Commercial Supported Gold Nanoparticles Catalyzed Alkyne Hydroamination and Indole Synthesis

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Abstract: Commercial gold nanoparticles supported on titanium dioxide (TiO_2) were found to be a highly efficient catalyst for alkyne hydroamination. Terminal alkynes could easily undergo intermolecular hydroamination with low catalyst loadings (0.2 mol% Au) under solvent-free conditions. Indoles were efficiently synthesized using microwave heating through intramolecular hydroamination.

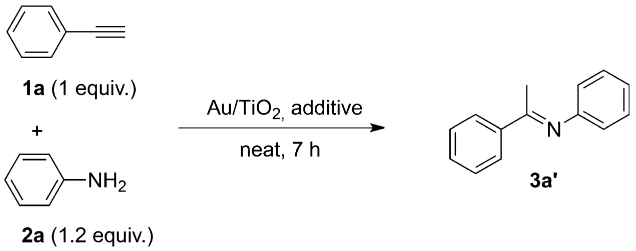
Keywords: Au/TiO_2; hydroamination; indoles; recyclable; supported gold nanoparticles

Nitrogen-containing compounds such as amines and nitrogen heterocycles are widely encountered in the scaffolds of various bioactive natural products, pharmaceuticals, and materials.[1] Therefore, many methods such as reductive amination[2] and C–N cross-coupling[3] have emerged for their construction.[4] Among these methods, hydroamination represents an atom-economical strategy because of the direct addition of amines to readily accessible alkenes, alkynes and allenes.[5] On the one hand, intermolecular hydroamination affords structurally complex amines; on the other hand, intramolecular hydroamination provides access to a wide range of N-containing cyclic compounds. Various transition metal catalysts have proven their value in the hydroamination of alkynes,[6] of which homogeneous cationic gold catalysis has attracted significant attention because of its excellent activity under mild reaction conditions.[7] However, the non-recyclability of homogeneous gold catalysts and the decay of cationic gold greatly limit their application in organic synthesis.[8] In this regard, heterogeneous gold catalysts, especially gold nanoparticles, are highly desirable in such transformations due to their stability and ease of manipulation.[9]

Gold nanoparticles (Au/NPs) have been successfully applied in many organic reactions such as oxidation,[10] reduction,[11] hydrosilylation,[12] and cross-coupling,[13] but reports of Au/NPs-mediated hydroamination, through π bond activation, are scarce.[14] It is believed that the cationic gold species present in gold nanoparticles is responsible for the activation of the unsaturated bond (see also the Supporting Information, Figure S-2).[15] Herein we are glad to report an alkyne hydroamination catalyzed by commercially available supported gold nanoparticles (Au/TiO_2). Through our methodology, a wide range of terminal alkynes were regioselectively converted to amines through intermolecular hydroamination, using molar fraction amounts of catalyst and no additional solvent; on the other hand, intramolecular hydroamination furnished indole derivatives in high yields.

We used the hydroamination of phenylacetylene **1a** with aniline **2a** as our model reaction (Table 1). When Au/TiO_2 (0.2 mol% Au) was utilized, the corresponding imine product **3a′** was obtained in 55% yield after 711hours at 80 °C. Extending the reaction time to 24 hours led to only a minor increase in yield (Table 1, entry 1). Higher temperatures did not increase the yield significantly (Table 1, entry 2). Inspired by homogeneous gold catalysis, we added acid promoters into the reaction. To our delight, all of the acid additives tested were able to facilitate the formation of **3a′** with similar efficiency (Table 1, entries 3–6). The easy-to-handle solid phosphotungstic acid was chosen as additive in our study. An attempt to achieve higher yield by increasing the temperature (100 °C) failed (Table 1, entry 7). A lower temperature (60 °C) furnished the desired product in 20% yield (Table 1, entry 8). Finally, when only the acid additive was used, or the support TiO_2 was used as catalyst, no

Table 1. Screening of Au/TiO_2.catalyzed intermolecular hydroamination.



