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Sustainable Gold Catalysis

Efficient and Selective Room-Temperature Gold-Catalyzed Reduction of Nitro Compounds with CO and H_2O as the Hydrogen Source**

Lin He, Lu-Cun Wang, Hao Sun, Ji Ni, Yong Cao,* He-Yong He, and Kang-Nian Fan

The selective reduction of nitro compounds to the corresponding amines is one of the most important transformations in synthetic organic chemistry.[1] Although a number of methods have been developed, the search for new facile, chemoselective, cost-effective, and environmentally friendly procedures that avoid the use of expensive and hazardous stoichiometric reducing agents in large excess has attracted substantial interest.[2] An attractive alternative is the catalytic reduction of nitro compounds with cheap and readily available CO and H_2O as the hydrogen source. In particular, the specific reduction of a nitro group under mild conditions in the presence of other functionalities is desirable. As opposed to commonly used catalytic hydrogenation, which involves H_2 as the reductant,[3] the use of CO and H_2O as the hydrogen source leads to remarkable chemoselectivity and is of great industrial potential,[4] especially when an efficient and reusable catalytic system can be employed. However, relevant studies have largely focused on various ruthenium- or rhodium-based homogeneous systems,[5] which are not practically useful because of their low turnover numbers (TONs) and turnover frequencies (TOFs), and the requirement of organic and/or inorganic bases in large excess as cocatalysts. Despite tremendous efforts in the last two decades,[6] few examples of heterogeneous catalyst systems for the reduction of a nitro compounds with CO/H_2O as the reductant have appeared, and these systems have often suffered from low efficiency as well as limited substrate scope and catalyst reusability.

Supported gold nanoparticles have emerged as active and extremely selective catalysts for a broad array of organic reactions owing to their unique catalytic properties under mild conditions.[7] Whereas the potential of gold-catalyzed selective oxidation reactions for atom-economical and sustainable organic synthesis is widely recognized,[8] the possibilities offered by catalytic reduction with supported gold nanoparticles have remained largely unexplored.[9] Recently, Corma and Serna reported that the chemoselective reduction of a nitro group in the presence of other reducible functionalities is possible with supported gold nanoparticles.[7d,10] One critical limitation associated with the current gold-catalyzed processes for the reduction of nitro compounds, however, is that the hydrogen-delivery rate is too low for practical applications.[9a,11] Herein, we describe a highly effective gold-catalyzed, CO/H_2O-mediated reduction that circumvents inconvenient H_2 activation to enable the rapid, efficient, and chemoselective reduction of a wide range of organic nitro compounds under mild conditions. The reaction is general and proceeds efficiently under an atmosphere of CO at room temperature. To the best of our knowledge, this gold-based catalytic system is the most efficient, simple, and environmentally friendly catalytic system for the selective reduction of nitro compounds that has been developed to date.

Initially, nitrobenzene was used as a model substrate in investigations of the catalytic activity of different solid catalysts under a CO atmosphere at room temperature. The Pt, Pd, and Ru catalysts tested were not active for this reaction. Of the various gold catalysts tested, very small Au nanoparticles (with a diameter of about 1.9 nm) supported on TiO_2 showed the highest activity (this catalyst system is denoted as Au/TiO_2-VS; see details in the Supporting Information). As observed for other gold-catalyzed processes,[12] both the nature of the support and the particle size had a strong influence on the activity of the Au nanoparticles. Thus, at 25 °C under 1 atm of CO, aniline was produced exclusively with an average TOF in the range of 0.9–33 h^{-1} (Table 1, entries 1–4). No trace of azo or azoxy compounds, byproducts frequently formed under homogeneous CO/H_2O catalysis,[5] was observed. Of particular note is that the reaction proceeded efficiently at a pressure of only 1 atm, which enables the use of common glass reactors. There are very few catalysts that are effective under such mild conditions, the most active of which is a homogeneous $[Rh(CO)_2(acac)]$ complex in the presence of a large excess of NaOH.[5b] However, the TOF of Au/TiO_2-VS is 97 times greater than that of $[Rh(CO)_2(acac)]$ under base-free reaction conditions (Table 1, entry 9). The high activity of Au/TiO_2-VS under ambient conditions significantly improves the economical and environmental impact of this gold-catalyzed reduction process.

