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A General and Efficient Heterogeneous Gold-Catalyzed Hydration of Nitriles in Neat Water under Mild Atmospheric Conditions

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Amides constitute one of the most important functional groups in contemporary chemistry. They are essential for sustaining life, linking the amino acids in proteins such as enzymes. They are found in numerous natural products and are among the most prolific moieties in pharmaceutical molecules.^[1] Despite their obvious importance, the majority of amide bond syntheses require stoichiometric amounts of coupling reagents, making them generally expensive and wasteful procedures.^[2] Not surprisingly, in 2007 the Pharmaceutical Roundtable of the ACS Green Chemistry Institute declared "amide formation avoiding poor-atom-economy reagents" a high priority in modern organic synthesis.^[3] An essentially atom-economical method that fulfills the above described requirements is the catalytic hydration of nitriles, which represents an extremely attractive sustainable technology for amide production. A variety of metalloenzymes^[4] and homogeneous transition-metal catalysts,^[5] including rhodium, platinum, ruthenium, palladium, and gold complexes, have been developed for this transformation. These systems can offer selective amide formation under relatively mild conditions but have several drawbacks, especially the difficulty in catalyst/product separation and the necessity of special procedures to handle microorganisms and air-sensitive metal complexes.

An ideal protocol to overcome these limitations is the use of heterogeneous catalysts. Indeed, heterogeneous catalysis offers many advantages, such as easy handling, stability, easy recovery, and reusability. Despite these merits, only a handful of heterogeneous systems were found to be effective for the selective hydration of nitriles,^[6] including Raney copper,^[6a] ruthenium hydroxide loaded on alumina [i.e., Ru(OH)_x/Al₂O₃],^[6c] hydroxylapatite-supported silver nanoclusters [Ag/HAP, where HAP is Ca₁₀(PO₄)₆(OH)₂]^[6e] and CeO₂.^[6g] Unfortunately, these catalysts commonly require an inconvenient inert atmosphere for their successful use, which has greatly restricted the utility of these procedures. Furthermore, most of these heterogeneous hydrations still suffered from harsh conditions (generally, *T* > 140 °C), and low efficiency as well as limited substrate scope. From both green and synthetic points of view, it is imperative to develop advanced reusable catalyst systems that can offer a simple, general, and more efficient hydration of nitriles, pref-

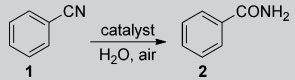
erably in neutral water, under convenient and mild atmospheric conditions.

Catalysts based on supported gold nanoparticles (NPs) have gained considerable attention in the past decade owing to their unique capability to promote selective reactions at low temperatures.^[7] In particular, various supported-gold catalysts have been reported to show catalytic activities far superior to those of conventional platinum group metal (PGM)-based catalysts for a number of industrially important processes, which is believed to be essential for the development of alternative and greener routes toward sustainability.^[8] Herein, we report that easily handled and ligand-free nanosized gold-decorated TiO₂ can catalyze the conversion of a large number of chemically and structurally diverse nitriles into their corresponding amides in pure neutral water under air at near-ambient conditions. The high efficiency of the catalytic system has allowed us to extend the process to the one-pot direct synthesis of industrially important ϵ -caprolactam (CPL) via a hydration–cyclization sequence starting with 6-aminocapronitrile (ANC). This hydration method, using a robust and reusable gold catalyst with neat water as solvent under ambient conditions, can make a significant contribution not only to reveal the intrinsic catalytic potential of supported gold nanoparticles, but also to establish a more sustainable and industrially viable process.