Entry	Au/TiO_2 [mol% Au]	Additive (mol%)	*T* [°C]	Yield [%][a]
1	0.2	–	80	55
2	0.2	–	100	62
3	0.2	HOTf (0.1%)	80	88
4	0.2	$HNTf_2$ (0.1%)	80	88
5	0.2	$HCTf_3$ (0.1%)	80	83
6	0.2	$H_3PO_4{\cdot}12WO_3$ (0.1%)	80	86
7	0.2	$H_3PO_4{\cdot}12WO_3$ (0.1%)	100	71
8	0.2	$H_3PO_4{\cdot}12WO_3$ (0.1%)	60	20
9	–	$H_3PO_4{\cdot}12WO_3$ (0.1%)	80	0
10[b]	–	$H_3PO_4{\cdot}12WO_3$ (0.1%)	80	0

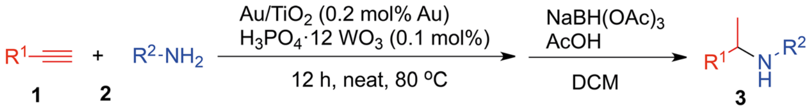
[a] Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

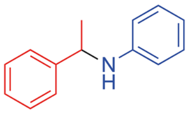
[b] TiO_2 (50 mol%) was used.

imine product was observed, underscoring the crucial role of gold nanoparticles (Table 1, entries 9 and 10).

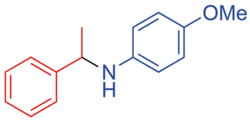
With the optimized conditions in hand, the substrate scope of intermolecular hydroamination was next evaluated (Table 2). Due to the instability of the resulting imines, they were immediately reduced to amines after the reaction was completed. Both electron-donating and electron-withdrawing substituents on aniline were well tolerated (Table 2, **3a**–**3f**). Anilines with substituents on sterically hindered positions (*o*-methyl and phenyl) could also provide the desired amines in high yields, although more catalyst and longer reaction times were required (Table 2, **3g** and **3h**). The functional groups on phenylacetylene did not affect the efficiency of the hydroamination (Table 2, **3i**–**3l**). Harsher conditions were needed to achieve good yields when aliphatic alkynes were examined (Table 2, **3m**–**3p**). Indole rings are one of the most ubiquitous and important heterocycles in nature.[16] A plethora of methodologies exist for indole ring synthesis,[17] but among them, the cycloisomerization of 2-alkynylanilines is the most straightforward and atom-economical. However, this straightforward synthesis of indoles has not received much attention using recyclable heterogeneous gold catalysts. The only reported work by Helaja and co-workers used home-made gold nanoparticles, which limits its application.[18] Capitalizing on our success with intermolecular hydroamination of alkynes, we envisioned that commercially available Au/TiO_2 would enable

Table 2. Au/TiO_2-catalyzed intermolecular hydroamination of terminal alkynes.[a]

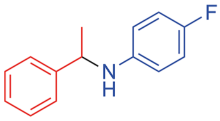




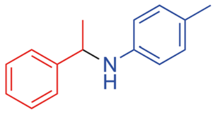
3a, (92%)



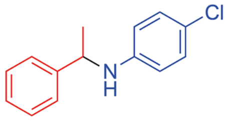
3b, (93%)



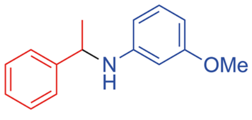
3c, (89%)



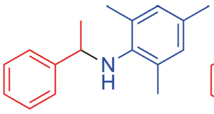
3d, (90%)



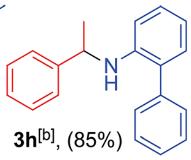
3e, (88%)



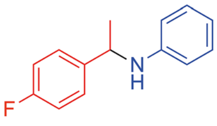
3f, (91%)



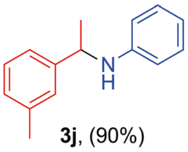
3g[b], (82%)



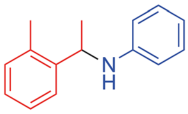
3h[b], (85%)



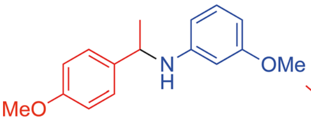
3i, (84%)



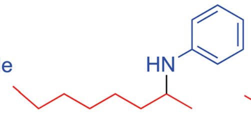
3j, (90%)



