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# Supported Gold Catalysis: From Small Molecule Activation to Green Chemical Synthesis

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## CONSPECTUS

With diminishing natural resources, there is an ever-increasing demand for cost-effective and sustainable production of fine and commodity chemicals. For this purpose, there is a need for new catalytic methods that can permit efficient and targeted conversion of fossil and biorenewable feedstocks with lower energy requirements and environmental impact. A significant number of industrial catalytic processes are performed by platinum-group-metal (PGM)-based heterogeneous catalysts capable of activating a range of important small molecules, such as CO, $O_2$, $H_2$, and $N_2$. In contrast, there is a general feeling that gold (Au) cannot act as an efficient catalyst because of its inability to activate most molecules, which is essential to any catalytic processes. As a consequence, researchers have long neglected the potential for use of gold as a catalyst.



be selective

In recent years, however, chemists have put forth tremendous effort and progress in the use of supported gold catalysts to facilitate a variety of useful synthetic transformations. The seminal discovery by Haruta in 1987 that suitably prepared Au-based catalysts were surprisingly active for CO oxidation even at 200 K initiated rapid development of the field. Since then, researchers have widely employed Au-based catalysts in many types of mild chemical processes, with special focus on selective reactions involving small molecules (for example, CO, $H_2O$, $O_2$, or $H_2$) as a reactant. That gold in the form of tiny nanoparticles (NPs, generally less than 5 nm in diameter) can subtly activate the reactant molecules under mild conditions has been evoked to explain the superior effectiveness of gold compared with conventional PGMs. In this context, Au-based catalysts are gaining great significance in developing new green processes with improved selectivity and energy minimization.

In this Account, we describe our efforts toward the development of a range of green and selective processes largely through the appropriate choice of Au catalysts coupled with the coactivation of a plethora of simple small molecules. We have focused on developing new mild and selective reductive transformations that can offer efficient alternatives to conventional Au-catalyzed hydrogenation processes. We have demonstrated Au-catalyzed selective transformation involving HCOOH activation, Au-catalyzed selective reduction involving CO and $H_2O$ activation, and Au-catalyzed C—N/C—C bond formation via alcohol activation with high selectivity. The interplay between the support and gold plays a critical role in the success of these transformations, thus highlighting the crucial importance of support in tuning the performance of supported Au NPs. Most of the reactions can tolerate a range of functional groups, and some can occur under ambient conditions. Depending on the specific process, we propose several mechanistic scenarios that describe the plausible small-molecule-mediated reaction pathways.

Additionally, we have observed an unusual reactant-promoted $H_2O$ or $H_2$ activation over supported Au NPs, thus offering new strategies for green and facile synthesis of diverse amides and heteroaromatic nitrogen compounds. We anticipate that key insights into how simple small molecules are activated for further reaction over Au NPs should lead to a better understanding of gold catalysis and the development of new innovative PGM-free technologies.
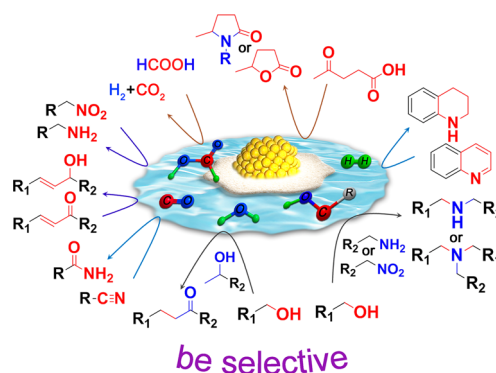
## I. Introduction and Background

Catalysis is at the heart of chemistry, providing essential tools for the synthesis of useful products in a sustainable fashion. A major challenge of catalysis today is to identify and develop new efficient heterogeneous catalytic processes that can achieve targeted conversion of fossil and biorenewable feedstocks with lower energy requirements and environmental impact. Thanks to their high capability
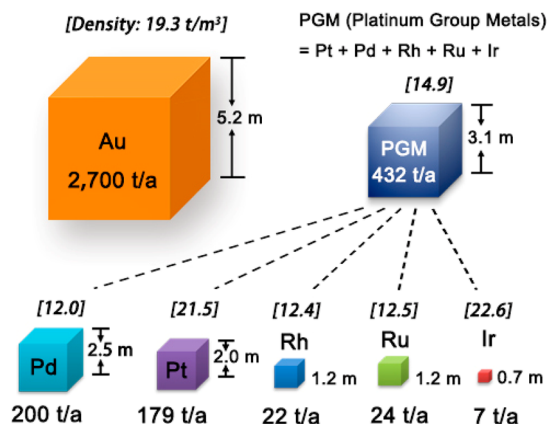
**FIGURE 1.** Global annual mine production of noble metals in 2012.

for activating industrially and economically important molecules ($CO$, $H_2$, $O_2$, $H_2O$, and so on), as well as high resistance to chemical attack, catalysts based on supported platinum-group metals (PGMs) are essential to a wide variety of commercially important processes.[1] Of the many possible applications, ranging from environmental remediation to energy conversion, green and sustainable chemical synthesis is especially attractive. However, as the PGM resources become scarcer and more expensive, the high cost of PGM-based catalysts has hampered the widespread implementation of green chemical processes.[2] In this respect, the findings that more abundant gold (Figure 1) shows unexpectedly higher activity and selectivity for various reactions than PGM catalysts are of special interest,[3] because they can open up many new possibilities for development of PGM-free catalytic technologies.

Gold has been historically considered catalytically inert. However, ever since the breakthrough discoveries by Hutchings[4] and Haruta[5] in the 1980s, it has become clear that suitably prepared gold nanoparticles (NPs) can show dramatic chemical activity for several key reactions. Accordingly, there has been an explosion of interest, particularly in the past few years, in using finely dispersed Au as catalyst for a variety of synthetic transformations, including partial oxidations, selective hydrogenations, addition of multiple C—C bonds, cyclization reactions, rearrangements, and C—C coupling reactions.[6] Compared with other metals, one of the most fascinating properties of gold in these processes is represented by the high selectivity that allows discrimination within chemical groups and geometrical positions, favoring high yields of the desired product. It is in this context that gold has turned out to be a very promising candidate as a next-generation "green" catalyst for sustainable processes using clean reagents, particularly $O_2$ and $H_2$,

often under mild, ecofriendly, and organic solvent-free conditions.