Next, the reaction conditions were optimized for the reduction of nitrobenzene through variation of the pressure and solvent. First, the effect of the pressure of CO (P_{CO}) was investigated. The reaction rate increased dramatically as P_{CO} was raised from 1 to 5 atm (Table 1, entries 1, 10, and 11)[13] but leveled off at 5–15 atm (Table 1, entries 12 and 13). These

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[*] L. He, Dr. L. C. Wang, H. Sun, J. Ni, Prof. Y. Cao, Prof. H. Y. He, Prof. K. N. Fan
Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials
Department of Chemistry, Fudan University
Shanghai 200433 (China)
Fax: (+86) 21-6564-3774
E-mail: yongcao@fudan.edu.cn

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Table 1: Reduction of nitrobenzene to aniline with CO/H_2O in the presence of various catalysts at 25 °C.[a]

Entry	Catalyst	P_{CO} [atm]	t [h]	Yield[b] [%]	Average TOF [h^{-1}]
1	Au/TiO_2-VS	1	3	> 99	33
2[c]	Au/TiO_2	1	3	57	19
3[c]	Au/Fe_2O_3	1	3	3	0.9
4[c]	Au/CeO_2	1	3	17	5.7
5[c]	Pt/TiO_2	1	3	n.r.	–
6[c]	Pd/C	1	3	n.r.	–
7[c]	Ru/Al_2O_3	1	3	n.r.	–
8	TiO_2 (P25)	1	3	n.r.	–
9[d]	[Rh(CO)$_2$(acac)]	1	3	0.4 (15)	0.34 (12.5)
10	Au/TiO_2-VS	3	2	> 99	50
11	Au/TiO_2-VS	5	1	> 99	99
12	Au/TiO_2-VS	10	1	> 99	99
13	Au/TiO_2-VS	15	1	> 99	99
14[e]	Au/TiO_2-VS	5	2.5	> 99	40

[a] Reaction conditions: $PhNO_2$ (1 mmol), metal (1 mol%), EtOH/H_2O (15 mL, 2:1 v/v), 25 °C; acac = acetylacetonate, n.r. = no reaction. [b] The yield was determined by GC (internal standard: *n*-decane). [c] Au/TiO_2 and Au/Fe_2O_3 were provided by the World Gold Council. Au/CeO_2 and Pt/TiO_2 were prepared according to references [7e] and [2e], respectively. Pd/C and Ru/Al_2O_3 were provided by Alfa Aesar. [d] Reference [5b]: $PhNO_2$ (5 mmol), Rh (0.4 mol%), 2-methoxyethanol/H_2O (20 mL, 3:1 v/v), 25 °C. Values in parentheses refer to a reaction carried out under the following conditions: $PhNO_2$ (5 mmol), Rh (0.4 mol%), 2-methoxyethanol/5 N NaOH (20 mL, 3:1 v/v), 25 °C. [e] The reaction was carried out under the following conditions: $PhNO_2$ (1 mmol), Au/TiO_2-VS (1 mol% Au), H_2O (15 mL), 25 °C.

experiments were conducted in a closed autoclave with CO at a constant reaction pressure, so that as the reaction proceeded and CO was consumed, this reductant was replenished. Studies on the effect of the solvent revealed that ethanol was the solvent of choice.[14] When the solvent was changed to THF or *N*,*N*-dimethylformamide (DMF), the conversion of nitrobenzene decreased to 65 and 52%, respectively (see Table S1, entries 2 and 3 in the Supporting Information). An even lower conversion was found when the solvent was changed to acetone (see Table S1, entry 4 in the Supporting Information). Interestingly, it was found that the reaction proceeded smoothly even in neat water in the absence of an organic solvent (Table 1, entry 14). This result was extremely welcome, not only because the reaction in water was very clean, but also because in this particular case with Au/TiO_2-VS, a triphasic system of an aqueous phase, an organic phase, and an inorganic solid was formed, which enabled the straightforward separation of both the catalyst and the product from the reaction mixture. No reduction of nitro compounds has been reported previously that proceeds with CO/H_2O in neat water at room temperature under base-free conditions in the presence of a heterogeneous catalyst.

