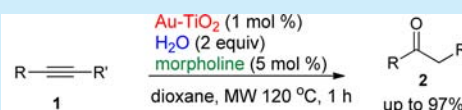


Supported Gold Nanoparticle-Catalyzed Hydration of Alkynes under Basic Conditions

Shengzong Liang,[†] Jacek Jasinski,[‡] Gerald B. Hammond,^{*,†} and Bo Xu^{*,†}[†]Department of Chemistry and [‡]Institute for Advanced Materials and Renewable Energy, University of Louisville, Louisville, Kentucky 40292, United States

Supporting Information

ABSTRACT: TiO₂-supported nanosize gold particles catalyze the hydration of alkynes using morpholine as a basic cocatalyst. Unlike most homogeneous cationic gold catalysts, the TiO₂-Au/morpholine system is weakly basic and is compatible with acid-sensitive functional groups (e.g., silyl ethers, ketals) or with a strongly coordinating group such as pyridine. What's more, this gold catalyst can be recycled by simple filtration and works well in flow reactors.



1. compatible with acid-sensitive functional groups (e.g. silyl ether, ketal);
2. compatible with strongly coordinating group (e.g. pyridine)
3. catalyst can be recycled by filtration
4. works well in flow reactors

Homogeneous cationic gold catalysis is a landmark addition to the field of organic synthesis.¹ Cationic gold catalysts are regarded as the most powerful catalysts for the electrophilic activation of alkynes toward a variety of nucleophiles.^{1a} However, a cationic gold catalytic system may not be compatible with substrates containing highly acid-sensitive functional groups such as silyl ethers or ketals because of the acidity of cationic gold catalysts and the acid promoters that are used to generate cationic gold. Although addition of bases to the reaction system may stabilize substrates containing acid-sensitive functional groups, more often than not, a base will quench the reactivity of cationic gold catalysts by inhibiting or slowing down multiple stages in the cationic gold catalytic cycle.²

Supported gold nanosize particles (AuNPs) have been used as heterogeneous catalysts for oxidation, reduction, silylation, and C–C coupling reactions,³ but their use in the electrophilic activation of alkynes/alkenes has received less attention.⁴ The catalytic activity of AuNPs could be attributed to its partial oxidation, by oxygen or other oxidants, to higher valence gold species.⁵ We speculated that AuNPs activated by partial oxidation could be more tolerant toward bases. AuNP-based catalysts are softer and weaker Lewis acids, and they may be less affected by the presence of bases, although on the other hand, their electrophilic activation ability may be weaker than that of homogeneous cationic gold catalysts because of their weaker cationic character. Thus, a combination of supported AuNPs and a suitable basic cocatalyst could work well for substrates containing acid-sensitive functional groups.

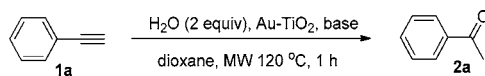
For a proof of concept, we chose the hydration of alkynes, which is a straightforward and atom-economical way to prepare carbonyl compounds.⁶ Many homogeneous catalysts like Hg,⁷ Pd,⁸ Pt,⁹ Fe,¹⁰ Ag,¹¹ Co,¹² Ir,¹³ Ru,¹⁴ and Brønsted acids¹⁵ can catalyze this reaction. Homogeneous gold catalysts are particularly effective.¹⁶ Notable examples include the [(PPh₃)₃AuMe]/H₂SO₄ system reported by Hayashi and co-workers,^{16f,17} the IPrAuCl/AgSbF₆ system reported by Nolan and co-workers,¹⁸ and the small gold clusters/HCl system reported by

Corma and co-workers.^{3d} Although the above systems are efficient, they do have the following shortcomings: (1) they are not compatible with substrates containing acid-sensitive functional groups; (2) they are not suitable for use with strongly coordinating groups like pyridine because of the strong affinity between the cationic gold and bases; and (3) they cannot be easily recycled. Even the silver-free gold (L–Au–NTf₂)-catalyzed hydration of alkynes reported by Corma and co-workers¹⁹—performed at room temperature in the absence of other acid promoters—led to non-negligible amounts of decomposition products (from 15% to 100%) when acid-sensitive groups such as silyl ethers and triphenylmethyl (Tr) were present in the starting material. This phenomenon could have been caused by the Lewis acidity of the cationic gold itself.