In the first stage of our work, benzonitrile (**1**) was selected as the substrate, and the hydration was conducted in pure water at a mild temperature of 60 °C under an atmosphere of air. We initially examined the hydration of **1** over a benchmark Au/TiO₂ catalyst (average gold particle size ca. 3.5 nm, supplied by the World Gold Council). This catalyst has been widely studied and proved to be highly active for a variety of organic transformations,^[9] including chemoselective nitro reduction,^[9a] selective alcohol oxidation,^[9b] aerobic olefin epoxidation,^[9c,d] and cross-coupling reactions for carbon-nitrogen bond formation.^[9e] The high versatility of the Au catalyst is due in part to its low reactant affinity,^[10] which has notably permitted the activation of a wide range of functional groups or raw materials. We were pleased to find that Au/TiO₂ delivered a notable conversion of **1** under the mild conditions probed (Table 1, entry 1). Importantly, the reaction proceeded smoothly and ran to completion within 15 h at 60 °C.^[11] Benzamide (**2**) was the only product formed in a yield greater than 97% (entry 2). Prompted by this result, we examined a series of catalysts with Au on other mineral supports, such as Fe₂O₃, Al₂O₃, SiO₂, CeO₂, HAP, and activated carbon. These catalysts, however, were not found to be particularly active, although in all cases the desired amide could be produced exclusively (entries 3–8). In addition, the hydration did not take place when using TiO₂ or the catalyst precursor HAuCl₄, nor with other Au compounds including Au(PPh₃)₃Cl, Au₂O₃, bulk Au⁰ powder (mean particle

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Table 1. Hydration of benzonitrile with various solid catalysts.^[a]


Entry	Catalyst	T [°C]	t [h]	Conv. ^[b] [%]	Yield ^[b] [%]
1 ^[c]	Au/TiO ₂	60	4	30	30
2 ^[c]	Au/TiO ₂	60	15	97	97
3 ^[c]	Au/Fe ₂ O ₃	60	4	12	11
4 ^[d]	Au/Al ₂ O ₃	60	4	10	10
5	Au/SiO ₂	60	4	3	3
6	Au/HAP	60	4	2	2
7	Au/CeO ₂	60	4	21	20
8	Au/C	60	4	4	4
9	Au/TiO ₂ -VS	60	4	> 99	99
10 ^[e]	Au/TiO ₂ -VS	25	18	> 99	99
11	Au/TiO ₂ -VS	80	1	99	99
12	Pd/TiO ₂	60	4	n.r.	/
13	Pt/TiO ₂	60	4	1	1
14 ^[f]	Ag/HAP	60	4	1	0.5
15 ^[g]	Ru(OH) _x /Al ₂ O ₃	60	4	2	1.6

[a] Reaction conditions: benzonitrile (1 mmol), catalyst (metal: 1 mol %), H₂O (3 mL), under air. [b] Conversion and yield were determined by HPLC. Trace of the carboxylic acids formed as by-products in some case. n.r. = no reaction. [c] Au/TiO₂ and Au/Fe₂O₃ provided by the World Gold Council (WGC). [d] Au/Al₂O₃ provided by Mintek. [e] Au: 2 mol %. [f] Ag/HAP prepared according to Reference [6e]. [g] Ru(OH)_x/Al₂O₃ prepared according to Reference [6c].

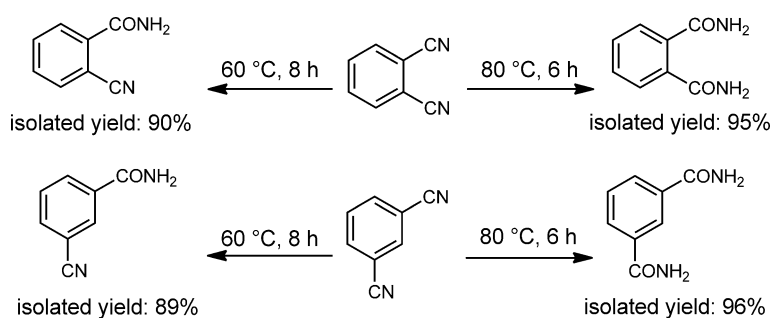
size, ca. 150 nm), or even unsupported Au⁰ NPs in place of Au/TiO₂ (Supporting Information, Table S1). These results demonstrate that the combination of Au NPs with TiO₂ is essential for achieving a high catalytic activity for the selective hydration of **1** into **2** under ambient conditions. Moreover, it was confirmed that the use of other metals (Pt, Pd, Ru, and Ag) instead of Au did not promote the hydration at all (entries 12–15). Note that a previously reported solid catalyst, HAP-supported silver NPs (Ag/HAP),^[6e] which required O₂-free conditions at an elevated temperature of 140 °C to promote the hydration, showed only very little activity under conditions employed in the above reaction (entry 14).