The origin of Au catalytic activity is still a hot topic of debate. In general, gold in the form of very small NPs, small enough to chemisorb reactant molecules, seems to be an essential parameter in heterogeneous gold-based catalysis.[5] An equally if not more important aspect is the synergism between gold and the underlying support.[7] It should be noted, however, that most Au-mediated selective reactions involve the use of ubiquitous small molecules (for example, $CO$, $O_2$, $H_2$, $H_2O$, etc.) as a reagent or reactant. Whereas the overall interaction of Au with these small molecules could be very weak, it is important to keep in mind that one essential aspect of catalysis is the formation of surface intermediate species of moderate stability.[8] In this context, one may envision that using supported Au to promote subtly small molecule activation can offer exciting opportunities to develop new catalytic processes that would achieve better efficiency and selectivity or even permit previously unknown reactivity under mild conditions.

Developing green catalysis for sustainable chemical synthesis has been a long-standing objective of our group. The present Account describes our recent efforts on the development of a range of novel gold-catalyzed synthetic reactions. By centering our research in Au catalysis on the activation and further reaction of a plethora of important small molecules, not only have we been able to achieve unprecedented reaction efficiency, but we have also taken advantage of reactant-promoted $H_2O$ or $H_2$ activation to discover a couple of new hydration and chemoselective hydrogenation reactions. For our laboratory, this concept has served as a crucial platform for both reaction development and studying heterogeneous Au-catalyzed selective transformations.

## II. Reaction Involving HCOOH Activation

Formic acid (FA, $HCOOH$) has attracted considerable recent interest in the area of green and sustainable chemistry because of its potential as a hydrogen carrier and as a means of utilizing $CO_2$.[9] The history behind the FA activation dates back at least a century in the pioneering work of Sabatier,[10] who identified that the decomposition of FA may occur via two distinct reaction pathways, namely, the decarboxylation, yielding $H_2$ and $CO_2$, or the dehydration into CO and $H_2O$ (see Scheme 1). Later on, the decomposition of FA vapors was widely investigated as a probe reaction to characterize the surface properties of metals and metal oxides.[11] From the stand point of catalysis, what is especially

**SCHEME 1.** Possible Reaction Pathways for the Decomposition of FA

HCOOH

a) dehydrogenation · b) dehydration

(R) WGS

$H_2 + CO_2$ ⇄ $CO + H_2O$
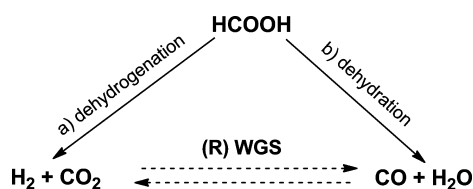
of interest is that the selectivity of the two possible pathways can be controlled by the choice of catalyst. Based upon extensive kinetic data concerning the molecular interaction of FA with metal single crystals, it was established in the 1990s that the heat of formation of the corresponding formate plays an important part in the catalysis of FA decomposition; this produces the well-known "volcano curve".[12] It is to be pointed out that according to these early research efforts, Au was grouped among the least active metals, in sharp contrast to the high activities displayed by PGMs.

During the past few years, a significantly renewed interest was devoted to FA decomposition, essentially owing to the inherent advantages of FA over other substrates in terms of being able to release high quality hydrogen gas under practical and convenient conditions. Particularly given that it is one of the major byproducts formed during biomass processing and has an energy content at least 5 times higher than that of commercially available lithium ion batteries, FA represents a convenient liquid hydrogen carrier in fuel cells designed for portable use.[10] This has prompted great efforts directed toward the catalytic FA decomposition in the liquid phase, where the production of CO-free $H_2$ at convenient temperatures is of great importance. Until recently, studies on liquid FA decomposition have been mostly concentrated on the use of homogeneous catalysis.[10] Our recent work in this area was partially inspired by the observations that Au finely dispersed on alumina can selectively decompose FA in the gas phase at 80 °C.[13] We considered the possibility that suitably prepared gold catalysts might offer significant advantages to develop new efficient catalytic processes to release the $H_2$ stored in liquid FA.[14]
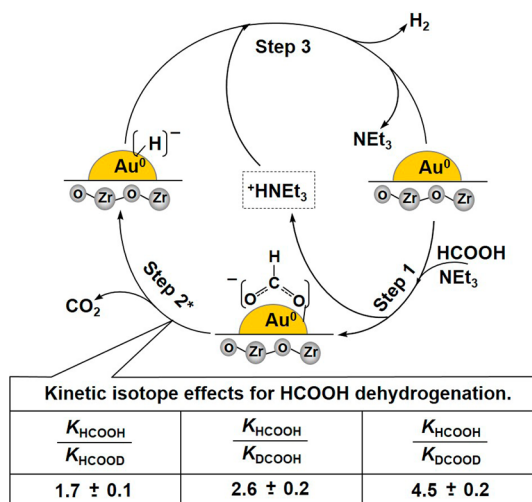
In our initial efforts to achieve the $H_2$ evolution from liquid FA, we examined the decomposition of a highly acidic 10.5 M aqueous FA solution catalyzed by small Au NPs (ca. 1.8 nm) deposited on acid-tolerant zirconia (Au/ZrO$_2$) at 80 °C.[14] With this catalyst, a high initial turnover frequency (TOF, calculated from the initial reaction rate, as the number of $H_2$ molecules formed per hour per gold atom) of up to 550 h$^{-1}$ was achieved with exclusive formation of $H_2$ and $CO_2$.
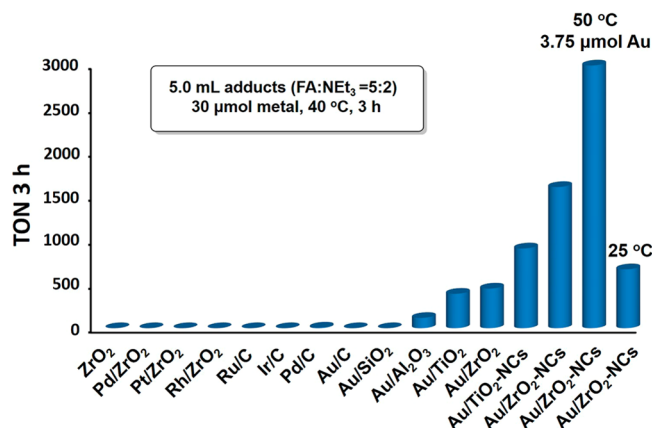


**FIGURE 2.** Activity of various catalysts for FA dehydrogenation at 40 °C.

Despite encouraging preliminary results, modest gas evolution was observed for the reaction performed at 40 °C, a more suitable temperature for mobile applications. Subsequent examination of the influence of various base additives showed that an efficient decomposition of a FA–NEt$_3$ mixture can be achieved by using the easily handled solid Au/ZrO$_2$ catalyst at 40 °C. It is noteworthy that Au/ZrO$_2$ can catalyze the decomposition of a 5:2 FA–NEt$_3$ azeotropic mixture (TEAF) to produce $H_2$ with initial TOF up to 250 h$^{-1}$ at 40 °C. These results revealed that the composition of the reaction medium was one of the key aspects in facilitating the desired $H_2$ evolution.