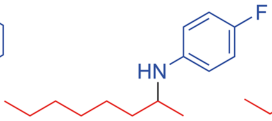
3k[b], (92%)



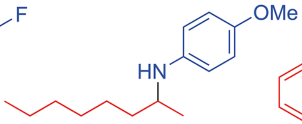
3l, (93%)



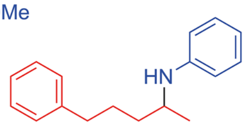
3m[b], (83%)



3n[b], (85%)



3o[b], (77%)

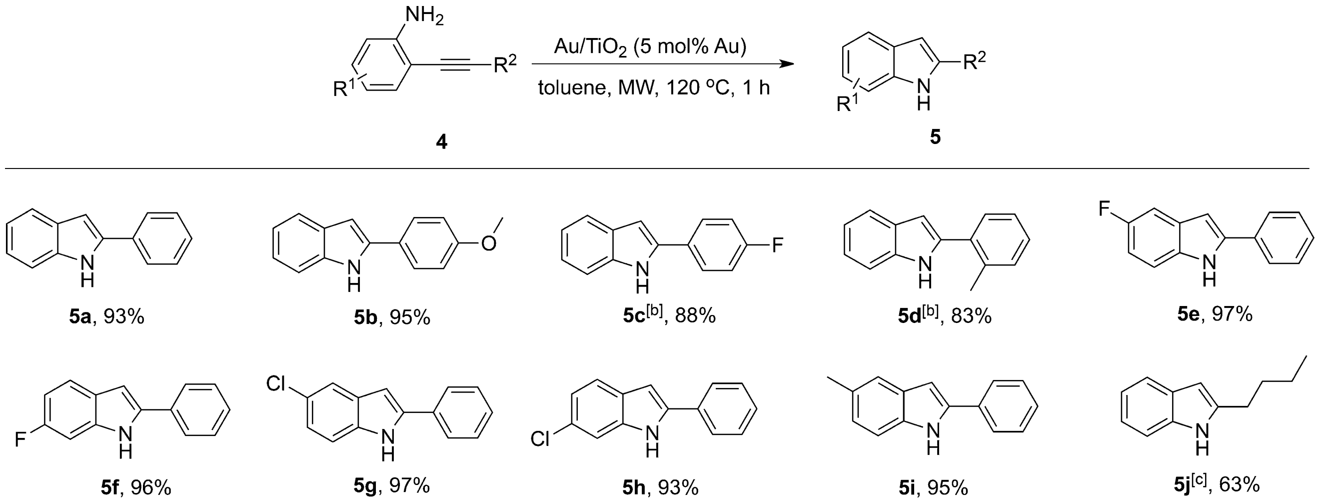


3p[b], (85%)

[a] *Reaction conditions*: **1** (1 mmol), **2** (1.2 mmol), Au/TiO_2 (0.2 mol% Au), $H_3PO_4{\cdot}12WO_3$ (0.1 mol%), neat at 80°C. Isolated yields ae shown in parentheses.

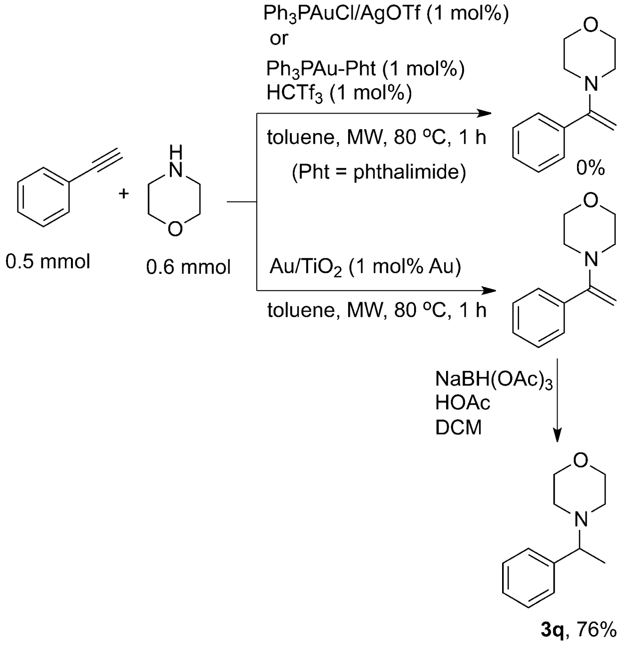
[b] Au/TiO_2 (0.5 mol% Au), $H_3PO_4{\cdot}12WO_3$ (0.5 mol%) were used in 24 h.

