Heterogeneous Catalysis

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Highly Efficient Amide Synthesis from Alcohols and Amines by Virtue of a Water-Soluble Gold/DNA Catalyst**

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Amides represent an important class of compounds and are ubiquitous in the pharmaceutical industry, materials science, and chemical biology.[1] Generally, the traditional syntheses of amides are limited by toxicity issues and the harsh conditions employed. Alternative methods,[2] such as the Beckmann rearrangement,[3a,b] Staudinger reaction,[3c,d] aminocarbonylation of aryl halides,[3e–h] hydration of the nitriles,[3i] oxidation of the terminal alkynes,[3j,k] and ligation of α-halo nitroalkanes with amines[3l] have emerged to improve the preparation of amides. Recently, amidation of aldehydes with amines under the catalysis of metal complexes was reported.[4] Considering the stability and the availability of alcohols, chemists are now focusing on the direct conversion of alcohols and amines into amides, which is more atom economical and environmentally benign.[5–7] However, one limitation of these direct amidations is the low yields of aromatic amine substrates. Also, the requirements of special handling and high temperatures hinder its application as one of the most straightforward protocols for amide synthesis. Therefore the development of a more efficient and feasible catalyst for such direct amidation from alcohols and amines is highly desirable.

In contrast, heterogeneous catalysts have received more and more attention because of the advantages of high catalytic efficiency and easy recycling, which are important for precious metal catalysts and flow chemistry processes.[8] Metal nanoparticles supported on different substrates have been widely used as heterogeneous catalysts in recent years.[9,10] However, little progress has been made on the direct amidation from alcohols and amines by using supported heterogeneous catalysts. Shimizu et al. reported a direct amidation by using a heterogeneous Ag/Al_2O_3 nanocluster.[11] A few heterogeneous gold catalysts were employed in the amidation,[12a] acylation,[12b,c] and the formylation of amines[12d,e] and some homogeneous and heterogeneous gold catalysts were used in the oxidative esterification directly from alcohols.[13] Moreover, the catalytic efficiency and the scope of the substrates for the direct amidation still need further improvement. We have been focusing on the heterogeneous catalysts for a long time.[14] DNA as a new template for heterogeneous catalysts was investigated in our group recently.[14e] Herein, we report a water-soluble gold catalyst immobilized on DNA (Au/DNA nanohybrid) and its application in amide formation from various alcohols and amines under mild reaction conditions. The high efficiency of the reported catalyst was demonstrated by using less-basic aromatic amines as substrates. The reaction time was shortened to 12 hours and the reaction temperature was decreased to 50 °C. More importantly, this Au/DNA catalyst can be recycled.

First of all, Au/DNA, Pd/DNA, Pt/DNA, and Ag/DNA nanohybrids were prepared as reported previously, wherein an inexpensive natural fish sperm DNA was used as the template and metal salts were used as precursors.[14e] The metal nanoparticles were chelated by DNA and the metal/DNA complex was stable in air with good reversible solubility in water and ethanol. Similarly, several water-soluble gold nanoparticles supported on different templates, such as Au/PVA, Au/PVP, Au/starch, and Au/gum arabic, were synthesized. Gold catalysts supported on metal oxide were also prepared. All of these gold catalysts were characterized by transmission electron microscopy (TEM) and the average particle diameters were 3–14 nm (3–5 nm for most of them). The reaction of benzyl alcohol with aniline was then used as a model reaction to optimize the catalysts. Generally, the water-insoluble gold catalysts supported on metal oxide could catalyze this amidation but the reaction yields were unsatisfactory (Table 1, entries 1–5). This can be ascribed to the poor dispersion of the gold catalysts in water. As for the water-soluble catalysts, the catalytic activity perhaps depended on both the stability of the templates and the binding between the templates and gold nanoparticles. For instance, the low catalytic activity of Au/PVA, Au/Starch, and Au/gum arabic could originate from the poor stability of these templates under the reaction conditions (Table 1, entries 6–8). ^{13}C NMR spectra (see Figures S3–S5 in the Supporting Information) showed that these polyalcohol templates were oxidized under the reaction conditions. As a result, the gold nanoparticles on the templates aggregated and lost their catalytic activity. For another water-soluble Au/PVP, the low catalytic activity (Table 1, entries 9) perhaps resulted from the stronger binding (see Figure S9 in the Supporting Information) between PVP and the gold nanoparticles although this template was resistant to oxidation in the reaction. We assumed that too strong of an interaction probably hindered the osculation of the reaction substrate with the gold nanoparticles, thereby resulting in a lower catalytic activity of the gold catalyst. When Au/DNA was employed as the catalyst, the highest yield was achieved (Table 1, entry 10) and the