In further experiments, a new Au catalyst sample composed of ultrasmall Au nanoclusters (size ca. 0.8 nm) finely dispersed on ZrO$_2$ (Au/ZrO$_2$-NCs) proved to be uniquely successful (Figure 2), enabling controlled and efficient CO-free $H_2$ liberation from TEAF at temperatures as low as 25 °C. It is important to point out that while the other noble metals were inactive even at a higher temperature of 40 °C, the rate of FA decomposition (TOF = 1593 h$^{-1}$ at 50 °C) obtained with this subnanometric gold material constitutes the highest activity ever reported for heterogeneously catalyzed FA decomposition. The detailed investigation on this particular FA decomposition system led to a discovery that the ultrasmall Au particle size[15] was critical for the success of the reaction. Moreover, the amphoteric character of the underlying support, particularly ZrO$_2$, was also essential to the transformation.

A possible catalytic cycle for hydrogen evolution from the TEAF system over the Au/ZrO$_2$–NCs catalyst was proposed in Scheme 2.[14] First, the key aspect of NEt$_3$ is to facilitate the O–H bond cleavage as a proton scavenger, leading to the formation of a metal–formate species during the initial step of the reaction. The Au–formate may undergo further

**SCHEME 2.** Possible Reaction Pathway for H$_2$ Evolution from the TEAF System over Au/ZrO$_2$-NCs



| Kinetic isotope effects for HCOOH dehydrogenation. | | |
|:---:|:---:|:---:|
| $\dfrac{K_{HCOOH}}{K_{HCOOD}}$ | $\dfrac{K_{HCOOH}}{K_{DCOOH}}$ | $\dfrac{K_{HCOOH}}{K_{DCOOD}}$ |
| 1.7 ± 0.1 | 2.6 ± 0.2 | 4.5 ± 0.2 |

dehydrogenation, in association with the $^+$HNEt$_3$ species formed via the reaction of NEt$_3$ with FA, to produce H$_2$ along with CO$_2$ via a $\beta$-elimination pathway. On the basis of kinetic isotope effect (KIE) measurements with HCOOD, DCOOH, and DCOOD, the decomposition of the transient Au—formate species could be involved in the rate-determining step, albeit the precise nature of such Au—formate species remains to be clarified at this stage. In the overall reaction for FA dehydrogenation, the cooperative action between ZrO$_2$ and ultrasmall Au clusters is essential. This can be argued to be an enhanced back-donation of electrons from Au to the HCOO* intermediate,[16] leading to the crucial Au—formate activation under mild conditions. Thus, one of the most important roles of the ZrO$_2$ may be to create negatively charged Au clusters, allowing for a facile C—H bond cleavage in Au—formate species.

The catalytic chemistry of gold toward FA activation presented above is very attractive because of its high efficiency and selectivity. In connection with our interest in the search for new reductive transformations, we set out to explore the potential of using FA as a convenient hydrogen source for reduction of levulinic acid (LA) to produce $\gamma$-valerolactone (GVL), an important transformation for biorefinery concepts based on platform chemicals.[17] Because an equimolar amount of FA is always coproduced with LA during the hydrolysis of biomass, the critical challenge for this important transformation lies in the development of a new versatile catalytic material that can facilitate rapid and selective FA decomposition and subsequent LA reduction using the in situ generated H$_2$.[18] We discovered that Au/ZrO$_2$ (Au size ca. 1.8 nm) catalyzed the selective conversion

**SCHEME 3.** Catalytic Conversion of Carbohydrate Biomass into GVL
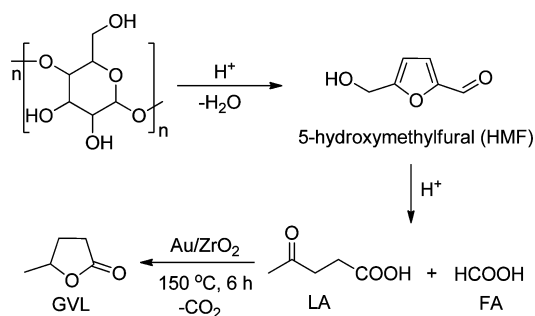


of bioderived LA/FA streams to afford GVL under mild and convenient conditions (Scheme 3).[19] The most salient feature of this process is the use of bio-FA as the sole hydrogen source for cost-competitive GVL production.

An interesting aspect of such Au—FA-mediated LA reduction is that the addition of CO to the reaction mixture exerted no influence on the GVL formation rate. Once again this contrasts with the results obtained for conventional Pd-based catalysts, where the crucial LA hydrogenation was almost completely suppressed by the presence of CO. Another key feature is that ZrO$_2$ is also established as the most suitable support for Au in this process because of its excellent acid tolerance under the harsh conditions. Other supports such as Al$_2$O$_3$, Fe$_2$O$_3$, or CeO$_2$ undergo leaching or even dissolution under the highly acidic conditions required for GVL production from LA/FA mixtures. Significantly, this Au—FA-mediated protocol can also be applied as a suitable reductive amination method for the direct one-pot synthesis of highly valuable pyrrolidone derivatives if a primary amine is present in the reaction mixture (Scheme 4).

## III. Reaction Involving CO and H$_2$O Activation

Of all important reactions involving the use of CO as an essential reactant, the water—gas shift (WGS, CO + H$_2$O $\leftrightarrow$ CO$_2$ + H$_2$) reaction occupies a special position due to its key relevance to several current industrial catalytic technologies such as ammonia synthesis, methanol synthesis, and Fischer—Tropsch processes.[1] From a conceptual point of view, the WGS allows the use of cheap and easily accessible CO and water as a source of hydrogen for fine chemical synthesis. In this sense, catalytic hydrogenations might be performed with a mixture of CO and liquid H$_2$O as the reductant. As opposed to the commonly used molecular H$_2$, the use of CO/H$_2$O couple in catalytic hydrogenations can provide a more straightforward route pertaining to improved chemoselectivity and operational simplicity under