Table 3. Au/TiO_2-catalyzed indole synthesis through intramolecular hydroamination.[a]



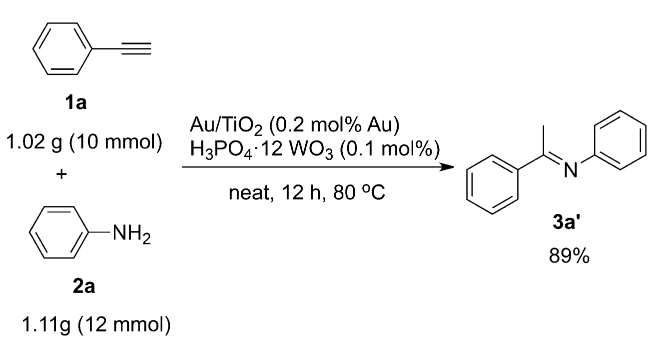
[a] *Reaction conditions:* **4** (0.1 mmol), Au/TiO_2 (5 mol% Au), in toluene (1 mL) at 120 °C for 1 h; Isolated yields.
[b] At 140 °C.
[c] $H_3PO_4{\cdot}12WO_3$ (5 mol%) was used.

the intramolecular version. Indeed, when microwave heating was applied, various 2-alkynylanilines were easily converted to the corresponding indole derivatives. As shown in Table 3, different substituted 2-alkynylanilines furnished the corresponding indole products in very good to excellent yields (Table 3, **5a**–**5d**). The halogens (F and Cl) and methyl group at the 4- or 5- positions of aniline proved beneficial, allowing indole products to be obtained in excellent yields (Table 3, **5e**–**5i**). When R^2 was replaced by an aliphatic group, an acid promoter was required (Table 3, **5j**).

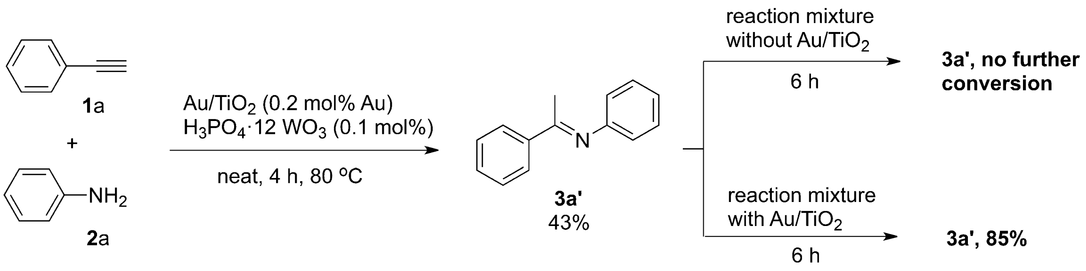


Scheme 1. Comparison of homogeneous gold catalyst and gold nanoparticles in the hydroamination of basic amines.

The hydroamination of basic amines catalyzed by cationic gold is a challenge. This is because a basic amine (e.g., morpholine) has much stronger affinity towards cationic gold than towards the alkyne substrate, thus, impairing the cationic gold.[19] This is one reason why most homogeneous gold catalysts cannot work in the strong basic environment created by basic amines.[7c,d] We speculated that the cationic gold species present in Au/NPs might be more tolerant towards bases and, consequently, they could efficiently activate alkynes in the presence of basic amines. To examine this assumption, the hydroamination of phenylacetylene with morpholine was carried out using Au/TiO_2 as catalyst. To our delight, after reduction, the desired amine product was obtained in 76% yield. In contrast, a commonly used L-AuCl/AgOTf or an otherwise efficient imido gold pre-catalyst completely lost their activities in the presence of morpholine (Scheme 1).[20] However, when thiomorpholine and pyrrolidine were used as basic amine partners, the hydroamination reaction did not occur; piperidine gave



Scheme 2. Gram-scale intermolecular hydroamination of **1a** and **2a**.