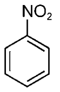
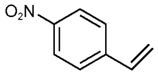
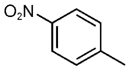
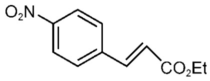
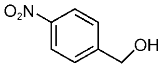
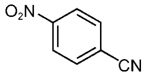
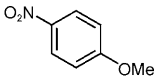
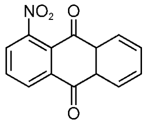
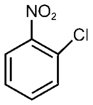
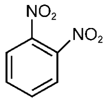
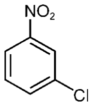
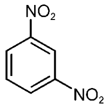
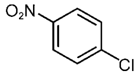
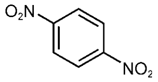
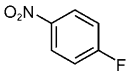
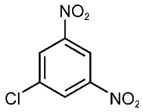
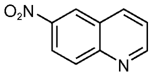
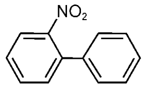
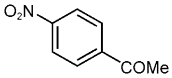
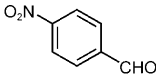
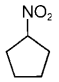
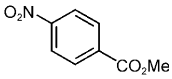
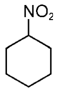
To verify whether the observed catalysis was due to solid Au/TiO_2-VS or leached gold species, we carried out the reduction of nitrobenzene under the conditions described in entry 1 of Table 1 and removed the Au/TiO_2-VS catalyst from the reaction mixture by filtration at approximately 40% conversion of nitrobenzene. After removal of the Au/TiO_2-VS catalyst, the filtrate was again held at 25 °C under CO (5 atm). In this case, no reaction proceeded. It was confirmed by inductively coupled plasma (ICP) analysis that no gold was present in the filtrate (below 0.10 ppm). These results ruled out any contribution to the observed catalysis from gold species that had leached into the reaction solution and showed that the observed catalysis was intrinsically heterogeneous.

To examine the scope of the CO/H_2O reduction of nitro groups with Au/TiO_2-VS, we investigated the reduction of a series of structurally diverse nitro compounds. The reaction was remarkably selective for the synthesis of a variety of aminoaromatic compounds, regardless of the presence of electron-donor or electron-acceptor substituents (Table 2, entries 2–4). Halogen-substituted nitrobenzenes were reduced cleanly to the corresponding chloro- or fluoroanilines without any dehalogenation (Table 2, entries 5–8), a side reaction often encountered with other procedures, including catalytic hydrogenation. 6-Nitroquinoline was reduced to 6-aminoquinoline; thus, the heterocyclic ring remained intact (Table 2, entry 9). *p*-Nitroacetophenone, *p*-cyanonitrobenzene, and 1-nitroanthraquinone were also reduced to the corresponding amines (aminoanthraquinone is a key fragment in dyes), without reduction of the C=O or C≡N groups (Table 2, entries 10, 15, and 16). Aldehyde, ester, and alkene functionalities present as substituents on the aromatic ring also remained unaffected during the reduction of nitrobenzenes by this procedure (Table 2, entries 11–14).[14] Notably, the monoreduction of dinitrobenzenes also occurred selectively to give the corresponding nitroanilines as the major products (Table 2, entries 17–20). Many conventional procedures involving hydride reducing agents, hydrogenation, or indium reagents failed to show such high chemoselectivity.[2] Moreover, this CO/H_2O reduction system was applicable to non-activated aliphatic nitro compounds; the corresponding amines were obtained in almost quantitative yield (Table 2, entries 22–24).