mild conditions.[20] Despite intense research efforts over the last few decades, there is yet to be developed a CO/H$_2$O-mediated reduction process that can compete from an economic point of view with the established technology. This is mostly due to the extremely slow WGS reaction rate although it is thermodynamically favored at lower temperatures ($K_{1073K}$ = 1.105, $K_{300K}$ = 1.5 × 10$^3$).[21]
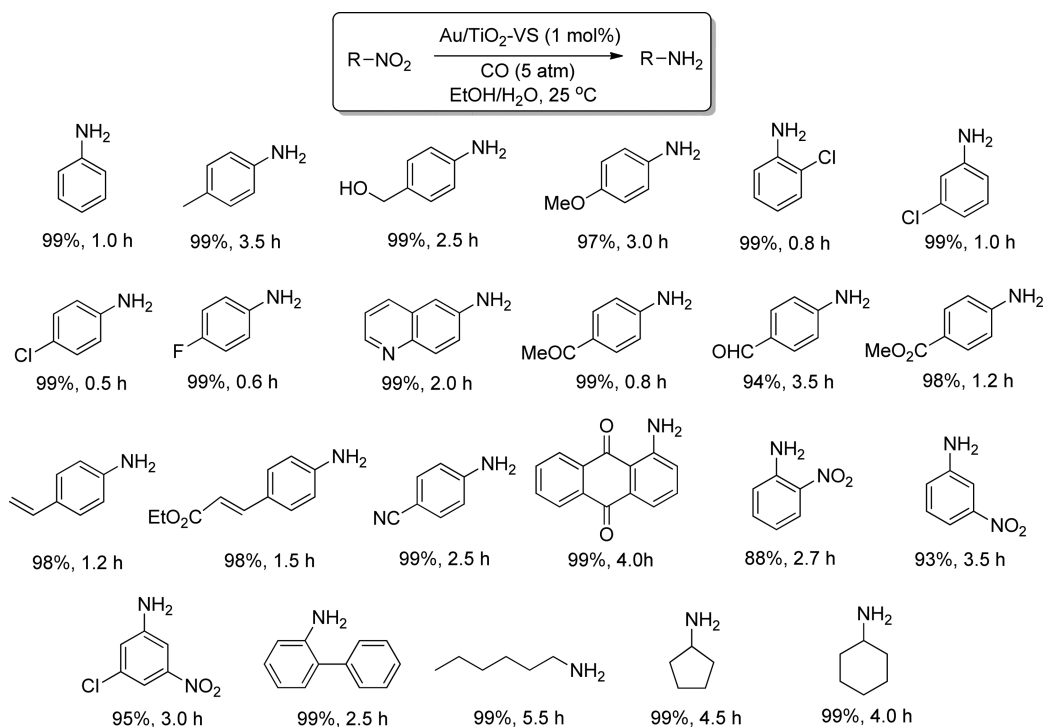
**SCHEME 4.** Pyrrolidone Derivative Production by the Reductive Amination of LA with Primary Amines (or Ammonia)



| 97%, 12 h | 95%, 12 h | 94%, 12 h | 91%, 16 h |

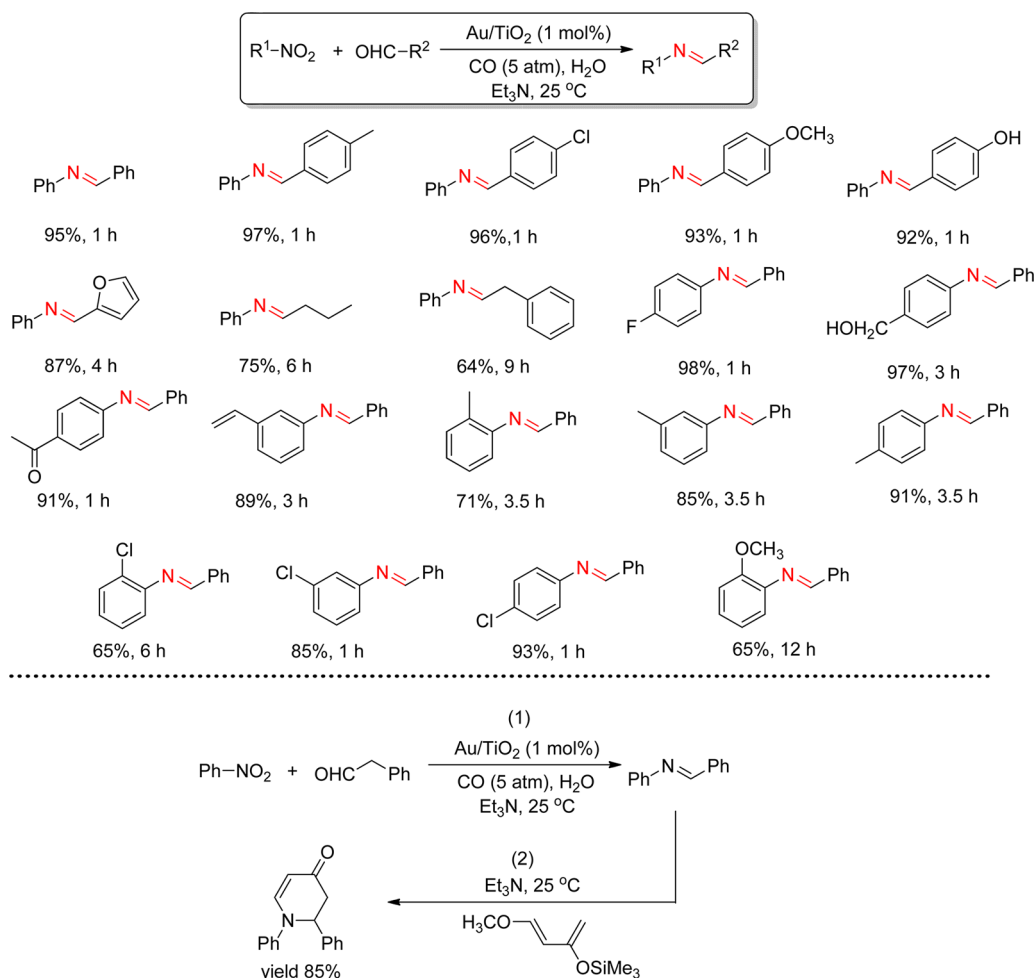| 93%, 16 h | 85%, 16 h | 88%, 24 h | 88%, 24 h |
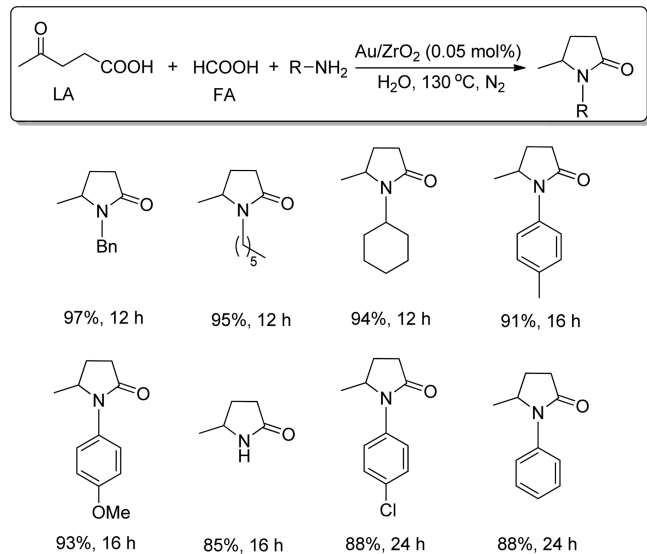
For some time, we have been interested in developing Au-based catalytic transfer hydrogenation (TH) processes that can circumvent the limited hydrogen delivery rate that has plagued previously reported Au-catalyzed selective hydrogenation processes involving H$_2$ as the reductant.[22] Believing that the Au−CO/H$_2$O-mediated reduction would be promoted under mild conditions, we initially investigated the ability of supported gold to catalyze selective reduction of nitro compounds using CO and H$_2$O as the hydrogen source. The nitro to amino group reduction is a process of high practical interest, because anilines and amines are important substances in the chemical industry. Corma et al.[23] showed in a pioneering work that TiO$_2$-supported Au NPs catalyze the highly chemoselective hydrogenation of several functionalized nitroarenes without affecting the integrity of other potentially reducible moieties, but an elevated temperature and high pressure of hydrogen gas are required. Much to our surprise we found that Au/TiO$_2$ can promote highly efficient and chemoselective reduction of nitro compounds in the presence of CO and H$_2$O under exceedingly mild conditions (Scheme 5).[24]