Taking into account that particle size has proven especially influential for supported-gold catalysts, we envisioned that smaller gold NPs deposited on TiO₂ could be more effective for the desired hydration. To explore this possibility, a gold catalyst bearing much smaller gold NPs (mean size < 2 nm) supported on TiO₂ (denoted as Au/TiO₂-VS; see Supporting Information for preparation details) was prepared. As disclosed by high resolution transmission electron microscopy (HRTEM) and the Au L₃-edge extended X-ray absorption fine structure (EXAFS), the Au/TiO₂-VS sample contained very fine gold NPs whose particle size was as small as 1.9 nm (see Figures S1 and S2 in the Supporting Information).

To our delight, we found that the use of Au/TiO₂-VS afforded a rapid and quantitative formation of **2** in 4 h (Table 1, entry 9). This hydration proceeded smoothly even at room temperature (entry 10).^[12] Moreover, the rates of the hydration could be greatly accelerated when using higher temperatures (entry 11). After the reaction, the Au/TiO₂-VS was easily separated by filtration. Analysis by inductively coupled plasma-atomic emission spectrometry (ICP-AES) confirmed that no Au was present in the filtrate, indicating that the observed catalysis is truly heterogeneous. To our knowledge, this is the first successful conversion of **1** into **2** in high yield by a heterogeneous catalyst in neat water under air at ambient temperature.

One distinct advantage of the above Au-mediated hydration of **1** is that the reaction rate did not depend on the O₂ concentration in the reaction atmosphere (Table S1, entries 8–9), thus offering practical and real advantages over existing technology or methods to establish a more industrially viable process for the clean synthesis of amide compounds. Of yet further interest is the high efficiency of the Au/TiO₂-VS system for the catalytic hydration of a diverse range of structurally different nitriles. As depicted in Table 2, various nitriles, including activated, inactivated, and heterocyclic ones, can be transformed into the corresponding amides in excellent yields, demonstrating the wide scope and synthetic utility of this catalytic system. Significantly, the hydration tolerates a wide variety of synthetically useful functional groups, including halide, nitro, hydroxy, ether, thioether, amino, aldehyde, ketone, ester, and alkyne substituents on the aromatic ring (entries 2–19). More interestingly, with *o*-benzenedinitrile and *m*-benzenedinitrile, that is, aromatic substrates bearing two nitrile groups, monohydration or double hydration was easily achieved in a selective manner with Au/TiO₂-VS by controlling the reaction time and temperature (Scheme 1). This result is in sharp contrast with previously reported catalytic performances using conventional catalysts.^[5f]

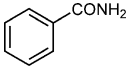
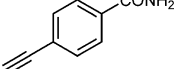
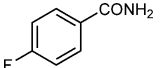
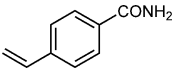
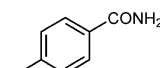
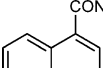
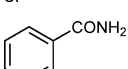
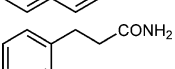
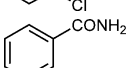
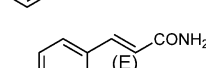
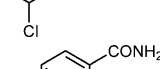
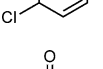
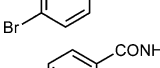
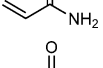
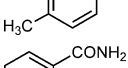
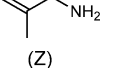
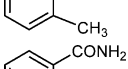
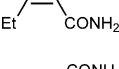
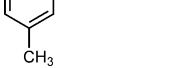
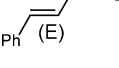
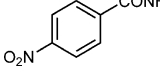

