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## Aerobic oxidative transformation of primary alcohols and amines to amides promoted by a hydroxyapatite-supported gold catalyst in water

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### Introduction

Amide groups are among the highly important and abundant functional groups in chemistry and can be found in the pharmaceutical industry, natural products, and materials science.<sup>1</sup> The traditional synthesis of amides involves carboxylic acids and their derivatives, often using promoters, organic solvents, or coupling reagents and leading to much waste.<sup>2</sup> Great efforts have been made to update this old process.<sup>3</sup> In this context, the direct catalytic aerobic oxidative coupling of alcohols and amines to form amides in the presence of heterogeneous catalysts represents a step forward toward green, economic, and sustainable process.<sup>4</sup> Nevertheless there are few efficient examples despite offering significant advantages from an environmental standpoint. In 2011, Wang et al. demonstrated the first highly efficient amide synthesis from aromatic alcohols and amines by a water-soluble gold/DNA catalyst.4b Meanwhile, Kobayashi and co-workers introduced powerful PICB (polymer-incarcerated carbon black)-supported Au/Co bimetallic catalysts for the reaction to afford various amides with good to excellent yields.<sup>4c</sup> However, tedious procedure for the catalyst synthesis or organic solvent was involved in these cases. Furthermore, organic synthesis reactions using water as solvent have some significant advantages: low cost, abundance, safety, and easy separation because most of organic products are water-insoluble. Thus, searching for facile catalysts that could achieve high reactivity and selectivity in water and extending the substrate scope (especially for aliphatic alcohols) are highly desirable and challenging in this field.

On the other hand, heterogeneous catalysts based on supported gold nanoparticles have attracted considerable research interest because of their unique catalytic properties for a broad array of organic transformations.<sup>5</sup> Recently, we have been interested in unique catalytic activities and selectivities of supported gold nanoparticle catalysts and involved in their application for fine chemical synthesis.<sup>4i,6</sup> With our ongoing interest in this area, herein, we wish to demonstrate that gold nanoparticle supported on hydroxylapatite (HAP:  $Ca_{10}(PO_4)_6(OH)_2$ ) can act as a highly efficient heterogeneous catalyst for the aerobic oxidative transformation of primary alcohols and amines to amides under aqueous conditions. Our Au/HAP is applicable to various alcohols and amines, particularly for aliphatic alcohols, which are notoriously difficult to oxidize, with up to 99% yield.

# Preparation of the Au/HAP catalyst and optimization of the reaction conditions

Initially, we selected the oxidative coupling reaction of ethanol **1a** and aniline **2a** as the model reaction, which would readily give access to acetanilide **3a**, an important intermediate in pharmaceutical industry. Different gold catalysts were tested in water at a mild temperature of 40 °C with NaOH as the base under  $O_2$  atmosphere. Table 1 summarizes some results obtained during the

ABSTRACT

In the presence of an easily prepared hydroxyapatite-supported gold catalyst, namely Au/HAP, various kinds of structurally diverse primary alcohols including benzylic and aliphatic ones, and amines involving aromatic and secondary ones could be converted into the corresponding amides in water with up to 99% yield. Meanwhile, on the basis of experimental observations and literatures, a plausible reaction pathway was described to elucidate the reaction mechanism.

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optimization of the reaction. Acetanilide **3a** was formed in a yield of 46% (Table 1, entry 1) with the catalyst Au/TiO<sub>2</sub> (average gold particle size ca. 3.5 nm, supplied by the World Gold Council). Prompted by this result, we examined a series of catalysts with Au on other inorganic supports, such as Fe<sub>2</sub>O<sub>3</sub>, hydrotalcite, HAP, CeO<sub>2</sub>, and ZnO. Among them, Au/HAP showed the highest catalytic activity for the transformation with up to 99% yield (Table 1, entry 6 vs entries 1-5). Other reaction parameters were also screened including base and catalyst loading, and no further improvement could be achieved with this catalyst (Table 1, entries 7–9). The Au/HAP was prepared with homogeneous deposition precipitation (HDP)-NaBH<sub>4</sub> reduction method<sup>7</sup> and characterized by X-ray Powder Diffraction (XRD) and HAADF-STEM analysis. As shown in Figure 1, the XRD peak positions of the Au/HAP were similar to those of a parent HAP, and no diffraction peak of Au was observed, implying that Au nanoparticles were highly dispersed