It is noteworthy that other noble metal NPs on TiO$_2$ did not promote the reaction, essentially owing to the intrinsically high affinity of PGMs for CO adsorption, which blocks their activity relative to Au. In this unprecedented

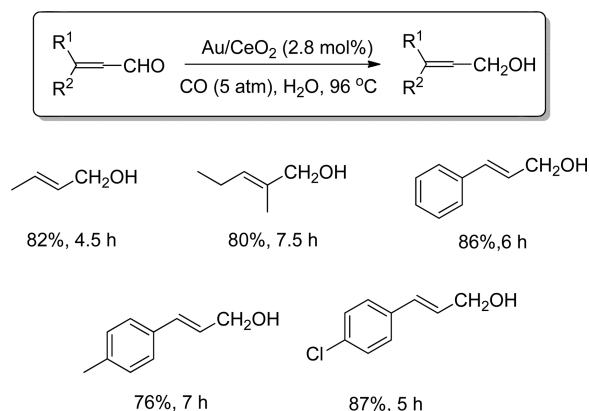**SCHEME 5.** Selected Examples from Reduction of Nitrobenzene to Aniline with CO/H$_2$O



| 99%, 1.0 h | 99%, 3.5 h | 99%, 2.5 h | 97%, 3.0 h | 99%, 0.8 h | 99%, 1.0 h |

| 99%, 0.5 h | 99%, 0.6 h | 99%, 2.0 h | 99%, 0.8 h | 94%, 3.5 h | 98%, 1.2 h |

| 98%, 1.2 h | 98%, 1.5 h | 99%, 2.5 h | 99%, 4.0h | 88%, 2.7 h | 93%, 3.5 h |

| 95%, 3.0 h | 99%, 2.5 h | 99%, 5.5 h | 99%, 4.5 h | 99%, 4.0 h |

**SCHEME 6.** Synthesis of Imines from Nitrobenzenes and Aldehydes



CO/$H_2$O-mediated mild nitro reduction, the combination of very small gold NPS (mean size ca. 1.9 nm) and $TiO_2$ affords the optimal results, demonstrating that both the Au particle size and the nature of the underlying support are essential for obtaining high activity in this reduction. Of note is that at 25 °C and 1 atm of CO, aniline can be exclusively produced over Au/$TiO_2$-VS (VS denotes very small) with an average TOF up to 33 h$^{-1}$, a value that is 97 times greater than that of the reported catalyst under base-free reaction conditions.[25] The reaction shows wide substrate scope for both ring-substituted nitrobenzenes and aliphatic nitro compounds. The advantages of this method were exemplified in a large-scale experiment, where nitrobenzene (0.25 mol scale) was reduced within 2.5 h to aniline in 97% isolated yield using 0.01 mol % Au/$TiO_2$-VS, under a 15 atm CO atmosphere at 100 °C. The Au−CO/$H_2$O-mediated reduction protocol also finds use in the direct one-pot reductive coupling of nitroarenes with various aldehydes to afford corresponding imines (Scheme 6).[26]

An inevitable question is why the Au/$TiO_2$ catalyst is so effective in promoting the CO/$H_2$O-mediated nitro reduction.[24] We believe that the formation of a key gold hydride species via a facile CO-induced reduction of $H_2$O is favored over the Au/$TiO_2$-VS sample under the reaction conditions, although the precise mechanism[23] remains unclear at this stage. In line with this view, the reduction practically did not occur when $H_2$ was applied instead of CO as a reductant. In addition, a stoichiometric amount of $CO_2$ (3 mol of CO uptake per mole of substrate conversion) without accompanying $H_2$ was formed at the end of the reduction. Evidence in support of the chemoselective nature of the reaction comes from the fact that the reduction did not proceed for other unsaturated substrates (styrene, acetophenone, benzaldehyde, and benzonitrile) under otherwise identical conditions. A further mechanistic insight into the reaction pathway is seen in the observation of an intermolecular kinetic isotope effect of $k_H/k_D = 1.54$ upon switching the solvent from $H_2$O to $D_2$O. However, this observation does

**SCHEME 7.** Reduction of $\alpha,\beta$-Unsaturated Aldehydes to Unsaturated Alcohols by CO/H$_2$O Using Au/CeO$_2$



82%, 4.5 h

80%, 7.5 h

86%, 6 h

76%, 7 h

87%, 5 h

**SCHEME 8.** Deoxygenation of Various Epoxides by CO/H$_2$O Using Au/TiO$_2$-VS



99%, 0.7 h    96%, 2 h    97%, 2 h    97%, 2 h    99%, 5 h

97%, 5 h    96%, 4 h    99%, 10 h    98%, 10 h

**SCHEME 9.** Deoxygenation of N-Oxides and Sulfoxides by CO/H$_2$O Using Au/TiO$_2$-VS



84%, 10 h

99%, 5 h

92%, 5 h

not necessarily provide solid evidence regarding the rate-determining step of the reduction.