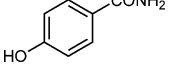
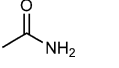
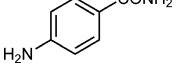
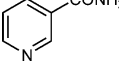
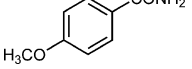
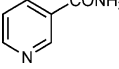
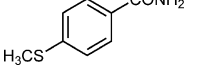
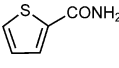
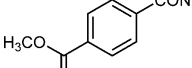
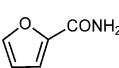
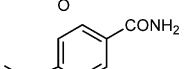
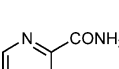
As shown in Table 2, this Au-mediated hydration process is not limited to aromatic nitriles: the hydration of substrates

**Scheme 1.** Tunable hydration of dicyano derivatives with Au/TiO₂-VS catalyst.

containing alkyl C≡N bonds was also readily and efficiently (GC yields ≥ 95%) achieved under the standard reaction conditions (entries 21–28). Remarkably, the hydration of acrylonitrile, which is currently used to produce more than 5 × 10⁵ tons of acrylamide per year for the industrial production of acrylic-based polymers, proceeded cleanly in the presence of Au/TiO₂-VS to afford the desired amide in 95% GC yield after 12 h

Table 2. Hydration of benzonitrile with various solid catalysts.^[a]

$$\text{R}-\text{C}\equiv\text{N} + \text{H}_2\text{O} \xrightarrow{\text{Au/TiO}_2\text{-VS}} \text{R}-\text{C}(=\text{O})\text{NH}_2$$

Entry	R	T [°C]	t [h]	Product	Yield ^[b] [%]	Entry	R	T [°C]	t [h]	Product	Yield [%] ^[b]
1	Ph	60	4		99 (91)	18	4-HC≡C-Ph	80	10		95
2	4-F-Ph	60	3		99	19	4-H ₂ C=CH-Ph	80	10		97
3	4-Cl-Ph	60	3		99	20	1-naphthyl	80	6		96 (89)
4	2-Cl-Ph	60	6		99	21 ^[c]	PhCH ₂ CH ₂	80	8		95
5	3-Cl-Ph	60	6		99	22	4-Cl-PhCH=CH(E)	80	10		96
6	4-Br-Ph	60	3		99 (93)	23 ^[c,d]	CH ₂ =CH	80	12		95 (89)
7	4-Me-Ph	80	3		99	24 ^[d,e]	CH ₂ =CCH ₃	80	24		97
8 ^[c]	2-Me-Ph	80	4		99	25 ^[c,d]	EtCH=CH(Z)	80	10		96
9 ^[c]	3-Me-Ph	80	4		98	26 ^[c]	PhCH=CH(E)	80	8		97
10	4-NO ₂ -Ph	60	2		99 (90)	27 ^[d,e]	<i>n</i> -Pr	80	20		95
11 ^[c]	4-OH-Ph	80	10		96	28 ^[d,e]	Me	80	24		96
12	4-NH ₂ -Ph	80	10		98	29	3-Py	60	2		99 (93)
13 ^[c]	4-MeO-Ph	80	8		99	30	3-Py	25	12		98
14	4-MeS-Ph	80	10		97	31	2-thienyl	60	2		95
15	4-CO ₂ Me-Ph	80	3		98 (91)	32	2-furanyl	60	2		99
16	4-MeCO-Ph	80	6		97	33	pyrazinyl	60	1		97
17	4-CHO-Ph	80	8		96	34 ^[f]	pyrazinyl	140	4		99 (94)