We chose the hydration of phenylacetylene **1a** as our model reaction together with the commercially available AUROLite series (AuNPs supported by TiO₂, ZnO or Al₂O₃, 1 wt %/wt loading, average size of AuNPs 2–3 nm). Au–TiO₂ itself performed poorly at 120 °C for 1 h under microwave conditions (Table 1, entry 1). A strong inorganic base like NaOH (20 mol %) (Table 1, entry 2) did not fare better. Tertiary amines (triethylamine and DMAP, Table 1, entries 3 and 4) inhibited the reaction; however, primary and secondary amine bases (*p*-toluenesulfonamide, 4-chloroaniline, benzylamine, diphenylamine, piperazine, piperidine, *N*-methylaniline, and morpholine) accelerated the hydration, affording the product in yields ranging from 17% to 76% (Table 1, entries 5–12). Morpholine proved to be the best cocatalyst in the lot (Table 1, entry 12), although morpholine itself did not catalyze the hydration (Table 1, entry 13). Using a higher loading of Au–TiO₂ (1 mol %) (Table 1, entry 14) and reducing the amount of morpholine (5%) (Table 1, entry 15) further improved the yield of the reaction. Toluene and nitromethane were not as good solvents as dioxane (Table 1,

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Table 1. Screening of Reaction Conditions^a


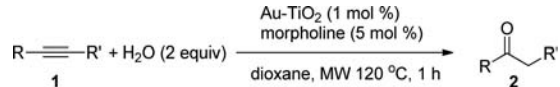
entry	base (mol %)	Au–TiO ₂ (mol %)	solvent	yield (%)
1		0.5	dioxane	6
2	NaOH (20)	0.5	dioxane	2
3	Et ₃ N (20)	0.5	dioxane	4
4	DMAP (20)	0.5	dioxane	0
5	TsNH ₂ (20)	0.5	dioxane	20
6	4-chloroaniline (20)	0.5	dioxane	57
7	benzylamine (20)	0.5	dioxane	30
8	diphenylamine (20)	0.5	dioxane	17
9	piperazine (20)	0.5	dioxane	33
10	piperidine (20)	0.5	dioxane	29
11	N-methylaniline (20)	0.5	dioxane	30
12	morpholine (20)	0.5	dioxane	76
13	morpholine (20)		dioxane	0
14	morpholine (20)	1	dioxane	88
15	morpholine (5)	1	dioxane	90
16	morpholine (5)	1	toluene	18
17	morpholine (5)	1	MeNO ₂	0
18 ^b	morpholine (5)	1	dioxane	85
19 ^c	morpholine (5)	1	dioxane	81
20 ^d	morpholine (5)	1	dioxane	^e

^aReaction conditions: concentration of phenylacetylene is 1 M, microwave at 120 °C for 1 h, yields were determined by ¹H NMR. ^bH₂O (1 equiv) was used. ^cH₂O (5 equiv) was used. ^dAu/ZnO or Au/Al₂O₃ was used. ^eA relative complex mixture.

entries 16 and 17). The amount of water had a minor influence on the reaction (Table 1, entries 18 and 19). We also tested other gold supports (Au/ZnO or Au/Al₂O₃), but they produced complex mixtures (Table 1, entry 20).

With optimized conditions in hand, we investigated the substrate scope (Table 2). Phenylacetylenes substituted with electron-donating or electron-withdrawing groups gave good yields of hydration product **2** (Table 2, entries 1–4). Terminal aliphatic alkynes also worked well if higher gold catalyst loading (4 mol %) and lower temperature (110 °C) were used (Table 2, entries 5 and 6).