#### Table 1

Reaction condition screening

∕_OH 1a	+ Ph-NH <sub>2</sub> 2a	1% Au, O <sub>2</sub> balloon aOH, H <sub>2</sub> O	O N H 3a	∕ <sup>Ph</sup> + 2 H <sub>2</sub> O
Entry <sup>a</sup>	Catalysts	Temp (°C)	<i>T</i> (h)	Yield <sup>b</sup> (%)
1	Au/TiO <sub>2</sub> (1.5 wt %)	40	20	46
2	Au/Fe <sub>2</sub> O <sub>3</sub> (4 wt %)	40	20	42
3	$Au/CeO_2$ (2 wt %)	40	24	29
4	Au/ZnO (1 wt %)	40	20	22
5	Au/HT (2 wt %)	40	24	45
6	Au/HAP (1.69 wt %)	40	24	99
7 <sup>c</sup>	Au/HAP (1.69 wt %)	40	24	55
8 <sup>d</sup>	Au/HAP (1.69 wt %)	40	24	20
9 <sup>e</sup>	Au/HAP (1.69 wt %)	40	24	71
10 <sup>f</sup>	Au(III)/HAP	40	24	N.R.
11 <sup>f</sup>	HAP	40	24	N.R.
12 <sup>g</sup>	Au/HAP (1.69 wt %)	40	24	Trace
13 <sup>h</sup>	Au/HAP (1.69 wt %)	40	24	Trace

<sup>a</sup> Unless otherwise noted, reactions were carried out with **1a** (10 mmol), aniline 2a (0.5 mmol), 0.77 mol % Au, and NaOH (0.5 mmol) in H<sub>2</sub>O (0.5 mL) at 40 °C under

oxygen balloon

Isolated yields. с

0.3 equiv NaOH was used. d

0.18 mol % Au was used. 5.0 mmol **1a** was used

f

N.R. = no reaction.

<sup>g</sup> Without NaOH.

<sup>h</sup> In the presence of N<sub>2</sub>.



Figure 1. XRD patterns of HAP and Au/HAP.

on HAP. HAADF-STEM images of the Au/HAP catalyst showed gold particles with an average size of 2.8 nm were uniformly dispersed on the support (Fig. 2). The loading of Au was determined to be 1.69 wt % by inductively coupled plasma-atomic emission spectrometry (ICP-AES). In addition, the use of Au(III)/HAP and HAP



Figure 2. HAADF-STEM image of Au/HAP (Au: 1.69 wt %) and histogram of the Au particle size distribution.

#### Table 2 The substrate scope for the reaction<sup>a</sup>

H Au/HAP (0.77 mol% Au), $O_2$ balloon $H$ $B^3$							
$R^{1}$ OH + $R^{3}$ $R^{2}$ $H_{2}O, NaOH, 40 \circ C, 24 h$ $R^{1}$ $N$ + 2 $H_{2}O$							
1	2			3 8	2		
•	-			•			
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Product	Yield <sup>b</sup> (%)		
1	Me	Ph	Н	3a	99		
2	Et	Ph	Н	3b	97		
3	Pr	Ph	Н	3c	98		
4	Bu	Ph	Н	3d	89		
5	$CH_3(CH_2)_4$	Ph	Н	3e	96		
6	$CH_3(CH_2)_6$	Ph	Н	3f	72		
7	i-Pr	Ph	Н	3g	91		
8	Су	Ph	Н	3h	85		
9	Me	3-MeOC <sub>6</sub> H <sub>4</sub>	Н	3i	93		
10	Me	2-MeOC <sub>6</sub> H <sub>4</sub>	Н	3j	79		
11	Me	3-MeC <sub>6</sub> H <sub>4</sub>	Н	3k	88		
12	Me	2-MeC <sub>6</sub> H <sub>4</sub>	Н	31	68		
13	Me	Bn	Н	3m	91		
14	Ph	Ph	Н	3n	94		
15	4-MeC <sub>6</sub> H <sub>4</sub>	Ph	Н	30	93		
16	3-MeC <sub>6</sub> H <sub>4</sub>	Ph	Н	3р	70		
17 <sup>c</sup>	2-MeC <sub>6</sub> H <sub>4</sub>	Ph	Н	3q	73		
18	4-i-PrC <sub>6</sub> H <sub>4</sub>	Ph	Н	3r	87		
19	4-MeOC <sub>6</sub> H <sub>4</sub>	Ph	Н	3s	99		
20	3-MeOC <sub>6</sub> H <sub>4</sub>	Ph	Н	3t	74		
21	3,4-0CH <sub>2</sub> 0-C <sub>6</sub> H <sub>3</sub>	Ph	Н	3u	65		
22	$4-FC_6H_4$	Ph	Н	3v	71		
23	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	Н	3w	76		
24	2-Furyl	Ph	Н	3x	50		
25	2-Pyridyl	Ph	Н	Зу	71		
26	Ph	Bn	Н	3z	89		
27	Ph	4-MeC <sub>6</sub> H <sub>4</sub>	Н	3aa	61		
28	Ph	3-MeOC <sub>6</sub> H <sub>4</sub>	Н	3ab	85		
29 <sup>d</sup>	Ph	Me	Me	3ac	90		
30 <sup>d</sup>	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	Me	3ad	98		
31 <sup>d,e</sup>	2-Naphthyl	Me	Me	3ae	87		
32 <sup>d</sup>	$4-BrC_6H_4$	Me	Me	3af	96		
33 <sup>d</sup>	Ph	Н	Н	3ag	60		
34 <sup>d</sup>	4-MeOC <sub>6</sub> H <sub>4</sub>	Н	Н	3ah	67		