Scheme 3. Leaching experiment in the hydroamination with Au/TiO_2.

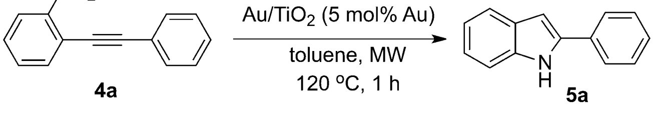
a low yield (25%) of imine product according to ^{1}H NMR. This result indicated that gold nanoparticles might be a better activator for triple bonds in the presence of some specific strong bases such as morpholine.

The scalability of the present method was also investigated through a gram-scale experiment (Scheme 2). The hydroamination proceeded smoothly, giving the corresponding imine product **3a′** in 89% yield.

A leaching experiment was also carried out (Scheme 3). The hydroamination of **1a** and **2a** provided the desired imine **3a′** in 43% yield after 4 hours under the optimized conditions; then a portion of the supernatant (150 μL) was transferred to another vial. Both the reaction mixture with Au/TiO_2 and the supernatant without Au/TiO_2 were allowed to react for another 2 hours. We found that the mixture containing Au/TiO_2 afforded **3a′** in 85% yield; In contrast, the supernatant without Au/TiO_2 did not produce additional **3a′**. These results demonstrate that the hydroamination is catalyzed by gold species present in gold nanoparticles rather than species leached into solution.

The recyclability of gold nanoparticles was also investigated through five straight runs of cycloisomerization (Scheme 4). After each run Au/TiO_2 was filtered out and washed with fresh toluene. We found that gold nanoparticles were efficiently reused without loss of catalytic activity.

In conclusion, we have developed a highly efficient hydroamination protocol using commercially available gold nanoparticles (Au/TiO_2). Compared with commonly used homogeneous gold catalysts, this heterogeneous gold catalyst is cost-effective, easy-to-manipulate, and reusable. Au/TiO_2 catalyzed the intermolecular hydroamination of terminal alkynes affording amines under solvent-free condition. What's more, a series of indole derivatives were synthesized through intramolecular hydroamination under microwave heating.



1st run: 96%; 2nd run: 96%; 3rd run: 96%; 4th run: 95%; 5th run: 95%

Scheme 4. Recyclability test of Au/TiO_2 in indole **5a** synthesis.

Experimental Section

General Procedure for Hydroamination of Terminal Alkynes 1 and Anilines 2

Au/TiO_2 (39.4 mg, 0.2 mol% Au) and $H_3PO_4 \cdot 12WO_3$ (2.88 mg, 0.1 mol%) were placed in a dry and clean vial which was then vacuumed and purged with argon three times. Then a mixture of alkyne **1** (1 mmol) and aniline **2** (1.2 mmol) was added into the vial. The reaction mixture was stirred in an oil bath at 80 °C for the designated time and cooled down to room temperature. Then Au/TiO_2 was filtered, the residual was dissolved in DCM (6 mL). $NaBH(OAc)_3$ (424 mg, 2 equiv.) and AcOH (114 μL, 2 equiv.) were then added into the solution. The mixture was allowed to stir at room temperature for 24 hours. The reaction was quenched with 1 M NaOH aqueous solution, extracted with DCM (5 mL × 2), the combined organic phase was dried over Na_2SO_4, and after filtration of Na_2SO_4 the filtrate was concentrated to dryness and the residue was subjected to flash chromatography (silica gel; EA/hexane).

General Procedure for Indole 5 Synthesis through Cycloisomerization of 2-Alkynylanilines 4

2-Alkynylaniline **4** (0.1 mmol) was placed in a clean and dry microwave vial and dissolved in toluene (1 mL). Au/TiO_2 (98.5 mg, 5 mol% Au) was then added into the solution. The mixture was reacted in the microwave reactor for 1 hour at 120 °C and cooled down to room temperature. Then Au/TiO_2 was filtered, the filtrate was concentrated to dryness and subjected to flash chromatography (silica gel; EA/hexane).

Acknowledgements

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