Common functional groups such as nitrile, ester or, alkene groups were well tolerated in the hydration (Table 2, entries 7, 8, and 17). We were pleased to find that our catalyst system was compatible with a wide range of acid-sensitive functional groups. Alkynes containing triisopropylsilyl (TIPS), *tert*-butyldimethylsilyl (TBDMS), and *tert*-butyldiphenylsilyl (TBDPS) ethers gave the desired hydration product with excellent yields (Table 2, entries 9–11). No deprotection products were detected. Two other acid-labile functional groups, triphenylmethyl (Tr) and allyl ether, were compatible with our reaction conditions (entries 12 and 13). Acetals or ketals are usually more acid sensitive than silyl ethers or Tr, but to our delight, they withstood the reaction conditions. Indeed, alkynes containing a cyclic tetrahydropyranyl ether (THP) moiety (**1n**), a noncyclic acetal group (**1o**), or a structurally complex glycoside (**1p**) yielded the corresponding hydration products in excellent yields (Table 2, entries 14–16). Most of these acid-sensitive groups could not have withstood the strong Lewis acidic catalysts reported in the literature.⁶ 2-Ethynylpyridine (**1r**) was also a challenging substrate because the nitrogen in pyridine strongly binds to most metal catalysts used in hydration.⁶ However, **1r** gave a very good yield of the

Table 2. Substrate Scope of Alkyne Hydration Catalyzed by Au–TiO₂/Morpholine


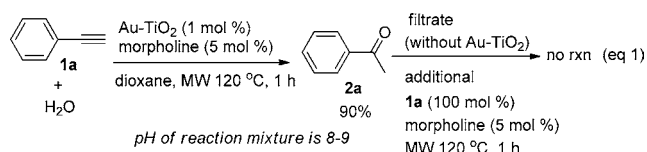
entry	1	2	yield (%) ^a
1 ^b			87
2 ^b			89
3 ^b			80
4 ^b			90
5 ^c			92
6 ^c			90
7 ^c			76
8 ^c			84
9 ^c			97
10 ^c			95
11 ^c			93
12 ^c			89
13 ^c			92
14 ^c			90
15 ^c			88
16 ^c			91
17 ^d			89
18 ^d			75
19 ^e			80
20 ^f			65

^aIsolated yields. ^bConditions A: Au–TiO₂ (1 mol %), morpholine (5 mol %), H₂O (2 equiv), MW 120 °C for 1 h. ^cConditions B: Au–TiO₂ (4 mol %), morpholine (10 mol %), H₂O (2 equiv), MW 110 °C for 2 h. ^dConditions A with Au–TiO₂ (2 mol %). ^eConditions B except reaction time is 1 h. ^fAu–TiO₂ (4 mol %), morpholine (20 mol %), H₂O (4 equiv), MW 140 °C for 2 h.

hydration product using our methodology (Table 2, entry 18). The internal alkyne diphenylacetylene (**1s**) gave the corresponding hydration product (**2s**) in 80% yield (Table 2, entry 19) and

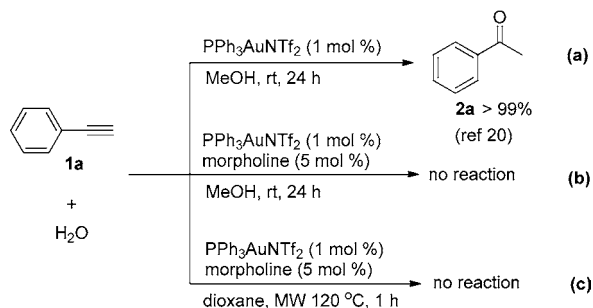
so did a diyne such as 1,4-diethynylbenzene (**1t**), although higher temperatures were needed in the reaction (Table 2, entry 20).

The pH of the reaction mixture remained weakly basic (pH 8–9) throughout the reaction. This could explain why acid-sensitive compounds were well tolerated. To learn whether the leaching of gold species from the TiO₂ support promoted the reactivity of our system, we filtered off the solid Au–TiO₂ after the reaction, added more **1a** (1 equiv) and morpholine (5 mol %) to the filtrate, and subjected the resulting mixture to our standard reaction conditions (eq 1). We found that no conversion took place in this manner, an indication that the catalysis was heterogeneous in nature.