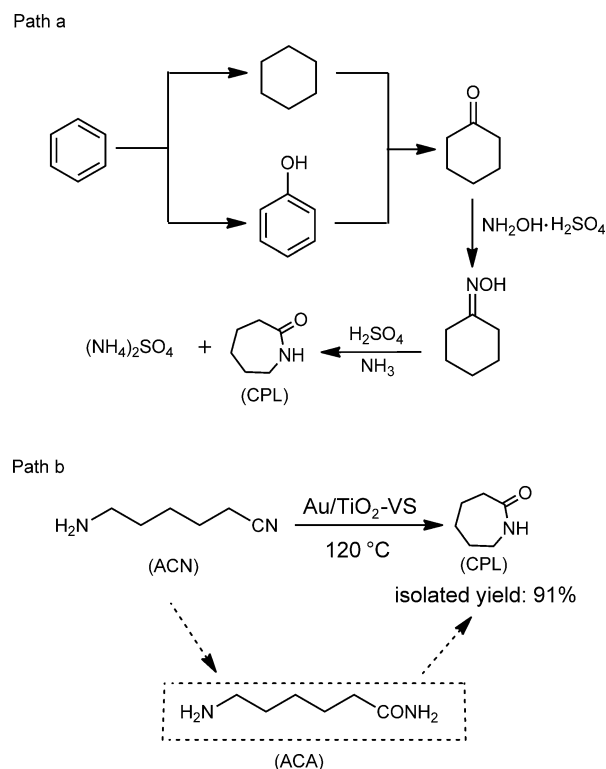
[a] Reaction conditions: nitrile (1 mmol), Au (1 mol%), H₂O (3 mL), under air. [b] Yields based on HPLC analysis (yields of isolated products are given in brackets). [c] Au: 2 mol%. [d] Yields based on GC analysis and confirmed by ¹H NMR spectroscopy. [e] Au: 4 mol%. [f] Nitrile (100 mmol), Au (0.001 mol%), H₂O (35 mL).

(entry 23). Neither hydration of the carbon–carbon double bond nor polymerization of acrylonitrile and/or acrylamide occurred. The same behavior was also observed for the related α,β -unsaturated nitriles, 4-chlorocinnamitrile (entry 22), cis-2-pentenenitrile (entry 25), and cinnamitrile (entry 26). A notable feature of catalytic nitrile hydration mediated by Au/TiO₂-VS is that nonactivated aliphatic nitriles (i.e., acetonitrile and butyronitrile) were transformed into the corresponding amides in good to excellent yields (entries 27 and 28).

Furthermore, the Au/TiO₂-VS catalyst also showed excellent promise for hydration of a range of heteroaromatic nitriles. In general, the strong coordinating capability of these molecules makes it more difficult for hydration to proceed.^[6e] Surprisingly, most of the heterocyclic nitriles were effectively converted into the corresponding amides within only 2 h (Table 2, entries 29, 31–33). For example, the hydration of 3-cyanopyridine to afford nicotinamide, which is part of the vitamin B group, was complete in 2 h. It should be emphasized that this hydration can work efficiently even at 25 °C (entry 30); hence, it might be useful in overcoming challenges confronted by current commercial biocatalytic processes for the manufacture of nicotinamide.^[13] In the hydration of pyrazinecarbonitrile to produce pyrazinecarboxamide, an antibacterial agent used for the treatment of tuberculosis,^[13,14] the reaction completed within only 1 h (entry 33). A large-scale experiment (scaled up 100-fold, 10 repetitions, Figure S3) of present heterogeneous Au-mediated pyrazinecarbonitrile hydration at 140 °C showed an average turnover frequency (TOF) of 25 000 h⁻¹; this value is at least 2 orders of magnitude higher than the highest activity ever reported for the catalytic hydration of nitrile (entry 34),^[6e] and an unprecedented total turnover number (TON) up to 1 000 000 was realized.

