \frac{2 \times n3_t}{n1_0 - n1_t} \times 100 \quad (3)$$

Synthesis of benzimidazoylquinoxaline with different substituents in each aromatic ring: In a glass reactor of 3.0 mL, 1,2-phenylenediamine derivative (**1**, 0.5 mmol), glyceraldehyde (**10**, 0.5 mmol), water (2.0 mL), and an amount of 42 mg of $Au/CeO_2$ (2.33 wt%) were added. Subsequently the reactor was pressurized at 3 bar of pure oxygen and the reaction performed under continuous stirring at RT during 4 h. After that, the system was depressurized and then another 1,2-phenylenediamine derivative (**1′**, 0.6 mmol) and diglyme (1.5 mL) as a solvent were added. Subsequently, the flask was connected to a refrigerant attached with a Dean Stark system to remove the water from the reaction mix-

ture by heating during 1 h at 120 °C in a silicone bath. Later, the temperature was increased up to 140 °C and the mixture stirred under atmospheric pressure until the reaction was finished. Yield, conversion of the global reaction, and the selectivity into the desired product **3** were calculated according to Equations (4), (5) and (6).

$$\text{Yield}\,(\%) = \text{Yield}\,(\text{step 1}) \times \text{Yield}\,(\text{step 2}) = \frac{n5_t \times n3_t}{n1_0 \times n5_0} \times 100 \quad (4)$$

$$\text{Conv.}\,(\%) = \text{Conv.}\,(\text{step 1}) \times \text{Conv.}\,(\text{step 2}) = \frac{(n1_0 - n1_t) \times (n5_0 - n5_t)}{n1_0 \times n5_0} \times 100 \quad (5)$$

$$\text{Sel.}\,(\%) = \frac{\text{Yield}}{\text{Conv.}} = \frac{n3_t \times n5_0}{(n1_0 - n1_t) \times (n5_0 - n5_t)} \times 100 \quad (6)$$

The progress of both reactions was followed by taking samples at regular time periods and analyzing them by gas chromatography using a flame ionization detector and a capillary column (HP5, 30 m × 0.25 mm × 0.25 μm). All samples were silylated with N,O-bis-(trimethylsilyl)trifluoroacetamide and dissolved in AcOEt prior to analysis by gas chromatography. Nitrobenzene was used as an external standard. At the end of the reaction the catalyst was filtered and washed according to the method described in the previous section. The extract was concentrated and quantified in the final outcome of the reaction and the catalyst was ready to be reused. In all cases the total final mass of the reaction (including the filtered extract) was over 90% of the initial amount weighed.

Purification of the different products obtained was performed by column chromatography on silica gel using hexane/ethyl acetate as an eluent, and after that, they were characterized by $^1$H NMR (300 MHz Bruker Avance). Additionally, products identification was also performed by GC–MS using a Fisons GC 8000 gas chromatograph equipped with a DB5 capillary column with a mass spectrometry detector (Fisons MD 800 quadrupole detector). This experimental data is collected in the Supporting Information.

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**Keywords:** biomass · cerium · cyclization · gold · oxidation

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