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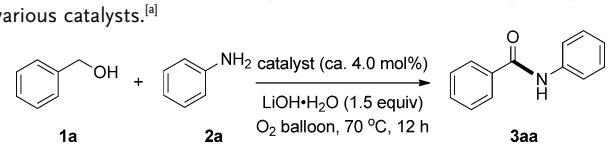
Table 1: The amidation of benzyl alcohol with aniline catalyzed by various catalysts.[a]

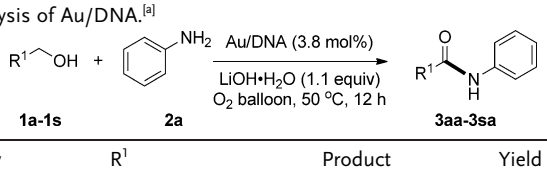


1a 2a 3aa

Entry	Catalyst	Yield [%][b]
1	Au/TiO_2 (3.08 nm)	26
2	Au/SiO_2 (3.36 nm)	30
3	Au/CeO_2 (3.39 nm)	36
4	Au/Al_2O_3 (3.94 nm)	39
5	Au/NiO (4.80 nm)	12
6[c]	Au/PVA (14.40 nm)	11
7[d]	Au/starch (10.97 nm)	10
8[c]	Au/gum arabic(5.26 nm)	41
9	Au/PVP (4.63 nm)	23
10	**Au/DNA (4.03 nm)**	**61 (55[e])**
11	Pd/DNA	trace
12	Pt/DNA	trace
13	Ag/DNA	n.d.
14	$KAuCl_4$	n.d.

[a] Reaction conditions: **1a** (0.50 mmol) and **2a** (0.25 mmol) in 2 mL H_2O. The values in the parentheses following the catalyst indicate the average diameter of the particle. [b] Yield determined by GC methods using 1,3,5-trimethylbenzene as an internal standard. [c] Nanoparticles were aggregated and the homogeneous solution was partly destroyed after the reaction. [d] Nanoparticles were completely oxidized to gold ions after the reaction. [e] Average yield of isolated product from using three different batches of Au/DNA. n.d. = not detected, PVA = polyvinyl alcohol, PVP = polyvinyl pyrrolidone.

Table 2: The amidation of aniline with different alcohols under the catalysis of Au/DNA.[a]



1a-1s 2a 3aa-3sa

Entry	R^1	Product	Yield [%][b]
1	Ph	**3aa**	91
2	4-MeC_6H_4	**3ba**	95
3	4-$OMeC_6H_4$	**3ca**	85
4	4-ClC_6H_4	**3da**	94
5	4-BrC_6H_4	**3ea**	83
6	4-FC_6H_4	**3fa**	91
7	4-$NO_2C_6H_4$	**3ga**	96
8	4-$CF_3C_6H_4$	**3ha**	90
9	3-MeC_6H_4	**3ia**	89
10[c]	2-MeC_6H_4	**3ja**	60
11[c]	2-ClC_6H_4	**3ka**	66
12[c]	2-BrC_6H_4	**3la**	52
13	1-naphthyl	**3ma**	58
14	2-py	**3na**	96
15	2-furyl	**3oa**	68
16[d]	Me	**3pa**	86
17	1-butyl	**3qa**	63
18[e]	benzyl	**3ra**	51
19	cyclohexyl	**3sa**	92