Given the excellent activity of supported gold NPs for selective nitrile hydration, we explored the possibility of a one-pot conversion of ACN into CPL, an important chemical intermediate for production of Nylon-6.^[15] CPL is currently manufactured on a massive scale through two popular multistep processes starting from cyclohexanone (Scheme 2a). Both methods require the use of highly aggressive reagents and generate substantial quantities of largely unwanted ammonium sulfate as a byproduct.^[16] The inherent deficiency of the existing synthetic routes reinforces the need for new, efficient, and sulfate-free processes. An attractive alternative to produce CPL is from adiponitrile via ACN, in which the intermediate 6-aminocaproic amide (ACA) generated from the hydration reaction undergoes subsequent cyclization to the target molecule, as depicted in Scheme 2b. The patent literature has several reports of this reaction being carried out catalytically in organic solvents at elevated temperatures under an inert atmosphere.^[15a–c] We have performed the one-pot reaction in neutral water under air at 120 °C using the Au/TiO₂-VS catalyst. The results, presented in Scheme 2b, show that it is possible to achieve high conversion of ACN with excellent selectivity to CPL through this clean one-pot procedure.

To shed light on the hydration mechanism, we have examined the interaction between nitriles and the Au-TiO₂ surface using diffuse reflectance Fourier transform infrared (DRIFT)



Scheme 2. a) Current CPL manufacturing process. b) One-pot synthesis of CPL from ACN via a hydration-cyclization sequence.

spectroscopy (Figure S4). Following the adsorption of **1** onto Au/TiO₂-VS, a band at 2230 cm⁻¹, assigned to the C≡N stretching vibration, shifted to ca. 2269 cm⁻¹. This finding revealed the strong adsorption of **1** through a side-on coordination of the nitrile group to the gold NPs on the Au-TiO₂ surface.^[17] Furthermore, **1** adsorbed onto the Au/TiO₂-VS catalyst was also exposed to water vapor at 25 °C. Time-resolved DRIFT spectra showed that the nitrile band gradually decreased with the increase of a new band corresponding to a C=O stretching vibration. Comparing the rate of disappearance of adsorbed nitrile species for Au NPs deposited on different supports (Figure S5), we observed that the hydration over Au/TiO₂-VS occurred with much higher rates than that over other catalysts. In line with the catalytic data as reported in Table 1, this indicates that the nitrile species adsorbed on the Au-TiO₂ interface can be more active for a relevant transformation. Moreover, when the hydration was carried out using D₂O instead of H₂O, a significant kinetic isotope effect ($k_H/k_D = 1.43 \pm 0.02$) was observed for Au/TiO₂-VS-catalyzed hydration of **1** (Figure S6), suggesting that O–H bond cleavage could be involved in the rate-determining step.

On the basis of the above results and the known chemistry of the transition-metal-mediated nitrile activation,^[16,17] a possible mechanism is proposed as follows: Initially, the C≡N bond in the nitrile molecule is strongly activated through coordination to the dispersed gold NPs as shown in Scheme S1. Subsequently, a nucleophilic OH species from H₂O, activated on the Au-TiO₂ interface, attacks the adsorbed nitrile to form the amide through an iminol intermediate. In the overall reaction,

the cooperative interaction between small gold NPs and TiO₂ plays an important role in leading to a unique activation of nitriles in association with H₂O under exceptionally mild conditions. In addition, a positive Hammett ρ value ($\rho=0.79$, $r^2=0.99$, see Figure S7) was identified when an Au/TiO₂-catalyzed competitive hydration of *p*-substituted benzonitriles was examined, indicating a negatively charged transition state, which is also consistent with the proposed mechanism.

In summary, an unprecedented heterogeneous-gold-catalyzed selective hydration of nitriles has been developed. To the best of our knowledge, this gold catalysis represents the most efficient, simple, and ecofriendly catalytic system available for clean and selective hydration of nitriles. Whereas this hydration reaction reveals for the first time the catalytic potential of Au NPs towards C≡N bond activation, and promises a new area of gold catalysis research, the results presented herein open up a new avenue for facile, convenient, and green synthesis of amide motifs.

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