We subsequently studied the gold-catalyzed chemoselective reduction of $\alpha,\beta$-unsaturated aldehydes (UALs) in the presence of CO and H$_2$O.[27] We found that chemoselective reduction of UALs with CO/H$_2$O proceeds effectively over a supported gold NP catalyst system (Scheme 7); specifically, CeO$_2$ turns out to be the most effective support, showing that both gold and the support surface are required for this particular transformation. This Au/CeO$_2$−CO/H$_2$O system can reduce a range of aliphatic and aromatic UALs to afford the corresponding unsaturated alcohols in good to high yields providing a novel efficient and clean approach to produce useful primary allyl alcohols. It seems that depending on the type of reactant involved in the catalytic process, a certain Au−support combination would be required for a CO/H$_2$O-mediated reduction. As a result of the cooperative interaction between Au and CeO$_2$, this Au−CO/H$_2$O-based protocol can overcome the inherent problem of low efficiency associated with the previously reported Au-based UAL hydrogenation systems.[28,29]

Furthermore, we have discovered the distinct ability of the Au−CO/H$_2$O protocol to catalyze de-epoxidation (Scheme 8).[30] Deoxygenation of epoxides to alkenes is a valuable reaction in organic synthesis and biological chemistry. From a sustainable and practical synthetic point of view, the development of a simple and efficient catalytic system for de-epoxidation is of high actual interest. We found that using CO/H$_2$O as a reducing agent along with Au/TiO$_2$-VS provides highly efficient deoxygenation of many epoxides into the corresponding alkenes. Further studies show that this Au−CO/H$_2$O protocol also works well in the deoxygenation of N-oxides and sulfoxides (Scheme 9).
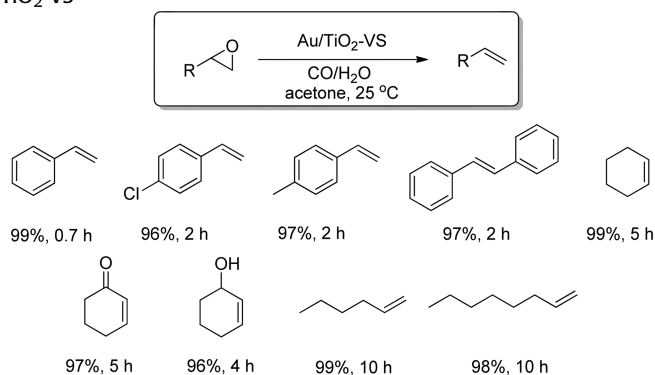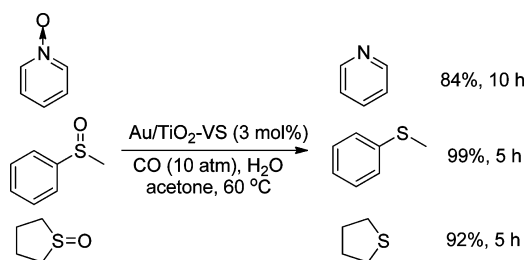
Notably, a correlation between the de-epoxidation and the corresponding low-temperature CO oxidation activity was observed for a series of gold catalysts deposited on different support materials, demonstrating that the adsorption/activation of CO is the essential step involved in these deoxygenation processes.

From the above-discussed reactions, it can be seen that the coactivation of CO and H$_2$O is essential for a relevant reduction process. Thus, it is also expected that supported Au can offer new opportunities to develop novel efficient hydration processes. The hydration of nitriles is the most atom-economical reaction and a sustainable method for the preparation of primary amides, which are versatile building blocks in synthetic organic chemistry. Traditional nitrile hydration protocols commonly require an inconvenient inert atmosphere and harsh conditions (generally above 140 °C) for their successful use. Very recently, we found that by using Au/TiO$_2$-VS, it is possible to realize a versatile and efficient hydration of a broad range of chemically diverse nitriles into valuable amides in neutral water, under mild atmospheric conditions.[31] Notably, an impressive TOF value of 25 000 h$^{-1}$ was reached in the hydration of pyrazinecarbonitrile to produce pyrazinecarboxamide, an antibacterial agent used for the treatment of tuberculosis (Scheme 10).

The reaction cleanly took place in neat water, under air, with a gold loading of only 0.001 mol %. In addition, after recycling the catalyst 10 times by simple filtration, an unprecedented cumulative TON of 1 000 000 can be realized. The high-yield synthesis of $\varepsilon$-caprolactam by hydration/ cyclization of 6-aminocapronitrile is another example of the synthetic usefulness of this heterogeneous system.

## IV. Reaction Involving Alcohol Activation

Carbon–nitrogen or carbon–carbon (C–X) bond formation, a vital approach to increase the molecular complexity of a

simple organic substrate, is one of the central themes in modern synthetic chemistry. Although a plethora of methods have been developed, the search for new, mild, efficient, and straightforward routes that minimize waste generation continues to be an active and challenging topical subject.[32] An elegant method is the transition-metal-catalyzed borrowing hydrogen (BH, also known as hydrogen autotransfer) strategy involving alcohol activation,[33] which provides most direct and clean access to C–X bond formation via cross-coupling of alcohols or amines. The excellent performance of supported gold NPs for transfer of hydrogen[23] has led us to investigate the possibilities offered by gold-mediated alcohol activation in facilitating versatile and efficient C–N or C–C bond formation.

Our studies indicate that Au/TiO$_2$-VS can act as an efficient solid catalyst for clean and atom-efficient N-alkylation of amines with equimolar amounts of alcohols in excellent yields under mild and base-free conditions (Scheme 11).[34] Various kinds of unsymmetrically substituted secondary amines can be synthesized in high yield. Notably, this gold-catalyzed transformation can also successfully facilitate the 100 mmol scale cross-coupling of aniline with benzyl alcohol under solvent-free conditions, and an
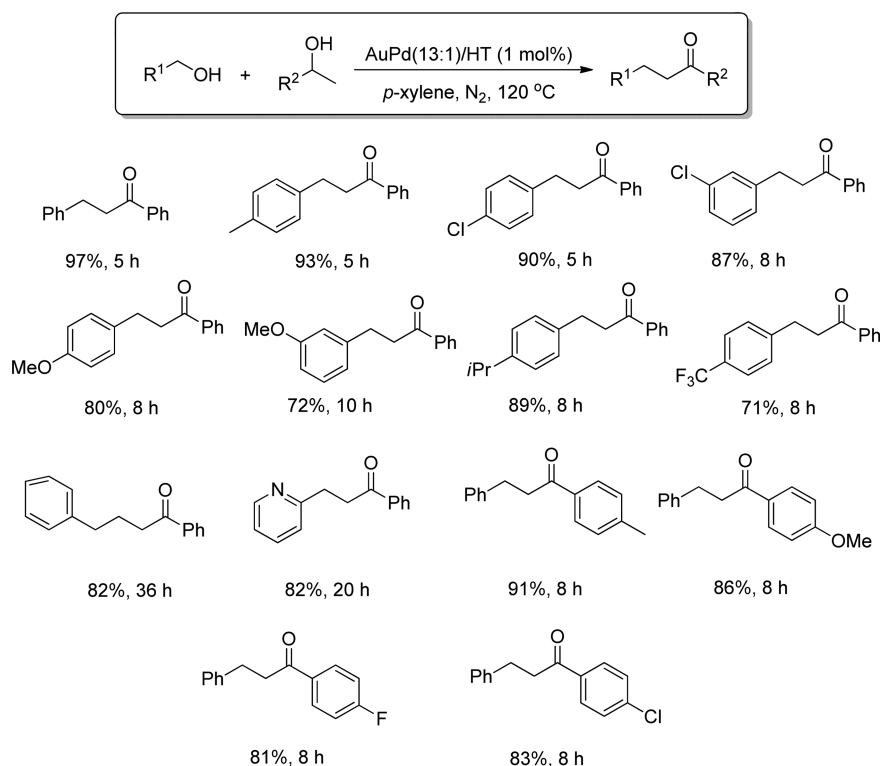
**SCHEME 10.** Pyrazinecarboxamide and $\varepsilon$-Caprolactam Synthesis from Corresponding Nitriles
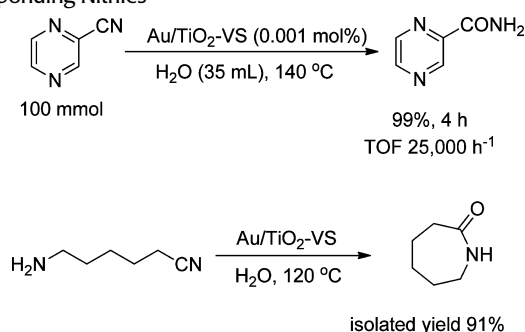