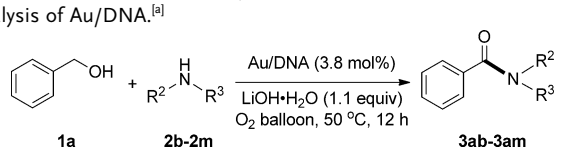
[a] Reaction conditions: **1** (0.50 mmol) and **2** (0.25 mmol) in 1 mL H_2O. [b] Yield of isolated product. [c] Au/DNA (Au loading = 7.6 mol%) was used. [d] EtOH (**1p**, 2.50 mmol) was used. [e] Reaction temperature was 80 °C. py = pyridyl.

catalyst remained stable in the reaction. IR and NMR tests (see Figures S6–S8 in the Supporting Information) showed that the DNA template scarcely changed before and after the amidation, and XPS showed that the interaction between the DNA and gold nanoparticles was weaker than that between the PVP and the gold nanoparticles (see Figure S9 in the Supporting Information). These results implied that both the water solubility of the catalysts and suitable interactions between gold nanoparticles and the templates had an important influence on the catalytic activity in this amidation. Other metal/DNA nanohybrids and gold salts did not effectively catalyze this amidation (Table 1, entries 11–14). After catalyst screening, Au/DNA proved to be the best catalyst for this direct amidation; the catalyst was water-soluble and stable under the reaction conditions. Moreover, in parallel experiments using different batches of Au/DNA, good reproducibility of the yield for the isolated product was achieved, thus demonstrating the stability of the composition and the catalytic activity of the Au/DNA nanohybrid.

After the catalyst optimization, the reaction conditions were optimized (see Table S1 in the Supporting Information). After detailed optimization, the standard reaction conditions were determined to be: 3.8 mol% of Au/DNA, 1.1 equivalents of $LiOH{\cdot}H_2O$, 1 mL of H_2O (solvent), reaction temperature at 50 °C under an oxygen atmosphere for 12 hours. A high yield (91%) of the isolated product for the model reaction could be obtained under these standard reaction conditions (Table 2, entry 1). The scope of the alcohol substrates was then investigated. As shown in Table 2, both aromatic and aliphatic alcohols were good substrates. The electron-withdrawing group on the aromatic ring favored this amidation slightly (Table 2, entries 4, 6, 7, 8, and 14) whereas steric bulk had a negative influence on this reaction (Table 2, entries 10–12). The aromatic rings of the reaction substrates could also be naphthyl, pyridyl, and furyl rings (Table 2, 13–15). Generally, the aliphatic alcohols were successfully employed in this reaction (Table 2, entries 16–19). For 2-phenylethanol, which was more difficult to oxidize, a higher temperature was needed (Table 2, entry 18). Importantly, acetylation of aniline could be realized smoothly by using EtOH as an acetyl source (Table 2, entry 16).

After this alcohol screening, the scope of the amine substrates was examined when using benzyl alcohol. The corresponding results are listed in Table 3. Previously, the aromatic amine substrates gave the corresponding amides with a low yield.[5c,7a,b,e] Under the catalysis of Au/DNA, various aniline derivatives gave the corresponding products with good yields. The yields for substrates having aromatic rings with 4-methoxy and 4-nitro substituents were lower because of the low water solubility of the amines. Some *t*BuOH was added in these two examples to increase the solubility and enhance the reaction yields (Table 3, entries 2 and 4). As for aliphatic amines, it was necessary to raise the reaction temperature to 80 °C (Table 3, entries 7 and 8) to improve the yields. It was found that the scope could be extended from primary to secondary amines (Table 3, entries 9 and 11). However, it was difficult to obtain the amide product for the secondary amines having steric bulk.