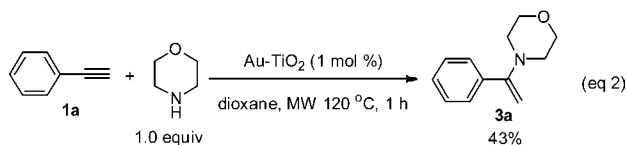
To support our previous assertion that a homogeneous cationic gold catalyst is usually incompatible with basic additives, we decided to investigate the effect of morpholine on the reactivity of a gold catalyst (Scheme 1). A homogeneous gold

Scheme 1. Effect of Base on the Reactivity of Homogeneous Gold Catalysis

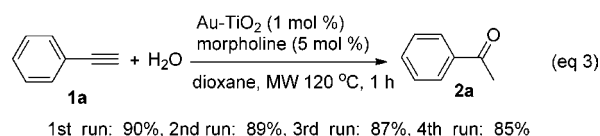


catalyst such as PPh₃AuNTf₂ catalyzed the hydration of alkyne **1a** efficiently at room temperature (Scheme 1a), but it became inactive in the presence of morpholine, either at room temperature (Scheme 1b) or under microwave conditions (Scheme 1c). This experiment proved that morpholine could deactivate a homogeneous gold catalyst but not a AuNP-based catalyst.

We also investigated the role of morpholine in the reaction. To this end, we conducted the hydration of phenylacetylene **1a** in dry dioxane and found significant amounts of the hydroamination product (eq 2).²⁰ This result seems to indicate that enamines are plausible intermediates in the hydration of alkynes.²¹



To investigate the recyclability of our supported AuNP catalyst, we carried out four straight runs of phenylacetylene hydration under the standard conditions. After each run, Au–TiO₂ was recovered by simple filtration. The yields after each run decreased only slightly (eq 3).



Flow chemistry has become a popular tool in many organic transformations.²² Compared with a conventional start-and-stop batch reaction, it has many advantages like better control of the reaction conditions, faster heat and mass transfer, a better safety profile, and an easier scale up.²³ Flow reactors are especially suitable for heterogeneous catalysis. Because our Au/TiO₂ could be recycled easily (see eq 3), we designed a flow reactor to take full advantage of this recyclability (Figure S-4, Supporting Information). Our catalyst worked quite well under flow conditions. We found that the conversion decreased slowly over time, a common phenomenon in industrial heterogeneous catalysis because of deactivation.

Frequent reasons given for heterogeneous metal catalyst deactivation include agglomeration of metal nanoparticles, change of oxidation state,²⁴ poisoning, or physical loss of metal.²⁵ We studied the STEM images of fresh and spent gold catalyst. These images clearly showed that agglomeration of gold nanoparticles took place in the spent catalyst (Figure 1).

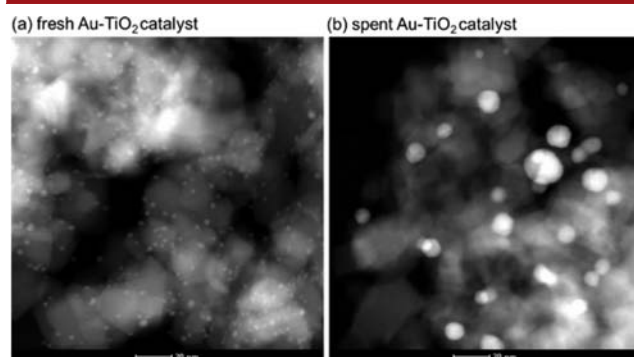


Figure 1. STEM images of fresh and spent catalysts.

Furthermore, XPS studies determined that there was no significant change in the oxidation state of AuNPs before or after the reaction (Figure S-5, Supporting Information). We concluded that agglomeration was the major reason for the partial deactivation of AuNPs over time.

In summary, we have developed an efficient alkyne hydration catalyzed by heterogeneous gold under basic conditions. Our method worked well for various alkynes bearing different functional groups, and it was especially useful with substrates bearing acid-sensitive functionalities. This gold catalyst was easily handled and fairly air stable and could be recycled by simple filtration; furthermore, it worked well in flow reactors.

■ ASSOCIATED CONTENT

Supporting Information

General procedures, flow reactor experimental design, XPS studies, and STEM and TEM images of supported AuNPs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: gb.hammond@louisville.edu.

*E-mail: bo.xu@louisville.edu.

Notes

The authors declare no competing financial interest.

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