**SCHEME 11.** Au/TiO$_2$-VS-Catalyzed N-Alkylation of Amines with Alcohols
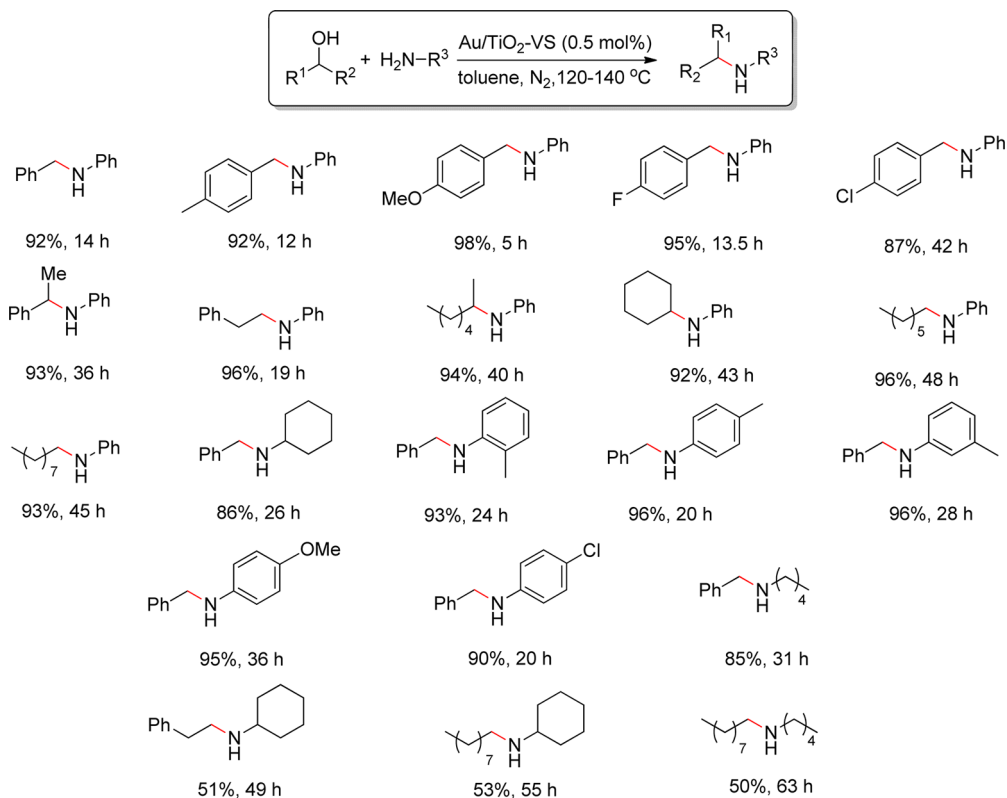
**SCHEME 12.** Cross-Coupling of Secondary and Primary Alcohols



impressive isolated yield (96%) was achieved after completion of the reaction. Although detailed mechanic studies remain to be carried out,[35] the Hammett kinetic experiments with a negative value ($\rho = -1.32$, $r^2 = 0.99$) indicated that initial $\beta$-hydride elimination of the alcohol may be involved in the rate-limiting step of the reaction. Moreover, this Au-catalyzed protocol can also be applied for the direct synthesis of secondary or tertiary amines from the amination of stoichiometric amounts of alcohols with inexpensive and readily available nitro compounds or urea as a convenient nitrogen source.[36,37]

Encouraged by the results of amine synthesis via BH strategy, C−C bond formation via cross-coupling of secondary and primary alcohols was subsequently investigated.[38] We found that gold NPs (ca. 2.4 nm) in combination with a basic layered clay of hydrotalcite (HT) can work as an efficient multitask catalyst capable of cross-coupling of secondary and primary benzylic alcohols via a facile sequential dehydrogenation/aldol condensation/TH pathway. Aiming to further improve the target product selectivity by promoting the rate-determining TH step, a series of bimetallic Au−Pd/HT catalysts with various Au/Pd atomic ratios (13:1−5:2) have been screened. It turns out that Au−Pd(13:1)/HT can deliver an excellent selectivity (97%) toward the target product. As depicted in Scheme 12, this direct

Au−Pd/HT-mediated C−C coupling protocol is applicable to a range of primary and secondary alcohols. To our knowledge, this novel one-pot Au-based catalytic protocol constitutes the first additive-free, recyclable catalytic system for clean and efficient C−C bond construction via alcohol cross-coupling.

## V. Reaction Involving $H_2$ Activation

Catalytic hydrogenations of unsaturated organic compounds constitute an important class of chemical transformations and find broad applications both in chemical industry and in laboratory organic synthesis.[39] The majority of hydrogenation reactions involve the direct use of $H_2$ as the hydrogen source, and they are catalyzed by conventional transition metal (e.g., Pt, Pd, and Ni) systems. Over the past decade, supported gold NPs have emerged as exceptionally selective catalysts for the reduction of a target functionality in multifunctional reactants.[6b] In this context, supported Au catalysts have contributed substantially to heterogeneous catalytic hydrogenation by improving the selectivity to an unprecedented level. However, the application of this new technique is largely limited by the inability of gold to split $H_2$.