<sup>a</sup> Unless otherwise noted, reactions were carried out with alcohol **1** (1–10 mmol), amine 2 (0.5 mmol), 0.77 mol % Au/HAP, and NaOH (0.5 mmol) in H<sub>2</sub>O (0.5 mL) at 40 °C under oxygen balloon for 24 h.

<sup>b</sup> Isolated yields.

с 1.54 mol % Au/HAP.

<sup>d</sup> Reactions were carried out with alcohol **1** (0.5 mmol), amine **2** (10 mmol), 0.77 mol % Au/HAP, and NaOH (0.5 mmol) in H2O (0.5 mL) at 25 °C under oxygen balloon for 24 h.

<sup>e</sup> *t*-BuOH (5.0 mmol) was added to improve the solubility of alcohol.

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$$\begin{array}{c} & & \\ & & \\ \hline OH & + & Ph - NH_2 & \\ \hline & NaOH, H_2O, 40 \ ^{\circ}C, 24 \ h \\ \hline & & \\ H \end{array} \begin{array}{c} & & \\ O \\ H \end{array} \begin{array}{c} & & \\ O \\ H \end{array} \begin{array}{c} & & \\ Ph & + & 2 \ H_2O \\ \hline & & \\ N \\ H \end{array}$$

Scheme 1. Au-catalyzed synthesis of acetanilide 3a on gram-scale.



**Figure 3.** HAADF-STEM image of Au/HAP after reuse experiment and histogram of the Au particle size distribution.

in place of Au/HAP did not promote the amidation at all (Table 1, entries 10 and 11). These results suggested that the high catalytic activity of the Au/HAP is ascribed to the intrinsic activity of the gold nanoparticles. It is evident from Table 1 (entries 12 and 13) that both the oxidant (O<sub>2</sub>) and base (NaOH) are also crucial for the oxidative amidation process.<sup>8</sup>

#### Extension of the methodology

To demonstrate the general applicability of our Au/HAP catalyst for direct amide synthesis and the scope of the process, various alcohols and amines were investigated, and the results are collected in Table 2.<sup>9</sup> First, a series of long-chain aliphatic alcohols, which are always difficult to oxidize, could be smoothly converted into the corresponding amides in high to excellent yields (Table 2, entries 1-8). We also explored the reactions of ethanol with substituted aromatic amines and benzylamine under similar reaction conditions, the catalyst still exhibited good activity in comparison with aniline (Table 2, entries 9–13). As shown in Table 2, benzyl alcohols with electron-donating groups (Me, *i*-Pr, MeO) reacted smoothly (Table 2, entries 14-21), however, steric hindrance had a negative influence on this reaction and 1.54 mol % Au was employed for 2-tolylmethanol (Table 2, entry 17). In addition, substitution with electron-withdrawing groups (F, Cl) on the benzene ring slightly decreased the reactivity (Table 2, entries 22 and 23). It is worth noting that heterocycles such as pyridin-2-ylmethanol and furan-2-methanol could also be used in this aerobic oxidative amidation and gave the corresponding products in moderate to good yields (Table 2, entries 24 and 25). Furthermore, besides alcohols, a series of amines 2 were also investigated (Table 2, entries 26–34) and the reaction proceeded smoothly. For sterically