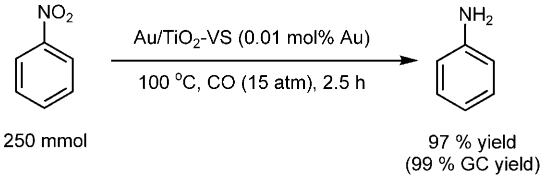
The applicability of the present synthetic protocol was highlighted by a reduction of nitrobenzene on a 250 mmol scale with 0.01 mol% Au at 100 °C under CO (15 atm; Scheme 1). The reduction was complete within 2.5 h, during which time the TON (based on Au) of nitrobenzene approached 9950 with an excellent average TOF of approximately 3980 h^{-1}. When the reaction was carried out on this scale, the Au/TiO_2-VS catalyst could also be reused without loss of activity (see the Supporting Information). These TON and TOF values observed with Au/TiO_2-VS are significantly higher than those for other active catalysts, such as [$Ru_3(CO)_{12}$]/Et_3N (TON = 1778, TOF = 889 h^{-1}, 20 atm, 150 °C),[6d] [$Ru_3(CO)_{12}$]/Ph-bian (TON = 512, TOF = 341 h^{-1}, 30 atm, 165 °C; Ph-bian = bis(phenylimino)acenaphtene),[6c] [$Ru_3(CO)_9$(peo-dppsa)$_3$] (TON = 975, TOF = 97.5 h^{-1}, 40 atm, 140 °C; peo-dppsa = poly(ethylene oxide)-substituted 4-(diphenylphosphanyl)benzenesulfonamide),[5e] and Au/Fe(OH)$_x$ (TON = 1960, TOF = 1287 h^{-1}, 15 atm, 100 °C).[6a]

In terms of the mechanism of reduction, one might envisage that the present gold-catalyzed reaction could proceed by the reduction of nitro compounds with hydrogen gas generated in situ from the low-temperature water–gas shift (LTWGS) reaction ($CO + H_2O \rightarrow CO_2 + H_2$, generally in the temperature range of 150–250 °C).[15] However, this

Table 2: Reduction of nitro compounds to the corresponding amines with CO/H_2O.[a]

Entry	Substrate	t [h]	Conv./Select.[b] [%]	Entry	Substrate	t [h]	Conv./Select.[b] [%]
1		1.0	99/>99	13		1.2	99/99
2		3.5	99/>99	14		1.5	99/99
3		2.5	99/>99	15		2.5	99/>99
4		3.0	98/99	16[c]		4.0	99/>99
5		0.8	99/>99	17		2.7	97/91[d]
6		1.0	99/>99	18		3.5	96/97[d]
7		0.5	99/>99	19[c]		4.0	98/94[d]
8		0.6	99/>99	20		3.0	99/96[d]
9		2.0	99/>99	21		2.5	99/>99
10		0.8	99/>99	22		5.5	99/>99
11		3.5	99/95	23		4.5	99/>99
12		1.2	99/99	24		4.0	99/>99

[a] Reaction conditions: substrate (1 mmol), Au/TiO_2-VS (1 mol% Au), EtOH/H_2O (15 mL, 2:1 v/v), CO (5 atm), 25 °C. [b] Conversion and selectivity were determined by GC (internal standard: *n*-decane). [c] DMF/H_2O (15 mL, 2:1 v/v). [d] Selectivity for the nitroaniline.



Scheme 1. Reduction of nitrobenzene on a 250 mmol scale.

possibility can be eliminated, as the reduction practically did not occur when H_2 was used instead of CO as the reductant (see the Supporting Information). Although the precise route and mechanism by which the reduction occurs are not yet fully understood, the transient Au–H species[16] formed by the CO-induced reduction of H_2O[7a] could be involved in the rate-determining step according to a kinetic study based on H_2O:D_2O switching ($k_H/k_D = 1.54 \pm 0.02$). Therefore, the fact that ultrasmall Au nanoparticles supported on titania can substantially facilitate the crucial Au–H bond-forming step appears to be a key factor in the high activity of the catalyst for nitro group reduction and is in line with the broad literature documenting the catalytic activity of supported gold nanoparticles.[17]

In conclusion, we have developed an exceedingly efficient and highly chemoselective gold-catalyzed approach for the clean reduction of a wide range of organic nitro compounds to the corresponding amines with cheap and readily accessible CO and H_2O as the hydrogen source. The unprecedented room-temperature activity coupled with the low operational pressure make this method readily adaptable to production on an industrial scale, where safety and environmental factors are of particular concern. We believe that the results presented herein open up a new avenue for the application of supported gold catalysts to green and sustainable organic synthesis.

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[14] The reduction did not proceed when other unsaturated compounds without a nitro group (styrene, acetophenone, benzaldehyde, and benzonitrile) were tested as substrates under the same conditions (see Table S2 in the Supporting Information).

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