We have recently found that gold NPs supported on high surface area titania (Au/HAS-TiO_2) catalyze the chemoselective

**SCHEME 13.** Hydrogenation of Heteroaromatic Nitrogen Compounds
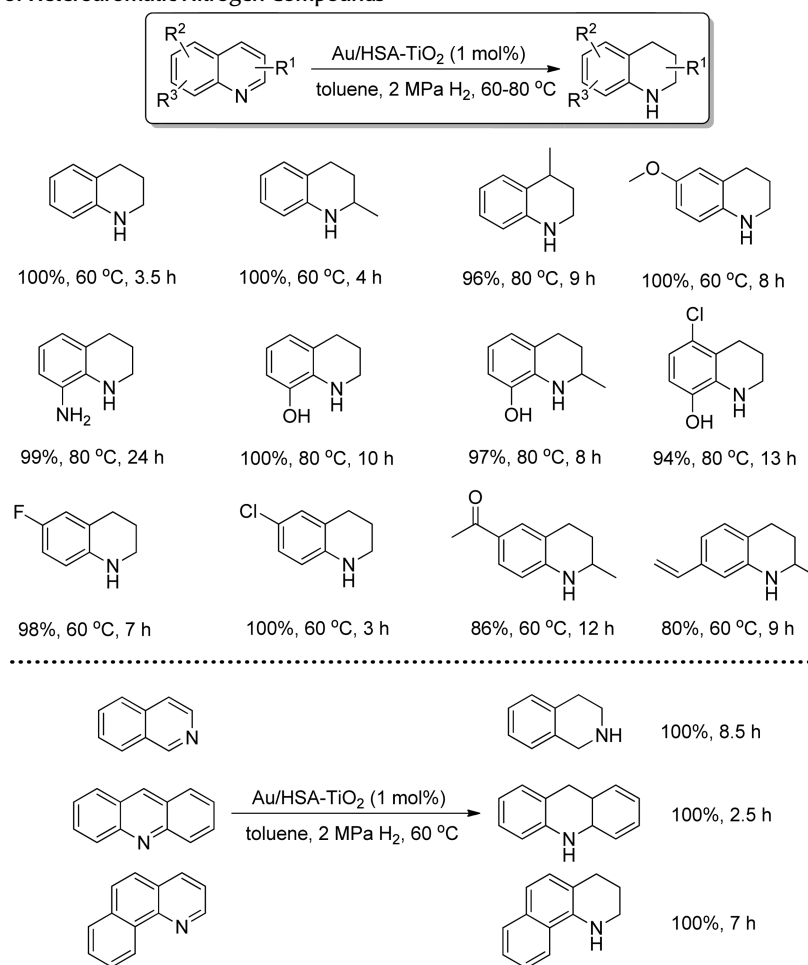


hydrogenation of functionalized quinolines with $H_2$ under mild reaction conditions (Scheme 13).[40] Our results point toward an unexpected role for quinolines in gold-mediated hydrogenation reactions, namely, that of promoter; this is in stark contrast to what prevails in the traditional PGM-based catalyst systems,[41] in which quinolines and their derivatives typically act as poisons. As a result of the remarkable promotional effect of quinoline molecules to $H_2$ activation over supported gold, the transformation can proceed smoothly under very mild conditions (even at 25 °C). Of note is that various synthetically useful functional groups including halogens and olefin remain intact during the hydrogenation of quinolines. Moreover, the protocol also shows promise for the regiospecific hydrogenation of the heterocyclic ring of a variety of other biologically important heteroaromatic nitrogen compounds such as isoquinoline, acridine, and 7,8-benzoquinoline in a facile manner.

To clarify the origin of this unusual phenomenon, we studied the $H_2$–$D_2$ exchange reaction over a variety of
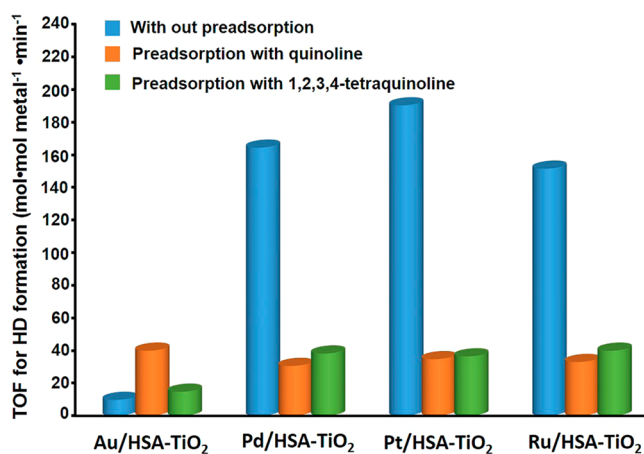


**FIGURE 3.** Rate for HD formation over various noble metal-based catalysts.

catalysts. The rate of HD formation and the turnover frequency (TOF) for each catalyst sample was estimated at 60 °C without or with preadsorbed quinoline or its hydrogenated products (Figure 3). It is revealed that as opposed to

the case without preadsorption or in the presence of pre-adsorbed tetrahydroquinoline, the $H_2-D_2$ exchange proceeds much more rapidly over Au/HSA-TiO$_2$ preadsorbed with quinoline molecules. This is in strong contrast to what occurs with the corresponding traditional PGM-based catalysts, in which the rate of HD formation was heavily decreased when the samples were preadsorbed with relevant N-heterocylic compounds. These results unambiguously demonstrate that quinoline, a poison for traditional noble metal-containing hydrogenation catalysts, can act as a promoter for the Au-catalyzed hydrogenation processes via facilitating the activation of H$_2$.

## VI. Concluding Remarks

Over the past few years, supported gold has emerged as an efficient catalyst with considerable synthetic potential for a wide array of organic transformations. In this Account, we have detailed our recent studies on the development of a range of novel Au-catalyzed green chemical reactions that can proceed under exceedingly mild and clean conditions guided by the textbook principle that catalysis simply requires the formation of surface intermediates of moderate stability. As an effort to develop green and sustainable chemistry in the field of chemical synthesis, a variety of simple and efficient methods for highly chemoselective transformation as well as C—C and C—N bond formations were established. A common theme throughout these studies is the important and indispensible role of the supported gold in promoting the activation of a plethora of industrially and economically important small molecules. These new methodologies may find synthetic applications in a broad spectrum of settings, including fine chemical synthesis, biomass valorization, and materials science. It is remarkable that in all the reactions practiced the supported gold NPs exhibited reactivity far superior to traditional PGM catalysts, including Pd, Pt, Ru, Rh, and Ir. The results presented here open an array of possibilities for further research in reactions where the less abundant PGM-based catalysts might be replaced by gold-based technologies.

## BIOGRAPHICAL INFORMATION

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