hindered secondary amine that are sluggish to perform the amidation (Table 2, entries 29–32), good to excellent yields of the corresponding amides were still obtained. Ammonia could also be a good substrate (Table 2, entries 33 and 34) though moderate yields of benzamides **3ag–3ah** were achieved. Gram scaled experiment was performed with ethanol and aniline. And acetanilide, an important intermediate in pharmaceutical industry, was achieved with 97% yield (Scheme 1). This indicates that Au/HAP can be used effectively as a catalyst for the large scale production of amides.

#### Mechanistic studies for the reaction

To clarify the essential role of Au/HAP for the title reaction, we further conducted several control experiments. The Au/HAP catalyst was filtered off from the reaction mixture after 75% conversion of aniline 2a. Continued stirring of the filtrate under identical reaction conditions did not promote the reaction to proceed any more. ICP-AES analysis of the filtrate showed only negligible amount of Au (0.28 ppm corresponding to 1.7 wt % of initial charge) was leached into the solution. This confirmed that the oxidative coupling reaction was indeed catalyzed by the heterogeneous catalyst. However, the average size of the gold particles obviously increased after the catalytic reaction (up to 8.0 nm, Fig. 3). Furthermore, the color of Au/HAP changed from red to purple. Actually, the recycled catalysts showed very low activity and afforded 2a in only 7% yield under the optimal reaction conditions. The change of the catalyst state involved the gold nanoparticle size might account for the decrease in the catalytic performance. The size-specific catalytic activity of Au/HAP is somewhat explained in terms of the efficient activation of O<sub>2</sub> by small-sized gold nanoparticles to generate superoxo-like species, which in turn facilitated the  $\alpha$ -C-H bond breaking through a  $H_2O_2$  pathway.<sup>10</sup>

The amidation followed the mechanism in Scheme 2 and did not proceed through an intermediate ester.<sup>11</sup> The latter was confirmed by treating ethyl acetate with aniline **2a** under the standard reaction conditions, which afforded none of the amide **3a**. The reaction between acetaldehyde and aniline **2a** under the same conditions led to the formation of the corresponding imine and amide **3a** was not observed. This result indicated that the reaction would proceed through an aldehyde route, but that the aldehyde kept adsorbed on Au nanoparticles. Subsequent attack of the intermediate by the amine afforded the hemiaminal which also kept adsorbed to Au nanoparticles. The amide was then formed after  $\beta$ -hydride elimination. The reaction intermediate could not be a free aldehyde or hemiaminal released from the catalyst since this would lead to the formation of an unreactive imine.

#### Conclusion

In summary, we have successfully developed a hydroxyapatitesupported gold catalyst for aerobic oxidative coupling of alcohols and amines. The reaction can be performed smoothly under mild



Scheme 2. Probable reaction pathway for the conversion of alcohols and amines to amides over Au/HAP.

reaction conditions in water and various aliphatic and aromatic amines and alcohols were tolerant to afford the corresponding amides with good to excellent yields. This catalytic system can provide a versatile and environmentally benign protocol for the economic synthesis of amides. Further investigations of gold nanoparticles in fine chemical synthesis are currently under investigation in our laboratory.

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#### Supplementary data

Supplementary data (complete experimental procedures are provided, including preparation of Au/HAP, general procedure for the synthesis of amides and NMR spectra of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.133.

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- 9. General procedure for the synthesis of amide **3**. Unless otherwise noted, reactions were carried out as following: a mixture of alcohol **1** (1.00 mmol, 2.0 equiv), amine **2** (0.50 mmol), sodium hydroxide, (0.50 mmol) and Au/HAP (45 mg, 1.69 wt %) were vigorously stirred in 0.5 mL of H<sub>2</sub>O at 40 °C for 24 h under oxygen balloon. After completion of the reaction, the mixture is cooled to room temperature, diluted with ethyl acetate. The catalyst was separated by centrifugation and washed with ethyl acetate ( $3 \times 15.0$  mL). The combined organic layer was washed by saturated NaCl solution and dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. The residue was purified by flash chromatography on a short silica gel (eluent: petroleum ether/ethyl acetate = 10:1, 2:1, or 1:1) to afford the corresponding amide **3**.
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