Table 3: The amidation of benzyl alcohol with different amines under the catalysis of Au/DNA.[a]



1a 2b-2m 3ab-3am

Entry	**2** R^2	R^3	Product	Yield [%][b]
1	4-MeC_6H_4	H	**3ab**	91
2[c]	4-$OMeC_6H_4$	H	**3ac**	76
3	4-ClC_6H_4	H	**3ad**	85
4[c]	4-$NO_2C_6H_4$	H	**3ae**	51
5	3-MeC_6H_4	H	**3af**	97
6	2-MeC_6H_4	H	**3ag**	90
7[d]	benzyl	H	**3ah**	80
8[d]	1-butyl	H	**3ai**	47
9	Me	Me	**3aj**	83
10[d]	Ph	Me	**3ak**	-[e]
11	piperidine	–	**3al**	91
12[f]	$NH_3·H_2O$	–	**3am**	50

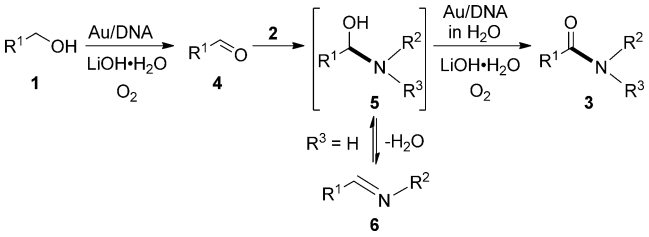
[a] Reaction conditions: **1** (0.50 mmol) and **2** (0.25 mmol) in 1 mL H_2O. [b] Yield of isolated product. [c] *t*BuOH (0.375 mol) was added to improve the solubility of amine. [d] Reaction temperature was 80°C. [e] Yield determined by GC methods to be $<5\%$. [f] $NH_3·H_2O$ (**2m**, 2.50 mmol) was used.

For example, only trace amounts of product could be detected by GC/MS when *N*-methylaniline was used as a substrate (Table 3, entry 10). Notably, ammonia could also be employed as the reaction substrate to deliver benzamide with a moderate yield of 50% (Table 3, entry 12).

By taking advantage of the reversible solubility of Au/DNA in water and ethanol, the catalyst could be easily recovered by a simple phase separation. Table 4 details the experimental results for the recyclability results of the catalyst. From Table 4, the catalytic activity of this heterogeneous catalyst was almost the same after the first round. After the fifth round, the catalyst still had a good catalytic activity and catalyzed the reaction to give the corresponding amide with a yield of 80%. The TEM image of Au/DNA after the fifth round (see Figure S1k in the Supporting Information) indicated that the gold nanoparticles were larger with an average diameter of 9.70 nm, and a little aggregation was also found.

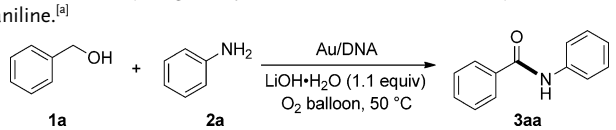
The reaction mechanism was investigated in our laboratory. Under the standard reaction conditions, the oxygen atmosphere and high pH value were both essential for this amidation. The imine was found to be the main by-product in the reaction. Moreover, the reaction of aniline with benzaldehyde can be carried out smoothly to give the amide **3aa** with a good yield (79%) whereas the reaction of aniline with benzoic acid did not work (see Scheme S1 in the Supporting Information). These results indicated that oxidation was the key step and that the aldehyde should be the intermediate of this transformation. In the control experiments, it was noted that water was crucial for this direct conversion of amides. The amidation did not occur and no amide was observed in the absence of water. When a different amount of water was added to this reaction mixture, the amide yield can be enhanced (see Table S2 in the Supporting Information). When neat water was employed as the reaction solvent and Au/DNA was used, the highest reaction yield was obtained (see Table S3 in the Supporting Information). In terms of these experimental results and the previous reports,[5c,11–13,15,16] a proposed mechanism is described.

First the alcohol **1** is oxidized into aldehyde **4** under the catalysis of Au/DNA (Scheme 1). Then the amine **2** attacks aldehyde **4** to generate the hemiaminal **5**, which can then be converted into either an imine (**6**) by losing one water molecule or an amide (**3**) by additional oxidation. Previous works have reported that the imine **6** was the main product when water-insoluble gold catalysts were employed under anhydrous reaction conditions.[10k,l] In this work, because of the presence of water, the high pH value, and the Au/DNA catalyst, OH^- and the hydroxides adsorbed at the gold/water interface could be generated.[16] This may promote the oxidation of **5** to form the desired product **3**. In contrast, the presence of water can perhaps affect the dehydration equilibrium towards **5** and thus most of **5** undergoes oxidation to form **3** in the presence of the Au/DNA catalyst.



Scheme 1. Proposed mechanism of amidation from alcohols and amines catalyzed by Au/DNA.

Table 4: The recycling of Au/DNA in the amidation of benzyl alcohol with aniline.[a]



1a 2a 3aa

Run	1	2	3	4	5[c]
Yield [%][b]	91	89	85	82	80

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.25 mmol), initial Au loading = 3.8 mol% in 1 mL H_2O, 12 h. [b] Yield of isolated product. [c] 18 h.

In summary, a water-soluble gold catalyst was prepared and employed in the direct amidation from alcohols and amines. The unique stability, solubility, and the suitable interaction between DNA and gold nanoparticles of this Au/DNA nanohybrid led to both the high reaction yields and the ability to recycle the catalyst. The reactions can be carried out smoothly under mild reaction conditions in neat water and the scope of the reaction substrates was extended to aromatic amines to afford the amides with good to excellent yields. To the best of our knowledge this is the first example of aromatic alcohols reacting with aromatic amines to obtain the desired

amides. The detailed structure of the Au/DNA nanohybrids in water and other applications in organic reactions are currently under investigation in our laboratory.

Experimental Section

Au/DNA nanohybrids were prepared as follows: $KAuCl_4$ (0.1 mmol) and fish sperm DNA (10 mg) were dissolved in Tris buffer (10 mL, 10 mM, pH 7.4). The combined solution was stirred for 24 h to ensure that the Au^{3+} thoroughly bound to the DNA. After this aging process, the solution was cooled to 0 °C and freshly dissolved $NaBH_4$ (0.5 mmol) in Tris buffer (10 mL) was added dropwise under an N_2 atmosphere. After reduction, the solution was stirred for another 24 h in N_2 after which it was warmed from 0 °C to room temperature to obtain the resulting Au/DNA nanohybrids (ca. 5 mM in Tris).

The as-synthesized Au/DNA nanohybrids (2 mL) were precipitated by adding excess EtOH (2–3 times the volume). After sitting for 1–2 h and then centrifuged at 5000 r min^{-1} for 5 min, the decantate was poured off. The obtained solid residue was dried by N_2 flow and redispersed in a water solution (1 mL) containing $LiOH{\cdot}H_2O$ (11.5 mg, 0.275 mmol). Benzyl alcohol (**1a**, 54.0 mg, 0.50 mmol) and aniline (**2a**, 23.3 mg, 0.25 mmol) were then added to the solution. The air in the reaction mixture was removed under vacuum and the reaction vessel refilled with O_2. This procedure was repeated for three times. The reaction mixture was then stirred under an O_2 balloon at 50 °C for 12 h. After the reaction was finished, 3 times the volume of EtOH and 5 times the volume of EtOAc was added to the reaction mixture. This mixture was left undisturbed for 2 h to allow precipitation and then centrifuged at 5000 r min^{-1} for 5 min. The decantate was poured off. The solid residue was dried and used as the catalyst for the next round. The decantate was evaporated with a rotary evaporator. The obtained residue was purified by column chromatography on silica gel (EtOAc/hexanes 1:1) to give *N*-phenylbenzamide (**3aa**) as a white solid in 91 % yield (45.0 mg, 0.228 mmol).

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